

HIV/AIDS: Update for Washington

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Answer Sheet/Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. In 1982, she received her PhD in Higher Education Administration from Peabody College of Vanderbilt University. In 1988, Dr. Norman took a position at Tennessee State University. There she has achieved tenure and full professor status. She is a member of Sigma Theta Tau National Nursing Honors Society. In 2005, she began her current position as Director of the Masters of Science in Nursing Program.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and

student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, Jane C. Norman, RN, MSN, CNE, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all dental professionals in Washington involved in the care of patients with HIV/AIDS.

Accreditations & Approvals

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Designations of Credit

NetCE designates this activity for 7 continuing education credits.

AGD Subject Code 148.

This course meets the Dental Board of California's requirements for 7 units of continuing education.

Dental Board of California course #07-3841-00356.

Special Approvals

This course is designed to fulfill the Washington requirement for HIV/AIDS education. Participants will receive 7 hours of continuing education for completing this course.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective

In view of the existing crisis in healthcare in the United States, the problems associated with providing the necessary care for persons with HIV infection or AIDS are significant. The purpose of this course is to address those problems in the discussion of epidemiology, organism characteristics, pathophysiology, transmission, clinical manifestations, complications, treatment advancements, prevention, ethical and legal aspects of care, and workplace concerns.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the background and significance of the AIDS epidemic, including geographic patterns of transmission.
2. Discuss the characteristics of the infecting organism and the various HIV tests available.
3. Describe the transmission and natural history of HIV infection, including risk behaviors and routes of contagion.
4. Describe the treatments available in the care of patients with HIV, including antiretroviral medications used in patient care.
5. Discuss the impact of the virus on women living with HIV infection.
6. Review the transmission of HIV to the infant and child, and discuss care of these infected children.
7. Summarize issues unique to older persons with HIV infection.
8. Outline approaches to AIDS prevention.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Despite scientific advances in our understanding of pathogenesis and transmission and expanded options for prevention and treatment, human immunodeficiency virus (HIV) remains a complex, challenging public health concern of epidemic proportion. In the United States, the prevalence of infection has increased substantially among young women and among the elderly in recent decades. The former has serious implications for maternal and child health; the latter presents new challenges for nurses and physicians who provide elder care. As yet, there is no cure or preventive vaccine; however, combination antiretroviral therapy controls HIV infection and permits individuals to lead relatively healthy, productive lives for decades.

The purpose of this course is to provide a basic, practical review and update of knowledge concerning HIV infection and acquired immune deficiency syndrome (AIDS), addressing the key issues that impact clinical and public health practice. Topics to be addressed include immunopathogenesis, modes of transmission, natural history and clinical staging, risk behavior assessment, prevention (including postexposure prophylaxis [PEP]), diagnosis, management, and follow-up.

EPIDEMIOLOGY

GLOBAL IMPACT

Analysis reveals that the HIV pandemic continues to escalate throughout developing countries compared to a notable stabilization in new cases and fatalities in some developed countries. The established healthcare community became aware of the illness that has since become known as AIDS in 1981.

Two human immunodeficiency viruses, HIV-1 and HIV-2, have been identified and both cause AIDS. Researchers in the United States and England have traced the ancestry of the HIV-1 virus to two strains found in African red-capped mangabeys and greater spot-nosed monkeys. The strains most likely combined in chimpanzees that ate the monkeys, resulting in the chimpanzees developing simian immunodeficiency virus (SIV). Chimpanzees then transmitted the virus to humans, likely around 1908 [1]. Genetic studies suggest that the lower monkeys first became infected with SIV 100,000 years ago [2].

HIV-2 is believed to be endemic in West Africa, though even areas with previously high rates (e.g., Senegal) are seeing HIV-2 being increasingly overtaken by HIV-1 [1]. Several well-documented cases of HIV-2 infection have been reported in Europeans and among West Africans residing abroad. A total of 242 cases meeting the Centers for Disease Control and Prevention's (CDC's) definition of HIV-2 infection were reported between 1988 and 2010 in the United States, the majority of which were associated with immigration from, travel to, or a sexual partner from West Africa [3]. Differences in the global spread are attributed to differences in transmissibility and duration of infectiousness [4].

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), an estimated 38.4 million individuals worldwide were living with HIV/AIDS in 2021, more than one-half of whom are women [5]. Eastern and southern Africa account for 94% of new HIV infections [5]. It is important to note that despite increases in certain geographic areas and demographic groups, overall, the rate of new infections is declining. This is due, in part, to lower prices for antiviral medications and implementation of prevention programs [5].

Beginning in 2003, the U.S. government has worked to fight the disease in Africa, partially through the implementation of the President's Emergency Plan for AIDS Relief (PEPFAR) [6]. PEPFAR was reauthorized in 2008 and in 2013, with more than \$50 billion in funds to address HIV/AIDS and additional health issues, including malaria, tuberculosis, maternal health, and clean water [7]. This was extended to 2018 with the PEPFAR Stewardship and Oversight Act of 2013 [8]. At the end of 2021, \$21.4 billion in U.S. dollars were available for the AIDS response in low- and middle-income countries [5].

U.S. STATISTICS

As of 2021, an estimated 1.2 million individuals 13 years of age or older were living with HIV/AIDS in the United States [9]. The CDC estimates that approximately 15% to 20% of these individuals are unaware of their infection [9]. When reviewing trends in HIV transmission, one should keep in mind that the widespread use of antiretroviral therapy has resulted in fewer deaths and longer survival.

As of 2020, the CDC reports several trends in the HIV/AIDS epidemic [10]:

- By region, the rate of HIV diagnosis was highest in the South (14.7 per 100,000 population) and lowest in the Midwest (7.2 per 100,000 population).
- By race/ethnicity, the percentages of HIV infection were approximately 42% among Black/African Americans, 27% among Hispanic/Latino individuals, 26% among White Americans, 3% among those of multiple race, 2% among Asians, and less than 1% among American Indians/Alaska Natives or Hawaiian/Pacific Islanders.
- By sex, 80% of adults and adolescents living with HIV are male.

WASHINGTON STATE STATISTICS

As of 2020, an estimated 14,000 Washington residents are living with HIV, with the vast majority of cases occurring in King County (50%) and Pierce County (11%) [11]. Each year, there are approximately 383 new cases within the state. The demographics of HIV/AIDS infection in Washington reflect its unique population. The majority of persons living with HIV/AIDS in Washington are White (56%) and male (84%); however, the rate of White men contracting the disease has been decreasing over the past few decades [11]. In 2020, 43% of new cases were among people of color, compared with 32% in 1998. Among men, new cases of HIV were reported to be highest among White men and lowest among Asian men. Among women, new cases of HIV were highest among Black women and lowest among Asian women [11]. The number of new cases in Washington gradually increased from 2015–2019. The number of reported diagnoses dropped in 2020, but it is unclear whether this represents a change in incidence [11].

A BRIEF OVERVIEW OF HIV DISEASE

VIRAL PATHOGENESIS

HIV, known formerly as human T cell lymphotropic virus (HTLV-III), is a member of the retrovirus group and as such carries a ribonucleic acid (RNA) genome and a reverse transcriptase enzyme (RNA-directed DNA polymerase) that enables the virus to replicate within infected host cells. Susceptibility in humans is determined by the binding affinity of virion envelope proteins for a specific cell surface receptor molecule (CD4+) found on tissue dendritic cells, macrophages, and CD4+ T lymphocytes. The pathogenesis of infection, and the subsequent perpetuation of the disease state, involves a complex set of interactions by which HIV is able to take advantage of cellular pathways while avoiding or neutralizing various components of the immune system [12; 13].

The most common mode of HIV infection is sexual transmission across exposed mucosal epithelium. Dendritic cells and macrophages are found beneath the mucosal epithelium of the anogenital and cervicovaginal tracts, as well as within tonsillar and adenoidal tissue. Studies in primates demonstrate that after the virus penetrates the mucosal epithelium, infection is initiated within nearby dendritic cells and macrophages. Infected dendritic cells then fuse with CD4⁺ T lymphocytes and the infection extends to deeper tissue and, shortly thereafter, to regional lymph nodes [13]. Within days, this proliferation of infected CD4⁺ T lymphocytes, combined with the migration of infected macrophages, leads to the appearance of viral RNA in the blood stream. This is followed by widespread secondary amplification of infection within the lymphoid tissue of the gastrointestinal tract, spleen, and bone marrow.

Once the virus enters the cell, it may replicate, induce cell fusion and propagation of infection, or lead to cell death [13]. The defining characteristic of HIV disease is the immune deficiency state caused by ongoing viral replication and cell-to-cell transmission within lymphoid tissue. With chronicity of infection there is a progressive depletion of CD4 (helper-inducer) lymphocytes, the very T lymphocyte cohort whose function it is to direct other cells in the immune system, and to orchestrate the inactivation of virus antigen. The result is a depressed T lymphocyte functional capacity, characterized by depletion of helper T cells (T4), impaired killer T cell activity, and increased suppressor T cells (T8). In persons with intact lymphocyte immune systems, the normal number of CD4 T cells ranges from 600–1,200 cells/mcL, depending on the stage and duration of infection.

CLINICAL MANIFESTATIONS AND DISEASE COURSE

The clinical manifestations of HIV disease are determined by the stage of primary infection and the chronicity and degree of the resultant cellular immunodeficiency state. Acute, primary HIV infection may be asymptomatic, but most often it is manifest by a subacute viral syndrome of malaise and fatigue, fever, sore throat, rash, myalgia, headache, and lymphadenopathy—clinical features similar in many respects to that seen with Epstein-Barr virus mononucleosis, cytomegalovirus (CMV), and certain types of herpes simplex infections [13]. A variety of atypical symptoms and signs may be seen, including aseptic meningitis syndrome, genital ulcers, and ulcerations involving the gingiva, palate, or buccal mucosa. The acute illness usually resolves in less than 14 days but may follow a protracted course over many weeks [13].

Early in the chronic phase of HIV infection, when the CD4 lymphocyte population is only modestly depressed and declining slowly, patients are often asymptomatic or may exhibit generalized lymphadenopathy and recurrent oropharyngeal candidiasis (thrush). During this stage, a reservoir of HIV is established throughout the lymphoid tissue system, including the spleen. Gradually, wandering (infected) macrophages disseminate the virus to certain internal organs, notably the brain, kidney, and adrenal glands.

Chronic HIV disease follows a variable course but eventually leads to a variety of clinical manifestations, some of which are directly related to the impact of chronic infection on vital organs. Common syndromes include HIV encephalopathy and dementia, peripheral neuropathy, interstitial nephropathy, a variety of skin eruptions, and signs of adrenal insufficiency.

