Chapter 148: Human Immunodeficiency Virus Infection

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UPDATE SUMMARY

Update Summary

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The following sections, tables, and figures were updated:

- Pathogenesis: added information regarding the capsid inhibitor lenacapavir
- Table 148-3: added lenacapavir

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 42, Human Immunodeficiency Virus Infection.

KEY CONCEPTS

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1. Infection with human immunodeficiency virus (HIV) occurs through three primary routes: sexual, parenteral, and perinatal. Sexual intercourse, primarily receptive anal and vaginal intercourse, is the most common method for transmission.

2. HIV infects cells expressing cluster of differentiation 4 (CD4) receptors, such as T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. Infection occurs via an interaction between glycoprotein 160 (gp160) on HIV with CD4 (primary interaction) and chemokine coreceptors (secondary interactions) present on the surfaces of these cells.

3. The hallmark of untreated HIV infection is profound CD4 T-lymphocyte depletion and severe immunosuppression (Acquired Immunodeficiency Syndrome [AIDS]) that puts persons with HIV at significant risk for infectious diseases caused by opportunistic pathogens. Opportunistic infections (OIs) in settings without access to antiretroviral drugs are the chief cause of morbidity and mortality associated with HIV infection.

4. The current goal of combination antiretroviral therapy (ART) is to achieve maximal and durable suppression of HIV replication, measured as the level of HIV-RNA in plasma (viral load) less than the lower limit of quantitation, usually 20 to 50 copies/mL (20×10^3–50×10^3/L). Another equally important outcome is an increase in CD4 lymphocytes because this closely correlates with the risk for developing OIs.

5. General principles for the management of OIs include preventing or reversing immunosuppression with ART, preventing exposure to pathogens, vaccination, prospective immunologic monitoring, primary chemoprophylaxis, treatment of acute episodes, secondary chemoprophylaxis, and discontinuation of prophylaxes following ART and subsequent immune recovery.

6. Clinical use of antiretroviral agents is complicated by drug-drug interactions. Some interactions are beneficial and used purposely; others may be harmful, leading to dangerously elevated or inadequate drug concentrations. For these reasons, clinicians involved in the pharmacotherapy of HIV infection must exercise constant vigilance and maintain a current knowledge of drug interactions.

7. Recommendations for the initial treatment of HIV advocate a minimum of two or three active antiretroviral agents from at least two drug classes. The typical regimen consists of two nucleoside/nucleotide analogs with an integrase strand transfer inhibitor (InSTI).

8. Inadequate suppression of viral replication allows HIV to select for antiretroviral-resistant HIV variants, a major factor limiting the ability of antiretroviral drugs to inhibit virus replication. Recommendations for treating drug-resistant HIV include choosing at least two drugs (preferably three) of different classes to which the patient's virus is susceptible. Susceptibility can be assessed using either genotypic or phenotypic resistance testing.

9. The reduction of viral load with ART lowers the risk of transmission to others. Additionally, pre- and post-exposure prophylaxis with antiretroviral agents in at-risk persons lowers HIV acquisition risk.

10. The longer life span conferred by ART has given rise to other medical issues. A wide spectrum of complications associated with older age have become common, some of which overlap with adverse effects from antiretroviral drugs. Medical management of these contemporary HIV complications is constantly evolving.

BEYOND THE BOOK

BEYOND THE BOOK

Review and complete the "HIV Infection: The Antiretroviral-Naïve Patient Level II" patient case in the *Pharmacotherapy Casebook: A Patient-Focused Approach*.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) was first recognized in a cohort of young, previously healthy men who have sex with men (MSM) with new-onset profound immunologic deficits, *Pneumocystis carinii* (now *Pneumocystis jirovecii*) pneumonia (PCP), and/or Kaposi's sarcoma. A retrovirus, human immunodeficiency virus type 1 (HIV-1), is the major cause of AIDS. A second retrovirus, HIV-2, is also recognized to cause AIDS, although it is less virulent, transmissible, and prevalent than HIV-1. These retroviruses are transmitted primarily by sexual contact and by contact with infected blood or blood products. Several risk behaviors for the acquisition of HIV infection have been identified in the United States, most notably the practice of anorectal intercourse and the sharing of blood-contaminated needles by injection-drug users. In many resource-limited countries, the majority of HIV transmission occurs via heterosexual intercourse and from childbearing people to their offspring. Initially, the medical management of HIV consisted of repeated treatments for opportunistic infections (OIs) and eventual palliative care. In the mid-1990s, a new era in the pharmacotherapy for HIV, known as *combination antiretroviral therapy* (ART), was born. ART consists of combinations of antiretroviral agents with different mechanisms of action that potently and durably suppress HIV replication, delay the onset of AIDS, reverse HIV-associated immunologic deficits, reduce HIV transmission, and significantly prolong survival. Modern antiretroviral drugs and ART regimens have improved tolerability and efficacy. Nevertheless, therapeutic challenges remain in the present ART era including the need for continuous adherence to medications and care, drug-drug interactions, drug-resistant HIV, acute and long-term drug toxicities, and other complications associated with a prolonged life span. Despite progress in the treatment access for this disease, large numbers of persons with HIV remain outside of care, nationally and globally. Significant efforts to develop an HIV vaccine have not been fruitful. However, prophylactic use of antiretroviral drugs effectively prevents HIV infection in persons at high risk of exposure and those exposed to the virus.

EPIDEMIOLOGY

The epidemiologic characteristics of HIV infection differ according to geographic region and depend upon the mode of transmission, governmental prevention efforts and resources, and cultural factors.[1,2]

1 Infection with HIV occurs through three primary modes: sexual, parenteral, and perinatal. Sexual intercourse, primarily anal and vaginal intercourse, is the most common method for transmission. The probability of HIV transmission depends on the type of sexual exposure. The highest risk is from receptive anorectal intercourse at about 1.4 transmissions per 100 sexual acts.[3] Transmission risk is lower for receptive vaginal intercourse, and insertive sex acts have lower risk than receptive acts. Condom use reduces risk of transmission by approximately 80%.[3] Other factors that affect the probability of infection include the stage of HIV disease and viral load in the index partner. For example, transmission is significantly higher when the index partner has early or late HIV compared with asymptomatic HIV, as these disease stages are associated with higher viral loads.[3] Individuals with genital ulcers or sexually transmitted infections are at greater risk for contracting HIV. HIV incidence and prevalence are lower in cultures that advocate male circumcision, which reduces risk of male acquisition of HIV approximately 50%.[3] Casual contact with persons with HIV is not a significant risk factor for HIV transmission.

Prevention of sexual transmission has focused primarily on education that encourages safer sex practices such as use of condoms and reduction of high-risk behavior (eg, intercourse or promiscuity with partners of unknown HIV status).[4] A powerful tool for HIV prevention is combination ART for the infected individual, as this dramatically lowers viral replication and infectiousness, significantly reducing the risk of transmission to others.[3,5] In fact, the HIV scientific community has endorsed the notion that "U = U," which means undetectable (plasma HIV-RNA) = untransmittable (no HIV transmissions).[6] Another effective prevention tool is chemoprophylaxis with antiretroviral drugs, as this significantly reduces HIV acquisition risk among uninfected individuals.[7-9] A combined approach has been advocated for optimal prevention.[10] Prevention strategies under investigation include HIV vaccines and topical vaginal/rectal microbicides, such as vaginal rings containing antiretroviral drugs.[11,12]

Parenteral transmission of HIV broadly encompasses infections due to infected blood exposure from needle sticks, IV injection with used needles, receipt of blood products, and organ transplants. Use of contaminated needles or other injection-related paraphernalia by drug abusers has been the main cause of parenteral transmissions. The risk of HIV transmission from sharing needles is approximately 0.67 per 100 episodes.[3,13] Prevention strategies include stopping drug use, obtaining needles from credible sources (eg, pharmacies), never reusing or sharing any paraphernalia, using sterile procedures in all injecting activities, and safely disposing of used paraphernalia.[10]

Before widespread screening, HIV was readily transmitted in blood products.[13] However, blood and tissue products in the healthcare system are now rigorously screened for HIV. The estimated risk for receiving contaminated blood or blood products in the United States is well below 1:2,300,000 and that for receiving a contaminated tissue transplant is 1:55,000.[14,15] Healthcare workers have a small but definite occupational risk of contracting HIV through accidental exposure. Most cases of occupationally acquired HIV have been the result of a percutaneous needle stick injury, which carries an estimated 0.3% risk of transmitting HIV.[3,16] Mucocutaneous exposures (eg, blood splash in eyes, mouth, or nose) carries a transmission risk of approximately 0.09%.[16] Significant risk factors for seroconversion with a needle stick include deep injury, injury with a device visibly contaminated with blood, and advanced HIV disease in the index patient (high viral load). The risk of transmission from a healthcare worker with HIV to a patient is extremely remote. Comprehensive medical guidelines, including antiretroviral drug prophylaxis, have been developed to minimize the hazard of HIV transmission for healthcare workers and persons exposed by rape or other means.[13,16]

