HIV Curriculum

For the Health Professional

BIPAI
Baylor International
Pediatric AIDS Initiative
HIV Curriculum

For the Health Professional

Baylor International Pediatric AIDS Initiative
Baylor College of Medicine
Houston, Texas, U.S.A.
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Generously supported by the
Bristol-Myers Squibb Secure the Future Initiative

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This is the fourth edition of the HIV Curriculum for the Health Professional, a book written and produced by the Baylor College of Medicine International Pediatric AIDS Initiative in collaboration with international partners. The Baylor College of Medicine International Pediatric AIDS Initiative (BIPAI) is a multidisciplinary team of health professionals based at the Baylor College of Medicine. Prior to launching this curriculum project in 1999, the BIPAI team had experience with health-professional education in developing-country settings such as Romania, Mexico, and Panama. The idea of creating a comprehensive curriculum on HIV/AIDS for nurses was a direct result of lessons learned from those early experiences. In order to develop a curriculum that would be appropriate for use in southern Africa, we conducted a needs assessment in the region and relied heavily on our African partners for content and feedback. The curriculum that follows is the product of years of close collaboration between BIPAI and our African colleagues.

The first edition of this book was titled the HIV Nursing Curriculum. Nurses have been the front-line medical professionals responding to the pandemic, providing hands-on care to patients and comfort to families on a daily basis. It is critical that nurses be honored, respected, and valued for their professional and personal contributions to people living with HIV/AIDS. It is also critical that they be educated about the disease and empowered to serve as advocates for their patients and themselves. To this end, the first edition of this HIV training curriculum was written specifically for nurses. However, we soon learned that health professionals of all kinds were seeking and benefiting from the information in the “HIV Nursing Curriculum”. The subsequent three editions were written with the intent of providing nurses, physicians, social workers, counselors, home-care workers, and students with the information they need to understand HIV and to offer the highest standard of compassionate care for HIV-infected patients. This revised, fourth edition of the HIV Curriculum for the Health Professional updates these tools with the latest research and practice insights presented for immediate, effective use in the field.

This curriculum reflects our expertise and experience in pediatrics, but it is designed to improve the care of patients of all ages. Nearly 50,000 copies of the first three editions of this publication have been distributed in 51 countries since the first edition became available in 2001. The curriculum has evolved with each edition; we hope it is becoming ever more practical, user-friendly, and comprehensive.

This HIV Curriculum for the Health Professional was made possible by start-up funding from the Bristol-Myers Squibb Company’s SECURE THE FUTURE™ initiative. Working in partnership with the African nations of Botswana, Lesotho, Namibia, South Africa, and Swaziland, SECURE THE FUTURE™ is designed to find solutions for the management of HIV/AIDS in women and children and to provide resources to improve community education and patient support. The largest commitment of its kind ever made, the Bristol-Myers Squibb SECURE THE FUTURE™ program is intended to complement the broader efforts of governments to identify relevant and sustainable responses to the HIV/AIDS pandemic. Additional sponsorship for development, printing, and distribution of this edition of the HIV Curriculum for the Health Professional was provided by the Fogarty International Center of the National Institutes of Health (NIH/FIC), the President’s
HIV Curriculum for the Health Professional


One important difference between the fourth edition HIV Curriculum for the Health Professional and the versions that preceded it is that the fourth edition will not be printed and distributed centrally from the BIPAI headquarters in Houston, Texas, USA. This decision was not taken lightly, as we recognize that many end-users (health professionals in the field) will not have ready broadband access to the material at the bedside where it might be most useful to them. We have made the fourth edition available in print-ready format online for local production, and we encourage our partner organizations and other NGOs to print as needed. The reasons for decentralizing curriculum production are many, and include:

- More environmentally friendly (not using jet fuel to ship heavy books across the world)
- Provides work and revenue to local businesses (printing companies)
- Quality standard can be maintained by providing non-editable .pdf
- Programs can control their own inventory of curriculum
- Curriculum can be modified and edited on-line and kept up-to-date more easily than if large central stores are produced
- Resources previously allocated for shipping costs can be devoted to programs to benefit HIV-infected individuals more directly

Acknowledgments

We are indebted to our international cadre of partners, who have shaped each module in this publication. We would not have undertaken the development of a full curriculum on HIV/AIDS without the support and encouragement of our professional partners in Africa. This publication represents a global effort by talented authors and contributors from partner countries the world over.

Special thanks to graphic artist DeeDee Tomkins, who designed this book; to editor Gabe Waggonner, who reviewed and improved each module; and to photographer Smiley N. Pool, who provided many of the images, including the cover photo.

Over the past several years, the education team of the Baylor International Pediatric AIDS Initiative has worked intensely in the development and refinement of this material. Friendships have been forged and have deepened as we journeyed together, both literally and figuratively, in the development of this curriculum. We are grateful to all who have made this incredible experience possible.

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Epidemiology of HIV
Meg Gwynne Ferris, PhD, MPH

Objectives
1. Review the most recent data on the global effect of the human immunodeficiency virus (HIV)/AIDS pandemic.
2. Summarize theories about the origin of HIV.
3. Review the modes of HIV transmission.
4. Identify risk behaviors that facilitate HIV transmission.
5. Analyze societal factors that are contributing to the expanding pandemic.
6. Analyze HIV’s effects on the future of people living in regions with a high HIV disease burden.

Key Points
1. HIV is a preventable infection.
2. The incidence of new HIV infections has leveled off but is not in rapid decline.
3. Approximately 90% of all HIV-positive people in the world live in developing countries.
4. Many societal factors are driving the spread of the epidemic, including people on the move, complex emergencies, cultural factors (e.g., the status of women), poverty, stigma, and denial.
5. HIV is most commonly transmitted during high-risk events such as unprotected sex with an infected person; blood-to-blood contact with an infected person; and pregnancy, childbirth, and breastfeeding by HIV-positive women.

Overview
Epidemiology is the study of the determinants and distribution of disease. In a world characterized by the rapid movement of people, goods, and information, human immunodeficiency virus (HIV)/AIDS has rapidly touched nearly every nation on this planet. This chapter considers the epidemiology of one of the most devastating and complex infectious diseases of the late 20th and early 21st centuries.

Global HIV/AIDS Statistics
According to UNAIDS, at the end of 2007, 33.2 million people worldwide were estimated to be living with HIV or AIDS. Most of them reside in the developing world; about 68% live in sub-Saharan Africa. The number of incident (new) HIV infections is believed to have peaked in the late 1990s at more than 3 million new infections per year and was at 2.5 million new infections in 2007. Among the new infections, 420,000 were among children younger than 15 years. This means that in 2007 there were nearly 6,850 new HIV infections globally per day, along with approximately 2.1 million AIDS-related deaths. The estimated 1.7 million new HIV infections in sub-Saharan Africa in 2007 mean that as many as 22.5 million Africans may now be living with the virus. Most are unaware that they are infected.

Between 2006 and 2007, UNAIDS downwardly revised its estimates of HIV infection globally. In 2006, the estimated number of people living with HIV/AIDS globally was 39.5 million; in 2007, the number was 33.2 million. UNAIDS has emphasized that although there are some localized reductions in HIV prevalence, the most important reason for this downward revision is several changes to how UNAIDS calculates its estimates. In other words, there has not been a major shift in patterns of HIV transmission or a true reduction in HIV prevalence. The estimates were previously inflated, and because of improved and more precise methods, the estimates have been revised to more accurately reflect reality.

Every country in the world was, at some point, a low-prevalence country. HIV prevalence among pregnant women attending antenatal clinics in South Africa was less than 1% in 1990, and today it is around 29%. To understand this pandemic, we must examine the origins of the disease as well as the many biological and socioeconomic factors that foment its growth.
Where Did HIV Come From?

AIDS did not come to wide public attention until mid-1981, after clusters of deaths from pneumocystis jirovecii (formerly known as PCP [pneumocystis carinii pneumonia]) and Kaposi sarcoma were reported among young, previously healthy homosexual men in New York City, Los Angeles, and San Francisco. Previously, PCP had been diagnosed only in people who were immunocompromised. The aggressive form of Kaposi sarcoma ravaging young men in the United States had previously been observed among older men of European or Mediterranean descent.

*Morbidity and Mortality Weekly Report* published a summary of these early cases in 1982. This article elicited similar reports from France, the Caribbean, and Central America. In the United States, the disease was first called “gay cancer” and then labeled “gay-related immune deficiency” because homosexual men first exhibited characteristic symptoms. In some areas in Africa, the disease was called “slim” or “slim disease” because of the profound wasting and the association of death with progressive weight loss and diarrhea. About the same time, pediatric immunologists noted more infants with unexplained immune problems.

It is widely believed that HIV is the result of an animal-to-human (zoonotic) transfer of a simian immunodeficiency virus. HIV type 2 (HIV-2), which is prevalent in West Africa and has spread to Europe and India, is almost indistinguishable from a simian immunodeficiency virus that infects sooty mangabey monkeys. An animal source for a new human infection is not unique to HIV. The bubonic plague in Europe was transmitted from rodents. Influenza reached humans via pigs. Variant Creutzfeldt-Jakob disease in the United Kingdom was transmitted to humans through consumption of infected “mad cows.” Like these other infections, once HIV was established in humans, it began to follow human habits and movements.

Modes of Transmission

The following fluids from an infected person contain HIV:
- Blood
- Semen
- Vaginal fluid
- Breast milk

HIV is usually transmitted via the following:
- Sex with an infected person
- Exposure to the blood of an infected person through contaminated needles and syringes, tainted transfusions, the sharing of unsterilized razors during cutting practices, or other mechanisms
- Pregnancy, birth, or breast-feeding from infected mother to child

Although HIV antibodies may be present in saliva, tears, and urine, there is no epidemiologic evidence that contact with these fluids has resulted in HIV infection. HIV is not transmitted by the respiratory route or by casual contact in any setting, whether household, social, work, school, or prison. HIV is not transmitted by food, water, toilets, swimming pools, shared eating and drinking utensils, or other objects such as second-hand clothing or telephones. Insects such as mosquitoes do not transmit HIV. When a

*Hopeful families crowd the waiting room at a busy clinic in Africa.*
mosquito bites, it sucks a small amount of blood from the person; the mosquito does not deposit any blood into the person.

HIV is not transmitted through casual contact. All people need to be aware of how HIV is and is not transmitted to reduce high-risk behaviors and to avoid unnecessary fears and stigmatization of HIV-infected people.

**Behavioral Risk and Vulnerable Groups**

Certain behaviors place people at greater risk of HIV infection, including unprotected sex with an infected person, blood-to-blood contact with an infected person, and injection drug use. Groups of people who engage in these high-risk behaviors (or who are involved in high-risk events such as childbirth and breast-feeding) are considered vulnerable to infection. The following section provides more information about high-risk events and behaviors as well as vulnerable groups.

**Exposure Through Sexual Contact**

Sexual intercourse is the major route of transmission of HIV throughout the world. The precise risk of HIV transmission from one act of sexual intercourse with an infected person is not known. Although some people have had multiple sexual contacts with an infected person without acquiring HIV, others have become infected from one sexual encounter. The probability that a person has acquired a sexually transmitted disease is, in general, proportional to the number of sexual partners that person has had in recent years. A study in Rwanda of behavioral risk factors for HIV infection found that infection rates were higher among women who were single and reported having more than one lifetime sexual partner. Rates of infection were lower among married women and women in monogamous partnerships. However, even among low-risk women, HIV prevalence was about 20%. For some women, a steady male partner who has sexual contact outside the primary relationship is the only source of HIV exposure. HIV is not just a disease of prostitutes and sexually promiscuous individuals.

There is now evidence from three randomized, controlled clinical trials conducted in Kenya, Uganda, and South Africa that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%. These results support long-term observations of a lower prevalence of HIV infection in countries where male circumcision is most commonly practiced. The evidence for a reduction of HIV acquisition risk in the context of male circumcision led the World Health Organization to formally announce recommendations on male circumcision for HIV prevention. The World Health Organization has stated that male circumcision should be a part of a comprehensive HIV prevention package. Of course, male circumcision services should be offered with full adherence to principles of basic human rights, including informed consent, confidentiality, and absence of coercion. Male circumcision is an important aspect to a comprehensive and integrated HIV/sexually transmitted illness prevention campaign.

**Exposure Through Blood or Blood Products**

Direct exposure to HIV-infected blood—whether through a tainted blood transfusion, the use of nonsterile razor blades for ritual scarring or traditional healing, or needle-stick accidents suffered by health care workers—is an efficient way to transmit HIV.

Compared with industrialized nations, countries in sub-Saharan Africa experience more transfusion-associated HIV transmission because of a higher prevalence of HIV infection in donor populations, a lack of HIV antibody screening in some areas, and a higher residual risk of contamination in blood supplies, despite antibody screening.

**Exposure through Pregnancy, Birth, or Breast-Feeding**

Transmission of HIV from mother to infant can occur at any point during pregnancy, labor, and delivery, or through breast milk after the baby is born. Without antiviral treatment, the rate of transmission of HIV from mothers to babies varies, depending on the region, from about 15% to 30% (in non-breast-feeding populations). Although HIV can be transmitted early in pregnancy, a particularly risky time for HIV transmission is the time of delivery, when the infant is directly exposed to maternal blood and secretions. Epidemiologic data indicate that breast-feeding approximately doubles the risk of HIV transmission. Prevention of perinatal HIV infection is one of the most powerful methods available to reduce the global effect of the virus. Please see the chapter on prevention of mother-to-child transmission of HIV for more information on this topic.
What Drives the Epidemic?

Epidemics are the result of complex interactions between biology and the environment. This section summarizes some of the principal societal factors driving the spread of this disease.

People and Goods on the Move
We are living in a global economy, with more people traveling than ever before. The most common reason for people to leave their homes and families is to seek work. HIV/AIDS has followed the routes of trade and commerce and the movement of labor, goods, and services. These are routes of legitimate commerce as well as illegal activities, such as trafficking in humans and illicit drugs. Migrant labor plays a particularly important role in southern Africa, where a thriving mining industry attracts workers from all over the region. Most miners live in single-sex dormitories, often hundreds of miles from their families. Many of these miners engage in sex with prostitutes, contract HIV, and transport the infection back home to their wives, who may in turn transmit the virus to infants during pregnancy.

People in Conflict and Complex Emergencies
War and instability are conducive to the spread of AIDS. The military can have a powerful effect on the general population’s exposure to HIV, whether through commercial sex, casual and consensual sex with other soldiers or civilians, or rape in times of conflict. Moreover, war and conflict often weaken or destroy public health systems, legitimate commerce, safe food supplies, and stable social arrangements. Sometimes war has stopped the spread of HIV (for example, Sierra Leone). This effect probably occurred because the conflict restricted movement within the country, and cross-border migration and trade became extremely difficult. In these situations, AIDS prevention efforts are a critical part of the reconstruction and normalization process.

Cultural Norms and the Status of Women
Cultural barriers often prevent women from taking necessary precautions to protect themselves and their babies from HIV. Domestic violence reduces women’s control over their exposure to HIV. In settings where supremacy and violence are regarded as a man’s right, women can seldom question their husbands about extramarital encounters, negotiate condom use, or refuse sex. In a recent study from Soweto, South Africa, 1,366 women who presented for antenatal care were interviewed privately about their experiences of partner violence and their perceived power in sexual relationships. Their HIV status was also determined. Researchers found that women who reported having been physically or sexually assaulted by an intimate male partner were more likely to be HIV infected. A high degree of male control in relationships was also associated with increased risk of HIV infection among women.

People in Poverty
AIDS tends to disproportionately affect the politically and economically disenfranchised. All over the world, HIV has settled into communities where people are poorly educated and living in poverty. Sadly, it is often poor, uneducated, and unempowered women and children who are most susceptible to this disease. Millions of people are vulnerable to HIV because they do not know the basic facts or because poverty constrains their life choices. Poverty can force women into situations where prostitution or transactional sex (sex exchanged for gifts and favors) becomes their only source of income.

Stigma and Denial
In many regions, denial and silence regarding HIV have been the norm for years. People are reluctant to admit that a fatal disease spread by behavior branded as immoral is rampaging through their community or their country. People who purport to explain the transmission of HIV among different populations but limit their analysis to such factors as sexual promiscuity and drug use tend to stigmatize or blame certain groups while failing to explain or understand larger issues involved in disease transmission. As mentioned earlier, it is not necessary to have multiple partners to acquire HIV, nor is everyone who has multiple partners HIV infected.

Ignorance fuels stigma and fear. Failure to provide accurate information about HIV leaves an information vacuum that is often filled by malevolent rumors and misinformation regarding disease spread, prevention, and treatment.

Denial about HIV can stigmatize HIV/AIDS and create an environment conducive to the continued spread of the virus. People living in such circumstances are less likely to want to know their HIV status, even if counseling and testing are offered. For example, people may be less likely to raise the issue of condom use before sex because they fear that their partner might interpret doing so as an
indication of possible HIV infection. Fear of revealing her HIV status to friends and family may prevent an infected woman from giving her baby replacement feeding as a way to avoid transmitting the virus through breast milk. An atmosphere of persecution, denial, and misinformation severely undermines prevention efforts.

**Prevention and Control**

Although there is hope that an effective anti-HIV treatment will be made available on a wide scale in the future, a cure or vaccine for AIDS is unlikely within the next several years. Therefore, prevention and treatment remain the most realistic strategies for dealing with the HIV epidemic.

Success in prevention requires consistent and persistent intervention over time, a clear understanding of the realities of target populations, and empowered participation by those affected by the interventions. Several barriers to successful prevention efforts have been identified around the world, including the following:

- Regional and national political instability
- A combination of growing populations and shrinking resources
- The presence of other endemic health problems (including childhood diseases, malaria, and tuberculosis)
- Poor governance, including inefficiency and corruption
- Apathy and silence at the international, national, and local organizational and governmental levels
- Lack of domestic spending on health care

HIV is clearly a preventable disease. If everyone who is currently infected did not transmit the virus to anyone else, the disease would eventually burn out and disappear. Stopping transmission through behavior change is a complicated challenge, but data indicate that HIV prevention and counseling efforts can be effective. A longitudinal study in Zambia of about 12,000 heterosexual couples evaluated the effect of prevention education and counseling on disease transmission. At baseline, 57% of the couples were concordant (both partners) HIV negative, 23% were concordant HIV positive, and 20% were serodiscordant (one partner was HIV negative; the other, HIV positive). All couples were counseled about HIV prevention and provided with condoms. Long-term follow-up showed reduced HIV acquisition rates among concordant negative couples, from approximately 3% to approximately 0.5% per year, and among serodiscordant couples, from about 23% to less than 10% per year.

Uganda, which has a strong prevention and control campaign, has reduced rates of HIV transmission, in part because of the ABC (Abstain, Be faithful, and use Condoms) campaign.

**Treatment and Its Influence on the Epidemic**

Fortunately, antiretroviral therapy is becoming increasingly available to people in developing countries. Some health professionals believe that treatment itself can help eliminate stigma. When treatment is available and AIDS is no longer considered a death sentence, more people may be motivated to seek counseling and testing. Knowing one’s status is more acceptable when treatment can improve and prolong life. We have seen evidence of this across the Baylor International Pediatric AIDS Initiative’s Children’s Clinical Centers of Excellence Network. Prior to the establishment of this network, some members of the community were concerned that the Centers of Excellence would be labeled as “AIDS clinics” and that families would be reluctant to bring their children for treatment for fear of being recognized and stigmatized. After several years of operation in countries across Africa, the network is providing comprehensive health services to more than 27,000 HIV-infected children and families (at the time of this printing), and the number is growing daily. In this case, access to treatment overshadowed concerns about stigma. As more treatment centers can offer highly active antiretroviral therapy, this phenomenon may be repeated throughout the developing world.

**Discussion**

Although the incidence of HIV may have plateaued, the HIV pandemic is not in rapid decline. More people are becoming infected with the virus than are dying from it. The numbers of incident infections and deaths remain unnecessarily high. Education, prevention, and treatment are currently the most promising strategies to slow the spread of the disease. Achieving greater levels of education, prevention, and treatment globally and curbing the growth of the HIV/AIDS pandemic may well be one of the greatest challenges of our time, and it is one
that we must embrace with a sense of total commitment and immediacy.

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Pathophysiology of the Human Immunodeficiency Virus

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**Objectives**
1. Provide an overview of the healthy immune system.
2. Describe the human immunodeficiency virus (HIV).
3. Describe the major components of the HIV life cycle.
4. Identify the various HIV types and subtypes.
5. Discuss HIV’s effects on the immune system.

**Key Points**
1. The immune system protects the body by recognizing invading antigens on pathogens (bacteria, viruses, fungi, and parasites) and reacting to them.
2. T lymphocytes, or T cells, regulate the immune system and destroy antigens.
3. HIV continuously uses new host cells to replicate itself.
4. The HIV life cycle includes six phases: binding and entry, reverse transcription, integration, replication, budding, and maturation.
5. Once HIV is in the circulatory system, it targets the CD4+ lymphocyte.
7. Primary infection refers to the time when HIV first enters the body.
8. Clinical latency refers to the time before onset of symptoms and complications in the HIV-infected individual. In HIV-infected adults, this phase may last 8-10 years.
9. Early signs and symptoms of HIV can include candidiasis, lymphadenopathy, cervical carcinoma, herpes zoster, and peripheral neuropathy.
10. Late signs and symptoms of HIV and AIDS-defining illnesses can include the development of life-threatening infections and malignancies.

**Overview**
The human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses. Retroviruses can use their RNA and host DNA to make viral DNA and are known for their long incubation periods. Like other retroviruses, HIV infects the body, has a long incubation period (clinical latency), and ultimately causes the signs and symptoms of disease, here AIDS. HIV causes severe damage to the immune system and eventually destroys it by using the DNA of CD4+ cells to replicate itself. In that process, the virus eventually destroys the CD4+ cells.

**The Healthy Immune System**
The immune system protects the body by recognizing antigens on invading bacteria and viruses and reacting to them. An antigen is any substance that induces a state of sensitivity and immune responsiveness. These antigens interact with antibodies and immune cells, initiating an immune response. This process destroys the antigen, allowing the body to be free of infections. Types of antigens include bacteria, viruses, fungi, and parasites. When the immune system is weakened or destroyed by a virus such as HIV, the body is left vulnerable to infections.

The immune system consists of lymphoid organs and tissues, including the bone marrow, thymus gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood, and lymphatic vessels (Figure 1). All components of the immune system are vital in the production and development of lymphocytes, or white blood cells. B lymphocytes (or B cells) and T lymphocytes (or T cells) are produced from stem cells in the bone marrow. B cells stay in the bone marrow to complete the maturation process, but T lymphocytes travel to the thymus gland to complete their maturation. There T lymphocytes become immunocompetent, multiply, and become more differentiated.
B Lymphocytes
The main function of B lymphocytes is humoral (antibody) immunity. Each B cell can recognize specific antigen targets and can secrete specific antibodies. Antibodies function by coating antigens, which makes the antigens more vulnerable to phagocytosis (engulfing and ingestion of invading organisms by leukocytes and/or macrophages), or by triggering the complement system, leading to an inflammatory response. Antibodies are highly specialized serum protein molecules. They are grouped into five classes, each having a specialized function: immunoglobulin G (IgG), IgA, IgM, IgE, and IgD.

T Lymphocytes
T lymphocytes have two major functions: regulation of the immune system and killing of cells that bear specific target antigens. Each T cell has a surface marker, such as CD4+, CD8+, and CD3+, that distinguishes it from other cells. CD4+ cells are helper cells that activate B cells, killer cells, and macrophages when a specific target antigen is present. There are two main types of CD8+ cells. The first type, cytotoxic CD8+ cells, kills cells infected by viruses or bacteria, as well as cancer cells. The second type of CD8+ cells, T-suppressor cells, inhibits or suppresses immune responses. Normal CD8+ cell count is between 300 and 1,000 cells in adults and children. The normal CD4+:CD8+ ratio is between 1.0 and 2.0.

T cells can secrete cytokines (chemicals that kill cells), such as interferon. Cytokines can bind to target cells and activate the inflammatory process. They also promote cell growth, activate phagocytes, and destroy target cells. Interleukins are cytokines that serve as messengers between white blood cells. Recombinant (laboratory synthesized) interleukins are currently being studied in clinical trials for patients with HIV infection.

Phagocytes
Phagocytes include monocytes and macrophages, large white blood cells that engulf and digest cells carrying antigenic particles. Found throughout the body, phagocytes rid the body of worn-out cells, initiate the immune response by presenting antigens to lymphocytes, are important in immune response regulation and inflammation, and carry receptors for cytokines. Dendritic cells, another type of phagocyte, also are antigen-presenting cells. They have long, threadlike extensions that help trap lymphocytes and antigens and are found in the spleen and lymph nodes. Neutrophils are granulocytic phagocytes that are important in the inflammatory response.

Complement
The complement system consists of 25 proteins. Complement can induce an inflammatory response when it functions with antibodies to facilitate phagocytosis or weaken the bacterial cell membrane. The complement proteins interact with one another in a sequential activation cascade, promoting the inflammatory process.

Despite the heavy artillery that the immune system has against foreign predators (Figures 2 and 3), HIV defeats it over time.

HIV’s Structure
HIV consists of a cylindrical center surrounded by a sphere-shaped lipid bilayer envelope. There are two major viral glycoproteins in this lipid bilayer, gp120 and gp41. The major function of these proteins is to mediate recognition of CD4+ cells and chemokine receptors, thereby enabling the virus to attach to and invade CD4+ cells. The inner sphere contains two single-stranded
Figure 2. Cells of the immune system

Figure 3. Immune response by white blood cells
copies of the genomic material, RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation: p24, p17, reverse transcriptase, integrase, and protease (Figure 4). Unlike other retroviruses, HIV uses nine genes to code for the necessary proteins and enzymes. The three principal genes are gag, pol, and env. The gag gene encodes core proteins. The pol gene encodes the enzymes reverse transcriptase, protease, and integrase. The env gene encodes the HIV structural components known as glycoproteins. The rest of the genes—rev, nef, vif, vpu, vpr, and tat—are important for viral replication and enhancing HIV’s infectivity rate.

**HIV’s Life Cycle**

Host cells infected with HIV have a shortened life span as a result of the virus’s using them as “factories” to produce multiple copies of new HIV. Thus, HIV continuously uses new host cells to replicate itself. As many as 10 million to 10 billion virions (individual viruses) are produced daily. In the first 24 h after exposure, HIV attacks or is captured by dendritic cells in the mucous membranes and skin. Within 5 days after exposure, these infected cells make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes rapid. CD4+ lymphocytes that are recruited to respond to viral antigen migrate to the lymph nodes. These become activated and then proliferate via complex interaction of cytokines released in the microenvironment of the lymph nodes. This sequence of events makes the CD4+ cells more susceptible to HIV infection, and it explains the generalized lymphadenopathy characteristic of the acute retroviral syndrome seen in adults and adolescents. In contrast, HIV-infected monocytes allow viral replication but resist killing. Thus, monocytes act as reservoirs of HIV and as effectors of tissue damage in organs such as the brain.

The HIV life cycle includes six phases: binding and entry, reverse transcription, integration, replication, budding, and maturation (Figure 5).

**Binding and Entry**

The envelope proteins gp120 and gp41 bind to CD4+ cell receptors and coreceptors on the outside of CD4+ cells.
Pathophysiology of the Human Immunodeficiency Virus

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and macrophages. The chemokine receptors CCR5 and CXCR4 facilitate viral entry. T-cell tropic viruses require CXCR4 to bind, and macrotropic strains of the virus require CCR5. R5 is the most common virus transmitted during acute infection, and later during infection X4 is the virus that is most common. The presence of a homozygous inactive mutation of the CCR5 allele has caused resistance to infection by the R5 virus.

The joining of the proteins and the receptors and coreceptors fuses the HIV membrane with the CD4+ cell membrane, and the virus enters the CD4+ cell and macrophage. The HIV membrane and the envelope proteins remain outside of the CD4+ cell, whereas the core of the virus enters the CD4+ cell. CD4+ cell enzymes interact with the viral core and stimulate the release of viral RNA and the viral enzymes reverse transcriptase, integrase, and protease.

**Reverse Transcription**
The HIV RNA must be converted to DNA before it can be incorporated into the DNA of the CD4+ cell. This incorporation must occur for the virus to multiply. The conversion of HIV RNA to DNA is known as reverse transcription and is mediated by the HIV enzyme reverse transcriptase. The result is the production of a single strand of DNA from the viral RNA. The single strand of this new DNA then undergoes replication into double-stranded HIV DNA.

**Integration**
Once reverse transcription has occurred, the viral DNA can enter the nucleus of the CD4+ cell. The viral enzyme integrase then inserts the viral DNA into the CD4+ cell’s DNA. This process is known as integration. The CD4+ cell has now been changed into a factory used to produce more HIV.

**Replication**
The new DNA, which has been formed by the integration of the viral DNA into the CD4+ cell, causes the production of messenger DNA that initiates the synthesis of HIV proteins.

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**Figure 5. The HIV life cycle** This depiction of the HIV life cycle shows the sites of action of some antiretroviral agents.
**Budding**
The HIV proteins and viral RNA, all the components needed to make a new virus, gather at the CD4+ cell membrane to form new viruses. These new viruses push through the different parts of the cell wall by budding. Many viruses can push through the wall of one CD4+ cell. These new viruses leave the CD4+ cell and contain all the components necessary to infect other CD4+ cells.

**Maturation**
The new virus has all the components necessary to infect other CD4+ cells but cannot do so until it has matured. During this process, the HIV protease enzyme cuts the long HIV proteins of the virus into smaller functional units that then reassemble to form a mature virus. The virus is now ready to infect other cells.

**HIV Types**
There are two types of HIV that cause AIDS: HIV type 1 (HIV-1) and HIV-2. We know little about HIV-2. Studies have shown striking similarities but also important differences between HIV-1 and HIV-2. They have the same modes of transmission and are associated with the same opportunistic infections, but HIV-2 appears to progress more slowly. Most HIV-2 cases are found in western Africa and in countries related to western Africa in some way such as Portugal, France, Angola, Mozambique, Brazil, and India.

Various subtypes of HIV-1 have been found in specific geographic areas and in specific high-risk groups. A person can be coinfected with different subtypes. The following are HIV-1 subtypes and their geographic distributions:

- **Subtype A:** Central Africa, sub-Saharan Africa
- **Subtype B:** South America, Brazil, United States, Thailand, Europe, Caribbean, India, Japan
- **Subtype C:** Brazil, India, South Africa
- **Subtype D:** Central Africa, sub-Saharan Africa
- **Subtype E:** Thailand, Central African Republic, Southeast Asia
- **Subtype F:** Brazil, Romania, Democratic Republic of Congo (Zaire)
- **Subtype G:** Democratic Republic of Congo (Zaire), Gabon, Thailand, Russia, Central Africa
- **Subtype H:** Democratic Republic of Congo (Zaire), Gabon, Russia, Central Africa
- **Subtype I:** Cyprus
- **Subtype O:** Cameroon, Gabon

Subtypes are unevenly distributed throughout the world. Subtype C currently accounts for more than half of all new HIV infections worldwide. Africa has most subtypes, although subtype B is less prevalent. There are no known subtypes of HIV-2.

**Effects on the Immune System**
The pathogenesis of HIV is basically a struggle between HIV replication and the immune responses of the patient, via cell-mediated and immune-mediated reactions. The HIV viral burden directly and indirectly mediates CD4+ T-cell destruction. There is destruction of mature CD4+ cells; CD4+ progenitor cells in bone marrow, the thymus, and peripheral lymphoid organs; as well as CD4+ cells within the nervous system, such as microglia. The result of this destruction is failure of T-cell production and eventual immune suppression.

There are many mechanisms of CD4+ cell depletion by HIV infection. Direct HIV-mediated cytopathic effects include single-cell killing as well as cell fusion, or syncytium formation. The syncytium is a fusion of multiple uninfected CD4+ cells with one HIV-infected CD4+ cell via CD4–gp120 interaction. This fusion results in a multinucleated syncytium, or giant cell, which may ultimately serve as a means to produce many virions. The host’s natural immune responses also play a role in CD4+ cell depletion, mainly through cytotoxic CD8+ T-cells, antibody-dependent cellular cytotoxicity, and natural killer cells. Other mechanisms include autoimmune responses, anergy, superantigen-mediated activation of T cells, and programmed cell death (apoptosis).

HIV can infect many types of cells. The spread of HIV outside lymphoid organs to the brain, spinal cord, lung, colon, liver, and kidney usually occurs late during illness. Table 1 gives a partial list of cells susceptible to HIV infection.

The immune systems of HIV-infected children undergo changes that are similar to those in adults. B-cell activation occurs in most children early in the infection, evidenced by the presence of hypergammaglobulinemia (>1.750 g/L) with high levels of anti–HIV-1 antibody. This reflects both dysregulation of T-cell suppression of B-cell antibody synthesis as well as active CD4+ enhancement of B-lymphocyte humoral response. Also, as HIV disease progresses through more severe immunosuppression and depletion of CD4+ cells, the CD8+ count increases, yielding an overall decrease in the CD4+:CD8+ ratio.
Children infected with HIV often have severe disease when first evaluated, or they may develop AIDS over time, much like adults infected with HIV. Infants and young children normally have higher CD4+ counts than those of adults. The normal CD4+ count in children varies with age, but it is equal to the adult value by the time the child is 6 years old. Immunologic and clinical categories are used to evaluate the HIV disease status in children and to make treatment decisions.

Primary Infection, or Acute Retroviral Syndrome
Primary infection refers to the time when HIV first enters the body. At the time of primary infection with HIV, a person’s blood carries a high viral load, meaning that there are many individual viruses in the blood. The number of copies of virus per milliliter of plasma or blood can exceed 1 million. Newly infected adults often experience an acute retroviral syndrome. Signs and symptoms of acute retroviral syndrome include fever, myalgia (muscle pain), headache, nausea, vomiting, diarrhea, night sweats, weight loss, and rash. These signs and symptoms usually occur 2–4 weeks after infection, subside after a few days, and often are misdiagnosed as influenza or infectious mononucleosis. An important differentiating symptom that is often absent is the presence of a runny nose or nasal congestion.

During primary infection, the CD4+ count in the blood decreases remarkably but rarely drops to less than 200 cells/μL. The virus targets CD4+ cells in the lymph nodes and the thymus during this time, making the HIV-infected person vulnerable to opportunistic infections and limiting the thymus’s ability to produce T-lymphocytes. HIV antibody testing using an enzyme-linked immunoassorbent assay or enzyme immunoassay may yield positive or negative results depending on the time of seroconversion. DNA PCR and RNA PCR will be positive, but confirmation with Western blot analysis may yield an indeterminate result because seroconversion can take up to 2–8 weeks to occur. The average time to seroconversion is 25 days.

Clinical Categories of HIV Infection
Although patients recently infected with HIV usually experience a “clinically latent” period of years between HIV infection and clinical signs and symptoms of AIDS, evidence of HIV replication and host immune system destruction exists from the onset of infection. Early during this time, referred to as Clinical Stage 1, the immune system produces antibodies in an attempt to protect itself from HIV. This is when the “viral set point” is established. The viral load of the set point can be used to predict how quickly disease progression will occur. People with higher viral load set points tend to exhibit more rapid disease progression than those with lower viral load set points.

During latency, HIV-infected patients may or may not have signs and symptoms of HIV infection though persistent lymphadenopathy is common. In HIV-infected adults, this phase may last 8–10 years. The HIV enzyme-linked immunoassorbent assay and Western blot or immunofluorescence assay will be positive. The CD4+ count is greater than 500 cells/μL in children over 5 years of age.

Mild Signs and Symptoms of HIV (Clinical Stage 2)
HIV-infected people may appear to be healthy for years, and then minor signs and symptoms of HIV infection begin to appear. They may develop candidiasis, lymphadenopathy, molluscum contagiosum, persistent

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**Table 1. Cells Susceptible to HIV Infection**

<table>
<thead>
<tr>
<th>System</th>
<th>Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic</td>
<td>T-cells (CD4+ OR CD 8+)</td>
</tr>
<tr>
<td></td>
<td>Macrophages/monocytes</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
</tr>
<tr>
<td></td>
<td>Fetal thymocytes and thymic epithelium</td>
</tr>
<tr>
<td></td>
<td>B-cells</td>
</tr>
<tr>
<td></td>
<td>NK cells</td>
</tr>
<tr>
<td></td>
<td>Megakaryotic cells</td>
</tr>
<tr>
<td></td>
<td>Stem cells</td>
</tr>
<tr>
<td>Central Nervous</td>
<td>Microglia</td>
</tr>
<tr>
<td></td>
<td>Capillary endothelial cells</td>
</tr>
<tr>
<td></td>
<td>Astrocytes</td>
</tr>
<tr>
<td></td>
<td>Oligodendrocytes</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Columnar epithelium</td>
</tr>
<tr>
<td>Other</td>
<td>Kupfer cells (liver)</td>
</tr>
<tr>
<td></td>
<td>Synovial cells</td>
</tr>
<tr>
<td></td>
<td>Placental tophoblast cells</td>
</tr>
</tbody>
</table>

Adapted from Levy L.A. Microbiological Reviews, 57:188-289, March 1993
hepatosplenomegaly, popular pruritic eruptions, herpes zoster, and/or peripheral neuropathy. The viral load increases, and the CD4+ count falls is between 350-499/μL in children older than 5 years. Once patients are in this stage they remain in stage 2. They can be reassigned stage 3 or 4 if a condition from one of those occurs, but they cannot be reassigned to Clinical Stage 1 or 2 if they become asymptomatic.

**Advanced Signs and Symptoms of HIV (Clinical Stage 3)**
HIV-infected patients with weakened immune systems can develop life-threatening infections. The development of cryptosporidiosis, pulmonary and lymph node tuberculosis, wasting, persistent fever (longer than one month), persistent candidiasis, recurrent bacterial pneumonia, and other opportunistic infections is common. These patients may be wasting, or losing weight. Their viral load continues to increase, and the CD4+ count falls to less than 200-349 cells/μL in children older than 5 years.

**Clinical Stage 4**
Patients with advanced HIV disease, or AIDS, can continue to develop new opportunistic infections, such as Pneumocystis jirovecii pneumonia (formerly Pneumocystis carinii pneumonia), cytomegalovirus infection, toxoplasmosis, Mycobacterium avium complex, cryptococcal meningitis, progressive multifocal leukoencephalopathy, Kaposi sarcoma and other infections that commonly occur with a severely depressed immune system. The viral load is very high, and the CD4+ count is less than 200 cells/μL in children older than 5 years. At this point in the disease course death can be imminent.

**REFERENCES**
**Objectives**

1. Identify and understand the laboratory tests used to diagnose HIV in infants, children, and adults.
2. Understand the importance and the challenges of early infant diagnosis (EID).
3. Understand principles and algorithms for EID.
5. Review the Centers for Disease Control and Prevention and WHO staging systems for HIV disease in infants, children and adults.

**Key Points**

1. HIV disease is diagnosed using clinical signs and symptoms as well as specific laboratory tests.
2. The HIV rapid test and HIV enzyme-linked immunosorbent assay are the screening tests used to detect HIV antibodies. These tests determine HIV exposure in infants younger than 18 months and diagnose HIV infection in children older than 18 months and in adults.
3. Antibody tests cannot be used to definitively diagnose HIV in infants younger than 18 months because of passive placental transfer of maternal HIV immunoglobulin G antibody during pregnancy.
4. Virologic testing (e.g., DNA polymerase chain reaction [PCR]) can be used to definitively diagnose HIV infection in infants younger than 18 months.
5. Early diagnosis of HIV infection in infants on the basis of clinical signs and symptoms, rapid testing, and virologic testing is important to ensure timely enrollment of HIV-exposed infants into care, initiation of cotrimoxazole prophylaxis, and appropriate infant feeding counseling.
6. Dried blood spot collection is highly stable and increases access to DNA PCR testing because of convenient sample handling and transport.
7. If virologic testing is not readily available for infants younger than 18 months and an infant has a positive antibody test plus certain signs and symptoms of HIV, a presumptive diagnosis of HIV may be made and ARV therapy initiated as a potentially life-saving measure.
8. The WHO has established easy-to-use clinical and immunological staging systems to evaluate the severity of HIV disease in infected individuals and determine the need to initiate ARV therapy.
9. HIV testing results need to be clearly documented in patient records and collected in a functioning database to ensure proper patient follow-up and to guide prevention of mother-to-child transmission and ARV therapy program development.

World Health Organization (WHO) Core Competencies included the following:

- Understand human immunodeficiency virus (HIV) testing in infants and children.
- Determine clinical stage by using clinical signs for stage 1, 2, and 3 conditions.
- Evaluate the child’s eligibility for antiretroviral (ARV) therapy.

**Overview**

Diagnosing human immunodeficiency virus (HIV) in infants, children, adolescents, and adults is challenging but important. When HIV is diagnosed early and accurately, the patient and previously undiagnosed family members have the opportunity to access life-saving care and treatment for HIV and related infections. When a young child is determined to be HIV negative, health care providers and family members can plan and implement actions to ensure that the child remains negative.

Encounters with exposed infants provide opportunities to link mothers and other HIV-positive family members to services, and healthy caregivers will help ensure child survival.

HIV diagnosis and treatment rely on clinical and laboratory findings. HIV can present with a variety of
signs and symptoms. Understanding these signs allows providers to identify potentially infected children and evaluate them appropriately. Laboratory testing has been the standard for HIV diagnosis in resource-rich countries for many years, and these tests are becoming cheaper and increasingly available in resource-limited settings.

Several types of HIV diagnostic tests have been developed. The affordability and availability of these tests vary by country. Diagnostic tests fall into two main categories (Table 1): antibody tests (HIV rapid tests, HIV enzyme-linked immunosorbent assay [ELISA; also called EIA {enzyme immunoassay}], and Western blot) and virologic tests (HIV DNA polymerase chain reaction [PCR] assays, RNA assays, p24 antigen assays, and viral culture).

Once HIV infection is diagnosed, the stage of infection can be established clinically and immunologically. Staging the severity of the patient’s disease allows health care professionals to determine the best time to initiate treatment with antiretroviral (ARV) therapy.

**Role of HIV Epidemiology in HIV Diagnosis**

**HIV Type 1 and -2**

There are two primary types of HIV that cause AIDS—HIV type 1 (HIV-1) and HIV-2. HIV-2 is limited largely to western Africa, whereas the more contagious HIV-1 continues to drive the current pandemic. For this reason, most diagnostic laboratory tests focus on HIV-1; however, most standard ELISA technology will detect antibodies to both HIV-1 and -2. The diagnostic principles discussed here apply to HIV-2, but the particular tests needed to identify HIV-2 are sometimes different from those used for HIV-1, and providers must exercise caution when using HIV-1 lab tests in areas with higher rates of HIV-2 infection. The HIV epidemiology chapter discusses HIV-1 and HIV-2 in more detail.

**Table 1. Common HIV diagnostic tests**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Virologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV rapid test</td>
<td>HIV-1 DNA PCR</td>
</tr>
<tr>
<td>HIV ELISA (also called EIA)</td>
<td>HIV-1 RNA PCR (viral load)</td>
</tr>
<tr>
<td>Western blot</td>
<td>Ultrasensitive p24 antigen assay test</td>
</tr>
<tr>
<td></td>
<td>HIV culture</td>
</tr>
</tbody>
</table>

**HIV-1 Subtypes**

The subtypes of HIV-1 also differ by continent and region. Although most new infections are subtype C, the geographic distribution of HIV-1 subtypes is complex. Africa, for example, has most subtypes but little subtype B, whereas the United States has a higher prevalence of subtype B. HIV diagnostic tests detect specific proteins and/or genetic material (i.e., HIV DNA and RNA PCR), and many are designed to detect primarily subtype B. Therefore, test sensitivity and specificity may be compromised in populations where HIV subtype B does not predominate. One can eliminate this issue by making sure that the test is specifically engineered for the subtype(s) of HIV in a particular population. Health care workers must be familiar with the distribution of certain subtypes in their region and to understand the potential limitations of diagnostic tests depending on local prevalences. National and local guidelines should consider these variations and can serve as a reference when there are questions about HIV-1 subtypes. The HIV epidemiology chapter discusses HIV-1 subtypes in more detail.

**Laboratory Diagnostic Tests**

**Antibody Tests**

One type of laboratory test used to diagnose HIV is the antibody test. This category of test includes HIV rapid tests, ELISA, and Western blot. Antibody tests, as the name suggests, detect the antibodies that are produced during the immune response to HIV.

Because antibody tests are inexpensive and relatively easy to perform, they are the most widely available. Antibody tests remain the only diagnostic test available in many settings. Antibody tests have both advantages and disadvantages. Like most lab tests, they can yield false-negative and false-positive results. To use antibody tests appropriately, one must understand these limitations.

False-negative tests occur when HIV-infected individuals do not produce detectable antibodies, such as during the early, acute phase of the infection (the preantibody, or “window,” period) and the very late stages of infection (when immune suppression is severe and antibodies are no longer being produced in response to HIV infection). Usually, individuals produce antibodies within 6 weeks of infection, and almost all infected individuals have detectable antibodies by 12 weeks postinfection. However, some may take as long as 6 months to make detectable antibodies.
For this reason, the World Health Organization (WHO) recommends using the antibody test 6 weeks after exposure to HIV because almost all infected individuals will have detectable antibodies (also called seroconversion) by then. Regardless of exposure history, a negative antibody test should be interpreted with the window period in mind. Also, a negative test does not exclude HIV in an individual with continual or recent exposure to HIV (e.g., breast-feeding infants or persons engaging in high-risk behavior).

The other primary cause of false-negative antibody tests is severe immunosuppression. During the very late stages of HIV-infection, antibody levels can fall so far as to become undetectable. When a false negative is suspected in the presence of severe clinical symptoms, further testing is required.

One of the most important diagnostic limitations of antibody tests occurs in infants younger than 18 months. During pregnancy, HIV-infected mothers passively transfer immunoglobulin G HIV antibody to the infant through the placenta. The presence of these antibodies means that the infant is exposed and might be infected. The section of this module titled “HIV Diagnosis in Infants” will discuss antibody testing for this age group in more detail.

Next, we will briefly discuss the types of antibody tests currently in use.

**Rapid test.** The development of HIV rapid tests in the 1990s increased access to testing and care, especially in resource-limited settings. These simple antibody tests can be performed at the point of care and have a fast turnaround time, with results available within 15–30 min. These tests are inexpensive (US$1–2 per test) and are ideal for situations in which an immediate result is necessary (e.g., a pregnant woman in labor). Also, they can be done with a simple heel, toe, or finger prick. Rapid tests are highly sensitive (99.3%–100%) and specific (98.6%–100%). (A sensitivity of 99.3% means that the test is falsely negative only 0.7% of the time, and a specificity of 98.6% means that the rapid test is falsely positive only 1.4% of the time.)

There are several types of rapid tests available. For a list of the rapid tests that have been approved by the U.S. Food and Drug Administration, see http://www.fda.gov/cber/products/testkits.htm.

In resource-limited settings, diagnostic testing algorithms often call for using two types of rapid tests, either at the same time or one after the other. This dual approach minimizes false results. Professionals should refer to national guidelines for specific protocols relating to rapid testing in each clinical setting, including protocols for discordant HIV rapid tests (when one test is negative and one is positive).

Like all diagnostic tests, rapid tests need to be interpreted within the context of the clinical situation. The window period needs to be considered any time that there is a negative rapid test, and positive rapid tests need to be interpreted with care in infants.

**ELISA.** Like the rapid test, ELISAs (also called EIsAs) are inexpensive and highly sensitive in identifying antibodies to HIV (meaning rarely falsely negative). Though several conditions can cause an ELISA to be falsely positive—autoimmune disease, certain viral infections, syphilis, hematologic malignancies, pregnancy, and recent blood transfusions—the test is also specific (rarely falsely positive). Compared to the HIV rapid test, however, ELISA has several disadvantages, including the need to perform a venous blood draw (rather than a simple skin prick), the need for laboratory facilities, and the longer turnaround time for results.

Because of the low levels of antibodies during the window period, the first generation of ELISAs were frequently falsely negative for a long time after initial infection. ELISA generations two through four have since been developed to capture existing antibodies at lower levels. With each successive generation of ELISAs, the window period has decreased significantly and the test has become more useful.

ELISAs usually require serum samples for processing, but tests that use urine or oral fluid have also been developed. ELISA is usually a qualitative (i.e., positive–negative type) test, but semiquantitative ELISAs have also been developed. These tests can estimate the amount of antibody present and detect trends in the quantity of antibody over time. Although these tests are potentially useful in monitoring the decrease in an infant’s maternal antibodies during late infancy, they are less useful in the first months of life and are not included in most current guidelines.
A negative ELISA does not require confirmatory testing, provided that the patient was not tested during the window period. A positive ELISA, however, should be confirmed with a Western blot assay to further minimize the possibility of a false result.

**Western blot.** Western blot is another category of antibody test that detects the presence of antibodies against specific HIV proteins. Western blots are typically used to confirm a reactive ELISA result.

The Western blot test is a polyacrylamide gel electrophoresis that detects several proteins that are specific to HIV antibodies (p24, gp41, gp120, gp160). If these proteins are not seen, the Western blot is negative. If most or all of the proteins are seen, the Western blot is positive. A negative Western blot indicates that the positive ELISA or rapid test was a false positive. A positive Western blot confirms the presence of HIV-1 antibodies. An indeterminate Western blot could mean early infection or, in an uninfected, exposed infant, the partial loss of maternal HIV antibody. Pregnancy may also cause specific proteins to appear on the Western blot and lead to an indeterminate reading.

In the event of an inconclusive or indeterminate result, the test should be repeated on the same serum sample and then repeated again on another blood sample 2 weeks later. If the indeterminate pattern persists, the Western blot needs to be repeated periodically for 6 months. If the inconclusive pattern persists after 6 months, the person is most likely HIV negative.

**Virologic Tests**

Another type of laboratory test used to diagnose HIV is the virologic test. Unlike the antibody tests, which detect the body’s immunologic response to HIV, virologic tests directly detect the presence of the virus in the blood sample. Specifically, these tests detect the DNA, RNA, or protein of the virus.

**HIV-1 DNA PCR.** HIV-1 DNA PCR testing has historically been the “gold standard” of early infant diagnosis in the developed world. Fortunately, DNA PCR is now becoming less expensive and more available in resource-limited settings worldwide. This test, currently priced at US$8–$18 per test, detects HIV DNA material located inside host cells. DNA PCR can be run using either serum or dried blood spots and can detect HIV DNA in replicating and nonreplicating cells. The test has an excellent sensitivity and specificity, even in the first months of life. Because almost all prenatal and perinatal infections are detectable by DNA PCR at 4 weeks of age (~96%), this test is excellent for early infant diagnosis. HIV infection acquired postpartum (via breast-feeding, for example) can be detected 6 weeks after the last exposure, and the test is highly sensitive even in infants taking ARVs. See the section titled “HIV Diagnosis in Infants” for more on DNA PCR in this age group.

**HIV-1 RNA PCR.** HIV-1 RNA PCR, another important virologic test, is commonly used to monitor response to HIV treatment. Whereas DNA PCR is a qualitative test providing positive or negative results, RNA PCR tests are quantitative and indicate how much HIV is in the blood. For this reason, RNA PCR is also known as the viral load and represents the number of copies of HIV per milliliter. RNA PCR is also an accurate method of HIV diagnosis in young infants (>10,000 copies/mL is considered diagnostic). RNA PCR sensitivity and specificity are similar to those of DNA PCR in this group (nearly 100% by 6 weeks of age for exposed, non–breast-feeding infants).

HIV RNA PCR tests are more expensive than DNA PCR tests, costing approximately US$50–$100 per test. The tests are also technologically complex and require uninterrupted electricity, air conditioning, and clean water—resources that are not available in many settings. Simpler, faster, and less expensive RNA PCR tests are in development. Also, nucleic acid amplification techniques are being developed to help ensure that small amounts of HIV RNA in blood samples (including pooled samples at blood banks) are not overlooked to result in false negatives. Nucleic acid amplification techniques, such as HIV RNA tests, remain expensive.

**Ultrasensitive p24 antigen assay.** Another laboratory test that directly detects HIV in the bloodstream is the p24 antigen test. The antigen p24 is a major core protein of HIV that can be found either free in the bloodstream of HIV-infected people or bound to anti-p24 antibody. An ultrasensitive p24 test has been developed that can be performed successfully using both serum and dried blood spot (DBS) collection techniques, with reported sensitivity and specificity of 98% and 100%, respectively. This ELISA-based technology is less expensive than DNA and RNA tests and involves simpler laboratory technique.
However, p24 lab equipment is not yet commercially available on a scale that would allow national coverage, and the recent decrease in the price of other virologic tests (e.g., DNA and RNA PCR) has decreased p24’s price advantage.

**HIV culture.** HIV culture is a virologic test that requires incubating peripheral blood cells from a patient to determine the presence of HIV in the blood sample. The sensitivity of HIV culture is the same as that of DNA PCR. However, HIV culture is expensive and time consuming, taking up to 6 weeks to obtain results. HIV culture is also unavailable in most settings and is no longer the test of choice for diagnosis of HIV in infants, children, or adults.

**DBS and HIV Testing**

Until recently, HIV testing required a phlebotomist, a centrifuge, and quick transport of the serum sample between the health clinic and the lab. The development of the DBS collection method has eliminated many of these logistical barriers and has provided increased access to HIV testing.

DBS simplifies blood sample collection and, owing to its high stability, allows for convenient sample handling and transport. Only a few drops of blood are required from a finger, toe, or heel stick, which are collected on special filter paper. The DBS cards are then dried; specially packaged; stored in a plastic, zip-locked bag; and transported to the lab at room temperature. See the “How to collect DBS” text box for more information on this collection technique.

DBS collection has been used successfully to perform virologic and antibody tests, including DNA PCR, RNA PCR, p24 antigen detection, and ELISA. Both DNA and RNA DBS samples are stable for more than a year when properly collected and stored. DNA PCR using DBS technology is as accurate as DNA PCR testing on whole blood (sensitivity of 100% and specificity of 99.6%). Testing programs using DBS are currently being implemented in various countries, and they have greatly facilitated the early infant diagnosis of HIV.

The rest of this chapter will build on the preceding overview of existing lab tests and discuss the principles of diagnosis in infants, children, and adults.

**HIV Diagnosis in Infants**

Early diagnosis and treatment of HIV can greatly affect child survival. The high mortality rates of infected infants underscore the importance of early diagnosis. Without interventions, up to 40% of infants born to HIV-positive mothers are infected during pregnancy, delivery, and breast-feeding. Median infant survival time after HIV infection in infancy is just over a year. Without treatment, one in five HIV-infected infants dies before 6 months, more than a third die by 1 year, and more than half die before 2 years.

**Antibody Testing in Infants**

Diagnostic testing for HIV-1 in infants younger than 18 months differs from that for older children, adolescents, and adults because of the presence of maternal antibodies. HIV-specific immunoglobulins such as immunoglobulin G HIV antibodies are passively transferred to the infant across the placenta. The mean age for clearing maternal antibody is just over 10 months, but maternal antibodies may persist in the infant until 18 months of age.

Because antibodies are transferred to the fetus during pregnancy, antibody tests such as rapid tests and ELISA are positive in all newborns of HIV-infected mothers, including infants who are not infected. Even if an infant becomes infected and begins making his or her own antibodies, antibody tests cannot differentiate between antibodies from the mother and those from the infant. Therefore, a positive antibody test in infancy indicates that an infant has been exposed and may or may not be infected.

Despite these factors, HIV antibody testing is still a useful screening tool later in infancy. Up to 93% of 9-month-old HIV-uninfected infants and 95% of 12-month-old HIV-uninfected infants will have lost their maternal antibodies. For this reason, a positive test later in infancy is more likely to indicate HIV infection. Many national guidelines recommend first doing a rapid test in infants aged 9 months to see if they are still antibody positive and then doing the more expensive virologic testing on those that still have circulating antibodies. This approach provides health care providers with a simple and relatively inexpensive strategy to exclude HIV infection in many infants aged 9 months because uninfected infants are likely to be antibody negative at that time.
A rapid antibody test (Figure 1) can also be used to definitively diagnose HIV infection, but only in children older than 18 months. Many countries with a high HIV prevalence have incorporated repeat rapid testing at 18 months of age for all children for confirmation of HIV status, regardless of prior testing.

**Virologic Testing in Infants**

During early infancy, when maternal HIV antibodies can complicate the interpretation of antibody tests, virologic tests can be used to determine whether the infant is HIV infected. Virologic testing is becoming increasingly available worldwide and has an increasing role in guiding early clinical decisions related to feeding choices, cotrimoxazole prophylaxis, and early HIV care and treatment.

In countries in which pediatric ARV therapy and infant formula are readily available and resources permit multiple tests, infants of HIV-positive mothers are tested at 14-21 days, 1-2 months, and 4-6 months. Some experts also recommend testing at birth to capture those infected during pregnancy. However, this approach is not practical in resource-limited settings, where often only one virologic test is available per child. In these settings, the DNA PCR test is often performed at 6 weeks of age or at the earliest clinical encounter thereafter. Testing at 6 weeks allows the provider to detect prenatal and perinatal infections and ensures that exposed infants begin to integrate into the child health care system (e.g., for immunizations and cotrimoxazole prophylaxis).

If resources permit, a second DNA PCR test can be done 6 weeks after breast-feeding has stopped. Because HIV exposure ends when a child is weaned from breast milk, this second DNA PCR allows for a definitive diagnosis in these children. DNA PCR tests are useful in other clinical scenarios as well, such as when an exposed infant older than 9 months with an unknown HIV status has a positive rapid test. Most HIV-negative infants are antibody negative by 9 months, and DNA PCR testing can offer a definitive diagnosis in this case. Finally, even if an infant has an initial DNA PCR test that is negative, the test should be repeated if the infant later develops signs and symptoms of HIV infection. This chapter includes several sample infant diagnosis algorithms.

**FIGURE 1. Rapid antibody test example**

**Virologic Testing and Infant Feeding**

Appropriate infant feeding is crucial to a child’s well-being and survival. Infant feeding counseling in the context of HIV should aim to provide the best possible nutrition to optimize growth, development, and survival while also preventing HIV transmission as much as possible. Nutritional counseling needs to balance the risk of HIV transmission through breast milk with the risks of replacement feeding—improper infant replacement feeding itself can lead to severe malnutrition and death.

For each patient, one must assess the acceptability, feasibility, affordability, sustainability, and safety (AFASS) criteria of replacement feeding to ensure that it is appropriate. Replacement feeding is possible only with access to clean water, a steady income to purchase formula and other supplies, fuel for safe preparation, HIV disclosure in the household, safe storage, and an understanding of the importance of proper preparation and delivery of formula.

In settings where replacement feeding with formula does not fulfill AFASS criteria, the WHO recommends exclusive breast-feeding for the first 6 months of life unless AFASS criteria can be fulfilled before then. Because HIV-positive mothers in many resource-limited areas cannot fulfill AFASS criteria, they are counseled to exclusively breast-feed. In these cases, the infant’s need for adequate nutrition requires continued HIV exposure.
**HIV Exposed Infant Age 6 Weeks to 9 Months**

Perform or Review **DNA PCR test**
- Give Cotrimoxazole prophylaxis
- Encourage exclusive BF until 6 months old, review feeding options at 6 months, then BF and complementary foods until AFASS met.
- For Mother: Clinically stage, check CD4, offer family planning

**DNA PCR POSITIVE**

**Sick Child?**
Repeat DNA PCR, if initial test was negative. Refer to doctor at any time if clinical suspicion of HIV.

**DNA PCR NEGATIVE**

**Breastfed in the 6 weeks before testing?**

**YES**

**Child is HIV POSITIVE**
- Refer to ARV clinic
- Continue Cotrimoxazole
- Continue BF as long as possible
- For Mother: Stage, check CD4, offer family planning

**Child is STILL EXPOSED**
- Continue Cotrimoxazole
- Review AFASS
- For Mother: Stage, check CD4, and offer family planning
  **Repeat DNA PCR test**
  6 weeks after cessation of BF

**Child is HIV NEGATIVE**
- Stop Cotrimoxazole
- For Mother: Clinically stage, check CD4, and offer family planning

**Repeat Rapid Test at 18 months for confirmation**

*Some national guidelines recommend DNA PCR for repeat HIV testing, 6 weeks post-weaning. Other guidelines recommend rapid testing, up to 3 months post-weaning, or repeating DNA PCR only if the child is ill-appearing. All DNA PCR tests should be confirmed at 18 months of age by repeat rapid test.

**FIGURE 2. HIV Diagnosis in Exposed Infants and Young Children**
HIV DIAGNOSIS IN EXPOSED INFANTS AND YOUNG CHILDREN

HIV Exposed Infant / Child Age 9 to 18 Months

Perform or Review Rapid test*  
• Give Cotrimoxazole prophylaxis  
• Continue BF and complementary foods until AFASS met.  
• For Mother: Clinically stage, check CD4, offer family planning

Rapid test POSITIVE  
Sick Child?  
Repeat Rapid test and DNA PCR, if initial test was negative. Refer to doctor at any time if clinical suspicion of HIV.

DNA PCR POSITIVE  
Child is HIV POSITIVE  
• Refer to ARV clinic  
• Continue Cotrimoxazole  
• Continue BF as long as possible  
• For Mother: Stage, check CD4, offer family planning

DNA PCR NEGATIVE  
Child is STILL EXPOSED  
• Continue Cotrimoxazole  
• Review AFASS  
• For Mother: Stage, check CD4, and offer family planning  
Repeat Rapid Testing  
6 weeks after cessation of BF***

Repeat Rapid Test at 18 months for confirmation

Rapid Test NEGATIVE

Breastfed in the 6 weeks before testing?***

YES

Child is HIV NEGATIVE  
• Stop Cotrimoxazole  
• For Mother: Clinically stage, check CD4, and offer family planning

NO

* WHO recommends that, from 9 months of age, antibody tests are performed first to ensure that virologic testing is only done on children who still have HIV antibodies. The use of a rapid tests in the 9-18 month age group varies by country.

**While awaiting DNA PCR results, CD4 evaluation is recommended in most settings due to a high likelihood of true infection. Clinical judgement should be used to determine if a patient should be referred to an ARV clinic at this time.

*** WHO recommends using a 6 week window period for rapid testing after 9 months of age. Several national guidelines use a 3 month window period for rapid testino. All DNA PCR tests should be confirmed at 18 months of age by repeat rapid test.

FIGURE 2. HIV Diagnosis in Exposed Infants and Young Children (continued)
FIGURE 2. HIV Diagnosis in Exposed Infants and Young Children (continued)

HIV Exposed Child Age 18 Months or Greater

Perform or Review **Rapid Test**
- Give Cotrimoxazole prophylaxis
- Continue BF and complementary foods until AFASS met.
- For Mother: Clinically stage, check CD4, and offer family planning

**Rapid Test POSITIVE**
- Sick Child?
  - Repeat Rapid test, if initial test was negative.
  - Refer to doctor at any time if clinical suspicion of HIV.

**Rapid Test NEGATIVE**
- Breastfed in the 6 weeks* before testing?
- YES
  - Child is **HIV POSITIVE**
    - Refer to ARV clinic
    - Continue Cotrimoxazole
    - Continue BF as long as possible
    - For Mother: Stage, check CD4, and offer family planning
- NO
  - Child is **HIV NEGATIVE**
    - Stop Cotrimoxazole
    - For Mother: Clinically stage, check CD4, and offer family planning
  - Child is **STILL EXPOSED**
    - Continue Cotrimoxazole
    - Review AFASS
    - For Mother: Stage, check CD4, and offer family planning
  - Repeat Rapid Testing
    - 6 weeks after cessation of BF*

* WHO recommends using a 6 week window period for rapid testing. Several national guidelines use a 3 month window period for rapid testing.
from breast milk. As a result, infant diagnosis becomes more complicated.

Early virologic testing at 6 weeks of age detects primarily those infections transmitted during pregnancy and delivery, and additional testing is needed in breast-feeding infants. DNA PCR testing can be performed 6 weeks after breast-feeding cessation, and antibody testing can be performed 12 weeks after breast-feeding cessation.

Infants with a positive DNA PCR test at age 6 weeks are presumed to be HIV infected and should breast-feed for at least the first 2 years of life to maximize the nutritional benefits of breast milk. For infants whose initial DNA PCR test is negative, AFASS criteria will determine infant feeding recommendations. (For more on infant feeding, see the chapter on prevention of mother-to-child transmission.)

**Early Infant Diagnosis Testing Algorithms**

Regional variations make recommending one diagnostic protocol for all settings difficult. Providers and policy makers must therefore decide which diagnostic approach maximizes access to care, minimizes the cost of testing, and best promotes child survival. Factors that influence diagnosis and testing include test availability, regional HIV prevalence, the age of the child, the child’s exposure history, infant feeding options, and clinical assessment of the infant or child.

**Figure 2** provides several algorithms as examples. The applicability of each algorithm to a particular setting varies, depending on the preceding factors.

**Diagnosing an Infant on the Basis of Clinical Criteria**

If diagnostic laboratory tests are not available or an infant is being assessed for the first time and lab results are pending, certain clinical signs and symptoms can be used to document likely HIV infection. Although infants who are HIV positive often have no symptoms, early clinical clues that the infant is HIV infected can guide clinical decision making. These clues include failure to thrive, oral candidiasis (thrush), chronic diarrhea, and hepatosplenomegaly (enlarged liver and spleen). These clinical findings are especially concerning in children who are orphaned or who have parents known to be HIV infected. Some of the physical exam findings that aid in the diagnosis of HIV have been formally summarized in the Integrated Management of Childhood Illness (IMCI) algorithm for suspected symptomatic HIV infection (**Figure 2**).

Though this algorithm is easy to use, this brief clinical assessment alone fails to identify many HIV-infected infants during a period when they are most vulnerable to rapid progression of illness. In one study, the most recent version of the IMCI HIV algorithm detected only between 50% and 70% of infected infants and missed up to 80% of infected 6-week-olds. In contrast, in a similar patient population, a careful clinical evaluation by a pediatrician achieved 90% sensitivity, whereas a DNA PCR test identifies nearly 100%.

The WHO has also developed a clinical assessment tool. It is designed to allow for a “presumptive diagnosis of HIV” in infants younger than 18 months. Like the IMCI protocol, this tool is useful in settings where it is too early for antibody testing and virologic testing is not available. However, these clinical criteria alone may miss many HIV-infected infants during a period when up to half will die without treatment (**Table 2b**).

In conclusion, the clinical evaluation of infants is an essential component of HIV diagnosis, and health care workers should strive to correlate clinical findings with available lab results. However, appropriate early infant diagnostic lab tests do more to ensure that exposed infants receive early diagnosis and, when needed, life-saving care and treatment.

**HIV Diagnosis in Children**

Because the maternal antibodies passed on to exposed infants during pregnancy do not persist beyond 18 months of age, the diagnosis of older children relies more heavily on antibody testing (HIV rapid tests or ELISA). For this reason, protocols for the diagnosis of older children are simpler than and usually similar to those for adults.

Where antibody tests are not available, young patients can also be evaluated clinically for signs of HIV. Signs and symptoms of early HIV infection—lethargy, malaise, sore throat, myalgias (muscle soreness), sweating, and fever—can be nonspecific and similar to those of many viral infections such as flu. The clinical manifestations seen later are often more suggestive of HIV in particular, but children can be HIV infected and yet have no signs
TABLE 2A. Integrated Management of Childhood Illness (IMCI) HIV Clinical Diagnosis Algorithm

**CHECK FOR HIV INFECTION**

- Does the mother or child have a HIV test done?
- Does the child have one or more of the following conditions:
  - Pneumonia*
  - Persistent diarrhea*
  - Ear discharge (acute or chronic)
  - Very low weight for age*

* Note that the severe forms such as severe pneumonia, severe persistent diarrhea and severe malnutrition can be used to enter the box. Complete assessment quickly and refer child.

If yes, enter the box below and look for the following conditions suggesting HIV infection:

<table>
<thead>
<tr>
<th>NOTE</th>
<th>LOOK and FEEL:</th>
<th>Classify for HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR ASK:</td>
<td>• Pneumonia?</td>
<td>• Oral thrush</td>
</tr>
<tr>
<td></td>
<td>• Persistent diarrhea?</td>
<td>• Parotid enlargement</td>
</tr>
<tr>
<td></td>
<td>• Ear discharge?</td>
<td>• Generalized persistent</td>
</tr>
<tr>
<td></td>
<td>• Very low weight?</td>
<td>• Lymphadenopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNS</th>
<th>CLASSIFY</th>
<th>INDENTIFY TREATMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Positive HIV antibody test in child 18 months and above OR • Positive HIV virological test AND • 2 or more conditions</td>
<td>CONFIRMED SYMPTOMATIC HIV INFECTION</td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give cotrimoxazole prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Check immunization status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give Vitamin A supplements from 6 months of age every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assess the child’s feeding and provide appropriate counseling to the mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Refer for further assessment including HIV care/ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise mother on home care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule</td>
</tr>
<tr>
<td>• No test results in child or positive antibody test in child &lt;18 months OR • Positive HIV virological test AND • Less than 2 conditions</td>
<td>CONFIRMED HIV INFECTION</td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give cotrimoxazole prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give Vitamin A supplements from 6 months of age every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assess the child’s feeding and provide appropriate counseling to the mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Test to confirm HIV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Refer for further assessment including HIV care/ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise mother on home care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule</td>
</tr>
<tr>
<td>• One or both of the following: • Mother HIV positive and no test result on child OR • Child less than 18 months with positive antibody test AND • Less than 2 conditions</td>
<td>SUSPECTED SYMPTOMATIC HIV INFECTION</td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give cotrimoxazole prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give Vitamin A supplements from 6 months of age every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assess the child’s feeding and provide appropriate counseling to the mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Test to confirm HIV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Refer for further assessment including HIV care/ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise mother on home care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule **</td>
</tr>
<tr>
<td>• No test result in child or positive antibody test in child &lt;18 months AND • 2 or more conditions</td>
<td>POSSIBLE HIV/HIV EXPOSED</td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give cotrimoxazole prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give Vitamin A supplements from 6 months of age every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assess the child’s feeding and provide appropriate counseling to the mother</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confirm HIV infection status of child as soon as possible with best available test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule **</td>
</tr>
<tr>
<td>• Negative HIV test in mother or child AND not enough signs to classify as suspected symptomatic HIV infection</td>
<td>SYMPTOMATIC HIV INFECTION UNLIKELY</td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise the mother about feeding and about her own health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Encourage HIV testing</td>
</tr>
<tr>
<td>• HIV INFECTION UNLIKELY</td>
<td></td>
<td>• Treat, counsel and follow-up existing infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advise the mother about feeding and about her own health</td>
</tr>
</tbody>
</table>

Integrated Management of Childhood Illness (IMCI) is a WHO/UNICEF strategy aimed at reducing mortality in children under five years by improving health care at a primary level. IMCI was introduced in 1995 and has been implemented in over 100 countries worldwide. IMCI provides a series of guidelines, often in the form of screening questions and symptom checklists, for assessing and treating common causes of childhood morbidity and mortality on the primary care level. IMCI has been adapted to include an algorithm to identify children with symptomatic HIV infection at the primary care level. Though this algorithm is useful where laboratory testing is not available, it fails to identify a large portion of infected children and should not be used alone for HIV diagnosis.

Source: Adapted from “Integrated Management of Childhood Illness for High HIV Settings”, WHO 2006
Clinical criteria for presumptive diagnosis of severe HIV disease among infants and children aged under 18 months in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:
- The infant is confirmed as HIV antibody-positive;
- Diagnosis of any AIDS-indicator condition(s)\(^a\) can be made;
- The infant is symptomatic with two or more of the following:
  - Oral thrush\(^b\)
  - Severe pneumonia\(^b\)
  - Severe sepsis\(^b\)

Other factors that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:
- Recent HIV-related maternal death or advanced HIV disease in the mother
- CD4 <20%\(^c\)

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

\(^a\)AIDS indicator conditions include some but not all HIV clinical stage 4 conditions seen in children such as Pneumocystis pneumonia, oesophageal candidiasis, cryptococcal meningitis, cerebral toxoplasmosis, unexplained wasting or malnutrition.

\(^b\) Defined in accordance with WHO Integrated Management of Childhood Illness guidelines:
- Oral thrush: Creamy white soft small plaques on red or normally colored mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
- Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the general danger signs outlined in the WHO Integrated Management of Childhood Illness guidelines: that is lethargic or unconscious, not able to drink or breastfeed, vomiting and presence or history of convulsions during current illness.
- Severe sepsis: Fever or low body temperature in a young infant with any severe sign, such as rapid breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, stiff neck.

\(^c\) It is unclear how often the CD4 count is lowered in these conditions in HIV-uninfected children.


Table 3. Physical findings suggestive of HIV infection*

<table>
<thead>
<tr>
<th>Highly suggestive of HIV infection in a child</th>
<th>Suggestive of HIV infection</th>
<th>Likely to be evidence of HIV infection but common in both HIV-infected and uninfected children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal candidiasis</td>
<td>Recurrent severe bacterial infection</td>
<td>Otitis media—persistent or recurrent</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Persistent or recurrent oral thrush</td>
<td>Diarrhea—persistent or recurrent</td>
</tr>
<tr>
<td>Invasive salmonella infection</td>
<td>Parotid enlargement</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>Generalized lymphadenopathy</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Extrapulmonary cryptococcosis</td>
<td>Hepatosplenomegaly</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Persistent or recurrent fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurologic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent generalized dermatitis</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from the African Network for the Care of Children Affected by HIV/AIDS’s Handbook on Paediatric AIDS in Africa.
or symptoms. Table 3 lists several physical findings that are suggestive of HIV infection in children. The staging section of this chapter and other chapters dedicated to the clinical manifestations of HIV will discuss many of these clinical findings of pediatric HIV in more detail.

**HIV Diagnosis in Adults**

HIV-infected adults, like children, can have nonspecific clinical signs and symptoms. Initial HIV infection (called acute retroviral syndrome [ARS]) can look similar to influenza, and HIV-infected adults can appear perfectly healthy for more than a decade after infection. Therefore, laboratory testing is the best way to determine whether an adult patient is HIV infected. As in older children, antibody tests such as rapid tests and ELISA are easy, inexpensive tools for diagnosing HIV infection in adults.

Though they have high sensitivity and specificity in patients who have made HIV antibodies, recently infected patients may not have detectable antibodies until 6–12 weeks after infection. Therefore, one must retest any patient who is negative by rapid test or ELISA if the patient has suspicious flulike symptoms or a recent exposure, for the patient might be in the window period. If the rapid test is not repeated and the diagnosis is missed, though the patient is likely to appear healthy, HIV will continue to attack and weaken the immune system. Also, the patient may unknowingly expose others and is in danger of contracting a sudden and life-threatening opportunistic infection. In those settings where virologic testing is available, ARS can be diagnosed earlier. Although antibody tests will probably be negative during and immediately after symptomatic ARS, DNA and RNA PCR will be positive.

**Staging**

Once a patient is diagnosed with HIV, the extent of damage to the immune system needs to be determined so that the patient can be treated if necessary. This assessment is called staging, which consists of two primary components: clinical staging and immunologic staging. For staging a patient, the primary objective is to determine when to start ARV therapy, or, in patients already on ARVs, when to consider changing therapy or stopping therapy. Both the WHO and Centers for Disease Control and Prevention (CDC) have developed standard clinical and immunologic staging criteria. (This chapter’s HIV staging section summarizes these criteria.)

**Clinical Staging**

Clinical staging is essentially the use of a careful history and physical exam to measure the severity of immunosuppression. Clinical staging, once established, can be repeated to monitor disease progression. Clinical staging systems are often adjusted and updated, and the reference tables in use at your site must be the most recent available.

**Clinical Staging after ARV Therapy Initiation**

Two different clinical staging guidelines are used worldwide. One is based on the recommendations of the CDC and one is based on WHO guidelines. This chapter’s HIV staging section discusses these staging systems. One of the major differences between the systems is how they are used after initiation of ARV treatment.

Most patients, after starting ARV therapy, will improve clinically. In the CDC staging system, their clinical stage does not change to a healthier stage when the patient improves on therapy. Hence, a child with extrapulmonary tuberculosis (TB) or another other AIDS-defining illness who was originally classified as “severe” (or “C”) would remain in this classification even after he or she improves on ARV therapy. The child would remain with a “C” staging even if all symptoms resolve.

The WHO has introduced the concept of treatment staging, or T staging. In this type of staging, the clinical stage is preceded by a T to indicate that a patient is on ARV treatment. The T staging system can be used after at least 6 months on a first-line ARV regimen and helps guide decision making about switching ARVs in the presence of disease progression. Patients on an effective ARV regimen should get better, not worse, and the development of a new or recurrent WHO clinical stage 3 or 4 condition while on ARVs may signal treatment failure. On the other hand, the disappearance of stage 3 or 4 diseases confirms improved health on ARVs, and the WHO clinical T stage changes to reflect this.

For example, a child who was instituted on ARVs because of persistent oral candidiasis (a WHO stage 3 condition) and later becomes asymptomatic on therapy would have a WHO clinical classification of T1. By changing the child’s stage to T1, the provider can document the improvement on ARV therapy. If the child later develops new manifestations of HIV while on ARV therapy (lymph node TB, for example), the stage would change again (to
T3 for lymph node TB, a stage 3 diagnosis. This chapter’s HIV staging section gives more specifics on T staging.

**Immunologic Staging**

The second primary component of staging is immunologic staging. Whereas clinical staging relies on a history and physical exam, immunologic staging relies primarily on CD4 cell counts. As discussed in the preceding chapter on the pathophysiology if HIV, the number of CD4+ lymphocytes helps measure the strength of the immune system. The CD4 count tells the health care provider many things, including approximately how much HIV is in the blood and what opportunistic infections the patient is in danger of getting. (For example, when the CD4 count is low, the viral load and opportunistic infection risk are high.)

**CD4 Absolute Count vs. CD4 Percentage**

A CD4 count can be reported as an absolute count or a percentage. The CD4 percentage is the absolute number of CD4 lymphocytes divided by the total number of lymphocytes in the blood. The absolute CD4 in the blood varies daily, especially in children, because of the immune system’s ongoing response to various pathogens. In children younger than 5 years, the large day-to-day fluctuations in absolute CD4 make interpreting the absolute count difficult. CD4 percentage is more consistent and therefore preferred for immunologic staging in this age group. In children older than 5 years, adolescents, and adults, CD4 percentage is typically disregarded and absolute CD4 count is used.

**CD4’s Natural Decrease in the First Years of Life**

Both the absolute count and percentage of CD4 cells decrease during the first 5 years of life. HIV-uninfected infants are therefore expected to have more CD4 cells than uninfected older children and uninfected adults. Immunologic staging tables incorporate these age variations, with adjusted CD4 count cutoffs for different age groups. (See the HIV staging section on the following pages for more.)
**Integrating Diagnostics into the Health Care System**

Although antibody and virologic testing are becoming more accurate and available, the ability of a health care system to accurately diagnose HIV in a population requires an understanding of human resource capacity and laboratory infrastructure. Without health care staff and laboratory professionals, an effective HIV diagnostic program is not achievable. In addition to personnel, a successful HIV diagnosis program requires a health care system that

1. is accessible to patients,
2. advocates for diagnostic testing in those patients,
3. provides adequate pretest and posttest counseling,
4. ensures the accuracy of its laboratory results,
5. links the patient to the appropriate posttest care, and
6. uses its collection of diagnostic data to inform and guide local and national HIV policy.

**Access**

An understanding of what tests are required to diagnose patients does not ensure that patients can get tested and enroll into care. For diagnostic protocols to function, patients need to be able to find their way to informed providers, and those providers need to have access to the materials needed for appropriate laboratory testing. Doing so is especially important for pregnant women and infants because the expecting mother’s HIV status will determine the need for prevention of mother-to-child transmission (PMTCT). If such a patient cannot access care, she may miss the opportunity to protect her child from HIV infection.

**Advocacy: Opt-Out and Provider-Initiated Diagnostic Testing**

In addition to maximizing access to care, providers should promote access to testing by instituting an opt-out policy. Opt-out testing means that all patients seen by a health care provider will receive diagnostic testing for HIV unless they request not to. This approach ensures that as many patients as possible know their HIV status. Another anticipatory strategy to maximize access to diagnostic testing is called provider-initiated testing, meaning that it becomes the responsibility of the health care professional to advocate that each patient is tested rather than waiting for the patient to request testing.

**Pre- and Posttest Counseling**

Any patient who is tested for HIV should receive an age-appropriate pretest and posttest counseling session. This session should include an explanation of the test, the implications of the results, and the availability of treatment for HIV-infected patients. Other issues—infant feeding, avoiding future infection/reinfection, and disclosure—are also key components of these counseling sessions. The counseling services that should accompany HIV diagnostic services are discussed in more detail in the chapter on HIV prevention counseling.

**Accuracy of Reported Lab Findings**

Lab results must be performed correctly, and clinical and laboratory personnel must invest time to understand the lab tests on site and minimize human error. A well-designed referral system for lab samples will minimize confusion and allow rapid turnaround. Once a result is available, it must be carefully communicated to both patient and provider. All lab results must also be included in the patient’s chart, along with immunizations and growth records.

**Linking Diagnosis and Treatment**

When an HIV-infected patient is identified, he or she must be referred to the appropriate care and treatment provider. Doing so requires careful linkage and coordination between PMTCT, maternal and child health, and ART centers.

**Monitoring**

Diagnostic testing is important to both individual patients and the population as a whole. Careful data collection will help guide patient care and help health care professionals better understand the local prevalence of HIV and the effectiveness of ongoing PMTCT programs. Such information minimizes the guesswork when shaping policy and enables informed health care providers to target HIV prevention, care, and treatment programs appropriately.
## How-to Stage HIV

### Contents

1. **Clinical Staging Tables:**
   - Table 1: WHO clinical staging system for children <15 years old
   - Table 2: WHO clinical staging system for adolescents >15 years old and adults
   - Table 3: WHO case definitions for HIV-related diseases (an expanded version of Table 2)

   *Regardless of the availability of lab tests for immunologic staging, HIV-infected patients can be diagnosed and classified clinically. In 2006, the World Health Organization updated several easy-to-use tables for this purpose. This staging system is used in many countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as 1 through 4, progressing from asymptomatic HIV infection to advanced HIV/AIDS. Each of these stages are defined by specific clinical conditions or symptoms.

2. **Immunologic Staging Tables:**
   - Table 4: WHO immunological classification for known HIV infection
   - Table 5: WHO total lymphocyte count (TLC) classification for known HIV infection

   **The CD4 cell count in infants and children who are not infected with HIV are considerably higher than those in uninfected adults. These values slowly decline to adult values by the age of about 6 years. Therefore, when monitoring CD4, age must be taken into account as a variable. Also, in children less than 5 years of age, the absolute CD4 count tends to vary within an individual child more than the % CD4. Therefore, the measurement of the % CD4 is thought to be more valuable in younger children. (For these reasons, the WHO table below is arranged by age group, and the younger age groups are staged by percentage.) Finally, because CD4 counts fluctuate some on a day-to-day basis, two or more CD4 values are better than one when staging a patient and planning treatment. Table 5 summarizes how total lymphocyte count (TLC) can be used to classify children immunologically. Where CD4 measurement is not available, a low TLC and clinical signs of HIV demonstrate severe immunodeficiency and the need for antiretroviral treatment.

3. **Combined Clinical and Immunological Staging Tables:**
   - Table 6: U.S. Centers for Disease Control and Prevention (CDC) classification system for children
   - Table 7: CDC classification system for adolescents and adults
   - Case examples for CDC classification

   ***Patients are classified under the CDC staging system based on both their CD4+ lymphocyte count and the clinical manifestations of disease. A patient’s disease status is classified by determining the degree of immunosuppression (1, 2, or 3) and the clinical category (N, A, B, C, or E). These categories are outlined in the Tables 6-7 below. “E” (not included in the tables) refers to infants who are vertically exposed but whose status is still unclear. Any of the CDC category C illnesses are considered AIDS-defining, though certain diseases (e.g. LIP) are considered AIDS-defining in children but not in adults. Unlike the WHO system, once classified using the CDC criteria, the patient cannot be reclassified into a less severe category even if clinical or immunological status improves. (See also “T staging” discussion below.)

4. **Treatment staging (“T staging”) Tables:**
   - Table 8: Using WHO pediatric clinical staging to guide decision-making on switching to second-line therapy for treatment failure
   - Table 9: Using WHO adolescent and adult clinical staging to guide decision-making on switching to second-line therapy for treatment failure

   ****Treatment staging (“T staging”) allows providers to monitor for treatment failure using the WHO clinical staging system. Patients on ARVs for more than six months should be getting better, not worse. If patients develop a WHO stage 3 or 4 condition after being on ARVs for more than 6 months, treatment failure is possible. In contrast, if the stage 3 or 4 conditions disappear, the T stage can document the patient’s improvement on ARVs.

5. **How-to Stage HIV**—Table 10: Images depicting common manifestations of WHO clinical staging diseases
### TABLE 1: Children less than 15 years old

<table>
<thead>
<tr>
<th>Clinical Stage 1</th>
<th>Clinical Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Unexplained moderate persistent hepatosplenomegaly</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>Papular pruritic eruptions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Stage 1</th>
<th>Clinical Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained moderate weight loss (&lt;10% of presumed or measured body weight)</td>
<td>Symptomatic HIV-associated nephropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Stage 3</th>
<th>Clinical Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained moderate malnutrition not adequately responding to standard therapy</td>
<td>HIV waste syndrome</td>
</tr>
<tr>
<td>Unexplained persistent diarrhea (14 days or more)</td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)</td>
<td>Recurrent severe bacterial pneumonia</td>
</tr>
<tr>
<td>Persistent oral candidiasis (after 6-8 weeks of life)</td>
<td>Chronic herpes simplex infection (orolabial, genital or anorectal)</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>(oral, or anorectal, or genital)</td>
</tr>
<tr>
<td>Acute necrotizing ulcerative gingivitis or periodontitis</td>
<td>more than one month's duration or visceral at any site)</td>
</tr>
<tr>
<td>Lymph node tuberculosis</td>
<td>Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>Extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>Severe recurrent bacterial pneumonia</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Symptomatic lymphoid interstitial pneumonitis</td>
<td>Cytomegalovirus infection (retinitis or infection of other organs)</td>
</tr>
<tr>
<td>Chronic HIV-associated lung disease including brochiectasis</td>
<td>HIV encephalopathy</td>
</tr>
<tr>
<td>Unexplained anaemia (&lt;8 g/dl), neutropaenia (&lt;0.5 x 10^9 per litre)</td>
<td>Extrapulmonary cryptococcosis including meningitis</td>
</tr>
<tr>
<td>and or chronic thrombocytopaenia (&lt;50 x 10^9 per litre</td>
<td>Disseminated non-tuberculous mycobacterial infection</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Chronic cryptosporidiosis</td>
</tr>
<tr>
<td>Papular pruritic eruptions</td>
<td>Chronic isosporiasis</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Recurrent septicaemia (including non-typhoidal <em>Salmonella</em>)</td>
</tr>
<tr>
<td>Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis or tonsillitis)</td>
<td>Lymphoma (cerebral or B-cell non-Hodgkin)</td>
</tr>
<tr>
<td>Unexplained severe weight loss (&gt;10% of presumed or measured body weight)</td>
<td>Invasive cervical carcinoma</td>
</tr>
<tr>
<td>Unexplained chronic diarrhea for no longer than one month</td>
<td>Atypical disseminated leishmaniasis</td>
</tr>
<tr>
<td>Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)</td>
<td>Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy</td>
</tr>
</tbody>
</table>

### TABLE 2: Children greater than 15 years old and adults

<table>
<thead>
<tr>
<th>Clinical Stage 1</th>
<th>Clinical Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Invasive cervical carcinoma</td>
<td>Angular cheilitis</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis or tonsillitis)</td>
</tr>
<tr>
<td>Papular pruritic eruptions</td>
<td>Lymphoma (cerebral or B-cell non-Hodgkin)</td>
</tr>
<tr>
<td>Disseminated non-tuberculous mycobacterial infection</td>
<td>Invasive cervical carcinoma</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Atypical disseminated leishmaniasis</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy</td>
</tr>
</tbody>
</table>

### How-to Stage HIV (continued)

#### TABLE 3: WHO case definitions for HIV-related diseases

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Characteristics</th>
<th>How to Diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL STAGE 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>No HIV-related symptoms reported and no clinical signs on examination</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Persistent Generalized Lymphadenopathy</td>
<td>Persistent swollen or enlarged lymph nodes &gt;1 cm at 2 or more non-contiguous sites (excluding inguinal) without known cause</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Unexplained persistent hepatosplenomegaly</td>
<td>Enlarged liver and spleen without obvious cause</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Papular pruritic eruptions</td>
<td>Papular pruritic vesicular lesions</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Extensive wart virus infection</td>
<td>Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat of sole of feet (plantar warts); facial, more than 5% of body area or disfiguring</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Extensive molluscum contagiosum infection</td>
<td>Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate more advanced immunodeficiency.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>Current event plus at least one previous episode in past 6 months. Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Unexplained persistent parotid enlargement</td>
<td>Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Lineal gingival erythema</td>
<td>Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td>Recurrent upper respiratory tract infection</td>
<td>Current event with at least 1 episode in the past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (laryngotracheal bronchitis). Persistent or recurrent ear discharge.</td>
<td>Clinical Diagnosis</td>
</tr>
<tr>
<td><strong>CLINICAL STAGE 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained moderate malnutrition</td>
<td>Weight Loss: low wt-for-age, up to -2 SD from the mean, not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.</td>
<td>Documented loss of body wt of -2 SD from the mean, failure to gain wt on standard mgmt and no other cause identified during investigation</td>
</tr>
<tr>
<td>Unexplained persistent diarrhea</td>
<td>Unexplained persistent (14 days or more) diarrhea (loose or watery stool, 3 or more times daily), not responding to standard treatment.</td>
<td>Stools observed and documented as unformed. Culture and microscopy reveal no pathogens.</td>
</tr>
<tr>
<td>Unexplained persistent fever (&gt;37.5 C intermittent or constant for longer than 1 month)</td>
<td>Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarial agents. No other obvious foci of disease reported or found on exam. Malaria must be excluded in malarious areas.</td>
<td>Documented fever of &gt;37.5c with negative blood culture negative malaria slide and normal or unchanged CXR and no other obvious foci of disease.</td>
</tr>
</tbody>
</table>
### How-to Stage HIV (continued)

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Appearance</th>
<th>How to Diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral candidiasis (after the first 6-8 weeks of life)</td>
<td>Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)</td>
<td>Microscopy or culture</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>Fine small linear patches on lateral borders of tongue, generally bilateral, that do not scrape off</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Acute necrotizing ulcerative gingivitis or stomatitis, or periodontitis</td>
<td>Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odor, and rapid loss of bone and/or soft tissue.</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Lymph node tuberculosis</td>
<td>Non-acute, painless “cold” enlargement of peripheral lymph nodes, localized to one region. Response to standard anti-TB treatment in one month.</td>
<td>Histology or fine needle aspirate positive for Ziehl-Nielson stain or culture.</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and wt loss. In the older child, also productive cough and hemoptyis. History of contact with adults with smear-positive pulmonary TB. No response to standard broad-spectrum antibiotic treatment.</td>
<td>One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities c/w active TB and/or culture-positive for Mycobacterium.</td>
</tr>
<tr>
<td>Severe recurrent bacterial pneumonia</td>
<td>Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.</td>
<td>Isolation of bacteria from appropriate clinical specimens (induced sputum, bronchoalveolar lavage and lung aspirate)</td>
</tr>
<tr>
<td>Symptomatic lymphocytic interstitial pneumonia</td>
<td>No presumptive clinical diagnosis</td>
<td>CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than 2 months with no response to antibiotic treatment and no other pathogen found. O2 saturations: &lt;90%, persistently. Cor pulmonale and increased exercise-induced fatigue. Characteristic histology.</td>
</tr>
<tr>
<td>Chronic HIV-associated lung disease (including bronchiectasis)</td>
<td>History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation</td>
<td>CXR may show honeycomb appearance (small cysts) and/or persistent area of opacification and/or widespread lung destruction, with fibrosis and loss of volume.</td>
</tr>
<tr>
<td>Unexplained anemia (&lt;8 g/dl), neutropenia (&lt;0.5 x 10⁹ /L) and or chronic thrombocytopenia (&lt;50 x 10⁹ /L)</td>
<td>No presumptive clinical diagnosis</td>
<td>Lab testing, not explained by other non-HIV conditions, not responding to standard therapy with hematinics, antimalarial, or antihelmintic agents as outlined in WHO IMCI guidelines.</td>
</tr>
</tbody>
</table>

### CLINICAL STAGE 4

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Appearance</th>
<th>How to Diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained severe wasting, stunting, or severe malnutrition not adequately responding to standard therapy</td>
<td>Persistent wt loss not explained by poor or inadequate feeding, other infections, and not adequately responding in 2 wks to standard therapy. Visible severe wasting of muscles, with or without edema of both feet, and/or wt-for-hht of -3 SD from the mean, as defined by WHO IMCI guidelines</td>
<td>Documented loss of over more than -3 SD from the mean with or without edema.</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>Dry cough, progressive difficulty in breathing, cyanosis, tachypnea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in WHO IMCI guidelines.) Rapid onset especially in infants younger than 6 months of age. Response to high-dose co-trimoxazole with or without prednisolone. CXR shows typical bilateral perihilar diffuse infiltrates.</td>
<td>Cytology or immuno-flourescent microscopy of induced sputum or bronchoalveolar lavage (BAL) or histology of lung tissue</td>
</tr>
</tbody>
</table>
### TABLE 3: WHO case definitions for HIV-related diseases (continued)

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Appearance</th>
<th>How to Diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL STAGE 4 (continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent severe bacterial infection, i.e.: Empyema, pyomyositis, bone/joint infection, meningitis, but excluding pneumonia</td>
<td>Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus 1 or more in previous 6 months.</td>
<td>Culture of appropriate clinical specimen.</td>
</tr>
<tr>
<td>Chronic herpes simplex infection; (orolabial/cutaneous of more than 1 month’s duration or visceral at any site)</td>
<td>Severe and progressive painful orolabial, genital, or anorectal lesions caused by herpes simplex virus infection present for more than 1 month.</td>
<td>Culture and/or histology</td>
</tr>
<tr>
<td>Esophageal candidiasis (or candidiasis of trachea, bronchi, lungs)</td>
<td>Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral Candida observed and food refusal occurs and/or difficulty or crying when feeding.</td>
<td>Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology</td>
</tr>
<tr>
<td>Extrapulmonary or disseminated TB</td>
<td>Systemic illness usually with prolonged fever, night sweats and wt loss. Clinical features of organs involved, such as sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, or orchitis, pericardial or abdominal</td>
<td>Positive microscopy showing acid-fast bacilli or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL. Biopsy and histology.</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise color, skin lesions that usually develop into nodules.</td>
<td>Not required but may be confirmed by: 1) typical red-purple lesions seen on bronchoscopy/endoscopy; 2) dense masses in lymph nodes, viscera, or lungs by palpation or radiology; and 3) histology.</td>
</tr>
<tr>
<td>CMV retinitis or CMV infection affecting another organ, with onset older than 1 month of age</td>
<td>CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic exam; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, hemorrhage and necrosis.</td>
<td>Definitive diagnosis required for other sites. Histology. CSF PCR.</td>
</tr>
<tr>
<td>CNS toxoplasmosis onset after 1 month of age</td>
<td>Fever, headache, focal nervous system signs and convulsions. Usually responds within 10 days to specific therapy.</td>
<td>Computed tomography scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast.</td>
</tr>
<tr>
<td>Extrapulmonary cryptococcosis (including meningitis)</td>
<td>Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion and behavioural changes that respond to cryptococcal therapy</td>
<td>CSF microscopy (India ink or Gram stain), serum or CSF cryptococcal antigen test or culture</td>
</tr>
</tbody>
</table>

TABLE 4: WHO immunological classification for known HIV infection

<table>
<thead>
<tr>
<th>HIV-associated immunodeficiency</th>
<th>&lt;11 months (% CD4+)</th>
<th>12-35 months (% CD4+)</th>
<th>36-59 months (% CD4+)</th>
<th>&gt;5 years (absolute number per mm³ or (% CD4+))</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or not significant</td>
<td>&gt;35</td>
<td>&gt;30</td>
<td>&gt;25</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mild</td>
<td>30-35</td>
<td>25-30</td>
<td>20-25</td>
<td>350-499</td>
</tr>
<tr>
<td>Advanced</td>
<td>25-29</td>
<td>20-24</td>
<td>15-19</td>
<td>200-349</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;25</td>
<td>&lt;20</td>
<td>&lt;15</td>
<td>&lt;200 or &lt;15%</td>
</tr>
</tbody>
</table>


TABLE 5: WHO total lymphocyte count (TLC) classification for known HIV infection

TLC Criteria for severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 HIV disease and where CD4 measurement is not available.

<table>
<thead>
<tr>
<th>Immunological marker</th>
<th>≤11 months</th>
<th>12 months to 35 months</th>
<th>36 months to 59 months</th>
<th>5 to 8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>&lt;4000 cells/mm³</td>
<td>&lt;3000 cells/mm³</td>
<td>&lt;2500 cells/mm³</td>
<td>&lt;2000 cells/mm³</td>
</tr>
</tbody>
</table>


TABLE 6A: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific CD4+ T-Lymphocyte Count and Percentage

<table>
<thead>
<tr>
<th>Immune Category</th>
<th>&lt;12 months No./uL (%)</th>
<th>1-5 years No./uL (%)</th>
<th>6-12 years No./uL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: No suppression</td>
<td>≥1500 (&gt;25%)</td>
<td>≥1000 (&gt;25%)</td>
<td>≥500 (&gt;25%)</td>
</tr>
<tr>
<td>2: Moderate suppression</td>
<td>750-1499 (15%-24%)</td>
<td>500-999 (15%-24%)</td>
<td>200-499 (15%-24%)</td>
</tr>
<tr>
<td>3: Severe suppression</td>
<td>&lt;750 (&lt;15%)</td>
<td>&lt;500 (&lt;15%)</td>
<td>&lt;200 (&lt;15%)</td>
</tr>
</tbody>
</table>

*Modified for CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43 (no. RR-12):1-10.
**TABLE 6B: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not Symptomatic</strong></td>
<td>Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.</td>
</tr>
<tr>
<td><strong>Mildly Symptomatic</strong></td>
<td>Children with 2 or more of the following conditions but none of the conditions listed in categories B and C:</td>
</tr>
<tr>
<td></td>
<td>✷ Lymphadenopathy (&gt;0.5 cm at more than 2 sites; bilateral at 1 site)</td>
</tr>
<tr>
<td></td>
<td>✷ Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>✷ Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>✷ Dermatitis</td>
</tr>
<tr>
<td></td>
<td>✷ Parotitis</td>
</tr>
<tr>
<td></td>
<td>✷ Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</td>
</tr>
<tr>
<td><strong>Moderately Symptomatic</strong></td>
<td>Children who have symptomatic conditions other than those listed in category A or category C that are attributed to HIV infection. Conditions in clinical category B include but are not limited to:</td>
</tr>
<tr>
<td></td>
<td>✷ Anemia (&lt;8 gm/dl), neutropenia (&lt;1000/mm$^3$), or thrombocytopenia (&lt;100000/mm$^3$) persisting &gt;30 days</td>
</tr>
<tr>
<td></td>
<td>✷ Bacterial meningitis, pneumonia, or sepsis (single episode)</td>
</tr>
<tr>
<td></td>
<td>✷ Candidiasis, oropharyngeal (thrush), lasting &gt;2 months</td>
</tr>
<tr>
<td></td>
<td>✷ Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>✷ Diarrhea, recurrent or chronic</td>
</tr>
<tr>
<td></td>
<td>✷ Hepatitis</td>
</tr>
<tr>
<td></td>
<td>✷ Herpes simplex virus, stomatitis, recurrent (&gt; 2 episodes in 1 year)</td>
</tr>
<tr>
<td></td>
<td>✷ Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome</td>
</tr>
<tr>
<td></td>
<td>✷ Leimyosarcoma</td>
</tr>
<tr>
<td></td>
<td>✷ Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia (PLH) complex</td>
</tr>
<tr>
<td></td>
<td>✷ Nephropathy</td>
</tr>
<tr>
<td></td>
<td>✷ Nocardiosis</td>
</tr>
<tr>
<td></td>
<td>✷ Fever lasting &gt;1 month</td>
</tr>
<tr>
<td></td>
<td>✷ Toxoplasmosis with onset before age 1 month</td>
</tr>
<tr>
<td></td>
<td>✷ Varicella, disseminated</td>
</tr>
<tr>
<td><strong>Severely Symptomatic</strong></td>
<td>Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP.</td>
</tr>
<tr>
<td></td>
<td>✷ Serious bacterial infections, multiple or recurrent (any combination of at least 2 culture-confirmed infections in a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections)</td>
</tr>
<tr>
<td></td>
<td>✷ Candidiasis, esophageal or pulmonary (bronchi, trachea, or lungs)</td>
</tr>
<tr>
<td></td>
<td>✷ Coccidiomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>✷ Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>✷ Cryptosporidiosis or Isosporiasis with diarrhea persisting &gt;1 month</td>
</tr>
<tr>
<td></td>
<td>✷ Cytomegalovirus disease with onset of symptoms at age &gt;1 month (at a site other than liver, spleen, or lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>✷ Encephalopathy (at least 1 of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children &lt;2 years of age); c) acquired symmetric motor deficit manifestations affecting a child &gt;1 month of age</td>
</tr>
<tr>
<td></td>
<td>✷ Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes</td>
</tr>
<tr>
<td></td>
<td>✷ Kaposi's sarcoma</td>
</tr>
<tr>
<td></td>
<td>✷ Lymphoma, primary, in brain</td>
</tr>
<tr>
<td></td>
<td>✷ Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large-cell lymphoma of B-cell or unknown immunologic phenotype</td>
</tr>
<tr>
<td></td>
<td>✷ Mycobacterium tuberculosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>✷ Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>✷ Mycobacterium avium complex or Mycobacterium kansasi, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</td>
</tr>
<tr>
<td></td>
<td>✷ Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td></td>
<td>✷ Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>✷ Salmonella (nontyphoid) septicemia, recurrent</td>
</tr>
<tr>
<td></td>
<td>✷ Toxoplasmosis of the brain with onset &gt;1 month of age</td>
</tr>
<tr>
<td></td>
<td>✷ Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following finding: a) persistent weight loss &gt;10% of baseline OR b) downward crossing of at least 2 percentile lines on the weight-for-age chart (95th, 75th, etc.) in a child &gt;1 year of age OR c) &lt;5th percentile on weight-for-height chart on 2 consecutive visits PLUS either a) diarrhea (at least 2 loose stools per day for &gt;30 days) OR b) documented fever for &gt;30 days, intermittent or constant</td>
</tr>
</tbody>
</table>

*Modified for CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43 (no. RR-12):1-10.*
How-to Stage HIV (continued)

**TABLE 7: CDC Revised Classification System for HIV Infection and Expanded AIDS Surveillance Case Definition for Adolescents and Adults**

<table>
<thead>
<tr>
<th>CD4+ Cell Categories</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: &gt;500 cells/uL</td>
<td>A1</td>
</tr>
<tr>
<td>2: 200-499 cells/uL</td>
<td>B1</td>
</tr>
<tr>
<td>3: &lt;200 cells/uL</td>
<td>C1**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4+ Cell Categories</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>2: 200-499 cells/uL</td>
<td>A2</td>
</tr>
<tr>
<td>3: &lt;200 cells/uL</td>
<td>B2</td>
</tr>
<tr>
<td></td>
<td>C2**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4+ Cell Categories</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>3: &lt;200 cells/uL</td>
<td>A3**</td>
</tr>
<tr>
<td></td>
<td>B3**</td>
</tr>
<tr>
<td></td>
<td>C3**</td>
</tr>
</tbody>
</table>

*Modified from MMWR, Vol. 41, 1992 RR-17 **AIDS

**CLINICAL CATEGORIES**

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

**Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical category B include, but are not limited to:**

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal, that is persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe) or cervical carcinoma in situ
- Constitutional symptoms, such as fever (>38.5 C) or diarrhea of >1 month’s duration
- Hairy leukoplakia, oral
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

**Category C includes the clinical conditions listed in the CDC’s AIDS surveillance case definition. For classification purposes, once a category C condition has occurred, the person will remain in category C.**

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidiodomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer (>1 month’s duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month)
- Kaposi’s sarcoma
- Lymphoma, Burkitt’s (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary of the brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain
- Wasting syndrome due to HIV (weight loss of >10% of body weight plus either unexplained chronic diarrhea >1 month or chronic weakness and unexplained prolonged fever >1 month)

**CDC CLASSIFICATION EXAMPLES**

- A 3-month-old infant with *Pneumocystis carinii* pneumonia and a CD4+ lymphocyte count of less than 750 cell/mm³ has a classification code of C3 in indicate severe clinical symptoms and severe immunosuppression.
- A 6-month-old infant who is not symptomatic with a CD4+ lymphocyte count of 1600 cell/mm³ (30%) is classified as N1 to indicate no signs or symptoms and no evidence of immunosuppression.
- A 7 year-old with a CD4 of 250 (18%) and oral thrush is classified as B2.
- A 28 year-old with Kaposi’s sarcoma and a CD4 of 50 has a classification of C3 (severe clinical symptoms and severe immunosuppression).
- A infant with HIV vertical exposure and indeterminate (unconfirmed) infection status has E (for vertically exposed) placed as a prefix to the appropriate classification code (e.g., EN1).
TABLE 8: Using WHO pediatric clinical staging events to guide decision making on switching to second-line therapy for treatment failure in children (“T staging”)

<table>
<thead>
<tr>
<th>New or recurrent event on ART(^{a,b})</th>
<th>Management options(^{c,d})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[A (IV)]</td>
</tr>
<tr>
<td>No new events or PGL (T1)</td>
<td>Do not switch to new regimen</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 events (T2)</td>
<td>Treat and manage staging event</td>
</tr>
<tr>
<td></td>
<td>Do not switch to new regimen</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 events (T3)</td>
<td>Treat and manage staging event and monitor response(^e)</td>
</tr>
<tr>
<td></td>
<td>Check if on treatment 24 weeks or more</td>
</tr>
<tr>
<td></td>
<td>Assess and offer adherence support</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4 events (T4)</td>
<td>Treat and manage staging event</td>
</tr>
<tr>
<td></td>
<td>Check if on treatment 24 weeks or more</td>
</tr>
<tr>
<td></td>
<td>Assess and offer adherence support</td>
</tr>
</tbody>
</table>

\(^{a}\) Strength of recommendation/level of evidence.

\(^{b}\) A clinical event refers to a new or recurrent condition as classified in the WHO clinical staging at the time of evaluating the infant or child on ART. Annex B provides more details about the clinical events.

\(^{c}\) It needs to be ensured that the child has had at least 24 weeks of treatment and that adherence to therapy has been assessed and considered adequate before considering switching to the second-line regimen.

\(^{d}\) Differentiation of opportunistic infections from IRIS is important.

\(^{e}\) In considering changing treatment because of growth failure, it should be ensured that the child has adequate nutrition and that any intercurrent infections have been treated and resolved.

\(^{f}\) Pulmonary or lymph node TB, which are clinical state 3 conditions, may not be an indication of treatment failure, and thus may not require consideration of second-line therapy. The response to tuberculosis therapy should be used to evaluate the need for switching therapy (Section XII).

CD4 is best performed once acute phase of presenting illness is resolved.

### How-to Stage HIV (continued)

**TABLE 9: Using WHO pediatric clinical staging events to guide decision making on switching to second-line therapy for treatment failure in adults ("T staging")**

<table>
<thead>
<tr>
<th>New or recurrent event on ART(^a)</th>
<th>Recommendations</th>
<th>Additional management options</th>
</tr>
</thead>
</table>
| Asymptomatic (T1)                   | Do not switch regimen | ◆ Maintain scheduled follow-up visits, including CD4 monitoring (if available)  
◆ Continue to offer adherence support |
| Stage 2 event (T2)                  | Do not switch regimen\(^b\) | ◆ Treat and manage staging event  
◆ Access and offer adherence support  
◆ Check if on treatment for at least six months  
◆ Assess continuation or reintroduction of OI prophylaxis  
◆ Schedule earlier visit for clinical review and consider CD4 (if available)\(^c\) |
| Stage 3 event (T3)                  | Consider switching regimen\(^b,d\) | ◆ Treat and manage staging event and monitor response  
◆ Assess and offer adherence support  
◆ Check if on treatment for at least six months  
◆ Check CD4 cell count (if available)\(^c,d\)  
◆ Assess continuation or reintroduction of OI prophylaxis  
◆ Institute more frequent follow-up |
| Stage 4 event (T4)                  | Switch regimen\(^b,e\) | ◆ Treat and manage staging event and monitor response  
◆ Check if on treatment for at least six months  
◆ Assess continuation or reintroduction of OI prophylaxis  
◆ Check CD4 cell count (if available)\(^c\)  
◆ Assess and offer adherence support |

\(^a\) Refers to clinical stages while on ART for at least six months (termed T1, T2, T3, T4).

\(^b\) Differentiation of opportunistic infections from immune reconstitution inflammatory syndrome is necessary.

\(^c\) Treat and manage the staging event before measuring CD4 cell count.

\(^d\) Certain WHO clinical stage 3 conditions (e.g., pulmonary TB, severe bacterial infections) may be indicators of treatment failure and thus require consideration of second-line therapy; response to appropriate therapy should be used to evaluate the need for switching of therapy.

\(^e\) Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy; response to appropriate antimicrobial therapy should be used to evaluate the need to switch therapy.

**Source:** World Health Organization, Antiretroviral Therapy for HIV infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006.
### Table 10: Imaged depicting common manifestations of WHO clinical staging diseases

#### Stage 2 Diagnosis - Selected examples

| Papular pruritic eruption | Unexplained persistent hepatomegaly | Two examples of extensive wart virus infection: 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>![Papular pruritic eruption]( Courtesy of Carrie Kovarik, M.D.)</td>
<td>![Unexplained persistent hepatomegaly]( Courtesy of Julia Kim, M.D.)</td>
<td>verruca planus verruca vulgaris</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Fungal nail infection</td>
<td>Recurrent oral ulcerations</td>
</tr>
<tr>
<td>![Herpes zoster]( Courtesy of BIPAI Image Library)</td>
<td>![Fungal nail infection]( Courtesy of I-TECH Public Image Library)</td>
<td>![Recurrent oral ulcerations]( Courtesy of I-TECH Public Image Library)</td>
</tr>
<tr>
<td>Extensive molluscum contagiosum</td>
<td>Unexplained persistent parotid enlargement</td>
<td></td>
</tr>
<tr>
<td>![Extensive molluscum contagiosum]( Courtesy of I-TECH Public Image Library)</td>
<td>![Unexplained persistent parotid enlargement]( Courtesy of BIPAI Image Library)</td>
<td></td>
</tr>
</tbody>
</table>
# How-to Stage HIV (concluded)

**TABLE 10: Imaged depicting common manifestations of WHO clinical staging diseases (continued)**

## Stage 3 Diagnosis - Selected examples

<table>
<thead>
<tr>
<th>Lymph node TB</th>
<th>Oral hairy leukoplakia</th>
<th>Persistent oral candidiasis</th>
<th>Symptomatic LIP (“Clubbing” a common finding)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>Courtesy of Julia Kim, M.D.</td>
<td>Courtesy of CDC Public Health Image Library</td>
<td>Courtesy of I-TECH Public Image Library</td>
<td>Courtesy of Helga Loeffler, M.D.</td>
</tr>
</tbody>
</table>

## Stage 4 Diagnosis - Selected examples

### Four examples of Kaposi’s sarcoma

- ![Image](image1) Courtesy of Carrie Kovarik, M.D.
- ![Image](image2) Courtesy of Carrie Kovarik, M.D.
- ![Image](image3) Courtesy of BIPAI Image Library
- ![Image](image4) Courtesy of Carrie Kovarik, M.D.

### Extrapulmonary TB (of spine)

- ![Image](image1) Courtesy of Liz Lowenthal, M.D.

### Persistent oral candidiasis

- ![Image](image1) Courtesy of BIPAI Image Library

### Hiv encephalopathy

- ![Image](image1) Courtesy of Helga Loeffler, M.D.

### Two examples of unexplained severe wasting, stunting, severe malnutrition

- ![Image](image1) Courtesy of Nanda Sugandhi, M.D.
- ![Image](image2) Courtesy of Nanda Sugandhi, M.D.
TABLE 11: How to collect DBS samples in infants and children for early diagnosis of HIV

1. Fill out appropriate paperwork: DBS card, lab order form, clinic logbook.
2. Choose the puncture site

<table>
<thead>
<tr>
<th>Stage</th>
<th>Puncture Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Infants</td>
<td>Heel</td>
</tr>
<tr>
<td>Medium Infants</td>
<td>Toe</td>
</tr>
<tr>
<td>Larger Infants</td>
<td>4th Finger</td>
</tr>
</tbody>
</table>

3. Warm the puncture site

4. Wash hands, put on gloves

5. Position baby with foot down
6. Clean the site with an alcohol swab and allow to dry for 30 seconds

7. Press lancet on to site, prick skin
8. Wipe away first drop

9. Allow large drop to collect
10. Touch blood drop to card
11. Fill entire circle with drop
12. Fill all 5 circles (at least 3)
13. Apply mild pressure and clean the puncture site

14. Dry and package the DBS samples for storage and transport to the laboratory

JOB WELL DONE!

Photos courtesy of Julia Kim, M.D.
REFERENCES


Objectives

1. Discuss the goals of treatment for human immunodeficiency virus (HIV) infection.
2. Present the basic principles of antiretroviral therapy (ART).
3. Review the ARV medicines currently being used around the world to treat HIV infection.
4. Discuss barriers to effective ART and some ways to overcome them.

Key Points

1. Many ARV drugs are available for the treatment of HIV infection. However, none of these medications can cure HIV.
2. Medications used to treat HIV reduce the ability of the virus to replicate (or reproduce) within the body.
3. When HIV cannot replicate, damage to the immune system and other vital organs is reduced, leading to improved health.
4. Patients receiving ART are less susceptible to opportunistic infections, malignancies, and other illnesses.
5. Many patients live longer because of ART.
6. One goal of ART is to reduce the patient’s viral load, preferably to below levels that can be detected with available tests.
7. ARV medications are designed to attack the virus at many points in its cycle.
8. The decision to begin ART in an HIV-infected person is determined by that person’s clinical, virologic, and immunologic condition.
9. ART often is changed when an HIV-infected child or adult experiences clinical, virologic, or immunologic failure.
10. Among the many barriers to ARV treatment are cost, time commitment, stigma, food security, and home environment.

Introduction

Although many medicines are used to treat human immunodeficiency virus (HIV) infection, none can cure HIV/AIDS. Antiretroviral (ARV) drugs can reduce the ability of the virus to replicate, and they can thus reduce the damage that the virus does over time to the person’s immune system and other vital organs.

Therapeutic Goals

The goals of ARV therapy (ART) include the following:

- Maximal and durable suppression of HIV replication
- Restoration and preservation of immune function
- Improvement in quality of life
- Reduction in HIV-related morbidity and mortality

Efficacy of these goals can be measured in three ways:

1. Clinically, by a reduction in the number and frequency of opportunistic infections (OIs)
2. Immunologically, by a gradual and steady rise in the CD4+ cell count
3. Virologically, by a decrease in the viral load, ideally to undetectable levels within 6 months after initiation of ART

The primary goal of ART is to improve the health and prolong the life of the HIV-infected child or adult. This goal is achieved by interfering with the ability of the virus to replicate, or reproduce, inside the body. When the virus cannot replicate, damage to the immune system is minimized. Because the immune system is functioning more normally, the treated individual is less susceptible to OIs, malignancies, and other illnesses. HIV-infected patients receiving ART also are less likely to develop other complications associated with HIV/AIDS, such as wasting syndrome and encephalopathy (a disorder of the brain). Most patients taking effective ART will live longer than they would without medications.
The health professional can monitor how well the goals of treatment are being met by talking with and examining the patient as well as by performing laboratory tests. Clinically, patients are evaluated for signs and symptoms of HIV disease progression, such as weight loss or new OIs. Children taking ARV drugs will often have improved growth and development. The two laboratory tests used most commonly to monitor the success of ARTs are measures of the viral load and the CD4+ cell count. A viral load (e.g., HIV RNA polymerase chain reaction) assay measures the concentration of the virus in the blood or plasma. Some types of highly active ART (HAART) can reduce the amount of virus circulating in the blood or plasma to below levels of detectability. Unfortunately, in such cases, the virus is still present in the body, and the concentration of circulating virus will increase if treatment is stopped.

ART typically produces a significant drop in viral load. However, viral-load test results may vary from day to day. Hence, changes in viral load are often expressed by logarithms, or logs. A 1-log change is a drop or increase by a factor of 10. A 1-log drop means that the level of HIV in the blood has decreased by 90%; a 1-log increase means that the level of HIV in the blood has increased 10-fold. In general, the larger the log drop, the stronger the sign that HIV replication is being slowed.

The concentration of a change in viral load varies with the age of the patient. In patients younger than 2 years, only changes of 0.7 log or more from the baseline level (the viral load before medications are started) are considered significant. In children 2 years and older and in adults, only viral-load increases or decreases of more than 0.5 log are considered meaningful. The viral load should be monitored at regular intervals. If the viral load decreases but then begins to increase, this may indicate nonadherence with medications, development of viral resistance to ARV drugs, or treatment failure.

The CD4+ cell count measures the concentration of a particular type of lymphocyte, the T-helper cell, in a specified volume of the patient’s blood. HIV infection severely affects the CD4+ cell. As detailed in Figure 1, in the body, HIV attaches to and enters CD4+ cells. Once inside, the virus subverts the CD4+ cell’s replication machinery, turning it into a virus factory. In copying itself, the virus destroys the CD4+ cell. Often when a patient begins ART, the CD4+ cell count will increase, a reflection of the immune system’s improved ability to fight infection. Determining a patient’s CD4+ cell count at regular intervals allows the health professional to monitor the strength of the patient’s immune system. Successful ART will cause the CD4+ cell count to rise and then remain elevated during therapy. A decrease in the concentration of CD4+ cells may represent failure of ART.

**Principles of Therapy**

**When to Start Therapy**

ART is not necessarily started when a patient is first infected with HIV. Although some evidence suggests that starting medicines before a patient is symptomatic can prolong life, there are many obstacles to such early treatment. ART can be costly. Also, the virus can develop resistance to these medications, in much the same way that bacteria can become resistant to the effects of antibiotics. The medicines can be difficult to take, causing many side effects. Patients who do not feel ill from their disease may not be motivated to take medicines. Once ARV medicines are started, they need to be taken consistently, according to instructions, every day. Patient motivation is important to ensure that medication schedules are followed precisely.

With these caveats in mind, most clinicians who treat adults follow standard criteria for starting medications.
Throughout the world, countries have their own guidelines for the use of ARV drugs. Most of the country-specific guidelines that have been developed are based on HIV treatment guidelines created and periodically updated by Working Groups organized under the U.S. Department of Health and Human Services (DHHS) and the National Institutes of Health (collectively referred to herein as the U.S. Guidelines), similar to those in use in most developed-country settings, and guidelines produced by the World Health Organization (WHO), which promote a public health-oriented approach for use in resource-limited settings.

For both pediatric and adult populations, three general categories of criteria are part of the decision-making process for initiating ART. These categories include the following:
- Clinical
- Immunologic
- Virologic

Clinical criteria for initiating ART are generally consistent across guidelines. As detailed in the previous chapter, clinical conditions indicating advanced HIV disease (CDC-C as well as WHO III and IV) are indications for initiating ART in both pediatric and adult populations.

With respect to immunologic and virologic status, most studies relating viral load and immune status to HIV disease progression have been conducted in developed countries. Many resource-limited settings tend to use more conservative criteria for initiating ARV medications, such as lower CD4+ cell count thresholds, than those in developed-country settings. These policies are based on drug availability as well as growing concern regarding the potential side effects of long-term ART.

In adults and adolescents, U.S. Guidelines recommend that ART be initiated (Table 1) in patients with a history of an AIDS-defining illness or with a CD4+ count of less than 350 cells/mm³. They also recommend treatment for the following groups regardless of CD4+ cell count:
- Pregnant patients
- Patients with HIV-associated nephropathy
- Patients coinfected with hepatitis B when treatment of hepatitis B is indicated

These guidelines comment that the optimal time to initiate ART in asymptomatic patients with a CD4+ greater than 350 cells/mm³ is not well defined. They recommend that the decision to start therapy or not in this set of patients depends on the potential benefits and risks of therapy, comorbidities, and patient readiness and willingness to adhere to long-term treatment. Some study data demonstrate immunologic benefits to initiating ART prior to a CD4+ count decline below 350 cells/mm³. In studies in Europe and the United States, patients who initiated ART at CD4+ counts greater than 350 cells/mm³ were more likely to have a normal CD4+ count (Europe,

### Table 1. Indications for initiating antiretroviral therapy for the chronically HIV-1 infected patient

<table>
<thead>
<tr>
<th>Clinical Condition and/or CD4 Count</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of AIDS-defining illness</td>
<td>Antiretroviral therapy should be initiated.</td>
</tr>
<tr>
<td>CD4 count &lt; 200 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>CD4 count 200-350 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>Pregnant women*</td>
<td></td>
</tr>
<tr>
<td>Persons with HIV-associated nephropathy</td>
<td></td>
</tr>
<tr>
<td>Persons coinfected with hepatitis B virus (HBV), when HBV treatment is indicated (Treatment with fully suppressive antiviral drugs active against both HIV and HBV is recommended.)</td>
<td></td>
</tr>
</tbody>
</table>

*For women who do not require antiretroviral therapy for their own health, consideration can be given to discontinuing antiretroviral drugs postpartum. For more detailed discussion, please refer to the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV-1 Transmission in the United States and the HIV-Infected Women of Reproductive Age and Pregnant Women section.
>800 cells/mm³; United States, >500 cells/mm³) after several years of therapy than those who initiated ART at CD4⁺ counts less than 350 cells/mm³.

When the CD4⁺ count is greater than 350 cells/mm³, viral loads are not strongly associated with short-term risk of developing or dying from AIDS. However, high viral loads do predict a more rapid progression to AIDS than lower viral load. Some experts take high viral loads (e.g., >100,000 copies/mL) into consideration when deciding whether ART should be initiated in a patient. As well, some experts believe that additional criteria, such as the rapidity with which CD4⁺ cell count is declining, should be used in making ART initiation decisions.

WHO guidelines for adults and adolescents make the point that viral loads are not commonly available in resource-limited settings, and so decisions regarding when to initiate ART for a patient must be made entirely on clinical and immunologic grounds. In many settings, still, CD4⁺ cell counts are not or are only unreliably available, leaving clinical grounds as the sole basis for ART initiation. Using these two criteria in tandem, the WHO makes the following recommendations (Table 2):

For WHO clinical stages I and II, HAART should be initiated only if the CD4⁺ cell count is less than 350 cells/mm³. For stage II, in the absence of CD4 availability, the total lymphocyte count (TLC) may be used as a surrogate marker for immune status—if it is less than 1200 cells/mm³, HAART should be initiated. WHO recommends that all patients in clinical stage III and IV be treated regardless of CD4⁺ cell count.

In some settings, ART may need to be started before the CD4⁺ cell count drops below even 350 cells/mm³. A cohort study in Cote d’Ivoire that monitored 792 adults for a median of 8 months after initiating ARVs found that although the rate of severe morbidity or mortality declined with increasing CD4 count, such rates were still considerable in some categories of patients with CD4 cell counts higher than 350 cells/mm³ who did not start ART. The study suggests that in sub-Saharan Africa, patients with low body mass index, low hemoglobin, and a history of tuberculosis may benefit from earlier initiation of ART, even if the CD4 count is greater than 350 cells/mm³. As well, in this study viral load was available to the investigators, and patients with high viral loads also were felt to benefit from earlier initiation.

### Table 2. Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers

<table>
<thead>
<tr>
<th>WHO Clinical Staging</th>
<th>When CD4 Cell Count Not Available</th>
<th>When CD4 Cell Count Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do not treat</td>
<td>Treat if CD4 count is below 350 cells/mm³^a^</td>
</tr>
<tr>
<td>2</td>
<td>Do not treat</td>
<td>Treat irrespective of CD4 cell count^b^</td>
</tr>
<tr>
<td>3</td>
<td>Treat</td>
<td>Treat irrespective of CD4 cell count^b^</td>
</tr>
<tr>
<td>4</td>
<td>Treat</td>
<td>Treat irrespective of CD4 cell count^b^</td>
</tr>
</tbody>
</table>

^a^ CD4 cell count advisable to assist with determining need for immediate therapy for situations such as pulmonary TB and severe bacterial infections, which may occur at any CD4 level.

^b^ A total lymphocyte count of 1200/mm³ or less can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exists. It is not useful in asymptomatic patients. Thus, in the absence of CD4 cell counts and TLCs, patients with WHO adult clinical stage 2 should not be treated.

^c^ The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells/mm³ (see Section 11.2).

^d^ The initiation of ART is recommended for all HIV-infected patients with CD4 counts below 350 cells/mm³ and pulmonary T8 (see Section 12.1) or severe bacterial infection.

^e^ The precise CD4 cell level above 200/mm³ at which ARV treatment should be started has not been established.
Opinions about when to start ART in an HIV-infected child also differ. An HIV-infected child’s clinical, virologic, and immunologic status should be evaluated at the time of diagnosis and monitored at regular intervals thereafter. Few experts would disagree that a symptomatic HIV-infected child should be treated. In particular, children who are experiencing growth failure or neurodevelopmental regression or who are failing to achieve developmental milestones normally should receive ART. Similarly, any child with a high or increasing viral load should be considered for ART. Finally, any child whose immune system has been compromised should be treated. Immunologic compromise is reflected in a lower-than-expected CD4+ cell count or percentage (<25%).

Available evidence suggests that infants younger than 12 months should be treated as soon as they are diagnosed with HIV. The rationale is that determining which infants will have rapid and which will have slow disease progression is difficult. A prediction of rate of disease progression cannot be made based on the viral-load determination or the CD4+ cell count or any other measure that is currently available. The WHO Technical Reference Group for Paediatric HIV/ART Care Guidelines recently endorsed treating such infants upon diagnosis.