The late clinical manifestations of HIV disease are most frequently the result of acquired immunodeficiency syndrome (AIDS) that follows progressive depletion of CD4⁺ T lymphocytes to levels <200 cells/mcL. AIDS-defining illnesses include secondary, opportunistic infections and certain malignancies usually encountered only in clinical settings of severely impaired cellular immunity.

Opportunistic infections are very common in persons with undiagnosed or poorly treated chronic HIV infection and are of two types. The first type is infection newly acquired by exposure to microorganisms normally nonpathogenic, or of low pathogenicity, for persons with a healthy immune system. Examples are *Pneumocystis jiroveci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and atypical mycobacteria, all of which are commonly associated with inhalational exposures and transient colonization of the respiratory tract in healthy individuals. The second type is reactivation of latent infection acquired earlier in life, which typically remains dormant throughout life. Examples of this type are CMV, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *Histoplasma capsulatum*. The advent of an opportunistic infection may serve as the herald sign of unrecognized, undiagnosed chronic HIV infection/AIDS.

Clinically, these infections tend to present in one of several distinct syndromes, with useful differential diagnosis considerations:

- Pneumonia: *Pneumocystis jiroveci* pneumonia (PJP), *Mycobacterium avium* complex (MAC), cryptococcosis, histoplasmosis
- Meningoencephalitis: Toxoplasmosis, cryptococcosis, tuberculosis
- Gastrointestinal disease (diarrhea): Common bacterial dysentery, cryptosporidium, fungal and atypical mycobacterial infection

- Fever of unknown origin (often with abdominal complaints, hepatosplenomegaly, and/or lymphadenopathy): CMV, MAC, tuberculosis, histoplasmosis

Late clinical manifestations related to HIV-induced malignancy include Kaposi sarcoma of the skin or respiratory tract and lymphoma presenting as lymphadenopathy, splenomegaly, or focal gastrointestinal disease.

Without satisfactory antiretroviral therapy, the usual patient with HIV/AIDS experiences a slow, inexorable wasting illness punctuated by periods of feverishness and diarrhea, becoming increasingly anorectic, malnourished, and lethargic. Late clinical signs include muscle wasting and weakness, anemia and thrombocytopenia, lymphadenopathy, pulmonary infiltrates, and neurologic abnormalities (such as dementia, peripheral neuropathy, and tremors). The median survival of patients with advanced HIV/AIDS (CD4 count <50 cells/mcL) is approximately 12 to 18 months. Patients succumb to complications of uncontrolled infection, malignancy, or critical organ failure (such as uremia or adrenal insufficiency).

HIV TESTING

There are several recommendations for HIV screening. The U.S. Preventive Services Task Force (USPSTF) and the Agency for Healthcare Research and Quality (AHRQ) recommend that all persons 15 to 65 years of age regardless of risk level have at least one test for HIV status and that all pregnant women be screened prior to childbirth [14; 15]. In addition, younger and older individuals at increased risk (e.g., new sexual partners) should also be screened.

The initial testing for HIV generally consists of an FDA-approved, fourth-generation antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to identify both established and acute infections [16; 17]. No further testing is required for specimens that are nonreactive on the initial immunoassay [16]. If this test is reactive, repeat testing is recommended to differentiate HIV-1 antibodies from HIV-2 antibodies [16; 17]. If this second test is non-reactive or indeterminate (or if acute HIV infection or recent exposure is suspected or reported), testing with an FDA-approved HIV-1 nucleic acid test is indicated [16; 17]. Specimens that are reactive on the initial immunoassay and nonreactive or indeterminate on the HIV-1/HIV-2 differentiation immunoassay should be tested with an FDA-approved HIV-1 nucleic acid test (HIV-1 NAT) [16; 17]. It is important to note that HIV-2 is not reliably identified by usual immunoblot antibody tests. Additional testing specific to HIV-2 should be considered if HIV-1 test results are atypical or inconsistent with clinical findings, especially for persons from West Africa [3; 16].

Other available tests, including enzyme-linked immunosorbent assay, may be used if the preferred combination immunoassay is not available. The HIV-1 Western blot and HIV-1 immunofluorescence assay, previously recommended to make a laboratory diagnosis of HIV-1 infection, are no longer part of the recommended testing algorithm [16].

CONSENT TO TEST

Informed consent should be obtained from each person being tested. Each individual should be fully aware of the limitations of the HIV-antibody test regarding HIV infection and the development of AIDS. The test and its meaning, the reason for ordering the test, and its potential adverse consequences should be understood. The consent also includes information about how the test information will be used. In the state of Washington, no person may undergo HIV testing without the person's consent except in cases of incompetence, double-blinded seroprevalence studies, and/or when the department of labor and industries determines that it is relevant [18; 19].

There have been court cases that have centered on testing without consent; therefore, it is imperative that all healthcare providers follow the procedures concerning consent to test. HIV testing may only be done with patient's consent. Informed consent includes: documentation of consent on the chart, pre-and post-test counseling and referrals. The physician ordering the test is required to tell the patient if the result is positive; offer counseling and appropriate referrals.

Cultural Considerations in Informed Consent

An individual's ability and prerogative to make decisions about treatment is now seen as a vital expression of autonomy and is a prerequisite to participation in treatment or interventions. Autonomy, individualism, and self-determination are belief systems that are highly valued in Western societies, especially in the United States. Autonomy may be categorized into two groups: first-order autonomy and second-order autonomy [20]. First-order autonomy is what Westerners espouse and value: self-determination and autonomy in decision making. Second-order autonomy, however, is prevalent in collectivistic societies where decision making is group-oriented and takes into account another decision-maker who is accorded authority and respect [20]. For example, in many Asian cultures, particularly if the family system is based on a patriarchal authority system, a male elder or leader who is regarded as the primary decision-maker is key in this process of informed consent.

The process of informed consent entails the explicit communication of information in order for the individual to make a decision. Again, Western cultures value explicit information, which is centered on American consumerism; believing in having choices and being able to exercise choices in purchases extends to healthcare. However, some cultures believe that language and information also shape reality [21]. In other words, explicit information, particularly if it is bad information, will affect the course of reality.

A signature is required on most Western informed consent forms to represent understanding and agreement on the part of the individual involved. Yet, this might be viewed as violation of social etiquette in some cultures. In some cultures (for example, Egypt), signatures are usually associated with major life events and legal matters. Therefore, requiring a signature outside these circumstances would imply a lack of trust, particularly when verbal consent has been given [22].

Furthermore, consent forms often contain technical and legal jargon that may be overwhelming to the native English-speaking individual but can be much more daunting for immigrants who may not be English proficient or familiar with various legal concepts. For some immigrants who have experienced political persecution in their homelands, asking for a signature on a consent form that contains foreign legal and technical terms can potentially place them at risk for secondary traumatization, as some were persecuted, tortured, and forced to sign documents in their homelands [23].

This cultural dissonance can be a challenge to many general healthcare and mental health practitioners. Cultural experts are highly recommended for consultations to assist in the interpretation and navigation of the complex web of cultural interactions.

CONFIDENTIALITY AND ANONYMOUS TESTING

It is important the healthcare professionals protect patients' rights to privacy and confidentiality and offer anonymous testing when appropriate. In Washington, local health officers are required to [24]:

- Ensure anonymous HIV testing is reasonably available.
- Make HIV testing, AIDS counseling, and pretest and post-test counseling available for voluntary, mandatory, and anonymous testing and counseling.
- Make information on anonymous HIV testing, AIDS counseling, and pretest and post-test counseling available.
- Use identifying information on HIV-infected individuals provided only:
 - For purposes of contacting the HIV-positive individual to provide test results and post-test counseling
 - To contact persons who have experienced substantial exposure, including sex and injection equipment-sharing partners and spouses
 - To link with other name-based public health disease registries when doing so will improve ability to provide needed care services and counseling and disease prevention
- Destroy documentation of referral information containing identities and identifying information on HIV-infected individuals and at-risk partners of those individuals immediately after notifying partners or within three months, whichever occurs first.

According to the Washington Department of Health, sharing the results of any sexually transmitted infection (STI) testing is restricted [25]. The exchange of medical information among healthcare providers and within facilities in order to provide healthcare services to the patient is permitted, and the results of HIV testing may be released to the following recipients:

- The subject of the test
- A person with a release of information from the tested person
- Health officials in accordance with reporting requirements for diagnosed STIs
- Facilities that collect blood, tissue, or semen
- Health officials, first responders, or victims of sexual assault who petition the court to order testing

- A person allowed access to information by a court order
- Local law enforcement if health officers have exhausted procedures to stop behaviors that present a danger to the health of the public
- Exposed persons who are notified because releasing the identity of the infected person is necessary
- Payers of health claims
- Agencies or guardians responsible for children younger than 14 years of age with an STI

However, HIV testing results should be released to approved parties with the following warning: “This information has been disclosed to you from records whose confidentiality is protected by state law. State law prohibits you from making any further disclosure of it without the specific written consent of the person to whom it pertains, or as otherwise permitted by state law. A general authorization for the release of medical or other information is NOT sufficient for this purpose” [25].

TRANSMISSION OF HIV

HIV is transmitted person-to-person across mucosal or cutaneous barriers by exposure to infected genital secretions or blood and blood products. The common modes of transmission are sexual intercourse, injection drug use, infusion of blood products, and perinatal transmission. The risk from whole blood, packed cell, and fresh frozen plasma is, at present, extremely low by virtue of more sensitive crossmatching and screening techniques.

RISK CATEGORIES

On the basis of newly reported cases, the transmission categories are [10]:

- Male-to-male sexual contact (MSM) (68%)
- Heterosexual contact (22%)
- Injecting drug users (IDUs) (7%)
- Male-to-male sexual contact and IDU (4%)
- Perinatal transmission (1%)
- Other (includes hemophilia, blood transfusion, and risk factor not reported or not identified) (1%)

The CDC has published guidelines for medical professionals to integrate HIV prevention into the regular medical care of those living with HIV. The three major components of the recommendation are: screening for HIV transmission risk behaviors and STIs; providing brief, behavioral risk-reduction interventions in the office setting and referring selected patients for additional prevention interventions and other related services; and facilitating notification and counseling for sex and needle-sharing partners of infected persons [26; 27].

MODES OF TRANSMISSION

Sexual Transmission of HIV

HIV has been isolated from blood, seminal fluid, spermatozoa, pre-ejaculate, vaginal secretions, urine, cerebrospinal fluid, saliva, tears, and breast milk of infected individuals. No cases of HIV infection have been traced to saliva or tears (though traces of the virus are present in these fluids) [28]. The virus is found in greater concentration in semen than in vaginal fluids, leading to a hypothesis that male-to-female transmission could occur more easily than female-to-male. Sexual behavior that involves exposure to blood is likely to increase transmission risks. Transmission could also occur through contact with infected bowel epithelial cells in anal intercourse, in addition to access to the bloodstream through breaks in the rectal mucosa.