Perinatal infection, or vertical transmission, is the most common cause of pediatric HIV infection. Most infections occur during or near to the time of birth, although a fraction can occur in utero.[2] The risk of mother-to-child transmission is approximately 25% in the absence of ART. Factors that increase the likelihood of vertical transmission include prolonged rupture of membranes, chorioamnionitis, genital infection during pregnancy, preterm delivery, vaginal delivery, birth weight less than 2.5 kg, illicit drug use and cigarette smoking during pregnancy, and high maternal viral load.[17] Breast-feeding in the absence of ART can also transmit HIV. The frequency of breast milk transmission is approximately 5% to 10% in the first 6 months and 15% to 20% through 18 to 24 months without interventions to reduce transmission.[18] High levels of virus in breast milk and in the mother are associated with higher risk of transmission. Formula feeding prevents breast milk transmission of HIV but may not improve mortality from other causes early in life in resource limited settings.[19] In the United States, mothers with HIV are recommended not to breastfeed.[19] A separate and comprehensive set of medical guidelines including antiretroviral drug prophylaxis have been developed to minimize the risk of mother-to-child HIV transmission.[19]

Persons with HIV infection are broadly categorized as those living with HIV and those with an AIDS diagnosis (stage 3). An AIDS diagnosis is made when the presence of HIV is laboratory-confirmed and the CD4 (T-helper cell) count drops below 200 cells/mm^3 (0.2×10^9/L) for those aged 6 years or older, or after an AIDS indicator condition is diagnosed.[20] Further distinctions regarding the stage of HIV and AIDS (stage 3) are given in the revised Centers for Disease Control and Prevention (CDC) surveillance case definition (Table 148-1).[20] In the United States, the CDC estimates HIV epidemiology using models that rely on surveillance data from state and local health departments.[10] Using these models about 1.2 million individuals are living with HIV (all stages) in the United States.[10] Approximately 13% of persons with HIV are unaware of their infection and only approximately 50% of those who are aware of their infection are consistently retained in care. Therefore, about half of persons with HIV are not receiving ART regularly, which significantly contributes to the ongoing transmission of HIV infection in the United States, totaling 36,800 new infections per annum.[21,22]

TABLE 148-1

Surveillance Case Definition for HIV Infection Stage Based on CD4+ T-lymphocyte Counts, United States, 2014

	Age on date of CD4+ T-lymphocyte test					
	<1 year		1-5 years		≥6 years	
Stage	**Cells/μL (×10⁶/L)**	**%**	**Cells/μL (×10⁶/L)**	**%**	**Cells/μL (×10⁶/L)**	**%**
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3 (AIDS)	<750	<26	<500	<22	<200	<14
AIDS-defining conditions						
Bacterial infections, multiple or recurrent (specific to children <6 years)						
Candidiasis of bronchi, trachea, or lungs			Lymphoma, Burkitt			
Candidiasis, esophageal			Lymphoma, immunoblastic			
Cervical cancer, invasive (specific to adults, adolescents, children >6 years)			Lymphoma, primary, or brain			
Coccidioidomycosis, disseminated or extrapulmonary			*Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary			
Cryptococcosis, extrapulmonary			*Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)			
Cryptosporidiosis, chronic intestinal (duration >1 month)			*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary			
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month			*Pneumocystis jirovecii* pneumonia (PCP)			
Cytomegalovirus retinitis (with loss of vision)			Pneumonia, recurrent (specific to adults, adolescents, children >6 years)			
Encephalopathy, HIV-related			Progressive multifocal leukoencephalopathy			
Herpes simplex: chronic ulcer(s) (duration >1 month); or bronchitis, pneumonitis, or esophagitis, onset at age >1 month			*Salmonella* septicemia, recurrent Toxoplasmosis of brain, onset at age >1 month			
Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (duration >1 month) Kaposi's sarcoma			Wasting syndrome due to HIV			

Data from Reference 20.

The epidemic in the United States was initially established in MSM, and this population continues to be prominently affected by HIV, accounting for

65% of new cases.[21]

Heterosexual transmissions accounted for approximately 23% of new cases and approximately 65% of these are women. Injection-drug use makes up about 7% of new cases. For women, the main risk factor for transmission is heterosexual intercourse (~85% of cases) and injection-drug use (~15% of cases). For men, the main risks are MSM (~81%), heterosexual sex (~10%), and injection-drug use (~10%).[21] Black and Hispanic communities are disproportionately affected by HIV infection. Of new infections in recent years, 42% were in Black persons and 29% were in Hispanic persons, although these populations only make up 12% and 18% of the US population, respectively. A relatively large proportion of these populations are not well linked to appropriate prevention, care, and treatment services, which represents a significant public health challenge.[10]

The number of individuals living with HIV globally has risen to 37.6 million persons.[1,23] Increases are due to longer lifespans due to wider implementation of ART worldwide. This has reduced the death rate and new infection rate. For example, the peak number of new infections was 3 million per year in 1997 and this has declined to 1.5 million in 2020. New infections in children (mostly due to perinatal transmission) have declined by 52% between 2010 and 2020, and overall deaths have declined by approximately 59% since 2004. Nevertheless, approximately 690,000 people succumbed to HIV in 2019 and HIV is still a major contributor to the global burden of disease.[1,23] The highest concentration of HIV cases in the world is in sub-Saharan Africa, where approximately 26 million people are infected. However, new infections have declined there by approximately 25% to 38% since 2010, depending on the region. Heterosexual transmission is the most common mode of transmission in sub-Saharan Africa and worldwide. Women in sub-Saharan Africa and resource-limited countries are at disproportionately high risk for acquiring HIV because of biological and cultural factors that foster HIV transmission, such as limited ability to negotiate condom use. Other important epidemiologic features of the HIV epidemic include growing incidence among injection-drug users in North Africa and the Middle East, as well as some regions of Eastern Europe and Central Asia (eg, Russia and Ukraine).[23]

ETIOLOGY

HIV is an enveloped single-stranded RNA virus and a member of the Lentivirinae (*lenti*, meaning “slow”) subfamily of retroviruses. Lentiviruses are characterized by their indolent infectious cycle. There are two related but distinct types of HIV: HIV-1 and HIV-2. HIV-2, found mostly in western Africa, consists of seven phylogenetic lineages designated as subtypes (clades) A through G. Four groups of HIV-1 are recognized: M (main or major), N (non-M, non-O), O (outlier), and P (pending the identification of further cases).[2] The nine subtypes of HIV-1 group M are identified as A through D, F through H, J, and K. Mixtures of subtypes are referred to as *circulating recombinant forms.* Group M, subtype B, is primarily responsible for the epidemic in North America and western Europe.[24]

HIV in humans was the result of a cross-species transmission (zoonosis) from primates infected with simian immunodeficiency virus (SIV).[24] Phylogenetic and geographic relationships suggest that HIV-2 arose from SIV that infects sooty mangabeys, and HIV-1 groups M and N arose from SIVcpz, a virus that infects chimpanzees (*Pan troglodytes troglodytes*). Groups O and P may have arisen from an SIV variant that infects wild gorillas. Cultural practices, such as preparation and eating of bush meat or keeping animals as pets, may have allowed the virus to cross from primates to humans. The earliest known human infection with HIV has been traced to central Africa in 1959, but cross-species transmissions probably date back to the early 1900s.[24] Modern transportation, promiscuity, and drug use have caused the rapid and continued spread of the virus within the United States and throughout the world. This chapter focuses on HIV-1 group M, which is the predominant strain likely to be encountered in the western world.