The most recent revision of U.S. infant and pediatric ART guidelines (July 2008) has adopted recommendations for when to initiate therapy (Table 3) according to three age ranges: infants younger than 12 months, children aged 1-4 years, and children aged 5 years or more. Because monitoring parameters such as CD4 percentage and viral load have less prognostic significance for children younger than 12 months than for those older than 12 months, the U.S. Guidelines recommendations are divided chiefly by a child’s status as younger or older than 12 months.

Adolescents are considered in the preceding section on adolescent and adult recommendations.

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**Table 3. Indications for initiation of antiretroviral therapy in children infected with human immunodeficiency virus (HIV) (Updated February 28, 2008)**

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number; the potential benefits and risks of therapy; and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed and addressed with the child, if age-appropriate, and caregiver before the decision to initiate therapy is made.

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>- Regardless of clinical symptoms, immune status, or viral load</td>
<td>Treat</td>
</tr>
<tr>
<td>1 - &lt;5 years</td>
<td>- AIDS or significant HIV-related symptoms*&lt;br&gt;- CD4 &lt;25%, regardless of symptoms or HIV RNA level²&lt;br&gt;- Asymptomatic or mild symptoms and&lt;br&gt;  - CD4 ≥25% and&lt;br&gt;  - HIV RNA &gt;100,000 copies/mL&lt;br&gt;- Asymptomatic or mild symptoms and&lt;br&gt;  - CD4 ≥25% and&lt;br&gt;  - HIV RNA &gt;100,000 copies/mL</td>
<td>Treat&lt;br&gt;Consider</td>
</tr>
<tr>
<td>≥5 years</td>
<td>- AIDS or significant HIV-related symptoms³&lt;br&gt;- CD4 &lt;350 cells/mm³&lt;br&gt;- Asymptomatic or mild symptoms and&lt;br&gt;  - CD4 ≥350 cells/mm³ and&lt;br&gt;  - HIV RNA &gt;100,000 copies/mL&lt;br&gt;- Asymptomatic or mild symptoms and&lt;br&gt;  - CD4 ≥350 cells/mm³ and&lt;br&gt;  - HIV RNA &lt;100,000 copies/mL</td>
<td>Treat&lt;br&gt;Consider&lt;br&gt;Defer⁴</td>
</tr>
</tbody>
</table>

* CDC Clinical Category C and B (except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

² The data supporting this recommendation are stronger for those with CD4 percentage <20% than for those with CD4 percentage between 20%-24%.

³ CDC Clinical Category A or N or the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

⁴ Clinical and laboratory data should be re-evaluated every 3 to 4 months.

⁵ The data supporting this recommendation are stronger for those with CD4 count <200 than for those with CD4 counts between 200-350 cells/mm³.
Because the risk of rapid disease progression is highest in the first year of life, U.S. Guidelines recommend that all ARV-naïve HIV-infected infants younger than 12 months be initiated on ART regardless of clinical status, CD4 percentage, or viral load.

After 12 months of age, the risk of rapid disease progression begins to slow, and expert opinion is that deferring treatment can be considered for older children. Data from the HIV Pediatric Prognostic Markers Collaborative Study identified CD4 percentage thresholds associated with either a 10% risk of progression to AIDS or a 5% risk of death within the next 12 months. These values have been adopted by the U.S. Guidelines as the recommended thresholds for initiating ART. For children aged 1-4 years, this threshold of CD4 percentage is 25%. As well, in age cohorts older than 1 year, very high viral loads (>100,000 copies/mL) have been associated with increased risk of disease progression.

For children aged 5 years or older, data from the HIV Pediatric Prognostic Markers Collaborative Study suggest that absolute CD4+ cell count is a useful prognostic marker, with the same threshold as that for adolescents and adults, 350 cells/mm³, below which risk of disease progression begins to rise.

Accordingly, for children older than 12 months, the U.S. Guidelines recommend initiating ART in children with AIDS or significant symptoms (CDC-C or -B diagnoses other than one episode of serious bacterial infection or lymphoid interstitial pneumonitis), regardless of CD4 percentage/absolute CD4+ cell count or viral load. As well, children who are asymptomatic or have mild symptoms (CDC-N, -A, or the -B diagnoses mentioned earlier) are recommended to initiate ART if CD4 percentage/absolute CD4+ cell count is less than the recommended thresholds (25% for ages 1-5 years, 350 cells/mm³ for age ≥5 years). For children with viral load greater than 100,000 copies/mL but CD4 percentage/absolute CD4+ cell count above the thresholds and who are asymptomatic (CDC-N) or with only mild symptoms (CDC-A) or CDC-B disease because of one episode of serious bacterial infection or lymphoid interstitial pneumonitis, the U.S. Guidelines advise that ART be considered. And for children with viral load less than 100,000 copies/mL, CD4 percentage/absolute CD4+ cell count above the thresholds, and asymptomatic or only mild symptoms, the U.S. Guidelines advise deferring initiation of ART.

The WHO’s most recently published recommendations on when to initiate ART in infants and children in resource-limited settings (Tables 4 and 5) are similar to the preceding U.S. Guidelines, although CD4 percentage thresholds for initiating ART are somewhat different. As in the U.S. Guidelines, all infants younger than 12 months should be initiated on ART. CD4+ percentage thresholds for ART initiation are less than 20% for children aged 1-5 years and less than 15% for children older than 5 years. Because at times in resource-limited settings only absolute CD4+ cell count values may be available, the WHO makes allowance for age-dependent CD4+ thresholds: less than 750 cells/mm³ for children aged 1-3 years and less than 350 cells/mm³ for children aged 3-5 years.

## Table 4. Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and availability of immunological Markers

<table>
<thead>
<tr>
<th>WHO Pediatric Stage</th>
<th>Availability of CD4 Cell Measurements</th>
<th>Age-Specific Treatment Recommendations (A (II))&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;12 Months</td>
</tr>
<tr>
<td>4&lt;sup&gt;+&lt;/sup&gt;</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Treat all</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
<td>Treat all</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Treat all</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Treat all</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
</tbody>
</table>

<sup>* Strength of recommendation/level of evidence.</sup>

<sup>a</sup> Stabilize any opportunistic infection before initiation of ART.

<sup>b</sup> Baseline CD4 is useful for monitoring ART even if it is not required to initiate ART.

<sup>c</sup> In children with pulmonary or lymph node tuberculosis the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment (see Section XII).

<sup>d</sup> Refer to Table 5 for CD4 and Table 6 for TLC values.
Antiretroviral Treatment

Table 5. CD4 criteria for severe HIV immunodeficiency

<table>
<thead>
<tr>
<th>Immunological Marker</th>
<th>Age-Specific Recommendation to Initiate ART a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12 Months</td>
</tr>
<tr>
<td>%CD4+</td>
<td>Treat all</td>
</tr>
<tr>
<td>CD4 Counts</td>
<td>&lt;750 cells/mm³</td>
</tr>
</tbody>
</table>

a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.
b ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.
c %CD4+ is preferred for children aged <5 years.

Table 6. TLC criteria for severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 and where CD4 measurement is not available

<table>
<thead>
<tr>
<th>Immunological Marker</th>
<th>Age-Specific Recommendation to Initiate ART b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12 Months</td>
</tr>
<tr>
<td>TLC</td>
<td>Treat all</td>
</tr>
</tbody>
</table>

a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging.
b A drop of TLC below these levels significantly increases the risk of disease progression and mortality.
c There are fewer data available on which to base recommendations on the use of TLC for decision-making in children aged over 8 years.

years. The WHO advises that children older than 5 years be treated per adult CD4+ cell count thresholds.

The WHO recommends that infants and children with clinically advanced disease (stage III or IV) be initiated on ART regardless of absolute CD4+ cell count or percentage, with some exceptions, such as for children older than 1 year where the stage III diagnosis is based solely on pulmonary or lymph node tuberculosis, in which cases CD4+ cell count should also be considered. All children with WHO stage IV disease should be initiated on ART, regardless of CD4+ cell count.

Where CD4+ cell count measurements are not available, the WHO advises that the TLC be used as a surrogate marker (Table 6). In such settings, all children in WHO stage III or IV disease should be initiated on ART. For children aged up to age 8 years with WHO stage II disease, TLC thresholds may be used (<4000 cells/mm³ for infants <1 year, <3000 cells/mm³ for children aged 1-3 years, <2500 cells/mm³ for children aged 3-5 years, and <2000 cells/mm³ for children aged 5-8 years) as an indication of the need to initiate ART.

In developed-country settings, virological testing for infant diagnosis is generally widely available. Although this mode (HIV DNA polymerase chain reaction) of establishing a definitive diagnosis of HIV in infants younger than 18 months is becoming more the norm in resource-limited settings, many settings still lack these diagnostic modalities. In these settings, there is a need for guidelines on presumptive diagnosis of severe HIV-related disease that allows for subsequent HIV management after treatment of the initial acute illness.

The WHO has developed criteria for such presumptive diagnosis. A presumptive diagnosis of severe HIV disease should be made when an infant is HIV antibody positive and an AIDS indicator condition (WHO IV conditions such as pneumocystis pneumonia, cryptococcal meningitis, HIV wasting, Kaposi sarcoma, and extrapulmonary tuberculosis) can be diagnosed. Further, if an infant is HIV antibody positive and symptomatic with two or more of oral thrush, severe pneumonia, or severe sepsis, a presumptive diagnosis of severe HIV disease may be made. Other factors that may support the diagnosis of severe HIV disease in a seropositive infant include recent HIV-related maternal death or advanced HIV disease in the mother or a CD4+ count of less than 20%. The WHO advises that whenever a presumptive diagnosis of HIV disease is made, the diagnosis should be confirmed as soon as possible.

When a presumptive diagnosis of severe HIV disease is made as outlined, the acute condition leading to the diagnosis should be treated first. Once the infant
or child’s clinical condition is stabilized, ART should be initiated. If HIV disease is subsequently ruled out, and the child is no longer exposed to the risk of HIV infection (e.g., through breastfeeding), ART should be discontinued.

**Which Therapy to Begin**

ARV drugs are grouped by how they work. Each class of medications interrupts HIV replication at a different point in the viral cycle (Figure 1). The groups of drugs include the following:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- PIs
- Entry inhibitors (EIs)
- Integrase inhibitors

The next section will discuss each group in more detail.

Patients with HIV infection almost always receive combinations of ARV drugs, and these combinations typically include drugs from more than one group or class. The rationale for combination ART is the same in adults and children: to target at least two points in the viral cycle. The more ways that different drugs attack HIV, the less likely it is that the virus will become resistant to treatment. This approach is similar to the use of combination therapy to treat tuberculosis.

Prevention of mother-to-child transmission (PMTCT) is the one instance where single-drug ART sometimes is given. Several studies have shown that treatment of the mother and infant with zidovudine (ZDV, azidothymidine [AZT]) can decrease transmission of the virus to the newborn. The same is true of the drug nevirapine (NVP). Regardless, one should not confuse these efforts to reduce mother-to-child HIV transmission with treatment of a child or adult with HIV/AIDS. Many current guidelines suggest starting ART with two NRTIs, usually in combination with an NNRTI or a PI.

**U.S. Adult and Adolescent Guidelines**

As of December 1, 2007, U.S. Guidelines recommend that most ART-naïve patients initiate either an NNRTI-based regimen (one NNRTI + two NRTIs) or a PI-based regimen (one PI + two NRTIs). Sometimes a triple-NRTI regimen (AZT + lamivudine [3TC] + abacavir [ABC]) may have utility. Regimens for which not enough data exist to recommend include NRTI-sparing regimens (such as NNRTI + PI or ritonavir-boosted monotherapy), quadruple-class regimens (such as NRTI + NNRTI + PI + EI); regimens containing EI as part of initial therapy; quadruple-NRTI regimens; or regimens containing five or more active agents, although alternative regimens are under investigation in several different settings.

**NNRTI-Based Regimens**

Strengths of NNRTI-based regimens include generally lower pill burden than that of PI-based regimens (particularly with the advent of the once-daily triple-drug fixed-dose combination [FDC] of tenofovir [TDF] plus emtricitabine plus efavirenz [EFV; marketed in the United States as Atripla]), avoidance of PI-associated side effects such as body habitus changes and lipid disorders, and the reservation of PIs for later use. U.S. Guidelines recommend efavirenz as the preferred NNRTI, except during the first trimester of pregnancy or in women of childbearing age who are not using an effective form of birth control because of efavirenz’s potential teratogenicity. Alternatively, nevirapine may be used in females with CD4+ cell counts less than or equal to 250 cells/mm³ and in males with CD4+ cell counts less than or equal to 400 cells/mm³; above these CD4+ cell count thresholds, the risk of nevirapine-associated hepatotoxicity is much greater.

Efavirenz-based regimens have shown strong efficacy in large randomized, controlled trials and cohort studies of treatment-naïve patients. The AIDS Clinical Trials Group 5412 study compared efavirenz plus two NRTIs with lopinavir/ritonavir plus two NRTIs and showed that the efavirenz-based regimen had significantly better virologic responses at 96 weeks than the lopinavir/ritonavir-based regimen (89% versus 77% with HIV RNA <50 copies/mL), whereas the regimen of lopinavir/ritonavir plus two NRTIs had significantly better CD4+ cell count improvements at 96 weeks (+268 cells/mm³ versus +241 cells/mm³) and lower rates of drug resistance in those patients who experienced virologic failure.

The randomized, controlled 2NN trial compared efavirenz versus nevirapine. When either efavirenz or nevirapine was given with stavudine plus lamivudine to treatment-naïve patients, both were effective and there were no statistically significant differences in the rates of treatment failure. However, there were two deaths in the study attributed to nevirapine use, one from fulminant
hepatitis and another from complications of Stevens-Johnson syndrome.

Although efavirenz and nevirapine are structurally distinct pharmaceuticals, either might cause hepatotoxicity or cutaneous reaction. When a severe cutaneous reaction, such as Stevens-Johnson syndrome, has taken place with either efavirenz or nevirapine, it is not recommended to replace the offending agent with the other. In such a case, future avoidance of the entire NNRTI drug class is recommended.

But for more minor skin rash—which is common in the early weeks of treatment, particularly with nevirapine—or for hepatotoxicity, the question arises in clinical practice whether it is safe to switch between efavirenz and nevirapine. A recently published review of the subject concluded that there was insufficient evidence to recommend substituting nevirapine for efavirenz after either cutaneous reaction or hepatotoxicity but that substituting efavirenz for nevirapine in similar circumstances was reasonable because the adverse reaction to nevirapine was not life threatening. This advice is in line with current WHO recommendations.

There are several second-generation NNRTI medications in development. The mechanism of action is similar to that of efavirenz or nevirapine, but the newer drugs are effective in patients who have developed common mutations to the current NNRTIs. These medications are taken orally, one once a day (rilpivirine) and another twice a day (etravirine). These medications are not yet approved by the U.S. Food and Drug Administration or other similar international bodies.

**PI-Based Regimens**

In wide use in resource-rich settings since the mid-1990s, PI-based regimens are traditionally effective in achieving sustained viral suppression, immunologic recovery, and clinical improvement in patients who take them. The U.S. Guidelines list several PIs as preferred products, including coformulated lopinavir/ritonavir and ritonavir-boosted azatanimavir and fosamprenavir. A randomized, placebo-controlled trial compared lopinavir/ritonavir with nelfinavir. In 653 patients who took either lopinavir/ritonavir plus two NRTIs or nelfinavir plus two NRTIs, the lopinavir/ritonavir arm of the study experienced better viral suppression at 48 weeks (84% versus 66%), and overall adverse event rates were similar between the two arms. Lopinavir/ritonavir was given twice daily, and the U.S. Guidelines recommend this administration schedule for lopinavir/ritonavir. Once-daily administration of lopinavir/ritonavir, unboosted azatanimavir, and both fosamprenavir and ritonavir-boosted fosamprenavir are listed by the U.S. Guidelines as alternatives to preferred PIs.

PI toxic effects, which sometimes limit and necessitate changes in therapy, include body habitus changes and hyperlipidemia, the latter occasionally necessitating pharmacologic therapy as management.

Some concern exists that PIs might be associated not only with increased risks of hyperlipidemia, requiring therapy, but also with an increased risk of myocardial infarction. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group analyzed data collected from a prospective observational study of 23,437 patients infected with HIV and compared myocardial infarction rates of patients exposed to PIs with those of patients exposed to NNRTIs. During 94,469 person-years of observation, 345 patients experienced a myocardial infarction. The incidence of myocardial infarction increased from 1.53 per 1000 person-years in those not exposed to PIs to 6.01 per 1000 person-years in those exposed to PIs for more than 6 years. After adjustment for exposure to the other drug class, established cardiovascular risk factors, and serum lipid levels, the relative rate of myocardial infarction per year of PI exposure was 1.10 (95% confidence interval, 1.04-1.18), whereas that per year of NNRTI exposure was 1.00 (95% confidence interval, 0.93-1.09), demonstrating an increased risk of myocardial infarction with exposure to PIs—a risk not seen with exposure to NNRTIs.

**Options for Dual-Nucleoside Backbone**

As described earlier, recommended NNRTI- and PI-based regimens use two NRTIs along with either the NNRTI or PI component. U.S. Guidelines recommend that the dual NRTIs be either tenofovir/emtricitabine (coformulated as Truvada) or zidovudine/lamivudine (coformulated as Combivir in North America and available in generic form in some settings, known as duovir.). Alternative dual NRTIs include abacavir/lamivudine (coformulated as Combivir in North America and available in generic form in some settings, known as duovir.) or didanosine plus lamivudine (or emtricitabine—U.S. Guidelines recommend that emtricitabine may generally be used in place of lamivudine or vice versa).
Resource-Limited Settings

In resource-limited settings, the WHO has recommended generating on a country-by-country basis standard first- and second-line regimens. If a child or adult fails the first-line regimen, he or she is switched, per the criteria and expert judgment outlined earlier, to the second-line regimen. The WHO recommends that resource-limited settings reserve PIs for second-line regimens. The choice of NRTI backbone depends on which NRTIs were used in the first-line regimen. For example, if a child were receiving stavudine (d4T) or AZT plus 3TC as the initial NRTI backbone, a second-line NRTI backbone could include ABC plus didanosine (ddI). If ABC plus 3TC were the initial dual NRTI, the second-line dual NRTI could be AZT plus ddI.

On the basis of available evidence, clinical experience, and feasibility for programmatic implementation by countries, the WHO recommends that first-line ART regimens for adults and adolescents consist of two NRTIs and one NNRTI. Particularly important to the feasibility and sustainability of implementing national-scope ART programs is the existence of FDC formulations containing two NRTIs and one NNRTI, particularly the combination of d4T, 3TC, and nevirapine that is the mainstay of many resource-limited setting programs. As well, not using PIs in the first-line regimen allows these potent, but expensive, drugs to be saved for second-line regimens in resource-limited settings.

The WHO recommends using a backbone approach to constructing first-line ART regimens. The preferred NRTI backbone is made up of either AZT or tenofovir along with 3TC or FTC. Efavirenz or nevirapine is added as the NNRTI component. Because of its associated toxic effects, d4T is no longer listed as a preferred NRTI, but rather as an alternative agent, typically used when a patient develops AZT-associated anemia. ABC is also listed as an alternative first-line NRTI.

Health professionals should reserve triple-NRTI regimens for certain classes of patients in whom NNRTIs may yield complications while continuing to reserve PIs for second-line use. These classes of patients may include the following:

- Women with CD4+ cell counts of 250–350 cells/mm³, in whom NVP may carry an increased risk of hepatotoxicity and for whom EFV may not be an option (i.e., those unable to ensure a reliable form of birth control)
- Patients who have coinfection with viral hepatitis or tuberculosis
- Patients who have experienced severe reactions to NVP or EFV
- Patients infected with HIV type 2, in whom NNRTIs are ineffective

The WHO-recommended triple-NRTI regimens are zidovudine-lamivudine-abacavir and zidovudine-lamivudine-tenofovir.

Because in resource-limited settings no potent or durable regimen has been identified for recommendation after initial PI failure, the WHO recommends that in such settings PIs be reserved for second-line therapy. However, the WHO allows for PIs to be used in first-line therapies in settings as mentioned, where NNRTIs may not be appropriate and triple NRTIs may not be available.

U.S. Pediatric Guidelines

U.S. Guidelines for administration of HAART to infants and children are to begin with a dual-NRTI backbone and add either an NNRTI or a PI. Because EFV is not recommended owing to toxicity concerns for children younger than 3 years or weighing less than 10 kg, the preferred NNRTI for children younger than 3 years is NVP. For those aged 3 or more years, it is EFV. Delavirdine is not recommended. Among PIs, lopinavir/ritonavir is preferred. Alternative PIs include atazanavir in combination with low-dose ritonavir plus two NRTIs, fosamprenavir in combination with low-dose ritonavir plus two NRTIs, and nelfinavir plus two NRTIs; atazanavir and fosamprenavir are indicated only for children aged at least 6 years, whereas nelfinavir is indicated for children aged at least 2 years. Unboosted atazanavir regimens are not recommended for children younger than 13 years and weighing less than 39 kg.

Favored two-NRTI combinations include the following:

- ABC plus 3TC or FTC (see comment later on human leukocyte antigen [HLA] B*5701 genetic testing, recommended prior to initiating ABC—ABC is not to be given if this test is positive)
- ddI plus FTC
- AZT plus 3TC or FTC
AZT plus either ABC or ddI is an alternative two-NRTI combination, with d4T plus either 3TC or FTC listed as available in special circumstances, such as a patient’s being unable to take or intolerant to other, more preferable two-NRTI combinations.

In special circumstances, much as discussed earlier for older patients, the U.S. Guidelines do allow for a three-NRTI regimen (zidovudine + lamivudine + abacavir) when an NNRTI-based or PI-based regimen cannot be used as first-line ART in a treatment-naive child.

ARV drug resistance testing is recommended prior to initiation of ART in all treatment-naive children. When infants who are receiving zidovudine prophylaxis as part of a PMTCT intervention are diagnosed as HIV infected in the first 6 weeks of life, zidovudine should be discontinued and combination ART with three drugs should be initiated, with choice of drug regimen based on results from ARV drug resistance testing.

**WHO Pediatric Guidelines**

In resource-limited settings, on the basis of ARVs both currently available in pediatric formulations and feasible on a cost basis, the WHO recommends that first-line regimens consist of one of the following two-NRTI-plus-1-NNRTI regimens:

- AZT plus 3TC plus either NVP or EFV
- d4T plus 3TC plus either NVP or EFV
- ABC plus 3TC plus either NVP or EFV

The choice of whether to use NVP or EFV is based on the age of the child (<3 years, NVP; ≥3 years, EFV). Of course, NVP should be used with caution in postpubertal adolescent girls with CD4+ cell count baseline values greater than 250 cells/mm³, and EFV likewise with caution in postpubertal adolescent girls who are sexually active, not on contraception, or (as discussed in the PMTCT section) in the first trimester of pregnancy. The most recent WHO guidelines (April 2008) recommend that infants younger than 12 months who have been exposed to an NVP regimen through either a PMTCT regimen or NNRTI-containing maternal ART should be initiated on a lopinavir/ritonavir-based regimen when feasible.

Where available, FTC may be used in place of 3TC in children older than 3 months; this approach reduces dose burden because FTC is administered only once daily.

ddi is generally saved for second-line regimens in most resource-limited settings. Again, for reasons as discussed earlier, triple-NRTI regimens may be used in special situations. Recommended regimens in this regard include either AZT or d4T plus 3TC/FTC plus ABC. The existence of AZT plus 3TC plus ABC in one FDC pill may be useful in adolescents with documented or significant potential for adherence issues.

In both wealthy and resource-poor settings, and in both pediatric and adult patients, certain NRTI combinations are not recommended, including the following:

- d4T plus AZT (antagonistic)
- d4T plus ddI (1. ddI reserved generally for second-line regimens in resource-poor settings; 2. toxicity concerns, particularly lactic acidosis)
- TDF plus 3TC plus ABC
- TDF plus 3TC plus ddI
- TDF plus ddI plus NNRTI

The last three are associated with a high incidence of early virological failure.

**FDCs**

At the beginning of 2007, the WHO and UNAIDS estimated that only 115,500 children worldwide had access to ART—a coverage rate of only 15% of those children in need. Furthermore, despite having the world’s highest pediatric HIV prevalences and the most children in need of ART, sub-Saharan Africa had the lowest ART coverage for children.

Reasons for this disparity are many, but one is the limited range of ARVs that are available and appropriate for pediatric use. Particularly lacking in the pediatric pharmaceutical armamentarium have been FDCs for treating smaller children. Because of the limitations of liquid formulations (which include sometimes complex storage requirements [refrigeration, shelf life], acceptance by the child [taste, volume required], and cost), there has been much effort directed at formulating a solid-form FDC. Beyond cost considerations, such a product would be expected to make country-level programming more facile, as well as improving adherence to ARV treatment regimens.

Several FDCs exist for adult use. Extensively used throughout sub-Saharan Africa is the FDC of d4T plus 3TC plus nevirapine, known by several brand names, including Triomune. Pediatric solid-form versions
of this FDC have recently moved into production by several generic drug manufacturers. The WHO Paediatric Antiretroviral Working Group (PAWG) evaluated the available d4T plus 3TC plus NVP FDCs and concluded that the ratio of nevirapine in relation to the NRTI components of a pediatric d4T-3TC-NVP FDC needs to be higher than in the comparable adult FDC. Of the solid-form versions reviewed, at the time this text went to print the PAWG believes that only the version FDC 6 (also known as Triomune Baby [Cipla Pharmaceuticals]) meets the specifications for ideal dosing of each component (6 mg of d4T, 30 mg of 3TC, 50 mg of NVP). There also exists an FDC solution composed of the same base ARVs (FDC 10—d4T, 10 mg/5 mL; 3TC, 40 mg/5 mL; NVP, 70 mg/5 mL), which can be used for even smaller children. Yet, because it contains d4T, it must be refrigerated at 40°C after reconstitution, and, although in use in some settings, is felt by the PAWG to generally not be a useful alternative to FDC 6 in resource-limited settings.

These FDCs, specially formulated for infant and small pediatric patients, have begun to see wider use in resource-limited settings. Early operational data show them to be effective in general use. A prospective study in India that looked at use of both pediatric-formulated d4T-3TC-NVP FDC solution and tablets showed statistically significant increases in CD4+ cell counts after 3 months of therapy in all age groups studied (<1 year, 1-5 years, ≥6 years), as well as improvements in clinical parameters and no incidence of drug-related adverse effects.

In some resource-limited settings, specially formulated pediatric FDCs remain unavailable. In some of these settings, full-strength FDCs of d4T-3TC-NVP are available and continue to be the mainstay of both adult and, when split into fragments for administration to children, pediatric ART programs. There is a paucity of data on the program-level effectiveness of this approach, but a study from India suggests that it may possess both feasibility and effectiveness for treatment of HIV in resource-limited settings. In this study, 25 consecutive HIV-positive, ART-naive children older than 18 months were started on split-pill, full-strength FDC d4T-3TC-NVP (30 mg of d4T, 150 mg of 3TC, 200 mg of NVP) dosed twice daily. In the cohort, substantial increases in weight were seen over the study period, as was a significant increase in mean...
Antiretroviral Treatment

CD4+ cell count. Low rates of drug adverse effects were seen, and adherence to medication and clinic visits were both high. However, a study conducted in Zambia and Malawi found that children taking half or one-quarter of a Triomune pill were often underdosed on nevirapine and were more stunted than those receiving optimal dosing. It is suggested that if split adult tablets are the only ART option, those with 30 mg of stavudine are preferable because they allow for higher nevirapine dosing.

Despite the improving availability of pediatric FDCs, and despite the feasibility and efficacy of the currently available formulations, much work remains to be done in increasing the number of FDC products available to children. At present, no WHO-recommended second-line ARV regimens are available in FDCs.

When to Change Therapy

ART should be changed when the child or adult experiences clinical, virologic, or immunologic failure. Evaluation for treatment failure should include a medical history and physical examination for evidence of disease progression, viral load, and CD4+ cell count. Adults who are responding well to treatment will maintain their weight and have few illnesses. Adults in whom treatment is no longer as effective will lose weight and develop more infections and illnesses. In children, it is important to measure growth, both length/height and weight, and monitor neurodevelopment. Neurodevelopment is the way a child achieves normal milestones, such as sitting, walking, and self-feeding. Such monitoring involves watching children closely during examinations and asking their caregivers about how the children have changed since the last visit. Children who are responding well to ART typically grow well and develop normally. Children who are failing ART often fail to grow, or they experience developmental problems.

The definition of virologic failure differs for each individual. A patient whose viral load is undetectable after a first course of ART but then rebounds to 10,000 or 20,000 copies/mL could be defined as having failed therapy. However, a patient who has had every available ARV drug but whose viral load decreases from 1,000,000 copies/mL to 10,000 or 20,000 copies/mL after a new course of treatment would be considered a treatment success.

As in treatment initiation, the decision to change treatment because of failure should be put into clinical context. Children and adults may have an initial drop in viral load, followed by a slow increase. But if their CD4+ lymphocytes continue to increase over time, this could indicate that the treatment is holding the virus at bay, preventing it from destroying the immune system, and thus the best course of action might be to continue the current medications.

Although a standard part of monitoring the effectiveness of ART in resource-rich settings, cost and operational considerations have kept viral load measurements beyond the reach of many resource-limited settings. Current WHO guidelines do not recommend viral load measurements for monitoring ART effectiveness in resource-limited settings. In these settings, decisions on switching therapy are typically made on the basis of those parameters available: clinical status and immunological status (CD4+ cell count); sometimes, when CD4+ cell counts are not available, clinical status is the sole criterion for switching decisions.

Concerns have been expressed over the inaccuracy with which changes in CD4+ cell count concord with changes in viral load. Studies in resource-limited settings have sometimes shown marked increases in CD4+ cell counts in patients without complete viral suppression and in others decreases in CD4+ cell count in patients with undetectable viral loads. By allowing prolonged periods of virological failure, delayed switching (based on CD4+ cell counts) of regimens may lead to the accumulation of resistance mutations. These mutations may have implications both for the patient (limiting the efficacy of available second-line regimens) and for populations, increasing the prevalence of primary resistance in the population. Such a development could limit the efficacy of both PMTCT interventions and common first-line therapies.

Making viral load testing more feasible for resource-limited settings could address the preceding concerns, as well as yield benefits to ART programs in areas such as adherence monitoring, infant diagnosis, quality assessment, and resistance surveillance. Although the cost, infrastructure, and personnel barriers are being overcome, new methods to monitor virological efficacy of ART in resource-poor countries are being proposed. Using the experiences of the Infectious Diseases Institute of the Makakere Medical School in Kampala, Uganda,
as their primary basis, Colebunders and colleagues recently presented a model that uses patients’ clinical and treatment history, adherence to treatment, hemoglobin level, and TLC to identify virological treatment failure and offer patients future treatment options. Although still needing to be tested in routine clinical care, this model poses an intriguing approach, relying heavily on good clinical skills and the evaluation of adherence in patients’ treatment histories. As well, the model suggests that it may be more cost-effective for resource-limited settings to invest in funding and training a multidisciplinary staff that can monitor each patient than to spend scarce funds on expensive laboratory testing—key considerations as programs in resource-limited settings face the challenges of scaling up services to meet the 2010 goal of universal access to HIV/AIDS care and treatment services.

**Treatment Options for Patients if ART Fails**

In all settings, when possible, ART regimen changes should involve all three drugs. Doing so is not always possible because some people have already received most of the ARVs available. One ARV may be changed or added, although this approach is not recommended because of concerns about viral resistance. Another option may be to continue the failing regimen. The definition of failure is different for each individual. A patient who has been on many ARV drugs and finds the viral load increasing while receiving HAART may still be deriving some clinical benefit from the drug combination. The failing treatment regimen may be continued even though full suppression of viral replication is not achieved. ARV drugs used in the patient’s past may be used again, but this approach is not generally considered as a first option. On rare occasions, ARVs are discontinued in a person with very advanced disease who has been through all available therapies and in whom therapy is producing toxicity or intolerance but no benefits.

**Limitations to Selection of Alternative ART**

Several possible limitations to the selection of alternative ART exist. There is cross-resistance among some agents. Hence, a patient who develops resistance to one PI may have resistance to most PIs. There is cross-resistance among the NNRTIs. The nucleoside agents are less prone to this classwide type of cross-resistance. There is cross-resistance between ddI and zalcitabine (ddC) and some potential cross-resistance between ddI and 3TC, particularly if 3TC is used prior to ddI. d4T is unique among ARV agents in that it does not have a genotypic marker for resistance, and high-grade resistance to d4T has been difficult to demonstrate in samples of virus taken from individual patients. Usually, the virus remains susceptible to d4T even in patients who have been treated with d4T monotherapy over a long period.

Accessory or secondary mutations of HIV invariably accumulate in patients who are treated with ARV agents. They are considered accessory mutations because they usually need to combine with other mutations to cause enough resistance to prevent the drug from working, whereas a primary mutation by itself can keep a drug from working effectively. A virus that has accumulated several accessory mutations over time will be resistant to therapy.

Resistance testing may also have a role to play when changing ART. Two types of resistance testing are available: genotyping and phenotyping. Genotyping is less expensive and can usually be completed in 1-2 weeks. Genotyping detects drug resistance mutations that are present in the relevant viral genes. In contrast, phenotyping assays measure the ability of viruses to grow in the presence of various concentrations of ARV drugs. They are more expensive and generally take 2-3 weeks to complete. Where available, resistance testing should be considered for cases of virologic failure that also are receiving HAART or suboptimal suppression of viral load after initiation of HAART. Resistance testing has several drawbacks, however: it is costly and lacks uniform quality assurance; moreover, it is insensitive for minor viral species. For example, if a patient has not taken ZDV in several years, ZDV-resistant virus may represent only a small percentage of circulating virus. Resistance testing may inaccurately report this patient as having a virus susceptible to ZDV. Were the patient to be restarted on ZDV, the resistant virus would quickly become dominant. Ultimately, each case is different. Decisions about when to declare failure and change treatment require the judgment of experienced professionals.
NNRTI plus PI, such as ddI plus EFV or nevirapine plus Kaletra.

Switching a child from a first-line to second-line ARV regimen in a resource-limited setting is fraught with potential challenges, not the least of which is the lack of further regimens should the second-line regimen fail. As a population experiences ARV administration over time, there is a natural rate of need to switch regimens. To date in resource-limited settings, there has been generally good success with first-line regimens. Recently published data from a multicountry survey carried out in 2006 by the AIDS Medicines and Diagnostics Service of the WHO showed the distribution of respective first-line use and second-line use among individuals on ART to be 96% and 4% for adults and 99% and 1% for children. More than 95% of respondents on first-line therapy in both populations were taking WHO-approved regimens, with the most common regimen in both populations being stavudine plus lamivudine plus nevirapine. Rates of first-year switching were low, estimated at between 1% and 15%.

Infants Who Have Acquired HIV Infection Despite ARV-based PMTCT

Special consideration is given to infants who have acquired HIV infection despite their mothers’ having received ARVs during pregnancy, either for treatment or as part of a PMTCT program, or themselves having received ARVs in the form of the infant component of PMTCT. In such cases, the infant might have HIV that is resistant to ARVs. Data from the HIVNET 012 single-dose nevirapine trial in Uganda showed that 46% of infants who acquired HIV infection despite the intervention had NNRTI-associated mutations. In a study of infants who had acquired HIV despite receiving one dose of nevirapine, there was a Substantially higher rate of virologic failure by the 6-month visit in infants who had received one dose of nevirapine than in those who had received placebo. Further investigation in this area is ongoing, and for now it is not definitively known whether ARV options for such infants should be modified from the standard regimens previously described. The WHO recommends that until there are more definitive data, children who require ARVs and who have previously received nevirapine (and/or 3TC, for which there are similar concerns) remain eligible for NNRTI-based regimens.

ARTs

Our discussion of the following five groups of ARV drugs includes tips for caregivers regarding difficulties that patients often have in taking medications, as well as some suggestions for overcoming these barriers. Table 7 lists doses and common side effects of all three classes of medications.

NRTIs

NRTIs were the first class of ARV medications approved by U.S. and European regulatory agencies, starting with zidovudine (ZDV, AZT) in 1987. NRTIs work by blocking an HIV protein called reverse transcriptase (Figure 1), thus preventing HIV RNA from changing into DNA. This is a critical point in HIV’s viral cycle. NRTIs in combination with one another and with other classes of drugs are the cornerstone therapy for HIV-infected children and adults.

- ZDV (Retrovir or zidovudine or AZT) can be taken with or without food and is available in oral solution, tablets, and capsules, all of which should be stored at room temperature. The capsules should be protected from moisture.
- d4T (Zerit or stavudine) can be taken with or without food. The oral solution needs to be refrigerated (oral solution that is not refrigerated may become ineffective) and shaken well before administering. The capsule can be opened and sprinkled over mashed potatoes or other soft foods. It should never be administered with ZDV, because the two medicines have the same mechanism of action and act at the same stage of the viral cycle. Hence, giving d4T and ZDV together would be the same as giving just one drug.
- ddI (Videx or didanosine) should be given on an empty stomach 1 h before or 2 h after a meal. The suspension needs to be refrigerated and shaken well before administering. If the solid formulation is used, two tablets must be given to ensure adequate buffering. The tablets may be dissolved in water or chewed. An enteric-coated capsule (Videx EC) is available. This form can be taken once a day by adults or twice a day by children, also on an empty stomach. The EC formulation is often more palatable for patients.
- 3TC (Epivir or lamivudine)/FTC (Emtriva or emtricitabine) can be given with or without food. Both are available in a tablet or oral-
solution formulation. The oral solution needs to be refrigerated. FTC can be given once daily, as opposed to 3TC, which is usually dosed twice daily.

- **Abacavir (Ziagen or ABC)** is available as a tablet or a yellow oral solution. It can be administered with or without food. The solution and tablets can be stored at room temperature. One of the NRTIs, abacavir (ABC), is associated, in up to 6% of patients who receive it, with a potentially fatal systemic hypersensitivity syndrome. A test has recently become available for an HLA type (HLA-B*5701) that is associated with a patient’s propensity to experience this reaction. DHHS recommends that HLA-B*5701 testing be performed prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction. Where HLA-B*5701 testing is not readily available, DHHS advises it to be reasonable to initiate abacavir with preinitiation counseling and monitoring for signs of abacavir-associated hypersensitivity reaction. HLA-B*5701-positive patients should not be prescribed abacavir, nor should patients with a history of prior hypersensitivity reaction to abacavir.

- **ddC (Hivid or zalcitabine)** comes in two different tablet formations. It should be taken on an empty stomach and is not approved for use in children.

- **Tenofovir (Viread)** is available in tablet form. It increased the concentration of didanosine, so these two should not be taken at the same time, or doses need to be adjusted appropriately. Tenofovir can decrease calcium absorption and affect long-term bone density. Calcium supplementation should be encouraged. Renal function can also be affected, and intermittent monitoring of serum creatine is recommended.

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**Table 7. Antiretroviral medications**

<table>
<thead>
<tr>
<th>Generic Name/Trade Name</th>
<th>How Supplied</th>
<th>Dosing</th>
<th>Notes</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td><strong>Abacavir (Ziagen)</strong></td>
<td>Film-coated 300-mg tablet, Oral solution 20 mg/mL</td>
<td>Pediatric: 8 mg/kg b.i.d., max 300 mg b.i.d.</td>
<td>Store at room temp</td>
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<td></td>
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<td>Adol/Adult: 300 mg b.i.d. or 600 mg daily</td>
<td>Required: warning card and PPI</td>
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<td>HLA-B*5701 testing recommended prior to use, if available</td>
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<td></td>
<td></td>
<td></td>
<td>Common: nausea/vomiting, diarrhea (N/V/D), loss of appetite, malaise, HA, rash</td>
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<td></td>
<td></td>
<td></td>
<td>Severe: hypersensitivity (do not rechallenge)</td>
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<tr>
<td><strong>Didanosine (ddI)</strong></td>
<td>Chew 25 mg, 50 mg, 100 mg, 150 mg, EC capsules: 125 mg, 200 mg, 250 mg, 400 mg Powder for oral solution in packets and bulk bottles</td>
<td>Neo (&lt;90 days): 50 mg/m² q 12 h</td>
<td>ddd liquid: mixed with antacids</td>
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<td></td>
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<td>Pediatrics: 90-120 mg/m² q 12 h</td>
<td>Shake well, refrigerate, stable for 30 days</td>
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<td>Adolescent (Adol)/Adult: &gt; 60 kg: 200 mg b.i.d. or 400 mg daily if EC &lt; 60 kg: 125 mg b.i.d. or 250 mg daily if EC</td>
<td>Take on empty stomach</td>
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<td>If using chew tabs, 2 tabs per dose recommended</td>
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<td>Do not coadminister with ganciclovir</td>
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<td></td>
<td></td>
<td></td>
<td>Common: N/V/D, abdominal pain</td>
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<td></td>
<td></td>
<td></td>
<td>Severe: peripheral neuropathy, electrolyte abnormalities, hyperuricemia, lactic acidosis with hepatic steatosis</td>
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<td></td>
<td></td>
<td></td>
<td>Uncommon: pancreatitis, increased LFTs, retinal depigmentation</td>
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<tr>
<td><strong>Emtricitabine (FTC)</strong></td>
<td>Capsule: 200 mg Solution: 10 mg/mL</td>
<td>Neo (&lt;90 days) 3 mg/kg daily</td>
<td>With or without food</td>
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<td></td>
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<td>Pediatric: 6 mg/kg daily, max dose: 240-mg solution. If &gt;33 kg may take capsule 200 mg daily</td>
<td>Capsule may not be opened</td>
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<tr>
<td></td>
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<td>Adol/Adult: 200 mg daily</td>
<td>Oral solution: refrigerate, but is stable at room temperature for 90 days (25°C max)</td>
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<td></td>
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<td></td>
<td>Common: HA, nausea, elevated liver functions</td>
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<td></td>
<td></td>
<td></td>
<td>Severe: hepatic steatosis, lactic acidemia</td>
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<td></td>
<td></td>
<td></td>
<td>Use with caution in hepatitis B coinfection</td>
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<table>
<thead>
<tr>
<th>Generic Name/Trade Name</th>
<th>How Supplied</th>
<th>Dosing</th>
<th>Notes</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td>Lamivudine (3TC) Epivir</td>
<td>Tablet 100 mg, 150 mg; Oral solution: 10 mg/mL</td>
<td>Neo (&lt;30 day): 2 mg/kg q 12 h&lt;br&gt;Pediatric: 4 mg/kg q 12 h&lt;br&gt;Adol/Adult: &lt;50 kg: 4 mg/kg q 12 h, max 150 mg b.i.d. &gt;50 kg: 150 mg b.i.d. or 300 mg daily</td>
<td>With or without food&lt;br&gt;Active against hepatitis B&lt;br&gt;Store oral solution at room temp</td>
<td>Common: N/D, HA, fatigue, skin rash, abdominal pain&lt;br&gt;Severe: pancreatitis, lactic acidosis with hepatic steatosis</td>
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<tr>
<td>Stavudine (d4T) Zerit</td>
<td>Capsule: 15 mg, 20 mg, 30 mg 40 mg&lt;br&gt;Oral powder for solution: 1 mg/mL</td>
<td>Pediatric: 1 mg/kg q 12 h&lt;br&gt;30-60 kg: 30 mg b.i.d. &gt;60 kg: 40 mg b.i.d.&lt;br&gt;Adol/Adult: &lt;60 kg: 30 mg b.i.d. &gt;60 kg: 40 mg b.i.d.</td>
<td>With or without food&lt;br&gt;Oral solution: shake, refrigerate, stable for 30 days</td>
<td>Common: HA, N/V/D, skin rash, increased LFTs&lt;br&gt;Severe: peripheral neuropathy, pancreatitis, lactic acidosis with hepatic steatosis, lipodystrophies</td>
</tr>
<tr>
<td>Tenofovir Disoproxil Fumarate Viread</td>
<td>300-mg tablet</td>
<td>Pediatric: 8 mg/kg daily (investigational)&lt;br&gt;Adol/Adult: 300 mg daily</td>
<td>Take 2 h before or 1 h after didanosine</td>
<td>Asthenia, HA, flatulence&lt;br&gt;Nausea&lt;br&gt;Lactic acidosis, decreased bone density (prepubertal children)</td>
</tr>
<tr>
<td>Zidovudine (ZDV) Retrovir</td>
<td>Capsule: 100 mg&lt;br&gt;Tablet: 300 mg&lt;br&gt;Syrup 10 mg/mL; IV 10 mg/mL</td>
<td>Premature (&lt;35 weeks): 1.5 mg/kg IV q 12 h&lt;br&gt;2 mg/kg p.o. q 12 h&lt;br&gt; Increase to q 8 h at 4 weeks of life if &lt;30 weeks GA and at 2 weeks of life if &gt;30 weeks GA&lt;br&gt;Neo: 2 mg/kg p.o. q 6 h&lt;br&gt;1.5 mg/kg IV q 6 h&lt;br&gt;Pediatric: 60-180 mg/m² p.o. q 6–8 h or 180-240 mg/m² p.o. q 12 h&lt;br&gt;IV intermittent: 60-120 mg/m² q 6 h&lt;br&gt;Adol/Adult: 200 mg t.i.d. or 300 mg b.i.d.</td>
<td>Take with food&lt;br&gt;Hematologic toxicity: interrupt therapy or decrease dose, or use erythropoietin, filgrastim, not recommended if baseline Hb is &lt;8.&lt;br&gt;IV: infuse over 1 h, dilute with D5W to 4 mg/mL, stable refrigerated for 24 h</td>
<td>Common: hematologic toxicity, HA&lt;br&gt;Other: myopathy, myositis, liver toxicity, lactic acidosis with hepatic steatosis</td>
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</table>

| **NNRTIs**             |              |        |       |              |
| Delavirdine (DLV) Rescriptor | Tablet: 100 mg | >13 years: 400 mg t.i.d. or 600 mg b.i.d. (investigational) | With or without food<br>Can crush tablets and disperse in water | Common: HA, fatigue, N/V/D, rash |

*Continued on next page*
Table 7. Antiretroviral medications (continued)

<table>
<thead>
<tr>
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<th>Notes</th>
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<tr>
<td><strong>NNRTIs</strong></td>
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<tr>
<td>Nevirapine (NVP) Viramune</td>
<td>Tablets: 200 mg, Oral liquid: 10 mg/mL</td>
<td>Neo (&lt;90 days): 150 mg/m² daily for 14 days and then b.i.d. Pediatric: 160-200 mg/m² daily for 14 days, then q 12 h (for &lt;8 years; may need to go as high as 200 mg/m²/dose) Adol/Adult: 200 mg daily for 14 days and then q 12 h</td>
<td>With or without food Do not crush tablets Oral liquid stable at room temp Use with caution in women with CD4 &gt;250 and men with CD4 &gt;400 (increased risk of hepatotoxicity)</td>
<td>Common: rash, sedative effects, HA, N/D Other: increased LFTs; rare, hepatitis</td>
</tr>
<tr>
<td>Efavirenz Sustiva/Stocrin</td>
<td>Capsule: 50 mg, 100 mg, 200 mg Tablet: 600 mg</td>
<td>10-15 kg: 200 mg p.o. qd 15-20 kg: 250 mg p.o. qd 20-25 kg: 300 mg p.o. qd 25-32.5 kg: 350 mg p.o. qd 32.5-40 kg: 400 mg p.o. qd &gt;40 kg: 600 mg p.o. qd</td>
<td>With or without food CNS side effects decreased if taken at night Avoid high fat</td>
<td>Common: rash CNS (dizziness, etc.) Other: increased LFTs</td>
</tr>
<tr>
<td>Etravirine Intelence</td>
<td>Tablet: 100 mg</td>
<td>Adult dosing: 100 mg p.o. b.i.d.</td>
<td>Must be taken with food May be dissolved in water Interactions with many PIs: OK with darunavir/ritonavir; use with caution with lopinavir/ritonavir, not advised with other PIs</td>
<td>Common: rash</td>
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<tr>
<td><strong>PIs</strong></td>
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<tr>
<td>Amprenavir Agenerase (no longer available in U.S.)</td>
<td>Oral capsule: 50 mg and 150 mg white oblong gel capsule Liquid: 15 mg/mL (grape, bubble gum, peppermint flavor)</td>
<td>Pediatric (&lt;3 yrs): &lt;50 kg: 22.5 mg/kg b.i.d. oral solution or 20 mg/kg b.i.d. capsules &gt;50 kg: 1200 mg b.i.d.</td>
<td>With or without food</td>
<td>Common: HA, N/V/D, rash</td>
</tr>
<tr>
<td>Atazanavir Reyataz</td>
<td>Capsule: 150 mg, 200 mg, 300 mg, 400 mg</td>
<td>Pediatric (6-13 years): 15-20 kg: atazanavir 8.5 mg/kg with ritonavir 4 mg/kg once daily with food. &gt;20 kg: atazanavir 7 mg/kg with ritonavir 4 mg/kg once daily with food, not to exceed atazanavir 300 mg and ritonavir 100 mg. Adol/Adult: Naive: 400 mg once daily or 300 mg + 100 mg RTV if with efavirenz Experienced: 300 mg + 100 mg RTV once daily</td>
<td>Administer 2 h before or 1 h after DDI EC Atazanavir/ddI/emtricitabine not recommended Take with food Do not take with proton pump inhibitors</td>
<td>Common: N/V/D, HA, rash Other: hyperbilirubinemia</td>
</tr>
</tbody>
</table>
## Table 7. Antiretroviral medications (continued)

<table>
<thead>
<tr>
<th>Generic Name/Trade Name</th>
<th>How Supplied</th>
<th>Dosing</th>
<th>Notes</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir Lexiva/Telzir</td>
<td>Tablet: 700 mg Liquid: 50 mg/mL</td>
<td>Pediatric: 2–5 years (PI naïve): 30 mg/kg b.i.d. 6 years (PI naïve): 30 mg/kg b.i.d. or 18 mg/kg + 3 mg/kg RTV b.i.d. (do not exceed adult dose) &gt;6 years (PI experienced): 18 mg/kg + 3 mg/kg RTV b.i.d. (do not exceed adult dose)</td>
<td>If given with efavirenz can give 1400 mg + 300 mg RTV daily</td>
<td>Common: N/V/D, HA, rash, hyperlipidemia, increased LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adol/Adult (or pediatric &gt;40 kg): PI naïve: 1400 mg b.i.d. or 1400 mg + 200 mg RTV daily or 700 mg + 100 mg RTV b.i.d. PI experienced: 700 mg + 100 mg RTV b.i.d.</td>
<td>With or without food Liquid stable at room temp</td>
<td></td>
</tr>
<tr>
<td>Indinavir (IDV) Crixivan</td>
<td>Capsules: 100 mg, 200 mg, 333 mg, 400 mg</td>
<td>Pediatrics: 500 mg/m² q 8 h (investigational) Adol/Adult: 800 mg p.o. q 8 h or 400 mg IDV + 400 mg RTV q 12 h or 800 mg IDV + 200 mg RTV daily</td>
<td>Take on empty stomach Take with water Store in original container</td>
<td>Common: N, abdominal pain, HA, asymptomatic hyperbilirubinemia Severe: nephrolithiasis Other: spontaneous bleeding, hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Oral powder: 50 mg/g</td>
<td>Pediatric: &lt;10 kg: 75 mg/kg b.i.d. 10 kg–19.9 kg: 60 mg/kg b.i.d. Adol/Adult (&gt;20 kg): 750 mg p.o. t.i.d. or 1250 mg b.i.d.</td>
<td>Take with food Powder can be mixed with water, milk, or pudding for 6 h Do not mix with acidic juices or food Tablets can be crushed in dispersed in water, milk</td>
<td>Common: N/V/D, HA especially if receiving ZDV Other: asthenia, abdominal pain, rash, hyperglycemia</td>
</tr>
<tr>
<td>Nelfinavir (NFV) Viracept</td>
<td>Tablets: 250 mg, 625 mg Oral powder: 50 mg/g</td>
<td>Pediatric: 250 mg/m² q 8 h 10 kg–19.9 kg: 60 mg/kg b.i.d. Adol/Adult (&gt;20 kg): 600 mg p.o. t.i.d. or 1250 mg b.i.d.</td>
<td>Take with food Store liquid in refrigerator in original container; can be stored at room temp for 30 days</td>
<td>Common: N/V/D, abdominal pain, anorexia Other: circumoral paresthesias, increased LFTs, spontaneous bleeding, pancreatitis, increased triglyceride and cholesterol, hyperglycemia</td>
</tr>
<tr>
<td>Ritonavir (RTV) Norvir</td>
<td>Capsules: 100 mg Liquid: 80 mg/mL</td>
<td>Pediatric: 400 mg/m² q 12 h Note: to minimize N/V, initiate at 250 mg/m² q 12 h and increase over 5 days Adol/Adult: 600 mg q 12 h</td>
<td>Take with food</td>
<td></td>
</tr>
<tr>
<td>Generic Name/Trade Name</td>
<td>How Supplied</td>
<td>Dosing</td>
<td>Notes</td>
<td>Side Effects</td>
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<tr>
<td>-------------------------</td>
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<tr>
<td><strong>PIs</strong></td>
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</tr>
<tr>
<td>Saquinavir (hard gelatin capsules) (SQV) Invirase</td>
<td>Capsule: 200 mg Tablet: 500 mg</td>
<td>Adol/Adult: 1000 mg + 100 mg RTV b.i.d. Otherwise not recommended</td>
<td>Take within 2 h of meal Photosensitivity</td>
<td>Common: N/V/D, abdominal pain, HA Other: Spontaneous bleeding, hyperglycemia</td>
</tr>
<tr>
<td>Darunavir Prezista</td>
<td>Tablet: 300 mg</td>
<td>Adol/Adult: 600 mg + 100 RTV b.i.d. Otherwise not recommended</td>
<td>Take with food</td>
<td>Common: N Other: dyslipidemia, increased amylase</td>
</tr>
<tr>
<td>Lopinavir/ritonavir Kaletra/Aluvia</td>
<td>Oral tablet: 200 mg lopinavir + 50 mg ritonavir 100 mg lopinavir + 25 mg ritonavir Liquid: 80 mg lopinavir + 20 mg ritonavir/mL</td>
<td>Infants (14 days-6 months): 300 mg LPV/75 mg RTV/m²/dose b.i.d. or 16 mg LPV/4 mg RTV/kg/dose b.i.d. Pediatric (&gt;6 mo): 7 to &lt;15 kg: 12 mg/kg lopinavir + 3 mg/kg RTV b.i.d. 15-40 kg: 10 mg/kg lopinavir + 2.5 mg RTV b.i.d. &gt;40 kg: 400 mg lopinavir + 100 mg RTV b.i.d. Adol/Adult: 400 mg lopinavir + 100 mg RTV b.i.d. Naïve Adult/Adult: 800 mg lopinavir + 200 mg RTV once daily</td>
<td>Take with food Refrigerate liquid, may be stable at room temp for 2 mo (avoid excessive heat) If given with NVP, EFV, NLV, increase dose</td>
<td>Common: N/V/D, HA Other: hyperglycemia, increased LFTs</td>
</tr>
<tr>
<td>Tipranavir Aptivus</td>
<td>Capsule: 250 mg Liquid: 100 mg/mL</td>
<td>Pediatric (2–18 years) treatment experienced only: 14 mg/kg TPV + 6 mg/kg RTV b.i.d., not to exceed adult dose Adol/Adult: 500 mg + 200 mg RTV b.i.d. Otherwise not recommended</td>
<td>Take with food Liquid contains vitamin E; further vitamin E supplementation should be avoided</td>
<td>Common: D Other: hyperglycemia, hyperlipidemia</td>
</tr>
<tr>
<td><strong>EIs</strong></td>
<td></td>
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</tr>
<tr>
<td>Enfuvirtide (T20) Fuzeon</td>
<td>Injectable: powder; 90 mg/mL once reconstituted</td>
<td>Pediatric: 6-16 years, 2 mg/kg SQ b.i.d. (max 90 mg/dose) Adol/Adult: 90 mg SQ b.i.d.</td>
<td>Must be reconstituted prior to use; if not used immediately refrigerate and use in 24 h. May take up to 45 min to become solution after reconstitution</td>
<td>Common: local skin site reactions Other: CPK elevation, increased LFTs</td>
</tr>
<tr>
<td>Generic Name/Trade Name</td>
<td>How Supplied</td>
<td>Dosing</td>
<td>Notes</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td><strong>EIs</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Maraviroc Selzentry/Celsentri</td>
<td>Tablet: 150 mg, 300 mg</td>
<td>Adol/Adult: 300 mg b.i.d. With PI (except tipranavir): 150 mg b.i.d. With efavirenz: 600 mg b.i.d.</td>
<td>CCR5 inhibitor, must do testing on patient to confirm CCR5 tropism prior to prescribing Dose adjustments with many medications, check carefully</td>
<td>Common: fever, upper respiratory infections Severe: increased LFTs, dyspepsia, abdominal pain</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir Isentress</td>
<td>Tablet: 400 mg</td>
<td>Adol/Adult: 400 mg b.i.d.</td>
<td>Take with or without food</td>
<td>Common: Hyperbilirubinemia, HA, pruritus Severe (rare): renal failure, renal tubular acidosis</td>
</tr>
<tr>
<td><strong>FDCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine/lamivudine Combivir/Douvir/Avocomb</td>
<td>Lamivudine 150 mg Zidovudine 300 mg</td>
<td>Pediatric: 14-19.9 kg: ½ tablet b.i.d. 19.9-29.9 kg: 1 tablet in a.m., 1/2 tablet in p.m. &gt;30 kg: 1 tablet b.i.d. Adol/Adult: 1 tablet b.i.d.</td>
<td>Lactic acidosis with hepatic steatosis</td>
<td></td>
</tr>
<tr>
<td>Zidovudine/lamivudine/abacavir Trizivir</td>
<td>Tablet: Zidovudine 300 mg Lamivudine 150 mg Abacavir 300 mg</td>
<td>Pediatric: 14-19.9 kg: ½ tablet b.i.d. 19.9-29.9 kg: 1 tablet in a.m., 1/2 tablet in p.m. &gt;30 kg: 1 tablet b.i.d. Adol/Adult: 1 tablet b.i.d.</td>
<td>Store at room temp Lactic acidosis with hepatic steatosis</td>
<td></td>
</tr>
<tr>
<td>Stavudine/lamivudine Lamivir S/Coviro</td>
<td>Tablet: 30 mg stavudine + 150 mg lamivudine or 40 mg stavudine +150 mg lamivudine or Lamivudine 60 mg + stavudine 12 mg (Junior) or lamivudine 30 + stavudine 6 (baby)</td>
<td>Pediatric: 14-24.9 kg: 1 tablet in a.m., 1/2 tablet in p.m. (30-mg stavudine tablet) &gt;25 kg: 1 tab b.i.d. (30-mg stavudine tablet) Adult: &lt;60 kg: 1 tab b.i.d. (30-mg stavudine tablet) &gt;60 kg: 1 tab b.i.d. (40-mg stavudine tablet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine + tenofovir Truvada</td>
<td>Tablet: 200-mg emtricitabine + 300-mg tenofovir</td>
<td>Adol/Adult: 1 tablet daily</td>
<td>Take with or without food Asthenia, HA, flatulence, N Lactic acidosis, decreased bone density (prepubertal children)</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine + tenofovir + efavirenz Atripla</td>
<td>Tablet: 200-mg emtricitabine + 300-mg tenofovir + 600-mg efavirenz</td>
<td>Adol/Adult: 1 tablet daily</td>
<td>Take at night to avoid CNS side effects Asthenia, HA, flatulence, N rash, CNS (dizziness), dream changes (efavirenz) Lactic acidosis, decreased bone density (prepubertal children)</td>
<td></td>
</tr>
</tbody>
</table>

*Continued on next page*
### Table 7. Antiretroviral medications (concluded)

<table>
<thead>
<tr>
<th>Generic Name/Trade Name</th>
<th>How Supplied</th>
<th>Dosing notes</th>
<th>Notes</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDCs*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine + stavudine + nevirapine Triomune or Triviro</td>
<td>Tablet: lamivudine 150 mg + stavudine 30 mg + nevirapine 200 mg (Triomune 30/Triviro) or lamivudine 150 mg + stavudine 40 mg + nevirapine 200 mg (Triomune 40/Triviro) or lamivudine 60 mg + stavudine 12 mg + nevirapine 100 mg (Triomune Junior) or lamivudine 30 mg + stavudine 6 mg + nevirapine 50 mg (Triomune baby) or lamivudine 20 mg + stavudine 5 mg + nevirapine 35 mg (Triomune KIDS DS) or lamivudine 40 mg + stavudine 10 mg + nevirapine 70 mg (Triomune KIDS DS)</td>
<td>Dosing depends on tablet size; please see table 4.</td>
<td>With or without food. Cannot use FDC for 2-week lead-in period (nevirapine to be given once daily for first 2 weeks)</td>
<td></td>
</tr>
<tr>
<td>Lamivudinide + zidovudine + nevirapine Duovir N</td>
<td>Lamivudine 150 mg + zidovudine 300 mg + nevirapine 200 mg</td>
<td>Adol/Adult: 1 tablet b.i.d.</td>
<td>With or without food. Cannot use FDC for 2-week lead-in period (nevirapine to be given once daily for first 2 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EI, entry inhibitor; Adol, adolescent; HA, headache; EC, enteric coated; N, nausea; V, vomiting; D, diarrhea; LFT, liver function test; CNS, central nervous system; SQ, subcutaneous; CPK, creatine phosphokinase; FDC, fixed-dose combination.

*If using FDCs of different sizes, please refer to individual drugs for weight-based dosing or Table 4 for complete FDC dosing.

Table courtesy of Stephanie Maciejewski, PharmD, modified 2007.

**NNRTIs**

NNRTIs also work by blocking the HIV enzyme reverse transcriptase, but they do so in a slightly different way from that of NRTIs. These drugs have been used in combination with NRTIs and PIs and are generally well tolerated and safe.

- Nevirapine (Viramune) is available as a tablet and an oral solution. It can be administered with or without food. The tablets are scored and may be broken in half for ease of administration. The solution should be shaken well prior to use. Nevirapine sometimes produces a measles-like rash in the first 6 weeks after initiating therapy. The likelihood of rash can be reduced by giving the medicine at half-dose for the first 14 days. It is important to increase to full dose after the first 14 days to prevent the occurrence of subtherapeutic nevirapine levels, which can lead to the development of resistance. Patients and parents should be taught to contact the health care provider if a rash appears. The rash is usually self-limited. However, involvement of mucous membranes (eyes, mouth, and urethra) signals a more serious condition and may require permanent discontinuation of the drug. Antihistamines may help with the itching that often accompanies a nevirapine rash.
Efavirenz (Sustiva) can be given with or without food, but high-fat meals should be avoided for proper absorption. Efavirenz capsules can be opened and sprinkled over food. The drug may cause hyperactivity, impaired concentration, abnormal dreams, and other central nervous system effects. These side effects can be reduced by giving the once-daily dose at bedtime. Efavirenz can cause a rash similar to that seen with nevirapine.

Delavirdine (Rescriptor) can be taken with or without food. It is not recommended for children. It can also cause a rash similar to that experienced with nevirapine.

Table 7 has dosing guidelines and common side effects of ARVs, and Table 8 describes dosing of pediatric FDC ARVs in resource-constrained settings.

### PIs

PIs are ARV drugs that work differently from NRTIs and NNRTIs. PIs prevent the protease enzyme from cleaving large HIV precursor proteins into smaller functional units, a process that causes the production of defective virus particles incapable of infecting CD4+ cells and replicating. PIs are powerful, but when they are taken alone the virus quickly becomes resistant to their anti-HIV effects, and the benefit of therapy is short lived. For this reason, PIs are always combined with other anti-HIV medications. Taking PIs in the correct dose and on time is crucial. Missed doses can lead to viral resistance and drug failure. Combining a small dose of one PI called ritonavir with a therapeutic dose of several other PIs can boost the concentration of those other PIs in the blood, improving the effectiveness of treatment. Kaletra (lopinavir/ritonavir) is a PI that combines one PI (lopinavir) with a small amount of another PI, ritonavir, in one pill.

### Table 8. Pediatric FDC ARV dosing: pediatric dosing in resource-constrained settings

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Cipla (6/30/50 mg per pill)</th>
<th>Cipla (12/60/100 mg per pill)</th>
<th>Rambaxy (5/20/35 mg per pill)</th>
<th>Rambaxy (10/40/70 mg per pill)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–3.9</td>
<td>D4T: 1 mg/kg/dose b.i.d.</td>
<td>D4T: 1 mg/kg/dose b.i.d.</td>
<td>D4T: 1 mg/kg/dose b.i.d.</td>
<td>D4T: 1 mg/kg/dose b.i.d.</td>
</tr>
<tr>
<td></td>
<td>3TC: 4 mg/kg/dose b.i.d.</td>
<td>3TC: 4 mg/kg/dose b.i.d.</td>
<td>3TC: 4 mg/kg/dose b.i.d.</td>
<td>3TC: 4 mg/kg/dose b.i.d.</td>
</tr>
<tr>
<td></td>
<td>NVP: 160–200 mg/m²/dose b.i.d. (maintenance dose)</td>
<td>NVP: 160–200 mg/m²/dose b.i.d. (maintenance dose)</td>
<td>NVP: 160–200 mg/m²/dose b.i.d. (maintenance dose)</td>
<td>NVP: 160–200 mg/m²/dose b.i.d. (maintenance dose)</td>
</tr>
<tr>
<td>4–4.9</td>
<td>1 pill b.i.d.</td>
<td>1/2 pill b.i.d.</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>5–5.9</td>
<td>1 pill b.i.d.</td>
<td>1/2 pill b.i.d.</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Cipla (6/30/50 mg per pill)</th>
<th>Cipla (12/60/100 mg per pill)</th>
<th>Rambaxy (5/20/35 mg per pill)</th>
<th>Rambaxy (10/40/70 mg per pill)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–6.9</td>
<td>1.5 pills b.i.d.</td>
<td>1 pill a.m.</td>
<td>2 pills b.i.d.*</td>
<td>1 pill b.i.d.*</td>
</tr>
<tr>
<td></td>
<td>1/2 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–7.9</td>
<td>1.5 pills b.i.d.</td>
<td>1 pill a.m.</td>
<td>2 pills b.i.d.*</td>
<td>1 pill b.i.d.*</td>
</tr>
<tr>
<td></td>
<td>1/2 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–8.9</td>
<td>1.5 pills b.i.d.</td>
<td>1 pill a.m.</td>
<td>2 pills b.i.d.</td>
<td>1 pill b.i.d.</td>
</tr>
<tr>
<td></td>
<td>1/2 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–9.9</td>
<td>1.5 pills b.i.d.</td>
<td>1 pill a.m.</td>
<td>2 pills b.i.d.</td>
<td>1 pill b.i.d.</td>
</tr>
<tr>
<td></td>
<td>1/2 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–10.9</td>
<td>2 pills b.i.d.</td>
<td>1 pill b.i.d.</td>
<td>2.5 pills b.i.d.</td>
<td>1.5 pills a.m.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 pill p.m.</td>
</tr>
<tr>
<td>11–11.9</td>
<td>2 pills b.i.d.</td>
<td>1 pill b.i.d.</td>
<td>2.5 pills b.i.d.</td>
<td>1.5 pills b.i.d.</td>
</tr>
<tr>
<td>12–13.9</td>
<td>2 pills b.i.d.</td>
<td>1 pill b.i.d.</td>
<td>3 pills b.i.d.</td>
<td>1.5 pills b.i.d.</td>
</tr>
<tr>
<td>14–16.9</td>
<td>2.5 pills b.i.d.</td>
<td>1.5 pill a.m.</td>
<td>3.5 pills b.i.d.</td>
<td>2 pills b.i.d.</td>
</tr>
<tr>
<td></td>
<td>1 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–19.9</td>
<td>2.5 pills b.i.d.</td>
<td>1.5 pill a.m.</td>
<td>4 pills b.i.d.</td>
<td>2 pills b.i.d.</td>
</tr>
<tr>
<td></td>
<td>1 pill p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24.9</td>
<td>3 pills b.i.d.</td>
<td>1.5 pill b.i.d.</td>
<td>4.5 pills b.i.d.</td>
<td>2.5 pills b.i.d.</td>
</tr>
<tr>
<td>25–29.9</td>
<td>4 pills b.i.d.</td>
<td>2 pills b.i.d.</td>
<td>6 pills b.i.d.</td>
<td>3 pills b.i.d.</td>
</tr>
<tr>
<td>30–34.9</td>
<td>4 pills b.i.d.**</td>
<td>2 pills b.i.d.**</td>
<td>6 pills b.i.d.**</td>
<td>3 pills b.i.d.**</td>
</tr>
</tbody>
</table>

*The stavudine (d4T) dose in this weight range for FDC 5/20/35 mg and 10/40/70 mg are consistently higher than the recommended 1-mg/kg/dose. Consider liquid formulations for this weight range if available.

**May substitute with adult-strength 30/150/200 mg FDC pills for those children weighing more than 30 kg.
Nelfinavir (Viracept) should be given with a light meal or snack. It is available as a blue tablet or a powder formulation. The tablets can be crushed, pulverized, or dissolved in water. It should not be given with citrus juices or applesauce. The powder has a low bioavailability, so a large amount of the powder must be administered to equal one dose. Because the powder has the consistency of sand, the tablets are usually preferred if the weight-based dose required by the patient is equivalent to at least one tablet. One can improve the taste of the powder by mixing it with milk, chocolate milk, pudding, or vanilla ice cream.

Ritonavir (Norvir) can be given with or without food, but food seems to make it more tolerable. It is available as an oral solution or a soft gelatin capsule. The solution needs to be refrigerated, and the gel capsules need to be kept cool. Ritonavir has a bad taste and is not well tolerated by most patients. Several methods have been used to make it more palatable, including mixing it with milk, chocolate milk, or vanilla or chocolate pudding; dulling the taste buds by giving ice or frozen treats prior to dosing; and coating the mouth with peanut butter.

Indinavir (Crixivan) is available only in a capsule formulation. It should be administered 1 h before or 2 h after a meal. Those who take it should drink 48 oz. of fluid per day to prevent the formation of kidney stones (renal calculi). It should not be taken with grapefruit juice, but it can be taken with water, skim milk, or apple juice.

Saquinavir (Invirase) should be given with a meal or no more than 2 h after a meal to ensure adequate drug levels. It is available as a tablet. Saquinavir can cause photosensitivity, patients should wear protective clothing or sunscreen when outdoors. Patients initiating saquinavir and ritonavir have reported nausea, vomiting, and abdominal pain. To promote adherence, supportive treatment of side effects is particularly important when initiating therapy.

Fosamprenavir (Lexiva) comes as both a tablet and a liquid. The tablet can be administered with or without food. The liquid should be administered to adults without food and to children with food. The liquid does not have to be refrigerated but should not exceed 30°C. It can be administered alone to PI-naive patients and with a ritonavir booster to experienced patients. This is a reformulation of amprenavir (Agenerase). Amprenavir is no longer available in the United States.

Azatranavir (Reyataz) can be administered with or without food. It comes in a capsule form. It can be administered by itself to PI-naive patients but is most commonly prescribed with a ritonavir booster. It is given daily. Azatranavir seems to cause less dyslipidemia than some of the other PIs but can cause a benign hyperbilirubinemia that may lead to scleral icterus.

Second-Generation PIs
These PIs are all given with a ritonavir booster. They are considered second generation because patients who have developed resistance to some of the other PIs may still be sensitive to these PIs. This designation is not the same necessarily as being part of a second-line regimen in country-specific guidelines.

Darunavir (Prezista) is always coadministered with a ritonavir booster twice daily. It is available only as a tablet and should be taken with food. It is generally well tolerated.

Lopinavir/ritonavir (Kaletra) should be administered with food. It comes as a tablet (two strengths) or an oral solution. The oral solution should be refrigerated but can be stable at room temperature for up to 60 days (<30°C).

Tipranavir (Aptivus) comes as a capsule and is administered twice daily with ritonavir boosting. It should be given with a high-fat meal. Patients taking this medication and ritonavir have experienced intracranial hemorrhage, but no causal relationship has been determined.

Atazanavir-, tipranavir-, and darunavir-containing regimens are not recommended (February 2008 U.S. Guidelines) as initial therapy in children or prepubertal adolescents because of lack of pediatric data on appropriate dosage.

EIs
For HIV to enter a CD4+ cell, steps need to be completed: attachment, coreceptor binding, and fusion. Theses steps use the gp41 and gp120 HIV envelope glycoproteins. These glycoproteins interact with the CD4 cell receptor and a coreceptor, either CCR5 or CXCR4. EIs are another class of HIV medications interrupting the process of
attachment, binding, and fusion. These medications inhibit the virus from completing the steps needed to infect the CD4+ cell. For enfuvirtide this is accomplished by binding to gp41 on the HIV cell membrane and stopping fusion with CD4+ cells. Other entry inhibitors use different mechanisms. CCR5 antagonists bind to the CCR5 coreceptor on the CD4+ cell surface and inhibit gp120 binding and therefore HIV entry into the cell. CCR5 antagonists can be used only in patients with CCR5-tropic virus. Hence, testing must be performed on the patient’s specific virus to determine tropism prior to administering this class of medications. CCR5 antagonists have the theoretical risk of decreasing the body’s ability to effectively mount an immune response to other viral infections (e.g., West Nile virus). Other entry inhibitors (such as CXCR4 antagonists) are in development.

- T-20/enfuvirtide (Fuzeon) is given via subcutaneous injection. It is supplied in powder form and needs to be reconstituted with sterile water. Each vial will supply enough medication for two doses (a day’s worth of medication) at adult levels. If the vial is reconstituted it must be kept refrigerated and then allowed to warm to room temperature prior to administration. Use of small needles and routine rotation of injection sites decrease injection site complications. Enfuvirtide doses for children younger than 6 years have not been established.

- Maraviroc (Selzentry) comes in a tablet form and is taken orally. It is given twice daily, and dosing depends on other ARVs given concomitantly (Table 7). It may be stored at room temperature (<30°C) and taken with or without food. The most common side effects seen with maraviroc are cough, fever, upper respiratory tract infections, rash, myalgia, abdominal pain, and nausea. Maraviroc is not yet approved for use in children.

### Integrase Inhibitors
Integrase inhibitors prevent HIV type 1 integrase from incorporating the HIV cDNA into the host cell genome, thereby preventing HIV replication. At present, the U.S. Food and Drug Administration has approved only one such medication. However, several others are being studied. One of these is raltegravir (Isentress), which comes as a tablet and is taken orally twice daily. It can be taken with or without food and stored at room temperature.

### Monitoring During Therapy
Monitoring patients taking ARV medications is important. Many of the preceding medications have potentially serious side effects (Table 7). Many of them also interact with other medications (Table 9). Current practice guidelines recommend evaluating patients at regular intervals while they are receiving these medications. Side effects experienced by the patient should be reviewed. If available, a complete (or full) blood count and routine blood chemistries should be checked. Urinalysis also should be checked at intervals. In resource-limited settings, specific approaches to monitoring during therapy will vary by center, according to local and national policies. These may differ somewhat from the U.S. Guidelines and/or the WHO recommendations.

### Table 9. Common Drug–drug interactions

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Lopinavir + Ritonavir</th>
<th>Nelfinavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>No adjustment necessary</td>
<td>No adjustment necessary</td>
<td>No adjustment necessary</td>
<td>No adjustment necessary</td>
<td>Increased risk hepatotoxicity; monitor NVP toxicity</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Do not exceed 200 mg/ day or monitor levels</td>
<td>Monitor for toxicity</td>
<td>Dose adjustment of RTV maybe needed if itraconazole &gt; 400-mg dose</td>
<td>No adjustment necessary</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>LPV decreases Do not exceed 200 mg/ day ketoconazole</td>
<td>No adjustment</td>
<td>Do not exceed 200 mg/day ketoconazole</td>
<td>No data</td>
<td>Do not coadminister</td>
</tr>
</tbody>
</table>

*Continued on next page*
**Table 9. Common Drug–drug interactions (continued)**

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Lopinavir + Ritonavir</th>
<th>Nelfinavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Not recommended</td>
<td>Monitor closely</td>
<td>Do not use with RTV 400 mg/dose or higher, not recommended with 100 mg RTV unless benefits outweigh risks</td>
<td>Do not coadminister</td>
<td>Carefully monitor for NVP toxicity and antifungal outcome</td>
</tr>
<tr>
<td><strong>Antimycobacterials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Adjust clarithromycin for moderate and severe renal impairment</td>
<td>No data</td>
<td>Adjust clarithromycin for moderate and severe renal impairment</td>
<td>Clarithromycin dose decreased, monitor carefully</td>
<td>Clarithromycin dose decreased, monitor carefully</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Decrease rifabutin to 150 mg or administer 3×/week</td>
<td>Decrease rifabutin to 150 mg daily or 300 mg 3×/wk</td>
<td>Decrease rifabutin to 150 mg every other day or administer 3×/week</td>
<td>Increase rifabutin to 450-600 mg daily or 600 mg 3×/week</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>&lt;50 kg pt., continue EFV 600 mg daily, if &gt;50 kg pt; increase EFV 800 mg daily</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td><strong>Herbal/complementary and alternative medicines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>Do not coadminister coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td><strong>Hormonal contraceptives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen/ progesterone</td>
<td>Use alternative or additional method</td>
<td>Use alternative or additional method</td>
<td>Use alternative or additional method</td>
<td>Use alternative or additional method</td>
<td>Use alternative or additional method</td>
</tr>
<tr>
<td><strong>Lipid-lowering agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastin</td>
<td>Lowest possible starting dose of atorvastatin, monitor atorvastatin carefully</td>
<td>Lowest possible starting dose of atorvastatin, monitor atorvastatin carefully</td>
<td>Lowest possible starting dose of atorvastatin, monitor atorvastatin carefully</td>
<td>Adjust dose of atorvastatin according to lipid response, do not exceed maximum recommended dose</td>
<td>No data</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No dose adjustment</td>
<td>No data</td>
<td>Pravastatin dosage adjustment based on lipid response (decreased when administered with SQV/RTV)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Simvastatin Lovastatin</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Adjust dose of simvastatin according to lipid response; do not exceed maximum recommended dose</td>
<td>No data</td>
</tr>
</tbody>
</table>

Continued on next page
Antiretroviral Treatment

For example, the Baylor College of Medicine/Bristol-Myers Squibb Foundation Children’s Clinical Center of Excellence in Maseru, Lesotho, one of the Baylor Pediatric AIDS Initiative’s HIV/AIDS care and treatment centers in Africa, has more than 2200 patients in care and 1200 patients on ART in its local network (the Centre and satellites). It uses the following monitoring approach, in accordance with Lesotho national guidelines:

- After ART begins, clinical assessments take place by a doctor or a nurse at 2 weeks, 1 month, 2 months, 3 months, 6 months, and every 3-6 months thereafter.
- Clinical monitoring
  - At baseline and at each visit, monitoring of weight, height, head circumference (children <3 years), developmental status, and nutritional status
  - Diagnosis and management of interim or new illnesses
  - Medication review, including side effects, adherence and dosing, and other medications, including traditional medications
  - Early diagnosis of pregnancy and linkage to longitudinal PMTCT program at the Centre/satellites

- Changes in social situation that may affect adherence to ART
- Laboratory monitoring
  - Baseline laboratory investigations (prior to starting ART)
    - CD4+ cell count (percentage in children ≤5 years)
    - Full (complete) blood count
    - ALT (alanine aminotransferase)
    - Serum creatinine when TDF being considered, followed by calculation of the rate of creatinine clearance
    - Pregnancy test in all women of childbearing age
  - Routine laboratory investigations (depend on specific ARVs in the patient’s regimen)
    - For AZT: check hemoglobin at 1 month, 2 months, 3 months, 6 months, and every 3-6 months thereafter.
    - For NVP, ALT checked at 1 month, 2 months, 3 months, 6 months, and every 3-6 months thereafter. If CD4+ cell count is more than 250 cells/mm³, there is additional risk of hepatotoxicity, so ALT should also be checked at 2 weeks.

### Table 9. Common Drug–drug interactions (concluded)

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Lopinavir + Ritonavir</th>
<th>Nelfinavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Monitor LPV level and</td>
<td>Monitor anticon-</td>
<td>Monitor anticon-</td>
<td>Use with caution,</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>anticonvulsant levels;</td>
<td>voulusant levels;</td>
<td>voulusant levels and EFV effective-</td>
<td>monitor anticon-</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>use alternative anti-</td>
<td>monitor carefully</td>
<td>ness. If possible,</td>
<td>voulusant levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>convulsant or ART if possible</td>
<td></td>
<td>use alternative anticonvulsant</td>
<td>if possible</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No interaction</td>
<td>No interaction</td>
<td>No interaction</td>
<td>Buprenorphine levels decreased; monitor for withdrawal</td>
<td>No data</td>
</tr>
<tr>
<td>Methadone</td>
<td>Monitor; may need increased methadone level</td>
<td>Monitor; may need increased methadone level</td>
<td>Monitor; may need increased methadone level</td>
<td>Monitor; may need increased methadone level</td>
<td>Monitor; may need increased methadone level</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>No interactions</td>
</tr>
<tr>
<td>Pluticasone</td>
<td>Do not coadminister</td>
<td>Monitor for steroid side effects</td>
<td>Do not coadminister</td>
<td>Monitor for steroid side effects</td>
<td>No interactions</td>
</tr>
<tr>
<td>Methadone</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
<td>Do not coadminister</td>
</tr>
</tbody>
</table>

Note: This table includes the most common interactions only; please review all medications a patient is taking carefully prior to prescribing new medications.
For tenofovir (TDF), serum creatinine (and rate of creatinine clearance) should be checked 6 months after initiation and every 6 months thereafter.

CD4 counts are checked at 3 and 6 months, and every 3-6 months thereafter; this is, with the lack of viral load testing along with clinical status, the chief determinant of regimen efficacy.

- Additional laboratory investigations
  - Lactate measurement, if patient is on an NRTI (especially d4T or ddI) for longer than 4 months and losing weight or having other symptoms that suggest hyperlactatemia
  - Glucose and lipid measurements, if the patient is taking a PI, such as lopinavir/ritonavir (Kaletra) or azatanavir/ritonavir

Different algorithms exist for how to handle abnormal laboratory values or adverse clinical situations. One such approach is to assign grades to toxic effects and specific clinical situations and to provide advice on how to clinically act on each grade. Table 10 is from South Africa’s most recent national guidelines and divides toxic effects into four grades.

In this model, for toxic effects of grades 1 and 2, the patient remains on therapy, the test is repeated, and the patient is reassessed clinically within 2 weeks. For grade 3 toxicity, the test should be repeated within 1 week; if grade 3 persists, stop all ARVs and seek expert medical advice. If the toxicity is grade 4, all drugs should be stopped immediately and specialist advice is sought.

**Alternative Approaches to ART**

Standard ART includes the continuous administration of three ARVs in the combinations previously described. At the moment, periodic interruptions in therapy are not recommended, nor are combinations of ARVs of fewer than or more than three agents, except in special circumstances, such as treatment-experienced patients with significant limitations in terms of therapeutic ARV options, in whom atypical multidrug regimens may be used by expert clinicians on a case-by-case basis.

Nevertheless, there is considerable interest in alternative approaches to ART, and study of such strategies is ongoing. Of particular interest is the possibility that patients with sustained periods of virologic suppression and immunologic recovery may be able to periodically interrupt therapy, with reinitiation guided by specified parameters, such as CD4⁺ cell count. Potential benefits ascribed to such an approach include reductions in ART-associated adverse events, such as metabolic and cardiovascular complications, and reductions in patient nonadherence due to medication fatigue.

Although some small studies have shown promising clinical results, the Strategies for Management of Antiretroviral Therapy (SMART) Study Group recently reported the results of a randomized, controlled clinical

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**Table 10. Grading the severity of pediatric adverse reactions (PACTG)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Grade 1 toxicity</th>
<th>Grade 2 toxicity</th>
<th>Grade 3 toxicity</th>
<th>Grade 4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin 3 months up to 2 yrs</td>
<td>9.0-9.9 g/dL</td>
<td>7.0-8.9 g/dL</td>
<td>&lt;7.0 g/dL</td>
<td>Cardiac failure secondary to anaemia</td>
</tr>
<tr>
<td>Hemoglobin 2 years and over</td>
<td>10-10.9 g/dL</td>
<td>7.0-9.9 g/dL</td>
<td>&lt;7.0 g/dL</td>
<td>Cardiac failure secondary to anaemia</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>0.75-1.2 x 10⁹/L</td>
<td>0.4-0.749 x 10⁹/L</td>
<td>0.25-0.399 x 10⁹/L</td>
<td>&lt;0.25 x 10⁹/L</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.1-4.9 x upper normal limit</td>
<td>5.0-9.9 x upper normal limit</td>
<td>10.0-15.0 x upper normal limit</td>
<td>&gt;15 x upper normal limit</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>---</td>
<td>1.54-8.46 mmol/L</td>
<td>8.47-13.55 mmol/L</td>
<td>&gt;13.56 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>---</td>
<td>4.43-12.92 mmol/L</td>
<td>12.93-19.4 mmol/L</td>
<td>&gt;19.4 mmol/L</td>
</tr>
</tbody>
</table>
trial in which 5472 patients with CD4+ cell counts greater
than 350 cells/mm³ were divided into continuous and
intermittent ART groups. In the intermittent-use group,
therapy was held until the CD4+ cell count declined to
below 250 cells/mm³, when therapy was restarted until
the CD4+ cell count again reached 350 cells/mm³, at which
time it was again discontinued. In this study, intermittent
therapy was associated with a significantly increased risk
of OI or death compared with continuous therapy, which
was felt to be due chiefly to allowing the CD4+ cell count
to decline and viral load to increase. As well, in this study,
intermittent ART was not associated with a reduction in
the risk of adverse events associated with ART.

Another alternative to conventional ART that is
under study in adults is the use of ritonavir-boosted
PIs as monotherapy after a period of induction
(with concomitant sustained viral suppression) with
conventional three-drug ART. Proposed benefits to this
strategy include simplification of patients’ long-term ARV
regimens, as well as the avoidance of NRTI-associated
mitochondrial dysfunction, which may be related to
adverse ARV events such as peripheral neuropathy,
hepatotoxicity, lipodystrophies, and pancreatitis. Studies
of this concept have generally been small so far. In a
Spanish study of 51 patients whose postinduction HIV
type 1 viral loads were less than 50 copies/mL (75% of
whom were on lopinavir/ritonavir-based regimens) and
were then switched to lopinavir/ritonavir monotherapy,
95% of patients who were available for assessment at
week 48 (38/40) maintained viral suppression (if patients
lost to follow-up are considered treatment failures,
the rate of sustained viral suppression drops to 74.5%
[38/51]). Mean CD4+ cell counts significantly increased in
the monotherapy group (from 541 to 609; \( P = 0.034 \)) and
levels of triglycerides decreased significantly (\( P = 0.029 \)).

Ritonavir-boosted atazanavir has also been studied
as monotherapy in adult patients with sustained viral
suppression after conventional ART, yet a pilot study of
such an approach showed significant rates of early viral
rebound.

Although few data are available on head-to-head
comparisons of PI monotherapy after standard
ART induction versus conventional ART, what data
are available suggest that standard therapy is more
efficacious. For example, in a trial that compared
lopinavir/ritonavir monotherapy after initial induction
with efavirenz-based three-drug therapy, the efficacy of
lopinavir/ritonavir monotherapy, although appreciable,
was statistically significantly lower than that of efavirenz-
based three-drug therapy.

At present, although neither the U.S. Guidelines nor the
WHO recommends PI monotherapy, even in patients
who have experienced sustained viral suppression with
standard ART, these and similar simplification strategies
continue to be studied.

When beginning ART, patients should be advised not
to stop their medications without first speaking with
a health care provider. Often, simple interventions
can minimize side effects. Stopping one or two of the
medications can increase the likelihood that HIV will
become resistant to treatment.

**Drug Interactions**

Various ARV drugs interact with one another as well
as with other common medications (Table 9). All
medications that a patient is taking should be reviewed
periodically for possible interactions. There are also
many interactions between ARVs and the drugs used
to treat tuberculosis. Before treating a patient for both
conditions, one should consult a specialist. See the
module on tuberculosis for a more detailed discussion
of the interactions between ARV and antituberculosis
treatment.

**Adherence**

Treatment success depends highly on a patient’s ability
to adhere to the medication schedule. Strict scheduling
guidelines, side effects, and the need to take multiple (and
at times unpalatable) medications make it difficult for
adults and children to take their medications at the right
time and in proper coordination with their meals. Yet
adhering to the medication schedule is critical to prevent
the development of resistant forms of HIV. The health
care team, family, and friends are vital components in the
patient’s success in adhering to treatment.

Adherence needs to be discussed at every clinic visit
and does not depend solely on the patient’s ability to
remember to take his or her medications. Barriers to
adherence can include lack of access to refills, insufficient
food and water with which to take the medications,
inability to get to the clinic for scheduled appointments
because of problems with transportation, stigma, and lack of a personal support system. These are all issues that should be discussed with the patient before he or she starts ARV medications and at every clinic visit after the patient has started ART.

The entire health care team is responsible for assisting patients with adherence through use of multiple interventions. Interventions should not be delayed until patients start having problems. Interventions should begin during the first discussions about starting ARVs and should continue at every clinic visit. Interventions include education, counseling, assistance with problem solving, and motivational strategies. Patient education can include the pathophysiology of HIV, routes of transmission, modes of prevention, the benefits of good adherence (including problems that can result from nonadherence), and adverse events related to ARV medications. Counseling can help patients to identify factors that may prevent them from taking their medications as scheduled. Health care providers can help by developing a written schedule that is individualized to a patient’s daily life and by assisting the patient to develop cues for remembering to take the medications. One way to achieve this goal is to incorporate taking medication into everyday activities. The patient may brush his or her teeth every morning and use this activity as a cue to take the morning dose of medication.

It is just as important for children to adhere to their ARV medication schedule as it is for adults. Discussions of the importance of medication adherence should begin as early as possible. The discussions should be based on the child’s developmental level. Disclosure of HIV status and discussion of the importance of medication adherence do not necessarily have to occur simultaneously. Children can be taught early in life to take their medications before they are developmentally mature enough to understand why they are taking them. Parent-child interaction and discipline are critical to the effectiveness of long-term medication maintenance. Parents or guardians need to be taught how to intervene appropriately when a child refuses to take the medications. Coercion and bribery are not recommended. These methods may promote short-term but not long-term adherence. Caregiver education can include teaching that if their child refuses to take the medications, everything in the child’s life stops until the medications are taken. Advise the caregiver to refrain from cajoling the child to take the medications. The child should simply not be allowed to do anything until he or she consumes the medicines. Children should be taught that medication taking is part of their daily lives. Motivational tools, such as videotapes of other children who take ARVs, and personal medication calendars may be useful for children. By focusing on factors that will help the patient and family adhere to the demanding regimens of ARVs over time, the entire team working together can help accomplish this difficult task.

Several ARV centers use a buddy system to help patients adhere to medications. Others use an adherence contract that patients must complete with their health care providers prior to starting medications. An example of one adherence contract (Appendix 1) is included in the toolkit at the end of this chapter.

**Barriers to Treatment**

One can find barriers to treatment at both the community and individual levels. At the community level, ARV medications can be too expensive for a government or community to supply to everyone who needs them. Current studies are evaluating more cost-effective treatment regimens that may reduce this problem. Cost can also be a barrier for an individual. Lack of transportation and other logistical problems can hinder treatment. Also, the toxicity of ARVs may deter some people from taking the medications. Combination ART can be complicated and time-consuming and may not be seen as compatible with some people’s lifestyles. Some medications need to be refrigerated, which may limit their usefulness in areas where refrigeration is not available. The development of resistance can also be a barrier to treatment. Patients who are noncompliant with their medications can develop resistance and then spread the resistant virus. These issues are decreasing as once-daily, single-pill regimens become more widely available. Such a regimen would make directly observed therapy a possibility.

**References**

Antiretroviral Treatment


6. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater. J. Acquir. Immune Defic. Syndr. 2007;45:183-192.


Antiretroviral Treatment

Please tick after each statement once it has been reviewed with the applicable individual(s):

1. I understand that antiretroviral drugs (ARVs) against HIV stop the virus from multiplying, leading to a better quality of life, although they are not a cure for HIV. HIV is a lifelong infection and ARVs are a lifelong treatment. Therefore, even if I/my child feels better after starting the ARVs, I understand that if the ARVs are stopped, sickness will resume.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

2. I understand that taking all of the ARV medications together as prescribed is critical to treatment success, and that missing even one dose may result in permanent drug failure and sickness. I will not miss any doses. If I do miss doses, I will ask the clinic for help because it is so important.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

3. I understand that I/my child cannot miss any doses. Therefore, I will return on time for each clinic appointment for ARV refills. If I run out of ARVs in advance of my/my child’s appointment because of an accident/spill, then I will return to the clinic immediately for a refill on a clinic day.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

4. I understand that because all the ARVs must be taken together to work, I will stop no medications without consultation with a doctor. I will not give away or sell the ARVs to anyone because doing so will be hurtful to me/my child and to the other person. I understand that if I stop one or more ARVs without the advice of a doctor, I may seriously hurt my/my child’s future treatment options because of HIV resistance. The first ARV regimen is the most important/effective. If it fails, the options are limited.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

5. I understand that the ARVs must be taken at the same time of day every day. However, should I forget to administer/take a dose, I should administer/take it as soon as I remember. However, if it is 6 hours past the time that the dose was due (for twice-daily ARVs) or 12 hours past the time that the dose was due (for once-daily ARVs), then I will skip the missed dose and continue the regular dosing schedule. I will not take a double dose to make up for a missed one.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

6. I understand that all medications may have associated side effects. These may include temporary weakness, rash, tiredness or lack of blood, loose stools, tingling sensation in the feet, vivid dreams, or others. I will come to the clinic if any side effects occur and will not stop any medications unless directed to do so by a doctor.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

7. If I/my child vomits within 30 minutes of taking the medication, or if I can see the ARVs in the vomit itself, then I will repeat the dose.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable

8. I will bring my/my child’s ARVs and/or pill box to every visit.

   [ ] Primary Caretaker   [ ] Patient (if disclosed to)
   [ ] Caretaker #2, if applicable   [ ] Caretaker #3, if applicable
9. For caretaker(s): I am fully committed to making certain that the child I am caring for receives his/her ARVs. If I can no longer care for the child, I will let the clinic counselor know as far in advance as possible so that another adult may be counseled to do so.

[ ] Primary Caretaker     [ ] Caretaker #2, if applicable
[ ] Caretaker #3, if applicable

10. For caretaker(s) of children only: I understand that I should encourage my child(ren) to be responsible for taking his or her ARVs; however, I understand that children must be directly monitored while swallowing the ARVs, and I will closely supervise their successfully taking the ARVs.

[ ] Primary Caretaker     [ ] Caretaker #2, if applicable
[ ] Caretaker #3, if applicable

11. For all patients if disclosed to: I understand that because ARVs are not a cure, I can still pass on the virus to someone else through my blood or through sexual intercourse. I understand how to avoid passing the virus to others, and I understand that it I can contract another strain of HIV, such that it is also in my best interest to protect myself from further infection.

[ ] Patient (if disclosed to)

12. For all female patients if disclosed to: I understand that I can still transmit HIV on a mother-to-child basis during pregnancy, delivery, or breast-feeding even while taking ARVs, although this risk is lower than among HIV-positive women not on ARVs. Because some ARVs may harm the developing fetus, I will inform my doctor if I am or plan to become sexually active or pregnant.

[ ] Patient (if disclosed to)

ADHERENCE COMMITMENT

By signing below, I commit to adhering to each and every dose of ARV medication for the rest of my/the child I care for’s life:

_________________________________ _________________________________ Date: ________________
Primary Caretaker Name                      Primary Caretaker Signature

_________________________________ _________________________________ Date: ________________
Patient’s Name (if disclosed to)            Patient’s Signature

_________________________________ _________________________________ Date: ________________
Caretaker #2 Name (if applicable; required if high risk) Caretaker #2 Signature

_________________________________ _________________________________ Date: ________________
Caretaker #3 Name (if applicable) Caretaker #3 Signature

_________________________________ _________________________________ Date: ________________
Counselor Name                             Counselor Signature
OBJECTIVES

1. Discuss the definition, pathogenesis, diagnosis, and treatment of immune reconstitution syndrome (IRS).
2. Discuss the metabolic changes associated with human immunodeficiency virus (HIV) infection and antiretroviral therapy, specifically dyslipidemia, lipodystrophy, insulin resistance, lactic acidemia, and decreased bone density.
3. Discuss the etiology and mechanisms of these changes.
4. Discuss treatment strategies.

KEY POINTS

1. IRS occurs most often in sicker patients who have a rapid response to therapy.
2. Usually, treatment with antiretroviral medications should continue through IRS.
3. HIV infection and its treatment are associated with a variety of endocrine and metabolic abnormalities.
4. The etiologies of these abnormalities are multifactorial.
5. These abnormalities may result in life-threatening complications and/or increase risk of serious chronic illnesses.
6. These abnormalities may be responsible for nonadherence to antiretroviral therapy.

OVERVIEW

Patients first beginning treatment with antiretroviral therapy (ART) sometimes paradoxically become sicker. This outcome is thought to be an immune-modulated reaction to the reconstitution of the previously depleted immune system. The exact nature of this reaction depends on many factors, including the state of the patient’s immune system prior to medications as well as past opportunistic infections. This reaction is commonly known as immune reconstitution syndrome (IRS). Human immunodeficiency virus (HIV) infection is associated with a wide array of endocrine and metabolic abnormalities, including hypercholesterolemia, hypertriglyceridemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis, adrenal insufficiency, hypoaldosteronism, thyroiditis, hypogonadism, and hypopituitarism (Figure 1). The pathophysiology of these changes is equally varied and may include direct damage by HIV, opportunistic infection, malnutrition, systemic inflammatory responses, neoplasms, and the complications of HIV therapy. These abnormalities may also increase the possibility of more long-term, secondary diseases, such as cardiovascular disease. Furthermore, adherence to potent ART may be compromised. An understanding of the adverse events and their management will help to maximize the effectiveness of available treatment.

Figure 1. Adverse effects of antiretroviral therapy

<table>
<thead>
<tr>
<th>Alopecia</th>
<th>Headache (AZT, D4T, efavirenz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia, depression (efavirenz)</td>
<td>Anemia (AZT)</td>
</tr>
<tr>
<td>Headache (AZT, D4T, efavirenz)</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Breast hypertrophy</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Nephrolithiasis (indinavir)</td>
<td>Thinning extremities</td>
</tr>
<tr>
<td>Central adiposity</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Pruritic skin</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Ingrown toenails</td>
</tr>
</tbody>
</table>
**Immune Reconstitution Syndrome**

**Definition**
IRS, the term we will use herein, has been referred to by many names: immune reconstitution disease, immune recovery disease, and immune restoration disease. IRS is a paradoxical worsening of symptoms after the initiation of ART medications.

There is no agreed-upon definition of IRS; however, most experts, including the World Health Organization (WHO), believe that for an illness to be considered IRS it should have the following elements:
- Temporally related to the start of ART—usually within the first 12 weeks.
- Documented improvement of immune status (a 1-log or greater decrease in viral load or a documented increase in CD4 lymphocyte cells). IRS is more likely to occur in those with worse disease at the time of ART initiation (CD4 <50 cells/μL).
- No evidence of new infectious process or drug toxicity.
- Patient has previously been treated for this disease (this is not always consistent because IRS may “unmask” previously undiagnosed illness).
- Clinical evidence of an inflammatory condition.

**Epidemiology/Pathophysiology**

Few prospective studies on IRS have been conducted. Retrospective studies imply that 10% of patients starting on ART will experience some form of IRS. Those more likely to experience IRS are those with a lower CD4 cell count at initiation of ART who exhibit rapid viral suppression and reconstitution of the immune system. Almost all organisms causing opportunistic infections and/or comorbidities with HIV have been associated with IRS. Diagnosis and treatment for the associated infection within a few months of initiating highly active ART (HAART) increases the risk of an IRS. The most common are the following:
- *Mycobacterium* (*Mycobacterium tuberculosis*, *M. avium* complex, and leprosy)
- Cryptococcal disease
- Herpes family viruses: varicella-zoster virus, herpes simplex virus
- Kaposi sarcoma
- Cytomegalovirus
- JC virus
- Noninfectious diseases (sarcoidosis, Guillain-Barré, Graves’ disease)

Paradoxical worsening of disease after initiation of therapy is not unique to ART. IRS has been described in the treatment of tuberculosis. Both syndromes are thought to be related to the increase of various immune cell lines and an increase in the release of interleukins and other immune modulators. It is postulated that the “reawakening” immune system is often dysregulated and can therefore lead to lymphadenopathy, early weight loss, or reactivation of dormant disease.

**Management**

Management of IRS is similar regardless of the associated organism. In most cases, HAART should be continued. Only when severe central nervous system (CNS) or pulmonary symptoms are...
seen and considered life-threatening should HAART be discontinued. This scenario is most likely with cryptococcal neoformans or KS. For moderate to severe symptoms, these symptoms can be lessened with adjunctive steroid or nonsteroidal anti-inflammatory drug (NSAID) therapy. Prednisone dosing would be 0.5-1 mg/kg of body weight/day for 5-10 days; dexamethasone is reserved for CNS symptoms and would be 8-10 mg/day divided twice daily for adults and 0.08-0.3 mg/kg/day divided twice daily for children. If steroids are used at higher doses and/or for longer than 5 days, a taper of the medication is recommended to avoid complications of steroid use.

**Mycobacterium-Associated IRS**

*M. tuberculosis* IRS is the most common seen internationally. It will manifest as fever, lymphadenopathy, new findings on chest radiograph, and perhaps weight loss. It is important to distinguish IRS from new-onset disease and/or tuberculosis (TB) that is resistant to the medication regimen that the patient is taking. In TB IRS, cultures of blood, sputum, and/or lymph biopsy samples will be negative for the organism but will show evidence of granulomas and inflammatory reaction. Patients with a previously anergic Mantoux skin test will now exhibit a reaction. TB IRS is more commonly seen in patients who begin HAART within 2 months of initiating TB treatment. It may also be seen in those with previously treated TB. Treatment depends on the severity of illness. Often, continuing HAART and TB treatment is enough for symptoms to subside. If severe pulmonary or CNS symptoms are seen, HAART may have to be temporarily discontinued. Occasionally, steroids (prednisone or dexamethasone) are needed to decrease symptoms. NSAIDS can also be used to alleviate symptoms.

*M. avium* complex-associated IRS often presents with lymphadenitis (painful) and fever. Blood and bone marrow cultures for *M. avium* complex will be negative; lymph aspirates usually show no organism but will show granulomas. Symptoms can be more diffuse, including abdominal pain or lung infiltrates. Treatment includes continuing HAART; incision and drainage of lymphadenitis; and, if severe, corticosteroids. Again, it is usually self-limited disease.

Bacillus Calmette-Guérin (BCG)-associated IRS has been reported in infants or children who have recently received the BCG vaccine prior to initiation of HAART. It may present as drainage and swelling at the site of BCG or ipsilateral lymph swelling. Culture of drainage would reveal BCG strains. Treatment is continuation of HAART and incision and drainage. See “Immunizations and HIV” for updated immunization recommendations.

Finally, limited case reports exist of IRS-associated leprosy. Most were previously undiagnosed cases, limited disease, and amiable to standard treatments. Most experts expect that the incidence will increase as access to HAART in leprosy-endemic areas increases.

**Cryptococcus neoformans-Associated IRS**

Lymphadenitis, CNS manifestations (mass lesions or meningitis), and pulmonary symptoms are the most common presentations of cryptococcus-associated IRS. Most patients have had identified cryptococcal disease prior to HAART initiation and a very low initial CD4 cell count (<50 copies/μL). Patients will often present with headache and neck stiffness despite being on preventive antifungal medications. Lumbar puncture will reveal a high opening pressure but negative cultures. Symptoms typically develop in the first 6 months after HAART initiation. Symptoms will develop more rapidly in severely immunocompromised patients. Treatment includes continuing ART medications, antifungal medications, and anti-inflammatory medications in cases of severe respiratory distress or mental status changes.

**Herpesvirus-Associated IRS**

Many herpetic viruses can cause IRS reactions in immunocompromised patients starting HAART.

Varicella-zoster virus most commonly presents as dermatomal zoster. Zoster is seen more frequently in HIV-positive patients receiving ART than in those who are not taking antiretrovirals (ARVs). Most cases are self-limited and can be treated with acyclovir or famciclovir. Continuation of HAART is recommended.

HSV labialis has been described in pediatric patients initiating HAART as well as adults. Again, symptomatic treatment and continuation of HAART are the recommended treatment, with few serious consequences.

**Kaposi Sarcoma**

Kaposi sarcoma (KS) resurgence has been reported with HAART initiation. Most are in patients with previously diagnosed KS and present within the first 3-8 weeks of
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HAART initiation or switch. Those with lower CD4+ cell counts at initiation of HAART are at higher risk for IRS-associated KS. Deaths have been reported, primarily in those with pulmonary complications. HAART can be continued; however, patients should be monitored for new lesions and/or symptoms. Rapidly progressing KS, particularly visceral KS, should also be treated with antineoplastic agents. Such treatment has led to favorable outcomes for patients.

**Cytomegalovirus**

Cytomegalovirus (CMV) causes primarily ocular complications in patients with a CD4 cell count less than 100 cells/mm³. Cases present similar to primary disease: painless floaters, blurred vision, photophobia, decreased visual acuity, or ocular pain. Examination of the fundus will show marked inflammatory response. In rare cases, systemic disease can also occur. Incidence of IRS is high: up to 63% in those known to have CMV ocular disease prior to HAART initiation. Nontreatment can have high morbidity, including loss of sight. Patients should continue HAART, and steroid treatment should be initiated because it decreases complications. Many patients with previously diagnosed disease are already on CMV medications, and these should be continued at therapeutic doses (see chapter on opportunistic infections).

**JC Virus**

The JC virus is associated with progressive multifocal leukoencephalopathy in patients with AIDS. As many as 20% of patients can experience worsening neurologic symptoms with the initiation of HAART. Imaging of the brain with contrast may reveal enlarging lesions. Onset of IRS-associated JC is 3-8 weeks after HAART initiation. Continuation of HAART and adjunctive steroid therapy for severe cases usually leads to resolution in 3-6 months. Some fatalities have been reported, however.

**Noninfectious IRS**

Several different autoimmune diseases have been associated with IRS. Guillain-Barré, sarcoidosis, autoimmune thyroiditis, and Graves’ disease have all been reported. They present 3-12 weeks after HAART initiation, strengthening the evidence that they are IRS-associated illnesses. Sarcoidosis may, however, present up to 12 months after the start of therapy. Most patients had been previously diagnosed with sarcoidosis that had become inactive as the patient’s CD4 lymphocyte count deteriorated. Hence, this reactivation of disease appears to be related to the reconstitution of the immune system. IRS-associated sarcoidosis responds well to adjunctive steroid therapy. Any autoimmune illness previously quiescent secondary to immune suppression can be expected to flare as immune reconstitution takes place. Should this occur, steroids are one possible treatment.

**Metabolic Changes Related to ART**

Treatment of HIV with HAART has changed the natural history of the infection and has allowed children infected at birth to live into adulthood. HIV has become a chronic illness that requires lifelong treatment and care. HAART, however, is associated with the development of adverse effects that include hyperlipidemia, lipodystrophy, insulin resistance, lactic acidemia, and bone changes. These conditions may be associated with long-term complications such as risk for coronary artery disease in patients with persistent hyperlipidemia. Some of these conditions can also be stigmatizing and related to decreased adherence to ART. These complications and their treatment are discussed next.

**Dyslipidemia**

Dyslipidemia refers to changes in lipid metabolism, particularly increases in total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) cholesterol levels and increases of high-density lipoprotein (HDL) cholesterol levels in the blood. By unclear mechanisms, dyslipidemia can be caused by HIV disease independent of ART. These changes are also associated not only with protease inhibitors (Pis) but also with nonnucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs) in adult patients.

An estimated 20%-50% of children receiving HAART will have lipid abnormalities, including elevations in TC and LDL. Among 280 children evaluated by the European Paediatric Lipodystrophy Group, 27% of children had elevated TC and 21% had elevated TG, resulting in an overall prevalence of dyslipidemia of 38%.

Cross-sectional cohort studies comparing children treated with PI-containing and non-PI-containing HAART regimens revealed elevations in TC and LDL cholesterol in those patients receiving PIs. TG levels were elevated in some patients but may normalize after several months of therapy. Although PIs as a class of ART are most
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associated with elevated TG and TC levels, atazanavir (ATV) is less likely to cause changes in serum lipids. Patients who had hyperlipidemia with the use of other PIs may have normalization of lipid levels with the use of ATV. When ATV is used in combination with low-dose ritonavir, however, dyslipidemia is more common. NRTIs, particularly D4T ( stavudine), have also been implicated in increasing cholesterol and triglycerides. Tenofovir, an NRTI, is associated with fewer metabolic aberrations than stavudine. NNRTIs seem to be least likely to increase lipid levels.

In adults there is a strong association between elevated TC and LDL levels and the development of atherosclerosis and cardiovascular disease. As children are living longer and using more complex regimens, the recognition and treatment of this disorder is becoming more important. The assessment of dyslipidemia must include information about other risk factors for coronary heart disease. Such risk factors include the following:

- A family history of hypercholesterolemia (elevated TC levels >240 mg/dL or 6.3 mmol/L)
- Hypertriglyceridemia (triglyceride level >500 mg/dL or 5.6 mmol/L)
- Low HDL levels (<40 mg/dL or 1.1 mmol/L)
- Hypertension (blood pressure greater than the 95th percentile for height or history of antihypertensive medications)
- A family history of premature coronary heart disease (in males younger than 55 years or females younger than 65 years)
- Age (older than 45 years for males, older than 55 years for females)
- Cigarette smoking

**Management of Dyslipidemia**

In adults the management of dyslipidemia begins with lifestyle changes. These changes include decreased fat intake, increased exercise, smoking cessation, decreased alcohol consumption, and weight loss if appropriate.

Dietary changes and exercise are important in the management of dyslipidemia in children as well. Increased dietary fiber, especially soluble fiber, has a modest cholesterol-lowering effect. Monounsaturated fats lower LDL cholesterol levels while maintaining or increasing HDL cholesterol levels. Foods that contain monounsaturated fats include olive oil, avocados, and many kinds of nuts (such as cashews) and seeds (such as sesame). An adequate trial period of 6-12 months should be given to these management strategies, except in patients at high risk for pancreatitis (TG >500 mg/dL).

If lifestyle changes are ineffective, drug therapy for dyslipidemia may be needed. Less is known about the available agents used to treat dyslipidemia and the long-term risks associated with lipid abnormalities in children with HIV infection. The available classes of drugs used to treat hyperlipidemias include the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, niacin, bile acid-sequestering agents, and cholesterol absorption inhibitors (ezetimibe).

The statins are the lipid-lowering drugs of choice for children with HIV infection. There are multiple drug interactions between this class of medications and ARVs, particularly PIs and NNRTIs. Lovastatin and simvastatin administration with PIs is contraindicated because PIs inhibit CYP3A4 isoenzyme activity, resulting in significantly increased serum concentrations of these agents’ increasing the potential for toxicity. Toxic effects include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Pravastatin is preferred for use in patients receiving PIs because pravastatin’s pharmacokinetics are minimally affected by PIs. NNRTIs are CYP3A inducers and may decrease statin concentrations; thus, higher statin doses may be needed to achieve the desired effect.

There are currently two statins that can be recommended to use in pediatric patients taking ARV agents: pravastatin (preferred) and atorvastatin (alternative). Therapy with pravastatin and atorvastatin should be initiated at the lowest possible dose and titrated to response at intervals of at least every 4 weeks as needed to reduce cholesterol levels. Short-term toxicities in children and adolescents include elevations of hepatic transaminases without clinical hepatotoxicity. These elevations are usually mild, asymptomatic, and reversible. Patients should be instructed to recognize symptoms of idiosyncratic hepatotoxicity and rhabdomyolysis. Statins are teratogenic but may be used in female patients who might become pregnant with adequate counseling about teratogenicity. Effective contraception should be prescribed to those patients who are sexually active.

Patients with HIV/AIDS who have elevated LDL and whose triglyceride levels are above normal (200-500 mg/
dL or 2.2-5.6 mmol/L) may use pravastatin at a dose of 10-40 mg per day or atorvastatin at 10 mg per day, because these drugs are least likely to interact with ARV medications. Patients with triglyceride levels above 500 mg/dL (5.6 mmol/L) regardless of LDL cholesterol levels may be treated with gemfibrozil 600 mg twice daily or fenofibrate 54-160 mg per day. There are no established pediatric doses for these medications.

**Lipodystrophy**

Lipodystrophy is a clinical syndrome characterized by changes in body habitus attributable to fat redistribution and may be associated with many metabolic derangements, including dyslipidemia and insulin resistance. Some of these metabolic derangements are addressed separately in this chapter. The changes of lipodystrophy can include the loss of subcutaneous fat, termed lipoatrophy; deposition of fat tissue subcutaneously or in visceral stores, referred to as lipohypertrophy; or a combination of the two conditions. Lipodystrophy occurs in as many as 33% of children and is more common in adolescents than in prepubertal children. Body habitus changes occur gradually and may not become apparent until months after initiation of combination ART.

Patient self-report and physical examination by an experienced clinician are generally sufficient for the diagnosis of lipodystrophic changes.

**Lipohypertrophy**

Features of lipohypertrophy include increased fat stores in the abdomen, breast, and the dorsocervical spine (Figure 3). Increases in visceral adipose tissue are reflected in increased abdominal girth and increased waist-to-hip ratio. In children, physical examination may reveal increased abdominal girth, dorsocervical fat deposition, and/or breast enlargement. More objective indices may include trunk/limb skinfold ratio of more than 2 standard deviations from the mean, dual energy absorptiometry (DEXA) examinations that demonstrate increases in the trunk/total fat, or trunk/limb fat ratios. Magnetic resonance imaging (MRI) and computed tomography can be used to demonstrate increased intra-abdominal adipose tissue. Cross-sectional measurements using these modalities allow comparisons of total adipose tissue, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT). Whole-body MRI allows comparison of SAT in the trunk and extremities.

**Lipoatrophy**

Lipoatrophy is characterized by thinning of subcutaneous fat in the face, buttocks, and extremities. A decrease in peripheral subcutaneous fat on the arms and legs results in a prominence of peripheral veins. Skinfold thickness near the triceps and biceps below the third percentile for sex and age further characterizes this condition. DEXA can be used to demonstrate a decrease in the ratio of limb/total fat or limb/trunkal fat. Whole-body MRI can be used to compare SAT in the trunk and extremities. In an individual patient, features of lipohypertrophy and lipoatrophy can occur concurrently.

Many studies suggest that lipodystrophy is more highly associated with HAART than with the pathogenesis of HIV disease itself. PIs have been most strongly implicated in the development of lipohypertrophy and its associated metabolic derangements. These changes can also be seen in PI-naïve patients. Thus, the body habitus changes of lipohypertrophy are related to an interrelation between patient genetic and lifestyle factors combined with HIV infection and its therapy. In contrast, lipoatrophy may be more specific to HIV infection and its treatment, specifically the use of NRTIs. Stavudine, didanosine, and zalcitabine are most strongly implicated in the development of this complication, which is postulated to be related to mitochondrial toxicity leading to a change in fat metabolism or even fat cell apoptosis or cell death.

**Treatment**

Diet and exercise are perhaps the most effective approach to increase the muscle-to-fat ratio and reversing the fat maldistribution and body habitus abnormalities of...
Management of Antiretroviral-Associated Complications

lipohypertrophy. Data on pharmacologic interventions are lacking. Hormone therapy has been attempted in some studies, particularly the use of testosterone, growth hormone, or steroids. Cosmetic surgery has also been employed. If therapy permits, changing from a PI-containing regimen may have some benefit. Because lipoatrophy is associated with use of certain NRTIs, avoidance of stavudine and didanosine is the most effective approach to lipoatrophy prevention. Discontinuation of PI therapy does not lead to improvement in lipoatrophy. Substitution of NRTIs less strongly associated with mitochondrial toxicity such as abacavir or tenofovir may improve limb fat, but if the regimen change is delayed, the improvement in peripheral fat may be slower and less complete. Any change in ART must be balanced against the risk of decreasing the effectiveness of the regimen and subsequent resurgence of HIV-associated illnesses.

Many studies have examined the effect of lipodystrophy on HIV-infected adults. Although not as abundant, some research regarding lipodystrophy in HIV-infected children suggests that children, especially prepubertal, are less susceptible to lipodystrophy syndrome than postpubertal adolescents and adults. In fact, it has been suggested that puberty-related changes may precipitate the development of lipodystrophy in some children taking HAART. These changes are not merely cosmetically significant; patient awareness of the disfiguring side effects of ART can be a significant hindrance to adherence. Also, lipodystrophy’s worldwide recognition causes some patients to fear stigmatization.

Hyperglycemia and Insulin Resistance
HIV disease and HIV treatment can alter glucose homeostasis. ARV therapy, especially PI-containing regimens, impair glucose tolerance as reflected in the following conditions:

- Insulin resistance without fasting hyperglycemia
- Asymptomatic fasting hyperglycemia
- New-onset diabetes mellitus
- Exacerbations of preexisting diabetes

However, distinguishing the contributions of ART to impaired glucose homeostasis from those of HIV disease is difficult.

ARV-associated hyperglycemia occurs in 3%-25% of adults receiving HAART, with a mean onset of 60 days after initiation of ARV therapy. The mechanism of hyperglycemia and insulin resistance in patients on ART is unknown and probably multifactorial. PIs can directly affect insulin resistance through the inhibition of insulin-stimulated glucose transport. NRTIs may contribute by increasing the VAT to SAT ratio, thereby altering fat and energy metabolism.

Insulin resistance occurs when there are higher circulating levels of insulin than are needed for maintaining normal glucose homeostasis. This condition occurs at the level of skeletal muscle, liver, and adipose tissues, which develop decreased sensitivity to the effects of insulin. Insulin resistance has often been associated with use of PIs. Studies performed on HIV-negative patients treated with PIs demonstrated definite signs of insulin resistance. However, several factors might contribute to insulin resistance, including changes in fat distribution (VAT:SAT ratio), age, and body mass index. Patients who acquire insulin resistance may have a higher risk of type 2 diabetes mellitus. There may also be an increased risk of atherosclerotic disease.

Insulin resistance can be diagnosed through a combination of physical and laboratory findings, such as polydipsia, polyphagia, polyuria, and increased fasting blood glucose level or a suspicious glucose tolerance test. If insulin resistance is suspected, an intravenous insulin tolerance test can be conducted to verify the diagnosis. Treatment of insulin resistance includes dietary changes, sensible weight reduction, and exercise. Medical management includes metformin at 500 mg twice daily and if feasible, cessation of PI use in ART.

Lactic Acidosis
ART can lead to alterations in mitochondrial function, resulting in the generation of excess lactic acid. Increases in serum lactate levels can range from asymptomatic mild elevations (2.1-5.0 mmol/L) without serum acidosis, referred to as hyperlactatemia, to severe lactic acid elevations (>5.1 mmol/L) with serum acidosis, or lactic acidosis.

Chronic, asymptomatic increases in serum lactate levels are relatively common among HIV-positive adults and children receiving NRTIs. As many as 15%-35% of adults and 29%-32% of children receiving ART for longer than 6 months may have asymptomatic increases in serum lactate levels. NRTIs inhibit mitochondrial replication
by disrupting mitochondrial DNA and oxidative phosphorylation. Stavudine, especially in combination with didanosine, has been implicated most commonly. In vitro studies have demonstrated that zalcitabine, followed by didanosine, stavudine, and zidovudine, has the highest affinity for mitochondrial DNA polymerase. Lamivudine, abacavir, emtricitabine, and tenofovir have lower affinity for this enzyme. Inhibition of mitochondrial DNA polymerase results in impaired synthesis of mitochondrial respiratory chain enzymes, deterioration of oxidative phosphorylation, and depletion of ATP levels. When the demand for energy is greater than what a cell can generate through oxidative phosphorylation, anaerobic respiration produces lactic acid and therefore excess hydrogen ions. When the production of hydrogen ions is greater than the clearance, a systemic metabolic acidosis can occur.

The more serious syndrome of lactic acidosis can occur abruptly after months or years of NRTI treatment. The clinical presentation of lactic acidosis can be acute or subacute. The health care worker should maintain a high index of suspicion for this diagnosis so that prompt evaluation and management can be implemented.

Symptoms typically occur a median of 4 months after starting therapy. Patients with lactic acidosis may be asymptomatic or may present with vague and nonspecific complaints. A prodrome may include generalized fatigue, weakness, and myalgias. Later, gastrointestinal, respiratory, and neurologic symptoms can occur: nausea, vomiting, abdominal pain, shortness of breath, tachypnea, and motor weakness. Hepatic failure occurs in some patients with lactic acidosis and may be associated with tender enlargement of the liver, ascites, and encephalopathy. More serious manifestations include cardiac arrhythmias, hypotension, shock, and even death.

Although there are identified risk factors for the development of lactic acidosis, there is no proven way to predict who will develop lactic acidosis. Routine monitoring of serum lactate levels in asymptomatic patients is not recommended. Mildly elevated serum lactate levels of 2-5 mmol/L should be correlated with symptoms. Patients with mild elevations in arterial or venous lactate (2.1-5.0 mmol/L) and a normal bicarbonate level are usually asymptomatic, and subsequent progression to the lactic acidosis syndrome is rare.

A confirmed moderately elevated lactate concentration of greater than 5 mmol/L in a symptomatic patient or a confirmed severely elevated lactate greater than 10 mmol/L regardless of clinical symptoms establishes the diagnosis of lactic acidosis and requires prompt evaluation and intervention.

Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis. Additional diagnostic evaluations include assessment of the following:

- Serum bicarbonate and anion gap
- Arterial blood gas to assess extent of acidosis
- Amylase and lipase to assess for pancreatitis
- Hepatic transaminases and serum albumin level to assess for hepatic dysfunction
- Imaging studies, such as abdominal ultrasound or computed tomography scan to evaluate for hepatic steatosis and/or pancreatitis

**Table 1. Management of lactic acidosis**

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Biochemical assays</th>
<th>Changes in ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Lactate &lt; 2 mmol/L</td>
<td>None</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Normal bicarbonate</td>
<td>None Evaluate for alternative causes of symptoms</td>
</tr>
<tr>
<td></td>
<td>Lactate &lt; 2 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Normal bicarbonate</td>
<td>Consider changing ddI and d4T Consider temporarily stopping ART while conducting additional workup</td>
</tr>
<tr>
<td></td>
<td>Lactate 2.1-5.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Lactate &gt; 5 mmol/L</td>
<td>Stop all ART</td>
</tr>
<tr>
<td>Asymptomatic or symptomatic</td>
<td>Lactate &gt; 10 mmol/L</td>
<td>Stop other potentially contributory medications Initiate supportive treatment for lactic acidosis</td>
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<td></td>
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</tbody>
</table>

**Treatment**

Treatment includes supportive care and correction of acid-base imbalance or other possible underlying causes. Supportive therapy may include intravenous fluids,
sedation, and respiratory support as needed to reduce oxygen demand and to ensure adequate oxygenation of tissues. Administration of bicarbonate to neutralize the lactic acid remains controversial. Anecdotal therapies to treat lactic acidosis include the administration of the following:

- High doses of riboflavin (vitamin B2) and thiamine (vitamin B1)
- Oral antioxidants, such as vitamins C, E, and K, or l-carnitine and coenzyme Q

Studies determining the efficacy of any of these agents in the treatment of NRTI-associated lactic acidosis are lacking.

**Changing ART Regimens**
The decision to modify ART depends on clinical symptoms and the presence of acidosis.

**Restarting ART**
After adults with lactic acidosis discontinue ART, lactate concentrations return to normal in about 3 months. If lactate levels are not available, ART should not be resumed until symptoms completely resolve, often not before 6-8 weeks. After resolution of symptoms, ARV therapy can be reinstituted. An NRTI-sparing regimen (i.e., an NNRTI and dual PI regimen) may be selected. If an NRTI is required for an effective regimen, then cautiously select NRTIs least likely to inhibit mitochondrial DNA polymerase. These include zidovudine and non-thymidine analog NRTIs: abacavir, tenofovir, lamivudine, and emtricitabine. Patients should be followed up with monthly monitoring of clinical status and lactate levels for at least 3 months.

**Bone Density Disorders**
Osteopenia, osteoporosis, and osteonecrosis are the most significant bone disorders affecting patients with HIV and AIDS. Osteopenia and osteoporosis represent decrease in bone mineral density (BMD). Osteonecrosis results in the cell death of various bone components, including fat marrow and mineralized tissue, as a result of impaired blood supply to the bone. Such abnormalities have been observed in both adults and children. Bone loss in children can be particularly serious because most bone creation takes place before the age of 30 years. The etiologies of bone loss are unclear. Some evidence points to HIV infection itself, whereas some evidence suggests that treatment regimens are the cause. Still other evidence suggests that ART might be protective. The pathogenesis seems to be multifactorial. Figure 4 shows some factors that may contribute to decreased BMD in HIV-infected patients.

A DEXA scan is used to assess BMD. Individual results are often summarized as a $T$ score, which refers to the number of standard deviations above or below the mean BMD of a young adult (usually about age 30) at peak bone density. The WHO criteria for osteoporosis are based on $T$ scores from DEXA scans:

- $T$ score greater than $–1$ is normal.
- $T$ score between $–1$ and $–2.5$ indicates osteopenia.
- $T$ score less than $–2.5$ indicates osteoporosis.

As the $T$ score declines below 0, the risk of fracture increases continuously. The BMD data may also be summarized as $Z$ scores, which are similar to $T$ scores but are normalized to patients who are the same age as the subject. Several recent studies have shown significant decreases in BMD in HIV-infected children, both on and off ART. Up to 66% of children in one study were found to have bone loss on DEXA scan.