Posing the highest risk of infection is unprotected anal receptive intercourse, followed by unprotected vaginal intercourse and unprotected insertive anal intercourse (particularly for uncircumcised men) [29; 30]. Risk is reduced through the use of latex condoms. For the wearer, latex condoms provide a mechanical barrier limiting penile exposure to infectious cervical, vaginal, vulvar, or rectal secretions or lesions. Likewise, the partner is protected from infectious pre-ejaculate, semen, and penile lesions. Oil-based lubricants may make latex condoms ineffective

and should not be used; water-soluble lubricants are considered safe. Natural membrane condoms (made from lamb cecum) contain small pores and do not block HIV passage. It is estimated that latex condom use reduces the risk of HIV transmission by approximately 70% to 80% [31; 32; 33]. Although abstinence from sexual contact is the sole way to absolutely prevent transmission, sexual activity in a mutually monogamous relationship in which neither partner is HIV-infected and no other risk factors are present is considered safe [4]. However, men who identify publicly as heterosexual and generally have committed relationships with women, but who also engage in sexual activity with other men, may be a transmission bridge to heterosexual women [34]. To better understand the actual extent of this behavior and its impact on HIV transmission, more research is necessary.

Numerous studies have demonstrated that oral sex can result in the transmission of HIV and other STIs. While the risk of HIV transmission through oral sex is much smaller than the risk from anal or vaginal sex, there are several co-factors that can increase this risk, including oral ulcers, bleeding gums, genital sores, and the presence of other STIs. Prevention includes the use of latex condoms, a natural rubber latex sheet, plastic food wrap, a cut open condom, or a dental dam, all of which serve as a physical barrier to transmission [35].

Blood Donor Products

It has been estimated that 1 mL of HIV-infected human blood contains up to 10,000 copies of the virus. In comparison, 1 mL of blood infected with hepatitis B virus has 100 million to 1 billion infective organisms [36]. Even so, HIV is transmitted via blood, primarily through sharing of contaminated needles among IDUs and, rarely, through blood transfusion. Transmission of HIV-1 has occurred after transfusion of the following components: whole blood, packed red blood cells (including washed and buffy coat poor), fresh frozen plasma, cryoprecipitate, platelets, and plasma-derived prod-

ucts, depending on the production process. With the implementation of a donor screening program of the nation's blood supply in 1985 and advances in the treatment of donated blood products, blood transfusion is now even safer; the current risk of transmission of HIV through this route is conservatively estimated to be between 1 in 1.5 million [37]. It is possible that before blood screening implementation, more than 12,000 people were infected [38]. A large percentage of persons with hemophilia acquired HIV in this manner. Donor screening, HIV testing, and heat treatment of the clotting factor have greatly reduced the risks.

Needle Sharing

More than 3,100 new HIV infections occurred in 2020 among IDUs [10]. Transmission of HIV among injecting drug users occurs primarily through contamination of injection paraphernalia with infected blood. The risk of sustaining HIV infection from a needle stick with infected blood is approximately 1 in 300 [39]. Behavior such as needle sharing, "booting" the injection with blood, and performing frequent injections increases the risk. Crack cocaine use (by injection or smoking) is associated with a higher prevalence of HIV infection. This may in part be attributed to the exchange of cocaine for sex. Sharing of equipment is common due to legal and financial restrictions and cultural norms, and some studies have linked higher levels of psychologic distress (e.g., anxiety and depressive symptoms) with an increased risk for needle sharing [40]. Secondary transmission occurs to children and sexual partners. Preventative strategies include medication-assisted drug treatment, onsite medical care in a drug treatment program, recruitment of "street" outreach workers for intensive drug and sex risk-reduction educational campaigns, teaching addicts to sterilize their equipment between use, the free provision or exchange of sterile injection equipment (as allowed by law), distribution of condoms and bleach to clean drug use equipment, or a combination of these interventions.

Syringe services programs (SSPs) are community-based prevention programs that provide a range of services, including access to and disposal of sterile syringes and injection equipment. SSPs can reduce needlestick injuries and overdose deaths. Studies show that SSPs protect first responders and the public by providing safe needle disposal. These programs can serve as a bridge to other health services, including HCV and HIV diagnosis and treatment [41].

Health professionals should stress the following messages when they counsel IDUs [42]:

- The best way for you to prevent HIV and hepatitis B and C virus transmission is to NOT inject drugs.
- Entering substance abuse treatment can help you reduce or stop injecting. This will lower your chances of infection.
- Get vaccinated against hepatitis A and hepatitis B. You can prevent these kinds of viral hepatitis if you get vaccinated.
- If you cannot or will not stop injecting, you should:
 - Use a new, sterile syringe obtained from a reliable source to prepare and divide drugs for each injection.
 - Never reuse or share syringes, water, cookers, or cottons.
 - Use sterile water to prepare drugs each time, or at least clean water from a reliable source.
 - Keep everything as clean as possible when injecting.
- If you cannot use a new, sterile syringe and clean equipment each time, then disinfecting with bleach may be better than doing nothing at all:
 1. Fill the syringe with clean water and shake or tap. Squirt out the water and throw it away. Repeat until you do not see any blood in the syringe.

2. Completely fill the syringe with fresh, full-strength household bleach. Keep it in the syringe for 30 seconds or more. Squirt it out and throw the bleach away.
 3. Fill the syringe with clean water and shake or tap. Squirt out the water and throw it away.
- If you do not have any bleach, use clean water to vigorously flush out the syringe. Fill the syringe with water and shake or tap it. Squirt out the water and throw it away. Repeat several times.

It is important to note that a disinfected syringe is not a sterile syringe. The best option is always to use a new, sterile syringe with every injection.

Perinatal Transmission

In the absence of prophylactic treatment, approximately 25% to 30% of children born to HIV-infected mothers will contract HIV infection; this increases to 50% with prolonged breastfeeding [43]. HIV is transmitted to infants by transplacental spread from mother to fetus in utero, during parturition, or through breastfeeding after birth. Because infants have underdeveloped natural resistance systems, they are highly susceptible to many infections, including HIV. Transmission usually occurs during labor and delivery and the early breastfeeding stage [44].

Worldwide, perinatal transmission accounts for most HIV infections among children. In the United States in 2019, an estimated 84 infants were born with HIV infection, a 41% decrease from 2015 [45]. Studies have shown the beneficial effect of treating pregnant women and newborns with zidovudine (ZDV) to prevent transmission to the child, resulting in dramatic declines in the incidence of perinatally acquired HIV [46]. Standard screening of all pregnant women is necessary to reduce transmission of HIV to infants.

Organ Transplantation

Because these procedures are less common than other transmission-related activities, there have been very few case reports of HIV acquisition by this route. HIV has been transmitted via transplanted kidneys, liver, heart, pancreas, bone, and, possibly, skin grafts and through artificial insemination. HIV testing is used in these circumstances to rule out infection. Most cases of transmission through transplants of organs, bone, or tissue occurred before HIV screening was available. However, in 2007, four organ transplant recipients contracted HIV and hepatitis C from a single organ donor, and in 2009, HIV was transmitted by a living kidney donor [47; 48]. These were the first cases of HIV infection resulting from transplantation since 1985. Though the donors were tested for HIV and hepatitis, the tests resulted in false negatives. As with blood transfusions, donors testing antibody seronegative may pass HIV infection on to recipients. The use of nucleic acid testing and reconsideration of the use of high-risk donors have both been recommended to ensure the safety of donor recipients [47].

The National Organ Transplant Act (NOTA) of 1984 established the Organ Procurement and Transplantation Network (OPTN) but banned the Network from using organs from donors “infected with the etiologic agent for AIDS” [49]. In 2013, in recognition of the growing need for organ transplantation in individuals with HIV, the HIV Organ Policy Equity (HOPE) Act was passed [50]. HOPE reversed the federal ban of 1984 by allowing for research into transplanting organs from HIV-positive donors (living and deceased) to HIV-positive recipients [51]. The HOPE Act initially only authorized kidney and liver transplants, but as a result of a 2020 update to protocols, organs of any type may now be transplanted [51]. A clinical trial is underway at Johns Hopkins University Medical Center to evaluate HIV-positive-to-HIV-positive kidney and liver transplantation [52]. In 2018, proposed amendments to the NOTA were introduced to expand the scope of the OPTN by addressing specific populations (e.g., minorities, children, other individuals) who live in rural areas [53].

Occupational Exposures

Transmission due to occupational exposure of healthcare workers has occurred in needlestick accidents and blood splashes to the mucous membranes. Needlestick is the most common route. Thousands of healthcare personnel who were so exposed have been studied, and only 58 cases of well-documented infection have been reported in the United States (24 of which were nurses), with only one case since 1999 [54]. The risk of infection through this route is low, and every effort should be made to decrease the exposure rate. Educational efforts, implementation of engineering controls in needled and sharp-edged medical devices, the use of hard plastic needle disposal units where these devices are most frequently used, and the development of procedural details to avoid blood and body fluid contact have greatly reduced the exposure rate. Healthcare personnel should apply Universal Precautions, as discussed in the Occupational Safety and Health Administration (OSHA) Bloodborne Pathogens standard regulations, to all activities to avoid contact with human fluids.

Postexposure Prophylaxis

The U.S. Public Health Service (PHS) has developed recommendations for situations where healthcare personnel have had exposure to a source person with HIV or where information suggests that there is a likelihood that the source person is HIV-infected. These recommendations are based on the risk for HIV infection after different types of exposure and limited data regarding efficacy and toxicity of PEP [55]. Because most occupational HIV exposures do not result in the transmission of HIV, potential toxicity should be carefully considered when prescribing PEP. When possible, these recommendations should be implemented in consultation with persons having expertise in antiretroviral therapy and HIV transmission.

It is recommended that PEP be started as soon as possible after the potential exposure and continue for four weeks [55]. The PHS no longer recommends that the severity of exposure be used to determine the number of drugs offered in an HIV PEP regimen [56]. A regimen containing three (or more) antiretroviral drugs is recommended routinely for all occupational exposures to HIV. The regimen should be administered as soon as possible but within 72 hours of exposure and should be continued for 28 days [57]. The suggested regimen is tenofovir/emtricitabine, plus dolutegravir or bictegravir. PEP should be initiated even if awaiting results of HIV testing on the individual [56; 57]. In the setting of pregnancy or breastfeeding, expert consultation is advised [57].