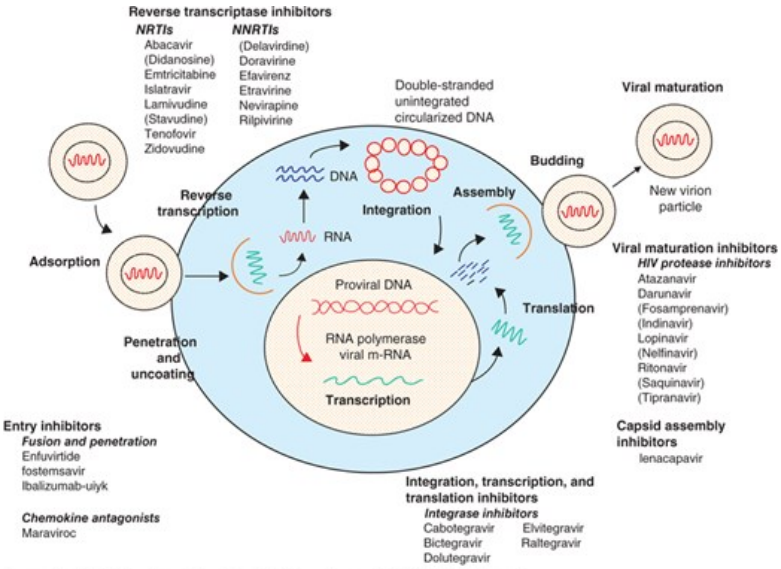
PATHOGENESIS

Understanding the life cycle of HIV (Fig. 148-1) is necessary because the current strategies used for HIV treatment target points in this cycle. Once HIV enters the human body, the outer glycoprotein (gp160) on its surface, which is composed of two subunits (gp120 and gp41), has affinity for CD4 receptors, which are proteins present on the surface of T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. The gp120 subunit is responsible for CD4 binding. Once initial binding occurs, the intimate association of HIV with the cell is enhanced by further binding to chemokine coreceptors. The two major chemokine receptors used by HIV are chemokine (C–C motif) receptor 5 (CCR5) and chemokine (C–X–C motif) receptor 4 (CXCR4). HIV isolates may contain a mixture of viruses that target one or the other of these coreceptors, and some viral strains may be dual-tropic (ie, can use both coreceptors). The HIV strain that preferentially uses CCR5, referred to as R5 viruses, is macrophage-tropic and typically implicated in most cases of sexually transmitted HIV.[25] Individuals with a common 32-base-pair deletion in the CCR5 gene are protected from

progression of HIV disease, and those who are homozygous for the 32-base-pair deletion have a degree of resistance to acquisition of HIV-1.[26] The HIV strain that targets CXCR4, designated X4 virus, is T-cell-tropic and often is predominant in the later stage of disease. CD4 and coreceptor attachment of HIV to the cell promotes membrane fusion, which is mediated by gp41, and finally internalization of the viral genetic material and enzymes necessary for replication.

FIGURE 148-1

Life cycle of human immunodeficiency virus with potential targets where replication may be interrupted. Italicized compounds were in development at the time of this writing. Parentheses indicate medications that are no longer used in clinical practice.



After internalization, the viral protein shell surrounding the nucleic acid (capsid) undergoes a disassembly process in preparation for replication.[27] The genetic material of HIV is positive-sense single-stranded RNA; the virus must transcribe this RNA into DNA (transcription normally occurs from DNA to RNA; HIV works backward, hence the name *retrovirus*). To do so, HIV is equipped with the unique enzyme RNA-dependent DNA polymerase (reverse transcriptase). HIV reverse transcriptase first synthesizes a complementary strand of DNA using the viral RNA as a template. The RNA portion of this DNA-RNA hybrid is then partially removed by ribonuclease H (RNase H), allowing HIV reverse transcriptase to complete the synthesis of a double-stranded DNA molecule. The fidelity of HIV reverse transcriptase is poor, and many mistakes are made during the process. These errors in the final DNA product contribute to the rapid mutation of the virus, which enables the virus to evade the immune response (thus complicating vaccine development), and promotes the evolution of drug resistance during partially suppressive therapy. Following reverse transcription, the final double-stranded DNA product migrates into the nucleus and is integrated into the host cell chromosome by integrase, another enzyme unique to HIV.

The integration of HIV into the host chromosome is critically important. Most notably, HIV can establish a persistent, latent infection, particularly in long-lived cells of the immune system such as memory T lymphocytes. The virus is effectively hidden in these cells until the cells become activated, and this characteristic has greatly complicated efforts to cure HIV infection.[28] It also necessitates continuous ART therapy because virus reemerges from this reservoir if therapy is suspended.

After integration, HIV preferentially replicates in activated cells. Activation by antigens, cytokines, or other factors stimulates the cell to produce nuclear factor kappa B (NF-κB), an enhancer-binding protein. NF-κB normally regulates the expression of T-lymphocyte genes involved in growth but also can inadvertently activate replication of HIV.[28] HIV encodes six regulatory and accessory proteins, such as Tat, Nef, Rev, Vpu, Vif, and Vpr, which enhance replication and inhibit innate immunity. For example, the Tat protein is a potent amplifier of HIV gene expression; it binds to a specific RNA sequence of HIV that initiates and stabilizes transcription elongation.[28] Vif is a viral protein that binds human APOBEC 3G, a cytidine deaminase that disrupts the virus' genetic code by converting viral RNA cytosine to uracil, thereby providing innate cellular immunity.[29] Vpu inhibits tetherin, a human cellular membrane protein that prevents release of virus particles after budding from infected cells. Assembly of new viral particles occurs in a stepwise

manner beginning with the coalescence of HIV proteins beneath the host cell lipid bilayer. The nucleocapsid is subsequently formed with viral single-stranded RNA and other components packaged inside. Once packaged, the virion then buds through the plasma membrane, acquiring the characteristics of the host lipid bilayer. After the virus buds, the maturation process begins. Within the virion, protease, another enzyme unique to HIV, cleaves large precursor polypeptides (gag and gag-pol) into functional proteins (capsid, protease, reverse transcriptase, and integrase) that are necessary to produce a complete and infectious virus. Without this enzyme, the virion is immature and unable to infect other cells. Capsid is key to this final maturation process, as well as many other roles in the HIV life-cycle such as facilitating reverse transcription, intracellular transport, nuclear entry, and integration.[30]

The natural history of HIV infection exhibits three general phases: acute, chronic, and terminal (AIDS). Initial rounds of HIV replication during acute infection take place largely in the mucosal CD4+, CCR5+ T-cell pools in the gut, resulting in a massive CD4 T-cell depletion in these tissues.[31] Cells are destroyed by various mechanisms, including cell lysis from newly budding virions, cytotoxic T-lymphocyte-induced cell killing, and induction of apoptosis. Following this destruction of the mucosal CD4 T-cell pool, which lasts for 2 to 3 weeks, a state of heightened immune activation ensues during the chronic infection phase, which can last for several years. The activated state is characterized by high levels of activation markers on circulating T cells (eg, HLA-DR and CD38) and proinflammatory cytokines, and may result from HIV antigen as well as translocation of microbial antigens from the T-cell-depleted gut mucosa. Heightened activation enables further HIV replication and ultimately leads to continued depletion of CD4+, CCR5+ T cells. HIV-1 exhibits a high turnover rate during this chronic phase, with an estimated 10 billion new viruses produced each day.[32] More than 99% of these viruses are produced in newly infected activated cells. Nevertheless, for much of the chronic phase, the immune system is able to operate well enough to prevent overt OIs that herald AIDS. However, the depletion of CD4 cells and continuous cellular activation eventually lead to a final collapse of the immune system, or AIDS. HIV may use the CXCR4 coreceptor during this last phase of infection, and these viruses infect a broader range of CD4 cells (naïve and central-memory) speeding the disease progression. It is this unrelenting destruction of CD4 cells that causes the profoundly compromised immune system and AIDS.

DIAGNOSIS

Detection of HIV and Surrogate Markers of Disease Progression

HIV is diagnosed through a multi-step process.[33] The presence of HIV infection is screened with an enzyme-linked immunosorbent assay (ELISA), which detects antibodies against HIV-1. Although ELISA has been the mainstay of HIV screening for decades, the technology has been evolving to detect infection earlier in the time course of the disease.[34] Older ELISA tests detected IgG (second-generation tests), but more modern tests detect IgG and IgM (third-generation tests) and may further include detection of p24 antigen, an early marker of infection (fourth-generation tests). These technological advances enable earlier detection of HIV by as much as 15 to 20 days compared with older second-generation tests. ELISA tests are generally highly sensitive (greater than 99%) and highly specific (greater than 99%), but rare false-positive results can occur particularly in those with autoimmune disorders.[33] False-negative results also occur and may be attributed to the “window period” before adequate production of antibodies or antigen. This “window period” between HIV acquisition and detection of HIV with fourth- and third-generation tests is approximately 2 and 3 weeks, respectively.[33] Positive screening tests are confirmed with another enzyme immunoassay to specify if the antibodies are to HIV-1 versus HIV-2 (although HIV-2 is rare in the United States, this step ensures proper diagnosis and treatment). If this follow-up assay is indeterminant or negative, an HIV nucleic acid test is performed for definitive diagnosis. HIV-RNA is the earliest indicator of infection, detectable ~10 days from acquisition and about 1 week before fourth-generation tests.[34] Several point-of-care screening kits are available for serum, plasma, whole blood, or oral fluids. While oral fluid tests are convenient, they are not as sensitive as blood assays, which may result in false-negatives early in infections; this is a particular disadvantage in the setting of HIV testing prior to initiating or continuing preexposure prophylaxis (PrEP).[34] Clinicians should be aware that HIV acquisition during PrEP may be associated with prolonged HIV suppression and delayed antibody expression.[35] HIV testing is recommended when HIV infection is suspected because of symptoms and/or high-risk behavior.[36] Additionally, the CDC recommends routine HIV screening at least once in all healthcare settings in all persons 13 to 64 years, a policy called “opt-out” testing.[37] A focus of the recommendations is to screen persons at high risk of HIV infection (eg, MSM) at least annually and to screen pregnant persons while they are in care. The policy states that consent for medical care will imply consent for HIV testing; however, the person must be informed of the test and can opt out of taking it. Because states may have different HIV consent laws, the local requirements for HIV testing should be consulted. The rationale for the opt-out strategy is to diagnose those who unknowingly carry HIV so as to initiate ART early, leading to improved prognosis and reduced forward transmissions.