When osteopenia is evaluated, vitamin D deficiency and hormonal imbalance must be ruled out, along with renal pathology. Management may include weight-bearing exercise, decreased...
alcohol consumption, smoking cessation, and vitamin D and calcium supplementation. Some suggest the use of alendronate at a dose of 5-10 mg per day. Alendronate acts by inhibiting osteoclast bone resorption.

**Conclusion**

Treatment with HAART has dramatically changed the natural history of HIV infection by allowing HIV-infected children to now survive for many years into adulthood. However, the use of HAART is associated with the development of metabolic alterations, each of which may independently affect the patient’s health and quality of life. Some metabolic abnormalities when combined, such as visceral fat accumulation, hyperlipidemia, and insulin resistance, which are components of the metabolic syndrome, can dramatically increase the individual’s risk for heart disease, diabetes mellitus, and stroke. For early diagnosis of these complications, patients should be screened for metabolic abnormalities regularly. Screening can often be accomplished through thorough history taking and physical examination. Many of the first-line treatments for metabolic abnormalities include diet and lifestyle changes. Such changes should be encouraged for all HIV-infected patients on ART. The effect of these adverse effects on adherence is extreme. For some, the task of having to take medicines every day for the rest of their lives without missing a dose is daunting. The difficulty is compounded by the idea that these medicines can cause such adverse physical reactions, especially the cosmetic changes. There is still stigma attached to HIV, and the fear that members of the community can identify someone’s serostatus simply by noticing lipoatrophy can be socially debilitating. Patients and health care workers must understand the adverse effects of ART as well as their management. This understanding is paramount in maximizing the effectiveness of adherence counseling as well as maximizing the benefits of available treatment regimens.

**References**


Prevention of Mother-to-Child Transmission of HIV Infection

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Daniel Dewey, MD

Objectives

1. Describe the scope of mother-to-child transmission of HIV within the context of the human immunodeficiency virus (HIV) pandemic.
2. Review current concepts on the timing of HIV transmission from mother to child.
3. Review the risk factors associated with transmission of HIV from mother to child.
4. Discuss the four components of the World Health Organization (WHO) framework for approaching the prevention of mother-to-child transmission (PMTCT).
5. Identify and discuss interventions applicable for each component of PMTCT.
6. Discuss WHO recommendations for infant feeding, including an explanation of the risk of transmitting HIV by breastfeeding and how this risk may be lowered.
7. Address efforts under way to scale up access to PMTCT services globally.

Key Points

1. A growing proportion of HIV-infected individuals worldwide, particularly in southern Africa, are young women of reproductive age.
2. Infants are infected with HIV through the perinatal route: in utero, during labor and delivery, or postpartum through breast milk.
3. Risk factors for mother-to-child transmission of HIV include maternal, obstetric, and postnatal factors, including choice of infant feeding strategy.
4. In a breastfeeding population, as much as 40% of total mother-to-child transmission of HIV may take place during breastfeeding.
5. Mixed feeding carries a higher risk of mother-to-child transmission than does either exclusive breastfeeding or exclusive formula feeding. With proper assessment, counseling, and support, mothers can successfully avoid mixed feeding.
6. Antiretroviral medications reduce mother-to-child transmission of HIV.
7. Mothers who qualify for highly active antiretroviral therapy on the basis of their own health should have access to such treatment.
8. PMTCT consists of more than simply giving antiretrovirals to an HIV-positive mother. The WHO offers a comprehensive strategic approach to the prevention of HIV infection in infants and young children that includes the following four components:
   - Primary prevention of HIV infection among women of childbearing age
   - Preventing unintended pregnancies among women living with HIV
   - Preventing HIV transmission from a woman living with HIV to her infant
   - Providing appropriate treatment, care, support to mothers living with HIV and their children and families
9. Globally, access to PMTCT is low, but specific advice on how to achieve improved access exists.
10. Application of a package of PMTCT interventions that have proven efficacy can reduce rates of mother-to-child transmission to less than 2%.
11. Effective PMTCT can be delivered in resource-limited settings.
12. Timely identification of HIV-positive status and enrollment in PMTCT services is crucial to the overall success of a PMTCT program.

Introduction

At the end of November 2009, UNAIDS released the latest data on the number and distribution of persons living with human immunodeficiency virus (HIV)/AIDS worldwide. Estimates are that of the more than 33 million persons living worldwide with HIV/AIDS, a growing proportion are young women of reproductive age. And as the World Health Organization (WHO) and UNICEF detail in the Guidance to Global Scale-up of the Prevention of
Prevention of Mother-to-Child Transmission of HIV Infection

Mother-to-Child Transmission of HIV, in countries with a high burden of HIV infection, AIDS has become a leading cause of illness and death among this population.

Women living with HIV infection can give birth to infants infected with HIV—a process known as mother-to-child transmission (MTCT), the prevention of which is known as the prevention of MTCT (PMTCT). More than 1,100 children younger than 15 years become infected with HIV every day—approximately 430,000 in 2008—almost all through MTCT. More than 90% of these are in southern Africa, and all told, children represent more than 15% of new HIV infections worldwide.

MTCT may take place during pregnancy, labor and delivery, or postpartum via breastfeeding. Risk factors for MTCT are well defined and include prenatal maternal factors such as high viral load, low CD4 cell count, and advanced clinical stage; obstetric factors such as prolonged rupture of membranes and invasive obstetrical procedures; and postnatal factors such as breastfeeding itself and breast conditions such as mastitis.

The overall population risk of MTCT varies with whether the population is breastfeeding or nonbreastfeeding and whether the population’s setting is in a developed country or is resource limited, owing to the relative ability to access a full range of MTCT interventions. In a nonbreastfeeding population, and with no intervention designed to decrease MTCT, the risk of MTCT is 15%-30%. Approximately 70% of transmission in a nonbreastfeeding population is believed to occur before delivery, with roughly 30% of transmission occurring during delivery and the passage of the infant through the birth canal.

In a breastfeeding population, the added risk of postnatal transmission from breastfeeding adds 5%-20% to the baseline risk, such that the total risk increases to as much as 50% (average range, 20%-50%). These percentages are averages of transmission rates; an individual patient could have much higher or lower risk depending on the particular clinical scenario.

Although historically most breastfeeding-associated MTCT has been believed to take place early in the postnatal period (first 6-8 weeks), it is now well appreciated that the risk of transmission from breastfeeding extends into the late postnatal period. In a study from Malawi of a population of HIV-positive mothers that breastfed up to age 24 months, the cumulative risk of transmission between the ages of 6-8 weeks and 24 months was 9.68%; of this figure, more than 85% of transmission was believed to have taken place after age 6 months.

The maximum effect demonstrated from strategies to reduce MTCT has differed by setting. In a nonbreastfeeding population in a developed country, the risk of MTCT can be reduced to less than 2% by a package of interventions that includes antiretroviral (ARV) drugs (highly active antiretroviral therapy [HAART]) given to women during pregnancy and labor, obstetrical interventions including cesarean delivery (prior to rupture of membranes), the complete avoidance of breastfeeding, and ARVs administered to the infant for the first several weeks of life.

In a resource-limited setting, several of these interventions may prove difficult to implement. Cesarean delivery is often not safely available. Patients often do not meet AFASS criteria (acceptable, feasible, affordable, sustainable, and safe), defined by WHO and UNICEF as necessarily present prior to replacement feeding being recommended. As a result, in resource-limited settings most of the PMTCT focus has traditionally been on strategies targeting transmission around the time of labor and delivery. A landmark study (HIVNET 012) from Uganda showed that even a regimen as simple as one dose of nevirapine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]) given to mother at the onset of labor and to the baby within the first 72 h of life (but as close to birth as possible) was associated with a 41% relative reduction in the risk of transmission through to 18 months. Many PMTCT programs in resource-limited settings with high HIV burdens have begun moving toward more effective prenatal ARV regimens, including initiating prophylaxis at or before 28 weeks of pregnancy.

Such expanded ARV prophylaxis strategies are effective, even in resource-limited settings, with reductions in MTCT rates as low as 2%-4%. But in breastfeeding populations, there is still sizable risk of postnatal transmission via breastfeeding, such that overall transmission rates remain considerable. There is significant interest in approaches that can reduce the risk of transmission during breastfeeding.

In developed-country settings, MTCT of HIV is a rare event, given the wide availability of a comprehensive package of MTCT prevention interventions. In contrast, in many resource-limited settings many pregnant,
HIV-infected women cannot access even basic PMTCT interventions, such as counseling and testing and ARV prophylaxis. As of the beginning of 2007, that only 20% of HIV-positive, pregnant women in low- and middle-income countries could access ARVs to reduce the risk of MTCT of HIV.

The global health community has paid considerable attention to this reality over the past several years, and, indeed, today’s figures, while still low, represent an improvement. In 2001, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS set specific targets for countries to aspire to in the provision on PMTCT services. In 2005, UNGASS raised the PMTCT ARV prophylaxis uptake target (on a country basis) to 40% and called for eventual universal PMTCT coverage (≥80% coverage within each country), with an eye toward an HIV/AIDS-free generation by 2015. By 2007, at least eight resource-constrained countries had achieved that mark (80% coverage), including one in sub-Saharan Africa, Botswana.

To approach PMTCT, the WHO in 2003 adopted a comprehensive strategic approach to the prevention of HIV infection in infants and young children that includes the following four components:

- Primary prevention of HIV infection among women of childbearing age
- Preventing unintended pregnancies among women living with HIV
- Preventing HIV transmission from a woman living with HIV to her infant, and
- Providing appropriate treatment, care, and support to mothers living with HIV and their children and families.

The rest of this chapter will examine each component.

**WHO PMTCT Component 1: Primary Prevention of HIV Infection Among Women of Childbearing Age**

**WHO PMTCT Component 2: Preventing Unintended Pregnancies Among Women Living with HIV**

As the building blocks of PMTCT, these first two strategies mesh. Women who do not get infected with HIV cannot, of course, transmit HIV perinatally to a child. Similarly, enabling women living with HIV to avoid unintended pregnancies reduces the demand on a given health system’s PMTCT program, allowing scarce resources to potentially flow into much needed scaleup of PMTCT services. As well, the interventions effective in enhancing these two strategies often synergize, so considering them in tandem is helpful.

Perhaps most important, interventions targeting these first two components of the WHO’s PMTCT strategy may be among the most effective interventions available. In the Guidance to Global Scale-up, authors comment on the fact that minimally reducing the prevalence of HIV infection among women of childbearing age and moderately reducing the number of unintended pregnancies among HIV-positive women of childbearing age can reduce infant HIV infection similarly to single-dose nevirapine (Sd-NVP)-based PMTCT interventions. Moving beyond “minimally” and “moderately,” the potential effects of these strategies are significant.

The primary route of infection with HIV among women of childbearing age is sexual transmission. Although this topic is well covered elsewhere in this text, the WHO recommends strategies to enhance efforts in this regard:

- Expanding entry points to service delivery, including
  - Antenatal, maternity, and postpartum care
  - Family planning
  - HIV/AIDS care and treatment (for adults and children)
  - Sexually transmitted infection (STI) diagnosis and treatment
  - Voluntary counseling and testing
- In high-burden countries, other entry points that could be expanded include
  - Child immunization and Under-5 clinics
  - Workplace clinics

Historically, in many resource-limited settings, PMTCT programs have not given significant attention to services for women who test HIV negative. Because a woman’s risk of acquiring HIV may be higher during pregnancy and lactation, women accessing antenatal care (ANC) services require increased access to primary HIV prevention services.

Institutionalization of provider-initiated testing and counseling (PITC) into standard maternal-child health packages (including ANC) is appreciated as a critical feature of programs in both developed-country and resource-limited settings that have high coverage of PMTCT and pediatric HIV services. Improving access to family planning improves the efficacy of PMTCT...
programs and is cost-effective in decreasing HIV infection in infants. In many high-prevalence settings, particularly in sub-Saharan Africa, where the burden of HIV and pressure on PMTCT programs is the greatest, up-to-date contraceptive prevalence rates are very low (<25%) and unmet need for family planning is high (13%-35%). A substantial opportunity exists for addressing these unmet needs and decreasing the number of infants exposed to HIV.

Specific services enhance primary prevention strategies and unintended pregnancies and can be provided in the preceding settings. Providing information and counseling on ways of reducing the risk of sexual transmission of HIV can extend its influence by involving male partners as well as increasing overall awareness of the issue of perinatal transmission of HIV infection. Also, such counseling can increase awareness that pregnant and postpartum women are at increased risk of HIV infection and help male partners appreciate their responsibility for practicing less risky sex.

By nature, HIV testing and counseling underpins prevention efforts. Specific items recommended to be promoted include augmenting PITC, including PMTCT and family planning counseling into general HIV counseling, and supporting couple counseling, partner testing, and safe and voluntary disclosure.

Promotion of male and female condom availability and use are a key part of prevention interventions. Of particular importance are the promotion of condom use during pregnancy and breastfeeding because of the significant risk of MTCT when HIV is contracted during these periods, as well as offering guidance on how to negotiate condom use with partners. In general, efforts should be made to increase the availability of a full range of contraception options within family planning services, including condoms. The issue of whether to promote using diaphragms in addition to condoms has been raised. A recent study showed no added protective benefit against HIV infection when diaphragm and lubricant gel were provided in addition to condoms and a comprehensive HIV prevention package.

With further respect to family planning services, recent emphasis has been given to the importance of promoting PITC and linking PITC to counseling on reproductive choices and awareness of PMTCT. A global approach that promotes family planning counseling and contraceptives through HIV care and treatment and voluntary counseling and testing, ANC, and postpartum services has been suggested.

Additional preventive benefit can be seen through improved management of STIs, including intensifying antenatal screening and treatment of STIs and targeting high-risk groups with prevention and treatment services for STIs.

Gender-based violence is appreciated as a contributing factor to increased risk of HIV transmission, particularly in high-prevalence settings such as southern Africa. Providing comprehensive management and support for victims of gender-based violence and involving men in reducing gender-based violence have been suggested as important priorities in addressing this concern.

Social and economic determinants play an important role in the risk of HIV acquisition. In Botswana and Swaziland, food insufficiency has been shown to be an important risk factor for sexual risk-taking among women. It has been suggested that targeting food assistance and income generation programs in conjunction with efforts to enhance women's legal and social rights be incorporated into a comprehensive approach to PMTCT.

Over the past several years there has emerged a growing interest in the role of preexposure prophylaxis in the prevention of HIV acquisition, and by extension, in a comprehensive approach to PMTCT. There is strong evidence that male circumcision markedly reduces a man’s likelihood of acquiring HIV infection, and it has been suggested that this measure also benefits women indirectly; on a population basis, fewer HIV-positive men should translate into fewer male-to-female HIV transmissions. The use of topical microbicides has been disappointing as a means of reducing HIV transmission. Doing so is either ineffective (C-31G) or actually increases the risk of transmission (cellulose sulfate), and no benefit has been shown from this approach. Also, ongoing research on a vaccine against HIV has thus far been disappointing.

Postexposure prophylaxis using a variety of ARVs has significant efficacy in many settings and is widely used, particularly in occupational or sexual assault exposure (see corresponding chapter in this text for details). Accordingly,
there is interest in the use of ARVs by high-risk populations before exposure (preexposure prophylaxis) as a means of reducing HIV transmission. Currently, tenofovir (TFV) and Truvada (a fixed-dose combination of tenofovir and emtricitabine) are being looked at for preexposure prophylaxis in a phase II study in the United States. In developing-country settings, TFV is being investigated in IVDU in Thailand, whereas Truvada is being studied in heterosexual men and women in Botswana and men who have sex with men in Peru and Ecuador.

**WHO PMTCT Component 3: Prevention of HIV Transmission from Mothers Living with HIV to Their Infants**

With no intervention, between 20% and 50% of infants born to HIV-infected mothers will themselves become infected with HIV. With an estimated risk of 5%-10% during pregnancy, 10%-20% during labor and delivery, and 5%-20% during breastfeeding, these risks can be reduced to less than 2% by applying a package of interventions.

**Risk Factors for MTCT of HIV**

Risk factors for MTCT of HIV are well defined. Maternal immunologic and virologic factors predictably influence the risk of HIV transmission. Lower CD4+ counts are associated with a higher risk of MTCT, and higher CD4+ counts are associated with a lower risk of MTCT. This association fits with the fact that low CD4+ counts are associated with more advanced disease, and sicker mothers are more likely to transmit the virus than HIV-infected mothers who are still clinically healthy.

There is a direct relationship between maternal viral load and perinatal transmission risk—the higher the viral load, the higher the transmission risk. Like low CD4 counts, high viral loads tend to be associated with more advanced disease. In a study of 552 HIV-infected women, MTCT did not occur among 57 women with RNA levels of less than 1,000 copies/mL. However, there are other reports of MTCT among women whose viral loads were too low to be counted. Therefore, it cannot be concluded that there is a viral load threshold below which there is no risk of perinatal transmission.

Any type of placental inflammation can increase the risk of MTCT. A study from Mombasa, Kenya, showed that chorioamnionitis (inflammation of the lining of the amniotic sac and the womb) slightly increased the risk of MTCT of HIV. Ordinarily, the placenta forms a barrier between maternal and fetal circulation. Although nutrients and waste products are exchanged between the mother and fetus, their circulatory systems are separate. HIV transmission is increased when there is placental inflammation or chorioamnionitis because the barrier that separates the mother’s and baby’s blood and other secretions is compromised. This breach could provide a portal for HIV to enter the baby’s circulation.

Delivery is a time of increased risk of HIV transmission, and a long duration of ruptured membranes increases this risk. During delivery, the baby of an HIV-infected woman is exposed to secretions in the maternal genital tract, which contain HIV. An analysis of 15 studies involving 4,721 deliveries to HIV-infected women illustrates this point. The risk of MTCT of HIV increased by about 2% for every additional hour of duration of ruptured membranes. For women diagnosed with AIDS (not simply HIV infection), the probability of transmission increased by 8% with duration of ruptured membranes of 2 h and by 31% with duration of 24 h. This association remained even after controlling for other risk factors, such as mode of delivery, receipt of ARV therapy, and maternal CD4+ count.

Also important during delivery are limitations on cervical examinations and avoiding unnecessary procedures and instrumentation, such as episiotomies and vacuum and forceps delivery. Whether birth canal exposure itself is a significant risk is controversial, with recent data from trials of birth canal cleansing with virucides showing no reduction in MTCT of HIV. Until recently it was thought that the first born of twins was more likely to contract HIV, but new data suggest this may not be the case.

The well-appreciated risk of transmitting HIV infection during breastfeeding appears to vary with several maternal and infant factors. Advanced clinical stage, lower CD4 counts, higher viral loads, and breast conditions such as mastitis are maternal factors increasing MTCT risk during breastfeeding. The underlying factor favoring transmission in the presence of these factors has been suggested to be that all are associated with increased levels of HIV in breast milk. Infant factors favoring breastfeeding-based MTCT include most importantly the failure to receive post-natal antiretrovirals (discussed below), mixed feeding (the mixing of breastfeeding with other non-breast milk liquids or solids) and the presence of infections such as oral or esophageal candidiasis which break down the infant’s protective gastrointestinal mucosal barrier. The concept
of a breakdown in mucosal barrier augmenting an infant’s propensity to be infected by HIV-infected breast milk underlies the recommendation that infants not mixed feed. The introduction of non-breast milk foods to the immature infantile gastrointestinal tract is believed to cause inflammation in the tract similar to that caused by infections, as mentioned above.

Timing of MTCT of HIV

Recently published work has tried to specify the timing of HIV transmission in both breastfeeding and nonbreastfeeding populations. Kourtis et al. analyzed 18 major clinical trials of ARV regimens used to reduce MTCT and concluded that for nonbreastfeeding populations, half of MTCT takes place at the end of pregnancy, near the time of labor, whereas for breastfeeding populations the largest fraction of transmissions take place in the postnatal period (Table 1).

For breastfeeding populations, this model suggests that if the period of breastfeeding is shortened from the 18-24 months (as is common in resource-limited settings) to the 6-12 months recommended by WHO, breastfeeding-associated HIV transmission falls markedly, as does the total rate of MTCT. This assertion has significant implications for infant feeding policies.

Testing and Counseling

The ability to offer a PMTCT intervention begins with the identification of HIV-positive expectant mothers—if a woman’s HIV status is unknown during pregnancy and the postnatal period, the opportunity for offering a PMTCT intervention is lost. In resource-rich settings, including the United States, opt-out testing—in which an HIV test is performed as part of standard prenatal laboratory testing unless the pregnant mother expressly refuses testing—is the norm, and similar provider-initiated testing is recommended by WHO for resource-limited settings.

The latest WHO guidance on testing and counseling refers to testing and counseling as a pivotal component of PMTCT programs. It is essential for identifying women who can benefit at the time of diagnosis either from HAART and other HIV/AIDS-related care and treatment services or from ARV prophylaxis and other interventions shown to prevent MTCT. WHO recommends that the offer to test and counsel all pregnant women, as early in pregnancy as possible, should be considered a routine part of ANC. If women miss the opportunity to be tested during pregnancy, they should have testing made available in labor or shortly after childbirth; indeed, WHO recommends that HIV testing and counseling be made a part of routine labor and delivery service for all women who present in labor without a known HIV test result. Even if not carried out until the postpartum period, and even if too late for antepartum and intrapartum PMTCT interventions, identification of HIV-positive status at any point allows a woman to access HIV prevention, care, and treatment services, as well as to receive counseling on infant feeding, all with the goal of reducing MTCT.

Opt-out testing increases the proportion of identified HIV-infected pregnant mothers compared with traditional patient-directed voluntary counseling and testing. This concomitantly increases the proportion of HIV-infected women obtaining a PMTCT intervention in a given locale.

Knowledge of and attitudes toward PMTCT of personnel involved in prenatal and maternity care are important factors in determining the degree to which PMTCT services, including testing and counseling, are offered in a given locale. Work from several resource-limited settings has shown less than universal appreciation of the importance and efficacy of PMTCT. Educational programs targeted at such personnel increase knowledge of and promote more favorable attitudes toward PMTCT. Such programs may increase the uptake of HIV testing and PMTCT interventions in resource-poor settings. Avoiding delays in HIV diagnosis and

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<tr>
<th>Table 1. Timing of MTCT of HIV by population</th>
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<td>Population</td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>Non-BF</td>
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<tr>
<td>BF to 6 mo</td>
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<td>BF 18-24 mo</td>
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BF, breastfeeding; N/A, not applicable.

enrollment in PMTCT services is crucial in achieving good PMTCT outcomes (see PMTCT Timeline at end of this chapter).

HAART versus Prophylaxis
Use of ARVs in Pregnant Women

In both developed-country and resource-limited settings, ARV medications, either alone or in combinations of two or three medications, lower the risk of MTCT. Through time, multiple trials and studies have monitored one another and evaluated many different ARV regimens. By decreasing viral replication in the mother and protecting the HIV-exposed fetus, these regimens are effective in reducing the risk of MTCT. Most regimens evaluated have also included a phase of administration of ARVs to the newborn infant, thereby protecting the infant after exposure as well.

Data from developed-country settings suggest that the effectiveness of PMTCT regimens that use three ARVs are superior to regimens that use only one or two. Results from the Women and Infants Transmission Study (WITS) conducted in the United States showed that HIV transmission was directly related to the complexity of ARV treatment. Transmission occurred with 20% of HIV-infected mothers who received no ARV therapy, 10.4% of those receiving zidovudine (known as ZDV or AZT) monotherapy, and 1.2% of those receiving three-drug ARV therapy, also known as HAART. Indeed, in developed-country settings the use of HAART has become the standard ARV regimen for the prevention of MTCT. Results similar to those observed in WITS have subsequently been shown in Brazil and other developing countries in Latin America, and in this region, too, HAART for the sole purpose of PMTCT has become the norm.

In discussing the use of ARVs in pregnant women, we must distinguish the use of ARVs for the treatment of HIV infection (with triple-drug HAART) in eligible women (as determined by clinical stage and, where available, by CD4 count) from prophylaxis against HIV transmission.

Treatment of HIV Infection

HAART to Protect a Mother’s Health

The chief priority in making decisions about whether to offer prophylaxis versus HAART to a pregnant woman is the protection of the pregnant woman’s health. Not only is HAART in such a case the most effective means of preventing MTCT, but for a woman with such an indication, HAART also reduces maternal mortality and morbidity. Particularly in resource-limited settings, a mother’s healthy survival is essential for ensuring her child’s survival. In Haiti and in several sub-Saharan African settings, healthy survival of mothers has been directly associated with the odds of their children surviving, regardless of the child’s HIV status. There is concern that progression of HIV disease or death in mothers may erode the likelihood of infant survival after effective PMTCT interventions.

WHO has published recommendations for initiating HAART in pregnancy that, like those described in the Antiretroviral Treatment chapter of this book, guide the decision whether to use HAART by assessing both the woman’s clinical stage (I-IV) and CD4 count. WHO emphasizes that CD4 testing is not universally available in many resource-limited settings; indeed, recent data from low- and middle-income countries demonstrate that less than 50% of HIV-positive pregnant women receiving ARVs for PMTCT were assessed for treatment eligibility. When CD4 counts are not available, WHO recommends initiating HAART in all women who meet clinical stage III or IV, but not clinical stage I or II. However, when CD4 counts are available, WHO recommends a CD4-guided approach that would initiate ART for all HIV-infected pregnant women with CD4 cell counts <350 cells/mm³, and for all HIV-infected pregnant women in WHO clinical stage III or IV.

Clearly, where CD4 counts are not available, some women who are clinical stage I or II will also have CD4 less than 350 these women will miss the opportunity to be initiated on HAART in the absence of CD4 availability. To this end, WHO emphasizes the need for broader CD4 availability in resource-limited settings where it currently is not available.

In developed-country settings, a decision-making process similar to that for the initiation of HAART in pregnancy is used. United States Public Health Service Task Force (USPHSTF) guidelines recommend that the same parameters (clinical stage and CD4 count) be used in making HAART-initiation decisions in pregnant women as are used in nonpregnant women, and that pregnant women be eligible for the same recommended HAART regimens as nonpregnant women.
**Safety of ARVs in Pregnancy**

When the decision has been made to initiate HAART, careful thought must be given to the choice of ARV agents to avoid adverse events in the developing fetus. Many studies have assessed the safety of using ARV agents during pregnancy.

**Nucleoside reverse transcriptase inhibitors (NRTIs).** Zidovudine (ZDV, AZT) and lamivudine (3TC) are the preferred NRTIs for use during pregnancy. Extensive experience in clinical trials indicates that they are both safe and efficacious; indeed, WHO recommends first-line ART regimens in pregnancy contain a ZDV + 3TC backbone. When ZDV or 3TC is unavailable, alternative agents include abacavir (ABC) and emtricitabine (FTC). The combination of stavudine (d4T) and didanosine (ddI) should be avoided during pregnancy because of a potential increased risk of lactic acidosis attributed to this combination of agents. Also, the combination of ZDV and d4T should always be avoided because of the potential for drug antagonism. Zalcitabine (ddC) is not recommended for use in pregnancy because of its potential for teratogenicity.

**NNRTIs.** Among NNRTIs, nevirapine (NVP) is the preferred agent. Extensive studies show that it is relatively safe for use in pregnancy. However, caution should be exercised in initiating this agent in women with CD4+ counts greater than 250 cells/µL because of an apparent increased risk of cutaneous and hepatic adverse events. Efavirenz (EFV), another NNRTI, should be avoided in the treatment of pregnant women in the first trimester of pregnancy and women of childbearing age who are not using a reliable method of family planning. This agent has been linked with the development of neural tube defects when the fetus is exposed to EFV during the first trimester. It is considered a safe alternative to NVP during the second and third trimesters. It is often used as part of HAART regimens when patients are receiving concomitant therapy for tuberculosis.

**Protease inhibitors (PIs).** Long-term use of PIs has been associated with certain metabolic derangements, including dyslipidemia, lipodystrophy, and hyperglycemia. Pregnancy itself is a risk factor for hyperglycemia, and pregnant patients who take PIs should be monitored for the development of hyperglycemia and gestational diabetes.

Given the increasing numbers of women worldwide who can access HAART when their own health requires, special attention should be directed at women who become pregnant while already on HAART. Although the chief consideration for a woman receiving HAART who becomes pregnant is always her health and the optimization of her treatment, consideration also needs to be given to the potential risks to the fetus of in utero exposure to ARV drugs. In general, with the exception of efavirenz, the ARVs recommended as adult first- and second-line therapies, in both resource-rich and resource-limited settings (see ART chapter), are considered to have benefits substantially greater than risks when used in pregnancy. The Antiretroviral Pregnancy Registry longitudinally assesses the risk of birth defects associated with ARVs. The prevalence of birth defects in infants exposed in utero to ARVs does not differ significantly from birth defect rates in the general population.

The case for efavirenz is somewhat different. Teratogenic effects observed in monkeys, and case reports of neural tube and other birth defects in human newborns exposed in utero to efavirenz, have led to recommendations that efavirenz not be used in the first trimester of pregnancy. Accordingly, many clinicians will not allow adolescent and women of childbearing age to use efavirenz as part of their HAART regimen unless a reliable form of birth control is also used.

When it is realized in the first trimester that a woman taking efavirenz has become pregnant, WHO recommends that nevirapine be substituted for efavirenz or that a triple NRTI- or PI-based regimen be given in replacement. When switching from efavirenz, nevirapine should be started at 200 mg twice daily, as opposed to the usual recommendation to start at once daily for the first 2 weeks and then titrate up, as in ARV-naïve patients being initiated on HAART.

Monitoring for hepatotoxicity, including laboratory assessment of liver enzyme levels, should be used in the first 12 weeks of therapy for women who have experienced a robust immune response to EFV-based HAART. NVP-associated hepatotoxicity is more frequent in women with CD4 counts greater than 250 (although chiefly seen in women who are naïve to ARVs at the time nevirapine is initiated), although data from several case series suggest that nevirapine is generally well tolerated in pregnancy and that there may be a significant
contribution to hepatotoxicity associated with nevirapine from underlying chronic viral hepatitis and other hepatobiliary disorders.

Outcome evidence from pregnancies in which infants were exposed to efavirenz in the first trimester is limited, particularly in the developing world. One study from Botswana showed no EFV-associated congenital anomalies among 22 consecutive first-trimester-exposed live born infants. WHO recommends that for women in whom pregnancy is not realized until the second or third trimester, efavirenz may be continued; the high-risk period of pregnancy (first trimester) has already concluded. Current recommendations are that exposure to efavirenz in utero not be considered an indication for abortion and that temporary cessation of HAART is not necessary.

Some concerns have been raised about the potential for tenofovir to be associated with abnormal fetal bone development. However, current recommendations are that women taking tenofovir who become pregnant should continue tenofovir; the benefits of continuing treatment exceed the theoretical orthopedic risk to the infant. Tenofovir + 3TC (or FTC) is a recommended alternative first-line backbone in pregnancy, when ZDV not available.

**Effects of HAART on Pregnancy Outcomes**

Although ZDV monotherapy prophylaxis appears to be safe to both mother and infant, the question of whether HAART is associated with adverse pregnancy outcomes has been difficult to definitively answer. Study data have been contradictory. Typical side effects of ARV drugs appear to be common, with a Swiss study showing that more than 75% of women experienced one or more of anemia, nausea/vomiting, elevation of liver enzymes, or hyperglycemia. In this study 10 of 30 infants were born prematurely. Further study data supporting an association of HAART with prematurity came from the European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study, which detailed the effects of combination ARVs in a population of 3,920 mother-child pairs. After adjusting for CD4 count and intravenous drug use, the study found a 2.6-fold (95% confidence interval, 1.4-4.8) increased odds of preterm delivery for infants exposed to HAART compared with no treatment. A limitation to the study was that only 323 (8%) of the women were exposed to HAART. ZDV monotherapy was not associated with prematurity.

However, in an observational study of pregnant women in the United States with HIV-1 infection (PACTG 367) in which 1,150 (78%) of the women received combination therapy, no association was found between having received combination therapy and preterm birth. Further evidence supporting a lack of association between HAART and significant adverse pregnancy outcome comes from a sizable meta-analysis of seven clinical trials that included 2,123 HIV-1-infected pregnant women who gave birth to infants during 1990-1998 and had received antenatal ARV therapy and 1,143 women who did not receive antenatal ARV therapy. In this meta-analysis, use of combination ARV therapy compared with one drug was not associated with a variety of adverse pregnancy outcomes, including rates of preterm labor, preterm birth, low birth weight, low Apgar scores, or stillbirth. More support for a lack of a specific association between ARV therapy and prematurity comes from a meta-analysis that looked at subjects recruited through 2002 and data published through 2006. This study showed only a small, non-statistically significant risk of prematurity with PI-containing regimens, slightly greater if the PI-containing regimen was started in the first trimester of pregnancy. In this analysis, monotherapy was associated with a small, non-statistically significant decrease in rates of prematurity, and non-PI HAART was associated with no difference.

**Use of ARVs for Prophylaxis Against MTCT**

ARVs have utility in the prevention of MTCT of HIV-1 infection even when mothers would not otherwise qualify for HAART (per WHO or developed-country criteria) on the basis of their own health. Over more than a decade, various prophylactic ARV regimens have been evaluated for safety and efficacy in the prevention of MTCT in both developed-country and resource-limited settings.

**Use of ARV prophylaxis in developed-country settings—ZDV monotherapy.**

PACTG 076, the Pediatric AIDS Clinical Trials Group Protocol 076, was the first major study of perinatal transmission prevention. This randomized, double-blind, placebo-controlled study evaluated the use of ARV prophylaxis with ZDV monotherapy. In this study, neither the woman nor her doctor knew whether she was receiving ZDV or a placebo (a sugar pill substitute). Women with CD4 counts greater than 200 cells/μL who had not received prior HIV treatment were randomized to a three-part regimen of ZDV versus placebo. The sample
size was 409. ZDV was given to the mother beginning at 14-34 weeks of pregnancy, at a dose of 100 mg, by mouth, five times per day. Therapy was avoided during the first trimester to reduce the risk of possible birth defects. During labor, intravenous ZDV was given to the mother as a loading dose of 2 mg/kg of body weight over 1 h followed by a continuous infusion of 1 mg/kg/h until delivery. Finally, oral ZDV was given to the newborn for the first 6 weeks of life, at a dose of 2 mg/kg every 6 h. Women in this study were instructed not to breastfeed their infants.

At 18 months, there was a dramatic relative risk reduction of 67.5% in MTCT in the ZDV treatment group compared with the placebo group. HIV transmission occurred with 25.5% of women receiving the placebo and with 8.3% of women receiving ZDV. Patients receiving ZDV also showed a slight reduction in viral load, but the researchers estimated that reduction in viral load accounted for only 17% of the reduction in HIV transmission. Experts speculate that ZDV may also exert its effect by reducing the concentration of HIV within cervicovaginal secretions. Furthermore, unlike other nucleoside drugs such as d4T and ddI, ZDV becomes fully active within the placenta, which may also explain some of its protective ability.

Infants in the ZDV group experienced temporarily lower hemoglobin concentrations than infants in the placebo group; however, this resolved without treatment. No significant differences were observed between the study groups in growth, neurodevelopment, or other developmental indicators. No unexpected ophthalmologic, cardiac, or other organ system problems were observed, and no malignancies have been observed in follow-up to 10 years of age.

Because PACTG 076 looked at the efficacy of ZDV chemoprophylaxis only in women with CD4 counts greater than 200, the question arose of whether ZDV chemoprophylaxis would be similarly effective in a population with different characteristics—i.e., clinically advanced HIV-1 disease and/or CD4 counts less than 200. Also, the question arose of whether ZDV chemoprophylaxis would be effective in women with prior exposure to ZDV. This question was evaluated by a separate perinatal transmission protocol, PACTG 185, which enrolled pregnant women with advanced HIV-1 disease and low CD4 counts who were receiving ARV therapy (24% had received ZDV before the current pregnancy). All women and infants received the preceding three-part ZDV regimen described as per PACTG 076 as well as either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies.

Use of ARV prophylaxis in resource-limited settings.
Because of its potent preventative benefit, the PACTG 076 ZDV prophylaxis regimen swiftly became part of routine practice in developed-country settings. But its complexity and cost (long prenatal and infant courses of ZDV, intravenous ZDV) have caused PACTG 076 to be difficult to implement in settings where not only are health care resources limited but there is often much higher prevalence of HIV than in North America and Europe. This has particularly been the case in sub-Saharan Africa.

With a need to find less complicated and less costly, but nonetheless effective, regimens for PMTCT, attention in resource-limited settings turned to ARV regimens focused on the periods of pregnancy and childbirth where transmission is believed to be most common: the critical intrapartum period, along with the late antepartum and early postpartum periods.

Short-course ZDV in resource-limited settings, nonbreastfeeding populations. The first study to address the needs of resource-poor settings was a trial conducted in Thailand in 1998, the CDC Short-Course ZDV trial, Thailand. In this study, a shorter course of ZDV therapy was provided than was used in the PACTG 076 protocol. This was a randomized, double-blind, placebo-
controlled trial of 397 HIV-infected women from two Bangkok hospitals. Oral ZDV (300 mg twice daily) was given to pregnant women, beginning at 36 weeks of gestation. This was followed by oral ZDV given to the mother during labor, at a dose of 300 mg administered every 3 h until delivery. Unlike PACTG 076, this trial had no newborn-treatment component. The mothers did not breastfeed. Results from this study showed that a shortened course of ZDV therapy can reduce the risk of MTCT by approximately 50%. The rate of HIV transmission was 18.9% in the placebo group and 9.4% in the ZDV group. The study also suggested that, in a nonbreastfeeding population, most cases of vertical transmission occur in the peripartum period.

Another trial carried out in Thailand looked at whether giving ZDV from a later point in pregnancy than did the CDC short-course ZDV trial, Thailand (38 weeks versus 36 weeks) as well as in labor but not to babies made a difference in the efficacy of ZDV. It did. Efficacy was markedly reduced (at 6 months in this nonbreastfeeding population), with only 9% MTCT risk reduction compared with CDC short-course ZDV trial, Thailand’s 50% figure, confirming the need to start ZDV earlier than 38 weeks for significant efficacy to be seen. As a result, starting AZT by 36 weeks has become standard practice in most resource-limited setting guidelines on the use of ZDV monotherapy prophylaxis, and whether a mother has received at least 4 weeks of prelabor ARV is a key point in the decision making recommended by the WHO and other authorities on choice of labor and postpartum prophylaxis regimens.

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Short-course ZDV in resource-limited settings—breastfeeding populations. PACTG 076 and the Thai trials showing efficacy for long-course and then short-course AZT prophylaxis were performed in nonbreastfeeding populations. But because most HIV-infected women in low-income settings do not have the resources to provide formula for their children, it has been essential to assess the efficacy of prophylaxis in sites where breastfeeding is unavoidable. The short-course regimen of ZDV used in Thai CDC was replicated in Abidjan, Cote d’Ivoire (CDC short-course ZDV trial, Cote d’Ivoire), in a population of 260 breastfeeding women. The use of ZDV resulted in a 44% reduction at age 4 weeks, a 37% reduction in the transmission of HIV by the time the infants were 3 months old, and 26% efficacy at 24 weeks. The Cote d’Ivoire study showed that the CDC short-course ZDV trial, Thailand, regimen of ZDV was effective in a breastfeeding population, although the reduction in transmission was not as large as that in the Thai CDC study, most likely because of postnatal transmission through breast milk.

The DITRAME trial also evaluated the use of a short course of ZDV prophylaxis in a breastfeeding population in Burkina Faso and Cote d’Ivoire. In this trial, ZDV was given as in the CDC short-course ZDV trial, Thailand, from 36 weeks; also, a postpartum maternal course of ZDV was given for 1 week, with the goal of reducing the transmission of HIV through breast milk. At 6 months, the treated group showed a 38% reduction in HIV transmission compared with the group receiving a placebo. The effect was sustained at 18 months postpartum, where the efficacy versus placebo was 30%. Hence, the added week of ZDV did not contribute to any further reduction in the transmission of HIV. Analysis of data from the Cote d’Ivoire (CDC short-course ZDV trial, Cote d’Ivoire) and DITRAME trials at 24 weeks postpartum revealed a persistent effect of short-course ZDV prophylaxis despite continuation of breastfeeding. At 24 weeks, the relative decrease in HIV transmission was 26% compared with placebo.

ZDV Plus 3TC in Resource-limited Settings—Breastfeeding Populations. Once short courses of ZDV were found to be effective, subsequent trials evaluated the efficacy of ARV prophylaxis combining ZDV with 3TC (lamivudine). A randomized, double-blind, placebo-controlled trial known as the PETRA trial, which was conducted in South Africa, Uganda, and Tanzania,
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evaluated the use of ZDV with 3TC in a resource-poor setting where the rate of breastfeeding was 74% and the median duration of breastfeeding was 28 weeks.

Between June 1996 and January 2000, 1,797 HIV-infected pregnant women were randomized to one of four (A, B, C, plus placebo) regimens (Table 2). At 6 weeks postpartum, results showed that regimens A and B were effective (5.7% and 8.9% transmission, respectively, versus 15.3% for placebo—efficacy, 63% and 42% versus placebo, respectively) in reducing HIV transmission, though the benefits had diminished considerably after 18 months. Regimen C (intrapartum ZDV + 3TC only) was not effective (14.2% transmission versus 15.3% for placebo). By 18 months postpartum, efficacy of the A and B regimens had diminished considerably (14.9% and 18.1% transmission versus 22.2% for placebo—efficacy, 34% and 18% versus placebo). As has been shown in other studies in resource-poor settings, this finding reflects continued HIV transmission via breastfeeding.

Nevertheless, short-course ZDV with 3TC remains a valid option for the prevention of MTCT of HIV in resource-poor settings. Indeed, a meta-analysis of individual data records from several African PMTCT trials indicates that the combination of ZDV and 3TC from 36 weeks of pregnancy is more effective in PMTCT than either ZDV from 36 weeks of pregnancy or Sd-NVP, and a recent Cochrane review supports regimens similar to PETRA A as among the most effective ARV prophylaxis regimens available in resource-limited settings.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HIV Transmission to the Baby at 6 Weeks of Life</th>
<th>HIV Transmission to the Baby at 18 Months of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ZDV+3TC starting at 36 weeks of gestation, oral intrapartum dosing, and 7 days postpartum dosing of mothers and infants</td>
<td>5.7%</td>
<td>15%</td>
</tr>
<tr>
<td>B. ZDV+3TC starting with oral intrapartum dosing and 7 days postpartum dosing of mothers and infants</td>
<td>8.9%</td>
<td>18%</td>
</tr>
<tr>
<td>C. ZDV+3TC oral intrapartum doses only</td>
<td>14.2%</td>
<td>20%</td>
</tr>
<tr>
<td>D. No intervention</td>
<td>15.3%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Sd-NVP. Although less expensive and less complicated than the long-course PACTG 076 AZT protocol used in resource-rich settings, short-course AZT and AZT + 3TC protocols still prove too financially and logistically challenging for some resource-limited settings. An even simpler and less expensive regimen uses a single-dose of nevirapine (Sd-NVP), an NNRTI ARV with a potent mechanism of action and a long half-life, given to the mother at the onset of labor and one dose of nevirapine given to the infant within 72 h of birth. This simple and inexpensive regimen is effective for PMTCT.

This regimen was formally evaluated in a landmark trial known as HIVNET 012, conducted among 619 HIV-infected pregnant women and their infants in Kampala, Uganda. In one arm of the study, one 200-mg oral dose of nevirapine was given to mothers at the onset of labor, and one 2 mg/kg oral dose of nevirapine was given to infants within 72 h of birth. The other study arm consisted of an ultrashort course of ZDV, in which oral ZDV was given to mothers beginning at the onset of labor, at an initial dose of 600 mg, followed by 300 mg every 3 h during labor. Oral ZDV was given to infants at a dose of 4 mg/kg twice per day for the first 7 days of life. In both arms of the study, infants were breastfed by their mothers. Infant infection status was analyzed at 6-8 weeks, 14-16 weeks, and 18 months of life.

The two doses of nevirapine reduced transmission by 47% compared with an ultrashort course of ZDV by 14-16 weeks postpartum. No significant adverse effects were noted. HIV transmission rates among the 311 infants receiving nevirapine and the 308 infants receiving ZDV were as follows:

- 8.1% versus 10.3% at birth
- 11.8% versus 20.0% at 6-8 weeks
- 13.6% versus 22.1% at 14-16 weeks
- 15.7% versus 24.1% at 18 months (42% reduction)

Advantages of the Sd-NVP approach include obvious cost and feasibility concerns. Nevirapine is relatively inexpensive. As well, the regimen is suitable for women who first come to medical attention at the onset of labor or who receive their first HIV-positive test result at such time. The medication may be stored at room temperature, is orally administered, and has a pediatric formulation widely available in resource-limited settings.
A traditional concern in resource-limited settings, particularly in sub-Saharan African locales where HIV rates are greatest and health systems among the world’s most poor functioning, is that results seen in a trial such as HIVNET 012 are not reproducible in a real-world operational context. Such concerns are particularly acute in sub-Saharan Africa. Yet, Sd-NVP can be implemented with effectiveness similar to that seen in clinical trials in a variety of sub-Saharan African settings, including rural health facilities and home births. And Sd-NVP is indeed an effective PMTCT regimen, recently validated in several systematic reviews of current ARV prophylaxis regimens. Ideally, however, national PMTCT programs will go beyond sd-NVP, utilizing other, more efficacious PMTCT regimens, as outlined in this chapter and recommended by WHO.

**Resistance to NNRTIs After Sd-NVP.** In addition to efficacy as compared with other PMTCT approaches, sd-NVP has other drawbacks. A chief concern is the development of NNRTI resistance. NNRTIs, such as nevirapine and efavirenz, need only one mutation to take place for the virus to obtain class resistance to other NNRTIs. Given nevirapine’s long half-life, administering one dose of nevirapine affects a relative monotherapy for the half-life of the drug (generally 24-30 h, but in some women it can persist for up to 21 days). With only one mutation required to impart resistance to the NNRTI class, resistance to Sd-NVP is common.

Indeed, such resistance has been seen in the follow-up to Sd-NVP trials in resource-limited settings. Sizable fractions of women (especially those with more advanced disease and higher viral loads) and of infants who become infected despite Sd-NVP develop resistance mutations to NNRTIs as a result of NVP-exposure. Because nevirapine is a first-line component of adult and pediatric HAART regimens in WHO’s current guidelines for ARV use in resource-limited settings, and efavirenz is commonly used as well around the world, the development of resistance to NNRTIs is of significant concern. Sd-NVP-induced resistance seems to wane over time, such that the effectiveness of Sd-NVP when used for PMTCT in subsequent pregnancies does not seem to be impaired. Sd-NVP-induced resistance compromises both subsequent maternal treatment with NVP-based HAART regimens (although the compromise is less if HAART started more than 6 months after exposure to Sd-NVP) and similar treatment in infants who become infected despite Sd-NVP.

Administering other ARVs, particularly a combination of zidovudine and lamivudine, can reduce the frequency with which nevirapine resistance develops after Sd-NVP. In particular, the TOPS study from South Africa showed that addition of intrapartum plus 4-7 days of maternal postpartum zidovudine-lamivudine reduced nevirapine resistance from 57% to 9%-13% in a population of women who received no antenatal ARVs. As a result of this data, WHO recommends that all women who receive Sd-NVP for PMTCT, whether as an isolated intervention or as part of an expanded antepartum-intrapartum regimen, receive a 7-day “tail” of zidovudine-lamivudine to reduce the likelihood of NNRTI resistance. A longer ZDV/3TC tail to cover the potentially persistent drug levels of Sd-NVP.
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is not recommended because of the possibility of 3TC resistance.

Recent results from a randomized clinical trial in Zambia suggest that a simpler method than 7 days of zidovudine-lamivudine may be possible for the reduction of NNRTI resistance after Sd-NVP. In this trial, 400 HIV-infected pregnant women who sought prenatal care at two public health facilities in Lusaka were enrolled to receive the local standard of care for PMTCT consisting of short-course antenatal zidovudine plus Sd-NVP at delivery. After one patient was excluded, 200 women were randomized into an arm where they received an additional at-delivery dose of 300 mg of tenofovir with 200 mg of emtricitabine under direct observation, whereas 199 received no study drug. Women who received the intervention were 53% less likely than control subjects to have a mutation that conferred NNRTI resistance at 6 weeks after delivery. Although the results of this study cannot be extended to women who take only Sd-NVP without antenatal zidovudine, current WHO recommendations recommend such short-course zidovudine plus Sd-NVP, as received by the women in this study. The study’s findings suggest that the addition of single-dose tenofovir-emtricitabine to short-course zidovudine and Sd-NVP is an effective approach that may prove more feasible than 7 days of postpartum zidovudine-lamivudine, while still conferring similar protection against the development of NNRTI resistance.

**Addition of Sd-NVP to ZDV-based ARV regimens for PMTCT.** Because a major cohort study conducted in the U.S. in the early 1990s showed that a combination of ARVs is more powerful than one agent, there has been interest in using combinations of ARVs for PMTCT. Indeed, in developed countries maternal HAART solely for PMTCT is the standard of care for women with detectable viral loads, as it is in many resource-limited settings such as Brazil, where data for the power of HAART to reduce transmission rates to less than 2% also exist.

Yet implementing HAART widely for the sole purpose of PMTCT faces sizable cost and operational feasibility issues in many resource-limited settings. As a result, much work has gone into looking closely at simpler combinations of prophylactic regimens that build on work done on ZDV-based short-course regimens and Sd-NVP.

**Combination ZDV-3TC versus Sd-NVP.** After PETRA and HIVNET 012 demonstrated the efficacy of short courses of medication in reducing MTCT, a study called SAINT (South African Intrapartum Nevirapine Trial) compared the two regimens. Women and their newborn infants were randomized to either nevirapine or ZDV-3TC arms. In the nevirapine arm, women received 200 mg orally in labor plus an additional 200 mg if still in labor after 48 h, as well as 200 mg 24-48 h postpartum; including the postpartum dose was a departure from the labor-only maternal dosing studied in HIVNET 012. In the ZDV-3TC arm, mothers received ZDV-3TC during labor (loading dose with subsequent dosing every 12 h until delivery) and twice daily for 7 days after delivery. Infants in the ZDV-3TC arm received ZDV and 3TC twice daily for 7 days (as in PETRA B [Table 3]). Results showed similar efficacy for intrapartum nevirapine and for combination ZDV-3TC at 8 weeks (12.3% and 9.3%, respectively, a non-statistically significant difference) in reducing MTCT of HIV. In this study, as in HIVNET 012, delivery near the time of nevirapine dosing increased the odds of transmission; the odds of intrapartum infection were threefold higher in SAINT when the maternal dose was given less than 2 h before delivery. This finding led the study authors to recommend that women who are tested during the antenatal period be given the Sd-NVP by the antenatal clinic and be advised to take it at the first sign of labor; this recommendation has gained widespread favor throughout sub-Saharan Africa and is now common practice in most PMTCT programs using maternal Sd-NVP.

**Combination nevirapine-ZDV in resource-limited settings.** To evaluate the efficacy of adding Sd-NVP to a short course of ZDV (300 mg by mouth twice a day starting at 28 weeks of gestation, 300 mg by mouth every 3 h intrapartum, and to the newborn 2 mg/kg by mouth every 6 h for 1 week), Perinatal HIV Prevention Trial (PHPT) investigators in Thailand in 2001-2003 randomized 1,844 nonbreastfeeding women to ZDV alone or ZDV combined with nevirapine. Results at 6 months revealed a transmission rate of 6.3% in the ZDV-alone group and 1.1% in the ZDV-nevirapine group. This finding confirmed that adding nevirapine to short-course ZDV further reduces MTCT of HIV in nonbreastfeeding women, and can, when added to short-course ZDV, achieve PMTCT results similar to those seen with full triple therapy (HAART)—less than 2%.
To assess the same regimen in a breastfeeding population, investigators in Cote d’Ivoire and Burkina Faso conducted an open-label study, called DITRAME-Plus, in which Sd-NVP was given along with short-course ZDV (similar to the CDC short-course ZDV study, Thailand). Combination therapy resulted in a transmission rate of 7% at 3 months postpartum, compared with 13% in previously documented cases without nevirapine. Thus, even in a population of breastfeeding women, adding Sd-NVP to short-course ZDV appears efficacious.

Because of the success of the Thai and DITRAME-Plus trials, the WHO recommends short-course ZDV with Sd-NVP as the best option for PMTCT of HIV in resource-limited settings when the mother does not otherwise qualify for HAART, recommending ZDV from as close to 28 weeks gestation as possible.

Investigators in Malawi tried adding a 1-week neonatal course of ZDV to the HIVNET 012 nevirapine protocol in a predominantly breastfeeding population. However, giving the newborn ZDV did not result in a statistically significant difference in the rates of transmission. At 6 weeks, the rate of transmission was 14.1% in infants who received only nevirapine and 16.3% in infants who received both nevirapine and ZDV.

**Combination nevirapine-ZDV in developed-country settings.** The PACTG 316 trial studied the effects of combining intrapartum/newborn nevirapine with standard ZDV-based antenatal prophylaxis in well-resourced settings. Nonbreastfeeding women in the United States, Europe, Brazil, and the Bahamas were randomized to standard ZDV-based ARV therapy (along with other ARVs required for treatment) with or without nevirapine. Results revealed no statistical difference in the rate of transmission: 1.4% with nevirapine and 1.6% without nevirapine. Hence, there appears to be no benefit to adding nevirapine to standard ZDV-based prophylaxis in more developed settings in which breastfeeding does not take place.

**WHO Recommendations on Adding Nevirapine to Short-Course ZDV Regimens in Resource-Limited Settings**

However, WHO recommends that where breastfeeding is common there is particular importance to including Sd-NVP as part of the PMTCT regimen because the long half-life of nevirapine prevents early postnatal transmission via breast milk. This is an effect not noted with zidovudine prophylaxis alone and is a significant contributor to the long-term efficacy of a PMTCT regimen, traditionally lower in breastfeeding populations because of the ongoing risk of acquiring HIV infection during the breastfeeding period. Early breast milk, with a high concentration of colostrum, has more HIV than breast milk that has transitioned.

Generally, it is recommended that in settings where breastfeeding is common both mother and baby receive nevirapine per the HIVNET 012 protocol. But data from a recent clinical trial in Botswana demonstrate that the maternal dose of nevirapine may be omitted if mother receives at least 4 weeks of AZT and the infant receives Sd-NVP as well as 4 weeks of AZT. In this trial, where all mothers received a background of zidovudine from 34 weeks, and all infants received Sd-NVP plus 4 weeks of zidovudine, mothers were randomized to either Sd-NVP or placebo at delivery. Transmission rates were very low in both arms—4.3% in the maternal nevirapine arm versus 3.7% in the placebo arm—a nonsignificant difference. That mothers may forgo the Sd-NVP dose if they receive at least 4 weeks of AZT is an important finding: not receiving Sd-NVP obviates a mother from having to receive intrapartum lamivudine or the 7-day zidovudine-lamivudine “tail” described in the previous section to reduce the risk of subsequent nevirapine resistance.

**HAART for PMTCT Regardless of CD4 Count**

In general, combinations of ARVs are more efficacious in preventing MTCT than one ARV. The Women and Infants Transmission Study (WITS) showed that transmission was directly related to the duration and complexity of ARV treatment. This and other studies confirm that the rate of MTCT of HIV correlates with the maternal serum HIV viral load at delivery: the higher the mother’s viral load, the greater the chance of HIV transmission. HAART provides the means to more effectively lower patients’ viral load and thus further reduce MTCT of HIV.

Accordingly, the use of HAART solely for PMTCT (i.e., otherwise not required for the mother’s health) has become standard practice in most of the developed world and in Latin America and other developing regions, where data show MTCT rates comparable to those in North America, Europe, and other wealthy settings. Current U.S. guidelines
advise that standard combination ARV regimens (typically two NRTIs and either a NNRTI, or more commonly in the U.S., a PI) for the treatment of HIV infection should be discussed and offered to all pregnant women with HIV infection regardless of viral load. For women with HIV RNA levels greater than 1,000 copies/mL they are recommended (when HAART is not used, ZDV monotherapy is used instead).

Until recently, little information was available on the efficacy and safety of HAART used exclusively for PMTCT in resource-limited settings with high HIV seroprevalence populations. But with much ongoing study in this area, this has changed. The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program is a large ARV treatment program financed by the Treatment Acceleration Program (TAP) of the World Bank. In addition to ARV treatment, the DREAM program also focuses on nutritional supplementation and a comprehensive approach to PMTCT. In the DREAM program, HIV-infected pregnant women are offered HAART, from as early as 25 weeks’ gestation, irrespective of their clinical, immunologic, or virologic status. All infants receive postexposure prophylaxis. From 2004 to 2006, in Mozambique, Malawi, and Tanzania, of 1,150 infants born to mothers who had received HAART, only 11 were HIV infected, a 0.95% rate of transmission, comparable to data from resource-rich settings. In this cohort, HAART when used for PMTCT was safe for both mothers and infants, as has been shown when HAART is used for treatment of mothers who qualify on clinical, immunologic, or virologic grounds.

In November 2009, WHO for the first time recommended as an option for all HIV-infected pregnant women not eligible for ART, prophylaxis with HAART starting from as early as 14 weeks of gestation until one week after all infant exposure to breast milk has ended; further discussion of antiretrovirals in the context of infant feeding will be discussed below.

**ARVs to the Infant after Birth**

As first shown in PACTG 076 and discussed earlier in the context of several trial results-based PMTCT regimens, provision of ARVs to the infant after birth is a key component of effective PMTCT. Postexposure prophylaxis is highly effective in noninfant populations exposed to HIV (see the HIV postexposure prophylaxis section of this text), and the same is true for the newborn, even when an HIV-infected mother has received no antepartum or intrapartum ARV-based PMTCT intervention. Although early data called into question the benefit of neonatal-only prophylaxis, later work has repeatedly shown a benefit, particularly when started within 12-24 h of birth, although benefit has still been shown with longer windows. Epidemiologic studies from New York State support the use of a 6-week course of neonatal-only ZDV to prevent the vertical transmission of HIV. In a nonbreastfeeding population, the risk of transmission dropped from 27% to 9% when neonatal-only prophylaxis was started within 48 h of delivery.

Investigators in South Africa compared the efficacy of single-dose, neonatal-only nevirapine against 6 weeks of neonatal-only ZDV for the prevention of vertical transmission of HIV in predominantly nonbreastfeeding women. Respective transmission rates were 11.9% and 13.5% at 6 weeks and 14.3% and 18.1% at 12 weeks. Hence, as an infant-only prophylaxis strategy, Sd-NVP may be at least as effective as neonatal-only ZDV for the prevention of MTCT of HIV.

Finally, the NVAZ Randomized Clinical Trial studied the effect of single-dose neonatal-only nevirapine compared to single-dose neonatal-only nevirapine combined with 1 week of neonatal-only ZDV in a predominantly breastfeeding population in Malawi. Results showed that postexposure prophylaxis with nevirapine and 1 week of ZDV was superior to nevirapine alone. Newborns receiving nevirapine alone had an infection rate of 12.1%, whereas newborns receiving the combination of nevirapine and ZDV had an infection rate of 7.7%, for a relative reduction of 36%.

Indeed, it is now believed that most of the benefit of regimens that cover only the peripartum and postnatal periods, such as Sd-NVP (HIVNET 012) or peripartum zidovudine-lamivudine is due to the newborn postnatal component, because the transmission rates reported in those studies differ little from those reporting data from studies involving infant postnatal prophylaxis only. This supposition is further supported by the findings from the PHPT trial in Thailand that added Sd-NVP to ZDV from 28 weeks and showed an 80% reduction in transmission risk, as well as the conclusion from the Mashi trial in Botswana that infant-only Sd-NVP gives similar benefit as Sd-NVP to both mother and infant.
The Mashi data indicate that infant-only Sd-NVP has comparable efficacy to mother-and-infant Sd-NVP only when mother has received at least 4 weeks of antepartum ARVs and the infant receives 4 weeks rather than 1 of postnatal zidovudine. Indeed, the PHPT investigators report that modeling based on their trials supports the key role of prolonged neonatal prophylaxis in averting late intrauterine transmissions to the infant, especially when the mother initiated ARV prophylaxis toward the end of pregnancy.

Longer courses of antiretrovirals for breastfeeding infants of HIV-infected mothers are now recommended by WHO, and will be discussed below.

**How ARVs Might Work to Prevent MTCT of HIV**

The question of how ARVs work to reduce transmission risk in an infant is not entirely clear. But it was recently shown that approximately 18% of uninfected (as shown by DNA PCR) infants born to HIV-1-infected mothers have evidence of only partially reverse-transcribed, and thus nonintegrated, HIV in their peripheral blood mononuclear cells. This finding gives rise to the hypothesis that until the “infected” cell receives the proper activation cues, which may take time after birth to occur, the HIV remains nonintegrated, and the mononuclear cell thus remains without an infection established. This “window” between the entry of HIV into the mononuclear cell and the activation of the mononuclear cell may provide the opportunity necessary for a critical intervention such as ARV therapy to avert establishing HIV infection in the newborn.

**Table 3. ARV-prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health**

<table>
<thead>
<tr>
<th>Option A - Maternal ZDV</th>
<th>Option B - Maternal triple ARV (HAART) prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td><strong>Mother</strong></td>
</tr>
<tr>
<td>Antepartum ZDV (from as early as 14 weeks gestation)*</td>
<td>Triple ARV from 14 weeks until one week after all exposure to breast milk has ended:</td>
</tr>
<tr>
<td>sd-NVP at onset of labor*</td>
<td>* ZDV+3TC+LPV/r</td>
</tr>
<tr>
<td>ZDV+3TC during labor and delivery*</td>
<td>ZDV+3TC+ABC</td>
</tr>
<tr>
<td>ZDV+3TC for 7 days postpartum*</td>
<td>ZDV+3TC+EFV</td>
</tr>
<tr>
<td>*sd-NVP and ZDV+3TC may be omitted if mother receives &gt;4 weeks of ZDV antepartum</td>
<td>ZDV+3TC (or FTC) + EFV</td>
</tr>
<tr>
<td><strong>Infant</strong></td>
<td><strong>Infant</strong></td>
</tr>
<tr>
<td>Breastfeeding infant</td>
<td>Breastfeeding infant</td>
</tr>
<tr>
<td>Daily NVP from birth until one week after all exposure to breast milk has ended</td>
<td>Daily NVP from birth to 6 weeks</td>
</tr>
<tr>
<td><strong>Non-breastfeeding infant</strong></td>
<td><strong>Non-breastfeeding infant</strong></td>
</tr>
<tr>
<td>ZDV or NVP daily for 6 weeks</td>
<td>ZDV or NVP daily for 6 weeks</td>
</tr>
</tbody>
</table>

Several obstetrical PMTCT principles should be implemented when possible. These standard procedures typically do not require significant resources, increased financial demand, or special training. Thus, implementation in resource-limited settings through proper training can be expected.

All intrapartum obstetrical recommendations are based on the core concepts of HIV transmission risks. Anything that increases maternal-to-fetal vaginal secretion exposure and maternal-to-fetal blood exposure, including inflammation, will increase the risk of HIV transmission to the newborn. Thus, it would follow that shortening the time of rupture of membranes to delivery whenever safely possible is recommended. HIV-positive pregnant women in labor should be monitored to ensure that they are progressing toward labor at an acceptable
rate. Pharmaceutical augmentation of labor should be used when acceptable according to standard obstetrical protocols to avoid prolonged labor. Cesarean delivery, when safely available, may be an acceptable alternative to prolonged labor but not used as a prevention measure after rupture of membranes. Cervical exams should be performed only when necessary, thus reducing the risk of chorioamnionitis and MTCT of HIV.

During vaginal delivery of the newborn, standard operating procedures should be followed for PMTCT. These include avoiding unnecessary instrumentation such as vacuum deliveries, forceps deliveries, and episiotomies. Most up-to-date obstetrical practitioners feel that episiotomies are rarely indicated and generally do not lead to improved newborn outcomes.

Health care providers should appropriately protect themselves from exposure as well through the use of gloves and protective eyewear, and they should use extreme caution with suturing and other sharp instrumentation.

In developed-country settings, cesarean delivery reduces MTCT. A meta-analysis of the mode of delivery was conducted using 15 prospective cohort studies representing 8,533 mother-infant pairs. The results of this analysis suggest that elective cesarean delivery reduces the risk of transmission of HIV from mother to infant independently of the effects of treatment with ZDV. Among women who had a cesarean delivery and no ZDV, the risk of transmission was 10.4%. Among women who received ZDV but had a vaginal delivery, the risk of transmission was 7.3%. Among women who had an elective cesarean delivery and received ZDV, the risk of transmission was 2%. For cesarean delivery to be most effective, it must be performed electively, prior to rupture of membranes.

Several studies have looked at whether HIV-infected women have an increased risk of postoperative complications after cesarean deliveries. In one early study, HIV-infected women appeared to be at increased risk. In a later study involving a much larger sample, complication rates for HIV-infected women overall were within the range of complication rates reported for HIV-negative women. However, women with CD4+ lymphocyte counts of fewer than 200 cells/µL did have an increased rate of complications. In summary, for most HIV-infected women, cesarean delivery is probably about as safe as it is for HIV-negative women, but for women with advanced disease or AIDS, cesarean delivery may carry a higher risk.

The U.S. Public Health Service Task Force (USPHSTF) recommends that scheduled cesarean delivery at 38 weeks be performed for women with HIV RNA levels of more than 1,000 copies/mL near delivery (whether receiving or not receiving antepartum ARV drugs) and for women with unknown HIV RNA levels near delivery. For women taking ARVs who have HIV RNA levels of fewer than 1,000 copies/mL, the USPHSTF advises that data are insufficient to evaluate the potential benefit of cesarean delivery to prevent MTCT. WHO recommendations for PMTCT in resource-limited settings do not include cesarean delivery as a part of standard PMTCT, largely because of cost and availability barriers and the limited benefit expected over properly applied ARV-based PMTCT regimens in such settings.

Finally, newborn care of HIV-exposed infants should ensure proper handling of the infant. The infant should be washed with clean water immediately after delivery so that the baby is free of maternal blood and secretions. It is especially important to clean the areas of the baby where newborn vitamin K and vaccines are given, so as not to introduce HIV to the newborn iatrogenically. If the newborn is to receive ARV prophylaxis, it should be started as soon as possible after delivery.

**INFANT FEEDING**

Implementing a package of PMTCT measures can generate HIV transmission rates at birth of 1%-2% in both high-income and resource-limited settings. And yet these impressive rates of PMTCT are not sustained in a breastfeeding population, where breastfeeding is the cause of up to 40% of overall transmission, and absolute risk approaches 15% if women carry out prolonged breastfeeding to 2 years.

Several factors increase the risk of breastfeeding transmission, including advanced maternal clinical stage, low maternal CD4 count, high maternal viral load, mastitis, and mixed feeding. The highest risk of HIV-1 transmission during breastfeeding is believed to be during early lactation; colostrum contains higher viral loads than milk produced later in lactation.

Yet transmission risk from breastfeeding is not restricted to the early lactation period. The Breastfeeding and HIV International Transmission Study (BHITS) meta-analysis has shown the risk to continue throughout the breastfeeding period. In BHITS, the risk of postnatal HIV
transmission after 4 weeks of age was 8.9 transmissions per 100 child-years of breastfeeding, and the rate was generally constant from 1 to 18 months of age. In follow-up of the NVAZ studies in Malawi, the risk of late postnatal transmission (after age 6 weeks) from breastfeeding was 9.68%; 85% of this occurred after 6 months. Data from NVAZ also suggest that in mothers who received Sd-NVP for PMTCT but whose infants still contracted HIV the risk of breastfeeding-associated MTCT may actually be higher after 6 months postpartum than before, owing to the propensity for Sd-NVP to induce resistant virus in the mother—virus that may have less fitness to be transferred to the infant but which regains its infectivity as resistance fades after 6 months.

**Issues Associated with Formula Feeding in Resource-Limited Settings**

Complete and exclusive formula feeding by nature obviates the risk of transmission through breastfeeding. Indeed, in high-income settings such an approach to infant feeding is the standard of care in the presence of maternal HIV infection. Yet in resource-limited settings, exclusive formula feeding is associated with several issues. Even when postnatal vertical HIV infection is dramatically reduced or eliminated by exclusive formula feeding, study data are mixed as to the overall infant survival benefits compared with breastfeeding. A randomized controlled trial conducted in a well-resourced PMTCT setting in urban Kenya where mothers had access to clean water, free and ready supplies of formula, and strong support by health workers showed a 40% lower risk of HIV transmission in the formula-fed versus the breastfed group, but findings showed similar 24-month mortalities. The DITRAME PLUS study carried out in Cote d’Ivoire showed a similar outcome. Also looking at an urban setting with strong support, DITRAME PLUS allowed women a choice of formula feeding or exclusively breastfeeding their infants with early weaning. Those who chose to formula feed were given free replacement feeds and supplies for 9 months. There were no significant differences in rates of infant illness and death at 24 months between formula-fed and breastfed infants, lending further support to the notion that where women have access to clean water, free transport to health care facilities and free health care, free formula and feeding supplies, and bountiful support, safe formula feeding can be accomplished in an overall resource-limited setting.

However, other studies in resource-limited settings have shown serious morbidity and mortality risks to be associated with formula feeding. In Botswana’s Mashi trial, cumulative all-cause mortality at 7 months was significantly higher (9.3% versus 4.9%, p=0.003) in infants randomly assigned to formula feeding versus those assigned to breastfeeding plus zidovudine, and HIV-free survival at 18 months was equivalent between the two groups, showing that the early mortality increase seen with formula feeding negates the benefits of reduced HIV transmission. Data from a Kenyan study showed higher early mortality (11% versus 9%) in formula-fed infants, and that from a South African study showed cumulative 3-month mortality in infants given replacement feeds of 15.1%, whereas the corresponding rate in exclusively breastfed infants was only 6.1%. And in the first quarter of 2006 more than 22,000 Botswanan infants experienced diarrhea (compared with 9,166 in the same period in 2005) and the number of deaths in children younger than 5 years increased by 20-fold. Almost all the deaths were in nonbreastfed infants, suggesting a lack of protective immunity in formula versus breastfed infants, a finding consistent with the long-appreciated benefit ascribed to breastfeeding of transfer of maternal mucosal protective immunity.

**Importance of and Barriers to Avoiding Mixed Feeding**

The risk of breastfeeding transmission varies by whether breastfeeding is exclusive (taking breast milk only, plus oral medicines, if required) or mixed (supplementing with non-breast milk liquids or solids). Several studies have associated mixed breastfeeding with increased risks of transmission compared with exclusive breastfeeding. Data extracted from two randomized controlled trials of the effects of vitamin A supplementation on MTCT (no effect seen) indicate approximately a threefold risk of mixed feeding compared with exclusive breastfeeding. A recently published large intervention cohort study from KwaZulu Natal, South Africa, found a twofold increased risk of transmission by age 6 months in infants who had been uninfected at age 6 weeks but were subject to mixed feeding with milk formula in addition to breast milk and found an 11-fold increase in risk if the mixed feeding included solids (generally home-prepared cereal or commercial infant porridges). Reasons hypothesized to increase risk of transmission among infants who mix feed include increased risk of maternal mastitis, which causes an increase in breast milk viral load, as well as the
introduction of proteins to the infant’s intestinal tract, which may provoke inflammation reducing the intestinal tract’s intrinsic integrity.

Complicating matters is the fact that mixed feeding is the most common form of breastfeeding worldwide and that even mothers who express a desire to breastfeed exclusively generally find it difficult to consistently do so. Data from two studies in South Africa and Zimbabwe that examined infant feeding and MTCT of HIV showed only 26% and 8% of infants, respectively, still being breastfed exclusively at 3 months. In the NVAZ studies, exclusive breastfeeding was common early (99% at week 1, 90% at week 6) but dropped to only 56% by age 3 months and further to 3% by age 6 months.

Several factors probably influence the difficulty women generally have in maintaining either exclusive breastfeeding or exclusive formula feeding. Studies in several different types of communities in South Africa suggest that neither exclusive breastfeeding nor exclusive nonbreastfeeding are the cultural norms in most African settings; indeed, this is probably also the case in a wide range of resource-limited settings outside Africa.

In one study set in the context of South Africa’s PMTCT program (where women are counseled to choose either exclusive breastfeeding with early weaning at 4-6 months or exclusive formula feeding with free infant formula provided until 6 months), 80% of women who had chosen exclusive breastfeeding had introduced other liquids in the first month because of pressures placed on them by the family. In the same study, nearly all the mothers reported periods when no formula was available from clinics, as well as high rates of confusion regarding their choice of infant feeding, a finding that suggests a lack of adequacy in initial counseling and community health worker follow-up. Also, mothers reported a lack of comfort with disclosing their HIV-positive status, even within the family—a finding shown consistently to be associated with low rates of adherence to multiple PMTCT interventions, including adherence to ARVs, and here to adherence to exclusive formula feeding.

And yet, quality data from the intervention cohort study in KwaZulu Natal showed that, with good support, HIV-infected women in a resource-limited setting can develop both appropriate and ideal feeding practices and sustain either exclusive breastfeeding for 6 months, as well as carry out a rapid wean, or exclusive formula feeding (and thus not the deleterious mixed feeding described earlier). In this study, mothers and infants were visited three or four times in the first 2 weeks of life and every 2 weeks thereafter until the infant was aged 6 months. Counselors and clinic nurses were tasked specifically with supporting mothers in one form of exclusive feeding or the other. Median duration of exclusive breastfeeding was 159 days, and 67% of mothers were still exclusively breastfeeding at 3 months, supporting the notion that with adequate support, exclusive breastfeeding can be achieved. The rate of transmission at 26 weeks in infants who were negative at 6 weeks was 4.04% and this in the setting of predominantly clade C virus, more likely to be transmitted perinatally than the A and D clades commonly encountered in other parts of Africa.

**WHO Infant Feeding Recommendations**

The WHO recommends that mothers known to be HIV-infected (and whose infants are HIV-uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complimentary foods thereafter, and ceasing breastfeeding only once a nutritionally adequate and safe diet without breast milk can be provided. Mothers known to be HIV-infected should only give commercial infant formula as a replacement feed to their HIV-uninfected infants or infants who are of unknown HIV status, when specific conditions are met: that replacement feeding is acceptable, feasible, affordable, sustainable, and safe (AFASS criteria).

WHO recommends that in all cases in which mothers choose not to breastfeed from birth or for any reason discontinue breastfeeding later, they should be provided with specific guidance and support for at least the first 2 years of the child’s life to ensure adequate replacement feeding. Because the cessation of breastfeeding is a time of increased risk to the infant in the form of increased transmission risk from mixed feeding and negative nutritional consequences from the withdrawal of this primary food source, WHO recommends that specific guidance and support be made available to mothers at the time of weaning, including specific assistance with avoiding malnutrition and poor breast health.
Quality Infant-Feeding Counseling and Support Is Critical
The quality of infant-feeding counseling given to mothers for whom replacement feeding is technically an option (such as in programs as Botswana’s and South Africa’s where free formula milk is available) must be improved. Deciding what the AFASS criteria mean in field operation is challenging, and some evidence suggests that more specific criteria should be applied when advising an HIV-infected woman on which choice of feeding strategy is best for her and her infant. Researchers in South Africa recently looked at factors that were associated with improved infant HIV-free survival among women choosing to formula feed in three sites across South Africa and found three such factors: piped water in the home; electricity, gas, or paraffin for fuel; and disclosure of HIV status. Of 311 women who met these criteria for formula feeding, 95 (30.5%) chose to breastfeed. Of 289 women who did not meet these criteria, 195 (67.4%) chose to formula feed. Infants of women who could have formula fed under these criteria were needlessly exposed to the risk of HIV infection. Even worse, infants of women who chose to formula feed without fulfilling the criteria had the highest risk of HIV transmission and/or death, with a hazard ratio of 3.63. Including an assessment of individual and environmental criteria in support of appropriate infant feeding choices when counseling mothers may improve the operational effectiveness of the WHO’s infant feeding guidelines.

What AFASS Criteria Should Mean in the Field
Recently, in Rapid Advice on HIV and Infant Feeding: Revised Principles and Recommendations, November 2009, WHO clarified in “everyday language” what AFASS criteria should mean in the field. This is summarized in Table 4.

Other Options for Infant Feeding
WHO lists other infant feeding options, including home-modified animal milk and heat-treated breast milk, as interim feeding methods appropriate for some instances.

For heat-treated breast milk, WHO lists two heating methods: direct boiling and pasteurization. Both options, however, are problematic. Direct boiling causes significant degradation of breast milk’s nutritional properties, whereas the pasteurization method commonly used in breast milk bank centers requires temperature gauges and timing devices not typically available in many resource-limited communities. Flash-heating, a simpler pasteurization method that is technically more feasible for resource-limited communities than traditional pasteurization, was recently studied in a cohort of HIV-positive mothers in a periurban settlement in South Africa. In this study, detectable HIV was found in the breast milk samples of 26 (31%) of 84 mothers. After flash-heat treatment all samples showed undetectable levels of cell-free HIV. With the simplicity of flash-heat treatment of breast milk, it has been suggested as an option for use during times of increased transmission risk, as during episodes of mastitis or during the transition from exclusive breastfeeding to replacement feeds or the addition of complementary foods. Flash-heat-treated breast milk retains breast milk’s nutritional and immunologic properties, critical elements lost by (boiled) animal milk is sometimes the only economically viable milk-based nutritional option for these mothers (although it is not recommended for infants less than 6 months of age). Many mothers have access to animal milk at a fraction of the price of formula or can access it for free because of animal ownership. In such situations, boiled animal milk may be utilized as part of a diet providing adequate micronutrient intake.

Table 4. Conditions needed to safely formula feed

| 1. Safe water and sanitation are assured at the household level and in the community, and, |
| 2. The mother or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant, and, |
| 3. The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhea and malnutrition, and, |
| 4. The mother or caregiver can, in the first six months, exclusively give infant formula milk, and, |
| 5. The family is supportive of this practice, and, |
| 6. The mother or caregiver can access health care that offers comprehensive child health services |
infants during weaning and necessary until the infant has established adequate replacement feeding.

ARV Drugs for Preventing HIV Transmission During Breastfeeding

Much recent attention has been given to other means of reducing the risk of mother-to-infant HIV transmission during lactation. Results from studies carried out in breastfeeding populations (HIVNET 012, PETRA, SAINT) have demonstrated efficacy in reducing MTCT without a reduction in maternal viral load (i.e., a prepartum course of ARVs of sufficient length). However, the regimens used in these studies did not address prevention of late breastfeeding transmission after the first few weeks of life—transmission described earlier to be a significant contributor to overall MTCT in breastfeeding populations.

Other interventions that do potentially address late breastfeeding-associated transmission of HIV, including prophylactic ARV administration to the uninfected infant during breastfeeding and the administration of HAART to mothers while breastfeeding, have been well-studied. Animal data from newborn macaques demonstrate the efficacy of tenofovir in preventing experimentally-induced simian immunodeficiency virus (SIV) infection, including when very high SIV doses and doses of partially tenofovir-resistant SIV were given.

Additional information on the efficacy of ARVs administered during breastfeeding in preventing breastfeeding-associated MTCT of HIV comes from several sources, including the Mashi trial and several extended NVP studies in breastfeeding infants.

Mashi Trial

Conducted in Botswana, the Mashi trial was a randomized 2 × 2 factorial clinical trial for HIV-infected pregnant women and their infants. It was designed to compare interventions for both preventing perinatal HIV transmission and reducing postnatal HIV infection and mortality. The postnatal portion of Mashi compared the efficacy and safety of breastfeeding plus infant ZDV prophylaxis for 6 months to formula feeding from birth plus 1 month of infant ZDV. A total of 1179 infants were studied, and points evaluated were HIV infection by age 7 months and HIV-free survival by 18 months. The study also evaluated safety in the form of occurrence of infant adverse events by 7 months of age. The 7-month HIV infection rates were 5.6% in the formula-fed group and 9.0% in the breastfed-plus-ZDV group (p = 0.04). Cumulative mortality or HIV infection rates at 18 months were 13.9% formula fed and 15.1% breastfed plus ZDV (p = 0.60). Infant mortality at 7 months was significantly higher for the formula-fed group (9.3%) versus the breastfed-plus-ZDV group (4.9%; p = 0.003), but this difference faded after 7 months to where time-to-mortality distributions through age 18 months were not significantly different. Conclusions of the Mashi trial were that breastfeeding with ZDV prophylaxis for 6 months was not as effective as formula feeding in PMTCT but was safer in the short term (to 7 months). Both strategies had comparable HIV-free survival at 18 months. Given the significant number of infant HIV infections that occurred after 1 month of age in the breastfed-plus-ZDV group compared with the formula-fed group, the study authors concluded they could not recommend extended infant ZDV prophylaxis for prevention of breastfeeding-related MTCT, despite the intervention being shown to be feasible.

Extended Nevirapine Regimens for Breastfeeding Infants

Recent work from sub-Saharan Africa and India has demonstrated that an extended course of NVP given to breastfeeding infants reduces both breastfeeding-associated HIV transmission and infant mortality when compared with Sd-NVP regimens, while demonstrating comparable safety.

Between 2001 and 2007, the SWEN studies enrolled nearly 2,000 mother-infant pairs in three coordinated studies in Ethiopia, India, and Uganda. When compared with infants receiving the local standard of care (Sd-NVP to mother during labor and to infant shortly after birth in all three settings), infants receiving the study regimen of Sd-NVP (2mg/kg) shortly after birth plus a daily dose of NVP (5mg) from days 8 to 42 (previous studies having shown that Sd-NVP shortly after birth protects against breastfeeding-associated HIV transmission for several days) had significantly lower combined rates of HIV infection or death at both 6 weeks (3.7% versus 6.4%) and 6 months of life (8.0% versus 11.0%).

A separate study, performed in Malawi (PEPI-Malawi) and having enrolled 3,276 mother-infant pairs between 2004 and 2007, investigated whether a 14-week course of NVP (2mg/kg/day during second week of life, then
4mg/kg/day during weeks 3-14) alone or in combination with ZDV could reduce HIV transmission and death in breastfeeding infants of HIV-infected mothers more than Malawi’s current standard of care for infants of Sd-NVP plus 1 week of ZDV. The combined rate of HIV infection or death for infants receiving the standard of care was 10.6% at 9 months, compared with 5.2% for extended NVP alone and 6.4% for extended NVP plus ZDV.

As a result of the data derived from extended infant NVP studies, WHO recently endorsed extended courses of NVP for breastfeeding infants, as detailed in Table 3.

**HAART to Mothers During Breastfeeding**

Another approach to reducing breastfeeding-associated MTCT of HIV involves administering ARVs to HIV-infected mothers during breastfeeding. It is logical that for an infant to become infected via breast milk there must be HIV present in the breast milk the infant consumes. Mothers with advanced clinical stage, lower CD4 counts, and higher serum viral loads have higher breast milk viral loads, and there is a well-demonstrated propensity for MTCT to be related to these factors. Data from the DREAM project in Mozambique discussed earlier show that in women receiving HAART (zidovudine, lamivudine, and nevirapine) from as early as 28 weeks gestation to 1 month postpartum, breast milk viral loads were significantly lower than in a comparison group of untreated women (2.3 log versus 3.4 log at delivery and 1.9 log versus 3.6 log at day 7). In this study, breast milk levels of ARVs were the same or higher than serum levels. Whether this or the reductions seen in breast milk HIV RNA would be similar with other ARV regimens is not known.

The DREAM project looked further at whether providing HAART during breastfeeding (in mothers who otherwise would not have qualified for HAART on the basis of clinical stage or CD4 count) was associated with a reduction in MTCT. In a Mozambican cohort studied between 2005 and 2006, women (otherwise nonqualifiers for HAART) receiving HAART from as early as the 25th week of pregnancy through up to 6 months of breastfeeding were compared with a cohort of women with similar characteristics who also received HAART similarly but chose to formula feed. Endpoints evaluated were HIV MTCT rates, infant morbidity, and mortality. At age 1 month 4 (1.2%) of 341 breastfed infants had contracted HIV, whereas 7 (0.8%) of 809 formula-fed infants had contracted HIV. At age 6 months, HIV transmission rates were 2 (0.8%) of 251 among breastfed infants and 15 (1.8%) of 809 among formula-fed infants, a difference that was non-statistically significant (p = 0.38). Nutritionally, both cohorts did better than the general infant population, as reflected by greater observed Z scores (a measure of nutritional status) in the study populations versus the general infant population. Rates of anemia were also lower than in the general infant population. Mortality rates, too, were lower than the general Mozambican infant population (101 per 1000 person-years): at age 6 months were 27/1000 person-years among formula-fed infants and 28.5 per 1,000 person-years among breastfed infants. Key conclusions of this study were that providing HAART to mothers in the third trimester and during breastfeeding was both safe and efficacious, with MTCT rates comparable to those seen in high-income countries and no additional risk of late postnatal HIV transmission to the infant by age 6 months.

WHO has recently endorsed the use of maternal triple ARV prophylaxis during breastfeeding, as outlined in Table 3. Indeed, where such strategies are available to breastfeeding mothers, WHO recommends continuing breastfeeding for up to 12 months, including after introduction of complementary foods when infants turn 6 months.

**INEFFECTIVE PMTCT APPROACHES**

**Vaginal Cleansing**

In resource-limited settings, where cost, personnel, and other logistic factors inhibit the scaleup of effective testing/ARV-based interventions, there has been much interest in low-cost, safe, and simple interventions that may be either used alone or in concert with ARV-based approaches to PMTCT. One such method that has been studied is the use of vaginal disinfection. Early studies confirmed the safety of disinfection of the vagina with aqueous chlorhexidine during labor, and the procedure was subsequently shown to reduce neonatal morbidity and mortality caused by Group B streptococci. In vitro, chlorhexidine at a concentration of 0.2% inactivates HIV-1.

A study in Malawi looked at whether vaginal cleansing with 0.25% chlorhexidine solution every 4 h during labor and washing the baby with chlorhexidine at birth was associated with a reduction in MTCT. Whereas global
MTCT was not affected by the procedure, in a subset of women with time since rupture of membranes greater than 4 hours, MTCT was significantly lower.

Whereas the Malawi study was performed using cotton wool soaked with chlorhexidine, a study in Kenya repeated the Malawi protocol with slight modifications. Disinfection was carried out every 3 h and via lavage rather than cotton wool sponging. This approach yielded no difference in either rates of global MTCT or intrapartum MTCT. A similar approach using benzalkonium chloride also failed to show a reduction in MTCT.

**Vitamin Supplementation**

Maternal nutritional factors may play a role in MTCT. Several studies have evaluated the contribution of maternal micronutrient levels, particularly vitamin A, to transmission risk. Vitamin A plays a key role in maintaining the surface integrity of the mucosa, and vitamin A deficiency is associated with immunologic alterations, including diminished CD4+ cell number and function. A study in Durban, South Africa, examined whether vitamin A supplementation was associated with reduced MTCT. Women were randomized to receive either vitamin A supplements or a placebo. The two groups showed no difference in the risk of HIV infection by 3 months of age. There was also no difference in overall fetal mortality. However, there were significantly fewer preterm births in the vitamin A group than in the group that received the placebo. Also, among the women who had preterm deliveries, those assigned to the vitamin A group were less likely to transmit HIV than those assigned to the placebo group.

Two other studies from Africa, looking at either vitamin A or multivitamin supplementation, have confirmed these findings. None of the three studies showed that vitamin supplementation was effective in reducing overall MTCT. However, all three showed that vitamin supplementation reduced adverse pregnancy outcomes. Multivitamin supplements are inexpensive and easy to administer and are recommended for HIV-infected pregnant women.

In one study carried out in a periurban South African setting, maternal multivitamin use was significantly correlated with increased levels of HIV RNA in the mothers’ breast milk. The clinical significance of this finding is not clear, but to date there have not been reports of maternal multivitamin use being linked to increased rates of breastfeeding-associated MTCT. Most clinicians recommend continuing to supplement lactating mothers with multivitamins, particularly given the well-credited nutritional stress that breastfeeding puts on mothers.

**HIV-2**

Throughout this chapter, when we have used the term “HIV,” we have generally referred to HIV-1. HIV-1 is far more common and geographically distributed than HIV-2, and most study data cited here refer to HIV-1. Yet HIV-2 infection also has consequences, and PMTCT of HIV-2 deserves special commentary.

Although transmitted in the same manner as HIV-1, data indicate HIV-2 to be much less transmissible from mother to child. Among breastfed infants and without any interventions, HIV-2 has rates of MTCT in the 0%-4% range. HIV-2 is endemic in West Africa, where testing for both HIV-1 and HIV-2 is recommended for PMTCT programs. A key feature of HIV-2 as relates specifically to PMTCT regimens recommended by the WHO for HIV-1 in resource-limited settings is that NNRTI drugs, including nevirapine, are not effective against HIV-2. HIV-2 may progress to AIDS in a similar fashion to HIV-1, although typically progression is much slower. When a woman living with HIV-2 infection requires HAART for her own health, a regimen of triple NRTIs is recommended rather than an NNRTI-based regimen (using nevirapine or efavirenz), because HIV-2 is inherently resistant to NNRTIs. Similarly, when a pregnant woman does not meet HAART treatment criteria for her own health she should be provided with ARV prophylaxis against MTCT.

The recommended regimen for ARV prophylaxis against MTCT in HIV-2-infected women is ZDV starting at 28 weeks’ gestation or as soon as is feasible thereafter and ZDV during labor. Because no nevirapine is given during labor (because of NNRTIs’ inherent inactivity versus HIV-2), the mother does not need ZDV and 3TC during labor, nor does she need the postpartum course of ZDV plus 3TC given to HIV-1-infected mothers who receive SD-NVP to prevent NNRTI resistance. Infants born to HIV-2-infected mothers should receive ZDV for 7 days after birth. WHO recommendations for infant feeding in the presence of maternal HIV-1 infection also apply in the presence of HIV-2 infection. In women coinfected with both HIV-1 and HIV-2, the recommendations detailed
for PMTCT in the presence of HIV-1 infection should be followed; HIV-1 is much more likely to be transmitted from mother to child than HIV-2 (Table 5).

**WHO PMTCT Component 4: Care, Treatment, and Support for Mothers Living With HIV, Their Children, and Families**

Traditionally, PMTCT has been focused on component 3 of the WHO four-component strategy—the prevention of transmission from mothers living with HIV to their children. As well, until recently PMTCT programs did not offer mothers much beyond these interventions. Yet it is well appreciated that the longitudinal health of a mother directly affects the health and survival of her child—HIV infected or not. Providing care, treatment, and support for mothers and their families after component 3 interventions, therefore, is critical to the ultimate goal of PMTCT: an HIV-free generation with a significant reduction in the number of children orphaned as a result of HIV/AIDS.

The concept of a continuum of care for maternal, newborn, and child health has been discussed in many forums and settings over the past recent years. Studies have suggested that high utilization and quality of essential packages of integrated, continuum-focused services could avert up to two-thirds of child and neonatal deaths in 60 priority countries worldwide, as well as assist major reductions in maternal mortality. Included in these proposed packages of services is a comprehensive approach to PMTCT, including linkages from prevention of HIV infection through diagnosis, PMTCT, to infant diagnosis and family-based HIV/AIDS care and treatment.

Indeed, for HIV-infected women, PMTCT programs offer an ideal opportunity to link diagnosis and PMTCT services with ongoing, longitudinal care. Although health systems are weak in many of the locales that have the highest prevalence of HIV, up to 70% of women in these locales attend at least one ANC visit. Using this encounter—possibly the only one a woman may ever make with the health system—as an opportunity to establish a longitudinal, family-based relationship with the mother is critical.

Opportunity exists for making PMTCT services a gateway for HIV-infected women and their families to longitudinal, comprehensive HIV care and treatment. Where this has been accomplished, even in part, evidence suggests a tangible benefit to global PMTCT success. In South Africa's Western Cape, all HIV-infected women identified via the province’s PMTCT program are stratified into “treatment” or “prophylaxis” groups by clinical stage and CD4 count, as described earlier. Treatment groups are fast-tracked to HAART initiation via a linkage to ART services provided by the PMTCT program. This linkage, and the more effective care provided through it, with less loss to follow-up than when the referral to ART is nonlinked, adds approximately 6%-8% to overall PMTCT efforts in the province and facilitates the entry of women into long-term HIV treatment. This approach can be key in obtaining good outcomes: for both adults and children, late entry into care is associated with poorer outcomes in response to HAART.

**Family-Based Care**

However, even in this improved system there is significant loss to follow-up because mothers still must move from one site (PMTCT clinic) to another (ART clinic). To combat this, cutting-edge models such as those created in Africa by MSF, ICAP, and BIPAI, among others, have begun to show the feasibility of offering longitudinal family-based care with mothers identified as HIV-positive during ANC screening as their index cases. Especially when such care can be delivered in one setting, even more so all family members together during one visit, rates of uptake of HIV/AIDS diagnosis, prevention, and care and treatment services can be maximally affected on a family- and community-wide basis. Particularly for HIV-infected children, a family-based approach may realize improved access to care-and-treatment services and reduce the risk of defaulting from care than if parents’ and children’s services are delivered separately. Indeed, there is growing

### Table 5. PMTCT considerations in the presence of HIV-2 Infection

<table>
<thead>
<tr>
<th></th>
<th>Maternal ART indicated</th>
<th>Maternal ART not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum</td>
<td>AZT+3TC+ABC</td>
<td>AZT starting at 28 weeks gestation or as soon as feasible thereafter</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>AZT+3TC+ABC</td>
<td>AZT</td>
</tr>
<tr>
<td>Postpartum</td>
<td>AZT+3TC+ABC</td>
<td></td>
</tr>
<tr>
<td>Infant</td>
<td>AZT x 7 days</td>
<td>AZT x 7 days</td>
</tr>
</tbody>
</table>
sentiment that, on the whole, PMTCT programs in resource-limited settings will ultimately not be able to duplicate the success seen in better-resourced settings without a successful merging of specific mother-child strategies with longitudinal care and treatment services.

**Scaling Up**

The recently released Guidance to Global PMTCT Scale-up promotes a country-targeted approach to reaching universal access to services. Key in the Guidance is the above-mentioned integration of all four components of the WHO PMTCT strategy into a comprehensive, longitudinal model of care.

The Guidance urges international coordinating bodies, such as WHO, UNAIDS, and UNICEF; national governments; and integral international nongovernmental organization partners (of which BIPAI is one) to work together in a common strategy to realize soon universal access to PMTCT services worldwide, on the way to an AIDS-free generation by 2015.

The Guidance offers 10 guiding principles in this regard:

1. Urgent scaleup to achieve national coverage and universal access
2. Country ownership and accountability
3. Emphasizing the participation of people living with HIV and communities
4. Strong, coordinated, and sustained partnerships
5. Aiming for both effectiveness and quality
6. Delivering a comprehensive package of services based on the United Nations four-element strategy, including links between services and integration with maternal, newborn, and child health services
7. Giving priority to providing ARV therapy for treating eligible pregnant women
8. Family-centered longitudinal care
9. The importance of male involvement
10. Improving maternal and child survival

**Conclusion**

The benefits of PMTCT are both obvious and substantial. Well supported with evidence and experience, PMTCT interventions offer an opportunity to significantly reduce the scope of the pediatric HIV pandemic. Extending the success seen in resource-rich settings to resource-limited locales is both a necessary and urgent ethically sound goal. PMTCT interventions do not exist in isolation from one another. Scaleup of the integration of all four components of the WHO approach into a family-based longitudinal care model offers the best opportunity for realizing the promise that PMTCT offers to individuals, families, and communities around the globe.

**References**

PMTCT timeline

<table>
<thead>
<tr>
<th>20 weeks</th>
<th>22 weeks</th>
<th>24 weeks</th>
<th>28 weeks</th>
<th>40 weeks</th>
<th>Birth to 4 week postpartum</th>
<th>Birth to 12 months postpartum</th>
<th>Ongoing longitudinal care and treatment for mother and affected family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient presents to ANC for voluntary care and testing and then draw CD4</td>
<td>Encourage disclosure, readiness for ART, start cotrimoxazole and multivitamins</td>
<td>Review CD4 results with patient—decide on HAART versus ARV prophylaxis</td>
<td>Start either HAART or ART prophylaxis</td>
<td>At onset of labor—HAART continues versus ART prophylaxis regimen; Delivery of newborn with safe delivery practices</td>
<td>Postpartum ART for mother and baby</td>
<td>Postpartum infant feeding counseling</td>
<td>Lifetime</td>
</tr>
</tbody>
</table>

This timeline presents the ideal for PMTCT: Early recognition of HIV-positive status, early evaluation of CD4 and decision as to HAART versus ARV prophylaxis as well as intrapartum, postpartum, and longitudinal care for mother, infant, and family. A key message is the realization that a delay in initiating the timeline (diagnosis of HIV positive, entry of mother into PMTCT services) delays all subsequent events. As the text of the chapter notes, ideally mothers receive at least 4 weeks of ART prior to delivery. This goal becomes difficult to achieve—and PMTCT efficacy suffers—when the initiation of the timeline is delayed.


72. HIV Prevention Trials Network. HPTN 046: Phase III Trial to Determine the Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV Infected Women to Prevent Vertical HIV Transmission During Breastfeeding.


Objectives

1. Review the factors associated with the sexual transmission of human immunodeficiency virus (HIV).
2. Evaluate the risk factors related to the sexual transmission of HIV.
3. Address the importance of safer-sex education.
4. Analyze key components of a successful prevention program to stop sexual transmission of HIV.

Overview

Sexual intercourse is the major route of transmission of human immunodeficiency virus (HIV) throughout the world. Although we maintain hope that an effective anti-HIV treatment or vaccine will be made available on a wide scale in the future, a cure or vaccine for AIDS is unlikely within the next several years. Therefore, prevention remains the most realistic strategy for slowing the HIV pandemic. The power of preventive interventions makes it theoretically possible to eradicate HIV from the planet. If everyone who is currently infected with HIV did not transmit it to anyone else, the virus would burn out and disappear. Thus it is vitally important to design, implement, analyze, and continually improve our prevention efforts. This module reviews facts about the sexual transmission of HIV. These include risk factors for sexual transmission of the virus and specific interventions known to be effective in reducing its spread. This module also provides evidence that prevention programs can be effective and describes essential elements found in most successful interventions.

Risk Factors for Sexual Transmission

The precise risk of HIV transmission from one act of sexual intercourse is not known. Whereas some people have had multiple sexual contacts with an infected person without acquiring HIV, others have become infected from one sexual encounter. Repeated intercourse with an HIV-infected person increases the risk of infection. The risk of becoming infected with HIV as a result of sexual intercourse depends on the following:

- Probability that the sexual partner is infected
- Number of sexual partners
- Type of sexual contact involved
- Amount of virus present in the blood or secretions of the infected partner

Key Points

1. HIV can be transmitted through exposure to any of four body fluids: blood, semen, vaginal fluids, and breast milk.
2. Sexual intercourse is the major route of transmission throughout the world.
3. Prevention of transmission is the most realistic strategy for slowing the HIV pandemic.
4. To sustain a sexually transmitted pandemic, an individual must have unprotected sex with at least two partners, becoming infected by one and passing the infection on to at least one other.
5. The presence of another sexually transmitted infection may increase the risk of HIV transmission.
6. Safer-sex practices reduce the risk of acquiring HIV.
7. Correct and consistent use of latex condoms during sexual intercourse can greatly reduce the chances of acquiring or transmitting HIV.
8. Even when both partners are infected, latex condoms should still be used to prevent transmission of different strains of HIV.
9. Evidence suggests that male circumcision can reduce the chances that a man will acquire HIV during a sexual encounter.
10. Combination prevention should be encouraged as the risk-reduction standard.
Presence in either partner of other sexually transmitted infections (STIs) and/or genital lesions, which increase the risk of HIV transmission

**Probability that Sexual Partner Is HIV Infected**
The prevalence of HIV infection among sexually active people varies in different areas and among population subgroups within each area. The extent to which HIV spreads between groups with high-risk behavior and the larger population depends on whether members of those high-risk groups have sex with people who do not share their high-risk behaviors and on whether condoms are used in those sexual encounters. For example, a married man who has sex with a sex worker is engaging in a high-risk behavior. If that man also has sex with his wife without a condom, the wife is at risk of acquiring HIV. If the wife becomes HIV infected, she may pass the virus to the couple’s children during pregnancy, birth, or breastfeeding. This is an example of how HIV spreads from high-risk groups into the general population. As infection rises in the general population, so does the likelihood of encountering an infected person early in one’s sexual career.

To help sustain a sexually transmitted pandemic, a person must have unprotected sex with at least two partners, becoming infected by one and passing the infection on to at least one other. In fact, because not every encounter between an HIV-positive and an HIV-negative partner results in a new infection, a sustained heterosexual pandemic suggests that a substantial proportion of the population, both male and female, have several sexual partners over their lifetimes. The risk of acquiring HIV from each sexual encounter depends, in part, on the likelihood that the partner is infected. This risk varies based on regional HIV prevalence rates and the type of risk behavior of each potential partner.

**Number of Sexual Partners**
The probability that a person has acquired an STI is, in general, proportional to the number of sexual partners that person has had in recent years. However, in areas where the prevalence of HIV is high, people may become infected who have had only one partner. This fact was illustrated in a study done to determine behavioral and demographic risk factors for HIV infection in Rwanda. Infection rates were higher among women who were single and reported more than one lifetime sexual partner. Women in legal marriages or monogamous partnerships had lower rates of infection, but even among low-risk women, the prevalence of HIV was about 20%. For most of these women, a steady male partner was the source of their HIV risk.

In places where efforts to reduce HIV prevalence have been successful, reducing the number of sexual partners has been a consistent element of prevention programs. Partner reduction was a key factor in the drop in HIV transmission in the homosexual populations of the United States and Europe in the mid-1980s. Community education and a dramatic reduction in the number of gay bathhouses (where men often met for casual sex) were strategies that limited the spread of HIV. Partner reduction is also credited for the drop in HIV prevalence in Uganda in the 1990s. Slogans such as “zero grazing” (faithfulness to one partner) and “love faithfully” were an important part of Uganda’s early response to HIV.

**Type of Sexual Contact Involved**
All types of sexual intercourse carry a risk of HIV transmission. Although existing data suggest differences in the relative risks of various types of intercourse, the precise level of risk associated with each is not known. Trauma to the mucous membranes of the rectum or vagina may make transmission of HIV more efficient, but it is not essential for transmission to occur. The highest risk of HIV infection occurs among women and men who engage in receptive anal intercourse with an infected partner. Vaginal intercourse carries a higher risk for men and women than oral sex.

Sexual intercourse refers to penetration of the penis into an orifice: vagina, rectum, or mouth. Sexual behavior is any act of sexual gratification, whether between two or more individuals or by oneself. Sexual intercourse is a risk behavior for acquiring HIV and other STIs, but not all sexual behaviors promote risk. Sexual behavior in which the exposure of infectious body fluids is minimized, such as intercourse using a condom, is considered risk reduction, or safer sex. Sexual practices with no exposure or exchange of infectious body fluids are considered prevention, or safe sex. These include but are not limited to hugging, dry kissing, masturbation, and frottage (rubbing).

HIV can be transmitted through exposure to blood, semen, vaginal fluids, or breast milk. Any activity that
directly exposes a person to any of these body fluids is risky.

**Amount of Virus Present in Blood or Secretions of the Infected Partner**

A person infected with HIV remains infectious throughout their or her lifetime and may transmit the virus sexually at any time or stage of disease. Although a person may be tested for HIV infection, screening alone will not prevent transmission because an HIV-infected person may transmit the virus for a period of time before the infection can be detected. The period between initial infection and detection of the virus by such means as PCR (polymerase chain reaction) is called the "eclipse period," and the period between initial infection and the time antibodies are detected is referred to as the "window period." An HIV-infected person is infectious during both the eclipse and window periods regardless of diagnosis of infection. This is an important aspect of prevention that underscores the need for consistent risk reduction behaviors even if a partner appears healthy and their or her HIV status is negative.

HIV-infected individuals are believed to become more infectious if newly infected (during the acute retroviral period) or as they progress to AIDS. In theory, those who have fewer particles of virus circulating in their bodies have fewer particles of virus to pass to their partners during unprotected sex. However, even newly infected persons who show no overt signs of immune compromise can transmit HIV infection. Also, they are more likely to have many sexual partners than are people who have clear symptoms of disease. Mathematical models suggest that the primary HIV infection interval—the time before an infected person shows symptoms of HIV—may account for as many as half of all infections. If this is true, the primary infection interval presents a special window within which it is possible to have a major effect on the spread of HIV.

**Presence of Other STIs**

There is increasing evidence that the presence of another STI in one or both partners increases the risk of HIV transmission. Genital ulceration, such as may occur with chancroid, syphilis, or herpes simplex virus infection, appears to increase susceptibility to infection. This may be because blisters, small tears, and other openings in the mucosal lining of the vagina or on the skin of the penis provide a portal that allows HIV to enter the body.

**Prevention of Further Sexual Transmission Within the HIV-Positive Population**

This module focuses on prevention of sexual transmission of HIV from an infected partner to an uninfected partner. However, even if both partners are infected, condoms still should be used to prevent further transmission. There are different types (strains) of HIV, and partners infected with different types might infect each other. Some researchers believe that certain types of HIV may be stronger and inflict more damage on the immune system than others. Reinfection occurs when a person gets more (different) HIV types in his or her system. If partners have different treatment histories with antiretroviral medications, medication-resistant strains could be transmitted from one partner to another. Safer-sex practices such as condom use help protect against reinfection. They also protect against other STIs, such as hepatitis, syphilis, gonorrhea, parasites, and herpes.

**Safer-Sex Education**

A person can take certain actions to reduce the risk of acquiring HIV. Education about these actions is an essential element of every successful prevention campaign. Everyone must be made aware of how to avoid acquiring HIV and must be empowered to act on that information. The following concepts are widely known as the elements of ABC prevention campaigns.

**ABC Prevention Campaign Elements**

**Know Your Status.** This element encourages individuals to seek voluntary counseling and testing (VCT) services in order to access personal risk and determine their HIV status and is considered by many as a prerequisite to
Abstinence. Refraining from sexual intercourse is the best way to prevent transmission of HIV and other STIs. Abstinence means not engaging in any sexual activity in which there is a direct or theoretical risk of exposure to blood, semen, or vaginal fluid.

Be faithful. If two partners are tested for HIV and found to be uninfected, they may enter into a strictly monogamous sexual relationship, and neither will be at risk of contracting HIV infection sexually. However, if one partner engages in sex with a third party, even one time, both partners are at risk of acquiring the virus. Monogamy works as a prevention strategy only if both partners are known to be uninfected when their sexual relationship begins and if neither partner has sex, even one time, outside this relationship.

Condoms. Correct and consistent use of latex condoms during sexual intercourse (vaginal, anal, and oral) can greatly reduce the chances of acquiring or transmitting HIV and other STIs. Natural-membrane condoms, often made from sheep gut, are not recommended, because they have tiny pores through which HIV can pass.

“Consistent use” means using a condom with each act of intercourse. Correct condom use involves all the following steps:

- Use a new condom for each act of vaginal, anal, or oral intercourse.
- Always check the expiration date on the condom package. Discard expired condoms.
- Put on the condom as soon as erection occurs and before any vaginal, anal, or oral contact with the penis.
- Hold the tip of the condom and unroll the condom onto the erect penis, leaving space at the tip of the condom but ensuring that no air is trapped in the tip.
- Adequate lubrication is important to prevent condom breakage, but use only water-based lubricants, such as glycerin. Oil-based lubricants, such as petroleum jelly, cold cream, hand lotion, and baby oil, can weaken the condom.
- Withdraw from the partner immediately after ejaculation, holding the condom firmly at the base of the penis to keep it from slipping off.
- Dispose of condoms after each and every use. Never reuse or share a condom.

The promotion and supply of condoms should be viewed as specific disease-control measures. Condoms should not be seen merely as contraceptives or as associated with a particular social or sexual lifestyle.

Common myths about condom use include the following:

- Condoms don’t work: If used correctly and consistently (during every sexual encounter), latex condoms are highly effective in preventing transmission of HIV and other STIs.
- Condoms often break: Condom breakage is extremely rare when condoms are used correctly. Using oil-based lubricants can weaken latex, causing the condom to break.
- HIV can pass through condoms: Intact latex condoms provide a barrier to HIV and much smaller microorganisms, such as hepatitis B. Natural-membrane condoms, often made from sheep gut, have tiny pores through which HIV can pass, so they are not recommended.
- Education about condom efficacy promotes sexual activity: The World Health Organization (WHO) reviewed 19 studies and found no evidence that sex education programs increased sexual activity among young people. In fact, five of the studies showed that such programs can lead young people to delay or decrease sexual activity.

Postponement

Another potentially powerful prevention message is postponement. Postponement means delaying intercourse until two partners are tested and found to be uninfected. Postponement is an empowering concept, especially for young people, for whom abstinence may have an “eternal” or “forever” connotation.

Microbicides

Microbicides are substances that are designed to block the transmission of or inactivate HIV when applied vaginally or rectally prior to intercourse. The advantage of such agents is that they are receptive partner controlled and could be used by both men and women. The ideal microbicide would...
1. come in many forms (e.g., cream, gel, suppository, films, lubricants),
2. prevent other STIs,
3. have both contraceptive and noncontraceptive forms,
4. be stable at tropical temperatures,
5. be nonteratogenic (not causing birth defects),
6. be compatible with latex,
7. be inexpensive,
8. be easy to use, and
9. be accessible to all.

To date, however, microbicides are still under development and have not yet been found to be effective in preventing the transmission of HIV or other STIs. Recent trials studying the microbicidal effects of a detergent with antifertility activities (cellulose sulfate) were discontinued by an independent data monitoring committee because preliminary results suggested a potential increased risk of HIV in women who used the compound. There has been no further explanation for why cellulose sulfate was associated with a higher risk of HIV infection than placebo. Previous studies with the use of a spermicidal compound containing nonoxynol-9 also demonstrated an increased risk of HIV acquisition, but this was postulated to be due to the vaginal irritation associated with its use. This does not appear to be the case with cellulose sulfate because colposcopy, evaluation of the microflora, and the assessment of inflammatory cytokines did not demonstrate genital irritation after 6-14 days or at 6 months of use. According to a review of microbicide drug candidates by the WHO, many candidate compounds are still under development and evaluation. There are possibilities that first-generation microbicidal products could be available by 2009. If they fail, second-generation products could become available by 2012.

**Male Circumcision**

There is now evidence from three randomized, controlled clinical trials conducted in Kenya, Uganda, and South Africa that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%. These results support long-term observations of a lower prevalence of HIV infection in countries where male circumcision is most commonly practiced. There are several factors that may contribute to the biologic basis for this finding. First, the foreskin of the penis has a more dense concentration of certain cells (called Langerhans cells) that are known to be more susceptible to HIV infection than other skin cells. Also, the foreskin may be more likely to get microscopic tears during intercourse that which could provide a “door” portal for HIV to enter the body. Third, HIV-containing secretions may stay in the retracted foreskin for a longer period of time after intercourse, which would increase the duration of exposure to the virus. Finally, there is also a higher prevalence of other sexually transmitted infections in non-circumcised men, and the presence of other STIs can increase the risk of acquisition of HIV. The evidence for a reduction of HIV acquisition risk in the context of male circumcision has led the World Health Organization to formally announce recommendations on male circumcision for HIV prevention. The WHO has stated that male circumcision should be a part of a comprehensive HIV prevention package. Of course, male circumcision services should be offered with full adherence to principles of basic humans rights, including informed consent, confidentiality, and absence of coercion. Male circumcision is an important aspect to a comprehensive integrated HIV/STI prevention campaign. It is an additive component and when included with the ABCs provides for an effective combination prevention spectrum of interventions.

**Female Condom**

The recent marketing of the female condom has generated considerable interest, especially among those who are allergic to latex. The female condom is made of polyurethane, not latex, so someone who is allergic to latex can use it without reaction. Although laboratory studies indicate that the device serves as a barrier to HIV, further research is needed to determine its effectiveness in preventing transmission of HIV. If a male condom cannot be used, consider using a female condom.

In settings with limited or no access to condoms (e.g., prisons and rural or remote areas), promoting “anything is better than nothing” with respect to risk reduction should always be encouraged. Helpful steps include limiting a person’s number of sexual partners, withdrawal prior to ejaculation, and abstaining from intercourse during menstruation.

**Preexposure Prophylaxis for HIV Infections**

Preexposure prophylaxis (PrEP) describes the use of antiretroviral treatments by HIV-seronegative people at
high risk for exposure to HIV in an attempt to prevent the infection. Limited animal data suggest that medications taken prior to and at the time of exposure can prevent the development of HIV infection. Individuals would therefore begin antiretroviral medications prior to the HIV exposure and continue the medications throughout the risk period. PrEP studies to date have been done using tenofovir alone or in a fixed-dose combination with emtricitabine (known as combo-PrEP). PrEP is one of the most promising HIV prevention methods currently being tested, but its safety and effectiveness are currently unknown. Many of the medical trials have been stopped because of ethical concerns such as exposing members of control groups to HIV. Also, there is concern that PrEP might provide people with a false sense of security, thereby encouraging risky sexual behavior. PrEP is not intended to be an alternative to condom use or other accepted preventive approaches. Although PrEP will not be able to rid the world of HIV, it will be widely used if its efficacy and safety are demonstrated because compared with vaccines or microbicides, these medications are currently widely available. This intervention will therefore require substantial resources and infrastructure support as well as continued medical education for users and providers.

“downhill phenomenon,” in which people always compare their own risk with that of someone who is at much greater risk. Doing so leads to an incorrect assessment in which the person sees himself or herself as being at lower risk for HIV than objective evidence would suggest.

- Most models of behavior change have been developed in North America and emphasize actions that an individual can take to reduce his or her risk of HIV infection. However, much of the world’s population lives in collectivistic rather than individualistic societies. In this context, the emphasis on and opportunity for individual behavior change are decreased.

- Those most exposed to HIV prevention messages often acquire “prevention fatigue.” In high-income countries, this phenomenon has been implicated in the rise of HIV-infection rates among risk groups who are well educated and well informed about HIV and HIV prevention.

- Myths about how to cure HIV exist in all parts of the world. There currently is no cure for HIV. One particularly damaging myth that is prevalent in southern Africa is that having sex with a virgin will cure a person of HIV infection. This myth is responsible for a growing epidemic of child sexual...
assault and rape. Having sex with a virgin will not cure HIV and will expose the virgin (often a child) to the infection.

- In developed countries where access to effective treatments has dramatically improved healthy survival rates, prevention efforts have been stymied by attitudes among risk subpopulations that there is a “cure.” This will be a challenge in other regions as populations see a marked improvement in health outcomes because of access to antiretroviral therapy.

**Aspects of Successful Sexual Prevention Interventions**

Stopping HIV transmission through behavior change is a complicated challenge, but data indicate that HIV prevention efforts can indeed work. Even modest gains through behavior change in key subpopulations (e.g., commercial sex workers and at-risk adolescents) can produce substantial gains for the entire population. In Uganda, reduction of HIV transmission through behavior change has been equivalent to a vaccine of 80% effectiveness. Aspects of successful HIV prevention campaigns include the following:

- **Education on how HIV is transmitted and how exposure to it can be minimized or eliminated** is a central element of all HIV prevention campaigns. Consistent and persistent education over time is important. Complicated behavior changes (such as those involving an person’s decision making regarding sexual practices) are unlikely after a one-time-only intervention. Because sexual behavior is private and many sexual behaviors meet with community disapproval, education must be provided for the entire population to reach all those at risk. Particular attention should be paid to adolescents and young adults, who are entering the age of sexual exploration.

- **Successful interventions are usually based on a clear understanding of the realities of target populations and involvement of members of those populations in the development of prevention efforts.** Support from the community is crucial. If HIV is so heavily stigmatized that people do not even discuss it, prevention interventions such as condom distribution are unlikely to be effective.

- **Interventions that emphasize clarity, simplicity, and feasibility for the target population have the greatest chance of success.** The concept of harm reduction is helpful in guiding feasible interventions. This concept emphasizes specific behaviors that can minimize risk when eliminating risk is not feasible. For example, if it is not feasible to shut down the industry of sex workers in a region, providing education and condoms to sex workers and their customers may minimize the number of cases of HIV transmission that occur.

- **Successful prevention programs often include training in interpersonal skills,** such as talking about sexual practices, discussing the avoidance of risks with a partner, and asserting personal preference in a sexual relationship (including abstinence from sex, nonpenetrative sex, or the use of condoms).

An example of a successful behaviorally based prevention model comes from Uganda. In Uganda, HIV prevalence nationally among pregnant women peaked in 1991 at 21.1% and by 1998 declined to 9.7%. By 2000, prevalence had declined further to 6%. Although population-based surveys show that there was an increase in the age of sexual debut and an increase in condom use during this period, this striking reduction in HIV prevalence is believed to be due largely to a decrease in the number of casual or nonregular sexual partners. From the beginning of the Ugandan HIV/AIDS pandemic, the government communicated a clear warning and prevention recommendation: AIDS, or “slim,” was fatal and required an immediate population response based on “zero grazing” (faithfulness to one partner). In addition to the government’s efforts, data suggest that social networks played a crucial role in information dissemination in Uganda. By 1995, 91.5% of men and 86.4% of women in Uganda were aware of AIDS as having infected or killed someone they knew. This finding suggests that credible communication of alarm and advice had taken root in discussions in social networks to a greater extent in Uganda than in neighboring countries. Furthermore, the communication process may have provided greater personal exposure to the fear-evoking consequences of the pandemic and thus catalyzed the process of behavior change.
Summary

This module provides educates and informs on the prevention of sexual transmission of HIV. Other modules go into more detail about issues such as counseling and common psychological responses to a positive HIV test result. The precise risk of HIV transmission from one act of sexual intercourse is not known. The risk of becoming infected with HIV as a result of sexual intercourse depends on several factors, including the number of sexual partners a person has, the presence of other STIs, and the type of sexual contact involved. Refraining from sexual intercourse with an infected partner is the best way to prevent transmission of HIV and other STIs. Correct and consistent use of latex condoms during sexual intercourse (vaginal, anal, and oral) can greatly reduce the chances of acquiring or transmitting HIV and other STIs. Finally, there is the encouraging fact that HIV prevention programs can indeed work. At this point, prevention is the most realistic strategy for slowing the HIV pandemic. Thus it is vitally important to design, implement, analyze, and continually improve our prevention efforts.

References

Standard Precautions and HIV Postexposure Prophylaxis in the Health Care Setting

Nancy R. Calles, MSN, RN, PNP, ACRN, MPH
Andreea C. Cazacu, MD

Objectives

1. Define standard (universal) precautions recommended by the World Health Organization (WHO) for protection against the transmission of infectious pathogens.
2. Review infectious versus noninfectious types of body fluids.
3. Describe examples of protective barriers that can prevent exposure to human immunodeficiency virus (HIV).
4. Evaluate the management of HIV exposure in the health care setting.
5. Explore options for postexposure management.
6. Review recommendations for follow-up and monitoring after exposure to HIV.
8. Treatment to reduce the risk of contracting HIV from the exposure depends on the risk of exposure and information about the exposure source.
9. Seroconversion later than 6 months after exposure is rare.

Key Points

1. WHO standard precautions recommend that all individuals be treated as if they were infected with HIV or other infectious pathogens.
2. Exposures that place health care workers at risk of infection include injuries, such as needle sticks, and contact of infectious fluids with mucous membranes or nonintact (cut or abraded) skin.
3. The most effective infection control measure that health care workers can perform is handwashing with soap and water before and after patient contact.
4. Precautions should be taken to avoid having the skin, eyes, and mucous membranes come into contact with blood.
5. Needles should never be recap, bent, or broken; they should be discarded into sealed, puncture-resistant containers.
6. Spills of blood or other infectious fluids should be cleaned while wearing gloves, using a solution of one part household bleach to 10 parts water.
7. When exposure occurs, the source patient and health care worker should be tested for HIV and for hepatitis B and C.

Overview

All health care workers—defined by the U.S. Centers for Disease Control and Prevention as all persons (employees, students, contractors, attending clinicians, public safety workers, or volunteers) whose activities include contact with patients or blood or other body fluids from patients in a health care or laboratory setting—should be taught how to practice infection control in all health care settings. Health care workers must be educated about appropriate measures to be taken if an exposure to a potentially infectious substance occurs. All health care settings should have a written plan of action that conforms to national policy for infection control, including counseling and follow-up for exposures. All health care workers should be made aware of the plan. One option for ensuring that all health care workers are aware of infection control measures is to make annual review of infection control policies mandatory for all health care workers.

Occupational exposure can occur in other settings other than the health care setting. Other settings in which exposure could occur include waste disposal, law enforcement, fire fighting, and prostitution. Non-occupational exposure can occur via sexual assault, via sharing of needles, and via pregnant women to her fetuses. This chapter will focus on occupational exposure to the human immunodeficiency virus (HIV) in the health care setting and will address the importance of following standard precautions when caring for individuals with HIV/AIDS.


**Standard Precautions**

The Centers for Disease Control and Prevention developed Universal Blood and Body Fluid Precautions, or universal precautions, in 1996 and included fluids containing blood. These precautions have been revised and now include all potentially infectious pathogens. The precautions are now called standard precautions. The World Health Organization also recommends using these precautions. The guidelines consider certain body fluids as potential sources of infection, whereas others are not considered infectious (Table 1). In general, any body fluid that contains visible blood is potentially infectious, but body fluids that do not appear to contain blood also may be infectious. These fluids include vaginal secretions, semen, pericardial fluid, pleural fluid, cerebrospinal fluid, amniotic fluid, peritoneal fluid, and synovial fluid. Noninfectious body fluids include tears, feces, urine, saliva, nasal secretions, sputum, vomit, and sweat. Health care worker exposure to breast milk is not considered a threat for HIV transmission, but gloves should be worn when breast milk is handled for an extended period, such as in a milk bank.

Exposures that most often put a health care worker at risk of infection include percutaneous injuries, such as needle sticks, or contact of infectious fluids with mucous membranes or nonintact skin. The risk of HIV transmission from a percutaneous exposure is very low, approximately 0.3%. The risk after a mucous membrane exposure is about 0.09%. Transmission of HIV from exposure to intact skin has not been documented. Studies suggest that several factors affect the risk of HIV transmission through percutaneous exposure: the amount of blood to which the person was exposed and the patient’s viral load and stage of disease. The risk of HIV transmission is higher if the health care worker is exposed to more blood through injury from a needle that has been in a vein or artery, or through a deep injury, or through a device that is visibly contaminated with blood. Exposure to the bodily fluid of a patient who has end-stage AIDS carries a higher risk of transmission because the patient will most likely have a high viral load. However, the presence of a low viral load cannot guarantee that transmission will not occur. HIV is fragile and will survive for only a short time outside the human body. According to studies, HIV can live for up to 1 day outside the body, but these studies used a large amount of virus. Thus, the survival time of the virus outside the human body seems to depend on the viral load of the person. Other factors that affect the viability of the virus outside the human body include conditions in the environment, such as temperature and chemicals.

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**Table 1. Infectious and Non-Infectious Body Fluids**

<table>
<thead>
<tr>
<th>Infectious Body Fluids</th>
<th>Non-Infectious Body Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>All body fluids containing visible blood</td>
<td>Tears</td>
</tr>
<tr>
<td>Vaginal secretions</td>
<td>Feces</td>
</tr>
<tr>
<td>Semen</td>
<td>Urine</td>
</tr>
<tr>
<td>Pericardial fluid</td>
<td>Saliva</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>Nasal secretions</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Sputum</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>Vomit</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>Sweat</td>
</tr>
</tbody>
</table>

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**Figure 1. Standard Precautions** Adapted from World Health Organization, Regional Office for the Western Pacific, Manila. HIV/AIDS Reference Library for Nurses: Infection Control. (1993):3,14.
How to Prevent Exposure

Exposure can be prevented through the use of standard precautions supplemented by simple infection control measures (Figure 1). The most effective infection control measure that health care workers can take is handwashing with soap and water or alcohol-based disinfectant products before and after all patient contact. For effective cleaning, the hands and forearms should be wet, and soap should be applied over all surfaces by using friction; they should then be rinsed completely of soap by using running water and dried with a paper towel. If paper towels are not available, a cloth towel that is laundered after each use can be used. Communal towels should never be used. If paper towels and cloth towels are not available, allow the hands and forearms to air-dry. Wet hands should not be dried on clothes. Soap bars can be used but should be cut into small pieces and put into soap dishes that allow water drainage. When running water is not available, hands can be washed using soap and a clean bowl of water and then rinsed using a clean water source that is poured from a cup or bucket over the arms and forearms. The water in the bowl should be discarded after each use, and the bowl should be washed. An alcohol-based hand rub can be prepared by combining 2 mL of glycerin, propylene glycol, or sorbitol and 100 mL of 60%-90% alcohol. To use this hand rub, pour 3-5 mL into the palm of one hand and vigorously rub it into all parts of both hands until dry.

Protective Barriers

Examples of protective barriers include gloves, gowns, goggles, and masks. Using all these barriers in all situations is impractical; one should use judgment as to when they are needed. A procedure in which the eyes could be splashed (such as removing a chest tube or preparing a body for embalming) calls for gloves, gown, and eye protection. Gloves should be changed and hands should be washed between patients. Gloves should never be washed, because washing can cause breakdown of the gloves. If barriers such as gloves and gowns are not available, other items may be used as a barrier. For example, a clean, thick cloth can be used to put pressure on a bleeding wound. Precautions should always be taken to avoid contact of blood with the skin, eyes, and mucous membranes. Hands should be washed with soap and water after all direct patient contacts.

If a phlebotomy is to be performed, using gloves is the only necessary barrier. Remember that gloves protect a health care worker only from getting blood on the skin or in cuts. They do not protect against percutaneous injuries. Percutaneous injuries most often occur when the phlebotomist is inexperienced, in a hurry, or tired, or when the patient is uncooperative.

Handling Potentially Infectious Items

Contaminated waste, such as disposable needles, disposable syringes, and bloody bandages, should be discarded appropriately. Needles should be discarded into sealed puncture-resistant containers. Needles should not be removed from the syringe and should never be recapped, bent, or broken. If possible, needles with a safety device should be used (retractable, self-blunting, or shielded needles). Puncture-resistant containers should be kept within easy access of medical procedure areas, thereby decreasing the handling of needles and sharps and reducing the risk of accidental injury.