Nonoccupational Postexposure Prophylaxis (nPEP)

In 2016, the CDC published updated guidelines for the recommendation of PEP for nonoccupational exposures. This section is taken from Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016 [58].

Healthcare providers should evaluate persons rapidly for nPEP when care is sought within 72 hours after a potential nonoccupational exposure that presents a substantial risk for HIV acquisition. All persons considered for nPEP should have determination of their HIV infection status by HIV testing, preferably by using rapid combined Ag/Ab, or antibody blood tests. If rapid HIV blood test results are unavailable, and nPEP is otherwise indicated, it should be initiated without delay and can be discontinued if the patient is later determined to have HIV infection already or the source is determined not to have HIV infection. nPEP is recommended when the source of the body fluids is known to be HIV-positive and the reported exposure presents a substantial risk for transmission. nPEP is not recommended when the reported exposure presents no substantial risk of HIV transmission or when care is sought more than 72 hours after potential exposure. A case-by-case determination about the nPEP is recommended

when the HIV infection status of the source of the body fluids is unknown and the reported exposure presents a substantial risk for transmission if the source did have HIV infection.

All persons evaluated for possible nPEP should be provided any indicated prevention, treatment, or supportive care for other exposure-associated health risks and conditions (e.g., bacterial sexually transmitted infections, traumatic injuries, hepatitis B virus and hepatitis C virus infection, or pregnancy). All persons who report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., injection drug use, sex without condoms) or who report receipt of a course of nPEP in the past year should be provided risk-reduction counseling and intervention services, including consideration of pre-exposure prophylaxis.

NATURAL HISTORY AND CLASSIFICATION OF HIV INFECTION

LATENCY PERIOD

Clinical latency, sometimes referred to as the window period, is the time elapsed between acquisition of the virus and the body's immune response sufficient to generate detectable antibody. This latent period is longer for HIV than for most other viral pathogens and is variable among newly infected individuals.

ACUTE HIV INFECTION

As discussed, HIV infection is a protracted illness that passes through several stages and, if untreated, carries an 80% mortality rate at 10 years. Within 15 to 30 days after acquisition of HIV infection, the majority of patients (50% to 90% in reported series) develop an acute retroviral syndrome similar to infectious mononucleosis [13]. Symptoms include fever, sore throat, malaise, rash, diarrhea, lymphadenopathy, mucocutaneous ulcerations and weight loss averaging 10 pounds. A variety of neurologic syndromes including encephalitis may occur. The illness is self-limited, with an average duration of two

to three weeks. Laboratory abnormalities include lymphopenia, atypical lymphocytosis, thrombocytopenia, and a decreased CD4 cell count. During this early phase of clinical illness, HIV antibody tests are often negative and the diagnosis rests on the demonstration of HIV P24 antigen or, preferably, quantitative plasma HIV RNA. Concentrations of HIV RNA in the blood (viral load) are high during the acute syndrome.

Following the host immune response, coincident with seroconversion and the rise in CD8 cytotoxic T cells, the viral load decreases steadily, reaching a relatively stable level at about six months. At this juncture, the degree of viral load correlates with the subsequent pace of disease progression. Patients having the highest viral loads, exhibit the most rapid progression to AIDS. As a result of the ongoing, protracted infection of target lymphocytes, the CD4 count gradually declines over time in the absence of treatment, at the average annual rate of about 50 cells/mcL.

ASYMPTOMATIC HIV INFECTION

Approximately 10% to 20% of persons with newly acquired HIV are asymptomatic during the initial two months following acute infection. While initial routine laboratory studies are relatively normal, serologic and virologic studies are positive and these patients show the same host-virus dynamics, including gradual decline in CD4 count, as that seen in symptomatic patients.

The serologic diagnosis of HIV infection in an asymptomatic patient does not, in and of itself, establish how recently the patient became infected. The stage of infection may be estimated on the basis of careful history and physical examination, and a standard laboratory evaluation that includes complete blood counts, lymphocyte subsets or CD4 count, and viral load. The duration of this asymptomatic stage is variable depending on prevailing CD4 count and viral load and is amenable to treatment with combination antiretroviral therapy (cART).

PERSISTENT GENERALIZED LYMPHADENOPATHY

In the months following acute infection, whether symptomatic or not, many patients have persistent, painless generalized lymphadenopathy (PGL) without other disease manifestations. PGL is defined as palpable lymph node enlargement of 1 cm or greater at two or more extrainguinal sites that persists for more than three months in the absence of a concurrent illness or explanation other than HIV infection. In some cases, lymphadenopathy regresses as HIV disease advances, probably because the architecture of the lymph node is gradually destroyed [4].

CHRONIC HIV AND DISEASE PROGRESSION

Chronic, asymptomatic HIV infection with ongoing low-level viral activity may last for many years before eventual progression to AIDS. Symptomatic illness can be expected to supervene as the CD4 count declines to a level less than 200 cells/mcL, as this correlates with severe immunodeficiency. The CDC defines late-stage HIV infection as AIDS on the basis of two criteria: CD4 count less than 200 cells/mcL or a characteristic AIDS-defining illness such as PJP, central nervous system (CNS) toxoplasmosis, or other opportunistic infections or tumors (Kaposi sarcoma). A variety of clinical syndromes may supervene at this juncture including dementia, peripheral neuropathy, wasting syndrome, and chronic diarrhea. In the United States, common AIDS-defining opportunistic diseases include: PJP, Kaposi sarcoma, candidiasis, cryptococcosis, cryptosporidiosis, CMV, atypical mycobacteriosis, systemic herpes, toxoplasmosis, and tuberculosis [59].

In the absence of effective therapy, the average survival is approximately 3.5 years after the patient's CD4 count has reached 200 cells/mcL and 1.5 years for the patient who has developed an AIDS-defining diagnosis. The natural history and the prognosis for the patient with chronic HIV infection have been dramatically altered by antiretroviral therapy, especially by the use of cART that followed the introduction of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in 1996.

MANAGEMENT OF HIV INFECTION

Primary care providers in consultation with specialists are playing an increasing role in the care of HIV-infected individuals. It is not possible for all care to be delivered by infectious disease and oncology specialists. Moreover, with early cART and prophylaxis for opportunistic infections, HIV disease shares features of other multisystem, chronic diseases characterized by acute exacerbations and end-stage manifestations. A study of serodifferent heterosexual and MSM couples in which the HIV-positive partner was on cART found no documented cases of within-couple transmission of HIV, despite engaging in condomless sex, after an average of 1.3 years [60].

Primary care providers should conduct risk factor assessment of their patients and, when appropriate, screen for HIV infection with pretest and post-test counseling. For persons who test positive, information on available medical and mental health services should be provided as well as guidance for contacting sexual or needle-sharing partners. Patients with HIV infection should be seen at regular intervals by a primary care provider to perform periodic physical examinations, monitor prognostic markers (e.g., CD4 count, viral load), initiate and monitor antiviral and prophylactic therapy, and provide supportive counseling. Specialists should be consulted for patients intolerant of standard drugs, those in need of systemic chemotherapy, and those with complicated opportunistic infections. In some cases, a single specialist consultation with follow-up to the primary care physician will provide the needed expertise while ensuring continuity of care.

Standard laboratory tests for patients with HIV infection may include:

- HIV serology
- Quantitative HIV RNA
- CD4 count
- Complete blood count (CBC)

- Chest x-ray
- Hepatitis serology and liver chemistry panel
- Syphilis serology
- Purified protein derivative (PPD) skin test to diagnose tuberculosis

COMBINATION ANTIRETROVIRAL THERAPY

More than 30 ARV drugs in several mechanistic classes are FDA-approved for treatment of HIV infection. These classes are: nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs), chemokine (C-C motif) receptor 5 (CCR5) antagonists, CD4 T lymphocyte (CD4) post-attachment inhibitors, gp120 attachment inhibitors, and capsid inhibitors. In addition, two drugs, ritonavir and cobicistat, are used as pharmacokinetic enhancers (or boosters) to improve the pharmacokinetic profiles of PIs [61].

Initiated in 1995 in the United States, cART regimens have been effective in dramatically decreasing HIV-related morbidity and mortality and should be considered for all HIV-infected persons who qualify for such therapy. In addition to combination therapy, the sequencing of drugs and the preservation of future treatment options are also important.

An initial regimen generally consists of two NRTIs administered in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, a NNRTI, or a PI with a pharmacokinetic enhancer booster. Data also support the use of the two-drug regimen dolutegravir plus lamivudine for initial treatment [61]. The goal of these regimens is to effectively reduce HIV-associated morbidity, prolong the duration and quality of survival, restore and preserve immunologic function, and prevent HIV transmission while also avoiding drug resistance [61]. A significant proportion of patients starting cART are infected with drug-resistant strains of HIV, which may lead to suboptimal virologic responses.

Therefore, pretreatment genotypic resistance testing should be used to guide selection of the most optimal initial regimen [61].

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs, used singularly or in combination, can increase CD4 count, decrease viral load, and prolong survival. Sequential monotherapy is followed eventually by clinical failure based on the emergence of drug resistance in HIV. Combinations of two NRTIs result in better viral suppression, more sustained CD4 counts, and decreased emergence of resistance. Available NRTI agents include: abacavir (Ziagen, ABC); zidovudine (Retrovir, ZDV, AZT); lamivudine (Epivir, 3TC); and emtricitabine (Emtriva, Coviracil, FTC) [62]. Tenofovir (Viread, TDF) is often categorized as an NRTI but is actually a nucleotide reverse transcriptase inhibitor.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs have a high affinity for the active site of HIV-RT. When used as a single agent, this class is associated with rapid emergence of resistance in as little as six weeks. Thus, these drugs should not be used as single agents but are best employed in combination regimens for patients who have not received prior antiretroviral therapy. Available agents include: doravirine (Pifeltro); efavirenz (Sustiva, EFV); nevirapine (Viramune, NVP); etravirine (Intelence); and rilpivirine (Edurant) [62].

Protease Inhibitors (PIs)

Development of mature infectious virus depends upon enzymatic cleavage of HIV transcribed polyprotein by HIV protease. In binding to the active site of the HIV protease, PIs interrupt the formation of mature infectious particles and reduce viral replication by as much as 99%. Resistance to PIs develops rapidly when these agents are used alone. However, in combination with nucleoside analogs the effect can last for years, often resulting in a reduction of

viral load to undetectable levels. Available agents include: ritonavir (Norvir, RTV); saquinavir (Invirase, Fortovase, SQV); atazanavir (Reyataz, ATZ); tipranavir (Aptivus, TPV); darunavir (Prezista; DRV); and fosamprenavir (Lexiva, FPV) [62].