Once diagnosed, HIV disease is monitored primarily by two surrogate biomarkers, viral load and CD4 cell count.[38] The viral load test quantifies the degree of viremia by measuring the number of copies of viral RNA (HIV-RNA) in the plasma. Methods for determining HIV-RNA include reverse-transcription polymerase chain reaction (RT-PCR), branched-chain DNA, transcription-mediated amplification, and nucleic acid sequence-based assay. RT-PCR is used more widely than the other techniques.[34] Irrespective of the method used, viral load is reported as the number of viral RNA copies per milliliter of plasma. Each assay has its own lower limit of quantitation, and results can vary from one assay method to the other; therefore, the same assay method should be used consistently for each patient. Reductions in viral load often are reported in base 10 logarithm. For example, if a patient presents initially with a viral load of 100,000 copies/mL (10^5 copies/mL or 10^8 copies/L) and subsequently has a viral load of 10,000 copies/mL (10^4 copies/mL or 10^7 copies/L), the decrease is 1 $\log_{10}$. Given that HIV-RNA varies within a patient, a perceptible clinical response is generally considered when the decline in viral load is more than 0.5 $\log_{10}$.[38] Viral load is a major prognostic factor for disease progression, CD4 count decline, and death.[38] It is also the predominant way to assess the effectiveness of treatment.

Because HIV attacks and leads to the destruction of cells bearing the CD4 receptor, the number of CD4 lymphocytes (T-helper cells) in the blood is a critical surrogate marker of disease progression and immune system status.[38] The normal adult CD4 lymphocyte count ranges from 500 to 1,600 cells/mm^3 (0.5×10^9–1.6×10^9/L), or 40% to 70% (0.4-0.7) of total lymphocytes. CD4 counts in children are age dependent, with younger children having higher CD4 counts (see Table 148-1). The hallmark of HIV disease is depletion of CD4 cells and the associated development of OIs and malignancies, especially at lower CD4 cell counts.

CLINICAL PRESENTATION

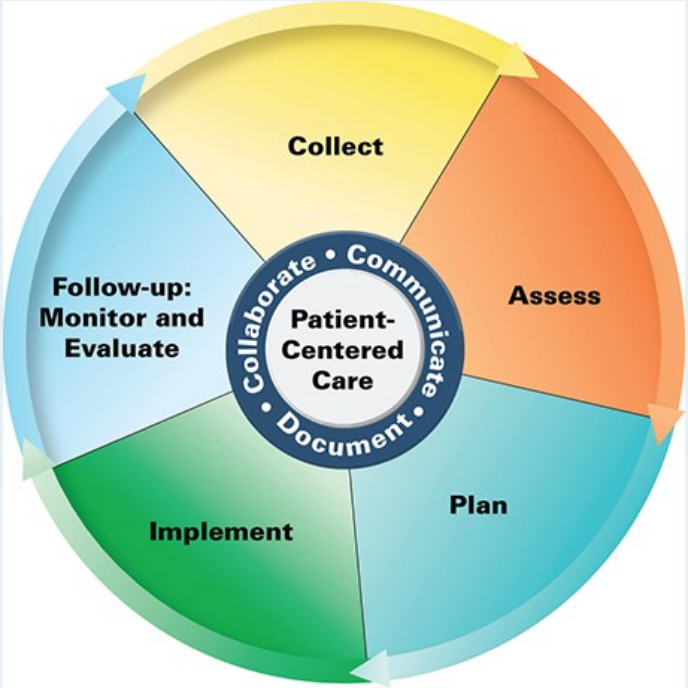
3 Clinical presentation of primary HIV infection varies, but most patients (50%-90%) have an acute retroviral syndrome or mononucleosis-like illness, presumably due to the host immune response to the virus (ie, “cytokine storm”).[39] Although many of these symptoms are nonspecific (eg, fever, headache, fatigue, lymphadenopathy, pharyngitis, rash), the presence of aseptic meningitis, oral or genital ulcers, and leukopenia should raise suspicion of acute HIV infection in the setting of a potential exposure. Symptoms often last 2 weeks, and hospitalization may be required for a small fraction of patients. Primary infection is associated with a high viral load (more than 10^6 copies/mL [10^9/L]) and a precipitous drop in CD4 cells. After several weeks, an immune response is mounted, the amount of HIV-RNA in plasma falls substantially, CD4 cells rebound slightly, and symptoms resolve gradually. However, as described above, this clinically latent period is not virologically latent because HIV replication is continuous (~10 billion viruses per day) and immune system destruction is ongoing. A steady decrease in CD4 cells (~50 cells/μL [0.05×10^9/L] per year) is the most measurable aspect of this immune system deterioration during the asymptomatic phase. Plasma viral load, on the other hand, is stabilized at a particular level or “set point.” The set point correlates strongly with the CD4 cell decline and time to AIDS and morbidity. For example, prior to ART, the Multicenter AIDS Cohort Study measured viral load in 1,604 HIV-positive men and followed them for as long as 11 years. The CD4 cell count decline was approximately twice as fast in those with HIV-RNA above 30,000 copies/mL (30×10^6/L) compared with those with HIV-RNA less than or equal to 500 copies/mL (500×10^3/L) and mortality rates (within 6 years) were 69.5% versus 0.9%, respectively.[40] Thus, a higher viral set point is associated with faster disease progression and poorer prognosis. Not all individuals infected with HIV progress to AIDS—these so-called “long-term nonprogressors” (also known as “elite controllers”) may be infected with a defective virus (eg, Nef-deficient HIV) or may have an intrinsic ability to resist infection (eg, CCR5 mutation).

Most children born with HIV are asymptomatic. On physical examination, children often present with nonspecific signs, such as lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, weight loss or unexplained low birth weight (in prenatally exposed infants), and fever of unknown origin.[41] Laboratory findings include anemia, hypergammaglobulinemia (primarily IgA and IgM), altered mononuclear cell function, and altered T-cell subset ratios. Of note, the normal range for CD4 cell counts in young children is much different from the range in adults (Table 148-1). Children have different susceptibility and/or exposures to OIs compared with adults. Bacterial infections, including *Streptococcus pneumoniae*, *Salmonella* spp., and *Mycobacterium tuberculosis*, may be more prevalent in children with AIDS than in adults with the disease. Kaposi’s sarcoma is rare in children. Children with HIV infection may develop lymphocytic interstitial pneumonitis without evidence of *P. jirovecii* or other pathogens on lung biopsy.

Some children (~25%) will progress to AIDS rapidly within the first year of life. A presentation of serious OIs such as *P. jirovecii* pneumonia, encephalopathy, failure to thrive, and a precipitous drop in CD4 cells are common in these infants. General management of children with HIV involves principles similar to those used for adults: ART, treatment and prophylaxis of OIs, and supportive care.[42,43]

PATIENT CARE PROCESS

Patient Care Process for Human Immunodeficiency Virus (HIV)



Collect

- Patient characteristics (eg, age, sex at birth, gender identity, race, ethnicity, contraception methods, or pregnancy intentions)
- Patient medical history (eg, HBV, HCV, STIs, other chronic/acute illnesses)
- Previous HIV history (mode of transmission, date of diagnosis, nadir $CD4^+$ T-cell count, history of previous opportunistic infections, history of antiretroviral resistance)
- Social history (eg, drug use, sexual history, high-risk behaviors)
- Current prescription and nonprescription medications including herbal products, dietary supplements, and any previous antiretroviral regimens
- Objective data
  - HIV screening and confirmatory tests
  - HIV-RNA and $CD4^+$ cell count
  - Baseline antiretroviral resistance testing
  - HLA-B*5701 testing
  - Complete blood count, basic metabolic panel, liver function panel, sexually transmitted infection screening