Reusable needles and syringes should be disinfected after each use. The needles and syringes should be washed as quickly as possible after use to prevent the formation of clots, which can be difficult to remove. Two methods exist for cleaning used needles and syringes. For the first method, take the needle and syringe apart and clean them with soap and water, paying special attention to the area around the fittings. Put the needle and syringe back together. Fill the syringe with water through the needle, shake it, and expel the water through the needle; repeat these steps until the water that is expelled looks clear. For the second method, fill a clean cup with undiluted bleach. Fill the syringe with the bleach through the needle, shake it, and expel the water through the needle; repeat these steps until the water that is expelled looks clear. For the second method, fill a clean cup with undiluted bleach. Fill the syringe with the bleach through the needle, and let the syringe and needle sit in the bleach-filled cup for 30 seconds. After the 30 seconds has elapsed, expel the bleach from the syringe through the needle, and rinse the syringe with water at least three times to remove all bleach. The bleach in the cup should be discarded and not reused.

Bloody bandages should be discarded according to local guidelines. All trash should be discarded into leakproof plastic bags. Heavily contaminated trash containing wet, bloody bandages or other infectious fluids should be put into a separate plastic bag before being put into a general trash container. Soiled linens and clothes do not need to be separated from other linen or laundry before washing. Laundry workers should always wear gloves when handling dirty laundry. Spills of blood or other infectious fluids should be cleaned while wearing gloves, using a solution...
of one part household bleach to 10 parts water. If gloves are not available, use some type of barrier between the hands and the spill, such as paper towels. Hands should be washed with soap and water immediately after the cleanup.

**HIV Exposure in the Health Care Setting**

**Background**
Health care workers are often at risk of exposure to HIV and other infectious diseases because of the environment in which they work. Following standard precautions easily minimizes this risk. All health care settings should have a written plan of action that conforms to national guidelines for handling HIV exposures. All health care workers should be familiar with this plan of action and should know where to find a copy of it. The plan should include instructions for reporting the exposure, instructions for managing the exposure; information on testing and counseling; and information on postexposure prophylaxis (PEP; treatment to try to prevent the acquisition of HIV infection), follow-up, and monitoring.

Data on time to HIV seroconversion are limited because of the low prevalence of infection after work-related exposure among health care workers. Among those health care workers who do seroconvert, available data indicate that 81% will seroconvert at a mean interval of 65 days after exposure and an estimated 95% will seroconvert by 6 months after initial exposure.

In theory, there is a short time between HIV exposure and infection during which transmission of HIV may be prevented. In the first 24 hours after exposure, HIV attacks dendritic-like cells in the mucous membranes and skin. Within 5 days after exposure, these infected cells then make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes rapid. According to this theory of pathogenesis, preventing HIV infection should be possible if antiretrovirals are used before 24-48 hours after exposure. Animal studies have indicated that PEP is not effective when it is received more later than 72 hours after the exposure.

**Reporting Exposures**
All exposures to potentially infectious fluids should be reported so that appropriate action can be taken. The report should include the date and time of the exposure, details of the procedure being performed, details of the exposure, and details about the exposure source. The wound or skin site should be washed immediately with soap and water, and exposed mucous membranes should be flushed with water. The use of caustic agents or antiseptics or disinfectants at the wound site is not recommended. Squeezing the site to encourage bleeding does not decrease the risk seem of transmission. The source patient and the health care worker should then be tested for HIV and for hepatitis B and C, and the need for HIV PEP should be assessed.

The person who is the source of the exposure should be evaluated for the presence of HIV (Appendix 2). The evaluation should include information on risk factors for HIV, questions about HIV-related symptoms, and HIV testing. If the source is known to be HIV infected, information about viral load and CD4+ count should be obtained. This information may be used in the consideration of PEP, but PEP should not be delayed pending these results. Changes to PEP can always be made after treatment has begun. If the source of the exposure is unknown, an epidemiologic evaluation should be performed. An epidemiologic evaluation includes assessing the geographic area in which the exposure occurred for its prevalence of HIV. The geographic area would include the country, the province, the city, the village, the hospital, and the hospital ward. If HIV exists at a high rate in any of these areas, the exposure should be considered high risk and PEP should be started. Testing of needles and other sharp instruments for the presence of HIV is not recommended because the reliability of this type of testing is unknown.

Occupational exposure to HIV among pediatricians was previously underestimated. New studies suggest that pediatricians represent a high-risk group.
**Evaluation and Testing**

Health care workers who are exposed to potentially infectious fluids should have baseline testing performed within hours of exposure to check for the presence of HIV antibodies. Evaluation of the health care worker also should include questions about medications and current or past medical conditions. PEP should not be started in a person who is found to be HIV positive to prevent the possible development of resistance from a two-drug regimen and to prevent the waste of PEP medications on a person who is already HIV positive. Baseline testing is not required prior to initiating PEP but should be strongly encouraged for the aforementioned reasons.

All women should be offered pregnancy testing. If the woman is pregnant, her evaluation for the risk of acquiring HIV should not be different from that of any other health care worker. Pregnancy is not a contraindication for PEP. PEP should be explained to the health care worker. The health care worker should be informed about the rationale for using PEP and about the risks and benefits of receiving it.

**PEP**

Factors that have influenced the recommendation of PEP include knowledge about the pathogenesis of the infection, experience in preventing perinatal transmission, and studies of the risks versus the benefits of receiving PEP. Animal and human studies have provided direct and indirect information indicating that postexposure treatment with zidovudine (ZDV, AZT) prevents infection. Some animal studies have shown that treatment with other antiretrovirals also works, but human study data are very limited.

The three types of antiretroviral drugs most commonly used in PEP include the following:

1. Nucleoside reverse transcriptase inhibitors, such as ZDV, stavudine (d4T), lamivudine (3TC), and didanosine (ddI)
2. Nonnucleoside reverse transcriptase inhibitors, such as nevirapine and delavirdine
3. Protease inhibitors, such as saquinavir, nelfinavir, and ritonavir

ZDV and nevirapine are the only drugs proven to prevent perinatal HIV transmission as indicated by the ACTG 076 trial and HIVNET 012 trial in Uganda. Limited data are available to indicate that adding other antiretrovirals is additive or synergistic in preventing transmission, but the use of combination therapy in HIV-infected patients suppresses viral replication better than monotherapy. Thus, use of combination therapy in PEP might be even more effective than single-agent treatment in reducing the risk of transmission.

Current HIV treatment guidelines recommend the use of at least three drugs for HIV-infected adults, but the use of all three drugs in PEP is not always considered necessary. The decision to use two or three drugs is based on the risk of transmission after exposure. The WHO recommends the use of two nucleosides. The nucleoside combinations recommended for PEP include ZDV-3TC, 3TC-d4T, and tenofovir–3TC. ZDV is recommended because of the ACTG 076 results, and 3TC is recommended because experts believe that the combination of ZDV and 3TC suppresses HIV replication more potently than does ZDV alone, with less chance of developing viral resistance. The other combinations may be preferred when resistance to ZDV and/or 3TC is thought to be present or believed to be necessary. The third drug can be chosen from any currently approved for use for HIV by the U.S. Food and Drug Administration boosted by the protease inhibitor, ritonavir. These include the protease inhibitors nelfinavir, indinavir, saquinavir, ritonavir, and lopinavir-ritonavir. The nonnucleoside reverse transcriptase inhibitor efavirenz can be used when there is suspicion of protease inhibitor resistance. It is not recommended for use during pregnancy. Abacavir can also be used, but because it has been associated with serious hypersensitivity reactions, patients taking this medication should be monitored. The WHO guidelines for PEP recommend a preferred two-drug regimen and several alternative two-drug regimens, plus a preferred three-drug and alternative three-drug regimens. (Appendix 3). PEP needs to be taken for at least 4 weeks. It is important to minimize the possibility of side effects when choosing which medications to use.

The selection of which postexposure regimen to use—the basic regimen (two drugs) or the expanded regimen (three drugs)—should be based on the severity of exposure and information about the exposure source (Appendix 4 and Appendix 5). Information about the exposure source would include information about antiretroviral history, the presence of possible resistance to anti-HIV drugs, CD4+ count, viral load, and disease stage. Most exposures will require only the basic regimen of two nucleoside reverse transcriptase inhibitors. In exposures in which the risk of transmission is considered great, or when
resistance may be an issue, a protease inhibitor should be added.

Pregnant women should be informed of the possible risks of receiving and of not receiving PEP. Education should include information on the limited data available about the effects of many of these medications on the fetus. Efavirenz is teratogenic (causing birth defects) in primates and thus is not recommended for use in pregnant women. Indinavir can cause hyperbilirubinemia and renal stones and should be used cautiously in pregnant women. Reports of the development of fatal and nonfatal lactic acidosis with concomitant use of d4T and ddI during pregnancy suggest that this combination should be used only when the benefits are believed to outweigh the risks. Studies with women who received ZDV after 14 weeks of gestation suggest that the drug is safe. The decrease in risk of transmission of HIV to the fetus outweighs any risk associated with receipt of ZDV.

The education and information provided to the pregnant woman should also include that the fact that there is an increased risk of infecting the baby via breast-feeding if seroconversion occurs during breastfeeding. If possible, the woman should exclusively bottle-feed her baby, and if it is not possible she should exclusively breast-feed.

PEP should be started as soon as possible. If the HIV status of the source is not known, the basic regimen may be started based on the source and geographic prevalence of HIV. The regimen can be stopped when it is proven that the source is not HIV infected. Some animal studies have shown that PEP is not effective when started more than 24-36 hours after exposure. However, in current practice, PEP is begun as late as 72 hours after exposure when the risk of transmission is high. Once PEP is started, it should be given for at least 4 weeks. Antiretroviral adherence rates of at least 95% or more are required to achieve the maximum benefits from treatment regimen. It is important to provide education, counseling, and support related to adherence.

Follow-Up and Monitoring
HIV counseling, medical follow-up, and HIV testing after exposure should be carried out for at least 6 months after exposure. Recommended testing intervals are 6 weeks, 12 weeks, and 6 months after exposure. Seroconversion after 6 months is rare. However, any health care worker who experiences acute retroviral syndrome (fever, rash, pharyngitis, and lymphadenopathy) should be tested for HIV, even if more than 6 months has elapsed since the known exposure. HIV antibody tests using enzyme immunoassay should be used to test for seroconversion, and Western blot can confirm any positive results. Direct virus assays such as cultures or PCR are not recommended in cases of exposed health care workers because few actually acquire the virus this way and direct virus assays are expensive.

If PEP is used in health care workers, it is important to monitor the individual with laboratory tests for drug-associated toxic effects. Baseline screening including a complete blood count and liver and renal function tests should be performed prior to starting therapy and again 2 weeks after the initiation of therapy. Serum glucose should be tested in individuals receiving a protease inhibitor. Some patients cannot complete the course of medication required for PEP because of medication side effects, including nausea and diarrhea. Administration of antiemetics and antidiarrheals often helps to prevent or relieve these symptoms.

Counseling
Health care workers who are exposed to HIV need to be counseled about the effect that the exposure will have on their lives. This includes the possibility of HIV seroconversion, the importance of starting prophylaxis, and behavioral changes that will have to be made for at

APPENDIX 1. Factors to be assessed after possible occupational exposure to HIV

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Type and Amount of Fluid/Tissue</th>
<th>Infectious Status of Source</th>
<th>Susceptibility of Exposed Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous injury</td>
<td>Blood</td>
<td>Presence of HIV antibody</td>
<td>HIV immune status</td>
</tr>
<tr>
<td>Mucous-membrane exposure</td>
<td>Fluids containing blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-intact skin exposure</td>
<td>Potentially infectious fluid or tissue (semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bites resulting in blood exposure to either person involved</td>
<td>Direct contact with concentrated virus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**APPENDIX 2. Evaluating the occupational exposure source**

**Known Sources**

- Test known sources for HIV antibody.
- Direct virus assays for routine screening of source patients are not recommended.
- Consider using a rapid HIV-antibody test.
- If the source person is not infected with HIV, baseline testing or further follow-up of the exposed person is not necessary.
- For sources whose infection status remains unknown (e.g., if the source person refuses testing), consider medical diagnoses, clinical symptoms, and history of risk behaviors.
- Do not test discarded needles for HIV.

**Unknown Sources**

- For unknown sources, evaluate the likelihood of exposure to a source at high risk of infection.
- Consider the likelihood of HIV infection among patients in the exposure setting.

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**APPENDIX 3. WHO-recommended two- and three-drug therapy combinations**

### Two-drug therapy combinations

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV–3TC</td>
<td>TDF–3TC d4T–3TC</td>
</tr>
</tbody>
</table>

### Three-drug therapy combinations

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV–3TC–lopinavir/ritonavir</td>
<td>ZDV–3TC–atazanavir–ritonavir</td>
</tr>
<tr>
<td>ZDV–3TC–fosamprenavir–ritonavir</td>
<td>TDF–3TC–atazanavir–ritonavir</td>
</tr>
<tr>
<td>d4T–3TC–atazanavir–ritonavir</td>
<td>d4T–3TC–saquinavir–ritonavir</td>
</tr>
</tbody>
</table>

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**APPENDIX 4. Recommended HIV post-exposure prophylaxis for percutaneous injuries**

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>HIV Infection Status of Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-Positive Class 1*</td>
</tr>
<tr>
<td>Less Severe‡</td>
<td>Basic 2-drug PEP</td>
</tr>
<tr>
<td>More Severe††</td>
<td>Expanded 3-drug PEP</td>
</tr>
</tbody>
</table>

* HIV-Positive Class 1: Asymptomatic HIV infection or known low viral load (e.g. <1,500 copies/ml). HIV-Positive Class 2: Symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† Source is of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

‡ Source is unknown (e.g., a needle from a sharps-disposal container).

++ If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

†† More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient’s artery or vein).
APPENDIX 5. Recommended HIV post-exposure prophylaxis for mucous-membrane exposures and non-intact skin* exposures†

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>HIV Infection Status of Source</th>
<th>HIV-Positive Class 1*</th>
<th>HIV-Positive Class 2*</th>
<th>HIV Status of Source Is Unknown+</th>
<th>Unknown Source†</th>
<th>HIV-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Volume†</td>
<td>Consider basic 2-drug PEP**</td>
<td>Basic 2-drug PEP</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** if source has HIV risk factors++</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely</td>
<td>No PEP</td>
<td></td>
</tr>
<tr>
<td>Large Volume††</td>
<td>Basic 2-drug PEP</td>
<td>Expanded 3-drug PEP</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** if source has HIV risk factors++</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely</td>
<td>No PEP</td>
<td></td>
</tr>
</tbody>
</table>

* For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g. dermatitis, abrasion, or open wound).

† HIV-Positive Class 1: Asymptomatic HIV infection or known low viral load (e.g. <1,500 copies/ml). HIV-Positive Class 2: Symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

†† Source is of unknown HIV status (e.g. deceased source person with no samples available for HIV testing).

‡ Small volume (i.e. a few drops)

** The designation “consider PEP” indicates that PEP is optional and should be based on an individualized decision by the exposed person and the treating clinician.

++ If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

††† Large volume (i.e. major blood splash)

least 6 months to prevent the possibility of transmitting HIV to others. These changes include sexual abstinence or condom use and cessation of breast-feeding, if appropriate. Access to information about HIV/AIDS should be provided, and appropriate referrals should be made for further counseling and medical care.

HIV-infected health care workers need not discontinue patient contact. HIV-infected health care workers should be allowed to continue to work without fear of stigmatization or discrimination. The diagnosis of HIV infection should be strictly confidential. HIV-infected health care workers should continue to follow infection control measures and standard precautions to prevent acquiring other infections and prevent transmitting HIV to others.

Components of Standard Precautions

1. Respiratory hygiene/cough etiquette.
   - Persons with respiratory illnesses who enter a health care facility should wear masks.
   - Handwashing is recommended after coughing/sneezing.
   - Maintain a distance of at least 3 feet from a person who has a respiratory illness.

2. Hand hygiene: enforce handwashing with soap and water before and after every patient contact or use of alcohol-based solutions.

3. Use of protective equipment as deemed necessary based on procedures/risks of contamination. Precautions should be taken to avoid having the skin, eyes, and mucous membranes come into contact with blood.
• Gloves should be worn for most procedures (e.g., venipuncture).
• Goggles should be worn if there is a risk of splashing with body fluids.
• Gown should be worn.
• Mask should be worn to prevent contamination of sterile sites with respiratory secretions.

4. Environmental cleaning.
• Needles/sharps disposal: needles should never be recapped, bent, or broken; they should be discarded into sealed, puncture-resistant containers.
• Waste/linen disposal: spills of blood or other infectious fluids should be cleaned while wearing gloves, using a solution of one part household bleach to 10 parts water.

**Summary of Management of HIV Exposure in the Health Care Setting**

Following standard precautions can prevent exposure to HIV. Treat all individuals as if they were infected with HIV or other infectious pathogens. *If an exposure does occur, carry out the following steps:*

1. Wash the exposure site:
   - Either broken or intact skin should be washed with soap and water, or flush it with water or a gel or hand-rub solution immediately.
   - A splash to the eye should be flushed with water immediately.
   - A splash to the mouth should be spit out immediately, and then the mouth should be rinsed with water, which should then be spit out. Repeat several times. Do not use soap or disinfectant in the mouth.

2. Report the exposure as soon as possible so that appropriate interventions can be started.
3. Assess the exposure’s potential to transmit HIV on the basis of the type of fluid involved, the route, and the severity of the exposure.
4. Evaluate the person who is the source of the exposure for the presence of HIV.
5. Gather information on risk factors for HIV and questions about HIV-related symptoms.
6. Counsel the exposed health care worker about HIV.
7. Perform baseline HIV testing for the exposed health care worker.
8. Evaluate the risks and benefits of receiving post-exposure prophylaxis (PEP).
9. Initiate PEP if warranted within in 72 hours of the exposure—the health care worker needs to be an active participant in the decision of whether to start PEP.
10. Repeat the HIV testing for at least 6 months after the exposure, usually at the intervals of 6 weeks, 12 weeks, and 6 months.

**References**


Objectives

1. Define opportunistic infections (OIs) in people with human immunodeficiency virus (HIV)/AIDS.
2. Describe primary prophylaxis to prevent OIs in people with HIV/AIDS.
3. Evaluate the clinical manifestations of bacterial, viral, parasitic, and fungal OIs in people with HIV/AIDS.
4. Describe the treatment for bacterial, viral, parasitic, and fungal OIs in people with HIV/AIDS.
5. Review specific interventions that can decrease the development of OIs in people with HIV/AIDS.

Key Points

1. An OI is caused by organisms that would not produce significant disease in a person with a well-functioning immune system.
2. People with HIV/AIDS are susceptible to OIs because their immune systems have been suppressed and cannot fight disease.
3. People with HIV/AIDS may have OIs at diagnosis.
4. Primary prophylaxis, or preventive treatment, is used to prevent OIs in people with HIV/AIDS.
5. Viral infections found in people with HIV/AIDS include cytomegalovirus, varicella-zoster (shingles), herpes simplex, hepatitis, and Epstein-Barr virus.
6. Pneumocystis jirovecii can cause severe pneumonia in people with HIV/AIDS.
7. Prophylaxis for Pneumocystis jirovecii is recommended for people with HIV/AIDS.
8. Candida albicans is the most common fungal infection diagnosed in HIV-infected people.
9. Education regarding appropriate preparation of food and good hygiene principles is essential to prevent serious OIs.

Overview

Many people living with human immunodeficiency virus (HIV)/AIDS acquire diseases that also affect otherwise healthy people. In such cases, HIV-infected patients may have a more severe disease course than uninfected people or may develop symptoms that uninfected people do not. However, HIV-infected people are also susceptible to opportunistic infections (OIs), which are infections caused by organisms that in a healthy host would not cause significant disease. This module discusses both types of infection. The most common OIs vary with geographic location. This module will give a broad overview of the concepts of preventing OIs and will discuss the most commonly diagnosed diseases worldwide. The module will cover specific diseases, how to recognize them, and which medicines are recommended to treat them. Treatment recommendations are based on available information and research. Not every recommendation will be feasible in every setting. Each country and health department will need to decide which treatments are appropriate in a particular area.

People with HIV/AIDS are susceptible to OIs because of how HIV/AIDS suppresses the immune system. Many people do not know that they have HIV until the first time that they have an OI. When counseling patients with HIV, one must emphasize how to avoid OIs. Easy ways to avoid some of these infections are through general good hygiene, including thorough washing of food and hands.

People with HIV need to be especially careful about how they prepare food. Meats and poultry should be cooked thoroughly. Fruits and vegetables should be washed well. Water should be taken from the cleanest source available. If clean water is not available, water should be boiled before drinking. Infections can also be passed from person to person and through contact with fecal material. Immunocompromised people should avoid contact with ill persons and with human and animal feces.
These measures can help prevent a person from getting a serious infection.

Vaccines can also reduce an HIV-infected patient’s risk of certain infections. See the chapter on immunizations for HIV-infected children for more details.

**Primary and Secondary Prophylaxis**

Oftentimes people known to be HIV infected are given medicines to prevent developing an OI. This approach is known as primary prophylaxis. The appropriate time to begin prophylaxis depends on the age of the patient, which infection is being prevented, and what laboratory support and medications are available in a particular area. The patient’s CD4+ lymphocyte count helps to determine when to begin primary prophylaxis. For example, when CD4+ lymphocyte counts are less than 200 cells/µL or total lymphocyte counts are less than 1,200 cells/µL, adults begin taking trimethoprim-sulfamethoxazole (TMP-SMX) to prevent *Pneumocystis jirovecii* pneumonia (formerly PCP [*Pneumocystis carinii* pneumonia]) as well as other diseases, such as toxoplasmosis, malaria, and diarrheal diseases.

When a person with AIDS dies, the cause of death is most often an OI. Primary prophylaxis is a way to help patients lead longer, healthier lives. After HIV-infected patients have been treated for an OI, they should stay on a lower dose of the medicine for the rest of their lives to prevent a relapse. This approach is known as secondary prophylaxis. Many medicines used for prophylaxis have side effects. If a patient will be taking prophylactic medications for a long time, the health professional must assess for side effects each time that the patient is examined. This requirement applies regardless of whether a patient is receiving primary or secondary prophylaxis. In places where highly active antiretroviral therapy (HAART) is available, one can sometimes discontinue prophylaxis. Although these recommendations are discussed as each organism is discussed, Table 1 provides a summary.

### Table 1. Criteria for discontinuing and restarting opportunistic infection prophylaxis for HIV-infected persons

<table>
<thead>
<tr>
<th>Opportunistic Illness</th>
<th>Criteria for Discontinuing Primary Prophylaxis</th>
<th>Criteria for Restarting Primary Prophylaxis</th>
<th>Criteria for Discontinuing Secondary Prophylaxis</th>
<th>Criteria for Restarting Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis Pneumonia</em> (PCP)</td>
<td>- Do not discontinue in children aged &lt; 1 year</td>
<td>- Age 1 to 5 years with CD4 percentage &lt; 15% or count &lt; 500 cells/mm³</td>
<td>- If fulfill all of the following criteria:</td>
<td>- Age 1 to 5 years with CD4 percentage &lt; 15% or count &lt; 500 cells/mm³ or recurrence PCP</td>
</tr>
<tr>
<td></td>
<td>- After ≥ 6 months of HAART and:</td>
<td>- Age 6 years with CD4 percentage &lt; 15% or count &lt; 200 cells/mm³</td>
<td>- Completed ≥ 6 months of HAART</td>
<td>- Age ≥ 6 years with CD4 percentage &lt; 15% or CD4 count &lt; 200 cells/mm³ or recurrence PCP</td>
</tr>
<tr>
<td></td>
<td>- Age 1 to 5 years, CD4 percentage or count is ≥ 15% or ≥ 500 cells/mm³ for &gt; 3 consecutive months</td>
<td>- Age ≥ 6 years with CD4 percentage or count is &gt; 15% or ≥ 200 cells/mm³ for &gt; 3 consecutive months</td>
<td>- Age 1 to 5 years, CD4 percentage or count is ≥ 15% or ≥ 200 cells/mm³ for &gt; 3 consecutive months</td>
<td>- Age ≥ 6 years with CD4 percentage &lt; 15% or CD4 count &lt; 200 cells/mm³ or recurrence PCP</td>
</tr>
<tr>
<td></td>
<td>- Age ≥ 6 years, CD4 percentage or count is ≥ 15% or ≥ 200 cells/mm³ for &gt; 3 consecutive months</td>
<td></td>
<td>- Age 1 to 5 years, CD4 percentage or count is ≥ 15% or ≥ 200 cells/mm³ for &gt; 3 consecutive months</td>
<td>- Age 1 to 5 years with CD4 percentage &lt; 15% or CD4 count &lt; 200 cells/mm³ or recurrence PCP</td>
</tr>
</tbody>
</table>

| *Toxoplasma gondii* Encephalitis (TE) | - Do not discontinue in children aged < 1 year                                                                | - Age 1 to 5 years with CD4 percentage < 15% (CIII)                                                           | - If fulfill all of the following criteria:                                                                     | - Age 1 to 5 years with CD4 percentage < 15% or CD4 count < 200 cells/mm³ or recurrence PCP                      |
|                                      | - Age 1 to 5 years, CD4 percentage or count is ≥ 15% for > 5 consecutive months                           | - Age ≥ 6 years with CD4 percentage or count is ≥ 100-200 cells/mm³                                          | - Completed ≥ 6 months of HAART                                                                                 | - Age ≥ 6 years with CD4 percentage < 15% or CD4 count < 200 cells/mm³ or recurrence PCP                      |
|                                      | - Age ≥ 6 years, CD4 percentage or count is ≥ 15% or ≥ 100-200 cells/mm³ for > 3 consecutive months   |                                                                                                               | - Complete initial therapy for TE                                                                                | - Age ≥ 6 years with CD4 percentage < 15% or CD4 count < 200 cells/mm³ or recurrence PCP                      |
|                                      |                                                                                                               | - Age 1 to 5 years, CD4 percentage is ≥ 15% for > 3 consecutive months                                        | - Asymptomatic for TE                                                                                          | - Age ≥ 6 years with CD4 percentage < 15% or CD4 count < 200 cells/mm³ or recurrence PCP                      |

Continued on next page
Table 1. Criteria for discontinuing and restarting opportunistic infection prophylaxis for HIV-infected persons

<table>
<thead>
<tr>
<th>Opportunistic Illness</th>
<th>Criteria for Discontinuing Primary Prophylaxis</th>
<th>Criteria for Restarting Primary Prophylaxis</th>
<th>Criteria for Discontinuing Secondary Prophylaxis</th>
<th>Criteria for Restarting Secondary Prophylaxis</th>
</tr>
</thead>
</table>
| **Mycobacterium avium complex (MAC) disease** | Do not discontinue in children aged <2 years  
If age >2 years, after ≥6 months of HAART and:  
Age 2 to 5 years with CD4 count >200 cells/mm³ for >3 consecutive months  
Age ≥6 years with CD4 count >100 cells/mm³ for >3 consecutive months | Age 2 to 5 years with CD4 count <200 cells/mm³  
Age ≥6 years with CD4 count <100 cells/mm³ | If fulfill all of the following criteria:  
Completed ≥6 months of HAART  
Completed ≥12 months of MAC therapy  
Asymptomatic for signs and symptoms of MAC  
Age 2 to 5 years with CD4 count >200 cells/mm³ for ≥6 consecutive months  
Age ≥6 years with CD4 count >100 cells/mm³ for ≥6 consecutive months | Age 2 to 5 years with CD4 count <200 cells/mm³  
Age ≥6 years with CD4 count <100 cells/mm³ |
| **Cytomegalovirus retinitis** | Not Applicable | Not applicable | If fulfill all of the following criteria:  
Completed ≥6 months of HAART  
Consultation with ophthalmologist  
Asymptomatic for TE  
Age 1 to 6 years with CD4 percentage ≥15% or CD4 count ≥500 cells/mm³ for >3 consecutive months  
Age >6 years with CD4 count >100 cells/mm³ for >3 consecutive months  
Routine (every 3 to 6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis | Age 1 to 6 years with CD4 percentage <15% or count <500 cells/mm³  
Age >6 years with CD4 count <100 cells/mm³ or CD4 percentage <15% |
| **Cryptococcal meningitis** | Not Applicable | Not applicable | If fulfill all of the following criteria:  
Asymptomatic on ≥6 months of secondary prophylaxis for cryptococcosis  
Completed ≥6 months of HAART  
Age >6 years with CD4 count ≥200 cells/mm³ for >6 consecutive months | CD4 count <200 cells/mm³ |
| **Histoplasma capsulatum infection** | | | If fulfill all of the following criteria:  
Age >6 years  
Received ≥1 year itraconazole  
Completed ≥6 months of HAART  
CD4 count ≥150 cells/mm³ and percentage ≥15%  
Negative Histoplasma blood cultures  
Serum Histoplasma antigen <2 ng/mL | CD4 count <150 cells/mm³ or percentage <15% |
BACTERIAL INFECTIONS

Streptococcus pneumoniae
One of the most common serious bacterial infections is Streptococcus pneumoniae, which causes pneumonia, otitis media, septicemia, and other invasive illnesses. All patients with HIV who are older than 2 years should be given the 23-valent polysaccharide vaccine for pneumococcus with one revaccination 3-5 years later if the child is younger than 10 years or after 5 years if the child is older than 10 years. The heptavalent pneumococcal conjugate vaccine (PCV-7) for pneumococcus is recommended for all children as young as 2 months where available.

Treponema pallidum
Treponema pallidum is the anaerobic bacterium responsible for syphilis. Syphilis is not an OI in a strict sense, but coinfection with HIV and syphilis is common. In the United States, the median HIV seroprevalence among persons infected with syphilis was 15.7%. There also are indications that HIV type 1 alters the diagnosis, natural history, management, and outcome of syphilis infections. Treponema pallidum can be transmitted from mother to child at any stage of pregnancy or delivery.

Primary syphilis ordinarily presents as one painless nodule at the site of inoculation or contact that ulcerates into a chancre. Such ulcerations might facilitate transmission of HIV infection between partners. In an HIV-infected person, multiple or atypical chancres can occur, and primary lesions may be absent or missed. Asymptomatic primary syphilis occurs at a higher rate in HIV-infected patients.

Secondary syphilis occurs 2-8 weeks after primary inoculation. Manifestations involve all organ systems. Skin lesions (macular, maculopapular, pustular, or condyloma lata in moist or intertrigonal areas) usually begin on the trunk and spread peripherally. Characteristically they are found on the palms and soles and are accompanied by generalized lymphadenopathy and constitutional symptoms (fever, malaise, anorexia, arthralgias, headache). Secondary syphilis can be difficult to distinguish from primary HIV infection. HIV infection can cause more rapid progression of syphilis.

Late syphilis includes neurosyphilis, cardiovascular syphilis, and gummatous syphilis. Neurosyphilis can have a more rapid progression in HIV-infected patients. Although in general neurosyphilis manifests similarly in HIV-infected and uninfected individuals, concomitant uveitis and meningitis may be more common in HIV-infected persons with syphilis.

Congenital syphilis has been found in 60%-100% of infants born to mothers who are untreated or inadequately treated for primary or secondary syphilis. Infants born to HIV-infected women have a higher rate of congenital syphilis than that of the general population. Coinfection may also increase the rate of perinatal HIV transmission. Clinical manifestations may be asymptomatic. Other manifestations are classified as either early or late. Early manifestations include hepatosplenomegaly, jaundice, mucocutaneous lesions, skin rash, nasal discharge (“snuffles”), pseudoparalysis of an extremity, anemia, thrombocytopenia, and osteochondritis. Late manifestations occur after 2 years of age and may involve the central nervous system, bones, teeth, eyes, and skin.

The diagnosis of syphilis is generally made either with tests that detect the organism directly (e.g., dark-field microscopy or direct fluorescent antibody to Treponema pallidum [DFA-TP]) or with serology that detects serum antibodies against the organism (e.g., fluorescent treponemal antibody absorption [FTA-ABS] and T. pallidum particle agglutination [TP-PA]) or nontreponemal antibodies generated during infection (e.g., venereal disease research laboratory [VDRL] and rapid plasma reagin [RPR]). However, there is a potential for false-negative serology.

Treatment of syphilis is the same for patients infected or uninfected with HIV, i.e., a penicillin-based regimen with adequate coverage for neurosyphilis. A pregnant woman infected with syphilis must be treated 30 or more days before delivery to effectively prevent perinatal transmission. Careful follow-up is required in all cases, because relapse is more likely in HIV-positive patients.

Mycobacterium tuberculosis
Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is not an OI, but it is the most common cause of death of HIV-infected people worldwide. HIV attacks T-lymphocyte cells, the body’s main defense against TB. Therefore, patients with HIV are more susceptible to TB infection. As the HIV epidemic grows,
transmission of TB becomes harder to control. Please refer to the chapter on TB for details regarding the diagnosis and management of its coinfection with HIV.

Preventive therapy against TB includes one or more anti-TB drugs given to HIV-infected patients who have a latent infection with *M. tuberculosis* to prevent progression to active disease. Before considering a patient for preventive therapy, one must exclude active disease. In 1998, the World Health Organization (WHO) and UNAIDS developed recommendations for preventive therapy. Preventive therapy is recommended in areas that have established HIV care and TB control programs. The resources must also be available to

- distinguish active from latent tuberculosis,
- ensure appropriate monitoring and follow-up,
- ensure a consistent supply of medication, and
- link preventive therapy against TB to voluntary counseling and testing for HIV.

Preventive therapy is recommended for HIV-infected patients with a positive Mantoux skin test who do not have active TB (i.e., have a normal chest radiograph). In areas where skin testing is not feasible, one should consider preventive therapy for the following high-risk patients if they have HIV:

- Persons living in populations with a high prevalence (>30%) of TB infection
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners

Preventive therapy with isoniazid (INH) is recommended. The dose should be 5 mg/kg of body weight (maximum, 300 mg) by mouth daily for at least 6 months, with clinical monitoring for adverse effects and active TB.

### Table 2. Treatment and prophylaxis dosing for MAC*

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Prophylaxis</th>
<th>Alternative Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Clarithromycin (7.5 mg/kg/dose twice daily) or Azithromycin (10-12 mg/kg/dose once daily) plus Ethambutal (15 mg/kg/day)</td>
<td>Clarithromycin 7.5 mg/kg twice daily</td>
<td>Azithromycin 20 mg/kg by mouth weekly or rifabutin (&gt;6 y/o) 300 mg daily</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Clarithromycin (500 mg twice daily) or Azithromycin (600 mg twice daily) plus Ethambutal (15 mg/kg/day) for at least 12 months</td>
<td>Clarithromycin 500 mg twice daily</td>
<td>Azithromycin 1.2 g by mouth weekly or rifabutin 300 mg daily</td>
</tr>
</tbody>
</table>

*Doses for medications given by mouth

### Table 3. Treatment and prophylaxis dosing for CMV retinitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Prophylaxis</th>
<th>Alternative Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Ganciclovir 5 mg/kg IV twice daily for 14 days</td>
<td>Ganciclovir 5 mg/kg IV once daily</td>
<td>Ganciclovir 6 mg/kg IV once daily for 5 days per week</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Ganciclovir 5 mg/kg IV twice daily for 14 days OR Valganciclovir 900 mg orally twice daily for 21 days</td>
<td>Ganciclovir 5 mg/kg IV once daily</td>
<td>Ganciclovir 1000 mg orally 3 times daily or Valganciclovir 900 mg orally once daily</td>
</tr>
</tbody>
</table>
**Mycobacterium avium Complex**

Mycobacterium avium complex (MAC) occurs all over the world. Symptoms of disseminated MAC are nonspecific and include weight loss or failure to thrive (in children), recurrent fever, abdominal pain, diarrhea, and lymphadenopathy. MAC can be grown in culture, albeit slowly. Acid-fast staining, if available, will be positive. Treatment for MAC requires at minimum a two-drug regimen of either clarithromycin or azithromycin plus ethambutol.

The age and CD4+ lymphocyte count of the patient indicate when to start primary prophylaxis. In adults, prophylaxis is recommended once the CD4+ lymphocyte count is less than 100 cells/µL. In children, CD4+ lymphocyte cell counts vary with age, but if the counts are below 15% for the child’s age group, prophylaxis is recommended.

Once patients receive HAART for at least 6 months and their CD4+ lymphocyte cell counts increase to more than 100 cells/µL (or >200 cells/µL for children aged 2-5 years) for 3 months, one may stop primary prophylaxis. Stop secondary prophylaxis only if the patient has completed at least 12 months of therapy and has maintained a CD4+ lymphocyte cell count of more than 100 cells/µL (or >200 cells/µL for children aged 2-5 years) for 6 months. Currently, stopping prophylaxis is not recommended for children younger than 2 years. See Table 2 for treatment and prophylaxis guidelines.

**Viral Infections**

**Cytomegalovirus**

Cytomegalovirus (CMV) is a common viral infection worldwide. Most people with CMV develop few or no symptoms. However, a fetus exposed to CMV can suffer severe consequences, including mental retardation and even death. In patients with HIV/AIDS, the most common complication of CMV is retinitis (Figure 1). CMV can also cause hepatitis, diarrhea, and encephalitis. CMV retinitis is most commonly seen in patients with CD4+ lymphocyte counts of less than 50 cells/µL and can lead to blindness if untreated. One should advise patients to report to the clinic if they notice changes in their vision, including blurry vision or “floaters.” Many patients are asymptomatic. If possible, patients should have regular fundoscopic examinations (visualizing the deep structures of the eye) to check for changes and if necessary should be referred to an eye specialist.

Ganciclovir intravenously or valganciclovir orally are the antiviral medications recommended for treating CMV. An intraocular form of ganciclovir can be used to treat isolated CMV retinitis. However, using intraocular ganciclovir without adjunctive therapy of a systemic anti-CMV agent increases the incidence of further systemic disease. See Table 3 for the dosing schedule for treatment and posttreatment prophylaxis (also referred to as maintenance therapy). The main side effect of ganciclovir is neutropenia. Other side effects include anemia, thrombocytopenia, and occasionally renal insufficiency. Currently, valganciclovir is not recommended for children.

Recent studies in adults, adolescents, and children older than 12 months suggest that one may discontinue CMV secondary prophylaxis in patients who have maintained a CD4+ lymphocyte cell count of more than 100-150 cells/µL (or 15%) in response to HAART for at least 6 months. If prophylaxis is discontinued, maintain regular ophthalmologic examinations.

**Varicella-Zoster Virus**

Varicella-zoster is the virus that causes chickenpox and shingles in children and adults. Infection with this virus can be much more serious in a person with HIV/AIDS. Primary varicella is spread by aerosolized viral particles. A person is contagious for 24-48 h before a vesicular rash (raised, fluid-filled lesions) is observed and remains contagious until all lesions are crusted over. Diagnosis is mainly clinical.

A vaccine is available to protect patients against this virus. If an HIV-infected child has an age-specific CD4+ lymphocyte percentage greater than 15%, the vaccine may be administered. HIV-infected children require two doses of the varicella vaccine, separated by at least 3 months. If an immunocompromised person comes into contact with someone with varicella, he or she can be protected with varicella-zoster immunoglobulin. Acyclovir, an antiviral medication, decreases the duration of disease. In children, acyclovir can be given intravenously or orally. The pediatric oral dose is 20 mg/kg/dose every 6 h for 5 days. The adult dose is 800 mg four times a day for 5-7 days. Acyclovir can cause pancytopenia (a decrease in all forms of blood cells), particularly when given in conjunction with zidovudine (AZT). Patients must increase the intake of fluids while on acyclovir to avoid crystalluria (the presence of crystals in the urine as a symptom of irritation) and possible acute renal failure.
Reactivation can cause painful grouped vesicles usually isolated to one dermatome months or years after primary infection. This development is referred to as zoster or shingles. Treatment with acyclovir can lessen the severity.

**Herpes Simplex Virus**

Herpes simplex virus type 1 (HSV-1) and HSV-2 infections also can be severe in patients with HIV/AIDS. HSV can cause ulcers around the mouth, known as cold sores. HSV can cause encephalitis as well.

Diagnosis is mainly clinical. Acute disease usually resolves spontaneously, but treatment for pain associated with the lesions may help the patient feel more comfortable. Genital herpes is a sexually transmitted infection. Using condoms can decrease a patient’s risk of contracting HSV. HSV infection can be transmitted from mother to child, and this occurs at a rate of one case per 2,000-5,000 deliveries. HIV-infected women coinfected with HSV-2 are much more likely to be actively shedding virus at the time of delivery and therefore are at greater risk for transmitting HSV-2 to their infants than are HIV-negative women. Oral or genital herpes can be treated with acyclovir in severe cases. Patients with HSV and HIV/AIDS often have severe recurrent attacks. For these patients, prophylaxis with daily acyclovir can help. The pediatric prophylactic dose is 10 mg/kg/dose twice daily orally. The adult prophylactic dose is 200 mg three times a day or 400 mg twice a day orally.

**Epstein-Barr Virus**

Epstein-Barr virus (EBV) usually causes minor symptoms, much like the common cold or strep throat. However, EBV infection of HIV-infected children can be associated with a pulmonary disease known as lymphoid interstitial pneumonia (LIP). LIP occurs in 20%-30% of HIV-infected children. It usually occurs in children older than 2 years. The diagnosis of LIP is usually made based on clinical criteria; definitive diagnosis requires lung biopsy.

Patients with LIP may initially be asymptomatic. As the disease progresses, they may present with generalized lymphadenopathy, hepatomegaly, and/or digital clubbing. Children may also have nontender, bilateral enlargement of the parotid glands. Respiratory difficulties may become evident because of secondary bacterial infections. In areas where tuberculosis is endemic, one must rule out TB before making a diagnosis of LIP. The chest radiograph associated with LIP will show bilateral diffuse reticulonodular infiltrations and mediastinal lymphadenopathy, which may be confused with TB. Patients often respond well to steroid therapy. Also, antiretroviral treatment can decrease the complications associated with LIP. EBV also has been associated with Burkitt’s lymphoma.

**JC Virus**

JC virus is the virus believed to be associated with progressive multifocal leukoencephalopathy, a disease characterized by altered mental status, limb weakness, or both. Patients may also exhibit personality changes with frequent emotional outbursts. This disease has a course that can vary. It occurs in patients with severe immune suppression and is rarely seen in children. Definitive diagnosis is confirmed by brain biopsy. On an image from computed tomography, one can see diminished density or demyelination (deterioration of the covering of the nerve). There is no treatment for this illness, but strong antiretroviral medications can sometimes improve the symptoms.

**Virus-Associated Malignancies**

**Kaposi Sarcoma**

Kaposi sarcoma is primarily a skin malignancy, but it can also involve internal organs such as the lungs, liver, and spleen. It is associated with the human herpesvirus 8 (HHV-8). Although Kaposi sarcoma has been observed in immunocompetent children in Africa, it is more common in children and adults with HIV/AIDS. In HIV-infected children, the median age of onset of Kaposi sarcoma is 33 months. Kaposi sarcoma associated with HIV/AIDS can present in two forms: mucocutaneous and lymphadenopathic. The mucocutaneous form may be an early type of the lymphadenopathic form. Cutaneous lesions characterizing Kaposi sarcoma can be flat, raised, or nodular and usually are purple or brown. They can occur anywhere on the body, including the palms of the hands, as well as inside the mouth. The most effective treatment for Kaposi sarcoma is antiretroviral therapy. Chemotherapy is often used, particularly when viscera are involved. Limited research also shows that ganciclovir may be associated with reduced disease progression or with lesion regression. Prognosis for Kaposi sarcoma seems to be related to the patient’s overall immune status and the organ systems involved.

HHV-8 can be transmitted through sexual intercourse, blood via needle sharing, and possibly deep kissing (oral secretions). Health providers should counsel HIV-infected
Opportunistic Infections

Human Papillomavirus

Human papillomavirus (HPV) infects cutaneous and mucosal squamous epithelium. It can cause genital, anal, conjunctival, nasal, oral, and laryngeal warts. In young children, genital warts may be a sign of sexual abuse. However, HPV can be transmitted perinatally. Such transmission is more likely to result in respiratory symptoms from HPV in toddlers (recurrent respiratory palomatos). Men who have sex with men have a high prevalence of anal HPV infection.

HPV infection is commonly associated with cervical cancer. Women who are immunocompromised have a higher rate of cervical cancer, as well as a higher rate of recurrence of cervical cancer after treatment. Using condoms can reduce the risk of transmission of sexually transmitted infections and may reduce the risk of transmitting HPV. Women with HIV should have a Papanicolaou (Pap) smear every 6 months for the first year after diagnosis of HIV. If these smears are negative, women with no other risk factors for cervical cancer should have a Pap smear once a year.

A vaccine for HPV is now available in some settings. This vaccine is safe for use in HIV-infected women and recommended in all women and female youth aged 9-26 years for prevention of HPV and cervical cancer. Multiple treatments for HPV-associated skin and external lesions are available. Specific treatments must be catered to the circumstances of the patient.

Parasitic Infections

Pneumocystis jiroveci

Pneumocystis jiroveci (formerly Pneumocystis carinii) is an organism that does not cause illness in immunocompetent hosts. However, it can cause severe pneumonia in patients with HIV/AIDS. This infection is prevalent worldwide. One should suspect Pneumocystis jiroveci pneumonia (formerly called PCP) in patients with tachypnea (increased rate of respiration), cough, and shortness of breath. Lung auscultation (sounds) may be normal because rales and rhonchi may develop late in the clinical course. Patients are commonly hypoxic with a normal chest radiograph. The chest radiograph may show bilateral interstitial infiltrates (Figures 2 and 3). Children can be severely ill with this disease, and it is often the first AIDS-defining illness in a child. Definitive diagnosis requires identifying the organism, usually from a bronchoalveolar lavage (a washing that can retrieve cells or tissue from the lungs and the alveoli in them) or an induced sputum sample. PCP is best treated with TMP-SMX.
The WHO recommends TMP-SMX primary and secondary prophylaxis for all symptomatic people with HIV and particularly in resource-limited settings where bacterial infections and malaria are prevalent among people living with HIV. For prevention of PCP and toxoplasmosis, the WHO recommends TMP-SMX for adults with CD4 counts less than 350 cells/µL or WHO stage 2, 3, and 4. The WHO recommends TMP-SMX prophylaxis for children according to age:

- Younger than 1 year, irrespective of CD4 cell count
- 1-5 years old, symptomatic children (WHO stages 2-4) or CD4 less than 25%
- 6 years or older who are symptomatic (WHO stages 2-4) or CD4 cell count <350 cells/µL

Infants born to HIV-infected mothers should begin PCP prophylaxis when they are 4-6 weeks of age and should remain on prophylaxis until they are 12 months old or until it can be determined definitively whether they are HIV infected, taking into account the ongoing risk of exposure to HIV via breast-feeding. If they are HIV infected, their treatment should follow the guidelines for HIV-infected children.

Guidelines in the United States recommend initiation of primary prophylaxis if the CD4 cell count falls below 200 cells/µL or 15% for children younger than 6 years. See Table 4 for dosing guidelines.

Primary treatment of PCP includes TMP-SMX 15-20 mg TMP/kg/day divided every 6-8 h for 21 days, plus steroid therapy for severe disease. Supplemental oxygen should be given if needed. The prophylaxis dose (Table 4) for adults is TMP 160 mg and SMX 800 mg once a day orally for 3 consecutive days a week. If this regimen is not tolerated, one may half the dose instead. Some patients are given the full dose every day; this will also protect them against toxoplasmosis. The dose for children is TMP 150 mg/m² of body surface area and SMX 750 mg/m² in two divided doses three consecutive days a week. As in adults, this may be given to children every day to protect against toxoplasmosis. If patients cannot tolerate TMP-SMX, have G6PD (glucose-6-phosphate dehydrogenase) deficiency (an enzyme disorder affecting red blood cells), are allergic to sulfa drugs, or experience side effects, dapsone may be used. The main side effect of TMP-SMX is rash. As with all sulfonamides, TMP-SMX can on rare occasions cause agranulocytosis (destruction of certain white blood cells), aplastic anemia (loss of bone marrow production), other blood disorders, Stevens-Johnson syndrome (a severe allergic reaction characterized by breakdown of mucous membranes), and hepatic necrosis (death of liver cells), or interstitial nephritis. The dose of dapsone for adults is 100 mg once daily. For children, the recommended dose is 2 mg/kg daily, with a maximum dose of 100 mg/day. Other alternative drugs include clindamycin-primaquine, dapsone-trimethoprim, atovaquone, pentamidine isethionate, and trimetrexate glucuronate.

Both primary and secondary prophylaxis can be discontinued in adults and adolescents who have maintained a CD4⁺ lymphocyte cell count of more than 200 cells/µL for at least 3 months after 6 months of HAART. Children older than 1 year may discontinue primary or secondary prophylaxis if their CD4 cell count remains above 15% for 3 months after 6 months of HAART. The WHO recommends stopping primary or secondary prophylaxis when two consecutive CD4 counts are greater than 200 cells/µL and the patient is on antiretroviral therapy for more than 6 months with good adherence once a child is older than 5 years. One should reinitiate prophylaxis if the CD4 cell count falls below 200 cells/µL or 15%. Malaria-endemic areas and/or places where CD4 cell counts are not regularly available may continue TMP-SMX prophylaxis indefinitely in HIV-infected children.

### Table 4. Prophylaxis for PCP – Once-daily dosing

<table>
<thead>
<tr>
<th>Weight</th>
<th>Suspension: 40 mg TMP + 200mg SMX/5ml</th>
<th>Tablets (SS): 80 mg TMP/400mg SMX</th>
<th>Tablets (SS): 160 mg TMP/800mg SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 kg</td>
<td>2.5 ml</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5-8 kg</td>
<td>5 ml</td>
<td>1/2 tab</td>
<td>–</td>
</tr>
<tr>
<td>9-16 kg</td>
<td>10 ml</td>
<td>1 tab</td>
<td>1/2 tab</td>
</tr>
<tr>
<td>17-50 kg</td>
<td>20 ml</td>
<td>2 tabs</td>
<td>1 tab</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>20 ml</td>
<td>2 tabs</td>
<td>1 tab</td>
</tr>
</tbody>
</table>
Opportunistic Infections

Cryptosporidium

Cryptosporidium is a parasite that causes persistent diarrhea and cholecystitis (gall bladder inflammation) in immunocompromised patients. Cryptosporidium is spread by direct contact with infected adults, children in diapers or of the age to be in diapers, and infected animals. Food and water contaminated with feces can spread infection as well. People with HIV/AIDS should be careful when coming in contact with human feces (e.g., changing diapers) or animal feces, as well as when working with the soil. Good hand washing and boiling water when advised are important for preventing infection.

Patients with cryptosporidiosis will have frequent, watery, voluminous stools, often lasting longer than 2 weeks. They also may experience abdominal cramping. If the biliary system (gall bladder and biliary ducts) is involved, they also may have nausea and right-upper-quadrant abdominal pain. Cryptosporidia in stool can be seen under a microscope with a modified acid-fast staining method. Nitazoxanide effectively treats cryptosporidiosis in immunocompetent patients. Dosing for adults is 500 mg by mouth twice daily for 3 days. Children aged 12-47 months should receive 100 mg by mouth twice daily for 3 days; children aged 4-11 years should receive 200 mg by mouth twice daily for 3 days; and those aged 12 years and older should receive the adult dose. Nitazoxanide was ineffective in HIV-infected children; however, one may consider an extended course of 6 days because in more immunocompetent children this dose may lessen the course of illness. Metronidazole and azithromycin have been used to treat Cryptosporidium with various degrees of success. Effective HAART is the recommended treatment for Cryptosporidium infections.

Isospora belli

Isospora belli spreads by the same routes of transmission as Cryptosporidium and has the same symptoms. Isospora can be diagnosed on acid-fast stain of stool. TMP-SMX can treat Isospora, but there is a 50% relapse rate among adults. Prophylaxis with TMP-SMX may be needed to prevent relapses. The dosing and side effects of TMP-SMX for Isospora belli are the same as for Pneumocystis jirovecii (Table 4).

Malaria

Malaria is a disease caused by several species of Plasmodium, a parasite transmitted via mosquito bites. It is found primarily in tropical regions of the world. About 90% of malaria cases occur in sub-Saharan Africa, which poses substantial problems because HIV prevalence there is also high. The two infections can have several harmful interactions.

Pregnant women with HIV infection are at increased risk of malaria. HIV increases the chances of placental malaria, which is associated with a greater risk of HIV transmission to the infant, low birth weight, and mortality. Patients suffering from AIDS (and possibly young children) are at increased risk of symptomatic malaria. They may present with a higher parasite burden. A study in Malawi suggests that malaria infection might increase HIV viral load.

Prevention is the mainstay of malaria reduction in many areas. One of the most effective prevention strategies is the use of insecticide-treated nets (ITNs) over the bed. ITN use decreases pediatric morbidity and mortality from malaria. Most nets need to be retreated with insecticide every 6 months. Wearing long sleeves and long pants can also prevent infection. So can remaining indoors at dawn and dusk, the times of highest transmission risk. Intermittent prophylaxis with medication for pregnant women and children is being studied. Finally, community efforts to eliminate or cover standing water can prevent mosquito breeding. A combination of TMP-SMX and ITNs is associated with a marked reduction in malaria incidence among HIV-infected persons.

Proper treatment of malaria is imperative to minimize morbidity and mortality. Different regions of the world have different types of malaria, some of which can be drug resistant. Treatment regimens for a particular setting depend on national guidelines. Examples of drugs used to treat malaria are chloroquine, quinine, primaquine, mefloquine, pyrimethamine-sulfadoxine, and atovaquone plus proguanil.

Toxoplasma gondii

Toxoplasma gondii is transmitted via raw or undercooked meat, particularly pork, lamb, and venison. It also can be transmitted via cat feces. Meat should be thoroughly cooked, and immunosuppressed individuals should avoid
contact with stray cats and cat feces. Good hand washing can prevent infection.

Toxoplasmosis in the immunocompromised host usually causes central nervous system disease, specifically brain abscesses. Toxoplasmosis commonly reactivates, causing repeated infections. Patients have focal neurologic deficits, including seizures, hemiparesis, hemiplegia, cerebellar tremor, cranial nerve palsies (e.g., unilateral facial droop), hemisensory loss, visual problems or blindness, personality changes, and cognitive disorders. Severe localized headache that does not respond to analgesics may be present. *Toxoplasma gondii* infection is classically seen as multiple-ring enhancing lesions on a computed tomography scan. Antibodies often can be detected in the blood or other body fluids (cerebrospinal fluid). This disease is much more common in adults than in children. However, infants infected in utero are at high risk for toxoplasmosis encephalitis.

Treat toxoplasmosis with pyrimethamine and sulfadiazine. Treatment for toxoplasmosis should continue for at least 4 weeks after complete resolution of disease. See Table 5 for treatment and secondary prophylaxis guidelines. Folinic acid is usually also given during treatment because pyrimethamine inhibits folate metabolism. Alternative treatment and secondary prophylaxis regimens include pyrimethamine-clindamycin, pyrimethamine-azithromycin, and pyrimethamine-atovaquone. However, one should use these combinations only when the risks of using pyrimethamine-sulphadiazine outweigh the benefits. Limited data also support using alternative regimens in children. Primary prophylaxis is recommended with TMP-SMX daily for severely immunocompromised patients (see Table 4 for dosing guidelines).

Patients who have experienced an increase in CD4+ lymphocyte cell count after at least 6 months of HAART to more than 200 cells/µL (or >15%) for at least 3 months may stop primary prophylaxis for toxoplasmosis. One may discontinue secondary prophylaxis if a patient maintains a CD4+ cell count of more than 200 cells/µL for at least 6 months. The WHO recommends stopping primary or secondary prophylaxis when two consecutive CD4 counts are greater than 200 cells/µL and the patient is on antiretroviral therapy for more than 6 months with good adherence and is older than 5 years.

### Fungal Infections

**Candida albicans**

*Candida albicans* is the most common fungal infection diagnosed in HIV-infected patients. Oral candidiasis (also called thrush) is particularly common. It is often one of the presenting signs of HIV infection in patients who do not have other reasons (e.g., recent antibiotic use) to have fungal disease. Patients have white or yellow plaques on the oropharyngeal mucosa and on the tongue. If esophageal infection is also present, the patient may complain of inability to swallow or retrosternal chest pain when swallowing. Infants may begin to feed and then stop after the first few swallows, arching their backs and

#### Table 5. Treatment and secondary prophylaxis for *Toxoplasma gondii*

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Pyrimethamine: 1-2 mg/kg/day orally for 2 days, then 1 mg/kg/day orally for 2 months, then 1 mg/kg/day orally 3 days/wk (maximum 50 mg) AND Sulfadiazine: 100 mg/kg oral loading dose, then 50 mg/kg twice daily by mouth AND Folinic acid: 5-10 mg orally or intramuscularly 3 times a week</td>
<td>Pyrimethamine: 1 mg/kg orally daily (maximum 25 mg) AND Sulfadiazine: 40 mg/kg/day orally 3 times a day AND Folinic acid: 5 mg orally every 3 days</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Pyrimethamine: 200 mg orally in divided doses, then 50 mg orally daily AND Sulfadiazine: 2000 mg orally 3 times daily AND Folinic acid: 15 mg orally daily</td>
<td>Pyrimethamine: 25 mg orally daily AND Sulfadiazine: 1000 mg orally 3 times a day AND Folinic acid: 15 mg orally daily</td>
</tr>
</tbody>
</table>
Opportunistic Infections

turning their heads because of difficulty in swallowing. Patients who are critically ill, have been treated with long-term systemic antibiotics, or have an indwelling catheter (e.g., central venous access device) may develop systemic candidiasis or candidemia. Diagnosis is mainly clinical; however, potassium hydroxide preparation can be used for microscopic demonstration of pseudohyphae. One can treat oral candidiasis with gentian violet applied directly to the lesions or with nystatin (or other topical antifungals) in liquid or tablet form taken orally. If one suspects candidal esophagitis, treat with ketoconazole or fluconazole. Treat vaginal candidiasis with topical antifungal agents.

Amphotericin B can treat systemic candidiasis that does not respond to other antifungal agents. The dose of amphotericin B will depend on the severity of the illness, ranging from 0.5 mg/kg/day to 1.5 mg/kg/day. Patients who receive this drug should be monitored when they are in the hospital. Administration of amphotericin B can be associated with shaking chills or rigors during infusion. Amphotericin B also causes hypokalemia (decreased potassium in the serum), bone marrow suppression, and nephrotoxicity.

Prophylaxis is recommended only for frequent and severe recurrences of candidiasis. The Centers for Disease Control and Prevention recommends daily fluconazole for prophylaxis of frequent and severe recurrences of candidiasis. However, daily fluconazole treatment can lead to the development of fluconazole-resistant candidiasis. An alternative is to use daily nystatin for prophylaxis, particularly for oral thrush. The prophylaxis dose of fluconazole is the same as the treatment dose (Table 6).

Cryptococcosis
Cryptococcosis usually occurs in HIV-infected patients with severe immune suppression and most commonly causes cryptococcal meningitis. Mortality during the first 6 weeks after diagnosis can be as high as 20%. Clinical signs and symptoms of this infection can be subtle. The most common clinical manifestation is indolent fever. Patients may have headache and altered mental status. Cutaneous manifestations can mimic molluscum contagiosum. These symptoms usually evolve over weeks or months. Meningitis is often associated with a high opening pressure on spinal tap. It is also fatal without treatment. Treatment is usually amphotericin B and flucytosine for 2 weeks, followed by fluconazole (400 mg/day for 8-10 weeks). The WHO recommends initial treatment with amphotericin B for 2 weeks followed by itraconazole or fluconazole for 8 weeks and maintenance therapy with itraconazole or fluconazole. Monitor patients for increased intracranial pressure, particularly in the first 2 weeks of treatment.

After initial treatment, secondary prophylaxis with fluconazole is recommended for both adults and children. The doses are the same as the maximum doses listed for candidiasis (Table 6).

Adults, adolescents, and children older than 6 years appear to be at low risk for recurrence of cryptococcosis if they have completed primary treatment, remained asymptomatic, and maintained a CD4 lymphocyte cell count greater than 100-200 cells/µL for more than 6 months. Some experts would recommend a repeat

### Table 6. Recommended dosing for prevention of severe and recurrent candidiasis

<table>
<thead>
<tr>
<th>Age</th>
<th>Nystatin Dose</th>
<th>Fluconazole Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates (&lt;1 month)</td>
<td>100 000 units 4 times daily by mouth</td>
<td>3-6 mg/kg by mouth every 72 hours (if ≥14 days old, use infant dose)</td>
</tr>
<tr>
<td>Infants (1-12 months)</td>
<td>200 000 units 4 times daily by mouth</td>
<td>3-6 mg/kg by mouth daily</td>
</tr>
<tr>
<td>Children (1-12 years)</td>
<td>400 000 units 4 times daily by mouth</td>
<td>3-6 mg/kg by mouth daily</td>
</tr>
<tr>
<td>Adults (&gt;12 years)</td>
<td>400 000-600 000 units 4 times daily by mouth</td>
<td>100-200 mg by mouth daily</td>
</tr>
</tbody>
</table>

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evaluation of cerebrospinal fluid to document a negative culture in an asymptomatic patient prior to stopping prophylaxis. Reinitiate prophylaxis if the CD4 cell count again falls below 200 cells/µL.

**Histoplasmosis**

*Histoplasma capsulatum* is a fungus endemic to certain parts of the United States, Latin America, and other parts of the world. In endemic areas, more than 25% of HIV-infected patients develop disseminated histoplasmosis. *H. capsulatum* can infect the lungs and the oropharyngeal and gastrointestinal tract as well as skin, brain, adrenal glands, and bone marrow. Patients may present with fever and weight loss, lymphadenopathy, splenomegaly, and diarrhea or abdominal pain. Some HIV-infected patients may present with intestinal ulcers. Those with pulmonary infection may be asymptomatic or may present with dyspnea. A chest radiograph will be abnormal in 70% of patients with histoplasmosis. A radiograph may show diffuse interstitial or reticulonodular infiltrates.

One can use culture, antigen testing, or fungal stain of the tissues to make the diagnosis. Depending on the site of infection, patients may present with anemia, leukopenia, elevated hepatic enzymes, or an elevated serum lactate dehydrogenase level. Treatment is with amphotericin B (0.7-1 mg/kg/day) initially, followed by itraconazole 200 mg once or twice daily. Itraconazole is more effective than ketoconazole or fluconazole. Treatment may last for up to 1 year. In patients with CD4+ lymphocyte counts of less than 150 cells/µL, lifelong maintenance therapy is recommended at the same dose of itraconazole. Itraconazole can interact with many different medications, including rifampin, so it must be monitored.

**References**


**Objectives**

1. Describe the epidemiology, clinical manifestations, diagnosis, and treatment of tuberculosis (TB).
2. Describe the interaction between anti-TB and antiretroviral drugs.
3. Describe preventive therapy for TB.

**Key Points**

1. Tuberculosis is the leading cause of death among human immunodeficiency virus (HIV)-infected individuals worldwide.
2. In settings of high HIV prevalence, all patients with TB should be offered HIV testing and counseling, and those who are found to be HIV infected should be offered the full range of available HIV services.
3. A negative Mantoux test does not exclude TB.
4. All children younger than 5 years and those aged 5 or more years who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB.
5. When any child (<15 years) is diagnosed with TB, an effort should be made to detect the source case (usually a smear-positive adult) and any other undiagnosed cases in the household.
6. Bacteriologic confirmation of Pulmonary TB (AFB smear and culture) using 3 specimens of expectorated sputum, induced sputum or early-morning gastric aspirates should be done whenever possible.
7. Principles of treating TB in HIV-infected and noninfected patients are the same, and cure is largely unaffected by HIV status.

**Epidemiology of Tuberculosis**

An estimated one-third of the world population is infected with *Mycobacterium tuberculosis* (the bacterium that causes tuberculosis [TB]), and each year an estimated 9 million people develop TB, of whom about 2 million die.

Of the 9 million annual TB cases, 1 million (11%) occur in children younger than 15 years. Of these childhood cases, 75% occur annually in 22 high-burden countries, most of which are in sub-Saharan Africa. Primary pulmonary infection with *M. tuberculosis* often is silent, with no obvious signs, symptoms, or radiographic abnormalities.

The likelihood of symptom development is age dependent, being greatest in infants and the elderly mainly because of their underdeveloped and waning immune systems, respectively. The risk of active TB in individuals with latent infection is increased 100-fold by HIV coinfection. TB is the most common cause of death among HIV-infected people worldwide.

HIV produces progressive loss of CD4+ lymphocytes (T cells), cells critical to the body’s defense against *M. tuberculosis*. HIV promotes the occurrence of TB at any stage of HIV disease, but clinical features of TB do vary by CD4+ lymphocyte count. Adults with HIV and CD4+ lymphocyte counts of more than 350 cells/µL typically manifest pulmonary disease alone, with predominantly upper-lobe infiltrates and/or cavitations. Extrapulmonary TB (including pleuritis, pericarditis, meningitis, and disseminated disease) often is observed among HIV-infected adults with CD4+ lymphocyte counts of less than 50 cells/µL. Chest radiographs often show lower- and/or middle-lobe infiltrates, sometimes miliary and typically without cavitation. The occurrence of TB is also associated with higher HIV viral load and more rapid progression of HIV disease.

A review of the natural history of pulmonary tuberculosis in childhood indicates that 50%-75% of children develop radiographically visible hilar adenopathy after primary infection with *M. tuberculosis*, but more than 90% of these do not progress to TB disease. Children with the highest risk of disease progression are those younger than 2 years mainly because of their underdeveloped immune systems. Younger children tend to develop noncavitary, segmental...
lung lesions, whereas older children can have reactivation pulmonary TB that resembles adult disease.

Key risk factors for TB in children include the following:
1. Household contact with a newly diagnosed smear-positive TB case
2. Age younger than 5 years
3. HIV infection
4. Severe malnutrition

**Diagnosis**
The recommended approach to diagnosis of TB in children includes the following:
1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary TB (mainly chest radiograph) and suspected extrapulmonary TB
6. HIV testing (in high-HIV prevalence areas)

**Careful History, Including History of TB Contact and Symptoms Consistent with TB**
A close contact is defined as one living in the same household as or in frequent contact with a source case with sputum smear-positive pulmonary TB. Source cases that are sputum smear negative but culture positive are also infectious, albeit to a lesser degree.

All children younger than 5 years and those aged 5 or more years who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB. When any child (<15 years) is diagnosed with TB, an effort should be made to detect the source case (usually a smear-positive adult) and any other undiagnosed cases in the household. If a child presents with smear-positive or cavitary pulmonary TB, child contacts must be looked for and screened. The commonest symptoms that should be looked for include:
- chronic cough not improving and that has been present for more than 21 days;
- fever of more than 38°C for 14 days, after common causes such as malaria or pneumonia have been excluded; and
- weight loss or failure to thrive, for which it is necessary to look at the child’s growth chart.

**Clinical Examination**
Physical signs suggestive of extrapulmonary TB include the following:
- Meningitis not responding to antibiotic treatment, with a subacute onset or raised intracranial pressure.
- Pleural effusion.
- Pericardial effusion.
- Ascites.
- Nonpainful enlarged lymph nodes without fistula formation.
- Documented weight loss or failure to gain weight—especially after treatment in a nutritional rehabilitation program—is a good indicator of chronic disease, of which TB may be the cause.
Mantoux Tuberculin Skin Testing
Tuberculin skin testing using purified protein derivative is performed in many settings to screen for infection with *M. tuberculosis*. However, HIV-infected individuals often are anergic (nonreactive) to purified protein derivative as a consequence of HIV-related impairment of cell-mediated (T cell) immunity. Also, interpretation of the Mantoux test in patients who have received bacillus Calmette-Guérin bacillus (BCG) vaccine can be complicated. In general, the Mantoux test should be interpreted irrespective of whether the patient has received the BCG vaccine. In HIV-infected patients and children with severe malnutrition, a Mantoux test reaction (induration) measuring 5 mm or greater in diameter is considered positive. This is in contrast with HIV-uninfected individuals, in whom a Mantoux test reaction of 10 mm or greater is considered positive. A negative Mantoux test does not exclude TB.

Bacteriological Confirmation
Bacterial confirmation for pulmonary TB consists of three morning expectorated sputum samples for acid-fast bacillus (AFB) smear and culture. If there is no sputum production, induced sputum (using hypertonic saline) or early-morning gastric aspiration can be used. The sensitivity of expectorated sputum samples for diagnosis of TB in adults with or without HIV is about 50%. This figure is comparable to that of induced sputum or bronchoscopy. Several DNA probe and nucleic acid amplification methods have been evaluated in the diagnosis of TB. The best of these may have sensitivity greater than that of AFB smear and culture. Such tests also are highly specific for *M. tuberculosis*, and their use hastens bacterial identification, but cost is prohibitive in many settings (US$50-$100 per test). Where available, these newer tests can be helpful in confirming the diagnosis of TB in moderate- or high-risk patients where other clinical and laboratory findings present a confusing picture.

Diagnosis of TB in young children (<5 years) is made more difficult by their inability to expectorate sputum suitable for AFB smear and culture. In addition, most children (especially those <5 years) have pausibacillary tuberculosis (TB with few tubercle bacilli) and therefore tend to be sputum smear negative. In children who are unable to expectorate sputum, an attempt should be made to obtain 3 specimens of induced sputum, or early morning gastric aspirates. Several recent studies have found that sputum induction using hypertonic saline and a bronchodilator such as salbutamol is safe, effective and well-tolerated in children of all ages and the bacterial yields are as good or better than for gastric aspirates. Induced sputum specimens should be sent for AFB smear and culture. Where sputum induction is not available, 3 early-morning gastric aspirate specimens should be collected on separate days, using a nasogastric tube, on awakening the child before they ambulate or eat. Gastric aspirate specimens should be cultured for *M. tuberculosis*, AFB smears are generally not useful.

Because *M. tuberculosis* is slow growing, culture confirmation prior to initiation of therapy is not always practical. A presumed diagnosis of TB can be made based on a history of contact with an individual with TB, appropriate clinical signs and symptoms, a positive Mantoux tuberculin skin test, and typical chest radiographic features. Classic signs and symptoms include chronic cough, hemoptysis (blood-stained or bloody sputum), night sweats, fever, and weight loss. Common chest radiographic findings include hilar adenopathy, pleural effusion, focal infiltrates in the upper and hilar regions, and cavitations.

Key features suggestive of TB in children include

1. chronic symptoms suggestive of TB,
2. physical signs highly suggestive of TB,
3. a positive tuberculin (Mantoux) skin test, and
4. chest x-ray features suggestive of TB.

HIV Testing
In settings of high HIV prevalence, all patients with TB should be offered HIV testing and counseling, and those who are found to be HIV infected should be offered the full range of available HIV services.
HIV-infected individuals are more prone than HIV-uninfected individuals to develop extrapulmonary TB. One form appears as diffuse lymphadenopathy. Biopsy or fine-needle aspirate will reveal necrotizing and nonnecrotizing granulomas. Young children with TB are at increased risk of extrapulmonary TB and disseminated disease with meningitis, pleural or pericardial effusion, or involvement of the spine. **Table 1** summarizes forms of extrapulmonary TB in children and the practical approach to diagnosis.

**Table 1. Forms of extrapulmonary TB in children and relevant investigations**

<table>
<thead>
<tr>
<th>Site</th>
<th>Practical Approach to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral lymph nodes (especially cervical)</td>
<td>Lymph node biopsy or fine needle aspiration</td>
</tr>
<tr>
<td>Military TB (e.g., disseminated)</td>
<td>Chest x-ray and lumbar puncture (to test for meningitis)</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Lumbar puncture (and computerized tomography where available)</td>
</tr>
<tr>
<td>Pleural effusion (older children and adolescents)</td>
<td>Chest x-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture</td>
</tr>
<tr>
<td>Abdominal TB (e.g., peritoneal)</td>
<td>Abdominal ultrasound and ascitic tap</td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>X-ray, joint tap or synovial biopsy</td>
</tr>
<tr>
<td>Pericardial TB</td>
<td>Ultrasound and pericardial tap</td>
</tr>
</tbody>
</table>
**Management and Treatment**

The main objectives of anti-TB treatment are to

1. cure the patient of TB (by rapidly eliminating most of the tubercle bacilli),
2. prevent death from active TB or its late effects,
3. prevent relapse of TB (by eliminating the dormant tubercle bacilli),
4. prevent development of drug resistance (by using a combination of effective drugs), and
5. decrease TB transmission.

Children usually have paucibacillary pulmonary tuberculosis (i.e., TB with low numbers of organism); cavitating TB is relatively rare (≤6%) in those younger than 13 years. Extrapulmonary disease and severe or disseminated TB occur especially more commonly in the youngest children (<2 years). Both the organism load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are, however, generally good even in young and immunocompromised children, provided that treatment is commenced promptly.

Ideally, patients newly diagnosed with TB should be managed in coordination with public health professionals (e.g., the National TB Control Program) who are well versed in contact investigation, local factors influencing treatment choices (e.g., local prevalence of drug resistance), and available local resources. Treatment choices generally are dictated by relevant national protocols.

Principles of treating TB in the HIV-infected and non-infected patients are the same:

- Goals and case definitions are the same.
- Dosing and duration of anti-TB therapy regimens are the same.

In both adults and children, a commonly prescribed regimen for drug-susceptible TB is isoniazid, rifampicin, and pyrazinamide (with ethambutol often added for adults and older children and for children with severe forms of tuberculosis or TB with severe HIV/AIDS) for 1 or 2 months, followed by isoniazid and rifampicin alone. Rifabutin can be substituted for rifampicin. In settings where directly observed therapy for TB is available, twice-weekly treatment with isoniazid and rifampicin often is given after an initial 1- or 2-month period of daily three- or four-drug treatment. Response to TB treatment is largely unaffected by HIV status. Thus, most current international guidelines recommend that TB in HIV-infected adults and children should be treated with a 6-month regimen, as in HIV-uninfected patients. However, some national guidelines recommend that patients with pulmonary TB be treated for 9 months and those with extrapulmonary TB be treated for 12 months.

The recommended daily dose of ethambutol is higher in children (20 mg/kg of body weight) than in adults (15 mg/kg) because the pharmacokinetics is different—peak serum concentrations are lower in children than in adults receiving the same milligram-per-kilogram dose. Although ethambutol was frequently omitted from treatment guidelines partly because of concerns about difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, recent data indicate that it is safe in children at a dose of 20 mg/kg (range, 15-25 mg/kg) daily. Streptomycin should be avoided when possible in children because the injections are painful and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Dose and range (mg/kg of body weight)</strong></td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>25 (20-30)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Children 20 (15-25)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Adults 15 (15-20)</td>
<td>—</td>
</tr>
<tr>
<td>Streptomycin</td>
<td></td>
<td>15 (12-18)</td>
</tr>
</tbody>
</table>

**Tuberculosis**

Irreversible auditory nerve damage may occur. The use of streptomycin in children is reserved mainly for the first 2 months of treatment of TB meningitis.

Corticosteroids may be used for the management of some complicated forms of TB, such as TB meningitis, complications of airway obstruction by tuberculous lymphadenopathy, and TB pericarditis. Steroids are recommended for all cases of TB meningitis, where they improve both survival and morbidity. The most commonly used drug is prednisone 2 mg/kg daily, increased up to 4 mg/kg daily in the most severe cases, with a maximum dose of 60 mg/day for 4 weeks. The dose should then be tapered over 1-2 weeks before stopping.

### Multidrug-Resistant TB

Multidrug-resistant (MDR) TB is resistant to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. In children MDR-TB is usually a result of transmission of a resistant strain of TB from an adult source. As a result MDR is usually diagnosed late in children unless there is a clear history of contact with an adult case of MDR-TB. Treatment of MDR-TB is difficult and referral to a specialist is highly recommended. Some basic principles of management of MDR-TB are as follows:

- Do not add one drug to a failing regimen.
- It is best to treat MDR-TB according to drug-susceptibility patterns (use the adult source case susceptibility pattern if the child’s is not available).
- Use at least four drugs.
- Daily directly observed therapy is essential.
- Provide consistent ongoing counseling and support to the caregiver and educate about the importance of completion of the treatment course.
- Clinical, radiological, and bacteriological follow-up are essential.
- Treatment duration depends on the extent of disease but is generally 12 months or longer (or ≥12 months after the last positive culture).
- With correct dosing, few long-term adverse events are seen with any of the more toxic second-line TB drugs, including ethionamide and the fluoroquinolones.

**Table 3. Recommended treatment regimens according to each diagnostic category**

<table>
<thead>
<tr>
<th>TB Diagnostic Category</th>
<th>TB Cases</th>
<th>Regimen</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>New smear-negative pulmonary TB (other than in category I)</td>
<td>2HRZ</td>
<td>4HR or 6HE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less severe forms of extrapulmonary TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>New smear-positive pulmonary TB</td>
<td>2HRZE</td>
<td>4HR or 6HE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New smear-negative pulmonary TB with extensive parenchymal involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe forms of extrapulmonary TB (other than TB meningitis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe concomitant HIV/AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>TB meningitis</td>
<td>2HRZS</td>
<td>4HR</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Previously treated smear positive pulmonary TB:</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ Relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ Treatment after interruption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>♦ Treatment failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Chronic and MDR TB</td>
<td>Specially designed standardized or individualized regimens (managed by experts at tertiary level)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Directly observed therapy is recommended during initiation phase and whenever the continuation phase contains rifampicin.

The regimen 2HRZE/6HE may be associated with higher rates of treatment failure and relapse than a 6-month regimen with rifampicin in the continuation phase. Source: WHO TB guidelines 2006.

**Table 4** summarizes the second-line (reserve) drugs used to treat MDTR-TB in children.
Extensively Drug-Resistant TB

Extensively drug-resistant (XDR) TB is resistant to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, capreomycin, kanamycin) in addition to isoniazid and rifampicin. This form of TB should be managed by experts in tertiary centers. Detailed discussion of XDR TB is beyond the scope of this publication.

Follow-Up and Monitoring

Patients on anti-TB therapy should ideally be monitored at least at the following intervals: 2 weeks after initiation of treatment, at the end of the intensive phase (usually 2 months), and every 2 months until completion of the treatment. Assessment should include (but not be limited to) assessment of symptoms and signs, medication adherence, drug toxicity and other adverse events, and weight gain. Doses should be adjusted according to weight gain. Liver enzymes must be monitored in patients concomitantly receiving antiretroviral and TB medications. Pyridoxine (10 mg by mouth daily) is recommended for all HIV-infected adults and children receiving isoniazid to help prevent drug-associated peripheral neuropathy. Signs and symptoms of peripheral neuropathy include numbness, tingling or prickling sensations in the hands and feet, absent deep-tendon reflexes, and foot drop. A follow-up sputum sample at 2 months post anti-TB therapy initiation should be obtained for all patients who were sputum positive at baseline. Follow-up chest radiographs are not routinely required, especially in children, who tend to have slow radiological response to treatment.

Interactions Between Anti-TB and Antiretroviral Drugs

Many medications used to treat TB interact with medications used to treat HIV. Of particular note is the interaction between rifampicin and either nonnucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs). Also, anti-TB and antiretroviral drugs have overlapping toxicities; the many drugs involved in treating the two diseases concomitantly poses significant adherence challenges, and paradoxical reactions due to immune reactivation or reconstitution after initiation of antiretroviral therapy may occur in 7%-36% of patients. In addition, very few studies have examined the optimal timing of antiretroviral therapy in TB/HIV co-infected individuals.

Because of these considerations, most physicians have been reluctant to simultaneously start anti-TB and antiretroviral medications. However, there is some recent evidence which suggests that starting HAART as soon as possible after starting anti-TB medications may improve survival in TB/HIV co-infected individuals. A recent Randomized Controlled Trial (SAPIT trial) done in South Africa found that starting Anti-retroviral therapy in TB/

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**Table 4. Second-line (reserve) drugs used to treat MDR-TB in children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Common Side-effects</th>
<th>Recommended daily dose Range</th>
<th>Maximum (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide or prothionamide</td>
<td>Bactericidal</td>
<td>Vomiting, GI upset</td>
<td>15-20</td>
<td>1000</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ofloxacin</td>
<td>Bactericidal</td>
<td>Arthropathy, arthritis</td>
<td>15-20</td>
<td>800</td>
</tr>
<tr>
<td>• Levofoxacin</td>
<td>Bactericidal</td>
<td></td>
<td>7.5-10</td>
<td>—</td>
</tr>
<tr>
<td>• Moxifloxacin</td>
<td>Bactericidal</td>
<td></td>
<td>7.5-10</td>
<td>—</td>
</tr>
<tr>
<td>• Gatifloxacin</td>
<td>Bactericidal</td>
<td></td>
<td>7.5-10</td>
<td>—</td>
</tr>
<tr>
<td>• Ciprofloxacin</td>
<td>Bactericidal</td>
<td></td>
<td>20-30</td>
<td>1500</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Amikacin</td>
<td>Bactericidal</td>
<td>Ototoxicity hepatotoxicity</td>
<td>15-22.5</td>
<td>1000</td>
</tr>
<tr>
<td>• Kanamycin</td>
<td>Bactericidal</td>
<td></td>
<td>15-30</td>
<td>1000</td>
</tr>
<tr>
<td>• Capreomycin</td>
<td>Bactericidal</td>
<td></td>
<td>15-30</td>
<td>1000</td>
</tr>
<tr>
<td>Cycloserine or Terizidone</td>
<td>Bacteriostatic</td>
<td>Psychiatric neurological</td>
<td>10-20</td>
<td>1000</td>
</tr>
<tr>
<td>Para-Aminosalicylic Acid</td>
<td>Bacteriostatic</td>
<td>Vomiting, GI upset</td>
<td>150</td>
<td>12000</td>
</tr>
</tbody>
</table>

Although fluoroquinolones are not approved for use in children in many countries, the benefit of treating a child with MDR-TB with a fluoroquinolone may often outweigh the risks.
HIV co-infected patients with CD4 counts less than 500 cells/mm³ who are on anti-TB medications (concurrent regimen) reduced mortality by up to 55% (HR 0.451, 95% CI: 0.26 to 0.79; p = 0.0049) when compared to delaying HAART until after completion of anti-TB therapy (sequential regimen). In this study, those on the concurrent regimen started HAART, on average, 67 days after starting anti-TB treatment compared to a 261 days delay for those on the sequential regimen. The observed mortality reduction was significant regardless of CD4 count. In addition, mathematical modeling done in Russia suggests that universal HAART coverage among TB/HIV co-infected individuals would significantly reduce TB incidence and mortality. World Health Organization (WHO) recommendations are as follows:

1. Start ART in all HIV-infected individuals with active tuberculosis (TB) irrespective of CD4 cell count.
2. Start TB treatment first, followed by ART as soon as possible after starting TB treatment.
3. Use efavirenz (EFV) as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment.

If a patient already is receiving antiretroviral medications when TB is diagnosed, these medications should not be discontinued. If possible, anti-TB medications that have fewer interactions with antiretroviral medications should be used (e.g., substituting rifabutin for rifampicin). Alternatively, one may consider using an antiretroviral regimen with fewer interactions with the anti-TB medications.

Interaction between rifampicin and many antiretroviral drugs occurs largely because these antiretroviral drugs are metabolized by the cytochrome P450 system of enzymes that is induced by rifampicin. The affected antiretroviral drugs are broken down at an accelerated rate, thus lowering their blood levels. Nucleoside reverse transcriptase inhibitors (NRTIs) are not metabolized by cytochrome P450 and are unaffected by rifampicin.

Pharmacological studies with few patients indicate that serum levels of the NNRTIs (nevirapine and efavirenz) and PIs are reduced in patients who are simultaneously treated with rifampicin. Blood levels of antiretroviral drugs are affected by coadministration of rifampicin as follows:
- Nevirapine, reduced by 37%
- Efavirenz, reduced by 25%
- Indinavir, reduced by 89%
- Ritonavir, reduced by 35%
- Saquinavir, reduced by 84%
- Nelfinavir, reduced by 82%
- Lopinavir/r, reduced by 75%

It is not known whether this type of interaction is serious enough to compromise the antiretroviral efficacy of NNRTIs; there are few clinical outcome data from controlled studies. Further, it is not known whether there are racial differences in these drug interactions. However, some recent data indicate that rifampicin can be used for treatment of active TB in patients whose antiretroviral regimen includes the NNRTI efavirenz and two NRTIs. The U.S. Centers for Disease Control and Prevention (CDC) guidelines suggest that rifampicin may also be used in antiretroviral regimens that include the NNRTI nevirapine.

The interaction between rifampicin and the PI class of drugs is problematic; there is strong evidence to indicate that rifampicin-induced reductions in the blood level of PIs may cause failure of antiretroviral treatment. In industrialized countries, rifabutin often is substituted for rifampicin. However, rifabutin is not part of TB treatment guidelines in most developing countries; it is expensive, and problems have been reported in obtaining sufficient supplies because of a world shortage of the drug. One way to overcome the difficulty of low PI serum levels is to give ritonavir concomitantly with the PI. Because ritonavir is the preferred substrate of the cytochrome P450 system, the system metabolizes ritonavir while allowing the concentration of the other PI to rise to levels similar to those that would be achieved without rifampicin. This is the principle that underpins PI boosting.

Table 5. Overlapping toxicities between anti-TB and anti-retroviral medications.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Antituberculosis Drugs</th>
<th>Antiretroviral Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>INH</td>
<td>D4T, DDI (also HIV)</td>
</tr>
<tr>
<td>Rash</td>
<td>SM, PZA, RIF, INH, EMB</td>
<td>NVP, EFV, ABC (also CTX)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>PZA, RIF, INH</td>
<td>ZDV, PIs</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PZA, RIF, INH</td>
<td>NVP, EFV, PIs</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>RIF</td>
<td>ZDV (also CTX)</td>
</tr>
</tbody>
</table>

**Immune Reconstitution Inflammatory Syndrome**

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical deterioration, with new or worsening symptoms, signs, or radiological...
manifestations. IRIS sometimes occurs after beginning anti-TB therapy with or without antiretroviral therapy because of restoration of the capacity to mount an inflammatory immune response. This can simulate worsening disease, with fever and increased size of lymph nodes or tuberculomas. In TB patients who are coinfected with HIV, clinical deterioration due to immune reconstitution commonly occurs after initiation of antiretroviral therapy. This is especially more likely in those patients who begin anti-TB and antiretroviral therapy when they are severely immunocompromised (with very low CD4 counts) and who have a rapid improvement in their CD4 counts. In all cases of IRIS, anti-TB therapy should be continued. In some severe cases of IRIS, corticosteroids can be helpful in dampening the vigorous immune response. If there is any doubt, the patient should be referred to the next level of care, ideally to be managed by experts in a tertiary setting.

**TB Preventive Therapy (Isoniazid TB Preventive Therapy)**

Preventive therapy against TB includes giving one or more anti-TB drugs to individuals with latent *M. tuberculosis* infection to prevent progression to active disease. Before a person is considered for TB preventive therapy, active TB should be excluded. In 1998, the WHO and UNAIDS developed recommendations for preventive therapy. Preventive therapy is recommended in countries that have established HIV care and TB control programs. Also, resources must be available to

1. distinguish active from latent TB,
2. ensure appropriate monitoring and follow-up,
3. ensure consistent supply of medications, and
4. link preventive therapy against TB to voluntary counseling and testing for HIV.

Preventive TB therapy is recommended for HIV-infected individuals with a positive Mantoux skin test who do not have evidence of active TB (i.e., who have a normal chest radiograph and no suggestive clinical symptoms). In areas where Mantoux testing is not feasible, preventive therapy should be considered for the following high-risk individuals if they are infected with HIV:

♦ Persons living in populations with a high prevalence of TB (>30%)
♦ Health care workers
♦ Household contacts of TB patients
♦ Prisoners
♦ Miners

Preventive therapy with isoniazid in adults is recommended at the dose of 5 mg/kg (maximum, 300 mg) by mouth daily for 6 months with clinical monitoring for adverse effects and active TB.

Until recently, isoniazid preventive therapy had not been studied in HIV-infected children. In a recent placebo-controlled randomized trial, isoniazid dosed at 10 mg/kg orally once daily or three times weekly was associated with a 53% reduction in mortality. The survival benefit occurred early (within 50 days) and was apparent in all CDC HIV categories of disease. The population studied lived in the Western Cape Province of South Africa, a region with one of the highest incidence rates of TB worldwide (4.1% annualized risk for children); therefore, the study’s findings are highly applicable to other countries with high TB prevalence. WHO recommends isoniazid prophylaxis (5 mg/kg daily) for at least 6 months for all asymptomatic children younger than 5 years and for all HIV-infected children, including those aged 5 or more years who are household contacts of adults with smear-positive tuberculosis. In all these cases it is essential that clinicians rule out active TB prior to commencing the children on isoniazid TB preventive therapy. The best way to detect TB infection is tuberculin skin testing, and chest x-ray is the best method to screen for TB disease among contacts. These tests should be used where they are readily available to screen exposed contacts. However, doing so may not be possible when tuberculin solution is unavailable, as is often the case in many developing countries. Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. Routine assessment of exposed contacts does not require chest x-ray or tuberculin skin testing.

**BCG Disease**

BCG is a live, attenuated vaccine derived from *Mycobacterium bovis*. WHO’s Expanded Program on Immunization recommends BCG vaccination for all newborns in high-burden countries.

BCG is a safe vaccine. However, 1%-2% of children will develop some complications after BCG vaccination. The most common complications include local reactions, localized abscesses, bacterial superinfection, supplicative adenitis, and local keloid formation. Most of these reactions resolve within a few weeks. However, those children who develop disseminated BCG disease should be investigated for immunosuppression (mainly HIV) and treated for TB with a standard first-line regimen (excluding pyrazinamide, to which *M. bovis* is universally resistant). Some children with persistent localized
abscesses may require surgical drainage. Management of adverse reactions in the setting of advanced HIV/AIDS or other immunodeficiencies is more complicated and may be best managed by specialists at tertiary centers.

**References**


OBJECTIVES

1. Describe the types of malignancies commonly found in children and adolescents with human immunodeficiency virus (HIV)/AIDS.
3. Discuss the clinical manifestations and treatment of the various HIV-associated malignancies.
4. Discuss the specific supportive-care measures necessary for children receiving chemotherapy and radiation therapy.

KEY POINTS

1. Children with HIV infection are at increased risk of developing malignancies as a result of the dysregulated immune system and the interplay of other oncogenic viruses.
2. The most common malignancies found in children with HIV/AIDS are NHL, KS, and leiomyosarcoma.
3. Treatment for HIV-associated malignancies may be complicated by HIV-associated organ dysfunction, infectious complications, and drug interactions between chemotherapy and antiretroviral drugs as well as combined immunosuppression between HIV infection and chemotherapy.
4. Treatment of HIV infection with highly active antiretroviral therapy is critical to the treatment of HIV-related malignancies and must be instituted alongside chemotherapy.

OVERVIEW

Evidence of the relationship between human immunodeficiency virus (HIV) and cancer became evident early in the HIV/AIDS epidemic. In 1981, the U.S. Centers for Disease Control and Prevention (CDC) described a clustering of cases of Kaposi sarcoma (KS), until then a rare form of cancer, among homosexual men in New York and California. The following year, the CDC reported a clustering of cases of gay men in San Francisco with diffuse, undifferentiated non-Hodgkin’s lymphoma (NHL), another rare cancer. In time, it became apparent that these unusual forms of cancer were appearing as a result of infection with HIV. However, this association would not be limited to these two forms of malignancy. Many other neoplastic disorders, most notably primary central nervous system (CNS) lymphoma, leiomyosarcoma, anal cancer, and cervical cancer, have also been linked to HIV infection.

This module will discuss the relationship between HIV and malignancy, with special attention to the tumors most commonly seen in the pediatric and adolescent populations. An overview of the epidemiology of HIV-related malignancy will be followed by discussions of the pathogenesis, clinical manifestations, and treatment of each cancer.

EPIDEMIOLOGY AND PATHOGENESIS

Malignancy occurs much more commonly in HIV-infected children than in uninfected children. HIV-infected children are at about a 40 times higher risk of developing malignancy than the general population. Among HIV-infected children in the United States, the incidence of malignancy is about one case per 1,000 children per year. In contrast, the incidence of cancer among all U.S. children is about one to two cases per 10,000 per year.

Children with HIV also have a predilection for developing rare tumors. In the general U.S. pediatric population, leukemia and brain tumors make up almost all new cases of malignancy each year. However, among U.S. children infected with HIV, NHL is the most common type of cancer, followed by KS and leiomyosarcoma.
In response to these epidemiologic data, the CDC added NHL, primary CNS lymphoma (PCNSL), and KS to the list of Category C symptoms (AIDS-defining illnesses) for children and has added leiomyosarcoma to the list of Category B (symptomatic HIV-infection entities not included in Category C) symptoms. The World Health Organization lists all of these under Clinical Stage 4 and does not classify leiomyosarcoma. (See the chapter on HIV/AIDS diagnostic criteria for a discussion of the CDC and WHO clinical categories.)

Furthermore, invasive cervical cancer occurs much more commonly in female HIV-infected adolescents (and adults) than in the general population. As a result, the CDC included invasive cervical cancer as a Category C symptom for HIV-infected adolescents (and adults) and has added cervical dysplasia (moderate to severe) and noninvasive cervical carcinoma to the list of Category B symptoms for adolescents (and adults). The WHO classifies invasive cervical cancer as Clinical Stage 4 and does not classify cervical dysplasia and noninvasive cervical cancer.

Though not listed in the CDC revised classification or WHO Clinical Staging classification systems, cancers such as Hodgkin’s disease, anal cancer, lung cancer, lip cancer, and testicular cancer are also more common with HIV infection.

The incidence of cancer is lower among children with HIV than among adults with HIV (0.1% per year versus 4% per year). Also, the relative incidence of specific cancers differs between children and adults. For example, in the United States, KS is the most common HIV-associated cancer in adults with HIV, whereas it is much less common in children with HIV. In contrast, leiomyosarcoma is found more commonly among children than among adults with HIV.

Regional variations in the prevalence of pediatric HIV-related malignancy exist. Although NHL is the most common pediatric HIV-related malignancy in the United States, KS remains the most common pediatric HIV-related malignancy in sub-Saharan Africa. Why these differences exist is not entirely clear. However, the prevalence of human herpesvirus 8 (HHV-8), the virus necessary for the development of KS, is much higher in central Africa than in the United States.

The pathogenesis of HIV-related malignancy is related to several factors. HIV weakens the immune system, thus diminishing the body’s innate tumor surveillance ability, much in the way that immunosuppressive agents put transplant patients at risk of malignancy. Furthermore, viruses such as the Epstein-Barr virus (EBV), human papilloma virus (HPV), and HHV-8 interact with HIV to create an environment that enhances tumor growth. The relationship between HIV-related malignancy and certain viruses is well established. For example, nearly every case of KS is linked with the presence of HHV-8, and nearly every case of HIV-related PCNSL is linked with the presence of EBV infection. Also, EBV is often isolated from HIV-related leiomyosarcoma, systemic NHL, and Hodgkin’s disease.

**Common Cancers Diagnosed in HIV-Infected Children and Adolescents**

**Non-Hodgkin’s Lymphoma**

The spectrum of HIV lymphoid malignancies spans lymphoproliferative disease such as lymphoid interstitial pneumonitis to high-grade NHL and CNS lymphoma as well as Hodgkin’s disease. NHL is the most common HIV-related malignancy (HRM) and usually presents as an extranodal high-grade B-cell lymphoma, although T-cell malignancies can be seen as well. One study from Malawi demonstrated that more than half of the cancers in children with HIV infection were lymphomas.

NHL accounts for about 7% of cancers among all U.S. children younger than 20 years. In contrast, NHL is one of the most common types of malignancy among HIV-infected children, accounting for more than 80% of HIV-related cancers. HIV-infected children most commonly develop Burkitt’s (small noncleaved cell) lymphoma and immunoblastic (large cell) lymphoma.

**Clinical presentation.** HIV-infected children who are diagnosed with NHL often have extranodal disease (disease spread outside the lymph nodes) at the time of presentation. Indeed, the cancer will probably have already metastasized to such places as the brain, bone marrow, and gastrointestinal tract.

Symptoms of cancer, including NHL, can be indistinguishable from symptoms of chronic HIV infection. Symptoms such as fever, fatigue, weight
loss, night sweats, anorexia, hepatosplenomegaly, and lymphadenopathy may reflect underlying HIV infection, but they may also reflect the presence of lymphoma. NHL includes many organ-specific symptoms (Table 1).

**Diagnosis and staging.** Diagnosis of NHL is made through biopsy of affected tissue. Staging involves the use of computed tomography (CT) scans (particularly of the head, abdomen, and pelvis), bone marrow biopsy, and cerebrospinal fluid (CSF) analysis.

Prognosis is better in patients with CD4+ counts greater than 100 per microliter, a near-normal serum lactate dehydrogenase level, no history of opportunistic infections, and a good performance status (i.e., the ability to function at a near-normal ability during daily activities).

**Treatment.** The therapies used in HIV NHL in children have been varied, including standard chemotherapy regimens, the current first line of which is CHOP, a regimen combining cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), and prednisone. Other variations such as BACOD (bleomycin, Adriamycin, cyclophosphamide, Oncovin, dexamethasone) and ABVD (Adriamycin, bleomycin, vincristine, dexamethasone) or some combination of these have been attempted in small case series. The results were poor, with median survival of 6 months. The experience in adults in the pre-highly active antiretroviral therapy (HAART) era has been equally disappointing. However, meta-analysis of these various regimens revealed cyclophosphamide and methotrexate to be most active, whereas dose escalation of doxorubicin, prednisone, and vincristine was clinically and statistically insignificant. These studies have led to the use of cyclophosphamide and methotrexate at high dose rates with successful treatment of children along with well-tolerated toxicity (per National Cancer Institute protocol). Because HIV NHL often spreads to the brain, treatment includes CNS prophylaxis with intrathecal (chemotherapy into the spinal fluid) methotrexate or cytarabine.

**Table 1. Site-dependent symptoms of NHL**

<table>
<thead>
<tr>
<th>Mediastinal or pharyngeal tumor</th>
<th>Abdominal tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>Ascites</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Retractions</td>
<td>Pain</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Palpable mass</td>
</tr>
<tr>
<td>CNS disease</td>
<td>Maxillofacial tumor</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>Asymmetric facial expression</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Jaw mass</td>
</tr>
<tr>
<td>Gait instability</td>
<td>Numbness of the chin (peripheral facial nerve compression)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td></td>
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</tbody>
</table>
Primary CNS Lymphoma
PCNSL is a subtype of NHL that is limited to the brain tissue. PCNSL is much more common in HIV-infected children than in uninfected children. The differential diagnosis of CNS lymphoma includes opportunistic infections such as toxoplasmosis or cryptococcosis. Unlike adults with HIV, in whom toxoplasmosis is the most common cause of a brain mass, PCNSL is the most common cause of an isolated brain mass in HIV-infected children. One should suspect PCNSL in any HIV-infected child with neurological abnormalities accompanied by mass lesions on a CT or magnetic resonance imaging scan of the brain. Although about 30%-50% of HIV-related systemic lymphomas are associated with EBV, HIV-related PCNSL appears to have a near-100% association with EBV.

Diagnosis. Diagnosis of PCNSL begins with cytological assessment of the CSF for malignant cells. These cells are present in up to 23% of patients. Analysis of CSF for the presence of EBV DNA by using polymerase chain reaction is also useful in suggesting the presence of PCNSL. Definitive diagnosis of PCNSL requires a brain biopsy. Assessment of serum for toxoplasma immunoglobulin G can help in determining the likelihood of CNS infection with toxoplasmosis. Negative titers make toxoplasmosis an unlikely diagnosis. Imaging can be helpful in distinguishing between the two diagnoses. Multiple ring-enhancing lesions on CT or magnetic resonance imaging are more suggestive of toxoplasmosis, whereas single lesions are more likely to be PCNSL.

Treatment. Treatment for PCNSL involves either the use of whole-brain radiation or high-dose intravenous (IV) methotrexate along with intrathecal therapy. Unfortunately, prognosis for this tumor remains poor. Without treatment, survival is less than 1 month; with treatment, survival is 2-4 months.

When a definitive diagnosis cannot be made and toxoplasmosis is under serious consideration as the etiology of disease, a trial of therapy for toxoplasmosis can help determine the true diagnosis. Lesions’ failing to respond would be suggestive of and near diagnostic for PCNSL.

Lymphoproliferative Disorders
Children with HIV are at high risk of developing lymphoproliferative disorders. Examples include lymphoid interstitial pneumonitis, pulmonary lymphoid hyperplasia, diffuse interstitial lymphocytosis syndrome, and mucosa-associated lymphoid tumors.

Lymphoproliferative disorders respond well to HAART. If the lymphoproliferative disorder progresses to lymphoma, the treatment would then be as described earlier for HIV-related NHL.

Kaposi Sarcoma
KS was first described in 1872 by the Hungarian physician Moritz Kaposi as a disease of “multiple idiopathic pigmented hemangiosarcomas” affecting mainly men older than 40 years. In the era of HIV/AIDS, KS became the first AIDS-defining cancer, initially noted in men who have sex with men. In the United States, KS is the AIDS-defining illness in less than 1% of children younger than 13 years, increasing to 3% in the adolescent years. Where the prevalence of infection with HIV and HHV-8 is higher, these numbers are dramatically increased. In Zambia, for example, KS accounts for almost 20% of all childhood cancers.

Pathogenesis. Immunosuppression is believed to be an integral factor in the pathogenesis of KS. An increased incidence of KS is found in other immunosuppressed patients, in particular among transplant patients receiving immunosuppressive agents. Recent data have also revealed a strong link between underlying infection with HHV-8 and the development of KS. HHV-8 has also been implicated in the pathogenesis of other neoplastic conditions, such as primary effusion lymphoma (a rare form of NHL also known as body cavity lymphoma) as well as multicentric Castleman’s disease (a rare disorder of the lymph nodes). Finally, the pathogenesis of KS depends strongly on angiogenesis, or the proliferation of new blood vessels, and medications are being explored to target this aspect of KS development.

Figure 2. Typical cutaneous Kaposi’s sarcoma lesion
**Clinical presentation.** KS most commonly affects the skin and oral mucosa. Its lesions are often found on the tip of the nose; on the trunk, arms, or neck; or in the mouth. On patients with dark skin, the lesions appear as dark plaques or nodules. On lighter-skinned people, the lesions are reddish-purplish or brownish. Skin lesions may first appear as erythematous macules, but over time they darken and become raised or nodular. Cutaneous lesions, specifically of the lower extremities, have been associated with peripheral edema, which can be debilitating. Nearly 30% of patients with KS also have lesions of the oral mucosa, most commonly on the hard palate. As these lesions grow, they may interfere with eating and speaking.

The differential diagnosis for cutaneous KS lesions includes hemangiomas, nevi, dermatofibromas, and bacillary angiomatosis. Distinguishing bacillary angiomatosis from KS is particularly important, because bacillary angiomatosis is caused by gram-negative bacteria (a *Bartonella* species) and thus may be readily treated with antibiotics. When necessary, performing a punch biopsy will help in making the correct diagnosis.

In addition to causing skin disease, KS may spread to the lymphatic system, the lungs, and the digestive tract. A physical exam may reveal lymphadenopathy (enlarged lymph nodes), which may be firm and nontender. Lesions in the oral mucosa often correlate with the presence of other gastrointestinal lesions. These lesions may be asymptomatic (often found at autopsy) or can lead to such problems as diarrhea and rectal bleeding. Metastases to the lungs may cause shortness of breath or hemoptysis (bloody cough). Though less common, some patients may present with pulmonary or gastrointestinal KS with no apparent skin lesions.

**Treatment of localized disease.** Most forms of KS will regress with the initiation of HAART, with response rates of 60%-80%. Thus, one should always incorporate treatment with antiretrovirals in the treatment of KS. Incorporating a protease inhibitor is more effective than a non-protease inhibitor regimen for KS in adults. This finding has not been clearly demonstrated in the pediatric population, and studies need to be carried out to unequivocally confirm such in this population.

For patients who do not respond adequately to antiretroviral therapy alone, other forms of treatment are effective. One can treat isolated lesions on the skin or in the mouth with alitretinoin gel, intralesional vinblastine, liquid nitrogen, laser ablation, or radiotherapy.

Subcutaneous interferon α (IFN-α) has been used in children with early disease. Though IFN-α can induce clinical responses in 32%-40% of patients, the development of flulike symptoms, such as fever, chills, headaches, and myalgias, often complicates IFN-α therapy. Nonsteroidal anti-inflammatory agents may help ameliorate some of these symptoms.

**Treatment of diffuse disease.** For patients with widespread cutaneous disease or organ involvement, systemic chemotherapy is often required. Currently, the treatment of choice is liposomal doxorubicin or liposomal daunorubicin, where response rates of 40%-80% have been demonstrated with liposomal doxorubicin at 20 mg/m² of body surface area every 2 or 3 weeks for six cycles. Recent studies have shown them to be more effective and less toxic than combination chemotherapy, which usually includes doxorubicin, vincristine, and bleomycin and which until recently was the standard of care. Side effects of liposomal doxorubicin and daunorubicin include myelosuppression and alopecia. Liposomal doxorubicin has also been associated with hand-foot syndrome (painful erythema and desquamation of the palms and soles).

One older study compared dactinomycin plus vincristine versus both plus imidazole carboxamide (DTIC) and demonstrated 94% complete remission with DTIC compared with 55% complete remission without it.

When liposomal agents fail, paclitaxel (Taxol) is often used next. Response rates of 70%-90% have been reported. Paclitaxel has been associated with myelosuppression, alopecia, peripheral neuropathy, and hypersensitivity reactions.

Though treatment of KS has evolved tremendously since the onset of the HIV epidemic, there is no effective cure for this cancer. The goal of treatment should be the palliation of symptoms. However, experimental therapy with angiogenesis inhibitors is being explored and is expected to be promising given what is known about the pathogenesis of KS.
**Smooth-Muscle Tumors: Leiomyosarcoma**

Leiomyosarcoma occurs rarely in children without HIV infection, and the incidence is estimated to be only two cases per 10 million children annually. However, with the onset of the AIDS epidemic, increased numbers of leiomyosarcoma have been reported in HIV-infected children. One large case series of HIV-infected children with cancer reported that 17% of their patients had leiomyosarcoma. This increased incidence in HIV-infected children led the CDC to classify leiomyosarcoma as a Category B symptom. Interestingly, there has not been a parallel rise in the incidence of leiomyosarcoma in HIV-infected adults.

The etiology of HIV-related leiomyosarcoma is unknown. However, EBV has been isolated in relatively high titers from leiomyosarcomas in pediatric patients with HIV. Also, these tumors present relatively late in the course of children with AIDS, suggesting a role of chronic immune suppression in tumor pathogenesis.

**Clinical Presentation.** Leiomyosarcoma most commonly presents within the gastrointestinal tract. Children with HIV, however, may present with tumors in unusual locations, such as the lungs, spleen, adrenal glands, pleural space, or intracranially. The course of the disease varies, with slow-growing tumors often not requiring intervention, whereas more aggressive, disseminated tumors require multimodal treatment with surgery and chemotherapy.

Gastrointestinal lesions may cause abdominal pain, rectal bleeding with anemia, abdominal masses, and bowel obstruction. Children with lung disease may appear cyanotic (blue around the face or lips). Respiratory insufficiency may be related to bronchial obstruction causing wheezing or secondary to persistent respiratory infections. Chest radiography often shows multiple pulmonary nodules. Children with brain lesions often show signs of increased intracranial pressure, such as nausea, vomiting, and headaches. Other neurological findings may also be present, such as visual disturbances, gait instability, and difficulty with coordination.

**Treatment.** Because smooth-muscle tumors are not particularly responsive to chemotherapy or radiotherapy, surgery is the treatment of choice. When surgery fails or is not an option, treatment involves the regimen VAC (vincristine, actinomycin, cyclophosphamide), often alternating with VAdriaC (Adriamycin in place of actinomycin). Ifosfamide and etoposide can be used as another alternating regimen. The course of therapy is generally 6 months to 1 year. Radiation therapy is sometimes given in addition to chemotherapy.

**Cervical Cancer**

Cervical cancer is the second most common cancer in women worldwide. Furthermore, HIV-infected women develop cervical cancer more often than non-HIV-infected women. For women with HIV, the risk of developing invasive cervical cancer is five to nine times as high as that for women without HIV. These findings have recently been confirmed in other parts of the world. In Nigeria, for example, one study found that high-grade lesions occurred more than three times more often in women with HIV infection than in women without infection. Because of this increased risk in HIV-infected women, the CDC added invasive cervical cancer to the list of AIDS-defining illnesses for adolescents and adults (WHO Clinical Stage 4) and has added moderate to severe cervical dysplasia and cervical carcinoma in situ to the list of Category B symptoms for these age groups.

**Pathogenesis.** HPV is a sexually transmitted virus that has been implicated in the development of cervical cancer. HPV is found in more than 99% of cervical cancer specimens; types 16 and 18 make up more than 60% of these oncogenic HPV subtypes. HIV-infected women are more likely to be infected with HPV, to be infected with multiple types of HPV, and to have persistent HPV infection than are HIV-negative women. Also, HIV-positive women are more likely to develop cervical dysplasia when infected with HPV than are women who are HIV negative. Several studies comparing women with cervical dysplasia found that risk factors for dysplasia included HIV-positive status and persistent HPV infection. Interestingly, unlike other HIV-related malignancies, there has not been a consistent relation to CD4 count.

**Screening and prevention.** The Papanicolaou (Pap) smear is an important screening tool for early detection of cervical cancer in all sexually active women. Most preventive health guidelines recommend that all sexually active adolescents obtain yearly Pap smears. However, because of the heightened risk of cervical cancer in HIV-positive women, both the U.S. Public Health Service and
the Infectious Diseases Society of America recommend Pap smears every 6 months for all HIV-infected women during the first year after HIV diagnosis, with yearly Pap smears thereafter if the initial two smears are negative.

Conventional Pap smears are as sensitive and specific in women with HIV as in women without HIV. HPV DNA tests of cervical cell scrapings are not recommended as a screening tool, although they may assist in triaging women without HIV to colposcopy in the presence of low-grade squamous intraepithelial lesions.

Although HPV is sexually transmitted, male condoms do not decrease HPV transmission to women. Male condoms may offer a protective benefit to men, but study results have been conflicting and often confounded. Data on female condoms and spermicidals are scant. Unlike other bacterial and viral sexually transmitted infections, including HIV, HPV also infects external genital tissue, which may account for the lack of protection via barrier methods. Although barrier and microbicidal methods may theoretically decrease viral exposure, they have not been proven to have a protective effect.

The ultimate primary prevention of genital HPV may be a vaccine, one of which completed clinical trials and became available in June 2007. It covers the two most common serotypes of HPV. Please refer to the module covering immunizations for more information.

Management of abnormal Pap smear results. Pap smears that are abnormal often require further investigation with colposcopy—especially for women infected with HIV. For example, HIV-infected women are more likely (>10%) to have high-grade squamous intraepithelial lesions on workup of ASCUS (atypical squamous cells of undetermined significance) than are women who are HIV negative, and therefore even ASCUS should be colposcopically evaluated in HIV-positive women, regardless of HPV status. Colposcopy here should be used to examine the vagina and vulva in addition to the cervix, given the increased risk of other genital tract dysplasias and cancers in HIV-positive women.

Dysplasia, specifically low-grade squamous intraepithelial lesions that persist for more than 1 or 2 years and high-grade squamous intraepithelial lesions, should be treated with excision or ablation. Conical excision may be accomplished through laser, “cold knife,” or loop electrosurgical excisional procedure cautery. Ablative modalities include laser and liquid nitrogen (cryotherapy). Postexcisional bleeding was substantially higher (>20%) in a small series of women with HIV.

Women with HIV are more likely to have multiple recurrences of dysplasia after therapy than women without HIV infection (62% and 18%, respectively), independent of ablational or excisional procedure type. Thus, HIV-infected women require diligent gynecologic follow-up. Women on HAART may have a more favorable natural history of dysplasia, although the data are inconclusive. Although women on HAART may have better immune control of their HPV, they may be at increased risk of infection with multiple HPV strains.

Treatment. Cervical cancer is managed through surgery with or without radiation and chemotherapy, depending on the extent of invasion. Recurrence or persistence of cervical cancer occurs in 35% of women. Patients with HIV have a higher mortality rate from cervical cancer than HIV-negative women. The data on the effect of HAART on cervical cancer progression is limited; long-term follow-up of larger groups of women is needed.

Early detection is crucial. One recent retrospective study in Nigeria demonstrated that 86% of 36 cases of confirmed cervical cancer were late stage at presentation, mitigating the ability to effectively treat these women.

Anal Cancer
Anal cancer is uncommon; however, the incidence is increasing in the population at risk, particularly those infected with HPV and HIV. The National Cancer Institute estimated 4,000 cases of anal cancer in 2004. The incidence is 35 times greater in men who are receptive for anal intercourse than in the general population in the United States. It is not limited to men, however, and women who practice anoreceptive intercourse, as a means to maintain virginity, for example, are also considered to be at high risk. About 85% of patients with anal cancer were found to have HPV infection as well. The association between AIDS and anal cancer is strong, although it is currently not categorized as an AIDS-defining illness. Individuals tend to have persistent HPV infection and high viral loads, contributing to the development of cancer.
**Table 2. Supportive care for children receiving chemotherapy**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Definition</th>
<th>Management</th>
<th>Care Guidelines</th>
</tr>
</thead>
</table>
| **Neutropenia** | Absolute neutrophil count <1000/mL| • Monitor for fever, skin ulcerations, pain, respiratory symptoms, stomatitis, perirectal pain, and fissures  
  • Obtain blood (including central line) and urine cultures and provide broad-spectrum antibiotics for fever >38.5°C or >38°C three times in 24 h  
  • Detailed exam to identify source with further workup when necessary | Neutropenic precautions  
  • Monitor temperature  
  • Avoid ill contacts, fresh flowers, unpasteurized foods, and dental work  
  • Avoid invasive procedures including rectal temperatures and exams, urinary catheterization and intramuscular injections  
  • Antibiotics |
| **Thrombocytopenia** | Platelet count <100,000/µL | • Assess for bleeding, bruising, petechiae, purpura  
  • Transfuse platelets 10 mL/kg to keep platelets >20,000  
  • Keep platelets >50,000 if active bleeding, before lumbar puncture or intramuscular injections, and other minor procedures other than bone marrow procedures | Thrombocytopenic precautions  
  • Avoid procedures if possible  
  • No rectal temperatures or exams  
  • Use pressure dressing for bone marrow procedures  
  • Transfusion therapy |
| **Anemia**       | Hemoglobin <10 g/dL               | • Assess for tachycardia, murmur, pallor, tachypnea, dyspnea, level of consciousness  
  • Transfuse with leukoreduced, irradiated packed red blood cells 10-15 mL/kg when necessary when symptomatic or hemoglobin <7 g/dL | Monitor for associated symptoms of fatigue, irritability, shortness of breath, chest pain with exertion, and headaches  
  • Transfusion therapy |
| **Nausea and Vomiting** | Serotonin receptor antagonists: ondansetron 4 mg p.o./IV t.i.d. (4-11 yrs old), 8 mg p.o./IV t.i.d. (>11 yrs old). Give just prior to chemotherapy for prevention of N/V  
  • Phenothiazines (>2 yrs old): Promethazine 0.25 mg/kg of body wt p.o./IV every 6 h when necessary; max dose, 50 mg  
  • Dexamethasone 6 mg/m² IV as one dose with the first daily dose of ondansetron  
  • Other antiemetics: dimenhydrinate, lorazepam, granisetron, dolasetron, prochlorperazine, chlorpromazine, meclizine, dronabinol | Assess frequency of vomiting and level of hydration  
  • Strict monitoring of input and output  
  • Offer small quantities of food  
  • IV hydration and oral rehydration solution as needed  
  • Antiemetic therapy, use to prevent N/V |
| **Mucositis**    | Breakdown of oral and/or gastrointestinal mucosa with or without secondary infection | • Rinse with a solution of 1 tablespoon of salt and baking soda in 1 L of water for several minutes 4–6 times per day  
  • Acetaminophen 10–15 mg/kg p.o. every 4 h and/or codeine 1 mg/kg every 6 h  
  • Severe mucositis may require morphine therapy for pain  
  • Benadryl:Maalox:Viscous Lidocaine at 1:1:0.5 solution swish and spit every 4-6 h  
  • Nystatin oral suspension 100,000 U/mL, 5 mL p.o. swish and swallow every 4-6 h | Frequent oral examination for evidence of erythema and ulcers  
  • Meticulous oral hygiene when awake  
  • Pain medication therapy |

p.o., per os; N/V, nausea and vomiting; t.i.d., three times daily.
The pathogenesis of anal cancer is felt to be equivalent to that of cervical cancer, in which HIV probably interacts and affects the oncogenicity of HPV, leading to malignant change.

The therapy of anal cancer is combined-modality treatment with chemotherapy and radiation. Most patients will have clinical regression. Peddada et al. demonstrated that all HIV-positive patients achieved complete remission with radiation along with 5-fluorouracil and mitomycin on day 1.

**Postchemotherapy and Radiation Therapy Care and Considerations**

Supportive care for patients receiving chemotherapy is important and should include *Pneumocystis jirovecii* prophylaxis, regardless of the CD4+ count; monitoring for fevers and infections during periods of neutropenia; thrombocytopenic precautions when the patient has a decreased platelet count; and blood transfusion therapy and epoetin therapy for symptomatic anemia (Table 2).

General side effects of radiation therapy include radiation dermatitis (skin inflammation) and myelosuppression (suppression of the bone marrow). Site-specific side effects may also occur. Children receiving radiation therapy who experience side effects will require symptom management (Table 3).

Children receiving IFN-α therapy may experience flu-like symptoms (fever, chills, muscle or joint pain, headache), fatigue and malaise, anorexia (loss of appetite), diarrhea, changes in mental status (e.g., poor concentration, somnolence, depression, forgetfulness, irritability), abnormal liver function tests, neutropenia, thrombocytopenia, and bone pain.

Avoid using zidovudine along with myelosuppressive (bone marrow toxic) chemotherapy, if possible, because the combination may heighten the potential for anemia, neutropenia, and thrombocytopenia.

Childhood cancer chemotherapy and radiation may cause several acute as well as late effects (Table 4). Late effects in long-term survivors might include neurocognitive deficits, neuroendocrine disturbances, gonadal dysfunction, secondary tumors, and multiorgan damage. Radiation to the brain or intrathecal chemotherapy places long-term survivors of childhood cancer at risk of cognitive deficits and developmental delay. Risk factors for therapy-induced neurocognitive damage include early

### Table 3. Symptom management for children receiving radiation therapy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
<th>Care Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/V</td>
<td>See Table 2</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>See Table 2</td>
<td></td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>✦ Aloe vera lotion 4–6 times daily</td>
<td>✦ Frequent skin exam for erythema, erosions, ulcers, blisters</td>
</tr>
<tr>
<td></td>
<td>✦ Diphenhydramine 1 mg/kg/dose p.o. every 6 h when necessary for itching</td>
<td>✦ Avoid excess heat and cold, sun exposure, and perfumed ointments</td>
</tr>
<tr>
<td></td>
<td>✦ 1% Hydrocortisone cream for itching or moderate erythema</td>
<td>✦ Use gentle soap; rinse off and pat dry</td>
</tr>
<tr>
<td></td>
<td>✦ Silvadene cream 1–2 times daily for moist desquamation</td>
<td>✦ Avoid adhesive tape or perfumed lotions in the radiation field</td>
</tr>
<tr>
<td></td>
<td>✦ Do not scrub skin when removing ink markings</td>
<td>✦ Do not scrub skin when removing ink markings</td>
</tr>
<tr>
<td>Enteritis</td>
<td>✦ Loperamide 1 mg p.o. t.i.d. (2–5 yrs old); 2 mg p.o. b.i.d. (6–8 yrs old); 2 mg p.o. t.i.d. (8-12 yrs old)</td>
<td>✦ Assess frequency of diarrhea</td>
</tr>
<tr>
<td></td>
<td>✦ 3- to 4-day rest period from radiation therapy if dehydration occurs</td>
<td>✦ Monitor level of hydration</td>
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<tr>
<td></td>
<td></td>
<td>✦ Restrict roughage in diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ Restrict dietary lactose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ Provide elemental diet to relieve symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ Strict monitoring of input and output</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ Daily weight assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ IV or oral hydration as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✦ Antidiarrheal medications</td>
</tr>
</tbody>
</table>

N/V, nausea and vomiting; p.o., per os; b.i.d., twice daily; t.i.d., three times daily.
HIV-Associated Malignancies

Irradiation and some chemotherapeutics may affect hearing, vision, and dentition. Systemic effects may include hepatotoxicity, renal toxicity, cardiac toxicity (primarily by anthracyclines and thoracic radiation), vascular damage, lung fibrosis, endocrine dysfunction (particularly thyroid disturbance and growth effects), osteoporosis, and sterility. Second malignant neoplasms are 6.38 (95% confidence interval, 5.69-7.13) times as likely among childhood cancer survivors as in the general population, with breast and secondary leukemias occurring at up to 16 and 19 times the expected incidence rates, respectively. In a childhood cancer survivor study, second malignant neoplasms of any type were reported to be independently and statistically significantly associated with younger age of the child at primary cancer diagnosis, primary childhood Hodgkin’s disease or soft-tissue sarcoma, female sex, and increased exposure to anthracyclines and/or epipodophyllotoxins.

Table 4. Chemotherapy agents and side effect profiles

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin-D</td>
<td>Antitumor antibiotic</td>
<td>Stimulates apoptosis; inhibits topoisomerase II</td>
<td>N/V, alopecia, mucositis, vesicant, hepatic vaso-occlusive disease</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Antitumor antibiotic</td>
<td>Oxidative cleavage of DNA</td>
<td>N/V, pulmonary fibrosis, mucositis, alopecia, hypersensitivity</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>Prevents DNA synthesis through alkylation of DNA and RNA</td>
<td>Myelosuppression, N/V, cystitis, water retention, cardiac, second cancers</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Antimetabolite</td>
<td>Inhibits DNA polymerase, cell cycle specific for S phase</td>
<td>Myelosuppression, N/V, mucositis, eye irritation</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>Anthracycline antibiotic</td>
<td>Stimulates apoptosis; inhibits topoisomerase II</td>
<td>Mucositis, N/V, myelosuppression, vesicant, cardiac (acute and long term), secondary cancer</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Steroid</td>
<td>Induces lymphoblast apoptosis</td>
<td>Hypertension, polyphagia, water retention, moon facies, nightmares, immunosuppression</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Anthracycline antibiotic</td>
<td>Stimulates apoptosis; inhibits topoisomerase II</td>
<td>Mucositis, N/V, alopecia, myelosuppression, vesicant, cardiac (acute and long term), secondary cancer</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Epipodophyllotoxin</td>
<td>Antimitotic agent binds tubulin</td>
<td>Mucositis, myelosuppression, alopecia, N/V, secondary leukemia, hypersensitivity</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Alkylating agent</td>
<td>Prevents DNA synthesis through alkylation of DNA and RNA</td>
<td>Myelosuppression, N/V, cystitis, water retention, cardiac, renal</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Antifolate antimetabolite</td>
<td>Inhibits thymidylate and purine synthesis</td>
<td>Mucositis, mild myelosuppression, neurotoxicity, hepatic toxicity, renal toxicity</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Taxol</td>
<td>Blocks microtubule depolarization</td>
<td>Hypersensitivity, mucositis, alopecia, myelosuppression, cardiac, EtOH poisoning</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Steroid</td>
<td>Induces lymphoblast apoptosis</td>
<td>Hypertension, polyphagia, water retention, moon facies, nightmares, immunosuppression</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Vinca alkaloid</td>
<td>Antimitotic agent M phase specific and active in S phase</td>
<td>Neurotoxicity, vesicant, alopecia, syndrome of inappropriate antidiuretic hormone, fatal if given intrathecally</td>
</tr>
</tbody>
</table>

N/V, nausea and vomiting.

References


**Cutaneous Manifestations of HIV Infection**

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Heidi Schwarzwald, MD, MPH

**Objectives**

1. Review the most common cutaneous manifestations of human immunodeficiency virus (HIV) infection.
2. Describe the methods of diagnosis and treatment for each cutaneous disease.

**Key Points**

1. Cutaneous lesions are often the first manifestation of HIV noted by patients and health professionals.
2. Cutaneous lesions occur frequently in both adults and children infected with HIV.
3. Diagnosis of several mucocutaneous diseases in the setting of HIV will allow appropriate treatment and prevention of complications.

**Overview**

Many people with human immunodeficiency virus (HIV) infection develop cutaneous lesions. The risk of developing cutaneous manifestations increases with disease progression. As immunosuppression increases, patients may develop multiple skin diseases at once, atypical-appearing skin lesions, or diseases that are refractory to standard treatment. Skin conditions that have been associated with HIV infection are listed in Table 1.

Once HIV infection has been confirmed, the diagnosis of certain mucocutaneous conditions in children (Table 2) and adults (Table 3) can be used to clinically stage the patient. The World Health Organization (WHO) clinically stages patients as having HIV that is asymptomatic (stage 1) or with mild symptoms (stage 2), advanced symptoms (stage 3), or severe symptoms (stage 4).

**Table 1. Cutaneous manifestations of HIV**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Infectious</td>
<td>Herpes zoster</td>
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<tr>
<td></td>
<td>Herpes simplex virus infections</td>
</tr>
<tr>
<td></td>
<td>Superficial fungal infections</td>
</tr>
<tr>
<td></td>
<td>Angular cheilitis</td>
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<tr>
<td></td>
<td>Chancroid</td>
</tr>
<tr>
<td></td>
<td>Cryptococcus</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Human papillomavirus (verruca vulgaris, verruca plana, condyloma)</td>
</tr>
<tr>
<td></td>
<td>Impetigo</td>
</tr>
<tr>
<td></td>
<td>Lymphogranuloma venereum</td>
</tr>
<tr>
<td></td>
<td>Molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Furunculosis</td>
</tr>
<tr>
<td></td>
<td>Folliculitis</td>
</tr>
<tr>
<td></td>
<td>Pyomyositis</td>
</tr>
<tr>
<td>Other</td>
<td>Pruritic papular eruption</td>
</tr>
<tr>
<td></td>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
<td></td>
<td>Drug eruption</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td>Photodermatitis</td>
</tr>
<tr>
<td></td>
<td>Atopic Dermatitis</td>
</tr>
<tr>
<td></td>
<td>Hair changes</td>
</tr>
</tbody>
</table>

Clinical staging is useful in the initial assessment of a patient, at the time the patient enters into long-term HIV care, and for monitoring a patient’s disease progression. The clinical stage of a patient has been shown to be related to survival, prognosis, and disease progression. As shown in Tables 2 and 3, the skin examination plays a significant role in the clinical staging process of patients with HIV. Also, the diagnosis of these cutaneous diseases may lead to the early testing and diagnosis of HIV in children and adults if recognized with other signs and symptoms of HIV infection.
This module focuses on many of the most common and/or significant cutaneous manifestations of HIV; however, other sections cover several mucocutaneous manifestations in depth. To avoid duplication, we will mention them here only briefly.