Fusion Inhibitors (FIs)

In 2003, the FDA approved the drug enfuvirtide (Fuzeon), the first new class of anti-HIV drug in seven years [62]. Enfuvirtide, a fusion inhibitor, works by blocking the ability of HIV to infect healthy CD4 cells. When used in combination with other anti-HIV medications, enfuvirtide can reduce the amount of HIV in the blood and increase the number of CD4 cells, slowing the progression of HIV in patients who have developed resistance to currently available medications.

CCR5 Antagonists

In 2007, maraviroc was approved by the FDA for patients with CCR5-tropic HIV-1 infection [63]. Maraviroc is a CCR5 antagonist; it blocks replication of the virus by preventing it from entering noninfected CD4 cells via the predominant route of entry, the CCR5 co-receptor [63]. This medication is intended for use in combination with other antiretroviral agents in treatment-experienced patients with evidence of viral replication and HIV-1 strains resistant to multiple agents [63]. Because both fusion inhibitors and CCR5 antagonists block HIV from entering CD4 cells, they are sometimes grouped together under the category of entry inhibitors. In 2016, the FDA expanded use of maraviroc to include pediatric patients with CCR5-tropic HIV-1 infection who are 2 years of age or older and who weigh at least 10 kilograms [64].

Integrase Strand Transfer Inhibitors (INSTIs)

In 2007, the FDA approved raltegravir, the first agent in a class known as integrase strand transfer inhibitors, or INSTIs [65]. Two additional integrase inhibitors, dolutegravir and elvitegravir, were approved by the FDA in 2013 and 2014, respectively [62; 66].

These agents act by preventing the viral DNA from inserting into the host DNA, effectively limiting infection of additional cells and decreasing viral load [65]. INSTIs are approved for use in combination with other antiretrovirals in treatment-experienced and treatment-naïve patients with evidence of HIV replication. In 2017, the FDA expanded use of raltegravir for treatment of HIV-1 in newborns from birth to four weeks of age [67].

gp120 Attachment Inhibitors

In 2020, the FDA approved the first gp120 attachment inhibitor, fostemsavir, for the treatment of HIV in patients whose infection cannot be successfully treated with other therapies because of resistance, intolerance, or safety considerations [68].

Capsid Inhibitors

In 2022, the FDA approved Sunlenca (lenacapavir) for adult patients living with HIV-1 whose infections cannot be successfully treated with other available treatments due to resistance, intolerance, or safety considerations [68]. Lenacapavir is the first of a new class of drugs called capsid inhibitors to be FDA-approved for treating HIV-1. Lenacapavir works by blocking the protein shell (the capsid) of the HIV virus, thereby interfering with essential steps in the viral lifecycle. The two recommended dosage regimens include oral tablets and subcutaneous injections [68].

Pharmacokinetic Enhancers

In an effort to improve the efficacy of other antiretroviral medications in a cART regimen, a pharmacokinetic enhancer may also be included. The agents most commonly used for this purpose are ritonavir (a PI) and cobicistat. Both of these agents inhibit cytochrome P450 (CYP) 3A enzymes, prolonging the effects of other medications [69]. However, they are not interchangeable; cobicistat is a more potent inhibitor of CYP [69]. The use of pharmacokinetic enhancers increases systemic exposure of effective antiretroviral medications, allowing for less frequent dosing and a lower pill burden.

Multi-Class Combination Products

Patient compliance may be improved with therapies that combine more than one drug into a single pill, making it easier for patients to comply with their medication regimen. As of 2023, there were 23 combination medications available [62]:

- Atripla: Efavirenz, emtricitabine, and tenofovir
- Biktarvy: Bictegravir, emtricitabine, and tenofovir
- Cabenuva: cabotegravir and rilpivirine
- Cimduo: Lamivudine and tenofovir
- Combivir: Lamivudine and zidovudine
- Complera: Emtricitabine, rilpivirine, and tenofovir
- Delstrigo: Doravirine, lamivudine, and tenofovir
- Descovy: Emtricitabine and tenofovir
- Dovato: Dolutegravir and lamivudine
- Epzicom: Abacavir and lamivudine
- Evotaz: Atazanavir and cobicistat
- Genvoya: Elvitegravir, cobicistat, emtricitabine, and tenofovir
- Juluca: Dolutegravir and rilpivirine
- Kaletra: Lopinavir and ritonavir
- Odefsey: Emtricitabine, rilpivirine, and tenofovir
- Prezcobix: Darunavir and cobicistat
- Stribild: Elvitegravir, cobicistat, emtricitabine, and tenofovir
- Symfi/Symfi Lo: Efavirenz, lamivudine, and tenofovir
- Symtuza: darunavir, cobicistat, emtricitabine, and tenofovir
- Triumeq: Abacavir, dolutegravir, and lamivudine
- Trizivir: Abacavir, lamivudine, and zidovudine
- Truvada: Emtricitabine and tenofovir

In 2021, the FDA approved the first monthly injectable cART—Cabenuva (cabotegravir/rilpivirine) [70]. This monthly injectable is intended to improve compliance and quality of life in patients with controlled HIV. Prior to initiating injectable therapy, oral therapy with cabotegravir/rilpivirine is started to ensure the agents are well-tolerated.

In addition to those medications that have been FDA-approved for the treatment of HIV, there is a long list of investigational, or “pipeline,” drugs being tested in clinical trials. For more information on those agents and the trials, please visit the National Institutes of Health information website at <https://hivinfo.nih.gov/understanding-hiv/fact-sheets/what-investigational-hiv-drug>.

Initiation of Therapy

The decision to initiate antiretroviral therapy is one that requires careful discussion with the patient, usually in consultation with an infectious disease specialist or other physician well versed in the use of cART. Physicians and patients alike should be aware of the advantages, potential toxicities, and complexity of monitoring therapy. At the present time, the most active triple-drug regimen in a previously untreated patient can be expected to reduce the viral load below detectable levels, increase CD4 counts by an average of 100–150 cells/mcL, reduce the risk of HIV-associated complications, and prolong survival. However, the ability to achieve this advantage depends on the patient’s willingness to accept a complex medical regimen that requires “many pills,” rigorous compliance, frequent follow-up, and moderate risk for drug toxicity. In reaching a decision it is helpful to bear in mind that prognosis is determined by viral load and the CD4 count. Patients having a viral load in excess of 60,000 copies per milliliter have a relatively rapid course and average survival of a little more than four years. In contrast, those with less than 6,000 copies per milliliter have an average survival of more than 10 years. The CD4 count is also a prognostic factor, as counts less than 350 cells/mcL indicate severe damage to immune function and corresponding risk for opportunistic infection.

Antiretroviral therapy should be initiated immediately for all patients infected with HIV in order to reduce the risk of disease progression and limit transmission [61]. There is growing evidence that early initiation of cART is effective in preventing clinical events (e.g., non-AIDS malignancies, infection, AIDS-defining illness) regardless of pre-treatment CD4 count [71; 72]. Advances in the development of antiretroviral medications and combination tablets makes adherence to therapy more effective, more convenient, and better tolerated than regimens used in the past. Deferral of therapy may be considered in patients with high CD4 counts (e.g., more than 500 cells/mcL) if adherence will be very difficult or impossible, comorbidities complicate or prohibit antiviral therapy, or a patient is considered a long-term non-progressor [61].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

According to the Panel on Antiretroviral Guidelines for Adults and Adolescents, antiretroviral therapy should be initiated in all patients with HIV infection regardless of CD4 count.

(<https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf>. Last accessed March 7, 2023.)

Strength of Recommendation: AI (Strong recommendation based on one or more randomized trials with clinical outcomes and/or validated laboratory endpoints)

For treatment-naïve patients, initial recommended therapy generally consists of two NRTIs in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, an NNRTI, or a PI with a pharmacokinetic enhancer (cobicistat or ritonavir) [61]. These regimens result in maximum reduction of viral load for the longest period of time. When used as initial therapy, these regimens will achieve the goal of no detectable virus in the majority of patients after four to six months [61].

PREVENTION OF OPPORTUNISTIC INFECTIONS

Depending on the CD4 count and other risk factors, asymptomatic patients may benefit from treatment to prevent opportunistic infections. In many cases, cART is useful in the prevention and treatment of these infections. Recommendations for antimicrobial prophylaxis of opportunistic infections are summarized in **Table 1** according to guidelines provided by the CDC, the National Institutes of Health, HIV Medicine Association, and the Infectious Diseases Society of America (IDSA) [73]. Prophylactic therapy for these conditions is strongly recommended because these infections are relatively common in HIV patients, preventive therapy is simple and cost effective, and efficacy has been established in clinical studies. In addition, all patients should be vaccinated with pneumococcal vaccine. Hepatitis B vaccination should be considered in patients whose serologic testing indicates susceptibility.

The CDC, the National Institutes of Health, and the IDSA have developed guidelines for the prevention of opportunistic infections among HIV-infected individuals [73]. The report offers guidelines specific to each type of opportunistic infection and can be viewed at <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf>.

TUBERCULOSIS AND HIV

People dually infected with HIV and tuberculosis have a 20 to 30 times greater risk of developing active tuberculosis and becoming infectious compared to people not infected with HIV [74]. However, cART significantly decreases the risk of conversion from latent to active disease, though patients with HIV remain at higher risk of TB disease than the general population [73]. Among individuals in the United States with tuberculosis, an estimated 8.6% are coinfecting with HIV [74].

In addition to the recommended prophylaxis to prevent a first episode of opportunistic tuberculosis, guidelines for the treatment of HIV-related tuberculosis have been developed. These guidelines call for directly observed therapy for all patients with HIV-related tuberculosis; prolonged treatment (up to nine months) for patients with a delayed clinical or bacteriologic response to therapy or perhaps with cavitory disease on chest radiograph; and rifabutin-based regimens given at least three times a week for patients with tuberculosis and advanced HIV disease [75]. Special considerations apply to children and pregnant women with HIV-related tuberculosis.

Healthcare professionals should be familiar with the guidelines to ensure the use of the most effective management strategies for patients with tuberculosis and HIV, while concurrently promoting optimal cART for these patients.

PROVIDING CARE FOR THOSE INFECTED

The HIV/AIDS Bureau of the U.S. Department of Health and Human Services has established guidelines for the clinical care of patients living with HIV/AIDS. These guidelines stress the importance of establishing mechanisms for coordination and communication to ensure good care for people with HIV/AIDS [76]. A multidisciplinary approach, utilizing the special skills of nurses, pharmacists, nutritionists, social workers, and case managers, is highly desirable to best address patients' needs regarding housing, medical insurance, emotional support, financial benefits, substance abuse counseling, and legal issues.