Assess

- Understanding of disease state and goals of treatment

- Access to ART (ie, insurance and co-pays)
- Willingness to start and adhere to ART
- Potential drug-drug interactions
- Any contraindications or concerns related to recommended ART regimens (eg, chronic kidney disease, ART resistance, HLA-B*5701 genotype, history of cardiovascular disease, hyperlipidemia, uncontrolled psychiatric illness, pregnancy or desire to become pregnant, history of multiple bone fractures, or severe osteoporosis)
- Need for opportunistic infection prophylaxis (ie, $CD4^+$ cell count)

Plan*

- ART regimen including specific agents, dose, frequency, administration (eg, food requirements), drug-drug interactions (see Tables 148-2 and 148-3)
- Monitoring parameters including efficacy (eg, HIV-RNA, $CD4^+$ cell count) and safety (eg, adverse effects, SCr, LFTs, CBC)
- Follow-up every 3 months until HIV-RNA is undetectable
- Patient education (eg, purpose of treatment, importance of adherence, transmission risk, drug-specific information; see Table 148-3)
- Referrals to other providers when appropriate (eg, behavioral health, social work)

Implement*

- Provide patient education regarding all elements of treatment plan
- Emphasize need for adherence to ART regimen and provide resources that can be used to maximize adherence
- Schedule follow-up for assessment of ART efficacy, safety, and adherence

Follow-up: Monitor and Evaluate

- Therapeutic efficacy (ie, reduction in HIV-RNA) and safety
- Restoration of immune function (ie, increasing $CD4^+$ cell count)
- Presence of adverse effects (eg, GI upset, headache, nausea)
- Renal and hepatic function
- Patient access and adherence to ART

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Desired Outcomes

4 The central goals of ART are to decrease morbidity and mortality, improve quality of life, restore and preserve immune function, and prevent further transmission.[38] The most important and effective way to achieve these goals is maximal and durable suppression of HIV replication, which is interpreted as plasma HIV-RNA less than the lower limit of quantitation (ie, undetectable; usually less than 20 or 50 copies/mL [20×10^3 or 50×10^3/L]).

Such a profound reduction in HIV-RNA is associated with reduced transmissions and long-term response to therapy (ie, durability), as well as increases in CD4 lymphocytes that closely correlate with a reduced risk for developing OIs. While undetectable HIV-RNA almost always corresponds with a rise in CD4 lymphocytes, some patients respond virologically or immunologically without the other.

General Approach to Treatment

5 Contemporary combinations of two or three active antiretroviral agents from two pharmacologic classes potently inhibit HIV replication to undetectable plasma levels, prevent and reverse immune deficiency, and substantially decrease morbidity and mortality—constituting the modern ART era.[44] Principles that serve as a guide for the clinical use of antiretroviral agents include[45]:

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV-RNA levels indicate the magnitude of HIV replication and its associated rate of CD4 cell destruction, whereas CD4 cell counts indicate the extent of HIV-induced immune damage already suffered.
3. Use of potent combination ART to suppress HIV replication to below the levels of detection of sensitive plasma HIV-RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
4. The most effective means for accomplishing durable suppression of HIV replication is simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been treated previously and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
5. Each of the antiretroviral drugs used in combination therapy regimens always should be used according to optimal schedules and dosages.
6. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in ART increases future therapeutic constraints.
7. People of child-bearing potential should receive optimal ART regardless of pregnancy status.
8. The same principles of ART apply to both children and adults with HIV, although treatment of children with HIV involves unique pharmacologic, virologic, and immunologic considerations.
9. Persons with acute primary HIV infections should be treated with combination ART to suppress virus replication to levels below the limit of detection of sensitive plasma HIV-RNA assays.

The extent to which these principles will continue to stand the test of time is unknown; new information on the pathogenesis and treatment of HIV accrues constantly. As of October 2021, 34 antiretroviral compounds have been approved by the FDA; six (amprenavir, delavirdine, didanosine, indinavir, stavudine, and zalcitabine) have since been removed from the US market. Table 148-2 presents the state of the art for treatment of persons with HIV as of October 2021.[38] Treatment is recommended for all persons with HIV regardless of CD4 lymphocyte count, as long as the patient is ready to adhere to therapy. Urgent indications for therapy include pregnancy, history of AIDS-defining illness, CD4 counts below 200 cells/mm^3 (0.2 × 10^9/L), HIV-associated nephropathy, HIV/hepatitis C virus coinfection, and/or HIV/hepatitis B virus coinfection.

TABLE 148-2

Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended as Initial Therapy for Persons with HIV

	Regimen	Selected Limitations
Recommended Initial Regimens for Most Persons with HIV		
InSTI	Bictegravir + tenofovir alafenamide fumarate +	Not recommended if CrCl <30 mL/min (0.5 mL/s); interactions with polyvalent cations;

based	emtricitabine (coformulated) (AI)	bictegravir inhibits creatinine secretion increasing serum creatinine (distinguish vs renal dysfunction); CNS/psychiatric side effects (primarily in those with preexisting conditions)
	Dolutegravir + abacavir + lamivudine (coformulated) (AI)	Only if HLA-B*5701 negative; do not use in chronic hepatitis B infection; interactions with polyvalent cations; dolutegravir inhibits creatinine secretion increasing SCr (distinguish vs renal dysfunction); CNS/psychiatric side effects (primarily in those with preexisting conditions)
	Dolutegravir + (tenofovir disoproxil fumarate or tenofovir alafenamide fumarate)[a] + (emtricitabine or lamivudine)[b] (AI)	Same as above without HLA-B*5701 negative requirement
	Dolutegravir + lamivudine (AI)	Do not use if HIV VL ≥500,000 copies/mL (500 × 10^6/L), chronic hepatitis B infection or hepatitis B infection status is unknown, or if HIV genotype is unavailable or shows resistance to either component
Recommended initial regimens in certain clinical situations (some potential disadvantages vs previous category)		
InSTI based	Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (coformulated) (BI)	Initiation not recommended if CrCl <70 mL/min (1.17 mL/s); food requirement; interactions with polyvalent cations; CYP3A4 drug interactions; cobicistat inhibits creatinine secretion increasing SCr (distinguish vs renal dysfunction); CNS/psychiatric side effects (primarily in those with preexisting conditions)
	Elvitegravir + cobicistat + tenofovir alafenamide fumarate + emtricitabine (coformulated) (BI)	Not recommended if CrCl <30 mL/min (0.5 mL/s); otherwise, same as above
	Raltegravir + (tenofovir disoproxil fumarate or tenofovir alafenamide) + (emtricitabine or lamivudine) (BI for tenofovir disoproxil fumarate+ (emtricitabine or lamivudine)[b]; BII for tenofovir alafenamide + emtricitabine)	Raltegravir can be dosed once or twice daily depending on the formulation; interactions with polyvalent cations; creatine kinase increases; TDF/FTC not recommended if CrCl <50 mL/min (0.83 mL/s) and TAF/FTC not recommended if CrCl <30 mL/min (0.5 mL/s); CNS/psychiatric side effects (primarily in those with preexisting conditions)
HIV PI based[c]	Atazanavir + ritonavir (or cobicistat) + (tenofovir disoproxil fumarate or tenofovir alafenamide fumarate)[a] + (emtricitabine or lamivudine) (BI)	GI side effects; food requirement; CYP3A4 drug interactions; hyperbilirubinemia leading to drug discontinuation, especially in those with Gilbert's syndrome; use of cobicistat with TDF/FTC not recommended if CrCl <70 mL/min (1.17 mL/s); use of TAF/FTC not recommended if CrCl <30 mL/min (0.5 mL/s); cobicistat inhibits creatinine secretion increasing SCr (distinguish vs renal dysfunction)
	Darunavir + (ritonavir or cobicistat) + (tenofovir disoproxil fumarate or tenofovir alafenamide)[a] + (emtricitabine or lamivudine)[b] (AI)	Rash (darunavir has sulfonamide moiety); GI side effects; food requirement; CYP3A4 drug interactions; use of cobicistat with TDF/FTC not recommended if CrCl <70 mL/min (1.17 mL/s); use of TAF/FTC not recommended if CrCl <30 mL/min (0.5 mL/s); cobicistat inhibits creatinine secretion increasing serum creatinine (distinguish vs renal dysfunction)
	Darunavir + ritonavir (or cobicistat) + abacavir + lamivudine (BII)	Only if HLA-B*5701 negative; see issues above
NNRTI based	Doravirine + tenofovir disoproxil fumarate + lamivudine (coformulated) (BI)	Not recommended if CrCl <50 mL/min (0.83 mL/s); CNS side effects
	Doravirine + tenofovir alafenamide +	TAF/FTC not recommended if CrCl <30 mL/min (0.5 mL/s); CNS side effects