**Viral Skin Disease**

**Cutaneous Infection with Herpes Simplex Virus**

Herpes simplex virus (HSV) infection most commonly causes disease in the oral or anogenital region; however, widespread disease may be seen in immunocompromised patients (Figure 1). In adults, a relationship has been observed between decreased CD4+ lymphocyte counts and an increased incidence of cutaneous HSV. In children, herpes gingivostomatitis can be so severe that it leads to poor nutrition and dehydration (Figure 2). Chronic HSV infection (present for >1 month) may manifest as severe, progressive, and painful orolabial, genital, or anorectal lesions and is one of the criteria for severely symptomatic (WHO Clinical Stage 4) HIV infection (Figure 3).

**Figure 1. Herpes Simplex** Confirmed herpes simplex virus infection on the nose and cheek of an HIV-infected man. This patient also had similar ulcers on the genitals.

**Table 2. Criteria for recognizing HIV-related mucocutaneous clinical events in children (younger than 15 years)**

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Diagnosis</th>
<th>Definitive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritic papular eruptions</td>
<td>Papular lesions with intense pruritus.</td>
<td>Clinical diagnosis, exclude other causes, such as drug eruptions, atopic dermatitis, scabies.</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>Fungal paronychia (painful, red, and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onychomycosis is uncommon without immunodeficiency.</td>
<td>Clinical diagnosis, microscopic demonstration of fungal hyphae, or culture of the nail.</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>Splits or cracks at the angles of the mouth, usually with surrounding erythema, and not attributable to nutritional deficiency.</td>
<td>Clinical diagnosis or response to antifungal therapy.</td>
</tr>
<tr>
<td>Extensive wart virus infection</td>
<td>Characteristic warty skin lesions. Variants include flat, plantar, papular, and genital. More than 5% or body surface area or disfiguring.</td>
<td>Clinical or histologic diagnosis.</td>
</tr>
<tr>
<td>Extensive molluscum contagiosum</td>
<td>Characteristic skin lesions: small flesh-colored, pearly or pink, dome-shaped or umbilicated papules. May have surrounding redness. More than 5% or body surface area or disfiguring.</td>
<td>Clinical or histologic diagnosis.</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>Current event plus at least one previous episode in the past 6 mo. Aphthous ulceration, typically with a halo of inflammation and yellow–gray pseudomembrane.</td>
<td>Clinical diagnosis.</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Painful rash with fluid-filled blisters, dermatomal distribution, can be hemorrhagic on erythematosus background, and can become large and confluent. Should not cross the midline. Can become disseminated.</td>
<td>Clinical diagnosis, microscopic diagnosis with Tzanck smear, or culture.</td>
</tr>
</tbody>
</table>

Continued on next page
### Table 2. Criteria for recognizing HIV-related mucocutaneous clinical events in children (younger than 15 years) *(concluded)*

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Clinical Diagnosis</th>
<th>Definitive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Stage 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>Persistent or recurrent, creamy white to yellow, soft plaques that can be scraped off, or red patches on the tongue, palate or lining on the mouth, usually painful or tender (erythematous form).</td>
<td>Clinical, microscopic, or culture diagnosis.</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>Fine, small linear patches on lateral borders of the tongue, generally bilateral, that do not scrape off. Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odor, and rapid loss or bone or soft tissue.</td>
<td>Clinical diagnosis.</td>
</tr>
</tbody>
</table>

| **Clinical Stage 4** | | |
| Chronic herpes simplex infection (HSV) | Severe and progressive painful orolabial, genital, or anorectal, lesions caused by HSV and present for >1 mo. | Clinical diagnosis, microscopic diagnosis with Tzanck smear, or culture. |
| Extrapulmonary tuberculosis | Systemic illness, usually with prolonged fever, night sweats, and weight loss. Clinical features of organs involved, such as sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, or skin lesions. | Positive microscopy showing acid-fast bacilli or culture of Mycobacterium tuberculosis from blood or other relevant specimen/tissue except sputum or bronchoalveolar lavage. Biopsy and histology. |
| Kaposi sarcoma | Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or purple color. May develop into plaques, nodules, or tumors. | Clinical diagnosis, may need histologic confirmation. |
| Disseminated fungal infection (cryptococcosis, histoplasmosis, coccidioidomycosis) | Wide range of clinical presentations in the skin, including papules, nodules, and ulcerations. | Histology, antigen detection, and/or culture is needed. |
| Disseminated mycobacterial infection, other than tuberculosis | Wide range of clinical presentations in the skin, including papules, nodules, and ulcerations. | Nonspecific clinical symptoms (weight loss, fever, anemia) plus culture of atypical mycobacterial species from tissue other than lung. |

*Adapted from 2006 WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.*

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**Figure 2. Herpes Simplex**

Herpes simplex virus infection in an HIV-infected girl. Chronic or progressive herpes skin lesions are observed occasionally in HIV-infected children.

**Figure 3. Large ulceration on the upper lip due to herpes simplex virus infection.** This patient’s ulcer had been present for more than 3 months. 

HSV cutaneous disease presents as small grouped vesicles (or blisters) with redness on the surrounding skin. The spread of HSV infection to other areas of the skin is common and occurs through autoinoculation or sexual contact. The typical clinical course of HSV infection includes the rupture of the blisters over the course of a week, with subsequent healing in 2 weeks; however, this course can be significantly prolonged in the immunocompromised host.

The diagnosis of HSV infection can be reached through clinical examination, microscopic identification of virally infected keratinocytes from the blister cavity with a Tzanck stain, viral culture,
immunofluorescent antibody tests, or polymerase chain reaction (PCR). Initial infection is treated with acyclovir at a dose of 10-20 mg/kg of body weight four times per day in children and 400 mg three times per day in adults for 7-14 days. Adults have been treated with valacyclovir (1 g twice a day) and famciclovir (500 mg twice a day) for 7 days. Patients with severe or disseminated disease will probably need intravenous acyclovir. Patients taking acyclovir need to be instructed to drink plenty of fluids to maintain adequate hydration to reduce the risk of acyclovir-induced renal failure.

**Chickenpox (Primary Varicella Zoster Virus Disease)**

In resource-limited settings, where varicella vaccination is unavailable, chickenpox (primary varicella zoster virus [VZV] disease) remains a common childhood illness. Typically there is a prodromal phase with fever, fatigue, and headache. Skin lesions appear as successive crops of vesicles (or small blisters) with surrounding redness. The lesions are in different stages, including papules, vesicles, pustules, and crusts (Figure 4). The rash typically starts on the face and scalp and spreads toward the feet. Primary VZV infection in HIV-infected children or adults may cause severe
or complicated disease, depending on the patient’s level of immunosuppression. Severe disease may be characterized by near-confluent skin lesions and involvement of the mucous membranes. Other potential complications of primary VZV infection include hemorrhagic skin lesions, hepatitis, pneumonia, encephalitis, bacterial complications, and death. Bacterial superinfection of cutaneous lesions may present as erythema, impetiginous changes (honey-colored crusting), and persistent ulcerations. The most common pathogens responsible for superinfection include *Staphylococcus aureus* and group A *Streptococcus*. Appropriate antibiotic therapy is warranted.

Clinical examination, a Tzanck smear, viral culture, immunofluorescent antibody tests, or PCR can be used to diagnose VZV infection. An HIV-infected child who is exposed to chickenpox should receive varicella zoster immune globulin, where available, within 96 h of exposure.

There is a window of opportunity for effective therapy, and it is ideal to administer antiviral therapy within 72 h of disease onset. Immunocompromised children with uncomplicated cases of chickenpox may be treated with acyclovir at a dose of 20 mg/kg by mouth, administered four times per day for 5 days. The maximum dose is 800 mg administered four times daily in children and 800 mg five times daily in adults. Patients with complicated disease may need intravenous acyclovir. Adequate hydration while on acyclovir therapy is imperative.

If a patient is identified as having chickenpox, all efforts should be made to isolate the patient to limit exposure to other children.

**Herpes Zoster**

Patients with HIV infection may also experience reactivation of latent VZV infection (also known as herpes zoster or shingles). One study reported that nearly half of HIV-infected children with chickenpox will have reactivation of disease within 24 months. Herpes zoster is one of the criteria for mildly symptomatic (WHO Clinical Stage 2) HIV infection in children and adults (Figure 5).
Herpes zoster is characterized by painful, grouped, vesicular lesions that appear in a dermatomal pattern (Figure 6). Complications include severe painful ulcerations, postherpetic neuralgia (pain along the course of a nerve), herpes keratitis (if eye involvement occurs), and disseminated disease. Herpes zoster lesions can be distinguished from other vesicular (blisterlike) eruptions because they do not cross the midline.

Clinical examination, a Tzanck smear, viral culture, immunofluorescent antibody tests, or PCR can be used to diagnose VZV infection. As with primary VZV infection, therapy is most effective if introduced within 72 h of disease onset. The treatment of choice for herpes zoster in children is acyclovir 20 mg/kg by mouth, administered four times per day for 7 days; the maximum dose is 800 mg administered four times daily. Adults may take up to 800 mg five times daily. Patients who have severe disease or who cannot take liquids should be treated with acyclovir at a dose of 10-20 mg/kg intravenously every 8 h for 7 days. Adequate hydration is imperative.

Molluscum Contagiosum
Molluscum contagiosum is caused by a poxvirus and is commonly found in persons with advanced HIV infection. In adults, it occurs more commonly with CD4+ lymphocyte counts of less than 200 cells/µL. Adults with CD4+ lymphocyte counts of less than 50 cells/µL are more prone to many lesions and to giant lesions larger than 1 cm. Extensive molluscum (involving >5% of body surface area or disfiguring) is one of the criteria for mildly symptomatic (WHO Clinical Stage 2) HIV infection in children (but not adults).

Molluscum contagiosum lesions are pearly or flesh-colored, dome-shaped, umbilicated papules, ranging from 2 to 5 mm, with a central core (Figure 7). Giant lesions often occur on the face, and they can be disfiguring (Figure 8). These lesions can be spread by autoinoculation, sexual contact, or into a linear configuration by scratching (a phenomenon known as koebnerization).

Diagnosis is either made clinically, by microscopic demonstration of virally infected cells within material expressed from lesions, or histologically. Treatment options include curettage, liquid nitrogen, topical retinoids, imiquimod, topical acids, or electrodesiccation. Despite treatment, the recurrence rate is high. Highly active antiretroviral treatment coupled with increasing CD4+ lymphocyte cell counts lessens the severity of disease or assists in the resolution of disease.

Kaposi Sarcoma
Kaposi sarcoma (KS) is an HIV-related vascular neoplasm that is associated with human herpes virus 8 infection. Cutaneous KS presents as red, violaceous (purple), or brown lesions, which vary from macules or patches to papules, nodules, or tumors (Figure 9). KS can present as lesions on the skin or mucous membranes; however, disseminated disease may involve in any organ. The most common sites of disseminated disease include the skin, mucosal surfaces, respiratory tract, and lymph nodes, and extensive disseminated disease is often associated with lymphedema. Pulmonary and lymph node disease may mimic those of tuberculosis. KS is one of the criteria for severely symptomatic (WHO Clinical Stage 4) HIV infection in children and adults. Please see the chapter on opportunistic infections for a more detailed description of KS.
Cutaneous Manifestations of HIV Infection

Bacterial Skin Disease

Superficial Bacterial Skin Infections

Superficial bacterial skin infections include impetigo, folliculitis, cellulitis, skin abscesses, furunculosis, and paronychia (Table 4). *Staphylococcus aureus* is the cause in most bacterial skin infections, and *S. aureus* colonization is substantially increased in HIV-infected patients.

<table>
<thead>
<tr>
<th>Bacterial Skin Infection</th>
<th>Causative Organism(s)</th>
<th>Clinical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impetigo</td>
<td><em>Staphylococcus aureus</em> majority, <em>Streptococcus pyogenes</em> minority.</td>
<td>Small erythematous macule, papule, or blister that eventually erodes and develops a characteristic honey-colored crust. May be primary or secondary to other skin conditions, such as eczema, scabies, or herpes.</td>
</tr>
<tr>
<td>Folliculitis</td>
<td><em>Staphylococcus aureus</em> most common cause; other causes include <em>Pseudomonas aeruginosa</em>.</td>
<td>Infection or inflammation within the hair follicle, manifesting as erythematous perifollicular pustules. Common sites include head, neck, trunk, axilla, buttocks.</td>
</tr>
<tr>
<td>Furunculosis</td>
<td><em>Staphylococcus aureus</em> most common cause.</td>
<td>Infection or inflammation of the skin and soft tissue surrounding the hair follicle. Lesions are larger than folliculitis.</td>
</tr>
<tr>
<td>Abscess</td>
<td><em>Staphylococcus aureus</em> majority, <em>Streptococcus pyogenes</em> minority.</td>
<td>Localized collection of pus in the skin or soft tissue. May be a complication of untreated cellulitis.</td>
</tr>
<tr>
<td>Cellulitis</td>
<td><em>Staphylococcus aureus</em> majority, <em>Streptococcus pyogenes</em> minority.</td>
<td>Inflammation of the skin, characterized by a painful, edematous, erythematous expanding lesion (plaque).</td>
</tr>
<tr>
<td>Paronychia</td>
<td><em>Staphylococcus aureus</em> (acute), <em>Candida</em> (chronic). May be multifactorial or complicated by other organisms, such as gram-negative rods.</td>
<td>Inflammation, pain, and tenderness of the folds of tissue surrounding the fingernail or toenail.</td>
</tr>
</tbody>
</table>

More severe cases of impetigo, folliculitis, or bacterial skin infections can be treated with an oral penicillinase-resistant penicillin, such as dicloxacillin. Dicloxacillin can be dosed in children as 20-25 mg/kg/day divided four times a day (maximum of 1 g/day) for 7 days. Adults may take 250 mg every 6 h for 7 days.

In areas where methicillin-resistant *Staphylococcus aureus* (MRSA) is prevalent, empiric antibiotic coverage of skin infections should include coverage of this organism. Appropriate coverage will change depending on the setting, but MRSA acquired in the community is often sensitive to trimethoprim-sulfamethoxazole and clindamycin. MRSA should be suspected if bacterial skin infections, such as impetigo or furunculosis, are not responsive to first-line antistaphylococcal antibiotics, such as dicloxacillin.

Disseminated Mycobacterial Infections

HIV-infected patients are at risk for disseminated mycobacterial infections. Extrapulmonary tuberculosis and disseminated nontuberculous mycobacterial infections are both criteria for severely symptomatic (WHO Clinical Stage 4) HIV infection in children and adults.

HIV-infected patients have an increased risk of developing extrapulmonary tuberculosis as CD4 counts decline. The most common forms of extrapulmonary
tuberculosis include pleural effusions, lymphadenopathy, pericardial disease, meningitis, and miliary disease. Miliary tuberculosis is a progressive and disseminated form of the disease caused by hematogenous dissemination with potential involvement of any organ system, including the skin. Young children with HIV and tuberculosis are at increased risk of disseminated disease, especially tuberculous meningitis, lymphadenopathy, and miliary disease. Please see the chapter on tuberculosis for a more detailed description.

Disseminated nontuberculous mycobacterial infections, caused by Mycobacterium avium complex, M. kansasii, M. chelonae, M. abscessus, or M. genavense, may occur in HIV-infected patients with severe immunosuppression or as an immune reconstitution syndrome. These disseminated infections typically cause lymph node, intraabdominal, and thoracic disease; however, skin lesions may also be present.

**Fungal Skin Disease**

**Superficial Fungal Skin Infections**

Fungal skin infections among people with HIV/AIDS include candidiasis and dermatophytosis.

In HIV-infected patients, candidiasis commonly manifests as oral disease, such as thrush or angular cheilitis. Mucocutaneous candidiasis is one of the most frequently reported mucocutaneous manifestations of pediatric HIV infection and is often the first manifestation of disease. (Please see the chapter on oral manifestations of HIV infection for a more detailed description.) Candidiasis is also seen frequently in the diaper area and within skin folds as a brightly erythematous (red) rash with well-demarcated borders and satellite lesions (pustules or papules).

Cutaneous candidiasis can be treated topically with 1% aqueous solution of gentian violet applied to lesions three times per day for 3 days or with nystatin ointment applied to lesions three times per day until the rash resolves. If there is no response to topical treatment, systemic treatment with ketoconazole or fluconazole can be used. Dosages in children are the following: ketoconazole 3.3-6.6 mg/kg/day given by mouth, once a day for 2-4 weeks, or fluconazole 3-6 mg/kg/day (maximum, 100-200 mg) once daily for 14 days. Dosages in adults are the following: ketoconazole 200-400 mg/day or fluconazole 100-400 mg/day. Ketoconazole interacts with many antiretroviral medications, so a thorough drug history should be taken prior to initiating therapy. Patients should be instructed to take ketoconazole with food to prevent stomach upset.

Dermatophytosis occurs as tinea corporis, tinea capitis, or onychomycosis. Tinea corporis is characterized by erythematous, sometimes annular (circular), scaling lesions with raised borders. Tinea capitis often presents as diffuse, round, scaly patches of hair loss and may be associated with tinea on other parts of the body (Figure 10). The lesions may be extensive and refractory to treatment in HIV-infected persons. Fungal nail infections, such as fungal paronychia (chronic, painful, red, and swollen nail beds) or proximal white subungual onychomycosis (a white, thickened, and brittle nail near the proximal nail fold) occur more frequently in immunosuppressed patients with HIV infection. Fungal nail infections are criteria for mildly symptomatic (WHO Clinical Stage 2) HIV infection in children and adults.

Dermatophytosis is treated with a topical broad-spectrum antifungal, such as clotrimazole or miconazole cream applied to lesions twice daily until the rash resolves. Whitfield’s ointment may also be effective. Tinea corporis usually responds to topical medications alone, and topical treatments may also be tried for tinea capitis if the infection is mild, no griseofulvin is available, or patients are taking concomitant hepatotoxic medications. More
severe cases of dermatophyte infections can be treated with systemic medications such as griseofulvin microsize tablets, 20 mg/kg per day (or 500 mg/day in adults) given once daily by mouth. Patients should be instructed to take griseofulvin with a meal that is high in fat to enhance absorption. Monitor complete blood count, electrolytes, blood urea nitrogen, creatinine, and liver function test after 4 weeks of receiving griseofulvin, when available. Duration of therapy depends on the location of infection. Tinea corporis should be treated for 2-4 weeks; tinea capitis should be treated for 4-6 weeks.

Itraconazole, ketoconazole, or terbinafine may also be used for severe tinea corporis or fungal nail disease.

**Disseminated Fungal Infections**

Disseminated fungal infections, including cryptococcosis and histoplasmosis, may occur in severely immunosuppressed patients with HIV infection and cause cutaneous manifestation in 10%-20% of these patients. These infections may present with a wide range of skin lesions, including papules, nodules, and ulcerations. Disseminated fungal infections are criteria for severely symptomatic (WHO Clinical Stage 4) HIV infection in children and adults. Please see the chapter on opportunistic infections for a more detailed description.

**Other Skin Conditions**

**Pruritic Papular Eruption**

Pruritic papular eruption (PPE) is a chronic eruption of papular lesions on the skin whose etiology is unclear. (Figure 11). Patients with PPE show evidence of increased immunoglobulin E and eosinophilia. Some studies suggest that PPE may represent an overexuberant reaction to insect bites. As the name suggests, PPE is pruritic. The rash most often presents as symmetric and evenly distributed skin-colored to hyperpigmented papules on the trunk and extremities. Before diagnosing a patient with PPE, it is important to consider other potential treatable causes for the rash, including scabies, atopic dermatitis, folliculitis, a drug eruption, urticaria (hives), or syphilis.

Between 11% and 45% of HIV-infected patients will present with PPE. PPE is believed to be a marker of worsening immunosuppression and is more commonly associated with a CD4+ lymphocyte count of less than 50 cells/µL. PPE can create substantial morbidity in both children and adults because it causes significant distress to the patient and often becomes superinfected with *Staphylococcus aureus*. In many regions of the world, the characteristic PPE rash has become associated with HIV and may be stigmatizing. Treatment of PPE is difficult and usually requires antihistamines and topical steroids with or without antibiotics. This treatment may be required for symptomatic relief for months, until the CD4 count recovers with concomitant antiretroviral medications. Ultraviolet-B light may assist with symptomatic treatment. PPE is one of the criteria for mildly symptomatic (WHO Clinical Stage 2) HIV infection in children and adults.

**Drug Eruptions**

Drug eruptions often occur in patients receiving treatment for HIV infection. Antibiotics that are used in the treatment of HIV patients, including sulfa drugs,
penicillin, cephalosporins, and dapsone, may cause drug eruptions, ranging from benign maculopapular lesions to fatal hypersensitivity reactions.

Antiretroviral medications also have many cutaneous side effects. Abacavir, a nucleoside reverse transcriptase inhibitor, may cause a potentially fatal hypersensitivity syndrome, which manifests as progressive, multiorgan system symptoms, including fever; shortness of breath; malaise; gastrointestinal side effects including nausea, vomiting, and diarrhea; and an erythematous (red) rash. Nonnucleoside reverse transcriptase inhibitors, most notably nevirapine, are frequently associated with pruritic, maculopapular skin eruptions. Nonnucleoside reverse transcriptase inhibitors are also rarely associated with Stevens-Johnson syndrome and toxic epidermal necrolysis, a potentially fatal drug eruption with sloughing of the skin and mucous membranes. Pro tease inhibitors may also cause a rash and have been rarely implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis.

Drug eruptions range in appearance from pink to erythematous (red) macules and papules (Figure 12), scaling papules, hives, mucous membrane erosions, skin sloughing, or light sensitivity. Most drug eruptions are mild, and the medication can be continued with eventual spontaneous resolution of the eruption. To promote comfort, the patient can be given an oral antihistamine, such as diphenhydramine HCl 1 mg/kg every 6 h. In more severe cases, such as eruptions with blisters, skin sloughing, or mucous membrane involvement, the medication must be discontinued and supportive care should be provided.

Seborrheic Dermatitis
Seborrheic dermatitis occurs in up to 85% of adults and children with HIV infection and may be an early sign of HIV. Seborrheic dermatitis is characterized by thick, yellow scaling areas that may have surrounding erythema (redness) and may occur on the scalp, face, skin folds, and/or diaper area. Older children and adults may also have involvement of the nasolabial folds, the skin behind the ears, and the eyebrows.

Treatment consists of selenium sulfide or ketoconazole shampoo, topical coal tar, or salicylic acid. To decrease inflammation, 1% hydrocortisone cream can be applied to the affected area three times per day. Hydrocortisone cream should be used sparingly in the diaper area and on the face.

Scabies
Scabies infection in adults and children is characterized by pruritic papular lesions and/or linear burrows found most commonly in the webs of the fingers and toes, folds of the wrist, antecubital area, axilla, and genitals. Infants may also have lesions on the palms and soles of the feet that often become pustular (Figure 13). Scrapings observed under the microscope may reveal the mite, eggs, or feces.

Treatment consists of an application of topical benzyl benzoate lotion, 25%, which is applied from the neck down, left on the skin overnight, and washed off in the morning; the process is repeated 1 week later. HIV-infected patients with advanced disease can experience a variant of scabies known as crusted scabies, which is characterized by generalized scaling and enlarged, crusted plaques (Figure 14). After a patient is treated for scabies,
the family should be advised to wash all clothing and bedclothes in hot water and iron them to kill mites that may live in the cloth.

**Clinical Considerations**

Patients should be encouraged to complete all medications as prescribed and to report any lesions that get worse or do not heal. Patients should be instructed to monitor for the development of bacterial superinfection of lesions. Superinfection, or secondary infection, occurs when a primary lesion becomes infected with a secondary organism, such as a varicella lesion that becomes infected with *Staphylococcus aureus*.

Patients should be instructed on how to maintain hygiene without producing dry skin. They should be instructed to avoid deodorant soaps and to use tepid water when bathing. Skin should be patted dry without rubbing, and moisturizer should be applied to the skin immediately after bathing. Bedridden patients should be turned every 2 h to avoid skin breakdown. Patients should keep their nails short and smooth and be discouraged from scratching lesions. Scratching can lead to open lesions and secondary infections. If open lesions are present, patients should be instructed to avoid contact with other areas of the skin to prevent spread of the infection.

**References**

Objectives

1. Discuss the importance of oral and dental care for patients with human immunodeficiency virus (HIV) infection.
2. Review the classification of orofacial lesions associated with HIV infection in adults and children.
3. Describe the clinical presentation and management of the most common oral manifestations of HIV infection.

Key Points

1. Oral health care is an important part of HIV primary care.
2. Oral manifestations are common clinical findings in children and adults with HIV infection.
3. Early diagnosis and management of oral manifestations is important to prevent complications and improve quality of life.

Importance of Oral Manifestations of HIV Infection

Since human immunodeficiency virus (HIV) infection was first described in 1981, a variety of oral conditions associated with HIV disease have been documented. Studies have shown that 70%-90% of HIV-infected individuals will develop at least one oral manifestation during the course of the disease. A review of the dental literature shows that HIV-associated orofacial lesions have been considered

- clinical indicators of HIV infection in otherwise healthy, undiagnosed individuals;
- early clinical features of HIV infection;
- clinical markers for the classification and staging of HIV disease; and
- predictors of HIV disease progression.

In developed countries, HIV disease progression is monitored by two key laboratory markers: CD4+ lymphocyte count and HIV viral load. Unfortunately, these tests are not readily available in many developing countries. There, other important clinical findings guide clinicians in the evaluation and treatment of HIV disease. Because the oral cavity is easily accessible to clinical examination, orofacial lesions associated with HIV infection may be used as clinical markers of HIV disease progression.

The advent of highly active antiretroviral therapy (HAART) in 1996 greatly reduced the mortality and morbidity of HIV-infected patients who have access to treatment. The incidence rates of many opportunistic infections associated with HIV disease have decreased, including that of HIV-associated orofacial lesions.

Evaluation of oral health status is an important part of routine health care. A thorough oral examination is important at every stage in the management of HIV disease. It is also desirable to encourage collaboration among general medical practitioners, infectious-disease doctors, general and pediatric dentists, and oral pathologists to provide the best care possible for HIV-infected patients.

Classification of Orofacial Lesions Associated with HIV

There are two main classification systems of oral lesions associated with HIV infection. The first is based on the etiology of the oral lesions. According to this system, orofacial lesions are classified as bacterial, viral, or fungal infections or as neoplastic lesions or other conditions. The second, more widely used, system—recommended by the EC Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Human Immunodeficiency Virus—classifies orofacial lesions into three groups according to the degree of their association with HIV infection.
Tables 1 and 2 show this classification of orofacial lesions associated with HIV/AIDS in adults and children, respectively.

**Clinical Presentation and Management**

**Oral Candidiasis**

Oral candidiasis is the most common orofacial manifestation of HIV infection. Its prevalence may depend on study population, diagnostic criteria, study design, and availability of antiretroviral therapy. Reported prevalence rates have varied widely, to as high as 72% in children and 94% in adults. Oral candidiasis is also a significant predictor of HIV disease progression in both adults and children. The median time of survival from its clinical diagnosis to death is 3.4 years among HIV-infected children. The main etiologic factor of oral candidiasis is the fungus *Candida albicans*, although other species of *Candida* may be involved.

**Clinical appearance.** Oral candidiasis is often observed in one of the following four clinical forms: erythematous (atrophic) candidiasis, pseudomembranous candidiasis, hyperplastic candidiasis, and angular cheilitis.

1. Erythematous (atrophic) candidiasis appears clinically as multiple small or large patches, most often localized on the tongue and/or palate (Figure 1).

2. Pseudomembranous candidiasis (oral thrush) is characterized by the presence of multiple superficial, creamy white plaques that can be easily wiped off, revealing an erythematous base (Figure 2). They are usually located on the buccal mucosa, oropharynx, and/or dorsal face of the tongue.

3. Hyperplastic candidiasis lesions appear white and hyperplastic and cannot be removed by scraping. This form of oral candidiasis is rare in HIV-infected individuals.

**Table 1. Orofacial lesions associated with HIV/AIDS in adults**

<table>
<thead>
<tr>
<th>Lesions strongly associated with HIV infection</th>
<th>Lesions less commonly associated with HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Candidiasis</td>
<td>• Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>◆ Erythematous</td>
<td>◆ Periodontal disease</td>
</tr>
<tr>
<td>◆ Pseudomembranous</td>
<td>◆ Linear gingival erythema</td>
</tr>
<tr>
<td>• Hairy leukoplakia</td>
<td>◆ Necrotizing (ulcerative) gingivitis</td>
</tr>
<tr>
<td>• Kaposi's sarcoma</td>
<td>◆ Necrotizing (ulcerative) periodontitis</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions less commonly associated with HIV infection</th>
<th>Lesions seen in HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bacterial infections</td>
<td>• Fungal infection other than candidiasis</td>
</tr>
<tr>
<td>◆ Mycobacterium avium-intracellulare</td>
<td>◆ Cryptococcus neoformans</td>
</tr>
<tr>
<td>◆ Mycobacterium tuberculosis</td>
<td>◆ Geotrichum candidum</td>
</tr>
<tr>
<td>• Melanotic hyperpigmentation</td>
<td>◆ Histoplasma capsulatum</td>
</tr>
<tr>
<td>• Necrotizing (ulcerative) stomatitis</td>
<td>◆ Aspergillus flavus</td>
</tr>
<tr>
<td>• Salivary gland disease</td>
<td>◆ Recurrent aphthous stomatitis</td>
</tr>
<tr>
<td>◆ Dry mouth due to decreased salivary flow rate</td>
<td>◆ Viral infections</td>
</tr>
<tr>
<td>◆ Unilateral or bilateral swelling of the major salivary glands</td>
<td>◆ Herpes zoster</td>
</tr>
<tr>
<td>• Thrombocytopenic purpura</td>
<td>◆ Varicella</td>
</tr>
<tr>
<td>• Ulceration NOS (not otherwise specified)</td>
<td>◆ Molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions seen in HIV infection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bacterial infections</td>
<td>• Viral infections</td>
</tr>
<tr>
<td>◆ Actinomyces Israel</td>
<td>◆ Herpes simplex virus</td>
</tr>
<tr>
<td>◆ Escherichia coli</td>
<td>◆ Human papillomavirus (wart-like lesions)</td>
</tr>
<tr>
<td>◆ Klebsiella pneumoniae</td>
<td>◆ Condyloma acuminatum</td>
</tr>
<tr>
<td>• Cat-scratch disease</td>
<td>◆ Focal epithelial hyperplasia</td>
</tr>
<tr>
<td>• Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)</td>
<td>◆ Verruca vulgaris</td>
</tr>
<tr>
<td>• Epithelioid (bacillary) angiomatosis</td>
<td>◆ Varicella zoster virus</td>
</tr>
<tr>
<td>• Neurologic disturbances</td>
<td>◆ Herpes zoster</td>
</tr>
<tr>
<td>◆ Facial palsy</td>
<td>◆ Varicella</td>
</tr>
<tr>
<td>◆ Trigeminal neuralgia</td>
<td></td>
</tr>
</tbody>
</table>
Angular cheilitis is characterized by the presence of erythematous fissures at the corners of the mouth. It is usually accompanied by another form of intraoral candidiasis.

**Treatment.** Treatment with topical and systemic antifungal agents is recommended (Table 3).

**Oral Hairy Leukoplakia**

Oral hairy leukoplakia (OHL) is more common among HIV-infected adults than among HIV-infected children. The reported prevalence of OHL in adults is about 20%-25%, increasing as the CD4+ lymphocyte count decreases, whereas in children the prevalence is about 2%-3%. The presence of OHL is a sign of severe immunosuppression. OHL is a significant predictor of HIV disease progression in adults. Although its etiology is not clear, OHL seems to be caused by Epstein-Barr virus infection.

**Clinical appearance.** OHL presents as white, thick patches that do not wipe away and that may exhibit vertical corrugations with a hairlike appearance (Figure 3). The lesions usually start on the lateral margins of the tongue and sometimes inside the cheeks and lower lip. They may be unilateral or bilateral, and they are asymptomatic. OHL is often associated with oral candidiasis.

**Figure 1.** Erythematous candidiasis in an HIV-infected child

**Figure 2.** Pseudomembranous candidiasis in an HIV-infected child

### Table 2. Orofacial lesions associated with pediatric HIV infection

<table>
<thead>
<tr>
<th>Lesions commonly associated with pediatric HIV infection</th>
<th>Lesions less commonly associated with pediatric HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral candidiasis</td>
<td>Viral infections</td>
</tr>
<tr>
<td>– Pseudomembranous</td>
<td>– Cytomegalovirus</td>
</tr>
<tr>
<td>– Erythematous</td>
<td>– Human papillomavirus</td>
</tr>
<tr>
<td>– Angular cheilitis</td>
<td>– Molluscum contagiosum</td>
</tr>
<tr>
<td>Herpes simplex virus infection</td>
<td>– Varicella zoster virus</td>
</tr>
<tr>
<td>Linear gingival erythema</td>
<td>– Herpes zoster</td>
</tr>
<tr>
<td></td>
<td>– Varicella</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions strongly associated with HIV infection but rare in children</th>
<th>Lesions strongly associated with HIV infection but rare in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>– Kaposi’s sarcoma and non-Hodgkin’s lymphoma</td>
<td>– Kaposi’s sarcoma and non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>Oral hairy leukoplakia</td>
</tr>
<tr>
<td>Tuberculosis-related ulcers</td>
<td>Tuberculosis-related ulcers</td>
</tr>
</tbody>
</table>

1. Bacterial infections of oral tissues
   - Necrotizing ulcerative gingivitis
   - Necrotizing ulcerative periodontitis
   - Necrotizing stomatitis
2. Xerostomia
   - Seborrheic dermatitis
3. Viral infections
   - Cytomegalovirus
   - Human papillomavirus
   - Molluscum contagiosum
   - Varicella zoster virus
   - Herpes zoster
   - Varicella
Oral Hairy Leukoplakia in an HIV-infected adult

**Oral Manifestations of HIV Infection**

**Treatment.** OHL usually does not require any treatment, but in severe cases systemic antivirals are recommended (Table 3). When OHL is associated with oral candidiasis, therapeutic management of oral candidiasis is required.

**HIV-Associated Periodontal Disease**

Periodontal (gum) disease is common among HIV-infected patients. It is characterized by bleeding gums, bad breath, pain/discomfort, mobile teeth, and sometimes sores. Its reported prevalence ranges widely, between 0% and 50%. Left untreated, HIV-associated periodontal disease may progress to life-threatening infections, such as Ludwig’s angina and noma (cancrum oris).

**Clinical appearance.** Four forms of HIV-associated periodontal disease have been described: linear gingival erythema, necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing stomatitis.

1. Linear gingival erythema is characterized by the presence of a 2- to 3-mm red band along the marginal gingiva, associated with diffuse erythema on the attached gingiva and oral mucosa (Figure 4). The degree of erythema is disproportionately intense compared with the amount of plaque present on the teeth.
2. NUG is more common in adults than in children. It is characterized by the presence of ulceration, sloughing, and necrosis of one or more interdental papillae, accompanied by pain, bleeding, and fetid halitosis.
3. NUP is characterized by the extensive and rapid loss of soft tissue and teeth.
4. Necrotizing stomatitis is thought to be a consequence of severe, untreated NUP. It is characterized by acute and painful ulceronecrotic lesions on the oral mucosa that expose underlying alveolar bone.

**Treatment.** Management and control of HIV-associated periodontal disease begin with good daily oral hygiene. In addition to brushing, flossing and use of mouthwash solutions are effective ways to prevent and control periodontal disease. Table 3 presents various therapeutic options.
Table 3. Therapeutic options for the most common HIV-associated oral manifestations23,34,35,36,37

<table>
<thead>
<tr>
<th>Oral Lesion</th>
<th>Treatment for Adults</th>
<th>Treatment for Children</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Candidiasis (Erythematous, Pseudomembranous, and Hyperplastic)</td>
<td><strong>Topical</strong></td>
<td><strong>Topical</strong></td>
<td>Different forms of oral candidiasis may occur simultaneously.</td>
</tr>
<tr>
<td></td>
<td>- Nystatin (Mycostatin)</td>
<td>- Nystatin suspension 200,000-400,000 U/day divided in 4-6 doses, for 14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Oral gel: apply gel q8h or q6h, for 10-14 days</td>
<td>- Clotrimazole troches 10 mg q6h or q6h, for 4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cream: Apply q12h, for 10-14 days</td>
<td>- Gentian violet 1% aqueous solution painted in the affected areas q8h</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nystatin (Mycostatin) 400,000-600,000 U q6h, for 14 days</td>
<td>- Ketoconazole 3.5-6.6 mg/kg/day in a single dose</td>
<td></td>
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<tr>
<td></td>
<td>- Ketoconazole (Nizoral) 200-400 mg PO q.d.</td>
<td>- Fluconazole 6 mg/kg on day 1, then 3 mg/kg qd, up to 2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fluconazole (Diffucan) 50-100 mg PO q.d.</td>
<td>- Itraconazole 100 mg PO, daily for children older than 3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Itraconazole (Sporanox) (Capsules or solution) 200 mg PO qd for 7 days</td>
<td>- Amphotericin B may be used in azole-resistant infections.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Amphotericin B 10 mg IVq6h, for 10 days</td>
<td>- Fluconazole 100 mg PO q8h or q12h for long period</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Prophylaxis</strong></td>
<td>- Nystatin 100,000-400,000 U PO q12h for long period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fluconazole 100 mg PO qwk, for long period</td>
<td>- Fluconazole 3-6 mg/kg PO daily or weekly for long period</td>
<td></td>
</tr>
<tr>
<td>Angular Cheilitis</td>
<td><strong>Topical</strong></td>
<td><strong>Topical</strong></td>
<td>Lesions tend to heal slowly because of the repeated opening of the mouth.</td>
</tr>
<tr>
<td></td>
<td>- Nystatin-triamcinolone (Mycolog II) ointment applied on the affected areas after meals and at bedtime</td>
<td>- Nystatin-triamcinolone (Mycolog II) ointment applied on the affected areas after meals and at bedtime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Clotrimazole 1% (Mycelex) cream</td>
<td>- Clotrimazole 1% (Mycelex) cream</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Miconazole 2% cream applied q12h on the affected areas, for 1-2 weeks</td>
<td>- Miconazole 2% cream applied q12h on the affected areas, for 1-2 weeks</td>
<td></td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV) Infection</td>
<td><strong>Systemic</strong></td>
<td><strong>Systemic</strong></td>
<td>Ganciclovir, Valacyclovir and Famiclovir are probably effective.</td>
</tr>
<tr>
<td></td>
<td>- Acyclovir (Zovirax) 800 mg PO q4h, for 10 days</td>
<td>- Acyclovir 10 mg/kg PO q4h or q6h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Foscarnet 24-40 mg/kg PO q8h, for resistant herpetic lesions</td>
<td>- Acyclovir 10 mg/kg IV q8h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Foscarnet 24-40 mg/kg PO q8h, for resistant herpetic lesions</td>
<td></td>
</tr>
<tr>
<td>Linear Gingival Erythema (LGE)</td>
<td><strong>Local</strong></td>
<td><strong>Local</strong></td>
<td>Prophylaxis is recommended: brushing, flossing, and use of mouth rinses.</td>
</tr>
<tr>
<td></td>
<td>- Scaling and root planing 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit</td>
<td>- Scaling and root planing 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit</td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page
Table 3. Therapeutic options for the most common HIV-associated oral manifestations\textsuperscript{23,34,35,36,37} (continued)

<table>
<thead>
<tr>
<th>Oral Lesion</th>
<th>Treatment for Adults</th>
<th>Treatment for Children</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Gingival Erythema (LGE)</td>
<td><strong>Local</strong>&lt;br&gt;• Scaling and root planing&lt;br&gt;• 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit</td>
<td><strong>Local</strong>&lt;br&gt;• Scaling and root planing&lt;br&gt;• 0.12% Chlorhexidine gluconate (Periogard, Peridex) 0.5 oz q12h rinse, for 30 sec. and spit</td>
<td>• Prophylaxis is recommended: brushing, flossing, and use of mouth rinses.&lt;br&gt;• Antifungal agents may be useful in the treatment of LGE.</td>
</tr>
<tr>
<td>Xerostomia</td>
<td><strong>Topical</strong>&lt;br&gt;• Chewing or sucking sugarless candy&lt;br&gt;• Frequent sips of water&lt;br&gt;• Commercial artificial saliva substitutes&lt;br&gt;• Topical fluoride products</td>
<td><strong>Topical</strong>&lt;br&gt;• Chewing or sucking sugarless candy&lt;br&gt;• Frequent sips of water&lt;br&gt;• Commercial artificial saliva substitutes&lt;br&gt;• Topical fluoride products</td>
<td>• Good oral hygiene measures and diet control (control of sugar and sugary foods) are recommended to prevent dental caries.&lt;br&gt;• Mouth rinses with high alcohol content should be avoided due to drying effect.</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic</strong>&lt;br&gt;• Pilocarpine (Salagen) 5 mg PO q8h before meals; it may increase to 7.5 mg PO q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid Enlargement (of major salivary glands)</td>
<td><strong>Systemic</strong>&lt;br&gt;• Non-steroidal anti-inflammatories&lt;br&gt;• Analgesics&lt;br&gt;• Antibiotics&lt;br&gt;• Steroids</td>
<td><strong>Systemic</strong>&lt;br&gt;• Non-steroidal anti-inflammatories&lt;br&gt;• Analgesics&lt;br&gt;• Antibiotics&lt;br&gt;• Steroids</td>
<td>• Surgical removal of the parotid gland may be necessary for esthetic reasons.</td>
</tr>
<tr>
<td>Oral Hairy Leukoplakia (OHL)</td>
<td><strong>Local</strong>&lt;br&gt;• Podophyllin resin 25% 1-2 applications on the affected areas, at 1 week apart&lt;br&gt;• Retinoic acid (Tretinoin)&lt;br&gt;• Surgical excision</td>
<td><strong>Local</strong>&lt;br&gt;• Podophyllin resin 25% 1-2 applications on the affected areas, at 1 week apart&lt;br&gt;• Retinoic acid (Tretinoin)&lt;br&gt;• Surgical excision</td>
<td>• Recurrence often occurs after the treatment is discontinued.&lt;br&gt;• OHL is rare in children. Symptomatic and extensive lesions may require topical treatment.&lt;br&gt;• OHL has been shown to disappear in patients receiving zidovudine (AZT).</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic</strong>&lt;br&gt;• Acyclovir (Zovirax) 800 mg PO q4h or q6h, for 14 days&lt;br&gt;• Famciclovir 500 mg PO q8h, for 5-10 days&lt;br&gt;• Valacyclovir 1000 mg PO q8h, for 5-10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP), Necrotizing Stomatitis (NS)</td>
<td><strong>Local</strong>&lt;br&gt;• Debridement of affected areas&lt;br&gt;• Irrigation with povidon-iodine (10% Betadine)&lt;br&gt;• 0.12% chlorhexidine gluconate (Peridex, Periogard) mouth rinse q12h</td>
<td><strong>Local</strong>&lt;br&gt;• Debridement of affected areas&lt;br&gt;• Irrigation with povidon-iodine (10% Betadine)&lt;br&gt;• 0.12% chlorhexidine gluconate (Peridex, Periogard) mouth rinse q12h</td>
<td>• Prolonged use of chlorhexidine may cause staining of teeth, tongue, and restorations; taste alteration; and mucosal desquamation and irritation.&lt;br&gt;• Metronidazole should not be given to patients taking didanosine (ddI) or zalcitabine (ddC), because it may potentiate peripheral neuropathy.</td>
</tr>
</tbody>
</table>

\textit{Continued on next page}
Table 3. Therapeutic options for the most common HIV-associated oral manifestations\textsuperscript{23,34,35,36,37} (concluded)

<table>
<thead>
<tr>
<th>Oral Lesion (Recurrent Aphthous Ulcers)</th>
<th>Treatment for Adults</th>
<th>Treatment for Children</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Ulcers (NUG), Necrotizing Ulcerative Periodontitis (NUP), Necrotizing Stomatitis (NS)</td>
<td><strong>Systemic</strong>&lt;br&gt; Metronidazole (Flagyl) 250 mg PO q8h or 500 mg q12h, for 7-10 days&lt;br&gt; Clindamycin (Cleocin) 150 mg PO q6h or 300 mg PO q8h, for 7 days&lt;br&gt; Amoxicillin clavulanate (Augmentin) 250 mg PO q12h, for 7 days</td>
<td><strong>Systemic</strong>&lt;br&gt; Metronidazole (Flagyl) 15-35 mg/kg PO q8h, for 7-10 days&lt;br&gt; Clindamycin (Cleocin) 20-30 mg/kg PO q6h, for 7 days&lt;br&gt; Amoxicillin clavulanate (Augmentin) 40 mg/kg PO q8h, for 7 days</td>
<td>(See chart on previous page)</td>
</tr>
<tr>
<td>Oral Warts</td>
<td><strong>Topical</strong>&lt;br&gt; Triamcinolone in Carboxymethylcellulose 0.1% paste&lt;br&gt; Betamethasone phosphate: - 0.5 mg tablet dissolved in 10 ml mouthwash and rinse q4h - spray on ulcer (1 spray = 100 µg) up to 800 µg&lt;br&gt; Fluocinonide (Lidex) 0.05% ointment applied on ulcer q4h&lt;br&gt; Dexamethasone elixir (0.5 mg/5ml) rinse and expectorate</td>
<td><strong>Topical</strong>&lt;br&gt; Triamcinolone in Carboxymethylcellulose 0.1% paste applied in a thin layer q6h daily&lt;br&gt; Betamethasone phosphate: - 0.5 mg tablet dissolved in 10 ml mouthwash and rinse q4h - spray on ulcer (1 spray = 100 µg) up to 800 µg&lt;br&gt; Fluocinonide (Lidex) 0.05% ointment q4h&lt;br&gt; Dexamethasone elixir (0.5 mg/5ml) rinse and expectorate&lt;br&gt; <strong>Systemic</strong>&lt;br&gt; Prednisone 2 mg/kg q6h, for 5-7 days with gradual tapering</td>
<td>Major aphthous ulcers usually require systemic steroids.&lt;br&gt; Aphthous ulcers may be exacerbated by stress.&lt;br&gt; Iron, vitamin B12, and folate deficiencies should be ruled out.&lt;br&gt; Dexamethasone elixir should be used for multiple ulcers or ulcers not accessible for topical application.&lt;br&gt; Thalidomide is indicated only when recurrences are severe and frequent.&lt;br&gt; The treatment with Thalidomide should be monitored thoroughly due to its teratogenicity. Birth control measures are required.</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic</strong>&lt;br&gt; Prednisone starting at 30-40 mg PO daily with taper over 1 month for severe disease resistant to topical agents&lt;br&gt; Thalidomide 200 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Warts</td>
<td><strong>Topical</strong>&lt;br&gt; Podophyllin resin 25% applications q6h for long period&lt;br&gt; Surgical excision&lt;br&gt; Laser ablation&lt;br&gt; Cryotherapy</td>
<td><strong>Topical</strong>&lt;br&gt; Podophyllin resin 25% applications q6h for long period&lt;br&gt; Surgical excision&lt;br&gt; Laser ablation&lt;br&gt; Cryotherapy</td>
<td>The recurrence rate is high.&lt;br&gt; Concurrent therapeutic approaches should be considered.</td>
</tr>
<tr>
<td>Oral Warts</td>
<td><strong>Systemic</strong>&lt;br&gt; Cimetidine (Tagamet) 600 mg PO q6h, for long period (months)&lt;br&gt; Interferon alfa–n3 SC/IM 3,000,000 U (1 ml) qwk, for several weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used in Table 3: **PO** = per os (by mouth); **IV** = intravenous; **qd** = every day; **qwk** = every week; **q2h** = every two hours; **q4h** = every four hours; **q6h** = every six hours; **q8h** = every 8 hours; **q12h** = every 12 hours.
Oral Manifestations of HIV Infection

Noma, also known as cancrum oris, is a gangrenous condition that affects primarily children. Noma has been reported mainly in developing countries in West Africa, but cases have also been described in other parts of the world. It is a multifactorial disease. The most important risk factors are poverty, chronic malnutrition, poor oral hygiene, and severe immunosuppression. Though considered a preventable disease, noma has a case fatality rate of 70%-90% if left untreated.

**Herpes Simplex Virus Infection**
Herpes simplex virus (HSV) infection may be either primary (herpetic gingivostomatitis) or secondary (herpes labialis). The prevalence of oral HSV infection varies between 10% and 35% in HIV-infected adults and children. The presence of HSV infection for more than 1 month constitutes an AIDS-defining condition.

**Clinical appearance.** HSV infection appears as a crop of vesicles usually localized on the keratinized mucosa (hard palate, gingiva) and/or vermilion borders of the lips and perioral skin (**Figure 5**). The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.

**Treatment.** Systemic therapy with antiviral agents is recommended (**Table 3**). The treatment is more effective if it is instituted in the prodromal stage of infection.

**Recurrent Aphthous Ulcers**
Recurrent aphthous ulcers (RAUs) occur in about 1%-7% of HIV-infected patients. They are painful ulcers on the nonkeratinized oral mucosa, such as labial and buccal mucosa, soft palate, and ventral aspect of the tongue. Severe recurrent aphthous lesions usually occur when the CD4+ lymphocyte count is less than 100 cells/µL. This result may be suggestive of HIV disease progression. The etiology of RAUs is not well known.

**Clinical appearance.** RAUs may present as minor, major, or herpetiform aphthae. Minor aphthous ulcers are ulcers less than 5 mm in diameter covered by pseudomembrane and surrounded by an erythematous halo. They usually heal spontaneously without scarring (**Figure 6**). Major aphthous ulcers resemble minor aphthous ulcers, but they are fewer and larger in diameter (1-3 cm), are more painful, and may persist longer. Their presence interferes with mastication, swallowing, and speaking. Healing occurs over 2-6 weeks. Scarring is common. Herpetiform aphthous ulcers occur as a crop of many small lesions (1-2 mm) disseminated on the soft palate, tonsils, tongue, and/or buccal mucosa.

**Treatment.** The first line of management of RAUs is pain control and prevention of superinfection. Depending on the severity of the ulcers, topical and/or systemic steroid agents are recommended (**Table 3**).

**Parotid Enlargement and Xerostomia**
Parotid enlargement is commonly associated with HIV infection in children (10%-30%) and less commonly in adults. It occurs in the late course of HIV infection and is associated with a slower rate of HIV disease progression. The median time from its diagnosis to death has been reported to be 5.4 years among HIV-infected children. Lymphocytic infiltration of the salivary glands may be an etiologic factor.

**Clinical appearance.** Parotid enlargement occurs as unilateral or bilateral swelling of the parotid glands. It is usually asymptomatic and may be accompanied by decreased salivary flow (xerostomia or dry mouth). Problems with dry mouth in HIV-infected patients are often caused by medications that interfere with salivary secretion, such as antihistamines, antianxiety medications, antidepressants, and some antiretroviral drugs (didanosine and zalcitabine).

**Treatment.** Treatment is required only in severe cases and may consist of systemic analgesics, anti-inflammatories, antibiotics, and/or steroids (**Table 3**).

**Human Papillomavirus Infection (Oral Warts)**
The incidence of oral warts due to human papillomavirus infection has increased dramatically since the era of HAART. The lesions are more prevalent in adults (1%-4% of cases) than in children.

**Clinical appearance.** Oral warts may appear cauliflower-like, spiked, or raised with a flat surface. They are asymptomatic. The most common location is the labial and buccal mucosa. The most common clinical presentation is multifocal flat lesions resembling focal epithelial hyperplasia (Heck’s disease).

**Treatment.** Treatment may be required for patients with multiple lesions. Topical and systemic agents and various surgical approaches are available (**Table 3**).
GENERAL MANAGEMENT CONSIDERATIONS

To prevent the need for expensive dental services, it is imperative to treat the oral manifestations of HIV infection at all levels of care. Personal oral hygiene practices, such as tooth brushing and use of interdental cleaning aids, are the most effective ways of maintaining good oral health.

At the primary level of oral care, prevention of oral diseases takes priority. Prevention involves improving oral hygiene awareness through health education at the individual and community levels. Oral health education messages should be made visible in all community forums. Home-based care providers should undergo training in basic oral hygiene practices so that they can impart these to patients under their care. Use of simple materials such as warm salty mouth rinse or commercial mouthwash (chlorhexidine) can improve basic oral hygiene cost-effectively. Patients whose manual dexterity is intact should be taught appropriate brushing techniques. Other adjuvant oral hygiene methods, such as flossing and use of interdental toothbrushes, will depend on the availability and affordability of supplies.

The secondary level of oral care involves visits to clinical care facilities. Depending on local resources, the health cadre available at this level may range from nursing staff at a health center to primary care physicians. In some countries, health centers may have no oral health personnel or may offer only relief of pain with analgesics and extractions. Health care workers at this level should be trained to recognize suspicious lesions that may be oral manifestations of HIV infection, and they should know when and where to refer patients to a higher level of oral care.

At the tertiary level of oral care, a dentist should be available to make definitive diagnoses of oral lesions and provide professional oral services such as prophylaxis, restorations, biopsies, and the prescription of appropriate medication.

ACKNOWLEDGMENT

We thank Professor Sudeshi Naidoo, Department of Community Dentistry, Faculty of Dentistry and WHO Collaborating Centre, University of the Western Cape, South Africa, for providing the pictures of oral lesions used in this chapter.

REFERENCES


Objectives

1. Present an overview of normal neurodevelopment in children.
2. Describe how human immunodeficiency virus (HIV) affects the nervous system.
3. Discuss how to monitor neurodevelopment in HIV-infected children.
4. Review common nervous system abnormalities in children with HIV infection.
5. Review guidelines for the diagnosis and management of children with neurologic and psychiatric manifestations of HIV.

Key Points

1. HIV can profoundly affect the developing nervous system.
2. Monitoring the development of HIV-infected children is essential.
3. Children with HIV are at increased risk of developing a variety of infectious and noninfectious abnormalities of the nervous system.
4. Prompt diagnosis and treatment of many nervous system abnormalities can significantly affect long-term outcomes.

The nervous system is a major target of human immunodeficiency virus (HIV) infection, and the consequences of nervous system involvement are often serious. Clinically significant nervous system involvement most often occurs in conjunction with profound immunosuppression and in the presence of other AIDS-defining illnesses. HIV-associated neurologic disorders can, however, be the first problems with which children and adults with AIDS appear for treatment. A variety of abnormalities of the central nervous system (CNS) and peripheral nervous system (PNS) are associated with HIV and AIDS. These abnormalities may be attributable to the following causes:

- HIV’s direct effects on the nervous system
- Opportunistic infections and malignancies occurring because of immunosuppression
- Neurotoxic effects of antiretroviral treatments
- Other systemic complications of HIV that affect brain function.

Neurologic disorders in people with HIV infection include peripheral neuropathies (nerve disorders that affect the feet, hands, and limbs), myelopathy (disorders of the spinal cord), focal cerebral mass lesions (brain tumors such as CNS lymphoma), CNS complications of opportunistic infections, vascular (blood vessel) abnormalities, seizures, and encephalopathy. Children and adults with HIV often suffer similar neurologic and psychiatric manifestations. However, because children’s nervous systems are still growing and developing, special attention must be paid to the early detection of neurologic problems in pediatric patients. Early detection and appropriate treatment of HIV-associated neurologic problems in children often leads to favorable outcomes.

HIV has been found in the brain and spinal fluid of children infected by HIV. The neurons themselves are not infected by HIV, but neuronal function is impaired via complex mechanisms. Other cells in and around the brain such as microglia, astrocytes, oligodendroglia, and cells of the monocyte-macrophage lineage have CD4+ receptors, allowing for direct infection by the virus. Monocytes and microglial cells serve as the main CNS reservoirs for HIV. Once infected, these cells secrete several substances (e.g., tumor necrosis factor α and nitric oxide) that are toxic to the brain. HIV-infected microglial cells secrete chemokines that amplify recruitment of HIV-infected monocytes, leading to a self-perpetuating feedback loop. The viral coat protein, gp120, can enter the CNS independent of the rest of the virus and is directly neurotoxic. Brain endothelial cells react to substances associated with HIV infection, such as Tat and cytokines, by releasing neurotoxic substances at the surface abutting the brain. A selective barrier (the blood-brain barrier [BBB]) between circulating blood and brain tissues prevents many damaging substances from reaching the brain. Certain compounds readily cross the
BBB; others are blocked. HIV can cause changes in the BBB that increase its permeability to other substances. Because HIV does not directly infect neurons, its effects on the PNS are also related to indirect effects of infection. Neurotoxic side effects of antiretroviral medications can also have a major effect on the PNS.

Neurologic and psychiatric manifestations of HIV infection can be either sudden or gradual in onset. In children, the effects of HIV infection on the brain often manifest as a failure to reach age-appropriate developmental milestones. Brain growth and head size may also be affected in young children. Careful clinical evaluations are necessary to ensure that these manifestations do not go unnoticed. Clinicians must maintain a high index of suspicion for neurologic abnormalities in children with HIV and must ask appropriate questions to ensure that neurologic, psychiatric, and developmental problems in children are promptly recognized.

Neurodevelopmental Assessment

People who provide health care to children must understand basic principles of neurodevelopmental assessment. This understanding is especially important for those providing care to HIV-infected children because neurodevelopmental delays are often early signs of disease progression. Neurodevelopmental difficulties can be the first indicator of a CNS abnormality.

Many standardized tools have been developed for screening neurodevelopment. Because some children may not have regular exposure to elements of standardized screening tools, these tools may underestimate the knowledge and abilities of children in certain cultures. Cultural practices may influence the “normal” age of development for even basic motor tasks such as crawling and walking. Therefore, whenever possible, one should use a tool that has been researched and validated for use among children of similar backgrounds.

When standardized tools are unavailable or time does not permit their widespread use, medical providers should keep a simple record of the developmental milestones achieved by their pediatric patients. Failure to achieve key milestones by certain ages can be considered “red flags” that should alert medical practitioners to the need for further evaluation and the consideration of interventions such as highly active antiretroviral therapy. Tables 1 and 2 provide basic guidelines for normal milestone progression in young children. Older children can be compared with their same-age peers to give an indication of whether they are functioning appropriately. Asking simple questions regarding children’s learning in the classroom, whether they can perform necessary activities of daily living and whether they interact appropriately with others can give valuable insight into a child’s development. Sustained developmental regressions (loss of the ability to perform previously acquired skills) are never normal and should prompt appropriate additional evaluations and interventions.

Children who fail to reach age-appropriate milestones as expected should be evaluated for conditions that lead to developmental and neurological deficits. Neurodevelopmental delays may also be related to factors other than HIV such as environmental, psychosocial, and nutritional factors. Whenever possible, neurodevelopmental testing should be coordinated with a comprehensive history, clinical examination, and laboratory data to confirm the appropriate diagnosis.

Neurodevelopmental Delays in HIV-Infected Children

Cognitive delays are common among HIV-infected infants and young children. Sometimes the problems are subtle. They may manifest as deficits in attentional focus and executive functioning, which refers to the ability to direct one’s actions to actively solve a problem. Children with these problems may be more distractible and impulsive, have difficulties planning and organizing, and be inefficient problem solvers. Deficits in visual-spatial processing, visual-motor integration, and fine-motor skills have also been demonstrated among HIV-infected children and can manifest as difficulties with mathematics, poor handwriting, and problems completing certain activities of daily living (e.g., dressing). The domain-specific deficits mentioned here are thought to relate to abnormalities in the brain’s white matter, frontal system, and basal ganglia. Medical providers must consider domain-specific functioning among HIV-infected children and can manifest as difficulties with mathematics, poor handwriting, and problems completing certain activities of daily living in home, school, and social settings.

If neurodevelopmental weaknesses occur, several options exist for intervention, ranging from therapeutic services to environmental support. Even in low-resource settings,
### Table 1. Developmental milestones: birth through age 12 years

<table>
<thead>
<tr>
<th>Age</th>
<th>Psychosocial</th>
<th>Gross Motor</th>
<th>Fine-Motor</th>
<th>Communication/Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>• Follows faces to the midline</td>
<td>• Moves all extremities</td>
<td>• Opens hands spontaneously</td>
<td>• Startled by loud sounds</td>
</tr>
<tr>
<td></td>
<td>• Follows faces past midline</td>
<td>• Lifts head when lying on stomach</td>
<td>• Cries</td>
<td>• Quiets when fed and comforted</td>
</tr>
<tr>
<td></td>
<td>• Smiles responsively</td>
<td>• lift head up 45° when on stomach</td>
<td>• Looks at own hand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recognizes parent's voice or touch</td>
<td>• Supports head for a few seconds when upright</td>
<td>• Looks at close objects</td>
<td>• Coos, squeals, gurgles</td>
</tr>
<tr>
<td>2 mo</td>
<td>• Recognizes parent's voice or touch</td>
<td>• Bears weight on legs</td>
<td>• Clasps hands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Follows an object with eyes for 180°</td>
<td>• Good neck control when pulled to sitting position</td>
<td>• Grabs a small object</td>
<td>• Turns head to sound</td>
</tr>
<tr>
<td></td>
<td>• Anticipates food on sight</td>
<td>• Can lift chest and support self on elbows when lying on stomach</td>
<td>• Reaches for object</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>• Indicates wants</td>
<td>• Sits without support</td>
<td>• Takes toy in each hand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Waves &quot;bye-bye&quot;</td>
<td>• Creeps or crawls</td>
<td>• Transfers toy from one hand to the other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Has separation anxiety</td>
<td>• Has stranger anxiety</td>
<td>• Imitates speech sounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Imitates gestures</td>
<td>• Pulls self up to standing position</td>
<td>• Understands &quot;no&quot;</td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>• Explores people and surroundings</td>
<td>• Walks with support</td>
<td>• Takes toy in each hand</td>
<td>• Looks for a toy when it has fallen or is hidden</td>
</tr>
<tr>
<td></td>
<td>• Imitates activities/speech</td>
<td>• Can stack one cube on another</td>
<td>• Imitates speech sounds</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>• Calls adult to initiate interactions</td>
<td>• Rolls from stomach to back or vice versa</td>
<td>• Plays with hands by touching them together</td>
<td></td>
</tr>
<tr>
<td>9 mo</td>
<td>• Tries to please others</td>
<td>• Sits without support</td>
<td>• Responds to name</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Engages in parallel (imitative) play</td>
<td>• Creeps or crawls</td>
<td>• Babbles</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>• Takes turn in games</td>
<td>• Pulls self up to standing position</td>
<td>• Responds to name</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Plays make-believe with toys and people</td>
<td>• Walks with support</td>
<td>• Imitates speech sounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Engages in fantasy play; may have imaginary friends</td>
<td>• Can learn to tie shoelaces</td>
<td>• Imitates speech sounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• More independent</td>
<td>• Can use fork and spoon</td>
<td>• Vocabulary of hundreds of words</td>
<td></td>
</tr>
<tr>
<td>15 mo</td>
<td>• Explores people and surroundings</td>
<td>• Can go upstairs/downstairs without help</td>
<td>• Uses four- to five-word sentences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Imitates activities/speech</td>
<td>• Can draw circles and squares</td>
<td>• Nearly all speech is intelligible to others</td>
<td></td>
</tr>
<tr>
<td>18 mo</td>
<td>• Peer groups become important</td>
<td>• Can draw circles and squares</td>
<td>• Can sort objects by shapes and colors</td>
<td></td>
</tr>
<tr>
<td>2 yrs</td>
<td>• Peer groups become important</td>
<td>• Can build a tower of more than six blocks</td>
<td>• Tells stories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Engages in fantasy play; may have imaginary friends</td>
<td>• Can draw a vertical line, horizontal line and circular strokes</td>
<td>• Names some colors</td>
<td></td>
</tr>
<tr>
<td>3 yrs</td>
<td>• Tries to please others</td>
<td>• Can participate in team sports</td>
<td>• Executives functioning skills improve (e.g., planning, problem-solving)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Engages in parallel (imitative) play</td>
<td>• Can hop on 1 foot</td>
<td>• Learns to read</td>
<td></td>
</tr>
<tr>
<td>4 yrs</td>
<td>• Engages in fantasy play; may have imaginary friends</td>
<td>• Can go upstairs/downstairs without help</td>
<td>• Tells stories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• More independent</td>
<td>• Can draw circles and squares</td>
<td>• Names some colors</td>
<td></td>
</tr>
<tr>
<td>5 yrs</td>
<td>• Wants to be like friends</td>
<td>• Can draw circles and squares</td>
<td>• Tells stories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Questions others</td>
<td>• Can use fork and spoon</td>
<td>• Names some colors</td>
<td></td>
</tr>
<tr>
<td>6-12 yrs</td>
<td>• Peer groups become important</td>
<td>• Can stand on one foot for 10 s or longer</td>
<td>• Composes six- to eight-word sentences with all parts</td>
<td></td>
</tr>
</tbody>
</table>
one can take many measures to support children with neurodevelopmental problems. Behavioral strategies such as using firm limits to deter impulsive behaviors and providing tangible rewards to reinforce positive behaviors should be suggested by practitioners who recognize children with impulse-control and attention problems. Health care practitioners and families can also suggest environmental modifications such as sitting near the teacher or giving more time to complete school exams. Families and community members can also give children extra help with study skills and organizing their activities of daily living when needed. By recognizing deficits and educating families regarding simple interventions that can be undertaken at home and school, health practitioners can help children to maximize their potential. When developmental problems are identified and services are available, referrals for physical therapy, occupational therapy, speech therapy, and/or neuropsychologic evaluations can be helpful.

**CNS and PNS Abnormalities**

**HIV Encephalopathy**

HIV encephalopathy is defined by one or more of the following, progressing over at least 2 months in the absence of another causative illness:
- Failure to attain, or loss of, developmental milestones or intellectual ability
- Progressive impaired brain growth
- Acquired symmetric motor deficit accompanied by paresis, pathological reflexes, ataxia, and/or gait disturbances

HIV-related encephalopathy can occur without other signs and symptoms. Periodic neurologic and cognitive assessment can help with the recognition and monitoring of HIV encephalopathy. HIV-infected children with HIV encephalopathy can proceed along a variable neurodevelopmental course, with periods of spontaneous improvement and stabilization. Treatment with antiretroviral medications and early intervention programs for children with neurologic impairments and developmental delays can help mitigate the symptoms and improve the course of HIV encephalopathy.

Impaired brain growth in children with HIV encephalopathy can be observed both clinically and radiographically. In children younger than 2 years, a plateau in serial measurements of head circumference is an indicator of impaired brain growth. In older children whose cranial sutures are closed, measurements of head circumference are not as useful. If available, computed tomography imaging may be used to detect loss of brain tissue. Radiological findings may demonstrate signs of cerebral atrophy: enlargement of the sulci, the subarachnoid space, and the ventricles. Brain atrophy is a significant predictor of HIV-related disease progression. Calcification

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### Table 2. Developmental red flags

<table>
<thead>
<tr>
<th>Age</th>
<th>Developmental Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-3 mo</td>
<td>• Failure to alert to environmental stimuli</td>
</tr>
<tr>
<td></td>
<td>• Rolling over before 2 mo (indicates hypertonia)</td>
</tr>
<tr>
<td></td>
<td>• Persistent fisting at 3 mo</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>• Poor head control</td>
</tr>
<tr>
<td></td>
<td>• Failure to smile</td>
</tr>
<tr>
<td></td>
<td>• Failure to reach for objects by 6 mo</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>• No baby sounds or babbling by 8 mo; no single words by 12 mo</td>
</tr>
<tr>
<td></td>
<td>• Does not bear some weight on legs by 7 mo; cannot stand with support by 12 mo</td>
</tr>
<tr>
<td></td>
<td>• Does not follow objects with both eyes at near and far (6 ft) ranges</td>
</tr>
<tr>
<td></td>
<td>• Does not gesture or point by 12 mo</td>
</tr>
<tr>
<td>12-24 mo</td>
<td>• Cannot walk by 18 mo</td>
</tr>
<tr>
<td></td>
<td>• Hand dominance prior to 18 mo (may indicate weakness on the non-dominant side)</td>
</tr>
<tr>
<td>2-3 yrs</td>
<td>• Unable to communicate in short phrases</td>
</tr>
<tr>
<td></td>
<td>• Little interest in other children</td>
</tr>
<tr>
<td></td>
<td>• Frequent falling by end of 3 yrs</td>
</tr>
<tr>
<td>3-4 yrs</td>
<td>• Cannot grasp a crayon between thumb and fingers by end of 4 yrs</td>
</tr>
<tr>
<td></td>
<td>• No interest in interactive games</td>
</tr>
<tr>
<td>4-5 yrs</td>
<td>• Unable to concentrate on single activity for more than 5 min</td>
</tr>
<tr>
<td></td>
<td>• Cannot understand two-part commands (e.g., “pick up the cup and put it on the table”)</td>
</tr>
<tr>
<td>Any age</td>
<td>• Loss of previously attained milestones</td>
</tr>
</tbody>
</table>
of the basal ganglia can be seen with HIV encephalopathy. Neuroimaging can also help exclude other disease processes.

Seizures
Seizures in children with HIV infection can have a variety of causes. Seizures in the context of HIV should raise suspicion of intracranial opportunistic infections, mass lesions, and vasculopathies. Metabolic imbalances, drug side effects or interactions, and cortical structural changes can also trigger seizures. Suspicion of a focal CNS lesion should be heightened whenever a focal neurologic deficit is discovered on history, physical exam, or electroencephalogram.

Unless neuroimaging (computed tomography or magnetic resonance imaging) is available, determining the etiology of seizures may be difficult. Laboratory studies may detect electrolyte or metabolic imbalances, and lumbar puncture may help to confirm suspected infection.

Anticonvulsant medications can help to control seizures. Their use in HIV-positive patients should be coordinated by providers knowledgeable about possible interactions between anticonvulsants and antiretroviral medicines.

Strokes
Strokes are more commonly seen in children with advanced HIV disease. HIV produces inflammation of blood vessels, including those in the brain. Children with HIV are at an increased risk of suffering strokes caused by the effects of HIV on the vessels of the brain. Many cases of stroke are hemorrhagic, which is sometimes related to HIV-associated thrombocytopenia, idiopathic thrombocytopenic purpura, or CNS neoplasia. Whenever possible, investigations should be carried out

Figure 1. Progressive HIV Encephalopathy. This is a 5-year-old girl with HIV infection and severe, progressive HIV encephalopathy. The girl is non-communicative and spastic. This condition may progress rapidly for a period of time and then stabilize or improve spontaneously.

Figure 2. Generalize Brain Atrophy. This is a computerized tomographic (CT) scan of the brain of an 8-year-old boy with HIV infection and generalized brain atrophy. Cerebral atrophy is observed commonly among children with HIV-associated encephalopathy, but it also may be observed among children who are normal neurologically and developmentally.
to determine the underlying cause of a stroke. Correction
of the underlying cause may help to prevent subsequent
episodes.

When thrombotic strokes occur, low-dose aspirin given
for at least 6 months can help prevent subsequent
strokes. In settings where anticardiolipin antibodies
and antiphospholipid antibodies can be measured,
these approaches can be helpful for deciding when to
discontinue aspirin therapy after a thrombotic event.
If these antibody levels are abnormal after the event,
some experts would recommend discontinuation of
prophylactic aspirin after the levels normalize, provided
that the patient has been on aspirin for at least 6 months.

Opportunistic Infections
Opportunistic infections (OIs) that involve the CNS are
often not readily apparent and should be considered in
cases of acute or chronic behavioral or mental status
changes, as well as in children with persistent headaches,
malaise, or fever. The most common pathogens that
cause CNS infections in immunocompromised patients
include Cryptococcus neoformans, herpes simplex virus,
Toxoplasma gondii, and cytomegalovirus (CMV). JC virus,
which leads to progressive multifocal demyelinating
leukoencephalopathy in about 5% of adults with AIDS, is
rarely found in children.

HIV-infected children who develop OIs in the CNS
may develop signs of increased intracranial pressure
(severe headache, nausea, vomiting, confusion, coma),
focal neurologic signs (hemiparesis, visual changes, gait
instability, fine or gross motor abnormalities), malaise,
fever, behavioral or personality changes, seizures, and
meningitic signs (headache, neck pain, and nuchal
rigidity). Table 3 provides guidance regarding the
diagnosis of CNS infections in patients with HIV.

Table 4 provides treatment options for the empiric
management of CNS infections. When possible,
cultures of the CNS should be obtained before initiating
antibiotics for suspected bacterial meningitis. The
recommended duration of treatment varies depending
on the organism identified. When bacterial meningitis
is suspected and cultures are not available, treatment
should be continued for 3 weeks in neonates and 10
days in older children. In countries where Haemophilus
influenzae type B (Hib) vaccine is not given, steroids are
more likely to be of benefit when given at the beginning
of meningitis treatment, particularly in children younger
than 2 years.

The neurologic impairment most frequently observed
in children with HIV is caused by HIV infection itself
rather than by OIs or CNS tumors. CNS OIs must
always be considered in HIV-infected children with CNS
manifestations; if these infections go untreated, death
may occur.

CNS Neoplasms
Non-Hodgkin’s lymphoma is the most common CNS
neoplasm in children with AIDS. CNS lymphomas
may be confused with other CNS conditions, such as
toxoplasmosis or cryptococcosis. They tend to grow
rapidly and to lead to headaches, nausea/vomiting
(primarily upon arising in the morning), altered mental
status, focal neurologic signs, and increased intracranial
pressure. Epstein-Barr virus infection is involved with
the pathogenesis of non-Hodgkin’s lymphoma in HIV-
infected children. Highly active antiretroviral therapy and
anticancer chemotherapies, including corticosteroids, can
improve prognosis.

Leiomyosarcomas have been reported with increased
frequency in children with HIV infection. The most
common sites of the lesion are the lungs, spleen,
and gastrointestinal tract. Leiomyosarcomas can be
found in the brain as well. Symptoms of intracranial
leiomyosarcoma are the same as those seen with other
CNS mass lesions.

Table 5 compares common features of HIV-associated
CNS mass lesions to assist with the differential diagnosis
of affected patients.

HIV Myopathy
This module includes myopathy because it is often part of
the differential diagnosis when neurologic problems are
being considered. Myopathy is characterized by muscular
pain and proximal muscle weakness. HIV-associated
myopathy is more common in adults than in children.
With the increased use of antiretroviral nucleoside
analogues (e.g., zidovudine) in children, however,
myopathies are occurring more frequently as a side effect
of these medications. Myopathy can also be caused by
direct effects of the virus or by secondary infections
(e.g., CMV). Diagnosis of myopathy may be made based
on clinical observations and elevated creatine kinase
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common Clinical Features</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis</td>
<td>Fever, Nuchal rigidity, Nausea/vomiting, Irritability or restlessness, Anorexia or poor feeding, Headache or bulging fontanelle, Confusion or change of behavior, Photophobia</td>
<td>CSF: usually elevated opening pressure, elevated WBCs, neutrophil predominance, elevated protein, low glucose, organisms on Gram stain and/or culture. If LP cannot be obtained immediately: obtain a blood culture, then begin antibiotics immediately.</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>Meningitis with subacute onset, not responding to standard antibiotics; sometimes with focal findings due to CNS tuberculoma, Other signs suggestive of TB: Persistent and unremitting cough, Failure to gain weight or weight loss, Fever</td>
<td>CSF usually elevated opening pressure with lymphocytosis, elevated protein, low glucose. AFB/TB culture insensitive. Evidence of TB elsewhere (by CXR, sputum/gastric aspirate, etc.). CT where available: obstructive hydrocephalus, basilar meningeal enhancement. TB skin test and history of TB contact can be helpful.</td>
</tr>
<tr>
<td>tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Common features: Subacute onset, Fever, Headache, May also have: Nuchal rigidity, Nausea and vomiting, Altered level of consciousness, Impaired mental function, Cranial nerve lesions, Visual deficits, CD4 &lt;100 cells/mL or equivalent percentage for age.</td>
<td>CSF: elevated opening pressure, mononuclear cell predominant, elevated protein, low glucose, India ink +, cryptococcal antigen from CSF/serum + CSF may appear normal in &gt;50% of cases. CT: communicating hydrocephalus, pseudocysts, mass lesions.</td>
</tr>
<tr>
<td>Toxoplasma encephalitis</td>
<td>Headache, Confusion, Fever, Lethargy, Focal neurologic signs (hemiparesis, cranial nerve palsies, ataxia, sensory deficits), May have seizures, associated hepatic involvement, pneumonitis, myocarditis, Intracranial mass lesions, Ocular: Marked loss of central vision, Hazy vision “Floaters”, CD4 &lt;100 cells/mL or equivalent percentage for age.</td>
<td>Presumptive on clinical and radiographic findings in context of T. gondii IgG seropositivity. CT with consistent lesions. Organisms in tissue or body fluids (e.g., CSF). Ophthalmologic exam: white or yellowish foci with elevated, edematous margins, surrounded by a zone of hyperemia (active lesion).</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis: Changes in visual acuity, Sees “Floaters”, Acquired inability to fix and follow (small infants), Abnormal light reflexes (small infants)</td>
<td>Ophthalmologic exam: yellowish-white granular areas with perivascular exudates and hemorrhage. Histology: coagulation necrosis, microvascular abnormalities.</td>
</tr>
</tbody>
</table>

Table 3. Diagnosis of CNS infections in children with HIV
### Table 3. Diagnosis of CNS infections in children with HIV (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common Clinical Features</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMV (continued)</strong></td>
<td>Subacute or chronic encephalitis/ventriculitis:</td>
<td>Confirms infection but not disease:</td>
</tr>
<tr>
<td></td>
<td>• Weakness</td>
<td>anti-CMV antibodies if &gt;12 mo</td>
</tr>
<tr>
<td></td>
<td>• Confusion</td>
<td>CSF pleocytosis in 50%, frequently PMN predominance, elevated protein,</td>
</tr>
<tr>
<td></td>
<td>• Loss of developmental milestones</td>
<td>occasionally with low glucose, CMV DNA by PCR</td>
</tr>
<tr>
<td></td>
<td>Axonal polyradiculopathy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Painful, ascending muscle weakness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Loss of deep tendon reflexes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Loss of bladder/bowel control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;50 cells/mL or equivalent percentage for age</td>
<td></td>
</tr>
<tr>
<td><strong>HSV encephalitis</strong></td>
<td>Acute or subacute encephalitis</td>
<td>CSF: elevated WBCs, RBCs present, elevated protein, normal glucose, HSV DNA</td>
</tr>
<tr>
<td></td>
<td>• Fever</td>
<td>PCR</td>
</tr>
<tr>
<td></td>
<td>• Altered level of consciousness</td>
<td>CT: early, unremarkable; late, low-density contrast-enhancing lesions in</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
<td>temporal area, mass effect, edema, and hemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Behavior changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Focal neurologic findings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May have associated vesicles and ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May have disseminated disease involving multiple organs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keratitis, conjunctivitis, retinitis</td>
<td></td>
</tr>
<tr>
<td><strong>Progressive multifocal</strong></td>
<td>Subacute onset</td>
<td>CT: multiple radiolucent areas in white matter without edema, mass effect,</td>
</tr>
<tr>
<td><strong>leukoencephalopathy</strong></td>
<td>• Weakness, hemiparesis</td>
<td>or contrast enhancement</td>
</tr>
<tr>
<td></td>
<td>• Cognitive impairment</td>
<td>CSF PCR for JC virus</td>
</tr>
<tr>
<td></td>
<td>• Speech impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vision impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sensory abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; WBCs, white blood cells; LP, lumbar puncture; AFB, acid-fast bacilli; TB, tuberculosis, CXR, chest x-ray; IgG, immunoglobulin G; PMN, polymorphonuclear leukocytes (neutrophils); PCR, polymerase chain reaction; HSV, herpes simplex virus; RBCs, red blood cells.

### Table 4. Treatment of secondary CNS infections in children with HIV

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial meningitis</strong></td>
<td><strong>Neonates &gt;2000 g:</strong></td>
</tr>
<tr>
<td></td>
<td>• Ampicillin IV</td>
</tr>
<tr>
<td></td>
<td>If age &lt;7 days, 200 mg/kg/day ÷ q 12 h</td>
</tr>
<tr>
<td></td>
<td>If age &gt;7 days, 300 mg/kg/day ÷ q 8 h</td>
</tr>
<tr>
<td></td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>• Gentamicin IV</td>
</tr>
<tr>
<td></td>
<td>If age &lt;7 days, 2.5 mg/kg/dose q 12 h</td>
</tr>
<tr>
<td></td>
<td>If age &gt;7 days, 2.5 mg/kg/dose q 8 h</td>
</tr>
<tr>
<td></td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>• Cefotaxime 100-180 mg/kg/day ÷ q 6 h IV</td>
</tr>
<tr>
<td></td>
<td><strong>Infants and children:</strong></td>
</tr>
<tr>
<td></td>
<td>• Chloramphenicol 100 mg/kg/day ÷ q 6 h IM/IV and</td>
</tr>
<tr>
<td></td>
<td>• Ampicillin 200 mg/kg/day ÷ q 6 h IM/IV or</td>
</tr>
<tr>
<td></td>
<td>• Benzylpenicillin 240 mg/kg/day (400,000 U/kg/day) ÷ q 6 h IM/IV</td>
</tr>
<tr>
<td></td>
<td>Consider dexamethasone 0.6 mg/kg/day ÷ q 6 h for 2 days (initiate before or with first dose of antibiotics)</td>
</tr>
</tbody>
</table>

Continued on next page
### Table 4. Treatment of secondary CNS infections in children with HIV (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **Mycobacterium tuberculosis meningitis** | Initial phase: 2 mo  
• Isoniazid 10-15 mg/kg PO daily  
• Rifampicin 10-20 mg/kg PO daily  
• Pyrazinamide 20-30 mg/kg PO daily, and  
• Streptomycin 20-40 mg/kg IM daily  
Prednisone 2 mg/kg daily, up to 4 mg/kg daily for the most seriously ill, for 4 weeks; then tapered over 1-2 weeks  
Continuation phase: 4 mo  
• Isoniazid 10-15 mg/kg PO daily  
• Rifampicin 10-20 mg/kg PO daily |
| **Cryptococcal meningitis**             | Induction: ≥14 days (until CSF culture negative)  
• Amphotericin B 1 mg/kg/day IV infusion  
(Note: adequate hydration must be maintained during amphotericin infusion)  
Consolidation: ≥8 weeks  
• Fluconazole 12-15 mg/kg daily  
Secondary prophylaxis:  
• Fluconazole 6-10 mg/kg daily until:  
  – Asymptomatic with last episode of Cryptococcus >12 months ago and  
  – If age >6 years old, CD4 >200 cells/µL, if age 2-6 years old, CD4% >25% (Do not stop secondary prophylaxis when age <2 years.)  
*Management of increased intracranial pressure by daily lumbar punctures. Lumbar punctures to control increased intracranial pressure are essential to successful treatment.* |
| **Toxoplasma encephalitis**             |  
• Pyrimethamine  
2 mg/kg/day ÷ q 12 h for 3 days, then  
1 mg/kg/day ÷ q 12-24 h for 4 weeks and  
• Sulfadiazine 100-200 mg/kg/day ÷ q 6 h for 3-4 weeks and  
• Leucovorin (folinic acid)  
Alternatives:  
High-dose TMP/SMX or pyrimethamine and clindamycin  
Corticosteroids appear useful in ocular or CNS disease  
Lifelong TMP/SMX prophylaxis |
| **CMV retinitis**                       | Intraocular ganciclovir  
Alternative: IV ganciclovir 10 mg/kg/day ÷ q 12 h IV for 14 days; followed by 5 mg/kg/day indefinitely or oral valganciclovir |
| **HSV encephalitis**                    | Acyclovir  
1500 mg/m²/day ÷ q 8 h IV or  
30 mg/kg/day ÷ q 8 h IV  
Total course: 21 days |
| **Progressive multifocal leukoencephalopathy** | HAART |

IV, intravenous; IM, intramuscular; PO, per os (by mouth); TMP/SMX, trimethoprim-sulfamethoxazole (Bactrim or cotrimoxazole)
levels. Evidence of myopathic changes can also be seen on electromyogram. Myopathies in HIV-infected patients may also be related to the use of corticosteroids or statin drugs (used to treat lipid disorders) or to hypothyroidism. Treatment involves addressing the causative agent.

**HIV Myelopathy**

Myelopathy is characterized by functional disturbance or pathologic changes in the spinal cord. Progressive difficulty walking and weakness in the lower extremities may be observed. The patient may develop sensory disturbances and urinary incontinence. As with myopathy, myelopathy is more commonly seen in HIV-infected adults than in children. Myelopathy may result from a reactivated infection with measles or CMV. The primary treatment for HIV-related myelopathy is antiretroviral therapy. Myelopathies may also be related to spinal cord tumors and epidural abscesses. These etiologies should be ruled out as part of the diagnosis and management of HIV-infected children with myelopathy.

**Peripheral Neuropathy**

There are many causes of peripheral neuropathy in children with HIV infection. Common etiologies include viral pathogens (including HIV itself), autoimmune effects, vitamin and mineral deficiencies, and side effects of drugs. The symptoms of peripheral neuropathy range from mild numbness or tingling to debilitating pain. Early peripheral neuropathy is often characterized by symmetric numbness and tingling of the extremities in a “stocking glove” distribution. Later stages may be characterized by paresthesias, pain (commonly burning pain that is worse at night), increased sensitivity to touch, diminished reflexes, and weakness. Children may not be able to describe their symptoms well. Thus, one must consider peripheral neuropathy as a possible cause of apparent pain or decreased activity in young children.

HIV can cause peripheral neuropathy by generating a tissue-specific autoimmune attack on peripheral nerves. Varicella-zoster virus causes symptoms along a sensory dermatome (shingles) more commonly in immunosuppressed patients. CMV-related polyradiculoneuropathy (inflammation of the nerve roots) also leads to peripheral neuropathy. HIV-infected children sometimes develop peripheral neuropathies related to vitamin B12 or pyridoxine deficiency. Certain antiretroviral nucleoside analogues (ddC, ddI, d4T) are neurotoxic and may exacerbate or trigger peripheral neuropathy. HIV-infected patients may be on other drugs such as isoniazid that can precipitate peripheral neuropathy. When a patient is suspected of having peripheral neuropathy, the provider should take a careful history to determine likely contributing factors.

Discontinuing drugs known to contribute to peripheral neuropathy often allows improvements in the patient’s condition. Several supplements and medications are also used to help improve symptoms. Some relatively low-cost options include B vitamins, folate, amitriptyline, and topical capsaicin.

**Sleep Problems**

Both quality and quantity of sleep are important to normal growth, development, and health of children. Sleep disturbances occur more commonly among HIV-
infected children and adults than among noninfected individuals. Sleep disturbances occur early in the course of HIV infection. HIV is thought to affect sleep via several mechanisms. Animal studies have suggested that HIV gp120 protein directly alters sleep architecture. Interleukin 1, which is considered a somnogenic lymphokine, is also produced in higher levels with HIV infection. Other medical problems, poor diet, and some medicines can also affect sleep in patients with HIV.

Patients taking efavirenz often report an increase in recollection of dreams and morning sluggishness. Sleep studies have shown that after the initiation of efavirenz, patients spend different amounts of time in various sleep stages such as REM (rapid eye movement) sleep. In most patients, these changes diminish over time and patients rarely report persistent sleep problems after a few months on efavirenz. In rare cases, the sleep problems are more severe and persistent, requiring a medication switch. For children on efavirenz, there must be a high index of suspicion for sleep problems. Children and their caregivers will rarely report such problems without direct questioning. When evaluating these patients, clinicians should ask about changes in daily activity levels (either decreased energy or hyperactivity), school performance in older children, and nightmares or nocturnal awakenings.

Problems other than poor sleep that should be considered in excessively fatigued patients with HIV include poor diet, anemia, hypothyroidism, inactivity, anxiety, and depression. Lifestyle changes including improving diet, getting regular exercise, and reducing stress can often have a profound effect on lessening fatigue.

**Psychiatric Manifestations of HIV in Children**

The World Health Organization estimates that one in four people presenting for health care has a mental health problem. Most of these conditions remain undiagnosed and untreated. Patients with HIV are at increased risk of several mental health problems. These conditions often profoundly affect quality of life. Psychiatric problems also lead to increased stigmatization and present significant challenges to medication adherence. In low-resource settings, specialized medical professionals are usually not available to perform comprehensive psychiatric evaluations. Treatments for psychiatric problems may also be limited. Health professionals in all settings, however, must screen for psychiatric problems so that they can provide the highest standard of care and support available.

Mental health problems that are seen more commonly in children with HIV include depression, delirium, anxiety disorders including posttraumatic stress disorder, attention deficit-hyperactivity disorder, and substance abuse problems. HIV-infected patients are at increased risk of mental health problems caused by the effects of HIV on the brain, the effects of secondary infections on the CNS, metabolic abnormalities, vitamin deficiencies, and side effects of medications used to treat HIV. Life stresses associated with HIV infection may also worsen mental health problems. Asking questions about signs and symptoms that are commonly associated with mental health problems can help identify children who are suffering from these difficulties.

Many case studies involving patients with late-stage HIV infection have documented psychotic and mood symptoms. The cause of the psychiatric symptoms is usually not clearly defined in such cases. In some patients, however, symptoms have improved when antiretroviral therapy was initiated. However, although antiretroviral medications often have a beneficial effect on psychiatric symptoms in late-stage HIV patients, the antiretroviral medicines themselves can also cause psychiatric symptoms. Efavirenz, in particular, has been associated with several adverse psychiatric side effects. Many patients who initiate efavirenz develop neuropsychiatric side effects, including depressed mood, sleep disturbances, anxiety, psychosis, impaired concentration, vivid dreams, and nightmares. Warning patients and family members that these side effects may occur is important. The problems usually resolve after a few weeks or months on efavirenz and discontinuation is usually not necessary.

In HIV-infected patients, depressed mood is rarely, if ever, due to direct effects of HIV on the brain. Therefore, the etiology of the mood symptoms should be intensely sought in patients with HIV and depression. Vitamin B12 and folate deficiencies have been associated with depression. Patients with HIV infection have an increased risk of vitamin B12 deficiency caused by malabsorption and altered metabolism. Thyroid dysfunction, another common contributor to depression, has been seen at an increased rate among HIV-infected children. These
conditions should be ruled out in patients presenting with depressive symptoms.

The evaluation of patients with HIV infection and psychiatric disorders should always include a full medical evaluation. When identified, contributors to psychiatric problems should always be addressed. Psychotropic medications should also be used in HIV-infected patients, including children, to help control symptoms. Patients with HIV may be treated with the same psychotropic medications that have proven to be effective in noninfected patients. Dosing may have to be altered, however, because of the presence of interactions between certain psychotropic and antiretroviral medications.

**References**

**Objectives**

1. Review specific subjective and objective information important in the assessment of nausea, vomiting, and diarrhea in patients with human immunodeficiency virus (HIV)/AIDS.
2. Discuss the possible causes of, types of, and management approaches to diarrhea in patients with HIV/AIDS.
3. Classify the signs of dehydration in relation to their level of severity.
4. Identify the appropriate rehydration plan for use with patients experiencing dehydration.
5. Describe the specific symptoms associated with wasting syndrome in patients with HIV/AIDS.
6. Describe the symptoms and causes of hepatitis in HIV-infected children.

**Key Points**

1. Patients with HIV/AIDS are at high risk of having gastrointestinal complications.
2. Careful assessment using subjective and objective information is important when evaluating patients with HIV/AIDS who are experiencing nausea, vomiting, or diarrhea.
3. Patients with diarrhea and/or vomiting should be monitored for signs and symptoms of dehydration.
4. Oral rehydration fluids should be used to prevent and treat dehydration.
5. Wasting syndrome is a severe form of weight loss associated with HIV/AIDS.
6. Hepatitis B and C are common coinfections in HIV-infected patients.

**Overview**

People infected with human immunodeficiency virus (HIV) have a high likelihood of developing gastrointestinal (GI) complications at some point during their illness. Diarrhea is the most common GI manifestation in HIV-infected patients. Others include vomiting, wasting, hepatitis, esophagitis, malabsorption, jaundice, and failure to thrive. Most of these GI problems are related to infections and may be caused by HIV itself or other viruses such as cytomegalovirus (CMV) and hepatitis B and C; by bacteria such as *Mycobacterium avium* complex (MAC), *Salmonella*, and *Shigella*; by parasites such as *Cryptosporidium* and *Giardia*; and by fungi such as *Candida*. This module will discuss the causes of the most common GI manifestations in HIV-infected patients and approaches to the assessment and treatment of these conditions.

**Nausea and Vomiting**

Nausea and vomiting are common physical complaints with many causes. Causes include infection and/or inflammation of the GI tract, gastroesophageal reflux, an overfilled stomach, protein intolerance, urinary tract infection, pregnancy, increased intracranial pressure, meningitis, hepatitis, biliary tract disease, pancreatitis, malignancies, mechanical obstruction, sepsis, food poisoning/toxins, and altered metabolism. Many medications can also cause nausea and vomiting, including antiretroviral agents, drugs used to treat or prevent opportunistic infections, and antineoplastic (anticancer) drugs. (Please refer to the chapter on antiretroviral treatment for a list of specific medications that may cause nausea and vomiting, hepatitis, or pancreatitis as side effects.) Determining the exact cause of an individual patient’s nausea and vomiting will often be difficult.

**Assessment**

The assessment of a patient with nausea and vomiting should include both subjective and objective data. Most episodes of nausea and vomiting are self-limited and not dangerous. The assessment should focus on determining the hydration status of the patient and evaluating for the presence of danger signs that might indicate a
serous cause of the patient’s symptoms. Some danger signs include bilius (dark green) emesis, hematemesis (vomit with blood), jaundice, severe headache, altered mental status, focal neurologic signs, and severe flank or abdominal tenderness on exam.

Subjective data include the following:

- Onset of vomiting, quantity of emesis, presence of blood or bile
- Relationship of vomiting to meals, time of day, activities, or medications
- History of trauma or ill contacts
- Presence of associated signs and symptoms, such as diarrhea, fever, pain, dysuria, flank or abdominal pain, vision changes, headache, seizures, high-pitched cry (especially in an infant), jaundice, irritability, behavior changes, polydipsia, polyuria, polyphagia, or anorexia
- Changes in patterns or quantity of urination and amount of oral intake

Objective data include the following:

- Patient’s current weight and last known weight.
- Volume of intake and output, as well as vital signs (temperature, heart rate, blood pressure, respiration rate).
- Assessment of skin turgor (skin pinch), mucous membranes, and the presence or absence of tears.
- Nuchal rigidity; level of consciousness; and any behavioral changes, such as irritability or lethargy.
- When laboratory studies can be obtained, a complete blood count, serum pH, electrolytes, blood urea nitrogen, creatinine, AST (aspartate aminotransferase), ALT (alanine aminotransferase), bilirubin, amylase, lipase, urine analysis, and urine culture may be helpful in determining the cause of nausea/vomiting and degree of dehydration.

Clinical Considerations

Considerations for patients with nausea and vomiting include restoring and/or maintaining adequate hydration and identifying the cause of nausea and vomiting. The patient and family should be educated about the signs of dehydration and the importance of maintaining adequate fluid intake. The patient’s weight, intake, and output should be assessed daily. Intake should include all oral and intravenous fluids; output should include urine, stool, and emesis. Hydration fluids should be administered as available. This module’s rehydration section discusses the types of fluids. Patients should be instructed to drink fluids frequently, small volumes at a time; eat five to six small meals a day; avoid greasy, high-fat foods; and eat food at room temperature.

In addition to restoring and maintaining adequate hydration, treatment should be directed at the underlying cause of nausea and vomiting if appropriate. Antiemetic medications can be sedating and may be harmful in the pediatric setting and are not recommended for children.

DIARRHEA

Overview

Diarrhea remains one of the most common causes of death worldwide among children younger than 5 years. It is also one of the most common manifestations of advanced HIV disease in both adults and children, and in Africa it is estimated that 60%-97% of children with AIDS suffer from diarrhea at some point. Diarrhea is an excessive loss of fluid and electrolytes in the stool resulting in three or more loose stools in a 24-h period. The consistency of the stools is the most important factor, and frequent passage of soft or well-formed stools should not be considered diarrhea.

Infections, toxins, medications, anatomic abnormalities such as tumors, and dietary intolerance can cause diarrhea. Infectious causes of diarrhea are the most common. These may be of bacterial, viral, fungal, or parasitic origin. Infections can be classified as causing predominantly watery, large-volume diarrhea due to a small-bowel infection or bloody, small-volume dysentery due to a predominant colonic infection. Pathogens that infect the GI tract are similar worldwide, but the likelihood of infection depends on the patient’s age, immune status, geographic location, and exposure history. Agents such as rotavirus, Norwalk virus, adenoviruses, enteroviruses, *Vibrio cholerae*, *Escherichia coli*, *Giardia*, and *Cryptosporidium* commonly cause watery diarrhea. See this module’s section on dysentery for common causes of bloody diarrhea. *Campylobacter* spp., *Salmonella*, *Shigella*, and MAC are particularly common bacterial causes of diarrhea in the setting of AIDS. Diarrhea caused by enteric viruses is no more common among children with AIDS than in the general population, although CMV and herpes simplex virus may cause opportunistic infection. *Candida albicans* can infect the GI tract of people with...
AIDS, and parasites such as *Cryptosporidium* and *Isospora* are more likely to cause chronic diarrhea in an immunosuppressed host.

Food- or waterborne pathogens may cause diarrheal infections in immunocompromised hosts at a smaller inoculum than that needed to infect healthy hosts; they may also cause opportunistic infections. Opportunistic AIDS-defining diarrheal illnesses include chronic *Cryptosporidium* (lasting >14 days in children or >1 month in adolescents and adults), CMV disease, histoplasmosis, isosporiasis, MAC, and septicemia from *Salmonella*. (The module on opportunistic infections gives more details regarding these infections and their treatment.)

Bacterial toxins present in food may also cause acute diarrhea, usually in association with vomiting. *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium perfringens* can cause food poisoning. Management of toxin ingestion is supportive care. Other causes of diarrhea include medications, such as antiretrovirals, which may cause diarrhea as a side effect (refer to the chapter on antiretroviral treatment for a listing of specific medications associated with diarrhea). Many antibiotics also cause loose stools because of their effect on normal flora, and *Clostridium difficile* infection may occur in the setting of recent broad-spectrum antibiotic therapy. Inflammatory processes such as celiac sprue (malabsorption syndrome characterized by marked atrophy and loss of function of the small intestinal lining), surgical procedures, and tumors can change the anatomy and function of the intestines and result in diarrhea. (Please refer to the chapter on HIV-associated malignancies for more information about Kaposi sarcoma and smooth-muscle tumors such as leiomyosarcomas and leiomyomas, which may present with diarrheal symptoms in patients with HIV/AIDS.) Osmotic diarrhea can occur with lactose deficiency and overfeeding, whereas bloody stools may occur with allergy to cow’s milk or soy protein.

Though diagnosis of the exact cause of diarrhea may be difficult, for treatment purposes one can usually divide diarrhea into four clinical types and then manage accordingly:

1. Acute diarrhea—diarrhea that has lasted less than 14 days
2. Dysentery—diarrhea with visible blood
3. Persistent diarrhea—diarrhea that has lasted more than 14 days
4. Diarrhea and severe acute malnutrition

**Assessment**

Assessment of a patient with diarrhea should include both subjective and objective information. The focus of the assessment should be twofold: to determine the degree of dehydration and to determine the type of diarrhea (acute, dysentery, persistent, or with severe acute malnutrition).

Subjective data include the following:
- Onset, duration, amount, frequency, odor, and appearance of stool—presence of mucus or blood
- Presence of any associated symptoms, such as fever, pain, vomiting, cramping, flatus, abdominal distension, tenesmus
- Dietary changes that might correlate with the increase in the amount of stool
- Family members with similar illness or other GI diseases and any unusual exposure history (travel, animals, antibiotics)

Objective data include the following:
- Assess for signs of dehydration, such as sunken fontanel in the infant, poor skin turgor, dry mucous membranes, lack of tears, decreased urine output, and changes in level of consciousness.
- Compare patient’s current weight and previous weight.
- Assess for alterations in tissue perfusion (e.g., tachycardia, delayed capillary refill, hypotension).
- Examine stool for color, consistency, blood, mucus, pus, odor, and volume.
- If possible, evaluate stool for ova and parasites, bacterial culture, and white blood cells.
- Assess for the presence of acute malnutrition—visible wasting, edema, mid-upper-arm circumference, weight for height (see chapter on nutrition).

**Clinical considerations.** Diagnosis of the cause of diarrhea is often difficult because of the many pathogens that produce infection. Whenever possible, appropriate enzyme immunoassays and bacterial, parasite, and special stool stains and cultures should be sent for definitive diagnosis. Bacterial, mycobacterial, and CMV blood cultures may facilitate diagnosis in febrile patients with HIV/AIDS and diarrhea.

Dehydration occurs when water output exceeds water intake. Patients with vomiting and diarrhea are at high
risk of dehydration. The patient’s weight and intake and output should be assessed daily or even more often if he or she is very sick. Intake should include all oral and intravenous fluids; output should include urine, stool, and emesis. For management purposes dehydration can be classified as none, some (mild or moderate), or severe (Table 1). As dehydration develops, signs include a sunken fontanel in infants, poor skin turgor, dry mucous membranes, lack of tears, decreased urine output, changes in the level of consciousness, increased heart rate, and decreased weight. Fluid and electrolyte replacement and maintenance are the mainstays of diarrhea management, and the next section lists recommended protocols for giving hydration fluids on the basis of the assessed level of dehydration. Dietary changes may alleviate diarrhea, and high-protein, high-calorie foods that are low in fat and free of lactose and caffeine may be helpful. Patients should increase soluble fiber and avoid hot, spicy foods.

Some general principles apply to managing all types of diarrhea. Support of appropriate nutrition, prevention and treatment of dehydration, and follow-up are the key components of management in all cases of diarrhea.

Antimicrobial agents may be indicated for the treatment of diarrhea in some situations but should not be used routinely on an empiric basis. When prescribing antimicrobial agents, one should instruct patients on the importance of finishing all medications prescribed. With patients and caregivers, emphasize good perineal hygiene to prevent skin breakdown and frequent hand washing to prevent transmission of infection. Antidiarrheal medications, such as loperamide, have no practical benefit for children with diarrhea, do not prevent dehydration or improve nutritional status, may have dangerous and even fatal side effects, and should not be given to children younger than 5 years. Avoid bismuth subsalicylate compounds in the setting of vomiting or flu because of their possible association with Reye syndrome.

Zinc deficiency is common in children in many resource-limited areas and may contribute to diarrhea in this setting. Many studies have now shown that giving zinc to children with diarrhea can reduce the severity, duration, and frequency of recurrence of diarrhea. The World Health Organization (WHO) recommends that all children with diarrhea be given zinc (10-20 mg/day) for 10-14 days.

**Acute Diarrhea**

Acute diarrhea is diarrhea that has lasted less than 14 days. The preceding section discussed the causes of acute diarrhea. The most important aspect of managing acute diarrhea is assessing the level of hydration (Table 1) and preventing and treating dehydration according to the following treatment plans. See Figures 1-3 for condensed versions of WHO Treatment Plans A, B, and C.

**Table 1. Assessment of level of dehydration in children with diarrhea**

<table>
<thead>
<tr>
<th>Action</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look at:</td>
<td>Condition*</td>
<td>Restless, irritable</td>
<td>Lethargic, unconscious</td>
</tr>
<tr>
<td>Eyes†</td>
<td>Well, alert</td>
<td>Sunken</td>
<td>Sunken</td>
</tr>
<tr>
<td>Thirst</td>
<td>Normal</td>
<td>Thirsty, drinks eagerly</td>
<td>Drinks poorly, or not able to drink</td>
</tr>
<tr>
<td>Feel:</td>
<td>Skin pinch‡</td>
<td>Goes back quickly</td>
<td>Goes back slowly (&lt;2 s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Goes back very slowly (&gt;2 s)</td>
</tr>
<tr>
<td>Decide</td>
<td>The patient has no signs of dehydration</td>
<td>If the patient has two or more signs in B, there is some dehydration</td>
<td>If the patient has two or more signs in C, there is severe dehydration</td>
</tr>
<tr>
<td>Treat</td>
<td>Use Treatment Plan A</td>
<td>Weigh the patient, if possible, and use Treatment Plan B</td>
<td>Weigh the patient and use Treatment Plan C urgently</td>
</tr>
</tbody>
</table>

*Being lethargic and sleepy are not the same. A lethargic child is not simply asleep—the child’s mental state is dull and the child cannot be fully awakened.
†In some infants and children the eyes normally appear somewhat sunken. It may help to ask the mother if the child’s eyes are normal or more sunken than usual.
‡The skin pinch is less useful in infants and children with marasmus or kwashiorkor. Signs of dehydration in severely malnourished children may be different from those in other children—see nutrition chapter for more information.

### Counsel the Caregiver on the 4 Rules of Home Treatment

#### Rule 1: Give the child more fluids than usual to prevent dehydration
- Instruct the caregiver to do the following:
  - Breast-feed frequently and for longer at each feed.
  - If the child is exclusively breast-fed, give ORS or clean water in addition to breast-feeding.
  - If the child is not exclusively breast-feeding, give ORS or clean water (if ORS is not available, soup, rice water, or yogurt drinks may be used).
  - Avoid inappropriate fluids: commercial carbonated beverages, commercial fruit juices, sweetened tea, coffee, medicinal teas.
- Teach the caregiver how to mix the ORS and make sure that he or she has at least 2 sachets.
- Tell the caregiver to give as much water as the child wants, but as a guide he or she should give the following in addition to the usual intake:
  - Younger than 2 years—give 50–100 mL with each watery stool.
  - Older than 2 years—give 100–200 mL with each watery stool.
- Teach the mother how to give the ORS:
  - Give frequent small sips from a cup or spoon.
  - If the child vomits, wait 10 min and then continue, but more slowly.
  - Continue giving the fluids as above until diarrhea resolves.

#### Rule 2: Give zinc supplements
- Tell the caregiver how much zinc to give:
  - Younger than 6 months—1/2 tab (10 mg) once daily for 10–14 days
  - 6 months and older—1 tab (20 mg) once daily for 10–14 days
- Instruct caregiver how to give the zinc—if child cannot chew tablet, crush or dissolve in small amount of clean water, ORS, or expressed breast milk and give with a cup or spoon.
- Remind the caregiver to give the zinc for the full 10–14 days, regardless of whether the diarrhea resolves.

#### Rule 3: Continue feeding
- Instruct the caregiver what food to give:
  - Infants who are breast-fed should continue to breast-feed as often and as much as they want. During diarrheal illness infants may want to breast-feed more than usual; this should be encouraged.
  - Infants who are not breast-fed should continue to be given their usual milk feeds at least every 3 h. Special commercial formulas are unnecessary and should not be routinely given.
  - If the child is taking soft foods he or she should continue taking these in addition to milk.
- Instruct the caregiver how much food to give and how often:
  - Offer the child foods every 3–4 h (at least 6 times per day)
  - Frequent, small feeds may be better tolerated than large feeds.
  - The child may need extra food for at least 2 weeks after an episode.

#### Rule 4: When to return
- Instruct the caregiver to return to a health worker if the child:
  - Begins passing frequent, watery stools
  - Has repeated vomiting
  - Becomes very thirsty
  - Is eating or drinking poorly
  - Develops a fever
  - Has blood in the stool
  - Does not get better in 3 days


**Figure 1. WHO Diarrhea Treatment Plan A: Treat Diarrhea at Home.**
Give recommended amount of ORS in the clinic over 4 h

Give ORS

- Determine the amount of ORS to give over 4 h—see table below
  - Use the age only when the weight can’t be determined. The approximate amount of ORS can be calculated by multiplying the weight by 75 (75 mL of ORS per kg).
  - If the child wants more ORS than shown, give it.

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;4 mo</th>
<th>4-11 mo</th>
<th>12 mo-2 yrs</th>
<th>2-4 yrs</th>
<th>5-14 yrs</th>
<th>≥15 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>&lt;6</td>
<td>6-7.9</td>
<td>8-10.9</td>
<td>11-15.9</td>
<td>16-29.9</td>
<td>≥30</td>
</tr>
<tr>
<td>ORS (mL)</td>
<td>200-400</td>
<td>400-600</td>
<td>600-800</td>
<td>800-1200</td>
<td>1200-2200</td>
<td>2200-400</td>
</tr>
</tbody>
</table>

- Instruct caregiver on how to give ORS.
  - Give frequent, small sips with a cup, spoon, or syringe.
  - Vomiting is not unusual in the first 1–2 h, especially if the child drinks too fast, but rarely prevents successful rehydration and usually stops. If the child vomits, wait 10 min and then continue but more slowly.
  - Continue breast-feeding whenever the child wants.
  - Children can also be offered as much clean water they want in addition to the ORS as above.
- Monitor during the 4 h to ensure that the child is taking the ORS appropriately.
- If the child develops signs of dehydration at any time switch to Treatment Plan C.

Reassess after 4 h

- Assess and classify the level of dehydration after 4 h of rehydration and select the appropriate treatment plan based on the new hydration assessment.
  - If now has no dehydration, switch to Treatment Plan A for home treatment.
  - If the child still has some dehydration, repeat Treatment Plan B.
  - If the child has severe dehydration, start Treatment Plan C immediately.
- Begin feeding the child in clinic if able—see below.

Give zinc

- After first 4 h of rehydration, begin supplemental zinc.
  - Younger than 6 months—1/2 tab (10 mg) once daily for 10–14 days
  - 6 months and older—1 tab (20 mg) once daily for 10–14 days

Begin giving food

- Except for breast milk, food should not be given during the first 3–4 h of rehydration
- After the first 4 h of rehydration, children should begin receiving food as described in Treatment Plan A and should be fed every 3–4 h.

If caregiver must leave before completing treatment

- Show the caregiver how to mix ORS.
- Instruct her on how much ORS to give to complete the 4 h of rehydration.
- Give her enough ORS to complete the rehydration and at least 2 packets for home treatment.
- Explain the 4 rules of home treatment—see Treatment Plan A.


Figure 2. WHO Diarrhea Treatment Plan B: Treat Some Dehydration with ORS.
HIV Curriculum for the Health Professional

**Guidelines for IV treatment**

- Rapid IV hydration is the preferred treatment - start IV fluid immediately
  - If child can drink give ORS by mouth while drip is set up
  - Give 100 mL/kg Ringer's lactate (LR) (or Normal Saline if LR not available) divided as below

<table>
<thead>
<tr>
<th>Age</th>
<th>First give 30 mL/kg in:</th>
<th>Then give 70 mL/kg in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (&lt;1 yr)</td>
<td>1 h*</td>
<td>5 h</td>
</tr>
<tr>
<td>Children (12 mo–5 yrs)</td>
<td>30 min*</td>
<td>2.5 h</td>
</tr>
</tbody>
</table>

*Repeat once if radial pulse is still very weak or undetectable.

- Reassess every 15–30 min until strong radial pulse is present and then at least every hour.
  - If the hydration status is not improving, give the IV drip more quickly.
  - As soon as the child can drink, usually after 3–4 h for infants or 1–2 h for children, all children should be given ORS (5 mL/kg/h) (may provide base and potassium not in the IVF)
- Reassess an infant after 6 h and a child after 3 h.
  - Classify dehydration
  - Choose the appropriate treatment plan—A, B, or C.

**What to do if IV treatment not available**

- Refer urgently to hospital for IV treatment.
- If the child can drink, provide the mother with ORS solution and show her how to give frequent sips during the trip.

  - Start rehydration orally or by NGT with ORS
    - Give 20 mL/kg/h for 6 h (total of 120 mL/kg).

- Reassess the child every 1–2 h.
  - If there is repeated vomiting or increasing abdominal distention, give the fluid more slowly.
  - If hydration status is not improving after 3 h, send the child for IV therapy.

- Reassess the child after 6 h.
  - Classify dehydration.
  - Choose the appropriate treatment plan—A, B, or C.


**Figure 3. WHO Diarrhea Treatment Plan C: For Patients with Severe Dehydration.**

**WHO Treatment Plan A.** The WHO has outlined the treatment of diarrhea at home as Treatment Plan A. Early intervention at home may prevent dehydration and nutritional deficits. Plan A should be used to treat patients who have

- been seen at a health facility and found to have no signs of dehydration,
- been treated at a health facility with Treatment Plan B or C until dehydration was corrected, or
- recently developed diarrhea but have not visited a health facility.

The four basic rules of home therapy using Plan A are as follows.

1. **Give the patient more fluids than usual to prevent dehydration.**

   Which fluids to give: Fluids that should be used at home to prevent dehydration include “recommended home fluids,” which include oral rehydration salt (ORS) solutions or any fluid recommended by the national WHO program for Control of Diarrhoeal Diseases, and other drinks usually available in the home. Many countries have recommended specific home fluids for use in oral replacement treatment.
These include food-based drinks, such as undiluted cereal gruel, and sugar-salt solution. These fluids are suitable for home treatment of most children with diarrhea. Some fluids, such as carbonated beverages, commercial fruit juices, and coffee, could be dangerous and should not be given to children with diarrhea.

For patients who have been treated for dehydration at a health facility using Treatment Plan B or C, ORS solution should also be used. Recipes for oral rehydration solutions are shown in Table 2. Please remember to measure all quantities precisely; even minor deviations from these recipes could be dangerous.

How much fluid and how often: In general, children having diarrhea should be given as much fluid as they want. The following is a general guide for the amount of fluid to be given at home after each loose stool; continue using until diarrhea resolves.

- Children aged 2 years or younger: 50-100 mL
- Children aged 2-10 years: 100-200 mL
- Children aged 10 years or older and adults: as much as they want

2. Give supplemental zinc (10-20 mg/day for 10-14 days) to the child.

3. Give the patient plenty of food to prevent undernutrition. The child’s usual diet should be continued, with the goal to give as much nutrient-rich food as the child can take. The appropriate food to give a child with diarrhea depends on the child’s age and his or her preillness feeding regimen. In general, foods suitable for a healthy child are what should continue to be given to a child with diarrhea. Breast-feeding should be continued without interruption in those children who are breast-feeding. Infants younger than 6 months who normally take formula or cow's milk and are not yet taking soft foods should continue to receive their usual feeds. Special formulas are not routinely necessary, and formula or cow’s milk should not be diluted. For other infants and children, the usual cow’s milk should be given throughout the illness.

Children who are aged 6 months or older, younger infants who have already begun to take soft foods, and adults should also be given soft or semisolid weaning foods. During diarrhea, give the patient as much food as he or she wants. Offer food every 3-4 h (six times a day). Small, frequent feedings are tolerated better than large feedings given less often.

4. Take the patient to a health facility if the diarrhea does not get better or if signs of dehydration or another serious illness develop.

WHO Treatment Plan B. Treatment Plan B should be used for children with some (i.e., mild to moderate) dehydration. Treatment Plan B is often initiated in the clinic or outpatient setting.

1. Giving oral rehydration therapy

- Estimate the amount of ORS solution to be given during the first 4 h with the following formula: 75 mL × weight (in kilograms) = amount of ORS solution. If the patient wants more ORS than shown, give more.
- Show family members how to give the solution. Give 1 teaspoonful (5 mL) of fluid every 1-2 min to children younger than 2 years; offer frequent sips from a cup to older children and adults. Give the determined amount of fluid in 4 h.
- If the patient vomits, wait 10 min and then continue giving ORS solution, but more slowly: 1 teaspoonful (5 mL) every 2-3 min.
- Meet normal fluid needs. Breast-feeding should continue. For infants younger than 6 months who are not breast-fed, also give 100-200 mL of clean water during this period. Older children during this time should be offered as much plain water as they would like in addition to the ORS.

Table 2. Recipes for rehydration solutions

<table>
<thead>
<tr>
<th>Homemade ORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 teaspoon of salt (2.5 g)</td>
</tr>
<tr>
<td>6 level teaspoons of sugar (30 g)</td>
</tr>
<tr>
<td>1 L of safe drinking water</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ReSoMal (for severely malnourished children with diarrhea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 packet of standard WHO-recommended ORS</td>
</tr>
<tr>
<td>Dilute in 2 L of safe drinking water</td>
</tr>
<tr>
<td>50 g of sugar (25g/L)</td>
</tr>
<tr>
<td>40 mL of mineral–vitamin mix (20 mL/L) or 1 scoop of Therapeutic CMV</td>
</tr>
</tbody>
</table>

ORS, oral rehydration solution; CMV, combined mineral–vitamin mix.
Monitor treatment and reassess the patient periodically until rehydration is completed. Identify patients who cannot be treated satisfactorily with ORS solution by mouth and adopt a more appropriate method of treatment.

2. Monitoring treatment
- Ensure that the caregiver is giving ORS solution correctly and that the patient is taking it satisfactorily.
- Record the amount of solution taken and the number of diarrhea stools.
- Observe for signs of worsening dehydration (e.g., further loss of skin elasticity, increasing lethargy) or increasing stools, and move to Treatment Plan C accordingly.
- Observe for puffy eyelids; swollen digits; or wet, coarse breath sounds, which can indicate overhydration; if these are seen, ORS solution should be stopped, although breast-feeding and the provision of plain water should continue. When the puffiness disappears, return to Treatment Plan A guidelines if stable.
- Reclassify patient to Treatment Plan A, B, or C after 4 h. If no signs of dehydration are present, give instructions for continuing treatment at home per Treatment Plan A. If signs of severe dehydration are present, proceed to Treatment Plan C.

3. Start supplemental zinc (10-20 mg/day) after the initial 4-h period of rehydration.

4. Giving food.
- Food should not be given during the first 4-h period with the exception of breast milk.
- After the first 4-h period, all children should resume taking foods as described in Treatment Plan A.

WHO Treatment Plan C. Treatment Plan C is for patients with severe dehydration. Patients with signs of severe dehydration can die quickly from hypovolemic shock. They should be treated immediately, per Treatment Plan C:
- Decide how the fluid will be given—by intravenous (IV) drip, by nasogastric (NG) infusion, or orally.
- Decide how much IV fluid to give, and then give the fluid and reassess the patient frequently.
- Shift to Treatment Plan B or A when the patient is no longer severely dehydrated.

1. Administration guidelines, Plan C

IV Replacement
The treatment of choice for severe dehydration is IV rehydration because it is the fastest way to restore the depleted blood volume. Ringer’s Lactate Solution (also called Hartmann’s Solution for Injection) and normal saline (0.9% NaCl) are the preferred commercially available solutions. If these are not available, half-strength Darrow’s solution with 2.5% or 5% dextrose or half-normal saline in 5% dextrose may be used. IV solutions containing only dextrose (glucose) should not be used.

Infants should be given IV fluid at a rate of 30 mL/kg of body weight in the first hour, followed by 70 mL/kg over the next 5 h, providing a total of 100 mL/kg in 6 h.

Older children and adults should be given IV fluid at a rate of 30 mL/kg within 30 min, followed by 70 mL/kg in the next 2.5 h, providing a total of 100 mL/kg in 3 h. After the first 30 mL/kg has been given, a strong radial pulse should be easily felt. If it is still weak and rapid, a second infusion of 30 mL/kg should be given at the same rate; however, doing so is rarely necessary. Small amounts of ORS solution should also be given by mouth (about 5 mL/kg/h) as soon as the patient can drink to provide additional potassium and base. Doing so is usually possible after 3-4 h in infants and after 1-2 h in older children and adults.

NG Replacement
If IV therapy is not possible, an NG tube can be used to give ORS solution, provided that there is a person trained in the tube’s placement and maintenance. This approach is not as satisfactory as IV infusion because the fluid cannot be given as rapidly, and additional time is required for it to be absorbed from the intestine. The maximum rate of fluid infusion is about 20 mL/kg/h. When higher volumes are administered, abdominal distension and repeated vomiting are frequent problems.

Oral Replacement
If IV and NG therapy are not possible or will be delayed, and if the patient can drink, ORS solution should be given by mouth at a rate of 20 mL/kg/h. This approach has the same disadvantages as those of NG therapy, and it cannot be used for patients who are lethargic or unconscious. Children younger than 2 years should be given ORS solution by spoon, about 1 teaspoonful (5 mL/min. Older
Children and adults may drink the solution from a cup.

Patients with abdominal distension caused by paralytic ileus should not be given ORS solution either orally or by NG tube.

2. Reassessing the patient

Signs of a satisfactory response to rehydration are return of a strong radial pulse, improved level of consciousness, ability to retain oral fluids, improved skin turgor, and urinary output nearly equal to fluid intake. When these signs are observed, the interval between assessments can be lengthened. If the signs of dehydration remain unchanged or worsen, and especially if the patient continues to pass watery stools, the rate of fluid administration and the total amount of fluid given for rehydration should be increased.

In addition to rehydration therapy, the patient's normal need for water must be met. Breast-feeding should be resumed as soon as an infant can suck. Infants younger than 6 months who are not breast-fed should be given 100-200 mL of plain water during the first 6 h if they can drink. Older children and adults should be given water to drink as soon as they desire it, provided that vomiting has subsided. This water is in addition to any ORS solution being given.

3. Transition to Treatment Plans B and A

At the end of the planned rehydration period outlined in Treatment Plan C (usually 3-6 h), the patient's hydration status should be carefully reassessed. If signs of severe dehydration are still present, rehydration therapy must be continued per Treatment Plan C. Otherwise, further treatment should follow Plan B if some signs of dehydration remain or Plan A if there are no signs of dehydration. In either case, ORS solution should be used. Before removing the IV line, however, it is wise to give ORS solution for at least 1 h to ensure that oral replacement therapy is feasible. If possible, patients presenting with severe dehydration should be hospitalized until the diarrhea subsides. Otherwise, they should be observed for at least 6 h after rehydration before returning home to make sure that the caregiver can maintain their hydration by using the ORS solution.

Dysentery

Dysentery is diarrhea with visible blood in the stool. Abdominal cramps, tenesmus (unproductive, painful straining), fever, and poor appetite are common associated symptoms. Infection with *Shigella* is the most common cause of dysentery, but other potential causes include infections with *Salmonella*, enterohemorrhagic and enteroinvasive *E. coli*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Schistosoma*, and *Entamoeba histolytica*. The diagnosis of dysentery can be made by history of blood in the stool or by visual inspection of stool for blood. A stool sample should be sent to a lab, if available, for microscopy for fecal leukocytes and ova and parasites, and for culture and sensitivities, though in many settings doing so may not possible. Populations at risk for severe disease and poor outcomes related to dysentery include the following: infants younger than 1 year, especially those not breast-feeding; malnourished children; children recovering from measles infection in the last 6 weeks; and those who develop severe dehydration, altered consciousness, or have an associated convulsion. Malnourished children with dysentery should be admitted to a hospital for inpatient care, and strong consideration should be given to admitting these other high-risk populations. In the absence of these risk factors, most children can be treated as outpatients.

Antibiotic treatment is recommended for children with dysentery, though resistance to routinely given antibiotics is a growing problem. The following antibiotics are ineffective against *Shigella*, and none of these should be given for the treatment of dysentery: metronidazole, tetracyclines, chloramphenicol, amoxicillin, aminoglycosides (gentamicin, kanamycin), nitrofurans (nitrofurantoin, furazolidone), and first- or second-generation cephalosporins. Cotrimoxazole and ampicillin were effective for *Shigella*, but there is now widespread resistance and these antibiotics should not be used empirically. Nalidixic acid is an antibiotic that was commonly used to treat dysentery but is currently not recommended for this indication.

Treatment of dysentery should be guided by the local sensitivity pattern of *Shigella* isolates. In the absence of known local resistance patterns, the WHO recommends ciprofloxacin as the first-line treatment for dysentery. The use of fluoroquinolones such as ciprofloxacin in children has been restricted because of the concern for joint damage that was seen as a side effect of these medications in animals. Sometimes, though, the benefits outweigh the small risks, and a short course of ciprofloxacin is both safe and effective for use in the treatment of dysentery in children. Other antibiotic options include extended-
spectrum cephalosporins (ceftriaxone, cefotaxime) and pivmecillinam. See Figure 4 for dosing information on these medications for adults and children. Empiric treatment for *E. histolytica* should not be given routinely because it is a rare cause of dysentery in children. Treatment for *E. histolytica* in children is recommended only when the results of stool microscopy from a reliable lab show evidence of infection or when a child has failed to respond to two antibiotics to which *Shigella* is susceptible.

See Figure 4 for an algorithm for the management of dysentery. Supportive care, including management of dehydration, appropriate feeding, provision of zinc, and control of fever and pain, should be given to all children just as in acute diarrhea according to the protocols referred to in the previous section. Malnourished children with dysentery should be admitted to a hospital for inpatient care. Most other children may be managed safely as outpatients. An antibiotic to which *Shigella* is sensitive should be given and its effect reassessed in 2 days. If the child is improved, as manifested by resolution of fever, fewer stools, less blood in the stools, and improved appetite and activity, the child should complete a 3- to 5-day course of the antibiotic. If the child is not improved after 2 days, the child should be given a second antibiotic to which *Shigella* is sensitive and reassessed 2 days later. If the child is improved at this point, a 5-day course of this antibiotic should be completed. If the child is still not improved, both admission to a hospital and a course of treatment for amoebiasis should be considered.