There are several special issues that often arise in the HIV/AIDS patient population. Because HIV occurs with greater frequency in gay and ethnic minority (particularly Black) communities, cultural competency and sensitivity are core elements of care. The guidelines recommend that providers demonstrate respect and provide excellent care to patients with various cultural backgrounds, beliefs, and sexual orientations [76]. Other socioeconomic issues, including poverty, professional and personal stigma, lack of insurance, and illegal immigration status, occur more frequently among these groups and can impact the ability to provide care.

PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE AMONG ADULTS AND ADOLESCENTS INFECTED WITH HIV			
Pathogen	Indication	Preventive Regimen	
		Preferred ^a	Alternative
<i>Pneumocystis jirovecii</i> pneumonia (PJP)	CD4 count <200 cells/mL (AI); or CD4 <14% (BII); or CD4 count ≥200 but <250 cells/mL and if monitoring CD4 cell count every three months is not possible (BII)	Trimethoprim-sulfamethoxazole (TMP-SMZ) 1 double-strength (DS) daily (AI), or TMP-SMX 1 single-strength (SS) daily (AI)	TMP-SMX 1 DS three times weekly (TIW) (BI); or dapsone 100 mg daily or 50 mg twice daily (BI); or dapsone 50 mg daily + pyrimethamine 50 mg + leucovorin 25 mg weekly (BI); or dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg weekly (BI); or aerosolized pentamidine 300 mg via Respigard II nebulizer every month (BI); or atovaquone 1,500 mg daily (BI); or atovaquone 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg daily (CIII)
<i>Toxoplasma gondii</i> encephalitis	<i>Toxoplasma</i> immunoglobulin G (IgG)-positive patients with CD4 count <100 cells/mL (AII). Seronegative patients receiving PJP prophylaxis not active against toxoplasmosis should have <i>Toxoplasma</i> serology retested if CD4 count decline to <100 cells/mL (CIII). Prophylaxis should be initiated if seroconversion occurred (AII).	TMP-SMX 1 DS daily (AII)	TMP-SMX 1 DS TIW (BIII); or TMP-SMX 1 SS daily (BIII); or dapsone 50 mg daily + pyrimethamine 50 mg + leucovorin 25 mg weekly (BI); or dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg weekly (BI); or atovaquone 1,500 mg daily (CIII); or atovaquone 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg daily (CIII)
Latent <i>Mycobacterium tuberculosis</i> infection (LTBI)	A positive screening test for LTBI, with no evidence of active TB and no prior treatment for active TB or LTBI (AI); or close contact with a person with infectious TB, regardless of screening test results (AII)	Isoniazid (INH) 300 mg + pyridoxine 25–50 mg daily for nine months (AII); or LTBI treatment and ART act independently to decrease the risk of TB disease. Thus, ART is recommended for all persons with HIV and LTBI (AI).	Rifapentine 750 mg weekly for person weighing 32.1–49.9 kg; 900 mg weekly for person weighing >50 kg + INH 900 mg + pyridoxine 50 mg once weekly for 12 weeks (AII); or rifampin 600 mg daily for four months (BI). For drug-resistant TB, consult an expert or public health authorities (AII).
Disseminated <i>Mycobacterium avium</i> complex (MAC) disease	CD4 count <50 cells/mL. Not recommended for those who immediately initiate ART (AII). Recommended for those who are not on fully suppressive ART, after ruling out active disseminated MAC disease based on clinical assessment (AI)	Azithromycin 1,200 mg once weekly (AI); or clarithromycin 500 mg twice daily (AI); or azithromycin 600 mg twice weekly (BIII)	Rifabutin 300 mg daily (dose adjusted based on concomitant ART) (BI); rule out active TB before starting

Table 1 continues on next page.

PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE AMONG ADULTS AND ADOLESCENTS INFECTED WITH HIV (Continued)			
Pathogen	Indication	Preventive Regimen	
		Preferred ^a	Alternative
<i>Streptococcus pneumoniae</i> infection	Individuals who have not received any pneumococcal vaccine, regardless of CD4 count	15-valent pneumococcal conjugate vaccine (PCV15); or 20-valent pneumococcal conjugate vaccine (PCV20) (AII). If PCV20 is used, vaccination is complete. If PCV15 is used, follow in eight weeks with PPV23 (AII). No additional vaccine doses recommended. If CD4 count \geq 200 cells/mcL, receive dose of PPV23 at least 8 weeks later (AI).	23-valent pneumococcal polysaccharide vaccine (PPV23) 0.5 mL IM (BII). For individuals who have previously received PPV23, one dose of PCV (either PCV20 or PCV15) should be given at least one year after the last receipt of PPV23 (BII).
	Re-vaccination is recommended for patients 19 to 64 years of age and \geq 5 years since the first PPV23 dose; or \geq 65 years of age and \geq 5 years since the previous PPV23 dose.	PPV23 0.5 mL IM or SQ (BIII)	—
Influenza A and B virus infection	All HIV-infected patients (AIII)	Inactivated influenza vaccine annually (AIII) Adults \geq 65 years to receive high-dose IIV (Fluzone) or adjuvanted IIV (Fluad) over standard-dose unadjuvanted vaccine (AII).	\geq 18 years also may use RIV (Flublok Quadrivalent). Pregnant women may receive inactivated influenza or recombinant vaccine at any time during pregnancy (AI). Note: Live-attenuated influenza vaccine is contraindicated in HIV-infected patients (AIII).
Syphilis	Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis, even if serologic test results are negative (AIII), or who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis $>$ 90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain (AIII).	Benzathine penicillin G 2.4 million units IM for 1 dose (AII)	Persons with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (AIII). For other penicillin-allergic patients: doxycycline 100 mg twice daily for 14 days (BII); or ceftriaxone 1 g IM or IV daily for 8–10–14 days (BII); or azithromycin 2 g for 1 dose (BII) (not recommended for MSM or pregnant women [AII])
<i>Histoplasma capsulatum</i> infection	CD4 count $<$ 150 cells/mcL and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis ($>$ 10 cases/100 patient-years) (BI)	Itraconazole 200 mg daily (BI)	—

Table 1 continues on next page.

PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE AMONG ADULTS AND ADOLESCENTS INFECTED WITH HIV (Continued)			
Pathogen	Indication	Preventive Regimen	
		Preferred ^a	Alternative
Coccidioidomycosis	A new positive IgM or IgG serologic test in patients who live in a disease-endemic area and with CD4 count <250 cells/mcL (AIII)	Fluconazole 400 mg daily (AIII)	—
Varicella-zoster virus (VZV) infection (pre-exposure)	Patients with CD4 counts ≥200 cells/mcL who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV (BIII)	Primary varicella vaccination (Varivax), 2 doses (0.5 mL SQ each) administered three months apart (BIII).	VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts (AIII). Long-term prophylaxis with anti-VZV drugs (e.g., acyclovir, valacyclovir) to prevent varicella is not recommended (AIII).
Varicella-zoster virus (VZV) infection (post-exposure)	Close contact with a person with chickenpox or herpes zoster and is susceptible (i.e., no history of vaccination or of either condition or known to be VZV seronegative) (AIII)	Varicella-zoster immune globulin (VariZIG) 125 IU IM per 10 kg (maximum: 625 IU), administered as soon as possible and within 10 days after exposure (AIII)	Acyclovir 800 mg five times per day for 5–7 days (BIII); or valacyclovir 1 g three times per day for 5–7 days (BIII)
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease, or who are injection-drug users, or MSM (AII).	Hepatitis A vaccine 1 mL IM x 2 doses at 0 and 6–12 months (AII). IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated when CD4 count >200 cells/mcL (BIII).	For patients susceptible to both HAV and hepatitis B: combined HAV and HBV vaccine (Twinrix), 1 mL IM as a 3-dose (0, 1, and 6 months) or 4-dose (days 0, 7, 21 to 30, and 12 months) series (AII)
Hepatitis B virus (HBV) infection	Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs <10 IU/mL) (AII); or patients with isolated anti-HBc and negative HBV DNA (BII). Early vaccination is recommended before CD4 count falls below 350 cells/mcL (AII). However, in patients with low CD4 cell counts, vaccination should not be deferred until CD4 count reaches >350 cells/mcL, because some patients with CD4 counts <200 cells/mcL do respond to vaccination (AII).	HBV vaccine IM (Engerix-B 20 mcg/mL or Recombivax HB 10 mcg/mL) at 0, 1, and 6 months (AII); or HBV vaccine IM (Engerix-B 40 mcg/mL or Recombivax HB 20 mcg/mL), 0, 1, 2 and 6 months (BI); or Heplisav 20 mcg in 0.5 mL IM at 0 and 1 month (CIII); or combined HAV and HBV vaccine (Twinrix) 1 mL IM as a 3-dose (0, 1, and 6 months) (AII); or 4-dose (days 0, 7, 21 to 30, and 12 months) series (BII)	Some experts recommend vaccinating with 40-mcg doses of either HBV vaccine.
	Vaccine non-responders: anti-HBs <10 IU/mL 1 month after vaccination series	Re-vaccinate with a second vaccine series (BIII)	HBV vaccine IM (Engerix-B 40 mcg/mL or Recombivax HB 20 mcg/mL), 0, 1, 2 and 6 months (BI)
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients.	—

Table 1 continues on next page.

PROPHYLAXIS TO PREVENT FIRST EPISODE OF OPPORTUNISTIC DISEASE AMONG ADULTS AND ADOLESCENTS INFECTED WITH HIV (<i>Continued</i>)			
Pathogen	Indication	Preventive Regimen	
		Preferred ^a	Alternative
Talaromycosis (Penicilliosis)	Patients with CD4 cell counts <100 cells/mcL who live or stay for a long period in rural areas in northern Thailand, Vietnam, or Southern China (BI); or who are from countries outside these areas who must travel to the region (BIII)	For persons residing in endemic areas: Itraconazole 200 mg once daily (BI) For persons traveling to highly endemic regions: Itraconazole 200 mg once daily 3 days prior to travel and continue for 1 week after leaving endemic area (BIII)	For persons residing in endemic areas: Fluconazole 400 mg once weekly (BII) For persons traveling to highly endemic regions: Take first dose of fluconazole 400 mg 3 days prior to travel and continue 400 mg once weekly; take final dose after leaving endemic area (BIII).
^a All medications are taken orally unless otherwise indicated.			
Source: [73]			Table 1

RECOMMENDATIONS RATING SCHEME	
Category	Definition
Strength of Recommendation	
A	Strong
B	Moderate
C	Optional
Level of Evidence	
I	One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II	One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III	Expert opinion

Patient education is a vital aspect of care that begins during the initial evaluation and continues throughout the course of care [76]. Using basic language and verifying patients' understanding of medical terms and concepts can strengthen information provided and ensure that issues are fully addressed. Patient education in the primary care setting should include [76]:

- A definition of HIV
- Natural history of HIV disease and consequences of immune system destruction
- HIV transmission
- Interpretation of laboratory results
- Indications and goals of treatment, including potential benefits and risks
- Transmission prevention techniques
- Early signs and symptoms and prophylaxis of opportunistic diseases
- Treatment options and compliance
- Insurance information and access to medication
- Support services and support groups

For comprehensive human services to assist those with HIV infection, please contact the Washington State Department of Health HIV Care Early Intervention Program (EIP) or the Medical Case Management Program at 877-376-9316 or visit their website at <https://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/HIV/ClientServices>.