	emtricitabine (BIII)	
	Efavirenz + tenofovir disoproxil fumarate + (emtricitabine or lamivudine)[b] (coformulated) (BI)	CNS side effects with efavirenz; CYP450 drug interactions; empty stomach dosing before bed; not recommended if CrCl <50 mL/min (0.83 mL/s)
	Efavirenz + tenofovir alafenamide + emtricitabine (BII)	CNS side effects with efavirenz; CYP450 drug interactions; empty stomach dosing before bed; TAF/FTC not recommended if CrCl <30 mL/min (0.5 mL/s)
	Rilpivirine + (tenofovir disoproxil fumarate or tenofovir alafenamide)[a] + emtricitabine (coformulated) (BI for TDF and BII for TAF)	Not recommended when HIV-RNA >100,000 copies/mL (100×10^6/L) or CD4 <200 cells/μL (0.2×10^9/L); no proton-pump inhibitors (rilpivirine); food requirement; antacid interactions
If abacavir and tenofovir cannot be used	Dolutegravir + lamivudine (AI)	Do not use if HIV VL ≥500,000 copies/mL (500×10^6/L), chronic hepatitis B infection or hepatitis B infection status is unknown, or if HIV genotype is unavailable or shows resistance to either component
	Darunavir + ritonavir + raltegravir (CI)	Only if HIV-RNA <100,000 copies/mL (100×10^6/L) and CD4 >200 cells/mm^3 (0.2×10^9/L); raltegravir must be dosed twice daily; do not use in chronic hepatitis B infection
	Darunavir + ritonavir + lamivudine (CI)	Do not use in chronic hepatitis B infection

Selected regimens or components that should not be used at any time

Regimen or component	Comment
Monotherapy with any single agent (AI)	Inferior virologic efficacy; risk of virologic rebound and resistance
Any NRTI only regimen (AI)	Inferior virologic efficacy
Unboosted PIs (ie, darunavir) (AII)	Inadequate bioavailability
Etravirine + unboosted PIs (AII)	Possible induction of PI metabolism, doses not established
Nevirapine in ARV naïve with higher CD4 counts (>250 cells/μL [0.25×10^9/L] for women, >400 cells/μL [0.4×10^9/L] for men) (BI)	High incidence of symptomatic hepatotoxicity

[a]TAF and TDF are prodrugs of tenofovir with differing pharmacology and safety profiles. Safety, cost, and access should be considered when deciding between which form to use.

Evidence-based rating definition. Rating strength of recommendation—A: Strong recommendation. B: Moderate recommendation. C: Optional recommendation. Rating Quality of Evidence Supporting the Recommendation—I: Evidence from randomized, controlled trials. II: Evidence from at least one well-designed clinical trial without randomization or observational cohorts with long-term clinical outcomes. III: Expert opinion. Lamivudine and emtricitabine are considered interchangeable endpoints.

[b]Emtricitabine and lamivudine are interchangeable.

[c]Boosted darunavir is generally preferred over boosted atazanavir.

Data from Reference 38.

The optimal time to initiate therapy in chronic HIV infection was a matter of debate. The main arguments for postponing therapy were the concern for cumulative drug toxicity and trepidation for drug resistance and loss of therapeutic options. These concerns were well-founded when older drugs such as lopinavir/ritonavir, stavudine, zidovudine, indinavir, and efavirenz were the mainstay of therapy. Today, the availability of newer medications with different mechanisms of action (eg, InSTIs) significantly improved adverse event profiles, and the convenience of single tablet regimens helps to mitigate these issues. Two large randomized controlled trials helped address the issue of whether initiating therapy immediately or waiting for a lower CD4 count provided clinical benefit.[46,47] In the START trial, immediate ART resulted in significantly fewer serious AIDS events (HR 0.28, 95% CI 0.15-0.50) and non-AIDS events (HR 0.61, 0.38-0.97) as compared with delaying ART until CD4 count fell below 350 cells/μL (0.35×10^9/L).[46] The TEMPRANO study also found that immediate ART resulted in fewer deaths or severe HIV-related illnesses as compared with deferred ART (HR among patients with a baseline CD4 greater than or equal to 500 cells/μL [0.5×10^9/L], 0.56; 95% CI, 0.33-0.94).[47] Immediate ART and subsequent suppressed viral load is also known to substantially prevent ongoing HIV transmissions compared with delayed ART.[48] Taken together, these studies provide high-quality evidence that untreated HIV is harmful even at high CD4 counts and immediate ART confers individual- and population-level benefit compared with delayed ART. Major policy-makers, including the WHO and US Department of Health and Human Services (DHHS), now recommend immediate ART regardless of CD4 count.[38,49]

More recent efforts have shifted toward immediate or rapid ART initiation, meaning that antiretroviral therapy is started on the same day or within a few days to weeks of HIV diagnosis. This strategy generally increases ART uptake, improves engagement and retention in HIV care, reduces time to viral suppression, and improves overall rates of those on ART with viral suppression. Several randomized controlled studies in resource-limited settings have shown marked improvements in these outcomes,[50] and prospective observational studies within the United States have shown similar patterns.[51] However, this approach requires the alignment of several resources within a short time frame and thus may be logistically challenging to implement in some settings.

An excellent source of information on updated treatment guidelines is available at https://clinicalinfo.hiv.gov/en/guidelines. Healthcare professionals involved in the care of persons with HIV are urged to consult the most current literature on the principles and strategies for ART therapy.

Pharmacologic Therapy

Several methods of therapeutic intervention have been evaluated against HIV, including systemic antiretroviral drugs (the focus of this chapter) for direct inhibition of chronic viral replication or prevention of HIV acquisition; vaccination; immunomodulators to help stimulate and restore the immune system; and topical antiretroviral drugs or virucides (chemicals that destroy intact viruses) to prevent HIV infection. Antiretroviral medications are the only FDA-approved options for HIV treatment, and the latter three approaches are now investigational. Several approaches for an HIV vaccine are in development, including whole killed virus, subunit and peptide vaccination, recombinant live vector, naked DNA delivery, adenovirus vectors, and mRNA. Historically, vaccine progress has been slow. Genetic variability in HIV and a nascent understanding of the role of the immune system in suppressing viral replication are significant barriers to the development of an effective HIV vaccine with long-lasting and protective immunity. Efforts are underway to understand the correlates of protection from various studies to inform the vaccine field going forward.[52,53] Immunomodulators have also been investigated as a way to restore immune function (eg, aldesleukin) and to potentially cure HIV through “shock and kill” strategies (activate the immune system to bring HIV out of latency, then suppress its replication).[54] Topical virucidal or antiretroviral drug formulations for vaginal or rectal use to prevent sexual transmission of HIV are in various phases of development.[11] Collectively, these agents have demonstrated modest efficacy and are discussed in more depth in the PrEP section.

Antiretroviral Agents

Systemic delivery of antiretroviral agents for direct inhibition of viral replication has been the most successful strategy for both treatment and prophylaxis. Six general classes of drugs are available: capsid inhibitors, entry inhibitors (fusion inhibitors, CD4 post-attachment inhibitors, gp120 attachment inhibitors, and chemokine receptor antagonists), nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (InSTIs), and HIV PIs (Table 148-3).[38] Newer agents exhibit significant advantages over first-generation drugs in terms of pharmacokinetics, tolerability, safety, and efficacy. This section will highlight specific advantages of newer agents over first-generation drugs and will focus the discussion on agents used most often. Updated drug information is available in the DHHS

guidelines including common adverse events and dosing recommendations for hepatic and renal insufficiency for all antiretroviral drugs.[38] There are other antiviral medications that exhibit modest, non-suppressive anti-HIV activity against HIV, such as the anti-herpes and anti-hepatitis B antivirals acyclovir, adefovir, entecavir, foscarnet, and interferon-alpha. These therapies should not be used as alternative options for HIV treatment but can be used in the setting of suppressive ART.