**Persistent diarrhea**
Persistent diarrhea is diarrhea, with or without blood, that lasts for more than 14 days. Persistent diarrhea may be

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**Figure 4. Algorithm for the management of dysentery.**
related to poor absorption of nutrients by the intestines because of damage done by previous infections. Changes in the diet may help to restore adequate nutrition and hydration while allowing the intestine to heal so that a normal diet can be resumed. In children with HIV it is more likely that persistent diarrhea is related to an infection. Organisms that almost never cause infection in immunocompetent children, such as CMV and MAC, may cause persistent diarrhea in HIV-infected children. Other organisms that usually cause a self-limited infection in immunocompetent children, such as Cryptosporidium spp.; Isospora spp.; Microspora spp.; and even common viral and bacterial infections such as rotavirus, adenovirus, Salmonella spp., Shigella spp., and Campylobacter spp., may result in persistent diarrhea in HIV-infected children. Giardia spp. is another infection that may cause persistent diarrhea with variable frequency. Most infectious causes of persistent diarrhea in HIV-infected children are more likely in the presence of advanced or severe immunodeficiency. Other causes of persistent diarrhea include HIV enteropathy (malabsorption without any other identifiable cause), postinfectious enteritis, inflammatory bowel disease, thyrotoxicosis, encopresis, and pancreatic or liver disease causing fat malabsorption—though these causes will be much less common than infections. When possible, stool specimens should be sent to the laboratory for an evaluation to include microscopy for leukocytes, ova, and parasites; culture and sensitivities; and any available tests for specific organisms.

Most children with persistent diarrhea can be managed as outpatients. Children with acute malnutrition and persistent diarrhea should be referred to a hospital for inpatient care. Inpatient referral should also be strongly considered for children with persistent diarrhea who are younger than 4 months, have signs of significant dehydration, or have other serious infections such as pneumonia or sepsis.

Treatment of persistent diarrhea includes four major components:

- Appropriate fluids to prevent and treat dehydration
- A nutritious diet that does not cause diarrhea to worsen
- Supplementary vitamins and minerals including zinc
- Antimicrobial treatment when appropriate

Patients should be assessed for dehydration and given appropriate fluids as described in previous sections. Children with persistent diarrhea require nutritious diets that are low in lactose. Infants younger than 6 months should be given exclusive breast-feeding if possible or, for those who cannot breast-feed, yogurt or lactose-free formula, if available. Children older than 6 months should be given one of the recommended diets as listed in Table 3. The first diet is low in lactose and will result in improved diarrhea for 65% of children. If the child fails the first diet, as indicated by an increase in stool frequency (usually >10 per day) and worsening dehydration, or a failure to gain weight after 7 days of the first diet, then the second diet, which is low in lactose and starch, should be given. All children with persistent diarrhea should receive supplementary vitamins and minerals once a day for at least 14 days.

For most children, routine treatment of persistent diarrhea with antimicrobials is not effective and should not be given but may be appropriate in certain circumstances. Any nonintestinal infections, such as pneumonia, sepsis, or urinary tract infection, should be identified and treated according to national guidelines.

Table 3. Recommended example diets for children older than 6 months with persistent diarrhea

<table>
<thead>
<tr>
<th>First Diet</th>
<th>Ingredient</th>
<th>Amt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full-fat dried milk</td>
<td>11 (or whole liquid milk 85 mL)</td>
</tr>
<tr>
<td></td>
<td>Rice</td>
<td>15 (uncooked rice)</td>
</tr>
<tr>
<td></td>
<td>Vegetable oil</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Cane sugar</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Water to make total vol of 200 mL</td>
<td></td>
</tr>
</tbody>
</table>

With this diet, 130 mL/kg gives 110 kcal/kg. This diet provides 83 kcal/100 g, 3.7 g of lactose/kg of body weight/day, and 11% of calories as protein.

<table>
<thead>
<tr>
<th>Second Diet</th>
<th>Ingredient</th>
<th>Amt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole egg</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Rice</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Vegetable oil</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Water to make total vol of 200 mL</td>
<td></td>
</tr>
</tbody>
</table>

With this diet, 145 mL/kg gives 110 kcal/kg. This diet provides 75 kcal/100 g. If finely ground, cooked chicken can replace the whole egg, giving 70 kcal/100 g.

Persistent diarrhea may not resolve until these non-intestinal infections have been adequately treated. Children with persistent diarrhea with blood should be treated as described in the section on dysentery. Patients should not be treated for amoebiasis or giardiasis unless laboratory examination confirms infection with these organisms. HIV-infected children with advanced or severe immunodeficiency are at higher risk for an infectious cause of their persistent diarrhea. When appropriate lab facilities are available, antibiotic treatment should not be given empirically and should be based on results of laboratory examination. In areas where lab facilities are not available, consideration may be given to empiric treatment of ill HIV-infected children with persistent diarrhea and advanced or severe immunosuppression with ciprofloxacin (to cover most bacterial causes), cotrimoxazole (to cover treatable parasitic infections), and metronidazole (to cover giardiasis). Persistent diarrhea lasting longer than 14 days and not responding to appropriate treatment is a WHO Clinical Stage 3 condition. Reconstitution of the HIV-infected child’s immune system with antiretroviral treatment will sometimes be the only effective way to treat persistent diarrhea in these children.

Diarrhea in severe acute malnutrition
Severely malnourished children who develop diarrhea have a higher risk of developing serious complications from their diarrhea and have much worse outcomes than those of well-nourished children. Children with severe malnutrition are also sensitive to fluids and can develop life-threatening heart failure from overhydration. For this reason, all children with diarrhea should have an assessment for severe acute malnutrition, and those who are noted to be malnourished should be assessed and managed according to the following protocol.

The assessment for the presence and severity of dehydration in malnourished children is difficult: many of the signs and symptoms described in the preceding section on dehydration are unreliable. Some signs and symptoms that are more reliable indicators of dehydration in malnourished children include a history of diarrhea, recently sunken eyes, cool hands and feet, weak or absent pulses, and diminished urine flow. A child’s mental state, skin elasticity/skin pinch, dry mouth, and lack of tears may be less reliable signs of hydration status in these children.

With the exception of the child with shock, rehydration in severely malnourished children should be done orally. The standard ORS solution has too much salt for these children, so ReSoMal should be used instead for rehydration. ReSoMal is commercially available but also can be prepared using ORS packets (see Table 2 for a ReSoMal recipe). Usually 70-100 mL/kg of fluid is enough to restore adequate hydration, but this volume should be given over 12 h. ReSoMal should be given at a dosage of 5 mL/kg every 30 min for 2 h. The total amount of fluid given should depend on resolution of the signs of dehydration, the child’s thirst, and passage of urine. If there is ongoing watery diarrhea, these fluid losses should be replaced with ReSoMal, with children younger than 2 years getting 50-100 mL with each watery stool and older children receiving 100-200 mL with each stool. These children should be monitored for any signs of overhydration, such as engorged neck veins, edema including puffy eyelids, and increased respiratory and heart rates. If any of these signs appear, rehydration should be stopped immediately. If the child refuses to or cannot take fluids orally, an NG tube should be placed and fluids administered through the tube.

IV fluids should be reserved for cases of shock, in which either half-strength Darrow’s solution with 5% glucose, Ringer’s Lactate with 5% glucose, or half-normal saline with 5% glucose should be given at 15 mL/kg over 1 h. When signs of shock have resolved, further rehydration can be continued orally as described earlier.

Feeding should begin promptly in severely malnourished children. Breast-feeding should not be interrupted, even during rehydration. F-75 should be given as soon as possible, usually within 2-3 h after starting rehydration. See the chapter on nutrition for further information on caring for severely malnourished children.

Wasting Syndrome
Wasting syndrome is an AIDS-defining condition and is a WHO Clinical Stage 4 diagnosis for both adults and children. For adults, the WHO defines wasting syndrome as

- unexplained involuntary weight loss (>10% of baseline body weight), with obvious wasting or body mass index less than 18.5 plus
- unexplained chronic diarrhea (loose or watery stools more than three times daily) reported for more than 1 month, or
Gastrointestinal Manifestations of HIV Infection

- reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarial agents. For children, WHO defines wasting as follows:
  - persistent weight loss not explained by poor or inadequate feeding or other infections; and/or
  - visible wasting of muscles, with or without edema of both feet; and/or
  - weight for height of –3 standard deviations from the mean, as defined by the WHO Integrated Management of Childhood Illness guidelines; and
  - not adequately responding in 2 weeks to standard therapy.

Wasting causes loss of lean body mass. In developing countries in Africa, failure to gain weight and weight loss are the most common presenting signs of HIV disease, explaining why HIV was known as "slim disease" in many places. Wasting syndrome can be attributed to inadequate caloric intake, malabsorption of nutrients from the GI tract, increased metabolic rates, and other direct effects of HIV infection. See the chapter on nutrition for a more in-depth discussion of causes of weight loss in HIV-infected patients.

Evaluation of a patient with wasting syndrome should include performing a nutritional assessment. The nutritional assessment should include growth measurements and dietary history (see chapter on nutrition). The patient should be assessed for any clinical signs or symptoms that suggest malabsorption, such as chronic diarrhea. Wasting can sometimes be alleviated with the use of antiretroviral agents and/or nutritional supplements. Oral supplementation should be offered to increase caloric intake. If oral supplementation fails, enteral supplementation should be used. See the nutrition chapter for more information on nutritional assessments and interventions.

Hepatitis

Hepatitis is inflammation of the liver. Signs and symptoms of hepatitis can include jaundice, fever, liver enlargement, abdominal tenderness, pruritus (itching), nausea/vomiting, and diarrhea. Often patients with hepatitis will have no symptoms, and the only indication of liver inflammation will be elevated liver enzymes in the blood (AST/ALT). The most common causes of hepatitis in HIV-infected patients are infections. Many different viral infections cause hepatitis, including hepatitis viruses A-E and G, Epstein-Barr virus, CMV, and HIV itself. Many of the medications taken commonly by HIV-infected adults and children can cause liver damage, which may present with signs, symptoms, and laboratory abnormalities identical to those of infectious hepatitis.

Some medications well known to cause liver damage include nevirapine, stavudine, ritonavir, trimethoprim-sulfamethoxazole, rifampicin, isoniazid, pyrazinamide, fluconazole, and ketoconazole.

Infection with two or more organisms is known as coinfection. Coinfection with HIV and the hepatitis viruses is common, and detailed discussions of hepatitis B and C infections follow.

Hepatitis A

Hepatitis A is a virus spread by fecal-oral route, often through contaminated food, and hand washing and good hygiene can help prevent transmission of the virus. Immunization to prevent hepatitis A is recommended in HIV-infected patients with chronic hepatitis B and C infection but may not be available in many settings. Hepatitis A infection is treated symptomatically, is usually self-limited, and rarely progresses to liver failure.

Hepatitis B

Hepatitis B is transmitted by contact with blood, through sexual contact, or from mother to child, but many cases have no known risk factor. Condoms can reduce the risk of sexual transmission. Hepatitis B may or may not cause a symptomatic hepatitis at the time of acute infection and sometimes may progress to chronic hepatitis. The likelihood of developing chronic hepatitis B depends strongly on age at the time of infection, with 90% of perinatally infected infants but only 2%-6% of people infected as older children or adults developing chronic infection. Adults and children with chronic hepatitis B are at high risk for developing other serious liver diseases, including cirrhosis and primary hepatocellular carcinoma, a cancer of the liver. Vaccination against hepatitis B is recommended for HIV-infected patients, and routine childhood vaccination is becoming more widespread. Indications for treatment of chronic hepatitis B infection include evidence of ongoing viral replication (detectable hepatitis B virus [HBV] DNA in the blood) for 6 months, persistent elevation of transaminases, and/or evidence of chronic hepatitis on liver biopsy. Medications approved for the treatment of chronic hepatitis B infection in adults include interferon α, lamivudine (3TC), adefovir, and entecavir, though only lamivudine and interferon α...
have been approved for use in children. New treatments for hepatitis B are currently being studied, including the antiretroviral medication tenofovir disoproxil fumarate (TDF). In HIV-HBV-coinfected adults and children, lamivudine and tenofovir should never be given alone as treatment for HBV because HIV will rapidly develop resistance. In many settings, these complex tests and treatments are not available, and the best intervention to offer HIV-HBV-coinfected patients with chronic hepatitis will be highly active antiretroviral therapy.

**Hepatitis C**

Hepatitis C coinfection with HIV is becoming more common worldwide, especially among IV drug users. Hepatitis C virus is spread primarily by contact with infected blood, and perinatal transmission of hepatitis C is increasing among children born to women who are coinfected with HIV and hepatitis C. As with hepatitis B, many cases have no known risk factor. Acute infection with hepatitis C is usually asymptomatic, but 50%-60% of children and 60%-70% of adults will go on to develop chronic hepatitis, of which many will progress to cirrhosis and primary hepatocellular carcinoma. All infants born to women coinfected with HIV and hepatitis C should be screened for hepatitis C if blood testing is available. Treatment for hepatitis C is available and does not appear to interfere with HIV treatment. Treatment should be started in patients with chronic hepatitis C progressing to cirrhosis. The two treatment regimens that are currently used are interferon alfa alone and interferon alfa in combination with ribavirin. A recent study of peginterferon alfa-2a plus ribavirin found that this combination was more effective in treating HIV-coinfected patients than the combination of interferon alfa and ribavirin or peginterferon alfa-2a alone. In many settings, these complex tests and treatments may not be available, and the best intervention to offer HIV-hepatitis C-coinfected patients with chronic hepatitis will be highly active antiretroviral therapy.

**REFERENCES**


Hematologic Manifestations of HIV/AIDS

Parth S. Mehta, MD

Objectives

1. Review the physiology of normal hematopoiesis.
2. Review the pathogenesis of the hematological manifestations of human immunodeficiency virus (HIV).
3. Identify the clinical manifestations of altered hematopoiesis resulting from HIV infection.
4. Discuss relevant laboratory findings in anemia, neutropenia, and thrombocytopenia.
5. Establish care guidelines for children with HIV infection and altered hematopoiesis resulting in anemia, neutropenia, and thrombocytopenia.

Key Points

1. Altered hematopoiesis in patients with HIV can affect all cell lines (white blood cells, red blood cells, and platelets).
2. Anemia is multifactorial in HIV infection, with causes including opportunistic infection, myelosuppressive drugs, nutritional deficiencies, and the direct effects of HIV on bone marrow progenitors and stromal elements.
3. The primary risk for children with HIV/AIDS with neutropenia is the risk for overwhelming and life-threatening infection.
4. The primary cause of thrombocytopenia in children with HIV/AIDS is an idiopathic thrombocytopenic purpura syndrome secondary to a dysregulated immune system as a result of HIV infection.

Overview

Altered hematopoiesis (blood cell production) occurs in patients with HIV infection. This change affects all three cell lines (red blood cells, white blood cells, and platelets) that come from stem cells in the marrow. Consequently, HIV-infected children may suffer from anemia (lowered levels of red cells), neutropenia (lowered levels of white blood cells called neutrophils), thrombocytopenia (lowered levels of platelets), or any combination of these three. The causes of these conditions are varied and are not fully understood. Evidence shows that HIV infects the progenitor cells in the bone marrow, the hematopoietic stem cells (HSCs), and causes abnormal function. When HSCs cannot produce adequate hematopoietic growth factors (the substances that stimulate the production of blood cells in the bone marrow), decreased production of blood cells occurs. Also, antiretroviral treatment for HIV infection, opportunistic infections and their treatment, and chemotherapy for treatment of HIV-associated malignancies also cause altered hematopoiesis, which can contribute to the problem.

This chapter reviews normal hematopoiesis and the clinical manifestations of children with altered hematopoiesis, followed by a discussion of the causes of the different manifestations of altered hematopoiesis and their management and treatment.

Normal Hematopoiesis

To understand abnormal blood cell production, one must know how normal hematopoiesis occurs. To have normal hematopoiesis, the HSC must be present because it is the cell from which all blood cells will be derived during a person’s lifetime.

HSCs are situated in the bone marrow, spleen, liver, and peripheral blood. HSCs in the bone marrow produce almost all blood cells, whereas the other sites assist in times of undue stress. Only about 5% of the HSCs in the bone marrow are functioning at any one time, yet they can maintain the hematopoietic system for the lifetime of the person.

In addition to the stem cell, supportive cells, called stromal cells, must be present for normal hematopoiesis to occur. T lymphocytes, macrophages, endothelial cells, and fibroblasts help to produce the hematopoietic system.
growth factors that are needed for production and differentiation of normal white blood cells in the bone marrow. Erythropoietin, produced in the kidney, and thrombopoietin, produced in the liver, are necessary for proliferation and production of red blood cells and platelets, respectively. The cells of the bone marrow grow in clumps known as colonies. Cells differentiate from the earliest progenitor cells, the HSCs, to progenitor cells of the different cell lineages, and these colonies then further mature toward becoming red blood cells, white blood cells (neutrophils, monocytes), and platelets. The progenitors of the red blood cells are in the erythroid lineage, whereas the white blood cells are derived from the granulocyte-macrophage colonies of progenitor cells, and finally the megakaryocytes of the bone marrow give rise to circulating platelets.

Alterations in hematopoiesis can lead to abnormalities in red cell, white cell, and platelet count in the peripheral blood. A decrease in the number of white cells is called leukopenia, and a decrease in the number of platelets is called thrombocytopenia. A decrease in the white blood cells known as neutrophils is called neutropenia. Anemia is a decrease in red cell number, hemoglobin, or hematocrit. Anemia is further classified by the size of the red cells in the peripheral blood as microcytic (smaller than normal), normocytic (normal), or macrocytic (larger than normal).

**Clinical Manifestations of Altered Hematopoiesis**

Children with alterations in hematopoiesis should have a comprehensive patient history, physical examination, complete blood count, and liver function tests. Children with anemia should also have a reticulocyte count, lactate dehydrogenase test, and Coombs’ test. A peripheral smear should be examined because it provides a great deal of information on cell morphology and can give clues to the cause of the alteration in hematopoiesis. Bone marrow aspiration and biopsy may be necessary to determine the cause. The following sections review the signs and symptoms of anemia, neutropenia, and thrombocytopenia.

**Clinical Presentation of a Child with Anemia**

- Pale conjunctivae or palmar creases, jaundice
- Fatigue or irritability
- Decreased ability to concentrate

**Clinical Presentation of a Child with Neutropenia**

- May be asymptomatic
- Fever
- Skin ulcerations or lesions
- Tachypnea, cough, wheezing, rales
- Stomatitis, dysphagia
- Abdominal pain, diarrhea
- Perirectal pain or fissure

**Clinical Presentation of a Child with Thrombocytopenia**

- Bruising, petechiae, purpura
- Epistaxis
- Gingival bleeding
- Hematuria
- Hematochezia

**Pathogenesis of Hematological Manifestations of HIV Infection**

**Abnormalities of Bone Marrow**

Bone marrow in HIV-infected children undergoes changes. The most common changes seen in morphology of the marrow architecture include decreased cellularity and myelodysplasia (abnormal change of the cellular structure) affecting the cells of the erythroid lineage and the megakaryocytes. Dysplastic changes of the granulocyte-macrophage lineage with arrest of maturation can occur in the marrow of children with HIV infection.

These changes impair growth of bone marrow cultures in vitro from patients with HIV infection. There is a decrease in the number of HSCs in the bone marrow of patients with HIV infection. Furthermore, HIV can directly infect the bone marrow stromal cells, leading to aberrations in their function. This development in turn leads to abnormal maturation of the different bone marrow cell lineages and may explain the preceding structural changes.

One can also observe drug-induced suppression of bone marrow in children with HIV infection. The most common cause is the antiretroviral drug zidovudine (AZT). This
drug inhibits the colony formation of stem cells as well as erythroid and granulocyte-macrophage progenitor cells. Other drugs can affect the bone marrow, and drugs used to treat opportunistic infections in HIV-infected children suppress the bone marrow. Acyclovir and ganciclovir used in the prevention and treatment of herpes simplex virus infection and cytomegalovirus (CMV) infection can both suppress the marrow. Trimethoprim-sulfamethoxazole used to prevent and treat *Pneumocystis jirovecii* pneumonia also suppresses the bone marrow. Finally, opportunistic infections can cause marrow suppression, particularly CMV, parvovirus B19, and *Mycobacterium avium* complex (MAC) infections.

One should consider the diagnosis of marrow suppression in any child with HIV infection when the blood count demonstrates a decrease in white cell (leukopenia), platelet (thrombocytopenia), or reticulocyte (immature red cells) count. One should consider the diagnosis of bone marrow dysfunction especially if there are decreases in more than one cell line. Many other factors can cause anemia, which when present alone is not as concerning for bone marrow suppression. Evaluating a child for marrow suppression requires bone marrow aspiration and biopsy, and the marrow should also be sent for mycobacterial stains and culture.

Treatment of bone marrow suppression is predicated on therapy for the underlying cause. In the child with HIV infection, optimization of antiretroviral therapy and decrease in the viral load alone is often effective in resolving the marrow suppression. Identification and treatment of opportunistic infections is also critical.

**Anemia**

Anemia is the most common hematological abnormality found in children with HIV infection. Indeed, anemia was the initial manifestation of HIV infection in about 10% of children in a recent study in Italy. The importance of finding and treating anemia in children with HIV infection is underscored by data from their study showing anemia to be an independent prognostic factor of mortality in children with HIV infection. The prognostic significance of anemia at baseline is statistically significant in multiple retrospective studies in adults in the United States and Europe both in the pre-highly active antiretroviral therapy (HAART) and HAART eras.

The etiology of anemia in children with HIV infection is multifactorial, and managing anemia can involve a variety of modalities (Table 1). HIV infection and its direct effects on HSCs and stromal elements can lead to anemia. Opportunistic infection and myelosuppressive drugs might also cause anemia. Furthermore, children with HIV infection often have abnormally low levels of iron and possibly cobalamin (vitamin B12), substances necessary for normal red blood cell production. Iron deficiency, the most common cause of anemia worldwide, is a frequent comorbid and treatable condition in children with HIV infection. The association of vitamin B12 is less clear: one study showed serum B12 levels to be low in only 20% of adults with HIV infection. Anemia due to iron deficiency is microcytic, and that due to B12 deficiency has associated changes in the neutrophils known as megaloblastic change.

Another well-known cause of anemia is pure red cell aplasia, caused by infection with parvovirus B19, and should be considered in children with HIV infection that have isolated anemia. Other marrow-suppressive infections such as CMV and MAC often affect the white cell lineage, first leading to neutropenia rather than anemia. Anemia of chronic infection as caused by these agents is normocytic.

Myelosuppressive drugs such as zidovudine and trimethoprim-sulfamethoxazole can also lead to anemia. The anemia associated with zidovudine treatment is macrocytic, and indeed the red cells may be macrocytic even without anemia. Some practitioners use this finding to assess adherence to zidovudine therapy.

Finally, anemia can be a result of red cell destruction, or hemolysis, as opposed to an aberration of production. Clinically significant hemolysis in patients with HIV infection is rare. However, in children with G6PD (glucose-6-phosphate dehydrogenase) deficiency, administering medications such as those commonly used in the prophylaxis and treatment of *Pneumocystis jirovecii* infection can lead to clinically significant hemolysis.

**Table 1** shows the management and treatment of anemia in children with HIV infection. Although many approaches to the workup and management of anemia in children exist, the basic fundamentals include obtaining a complete blood count with red cell indices and a reticulocyte count where available. The formulation of a diagnosis is based on the size of red cells along with
Hematologic Manifestations of HIV/AIDS

**Table 1. Guidelines for diagnosis and treatment of anemia in children with HIV infection**

<table>
<thead>
<tr>
<th>Cause of Anemia</th>
<th>Laboratory Findings</th>
<th>Management Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased production due to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Microcytic anemia with decreased reticulocyte count Bone marrow normocellular with decreased iron</td>
<td>Iron therapy at 6 mg elemental Fe/kg/day divided b.i.d. and t.i.d. orally and continue for 3 mos to ensure adequate iron stores</td>
</tr>
<tr>
<td>Consider thalassemia syndrome and lead poisoning</td>
<td></td>
<td>In patients with poor absorption of iron, consider adding vitamin C or may consider intravenous iron therapy</td>
</tr>
</tbody>
</table>

Decreased production due to:
- Vitamin B12 and/or folate deficiency
- Medication toxicity

Macrocytic anemia with decreased reticulocyte count Hypersegmented neutrophils on peripheral smear Megaloblastic bone marrow with normal cellularity with immature progenitors

If patient on zidovudine consider switching to another medication
Supplementation with oral folate 1 mg daily and vitamin B12 intramuscularly monthly, although these are rare causes in children

Decreased production due to:
- Medication toxicity
- Viral suppression
- Marrow infiltration by malignancy
- Nutritional deficiencies
- Other infection (MAC)

Normocytic anemia with decreased reticulocyte count Bone marrow with decreased erythroid progenitors and decreased cellularity

Transfusion therapy with 10-15 mL/kg of packed red blood cells (pRBCs) for hemoglobin <7 g/dL or symptomatic anemia
Optimize HAART
Treatment of underlying infections (e.g., MAC)
Consider IVIG 0.5 g/kg every 4 weeks in pure red cell aplasia due to parvovirus B19
If patients needs chronic transfusion therapy, consider treatment with erythropoietin alfa at 150-600 U/kg 3 days/wk subcutaneously

Increased destruction due to:
- Nonimmune hemolysis due to genetic defect such as G6PD deficiency with medication exposure
- Autoimmune hemolytic anemia
- Infection with or without disseminated intravascular coagulopathy

Normocytic anemia with increased reticulocyte count and evidence of red cell destruction on peripheral smear Increased lactate dehydrogenase Positive Coombs’ test in autoimmune hemolysis Normal bone marrow

Discontinue medication (e.g. dapsone) in case of G6PD deficiency
IVIG and/or prednisone at 1 mg/kg/dose BID for autoimmune hemolysis
Consider transfusion of pRBCs only in life-threatening cases

The physiological reason (decrease in production or increase in destruction). So a common approach involves classifying anemia into macrocytic, normocytic, or (most commonly) microcytic, on the basis of mean cell volume. The reticulocyte count is 1%-2% in the presence of a normal hemoglobin value. In the presence of anemia, the corrected reticulocyte count can help distinguish between anemia due to decreased production (low corrected reticulocyte count) versus that due to increased destruction (elevated corrected reticulocyte count).

For macrocytic anemia in a child with HIV infection or on therapy, the most common cause is zidovudine toxicity. If a child is receiving zidovudine as part of his or her HAART regimen, the provider must recheck the dosing of zidovudine to ensure that it is not being overdosed. Furthermore, because there is a range of doses that can be used for zidovudine and still be therapeutically effective, one can consider decreasing the dose while remaining in that therapeutic range to alleviate the anemia. This approach was more commonly taken in the past with dosing every 6 h; today with twice-daily dosing it is commonly felt to be less of a problem, although to my knowledge there have been no unequivocal studies published demonstrating this commonly observed finding. Table 1 lists the other common causes of macrocytic anemia, along with their management.
Normocytic anemia is also common in children with HIV infection. In a child not on therapy, one can often find this development as a result of the chronic disease state. In this situation the most important therapy is to treat the HIV infection with HAART. If the child has severe anemia, with a hemoglobin level less than 7 g/dL, at presentation it may be necessary to omit zidovudine from the chosen regimen. In a child already on therapy, the chronic disease state is expected to play less of a role if the child’s HIV infection is well controlled. However, to my knowledge there are no unequivocal studies showing that a low viral load in the peripheral blood necessitates a lack of activity of HIV infection in the marrow microenvironment; nonetheless, a normocytic anemia should prompt further considerations in a child already on HAART with viral suppression. Table 1 lists some of the important causes of normocytic anemia.

A mixed nutritional problem of iron deficiency and folate or vitamin B12 deficiency can also lead to a normocytic anemia. In a developing, resource-poor country where nutritional problems are frequent, one should address this possibility with a trial of iron therapy (6 mg of elemental Fe/kg of body weight divided twice daily orally) along with folate (1 mg daily by mouth) for at least 1 month. Persistent normocytic anemia for a child on HAART warrants a bone marrow examination looking for a specific cause such as infiltrative disease or opportunistic infection of the marrow by MAC (Table 1).

Finally, the other possibility to consider in a child with normocytic anemia is a destructive process. In a child who has signs of hemolysis such as jaundice and splenomegaly, it is especially helpful for diagnosis to send a direct Coombs’ test and to prepare a peripheral smear for review. In a child with Coombs’ test-positive hemolysis, an immune-mediated hemolysis is of concern, and these children should receive transfusion therapy only in life-threatening situations because the transfused red blood cells will probably also be hemolyzed. The peripheral smear can be helpful in showing signs of hemolysis with red blood cell fragments, spherocytes (spherical red cells, normally donut shaped), or schistocytes (sometimes called helmet cells because of their shape). This approach can help to rapidly diagnose hemolytic anemia, and therefore a peripheral smear is strongly recommended whenever hemolytic anemia is a consideration.

The most common type of anemia worldwide is microcytic anemia as a result of iron deficiency. This development is particularly of concern in resource-poor settings where nutritional deficiencies abound. Iron therapy as described earlier is indicated. The health care provider must advise the patient and family to administer the iron supplementation without dairy products and preferably with a citrus product such as orange juice, or it can also be given with vitamin C. The duration of therapy is 6 weeks to 3 months depending on response. The hemoglobin level should start to rise within 2–4 weeks; however, one must treat long enough after normalization of the hemoglobin to replenish iron stores in the liver. Table 1 describes the other causes of microcytic anemia are described in Table 1, and once again a peripheral smear can be helpful in distinguishing both thalassemia and lead intoxication from iron deficiency.

Leukopenia and Neutropenia

A decrease in white blood cell count, leukopenia occurs in about one-third of children with untreated HIV infection with white counts less than 3000 cells/µL. Neutropenia is an absolute neutrophil count (ANC) of less than 1500 cells/µL and is observed in almost half of children with untreated HIV infection. The risk of serious bacterial infection increases when the ANC falls below 500 cells/µL. To calculate the ANC, multiply the total white blood cell count by the sum of the percentages of segmented neutrophils and bands. For a white blood cell count of 3,000 cells/µL, segmented neutrophils of 24%, and bands of 4%,

\[ \text{ANC} = 3,000 \text{ cells/µL} \times 0.28 = 840 \text{ cells/µL}. \]

Like anemia, neutropenia in children with HIV is caused by various factors. Decreased levels of the factor that stimulates production of white blood cells in the bone marrow (granulocyte colony-stimulating factor [G-CSF]) are present in some patients with HIV infection. A deficiency of G-CSF can lead to chronic neutropenia. As discussed earlier, HIV infection suppresses the bone marrow and affects the granulocyte-macrophage lineage, resulting in leukopenia and neutropenia. Furthermore, HIV infection can directly result in lymphopenia as the infection progresses, leading to a decrease in CD4+ lymphocytes.

A major cause of neutropenia in these patients is myelosuppressive medications. In the past when zidovudine was the only therapy available, a dose of
Hematologic Manifestations of HIV/AIDS

180 mg/m² of body surface area given every 6 h was associated with neutropenia in about half of children, resulting in an ANC count of less than 750 cells/µL. Even a dose of 100 mg/m² given every 6 h orally resulted in clinically significant neutropenia. However, other reverse transcriptase inhibitors do not cause clinically significant neutropenia. Other drugs that are commonly used in children with HIV infection that cause neutropenia include acyclovir, ganciclovir, and trimethoprim-sulfamethoxazole.

HIV infection in children increases circulating immunoglobulins as a result of abnormal stimulation of B lymphocytes. These increased immunoglobulins can be directed toward elements of the person’s body, called autoimmune antibodies. These autoimmune antibodies include antineutrophil antibodies, destroying neutrophils once they have matured in the bone marrow and have been released into the peripheral circulation. However, levels of antineutrophil antibodies are not necessarily associated with the degree of neutropenia, although this remains a potential mechanism of neutropenia in children with HIV infection.

As with other disorders discussed herein, optimizing antiretroviral therapy is always advised and starting therapy for a previously untreated patient is important. Nonetheless, treatment of neutropenia is generally geared toward preventing and treating serious bacterial infections that can result from severe neutropenia. However, one should consider a child with HIV infection and moderate neutropenia (ANC <1000) who is febrile for admission to the hospital. One should always admit a child with severe neutropenia (ANC <500) and fever to the hospital. One should draw blood cultures from all patients with febrile neutropenia blood cultures and should start the child on broad-spectrum IV antibiotics. Monitoring of the white blood cell count and ANC while the child is febrile is advised.

Using growth factors such as G-CSF to stimulate production of neutrophils has been tried, although it is not clear when this therapy should be initiated and what the long-term effects may be in a child with HIV infection. Another growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), has been associated with an increase in HIV replication and probably ought to be avoided. G-CSF, on the other hand, has not been associated with an increase in viral replication because it is more specific for neutrophil precursors. Nonetheless, judicious use of G-CSF (at doses of 5-10 µg/kg/day intravenously or subcutaneously) is advised because the long-term effects on the bone marrow and potential for the induction of malignancy in children with HIV infection are unknown. If G-CSF therapy is used, one must monitor the neutrophil count to assess the child’s response.

Finally, one must consider medication toxicity. In a child being treated with zidovudine, consider changing to another antiretroviral. Other medications that can lead to neutropenia, such as acyclovir or trimethoprim-sulfamethoxazole, must be evaluated for their need and discontinuation must be considered. However, when a child, for example, is being treated for *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole, this drug will probably need to be continued and the
neutropenia managed with meticulous hygiene and coverage with antibiotics.

**Thrombocytopenia**

Thrombocytopenia occurs often in patients with HIV infection and is the second most common hematological abnormality found in children with HIV infection. The cause is not clear, although studies suggest that the primary cause of thrombocytopenia in children with HIV infection is idiopathic thrombocytopenic purpura (ITP). This is an abnormal process in which an autoantibody targets and ultimately removes circulating platelets from the peripheral circulation as they travel through the spleen. These are cross-reacting antibodies that are directed toward HIV proteins, particularly gp120 and p-24. Also, some studies demonstrate a decreased production of platelets from the bone marrow. As discussed earlier, the effect of HIV infection on stromal cells in the marrow plays a role. However, the progenitor cell of platelets, the megakaryocyte, carries the CD4 receptor and thus HIV may directly infect these cells, resulting in their decrease and subsequently a decrease in platelet production. Also, infection can lead to thrombocytopenia, and the opportunistic infections seen in children with HIV infection are no exception.

Thrombocytopenia is associated with rapid progression of disease in patients with HIV infection. There is also an association between thrombocytopenia and mortality; one study showed a mortality rate of nearly 40% in children with HIV infection and thrombocytopenia. Furthermore, thrombocytopenia complicates treatment of HIV infection and associated malignancies because the medications used often affect the platelet level.

No clear guidelines for the treatment of thrombocytopenia in children with HIV infection exist. Indeed, this is a matter of ongoing research and frustration for professionals caring for children with HIV infection. Experts agree that initiation of HAART in children presenting with HIV infection and thrombocytopenia is critical. In these children, antiretroviral therapy often corrects the thrombocytopenia that is secondary to HIV infection alone. However, children with either persistent thrombocytopenia or thrombocytopenia later in the course of their illness do not respond as readily to HIV therapy.

Platelet transfusion is sometimes necessary in life-threatening situations or in children with active bleeding. However, the utility of transfusion therapy is limited in children with HIV infection when one considers the risks of long-term transfusion therapy and the pathogenesis of thrombocytopenia discussed earlier.

Therapies directed toward ITP, including intravenous immunoglobulin (1 g/kg) and corticosteroids (prednisone 2 mg/kg/day), are effective in increasing platelet counts in the short term; however, they often do not result in a sustained rise in platelet level. Another approach, using the anti-D preparation WinRho, effectively increases platelet levels; however, it is associated with a decrease in red cells—a potentially unacceptable and expected side effect of this intervention. Furthermore, there is an association with acute nephritis limiting its use in children with HIV infection. When the thrombocytopenia is felt to be secondary to an ITP process and the child is otherwise clinically well, splenectomy can (according to some data) be as safe in children with HIV infection as those without. However, only half of HIV-infected children so treated experience a long-term elevation, and with the long-term risk of spleen removal, this intervention is less attractive. Therapy using the growth factor thrombopoietin is still under investigation, and future research to identify other interventions will be necessary if we are to surmount this difficult problem.

**References**

**Objectives**

- Provide an overview of human immunodeficiency virus (HIV)–associated nephropathy and other pertinent renal disease in the context of pediatric HIV infection.
- Provide a basic understanding of the cardiac conditions in HIV-infected children.
- Review the causes of chronic lung disease in HIV-infected children, with a focus on lymphocytic interstitial pneumonitis (LIP).

**Key Points**

- Nephropathy in HIV-infected children, though rare, is a dangerous condition and can lead to end-stage renal failure and death.
- Clinicians must monitor children for clinical and laboratory signs of kidney disease and must refer and treat patients as appropriate.
- HIV-associated nephropathy is a World Health Organization Clinical Stage 4 condition, and patients with this disease require highly active antiretroviral therapy and follow-up.
- Left ventricular dysfunction and cardiomyopathy are common in children infected with HIV.
- Pericardial effusions are common and usually resolve spontaneously in HIV-infected children.
- Therapy for symptomatic congestive heart failure may require additional cardiac medications.
- Chronic lung disease, especially LIP, is common in children with HIV.
- Prednisone therapy may be beneficial in patients with severe LIP.

**Renal Disease**

Human immunodeficiency virus (HIV) infection is associated with several different types of renal disease. The most common clinical entity encountered in children and adults is HIV-associated nephropathy (HIVAN), a disease that leads to progressive renal damage, urine protein loss, and sometimes end-stage renal disease. HIVAN is often characterized by collapsing focal segmental glomerulosclerosis on renal biopsy, but children sometimes demonstrate clinical signs of HIVAN without underlying focal segmental glomerulosclerosis. Other less common renal manifestations of HIV infection are HIV-related immune complex glomerulonephritis and membranous nephropathy.

Though present in up to 10% of adults, HIVAN is an unusual feature of childhood HIV infection. The incidence of HIV-associated kidney disease in children is estimated at between 2% and 5% and at up to 15% in populations of African descent. Risk factors for HIVAN include high viral load, low CD4+ T-lymphocyte cell counts, and longstanding HIV disease. Many centers do not routinely perform renal biopsies on patients (adult or child) with HIV and elevated urine protein (proteinuria), and therefore the true prevalence of HIVAN is not known. Though HIVAN is believed to be the most common form of kidney disease in HIV-infected adults of African descent, biopsy data have confirmed HIVAN in only about half of suspected cases. Available data from kidney biopsy series suggest that the most common diagnoses encountered among HIV-infected individuals are the following:

- Focal segmental glomerulosclerosis, thought to be due to the direct pathogenic effect of HIV in the kidney
- Immune complex glomerulonephritis, related to the deposition of antigen–antibody complexes
- Membranous nephropathy, usually related to ongoing hepatitis B or C infection

Other non-HIVAN disorders of the kidney that sometimes occur in HIV-infected patients include

- acute renal failure resulting from hypotension or infection,
- drug-induced kidney disease (e.g., aminoglycosides, amphotericin B, some antiretroviral [ARV] drugs), and
- postinfectious glomerulonephritis due to bacterial infection.
Clinical Presentation and Diagnosis

Classic HIVAN can present at any stage of HIV infection and with various degrees of renal disease. Though many affected patients have urine protein loss with no symptoms, HIVAN can lead to a nephrotic syndrome characterized by high urine protein loss, low serum albumin, and edema. In children, edema is often first noticeable around the eyes (called periorbital edema) (Figure 1). This swelling is often incorrectly identified as an allergy because it decreases throughout the day. However, as the kidney disease progresses, the edema will become generalized and patients can develop ascites, pleural effusions, leg swelling, and/or genital swelling. Complaints of anorexia, irritability, abdominal pain, and diarrhea are common, whereas hypertension is usually not present. The differential diagnosis of edema in children, in addition to kidney disease, includes protein-loss enteropathy, protein–energy malnutrition, hepatic failure, and congestive heart failure. Some helpful clinical criteria for HIVAN include proteinuria, edema, high blood pressure, and black race. However, a laboratory evaluation is needed to distinguish HIVAN from these nonrenal causes of edema. Ray et al. (Table 1) used clinical criteria to help distinguish between HIVAN and other kidney lesions in HIV-infected patients, but only renal biopsy provides a definitive diagnosis.

Common abnormal lab values in patients with HIVAN are those suggestive of nephrotic syndrome: high urine protein (3+ to 4+ or a urine protein/creatinine ratio of >0.2) and low serum albumin (<2.5 g/dL). Serum cholesterol and triglycerides may be elevated, and azotemia (a high level of nitrogen-containing compounds in the blood) may be present. Urine should not have more than a few red or white blood cells; gross blood in the urine is uncommon. Renal ultrasound, if available, will probably demonstrate large kidneys that are echogenic (i.e., appear brighter than usual).

![Figure 1. Above left, a child with generalized edema caused by urine protein loss. Notice the prominent swelling around the eyes (“periorbital edema”) and cheeks, the distended abdomen, and the swollen arms. Periorbital edema is often the first clinical sign of renal disease in less severe cases. Lower extremity edema (as pictured above right) can also be seen in children with kidney disease and other diseases such as kwashiorkor. Photos courtesy of http://phil.cdc.gov.](image)

Clinical Course

In children, renal disease associated with HIV progresses at a slower rate than in adults, with most children developing proteinuria within 2-5 years after HIV infection. After the onset of proteinuria, end-stage renal disease can develop within 3 years. However, the rate of progression depends on the underlying cause of

| Table 1. Clinical evaluation for HIVAN in HIV-infected children |
|-----------------|------------------------|
| **Diagnosis**   | **Clinical Parameters** |
| HIVAN           | Persistent proteinuria*|
|                 | Abnormal microscopic examination of the urinary sediment, which might include microcysts |
|                 | Presence of enlarged echogenic kidneys by renal ultrasound on at least two different studies performed 2 mo apart |
|                 | Black race and clinical history consistent with the diagnosis of HIVAN |
| Non-HIVAN       | Macroscopic hematuria |
|                 | Microscopic hematuria without proteinuria |
|                 | Elevated blood urea nitrogen and serum creatinine levels without significant proteinuria |
|                 | Hematuria and/or proteinuria in white or Hispanic HIV-infected children |

*Urine dipstick for protein above 1+ or a urinary protein creatinine clearance ratio greater than 0.1 for more than 2 months without acute infection.
the disease and the presence of other AIDS-associated illnesses. Some children can have chronic urine protein loss without developing clinically significant edema or end-stage renal disease. Baseline screening urinalyses are helpful to identify those patients with proteinuria, but the value of treating these patients is unclear, and both screening and treatment should be guided by other symptoms.

Although nephropathy is a World Health Organization (WHO) Clinical Stage 4 disease, HIVAN and non-HIVAN are typically late manifestations of HIV/AIDS. HIV-infected children rarely die of end-stage renal disease, and a patient’s prognosis depends heavily on other Stage 3 and 4 diseases (e.g., opportunistic infections and cardiomyopathy) and whether the child is receiving highly active antiretroviral therapy (HAART). Treating HIV should take priority over treating mild or asymptomatic renal disease.

**Treatment**

Patients with HIVAN should be on HAART. HAART reduces the risk of developing HIVAN by more than half and significantly reduces the rate at which HIVAN progresses to renal failure. In the era before HAART, HIV-infected children with HIVAN died on average less than a year after the diagnosis of renal disease. HAART can slow or even stop this progression toward renal failure.

Prednisone is the medication of choice for treating children with nephrotic syndrome. Prior to using prednisone therapy, however, the clinician should have excluded tuberculosis (TB) as a cause of the renal problems or have the patient on appropriate therapy for TB. Prednisone therapy readily reduces the edema, proteinuria, and serum cholesterol level. Patients in the early stages of HIVAN, however, usually have normal or low serum cholesterol levels and no significant edema. The potential beneficial effect of prednisone therapy in HIVAN is limited to improving the proteinuria and reducing the underlying renal inflammation, but there are few conclusive data supporting its use and some centers have found that the response in patients is minimal.

If the use of prednisone is indicated, the recommended dose is the same as that for other types of nephrotic syndrome: 60 mg/m² of body surface area/day divided into two to three daily doses for 4-6 consecutive weeks, with a maximum daily dose of 80 mg. In patients who respond to prednisone therapy, the urine should become negative for protein or remain only trace positive for 3 consecutive days after 2 weeks of therapy. After the initial 4- to 6-week course of prednisone, the dose should be tapered to 40 mg/m²/day given every other day as one dose. This alternate-day dosing can then be slowly tapered and discontinued over the next 2-3 months. Patients who continue to have proteinuria (≥2+) after 4-8 weeks of prednisone therapy should be considered steroid resistant. Such resistance is common in HIVAN and non-HIVAN nephropathy.

Several smaller retrospective studies in adults with HIVAN have demonstrated that another class of drug, angiotensin-converting enzyme inhibitors (ACEIs), can reduce proteinuria and hypertension during late-stage HIVAN. The exact mechanism by which ACEIs help improve renal function is unknown. To date, no prospective, randomized, controlled trials have proven the benefits of HAART, prednisone, or ACEIs in the treatment of renal disease in HIV-infected children. On the basis of available data, however, HAART is the current drug regimen of choice to limit progression of this life-threatening WHO Stage 4 condition. Many experts recommend adding an ACEI and using a trial of prednisone in these patients. There are differences between ACEIs and their interactions with ARVs. For instance, lopinavir–ritonavir is a strong inducer of CYP2D6, affecting levels of captopril (but not enalapril), whereas efavirenz induces CYP3A4, affecting levels of enalapril (but not captopril). If available, hemodialysis and renal transplantation are therapeutic options for those patients who progress to end-stage renal disease.

**ARV Drugs and Nephrotoxicity**

ARV drugs are a rare cause of significant nephrotoxicity, but renal side effects can occur. Ritonavir has been associated with acute renal failure and indinavir has caused some adverse renal and urological effects, including stone formation. Also, tenofovir has caused tubular dysfunction leading to renal toxicity. All these complications of ARVs are uncommon.

**Cardiac Disease**

Children infected with HIV might develop a wide range of cardiovascular problems from the subclinical (e.g., electrocardiographic changes) to the life threatening (e.g., cardiomyopathy). The exact causes of many of
these cardiac abnormalities are unknown and probably multifactorial. In the era of HAART and increased life expectancy, cardiac complications are increasingly recognized as important health problems in children. In HIV-infected children, death from cardiac disease becomes more common with increasing age. It is uncommon in infants and younger children but is responsible for up to 25% of deaths in children older than 10 years who die of an HIV-related illness. Half these children suffer from chronic cardiac disease prior to death. Risk factors for cardiac complications in children with HIV infection include rapid progression of HIV infection, wasting, low CD4 count, previous serious cardiac event, and advanced neurologic disease (e.g., encephalopathy). Therefore, routine cardiac evaluation is recommended, which should include a complete physical examination, electrocardiograph (ECG), and ideally echocardiography. Aggressive treatment of cardiac complications is also essential.

Left Ventricular Dysfunction and Cardiomyopathy
Cardiomyopathy is common in HIV-infected children and initially manifests itself as left ventricular (LV) dysfunction. A recent study demonstrated that as many as 28% of children developed a decrease in cardiac function over 5 years, whereas as many as 39% developed cardiomegaly. LV dysfunction is characterized by a decrease in the shortening fraction (SF) and the ejection fraction (EF) of the LV. The SF measures the change in the diameter of the LV between the contracted and relaxed states. Unlike the SF, the EF measures the amount of blood pumped out of the LV with each heartbeat. Healthy individuals have an SF between 28% and 40% and EFs greater than 55%. Many children develop LV hypertrophy and/or LV dilation in the context of LV dysfunction, both of which increase LV mass. LV dysfunction is commonly asymptomatic early in the course but may result in heart failure with progression. Children with depressed LV SF and contractility, increased LV dimensions, and increased LV mass at baseline have a higher mortality, particularly in children with rapid progression of HIV infection. The etiology of HIV cardiomyopathy remains unknown. It is probably a result of a combination of several mechanisms such as a complication of secondary viral or bacterial infections, certain ARV medications (e.g., zidovudine), chemotherapeutic agents that HIV-infected patients may have received (e.g., doxorubicin), nutritional deficiencies that are common in HIV-infected children from resource-limited areas (e.g., beriberi disease, wasting syndrome), anemia, or a combination of these factors. Although there has been significant correlation between the SF and CD4+ cell counts at baseline, the rates of CD4+ cell decline do not appear to be as useful as the viral load as a potential marker for cardiac deterioration.

Myocarditis
A common cause of LV dysfunction, myocarditis is signified by inflammation of the cardiac muscle. This inflammation can be the result of infection of the myocardium with certain viruses. Several studies have identified HIV particles in myocardial muscle cells, but the level of infection is commonly low, suggesting that HIV infection plays only an indirect role. Other viruses commonly encountered in HIV-infected individuals, such as parvovirus, cytomegalovirus, enterovirus, and adenovirus, have been implicated. Most recently however, certain alterations of the immune system are recognized to be associated with cardiomyopathy. Certain cytokines are part of an inflammatory response of the body and have been associated with cardiomyopathy and heart failure. In HIV-infected individuals, these cytokine pathways are more active than those in uninfected individuals, suggesting a direct role in the development of cardiomyopathy.

Pulmonary Arterial Hypertension
The incidence of pulmonary arterial hypertension (PAH) in adults with HIV infection is 0.5%, which is higher than that in the general population, whereas the incidence in HIV-infected children has not been established. As in myocarditis, the etiology of HIV PAH has not been well established but is probably related to an immunological process related to HIV infection, leading to chronic changes in pulmonary vasculature with resultant increase in pulmonary vascular resistance. However, other factors such as repeated pulmonary infections, severe lymphocytic interstitial pneumonitis (LIP), and LV failure may play a role. Longstanding PAH can lead to right ventricular failure and cor pulmonale.

Pericardial Effusions
Pericardial effusions can be found on echocardiography in approximately 10%-20% of HIV-infected patients. Pericardial effusions in HIV-infected patients might be related to opportunistic infections, malignancies (e.g., Kaposi sarcoma, non-Hodgkin’s lymphoma), or HIV itself, or it might be idiopathic. Pericardial effusions might present with a pericardial friction rub (if the effusion is small) and distant heart sounds on cardiac
auscultation or signs of hemodynamic compromise with impending cardiac tamponade. Most patients with pericardial effusions are asymptomatic because of the slow accumulation of fluid, and the fluid collection will usually resolve spontaneously. Evaluation of pericardial effusions by pericardiocentesis should be considered in certain situations, including the following:

- Systemic symptoms due to the pericardial effusion
- Large effusions
- Concern for purulent pericarditis
- Diagnostic evaluation of systemic illness
- Cardiac tamponade (hemodynamic compromise)

Appropriate therapy should be promptly initiated if an infectious cause for pericardial effusion is identified. Mortality rates for HIV-infected patients with pericardial effusions are higher even when the effusion resolves spontaneously. The effects of HAART on pericardial effusions are unknown.

**Other Cardiac Abnormalities**

Congenital heart disease occurs in from 2% to 5% of HIV-infected children, which is greater than that of the general population (0.8%). The most common lesions described to date have been ventricular and atrial septal defects. Congenital heart disease may be slightly more prevalent in HIV-infected children, although this may not be a result of HIV infection itself but rather of maternal risk factors such as smoking, drug abuse, and coinfection with other viruses. Sinus tachycardia also occurs more commonly in HIV-infected children than in uninfected children. The mechanism is unknown. No dysrhythmias have been noted to occur more commonly in HIV-infected children. Coronary artery disease and abnormalities of the great vessels also occur in children and adults living with HIV/AIDS. A recent pathologic study revealed coronary arteriopathy in half of children who died from HIV infection. Sixty-four percent of this cohort showed arteriopathy of the aorta and pulmonary arteries. Aortic root dilation can occur in children with HIV infection. The clinical relevance of these findings in children is unclear, but as life expectancy increases this may become relevant.

**Abnormalities Associated with ARV Therapy**

Certain ARV agents (e.g., zidovudine [AZT]) have been implicated to cause skeletal muscle myopathies as well as cardiomyopathy; however, a recent study failed to confirm this finding in children. Furthermore, the suspected adverse effects of fetal exposure to zidovudine could not be corroborated. In adults, metabolic derangements caused by protease inhibitors have been associated with an increase in coronary artery disease, in particular hypercholesterolemia, hypertriglyceridemia, insulin resistance, and impaired glucose tolerance. However, this complication is generally treated with dietary and lifestyle adjustments.

**Evaluation and Investigation**

The evaluation of HIV-infected children with suspected cardiac disease does not differ from that for the uninfected child. A thorough history and physical examination should be performed prior to other evaluations. In particular, patients should be evaluated for signs and symptoms of congestive heart failure, which include the following:

- Abdominal pain
- Bibasilar rales
- Chronic cough not associated with an infection
- Dyspnea on exertion
- Difficulty breathing
- Easy fatigability
- Gallop rhythm
- Generalized edema
- Hepatomegaly
- Holosystolic murmur
- Jugular venous distention
- Orthopnea
- Tachycardia
- Tachypnea
- Weight gain (poor weight gain more common in infants)

Patients who require further evaluation should have a chest radiograph and an ECG if available. The chest radiograph (Figure 2) will provide information on the heart size and shape, pulmonary blood flow, pulmonary edema, and other potential congenital abnormalities (e.g., abnormal...
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Vertebral. The ECG demonstrates anatomic and hemodynamic features by changes in the QRS and T-wave morphologies. A 13-lead ECG is recommended for use in children, including either lead V3R or V4R. The ECG is of only limited use in children for evaluating LV hypertrophy and is not a sensitive indicator of LV dysfunction; however, lead V1 and V3R may be useful for evaluating for right ventricular hypertrophy. Furthermore, the ECG allows evaluating the heart rhythm and may indicate abnormalities such as myocarditis (low QRS voltage and ST segment and T-wave abnormalities, as well as sinus tachycardia) and pericarditis (e.g., low QRS voltage from the effect of pericardial fluid in pericardial effusions).

For children with suspected LV dysfunction or any other child with significant cardiac disease, an echocardiogram is indicated. Echocardiography allows evaluating the cardiac structure, and it can noninvasively estimate intracardiac and pulmonary pressures, quantitate cardiac contractile function (e.g., SFs, EFs), and detect cardiac vegetations and pericardial effusions. Echocardiography, where available, should be performed at baseline and at reasonable intervals (in particular in patients with advanced disease or rapid progression) to evaluate cardiac function and structure, as well as for pericardial effusion.

**Therapy**

Patients with symptoms of congestive heart failure may require treatment with cardiac medications. Diuretics initially are the mainstay of therapy and are usually introduced first. The goal is relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema, by increasing the excretion of excess fluid via the urine. Diuretics may also be given in combination with other cardiac and ARV medications. The most widely available diuretic is furosemide and can be used both intravenously and orally. For acute treatment, a dose of 1-2 mg/kg intravenously usually results in rapid diuresis and prompt improvement of the patient’s clinical status. This treatment may be performed as often as four times daily. Chronic furosemide dosing is 1-2 mg/kg/dose given between one and four times a day orally (maximum dose, 6 mg/kg/day). One must monitor serum electrolytes, however, because furosemide might cause significant loss of serum potassium into the urine. Most patients on daily furosemide therapy will also require potassium supplementation or addition of spironolactone, a potassium-sparing diuretic. Care should be taken in patients who are also receiving digoxin because hypokalemia can potentiate digoxin toxicity.

In developed countries, most clinicians will use an ACEI (e.g., enalapril, captopril) during or after the optimization of diuretic therapy. In children, therapy should be started with low doses to reduce the likelihood of hypotension and azotemia. Blood should be obtained in all patients 1-2 weeks after starting or changing a dose and periodically thereafter to assess the plasma potassium concentration and renal function. The dosage for both enalapril and captopril needs to be reduced for patients with decreased renal function. There are differences between ACEIs and their interactions with ARVs. For instance, lopinavir–ritonavir is a strong inducer of CYP2D6, affecting levels of captopril (but not enalapril), whereas efavirenz induces CYP3A4, affecting levels of enalapril (but not captopril). For older adolescent and adult patients who cannot tolerate an ACEI, an angiotensin II receptor blocker can be used (e.g., candesartan, losartan). Many clinical trials in adults have shown that β blockade can be beneficial in the treatment of congestive heart failure. Studies have shown an increase in EF and a decrease in hospitalization in patients using β blockers. Studies in children have shown similar findings. The angiotensin II receptor blocker losartan can be affected by the use of the CYP3A4 inducers nevirapine and efavirenz, whereas candesartan does not appear to be affected by these medications. Providers can also start patients on β blockers such as carvedilol after the patients are stable on ACEIs, again beginning at low doses with titration to higher doses as tolerated. Protease inhibitors that induce CYP2D6 (e.g., lopinavir–ritonavir) can affect the levels of β blockers and may not be appropriate to use.

Digoxin (Table 2) has been the mainstay of medical therapy for children with heart failure for decades but is now added only when patients

**Table 2. Oral digoxin dosing**

<table>
<thead>
<tr>
<th>Age</th>
<th>Loading*</th>
<th>Maintenance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full term</td>
<td>30</td>
<td>8-10</td>
</tr>
<tr>
<td>&lt;2 yrs</td>
<td>40-50</td>
<td>10-12</td>
</tr>
<tr>
<td>2-10 yrs</td>
<td>30-40</td>
<td>8-10</td>
</tr>
<tr>
<td>&gt;10 yrs (and &lt;100 kg)</td>
<td>10-15</td>
<td>2.5-5</td>
</tr>
</tbody>
</table>

*Give half the total digitalizing dose (TDD) and then 1/4 of the TDD every 8-18 h for two doses; obtain ECG 6 h after each dose to assess for toxicity.

†Maintenance dose is started approximately 12 h after TDD is completed (for patients <10 years, divide into two daily doses). Slow initiation of digoxin can be achieved without the loading dose by initiating the maintenance dose but requires 7-10 days to reach maximum efficacy.
Renal, Cardiac, and Pulmonary Manifestations of HIV/AIDS

are failing the preceding regimen. In resource-limited areas, however, digoxin may be the only medication that is available to be used in addition to a diuretic. The kidneys eliminate digoxin, so dosing should be adjusted according to renal function. Baseline serum electrolytes should be measured before and after digitalization because hypokalemia, hyponatremia, hypomagnesemia, and hypercalcemia can exacerbate digoxin toxicity. Measurement of serum digoxin levels is recommended for chronic use in children. Therapeutic levels are 2–4 ng/mL in infants and 1-2 ng/mL in older children. Cardiac toxicity in children generally manifests as atrioventricular block, but any cardiac arrhythmia can be caused by digoxin toxicity (e.g., ST segment changes). Systemic symptoms include central nervous system disturbances, visual disturbances, anorexia, and vomiting. If toxicity is suspected, digoxin should be stopped immediately. Many medications interact with digoxin; some raise digoxin levels (e.g., tetracyclines), some lower digoxin levels (e.g., rifampicin), and some potentiate toxicity by causing electrolyte disturbances, especially hypokalemia (e.g., furosemide). The nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors do not appear to have significant interactions with digoxin, whereas one must take care with the use of protease inhibitors because these may increase digoxin levels. Because of all these potential complications, one should carefully consider the use of digoxin in a resource-limited setting.

Morbidity and mortality in heart failure is also influenced by commonly associated conditions, including arrhythmias, thromboembolism, and anemia. Therefore, management should also be directed at identifying and correcting these factors where possible.

Pulmonary Disease

Chronic lung disease is common in children with HIV and AIDS. Recurrent or chronic pulmonary infections can be caused by bacteria (e.g., Streptococcus pneumoniae), fungi (e.g., candidiasis, histoplasmosis, Pneumocystis jirovecii), viruses (e.g., cytomegalovirus and adenovirus), and mycobacteria (e.g., Mycobacterium tuberculosis and M. avium complex). Such infections can lead to chronic structural abnormalities, including bronchiectasis—the permanent dilation and scarring of the lungs’ bronchi (large airways) and bronchioles (small airways). In addition to infectious causes, malignancies (e.g., non-Hodgkin’s lymphoma, Kaposi sarcoma), immune reconstitution inflammatory syndrome and nonspecific interstitial lung disease may also contribute to the development of chronic lung disease. Of this long list of pulmonary manifestations of HIV, the most common chronic lower respiratory tract abnormality is LIP. Because the other pulmonary diseases listed are discussed in some detail elsewhere in this volume, the rest of this section will focus on this common and potentially fatal condition.

Epidemiology

LIP, a form of pulmonary lymphoproliferative disease, occurs in approximately 25%-40% of vertically infected children and usually presents in the second or third year of life. Adults with HIV are also affected, but adult LIP is less common and better tolerated. The etiology of this disorder is unknown, although serologic data suggest that an HIV–Epstein-Barr virus coinfection may be responsible. Other possibilities include an exaggerated immune response to inhaled or circulating antigens, the direct effect by HIV itself, immune dysregulation, or a combination of these factors. LIP occasionally occurs in children and adults without HIV, particularly those with autoimmune disorders.

Clinical Presentation

LIP is the result of a chronic process called pulmonary lymphoid hyperplasia (PLH) within the lining of the bronchi and bronchioles. Because lymphoid hyperplasia is a spectrum that results in LIP, many texts use the two terms together—LIP/PLH—when discussing patients with clinical features of a chronic lymphoproliferative pulmonary disease. When LIP/PLH occurs, the airway epithelium becomes congested with lymphoid cells, often leading to progressive blocking of the nearby capillaries. As the disease worsens and lung tissue is progressively damaged, many affected patients develop a chronic cough, rapid respirations, and low blood oxygen levels. On pulmonary examination, they may have few or no abnormal findings, though sometimes rales, or crackles, can be heard. Clubbing of the fingers and toes will be present in more advanced disease, probably representing low blood oxygenation (Figure 1). The proliferation of the lymphoid cells responsible for LIP may also affect other organs and cause findings such as generalized adenopathy, bilateral nontender parotid enlargement, and an enlarged liver and spleen (hepatosplenomegaly). The changes that accompany LIP occur slowly. Although most children present at approximately 18-24 months of age, a wide age range has been described (5-60 months).
Even though the onset is relatively late, LIP may be the first manifestation of advanced pediatric HIV disease that a clinician recognizes.

**Diagnosis**
The complete workup of pulmonary illness in the context of HIV requires a careful history and physical exam and, where available, laboratory studies and radiologic imaging. If feasible, pulmonary function tests and tissue biopsy are also sometimes indicated and diagnostically helpful. Differentiating LIP from other pulmonary illnesses can be difficult. Patients with acute bacterial lower respiratory tract infections typically have a rapid onset of illness with fever. Pneumocystis pneumonia usually has a rapid onset but typically does not cause fever and brings with it an acute and severe oxygen requirement. In comparison, LIP has a gradual onset. TB also has a gradual onset and is easily confused with LIP. However, on physical exam, patients with both Pneumocystis jirovecii pneumonia (formerly called Pneumocystis carinii pneumonia [PCP]) and TB are less likely to have digital clubbing and parotid swelling than are patients with LIP. LIP has x-ray findings that are often difficult to differentiate from common bacterial pneumonia, PCP, and miliary TB. On chest x-ray, common bacterial pneumonia often appears as a focal abnormality, but LIP, PCP, and miliary TB can all appear as bilateral, diffuse interstitial opacities (Figure 3).

Though x-rays of LIP are less likely than TB to have hilar adenopathy, distinguishing these pulmonary conditions is not possible on x-ray alone. Where available, high-resolution computed tomography of the chest may be helpful if the diagnosis of LIP is in question. Computed tomography will typically reveal micronodules (1-3 mm in diameter) with a perilymphatic distribution as well as subpleural nodules. In LIP, radiographic findings may improve even as the patient’s immune status worsens. If a lung biopsy is performed, microscopic inspection of the lung tissue will demonstrate abnormal collections of lymphocytes surrounding the airways. Pulmonary function testing in LIP patients typically demonstrates a pattern of restrictive disease, with reduced forced vital capacity (FVC), reduced FVC in 1 s (FEV1), and a normal FEV1/FVC ratio.

**Clinical Course and Treatment**
The clinical course of LIP varies and spontaneous remission occurs occasionally. Intercurrent respiratory illnesses can exacerbate existing disease, and when severe, LIP can cause progressive hypoxia and respiratory failure. Measuring oxygen saturation with pulse oximetry helps determine the severity of illness and the need for oxygen therapy. Some affected patients require continuous oxygen. Antibiotics may be required for acute pulmonary infections, and inhaled bronchodilators (e.g., albuterol or salbutamol) may provide some relief when LIP symptoms worsen. Although there are few data for its use, most patients respond to oral corticosteroid therapy and it is recommended for those with LIP and a chronic oxygen requirement. In affected children, prednisone (2 mg/kg/day) can be prescribed for 2-4 weeks or until the oxygen requirement improves, at which time the prednisone should be decreased to a dose of 0.5-0.75 mg/kg every other day. In severe disease, tapering is sometimes not possible and corticosteroid therapy may be required indefinitely. The most effective dose and treatment duration of corticosteroid therapy remains uncertain, and more studies are needed. Hydroxychloroquine is an alternative to oral corticosteroid therapy and is effective in some cases. The recommended hydroxychloroquine dose in children is 10 mg/kg per day. In addition to symptomatic therapy, HAART may also provide some improvement. Although LIP is a Stage 3 WHO disease, it is one of the four Stage 3 diseases (LIP, thrombocytopenia, pulmonary TB, and oral hairy leukoplakia) that do not require immediate initiation of ARV therapy, provided that the CD4+ cell count is adequate. Secondary infections (due to HIV-mediated or drug-mediated immunosuppression) are common in patients with LIP; without monitoring, diagnosis, and treatment, they can be life threatening.
REFERENCES

Renal Disease

Cardiac Disease

Pulmonary Disease
Objectives

1. Discuss the assessment of a child with human immunodeficiency virus (HIV) who presents with fever.
2. Discuss the differential diagnosis of serious causes of fever, which includes sepsis, pneumonia, meningitis, and urinary tract infections.
3. Describe common signs and symptoms associated with the serious causes of fever.
4. Discuss the appropriate management of fever on the basis of the child’s age.
5. Discuss the management of fever in children living in regions at high risk for malaria.

Key Points

1. Infection is the most common cause of fever in children with HIV. Other causes of fever rarely include HIV infection itself or medications used to treat HIV.
2. Serious causes of fever include sepsis, pneumonia, meningitis, and urinary tract infections. These infections may be more severe or more rapidly progressive in children with HIV.
3. Respiratory infection is the most common complaint in HIV-infected children and may be manifested by one or more of the following signs and symptoms: fever, cough, difficulty breathing, sore throat, runny nose/nasal congestion, and ear pain or ear drainage.
4. Treatment of febrile illnesses in children depends on the age of the child.
5. Measles remains a cause of fever for children in most developing countries.
6. Malaria should be considered for any child with fever who lives in areas at high risk for malaria transmission.
7. All children younger than 2 months with fever and/or pneumonia and older children with severe disease should be assessed, stabilized, and referred to a hospital as quickly as possible.

Overview

Regardless of human immunodeficiency virus (HIV) status, any sick child who is brought to a clinic or hospital requires a complete and thorough assessment. If the child is assessed only for the major complaint or symptom, other important signs of diseases such as pneumonia, tuberculosis, diarrhea, malaria, measles, or malnutrition may be overlooked. If left untreated, these diseases can be serious or even fatal in young children.

This module reviews the assessment and treatment of a child who presents with fever and/or respiratory symptoms in areas at both high and low risk of malaria transmission. This module first discusses common infections in children aged 2 months to 5 years such as meningitis, sepsis, malaria, measles, urinary tract infection, and respiratory infections including pneumonia, otitis media, mastoiditis and sore throat. Fever in infants aged 1 week to 2 months is discussed later. Fever in newborns (aged <7 days) is beyond the scope of this discussion. Other diseases, including diarrhea, pneumocystis jirovecii (previously pneumocystis carinii) pneumonia, tuberculosis, and neurological manifestations of HIV/AIDS, are reviewed in other modules.

Fever in Children Aged 2 Months to 5 Years

Fever is one of the most common parental concerns for a child with HIV. Caregivers often view fever as an illness rather than a sign or symptom. Fever is defined by the World Health Organization (WHO) as a temperature greater than 37.5°C (measured under the arm) continuously for more than 24 h or intermittently for more than 24 h in a 72-h period.

Assessment

The first step in assessing a sick child is to ask the mother or caregiver to describe the problem(s) that the child is having and to check for general danger signs.
Subjective data include the following:
1. What is the child’s temperature? What is the highest that it has been?
2. How long has the child had fever?
3. Has the child been alert and playful or lethargic and quiet?
4. How has the child’s appetite been? Has the child been able to drink liquids?
5. Is the child experiencing any other signs/symptoms, such as ear pain, runny nose, cough, sore throat, abdominal pain, vomiting, or diarrhea?
6. Has the child been in contact with anyone who is ill?
7. Which treatments or medications have been given?

Assessment for general danger signs should include asking the child’s caregiver the following:
1. Is the child unable to drink or breast-feed?
2. Does the child vomit every meal?
3. Has the child had convulsions?
4. Is the child unusually irritable or restless?
5. Has the child been less playful or sleeping more than usual?
6. Has the child been less interactive with the caregiver?
7. Has the child’s urine output decreased?
8. Has the child lost weight?
9. Is the child having difficulty in breathing?

### Differential Diagnosis of Fever in Children Aged 2 Months to 5 Years

Fever may be caused by infection (bacterial, viral, fungal, or protozoal) or malignancy but is rarely caused by HIV infection itself or by medications used to treat HIV infection. In children in the early stages of HIV infection, before substantial immune suppression develops, a child with fever should be evaluated as an immunocompetent host. It is not until the child develops severe immunosuppression (CD4+ count of <15%) that he or she becomes more susceptible to opportunistic infections. When severely immunocompromised children present with fever, the assessment and initial treatment, such as administering a dose of the appropriate antibiotic, should be completed as quickly as possible, and a referral should be made for further treatment at a hospital.

### Danger Signs
- Lethargy
- Poor oral intake
- Fever (>37.5°C) or hypothermia (<35°C)
- Tachypnea
- Wheezing
- Retractions
- Nasal flaring
- Cyanosis
- Stridor when calm
- Altered mental status
- Severe malnutrition

In children aged 2 months to 5 years, the differential diagnosis for fever may include the following:
- Severe bacterial infections
  - Meningitis
  - Severe pneumonia
  - Septicemia (overwhelming sepsis)
  - Severe malaria (in malaria-endemic areas)
This module will focus mainly on the prehospital care of the most common conditions; detailed inpatient management is beyond the scope of this module.

**Bacterial Meningitis**

Acute bacterial meningitis is a bacterial infection of the meninges and cerebrospinal fluid (CSF) resulting in meningeal inflammation, obstruction of the circulation of the CSF caused by purulent exudate, cerebral edema, and local necrosis of nerve fibers and cerebral vessels. Bacterial meningitis has high mortality and morbidity rates, especially if not treated early; therefore, early diagnosis and prompt effective treatment are essential. Diagnosis of bacterial meningitis includes the following:

- History
  - Vomiting
  - Inability to drink or breast-feed
  - Irritability

- Convulsions
- Lethargy
- Headache or pain in the back of the neck

Examination for bacterial meningitis includes the following:

- Neck stiffness (Figure 1)
- Repeated convulsions
- Petechial rash or purpura
- Lethargy
- Irritability
- Bulging fontanel
- Evidence of head trauma suggesting possibility of recent skull fracture
- Signs of raised intracranial pressure (Figure 2)
  - Unequal pupils
  - Opisthotonus or rigid posture
  - Irregular respirations
  - Focal paralysis in any of the limbs or trunk

Nuchal rigidity, or neck stiffness, is reflected in the inability of a patient to place the chin on the chest, limitation of passive neck flexion, and Kernig and Brudzinski signs. Kernig sign is present if the patient, in the supine position with the hip and knee flexed at 90°, cannot extend the knee more than 135° and/or there is flexion of the opposite knee.
The Brudzinski sign is present if the patient, while in the supine position, flexes the lower extremities during attempted passive flexion of the neck.

Any child showing any of the preceding symptoms and signs should be quickly assessed for clinical stability, treated empirically with intravenous (IV) or intramuscular (IM) antibiotics, and transferred urgently to a hospital for further assessment and inpatient management. In children known or suspected to have HIV/AIDS, the differential diagnosis includes bacterial, tuberculous, viral and fungal (particularly cryptococcal) meningitis.

**Laboratory investigations.** Whenever possible, the diagnosis of meningitis should be confirmed with a lumbar puncture and CSF collection prior to the administration of antibiotics. CSF should be examined for full blood count, gram stain, culture, glucose, and protein. A lumbar puncture should not be carried out if there are signs of raised intracranial pressure (as outlined earlier) or there is local infection at the lumbar puncture site. Also, because of the invasive nature of the lumbar puncture, lumbar puncture is not recommended in settings in which reliable examination and culture of the CSF obtained is not possible.

**Management.** In the prehospital setting, if there is high suspicion of meningitis, and a lumbar puncture is not possible, then antibiotic therapy should be commenced promptly before the child is transferred to the hospital. Choose one of the following regimens:

- Chloramphenicol, 25 mg/kg of body weight IV (or IM) every 6 h plus ampicillin, 50 mg/kg IV (or IM) every 6 h
- Chloramphenicol, 25 mg/kg IV (or IM) every 6 h plus benzylpenicillin, 60 mg/kg (100,000 U/kg) every 6 h IV (or IM)

Where there is known significant drug resistance of common organisms (*e.g.*, *Haemophilus influenzae* or *Streptococcus pneumoniae*) to the preceding antibiotics, national guidelines (based on susceptibility tests) should be followed. Often the most appropriate antibiotic will be a third-generation cephalosporin such as the following:

- Cefotaxime, 50 mg/kg IV (or IM) every 6 h
- Ceftriaxone, 50 mg/kg IV (or IM) over 30-60 min every 12 h

**Measles**

Measles is a highly contagious viral disease with serious complications (such as blindness in children with preexisting vitamin A deficiency) and a high mortality rate. It is rare in infants younger than 3 months. After a 1- to 2-week incubation period, the infection presents with a prodrome of high fever followed by cough, coryza (runny nose), conjunctivitis, and a fine maculopapular rash behind the ears and along the hairline, spreading to become generalized and blotchy and lasting for about 4 days. The rash may lead to skin desquamation. Sometimes pathognomonic small gray-white lesions (Koplik spots) appear on the posterior buccal mucosa.

**Diagnosis.** Measles often occurs in epidemics; therefore, recent episodes in the area should raise the suspicion of measles. A diagnosis of measles should be readily made if the mother clearly reports that the child has had a typical measles rash or if the child has the following symptoms:

- fever;
- generalized rash; and
- one of
  - cough,
  - runny nose, or
  - red eyes.

In children with HIV these symptoms and signs may not be present, and the diagnosis of measles may be difficult.

**Severe complicated measles.** A child with measles who presents with the following symptoms should be diagnosed as having severe measles:

- Inability to drink or breast-feed
- Vomiting all foods and liquids
- Convulsions

On examination, signs of late complications after the rash has disappeared should be looked for, including the following:

- Lethargy or unconsciousness
- Corneal clouding
- Deep or extensive mouth ulcers
- Pneumonia
- Dehydration from diarrhea or inability to drink
- Stridor caused by measles croup
- Severe malnutrition
Treatment. All children with severe or complicated measles require admission and management in a hospital. Vitamin A therapy should be given to all children with measles unless the child has had adequate vitamin A treatment for this illness as an outpatient or had received a preventive vitamin A supplement within 1 month. Two doses should be given: the first dose immediately upon diagnosis; the second dose, the next day. The dose varies according to the age of the child (Table 1).

**Table 1. Dose of vitamin A**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>50,000</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>100,000</td>
</tr>
<tr>
<td>12 mo-5 yrs</td>
<td>200,000</td>
</tr>
</tbody>
</table>

Those children who show eye signs compatible with vitamin A deficiency (xerophthalmia with corneal scarring) or are severely malnourished should receive a third dose of vitamin A 2-4 weeks after the second dose when the child comes for follow-up.

Supportive care for fever. If the temperature is ≥39°C or ≥102.2°F, the child should be given paracetamol at a dose of 15 mg/kg up to four to six times a day to relieve the fever. If the fever persists for more than 3-4 days, a secondary infection should be considered. Antimalarial medications should be given in areas of high malaria endemicity if the malaria smear is positive or if there is high clinical suspicion of malaria.

Nutritional support. Nutritional status should be determined by weighing the child and plotting on a growth chart (rehydrate before weighing). The mother should be encouraged to breast-feed and to give the child frequent, small meals. The mouth should be examined for ulcers that might discourage the child from eating or drinking. National Guidelines on nutritional management should be followed depending on the degree of malnutrition.

Complications. Eye problems such as conjunctivitis and corneal damage may occur because of infection, vitamin A deficiency, or harmful local remedies. In addition to vitamin A, any infection should be treated with an appropriate antibiotic such as tetracycline or gentamicin eye ointment three times a day. If there is no improvement after 7 days of treatment, the child should be referred to an ophthalmologist. A steroid eye ointment should never be used.

Neurologic complications. Convulsions, excessive sleepiness, drowsiness, or coma may be a symptom of encephalitis or severe dehydration. The child should be assessed for dehydration and treated accordingly (see the diarrhea chapter). The chapter on neurologic complications of HIV discusses management of convulsions. Other sections in this publication describe the management of other complications such as pneumonia, otitis media, and diarrhea.

Monitoring. The child’s temperature should be checked twice a day and there should be daily assessment for the preceding complications. In uncomplicated measles the temperature usually returns to normal within about 4 days after the appearance of the rash. The child should be weighed daily to monitor hydration and nutritional status.

Follow-up. Recovery after acute measles is often delayed for many weeks or even months, especially in malnourished children. Recovery may be complicated by failure to thrive, recurrent infections, and persistent pneumonia and diarrhea. The death rate during this phase is high. Upon discharge mothers should be advised of potential problems and asked to return if they arise. A third dose of vitamin A should be arranged before discharge.

Public health measures. Measles is preventable with use of measles vaccine. Measles vaccine should be encouraged to all children according to the national vaccine schedule. Whenever possible, a child with measles should be isolated for at least 4 days after the onset of the rash. In malnourished and immunocompromised children, the isolation should be continued throughout the duration of the illness. When there are children with measles in the hospital, immunize all other children older than 6 months. If children receive their measles vaccination at 6-9 months, ensure that they receive a second dose as soon as possible after 9 months. Check the immunization status of the staff and vaccinate accordingly.
Common Illnesses in Children with HIV/AIDS

Measles (nonsevere)—diagnosis. Nonsevere measles should be diagnosed in children whose mothers clearly report measles rash or if the child has
- fever;
- a generalized rash; and
- one of
  - cough,
  - runny nose, or
  - red eyes, but
- none of the features of severe or complicated measles.

Measles (nonsevere)—treatment. Nonsevere measles should be treated on an outpatient basis. The treatment is largely supportive and symptomatic. The supportive treatment is outlined in the management of severe measles. Vitamin A therapy should also be given as described earlier.

Malaria
In malaria-endemic regions, the diagnosis of malaria should be considered in any patient presenting with fever, particularly if no other source for the fever can be identified. Malaria is responsible for an estimated 300 million-500 million infections and 1 million-3 million deaths per year. In areas of high malaria transmission, children younger than 5 years are most at risk of severe malaria and death. Children with HIV/AIDS are more likely to be infected with malaria, and the infection is more likely to be symptomatic, more severe, and less responsive to treatment. HIV infection is associated with increased susceptibility, higher parasitemia, and an increased risk for recurrent malaria infections, especially in patients with CD4 counts less than 200 cells/µL.

Malaria is caused by infection of red blood cells (RBCs) with protozoan parasites of the genus *Plasmodium*. Human malaria is caused primarily by four species of plasmodia: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. A fifth species, *P. knowlesi*, was previously confined to infections in nonhuman primates but has also been implicated in human disease.

In humans, malaria parasites grow and multiply first in the liver cells and then in RBCs. Successive broods of parasites grow inside the RBCs and destroy them, releasing daughter parasites that continue the cycle by invading other RBCs. When certain forms of blood stage parasites are picked up by a female *Anopheles* mosquito during a blood meal, they start another, different cycle of growth and multiplication in the mosquito. The parasite eventually ends up in the mosquito’s salivary glands, ready to be injected into another human host.

Diagnosis. In stable high-transmission settings, malaria is usually the most common cause of fever in children younger than 5 years. For severe malaria, accurate prerereferral diagnosis and treatment are imperative to prevent illness and death associated with delays in the initiation of effective therapy. As immunity is acquired, however, malaria becomes less likely as a cause of fever. Thus, in children older than 5 years and in adults, the diagnosis of malaria should be based on parasitological confirmation.

The typical presentation of malarial infection may be nonspecific and be similar to that of a minor systemic viral illness. The prodrome often includes headache, coughing, malaise, fatigue, abdominal discomfort, and muscle and joint pain. These symptoms are followed by paroxysms of fever, shaking chills, and perspiration. Nausea, vomiting, diarrhea, abdominal pain and worsening malaise may accompany the fever. Physical examination may reveal splenomegaly and mild jaundice, but there is usually no lymphadenopathy.

Severe malaria is a medical emergency. Severe disease is life threatening and is manifested by the presence of one or more of the following conditions:
- Coma
- Metabolic acidosis
- Severe anemia
- Hypoglycemia
- Acute renal failure
- Acute pulmonary edema

In older children and adults, malaria diagnosis should be based on parasitological confirmation. Parasitological diagnostic techniques are important in confirming the diagnosis of malaria, quantifying the degree of parasitemia, and identifying the species of the parasite and confirming treatment failures. If the diagnosis of malaria is excluded by careful parasitologic diagnostics, then unnecessary exposure to antimalarial medications can be prevented, thereby reducing side effects, drug interactions, and selection pressure. Parasitological diagnosis should also be promoted in pregnant women to improve the differential diagnosis of fever and to
reduce the unnecessary use of antimalarial medications in pregnancy. Parasitological diagnosis is also important in settings with a high prevalence of HIV/AIDS because of the high incidence of febrile disease that is not malaria.

Light microscopy of Giemsa-stained thick or thin blood smear remains the mainstay of the diagnosis of malaria. Light microscopy has the advantage of low cost and high sensitivity and specificity when used by well-trained staff. The thick smear is more sensitive in diagnosing malaria. Examination of thin films allows the examination of the morphologic features of the parasites and the host RBC, which is useful for identifying the particular malaria species. The thin smear also allows quantification of the percentage of parasitized RBCs.

Rapid diagnostic tests for the detection of parasite antigens are available and generally more expensive than light microscopy. These tests may also be vulnerable to ambient conditions, such as heat and humidity, that might compromise their accuracy. These tests may be of benefit in allowing the diagnosis of malaria in settings where light microscopy is not possible.

**Treatment.** In uncomplicated infections, if prompt and effective treatment is provided, recovery is complete and case fatality is low. If treatment is delayed or if ineffective drugs are given, the parasite burden continues to increase and severe malaria may result. A patient can progress from having minor symptoms to having severe disease within a few hours. In severe malaria, if untreated, mortality approaches 100%. Even with treatment, risk of mortality remains as high as 15%-20%. Thus, it is imperative to consider malaria as a cause of fever of children in endemic regions and to provide prompt treatment to decrease associated illness and death. Delays in the recognition and treatment of malaria are directly associated with increases in morbidity and mortality.

If the patient presents only with fever but no danger signs, stiff neck, or signs of severe malaria, and if the patient has no cough with rapid breathing, then he is presumed to have uncomplicated malaria. This patient should receive oral antimalarial medications. If there is concern for pneumonia with cough and rapid breathing, then the patient should also be treated with an appropriate antibiotic.

To counter the threat of resistance of *P. falciparum* to single antimalarial medications and to improve treatment outcomes, treatment for malaria is based on the use of combinations of two or more antimalarial medications, each with independent modes of action and thus unrelated biochemical targets in the parasite. The potential disadvantage in the use of combinations of drugs is the possibility for increased risk of adverse effects and the increased cost of using multiple drugs.

Artemisinin-based combination therapy (ACT) is a preferred treatment option for malaria. Artemisinin and its derivatives (artesunate, artemether, artemotil, and dihydroartemisinin) produce rapid clearance of parasitemia and rapid resolution of symptoms. See Tables A1-A4 (in the appendix) for information of currently recommended ACTs. The choice of ACT in a country or region will be based on the level of resistance of the partner medication in the combination. Important features of ACT include the following:

1. The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.
2. Sulfadoxine-pyrimethamine should be avoided for malaria treatment in HIV-infected patients receiving cotrimoxazole prophylaxis.
3. Artemether-lumefantrine (Coartem) should be used with a six-dose regimen.
4. Amodiaquine plus sulfadoxine-pyrimethamine may be considered as an interim option in situations where ACTs cannot be made available.

Because the initial symptoms of malaria may include isolated cough or rapid breathing associated with metabolic acidosis, the caregiver must be advised to return promptly if the patient’s condition worsens (including the development of any of the danger signs or signs of severe malaria) or fails to improve.

If there are any of danger signs, neck stiffness, or any of the preceding signs of severe malaria, the patient is classified as having severe malaria. Young children and nonimmune adults may deteriorate quickly. Severe malaria is a clinical emergency. The physician or health care worker should use his clinical judgment and treat any patient suspected of having severe malaria appropriately. The risks of undertreating severe malaria greatly outweigh those of giving emergent treatment to a patient who does not need it.
The patient should be immediately given full doses of IV or IM antimalarial treatment with whichever effective antimalarial is first available for treatment of severe malaria as well as the first dose of appropriate broad-spectrum antibiotics for bacterial causes of fever.

For children in high-transmission areas, one of the following antimalarial medications is recommended for emergency prehospital use:

- Artesunate 2.4 mg/kg IV or IM given on admission (time = 0) and then at 12 h, 24 h, and then once daily.
- Artemether 3.2 mg/kg IM given on admission and then 1.6 mg/kg/day.
- Quinine 20 mg salt/kg on admission IV or divided IM injection and then 10 mg/kg every 8 h. IV infusion rate should not exceed 5 mg salt/kg/h.

Also, the patient should be treated to prevent or treat low blood sugar and treated with paracetamol if temperature is greater than 38.5°C. After these measures have been taken and the patient is stable, the patient should be referred urgently to the hospital, where he or she can be managed in an intensive care unit where clinical monitoring can be assured.

**Public health measures.** Prevention of malaria transmission remains a key measure to reduce the morbidity and mortality associated with malaria infection. Prevention of malaria in HIV-infected people living in endemic areas is increasingly regarded as part of basic HIV care. A combination of cotrimoxazole, antiretroviral therapy, and insecticide-treated bednets substantially reduces the frequency of malaria and thus the morbidity and mortality of malaria infection.

**Septicemia**

Septicemia should be suspected in any seriously ill child with fever and no apparent focus of the infection. Where meningococcal disease is common, a clinical diagnosis of meningococcal septicemia must be made if petechiae or purpura are present. Antibiotic therapy should be started promptly.

### Table 2. Estimated minimal incidence of bacteremia by causative organism among children in the catchment area of a rural Kenyan hospital

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incidence of bacteremia per 100,000 for age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 ($N = 26,968$)</td>
</tr>
<tr>
<td>Any organism</td>
<td>1457</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>241</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>89</td>
</tr>
<tr>
<td>Group A streptoccci</td>
<td>96</td>
</tr>
<tr>
<td>Group B streptoccci</td>
<td>74</td>
</tr>
<tr>
<td>Nontyphoidal salmonella species</td>
<td>170</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>159</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>204</td>
</tr>
</tbody>
</table>

A recent study by Berkley et al. reported the following estimated minimal incidence of bacteremia by causative organism among children in the catchment area of a rural Kenyan hospital (*Table 2*).

The following differential diagnoses must be ruled out.

- Malaria: do a blood film. Malaria can kill children quickly. In malaria-endemic areas, or if there is any suspicion of malaria, give antimalaria treatment as soon as possible. Do not wait for the result of the blood film. It is better to err on the side of caution.
- Meningitis: look for a stiff neck, Kernig sign, or Brudzinski sign; do a lumbar puncture.

**Laboratory investigations.** Wherever feasible, perform the following:

- Blood for microscopy, culture, and sensitivity
- Urine for microscopy, culture, and sensitivity
- Lumbar puncture for Gram stain, India ink, and CSF culture
- Malaria blood slide in malaria-endemic areas or if there is a history of travel to a malaria-endemic area

**Treatment.** Treatment options include the following:

- Benzylpenicillin 500,000 U/kg IV or IM every 6 h plus chloramphenicol 25 mg/kg IV or IM every 8 h for 7 days.
If there is no improvement on the preceding regimen, switch to chloramphenicol 25 mg/kg IV or IM every 8 h plus ampicillin 50 mg/kg IV or IM every 6 h.

Often, especially where there is known or suspected microbial resistance to the preceding antibiotics, the best antibiotic may be a third-generation cephalosporin such as ceftriaxone 80 mg/kg IV or IM once daily for 7 days.

**Complications.** Common complications of septicemia may include the following:
- Shock (septicemic shock)
- Cardiac failure
- Disseminated intravascular coagulation
- Anemia
- Convulsions
- Confusion
- Coma

Death from septicemic shock is common. A thorough history and physical examination and appropriate investigations should result in recognition of the preceding complications, and prompt appropriate treatment should be initiated to reduce the associated mortality.

**Public health measures.** Children should receive all the WHO-recommended childhood vaccinations to reduce the morbidity and mortality from preventable childhood illnesses.

**Respiratory Infections**

Respiratory infection may involve the upper or lower respiratory tract. The upper tract includes the nose, middle ear, and pharynx. The lower tract includes the trachea, bronchi, bronchioles, and lungs. Signs and symptoms of respiratory infection include cough, difficulty breathing, sore throat, runny nose, and ear pain or ear drainage. Fever is also common in children with respiratory infections.

Respiratory infections involving both the upper and lower respiratory tracts are common in children. Most respiratory infections in children are caused by viruses. The most frequently isolated viruses are respiratory syncytial virus, rhinoviruses, influenza viruses, and adenoviruses. Human metapneumovirus, identified in 2001, also has been associated with otitis media (ear infections) in children. Bacterial causes of respiratory infection in children include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Other bacterial causes include group A β-hemolytic streptococci, staphylococci, *Chlamydia trachomatis*, and mycoplasma.

Younger children are more susceptible to more severe infection because of anatomic differences. Young children’s airways are narrower and more easily obstructed by edema and secretions. The eustachian tube, the tube between the nasopharynx and middle ear, is shorter in infants and young children, which leads to increased susceptibility to otitis media.

In the early stages of HIV infection, before immune suppression develops, an older child with a respiratory infection involving both the upper and lower respiratory tracts should be evaluated as an immunocompetent host. It is not until the older child develops severe immunosuppression (CD4+ count of <15%) that he or she becomes more susceptible to opportunistic infections. However, young infants tend to be susceptible to opportunistic infections (especially pneumocystis jirovecii [previously pneumocystis carinii] pneumonia) even with high CD4 counts.

A child with a mild respiratory infection or cold may be treated symptomatically at home. A child with a more severe infection, such as pneumonia, may need to be treated in the hospital. According to the WHO, lower respiratory infections are responsible for 18% of all deaths in developing countries. Many of these deaths occur among children who are younger than 2 months. Early recognition and appropriate treatment of pneumonia can greatly reduce the number of deaths.

Most cases of pneumonia can be identified by checking for the most common signs of pneumonia, fever, fast breathing, and retractions. In this module, the student will learn how to differentiate between a cold and pneumonia and how to determine which cases of pneumonia can be treated in an outpatient clinic and which require admission to a hospital.

Assessment of a child with a respiratory infection should include both subjective data and objective data. Subjective data include the following:

1. Which signs/symptoms are present? Does the child have a cough? Is the child having difficulty breathing? Parents may describe such breathing as “fast,” “noisy,” or “interrupted.”
Common Illnesses in Children with HIV/AIDS

2. Does the child have fever? If yes, how high is the temperature, and how long has it been elevated?
3. Does the child have a sore throat or runny nose? Is there ear pain or ear drainage? How long have these symptoms been present?
4. Is the child complaining of chest pain? Is the pain localized or generalized, dull or sharp, deep or superficial, associated with rapid, shallow respirations or grunting?
5. Can the child drink and is he or she interested in drinking? When was the child’s last urine output?
6. What is the child’s activity level?
7. Has the child had convulsions?
8. Is the child abnormally sleepy or difficult to rouse?

Correct interpretation of objective findings will depend on the child’s age. Younger children normally have higher respiratory rates than those of older children. The respiratory rate should be counted for an entire minute, especially in infants, for whom variations in rate are normal. Respiratory rate should be counted while the child is quiet, where this is possible (See Table A5 in the appendix for normal vital signs.) gives age-specific vital signs. Objective data should include the following:

1. The child’s respirations should be observed for rate, depth, ease, and rhythm of breathing.
   a. Rate. Is the rate normal, rapid, or slow for the child?
   b. Depth. Is the depth of the respiration normal, too shallow, or too deep?
   c. Ease. Are the respirations effortless or labored? Does the child need to be upright to breathe? Are there intercostal or substernal retractions (sinking in of the chest with respiration)? Does nasal flaring or head bobbing accompany the child’s breathing? Is the child grunting or wheezing?
   d. Rhythm of breathing. Is there variation in rate and depth of respiration?
2. Is the chest movement symmetrical? Asymmetry may indicate pneumonia, pneumothorax (air in the normally closed pleural space between two membranes on the exterior of the lungs), atelectasis (collapse of a lobe of the lung), or foreign-body obstruction.
3. The lungs should ideally be auscultated (listened to) throughout all lung fields while the child is quiet. The stethoscope should be placed directly on the child’s skin. Are any abnormal sounds present? Chest auscultation usually reveals some of the following:
   a. Decreased breath sounds
   b. Bronchial breathing
   c. Crepitations (crackles)
   d. Increased vocal resonance (over consolidated lung tissue) or decreased vocal resonance (over a pleural effusion)
   e. Pleural rub
4. Is there other evidence of infection, such as enlarged cervical lymph nodes, inflamed nasal mucous membranes, or discharge from the nose (rhinorrhea) or lungs (sputum)?
5. Does the child have a cough? When is the cough most frequent (e.g., morning or night)? How frequent is the cough? Is the cough productive or nonproductive? If the cough is productive, note volume, color, viscosity, and odor of sputum. How does the cough sound—moist, dry, or croupy? Is the cough accompanied by wheezing or stridor?
6. Are there changes in skin color, such as mottling, pallor, or cyanosis? What is the distribution of the discoloration (peripheral, circumoral, central)? What is the capillary refill time? Is cyanosis associated with activity or present at rest?
7. Is clubbing present? Clubbing is an abnormal growth of tissue about the terminal phalanges (bones of the fingers and toes). Clubbing is usually associated with chronic hypoxia (decreased oxygen to body tissues) and in HIV-infected children is a common sign of lymphocytic interstitial pneumonitis or bronchiectasis.
8. Wherever possible, a chest radiograph should be obtained, which may clearly define the following:
   a. Consolidation
   b. Interstitial infiltrates
   c. Pleural effusion
   d. Empyema thoracis
   e. Pneumothorax or pneumatocele
Severe Pneumonia
A child is classified as having severe pneumonia if he or she has cough or respiratory distress plus at least one of the following:
- Central cyanosis
- Inability to drink or breast-feed or vomiting everything
- Convulsions, lethargy, or unconsciousness

The child’s respiratory rate needs to be adequately assessed to determine whether the child is in respiratory distress or faces impending respiratory failure. Cardinal signs of respiratory failure are restlessness, tachypnea (rapid respiration), tachycardia (rapid heart rate), and diaphoresis (profuse sweating). Early signs of respiratory failure include altered depth and pattern of respirations, shortness of breath, nasal flaring (Figure 3), chest wall retractions (Figure 4), expiratory grunt, and wheezing and/or prolonged expiration. See also Table 3.

Table 3. Differential diagnosis of a child presenting with cough and respiratory distress*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>In Favor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>• Cough with fast breathing</td>
</tr>
<tr>
<td></td>
<td>• Lower chest wall indrawing</td>
</tr>
<tr>
<td></td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td>• Coarse crackles on auscultation</td>
</tr>
<tr>
<td></td>
<td>• Nasal flaring</td>
</tr>
<tr>
<td></td>
<td>• Grunting</td>
</tr>
<tr>
<td></td>
<td>• Head nodding</td>
</tr>
<tr>
<td>Malaria</td>
<td>• Fast breathing in febrile child</td>
</tr>
<tr>
<td></td>
<td>• Blood smear: high parasitemia</td>
</tr>
<tr>
<td></td>
<td>• Lives in or travelled to a malarious area</td>
</tr>
<tr>
<td></td>
<td>• In severe malaria: deep (acidotic) breathing/lower chest wall indrawing</td>
</tr>
<tr>
<td></td>
<td>• Chest clear on auscultation</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>• Severe palmar pallor</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin &lt;6 g/dl</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>• Gallop rhythm</td>
</tr>
<tr>
<td></td>
<td>• Raised jugular venous pressure</td>
</tr>
<tr>
<td></td>
<td>• Basal fine crackles</td>
</tr>
<tr>
<td></td>
<td>• Apex beat displaced</td>
</tr>
<tr>
<td></td>
<td>• Enlarged palpable liver</td>
</tr>
<tr>
<td></td>
<td>• Heart murmur</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>• Central cyanosis</td>
</tr>
<tr>
<td></td>
<td>• Difficulty in feeding or breastfeeding</td>
</tr>
<tr>
<td></td>
<td>• Enlarged liver</td>
</tr>
<tr>
<td></td>
<td>• Heart murmur</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>• Chronic cough (more than 30 days)</td>
</tr>
<tr>
<td></td>
<td>• Poor growth/wasting or weight loss</td>
</tr>
<tr>
<td></td>
<td>• Positive contact history with tuberculosis patient</td>
</tr>
<tr>
<td></td>
<td>• Diagnostic chest x-ray such as primary complex or miliary tuberculosis</td>
</tr>
<tr>
<td>Pertussis</td>
<td>• Paroxysms of cough followed by whoop, vomiting, cyanosis or apnea</td>
</tr>
<tr>
<td></td>
<td>• No fever</td>
</tr>
<tr>
<td></td>
<td>• No history of DPT immunization</td>
</tr>
<tr>
<td>Foreign body</td>
<td>• History of sudden choking</td>
</tr>
<tr>
<td></td>
<td>• Sudden onset of stridor or respiratory distress</td>
</tr>
<tr>
<td></td>
<td>• Focal areas of wheeze or reduced breath sounds</td>
</tr>
<tr>
<td>Empyema</td>
<td>• Stony dullness to percussion</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>• Sudden onset</td>
</tr>
<tr>
<td></td>
<td>• Hyper-resonance on percussion on one side of the chest</td>
</tr>
<tr>
<td></td>
<td>• Shift in mediastinum</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>• 2-6-month-old child with central cyanosis</td>
</tr>
<tr>
<td></td>
<td>• Hyper-expanded chest</td>
</tr>
<tr>
<td></td>
<td>• Fast breathing</td>
</tr>
<tr>
<td></td>
<td>• Finger clubbing</td>
</tr>
<tr>
<td></td>
<td>• Chest x-ray changes, but chest clear on auscultation</td>
</tr>
<tr>
<td></td>
<td>• Enlarged liver, spleen, lymph nodes</td>
</tr>
<tr>
<td></td>
<td>• Wasting</td>
</tr>
<tr>
<td></td>
<td>• HIV test positive</td>
</tr>
</tbody>
</table>

*World Health Organization. Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries, 2000.)
**Treatment.** All children with severe pneumonia should be urgently transferred to a hospital for inpatient management with IV antibiotics and oxygen therapy. Whenever feasible, the child should be given the first antibiotic dose and placed on oxygen therapy if an oxygen cylinder is available prior to transfer.

Empiric antibiotic therapy should be guided by locally prevailing susceptibility patterns. Usually, however, benzylpenicillin 50,000 IU/kg IM or IV can be given prior to hospital transfer.

**Nonsevere Pneumonia**
Most pneumonia cases in children aged 2 months to 5 years will be characterized by rapid respirations without retractions. A child with pneumonia can be treated on an outpatient basis with oral antibiotics. The child’s caregiver should be instructed on how to administer the antibiotics; if feasible, the first dose should be given in the clinic to demonstrate proper administration. A child treated at home should return to the clinic in 2 days to be reassessed. The caregiver should be instructed to return to the clinic sooner if the child continues to have rapid respirations, develops retractions, continues to have fever, or does not improve on oral antibiotics. If any of these outcomes occurs, the child should be referred to a hospital. If the child improves on oral antibiotics, the antibiotics should be continued to complete at least 5 days of treatment. If the child’s signs and symptoms have not improved and the caregiver has been giving the antibiotics correctly, a different antibiotic should be given for 5-10 days, or an alternative etiology should be considered.

**No Pneumonia (Upper Respiratory Tract Infection or Cold)**
A child with cough or difficulty breathing but without any general danger signs is determined to have a cold. Young children average six to eight colds per year, each lasting about 2 weeks. Purulent nasal discharge is characteristic, and fever is common in children during the first 3 days of the illness. Other symptoms may include sore throat, cough, irritability, difficulty sleeping, and decreased appetite. Physical signs are nonspecific but may include erythema and swelling of the nasal mucosa, as well as moderate anterior cervical lymphadenopathy. The symptoms of the common cold can be caused by a variety of viruses. Rhinoviruses, respiratory syncytial virus, influenza viruses, parainfluenza viruses, and adenoviruses are commonly responsible for colds in preschool children.

Such a child does not require treatment with antibiotics. The child can be cared for at home. The caregiver should be instructed to watch for signs of respiratory distress (e.g., nasal flaring, abdominal or intercostal retractions, cyanosis, grunting) and to bring the child back immediately if any of these signs occur. If coughing has persisted for more than 30 days, the child should be referred to a hospital for assessment.

**Upper Respiratory Tract Infections, Otitis Media, and Sore Throat**
Otitis media, or infection of the middle ear, can be classified into four categories to help identify proper treatment:
- acute ear infection,
- chronic ear infection,
- mastoiditis, and
- no ear infection.

**Acute Ear Infection (Acute Otitis Media)**
A child with an ear infection may have ear pain, ear drainage, and/or fever. On physical examination, the child will have an erythematous (abnormally red), bulging, dull, immobile eardrum and/or pus draining from the ear. If the signs and symptoms have been present for less than 2 weeks, the child is classified as having acute otitis media. Acute otitis media is treated with oral antibiotics at home for 5 days. If the child has fever for more than 48 h on antibiotics, consider a change in the antibiotics and consider looking for other possible causes of the fever.

**Chronic Ear Infection (Chronic Otitis Media)**
Chronic suppurative otitis media is common in HIV-infected children. A child who has had ear drainage for longer than 2 weeks is considered to have chronic otitis media. The ear should be dried by a method known as wicking. This procedure should be done for the first time in the clinic to demonstrate the technique to the child’s caregiver. To dry the ear, roll a clean, soft, absorbent cotton cloth into a wick. Place the wick in the child’s ear, and remove it when it is wet. Repeat this step until the wick no longer gets wet; this indicates that the drainage has stopped. This treatment should be done at home at least three times per day. Antibiotics generally have no place in the management of chronic suppurative otitis media because they are usually ineffective and do not alter the course or the outcome.
Mastoiditis
Mastoiditis is a complication of otitis media. A child with mastoiditis will have a tender, swollen, erythematous, warm area behind the ear. Mastoiditis requires treatment with IV antibiotics and possible surgery. A child with mastoiditis should be referred to a hospital. The first dose of antibiotics should be given in the clinic, if feasible. The same antibiotics used to treat pneumonia are used in the treatment of mastoiditis.

Management. If antibiotics are given for an ear infection, the caregiver should be instructed to complete the full course of antibiotics even if the child is feeling better and to return for follow-up as instructed. The caregiver should be instructed not to put oil or any other fluid into the child’s ear, and the child should avoid getting water into the ear. Recurrent, chronic ear infections can cause deafness.

Sore Throat
Sore throat is one of the most common symptoms of an upper respiratory infection. Most cases of sore throat are caused by viruses, can be treated symptomatically, and resolve in a few days. Occasionally a child with a sore throat will require antibiotics. Antibiotics are necessary if the sore throat is caused by a throat abscess or streptococcal infection. A child with a throat abscess will not be able to swallow secretions, fluids, or food and should be referred to a hospital for drainage of the abscess. A child with a streptococcal throat infection will have tender, enlarged lymph nodes in the front of the neck and white exudate in the posterior oropharynx and/or on the tonsils.

Management. Most children with a sore throat get better in a few days with symptomatic treatment. Caregivers should be encouraged to offer frequent liquids to keep the mucosal surface of the throat moist. Paracetamol may be given by mouth at a dose of 15 mg/kg/dose every 4-6 h to relieve discomfort or fever. Caregivers should be instructed not to exceed six doses per day of paracetamol because an overdose can cause liver failure. The child’s temperature should be rechecked 30-60 min after the dose to confirm the effectiveness of the medication. If the child has a streptococcal infection, the best treatment is one injection of benzathine penicillin. If this is not available, the child should be treated with oral amoxicillin, ampicillin, or penicillin for 10 days. If oral antibiotics are given, the caregiver must understand the importance of completing the antibiotics to prevent complications such as rheumatic fever or a relapse of the illness.

Fever in Infants Aged 1 Week to 2 Months
Fever in a young infant represents a special clinical situation. Most young infants with fever will have a benign viral infection, but serious bacterial infections include pneumonia, sepsis, urinary tract infection, and meningitis. In young infants, these diseases may all present similarly; thus, clinical signs cannot reliably distinguish between these diagnoses. Therefore, the goal of the evaluation in the prehospital setting is to recognize that young infants are at high risk for serious illness. It is therefore imperative that the infant be promptly evaluated, that appropriate antibiotic treatment be initiated promptly, and that the infant be referred to the hospital even before a specific diagnosis is confirmed. In the referral hospital, laboratory investigations can be carried out and the infant can receive parenteral antibiotics and be monitored pending results of laboratory investigations and cultures.

History
In young infants, the symptoms of serious bacterial infection are often nonspecific and may include lethargy, poor feeding, vomiting, and/or convulsions. Other historical details to elicit might include the following:

- Associated symptoms
- Exposures to sick contacts
- Any previous illness or antibiotic use
- Birth history
  - Maternal fever
  - Maternal history of infections
  - Duration of rupture of membranes prior to delivery
  - Delivery at home or in hospital
  - Infant’s neonatal course

Objective
General appearance. The infant’s general appearance is a vitally important observation. Toxic-appearing infants are pale or cyanotic, lethargic, or inconsolably irritable. They may also have tachypnea and tachycardia with poor capillary refill.
Other physical findings include the following:

- Alterations in body temperature
  - Fever (axillary temperature ≥37.5°C or ≥99.5°F)
  - Hypothermia (axillary temperature ≤35.5°C or ≤95.9°F)
- Alterations in color
  - Pallor
  - Cyanosis
  - Jaundice
- Signs of respiratory distress
  - Fast or irregular breathing
  - Lower chest wall indrawing/retractions
  - Nasal flaring
  - Grunting
  - Apnea
- Abdominal distension
- Hepatosplenomegaly

Physical findings that might indicate the source of fever include

- Pus draining from the ear
- Painful joints, joint swelling, reduced movement and irritability if these parts are handled
- Umbilical redness extending to the periumbilical skin

Meningitis might be suspected if the following signs are present:

- Tense or bulging fontanel
- Neck stiffness
- High-pitched cry
- Apneic episodes
- Convulsions

All young infants must be assessed to determine if they should be classified as having possible serious bacterial infection or a local bacterial infection. Young HIV-infected infants tend to be susceptible to opportunistic infections (especially pneumocystis jirovecii [previously pneumocystis carinii] pneumonia, even with high CD4 counts.

**Severe Disease**

An infant is classified as having severe disease if any of the following danger signs are present: lethargy, decreased intake, wheezing, fever (>37.5°C) or low body temperature (<35°C), or severe malnutrition.

In this age group, all pneumonia is considered severe. A child is diagnosed as having pneumonia if the respiration rate is greater than 60 breaths per minute or the infant is having chest wall retractions. A young infant with pneumonia should be treated with IV antibiotics and referred to a hospital for inpatient management.

Meningitis should be suspected if the infant presents with general illness such as irritability, vomiting everything, abnormal cry, or lethargy. Physical examination might reveal bulging or tense fontanel, stiff neck, apneic episodes, or convulsions. A young infant with severe disease should be transferred immediately to a hospital where there is access to laboratory tests including a full blood count, blood culture, urinalysis and urine culture, chest radiograph, lumbar puncture, and CSF examination.

If possible, give one dose of one of the following antibiotic regimens before the transfer.

**For sepsis when the precise diagnosis is not yet established:**

- Ampicillin 50 mg/kg IV or IM every 6-8 h plus gentamicin 7.5 mg/kg IV or IM once daily
- Benzylpenicillin 50,000 U/kg IV or IM every 6-8 h plus gentamicin 7.5 mg/kg IV or IM once daily

**For meningitis:**

- Ampicillin 50 mg/kg IV or IM every 6-8 h plus gentamicin 7.5 mg/kg IV or IM once daily
- Benzylpenicillin 50,000 U/kg IV or IM every 6-8 h plus chloramphenicol 25 mg/kg IV or IM every 6 h

Chloramphenicol should not be given to premature infants (<37 weeks’ gestation) and should be avoided in all infants in the first week of life. For infants aged 1 week to 1 month, chloramphenicol should be given every 12 h.

**No Pneumonia (Upper Respiratory Tract Infection or Cold)**

A young infant without fever; without any danger signs (lethargy, decreased intake, wheezing, or low body temperature, severe malnutrition); and without fast breathing, retractions, or wheezing is determined to have a cold. The infant can be cared for at home. The caregiver should be encouraged to offer frequent fluids and to clear the infant’s nose prior to feeding. The caregiver should be instructed to watch for signs of respiratory distress (e.g., nasal flaring, retractions, cyanosis, grunting) and to take
the infant to the nearest clinic or hospital immediately if any of the signs occur.

**Conclusion**

Children with HIV present commonly for evaluation and treatment of illness. The integrated approach to management of childhood illness remains the most effective method for managing sick children. The health care provider must consider the subjective data revealed by taking a thorough history and the objective data obtained by performing a complete physical examination. These data allow the health care provider to accurately classify the condition and to identify the appropriate treatment actions.

Fever is a symptom of many conditions, some simple and others serious. It is imperative for the health care provider to rapidly assess the patient so that the appropriate treatment plan can be promptly initiated. Because malaria can evolve quickly into serious disease, malaria should be considered as a possible diagnosis in malaria-endemic areas. Young infants are susceptible to febrile infections and when ill, often show less specific clinical signs. Thus, if any danger signs are present, young infants should be referred emergently to the hospital for further management.

Many upper respiratory tract infections can be treated at home with oral antibiotics and/or simple treatments for symptoms. Children presenting with cough and/or difficulty breathing might be referred urgently to the hospital, treated with oral antibiotics, or treated only for symptoms depending upon whether they were assessed as having severe disease or severe pneumonia, uncomplicated pneumonia, or no pneumonia. Caregivers for the child should be given clear follow-up instructions. They should be educated on how to recognize symptoms that might indicate progression or complication of the condition. They should be instructed to urgently get the child to the nearest health facility upon earliest suspicion of deterioration in the child’s condition or development of danger signs.

**Appendix: Dosing schedules for antimalarial medications**

**Artemether-Lumefantrine (Coartem)**
Currently available as coformulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The total recommended treatment is a six-dose regimen of artemether-lumefantrine twice daily for 3 days.

**Artesunate Plus Amodiaquine**
Currently available as separate scored tablets containing 50 mg of artemunate and 153-mg base of amodiaquine. The total recommended treatment is 4 mg/kg of artemunate and 10 mg/kg of amodiaquine given once daily for 3 days.

**Artesunate Plus Sulfadoxine-Pyrimethamine**
Currently available as separate scored tablets containing 50 mg of artemunate and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine. The total recommended treatment is 4 mg/kg of artemunate given once a day for 3 days and one administration of sulfadoxine-pyrimethamine (25/1.25 mg of base/kg) on day 1.

---

**Table A1. Dosing schedule for artemether-lumefantrine (Coartem)**

<table>
<thead>
<tr>
<th>Body wt (kg)</th>
<th>Age (yrs)</th>
<th>No. of tablets at approximate timing of dosing (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5-14</td>
<td>&lt;3</td>
<td>1</td>
</tr>
<tr>
<td>15-24</td>
<td>≥3-8</td>
<td>2</td>
</tr>
<tr>
<td>25-34</td>
<td>≥8-14</td>
<td>3</td>
</tr>
<tr>
<td>&gt;34</td>
<td>≥14</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table A2. Dosing schedule for artemunate plus amodiaquine**

<table>
<thead>
<tr>
<th>Age</th>
<th>Artesunate (50 mg)</th>
<th>Amodiaquine (153 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>5-11 mo</td>
<td>25 (1/2)</td>
<td>25</td>
</tr>
<tr>
<td>≥1-6 yrs</td>
<td>50 (1)</td>
<td>50</td>
</tr>
<tr>
<td>≥7-13 yrs</td>
<td>100 (2)</td>
<td>100</td>
</tr>
<tr>
<td>≥13 yrs</td>
<td>200 (4)</td>
<td>200</td>
</tr>
</tbody>
</table>

**Table A3. Dosing schedule for artemunate plus sulfadoxine-pyrimethamine**

<table>
<thead>
<tr>
<th>Age</th>
<th>Artesunate (50 mg)</th>
<th>Sulfadoxine-pyrimethamine (500 mg/25 mg, respectively)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>5-11 mo</td>
<td>25 (1/2)</td>
<td>25</td>
</tr>
<tr>
<td>≥1-6 yrs</td>
<td>50 (1)</td>
<td>50</td>
</tr>
<tr>
<td>≥7-13 yrs</td>
<td>100 (2)</td>
<td>100</td>
</tr>
<tr>
<td>≥13 yrs</td>
<td>200 (4)</td>
<td>200</td>
</tr>
</tbody>
</table>
Artesunate Plus Mefloquine

Currently available as separate scored tablets containing 50 mg of artesunate and 250-mg base of mefloquine. Total recommended treatment is 4 mg/kg artesunate given once daily for 3 days and 25 mg of base/kg of mefloquine usually split over 2 or 3 days. Two different doses of mefloquine have been evaluated, 15 mg of base/kg and 25 mg of base/kg. The lower dose is associated with inferior efficacy and is not recommended. To reduce acute vomiting and optimize absorption, the 25 mg/kg dose is usually split and given as 15 mg/kg (usually on the second day) followed by 10 mg/kg 1 day later, or as 8.3 mg/kg per day for 3 days. Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria, and sleep disturbance in clinical trials, but these symptoms are seldom debilitating and mefloquine is generally well tolerated.

Table A4. Dosing schedule for artesunate plus mefloquine

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose, mg (No. of tablets)</th>
<th>Artesunate (50 mg)</th>
<th>Amodiaquine (153 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>5-11 mo</td>
<td>25 (1/2)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>≥1-6 yrs</td>
<td>50 (1)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>≥7-13 yrs</td>
<td>100 (2)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>≥13 yrs</td>
<td>200 (4)</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Table A5. Normal pediatric vital signs

<table>
<thead>
<tr>
<th>Age</th>
<th>Wt (kg)</th>
<th>Pulse/Respirations</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>min/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>1</td>
<td>145 &lt;40</td>
<td>42 ± 10</td>
<td>21 ± 8</td>
</tr>
<tr>
<td>Newborn</td>
<td>2-3</td>
<td>125 —</td>
<td>60 ± 10</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>1 mo</td>
<td>4</td>
<td>120 24-35</td>
<td>80 ± 16</td>
<td>46 ± 16</td>
</tr>
<tr>
<td>1 yr</td>
<td>10</td>
<td>120 20-30</td>
<td>96 ± 30</td>
<td>66 ± 25</td>
</tr>
<tr>
<td>2-5 yrs</td>
<td>12-14</td>
<td>115 —</td>
<td>99 ± 25</td>
<td>64 ± 25</td>
</tr>
<tr>
<td>6-9 yrs</td>
<td>20-26</td>
<td>100 12-25</td>
<td>100 ± 20</td>
<td>65 ± 15</td>
</tr>
<tr>
<td>10-12 yrs</td>
<td>32-42</td>
<td>75 —</td>
<td>112 ± 20</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>&gt;14 yrs</td>
<td>&gt;50</td>
<td>70 12-18</td>
<td>120 ± 20</td>
<td>75 ± 15</td>
</tr>
</tbody>
</table>

References

Growth in HIV-Infected Children

Elizabeth D. Lowenthal, MD
Ryan Phelps, MD, MPH

Objectives
3. Review the effects of highly active antiretroviral therapy on growth in HIV-infected children.
4. Discuss changes in bone formation and pubertal development in HIV-infected children.
5. Review how to perform and interpret basic anthropometric measurements in children.

Key Points
1. Growth is an important indicator of a child’s health.
2. HIV infection can lead to growth problems.
3. Bone problems and abnormal pubertal development are more commonly seen in HIV-infected children than in noninfected children.
4. Health care providers who care for children with HIV should evaluate each child’s growth at every visit.
5. When growth problems are found, the health care provider should attempt to identify and treat the underlying cause of the problem.

World Health Organization (WHO) Core Competencies included the following:
- Provide growth monitoring—weight, middle-upper arm circumference, height
- Recognize human immunodeficiency virus (HIV)-related conditions (growth failure)
- Determine eligibility for antiretroviral therapy (WHO growth-related clinical staging)

Overview
Growth is an important indicator of a child’s health. Accurate measurements of weight, length/height, and head circumference are essential parts of the health evaluation of growing children. Children who are unhealthy tend to grow and gain weight more slowly than healthy children their age. Human immunodeficiency virus (HIV)-infected children are at particular risk for problems related to growth. HIV and opportunistic infections often negatively influence the growth of young children. A lack of nutritious food necessary for normal growth complicates the lives of many HIV-infected children.

Health care providers who treat children should be able to assess whether a child’s growth is appropriate for the age of the child. By evaluating growth and development at every medical visit, we can learn much about the child’s health. This chapter discusses how HIV affects growth and provides practical tools for growth monitoring.

Newborns: Birth Weight Comparisons
Small size at birth is not clearly associated with HIV infection in full-term newborns. Many factors determine a full-term newborn’s birth weight, including maternal nutrition, placental function, and fetal genetics. Studies examining the role of maternal HIV infection in fetal growth have failed to show a consistent relationship. According to the European Collaborative Study and a study from Durban, South Africa, birth weight of infected and uninfected children born to HIV-positive mothers are not significantly different. In contrast, a study based on a U.S. inner-city population concluded that children born to HIV-infected mothers are at increased risk of low birth weight as well as prematurity. Further studies are needed to clarify the reasons for the inconsistencies seen between these populations. At this time, the evidence does not clearly imply a relationship between HIV infection and infant birth weight.

Although full-term newborns who are HIV infected or HIV exposed are not typically smaller than term unexposed infants, prematurity is more common among HIV-exposed infants. A study done prior to the
implementation of prenatal prophylaxis and the routine use of highly active antiretroviral therapy (HAART) showed that the rate of prematurity associated with HIV infection was as high as 19%, more than 30% higher than that in the uninfected population. HAART’s role in preventing prematurity is controversial. Some studies have suggested that HAART may increase the risk of prematurity. However, a recent meta-analysis of 14 separate studies concluded that treatment with antiretroviral regimens during pregnancy is not associated with an overall increased risk of premature delivery.

**Head Growth and HIV**

Head circumference (also called frontal occipital circumference [FOC]) is correlated with brain volume in small children. The brain is one of the primary targets of HIV infection. HIV infection in young children sometimes results in reduced brain growth. Smaller FOC at birth has been associated with developmental delays and reduced academic achievement. Studies have not shown a statistically significant difference in FOC at birth between HIV-infected and uninfected children. The Women and Infants Transmission Study (WITS) did, however, show a trend toward smaller FOC in HIV-infected infants. This study also showed that untreated infants infected with HIV have a decline in brain growth, as evidenced by an increased rate of microcephaly (FOC <5th percentile for age) as they aged. Because microcephaly has been correlated with adverse developmental outcomes, FOC measurements should be used as a tool for the identification of infants at risk for these unfavorable outcomes. FOC measurements are most useful during the first 2 years of life, when head circumference changes most rapidly.

**Variable Onset of Growth Failure**

Many factors affect children’s growth, including general nutrition, overall health, and caretaker nurturing. A child is said to be failing to thrive when he or she loses weight or fails to gain weight at a normal rate for a child of that age. Failure to thrive is a diagnosis that has multiple etiologies, one of which is HIV infection.

The onset of growth failure in children with HIV varies. Growth deceleration can occur as early as the first few months of life, though some children have normal growth for many years. On average, children with untreated HIV infection grow more slowly than uninfected children, a difference that becomes more significant with age. Asymptomatic infected children have growth patterns that are similar to those of mildly or moderately symptomatic children. However, children with severe illness tend to have significantly poorer growth, and high viral loads have been clearly associated with decreased growth.

**Growth as a Predictor of Prognosis**

Children infected with HIV have been classified in three clinical groups with regard to the timing of their disease progression. Infants who develop symptoms of AIDS or who die within the first year of life are rapid progressors. Children who suffer from an AIDS-defining illness or who die within 1-5 years of infection are intermediate progressors. Those children who do not develop symptoms and who survive past 5 years of age are slow progressors. Growth failure in children has been clearly associated with accelerated progression from asymptomatic HIV infection to AIDS. Rapid progressors have the highest incidence of growth failure.

Perinatally acquired HIV infection is sometimes associated with early and progressive reductions in weight and length. Studies in Thailand, Rwanda, and the United States suggest that growth failure can signal rapid disease progression. Babies who failed to gain 2 kg by 4 months of age were more likely to progress to AIDS rapidly. Also, height growth velocity (rate of growth) can predict survival independently of age, viral load, and CD4+ cell count. In resource-limited environments, where obtaining laboratory data is sometimes not possible, growth monitoring may be the best available tool for assessing risk of disease progression.

**Effects of HAART on Growth**

Early studies demonstrated that mono or dual antiretroviral therapies containing zidovudine, didanosine, or zalcitabine temporarily increased weight and linear growth rate. Because HAART is less likely to lead to resistance and treatment failure, more sustainable clinical growth responses are seen among children on HAART. Patients on HAART who achieve and maintain virologic suppression generally have corresponding long-term improvements in growth. After patients begin HAART, beneficial effects are first seen as increases in weight followed by increases in height (usually by 96 weeks on therapy).
Bone Growth: Osteopenia, Osteoporosis, and Osteonecrosis

Bone mass increases during childhood and adolescence. Peak bone mass is normally achieved during the third decade of life. When people have low bone density for their age, they are said to have osteopenia. Those whose bone density is less than 2.5 standard deviations below the mean have the severe form of bone wasting called osteoporosis. Children who fail to form bone normally are at increased risk for this complication because they accumulate bone density more slowly than noninfected children and because certain HAART regimens may further decrease bone density.

The mechanisms by which bone mass decreases among HIV-positive children are complicated. HIV can infect certain bone cells directly. The virus also elevates levels of several cytokines (interleukin 1, interleukin 6, and tumor necrosis factor α) that contribute to increased activity of osteoclasts (cells that break down bone). Vitamin D deficiency also contributes to abnormal bone metabolism and has been reported more frequently in patients with HIV. Although increased rates of bone fractures are not commonly seen among HIV-infected children, these children are at high risk of fractures later in life because of their early development of osteopenia and osteoporosis.

The appearance of bones on plain X rays can provide qualitative evidence for the existence of osteopenia or osteoporosis. Where available, one can quantify low bone density by using DEXA (dual-energy X-ray absorptiometry) or quantitative computed tomography scans.

Weight-bearing exercises (e.g., jogging, dancing, and weight lifting) can help children with HIV maximize their bone development. Providing a diet that is rich in vitamin D, especially in areas where children have limited exposure to sunlight, will also help to ensure the best possible bone growth. Studies evaluating the use of medicines and hormone replacement therapies to help rebuild bone in HIV-infected patients with osteopenia and osteoporosis are currently being carried out in several settings.

Children and adults with HIV infection are also at increased risk of osteonecrosis of the hip. In children, this condition is called Legg-Calve-Perthes disease (LCPD). A study of perinatally HIV-infected children demonstrated a prevalence of LCPD that was more than eight times that of the general population. LCPD is diagnosed on the basis of typical X-ray findings in a symptomatic patient. Treatments for LCPD include the use of nonsteroidal anti-inflammatory and pain control medications, temporarily avoiding weight bearing, and exercises to maintain the range of motion. Severe cases may require surgery or immobilization of the joint.

Puberty

Delay of sexual maturation is common among children with chronic diseases. Children with HIV infection have delays both in the age of onset of puberty and in their progression through the pubertal stages (Table 1 and Table 2). The median delay in pubertal onset is 2 years for girls and 1 year for boys. Entry into the late pubertal stage can be identified by the development of secondary sexual characteristics.

Table 1. Female pubertal (Tanner) staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normal Age Range (yrs)</th>
<th>Breast Growth</th>
<th>Pubic Hair Growth</th>
<th>Other Significant Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-15</td>
<td>No palpable glandular tissue; areola not pigmented</td>
<td>None</td>
<td>Preadolescent</td>
</tr>
<tr>
<td>II</td>
<td>8-15</td>
<td>Breast budding (thelarche); nipple and breast project as one mound</td>
<td>Downy pubic hair develops near the labia</td>
<td>Peak growth velocity often occurs with this stage in girls</td>
</tr>
<tr>
<td>III</td>
<td>10-15</td>
<td>Further enlargement of breast tissue beyond the areola; nipples enlarge and become pigmented</td>
<td>Hair increased in amount and distribution</td>
<td>Menarche occurs in a small percentage of girls late in Stage 3</td>
</tr>
<tr>
<td>IV</td>
<td>10-17</td>
<td>Separation of contours with areola and nipple forming a secondary mound above the breast tissue; increased areolar pigmentation</td>
<td>Adult in type; covers mons pubis, but not extending to thighs</td>
<td>Menarche occurs in most girls at this stage (usually 1–3 yrs after thelarche)</td>
</tr>
<tr>
<td>V</td>
<td>12.5-18</td>
<td>Adult-sized breast with mature contour</td>
<td>Adult distribution</td>
<td>Menarche occurs in 10% of girls in Stage V</td>
</tr>
</tbody>
</table>
Growth in HIV-Infected Children

Table 2. Male pubertal (Tanner) staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normal Age Range (yrs)</th>
<th>Testis Growth</th>
<th>Penis Growth</th>
<th>Pubic Hair Growth</th>
<th>Other Significant Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0–15</td>
<td>Preadolescent testes (&lt;2.5cm)</td>
<td>Preadolescent</td>
<td>None</td>
<td>Preadolescent</td>
</tr>
<tr>
<td>II</td>
<td>10–15</td>
<td>Enlargement of the testes (&gt;2.5–3 cm); scrotal sac darkening</td>
<td>Minimal or no enlargement</td>
<td>Downy pubic hair develops at base of the penis</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>10.5–16.5</td>
<td>Further enlargement (&gt;3.0–3.5 cm)</td>
<td>Significant enlargement, especially in diameter</td>
<td>Hair increased in amount; curling</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>12–17</td>
<td>Further enlargement (&gt;3.5–4.0 cm)</td>
<td>Further enlargement, especially in diameter</td>
<td>Adult in type, but more limited distribution</td>
<td>Development of axillary hair and some facial hair; most boys reach peak growth velocity during this stage</td>
</tr>
<tr>
<td>V</td>
<td>13–18</td>
<td>Adult sized (&gt;4.0 cm)</td>
<td>Adult sized</td>
<td>Adult distribution (medial aspect of thighs and linea alba)</td>
<td>Body hair continues to grow; muscles continue to increase in size</td>
</tr>
</tbody>
</table>

How Do We Measure Growth?