HIV INFECTION IN SPECIAL POPULATIONS

WOMEN LIVING WITH HIV INFECTION

As stated, worldwide in 2021, 38.4 million people were living with HIV. More than one-half of these were adult and adolescent women [77]. Women account for approximately 23% of all cases in the United States [10; 78]. In 1993, when the CDC expanded the case definition of AIDS, there was a 151% increase in the number of AIDS cases in women and a 105% increase in cases in men. More women were found to meet the AIDS case definition when the CD4+ T-lymphocyte count of <200 cells/mcL was added to the criteria. This may be evidence that the previous case definitions based on the clinical characteristics of men did not accurately reflect the clinical manifestations of HIV in women [79]. Although HIV diagnoses among women in the United States have declined in recent years, women comprised 18% (6,400) of the 34,800 new diagnoses in 2019 [10; 80].

As of 2023, AIDS was no longer among the top 10 causes of death for African American women in the United States [81]. Nevertheless, women of color have been disproportionately affected by HIV/AIDS. In 2019, African American women accounted for 54% of new HIV diagnoses among women in the United States [80]. Although HIV diagnoses among African American women decreased 31% between 2019 and 2018, the incidence rates remain much higher for Black and Hispanic women than for White women [78]. In 2020, the highest number of HIV cases reported were in women 25 to 34 years of age, followed by women 35 to 44 years of age, women 45 to 54 years of age, and women 55 years of age and older. The lowest number of cases were reported in females 13 to 24 years of age [82].

The risk for acquisition of HIV and the factors that may affect seroconversion in heterosexual women are areas of research. It is clear that, in the absence of protective measures, women are twice as likely to become infected with HIV through heterosexual

sex (i.e., vaginal or anal receptive sex) than men [83]. Although latex condoms are effective at preventing transmission of HIV when used correctly and consistently, some women may be afraid of the repercussions of insisting on condom use with their partners [80].

Clinical Manifestations

Many symptoms and signs of acute HIV infection and non-specific manifestations, such as fevers, weight loss, and fatigue, are the same for women and men. Because past research has either excluded women altogether or included only small cohorts of women, it has been difficult to determine gender differences in the clinical course of HIV disease. More recent research indicates that women with HIV initially present with lower viral loads but may be more likely than men to progress to AIDS, regardless of the viral load [84]. cART appears to be more effective in preventing opportunistic infections and disease progression among women with HIV than among men, but it is also more likely to result in toxicities among women and men [85; 86].

Gender-specific manifestations of HIV disease include irregular menstruation, recurrent vulvovaginal candidiasis, human papillomavirus (HPV)-related cervical dysplasia (abnormal, precancerous cell growth), and cervical cancer [87]. HIV-infected women have a higher prevalence of HPV infection, a higher risk of progression from infection to disease, and an increased risk of invasive cervical cancer and other HPV-related cancers than non-infected women [87]. Research indicates that cART does not significantly decrease the incidence of HPV-related cancers. As such, the American College of Obstetricians and Gynecologists recommends that women younger than 30 years of age with HIV should have cervical cytology screening once every three years rather than annually if they have had three consecutive normal annual results. Women with HIV who are 30 years of age and older can undergo either testing with cytology alone or co-testing with cytology and HPV testing. Women with three consecutive normal annual cytology tests can then be screened annually as can those with one normal co-test [88].

Hormonal contraception also has an effect on the manifestations of HIV, the risk of acquisition/transmission, and treatment efficacy. An older study found that combined oral contraceptive use was associated with lower absolute CD4 cell count [89]. Research focusing on HIV in women using hormonal contraceptive has indicated a slightly increased risk of acquisition and transmission, particularly with injectable methods of birth control [90; 91]. There has been some evidence of an increased risk of HIV transmission to an uninfected male partner if the woman is using hormonal contraceptives, but the evidence is inconclusive [92]. Hormonal birth control may interact with cART to create additional drug toxicities and treatment failures, and cART may reduce the effectiveness of some hormonal contraceptives [92].

Prognosis

Biologically, women and persons with vaginas are more vulnerable than men to HIV infection from heterosexual intercourse because of their substantial mucosal exposure to seminal fluids. These patients' risk is increased by other factors, such as non-consensual sex, sex without condoms, and the unknown or high-risk behaviors of their partners. Once infected with HIV, women can face obstacles in seeking and getting treatment. Frequently, they have difficulty accessing health care. They often lack social support and face other challenges (e.g., caring for children, caring for other family members) that may impede their ability to adhere to treatment. If they do follow through with treatment, studies have shown that women differ from men in the way they metabolize drugs, which could result in unexpected responses to antiretroviral therapy and an increase in adverse reactions to the drugs [93].

Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman

HIV counseling and the offer of HIV testing to pregnant women have been universally recommended in the United States and are now mandatory in some states. Care of the HIV-infected pregnant woman should involve collaboration between the HIV

specialist caring for the woman when she is not pregnant, her obstetrician, and the woman herself. Treatment recommendations for HIV-infected pregnant women are based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus, or infant that outweigh the potential benefit to the woman [46].

Initiation of cART is recommended for pregnant women with HIV in all stages of pregnancy. Regardless of the stage of pregnancy or childbirth, if a woman is found to be HIV-positive, there are treatment options that should be explored [46].

Patients should be registered with the Antiretroviral Pregnancy Registry, which collects observational, nonexperimental data. The registry is sponsored by GlaxoSmithKline, in affiliation with the CDC and Kendle International, Inc. Women who have been treated with cART at any time during their pregnancies are eligible for registry enrollment. The telephone number for registration is (800) 258-4263, and the website is <http://www.apregistry.com>.

INFANTS AND CHILDREN WITH HIV

In the United States today, the predominant route of infection with HIV in children is perinatal (from an infected pregnant woman to her fetus or infant) [45]. However, most women with HIV who give birth do not transmit HIV to their infants. In 2019, only 84 children younger than 13 years of age were diagnosed with HIV; less than 1% were perinatally infected [45].

Clinical Symptoms in Children with HIV Infection

Children with HIV/AIDS may have more than one infection at the same time or in succession (multiple opportunistic infections). Conditions associated with HIV infection in children are [94]:

- Serious bacterial infections, multiple or recurrent (only among children younger than 6 years of age)
- Candidiasis (esophageal or pulmonary)

- Invasive cervical cancer (only among adolescents and children 6 years of age or older)
- Disseminated coccidioidomycosis
- Extrapulmonary cryptococcosis
- Cryptosporidiosis or isosporiasis with diarrhea persisting longer than one month
- CMV disease
- Encephalopathy
- Herpes simplex virus infection causing bronchitis, pneumonitis, or esophagitis or causing a mucocutaneous ulcer that persists for longer than one month
- Disseminated or extrapulmonary histoplasmosis
- Kaposi sarcoma
- Lymphoma
- Disseminated or extrapulmonary *Mycobacterium tuberculosis*
- Disseminated *Mycobacterium avium* or *kansasii*
- PJP
- Progressive multifocal leukoencephalopathy
- Recurrent *Salmonella* septicemia (nontyphoid)
- Toxoplasmosis of the brain
- Wasting syndrome

Antiretroviral Treatment in Children

As with adults, cART is believed to play a major role in slowing progression of HIV in children and adolescents. For treatment-naïve children, preferred regimens for initial cART include INSTI-based, NNRTI-based, or boosted PI-based regimens [95]. Choice of regimen should be individualized based on several factors, including the patient's individual characteristics (especially age), the results of drug-resistance testing, potential adverse effects, and

dosing frequency [95]. Drug recommendations often include both age and weight limitations. Although age can be used as a rough guide, body weight (when available) is the preferred determinant for selecting a specific drug. An exception to this is infants younger than 14 days. Many drugs that are recommended for use in very young infants do not have dosing recommendations for premature infants [95].

Children receiving cART should be monitored for side effects, adherence, efficacy and toxicity. The U.S. Department of Health and Human Services recommends evaluating all pediatric patients within one to two weeks to monitor compliance, side effects, and response to treatment. Subsequently, a visit should be scheduled every three to four months [95]. Strategies to improve adherence should focus on selecting an appropriate regimen, educating the family/caregiver, and consistent follow-up.

OLDER PEOPLE WITH HIV

Approximately 17% of newly diagnosed cases of HIV in 2018 occurred in individuals 50 years of age or older; 12.5% of all persons living with HIV/AIDS are 50 years of age and older [96]. Until recently, there had been little attention given to this group. HIV/AIDS has traditionally been thought to be a disease of the young; therefore, in the past, prevention and education campaigns had not been targeted toward older adults. However, evidence points to the increasing number of infected older people and a need for change in prevention and education campaigns. Some older persons may have less knowledge about HIV and risk reduction strategies. Due to divorce or being widowed and the availability of medications to treat erectile dysfunction, increasing numbers of older people are becoming sexually active with multiple partners [96]. For postmenopausal women, contraception is no longer a concern, and they are less likely to use a

condom. Furthermore, vaginal drying and thinning associated with aging can result in small tears or cuts during sexual activity, which also raises the risk for infection with HIV/AIDS [96]. Studies indicate that at-risk individuals in this age group are significantly less likely than younger at-risk adults to use condoms during sex [97]. In addition, healthcare professionals are less likely to discuss sexual activity or take a sexual history if the patient is older than 50 years of age [97]. The combination of these factors increases the risk for unprotected sex with new or multiple partners in this age group, thereby increasing their risk for AIDS. This increase should be considered when evaluating older patients.

Early possible signs of immunosuppression that are frequently overlooked or mistakenly attributed to aging include thrush and skin problems, especially seborrheic dermatitis and herpes zoster. When HIV is not recognized or treated, the most typical opportunistic infections are PJP and recurrent bacterial pneumonia, CMV, and *Mycobacterium tuberculosis* or *Mycobacterium avium* complex. PJP can present as bacterial pneumonia, bronchitis, or congestive heart failure. Early HIV symptoms in the elderly, such as fatigue and weight loss, may appear to be a normal part of aging, and AIDS-related dementia is often mistaken for Alzheimer disease.