TABLE 148-3

Selected Pharmacologic Characteristics of Selected Antiretroviral Compounds for HIV Treatment

Drug	*F* (%)	$t_{1/2}$[a]	Adult Dosing Recommendation[b] (doses/day)	Plasma C_{max}/C_{min} (ng/mL or mcg/L)	Distinguishing Adverse Effects
Integrase inhibitors (InSTI)					
Bictegravir	?	17.3 hr	50 mg orally once daily	6,150/2,610	Diarrhea, nausea, headache, weight gain
Cabotegravir		41 hr	Oral lead-in: 30 mg orally once daily × 28 days	8,000/4,600	Headache, nausea, abnormal dreams, anxiety, insomnia, depressive disorders, hepatotoxicity
Cabotegravir LA	N/A	6-12 weeks (absorption-limited)	600 mg/3 mL IM × 1 (loading) 400 mg/2 mL every 4 weeks (continuation) Or 600 mg/3 mL every 8 weeks (continuation)	8,000/1,500 4,200/2,800	IM only: injection site reactions
Dolutegravir	?	14 hr	50 mg orally once daily *Or* 50 mg orally twice daily	3,670/1,110 4,150/2,120	Insomnia, headache, depression, and suicidal ideation (rare—usually patients with preexisting psychiatric conditions), weight gain, hepatotoxicity, hypersensitivity reactions including rash (can be severe)
Elvitegravir (coformulated with cobicistat)	?	13 hr	150 mg orally once daily	2,100/290	Diarrhea, nausea, depression and suicidal ideation (rare—usually patients with preexisting psychiatric conditions)
Raltegravir	?	9 hr	400 mg orally twice daily *Or* 1,200 mg orally once daily	2,171/68.5 7,575/51.6	Rash (can be severe), nausea, headache, diarrhea, pyrexia, creatine phosphokinase increases, weight gain, insomnia, depression, and suicidal ideation (rare—usually patients with preexisting psychiatric conditions)
Nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs)					
Abacavir	83	1.5/20 hr	300 mg orally twice daily *Or* 600 mg orally once daily	3,000/20 4,260[c]	Hypersensitivity (HLA-B*5701 test to predict); possible increased risk of MI with recent or current use but studies vary
Emtricitabine	93	10/39 hr	200 mg orally once daily	1,800/90	Rarely pigmentation on soles and palms in non-White

					populations
Lamivudine	86	5/22 hr	150 mg orally twice daily *Or* 300 mg orally once daily	1,400/370 2,410/110	Headache
Tenofovir alafenamide	?	0.4 (TAF) and 35/150 hr TAF and tenofovir components	25 mg orally once daily *Or* 10 mg orally once daily (when coformulated with cobicistat)	160 and 30/NA[c] and 10	Diarrhea, nausea, headache; increased lipids and weight gain vs TDF; less renal and bone toxicity vs TDF
Tenofovir disoproxil fumarate	25	17/150 hr (tenofovir component)	300 mg orally once daily	299/115	Renal dysfunction (proximal tubulopathy), bone demineralization
Zidovudine	85	2/7 hr	200 mg orally three times daily *Or* 300 mg orally twice daily	1,020/100 2,290/20	Anemia, neutropenia, myopathy
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)					
Doravirine	64	15 hr	100 mg orally once daily	962/396	Nausea, dizziness, abnormal dreams
Efavirenz	43	48 hr	600 mg orally once daily *Or* 400 mg orally once daily	4,072/1,768	CNS disturbances, rash, serum transaminase elevations, hiperlipidemia, QT prolongation
Etravirine	?	41 hr	200 mg orally twice daily	736/161	Rash (including SJS), nausea, hypersensitivity reactions
Nevirapine	93	25 hr	200 mg orally twice daily[d] *Or* 400 mg orally once daily	5,400/3,730 6,658/2,929	Potentially serious rash (including SJS) and symptomatic hepatotoxicity
Rilpivirine	?	50 hr	25 mg orally once daily	280/120	Rash, depression, insomnia, headache, hepatotoxicity, QT prolongation
Rilpivirine LA		13-28 weeks	900 mg/3 mL IM × 1 (loading) 600 mg/2 mL IM every 4 weeks (continuation) *Or* 900 mg/3 mL IM every 8 weeks (continuation)	139/37.2 116/82.2	IM only: injection site reactions
Protease inhibitors (PIs)					
Atazanavir	68	7 hr	400 mg orally once daily[e] *Or*	2,298/120 4,420/636	Unconjugated hyper bilirubinemia, cholelithiasis, nephrolithiasis, serum transaminase elevations

			300 mg orally once daily[f]		
Darunavir	82	15 hr	800 mg orally once daily[f] *Or* 600 mg orally twice daily[f]	7,070/3,860	Hepatotoxicity, rash, metabolic side effects
Lopinavir[g]	?	5.5 hr	800 mg orally once daily *Or* 400 mg orally twice daily	9,800/7,100	Hyperlipidemia, GI intolerance, metabolic side effects
Pharmacoenhancers					
Cobicistat	?	3-4 hr	150 mg orally once daily	990/30	SCr increases
Ritonavir	60	3-5 hr	100 mg orally once daily *Or* 100 mg orally twice daily		GI intolerance, hyperlipidemia
Fusion inhibitors					
Enfuvirtide	84	3.8 hr	90 mg/1 mL SQ twice daily	5,000/3,300	Injection-site reactions, rare hypersensitivity reactions
CCR5 antagonists					
Maraviroc	33	15 hr	300 mg orally twice daily[h]	618/33.6	Hepatotoxicity, abdominal pain, cough, dizziness
CD4 post-attachment inhibitors					
Ibalizumab-uiyk	N/A	79 hr	2,000 mg IV loading dose, then 800 mg every 2 weeks	567,000/230	Diarrhea, dizziness, nausea, rash, infusion reactions
Gp120 attachment inhibitors					
Fostemsavir	27	11 hr	600 mg orally twice daily	1,770/478	Nausea; QTc prolongation; transaminase and transient bilirubin elevations; sleep disturbance, dizziness
Capsid inhibitors					
Lenacapavir oral	8[i]	11 days	Initiation (option 1): 600 mg orally on days 1 and 2 only *or* Initiation (option 2): 600 mg orally on days 1 and 2, then 300 mg on Day 8	97/29	Nausea
Lenacapavir injection	100[i]	10 weeks	Initiation (option 1) & maintenance: 927 mg/3 mL SQ on day 1 and every 26 weeks thereafter	97/29	Injection site reaction (e.g. swelling, pain, erythema, nodules, induration, pruritus)

			or Initiation (option 2) & maintenance: 927 mg/3 mL SQ on day 15 and every 26 weeks thereafter		

C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; *F*, bioavailability; IM, intramuscular; IV, intravenous; LA, long acting; NA, not applicable; PO, by mouth; SQ, subcutaneous; $t_{1/2}$, elimination half-life.

[a]NtRTIs: Plasma NtRTI $t_{1/2}$/intracellular (peripheral blood mononuclear cells) NtRTI-triphosphate $t_{1/2}$; plasma $t_{1/2}$ only for other classes.

[b]Dose adjustment may be required for treatment-experienced patients with resistance mutations, weight, renal or hepatic disease, and drug interactions.

[c]C_{min} concentration typically below the limit of quantification.

[d]Initial dose escalation recommended to minimize side effects.

[e]Must be boosted with low doses of ritonavir (100-200 mg once or twice daily).

[f]Available as coformulation 4:1 lopinavir to ritonavir.

[h]Dose adjustment required with the concomitant use of medications that inhibit or induce CYP3A4

[i]*Relative to the long-acting injection formulation*

Data from Reference 38 and individual package inserts.

Reverse transcriptase inhibitors consist of two classes: those that are chemical derivatives of purine- and pyrimidine-based nucleosides and nucleotides (nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs]) and those that are not (nonnucleoside reverse transcriptase inhibitors [NNRTIs]). Recommended NRTIs include the thymidine analog zidovudine (AZT or ZDV); the deoxycytidine analogs emtricitabine (FTC) and lamivudine (3TC); the deoxyguanosine analog abacavir sulfate (ABC); and tenofovir, which is a deoxyadenosine-monophosphate nucleotide analog (a nucleotide is a nucleoside with one or more phosphates). **Note that drug abbreviations are provided here and below for reference, but their use is discouraged because they may lead to prescribing or administration errors.**

As a class, the NRTIs require phosphorylation in cells to the 5′-triphosphate moiety to become pharmacologically active. Intracellular phosphorylation occurs by cytoplasmic or mitochondrial kinases and phosphotransferases (not viral kinases). The 5′-triphosphate moiety acts in two ways: (1) it competes with endogenous deoxyribonucleotides for the catalytic site of reverse transcriptase, and (2) if taken up and incorporated by reverse transcriptase, it prematurely terminates DNA elongation, as it lacks the requisite 3′-hydroxyl for sugar-phosphate linking. NRTIs are active against both HIV-1 and HIV-2.[38] Emtricitabine, lamivudine, and tenofovir are also active against hepatitis B virus, and a combination of these agents should be used when possible in HIV–hepatitis B coinfected patients.