Growth monitoring in children requires obtaining accurate measurements of weight and length/height. Head circumference should also be monitored in children who are younger than 2 years.

Measuring Weight

When weighing young children, consider these basic guidelines to ensure accuracy:

- Use the same scale at each visit.
- Record the weight to the nearest 0.1 kg.
- When weighing infants, weigh them in the supine position with no clothing (except perhaps a dry diaper).
- If available, infant scales should be used for children weighing less than 20 kg. Another option is tared weighing, where the caregiver is weighed, the scale is tared (or “zeroed”), and then the undressed child is held by the caregiver, capturing the weight of the child only.
- If the child is older and will stand still, it is best to weigh the child standing alone on the scale.

Measuring Length and Height

Children younger than 2 years should be measured while they are lying on a flat surface. This measurement is called the child’s length. Older children who can stand should be measured in a standing position, which measures the child’s height. When measuring length and height, consider these basic guidelines to ensure accuracy:

- Measure the length of children aged 0-2 years when they are lying down with a length board, with back flat, knees straight, and ankles in neutral position. Record the measurement to the nearest 0.5 cm.
- If the child is aged 2 or more years, measure standing height (heels against wall, without shoes) by using a height board mounted at a right angle.
- Because standing height is about 0.7 cm less than recumbent length and growth charts for children older than 2 years assume that the child will be measured in the standing position, you must subtract 0.7 cm from the measurement of children aged 2 years or older who are measured lying down before plotting them on the standardized World Health Organization (WHO) growth charts.

Measuring Head Circumference

When measuring head circumference, consider these basic guidelines to ensure accuracy:

- Head circumference should be routinely checked for the first 24 months of life by using a nonstretchable tape (usually plastic coated or metallic) and recorded to the nearest 0.5 cm.
- The tape should encircle the bony prominence...
of both the forehead and the occiput and should reflect the head’s greatest diameter to avoid an underestimation.

- Ideally, the head circumference should be measured twice in moving children to ensure that the widest diameter has been measured.

**Plotting Measurements on Growth Charts**

Once weight and height (or length) are measured, they should be plotted and interpreted using a standard growth chart. The WHO has developed growth charts that reflect the range of growth potential for children worldwide who receive proper nutrition and health care. These growth charts depict age on the horizontal axis and weight, height, or head circumference on the vertical axis. They offer a simple, systematic way to document a child’s nutritional status at a point in time and allow the tracking of a child’s growth rate over time.

Using these charts or other locally validated charts, one should plot the weight, height, and head circumference of HIV-infected children at regular intervals. Weight should be checked each visit and height checked every 3 months throughout childhood. Head circumference should be plotted at least every 3 months until 24 months of age and more frequently during the first 6 months of life. Once weight and height are plotted on the growth chart according to the age of the patient, they offer a visual representation of the child’s growth compared with that of healthy children of the same age.

Weight and height also make it possible to define other essential growth parameters—weight-for-height ratio and body mass index (BMI). The weight-for-height ratio is a growth indicator that relates weight to length (for children <2 years) or height (for children ≥2 years). BMI, often used for older children and adolescents, indicates a person’s weight in proportion to height, calculated as kilograms per square meter of body surface area. Like other measurements, weight-for-height ratios and BMI are best interpreted while taking into consideration the age of the child, and standard charts and reference tables have been developed to assist the clinician. The most relevant WHO growth charts are included within this chapter. Additional charts are available through the WHO child growth standards Web site: http://www.who.int/childgrowth/en.

Once measurements have been plotted, the resulting growth curve makes it easy to determine whether the child is experiencing growth failure. Figure 1 shows two examples of the type of growth failure commonly observed among children with HIV infection.

**Figure 1.** This orphan had severe growth failure and malnutrition when he first presented to the Baylor clinic at age nine years, with a weight too low to fit on the WHO weight-for-age chart and no previous medical records. After treatment for TB and the initiation of HAART, the child’s nutritional status and weight for age improved dramatically. He is now almost ten years old, and his weight should continue to normalize as HAART and immune system recovery continue. Note the slower improvement in height in the height-for-age chart. Though his weight is recovering quickly, his height will lag behind, and he is likely to remained stunted, with a lower than average adult height.
Using Growth Plots To Classify Poor Growth and Nutritional Deficiency

In the short term, patients who are not growing well become thin, or “wasted.” Over time, if poor growth continues, the children will also fail to gain height at the normal rate. The failure to gain height results in short stature for age, or “stunting.” Children with HIV who have stunting have a poorer prognosis than that of children with more normal long-term growth. Health care providers should therefore aim to identify poor growth early before stunting occurs.

A variety of different criteria exist to aid in the timely diagnosis of clinically significant poor growth. Three criteria that are commonly used to indicate a growth abnormality are:

- Weight loss of 10% or more of body weight
- Deceleration in weight gain resulting in a downward crossing of two or more of the percentile lines for age (e.g., 97th, 85th, 50th, 15th, 3rd)
- Weight-for-height ratio or BMI of less than –1 standard deviation below the mean with failure to follow a normal upward curve

Measuring the middle-upper arm circumference (MUAC) provides another useful tool to identify a child with wasting syndrome. As a child loses subcutaneous fat and muscle, the MUAC becomes low for age.

In addition to looking at a child’s growth chart, one should always examine the child for other physical signs of malnutrition. Some children with severe protein energy malnutrition develop edema. The presence of edema makes the weight and MUAC appear falsely elevated. The nutrition chapter discusses other clinical signs of malnutrition in more detail.

**What To Do If a Child Has Poor Growth**

Children who fail to meet growth parameters should be targeted for treatment of potentially reversible causes of poor growth, including untreated HIV infection. Most countries currently use WHO clinical staging as a basis for determining eligibility for initiating HAART. Nutritional status plays an important role within these HAART eligibility criteria (Table 3).

**Table 3. WHO presumptive and definitive criteria for recognizing HIV-related growth problems**

<table>
<thead>
<tr>
<th>Clinical Stage and Diagnosis</th>
<th>Presumptive Diagnosis</th>
<th>Definitive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3: unexplained moderate malnutrition</td>
<td>Weight loss: low weight for age, up to –2 standard SDs, not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management.</td>
<td>Documented loss of body weight of –2 SDs, failure to gain weight on standard management and no other cause identified during investigation</td>
</tr>
<tr>
<td>Stage 4: unexplained severe wasting, stunting, or severe malnutrition not adequately responding to standard therapy</td>
<td>Persistent weight loss not explained by poor or inadequate feeding or other infections and not adequately responding in 2 weeks to standard therapy. Characterized by visible severe wasting of muscles, with or without edema of both feet, and/or weight for height of –3 SDs.</td>
<td>Documented weight loss of &gt;–3 SDs with or without edema. SDs, standard deviations</td>
</tr>
</tbody>
</table>

Other HIV-related conditions can profoundly affect nutritional status and should be considered in any child with poor growth. Opportunistic infections should also be considered in the presence of poor growth because they increase the body’s metabolism. Diarrheal illnesses can lead to poor absorption of nutrients. Painful oral or esophageal infections that interfere with eating are also common problems in HIV-infected patients. To ensure adequate intake, give children with poor growth counseling regarding adequate intake of high-energy and nutrient-rich foods. The nutrition chapter gives more information on nutrition in the context of HIV.
Body mass index-for-age percentiles:
Boys, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Stature-for-age percentiles: Boys, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Weight-for-age percentiles: Boys, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-stature percentiles: Girls

Revised and corrected November 21, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Body mass index-for-age percentiles: Girls, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-age percentiles: Girls, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Stature-for-age percentiles: Girls, 2 to 20 years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-length percentiles:
Boys, birth to 36 months

Revised and corrected June 8, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
Growth in HIV-Infected Children

CDC Growth Charts: United States

Head circumference-for-age percentiles:
Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-age percentiles: Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Growth in HIV-Infected Children

CDC Growth Charts: United States

Length-for-age percentiles: Boys, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-age percentiles: Girls, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Length-for-age percentiles: Girls, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
CDC Growth Charts: United States

Weight-for-length percentiles: Girls, birth to 36 months

Revised and corrected June 8, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Growth in HIV-Infected Children

CDC Growth Charts: United States

Head circumference-for-age percentiles:
Girls, birth to 36 months

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
References


Immunizations for Children with HIV/AIDS

Nancy R. Calles, MSN, RN, PNP, ACRN, MPH
Gordon E. Schutze, MD

Objectives
1. Describe the importance of immunizations for children with human immunodeficiency virus (HIV)/AIDs.
2. Discuss the specific types of immunizations that are available for HIV-infected patients.
3. Understand the side effects related to the administration of immunizations to HIV-infected patients.

Key Points
1. Immunizations play an important role in the prevention of childhood diseases.
2. It is recommended that children infected with HIV/AIDS follow an accelerated immunization schedule.
3. The bacille Calmette–Guérin vaccine is the most commonly used vaccine in the world and is the only vaccine available for Mycobacterium tuberculosis but should not be used in HIV-infected children.
4. The World Health Organization recommends the use of the oral polio vaccine in asymptomatic HIV-infected children in areas of the world where the inactivated polio vaccine is not available.
5. The measles and varicella vaccines are administered to HIV-infected children who are not severely immunocompromised.
6. The hepatitis B virus vaccine is recommended for HIV-infected children.
7. The yellow fever vaccine is recommended at 9 months of age and every 10 years thereafter for asymptomatic HIV-infected children living in or traveling to HIV-endemic areas of the world.

Importance of Immunizations for HIV-Infected Children

Immunization is one of the easiest ways to prevent dangerous diseases. Immunizations can also help human immunodeficiency virus (HIV)-infected children, who are more likely to acquire preventable diseases because of a compromised immune system. Appropriate immunizations vary by geographic location. There is limited information regarding routine immunization of HIV-infected children, but with some notable exceptions, immunization is generally safe and beneficial for HIV-infected patients.

Immune Response

Immune responses to vaccination vary, depending on the nature of the vaccine and the individual's immune status. Adult immune systems respond when exposed to a disease-causing antigen because of previous exposure to the antigen, either through vaccination or through acquisition of the infection. An unimmunized child who has never been exposed to the disease-causing antigen is reacting for the first time. The immune system dysfunction that occurs with advanced HIV infections can result in a blunted immune response to immunization, but this response does depend on how affected the immune system is at the time of vaccine receipt. Therefore, it is important to immunize HIV-infected children as quickly as possible so that they can mount protective responses prior to the failing of their immune system. One should consider HIV-infected patients with CD4+ lymphocyte percentages of less than 15% or an absolute CD4+ lymphocyte count that is lower than normal for age, those with a history of an AIDS-defining illness, or those with clinical manifestations of symptomatic HIV to have severe immunosuppression. Patients with CD4+ lymphocyte counts from 15% to 25% or those patients older than 6 years with counts of 200-500 are considered to have limited immune deficits. Patients who have been severely immunosuppressed but have had immune reconstitution with highly active antiretroviral therapy can also usually respond to immunizations. Patients should therefore be categorized based upon the increase in their CD4 count, not the nadir count. The exact time at which the immune-reconstituted
lymphocytes become fully functional is not known; therefore, it is prudent to delay postreconstitution immunizations for at least 3 months to maximize the immune response. Increases in HIV viral loads have been observed after administration with several different vaccines (e.g., influenza), but the clinical significance of these increases is not known and they are usually transient. The possibility of transient increases in viral load is not a contraindication for immunization.

**Immunization Schedule for HIV-Infected Children**

The Expanded Program on Immunizations (EPI) of the World Health Organization (WHO), in collaboration with UNICEF, recommends a narrow and accelerated immunization schedule for HIV-infected children (Table 1). The immunization schedule may vary slightly in each country. The EPI schedule accounts for limited resources, barriers in the health care delivery system, and the urgency to better control morbidity and mortality related to infectious diseases. The WHO has also made recommendations that serve to guide whether particular vaccines should be used in the asymptomatic or symptomatic HIV-infected child (Table 2).

**Specific Immunizations**

**Bacille Calmette-Guérin Vaccine**

Bacille Calmette-Guérin (BCG) is the most widely used vaccine in the world and is the only vaccine available for prevention of *Mycobacterium tuberculosis*. This live vaccine is prepared from attenuated strains of *M. bovis* and is currently used in more than 100 countries. BCG is used to help prevent disseminated and other life-threatening forms of tuberculosis in infants and children. There are various BCG vaccines used throughout the world, and they differ in their composition and efficacy. Recent data have demonstrated, however, that children who are HIV infected when immunized with BCG at birth, and who later progress to AIDS, are at increased risk of developing disseminated BCG disease later in life. In 2007 the WHO recommended that BCG vaccine not be given to any infant or child known to be HIV infected (symptomatic or asymptomatic). In 2007 the WHO recommended that BCG vaccine not be given to any infant or child known to be HIV infected (symptomatic or asymptomatic). Infants born to mothers with an unknown HIV status or those born to mothers who are known to be HIV infected but without signs or symptoms suggestive of HIV can receive the vaccine.

### Table 1. WHO Expanded Programme on Immunization for HIV-Exposed or -Infected Children

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>6 wks</th>
<th>10 wks</th>
<th>14 wks</th>
<th>9 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG†</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPV§</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae, type B</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Yellow fever§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Measles§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

† Not indicated for any infant or child known to be HIV infected.
§ In polio-endemic countries.

### Table 2. Immunizations for HIV-infected patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Asymptomatic HIV infection</th>
<th>Symptomatic HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
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<td>No</td>
</tr>
<tr>
<td>DTP</td>
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<td>Yes</td>
</tr>
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</tr>
<tr>
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<td>Haemophilus influenzae, type B</td>
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<td>Yes</td>
</tr>
<tr>
<td>HPV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza</td>
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</tr>
<tr>
<td>JBE</td>
<td>Yes                         No†</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Yes                         No†</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Yes                         Yes</td>
<td></td>
</tr>
<tr>
<td>Polio vaccine</td>
<td>Yes                         Yes‡</td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Yes                         No†</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Yes                         Yes</td>
<td></td>
</tr>
<tr>
<td>Typhoid</td>
<td>Yes                         Yes‡</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Yes                         No†</td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Yes                         No†</td>
<td></td>
</tr>
</tbody>
</table>

‡ Only the inactivated influenza vaccine that is given intramuscularly should be used.
† HIV-infected patients with CD4+ lymphocyte percentages of less than 15% or an absolute CD4+ lymphocyte count that is lower than normal for age, those with a history of an AIDS-defining illness, or those with clinical manifestations of symptomatic HIV should all be considered to have severe immunosuppression, and vaccine should not be given.

The inactivated polio vaccine that is given intramuscularly should be used.

The inactivated typhoid vaccine that is given intramuscularly should be used.
The recommended dose of BCG vaccine is 0.05 mL (0.05 mg) in children younger than 12 months and 0.1 mL (0.1 mg) in persons older than 12 months. It should be administered via the intradermal route. The best sites for injection are dorsogluteal and the lateral aspect of the upper arm, but in many countries the location is standardized. Attention should be given to how high on the upper arm one should give the injection. The higher the location, the greater the tendency for a scar to form. The best location is in the lower deltoid muscle. A papule with redness appears at the site of injection within 2-3 weeks. This improves slowly and is followed by a local lesion that may ulcerate 6-8 weeks later. This lesion will heal and leave a small flat scar 3-6 months after vaccination. Prolonged local reactions are common after receipt of the vaccine. The reactions usually consist of localized redness and swelling, which can last a few weeks to several months. Poor injection technique, such as giving the injection too deep, can cause the formation of large abscesses. In addition to the development of subcutaneous abscesses, regional lymphadenitis may also develop. Osteitis affecting the long bones underlying the injection site can occur up to several years after BCG immunization.

**Diphtheria–Tetanus–Pertussis Vaccine**

The diphtheria–tetanus–pertussis (DTP) vaccine is not contraindicated for HIV-infected children or their close contacts. Newer preparations of DTP vaccines using acellular pertussis (DTaP) for the primary series and booster doses or those including acellular pertussis for older adolescents and adults (Tdap) are available in many countries. When available, these are the preferred preparations to use. Recent recommendations providing acellular pertussis in the routine use of booster doses of diphtheria–tetanus immunizations (Tdap) to adolescents (>11 years) and adults (<65 years) also apply for symptomatic or asymptomatic HIV infected patients.

The vaccine is administered intramuscularly, usually in the anterolateral aspect of the thigh in infants and younger children and in the deltoid muscle in older children. Mild side effects after receipt of DPT vaccination include low-grade fever, mild irritability, and tenderness at the site of the injection. These side effects are usually due to the pertussis portion of the vaccine. Severe complications that may occur include fever; high-pitched, uncontrollable crying; febrile seizures; and shock. To help minimize postimmunization fever and muscle soreness, one may use acetaminophen (paracetamol) or ibuprofen every 4-6 h for the first 24 h after the vaccine is administered.

Parents should be instructed to return to the clinic if the child has a fever of more than 39.5°C, a seizure, or difficulty breathing or cries inconsolably for more than 3 h at a time.

**Hepatitis A Vaccine**

In the United States the hepatitis A vaccine is recommended for all children at 1 year and is given in a two-dose series, with the second dose being given 6-12 months after the first dose. There are both pediatric and adult formulations of the vaccine, and they differ in the dose of the hepatitis A antigen used. The adult formulations are recommended for persons aged at least 19 years. The vaccines are made from formalin-inactivated hepatitis A virus and are therefore safe for HIV-infected children and adults. As with other vaccines, however, patients with severe immunosuppression may have a suboptimal response. The need for booster doses has not been determined.

The hepatitis A vaccines are given intramuscularly, with the deltoid muscle being the preferred site of administration. The pediatric and adult forms vary based upon the amount antigen in the vaccine as well as the amount injected (e.g., 0.5 mL for pediatric and 1.0 mL for adult forms of the vaccine). The adverse reactions associated with the vaccine are mild and include local pain and induration at the injection site. There is a three-dose combination vaccine against hepatitis A and hepatitis B available for patients aged 18 or more years. Patients who have not had clinical disease or vaccine should receive immunoglobulin (0.02 mL/kg; 5-mL maximum) and hepatitis A vaccine for significant exposures occurring not more than 2 weeks in the past to prevent disease.

**Hepatitis B Vaccine**

Despite a short history of immunizing HIV-infected children with hepatitis B virus (HBV) vaccine, the WHO recommends the immunization for children and adults infected with HIV. To our knowledge, no adverse events associated with hepatitis vaccination of HIV-infected adults and children have been reported. However, in HIV-infected children, the antibody response mounted against HBV does not appear to be long lasting. For infants, two schedules are available. One is recommended in countries where perinatal transmission of HBV is frequent (birth,
6 weeks, 10 weeks, 14 weeks) and a second can be used where perinatal transmission is less frequent (6 weeks, 10 weeks, 14 weeks). For older children and adults, three doses would also be required (0, 1-2 months, 4-6 months).

There are two types of hepatitis vaccine available: plasma-derived vaccine and recombinant vaccine. The two are equal in terms of efficacy and length of immunogenicity. The hepatitis vaccine is available as a single-antigen or a combination-antigen product (e.g., hepatitis B–Haemophilus influenzae, type B; hepatitis A–hepatitis B) and should be administered intramuscularly, avoiding the dorsogluteal muscle because of possible reduced immunological response. Anaphylaxis (severe allergic reaction with symptoms that include swelling of the mouth, difficulty breathing, low blood pressure, and sometimes shock) is a rare but serious side effect of this or any immunization. In general, however, the HBV vaccine is well tolerated, with few reports of adverse events. If adverse events do occur, they are usually mild, consisting of irritability and soreness at the injection site. These symptoms usually appear within 24 h of receiving the vaccine and resolve within 1 or 2 days. For HIV-infected patients many experts suggest postvaccination antibody testing 1-2 months after the last dose is given. For patients who do not produce adequate anti-HBV titers (<10 mIU/mL) after the primary vaccine series, an additional three-dose series should be provided. Patients who remain anti-HBV negative after reimmunization are not likely to respond to additional doses. Unimmunized patients or those without a history of clinical disease should receive both HBV vaccine and hepatitis B immunoglobulin after a high-risk exposure to infected blood or body fluids (e.g., semen).

**Haemophilus influenzae, Type B Vaccine**

*Haemophilus influenzae*, type B (HIB) is a bacterium transmitted from person to person by sneezing and coughing, resulting in colonization of the nose and throat. Children whom this organism merely colonizes will be asymptomatic. In some children, however, the organism will cause significant and life-threatening disease. It can cause pneumonia, epiglottitis, bacteremia, meningitis, or pyogenic arthritis. Several HIB conjugate vaccines are available either as single-antigen products or in combination with other antigens (e.g., HBV–HIB, DTP–HBV–HIB). The immunization schedule for the HIB vaccine is a series of three injections that can be given on the same schedule as the DTP. An additional dose of HIB conjugate vaccine is given in some countries at 12-15 months of age regardless of which regimen was used for the primary series, though there is WHO recommendation for doing so at this time. One dose of the vaccine is sufficient for children aged 12-24 months who are late in receiving their vaccines.

The 0.5-mL dose is given intramuscularly in the outer mid thigh for infants and in the upper arm for older children. Adverse reactions to the vaccine are usually mild and involve simple pain, erythema, or swelling of the injection site. The HIB vaccine can be provided to asymptomatic or symptomatic HIV-infected children. Infants and children who are severely immunocompromised may not respond to the vaccine as well as those children who are immunocompetent.

**Human Papillomavirus Vaccine**

The transmission of genital human papillomavirus (HPV) is a common sexually transmitted infection. Although most of these infections are self-limited, persistent infection with HPV can cause anogenital cancers. Genital HPV types are categorized according to their epidemiologic association with cervical cancer. Infections with low-risk types (e.g., types 6 and 11) can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis. High-risk types (e.g., types 16 and 18) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical cancers; approximately 70% of cervical cancers worldwide are caused by types 16 and 18. The quadrivalent HPV vaccine is a mixture of four HPV type–specific noninfectious viruslike particles prepared from the proteins of HPV types 6, 11, 16, and 18 combined with an aluminum adjuvant. Clinical trials indicate that the vaccine has high efficacy in preventing persistent HPV infection; cervical cancer precursor lesions; vaginal and vulvar cancer precursor lesions; and genital warts caused by HPV types 6, 11, 16, or 18 among females who have not already been infected with the respective HPV type. There are currently no data available on the immunogenicity, safety, and efficacy of the HPV vaccine in HIV-infected persons. But because the HPV vaccine is a noninfectious vaccine, one can administer it to HIV-infected (asymptomatic or symptomatic) women. However, the immune response might be less vigorous in those individuals who are severely immunocompromised.
The HPV vaccine is indicated for girls and women aged 9–26 years and should be administered intramuscularly (deltoid region of the arm or in the higher anterolateral area of the thigh). After the initial 0.5-mL dose, a second dose is required 2 months later and a third dose should be given 6 months after the initial dose. Fainting may occur after any dose of the vaccine, so vaccinees should be observed for approximately 15 min after administration. Other adverse effects include fever; nausea; and pain, swelling, erythema, or pruritus of the injection site.

**Influenza Vaccine**

Influenza can cause severe infections and complications in HIV-infected children. HIV-infected adults with influenza have a longer, more severe disease course and are more likely to suffer from lower levels of oxygen in the blood than healthy adults. In the United States, influenza immunization is indicated for all HIV-infected children aged 6 months or older, as well as their close contacts. There are two types of trivalent vaccines available: an inactivated and a live-attenuated, cold-adapted vaccine. Patients with HIV should not receive the live-attenuated, cold-adapted vaccine, which is given intranasally. The inactivated vaccine should be the only vaccine used for HIV-infected patients. It should be administered in the autumn and repeated annually because of the vaccine’s low immunogenicity and changes in the type of influenza causing infection from year to year. For healthy close contacts of HIV-infected patients, the live-attenuated, cold-adapted vaccine can be used for contacts aged 5-49 years or the inactivated vaccine for those aged at least 6 months.

The influenza vaccine is administered as an intramuscular injection in the anterolateral upper side of the thigh in young children and the deltoid muscle in older children. A child receiving the influenza vaccine for the first time between the ages of 6 months and 8 years should receive a series of two shots separated by 1 month. Children aged 6-35 months should receive 0.25 mL, and those aged 3 years or older should receive 0.5 mL. Most adverse events are minor; they include fever, malaise, and soreness or redness at the injection site.

**Japanese B Encephalitis Vaccine**

Japanese B encephalitis (JBE) is the leading cause of viral encephalitis in Asia. Humans are dead-end hosts and become infected only through the bite of an infected mosquito. Most JBE infections are asymptomatic, but in its severe form patients may develop meningoencephalitis, aseptic meningitis, or a polio-like flaccid paralysis. Most cases occur in children younger than 10 years.

Three types of JBE vaccine are currently available: (1) inactivated mouse brain–derived vaccine, (2) cell culture–derived inactivated vaccine, and (3) cell culture–derived live-attenuated vaccine. There are some countries that include inactivated JBE vaccination in the WHO EPI vaccination schedule for children (e.g., Thailand), and some countries are routinely using the live-attenuated vaccine (e.g., China). HIV-infected patients may receive the inactivated vaccines, but live-attenuated vaccine should not be used in patients who are severely immunocompromised.

The recommended primary series of the inactivated vaccine for patients older than 3 years is three doses (1.0 mL each dose) administered subcutaneously on days 0, 7, and 30. An abbreviated schedule can be used for those who may be traveling (0, 7, 14 days). The dose for children aged 1–3 years is usually 0.5 mL. Few data are available on vaccine safety and efficacy for infants.

Local and mild systemic reactions occur in 15%-25% of vaccine recipients. Fever, headache, and myalgia are the most common complaints. This vaccine, however, also has the unique ability to produce delayed (>72 h after immunization) allergic reactions that can be life threatening. Therefore, patients should not travel internationally for at least 7 days after receipt of the vaccine.

**Measles Vaccine**

In some developing countries, measles continues to cause serious illness and death in children younger than 5 years. HIV-infected children have an increased risk of developing severe complications when infected with measles. A review of reported cases of measles infections in children with HIV indicates a 40% death rate. The WHO recommends that HIV-infected children be offered measles vaccination as soon as possible. Therefore, children who are HIV infected can receive measles vaccine at 6 months of age, followed by a second dose at 9 months of age.
Recommendations in the United States are to immunize asymptomatic HIV-infected children against measles, mumps, and rubella at age 12-15 months and again at 4-6 years. Some experts suggest that the second dose should be given 1 month after the first dose instead of waiting until 4-6 years of age. Any children who are severely immunocompromised should be excluded. Because there are fewer cases of measles in the United States than in the developing world, and the risk of acquiring the disease is lower, making this recommendation practical in this small group of children. In many other parts of the world, however, the accelerated dosage schedule is recommended, because HIV progressively harms the immune system, and antibody responses to the vaccine are less likely to be effective as the disease progresses. Close contacts of children with HIV infection also should be vaccinated at routine intervals unless they are HIV infected and have severe immunosuppression. Measles vaccine is made from a live-attenuated strain and is available as a monovalent formulation (measles alone) or in combinations such as measles–rubella (MR), measles–mumps–rubella (MMR), or measles–mumps–rubella–varicella (MMRV). MMRV should not be administered as a substitute for the component vaccines in children with HIV until more data are available.

Severely immunocompromised and symptomatic patients with HIV should receive intramuscular immunoglobulin (0.5 mL/kg; maximum dose, 15 mL) if exposed to measles, regardless of vaccine status. Previously immunized HIV-infected children and adolescents have developed wild-type measles.

The measles vaccine is administered as a subcutaneous injection in the anterolateral region of the thigh or upper arm. Minor adverse reactions that may occur include fever (>39.4°C in 5%-15% of patients) 1-2 weeks after the injection. The fever generally lasts 1-2 days but may last as long as 5 days. Approximately 5% of vaccine recipients will develop a transient rash that is similar to the rash seen with wild-type measles. Other minor adverse effects include cough, nasal drainage, redness, swelling, and tenderness at the injection site. Serious adverse events include seizures, hypersensitivity reactions, thrombocytopenia, and subacute sclerosing panencephalitis.

Neisseria meningitidis Vaccine

*Neisseria meningitidis* is a gram-negative diplococcus that is responsible for many cases of bacteremia and meningitis among children and adults. At least 13 different serogroups exist, but most disease is caused by five of these serogroups (A, B, C, Y, and W-135). There are currently two types of meningococcal vaccines available: polysaccharide (PS) vaccines and conjugate vaccines. Both will cover either a single or multiple serogroups of *N. meningitidis*. The main PS vaccines currently available cover two (A and C), three (A, C, and W-135), or four (A, C, Y, and W-135) serogroups. The problem with the PS vaccines is that they are not immunogenic in children younger than 2 years, fail to induce immunological memory, and do not provide protection for more than 3-5 years.

Similar to the HIB and pneumococcal vaccines, newer vaccines have incorporated a PS conjugated to a protein carrier (e.g., diphtheria toxoid), resulting in a vaccine that not only is immunogenic in children younger than 2 years but also will induce long term-immunity. Current conjugate vaccines may be against a single serogroup (e.g., C) or multiple serogroups (A, C, Y, and W-135). In contrast to the other serogroups that tend to cause invasive disease, development of a vaccine against serogroup B remains problematic. Despite the type of vaccine or the number of serogroups involved, these vaccines are safe for asymptomatic or symptomatic HIV patients. The type of vaccine used will dictate the age of receipt and the type of vaccine used.

Meningococcal vaccines are given intramuscularly, and the most common adverse effects include localized pain, headache, and fatigue. There has been a temporal association with the quadrivalent conjugate vaccine (A, C, Y, and W-135) and Guillain–Barré syndrome; therefore, this vaccine should be avoided in patients who have a previous history of Guillain–Barré syndrome.

Polio Vaccine

Polio has been eradicated in much of the world. The risk of an adverse event after receipt of oral polio vaccine (OPV) by HIV-infected children is low, but there have been cases of children with primary immunodeficiency syndromes (problems with which they were born such as the B-cell disorder or X-linked agammaglobulinemia) who developed vaccine-associated paralytic polio after receiving OPV. Inactivated polio vaccine (IPV) is
considered the safer choice and is used for HIV-infected children and household contacts in countries where it is available. The U.S. Centers for Disease Control and Prevention endorses the use of IPV for all children. Because of the ease of administration, the ability to provide herd immunity, and few reported adverse events, the WHO continues to recommend the use of OPV in infants and children with an unknown HIV status or for those HIV-infected children who are asymptomatic in resource-limited areas. Symptomatic HIV-infected children can receive the IPV.

OPV is administered by mouth. IPV is administered via subcutaneous injection in the upper arm or thigh. There are no immediate side effects secondary to OPV administration. Vaccine-associated paralytic polio usually occurs within 2 months after immunization, but the risk is low, estimated at 1:7.8 million doses. Few adverse events secondary to receiving IPV have been reported.

Rotavirus Vaccine
Rotaviruses are the leading cause of severe diarrheal disease and dehydration in infants and young children in both developed and developing countries. Virtually all children are infected by the time they reach 2-3 years of age. Most symptomatic episodes occur between 3 months and 2 years of age, with a peak incidence between 7 and 15 months. Infants and young children are most at risk for the development of life-threatening dehydration from this infection.

The current licensed pentavalent rotavirus vaccine is an oral vaccine that contains five active reassortant rotaviruses. The rotavirus parent strains were isolated from human and bovine strains. Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected HIV infection. No safety or efficacy data are available for the administration of rotavirus vaccine to infants who are HIV infected.

Three doses of the pentavalent rotavirus vaccine are administered orally at 2, 4, and 6 months of age. The first dose should be administered between 6 and 12 weeks of age; immunization should not be initiated for infants older than 12 weeks. Rotavirus vaccine can be given simultaneously with other childhood immunizations (e.g., DTP, HIB). If immunization with rotavirus vaccine is being considered for an HIV-infected infant, severe immunosuppression should be considered a contraindication to vaccine receipt. Rotavirus vaccine can be used for siblings living in the home of an HIV-infected patient. Fever and abdominal complaints are the most commonly reported adverse effects of the vaccine. Previous rotavirus vaccines were temporally associated with intussception, but this outcome has not been demonstrated with the current pentavalent vaccine.

Streptococcus pneumoniae Vaccine
Pneumococcus is the most common cause of bacterial invasive infections in children with HIV, causing frequent episodes of otitis media, sinusitis, and pneumonia. The pneumococcal conjugate vaccine (PCV7) and the pneumococcal polysaccharide vaccine (PPV23) are well tolerated in children with HIV. In the United States, PCV7 is recommended at 2, 4, 6, and 12-15 months of age, followed by PPV23 at 24 months of age and again 3-5 years later. If not previously vaccinated, patients aged at least 7 years should receive PPV23 with a single revaccination after 3-5 years. As the next generation of conjugate pneumococcal vaccines becomes available, countries that currently use PCV7 should assess the value of changing to the newer formulations to protect children against more invasive pneumococcal serotypes.

PCV7 is administered as a 0.5-mL dose by an intramuscular injection in the upper anterior thigh or upper arm. It may be given simultaneously with other age-appropriate childhood immunizations. PPV23 is given as a 0.5-mL dose either subcutaneously or intramuscularly in the deltoid muscle region or the lateral mid thigh with appropriate precautions to avoid intramuscular administration. About half of the people who receive the vaccine develop mild adverse events, such as tenderness and redness at the injection site. Only about 1% of pneumococcal vaccine recipients develop fever, muscle pain, or severe local reactions.

Typhoid Vaccine
Typhoid fever is a febrile illness that can include bacteremia and death. It is encountered most often in resource-limited areas because infection occurs as a result either of fecal–oral contamination from an infected person or by contact with an item (e.g., food) contaminated by a carrier. Typhoid vaccines are not routinely provided to patients but may be used as part of an outbreak control or before travel.
There are currently two types of vaccines available: the live oral vaccine (LOV) and the polysaccharide vaccine (PSV). The LOV can be used in patients older than 6 years but should not be used for immunosuppressed HIV patients. The PSV is indicated for patients aged 2 or more years and is the vaccine of choice for immunocompromised HIV patients.

The LOV is given in four doses (one capsule every 2 days for a total of four capsules), whereas the PSV (0.5 mL) is intramuscular. Booster doses of the LOV in circumstances of continued or repeated exposure are every 5 years, whereas booster doses should be given every 2 years for the PSV. There are no data available for the efficacy of any typhoid vaccine in children younger than 2 years. The LOV requires replication in the gastrointestinal tract for effectiveness, so it should not be administered during gastrointestinal tract illness. Also, concomitant use with some antimalarial medications (e.g., atovaquone/proguanil) resulted in a poor immune response. Antimicrobial agents should also be avoided for at least 24 h prior to the first dose of vaccine and not until 7 days after the fourth dose.

**Varicella (Chickenpox) Vaccine**

In HIV-infected patients, chickenpox, or varicella-zoster virus, can cause serious complications, including pneumonia and encephalitis. The varicella live-attenuated vaccine can be administered to HIV-infected children without a history of clinical disease who are asymptomatic or mildly symptomatic and have age-specific CD4+ lymphocyte percentages greater than 15%. Patients who are severely immunosuppressed should not receive the vaccine. Siblings of HIV-infected children should also be immunized with varicella vaccine. Combination vaccines such as the MMRV vaccine should not be used in HIV-infected patients.

The varicella vaccine is administered subcutaneously in the anterolateral region of the thigh or upper arm. HIV-infected patients who are eligible for the vaccine should receive two doses 3 months apart as soon as possible after their first birthday. HIV-infected adults without evidence of immunity or a history of clinical disease who are asymptomatic or mildly symptomatic and have age-specific CD4+ lymphocyte percentages greater than 15%. Patients who are severely immunosuppressed should not receive the vaccine. Siblings of HIV-infected children should also be immunized with varicella vaccine. Combination vaccines such as the MMRV vaccine should not be used in HIV-infected patients.

HIV-infected patients who have neither received the vaccine nor have had clinical disease and who are exposed to chickenpox (varicella) should receive varicella-zoster immunoglobulin (VariZIG) within the first 96 h after exposure. If VariZIG is not available, intravenous immunoglobulin (IVIG) can be used. Acyclovir is beneficial in the treatment of varicella infection, and some experts recommend using acyclovir for a susceptible immunocompromised patient who has been exposed to varicella-zoster virus.

**Yellow Fever Vaccine**

Besides mosquito control, the yellow fever vaccine is the only measure available to prevent yellow fever. Immunity occurs within 1 week in 95% of people vaccinated, and immunity lasts for at least 10 years. The EPI of the WHO recommends immunization at 9 months or older for asymptomatic HIV-infected children who are living in or visiting disease-endemic areas. A booster vaccine should be administered every 10 years thereafter. Patients with symptomatic HIV infection or those with severe immune suppression should generally not receive the vaccine. Where the risk of disease is very high, medical practitioners may consider the risk to the patient from the vaccine to be less than that from acquiring the disease and elect to give the vaccine.

The vaccine is a live-attenuated vaccine that should be administered subcutaneously in a single dose of 0.5 mL for those living or traveling to areas with endemic yellow fever. It is required every 10 years by international regulations for travel to and from certain countries. Consideration for using the vaccine in an outbreak setting in patients aged 4-9 months must be weighed against the potential for life-threatening side effects. Infants younger than 4 months should not be immunized because of an increased risk of vaccine-associated encephalitis. Yellow fever vaccine–associated viscerotropic disease and yellow fever vaccine–associated neurotropic disease can occur
but are rare. Family members of immunocompromised patients can receive the vaccine.

**Intravenous Immunoglobulin**

IVIG has been used in the past as protection against bacterial infections, especially pneumococcal infections, for children infected with HIV. It is now no longer indicated. HIV-infected children receiving *Pneumocystis jirovecii* (formerly PCP [*Pneumocystis carinii]*) pneumonia prophylaxis with trimethoprim–sulfamethoxazole do not derive additional benefit from IVIG. Hyperimmune globulins are available that may be used for specific indications. The use of hyperimmune globulins is recommended for children who have been exposed to particular antigens to prevent an infection or shorten the course of the disease. For example, VariZIG is recommended for children who have been exposed to varicella-zoster virus. Other hyperimmune products include hepatitis B immunoglobulin, rabies immunoglobulin, tetanus immunoglobulin, cytomegalovirus intravenous immunoglobulin, and respiratory syncytial virus intravenous immunoglobulin.

**REFERENCES**


Nutrition and HIV/AIDS

Anthony J. Garcia-Prats, MD
Ann R. McMeans, MS, RD, LD
George D. Ferry, MD
William J. Klish, MD

Objectives
1. Describe the complex interactions between nutrition and human immunodeficiency virus (HIV)/AIDS.
2. Describe the risk factors that contribute to malnutrition in HIV/AIDS.
3. Explain how to conduct a nutritional assessment of children and adults.
4. Explain how to determine nutrient needs of children and adults.
5. Describe how to classify malnutrition.
6. Describe nutrition intervention strategies for adults and children with HIV/AIDS.

Key Points
1. HIV infection can often result in nutritional deficiencies and growth failure.
2. Malnutrition associated with HIV/AIDS can severely affect an already compromised immune system, leading to increases in rates of opportunistic infections and a decreased survival rate.
3. A nutritional assessment is an indispensable component of the comprehensive management of HIV-infected individuals.
4. One must monitor and maintain adequate nutritional status in HIV-infected children and adults.
5. The management of moderately and severely malnourished HIV-infected individuals includes both aggressive nutritional support according to well-accepted protocols and antiretroviral medications.
6. Routine vitamin A supplementation and distribution of antihelminth medications are important contributions to good nutrition in many settings.

Overview
Severe weight loss and wasting were some of the earliest recognized signs of human immunodeficiency virus (HIV) infection, and in many African countries HIV was called “slim disease” because of the prominence of this feature. Wasting and weight loss are common features of HIV infection, especially in resource-limited settings, with some studies showing 40%-44% of adults and 59% of children having wasting and malnutrition as a part of their disease manifestations. There is a complex relationship between nutrition and HIV infection. Malnutrition, even without HIV, can compromise the immune system, and CD4 T cells can be decreased in malnourished, HIV-negative individuals. Nutritional status may indicate disease severity and may help indicate response to antiretroviral therapy (ART). Both macronutrient and micronutrient deficiencies are important in HIV-infected patients. For all these reasons, an assessment of nutritional status should be a routine part of the care of every HIV-infected patient. Prevention and management of nutritional deficiencies and malnutrition are crucial parts of the comprehensive management of HIV-infected children and adults. Metabolic abnormalities, usually related to ART, are common but will not be discussed in this chapter (see the chapter on metabolic abnormalities).

Reasons for Malnutrition/Growth Problems in HIV-Infected Individuals
HIV contributes to malnutrition in many different ways and can directly or indirectly result in decreased caloric intake, increased loss of nutrients, and increased use of nutrients/energy. Factors thought to contribute to wasting and malnutrition in people with HIV/AIDS include metabolic alterations, infection, fever, gastrointestinal (GI) changes and illnesses, developmental/neurological problems, and economic and psychosocial issues. HIV also seems to affect lean body or muscle mass more aggressively than other infections, resulting in a disproportionate loss of muscle compared with fat during the development of malnutrition.
Any infection, and HIV infection in particular, alters the metabolism of energy, carbohydrates, fats, proteins, vitamins, and minerals, increasing the body’s need for these nutrients. Fever may increase protein utilization and increases calorie needs by 12% for each degree Celsius above normal and 7% for each degree Fahrenheit above normal. Though there is some controversy, it is thought that HIV infection may increase resting energy expenditure (the amount of energy that the body uses to run basic cell and tissue functions at rest), which could lead to wasting. An increased production of cytokines in HIV infection may also contribute to wasting in HIV infection.

The interaction of HIV with the GI tract (see chapter on GI manifestations of HIV) can profoundly affect nutritional status. Diarrhea increases caloric needs by 25% and often leads to a decreased oral intake. Malabsorption, the inability of the body to absorb nutrients from the GI tract, may be associated with diarrhea or occur without diarrhea because of metabolic changes associated with HIV. It can lead to vitamin, mineral, protein, fat, and carbohydrate losses as well as a decrease in oral intake. Dehydration from diarrhea may result in an acute loss of weight from water loss and can be a life-threatening complication of diarrhea (see the chapter on GI manifestations of HIV infection for recommendations on treating dehydration). Severe oral candidiasis (yeast), esophageal candidiasis, herpes gingivostomatitis, viral esophagitis, and gastritis can make eating difficult and painful, leading to decreased oral intake or feeding refusal (see chapter on opportunistic infections for recommendations on treating these infections). Nausea and vomiting caused by drugs, infection, and/or illness can result in poor oral intake, dehydration, and loss of nutrients.

Children and adults with HIV/AIDS can develop feeding problems, often due to neurological deterioration related to HIV infection, leading to inadequate intake of nutrients. Infants with HIV can have a weak suck, resulting in inadequate intake of breast milk or formula. Older children may develop poor chewing and feeding skills. Difficulty swallowing can lead to poor oral intake or refusal to eat. There is a risk of aspiration and pneumonia with swallowing problems.

Economic issues leading to inadequate nutrient intake are a frequent contributor to malnutrition in many settings. These issues include a limited food supply, loss of household income or livelihood (such as farming) due to illness, and limited cooking and storage facilities. HIV-infected adults may be too ill or uninterested to care for themselves and their children. Depression in an adult or child can also lead to decreased appetite and poor nutrient intake.

**Importance of Malnutrition and Wasting in HIV/AIDS**

The interaction between malnutrition and HIV is complex. Recognizing malnutrition is important because it may predict disease progression and higher risk of morbidity and mortality. The presence of malnutrition is a predictor of worse outcomes in both HIV-infected adults and children. In HIV-infected children, measurements such as height growth velocity and low weight for age predict survival and disease progression. Malnutrition may be a secondary result of advanced HIV disease. Primary malnutrition may also
accelerate HIV disease progression. Malnutrition independent of HIV infection has a high morbidity and mortality, and this effect may be exaggerated in HIV-positive individuals.

Recognizing malnutrition is also important so that specific treatments directed at improving nutritional status can be used. Control of HIV infection using antiretroviral (ARV) medications and interventions directed at nutritional deficiencies, such as nutritional supplements, are often both necessary to adequately care for infected individuals. Use of ARVs without nutritional support, or nutritional support without ARVs, will often result in poor treatment responses and outcomes. With ARV medications and improvement in CD4 count and viral load, weight and some lean body mass can be restored. However, some patients see little to no improvement in lean body mass, so one must try to maintain good nutritional status in HIV-positive patients from the time of diagnosis.

**Nutrition Assessment**

A nutrition assessment is a critical part of evaluating every HIV-infected patient and has three major components:

1. A history and physical examination, including a diet and feeding history, to identify the causes that may be contributing to a patient’s current wasting or malnutrition, or risk factors for the development of nutritional problems in the future
2. Assessing objective measures of growth (height, weight, mid-upper arm circumference [MUAC], head circumference, weight gain, and linear growth) and comparing them to expected norms
3. A laboratory assessment when available and appropriate

**History, Physical Examination, Diet/Feeding History**
The history and physical examination in a nutrition assessment should focus on identifying symptoms and signs of malnutrition as well as any specific causes that are currently contributing or might contribute to malnutrition. The previous section discusses some of the more common factors contributing to malnutrition in HIV-infected patients. The physical exam should assess for pitting edema because this may be a sign of severe malnutrition, often without low weight or visible wasting. Signs of common micronutrient deficiencies are shown in Table 1.

<table>
<thead>
<tr>
<th>Vitamin or mineral</th>
<th>Clinical signs</th>
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<tbody>
<tr>
<td>B12</td>
<td>Macrocytic (larger than normal red blood cells) anemia, neurologic disturbances, altered mental status</td>
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<tr>
<td>C</td>
<td>Bleeding gums, petechial hemorrhages (small, purplish spots on the skin)</td>
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<td>A</td>
<td>Night blindness, xerophthalmia (dryness of the eyes), loss of appetite</td>
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<tr>
<td>B6, niacin, riboflavin</td>
<td>Cheilosis (fissures, redness, sores around lips)</td>
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<tr>
<td>Iron</td>
<td>Thin, brittle, concave fingernails, microcytic anemia</td>
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<tr>
<td>Zinc</td>
<td>Growth retardation, dermatitis (inflammation of the skin evidenced by itching, redness, and lesions), diarrhea, hair loss</td>
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<tr>
<td>Selenium</td>
<td>Cardiomyopathy (abnormalities of the heart muscles)</td>
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Dietary intake and feeding history are important aspects of a nutrition assessment. The adequacy of nutrient intake can be assessed based on a 24-h patient diet recall (a list of what the patient normally eats and/or ate in the past 24 h) or a 3-day food intake record (kept in writing by the patient or a caretaker). One must interview the patient/caretaker to find out the types and estimated amounts of foods, formula, fluids, and breast milk consumed. For those giving infant formula, determine how they are mixing the formula: over- and underdilution are common and potentially serious problems. Other important information includes how long it takes the patient to eat; the patient’s appetite; any chewing, sucking, or swallowing problems; presence of nausea, vomiting, diarrhea, and abdominal pain; and any feeding refusal, food intolerance, allergies, and fatigue. If the patient is a child, know who provides the food for the child, who feeds the child, and whether there is an adequate supply of food daily or intermittently.

**Objective Measures of Growth**
Weight, length or height, head circumference/frontal-occipital circumference (FOC), and MUAC are important objective measures of nutritional status. Body weight is one of the most fundamental ways to assess nutritional status in infants and children, especially when evaluated over time, and weight alone is adequate to assess growth when no other measurements are available. Dehydration
can affect weight, so determining whether the patient is dehydrated is important. Recent acute weight loss could indicate infection and/or changes in intake. Weight loss of more than 2% in one week, 5% in one month, 7.5% in 3 months, and 10% in 6 months are considered significant. One must take the time and effort to measure these values accurately (see chapter on growth). For children, rate of weight gain and linear growth are also important components of a nutrition assessment, and one should plot weights, heights, and FOCs on appropriate growth charts (see chapter on growth).

The MUAC is another objective measure of nutritional status that is becoming more widely used, especially in resource-limited settings. It is a simple, cheap, and less error prone method by which to assess for wasting, and MUAC might be a better indicator of mortality risk associated with malnutrition than weight for height (discussed in the following section). Many malnutrition programs in developing countries have moved toward using MUAC as the preferred measure for identifying/screening for acutely malnourished children, and health practitioners need to be familiar with its use. Because muscle mass is more affected in HIV than in primary malnutrition, for which MUAC norms were developed, there is a tendency to overestimate the degree of malnutrition with this technique. This is probably an advantage during the acute management of wasting in these children but may result in the maintenance of therapies longer than necessary. By convention the MUAC is usually taken on the left arm. With the patient’s arm bent at 90° at the elbow, use the MUAC band (a simple tape measure can be used) to measure the length of the upper arm, from shoulder bone to elbow, and mark the midpoint with a pen. Then, with the arm straightened, wrap the MUAC band around the child’s arm at the midpoint, such that all of it is in contact with the child’s skin. It should be neither too tight nor too loose. Read the MUAC, in millimeters or centimeters, to the nearest millimeter.

Other, more specialized, objective measures of determining body composition, such as the triceps skin fold, can be useful in a nutritional assessment but are outside the scope of this chapter. However, pinching the skin as part of the physical exam is an easy way to estimate the amount of subcutaneous fat and can help in determining the degree of acute malnutrition.

**Laboratory Assessment**

The laboratory component of a nutrition assessment in both children and adults when available should include evaluation of the complete/full blood count, total protein, albumin (dehydration can lead to falsely elevated serum levels), and prealbumin (which has a half-life of several days versus about 2 weeks for albumin). Albumin and prealbumin assess visceral protein status (muscle mass), with prealbumin, because of its shorter half-life, reflecting more recent protein intake.

**Classification of Malnutrition**

After having done an in-depth nutritional assessment, one must know how to interpret the results. To assess growth, the health care provider should plot the patient’s weight, height/length, and FOC on a growth chart. Any prior weights and lengths that are available, including birth weight, are helpful to plot trends in the patient’s growth (see the growth chapter).

Professionals often use $z$ scores to define the presence and severity of malnutrition. The $z$ score is the measure of distance in standard deviations that a value is from the mean. Tables of $z$ scores facilitate identification of malnutrition. In most resource-limited settings, the World Health Organization (WHO)-published $z$ scores are the most widely used standards for determining levels of childhood malnutrition. For completeness, this chapter also includes other well-accepted methods of defining malnutrition. The Waterlow criteria use the percentage of expected length/height for age and the percentage of expected weight for height to define malnutrition. Using standard growth charts, one can calculate the percentage of expected height for age and weight for length/height.

**Chronic Malnutrition**

Chronic malnutrition is indicated by the presence of stunting—when a child’s length/height is much lower than that of other children of the same age. Though used as a measure of chronic malnutrition, stunting has other causes, including chronic disease, genetic abnormalities, and endocrine disorders. Stunting may also be constitutional (short parents). The length/height-for-age $z$ score is one way to determine the presence and severity of stunting. Stunting is considered to be moderate when the length/height-for-age $z$ score is between –2 and –3, and severe when the $z$ score is less than –3. Stunting may also be determined by a patient’s percentage of expected height for age (Table 2).
Acute Malnutrition

Acute malnutrition is indicated by the presence of nutritional edema and/or wasting. Wasting is almost always the result of nutritional deprivation. The only exception is in primary muscle wasting diseases such as AIDS, in which case one must use clinical judgment. Determining whether wasting is related to nutritional deprivation or HIV/AIDS can be difficult, and managing both aggressively usually makes sense—with nutrition support as well as treatment directed at the patient’s HIV infection.

Edema is quantified as grade 1+ (mild, both feet/ankles), grade 2++ (moderate, feet plus lower legs, hands, or arms), or grade 3+++ (severe, generalized, including feet, legs, hands, arms, and face). The presence of nutritional edema of any grade indicates severe acute malnutrition. One can define the presence and severity of wasting by the weight-for-height z score. Wasting is considered to be mild when the weight-for-height z score is between –1 and –2, moderate when it is between –2 and –3, and severe when it is less than –3 (Table 3). One may also use MUAC to determine wasting. MUAC z scores are available by age for both males and females, but for simplicity many malnutrition programs consider a MUAC of less than 110 mm to be severe wasting and 110-125 mm to be moderate wasting for children aged 6-59 months.

The Waterlow criteria use percentage of expected weight for height to define wasting (Table 2). If one uses the percentage of the median weight for height, less than 70% would be considered severe wasting and 70%-80%, moderate wasting. One may use the Gomez criteria when a height measurement is unavailable, though they might be less accurate because they do not account for length/height (Table 2). One can also use the body mass index (BMI) to classify malnutrition, and doing so might be useful in adolescents and adults. BMI curves and z scores for age are available. For an adult, malnutrition can be defined as involuntary weight loss greater than 10% or weight less than 90% of ideal weight. To assess the nutritional status of an adult, a formula for estimating ideal body weight is available in Table 2.

Wasting Syndrome

Wasting syndrome is an AIDS-defining condition and is a WHO Clinical Stage 4 diagnosis for both adults and children. In adults, the WHO defines HIV wasting syndrome as unexplained involuntary weight loss (>10% of baseline body weight), with obvious wasting or BMI less than 18.5, plus

* unexplained chronic diarrhea (loose or watery stools more than three times daily) reported for more than 1 month or
* reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarial agents.

For children, WHO defines wasting as follows:

* persistent weight loss not explained by poor or inadequate feeding or other infections; and/or
* visible wasting of muscles, with or without edema of both feet; and/or

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<th>Table 2. Waterlow and Gomez criteria</th>
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<td><strong>Waterlow criteria—chronic malnutrition</strong></td>
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<tr>
<td>Stunting: Expected ht (cm) for age at 50%ile × 100</td>
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<td>Stage 0 (normal) &gt;95%</td>
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<td>Stage I (mild) 90%–95%</td>
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<td>Stage II (moderate) 85%–90%</td>
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<td>Stage III (severe) &lt;85%</td>
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<td><strong>Waterlow criteria—acute malnutrition</strong></td>
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<tr>
<td>Wasting or acute malnutrition: Expected wt (kg) at patient’s ht center × 100</td>
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<td>Stage 0 (normal) &gt;90%</td>
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<td>Stage I (mild) 80%–90%</td>
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<td>Stage II (moderate) 70%–80%</td>
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<td>Stage III (severe) &lt;70%</td>
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<td><strong>Gomez criteria—acute malnutrition</strong></td>
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<td>% of ideal body wt: Expected wt for age (kg) at 50%ile × 100</td>
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<td>1st degree (mild) 75%–85%</td>
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<td>2nd degree (moderate) 64%–74%</td>
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<td>3rd degree (severe) &lt;64%</td>
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<td><strong>Estimating ideal body wt for adults</strong></td>
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<tr>
<td>Male: 48 kg + 1.07 kg/cm if ht is over 152 cm</td>
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<td>Female: 45.5 kg + 0.9 kg/cm if ht is over 152 cm</td>
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**Nutrition and HIV/AIDS**

Table 3. WHO/NCHS normalized reference values for weight-for-length and weight-for-height

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<th>Boy's Weight (kg)</th>
<th>Length* (cm)</th>
<th>Girl's Weight (kg)</th>
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SD: standard deviation score (or Z-score). Although the interpretation of a fixed percent-of-median value varies across age and height and generally the two scales cannot be compared, the approximate percent-of-median values for -1 and -2 SD are 90% and 80% of median, respectively (Gorstein et al. Issues in the assessment of nutritional status using anthropometry. *Bulletin of the World Health Organization*, 1994, 72:273-283).

*Length is measured for children below 85 cm. For children 85 cm or more, height is measured. Recumbent length is on average 0.5 cm greater than standing height; although the difference is of no importance to individual children, a correction may be made by subtracting 0.5 cm from all lengths above 84.9 cm if standing height cannot be measured.*
**Table 3. WHO/NCHS normalized reference values for weight-for-length and weight-for-height (continued)**

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- weight for height of −3 standard deviations from the mean, as defined by the WHO Integrated Management of Childhood Illness guidelines; and
- not adequately responding in 2 weeks to standard therapy.

Wasting causes loss of lean body mass. Wasting has declined in many countries since the introduction of ART but is still a frequent complication of HIV, especially in resource-limited and food-insecure environments.

**Nutrition Interventions**

The level of nutritional support for HIV-infected patients should be guided by their current nutritional status as well as by the presence of risk factors for malnutrition. Causes of malnutrition and risk factors for the development of worsening nutritional status should be comprehensively addressed. Preventing malnutrition through education and increased caloric intake is the goal.
for patients with no malnutrition. Patients with moderate or severe acute malnutrition need aggressive inpatient or outpatient management depending on available resources and country-specific guidelines. Although other interventions to address muscle wasting/malnutrition in HIV-infected patients exist, such as administration of testosterone, growth hormone, or anabolic steroids, these are not widely available in most settings.

**Address Causes of an Individual’s Malnutrition**

To treat nausea and vomiting, recommend small frequent meals; cold foods and beverages; low-fat foods; and bland, nonspicy foods. See the chapter on GI manifestations for an in-depth approach to managing diarrhea. For oral lesions and esophageal pain, recommend smooth-textured, nonspicy foods; cold foods; drinking through a straw to bypass sores; and mild sauces and gravies on foods to make swallowing easier. Treat the underlying cause of the oral or esophageal lesions/pain if possible. When a patient has developmental delay or neurological deterioration, conduct a feeding and swallowing evaluation if possible. If the patient has problems chewing or swallowing, it may help to purée the food. Enteral (tube) feedings may be the best option if a patient cannot eat.

**Foodborne illness** can cause serious problems for HIV-infected patients, and patients and caregivers should be educated on simple techniques to avoid these. Teach patients and caretakers to wash their hands before and during food preparation, especially if handling raw meat; to wash fresh produce with clean water; to cook foods thoroughly; to avoid raw meat, fish, and eggs; to avoid unpasteurized dairy products and soft cheeses; to boil bottles and nipples if used (cups should be used, even

---

**Table 4. Equations to estimate energy requirements based on 2006 dietary reference intakes**

<table>
<thead>
<tr>
<th>Infants and young children</th>
<th>Estimated energy requirement (kcal/day) = total energy expenditure + energy deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 mo</td>
<td>EER = (89 × weight (kg) – 100) + 175</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>EER = (89 × weight (kg) – 100) + 56</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>EER = (89 × weight (kg) – 100) + 22</td>
</tr>
<tr>
<td>13-35 mo</td>
<td>EER = (89 × weight (kg) – 100) + 20</td>
</tr>
</tbody>
</table>

| Children and adolescents 3–18 yrs | Boys | 3-8 yrs | EER = 88.5 – (61.9 × age [yr]) + PA × [(26.7 × weight [kg]) + (903 × height [m])] + 20 |
|                                   |      | 9-18 yrs | EER = 88.5 – (61.9 × age [yr]) + PA × [(26.7 × weight [kg]) + (903 × height [m])] + 25 |

| Girls | 3-8 yrs | EER = 135.3 – (30.8 × age [yr]) + PA × [(10.0 × weight [kg]) + (934 × height [m])] + 20 |
|       | 9-18 yrs | EER = 135.3 – (30.8 × age [yr]) + PA × [(10.0 × weight [kg]) + (934 × height [m])] + 25 |

| Adults 19 yrs and older | Men | EER = 662 – (9.53 × age [yr]) + PA × [(15.91 × weight [kg]) + (539.6 × height [m])] |
|                        | Women | EER = 354 – (6.91 × age [yr]) + PA × [(9.36 × weight [kg]) + (726 × height [m])] |

| Pregnancy | Estimated energy requirement (kcal/day) = nonpregnant EER + pregnancy energy deposition |
|           | 1st Trimester | EER = Nonpregnant EER + 0 |
|           | 2nd Trimester | EER = Nonpregnant EER + 340 |
|           | 3rd Trimester | EER = Nonpregnant EER + 452 |

| Lactation | Estimated energy requirement (kcal/day) = nonpregnant EER + milk energy output – weight loss |
|           | 0-6 mo postpartum | EER = Nonpregnant EER + 500 – 170 |
|           | 7-12 mo postpartum | EER = Nonpregnant EER + 400 – 0 |

These equations provide an estimate of energy requirement. Relative body weight (i.e., loss, stable, gain) is the preferred indicator of energy adequacy.

*aEstimated energy requirement.

bPhysical activity coefficient (see Table 5).

### Table 5. Physical activity (PA) coefficients for use in EER<sup>a</sup> equations

<table>
<thead>
<tr>
<th>Sex and age group</th>
<th>Sedentary (PAL&lt;sup&gt;b&lt;/sup&gt; 1.0–1.39)</th>
<th>Low Active (PAL 1.4–1.59)</th>
<th>Active (PAL 1.6–1.89)</th>
<th>Very Active (PAL 1.9–2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical daily living activities (e.g., household tasks, walking to the bus)</td>
<td>Typical daily living activities plus 30-60 min of daily moderate activity (e.g., walking at 5-7 km/h)</td>
<td>Typical daily living activities plus at least 60 min of daily moderate activity</td>
<td>Typical daily living activities plus at least 60 min of daily moderate activity plus an additional 60 min of vigorous activity or 120 min of moderate activity</td>
</tr>
<tr>
<td>Boys 3–18 yrs</td>
<td>1.00</td>
<td>1.13</td>
<td>1.26</td>
<td>1.42</td>
</tr>
<tr>
<td>Girls 3–18 yrs</td>
<td>1.00</td>
<td>1.16</td>
<td>1.31</td>
<td>1.56</td>
</tr>
<tr>
<td>Men 19+ yrs</td>
<td>1.00</td>
<td>1.11</td>
<td>1.25</td>
<td>1.48</td>
</tr>
<tr>
<td>Women 19+ yrs</td>
<td>1.00</td>
<td>1.12</td>
<td>1.27</td>
<td>1.45</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated energy requirement.  
<sup>b</sup> Physical activity level.  

### Table 6. Dietary reference intakes for total protein by life stage group (g/kg/day)

<table>
<thead>
<tr>
<th>Life stage group</th>
<th>EAR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RDA&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AI&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>0-6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-12 mo</td>
<td>1.0</td>
<td>1.0</td>
<td>1.2 (11)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>0.87</td>
<td>0.87</td>
<td>1.05 (13)</td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>0.76</td>
<td>0.76</td>
<td>0.95 (19)</td>
</tr>
<tr>
<td>9-13 yrs</td>
<td>0.76</td>
<td>0.76</td>
<td>0.95 (34)</td>
</tr>
<tr>
<td>14-18 yrs</td>
<td>0.73</td>
<td>0.71</td>
<td>0.85 (52)</td>
</tr>
<tr>
<td>19-30 yrs</td>
<td>0.66</td>
<td>0.66</td>
<td>0.80 (56)</td>
</tr>
<tr>
<td>31-50 yrs</td>
<td>0.66</td>
<td>0.66</td>
<td>0.80 (56)</td>
</tr>
<tr>
<td>51-70 yrs</td>
<td>0.66</td>
<td>0.66</td>
<td>0.80 (56)</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>0.66</td>
<td>0.66</td>
<td>0.80 (56)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.88&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>1.1 (71)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lactation</td>
<td>1.05</td>
<td></td>
<td>1.3 (71)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated average requirement. An EAR is the average daily nutrient intake level estimated to meet the requirements of half the healthy individuals in a group.  
<sup>b</sup> Recommended dietary allowance. An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals in a group.  
<sup>c</sup> Adequate intake. If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, the AI is the mean intake.  
<sup>d</sup> Values in parentheses are examples of the total grams/day of protein calculated from grams/kilograms/day of reference weights.  
<sup>e</sup> EAR and RDA for pregnancy are only for second half of pregnancy. For first half of pregnancy protein requirements are the same as those of nonpregnant women.  
Nutrition and HIV/AIDS

for very small infants, rather than bottles); and to store foods at proper temperatures.

Preventing Malnutrition by Increasing Calories/Improving Diet

A healthful diet for everyone should include adequate amounts of essential macronutrients (protein, carbohydrates, and fat) and micronutrients (vitamins and minerals). To appropriately advise patients on increasing their caloric intake, knowing what their energy needs are is helpful. Equations to estimate energy requirements, along with adjustments for level of physical activity, are available in the Tables 4 and 5. These are starting points and need to be adjusted for fever, sepsis, lack of weight gain/growth, or continued weight loss. HIV/AIDS can also increase losses of protein. To help estimate protein requirements, Table 6 gives the dietary reference intakes for total protein intake, including estimated average requirements and recommended dietary allowance (RDA). For children with HIV/AIDS, protein may need to be increased to twice the RDA for protein but should not exceed 4 g/kg of body weight/day to prevent azotemia (too much urea in the blood). Adults with HIV should start with 2-2.5 g/kg/day of protein.

Because of time constraints, calculating the individual nutrient needs of each patient may not always be possible. The WHO recommends increasing the daily caloric intake of asymptomatic HIV-infected infants and children by 10% from the RDA for age and by 20%-30% if they are symptomatic or recovering from acute infections. This is a reasonable estimate, though some patients will have higher caloric needs.

If an illness is causing increased energy and/or protein needs, one must treat the underlying illness. One must also provide a high-calorie, high-protein diet and to teach the family how to increase nutritious foods in the diet that are high in vitamins and minerals. Foods high in calories help to maintain body weight and promote weight gain. Starchy foods make up a large part of the diet and are a good, inexpensive source of calories. These foods include bread, pap, porridge, mealies, sorghum, rice, potatoes, sweet potatoes, samp, millet, and pasta.

Foods high in protein help maintain muscle mass. Sources of protein include, meat (beef, mutton, pork), organ meats, fish, chicken, eggs, milk, dairy products such as yogurt and cheese, and mopani worms and other insects. Inexpensive sources of protein include legumes such as beans and peas, nuts, peanut butter, and seeds, as well as grains such as rice, maize, barley, oats, wheat, rye, sorghum, millet, and corn. Because the proteins of grains and legumes are low in selected amino acids, they have a lower biologic value than that of meat or dairy. Grains and legumes need to be combined to supplement each other or eaten with another protein source, such as meat, on the same day, or the protein they provide cannot be totally used to synthesize body protein and will be converted into energy. Vegetables and fruits are important sources of essential vitamins and minerals, especially vitamins A and C, and need to be eaten daily.

Fats and oils are also an important part of the diet, providing calories and essential vitamins and fatty acids. Sources of fat include butter, margarine, cooking oils, nuts, avocados, mayonnaise, and salad dressings.

Sugar, sweets, sodas, and desserts are good sources of calories but should not be used in place of more nutritious foods. They can be used in addition to a healthful diet to provide extra calories.

Patients with HIV/AIDS often lack vitamins and minerals because of inadequate dietary intake, infection, and malabsorption. The water-soluble vitamins, such as vitamin C and the B vitamins, need to be included in the diet daily. The fat-soluble vitamins, such as vitamin A, need to be consumed at least every other day. Vitamin D, important for bone development, can be obtained by spending at least 15 min in the sun every other day. Calcium, important in bone development, comes from milk and other dairy products, beans, and leafy green vegetables. Vitamins A, C, E, and B are important for immune system function. Vitamins A and C are important for wound healing, and vitamin A is important for vision. The B vitamins are also important for energy production, red blood cell production, and growth. Vitamin E is important in red blood cell production and as an antioxidant. Minerals such as zinc and selenium are important in immune system function and, along with other minerals such as iron, magnesium, potassium, phosphorus, and copper, are often depleted in association with HIV infection. Because vitamins and minerals play such an important role in the body, a daily multivitamin/mineral supplement can benefit both asymptomatic and symptomatic HIV-positive patients. If giving a vitamin is not feasible, it is especially critical to promote a healthful
diet with a variety of foods. Table 7 lists important vitamins and minerals and their sources.

<table>
<thead>
<tr>
<th>Vitamin or mineral</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins A and C</td>
<td>Fruits and vegetables including cabbage, dark green leafy vegetables, spinach, guava, carrots, beetroot, avocado, pumpkin, squash, potatoes, sweet yams, sweet potatoes, tomatoes, oranges, mangoes, pineapple, melons, papaya, and lemons</td>
</tr>
<tr>
<td>Vitamin B</td>
<td>Meats, whole grains, milk, eggs, and legumes</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Vegetable oils, dark green leafy vegetables, legumes, and nuts</td>
</tr>
<tr>
<td>Zinc</td>
<td>Meat, legumes, and whole-grain cereals</td>
</tr>
<tr>
<td>Selenium</td>
<td>Meat, seafood, and cereals</td>
</tr>
<tr>
<td>Iron</td>
<td>Meat, fish, poultry, whole-grain cereals, dark green leafy vegetables, and legumes</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Green leafy vegetables, legumes, and whole grains</td>
</tr>
<tr>
<td>Potassium</td>
<td>Meats, poultry, fish, fruits and vegetables including bananas, potatoes, carrots, tomatoes, and oranges</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Meats, milk, and whole-grain cereals</td>
</tr>
<tr>
<td>Copper</td>
<td>Organ meats, shellfish, legumes, nuts, and whole-grain cereals</td>
</tr>
</tbody>
</table>

**Inpatient Management of Severe Acute Malnutrition**

Severe acute malnutrition is an extremely serious condition, with substantial morbidity and mortality. Severely malnourished HIV-infected adults and children are at even higher risk of poor outcomes. Severe acute malnutrition has been considered a condition best managed in the inpatient setting, though this view is beginning to change (see the following section on outpatient management of severe acute malnutrition). The WHO has developed widely accepted protocols for the inpatient management of severe acute malnutrition that, if properly implemented, can result in less than 5%-10% mortality. HIV-infected children can be managed according to these protocols, though they may gain weight more slowly than HIV-negative children.

An in-depth review of the inpatient management of severe acute malnutrition is beyond the scope of this chapter, and country-specific guidelines based on international standards should be followed. Commercially available preparations of therapeutic milks (F-75/F-100) and rehydration solution (ReSoMal) are in use in many places, but when this is not available these solutions can be made from easily obtained ingredients according to the recipes in Table 8. The following is an overview of the steps in managing severe malnutrition.

1. **Treat/prevent hypoglycemia.** If unable to test the blood glucose level, assume that all severely malnourished children are hypoglycemic and treat accordingly. If the dextrostix is less than 3 mmol/L, treat with intravenous (IV) glucose (50-mL bolus of 10% glucose) if available or a 10% oral sucrose solution, with initiation of feeds within 30 min. Repeat the dextrostix if the initial one is low or if the child develops hypothermia or altered level of consciousness.

2. **Treat/prevent hypothermia.** Hypothermia can be the result of sepsis or lack of insulating fat. May need active rewarming, if rectal temperature is less than 35.5°C (95.9°F), by using warmed blanket, incandescent lamp, or heater; or put the child on mother’s bare chest (skin to skin). Ensure that the child is covered at all times, especially at night.

3. **Treat/prevent dehydration.** Dehydration can be difficult to reliably assess in severely malnourished children, and the mental state, moisture of mouth/tongue/tears, and skin pinch may not be reliable indicators of dehydration in these children. A history of diarrhea along with thirst, hypothermia, sunken eyes, weak or absent radial pulses, and cold hands and feet are usually reliable signs of dehydration—but may also indicate septic shock. Avoid IV fluids except for shock. Give ReSoMal (not ORS) orally or with nasogastric tube 70-100 mL/kg over 12 h (start at 5 mL/kg every 30 min for the first 2 h and then 5-10 mL/kg/h for the next 10 h). Stop ReSoMal if there are any signs of overhydration, which would include increased respiratory rate and pulse rate, engorged jugular veins, or increasing edema.

4. **Correct electrolyte imbalance.** Provide extra potassium and magnesium and a low-sodium diet.
at first. Most commercially available preparations of F-75/F-100 contain adequate amounts of these electrolytes, but when these preparations are not available, make and give an electrolyte-mineral solution as described in Table 8.

5. Treat/prevent infection. Infection is common, especially when hypothermia or hypoglycemia is present, though fever may be absent. Measles vaccine should be given if the child is not vaccinated and is more than 6 months old. Give broad-spectrum antibiotics with oral trimethoprim-sulfamethoxazole or amoxicillin if no complications are present, or IV ampicillin and gentamicin if the child is severely ill or there are signs of infection. Giving an antimalarial is important in malaria-endemic areas.

6. Correct micronutrient deficiencies. Ensure that vitamin A, multivitamin, folate, and adequate amounts of zinc and copper are given at recom-

| Table 8. Recipes for therapeutic feeds and other fluids |
|---------------------------------------------------------|----------------|
| Ingredient                                              | Amount         |
| **Recipe for ReSoMal**                                  |                |
| Water (boiled and cooled)                               | 2 L            |
| WHO-ORS                                                 | One 1-L packet |
| Sugar                                                   | 50 g           |
| Electrolyte/mineral solution                            | 40 mL (see recipe below) |
| **Recipe for F-75**                                     |                |
| Dried skim milk                                         | 25 g           |
| Sugar                                                   | 100 g          |
| Vegetable oil                                           | 30 g (or 35 mL) |
| Electrolyte/mineral mix                                 | 20 mL          |
| Water                                                   | Make up to 1 L or add 860 mL |
| Contents per 100 mL: energy, 75 kcal; protein, 0.9 g; lactose, 1.3 g; potassium, 4.0 mmol; sodium, 0.6 mmol |
| **Recipe for F-100**                                    |                |
| Dried skim milk                                         | 80 g           |
| Sugar                                                   | 50 g           |
| Vegetable oil                                           | 60 g (or 70 mL) |
| Electrolyte/mineral mix                                 | 20 mL          |
| Water                                                   | Make up to 1 L or add 810 mL |
| Contents per 100 mL: energy, 100 kcal; protein, 2.9 g; lactose, 4.2 g; potassium, 6.3 mmol; sodium, 1.9 mmol |
| **Recipe for electrolyte mineral solution**             |                |
| Potassium chloride                                      | 224            |
| 24 mmol                                                 |                |
| Tripotassium citrate ($C_3H_5K_3O_7H_2O$)              | 81 2 mmol      |
| Magnesium Chloride ($MgCl_2.2H_2O$)                     | 76 3 mmol      |
| Zinc Acetate, Zn($CH_2COO$)$_2.2H_2O$                   | 8.2 300 µmol   |
| Copper Sulphate, CuSO$_4$.5H$_2$O                        | 1.4 45 µmol    |
| Water                                                   | To make up to 2500 mL |
| If available, also add 0.028 g of sodium selenate (NaSeO4.10H20) and 0.012 g of potassium iodide (KI). Dissolve in cooled boiled water and store in sterile bottles in refrigerator. |

Alternative if electrolyte mineral mix unavailable

Potassium—make a 10% stock solution of potassium chloride (100 gm KCl in 1 L of water) For ReSoMal—add 45 mL of stock KCl instead of electrolyte mineral mix For F-75/F-100—add 22.5 mL of KCl stock solution instead of 20 mL of electrolyte mineral mix

Zinc—Make a 1.5% solution of zinc acetate (15 g of zinc acetate in 1 L of water) Give this solution orally at a dose of 1 mL/kg/day

Magnesium—Give a dose of 0.3 mL/kg (to a maximum of 2 mL) of 50% magnesium sulfate intramuscularly one time only

mended doses. Iron should not be started initially but should be given once the appetite returns and the child is gaining weight.

7. **Start cautious feeding.** Give feeds with F-75 as soon as possible, at a total daily volume of 130 mL/kg/day. Children with severe edema should be started on feeds with F-75 at a lower volume—100 mL/kg/day. Feed every 2 h for the first 1-2 days and then every 3 h for about 3 days. Feeding every 4 h should start at day 6-7. As feeding frequency decreases, feeding volume should increase so that the child continues to receive 130 mL/kg/day. This schedule can be sped up for children with good appetites.

8. **Achieve catchup growth.** When the appetite improves, replace the F-75 with the same volume of F-100 for 48 h. If after 2 days the feeds are well tolerated without any signs of heart failure, then increase each feeding by 10 mL until some of the feeding remains uneaten, and continue at that volume. Solid foods can be reintroduced when the child has been tolerating feeds within a range of 150-220 mL/kg/day for a few days. Weight gain of greater than 10 g/kg/day is optimal.

9. **Provide sensory stimulation and emotional support.** Provide tender-loving care, a cheerful environment, structured play 15-30 min/day, and physical activity as soon as the child is capable.

10. **Prepare for follow-up after recovery.** Prepare for discharge when weight for height approaches –1 standard deviation (–1 z score) of NCHS/WHO reference values. Nutrition education for parents will help to prevent relapse. Children recovering from AIDS will have greater stunting (height for age) than that of uninfected children and because of muscle wasting will appear to have some degree of prolonged wasting (weight for height) when plotted on standard reference weight-for-height or BMI charts.

**Outpatient Management of Acute Malnutrition**

Despite the well-documented effectiveness of inpatient protocols, the mortality of pediatric severe acute malnutrition remains high in many resource-limited settings. There are many reasons for this, including patient overcrowding, inadequate staff to implement the relatively labor-intensive protocols, poor infection control practices resulting in a high rate of hospital-acquired infections, and the limited number of hospitals and inaccessibility of inpatient treatment to large parts of the population. The high costs to caregivers who must leave their jobs, home responsibilities, and other children/family to care for a sick child in the hospital often result in caregivers’ postponing treatment until the malnutrition is far advanced and thus more difficult to treat and associated with worse outcomes. Therefore, focus has shifted to developing outpatient management strategies for pediatric severe acute malnutrition.

Ready-to-use therapeutic food (RUTF) has allowed the outpatient management of acute malnutrition and thus resulted in fewer hospital-acquired infections, increased accessibility to the general public, decreased burden on inpatient facilities, and decreased costs to families previously associated with inpatient treatment, resulting in earlier presentation for care, decreased levels of defaulting from care, and thus substantially improved outcomes. Outpatient management of malnutrition is most effective within the framework of a community-based therapeutic care model, which is becoming the basis for many countries’ malnutrition programs.

RUTF is an oil-based, energy dense, mineral/vitamin-enriched food used in the management of acute malnutrition in children. It is a type of therapeutic food that can be used in place of therapeutic milk such as F-100. There are many advantages to using RUTF over therapeutic milks. RUTF does not require preparation, may be stored at room temperature with minimal risk of contamination, and has a shelf life of up to 24 months. It is easier to adminster than therapeutic milk, facilitates shorter time to discharge from the hospital, and allows ongoing treatment of malnutrition at home.

Outpatient management has also brought about a new classification of malnutrition—complicated versus uncomplicated. Children with acute malnutrition and complications—such as severe pneumonia, severe dehydration, severe anemia, hypo- or hyperthermia, poor appetite, severe (grade 3+++ edema)—are admitted to an inpatient facility to start their treatment. Once these complications have been adequately treated, the children may be transitioned to RUTF and discharged to complete their treatment as outpatients. Acutely malnourished patients without complications who have a good appetite can be prescribed a ration of RUTF on the basis of their weight and then followed up as outpatients. The specific outpatient protocols for the use of RUTF in outpatient malnutrition are beyond the scope of this chapter. Where RUTF is available, local protocols should be followed.
Malnourished, HIV-infected children can be given RUTF per the same protocols as for HIV-negative individuals, and though the rate of weight gain may be slower, many of these children will respond well. ARV medications should be used in combination with nutritional support to have a good response (see the section on ART). Where available, RUTF can be a wonderful tool to treat malnourished, HIV-infected children.

Other Important Interventions
Vitamin A deficiency is a common micronutrient deficiency that can result in blindness as well as increased susceptibility to measles, diarrhea, and malaria. Children are the most susceptible, and in areas of high vitamin A deficiency, supplementation can reduce childhood mortality by more than 20%. In areas of high vitamin A deficiency, universal supplementation is recommended by the WHO, as described in Table 9.

Soil-transmitted helminths are a major public health problem in much of the world, including all of Africa. The three most prevalent worm infections that result in significant consequences for their hosts include roundworms (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale* and *Necator americanus*), and whipworms (*Trichuris trichiura*). Worm infection results in significant loss of micronutrients, causes malabsorption of vitamin A, and contributes to anemia and malnutrition, all of which can lead to poor cognitive development. Appropriate treatment can reverse these complications of worm infection. Preschool- and school-aged children and women of childbearing age are at the highest risk for infection and complications of infection. Deworming treatments are safe and effective. The WHO recommends routine and regular (every 6 months) deworming starting at 1 year of age. Medications and doses for antihelminthic agents are listed in Table 10. These medications may occasionally cause some minor nausea and abdominal pain, but because they are poorly absorbed rarely cause serious systemic side effects. Even if children younger than 1 year are accidentally given

### Table 9. Vitamin A supplementation

<table>
<thead>
<tr>
<th>Schedule of high-dose vitamin A distribution</th>
<th>Dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt;6 mo</td>
<td></td>
</tr>
<tr>
<td>Non-breastfed infants</td>
<td>50,000, orally</td>
</tr>
<tr>
<td>Breast-fed infants whose mothers did not receive vitamin A supplementation</td>
<td>50,000, orally</td>
</tr>
<tr>
<td>Infants 6–12 mo</td>
<td>100,000, orally, every 4–6 mo</td>
</tr>
<tr>
<td>Children &gt;12 mo</td>
<td>200,000, orally, every 4–6 mo</td>
</tr>
<tr>
<td>Mothers</td>
<td>200,000, orally, within 8 wks of delivery</td>
</tr>
</tbody>
</table>


### Table 10. Deworming drugs and doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose for preschool children</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12–23 mo</td>
<td>24 mo and older</td>
</tr>
<tr>
<td>Albendazole 400-mg tablet</td>
<td>1/2 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Mebendazole 500-mg tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Levamisole 40-mg tablet</td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td>Pyrantel palmoate 250-mg tablet</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
</tr>
</tbody>
</table>

an antihelminth, or if older children are given multiple repeated doses, harm will rarely be caused.

**ART for Malnourished Children**

HIV-infected children who are moderately or severely malnourished may benefit from ART, though the decision to initiate ARVs in these patients is complex. Little information on the safety, pharmacokinetics, or effectiveness of ART in severely malnourished children exists. The optimal timing of initiation of ARVs is not known, and studies are urgently needed. On the basis of expert opinion, the WHO recommends that severely malnourished, HIV-infected children be managed for their malnutrition according to standard protocols and reassessed after the initial management phase. Children with unexplained moderate or severe malnutrition who do not respond to standard nutritional treatment by definition have a WHO Clinical Stage 3 or 4 condition, respectively, and should receive ART. Control of HIV infection by using ARVs combined with nutritional support, will often both be necessary to adequately care for infected individuals. Use of ARVs without nutritional support, or nutritional support without ARVs, will often result in poor treatment responses and outcomes.

**Infant Feeding in HIV**

The complex interaction between nutrition and HIV is highlighted in the issue of appropriate feeding of infants born to HIV-infected mothers. When a mother who is HIV positive breast-feeds, she risks transmitting the virus to her child. Without safe and appropriate nutritional options for infants other then breast-feeding, weaning children from breast milk can have serious consequences. See the chapter on mother-to-child transmission of HIV for more information and recommendations regarding infant feeding in HIV infection.

Supporting the nutritional needs of mothers who choose to breast-feed is crucial to the outcome of the infant. A breast-feeding mother needs at least 500 extra calories per day. If she does not get enough calories, she can become malnourished, lose bone, and have a poor milk supply. Breast-feeding, HIV-infected mothers may need nutritional support in the form of both caloric and micronutrient supplements.

**References**


Traditional, Complementary, and Alternative Medicine

Elizabeth D. Lowenthal, MD
Ketlogetswe Montshiwa, MPhil, MSc

Objectives
1. Define allopathic medicine, traditional medicine, and complementary and alternative medicine (CAM).
2. Review various types of traditional therapies and CAM used in treating human immunodeficiency virus (HIV)-infected patients.
3. Discuss risks and benefits associated with the use of traditional therapies and CAM by HIV-infected patients.
4. Explore prevalent patient attitudes regarding traditional therapies and CAM.

Key Points
1. Health care professionals must be knowledgeable about traditional therapies and CAM to assist patients in making informed choices regarding their use.
2. Traditional therapies and CAM are often used in conjunction with conventional treatments for HIV/AIDS patients.
3. The risks and benefits of all therapies, including traditional medicines and CAM options, should be considered by patients and health care providers prior to the start of treatment.
4. When treatment failures and adverse effects of therapy are seen, the possible influence of traditional and complementary therapies needs to be considered.

Overview
The prevention, diagnosis, and treatment of disease using conventional, Western, evidence-based medical therapies is often referred to as allopathic medicine. The diagnostic modalities and therapies described in other chapters in this curriculum reflect primarily allopathic approaches to HIV and acquired immune deficiency syndrome (AIDS). Although evidence-based approaches such as the use of licensed antiretroviral medications can have an important effect on the lives of patients with HIV/AIDS, health care practitioners must recognize that for most patients worldwide nonallopathic beliefs and practices play a major role in health care.

In many settings, traditional medical practices are the most widely used forms of health care. These practices incorporate knowledge, beliefs, and health interventions that are based on locally available plants, animals, and minerals, as well as spiritual therapies, manual techniques, and exercises. The goals of these therapies are often similar to the goals of allopathic medicine: to diagnose, prevent, and treat illnesses and to promote well-being. In industrialized countries, adaptations of traditional therapies are termed CAM. Traditional, complementary, and alternative therapies are used by many HIV-infected patients worldwide. For simplicity, this module will use the abbreviation “CAM” to describe traditional, complementary, and alternative medicines.

The World Health Organization estimates that in Africa, North America, and Europe, three of four people living with HIV/AIDS use some form of CAM. In some populations, the numbers are even higher. For patients in many parts of the world, standard Western medical therapies are not easily accessible. In countries where conventional medicines are more readily available, the number of people using CAM therapies has nevertheless been increasing over the past few decades. The implications of the widespread use of CAM are great in terms of both potential benefits and potential risks to patients.

CAM includes a wide range of therapies not usually integrated into standard Western medical practice. These therapies are referred to as complementary when they are used in conjunction with conventional medical practices. Those used instead of conventional practices are considered alternative. A variety of approaches to diagnosis, treatment, and care that fall outside of conventional methods can be classified as CAM.
Defining CAM in a multicultural context presents certain difficulties. Because CAM includes a wide range of therapies and health systems, one must avoid generalizations. What is considered conventional in one setting may be out of the ordinary in another. The list of practices that are considered to be CAM changes as some CAM therapies that are proven safe and effective become a part of mainstream medicine. Health care providers must appreciate the CAM modalities commonly used by their patients. **Table 1** defines some commonly used CAM modalities. For some of these treatments, certain benefits and risks with regard to their use in HIV-infected adults and children have been identified through research studies. Some of these studies and their potential implications for HIV-infected patients are discussed briefly in Tables 1 and 2 and later in the chapter text.

**Traditional Healers**

In some countries, most of the population relies on traditional medicine for basic health care. Traditional healers are often the most accessible of all health care providers, especially for rural communities. In Ghana, for example, it has been estimated that there is one traditional healer for every 400 people but only one conventional medical doctor for every 12,000 people.

Surveys have shown that in Africa, about 70% of people see traditional providers first when confronted with health-related problems. A 2001 study of HIV-infected people in Cambodia revealed that most consulted a traditional healer for care.

International bodies such as the World Health Organization and UNAIDS have acknowledged and

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Theory and Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>Acupuncture is a component of traditional Chinese medicine. It is based on the theory that vital energy circulates through the body in channels called meridians. Disease occurs when the flow of vital energy is disrupted and healing occurs when the flow is restored through stimulation of specific points along the energy meridians. Stimulation occurs through a variety of techniques, including needle insertion and cupping. Acupuncture is commonly used for the treatment of pain. Studies have shown acupuncture to be effective in relieving some HIV-related symptoms, including HIV-related peripheral neuropathy.</td>
</tr>
<tr>
<td>Bioenergetic therapies</td>
<td>Reiki and other forms of therapeutic touch operate on the belief that energy can be transmitted from the healer to the patient. Practitioners of this form of therapy work either by direct physical contact or through visualization and energy transfer. Some HIV-infected patients report an increased sense of well-being after bioenergetic treatments.</td>
</tr>
<tr>
<td>Chiropractic</td>
<td>Chiropractic is based on an association between the spine and nervous system and on the self-healing properties of the human body. Chiropractors believe that misalignment of the joints, particularly the spine, is a major source of morbidity. Through manipulations of the spine and other joints, they seek to reestablish normal body functions. Chiropractic manipulations have been used in children to treat joint and gastrointestinal symptoms and to strengthen the immune system.</td>
</tr>
<tr>
<td>Faith healing</td>
<td>Faith healing is a component of many traditional therapeutic modalities. Some Christian communities stress that faith in God allows miraculous healing to take place. Many studies examined the effects of faith and prayer on health outcomes. Sometimes benefits have been seen among patients using faith healing modalities.</td>
</tr>
<tr>
<td>Herbs and supplements</td>
<td>Many herbal remedies are used throughout the world for the maintenance of health and treatment of disease. Vitamins and mineral supplements are sometimes added to or used with herbal treatments. Many conventional medicines are derived from natural plant products. Many ongoing studies are evaluating the safety and efficacy of commonly used herbal treatments.</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>Homeopathy is a system of medical treatment that operates based on the Law of Similars and the Law of Dilutions. The Law of Similars is the belief that a substance that would cause a symptom in a healthy person can treat the same symptom in a sick person (“like cures like”). According to the Law of Dilutions, the more a substance is diluted, the more powerful it becomes as a therapy. Thus, a very dilute solution made with poison ivy extracts would be a potential homeopathic remedy for an itchy rash. A few small studies have suggested a trend toward improvement of immune function and quality of life among HIV/AIDS patients using certain homeopathic remedies.</td>
</tr>
<tr>
<td>Massage</td>
<td>Several different types of massage aim to improve circulation, alleviate pain, promote relaxation, and stimulate the immune system. A study of HIV-infected children in the Dominican Republic suggested that the use of massage may enhance immune function.</td>
</tr>
<tr>
<td>Mind–body exercise</td>
<td>Yoga, tai chi, and qi gong are among exercises that are recommended to reduce stress and improve psychosocial function. These techniques can improve fitness and overall sense of well-being.</td>
</tr>
<tr>
<td>Traditional healers</td>
<td>In many societies, certain people are believed to be endowed with special healing powers. Traditional healers are widely used for spiritual support, problem solving, and health care. Healing techniques are often passed from one healer to another through apprenticeships. Traditional healing may take place in the form of a community ceremony or as a private healing ritual or treatment for a sick person.</td>
</tr>
</tbody>
</table>
studied the role and influence of traditional healers. Many international and regional groups are working to improve collaborations between traditional healers and government-sponsored health networks. For example, in Uganda, a nongovernmental organization called Traditional Healers and Modern Practitioners Together Against AIDS (THETA) has been a regional leader in building effective partnerships between traditional and modern practitioners for the care of patients with HIV infection. Their work has included training traditional healers in modern understanding of HIV pathogenesis and treatments as well as studies to document the efficacy of selected traditional herbal remedies. In Botswana, traditional healers are organized into the Dingaka ("doctors") Association of Botswana. Efforts to train Dingaka Association members regarding the spread of HIV have resulted in increased sexually transmitted disease prevention counseling in the communities that they serve.

The education of traditional healers in conventional medical theories and treatments can play an important role in stemming the transmission of HIV. A 3-year study of the practices of traditional healers in Nigeria revealed that 77% of their treatments involved incisions made with unsterilized blades. Herbal preparations were then rubbed into actively bleeding skin cuts, using unprotected fingers, which were in direct contact with the patient’s blood. Both healers and their patients are at great risk for contracting HIV and other infections through such practices.

As antiretroviral (ARV) medications become more widely available in areas where traditional healers work, it will be important for the healers to be trained in the basic principles of their use. The misuse of antibacterial drugs by untrained practitioners, such as the mixing of low doses of antibiotics into herbal remedies, has exacerbated the problem of antibiotic resistance. Similar practices using ARV drugs would harm patients by leading to the development of viral resistance to the ARVs.

Although the risks of some traditional medical practices are real, traditional healers often use a holistic approach that makes them especially well suited to assist with the management of symptoms and the maintenance of patients’ general well-being. By providing education and regarding traditional healers as partners in the care of HIV-infected individuals, we can maximize benefits to the patient and minimize potential harm. Traditional healers should be sensitized to the potential risk of infection to themselves as a result of certain practices.

**Attitudes Regarding CAM**

The use of CAM modalities is widespread among HIV-infected people around the world. Although most studies related to the use of CAM in HIV-infected patients have focused on adults, CAM practices are also known to be used to treat children with HIV. Because of the importance of CAM to families and the potential for interactions between CAM and conventional medicines, asking about CAM use should be a part of medical history taking for all pediatric HIV patients.

There are many reasons why people choose to use CAM. Commonly cited reasons for CAM use include the following:

- Ease of access
- CAM providers’ use of culturally familiar ways to explain the causes of ill health
- Perception of efficacy
- Perception of safety
- Lower cost
- Preference for natural over synthetic medicine
- Greater sense of patient autonomy and taking control over one’s health care
- Greater use of physical touch
- Belief that CAM providers can heal both the body and the spirit
- Pleasant therapeutic experiences
- Rejection of science and technology
- Failure of conventional therapy to provide a cure
- Dissatisfaction with practitioners of conventional medicine
- Frustration with side effects of conventional medicines
- Desperation

Most patients who use CAM do not discuss this use with their mainstream health care providers unless asked specifically in a nonthreatening manner. Patients cite many reasons for not discussing their CAM use with nurses, physicians, and other mainstream providers, including the following:

- They are not asked specifically about the use of CAM therapies.
- They think of the CAM therapies as separate from mainstream therapies and do not recognize that
one may change the efficacy of the other.

- They fear that mainstream providers will perceive their CAM use negatively.
- They fear that mainstream providers will provide lower quality of care if mainstream providers know of their CAM use.
- The use of CAM modalities provides them with an increased sense of control over the illness that may be compromised by disclosure to a paternalistic medical provider.

Despite the widespread use of CAM therapies, many health care providers do not routinely discuss CAM use with their patients. To best serve the interests of their patients, health care providers should establish and maintain trusting relationships with patients and their families; guard against personal biases; and provide balanced, evidence-based advice about therapeutic options. When evidence regarding the safety and efficacy of a treatment choice is lacking, the uncertainty should be discussed openly, and likely risks and benefits should be considered.

### Evaluating CAM Therapies

Health care providers must inform patients about known treatment-related risks and must be aware that unknown toxic effects or interactions may exist. Health care providers should seek information about CAM therapies that their patients are using. When studies related to the therapies are available, providers should review their quality and results. Health care professionals can often contact the providers of CAM therapies to help clarify the merits and the risks of the treatment approaches they recommend.

### Risks

Risks associated with the use of CAM therapies can be grouped as follows:

- Causing direct physical harm.
- Causing indirect physical harm as a result of delaying or avoiding the use of conventional treatment that is known to be effective (e.g., ARVs).

### Table 2. Selected potential side effects of CAM in children with HIV/AIDS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Common Uses</th>
<th>Risks of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>See Table 1</td>
<td>Complications are rare, but infections and serious tissue trauma (heart rupture, liver injury) have occurred in children.</td>
</tr>
<tr>
<td>Chiropractic manipulations</td>
<td>See Table 1</td>
<td>Upper spinal manipulations have been associated with serious adverse events in children, including paralysis, strokes, and vertebral artery dissection.</td>
</tr>
<tr>
<td>Cutting and bloodletting</td>
<td>Purging the body of hazardous substances, creating a dermal opening for the application of herbal remedies</td>
<td>Unsterile conditions and reuse of cutting instruments and other tools may lead to the spread of infections, including HIV.</td>
</tr>
<tr>
<td>Herb/food product: African potato (Hypoxis sp.)</td>
<td>Immune enhancement, anti-inflammatory</td>
<td>Interacts with cytochrome p450 metabolism. Because many antiretrovirals and other drugs are metabolized through the cytochrome p450 system, drug levels may be altered by concurrent use.</td>
</tr>
<tr>
<td>Herb: chaparral (Larrea tridentate)</td>
<td>Antioxidant; anti-fungal; also used for arthralgias, neuralgias, respiratory infections, rashes</td>
<td>Multiple cases of liver damage, including cirrhosis and fulminant liver failure, have been reported.</td>
</tr>
<tr>
<td>Herb: coneflower (Echinacea sp.)</td>
<td>Immune stimulant</td>
<td>Use in HIV-positive patients is controversial. Some in vitro studies suggest that it might aid progression of HIV disease.</td>
</tr>
<tr>
<td>Herb: ephedra/ma huang</td>
<td>Stimulant, increases energy level</td>
<td>Increases blood pressure, heart arrhythmias; has led to strokes and death.</td>
</tr>
<tr>
<td>Herb/food product: garlic (Allium sativum)</td>
<td>Antimicrobial and antiviral properties; inhibits platelet aggregation</td>
<td>Decreases plasma concentrations of protease inhibitors; increases bleeding tendency.</td>
</tr>
<tr>
<td>Herb: sutherlandia</td>
<td>Immune booster, antioxidant, anti-inflammatory</td>
<td>Interacts with cytochrome p450 metabolism. Because many antiretrovirals and other drugs are metabolized through the cytochrome p450 system, drug levels may be altered by concurrent use.</td>
</tr>
<tr>
<td>Herb: St. John’s wort (Hypericum perforatum)</td>
<td>Used for the treatment of mood disorders, particularly depression</td>
<td>Reduces the concentration of certain protease inhibitors and nonnucleoside reverse transcriptase inhibitors. (St. John’s wort is a potent inducer of CYP3A4 and inhibits several other CYPs.)</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>See Table 1</td>
<td>Most but not all homeopathic remedies are diluted beyond the threshold of toxicity. A case of mercury poisoning in an infant after ingestion of homeopathically diluted mercury has been reported.</td>
</tr>
</tbody>
</table>
Harm may also come from financial or emotional exploitation. The issue of financial exploitation is crucial because many of those infected with HIV are financially disadvantaged.

Many herbs and supplements contain undeclared pharmaceutical drugs, heavy metals, and other contaminants. A recent study of 260 Asian patent medicines sold in the United States revealed that one-third contained undeclared pharmaceuticals and/or heavy metals. The origin, contents, and quality of all remedies ingested or applied to the body should be investigated. Care should be taken to ensure that patients are not unknowingly consuming products that are likely to be harmful to them.

Patients and health care providers should consider the potential risks and benefits of all therapies. Part of this evaluation should include reflection regarding how different therapies may interact with each other. Just as certain prescription drugs should not be given together because of potential adverse effects, some CAM therapies should not be used in conjunction with prescription medications. In HIV-infected patients on ARVs, some herbs hasten the progression of HIV infection because of the herbs’ effects on ARV concentrations (Table 2). This effect is probably due to induction and inhibition of various cytochrome P450 enzymes involved in ARV metabolism. When patients fail to respond to prescribed therapies, health care professionals should always consider the possibility of such interactions.

Patients stand to gain much by increased understanding of the benefits and risks associated with CAM use. In 1998, the National Institutes of Health of the United States established the National Center for Complementary and Alternative Medicine (NCCAM) to help bridge some of the gaps between conventional and CAM providers. Through scientific studies, NCCAM investigates which CAM practices are effective and why. As of early 2008, 28 NCCAM trials related to the use of CAM for HIV/AIDS-related care were either completed or in progress. These included studies related to the use of acupuncture to treat chronic diarrhea in HIV patients and massage to improve immune function and quality of life in HIV-infected children. Several African and Asian countries are similarly putting considerable resources into analyzing the benefits and risks of locally popular CAM practices and disseminating results of their studies. Patients and health care providers should look for the results of these and similar studies to guide them in the rational evaluation of CAM therapies.

References


Objectives

1. Describe the complex nature of pain, focusing on the aspects of pain perception in children.
2. Understand the best ways to assess pain by using self-report, behavioral observation, and physiologic measures.
3. Describe the pain syndromes unique to patients with human immunodeficiency virus (HIV)/AIDS and specific measures useful to alleviate pain.
4. Understand how to use the World Health Organization (WHO) Pain Ladder to initiate and titrate pain medications.
5. Understand key facts about the most common analgesics used in pain control.
6. Describe symptom management at the end-of-life stage in individuals with HIV/AIDS, including dyspnea, diarrhea, constipation, nausea/vomiting, anorexia, peripheral edema, and intractable hiccups.

Key Points

1. Pain is a complex process involving both physiologic and nonphysiologic factors unique to each individual.
2. Pain in persons with HIV/AIDS is common and often undertreated.
3. Self-report is the best way to assess pain, but there are other ways to elicit pain cues from patients.
4. Pain relief should begin with a straightforward, developmentally appropriate explanation to the patient about the causes of pain.
5. Specific analgesic measures can help with pain localized to certain areas.
6. Pain management for people with HIV/AIDS should follow the WHO analgesic ladder when possible and should include behavioral interventions.
7. Symptom management at the end-of-life stage is complex and requires ongoing assessment and intervention.

“I’m in Pain”: The Complex Nature of Pain

As human immunodeficiency virus (HIV) alters the immune system of an infected individual, the number of infections and malignancies increases. These sequelae of immune suppression have a frequent common symptom of pain.

Pain is a sensation produced when a stimulated nerve signals the brain that something is wrong. The brain relays this sensation to other areas of the nervous system, setting off a cascade of responses, thoughts, and emotions.

Children with HIV/AIDS experience pain throughout their disease. The incidence of pain in HIV-infected children is comparable to that in childhood cancer. In one study, pain affected almost two-thirds of HIV-infected children in their daily lives, though only one-third received appropriate analgesia.

Pain is particularly underrecognized and undertreated in the pediatric population because children rely on adult caregivers to recognize and respond to their pain. The myth among caregivers that children do not feel pain the same way that adults do is a barrier to their treatment.

Children underreport pain because they fear
- talking to health care providers,
- disappointing others,
- receiving an injection, and
- returning to the hospital.

Failure of health care providers to account for the developmental level of a child as they assess pain can lead to a critical undertreatment of pain among infants, children, and adolescents throughout the world.
Pain is inherently subjective. Many factors beyond the physical experience of pain affect how pain is perceived (Figure 1). Adequately addressing chronic pain in HIV/AIDS requires astute attention to all these factors.

**Psychological Factors**

Pain control can modulate a child’s future response to pain. Newborns circumcised without analgesia showed more distress during later routine immunizations than uncircumcised infants or those circumcised with local anesthesia. Also, pediatric cancer patients given inadequate analgesia during an invasive procedure showed more severe distress during later procedures than those who received a potent opioid during the first procedure.

Emotional states such as depression also play a key role in the experience of pain. Sometimes the fear of pain, injury, or loss of physical ability may be more disabling than the pain itself. People dealing with chronic illness often experience feelings of depression and helplessness. Because approximately half of depressed patients express pain as a symptom of their illness, pain control must address the accompanying symptoms of depression and anxiety.

A child’s temperament and personality type also affect how pain is perceived. Children considered to have a more “difficult” temperament (e.g., negative mood, poorly adaptable, complaining) are more likely to display distress during a painful experience than children with “easy” personalities (e.g., adaptable, positive). This latter group of children may not receive appropriate analgesia because they might not report their pain to the same degree. Children with naturally good coping mechanisms such as information seeking or focusing attention away from the painful stimuli can better handle pain. Those who accept their illness as a challenge to overcome usually fare better than those who do not accept their illness or who see their illness as a sign that they are “damaged.”

When helping children deal with pain, health care providers should also keep in mind a child’s developmental level. Children at different ages perceive pain in different ways (Table 1). For example, a preschooler may not understand or gain comfort from a cause-and-effect explanation for a painful procedure (e.g., “This lumbar puncture will help us treat your infection and in the end you will feel better”), whereas this information would probably comfort a school-aged child.

**Familial and Social Attitudes**

The attitudes of family and society regarding the child’s illness and pain in general contribute significantly to a child’s perception of and reaction to pain. Parents and caregivers can model both positive and negative ways to tolerate and express pain. Caregivers can listen, comfort, and counsel children on dealing with pain appropriately, but caregivers can also inadvertently encourage children to stay in the “sick role” even if no longer necessary. If family members are in denial regarding the patient’s disease, the patient may feel emotionally isolated, depressed, or anxious; these feelings compound the physiologic pain. Parental denial of HIV status has also been linked to denial of the child’s pain.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Concept of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–6</td>
<td>Pain as physical, concrete or magical; may see pain as punishment for wrongdoing on their part or the part of a loved one</td>
</tr>
<tr>
<td>7–12</td>
<td>Some pain as psychological (e.g., grief), beginning cause–effect thinking, may fear bodily harm and death</td>
</tr>
<tr>
<td>≥13</td>
<td>Can verbalize reasons for pain and perceive several types of psychological pain but have limited abilities to cope</td>
</tr>
</tbody>
</table>

*Figure 1. Nonphysiologic factor contributing to pain*

*Table 1. Age and concept of pain*
Life Stressors
Children who have experienced a death in the family, particularly the death of a parent, are at risk to have more acute experiences of pain. Orphaned children are especially vulnerable to poor pain control. Parents are much better predictors of actual pain in children than health care providers; therefore, losing a parent takes away a child’s most important advocate for pain management. A family overwhelmed by financial stress, unemployment, a housing crisis, or other major life stressors may not have the resources to properly attend to the pain of a child in their midst.

Cultural and Spiritual Factors
A patient’s sex plays a role in how pain is experienced and expressed. Females tend to be more vocal about pain, whereas males may feel that they need to be “tough” and therefore see themselves as not free to ask for pain relief. Some cultures conceive of pain as punishment for wrongdoing, and children can incorporate and embody these same ideas. In HIV/AIDS, for which stigma still has a role in many societies, children may fear to speak up about pain from their disease in an effort to not draw attention to their disease. Health care providers should be attuned to the spiritual needs of their patients in their efforts to holistically address pain. Children may gain comfort from spiritual concepts of prayer and suffering.

“HOW BAD IS MY PAIN?”: PAIN ASSESSMENT
Several validated pain assessment tools exist to aid the clinician, but usually a combination of self-report, behavioral observation, and physiologic measures can work together to provide a comprehensive appraisal. Self-report is the “gold standard” of pain assessment, but this is obviously challenging in infants, nonverbal children, and children too critically ill to communicate verbally. In these situations, a therapeutic trial of comfort measures and analgesic medications may be helpful in interpreting distressed behavior. A health care provider should assess and document pain at regular intervals—with each new report of pain, as well as after a pharmacologic or nonpharmacologic intervention has been provided to offer the best possible pain management.

Self-Report
If a child is of sufficient age and developmental level, eliciting a full qualitative description of his or her pain is helpful. A pain history includes the following:
- Character (e.g., burning, dull, sharp)
- Location (including any radiation)
- Quality
- Duration
- Frequency
- Intensity

Beneficial direct dialogue with children includes topics such as how they have positively dealt with pain in the past, with whom they feel most comfortable discussing pain, and interventions that have helped and not helped in previously painful situations. Considering caregivers’ observations about their child’s past pain experience can also be helpful in making a plan to deal with the current pain.

Children aged 8 or more years can generally use a simple linear scale (Figure 2) to rate the intensity of their pain, giving a quantitative measure to pain.

One can assess a child’s ability to use a linear pain scale by putting the child through a simple test such as placing five bits of paper of different sizes in order from smallest to largest. This linear scale helps patients describe their pain better and can provide important information about whether pain management techniques are effective. For children aged 3-8 years, self-reported measures usually incorporate the faces scale to assess children’s perceptions of pain (Figure 3).
Children as young as 18 months can usually report pain or hurting in some fashion but have difficulty understanding gradation of pain (e.g., a little, a lot).

**Behavioral Observation**

Behavioral observation is the primary means of assessing pain in newborns, infants, children younger than 4 years, and children with developmental disabilities. Observations include facial expressions, limb and trunk motor responses, vocalizations (e.g., crying, moaning), body posture, activity, and appearance. These measures are imperfect; they cannot distinguish between forms of distress (e.g., pain versus fear or anxiety) and they underestimate pain relative to self-report. Children with chronic inadequately treated pain may use distraction techniques such as playing, sleeping, or remaining quiet to deal with pain, and these behaviors can mislead clinicians into thinking that the pain is under control. Behaviors to express pain can also vary; some infants might close their eyes, furrow their brows, or clench their fists rather than cry in pain. Caregivers most familiar with the child are often the best individuals to interpret behavioral cues.

**Physiologic Measures**

Pain leads to stress within the body that activates compensatory mechanisms of the autonomic nervous system. Responses include tachycardia (fast heart rate), elevated blood pressure, tachypnea (rapid breathing), restlessness, and dilation of the pupils. As with behavioral measures of pain, physiologic measures cannot discriminate well between a physical response to pain and other forms of stress on the body. As with the assessment of any symptom, a complete physical examination can yield much information in the attempt to link the pain complaint with the patient’s disease and find the best means to alleviate the cause of the pain.

“What Is Causing My Pain?”

HIV opens the body to attacks from infections and malignancies with a frequent common symptom of pain.
The etiology of pain with HIV is usually multifactorial but can be often be attributed to opportunistic infections, side effects of medication, and nonspecific factors related to the HIV infection itself. The cause of pain can be elusive but must be pursued to eradicate the underlying cause, choose the best analgesia, and provide prognostic counseling.

A patient with HIV can sprain an ankle or develop a headache like anyone else, requiring similar acute pain treatments. This chapter will focus on pain syndromes exclusive to or more common with HIV organized by anatomical location and a cluster of symptoms occurring late in AIDS. Figure 4 provides a useful tool for differential diagnosis of pain.

“What Can Be Done about My Pain?”

Many measures have been used with great success in pain relief for HIV-infected individuals. A working knowledge of the usual sources of pain in HIV and an understanding of some key principles in the proper use of analgesics are essential. Understanding various nonpharmacologic measures that help relieve pain is especially important in treating pain in children.

Specific Pain Syndromes by Anatomical Location

Mouth. Topical agents can relieve pain from oral manifestations such as candidiasis and aphthous ulcers. Magic Mouthwash (a preparation of a 1:1:1 solution of diphenhydramine elixir [12.5 mg/5 mL], an antacid, and viscous lidocaine) swished and spit out helps reduce pain in severe thrush, as can glycothymol mouthwash. Some clinicians have found that 1% gentian violet topically applied to aphthous ulcers can provide relief.

Esophagus and chest. Chest pain from either esophagitis or pleural inflammation from pneumonia often responds favorably to opioid analgesic agents. Cough medications containing codeine contribute to cough suppression and alleviate pleuritic pain. Viscous lidocaine taken by mouth is useful in mitigating pain for esophageal ulcers caused by *Candida* and herpesvirus.

Skin itching (pruritus). Severe itching commonly affects debilitated HIV/AIDS patients who suffer from chronic skin conditions, side effects of medications (e.g., opioids), and other systemic diseases.

Though symptomatic treatment for itching is readily available, identification and treatment of the underlying cause will achieve the best relief. Severe itching commonly results from skin conditions such as papular pruritic eruptions, scabies, fungal infections, and poorly cared for dry skin. Pruritus can be a manifestation of systemic diseases also common with HIV/AIDS, such as hepatitis, biliary disease, lymphoma, and renal failure. The provider should search for the systemic causes while starting routine antipruritic therapies.

Treatments for pruritus include the following:

- Skin moisturizers and emollients help to relieve the itching that commonly occurs from dry skin. Petroleum jelly is a readily available agent that is effective when applied two to three times daily. Using tepid water minimizes the drying effect of bathing.
- Oral antihistamines play a key role in reducing itching, which often results from histamine release in the skin. Diphenhydramine and hydroxyzine are useful, though they often cause mild sedation and dry mouth. Doxepin, a tricyclic antidepressant possessing antihistamine properties, is also effective for refractory cases.
- Keeping nails short and clean minimizes infection in scratched areas.
- Calamine lotion and menthol are mildly effective. Oatmeal baths are useful, and occasionally topical steroids, such as 1% hydrocortisone, are required.

Neuropathic pain. Neurologic complications such as herpes zoster radiculitis, peripheral neuropathy (either from HIV itself or from antiretroviral agents), and HIV encephalopathy often cause a unique kind of pain called neuropathic pain. Neuropathic pain is caused by an abnormal excitability in the peripheral or central nervous system that patients often describe as a burning or stabbing sensation. Neuropathic pain is notoriously unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDS) and to opioid analgesics, and therefore adjunctive agents such as antidepressants (e.g., tricyclic antidepressants) and anticonvulsants have been effectively used.

General Principles of Pain Management

Pain results not only from a physical sensation but also from many contributing psychosocial factors. The treatment of pain, therefore, should include medicinal and nonmedicinal stratagems.
When choosing a medicinal strategy, remember to proceed as the World Health Organization describes: 1) by the ladder, 2) by the mouth, and 3) by the clock whenever possible.

**By the ladder.** Figure 5 and Figure 6 are useful guides for starting a patient on analgesics. The key decision here is assessing the severity of the patient’s pain.

**By the mouth.** Oral administration is the easiest route for an alert patient. The patient is allowed a role in his or her own care and can feel empowered by this participation.

Intravenous or intramuscular routes of administration are useful for patients in excruciating pain or who are vomiting, but these routes are more difficult to administer, can cause pain themselves, and require more frequent dosing because of more rapid metabolism.

Transdermal administration is effective in patients who cannot take medicines by mouth. There is a delay of 12-24 h until therapeutic levels are reached once a patch is placed, and drug continues to be released for up to 24 h once the patch is removed. The titration of the medicine should occur only at 72-h intervals. A patient’s skin must also be clean, hairless, and dry. Profuse sweating can impair adhesion and alter absorption rates.

Many analgesic drugs are available as rectal suppositories. This mode of delivery has a role to play in pain control, but absorption of drugs by the rectal route can be inconsistent. Rectal medications should not be used in patients with neutropenia (low white blood cell levels) or thrombocytopenia (low platelet counts) because of the risk of infection and bleeding.

**By the clock.** Administering pain medication on a scheduled basis is the preferred method of achieving analgesia. Scheduled regimens account for the half-lives of the drugs and help to achieve a consistent level of the drug in the bloodstream, providing a consistent analgesic effect.

Clinicians argue that maintaining analgesia takes less medication than attaining it—it takes more medication to make pain go away than to keep pain away once it has been relieved.

With PRN (“as-needed”) regimens, patients may wait until their pain is unbearable before taking a dose and then have to accept the defeat of the pain prior to taking a needed treatment.

PRN dosing is useful in addition to scheduled medication as a breakthrough pain dose. The breakthrough medication is usually a short-acting opiate and should be 10% of the total daily dose of opiates. One can offer this treatment every 4 h, and one can use the number of daily breakthrough doses required to adjust the scheduled doses at the next provider encounter.

**Specifics about Drug Classes**

1. **Ibuprofen or other NSAIDS:** such drugs block the synthesis of specific prostaglandins through inhibiting cyclooxygenase.

   These medications are efficacious in relieving mild pain and as an addition to opiates for moderate to severe pain. Chronic scheduled use of these medications (greater than 2-4 weeks) can increase the risk of gastric ulcers. Patients with coexisting HIV-related gastrointestinal symptoms may not tolerate NSAIDS. Also, patients with renal or liver disease should avoid these medications because they
### Give only one drug from the opioid and non-opioid group at a time.*

*Exception: If no codeine, aspirin every 4 hours can be combined with paracetamol every 4 hours—overlap so one is given every 2 hours.

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Starting Dose in Adults</th>
<th>Range</th>
<th>Side Effects/ Cautions</th>
<th>Starting Dose in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-opioid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paracetamol</strong> (also lowers fever)</td>
<td>500 mg 2 tablets every 4-6 hours (skip dose at night or give another analgesic to keep total to 8 tablets).</td>
<td>Only 1 tablet may be required in elderly or very ill or when combined with opioid. Mild pain might be controlled with 6 hour dosing.</td>
<td>Do not exceed eight 500 mg tablets in 24 hours (more can cause serious liver toxicity).</td>
<td>10-15 mg per kg every 4 hours oral, not to exceed 75 mg/kg/day in infants and 100 mg/kg/day in children</td>
</tr>
<tr>
<td><strong>Aspirin</strong> (acetylsalicylic acid) (also anti-inflammatory and lowers fever).</td>
<td>600 mg (2 tablets of 300 mg) every 4 hours.</td>
<td></td>
<td>Avoid use if gastric problems. Stop if epigastric pain, indigestion, black stools petechiae or bleeding. Do not give to children under 12 years. Avoid if presence of any bleeding.</td>
<td>Avoid use if possible</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong> (also anti-inflammatory, lowers fever, for bone pain).</td>
<td>400 mg every 6 hours.</td>
<td>Max. 8 tablets per day.</td>
<td></td>
<td>5-10 mg per kg every 6-8 hours, not to exceed 40 mg/kg/day</td>
</tr>
<tr>
<td><strong>Opioid for mild to moderate pain</strong> (give in addition to aspirin, ibuprofen, or paracetamol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Codeine</strong> (if not available, consider alternating aspirin and paracetamol*).</td>
<td>30 mg every 4 hours.</td>
<td>30-60 mg every 4 to 8 hours.</td>
<td>Give laxative to avoid constipation unless diarrhea.</td>
<td>0.5-1 mg per kg per dose every 4-6 hours</td>
</tr>
<tr>
<td><strong>Opioid for moderate to severe pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral Morphine</strong> 5 mg/5 ml or 50 mg/5 ml.</td>
<td>2.5-5 mg every 4 hours (dose can be increased by 1.5 or doubled after 24 hours if pain persists).</td>
<td>According to need of patient and breathing.</td>
<td>Give laxative to avoid constipation unless diarrhea.</td>
<td>0.2-0.5 mg per kg every 4 hours</td>
</tr>
<tr>
<td>Drop into mouth. Can also be given rectally (by syringe).</td>
<td><strong>There is NO ceiling dose.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 6. Use of opioids and nonopioid analgesics. Adapted from WHO Guidelines on Palliative Care.*
can precipitate renal failure by their action on the kidneys’ glomerular regulation of blood flow.

2. **Salicylates (aspirin):** Pediatric use of aspirin for pain has declined since the 1970s because of its association with Reye’s hepatic encephalopathy. Aspirin does maintain a role, however, in rheumatologic conditions and for inhibiting platelet adhesion.

3. **Acetaminophen (paracetamol):** Paracetamol has replaced aspirin as the most widely used antipyretic and mild analgesic agent for children throughout the world. It has a good safety profile, often comes in oral and rectal preparations, and is not associated with the gastrointestinal or antiplatelet side effects of aspirin or NSAIDS. Unlike aspirin or NSAIDS, this agent has little anti-inflammatory action.

4. **Opiates (e.g., codeine, morphine):** Opiates are the backbone of any regimen for moderate to severe pain and are useful for other symptoms encountered near the end of life. Opiates are available in all dosing forms and have been formulated for slow and rapid effects (Table 2). These drugs activate special receptors that modulate pain. These opiate receptors are widely distributed throughout the body, explaining the many side effects that can occur with their use.

Side effects that need monitoring during opioid use include constipation, sedation, itching, and nausea and vomiting. Respiratory depression, although greatly feared among health care providers, is rare when opiates are used appropriately. Constipation is a particularly troubling problem, and patients should be started on a stool softener and/or laxative at the initiation of opioid medication.

### Nonpharmacologic Interventions

Although nonpharmacologic approaches to pain management should not be used as an excuse to withhold appropriate analgesics, there are measures that can be taken in the pediatric population to relieve the fear and anxiety that often amplify pain. Age-appropriate comfort measures can include the following:

- Infant-specific comforts (swaddling, carrying, and breast-feeding)
- Massage therapy (stroking, rubbing, or deep manipulation of muscles)
- Distractions (storytelling, playing a game, or listening to music)
- Relaxation techniques (progressive muscle relaxation and controlled-breathing exercises)
- Individual or group psychotherapy

Simply giving information regarding the disease process and medical procedures can help children and their families feel less out of control. Informing them of their pain control options and including children and their caregivers in decision making can go far to help make pain management more effective.

### Symptoms Near the End of Life

Certain troubling symptoms can occur near the end of life in patients with HIV/AIDS. Symptom management at the end-of-life stage must address the patient’s physical, psychological, and social needs. Being aware of the following symptoms and knowing how to manage them can provide much comfort and relief for the dying.

**Dyspnea**

Dyspnea is a frequent complaint for HIV/AIDS patients, who have often suffered from chronic pulmonary disease during the course of their illness. Breathing through a straw readily demonstrates the discomfort and anxiety produced for patients with severe dyspnea.

As in all cases, a careful search and empiric treatment for the underlying cause is critical to halt or reverse the parenchymal damage to the lungs. Pulmonary edema from heart, renal, or liver failure are key to recognize and treat with diuretics. A metabolic acidosis with compensatory respiratory alkalosis is a common cause of breathlessness.

Symptomatic treatment with opiates is effective while treating the underlying cause. Many providers fear

### Table 2. Equianalgesic dose of various opiates

<table>
<thead>
<tr>
<th>Medication</th>
<th>Oral Dose (mg)</th>
<th>IV Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>N/A</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 (acute)</td>
<td>10 (acute)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>N/A</td>
<td>0.1</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

N/A - Not applicable.
respiratory depression or blunting the respiratory drive, which may hasten the death of their patients. Prospective studies have investigated this question of respiratory depression, which does not occur when opiates are cautiously titrated in the breathless patient. In fact, respiratory depression does not occur without concomitant central nervous system depression, which a caregiver can easily identify. The caregiver can hold doses or notify the provider when this occurs.

Anticholinergic medicines such as scopolamine can help to reduce secretions. Providing supplemental oxygen and having the patient sit upright or elevated in bed can also help.

**Diarrhea**

Diarrhea is common in the end stage of HIV/AIDS and can persist despite appropriate specific treatments for common pathogens. Patients with diarrhea are at risk for volume depletion, electrolyte disturbances, and skin breakdown.

Diarrhea can persist because of resistant or difficult-to-treat pathogens such as *Isospora* or *Microsporidium*; malabsorption from pancreatic insufficiency, bowel wall edema, or bacterial overgrowth; or side effects from medications or overtreatment with laxatives used to offset the constipating effects of opiates. Additional “overflow diarrhea” from severe constipation or fecal impaction also commonly occurs.

Once the underlying causes for diarrhea have been investigated and treated, the following medicines can be useful:

- Kaolin or Pectin help to bulk the stool, but these can have a delayed onset of 48 h.
- Loperamide 4 mg at the onset of diarrhea and then 2 mg after each unformed stool. (Package insert lists 16 mg as the maximum per day.)
- Tincture of opium, which contains 10% morphine. Adult dose, 0.3-1 mL every 2-6 h to maximum of 6 mL/24 h. Child dose, 0.005-0.01 mL/kg of body weight every 3-4 h for a maximum of six doses/24 h.
- Others include bismuth, cholestyramine, and pancreatic enzymes.

**Constipation**

Constipation is often multifactorial and occurs from too much or too little solid waste, decreased water content in the stool, and poor motility. Being confined to bed can cause motility problems, as can the use of certain drugs (e.g., opioids). The cause of the constipation needs to be identified prior to initiating treatment by obtaining a thorough history of diet, fluid intake, level of activity, and medications. Physical examination should include palpation of the abdomen and a digital examination of the rectal vault to assess for stool.

Interventions for constipation can include the following:

- Fiber. Constipated patients may improve if fiber (e.g., psyllium) is added to their diet. However, patients with minimal fluid intake or poor gut motility at the end-of-life stage may develop a fecal impaction from eating more fiber.
- Laxatives and stool softeners. Magnesium hydroxide, senna, docusate, and bisacodyl are all medicines that soften stool and should be used with opiates.
- Sorbitol or lactulose. Stool water content can be increased by increasing the amount of fluid intake or adding osmotically active particles that retain water.
- Restriction of fruit juices. Juice draws water into the gut, exacerbating dehydration.
- Lubricants. Mineral oil taken orally and glycerin suppositories or soap-based enemas given rectally ease the passage of stool by lubrication.

**Nausea and Vomiting**

Nausea and vomiting often occur and can lead to medication nonadherence, dehydration, electrolyte imbalances, malnutrition, and wasting. Obstruction of the bowel caused by constipation, dysmotility, infection, inflammation, medications, and psychological factors can lead to nausea and vomiting. A thorough history should be obtained, with particular attention to associated symptoms and factors that increase or decrease these symptoms.

If possible, one should treat the underlying cause of nausea and vomiting. Otherwise, one can use several palliative interventions to help decrease symptoms and promote optimal hydration and nutrition, including the following:

- Avoid favorite foods when nauseated to prevent aversion to that food in the future.
- Avoid reclining or lying supine after eating; reflux and nausea may occur.
Pain Management

• Eat (or serve) small portions of food at mealtime.
• Foods and liquids at cool temperatures may be better tolerated by someone who is nauseated.

Anorexia
Patients near the end-of-life stage often experience significant weight loss from many factors. Weight loss of more than 10% of premorbid weight can cause significant morbidity and is a risk factor for early mortality.

Weight loss is caused by decreased intake from chronic nausea or early satiety, increased metabolism from HIV or an underlying malignancy, or psychological factors including depression.

Megestrol or Marinol can have limited efficacy in appetite stimulation. Cyproheptadine, or Periactin, is effective for appetite stimulation in children.

Peripheral Edema
Peripheral edema can occur in the end-stage patient from heart, liver, or renal failure, but it is commonly a result of hypoalbuminemia that results from chronic wasting and malnutrition. Identifying the cause via history, physical, and laboratory analysis is always indicated.

Peripheral edema may be only cosmetically disturbing when mild but can lead to pain, draining sores, infection, and decreased mobility when severe.