Adverse drug events from antiretroviral therapy and concomitant drugs may occur more frequently in older HIV-infected patients than in younger HIV-infected patients. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health

of older HIV-infected patients should be monitored closely.

(<https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf>. Last accessed March 7, 2023.)

Strength of Recommendation: Expert Opinion/
Consensus Statement

AIDS PREVENTION

PRE-EXPOSURE PROPHYLAXIS (PrEP)

In 2012, the FDA approved the first medication for the prevention of sexually transmitted HIV infection, the combination drug Truvada (emtricitabine/tenofovir DF) [98]. In 2019, another combination drug—Descovy (emtricitabine/tenofovir alafenamide)—was approved to prevent HIV infection [99]. In 2021, the FDA approved the first injectable agent for the prevention of HIV infection; cabotegravir is given first as two initiation injections administered one month apart, and then every two months thereafter [100]. In conjunction with safer sex practices, these agents have been found to be partially effective as pre-exposure prophylaxis in high-risk patients. The Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx, studied the effect of once daily Truvada in 2,499 HIV-seronegative men or transgender women who have sex with men compared to placebo [101]. Researchers found that persons receiving Truvada experienced a 44% reduction in the incidence of HIV after a median of 1.2 years compared to placebo. Pre-exposure prophylaxis was most effective among participants at particularly high risk for HIV (i.e., self-reports of unprotected receptive anal intercourse). Research has indicated that Descovy and cabotegravir are similarly effective [99].

In 2021, the CDC and the U.S. Department of Health and Human Services released updated clinical practice guidelines for pre-exposure prophylaxis for the prevention of HIV infection [102]. In 2022, the International Antiviral Society published recommendations for the treatment and prevention of HIV infection in adults [57]. These guidelines outline indications for prophylaxis as one prevention option for HIV transmission. The most important first step in determining if an individual is a candidate for pre-exposure prophylaxis is a thorough history, including sexual and injection drug activities.

All candidates will be adults without an acute or established HIV diagnosis. Pre-exposure prophylaxis should be offered to all sexually active adults and adolescents at substantial risk of acquiring HIV [57; 102]. PrEP is indicated for high-risk MSM, meaning those who have had any male sex partners in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative man, and have one of the following [102]:

- Anal sex without condoms (receptive or insertive) in the past six months
- Any STI diagnosed or reported in the past six months
- An ongoing sexual relationship with an HIV-positive man

Prophylaxis is also recommended for high-risk heterosexual adults who have had sex with an opposite sex partner(s) in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative partner, and one of the following [102]:

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with one or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

IDUs are also considered candidates for pre-exposure prophylaxis if they meet certain criteria. The guideline states that persons who have injected drugs not prescribed by a clinician in past six months may be candidates for prophylaxis if they also are positive for one of the following factors [102]:

- Any sharing of injection or drug preparation equipment in the past six months
- Been in a methadone, buprenorphine, or buprenorphine/naloxone treatment program in the past six months

- Increased risk of sexual acquisition (based on the previously outlined criteria)

Injection cabotegravir given bimonthly and fixed-dose combination tenofovir and emtricitabine (Truvada or Descovy) taken daily are approved for pre-exposure prophylaxis, and they are considered the recommended first-line option [98; 99; 100; 102]. However, because tenofovir alone has been proven effective in trials with IDU and heterosexually active men and women, it is the alternative option for these populations [102]. No other antiretroviral regimens should be used for pre-exposure prophylaxis. The optimal PrEP regimen is the one most acceptable to an individual and congruent with their sexual behavior, ability to reliably take prescribed medications, anticipated sexual activity, and adverse effect profile. Delaying PrEP is not recommended for individuals at risk [43]. Recommendations on the frequency and type of laboratory testing for people receiving PrEP vary according to the chosen regimen and patient risk profile [57].

All patients prescribed pre-exposure prophylaxis must have a negative HIV test prior to initiating treatment and every three months thereafter. In addition, patients should be advised regarding possible side effects and the continued necessity for safe sex practices. Eligible patients should also be screened for hepatitis B and have a confirmed creatinine clearance of 60 mL per minute or greater [102].

AIDS VACCINE

Achieving an end to the AIDS epidemic will require the development of an effective vaccine. Both preventive and therapeutic vaccines are being studied for use in the fight against HIV. Preventive vaccines are developed to protect individuals from contracting HIV, while the goal of therapeutic vaccines is to boost immune response to and better control existing HIV infection [103]. Of course, the ultimate goal in vaccine research is a vaccine that will prevent infection; however, despite several trials, no vaccine effective in preventing HIV has been discovered.

There are three types of preventive vaccines being studied for the prevention of HIV: subunit vaccines, recombinant vector vaccines, and DNA vaccines [104]. Subunit vaccines, also known as component or protein vaccines, contain only genetically engineered parts of HIV rather than the whole virus. Theoretically, these parts, or subunits, may induce an anti-HIV immune response, but the effectiveness of preventing future infection is unknown.

DNA vaccines contain a portion of a virus's genetic material. The partial HIV DNA is injected into the body, where existing cells produce HIV proteins. As a result, the body produces an immune response against HIV.

Finally, recombinant vector vaccines utilize as attenuated non-HIV virus, or vector, to carry a portion of HIV's genetic material into the recipient's body. As with the DNA vaccines, the HIV genes create proteins, which in turn stimulate an immune response. Because most HIV recombinant vector vaccines deliver several HIV genes, they may create a stronger immune response. Canarypox virus, cowpox virus, Venezuelan equine encephalitis, and adenovirus-5 are all being studied as possible vectors for future HIV vaccines [104].

The possibility of combining two or more types of vaccines in a booster system to strengthen immune response is being studied. This prime-boost vaccination strategy may stimulate different parts of the immune system and enhance the effectiveness of the vaccines [104].

It is important to note that none of these vaccines contains the viral material necessary to develop HIV infection. Those vaccines that contain genetic material from the virus do not carry the full virus or the complete set of genes necessary for infection [104].

The International AIDS Vaccine Initiative (IAVI) is working to speed the development and distribution of preventive AIDS vaccines, focusing on four areas: mobilizing support through advocacy and education; accelerating scientific progress; encouraging industrial participation in AIDS vaccine development; and assuring global access [105].

TOPICAL MICROBICIDES

Because HIV is spread predominantly through sexual transmission, the development of chemical and physical barriers that can be used intravaginally or intrarectally to inactivate HIV and other STI pathogens is critically important for controlling HIV infection.

Researchers are developing and testing new creams or gels (topical microbicides) that could be applied before intercourse to protect individuals against HIV and other sexually transmitted organisms [106]. One of the most promising is 1% vaginal gel formulation of tenofovir, which showed a 54% decrease in the incidence of HIV infection in high adherers in one clinical trial [107]. However, there are concerns regarding compliance with recommendations to ensure protection.

New topical microbicide candidates would ideally be non-irritating and inexpensive. In addition, they should be available in both spermicidal and non-spermicidal formulations so women do not have to put themselves at risk for acquiring HIV and other STIs in order to conceive a child.

EDUCATION TO PREVENT HIV INFECTION

Many adolescents engage in behaviors that put them at risk for HIV infection. According to the CDC, 37.4% of high school students reported being sexually active [108]. Approximately 54.3% of currently sexually active high school students had not used a condom at last sexual intercourse; 1.2% had ever injected an illegal drug [108]. Only 71% of U.S. high school districts have adopted a policy specifying that human sexuality is taught, and the content of these discussions may not provide adequate information on the subject. Furthermore, the American Academy of Pediatrics determined that school-based education and intervention programs do not provide the necessary opportunities of confidential discussions or targeted counseling [109]. Healthcare professionals have a unique opportunity to intervene in this population to provide accurate and complete information on HIV transmission and risk reduction.

EVIDENCE-BASED INTERVENTIONS

The CDC HIV/AIDS Prevention Research Synthesis Project collects and analyzes systematic reviews and identifies evidence-based interventions that have been proven effective in eliminating or reducing sex- or drug-related risk behaviors, reducing the rate of new HIV/STD infections, or increasing HIV-protective behaviors [110]. As of 2023, 78 best-evidence interventions had been identified, many of which target specific populations. Intervention packages and more information on these interventions are available at <https://www.cdc.gov/hiv/dhap/prb/prs/index.html>.

HIV/AIDS REPORTING

The state of Washington has specific laws and statutes governing HIV testing, including sections devoted to informed reporting, consent, and confidentiality. According to the Washington Administrative Code, healthcare professionals must report diagnoses of HIV and/or AIDS to local health departments within three business days [111]. According to the Washington Department of Health, laboratories are required to report each test result (except in King County or when another local health department is designated by the Department of Health), including [111]:

- Tests confirming HIV infection (e.g., positive Western Blot assays, p24 antigen tests, and viral culture tests): Within 2 business days
- HIV viral load results, both detectable and undetectable: Monthly
- CD4+ (T4) lymphocyte results of any value (patients aged thirteen or older): Monthly

For each result, the lab must provide the test result, date of collection, requesting health care provider, and patient information including name, sex, date of birth, address, and telephone number. As of July 1, 2011, healthcare providers requesting a laboratory test for HIV/AIDS are required to provide the following information [111]:

- Patient name
- Patient address including zip code
- Patient date of birth
- Patient sex
- Name of the principal healthcare provider
- Telephone number of the principal healthcare provider
- Type of test requested
- Type of specimen
- Date of ordering specimen collection

Many HIV and AIDS case reports are initiated from a laboratory result. However, when testing takes place outside of Washington, it is the healthcare provider's responsibility to ensure that the diagnosis is reported to the public health office. According to Washington Administrative Code, in these cases healthcare providers can meet this requirement by arranging for the referral laboratory to notify the local health department, the department, or both; or forwarding the notification of the test result from the referral laboratory to the local health department, the department, or both [111].

WASHINGTON STATUTES

Knowledge of statutes related to HIV/AIDS testing, reporting, and counseling may be useful in ensuring that public health is served and patients' rights are protected. To view the Washington Administrative Code Chapters 246-100 and 246-101 pertaining to communicable and notifiable diseases, please visit the Washington Legislature's website at <https://apps.leg.wa.gov/WAC/default.aspx?cite=246-101>.

SUMMARY

Although prevention and new medical interventions may reduce the pace of the epidemic, HIV will be a significant disease for many years both in the United States and the world. Education provides the opportunity to ensure that healthcare professionals have the information necessary to provide the best possible care for persons with HIV. Those who specialize in HIV care should identify ways to renew themselves through education, individual support, staff support, and variation of workload so that they can continue to contribute their valuable expertise to patients with HIV. With no easy cure in sight, healthcare professionals have the opportunity to work with patients to help them achieve and maintain their optimal level of health during the continuum of HIV disease.

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