Diuretics and salt restriction are key treatments for edema but should be used with caution where routine monitoring of electrolytes and volume status are limited; overdiuresis can hasten volume depletion, renal failure, and death.

To treat edema, using diuretics, such as HCTZ (hydrochlorothiazide) 12.5-50 mg once daily, is moderately useful, but only if the creatinine level is less than 1.5 mg/dL (132 µmol/L). This treatment approach does not work when the creatinine level is greater. Lasix 20 mg twice daily and up (adult dosing; pediatric dosing, 1 mg/kg of body weight/dose) is effective but requires potassium supplementation and creatinine monitoring. Elevation of the legs above the hips for 30 min three times per day is helpful. Compression stockings are useful for preventing edema and limiting accumulation when ambulating.

Intractable Hiccups
Although occasional hiccups can be amusing, intractable hiccuping can be disruptive and distressing to patients. Hiccups commonly occur from irritation of the vagus or phrenic nerves that innervate the diaphragm and can be irritated by infections of the lungs or gastrointestinal tract. Other causes include systemic diseases such as renal failure or liver disease.

Treatments for hiccups are limited and lacking in evidence but have been attempted because of the debilitating nature of hiccups. The following treatments include medicines that have many interactions with other drugs and should be used cautiously in HIV patients, who often are already on many other medications.

• Chlorpromazine 25-50 mg per os three times daily.
  Chlorpromazine is the only U.S. Food and Drug Administration-approved drug for hiccups.
• Baclofen 5 mg per os three times daily is also useful for symptom relief.

Summary
Pain can be a debilitating aspect of living with HIV/AIDS. The health care provider must assist each patient in being as pain free as possible. Children with HIV/AIDS in particular require special advocacy because they often rely on adult caregivers to respond to their pain. Effective medicinal and nonmedicinal mechanisms exist to recognize and treat pain. Attention to certain key symptoms at the end-of-life stage for terminally ill patients can relieve much suffering.

References


Objectives

1. Identify psychosocial factors that affect children and adolescents infected with human immunodeficiency virus (HIV)/AIDS and how these factors relate to general chronic illness.
2. Identify sources of stigma and discrimination against children and adolescents and explore how stigma affects disclosure of HIV status.
3. Examine issues of death and dying and the grief/bereavement process that follows for survivors.
4. Identify particularly vulnerable pediatric and adolescent populations and explore reasons why they are at increased risk of HIV/AIDS infection and progression.
5. Discuss special issues encountered by adolescents infected with and affected by HIV/AIDS.

Key Points

1. Pediatric patients with HIV/AIDS experience many of the stages and stresses of other pediatric chronic and terminal illnesses.
2. Stigma affects all aspects of caring for children and adolescents infected and affected by HIV/AIDS, especially as they face the issue of disclosure of HIV status.
3. Death and bereavement are important aspects of chronic illness that must be addressed with children and their families.
4. Orphans and young girls are at increased risk of contracting sexually transmitted infections, including HIV, and of receiving less support and education than their peers.
5. Adolescents are a unique population with a pivotal role in the future of the pandemic. They need special care and attention, with an emphasis on support and education.

Overview

Children and adolescents are an ever-growing part of the human immunodeficiency virus (HIV)/AIDS pandemic. In 2007, an estimated 2.1 million children younger than 15 years were living with HIV, and 290,000 children died from the disease in 2007 alone. HIV/AIDS takes an enormous physical toll on those infected by the virus as well as those who care for them. However, the psychological toll of the pandemic is just as significant. The psychological and social effects of HIV/AIDS are magnified in today’s youth.

Children involved in the pandemic face a set of psychological and social issues that must be addressed, not overlooked. This chapter will discuss how children and adolescents are affected by important aspects of the HIV/AIDS pandemic, including stigma, disclosure, and death, as well as how health care professionals can support them while dealing with these challenges.

HIV/AIDS as a Chronic Illness

In many parts of the world, HIV/AIDS is still viewed solely as a terminal illness, a disease from which there is no recovery. However, with the ever-improving availability of antiretroviral therapy, HIV is increasingly recognized as a chronic, rather than terminal, illness. This transition requires psychological adjustments, especially in the pediatric and adolescent populations.

A chronic illness is a disorder with a protracted course that can be progressive and fatal or associated with a relatively normal life span despite impaired mental and/or physical functioning. This broad definition encompasses multiple types of conditions, ranging from fatal to lifelong, including HIV/AIDS. Unlike acute conditions, which develop and resolve within a limited amount of time, chronic conditions are permanent.
and usually have no cure. Of the main characteristics experienced by children with chronic conditions, children with HIV infection may experience the following:

- Limitation of developmentally appropriate functioning
- Dependency on medication
- Need for more medical care than is normal for their age
- Disfigurement resulting from certain opportunistic infections or severe wasting accompanying progressive disease

Because chronic illness persists for an extended time, infected children and their caregivers go through psychosocial stages that can be sources of great stress, including the following:

- Initial diagnosis
- Disclosure of disease status to the child
- Difficulties resulting from long-term care, including financial and emotional strain
- Preparation for and acceptance of the patient’s eventual death

For pediatric patients with HIV, the preceding stages have increased psychological stress. Stigma surrounding HIV negatively affects disclosure, influences daily care of the patient, and even continues through to the patient’s death. With regard to difficulties with long-term care, adherence to HIV medication regimens is extremely taxing on the patient and his or her family. To prevent resistance, the child must take the medications with a greater than 95% rate of adherence. This task can be difficult for an adult patient and increasingly difficult when the patient is a child or adolescent. Oftentimes, caregivers fall into the pattern of “miscarried helping.” In miscarried helping the family feels the overwhelming need to help the patient with his or her medication regimen and becomes excessive in the frequency of their helping. They may also invoke negative feelings in the patient by telling him that he is “bad” when he misses his
pills. As the patient gets older, he wants to have a sense of autonomy from his caregivers. With the family’s need to help and the patient’s need for autonomy, conflict arises, which can lead to poor health outcomes for the patient. Health care providers must guide the caregiver to ask the patient how to best be helpful regarding medication adherence. By giving the patient the power to direct the help from their caregivers, the patient feels a sense of control over the helping while the family can remain involved in the care.

The stressors of a chronic illness can be more challenging when the patient is a child. This situation increases the necessity for caregivers and other family members to assist with medical care and activities of daily living. Chronic illness creates a series of challenges for those involved in the child’s care. These challenges fall into three general areas: emotional, cognitive, and behavioral. Emotionally, the family must come to accept the child’s diagnosis. Doing so includes grieving the loss of the idea of their once-healthy child, as well as guilt, sadness, and anger. If the child acquired HIV through mother-to-child transmission, the mother may feel enormous guilt and may be blamed by other family members for the child’s infection.

The cognitive challenge is to educate the child’s family about HIV/AIDS. They must understand the available treatment options and the importance of adherence to the prescribed medication regimen. If they understand how the medications work, family members can become an informed asset to the team providing the child’s medical care. The family should also be educated regarding the symptoms of disease progression and possible side effects of medications. This way the family will know what to look for when the child falls ill or develops new symptoms. The cognitive challenge also includes education specifically for the patient. The pediatric patient must have a developmentally appropriate understanding of why they see the doctor and why they take medications. This understanding may include using developmentally appropriate language such as “bugs” in place of HIV or “soldier cells” in place of CD4/T cells. Often, education with children is more successful with visual tools such as drawing and videos.

The behavioral challenge consists of incorporating the child’s chronic illness in the daily life of the child and the family. The child’s medications and clinic visits need to be a part of daily living, though they often require major adjustments and place strain on family relationships and routines. Amid the required behavioral changes, the child’s caregivers must also try to maintain a sense of normalcy for the child. Despite living with a chronic condition, children still need rules, discipline, and routines. Routines are especially important for children dealing with stressful or new situations because they help provide a sense of security.

Living with a chronic illness can lead to psychological stress that can build over a long time. People living with HIV are twice as likely to be diagnosed with major depressive disorder. Children living with HIV may have decreased social functioning in comparison with their peers. This decline in social functioning or peer relations may signify the child’s increased difficulty managing his or her HIV diagnosis and/or treatment regimen. This decline may be more apparent as the child grows older and the significance of his or her HIV infection changes with relation to developmental stage. Also, living with a long-term chronic condition also lends a patient to experience burnout. With burnout, a patient may feel depressed and isolated. He or she is frustrated with the medication regimen and the constant requirement to maintain greater than 95% adherence. Often families will shame or guilt their children into taking their medications consistently, which will wear down the patient mentally over time. Health care providers can help reduce patient burnout in chronic illness by using “the 4 Rs”:

1. Realistic goals
2. Reduce blame and criticism in medication adherence
3. Reach for progress, not perfection
4. Recognize negative feelings about disease management as normal and important for the patient to discuss

Children with a chronic illness such as HIV/AIDS face unique challenges that make their lives more difficult. It is important to understand the long-term effects that these challenges can have on the children and their caregivers. With proper support from their health care providers and their community, the challenges of living with childhood HIV/AIDS will be easier to surmount.

HIV/AIDS and Stigma

A major distinction between HIV/AIDS and other chronic or terminal illnesses is the stigma associated with the disease. This stigma often stems from a lack of knowledge
about HIV and how it is transmitted. Stigma can adversely affect children and their caregivers in ways that have long-term negative psychological and social effects.

Previous work has defined stigma as “a negative, moral, or judgmental definition of a person or social situation, often connected to discredit, disgrace, blame, and ascription of responsibility for the conditions.” The stigma that a person carries can alter how he or she perceives and interacts with the world, even affecting how a person thinks and feels about him- or herself as an individual. Stigma surrounding HIV/AIDS is not particular to one generation or one part of the world. It has been an evolving aspect of the disease since the first cases emerged in the early 1980s, and it has become prevalent in all geographic locations—even those with limited mass media influence.

The stigma surrounding HIV/AIDS originated with the association of the disease with homosexual men and intravenous drug users, two marginalized groups in which HIV/AIDS first gained medical attention. The mass media played a large role in increasing the level of stigma around HIV/AIDS. When the medical community initially thought that HIV was transmitted solely among homosexual men, the media came to refer to HIV as “the gay plague.” Through this language, people generalized HIV to be associated with perceived immoral behaviors such as sexual promiscuity and intravenous drug use. Although the medical community soon discovered that transmission was not limited to these groups and behaviors, stigma persisted. HIV/AIDS stigma is also reinforced by the fact that the disease can be fatal, has no cure, and has noticeable physical effects during its advanced stages.

The pediatric population was not a prominent part of the media attention in the initial phase of the pandemic. When HIV/AIDS was first being documented, few children were known to be infected. The first groups of HIV-positive children to be recognized were those who had received infected blood products, particularly young boys with hemophilia, and children born to HIV-positive mothers. Today, those infected through mother-to-child transmission make up nearly all HIV-positive patients younger than 15 years. Infection among adolescents (aged 15-24 years) is growing at an astounding rate, mostly through sexual transmission.

Three concepts are helpful in understanding stigma as it relates to the pediatric HIV population: associative stigma, internalized stigma, and stigma management.

Stigma is associative when it affects people because of their association with a stigmatized person, such as a person living with HIV. Associative stigma may affect caregivers who help care for infected children or affected children whose parents have died from the disease. Children may be affected by associative stigma if their parents are publicly known to be infected with HIV. Other examples include being friends with an HIV-positive person and attending a social or fundraising event aimed at people living with HIV.

Internalized stigma can be particularly damaging. Such stigma occurs when a person is aware of a social stigma and accepts, or internalizes, society’s negative views. Doing so damages the person’s self-esteem and gives him or her a negative sense of self-worth. Internalized stigma has a large effect on the pediatric population through its influence on parents’ decisions to disclose. If parents or caregivers have internalized the stigma and negative views of HIV/AIDS, their likelihood of telling the child about his or her diagnosis decreases significantly. If adolescents internalize the stigma regarding their diagnosis, they are more likely to become depressed and engage in denial regarding their HIV status. Adolescents may fear disclosing their status to others and feel shameful regarding their condition.

Stigma management is a way of coping with stigma by being aware of possible negative reactions and finding ways to minimize them. People living with HIV practice stigma management by choosing and limiting whom they disclose to in order to minimize the chance of negative reactions or rejection. They may also “test” potential friends or loved ones they wish to disclose to by discussing HIV education or using probing questions to discern the person’s understanding and personal opinions regarding people living with HIV.

Stigma surrounding HIV/AIDS can severely influence those infected with or affected by the virus. Many people living with HIV fear the stigma from their community more than they fear dying from the disease. Prone to both stigma internalization and stigma management, HIV-positive people are less likely to seek social support for fear of rejection and isolation. In some areas, because of
stigma HIV-positive children are banned from school and other community activities. In other regions, children are allowed to attend school but are required by law to reveal their HIV status.

To safeguard a child from experiencing stigma, caregivers often practice stigma management and delay disclosing the child’s diagnosis to the child. Between 25% and 90% of school-aged HIV-positive children are unaware of their own HIV status. Some caregivers feel that if children are unaware of their diagnosis, they are less likely to tell the wrong people. Other caregivers feel that if children know their diagnosis, they will internalize the stigma and give up hope. In this way, stigma leads to an atmosphere of secrecy within the family that the child often senses. Children become acutely aware of parents’ feelings toward their diagnosis, through observing interactions with other adults and how they discuss, or avoid, the topic in their presence. Labeling the diagnosis as a secret that cannot be discussed serves only to increase the stigma. Many parents are also afraid to disclose the child’s HIV-positive status because of deep feelings of guilt or shame. The parents may feel guilty about their role in infecting the child and fear that the child will become angry or blame them. Caregivers fear that disclosure of HIV status will eventually lead to questions related to modes of transmission for the adult, which may involve discussing family secrets such as infidelity or drug use.

Clinicians play a large role in assisting families with the disclosure process. Many families choose to disclose in the clinic setting so that they can receive the educational support of the physicians and other clinic staff. Disclosure is not one event but rather more of a process. The patient should be allowed to absorb the information at a pace that is comfortable, which often means that the discussion may start during one visit and continue through the next few visits. It is good to begin with universal terms that children and youth will understand, such as describing CD4 cells as “soldiers” and HIV as a “bug.” It is beneficial to use as many audio and visual aids as possible because many children learn better with these additional tools. If medications are available, discuss the diagnosis as a chronic illness and provide the patient with realistic hope. Because many disclosures take place in the clinic setting, it is important to ensure that clinic staff are trained and comfortable in participating in the disclosure process. Caregivers should also be prepared for disclosure: the caregiver may be asked additional questions when the family has returned home and the child begins mentally processing the disclosure.

Patient families need to be supported and educated, along with their communities. Through basic education about the virus, how it is transmitted, and treatment options, much of the stigma surrounding HIV/AIDS can be dispelled. With knowledge, long-standing myths and rumors can be laid to rest and the truth regarding HIV can replace fear and ignorance. Through educating the community at large, families and children infected with and affected by HIV/AIDS can receive much-needed support and will no longer feel alone in their struggle.

**Death and Bereavement**

Despite the increased availability of highly active antiretroviral therapy, many people lose their lives to HIV/AIDS each year. In addition to the children who die from HIV infection, millions of affected children lose one or both parents to AIDS. Often children’s psychosocial needs are overlooked during this time of loss, and children are not given full recognition or support. This problem is usually due to the belief that children are too young to understand what is happening or are better served not dwelling on their grief.

It is often difficult for medical professionals to work with dying patients. Medical training often does not address how to provide palliative care, and many of the lessons learned around dying are done informally and at the time of the patient’s death. Physicians often do not feel comfortable addressing death with patients for fear that the patient will lose hope and give up. It is important to have open and honest discussions with patients to help increase their understanding of the situation and feel supported by their medical team. In a study completed in Uganda, the three most important needs of the dying patient were control of pain and symptoms, counseling services around stigma and healing family relationships, and addressing financial needs for surviving family members. The preferred site of care in the end of life was at home. At home, a patient feels that he or she can better maintain privacy and can receive support from family and sometimes the larger community. Often, patients are most afraid of dying alone, and being able to spend their last days at home can calm this fear.

When a parent or caregiver approaches the end stages of AIDS, a plan of care must be created for the surviving
children. This process is referred to as permanency planning. When this step is not taken, children are left in a state of uncertainty about who will care for them, which can compound the loss felt by the child after a parent’s death. The child may be separated from siblings and may experience frequent shifts from place to place in search of a proper home. Children whose parents do not complete permanency planning are at increased risk of developing emotional and behavioral problems. Several things should be considered when creating a permanency plan. It is best to start with the needs expressed by the dying caregiver. Ask open-ended questions, such as “What do you feel are the most important issues for your family after you pass?” and “What will be left undone if you were to die sooner rather than later?” The caregiver should decide where the children will live once he or she has passed. This could be in the home with the surviving parent or with another family member. It is common if the surviving parent is the father to have the caring shifted to a female relative, potentially outside the home. Conversations with the person chosen to be the future caregiver should take place to make this person fully aware of this new responsibility and to ensure acceptance of the plan. If possible, financial planning should be discussed to help pay for food, clothing, and school fees if needed. For surviving children with medical conditions, education sessions should be conducted with the new caregivers prior to the parent’s passing. If possible, have the new caregiver attend a clinic visit with the parent and child. This way the new caregiver can become familiar with the setting and the clinic staff and can ask questions about the illness and/or required medications. Having a permanency plan in place will help ease the transition after the caregiver’s death.

For children who have lost parents or family members, grief can be overwhelming and hard to understand. The death of a parent is one of the most stressful life events that a child can experience. The effects of this loss can be found years after the death occurs, often not even manifesting until 1-2 years later. Some children even show symptoms of posttraumatic stress disorder after the loss of a parent. This disorder is more common in girls, children who are on average younger, and children who still live with a surviving parent. Losing a parent, particularly at a younger age, demonstrates early for a child that he or she is not invincible and brings into question his or her own mortality. This effect can then be compounded if the parent died from AIDS-related illness and the surviving child is HIV positive.

Grief and bereavement experiences are unique to each individual and often involve different types of responses, including physical, emotional, behavioral, cognitive, spiritual, and social. Grieving children must be able to discuss and acknowledge their loss and must have an opportunity to release their grief. For example, children could write letters addressed to the person they lost. Doing so gives them the opportunity to say feelings or thoughts that were not relayed prior to the person’s passing. Younger children might draw pictures instead of writing letters. Without such opportunities to release their grief, they may experience psychological ramifications well into adulthood.

Children commonly experience a regression in their behavior while grieving. They may begin to display behaviors that they have not exhibited in a long time. Some examples are wetting the bed, self-soothing actions such as sucking on their thumbs, or increasing their physical contact with adults—all actions that help increase their sense of security in a time of confusion. Attention helps children to remember that they have not been forgotten. Some children will try to gain attention through acting-out behaviors. Although acting-out behaviors often result in negative responses, children will ultimately be reassured by the one-on-one attention that they get through discipline from an adult.

One must understand how children’s views of death are shaped by their developmental age. For children younger than 4 years, comprehension of death is limited. Their limited language skills at this point in their development also affect this issue. The children recognize a change in their patterns of care and realize that the deceased person is no longer in the environment. These children may be more irritable than usual and may exhibit regressive behaviors. Maintaining consistency within the home and providing constant reassurance are both ways to help young children cope with the loss and change to their environment.

From 4 to 7 years of age, children believe that the deceased parent is just away for a short time and will eventually return. For them, death is something that is reversible. They have no comprehension of the finality of death. They may ask questions regarding the process of death and be curious regarding the “how” and the “why” of the person’s passing. The child may attempt to do tasks that were originally the responsibility of the deceased. Children of this age also begin to exhibit
forms of “magical thinking,” in which they believe that they have the power to affect things with their thoughts or actions that in reality are out of their control. For example, a child who made his mother angry shortly before her death may believe that he is responsible for her death. Children in this age range should be allowed to discuss the loss and to ask questions in a supportive environment.

At ages 7-11 years, children come to realize that death is final and irreversible. These children are concrete thinkers and have trouble comprehending anything beyond the physical death that has occurred. They may not understand why the person passed away and will ask detailed questions. Through experiencing the death of a loved one, the children in this age range worry about their own bodies and any bodily harm that could be done to them. They may also be concerned regarding how others are responding to the death. During this period, children may show aggressive tendencies, display risky behaviors, become excessively impulsive, and might also regress. It is important to be open and allow discussion if the child is interested; however, it is also important to allow the child to process his or her thoughts alone if needed.

During adolescence, ages 11-18 years, youths begin to understand death in an abstract sense. They think of death in terms of an afterlife as well as a physical death and try to make logical sense of death within the larger framework of life. As adolescents are developmentally separating from family and aligning with peer groups, they may often want to gain support from friends outside family relationships. Adolescents might experience random and intense emotional outbursts. Adolescents should be provided with opportunities to verbalize their grief and should have their feelings validated during this time, not minimized.

It may take years for a child or adolescent to fully accept a parent’s death. Support is a key factor in grieving. This support can come from their families, friends, and communities. Rituals are a central part of death and grieving for communities around the world. Often children have assigned roles during such rituals. For some, participating in rituals can help with the transitional period caused by the loss and help begin acceptance of the loved one’s passing. For others, these roles can increase the trauma experienced by the mourner. Children must be supported before and after the ritual to reduce the amount of stress that they experience. If participation in the ritual is optional, children should be allowed to choose whether they would like to participate.

The concepts of death and dying become more complicated when the dying patient is a child. When facing their own death, many experience anticipatory grief. With anticipatory grief, the dying person is still alive, but the patient and family members begin grieving prior to the death. Often, people experiencing anticipatory grief will project their feelings onto others. For example, children who are dying may be more afraid of their caregivers’ dying. They will panic at the thought of anything traumatic happening to their caregivers, when in fact they are afraid of their own death and what will happen to their loved ones when they are gone. Children may also show signs of knowing about their fate through symbolic play or art. They may pretend that toys are dead or draw death in their artwork. Children may become withdrawn, quiet, increasingly irritable, and display regressive behaviors. They will inevitably feel a loss of control in the world around them. To help children face this oncoming event, they must have the opportunity to express what they are feeling and to ask questions about what might happen. These talks must be at a developmentally appropriate level so that the child will understand, and the answers should be honest. Children should be allowed to participate in decisions affecting their care at the end of life. They are the best resource for determining what they want and how much they can tolerate in the end stages of their disease.

Unfortunately, death and grief are harsh realities in the HIV pandemic. Children’s experience of losing parents and loved ones is often compounded by their own illness and by other factors surrounding the loss, such as secrecy and stigma. These families need additional support and care from their health care providers during their time of mourning.

**Orphans and Vulnerable Children**

The HIV pandemic has increased the risk of children and youth suffering from poverty, illness, and abuse, in essence increasing the preexisting vulnerability of children. Vulnerability can be described in different forms and is affected by the age of the child. Children younger than 2 years are more at risk of parental neglect because of their dependence on adult caregivers. They suffer from
lack of food, shelter, and basic care needs if an adult caregiver does not provide for them. Between the ages of 3 and 10 years, children suffer increasingly from lack of educational opportunities, lack of available food, and an increased risk of losing a parent. Adolescents, aged 11-17 years, are made vulnerable by the poverty that surrounds and influences their family. They may be forced to work in jobs that exploit child labor, be forced into early marriages, or have to care for younger siblings. Two specific populations that are more heavily affected by the AIDS pandemic are orphans and young girls.

Approximately 15.2 million children younger than 18 years have lost one or both parents to AIDS, most of them living in sub-Saharan Africa. AIDS has also caused children to lose their siblings, friends, relatives, teachers, doctors, and other significant people in their lives. Also, the mortality rate for children who have HIV-positive mothers is significantly higher than those children with mothers who are HIV negative, showing that children are at a higher risk of losing their own life if their caregiver is HIV positive.

Children orphaned by AIDS are more likely to suffer economic hardship, including loss of property and inheritance. When the family loses a primary caregiver who provided economically for the family, the effects can be widespread. The family may be forced to move to a different region to help earn additional income. For some, doing so includes leaving the rural area to move to the city for more job opportunities or relocating to live with other relatives. Some orphans may not have family members to stay with after a parent’s death. These orphans may try to survive living on the streets or may be forced to stay in an orphanage or institution. Institutions often fail to provide adequately for the physical and psychosocial needs of children, and they actually cost more than direct monetary assistance to families that foster orphans. In some cultures, children will lose property or inheritance when the relatives of the deceased come to claim items such as cars, work equipment, or electronics. This process can compound the loss felt by the surviving children in the family. In addition to economic hardship, educational opportunities for orphans are often limited. New caregivers cannot pay school fees, and often orphans have to work to help maintain the family financial stability or care for younger siblings. Orphans of caregivers who have died from AIDS may also be infected with HIV. The loss of their caregiver may have direct negative effects on their clinical outcomes. Orphans may experience decreased access to medical care with overwhelmed new caregivers who cannot bring all children to a doctor when needed. In Kenya, HIV-positive orphans who were taking antiretroviral treatment were compared with nonorphans taking antiretroviral treatment. Overall, the orphan group had similar short-term outcomes to those of the non orphan group. However, the two groups differentiated with their long-term outcomes in terms of weight gain, with the orphan group decreasing significantly in weight gain after 70 weeks. Also, the orphan group tended to be older at treatment initiation. Fortunately, in terms of adherence and CD4 percentage, there were no differences between the orphans and nonorphans.

Psychologically, orphans may begin to express their difficulties prior to their parents’ passing. They have a hard time adjusting to their parents’ illness and inability to care for them in the final stages of the disease. Children who lose their parents often internalize their psychological turmoil and feel the negative effects from the parental death up to 2 years afterward. Often, the new caregiver does not notice the adjustment difficulties of the orphan in the first 6 months because the child may be well behaved with a new caregiver or too traumatized to externalize his or her negative feelings.

Young women are an equally vulnerable population in the HIV/AIDS pandemic. In countries all over the world, young girls are more often employed in the informal economic sector and are often paid less than their male counterparts, even when they are doing more work. In Northern Africa, the Middle East, Latin America, Asia, and sub-Saharan Africa, young women have a harder time finding employment because of poorer educational opportunities and other social constraints. Some of these constraints include restriction from extensive traveling for employment and lack of available jobs for young people overall. Educational opportunities are lacking for young girls. For example, in India more than half of women aged 15-19 years have no primary education. Sub-Saharan Africa also has a dearth of young girls in school. This lack of education for young women has a ripple effect throughout their lives, affecting their ability to make decisions about their future and their ability to obtain and maintain employment. Poverty within the
community can have an increased negative effect on young girls in the family because they are then made to perform daily chores for the household that detract from their ability to obtain an education. They may need to fetch water daily from the community well, which takes away from their ability to leave the homestead for education or outside work and often exposes them to opportunities for exploitation.

Worldwide, young women are at greater risk of contracting sexually transmitted infections, including HIV, and often do not have the power or skills to protect themselves. Many young women are coerced or forced into unprotected sex. A girl’s vaginal tissue tears easily, putting her at high risk of contracting HIV and other sexually transmitted infections from unprotected sex. A study in Uganda found that young women were nine times more likely to contract HIV than young men. Violence, forced prostitution, incest, and rape, including marital rape, all put girls and women at risk. Coercion can be extremely common among young girls who are living in disadvantaged conditions. Coercion can include forced sex, pressure to have sex in exchange for money or gifts, flattery/pestering/threatening from the male, or passive acceptance.

Every child’s situation is unique. Interventions will be most successful when children’s sex and sociocultural environment are taken into account. Early interventions that include community education and support are essential to help prevent orphans and young girls from being kept out of school and tracked into informal employment.

**Adolescents**

Adolescents are an increasingly important population that deserves special attention. Today’s young adults are becoming infected with HIV at an alarming rate. Also, as antiretroviral treatment becomes more widely available, HIV-infected children are now provided the opportunity to mature into young adults. Adolescence is a transitional period full of critical decisions and turning points for which proper guidance is often needed.

**Disclosure**

Adolescents deal with disclosure issues on multiple levels, from finding out their own HIV-positive status to deciding to disclose their HIV-positive status to others. The American Academy of Pediatrics states that adolescents should know their diagnosis in all cases. Teens should be fully informed of their health status so that they can make informed decisions regarding their actions and life choices. The youth will often need repetitive education around daily living with the virus and how it will mold decisions that they make in their social lives. These decisions involve managing their own health, disclosing to friends and significant others, and sexual choices. While the youth progress through different life stages, they will experience new and different realizations in relation to their diagnosis.

Youth living with HIV (YLH) face the decision of whom they will disclose their diagnosis to. Many youth have disclosed to their families, and many choose to disclose to close friends. Disclosing to others is associated with positive outcomes and lower stress levels. However, stigma surrounding HIV/AIDS makes people more cautious about disclosure. To manage stigma, YLH often are selective about whom they tell and when, protecting themselves against negative reactions and social isolation. Multiple factors must be considered when deciding whom an adolescent will disclose their HIV status to, including how they have adjusted to their own diagnosis, their assessment of their own disclosure skills, and their motivation to proceed with disclosure. Youths must also evaluate the circumstances of the person whom they plan to tell, anticipate what that person’s reaction may be, and determine how well they feel the person will be able to keep the information confidential. Many feel that they simply do not have the skills to disclose with positive outcomes. One study showed that HIV-positive women felt that deciding whom to tell was easy but that how to tell was hard. Clinic staff can role-play different scenarios with patients so that they can practice what they are comfortable saying and how they can also provide education to the recipient. Teens who can find a strong circle of support, including people who are aware of and accepting of their diagnosis, have greater self-esteem and outcomes that are more positive.

Once HIV-positive youth begin sexual activity, they have responsibilities toward their sexual partners. Whether it should be legally mandatory for HIV-positive people to disclose their status to sexual partners is widely debated. Despite what the law mandates, adolescents need to have feelings of confidence and trust to disclose their status to their sexual partners. Some YLH do not
disclose to sexual partners, especially during casual sexual encounters. But many youth feel a moral obligation to disclose their HIV status so that their partners are aware of the risk of transmission. YLH should be supported through these decisions and provided with opportunities to practice disclosure and learn explanations that they are most comfortable using. Disclosing disease status can be stressful, especially if the HIV-positive adolescents have deep feelings for their partners and are fearful of rejection. Adolescents feel a strong need to be similar to their peers and feel accepted. For many adolescents, the fear of rejection can even be stronger than their fear of potentially infecting their sexual partner. Strong support is needed at this time and should be offered before, during, and after disclosure. Offer to have the adolescent bring his or her partner to the clinic if the patient would like additional medical education and support.

**Medical Independence**

For adolescents living with a chronic illness, transitioning into adulthood includes an important shift toward medical independence. Despite their previous experience, or lack thereof, with the medical system, YLH need assistance in taking charge of their medical care. Health service involvement decreases in adolescence at the same time that family involvement in youth's health care also declines. This situation can have serious negative implications for the youth's future health as he or she may make poor health decisions, such as missing antiretroviral doses frequently, and are not supported by family members.

Youth should feel empowered to take over their medical care, which requires the clinic staff to use a different approach: involving the YLH in their own goal setting. The youth can no longer be passive in their health care decisions, and physicians must learn to share control over medical decisions with the youth themselves. To help provide this feeling of empowerment, providers must teach adolescents to manage specific tasks, such as managing their appointments, and discussing their medications, scheduling their appointments, and discussing their health concerns directly with their health care providers. To perform many of these tasks, teens must first be thoroughly educated on HIV and feel comfortable discussing it with the health care team. With increased HIV education, YLH will feel more confident in discussions regarding their own health care and will be able to make informed decisions about treatment and management.

Often, adolescents may need to transition to a new health care provider/clinic as they age. Many pediatric clinics do not have funding or capacity to keep youth as they age into adulthood. However, many YLH do not feel equipped to leave the clinic where they have managed most of their health care. Many youth feel that the clinic staff are the "keepers of their health history" and do not try to remember specific aspects of their medical care because they know that the staff keep it on record. When meeting with a new provider, some youth may feel unsure regarding which components of their health history are important to share with these new providers. To assist them, a health history summary can document the pertinent aspects of their medical past and help them make a more positive transition. Health history summary forms should include a list of medications (past and present), prior surgeries, laboratory work, any recurrent

Young people with HIV need psychosocial support as well as medication.
or major illnesses, as well as establish what the youth may have a family history of—for example, cancers or high blood pressure. For teens who are switching to a new provider, additional support is often needed to ensure a smooth transition. To assist YLH with the transition, a member of the pediatric office staff can accompany them to their first visit with their new provider or go with them on a tour of the new clinic and meet the staff prior to the first visit. It is beneficial to have a strong working relationship with the adult clinic/provider in your area to help ensure a smooth transition and prevent adolescents from falling out of care.

**Self-Esteem and Identity**

The adolescent years are one of the most important developmental stages prior to adulthood. Youth pass through three periods during this transition. Early adolescence focuses on a shift in attachments, from parents and caregivers to peer groups. During middle adolescence, youth work on their self-image and begin to develop abstract reasoning. Late adolescence is when youth begin to feel comfortable with who they are becoming as adult members of the greater society. They also gain awareness of others and their relationships. Youth living with HIV encounter additional challenges while passing through these three stages.

If the disease is untreated, the youth may have a delay in physical development, including pubescent changes. Consequently, HIV-positive youth may appear younger and smaller than other adolescents. They may also experience physical changes as a result of their illness, including wasting and opportunistic infections that may cause noticeable physical symptoms. If youth look different from their peers, they have a harder time bonding with them, adversely affecting the adolescents’ peer attachments and making it difficult for them to separate from their parents. These changes may also contribute to a negative self-image. YLH may feel unable to identify with their peers or feel singled out from others because of stigma. Individuals develop much of their identity, the sense of who they are, on the basis of how they compare to others. This sense of identity comes from actions within a social context and is based on whether their decisions are accepted or rejected by others in the group. Rejection from the group can have a serious negative influence on one’s self-esteem and identity. For instance, adolescents bullied excessively by peers can have low self-esteem and a negative self-image that lasts well into adulthood. Peer relationships have a stronger influence on behaviors during adolescence than in any other period in life, including childhood and adulthood. Conversely, not being accepted into a peer group can have an equally strong effect on adolescents. Peers have a strong influence not only on adolescent social behaviors but also on health-related behaviors. These influences can be negative, such as smoking tobacco, or positive, such as encouraging medication adherence in support groups. Connecting with a peer group allows caregivers and clinic staff to understand their adolescent patients. The gained understanding of peer influences allows health care providers to help benefit YLH via support groups and adherence buddies.

Adolescence is also a time of exploration. The stress of having a chronic illness may prevent some YLH from wanting to participate in psychological exploration—especially if they are in denial or are having trouble accepting their HIV status. Dealing with a chronic illness shapes and molds individual identities by altering the individual’s view of the world. Their diagnosis may affect their views of caregivers, affect the role of medical care, and influence whom they trust with confidential information or have romantic relationships with. If not accepting of their diagnosis, they may experience long periods of self-doubt and may be overly untrusting of the world around them. Developing an identity is a difficult task for any young person, a task that requires guidance and support—especially for young people living with HIV. As youth develop, they will systematically begin to organize their lives around who they feel they are as individuals and how this affects where they fit in the world around them, all of which is influenced by their HIV status. In turn, this perception of their place in society then shapes the personal and professional choices that they make, which belief system they align with, and which culture defines them. This sense of identity often becomes the measure of their worth as a person. If YLH are hindered by fear and denial of status, the ramifications on their perceptions of their place in the world can be hugely damaging.

**Sexuality**

Sexuality is an important topic for adolescents, who are at the age when sexual exploration begins. Their drive to explore their sexuality makes adolescents a pivotal population in the HIV/AIDS pandemic. A study done in Uganda found that by age 18 years, 64% of women and
50% of men already reported being sexually experienced. Many youth are poorly educated about sex and safe sex methods. This lack of education on practicing safe sex methods, and the subsequent likelihood that they will not use protection, leaves teens at high risk of contracting and transmitting sexually transmitted infections. Youth are also engaging in sexual exploration at younger ages than in the past. This trend is of great concern because younger groups are even less likely to be educated about sexual protection.

A study conducted in 1999 showed that if youth perceived themselves as more mature than their chronological age, they were more likely to engage in sex earlier than their peers. Their premature transition into adulthood also was a major factor in their remaining sexually active after their first sexual encounter. This factor is important in the discussion of HIV-positive youth because of the increasing number of families headed by young adults. With the absence of parental figures, often due to AIDS-related death, youth are being placed in caregiver roles at much younger ages. Many care for younger siblings, and some are the sole providers for their families. With these responsibilities, youth may feel greater autonomy and may engage in early sexual intercourse.

Some YLH are afraid to engage in sexual activity because of fear of transmission. Sexual expression is part of human nature and normal development. The ability to express oneself sexually and the opportunity to one day be a parent are an innate part of being human. Some YLH experience strong pressure from family members to abstain from sexual activity and even feel pressure to never have their own children. Clinicians involved with youth must educate them on ways to have safe sexual experiences for themselves and their partners, as well as on ways to have their own children without fear of passing on the infection. All teens and adults experience “prevention fatigue.” Similar to medication adherence fatigue, many find it difficult to always use protection. Females are more likely to use protection than males. However, in many places females are not in a position of power to protect themselves during sexual intercourse. Clinicians need to support youth in the ability to use protection consistently.

Receiving support around having a healthy and safe sexual experience can be difficult for some youth. First, some may not seek out safe sex education or tools for fear that their partner may suspect that they are HIV positive. Adolescents developmentally are at a point where they want to be similar to their peer group. However, YLH are aware of distinct differences within themselves that distinguish them from their peers. Youth may go to extra lengths to reduce the differences that they have between themselves and their peers. One example is engaging in sexual practices without protection. Second, education can sometimes be hard to find in a society that feels that sexual activity is against good morals and values. Sexuality in many societies is not openly discussed for fear that youth will then engage in sexual activity too early or because conversations regarding sex are traditionally held privately within families. However, despite these broadly held beliefs, one study found that 82% of 45 television shows most watched by youth contained sexual behavior or talk of sexual behavior. On average there were 11.1 sexual interactions per hour in these shows. However, rarely in these same shows did the characters discuss or refer to methods of sexual protection or the risks of negative outcomes. This situation highlights that even if family members or clinicians do not discuss sexual behaviors, youth are still being exposed to them through the media. Without education and support from adults around them, youth will be guided solely by their peers and the “education” that they receive from the media.

A group that requires special attention within the adolescent population is homosexual and bisexual youth. These youth face the additional stressor of “coming out” to their friends and family about their sexual orientation. This is a daunting task because of the large amount of public stigma and discrimination toward homosexuals and bisexuals. These teens feel different from their peers and experience the “gay-related stress” of growing up homosexual or bisexual in a hostile environment. Symptoms of gay-related stress can include anxiety about disclosing that they are gay, as well as fears that someone will inadvertently find out about their sexual orientation. These youth must learn to integrate their homosexuality into their greater identity. Stress increases if the teen is HIV positive because of the additional stigma carried by the disease. Young homosexual men are at increased risk of becoming infected with HIV and of transmitting the disease. This makes homosexual youth an important population to reach with HIV education and support, to provide them with the tools to protect themselves and others.
Illicit Substance Use and Abuse

Substance use and abuse are common risky behaviors among today’s youth. More young people often use tobacco products and consume alcohol socially. Behind tobacco and alcohol, marijuana is the third most commonly used substance by youth. Tobacco, alcohol, and marijuana are sometimes referred to as “gateway drugs.” People who use any or all of these substances may be more likely to experiment with other, more addictive, drugs. Drugs such as cocaine and heroin are used less frequently, but their presence on the adolescent scene is growing. In Eastern Europe and many parts of Latin America and Asia, injection drug use is a widespread problem that is also fueling the spread of HIV. Youth who begin using substances early tend to use more substances with increased frequency as time goes on.

Screening for substance use among YLH is important; multiple studies have found an increased prevalence of substance abuse-related disorders in this population. Increased substance use can also indicate poor adherence. Substance use can also have major negative medical consequences for YLH. Alcohol consumption can lead to increased susceptibility to opportunistic infections, suppress the immune system, and even compromise the activation of zidovudine (AZT). Most illicit substances can reduce immune system function, which may strengthen the virus. For instance, prolonged exposure to nicotine specifically inhibits T-cell activity. In teens on highly active antiretroviral therapy, these substances can have adverse effects and interactions with the medications, causing the youth to become ill. Like many antiretrovirals, many illegal substances are processed through the liver. Combining the two may lengthen the time that an illegal substance stays in the bloodstream, increasing toxicity and the chance of overdose. Substance use also tends to decrease behavioral inhibitions and increase other risky behaviors. Adolescents under the influence of substances may choose to engage in unprotected sex, putting their sexual partners at risk of contracting HIV.

Clinic staff should ask patients about their substance-using patterns to help provide them education on the negative health effects of the substances, as well as to provide a baseline for their patterns of substance use. These sessions should not be judgmental; such sessions will hinder the youth from fully disclosing their experience of using substances. Teens should also be reassured that their conversation is confidential so that the YLH will not fear repercussions from their caregivers. Educating teens on the adverse effects of substance use and abuse may guide them to make safer life choices.

Conclusion

Education and support are the most effective tools that help children and adolescents with HIV survive into psychologically healthy adulthood. Support can help children recover from the devastating loss of parents and loved ones. Proper support will also help children with HIV/AIDS to progress through the appropriate developmental stages and grow alongside their peers. Through education, children and adolescents can learn to take charge of their own medical care and protect themselves and those around them. They can also extend this education to others and help reduce the stigma within their larger communities. Through the many changes and challenges of childhood and adolescence, the support of family, friends, communities, and health care professionals is essential to the well-being of tomorrow’s adults.

References


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Objectives
1. Understand the complexity of factors that affect the life of an HIV-infected adult.
2. Evaluate and identify means of reducing the personal and socioeconomic effects of HIV/AIDS.
3. Identify and describe appropriate resources for care and support.
4. Identify how caring for people with HIV/AIDS affects health care providers.
5. Identify sources of stigma and discrimination and discuss ways of reducing their negative effects on patients and health care workers.

Key Points
1. The individual HIV disease happens in the context of an HIV epidemic; therefore, understanding psychosocial aspects of HIV in adults involves understanding the interrelations between the individual’s microenvironment and the macroenvironment.
2. Psychological and social factors influence the ability to cope with HIV/AIDS more than the severity of the disease. Stigma and discrimination are critical factors to be considered.
3. HIV has profound psychosocial effects on the HIV-infected person, the family, the community, and the society at large.
4. There is a specific individual dynamic in relation with different stages of chronic disease: disclosure and planning the treatment phase; accommodation with the disease stage; and the final, terminal stage.
5. Helping the patient in finding his or her own best possible adaptation to living with HIV implies interventions of reframing and finding meaning in the new life situation, as much as concrete, practical support.
6. The stressors of caring for patients with HIV affect health care providers, who need to develop resources for personal and occupational support.

Introduction
HIV as an illness affects the person first and foremost at the biological level in the form of an aggressive virus that compromises immunity. Every illness experience represents a unique and dramatic negative experience for the patient; it is associated with a profound and authentic psychological engagement of patients themselves and the significant people in their lives.

Psychologists conceptualize the disease developing based not only on an individual relationship with the nature and the aggressiveness of the viral subtype but also on the psychological response of the person, their experience with other pathologies, and their personality traits. For example, Kalichman et al. provide evidence that patients with personality disorders are at higher risk for HIV exposure than those diagnosed with only clinical symptoms because these patients display little confidence in their ability to enact safer sexual practices, little commitment to condom use, and higher anxiety associated with risk of contracting HIV.

Several studies have found that a substantial proportion of the chronically mentally ill report engaging in HIV risk behaviors. HIV infection adds stress to the already compromised coping skills of the mentally ill, while mental illness itself may increase the risk behavior and thus predispose the affected person to HIV.

HIV-infected adults live in a social and cultural environment, and the economic and political conditions of the state that they live in directly affect these people. In this complex context there are specific developmental stages that all adults, regardless of their HIV status, tend to go through. Developmental psychology described these stages decades ago, and we should consider them when we want to understand the effect of HIV on an adults’ lives and their movement toward achievement of life tasks (Vignette 1). HIV can affect an adult while he or she is forming a couple and developing a sense of intimacy and
trust, or while becoming a parent and moving toward a different life stage: parenthood. For a certain period the illness can take away the person’s ability to work and keep a job, thereby affecting the sense of productivity, self-control, and security of daily life. Redefining identity through the condition of HIV can be a big challenge because it can come in deep contradiction with life goals and plans. Sexuality is important during adulthood; however, having a sexually transmitted disease that is not curable will affect dynamics and form of sexual life. Having HIV can affect other social relationships because infected adults need to make decisions regarding levels of HIV diagnosis disclosure. Within the developmental stages of the adult, Ross et al. have also noted that the individual infected with HIV will move through personal psychological stages of response to finding out that he or she is infected. These stages tend to mirror Kübler-Ross’s stages of death and dying because HIV/AIDS is still seen as a threat to life; however, with the stigma associated with both AIDS and sexuality, it also contains aspects of adapting to, and protecting information about, a stigmatized identity (Vignette 2).

The individual HIV illness, even if it is subjectively experienced as unique and isolating, always happens in the context of the HIV epidemic. The face of the HIV epidemic may look different from country to country or even between rural and urban areas (Vignette 3). However, the epidemic of HIV is more deeply seated than the person’s body. Barnett (2002) notes that “an epidemic reveals many of the fractures, stresses, and strains in a society”; among these, one can enumerate long-term historical and societal structural inequalities and inequities (poverty, inequities in distribution of income and wealth, polarization by social class, levels of social justice, education, ethnicity) or other aspects such as social order and social cohesion, which may be affected by war or migration or similar social and physical dislocations. “The HIV/AIDS epidemic did not just happen. There are social, economic, and cultural reasons why such events occur” (Vignette 4).

When assisting and working with an HIV infected patient, health care providers must consider the preceding aspects. The HIV infection may, depending on context, be seen to a greater or lesser extent as a “lifestyle disease,” depending on the perceived mode of transmission. But becoming HIV infected and coping with the disease is not totally the individual’s

### Vignette 1: Developmental stages in adulthood (Vaillant, 1977)

- Age of establishment (20-30 years): moving from under the parents’ dominance to autonomy, finding a spouse, raising children, developing and deepening friendships
- Age of consolidation (25-35 years): doing what has to be done, consolidating career, strengthening marriage, not questioning goals
- Age of transition (~40 years): leaving the compulsive busywork of occupational apprenticeship to examine the inner world

### Vignette 2: Developmental stages of HIV disease in adulthood (Ross, Tebble, and Viliunas, 1977)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Psychological process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages 1 and 2: Shock, denial, anger</td>
<td>Guilt, powerlessness, anger</td>
</tr>
<tr>
<td>Stage 3: Withdrawal</td>
<td>Recognition of stigma, isolation</td>
</tr>
<tr>
<td>Stage 4: Bargaining</td>
<td>Testing others’ reactions and bargaining, stress displacement, need to be loved</td>
</tr>
<tr>
<td>4a: “Coming out” to significant others</td>
<td>Sharing, recognition, trust, positive reinforcement, social support</td>
</tr>
<tr>
<td>4b: Looking for other HIV positives</td>
<td>Turning alienation into a unique advantage, difference becomes special, needed by others</td>
</tr>
<tr>
<td>4c: Special status</td>
<td>Group commitment and cohesiveness, feeling of community</td>
</tr>
<tr>
<td>4d: Altruistic behavior</td>
<td>Integrated HIV status into self-identity, balance between altruism and self, coming to terms with condition</td>
</tr>
</tbody>
</table>


- Nascent epidemics: HIV less than 5% in one or more subpopulations with high-risk behavior
- Concentrated epidemics: more than 5% in one or more subpopulations with high-risk behaviors but less than 5% in antenatal clinics
- Generalized: HIV spread from the original subpopulation; prevalence in antenatal clinics more than 5%
responsibility, because everyone’s life is unfolding in a society and a social context that generates circumstances for risk environments, thus making the individual more or less susceptible to acquiring HIV and remaining at risk for higher morbidity and mortality. Stigma and discrimination are channels that funnel the epidemic, raising obstacles to prevention and treatment.

**Stigma, Discrimination, and HIV**

Probably the single most important factor in producing and extending the negative psychosocial effect of HIV and AIDS is stigma. Consequently, actions to reduce or protect against stigma may be the most significant step that can be taken to improve the psychosocial well-being of people with HIV/AIDS. Stigma can be defined as “an act of identifying, labeling, or attributing undesirable qualities targeted towards those who are perceived as being shamefully different and deviant from the social ideal” and as “an attribute that is significantly discrediting (and is) used to set the affected persons or groups apart from the normalized social order.” (Definitions from UNAIDS Intercountry Team for East and Southern Africa [D. Miller, Stigma and HIV/AIDS in Africa: setting the operational research agenda], Tanzania, June 2001.)

Discrimination can be defined as “an action or treatment based on the stigma and directed toward the stigmatized” and as “sanction, harassment, scapegoating, and violence based on infection or association with HIV/AIDS.” Stated more simply: stigma is the attitude, and discrimination is the act. Acting through discrimination, denial, and shame, stigmatization is an impediment to HIV prevention and treatment efforts. A broader definition of stigma argues that the concept can be understood only in relation to notions of power and domination. Power and control exerted over the devalued group create social inequality and result in the social exclusion of people with the stigmatized disease.

People with HIV/AIDS are stigmatized and discriminated against for many reasons, including the following:

- HIV is a slow, incurable disease that eventually results in suffering and death.
- Many people regard HIV as a death sentence.
- The public often poorly understands how HIV is transmitted and is irrationally afraid of acquiring HIV from people infected with it.
- HIV transmission is often associated with violations of social mores regarding proper sexual relationships, so people with HIV are associated with having done something “bad.” For example, in some cultures, people believe that a woman becomes infected with HIV because she has violated the mourning period after her husband died.
- Therapeutic protocols are lacking for anti-HIV medications that could control the spread of the epidemic and prolong lives.

Stigma prevents people from talking about and acknowledging HIV as a major cause of illness and death. Stigma prevents HIV-infected people from seeking counseling, obtaining medical and psychosocial care, and taking preventive measures to avoid infecting others. Prevention behaviors are also stigmatized, and people are reluctant to introduce behaviors that could associate them with the virus, such as use of condoms, certain medications, and infant formula when appropriate. A woman with HIV might want her partner to use a condom but might be reluctant to ask because of the stigma associated with the suggestion of HIV risk.

If one family member exhibits signs and symptoms of HIV, the entire family may face rejection and even violence from the community. The loss of social support results in isolation for the family, which may also fear loss of employment, denial of school admission, or denial of adequate housing. Stigma can attach to children of HIV-infected parents and to orphans whose parents died of AIDS. Globally, the AIDS epidemic has robbed 15 million children (12 million in sub-Saharan Africa) of one or both parents. Children may be ostracized at school if it is known that they have an HIV-infected family member, and HIV-infected children may be denied school services for fear that they might spread the virus through casual contact.

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**Vignette 4: Determinants of HIV epidemic**

(Barnett et al., 2000)

- Biology: virus subtypes, stage of infection, presence of other sexually transmitted diseases, patient’s sex, circumcision
- Behavior: rate of partner change, prevalence of concurrent partners, sexual mixing patterns, sexual practices and condom use, breast feeding
- Microenvironment: mobility, urbanization, access to health care, levels of violence, women’s rights and status
- Macroenvironment: wealth, income distribution, culture, religion, governance

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Stigma and discrimination also occur in the health care setting. Sometimes HIV-infected patients are denied appropriate care or are segregated from the general hospital population. Health care workers may selectively use universal precautions only with HIV-infected patients. Reasons may include a lack of medical resources, but health care workers’ ignorance and stigmatization of HIV can also be factors. A survey of 1000 physicians and nurses in West Africa in 2002 found that 20% of them felt that HIV-infected patients had behaved immorally and deserved their fate. Oftentimes health care workers who help patients with HIV may also be stigmatized because of their association with the virus.

Statistics indicate that close to 75% of the global HIV/AIDS caseload occurs in Africa. As in other places, stigma associated with HIV/AIDS in Africa involves attributions of other stigmatized behavior, such as homosexual acts among young men. Homosexuality is highly stigmatized and is even illegal in many parts of Africa and Asia. People often blame outside forces, such as foreigners or the devil, for HIV/AIDS. Stigma may even lead to violence against those blamed for introducing the disease. In 2003, schoolchildren in Ghana staged a demonstration to demand that all tourists be required to get HIV tests. Most societies stigmatize sex workers (prostitutes), who are an integral part of the spread of HIV. Stigma and discrimination prevent sex workers from playing a larger role in the fight against HIV/AIDS.

Anal sex is also widely stigmatized, independent of its association with HIV infection. Anal sex is a more common practice in Africa than previously thought: in a 2004 survey in South Africa, male-male sex accounted for 7% of sexual practices, and heterosexual anal intercourse is a common form of birth control. Stigma may cause people not to talk about risk behaviors and risk reduction. By association with HIV, stigma may also attach to HIV prevention methods, such as the use of condoms, and thus prevent HIV risk reduction among the uninfected.

Social dislocation carries with it not only additional risks of infection but also the stigma associated with being a foreigner or outsider. Many refugees may have contracted HIV in their own countries before seeking refuge elsewhere. Warring groups in Sudan, Congo, Uganda, and Rwanda have raped thousands of women and girls, putting them at high risk of contracting HIV. Among an estimated 250,000 rape survivors, up to 67% might be living with HIV.

Sex education may also be stigmatized, perhaps in the belief that it can contribute to sexual activity. As a result, young people may lack information to prevent the spread of HIV. Research shows that many girls in Africa contract HIV during their first sexual encounter. Remarkably, 8% of women surveyed reported having sex before the age of 13 years, and 15% said that they had sex before their first menstrual period. Only 27% reported using a condom during their first sexual experience. In areas of high HIV prevalence, infection during early sexual encounters is likely.

Most routes of HIV transmission are not exclusively associated with “immoral” behaviors. But such behaviors are attributed to those infected, thus doubly stigmatizing them—through infection and through attribution. Prevention efforts are also stigmatized through their association with HIV; the attribution is that those trying to protect themselves must be infected. Stigma is thus associated not only with psychosocial distress but also with a reduction in prevention efforts and practices. We must minimize the effects of stigmatization to improve prevention and treatment efforts. Because HIV/AIDS stigma is a social and cultural phenomenon of the entire community and not simply the result of individual actions, attempts to reduce stigma must address the community rather than focus on individuals.

Health care professionals must be aware of the stigma faced by their HIV-positive patients and must be scrupulous in protecting their patients’ confidentiality. At the same time, providers can take steps to reduce the effects of stigma on their patients. By promoting disclosure of a positive HIV test result to the patient’s family or spouse, health care providers can help build a support system for the patient and educate family members about HIV. They should provide supportive counseling to patients, caregivers, and fellow health care providers to reduce the stressful effects of stigma. Finally, all providers should regularly examine their personal values as they relate to caring for people with HIV/AIDS.

**Psychosocial Effects of HIV on the Individual**

Even if stigma is minimized, an incurable and often fatal disease requires enormous psychosocial adjustments. People diagnosed with HIV experience many of the emotional responses identified in people facing a terminal illness. They commonly go through an initial stage of denial, in which they do not acknowledge having
the disease or deny its likely consequences. HIV threatens a person’s life, goals, expectations, and significant relationships; no wonder that many people are reluctant to admit their diagnosis or their risk of infection. People who subject themselves to high-risk situations or behaviors commonly deny that they are at risk of HIV infection. They often avoid testing, and if they are tested, they avoid following up on results, as if avoiding a clinical diagnosis might prevent the disease. To battle HIV successfully, people must have some level of acceptance of the disease so that they can seek counseling, social support, and medical care.

**Individual Reactions to Disclosure of HIV Diagnosis in Adults**

Change, adaptation, and evolution are principles of life. Having a disease is discouraging, growth inhibiting, and fosters hopelessness and helplessness. Often denial and regression are the first processes that take place in the psychological life of persons newly disclosed to.

The level of distress felt by a person as a result of disclosure of HIV diagnosis may depend on the following:

- Method of acquiring the infection
- Personality characteristics and lifestyle
- Degree of support available
- Knowledge of and experience with AIDS-related issues
- Accessibility to HAART (highly active antiretroviral therapy)
- Self-evaluated risk of exposure to HIV

Many psychosocial reactions might appear (e.g., anxiety, depression, guilt, body image disturbance, social isolation, and ambivalence), and for many the HIV diagnosis is at least a highly stressful event, if not a traumatic one. On the basis of case histories in Australian men infected with HIV, Ross et al. (Vignette 2) have offered a model of the progress of psychological response. Although these data were based on responses of men having sex with men in the 1980s, clinical experience has suggested that these broad stages may categorize the response to being informed of infection in other people with HIV infection. However, there is a crucial interaction between the stigma of HIV and the progression through stages. Where stigma is high, people may be unlikely to progress into the fourth stage, because any self-exposure would lead to isolation and stigmatization. Progression through these stages is possible only to the extent that there is sufficient communication about HIV to make a common support grouping of people with HIV possible, and so they may be appropriate only to more Western and individualistic cultures where stigma management may be easier.

The nature and quality of disclosure are critical to preventing trauma. If the disclosure is blunt and aggressive (or has not been sought through voluntary testing), it can become an overwhelming and intrusive event that will affect the long-term psychological balance.

Although appreciating what is normal and what is pathologic is difficult when we talk about life-changing bad news, there are different types of reactions to stress and trauma:

- Normal (fear, fury, denial, depression, withdrawal)
- Neurotic (exaggerated reactions such as panic, extreme avoidance behaviors, and impairment
Psychosocial Aspects of HIV/AIDS: Adults

• of ability to love and work; patients can express emotional distress and attitudes toward illness
• Psychotic (depressive symptoms and depressive disorders are among the most common psychiatric sequelae of HIV infection)
• Psychosomatic (low ability to verbally express distress; focused on the disease of an organ)

Chronicity of HIV Infection as a Subjective Experience
From a psychological point of view, the disease is a period of many questions, self-explorations, and anxious expectations. All these can lead to new symptoms that can be structured in a second disease (e.g., secondary morbid state, a mental disorder) or an increase of somatic symptomatology through psychogenic factors that are activated by the awareness of the disease (e.g., hypertension). Health psychology suggests that mental mechanisms are geared toward maintenance or reestablishment of the overall health of an individual.

For antiretroviral therapy availability, one can consider HIV to be more a chronic disease. Whereas patients tend to consider any acute disease as an exterior, accidental, and transitional circumstance in one’s life, they often perceive a chronic disease as being developed from within, as being part of the body (this creates a paradoxical situation, because the conflict comes from wanting to avoid something that is inside and by this very nature it is a state that cannot be avoided).

The long-term progression of HIV, doubled by the uncertainties related to the disease prognosis, enhances these feelings. All these factors reinforce the anxiety felt by the patient with chronic disease (versus the trust that one experiences for an acute condition).

Depression may be common among people with HIV, especially as they adjust to the fact that they are no longer the healthy people they once thought they were. Adjustment to HIV is affected by the lack of hope that comes from a person’s inability to access or benefit from treatment and the anticipated rejection and need for secrecy because of HIV-associated stigma. Seeing many others become ill and experience alienation before succumbing to AIDS increases fear and depression. Suicidal impulses appear as complications of depression and failure to find significance and meaning in a life with HIV. However, suicidal behavior is not particularly common. A 20-year longitudinal study in a Romanian hospital showed that a somatic affection with serious risk for life does not increase suicidal impulses; instead, it is correlated with a tendency to overcome obstacles to survive.

Psychological Issues through Progression of HIV/AIDS
The issues facing HIV-positive people vary in accordance with the disease process, including whether the disease is symptomatic. In a study monitoring 80 homosexual men with HIV/AIDS for 15 years, Nilsson Schönnesson and Ross noted common themes that emerged at different points in the disease process. They found that HIV is a threat not only to people’s physical survival but also to their psychological survival. Early in the disease, people often see themselves as being “persecuted” by the virus—an external, alien, bad object. At later stages, physical and psychological anxieties and fears about death are common.

As the disease progresses, control (or power) issues emerge as patients face increasing loss of physical control. Self-efficacy and active involvement in their health can increase people’s sense of being in control and reduce their risk of feeling helpless. But hope may alternate with despair. Nilsson Schönnesson and Ross found that existential issues invariably emerged in response to threats to physical and psychological survival. Patients’ sense of the meaning of life may be shattered, and they will need to reconstruct new meanings that incorporate HIV. For some, this process may include personal and spiritual growth, with HIV as an impetus to do something with their life or for their family. Existential isolation—a fear of being rejected or abandoned—may lead to anxiety and depression. For many, the existential issues involve spirituality, often manifesting as a rediscovery of religion if the person has a history of religiosity. For such people, religious belief systems may be a major source of psychosocial support and consolation.

At the beginning of the disease process, issues of death tend to be dealt with indirectly as fears of psychological death. At the severe symptomatic stage of AIDS, patients experience these issues as much more direct concerns related to physical death. Views of the persecutory nature of HIV change over time. Initial bewilderment turns to fear as the disease becomes more severe. Denial is most typical in the early stages of infection. Control issues are more salient in the asymptomatic and mild symptomatic...
stages, and helplessness and hopelessness are most concentrated in the severe symptomatic and terminal phases of AIDS. Thus, one can characterize HIV disease as producing four major psychological concerns:

1. existential and spiritual issues,
2. a perception of HIV as a threat or persecutor,
3. feelings of vulnerability and loss of control, and
4. death-related concerns.

These concerns emerged from a longitudinal study of a Western, gay population, but the same issues and stages of dealing with HIV would probably emerge in non-Western countries.

Other psychological mechanisms that one is likely to encounter during different stages of the HIV progression include the following:

1. Denial (total refusal of acknowledging the truth of HIV infection), which can be cognitive, emotional, or behavioral. It is common in the initial shock-numbness-disbelief stage and is usually short term/rarely pathologic, taking years to manifest.

2. Splitting (always present, to a lesser or greater extent because it allows some degree of dissociation and denial). Clients appear with a nonchalant, hapless attitude toward HIV status. This comes in contrast with at least one intense feeling—beyond the usual expected intensity—that the client displays toward some other problems such as school problems/grades or relationship conflicts. (See Vignette 5.)

3. Projecting “bad” parts of self associated with illness (influenced by internalized stigma). The self-concept is altered: I am bad, I am without control, I anticipate failure in all my endeavors. All these cognitions create high levels of doubt and uncertainty regarding identity and self-effectiveness. “Magic” thinking and acting can replace more rational and common-sense practices—for example, when patients are looking for quasimedical cures. Persons are making constant efforts to seclude their felt badness from the rest of the world.

4. Limitation of the ability to process and integrate symbols (Greek: “to put together”) and our ability to operate with them holds a critical role in adapting to conflicting situations and mediates the healing process. It is about reframing and finding a new, positive meaning in difficult, existential issues.

Vignette 5: Splitting examples

- Patient unable to discuss HIV (taboo subject); patients find countless ways of avoiding or diverting the answer to a direct HIV-related question.
- Splitting may appear in relation to sexuality (“sex, badness, and death are associated in a fixed constellation” [Cartwright, 2002]).
  For example:
  - I will never have sex or marry.
  - I am not interested in boys/girls.
  - I do not spend time with school peers because they are all thinking only about sex (disgusting).

“Through symbols, human beings are trying to integrate everything into a system, to reduce the multiplicity to a unique and more transparent situation.”

—Mircea Eliade, 1992

Finding Meaning and Mediating Successful Adaptation to a Life with HIV

Professionals need to be able to recognize the aforementioned processes and help patients overcome denial and splitting, improve self-esteem, and restore the symbolic function of mind. The final goal is to assist the person to recognize the unpleasant reality of the disease while keeping hope and goals in life, to offer a safe mode of expressing fury and fear while keeping the love and support of significant ones, and finally integrating the disease into the self-concept. However, Ross et al. and Nilsson Schönnesson and Ross note that with successive health crises, people may regress briefly to earlier stages as they adapt to new health circumstances.

Professional counselors, social workers, health care workers, clergy, trained volunteers, friends, and family play crucial roles in providing psychosocial support. One of the first steps in providing adequate assistance for people with HIV is to ensure that the helper is thoroughly aware of and comfortable with the facts about HIV transmission. If helpers feel personally at risk from HIV-infected patients, they will convey those feelings to the patients, who will then feel even more isolated than before. Counselors need to educate themselves about HIV to adequately counsel people with HIV. Individual and supportive counseling can help patients come to terms with their HIV diagnosis and with how it will affect all aspects of their lives. Patient education should include information about how HIV is transmitted and should...
give the patient some idea of common physical and emotional responses to HIV. This type of education can help patients anticipate and plan for these experiences.

Professionals can also help patients assess controllability of HIV-related stressors and to design adaptive coping mechanisms. For example, the therapeutic focus can be on developing a problem-focused coping response when the stressor is controllable, whereas an uncontrollable stressor should focus interventions on finding, defining, and redefining meaning (Vignette 6).

**Vignette 6: Meaning- versus problem-focused coping**

- Meaning-focused coping refers to a positive reappraisal even if a stressor cannot be readily alleviated or changed.
- Problem-focused coping has the greatest effect on self-reported depressive symptoms when stressors are controllable (e.g., seeking information).

One useful tool to use is the self-report scale “Meaning of illness questionnaire” that helps evaluate illness-related meaning appraisals in five domains:

- Impact (Has this illness negatively affected how you live your day-to-day life?)
- Type of stress (Would you describe this illness as a loss?)
- Degree of stress (Are you pleased with the way you are handling stress?)
- Challenge, positive attitude, motivation, hope (Would you describe this illness as a challenge?)
- Nonanticipated vulnerability (Was this illness expected before the doctor told you?)

This tool can provide insight to both the patient and the professional that offers assistance on how the person subjectively experiences the illness, and it can be the starting point in designing a successful intervention plan.

Improved quality of life and successful adaptation to life challenges are the main goals of psychosocial intervention plans. These are developed by multidisciplinary teams, taking into consideration the many factors presented in the beginning of this chapter and their dynamics.

The general goal is then elaborated into more concrete objectives connected with designed interventions and anticipated outcomes. The interventions of the multidisciplinary team might focus on the following areas:

- Improved physical well-being
- Reduction or control of stigma and discrimination
- Improved access to health care
- Improved access to social support
- Activation of internal resources

Heckman (2003) presents the logic model of the preceding factors (Figure 1) that should be the goals of psychosocial interventions to ensure a good quality of life and the best possible successful adaptation to the HIV diagnosis and life with HIV for affected adults. The process depends on how each individual activates, combines, and uses different resources available, both internal and external. (See Vignette 7.)

**Figure 1. Model of factors influencing quality of life of HIV-infected persons.**

**Vignette 7: Resources activated for successful adaptation to HIV**

**Internal resources:**

- Cognitive reappraisal of a situation
- Realistic perception of current life events
- Strong self-concept and self-esteem
- Self-control and self-efficacy
- Positive appraisal of the future

**External resources:**

- Access to medical care
- Family and social support network
- Therapeutic alliance with the care team
- Psychotherapeutic and psychopharmacological support
- Support with issues regarding confidentiality
- Access to social services
Group counseling can also play an important role by allowing individuals with HIV to share experiences with one another. However, this approach is usually not a good idea until the person has been able to accept the diagnosis enough to come to the group and communicate honestly. Group support can help patients cope with their emotional responses to HIV on the basis of accurate information, shared experiences, empathetic listening, and assistance with problem solving. Counseling and support can help people with HIV share their feelings about secrecy and stigma and consider how these influence their emotional and physical health. Counseling and support can also help people consider how their own behaviors can promote health and well-being, such as seeking resources for adequate nutrition, shelter, proper medical follow-up, adequate sleep, and management of stress and anxiety.

Supporting the spiritual needs of HIV-infected people and their families is a critical component of good care and support. Patients with AIDS report significantly lower levels of spiritual well-being than do patients with cancer and other terminal illnesses. They also report greater feelings of loneliness, fewer support systems, and less satisfaction with the support systems that they have. Support from spiritual leaders who are significant to the patient helps the patient and family cope with the existential and intrapersonal questions raised by a life-threatening illness and with regrets that the person may feel about past actions, relationships, or experiences. Traditional healers, often the first care providers sought out by patients, can also be a source of support. When traditional healers and other medical providers work together and have a shared understanding of the goals of care, patients with HIV benefit. One can engender hope in terminally ill patients by controlling symptoms, encouraging relationships, assisting patients with practical needs, affirming their value, and helping them review their life experiences and personal worth positively.

**Types of Psychosocial Interventions for Adults**

All the preceding issues presented have stressed the complexity and variability of unique constellations of psychosocial factors that come together in the life of each patient. Good care can be provided through structured psychosocial services that involve a multidisciplinary team.

One key principle before designing any intervention that will address a specific need of our patient is to always involve the client in the design of his intervention plan and prioritize issues together.

The multidisciplinary team should have clear standards of care and intervention that will guide their actions (Figure 2). Clients might have different needs, starting with the need for information or legal support with respect to rights and responsibilities; continuing with need for know-how on accessing services available; and ending with needs for developing practical skills to improve adherence, disclose diagnosis to other parties, or change a specific life situation.

Support can be either intensive or nonintensive and usually comes in one of the following forms:
- Counseling
- Education
- Practical support and assistance
- Psychotherapy and psychiatric support

![Figure 2. General design of guiding procedures for multidisciplinary team interventions’ plan](image-url)
Counseling can be linked with many aspects, such as HIV testing and support for adaptation to the new status, promoting a healthy lifestyle (e.g., adherence to antiretroviral therapy, behavioral changes), decisions regarding current conflicting emotional situations, and confidentiality and its limits. It can be an individual process, but involving the couple or working with family members or in a group format might also be required.

Education includes several components, such as sexual education, education about HIV infection and opportunistic infections, and education about the legal framework that the patient should be aware of. It can also focus on, for example, developing parenting and nutritional skills for those caring for HIV-infected newborns and teaching nursing skills for caregivers of the terminally ill. Educational approaches can take a variety of forms, starting with professional guided education and ending with self-education based on printed materials or mediated by a peer educator.

However, situations often require practical support and assistance. Such interventions include providing free condoms, temporarily helping with transportation fares or medication, helping the patient to represent himself at different institutions to access his legal rights, or simply paying home visits for follow-up.

Because HIV infection is a chronic condition, the follow-up and monitoring of a patient does not end, even if he or she might not need intensive support at one time. Health care workers should have ongoing evaluations and keep track of changes that might negatively affect the person.

**Psychosocial Effects of HIV on the Family**

HIV affects the whole family, not only the infected individual. When one member of a family has HIV, often there are others who are as yet undiagnosed. When HIV infects one partner in a relationship, both partners are affected. The infection may indicate that sex or other risk behavior has occurred outside the relationship, but even if the infection predated the relationship, both partners will be involved in the emotional trauma of the discovery. Ideally, the couple should openly discuss sensitive matters such as condom use, sexual fidelity, and childbearing. This step does not always happen. Regardless of his or her own risk behavior, the undiagnosed partner may express anger and violence toward the person who has been diagnosed. The diagnosis of HIV infection in a child usually indicates the presence of the virus in the mother. The father and other siblings may carry the infection as well.

Cultural, social, biological, and economic pressures make women more vulnerable to HIV infection than men. In some areas, the high prevalence of rape puts some women at risk of acquiring HIV. In others, older men who may be infected with HIV pressure teenagers into sexual relationships. Women are often economically dependent on men and unable to negotiate safer-sex practices, including condom use. Women are usually the primary caregivers for their families and may have little support from others when they are ill themselves. As more people receive care for HIV/AIDS in their own homes or the homes of others, health care workers must keep in mind that HIV-infected women are likely to care for everyone else in the family, often to the detriment of the women's own health. Households led by women also face greater economic difficulties and have fewer supports.

Strengthening the family structure is especially important because of the tremendous stress that HIV puts on family systems. Besides caring for ill relatives and for orphans, families are often beset by economic and social problems as well as the grief that accompanies the loss of family and friends. They may benefit from group or family counseling, including counseling about their desire to have a family, perhaps the need to prevent unwanted pregnancies, and negotiation of risk-reduction practices such as condom use. Individuals may need training in assertiveness and how to communicate their needs. Remember also the more basic needs that the family is facing: food, shelter, and dwindling finances.

A common issue in counseling is who should be told of a person's HIV status and how and when the matter should be communicated. One approach is to educate the infected person about how HIV progresses. While the person is still asymptomatic, he or she should consider whom to tell about the infection before the illness begins to manifest itself. A counselor can help the patient identify family members and friends who are supportive and will be open to education regarding HIV. A related issue is disclosure to a sexual partner or spouse. Partner notification programs may help patients who want to tell their partners but do not feel comfortable doing so. Some patients may opt not to tell people with whom they live because they fear losing their home and family support. The reaction of a partner or other family member could
be violent. At times, it may be possible to give alternative explanations for changed behavior, such as wanting to use condoms to avoid pregnancy. In societies where a man’s virility and a woman’s worth are measured by how many children they have, this approach may be more difficult.

**Socioeconomic Effects of HIV/AIDS**

HIV/AIDS affects the economic well-being of families, businesses, and societies in many ways. When people become ill and die, society loses not only those people but also their productive potential. They no longer hold jobs, manufacture goods, provide services, or support their families. Families lose their breadwinners; the nation loses people who contribute to the well-being of society.

As families use their time and money to care for ill members, their energies are diverted from working to provide income or farming to provide food. Not only the present but also the future is affected, as family members discontinue education because of the financial needs of the family. Even burying the dead makes life more difficult for families and society. Funerals are costly, and people miss days from work to attend the rituals. The epidemic’s high death toll is producing cultural changes. In some communities with high rates of HIV infection, cemeteries have become overcrowded, creating pressure to accept practices not previously sanctioned by religious and cultural authorities, such as cremation. Funerals are a visible, potentially numbing reminder to all that a deadly disease threatens their survival.

HIV threatens workplace productivity because of deaths, absenteeism due to illness and funeral attendance, and lower productivity of sick or newly hired replacement workers. Other increased costs to the business sector include expenses for insurance and medical care for sick employees, which must be weighed against the cost of having to train new employees if more experienced employees become sick because of inadequate health care.

At the societal level, economic growth in many nations is lagging because so many skilled and experienced workers have died of AIDS. High unemployment and high rates of infection among skilled workers bode ill for countries’ ability to keep social supports intact. Studies of teachers and health care workers, for example, indicate that many in those professions have been infected with HIV. Society faces the challenges of having many of its productive members sick or dying, leaving few people to care for children and the elderly. In many countries, the number of people affected by HIV/AIDS is overburdening health care and social support resources.

The effect of HIV/AIDS on broader indicators of development, such as life expectancy, has been profound. In the 1950s, a child born in southern Africa had a life expectancy of 44 years. By the early 1990s, that figure had risen to almost 60 years. But life expectancy is expected to drop to 45 years between 2005 and 2010 because of the toll that AIDS has taken. Poor households are being pushed deeper into poverty. The effects of the AIDS epidemic will be felt for generations, because so many children are being deprived of adequate nurturing, nutrition, education, and good role models.

In sub-Saharan African countries such as Malawi, Mozambique, Tanzania, Uganda, and Zambia, determinants of long-term growth show sharp declines as a result of the AIDS pandemic. In South Africa, the gross domestic product is projected to decline by 17% between 2002 and 2010.

Frail economies, weak institutions, declining standards of living, and reduced social and governmental capacities indicate that the effect of HIV/AIDS on the future of African societies will be devastating. The assault on countries’ most productive segment, with the resultant undermining of their tax base and their ability to finance such critical infrastructure as health and education, are certain to hamper sustained economic, cultural, and societal development.

A United Nations Development Programme study carried out between 1980 and 1992 confirms the scale of the setback to human development by HIV/AIDS. The average loss of human development progress because of AIDS was estimated at 10 years in Zambia; 8 years in Tanzania; 7 years in Rwanda; 6 years in the Central African Republic; and 3-5 years in Burundi, Kenya, Malawi, Uganda, and Zimbabwe. Because the severity of the AIDS epidemic in sub-Saharan Africa has increased significantly since 1992, subsequent losses in human development are probably even greater.

Reduced productivity in important sectors of the economy feeds into economic instability, which in turn...
can undermine a country’s political stability. Civil unrest and war create social dislocation, refugees, and rape, fueling a vicious cycle whose hallmark is an increased incidence of HIV/AIDS.

**Effects of HIV on the Societal Level**

HIV places enormous and varied stresses on the political, cultural, and religious fabric of society. Among issues that become critical are the availability of health care, social supports for orphans and caregivers, legal rights and responsibilities of people with HIV, and the response of religious and cultural systems to the needs of their members who are infected with or affected by HIV/AIDS. Political instability may be exacerbated by growing frustration with the government’s inability to stop or slow the epidemic or to respond effectively to the needs created by it. Increased poverty and social inequality may encourage conflict and crime. How these critical issues are resolved will determine society’s survival and viability.

The effects will be most obvious in the area of health care as the need for services increases. Providing treatment for HIV/AIDS and the illnesses that accompany the infection is expensive. Often governments must choose between providing treatment and funding prevention programs. The choices are not easy.

Education systems face shortages as teachers become ill and die. A rare public-sector assessment commissioned by the Government of the Kingdom of Swaziland estimated that the country would have to train 13,000 teachers between 2003 and 2011, compared to 5,093 if no AIDS epidemic existed. Schools also must deal with significant numbers of infected and affected children with psychological, social, and economic problems caused by the epidemic. Enrollment rates in institutions of higher education may drop because fewer children live to adulthood.

**Societal Interventions**

Because of the complex effects of HIV/AIDS on the individual, family, community, and society, interventions on many levels are needed to mitigate the effect of the epidemic. Some interventions are targeted at individuals with or at risk of HIV, whereas others are aimed at the larger community. Their objective is prevention of HIV and reduction of societal factors that increase the risk of infection. Protecting the human rights of vulnerable members of society, who are often hardest hit by any health problem, is another important step in mitigating the effects of HIV. Destigmatization of HIV and legal protection from discrimination and physical harm of people with HIV are important because of the broad effects that stigma and fear have on prevention and treatment efforts.

Role modeling is an effective way to encourage behavior change, as for HIV testing in Siaya, Kenya. When three members of parliament took the lead by offering to be tested in public, many people joined them. The three parliament members later called on fellow legislators and civic leaders to follow suit and take the lead in motivating other districts to join in this voluntary counseling and testing initiative. Leading figures who discuss their HIV infection in public may also make a major contribution to reducing stigma.

Many projects try to help patients and families with basic needs and income generation. Reduction of poverty and improvement of the overall health of the population are important objectives in the fight against HIV/AIDS. Nongovernmental organizations and community-based organizations, often in conjunction with the government, are carrying out considerable work at the local level toward these objectives. Approaches range from institutionalized care to home-based care for terminally ill patients to training for lay counselors. To be successful, home-care interventions must be supported with structured programs from the health-service delivery system. Poor families without such basic resources as clean water and adequate food are likely to need extra training and resources to care for a sick family member at home. Health care providers should assess each family’s needs for support when making a home-care plan. Many families may benefit from simple support, such as a friendly visit, a referral for food assistance, latex gloves, or advice to improve caregiving skills. Families also need contact information, such as phone numbers or addresses, in the event of a problem or emergency.

On a larger scale, public and private industry policies regarding HIV and HIV prevention should be evaluated on an ongoing basis to examine their effects on the lives and health of the population. Advocacy for policies ensuring confidentiality of HIV status, access to medical care, and protection from discrimination are likely to help more people with HIV meet their physical and social needs and income generation.
needs. Education and advocacy within religious and cultural groups, and support from these groups, help patients and families living with HIV. Governments and nongovernmental organizations must devote resources to advocacy for increased attention to HIV prevention and the need for medications, medical care, and psychosocial and cultural support for individuals, families, and communities living with the virus.

**Prevention of Transmission**

People who find out that they have HIV may feel powerless against the virus. But they are not powerless to prevent its spread. The pandemic’s growth depends on an infected person who transmits the infection and an uninfected person who receives it. To slow the epidemic, people who are infected must be educated to avoid transmitting it. Thus, on diagnosis and during subsequent visits, prevention information needs to be provided and reinforced. As part of this reinforcement, a health care provider might emphasize that despite their infection, patients still have some control over where the epidemic goes in their community and a responsibility not to become another link in the chain of transmission. This emphasis will need to be balanced against the stigma of being identified as HIV infected, e.g., through condom use.

**ABC Prevention Approach**

Uganda has significantly reduced the transmission of HIV by using the ABC (Abstinence, Be faithful, use Condoms) approach. This harm-reduction approach gives each person several strategies for preventing HIV transmission to themselves and others.

Abstinence from intercourse is likely to be most useful with adolescents, who may be encouraged to delay intercourse, and in situations where families or partners are separated by work or travel.

Being faithful (staying with one sexual partner) will prevent HIV transmission if both partners have the same HIV status (both negative or both positive with the same strain of HIV), which can be known only through testing. If only one partner is faithful, the activities of the unfaithful partner may put the faithful one at risk. Where there is a high prevalence of HIV in the population, even one or two additional partners may make infection likely.

Using condoms consistently and properly prevents HIV transmission and significantly reduces transmission of other sexually transmitted infections (STIs) such as syphilis, gonorrhea, and chlamydia. Because having an STI greatly increases the risk of contracting HIV (via infected membranes and sores), both condom use and treatment of any STIs are important.

People must be given all relevant information and allowed to make their own choices as to which prevention method is most appropriate. What works for one person will not always work for another, and what works at one point in life may not work for the same person later. Regardless of their own points of view, health workers are ethically bound not to withhold any information from patients that might prevent transmission of HIV or other STIs. Health professionals must explain the benefits and drawbacks of each approach. We can give our patients the tools in the form of information, and it is up to them to use the most appropriate ones at the most appropriate times.

**Situational Approaches to Prevention**

Sometimes health care providers assume that patients have more individual power to practice prevention than they actually have. For example, someone may have the power to practice prevention in one situation but not in others. One useful approach is to ask patients to list the situations in which they can successfully use any of the ABC approaches and the situations in which they cannot. Issues of power and stigma will often determine prevention, with the weakest person in the situation having the least power. Ask patients to list “risk situations” rather than “risk behaviors.” Then ask how they might avoid getting into such a risk situation if at all possible or how they might reduce the risk if the situation is unavoidable. Explore ways in which patients have some power in the situation to control or modify risk.

**Knowledge, Attitudes, Beliefs, and HIV Prevention**

A common myth among many health professionals is that information about HIV/AIDS is an effective way to prevent HIV transmission. Although adequate information is a necessary condition to prevent transmission, it is often not a sufficient condition. In other words, there needs to be basic information, but by itself information will not always overcome barriers to actually doing preventive activities. The best predictor of whether people will carry out preventive activities is
their intention to do so. People will have good intentions if they see some value (for themselves, their family, and their community) in preventing the spread of HIV, either to themselves or from themselves.

Even with the best intentions, people may come up against barriers to prevention of HIV transmission. These barriers may be situational (low power in a situation; the influence of alcohol or other drugs; potential violence; no condoms; or a need for food, shelter, or money). They may also be emotional (when people are highly attracted to their partner, when they want children, when they are sexually aroused); often, despite what people know, their emotions override their intentions. It is useful to have people describe the situations in which emotions may override their knowledge and judgment and to identify the point of no return beyond which unsafe sex is likely to occur. A helpful concept to introduce is anticipated regret. Here you can ask patients to describe how they would feel after putting themselves or others at risk and how significant others in their family or community might feel about their actions. How might infected patients feel upon learning that they have infected their partner when that partner gets a positive HIV test result? Can they imagine explaining infection to their partner? Seeing risk situations by envisaging one’s regrets afterward can help to balance the emotional pressures at critical times.

Knowledge and Myths
Increasing knowledge about HIV transmission and prevention (or treatment) cannot occur where the mythology about HIV/AIDS is actively contradictory. Myths will often constitute “folk epidemiology”—a description of beliefs and explanations about HIV. These myths will underlie all aspects of HIV/AIDS: the stigma, HIV transmission beliefs, HIV treatment beliefs, and how people cope with HIV. Cultures will differ on these myths and beliefs, but health workers must be able to list the most prevalent myths. Attempting to deal with HIV/AIDS while ignoring the folk epidemiology will almost always fail. Health care personnel need to be able to credibly refute myths that contradict appropriate psychosocial approaches to HIV/AIDS, or that stigmatize such approaches, while reinforcing those that support optimal psychosocial care and prevention. Myths that have been reported include the following:

- People who look healthy cannot have HIV.
- There are medical and/or folk cures for HIV.
- Religious and cultural rituals can remove HIV/AIDS.
- Being a member of certain religions protects against HIV/AIDS.
- HIV/AIDS is a punishment.
- Intact condoms will allow transmission of HIV.
- HIV cannot be transmitted from females to males.
- Having only one partner will prevent HIV (one partner may put someone at risk, depending on what that one partner has done).
- HIV infection will not harm a person, and only AIDS is dangerous.
- Having sex with a virgin will cure HIV/AIDS.
- HIV does not cause AIDS.

All these myths can hinder HIV prevention or treatment, and health care providers must be prepared to counter them effectively.

Spirituality, Religion, and HIV/AIDS
Existential issues, including spirituality and religious belief, may take on increasing importance to people who get a diagnosis of what is still, despite advances in treatment and health care, a frequently fatal disease. Unfortunately, despite the importance of the spiritual and religious dimensions of life, some officials of some established religions seek to stigmatize, rather than help, people with HIV, even though all the major religions emphasize the importance of caring for the sick and suffering and clearly recognize the obligation to support personally and charitably those suffering from disease.

The health care worker also has a special obligation to help the sick live and die with respect and dignity. Regardless of whether the health care worker personally has a spiritual or religious belief, the patient has an absolute right to be cared for and respected. Stigma, which is a problem in the mind of judgmental others, not inherent in the disease, can be significantly lessened if the patient’s spiritual and religious beliefs are supported. One can do so by recognizing that the spiritual and religious needs of patients may be as important for their mental health and comfort as more widely recognized psychological and social supports. Particularly when medical interventions are of limited effectiveness, the health worker may sometimes, if requested by the patient, support or facilitate (but never impose) ways of meeting the patient’s religious or spiritual needs. Sometimes the consolations of traditional spirituality or religion may make a significant difference to psychosocial
adjustment and mental health. Health professionals should not overlook such existential issues in caring for the total needs of the person with HIV disease.

**Psychosocial Effects of HIV/AIDS on Health Care Professionals**

Eventually, health care professionals who have lost many patients to HIV/AIDS begin to suffer because they have inadequate time to grieve or deal with their losses. Like their patients, they display many of the symptoms of the stages of grief (denial, anger, guilt, bargaining, depression, and acceptance). However, as they experience loss after loss, the stages become intermingled. They have not worked through one loss before another occurs. Loss of multiple patients can lead to complicated and ongoing grief and can prevent the health care worker from processing the thoughts, feelings, and responses to patients in healthful and helpful ways. Over time, the unacknowledged sadness, anger, and guilt can become compressed and result in cynicism and decreased ability to invest emotionally in patients. It is painful to acknowledge the feelings associated with seeing patients suffer and die, so the professional becomes more hardened and expresses less sensitivity and sympathy for the needs of the next patient.

Symptoms of AIDS-related burnout may be physical (e.g., exhaustion, headaches, back pain, sleeplessness, malaise, and gastrointestinal disturbances) as well as behavioral (e.g., becoming easily irritated and angry, increased alcohol/drug use, marital/relationship problems, inflexibility in problem solving, impulsivity and acting out, and withdrawal from noncolleagues). Cognitive and emotional symptoms may include emotional numbness or hypersensitivity, overidentification with patients, grief and sadness, pessimism and hopelessness, cynicism, indecision and inattention, and depression.

Environmental factors contribute to the stress of health care professionals who care for people with HIV/AIDS. Providers suffer stigma similar to that of their patients and are often unable to talk with family and friends about their work with patients suffering from an often unmentionable disease. Also, HIV counselors must face their own fears about being HIV infected as they encounter patients who may have risk behaviors similar to their own. In a study of HIV counselors in Zambia, 72% worried about their HIV status, but less than one-fourth had been tested for HIV. Half of the counselors said that they did not want to be tested because they did not want to deal with the hopelessness of a positive result or they thought it pointless because there is no cure and only limited treatment. These factors would seem to have a detrimental effect on the ability to counsel effectively or encourage others to seek testing.

Health care providers working with HIV patients see many patients with complicated family situations and seemingly unlimited needs. Often, there are insufficient resources, such as medication and supplies, to meet the needs of such patients. A high caseload combined with inadequate staffing makes it difficult to provide sufficient counseling to the patient. Caregivers are acutely aware of personal limitations and powerlessness to fix the patient’s situation. The provider should remember the power that he or she does have—to provide the medical treatments

*Addressing spiritual and religious needs can be important for patients’ mental health.*
that are necessary and available, to try to comfort patients when they are suffering, to provide hope and humor in a potentially devastating situation, and to be a positive influence in the lives of patients and caregivers.

Health care providers can help one another by creating a supportive environment in which they feel free to express their feelings. Doing so reduces the isolation and emotional pain that can affect an individual's ability to provide sensitive care. Formal support groups for health care providers can not only reduce feelings of isolation but also lead to new ways to cope with the stress of work. In these settings, it is often more important to discuss how the person feels about and responds to difficult situations, and to develop new ways to think about and respond to them, than to discuss in detail the situation itself. Informal discussions are also helpful because they can occur directly after a stressful experience. The goal should be for the person to express feelings, to see things in a new light, and to develop new skills and strategies for coping. Humor is also an effective way of coping with stress.

The health care provider will need to evaluate the effects of stress on his or her life on an ongoing basis. Adequate rest, exercise, and nutrition are important for the promotion of health for the caregiver as well as the patient. Relaxation techniques such as progressive relaxation and breathing exercises can help the stressed professional to detach from stressful situations to address them more effectively. At various times, the health care provider may need to reexamine the stressors and positive factors in his or her life to find balance and positive physical and mental health to continue the important work of caring for patients with HIV/AIDS.

**References**

**Objectives**

1. Describe the benefits of human immunodeficiency virus (HIV) prevention counseling.
2. Describe specific skills that promote effective prevention counseling.
3. Discuss appropriate techniques for use during HIV prevention counseling, health education, and supportive counseling.
4. Discuss appropriate techniques for use during HIV prevention counseling with rapid tests.
5. Provide case studies to practice prevention counseling skills.

**Key Points**

1. HIV prevention counseling plays a role in education about HIV transmission and risk-reduction behaviors.
2. Using a prevention counseling assessment will help counselors and health care professionals promote optimal support and guidance of patients seeking HIV testing.
3. An organized approach to prevention counseling is essential to provide effective support to patients receiving HIV results.

**Overview**

Human immunodeficiency virus (HIV) prevention counseling strategies rely on interventions aimed at changing behaviors, including counseling and testing performed in a variety of settings. Prevention counseling is an important part of testing for HIV and providing test results. In many communities, there are specially designated HIV counselors who have been trained in HIV prevention counseling. However, because of the many people infected with HIV or at risk of being infected, all health care professionals should understand the basic principles involved in HIV prevention counseling. Doing so does not negate the benefit and importance of obtaining more in-depth training to provide HIV prevention counseling, which may indeed be a requirement in some areas.

**HIV Prevention Counseling’s Importance**

HIV/AIDS is a uniquely stigmatized disease. Stigma affects every aspect of medical and social care for people infected with HIV or at risk of infection. It is rare for the diagnosis of a disease to result in the possible loss of home, family, and religious or cultural supports, as well as the infected person’s feeling of connection with the community, but this is a real threat with a diagnosis of HIV/AIDS. Stigma may prevent people at risk of HIV infection from identifying their symptoms or risk factors at an early stage, because acknowledging personal risk of HIV forces them to face their own preconceptions about people with HIV and to associate those attitudes with themselves. Stigma may prevent people who have received positive test results from accepting them, seeking appropriate treatment, and implementing risk-reduction strategies to prevent transmission to others. By the same token, the severe stigma associated with HIV may prevent people from disclosing even an HIV-negative status. In addition to propagating prejudice, stigma also promotes patient denial. Patients in denial often do not take initiative on seeking treatment, care, or support. One aim of HIV prevention counseling is to reduce internalized stigma by providing information about HIV in a neutral, nonjudgmental manner. Health care professionals should extend the reduction of stigma by treating people at risk of HIV infection with respect, tolerance, and compassion in all encounters.
HIV prevention counseling helps patients and health care professionals identify risk factors and symptoms that may indicate HIV infection. It helps patients begin to anticipate a possible HIV-positive result and consider how they would respond to such a result. During the initial session, a patient can begin to think of a safe person whom he or she will tell about the HIV test. If the patient can talk with someone about being at risk of HIV infection, that patient will also be better prepared to talk to that person if the test is positive. Patients who have a supportive environment will find this support critical as they deal with their HIV-positive result. Also, by involving a trusted friend or supporter in the decision to test, the person being tested will have someone with whom to discuss the test results. If couples are tested at the same time, they avoid the potentially difficult situation in which only one partner is tested and then must reveal his or her diagnosis to the other.

HIV prevention counseling is an effective public-health intervention because it promotes the health status of someone living with HIV and plays a role in reducing HIV transmission. Client-centered interventions, education regarding transmission factors, and risk-reduction techniques are the main focus of HIV prevention counseling. A randomized trial conducted in Kenya, Tanzania, and Trinidad showed that people who received voluntary counseling and testing were significantly more likely to reduce unprotected intercourse with nonprimary partners than those who received only health education sessions. Couples in which one or both partners were HIV infected showed a reduction in unprotected intercourse with their primary partner after counseling and testing. Analysis shows that voluntary counseling and testing for HIV can reduce HIV transmission and is cost-effective, especially among women presenting individually for testing and men and women presenting as a couple.

**Informed Decision Making**

Before being tested for HIV, the patient should make an informed decision to test. His or her decision should be made with no coercion or duress but rather from free will. One factor that should be addressed is what legal, emotional, and social consequences would result from a positive test result. Does disclosure of the patient’s HIV status compromise that patient’s emotional well-being? Are test results reported to public health or government officials? If so, what are the consequences? Are significant others or relatives routinely notified of the results, along with the patient? Health care professionals must understand the legal and procedural reporting policies in their institutions.

Patients may consider the advantages and disadvantages of testing and of knowing a positive result, but often they focus mainly on the disadvantages of testing. Health care professionals may be able to help their patients by making a chart of the advantages and disadvantages of testing and of knowing one’s HIV status, compared with the advantages and disadvantages of not knowing one’s HIV status. Advantages may include the ability to seek medical care to prevent complications of HIV/AIDS, to prevent transmission to others, and to make healthful lifestyle changes. Knowing the cause of symptoms that one is experiencing also has value. Disadvantages may include increased fear of illness and death, fears related to family relations and parenting, guilt and anger about past decisions or relationships, and the stigma associated with HIV/AIDS. The patient should be informed of whether testing is voluntary or involuntary—confidential (with a name) or anonymous (without name or identifier); whether he or she can refuse testing; and what consequences, if any, will result from refusing the test. Health professionals must embrace a positive and empowering relationship with their patients. Provider fatalism, a belief that HIV-infected patients are unlikely to change risk behaviors, is a potential barrier that must be addressed when implementing HIV prevention counseling programs, regardless of the settings.

**Health Education**

Health education about the etiology and transmission of HIV is an important part of HIV prevention counseling. Most patients associate HIV with death and know little about what HIV is or how it affects the body. Residents of many African countries believe that witchcraft is the source of many HIV-related illnesses and that HIV itself does not exist. Family members believe that their loved one has been bewitched by someone who is jealous of the loved one’s success. Because of this many HIV-related illness are treated by use of magic, sorcery, and traditional methods, and HIV itself is not recognized as or believed to be a possible cause.

Health care providers can help reduce stigma and fear by explaining that HIV is a virus that enters the body and...
causes the immune system, which fights infections, to gradually become less effective, which makes people with HIV more susceptible to infections than people without HIV. Health care providers can further explain that HIV is transmitted in only a few ways, namely, through sexual contact; exchange of blood (e.g., through contaminated needles or cutting instruments); and from a mother to child during pregnancy, childbirth, or breast-feeding. Knowing these facts will help someone living with HIV think more clearly about HIV transmission rather than associating transmission with having done something “bad.” Such knowledge may also alleviate their concerns about the possibility of transmitting the virus to others during daily activities. For example, a mother need not fear that by being around her children, she is putting them at risk of HIV infection.

**Group Health Education**

Some facilities use a group setting for teaching about general aspects of HIV testing, HIV risk factors, and risk reduction. In a study of individual versus group health education for pregnant women in Burkina Faso, group counseling was generally more effective in increasing knowledge about HIV infection. This effect might have been caused by the interaction among patients and counselors as well as the possibility for patients to learn from answers to questions that they might not have been willing to ask for themselves. Patients in the groups were also given individual HIV risk assessments. Group health education may be a time- and cost-effective tool for increasing knowledge of HIV/AIDS and reducing high-risk behavior. In group-level interventions, confidentiality should always be emphasized and reiterated, especially if individuals reveal their HIV status.

**Couple and Family Counseling**

When culturally and socially appropriate and legal, counseling a couple together so that they can decide together to be tested and to return for results is often an effective strategy. When only one partner is tested and is diagnosed with HIV, that person often experiences feelings of shame and fear about disclosing to his or her partner. The disclosing partner may face rejection or blame for bringing HIV into the home. Some women may want to involve their families in the decision to receive testing. One reason to encourage family involvement is to prevent potential problems with treatment adherence. If a woman is diagnosed with HIV/AIDS, she may not receive support from her partner. For example, he may not understand steps taken to prevent transmission, such as using infant formula. A male partner who is not involved in an initial decision to be tested may never be tested once the woman is diagnosed because he fears that he, too, is HIV infected. Ideally, the spouse or partner should be included in initial HIV prevention counseling discussions. The counselor will need to listen carefully to each person and help resolve conflict. One must pay close attention to the cultural and family dynamics between the two partners, which will provide information about counseling techniques that may be helpful. For example, in some families, the counselor will need to show respect to the husband by speaking to him first or by not looking directly at him, which may be interpreted as a lack of respect. Some cultures mandate that women seek permission from their partners before seeking health care (such as antenatal clinical care) and treatment (e.g., voluntary counseling and testing for HIV). Considerations of culturally appropriate communication styles should not prevent the counselor from including the woman in the session. Obtaining an accurate assessment of individual risks when the couple is counseled together might be difficult because either person may be reluctant to be honest about risk factors in the presence of the other. Involving other family members in counseling can be beneficial for finding sources of potential ongoing treatment supporters.

Also, one should consider roles of the two sexes when discussing sexual risk behaviors. Some patients may feel less or more comfortable discussing sensitive sexual and risk-reduction issues with counselors of the opposite sex. In some cultures, open discussion of sexual risk behaviors is not customary, especially if the opposite sex is present in the room.

**Counseling Adolescents**

Adolescents need special considerations in HIV prevention counseling because it is at this growth stage where they experience physical changes and begin to explore their identity. It is at this bridge between childhood and adulthood where many adolescents explore many risky behaviors and the influence of friends and peers is most powerful. Counseling methods should consider these factors.
The national guidelines of the clinic site will tend to stipulate the age at which an adolescent can give his or her full consent for an HIV test without needing a caregiver. The health professional or counselor must ensure that the adolescent has been not pressured, coerced, or placed under duress in consenting to the HIV test. After giving consent, the adolescent must understand the confidential nature of the counseling sessions.

Building rapport with the adolescent patient is critical because such patients need to feel that they can trust the health care worker. The more comfortable adolescents are, the more open and honest they will be not only about their feelings but also about their previous sexual history. Such openness and honesty may be difficult, especially where the adolescent is involved in imbalanced sexual relationships, such as with wealthy, older men (so-called sugar daddies) or in commercial sex work. Many adolescents may not be making informed decisions to have sex, but they engage in it because of peer pressure or for financial gain. Peers tend to pressure one another without having received adequate and accurate information about the risks and implications involved in the behavior that they desire to engage in. The information that peers share tends to be imprecise and mythical. Therefore, they cannot always make informed decisions, placing them more at risk.

Many adolescents may come to a health facility because they need more information before engaging in sexual behavior. Many cultures do not openly discuss sex in the home—especially not to the children. Adolescents then may seek the support of a counselor. Here adolescents need counseling not only on HIV prevention but also on other sexually transmitted infections (STIs) and methods of contraception.

Discussing Reasons to Test

For patients who are seeking HIV testing voluntarily, a discussion of the reasons for testing will focus primarily on risk factors. However, many patients may be identified for testing because of symptoms indicative of HIV or because they have sought medical care for a related medical need, such as pregnancy or an STI. In such cases, health care providers will need to discuss the connections between the reasons that the patients are being seen for medical care and the reasons for and benefits of testing.

Sometimes a patient may identify as a perceived risk an activity or factor that is not associated with HIV infection. For example, the patient may be concerned about casual contact with a “risky” person, or the patient may fear that he or she is bewitched. The health care provider should respond respectfully to the patient’s beliefs and provide education about the known ways in which HIV is transmitted without being judgmental or biased. At times, patients may not feel comfortable talking about particular risky behaviors in which they have participated. In such cases, providers should support patients in being tested. Some patients may display anxious behavior and seek repeated testing, despite repeated negative test results. These patients may need...
help in identifying their fears of infection, more in-depth discussion of risk reduction, and/or increased education about HIV transmission and testing.

**Increasing the Odds That Patients Return for Results**

Often individuals may come for HIV testing but not return for results. Health care providers must reinforce the importance of returning for results. Providers should aid patients in setting up a plan for the return visit and prepare them for the anxiety that they might experience during the waiting period. Patients are often anxious and depressed in the time between being tested and receiving results, so strategies for reducing anxiety and stress are important. Counselors should help patients decide when they will return for results, whom they will tell about the test, and who may come with them when they return for results.

A study conducted in Ethiopia evaluated attendance for follow-up of HIV test results. Increased attendance of result counseling was related to greater knowledge and understanding of HIV infection and to the belief that good medical care will improve the course of HIV infection. Education about HIV and the positive effects of medical follow-up for HIV-infected patients should be discussed during initial HIV prevention counseling; doing so increases the likelihood that tested patients will return for results and follow-up counseling.

In a study of pregnant women, a positive test result was associated with failure to return for posttest counseling, suggesting that those who are most afraid of HIV-positive results may fail to return for them. Fear of violence from partners and feelings of lack of control over past and current risk factors also have been associated with failure to return for results. Likewise, feelings of fatalism may keep a patient from returning for results. Providing a sense of realistic hope is important. By using culturally appropriate counseling skills, counselors can help patients discuss the difficult subject of HIV testing and plan for the consequences of test results.

**HIV Counseling with Rapid Tests**

HIV prevention counseling with a rapid test completed in one visit has been a successful intervention in many settings in the United States over the past few years and has shown this approach to be feasible and well accepted by most clients.

HIV prevention counseling with rapid tests consists of two components: provision of information and prevention counseling. All patients must receive information about the rapid test and give consent for testing. Patients who can benefit should also receive prevention counseling.

**Information**

All patients tested with rapid tests should be given the same types of information as those tested with a standard enzyme immunoassay. Also, professionals should inform patients tested with rapid HIV tests that their test results will be made available during the same visit and that a reactive rapid test will require confirmatory testing. Information can be disseminated in a face-to-face meeting with the health professional or by way of brochures, pamphlets, or video and includes the following:

- Information about the HIV test, benefits, and consequences
- Ways that HIV is transmitted and how it can be prevented
- The meaning of the test results in understandable language
- Where to receive additional information and, if applicable, HIV prevention counseling
- How and where to obtain other health care services, including (if applicable) HIV/tuberculosis treatment and prevention of mother-to-child transmission
- How and where to obtain community support and resources

**HIV Prevention Counseling**

Fundamentals of HIV prevention counseling with rapid tests include but are not limited to the following:

- Keep the prevention counseling session focused on HIV risk reduction.
- Include comprehensive personalized risk assessment.
- Acknowledge and provide support for any positive steps already made, regardless of how minimal they may be perceived.
- Clarify critical rather than general misconceptions about risk of HIV.
- Negotiate concrete, achievable behavior change steps that will reduce HIV risk.
- Seek flexibility in the counseling process and avoid a one-size-fits-all approach.
The standard enzyme immunoassay setting always offers two test-associated opportunities for HIV prevention counseling for patients who return for their results; however, with rapid HIV testing there may be either one or two:

- Patients with reactive rapid HIV tests also have two associated opportunities—one during the day of testing and one during the day on which they return for their confirmatory test results.
- Patients with a nonreactive rapid test may have only the one test-associated opportunity. They may not have an opportunity to act upon their risk-reduction plan or discuss with the health professional their attempts at carrying it out prior to receiving their test result. If the health professional feels that the patient’s risks justify additional prevention counseling after negotiating a risk-reduction step(s), another appointment may be warranted and scheduled with the patient to further engage and empower the patient in his or her risk-reduction plan.

**Initial prevention counseling assessment.** The following guidelines are models for individual prevention counseling. The counseling assessment form can be used to guide the health care worker and to ensure that important topics covered in the guidelines are discussed with the patient, couple, or family. Group health education about HIV testing and risk factors can be used to convey information prior to counseling patients individually about their personal risk factors and risk-reduction strategies. Prevention counseling needs to be client centered, focusing on the client’s needs and concerns, and not on the completion of a risk-assessment tool. If particular risk factors do not apply to a particular client, the counselor should only briefly describe how those behaviors place one at risk of HIV infection. Discussing risk behaviors and fears is uncomfortable. Therefore the counselor will need to use good, insightful listening skills and supportive discussion to elicit the concerns surrounding the patient’s decision to be tested. Risk-reduction messages should be targeted to the patient’s particular risk factors and behavioral and psychosocial profile.

**Follow-up counseling.** Because the counselor will be the one providing the test results to the patient, the counselor must examine his or her own reactions to those results. The counselor should obtain the results and take time to review them alone or with a supervisor prior to delivering the results to the patient. If the counselor is shocked or distressed, that reaction will affect how he or she delivers the news of a positive or negative test. The counselor must enter the session focused on the patient’s needs and concerns. A quiet and confidential place to discuss results is essential. If possible, the same person who did the initial prevention counseling should provide follow-up counseling because the patient has already developed a relationship with that counselor.

**Assessing patient’s knowledge about HIV testing.** Before giving test results, the counselor should assess the patient’s knowledge about the HIV testing that he or she underwent. Most patients will have had initial prevention counseling and will know what HIV is and which risk factors place one at risk of HIV infection. However, some may have consented in haste or declined in-depth discussion of HIV and risk factors prior to testing. Other patients may have been tested without their knowledge because of, for example, insurance reasons, blood screening, or a concern by the medical provider. Testing people without their knowledge or consent is usually unethical, and doing so is illegal in some countries. Unfortunately, however, some people are tested without their knowledge or consent. Such patients may not be knowledgeable about HIV or prepared to receive HIV results. They may be angry at having been tested or shocked because they are getting unsolicited test results. Counselors will need to use their listening skills and help patients express their emotions and thoughts about the testing process and results.

**Assessing patient’s readiness to receive test results.** Prior to giving test results, the counselor must assess the patient’s readiness to receive them. The counselor should review what was discussed during the initial session of prevention counseling, including the meaning of a positive or negative test result and the patient’s understanding of the process and outcome of testing. The counselor should assess how the patient thinks that he or she is likely to respond to a positive test result. Many patients may be anxious about receiving HIV-positive test results and may plan threatening acts in such an event. This reaction indicates that a patient is not yet ready to hear the result. If a patient has communicated that he or she is not ready to receive HIV results at the time, the session can be deferred until that patient is ready. Counseling can then focus on the current patient
fears of receiving the result and on patient preparedness. However, the counselor will need to weigh the benefits of a delay against the risk that the patient may not return for the test result.

**Giving HIV test results.** If the patient is ready to receive the test result, the counselor should clearly and directly state the result using a neutral and calm tone of voice.

**Reactions to HIV test results.** People receiving a positive HIV test result have a variety of reactions, ranging from lack of emotion to profound and disruptive reactions resulting from anger and fear. The counselor must remain calm and comforting even if uncomfortable with the patient’s reactions. Here, counseling should focus on the client’s response to his or her newly learned status. If a patient has newly learned of his or her HIV-positive status, the counseling can address client reactions, fears, newly developed self-perceptions, and ideas of how others might perceive the patient and on new implications on his or her quality of life. The aim of these sessions would then be to empower the client to see beyond HIV status and not to concentrate on possible life constraints emerging because of HIV.

West (2007) argues that patients who are most at risk of HIV transmission (MART) who test HIV positive should change their behavior immediately. He further asserts that the primary focus of HIV prevention counseling for MART patients should be on short-term behavior change to reduce risky behaviors and thus stop the spread of HIV. To sustain this behavior change, though, MART patients can simultaneously benefit from long-term support services.

Providing the patient with HIV education about risk-reduction practices right after he or she has been diagnosed may not be possible. One may need to schedule a follow-up appointment to cover important topics and to offer ongoing supportive counseling. The module on psychosocial issues discusses some common issues that may need to be addressed. The counselor should not set a separate time for discussion of these topics just because he or she wishes to avoid the intense emotions of the patient. Instead, the separate appointment should be set only if it will benefit the patient.

If a patient has tested HIV negative, the counselor can review the patient’s initial reasons for testing and discuss prevention of future risk factors. The counselor can congratulate the patient for the results and encourage and empower him or her on ways of trying to remain HIV negative.

Skillful counseling can support patient needs. Listening skills, positive use of silence, and appropriate touch can help patients experiencing the immediate shock of an HIV-positive diagnosis.

Because denial is a prominent feature of patients’ response to a diagnosis of HIV infection, the patient should be shown a copy of the test result with his or her name on it as proof of the result. Many patients will want the test repeated, either at the same medical clinic or somewhere else. Patients with a positive test result should be provided with referrals to medical providers and social support networks or counseling services.

**Follow-up.** During a follow-up counseling session, the counselor may focus primarily on crisis intervention and supportive listening. As in the initial prevention counseling session, the counselor should reinforce the ways in which HIV is and is not transmitted, as well as the benefits of medical follow-up for HIV-positive patients.

Regardless of the test results, counselors should give patients information on reducing their personal risk of HIV infection or HIV transmission to others. Prevention messages should be tailored to the person’s risk factors and willingness and ability to change risk behaviors or situations. Practical information and assistance should be provided, and motivational factors that might prevent the use of risk-reduction practices should be discussed.

**HIV Prevention Counseling Guidelines**

**Before prevention counseling:**
- Obtain the patient’s identifying information as determined by the testing site.
- Take the patient to a quiet, designated counseling area to discuss testing and ensure confidentiality.

**Assess the patient’s risk factors and provide education:**
- Ask the patient’s reasons for seeking testing at this time or discuss the reasons that the patient is being engaged to discuss HIV testing.
- Discuss confidentiality of testing.
- Ask if the patient has had a previous HIV test.
HIV Prevention Counseling

- Ask if the patient has had any signs or symptoms that he or she fears are associated with HIV.
- Ask if the patient has ever had another sexually transmitted disease, and if so, ask when that was and what the circumstances were. Avoid making these questions seem like an interrogative session where patients are made to confess past transgressions—such an approach stifles the session and often hinders the patient from being honest and open.
- Provide education about HIV risk factors and about risk reduction based on risk factors that the patient has identified.

Assess the patient’s coping and support:
- With whom does the patient live? Who is a positive support in the patient’s life?
- What current life stressors is the patient experiencing?
- What other losses has the patient experienced, and how did he or she cope?
- Does the patient have a history of medical or psychiatric problems?
- Does the patient have a history of suicidal thoughts or attempts? Is the patient currently having thoughts about suicide? Has the patient attempted suicide?
- What experience has the patient had with people with HIV/AIDS?
- What individual strengths does the patient have that help him or her cope with difficulties?
- What are some family and cultural strengths that help the patient cope with difficulties?
- What social networks (e.g., faith-based or community organizations) help the patient cope with difficulties?
- What are the cultural or traditional beliefs around people living with HIV/AIDS?
- Does the patient’s culture facilitate safe, supportive disclosure of HIV, or does it make it harder?

Anticipation of results:
- Ask the patient what result he or she anticipates and why.
- Ask the patient what he or she will do if the result is different from the one that he or she anticipates, either positive or negative.
- Ask the patient what relationships or situations may change if the test is positive or negative.

Discuss the benefits of testing:
- The patient can seek medical intervention to prevent complications of opportunistic infections and to improve the course of the disease.
- The patient can reduce the risk of transmission to others, including children.
- The patient can make healthful lifestyle changes to improve his or her life.
- The patient can be empowered with new information and can actively seek help for signs and symptoms.

Discussion of HIV antibody tests:
- HIV antibody tests look for antibodies to HIV, which in adults and in many children means that the person has HIV.
- There is a window period during which an HIV-positive person can test negative because he or she has not yet developed antibodies (usually ≤3 months).
- Antibody screening and confirmatory testing are both performed before positive diagnosis.

Discuss medical treatment options if test results are positive:
- The patient may receive referrals to health care providers, referrals for support, and counseling and testing for other family members.
- Emphasize the positive effects of medical follow-up for HIV-positive patients.

Ensure that the person is making an informed decision to test:
- Does the patient understand the documenting requirements of the site? Yes No
- Does the patient understand who is notified of test results? Yes No
- Is testing voluntary? Yes No Reason if not voluntary:
- Does the patient understand the consequences of refusing testing?
- Is the patient of consenting age, and does he or she consent to testing at this time? Yes No

Emphasize the need for follow-up of results:
- Schedule a follow-up appointment for test results.
- Discuss what the patient will do to reduce anxiety and stress while waiting for results.
Help the patient envision coming back for results.
Ask if anyone will come with the patient for results.
Discuss date, time, and place to return for results.
Emphasize the benefits of returning for results and the courage that it took to come in for testing.

1. Sexual risk factors
   Assess
   - Has the patient had sex?
   - Does the patient have a known infected sexual contact?
   - Has the patient had any other sexually transmitted diseases?
   - Does the patient have a history of nonconsensual sex or sex for survival needs or drugs?
   Educate about the ABCs
   - Abstinence.
   - Be faithful.
   - Condom use—discuss techniques of proper use and negotiation of condom use.
   ABCs & SAVED—a dual approach
   - Safer practices—dual protection, be faithful, circumcision
   - Access to prescriptions—can the patient access treatment regularly?
   - Voluntary testing and counseling
   - Empowerment—can the patient (especially women and children) make informed decisions? Does he or she have decision-making power?
   - Disease Prevention and Control
   - Risk reduction—minimizing exchange of body fluids, using lubrication, and decreasing the number of partners.

2. Drug use risk factors
   Assess
   - Does the patient have a history of drug use?
   - What types of drugs does he or she use? How often? By what method (inhalation, injection, ingestion, topical application)?
   Educate
   - Changing method of use, e.g., from injection to inhalation or ingestion.
   - Changing frequency of use, e.g., from daily to less frequently.
   - Acquiring clean needles or cleaning needles with bleach and water.
   - Drug treatment to stop using drugs.

3. Medical/traditional practices with contaminated instruments or blood
   Assess
   - Has the patient ever had a blood transfusion?
   - Does the patient have a history of medical procedures with potentially contaminated instruments or needles?
   - Does the patient have a history of traditional practices with potentially contaminated razors or exchange of blood?
   Educate
   - Use personally owned razors. Clean razors.
   - Take universal precautions.

4. Mother-to-child transmission
   Assess
   - Does the child have an HIV-positive mother?
   - Does the child have a mother who died of unknown causes?
   - Is the woman pregnant or considering pregnancy?
   Educate
   - Educate the mother about perinatal transmission and risk reduction for future pregnancies.
   - Educate the mother about the risk of breast-feeding.
   - Educate HIV-positive women considering pregnancy about the risk of transmitting HIV to her infant and about treatment to reduce that risk.

5. Other risk factors
   Assess
   - Does the patient identify other risk factors for HIV?
   Educate
   - Correct misconceptions about transmission.

HIV Follow-Up Counseling Guidelines

Before prevention counseling:
- Obtain the patient’s identifying information as determined by the testing site.
- Take the patient to a quiet, designated counseling space to discuss testing and ensure confidentiality.

General guidelines:
- Make time to review all test results, either alone or with a supervisor, prior to delivering the results.
HIV Prevention Counseling

- Confirm the patient’s identity with the information acquired during the initial session.
- Greet the patient and take him or her to the room in which the results will be discussed.
- Assess his or her emotional and physical state of anxiety.
- Ask if the patient has told anyone that he or she has been tested and is coming for results.
- Did the patient receive initial HIV prevention counseling?
- Assess the patient’s level of HIV knowledge and awareness that he or she was tested for HIV.
- Discuss with the patient whether he or she is ready to receive the HIV test result. If the patient is not ready to receive the result at this time, discuss strategies to reduce anxiety and schedule a follow-up appointment.
- If the patient is ready to receive them, give the test results directly.
- Observe and assess the patient’s initial reactions to the test results.

When the HIV test is negative:
- Clarify that the test did not detect HIV antibodies and that this means the patient either does not have HIV or has not yet developed HIV antibodies.
- Listen to the patient’s thoughts and fears about the test results.
- Congratulate the person on the test results.
- Discuss risk-reduction methods.
- Discuss the current risk situations of the patient and help develop strategies to prevent infection.

When the HIV test is inconclusive:
- Clarify what the result means.
  - The test needs to be repeated.
  - It is not possible to assess a positive or negative result until the repeat testing is performed.
- Complete repeat testing.
- Reinforce risk-reduction behaviors or abstinence until the test results are back.
- Help the patient think of what he or she will do to reduce stress and anxiety.
- Help the patient think of personal coping strategies.
- Provide referrals for individual or group support.
- Reinforce the importance of returning for the test results.

When the HIV test is positive:
- Clarify that the test detected HIV antibodies and that a confirmatory test was done. In an adult, a positive test that has been confirmed usually means that the person is HIV infected.
- Acknowledge the patient’s shock or other reactions.
- Listen to the patient’s thoughts and fears about the test results.
- Avoid speculation on the patient’s prognosis.
- Explain in lay terms what HIV is and how it affects the immune system.
- Review routes of transmission and how to prevent transmission to others.
- Discuss the importance of informing current and previous partners.
- Discuss fears about disclosing the diagnosis.
  - Who might be a safe and positive person to talk to?
  - Discuss the possibility of waiting to tell others if it’s uncertain how they might respond.
  - Discuss safety concerns related to possible violent reactions or people who may not keep the diagnosis confidential.
- Listen to the patient.
  - Be willing to listen to feelings about HIV.
  - Ask about fears of illness and death.
  - Listen for expressions of guilt, rejection, fatalism, and spiritual beliefs.
- Help the patient recognize positive coping skills used in earlier times of crisis or in other areas of life.
- Anticipate previous negative coping responses or difficult social networks.
  - Encourage the patient to seek help if he or she becomes severely depressed or anxious.
  - Advise the patient to talk to someone if he or she has thoughts of suicide.
  - Assess the patient for current thoughts of suicide.
- Prepare the patient to anticipate emotional ups and downs.
- Prepare the patient to interpret common symptoms of HIV. Not all symptoms or problems are related to being HIV infected.
- Provide information on support networks and groups.
- Discuss the importance of receiving medical follow-up.
- Provide referrals for medical care and treatment.
For women, discuss considerations regarding childbearing and contraception.

Discuss healthful lifestyle adjustments that the patient can make.

Provide the patient with a sense of realistic hope.
- There is currently no cure for HIV.
- However, treatments are available that can prolong health and life.
- Emphasize that the patient should continue to pursue goals, e.g., at work or school.
- Encourage the patient to anticipate other goals that he or she might want to accomplish.
- Provide encouragement and appropriate follow-up. Schedule follow-up counseling.

### HIV Prevention Counseling Assessment

<table>
<thead>
<tr>
<th>Patient’s identifying information obtained?</th>
<th>☐ Yes ☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons for seeking testing:</td>
<td>____________________________</td>
</tr>
<tr>
<td>Previous HIV test? Date and result:</td>
<td>____________________________</td>
</tr>
<tr>
<td>Signs/symptoms of HIV:</td>
<td>____________________________</td>
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</tbody>
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Understanding of HIV risk factors: Discuss and mark patient’s risk factor(s)
- Sexual risk factors
  - Has had sex
  - Known HIV-infected sexual contact:
  - Other STIs:
    - When: ____________________________
    - History of nonconsensual sex or exchange of sex for survival needs/drugs?
    - Use of condoms as preventative strategy?
      - Always ☐ Sometimes ☐ Never ☐
- Drug use risk factors
  - Type of drug, frequency, and method
  - History of medical/traditional practices with contaminated instruments?
  - History of blood transfusion? When and where?
- Mother-to-child risk factors
  - Child of a known HIV-positive mother?
  - Child of a mother who died of unknown causes?
- Other risk factors identified by the client:
- Assessment of coping and support
- With whom does the patient live?
- Current stressors:
- Previous experiences of loss:
  - History of mental illness
  - History of suicidal thoughts or attempts
  - Current suicidal thoughts or attempts
  - Experiences with people with HIV/AIDS

### HIV Follow-Up Counseling Assessment

Patient’s identifying information obtained?

Did the patient tell anyone about the testing and about coming for results? ☐ Yes ☐ No

Did the patient receive initial HIV prevention counseling? ☐ Yes ☐ No

Does the patient understand HIV risk factors and that he or she was tested for HIV? ☐ Yes ☐ No

Is the patient ready to receive the HIV test result? ☐ Yes ☐ No

If not, follow-up appointment date:

- Patient’s test result
  - Negative test
  - Patient understands test did not detect antibodies.
  - Current risk situations discussed:
  - Risk-reduction methods discussed:
  - Follow-up testing needed? Date: ____________

- Inconclusive test
  - Patient understands test result was ambiguous and test must be repeated.
  - Current risk situations discussed:
  - Risk-reduction methods discussed:
    - Strategies for reducing anxiety reinforced.
  - Discussed importance of returning for result.
HIV Prevention Counseling

- Follow-up testing done? ☐ Yes ☐ No
- Follow-up appointment date: ________________
  - Positive test
  - Patient understands the test detected antibodies and a confirmatory test was done. This means that the person is HIV infected.
  - Patient understands what HIV is and what it does to the immune system.
  - Patient understands that medical follow-up can improve the course of HIV infection.
  - Partner notification discussed.
  - Disclosure-related concerns discussed.
  - Fears and concerns discussed.
  - Patient understands that he or she will experience emotional ups and downs and may interpret symptoms as being HIV related when that is not always the case.
  - Risk factors reviewed. Patient’s risk factors:
    - Risk-reduction techniques discussed:
    - Assessment of depression/suicidal thoughts:
    - Patient’s support system:
    - Patient’s beliefs that will influence reaction/treatment:
    - Positive coping skills:
    - Referrals to support groups/counseling:
    - Referrals to medical providers:
    - Reinforced hope and family relationships.
    - Follow-up date set:

Patient’s reaction to results: ______________________
Notes on session: ______________________________
Signature: _____________________________________

Review Questions and Role Plays

1. Mary, who is 14, has told you that she has been having a sexual relationship with a 30-year-old man and has had other sexual relationships.
   - What would you be thinking and feeling about this situation? How might your thoughts and feelings potentially interfere with your ability to communicate with Mary?
   - What important information would you discuss with Mary about the risks of HIV and other sexually transmitted infections?
   - How would you bring up the need for HIV testing with Mary?
   - What information would you want to know about Mary’s home situation and relationship with her sexual partners to help you provide prevention counseling and support to her?

Mary agrees to be tested for HIV but does not want to discuss this with her mother.
   - What information would you want to know about Mary’s relationship with her mother?
   - How might you talk to Mary about thinking of someone else whom she could tell about being tested for HIV?
   - How would you help her make that decision?

Mary’s test comes back inconclusive.
   - What information would you present to her, and how?
   - What would you tell her to do while awaiting a repeat test?

Upon repeat testing, Mary’s test is positive for HIV. She misses her first scheduled appointment for the test result.
   - What would you be thinking and feeling in this situation?
   - How would you go about contacting her to bring her back to the clinic to discuss the test result? What information that you obtained during the initial session of prevention counseling would be helpful in trying to contact her?

Mary comes back in for her HIV result. She is visibly anxious.
   - How would you connect with Mary during this return appointment?
   - What would you want to know about what Mary recalls from the initial prevention counseling session and about her thoughts and experiences since she first came for testing?
   - What would you want to review with Mary prior to giving her the test result?

Mary says that she is not sure if she wants to know her result.
   - What would you discuss with her about her feelings about receiving the test result and the pros and cons of knowing the result of the test?
   - Do you feel that patients have a right not to know their test results?
Mary says that she is ready to learn her test result. When you tell her, she begins to cry. She says she has a close friend who recently died of AIDS.

- How might you provide support to Mary?
- What would be the most important information to convey to Mary at this time?
- What strengths would you try to build in Mary at this time?
- What referrals might you make?
- How would you ensure follow-up for Mary?

2. The Dlaminis have been married for 5 years. Last month, after their 8-month-old child died of severe pneumonia, a physician recommended that the Dlaminis both be tested for HIV. They agreed to be tested and now have returned for their results. You have the results, which show that one of the Dlaminis is positive and the other is negative.

- Would you tell the couple their results together? Why or why not?
- If the woman were positive, would that change how you would handle the situation? What if it were the husband?
- What issues would you discuss with the person whose test is negative? What recommendations might you make? Would your approach be different if the couple were not married? Would it be different if you did not know the partner’s status?
- How would you tell the person who is positive? What would you counsel that person about the partner? Would your counsel be different if the positive partner is male or female? Why or why not?

3. Musa is a 12-year-old double orphan. His father died in his infancy and his mother died 2 months ago. His maternal grandmother has brought him you; she complains that he is showing signs and symptoms similar to those of her deceased daughter. His grandmother says that a week ago she told Musa that she would bring him for an HIV test at your site, but he has said nothing in response. She further explains that Musa has been depressed since his mother’s death. She believes that this is because Musa cared for her as she deteriorated and was at her bedside when she died. Musa presents to you with low affect. He is sad and often teary as his grandmother speaks. He says nothing to either of you through the session, even when spoken to.

- How do you approach the subject of HIV with Musa?
- What is Musa’s social story, and how has HIV affected him?
- What kind of emotions do you think that Musa is experiencing?
- What effect did watching his mother pass away have on him?
- Do you think that HIV testing should proceed? Why or why not?
- How should issues of consent be addressed in this case? Who should give it?
- How much say or decision-making power does Musa have?
- What effect would an HIV-positive result have on Musa?
- What about an HIV-negative result?

References