Tenofovir comes in two prodrug formulations, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Tenofovir disoproxil fumarate is an ester prodrug that releases tenofovir upon absorption and first pass metabolism, producing relatively high systemic concentrations of tenofovir, which confers some risk of proximal tubulopathy and bone demineralization (both usually mild and reversible). Tenofovir alafenamide contains a different prodrug configuration such that more of the intact prodrug reaches the systemic circulation and penetrates lymphoid cells. Once in lymphoid cells, tenofovir is released via hydrolysis by cathepsin A in lymphoid tissues or in hepatic cells via carboxylesterase 1. This strategy results in higher intracellular concentrations in cells of interest, but lower systemic tenofovir concentrations and less change in markers of proximal tubulopathy and bone demineralization.[55] However, TAF has been associated with weight gain and lipid abnormalities in comparison to TDF.[56,57]

Although NRTI triphosphates (or diphosphate for tenofovir) are specific for HIV reverse transcriptase, their adverse effects may be caused in part by inhibition of mitochondrial DNA or RNA synthesis.[38] It is largely this problem that differentiates the first-generation drugs (didanosine, stavudine, and

zidovudine) from the agents used most often (tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine, lamivudine, and abacavir). The mitochondrial toxicities associated with first-generation drugs include peripheral neuropathy, pancreatitis, lipoatrophy (subcutaneous fat loss), myopathy, anemia, and rarely life-threatening lactic acidosis with fatty liver. The newer agents exhibit less potential to cause these toxicities, but they still have their own adverse event profiles to be considered (see Table 148-3).

Most of the newer NRTIs are eliminated by the kidney, and dose adjustments are required for renal insufficiency; abacavir is an exception as it is metabolized in the liver and should not be used in advanced hepatic impairment. Resistance has been reported for all NRTIs, including cross-resistance within the class as multiple and/or specific mutations in the viral genome accrue.[58]

NNRTIs are a chemically heterogeneous group of agents that bind noncompetitively to reverse transcriptase adjacent to the catalytic site, forcing a conformation change to the enzyme. Unlike NRTIs, NNRTIs do not require intracellular activation, do not compete against endogenous deoxyribonucleotides, and do not have intrinsic antiviral activity against HIV-2. Recommended NNRTIs include doravirine (DOR), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine (RPV).[38] As a class, the NNRTIs are generally associated with rash and hepatotoxicity, including rare life-threatening cases, particularly for nevirapine.[38] The use of first-generation NNRTIs (nevirapine and efavirenz) are on the decline largely because of tolerability and/or safety concerns. However, some patients have remained on efavirenz-based therapy and both efavirenz and nevirapine are still used in certain regions of the world. NNRTIs tend to have long plasma half-lives and they are mainly cleared by liver and/or gut-mediated metabolism through the cytochrome P450 (CYP) enzyme system. Rilpivirine is the only NNRTI available in both an immediate release oral and a long-acting injectable formulation. Caution should be used for those with advanced hepatic insufficiency (nevirapine should not be used in moderate or advanced hepatic insufficiency). NNRTIs can be perpetrators of drug-drug interactions, most often induction of CYP metabolism. Exceptions to this are doravirine and rilpivirine, which do not induce or inhibit CYP metabolism. The older NNRTIs were unique in that a single mutation was needed to confer high-level cross-resistance for the class (not including etravirine and doravirine). This has been termed a *low-genetic barrier* to resistance.[58]

Recommended HIV PIs include atazanavir (ATV), darunavir (DRV), and lopinavir (LPV). Ritonavir (RTV) is also an older PI that is now used as a pharmacoenhancer for this class of drugs. HIV PIs competitively inhibit the cleavage of the gag-pol polyprotein, which is a crucial step in the viral maturation process, thereby resulting in the production of immature, noninfectious virions. HIV PIs have activity against HIV-1 and HIV-2 (particularly darunavir and lopinavir).[38] HIV PIs are generally associated with GI distress and metabolic changes, such as increased lipids, insulin insensitivity, and changes in body fat distribution. Some of these issues can be traced to formulation problems due to limited aqueous solubility, requiring high levels of excipients and large pill burdens. The first-generation HIV PIs (eg, indinavir, nelfinavir, saquinavir, lopinavir) exhibited poor solubility leading to erratic absorption (nelfinavir, saquinavir), crystallization of drug in urine (indinavir), gastrointestinal distress (nelfinavir, lopinavir), and hyperlipidemia (lopinavir). Generally, the newer HIV PIs, darunavir and atazanavir, improve upon, but do not eliminate, these issues. HIV PIs are cleared by liver- and gut-mediated metabolism (mainly CYP3A), and dose adjustments may be required in hepatic insufficiency. HIV PIs are almost always used with low doses of CYP3A inhibitors, ritonavir or cobicistat, to increase the plasma concentrations of the HIV PI of interest. Thus, CYP3A- and P-gp-mediated drug interactions with concomitant medications are important considerations for PIs. Resistance to the HIV PIs generally requires the buildup of multiple mutations, termed a *high-genetic barrier* to resistance. Multiple mutations can lead to cross-resistance.[58]

There are four drugs that block HIV entry and these are generally reserved for treatment-experienced patients. Enfuvirtide (T20) is a synthetic 36-amino-acid peptide that binds gp41, inhibiting envelope fusion of HIV-1 with the target cell. It does not have activity against HIV-2. Subcutaneous injection is the preferred route of administration and injection-site reactions (pain, erythema, nodules) are the most common adverse effects, nearing 100% incidence. Enfuvirtide is cleared via protein catabolism and amino acid recycling.[38] Maraviroc is a CCR5 antagonist with activity against HIV-1 and HIV-2. The long-term consequences of blocking CCR5 (a human receptor) are unknown but may include increased susceptibility to disease by flaviviruses (eg, West Nile virus and tickborne encephalitis virus).[59] One advantage of targeting a human receptor is that resistance to CCR5 antagonists may be more difficult to develop. Because CCR5 antagonists are only effective against R5 virus and not X4 virus, a viral tropism assay must be performed prior to using a CCR5 antagonist. Maraviroc is a CYP3A and P-glycoprotein substrate and is therefore susceptible to drug-drug interactions and caution should be used in those with advanced hepatic insufficiency. Maraviroc has been associated with rash and hepatotoxicity. Resistance mutations have been identified for enfuvirtide, which has a low-genetic barrier to resistance, but assays for maraviroc resistance have not been developed other than the R5 versus X4 tropism test.[38,58] Ibalizumab-uiyk is a recombinant humanized monoclonal antibody with activity against HIV-1 that binds to domain 2 of the CD4 receptor on host cells. The binding of ibalizumab-uiyk to the CD4 receptor does not affect its ability to bind gp120 on viral particles, but it interferes with the post-attachment steps necessary for the entry of HIV-1 into host cells. Ibalizumab-uiyk is administered by infusion and is indicated for heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who are failing their current antiretroviral

regimen.[60] It has activity against R5-tropic, X4-tropic, and dual-tropic viruses. The most common adverse effects associated with ibalizumab-uiyk include diarrhea, dizziness, nausea, and rash. Decreased susceptibility to ibalizumab-uiyk has been seen in some subjects, but the clinical significance of this is not well understood. There is no evidence of cross-resistance between ibalizumab-uiyk and any other antiretroviral class. Fostemsavir is an oral pro-drug of temsavir, which is an attachment inhibitor that binds near the CD4 receptor binding site to prevent conformational changes in gp120, thus preventing HIV from entering CD4 cells.[61] This medication is indicated as salvage therapy in heavily treatment-experienced patients. Temsavir is metabolized by esterases and CYP3A4 and is susceptible to drug-drug interactions with CYP3A4 inducers. Temsavir caused QTc prolongation at doses multiple-fold higher than those used clinically. Caution is advised in patients with a history of QTc prolongation or associated cardiac diseases, or in combination with other medications that may cause Torsades de Pointes.

InSTI options include bictegravir (BIC), cabotegravir (CAB), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL). Cabotegravir is the only InSTI available in both immediate release oral and long acting injectable forms. InSTIs bind to HIV integrase while it is in a specific complex with viral DNA and inhibit the strand transfer that incorporates the proviral DNA into the chromosomal DNA. InSTIs are active against HIV-1 and HIV-2. Cabotegravir, dolutegravir, and raltegravir are primarily glucuronidated by UGT1A1 and are not susceptible to major CYP-mediated drug interactions, although other kinds of interactions are important (Table 148-2). In particular, polyvalent cation containing antacids and mineral supplements bind InSTIs in the gut leading to reduced bioavailability. Recommendations vary on how to mitigate these interactions, including temporal separation (eg, elvitegravir and raltegravir), simultaneous administration with food (eg, bictegravir and dolutegravir), or consideration of an antacid with a different mechanism of action (eg, histamine-2 receptor antagonists or proton pump inhibitors). Bictegravir is metabolized by both UGT1A1 and CYP3A4 and is susceptible to interactions through both enzymatic pathways. Elvitegravir is extensively metabolized by CYP3A and is coformulated with cobicistat, a potent CYP3A inhibitor, to optimize drug exposure and enable once-daily dosing. InSTIs are relatively well tolerated with adverse events that include rash, nausea, and headache. This class of medications, particularly dolutegravir, has also been associated with CNS and psychiatric side effects (eg, insomnia, depression, and increased risk of suicidality) with a higher risk among those with a history of psychiatric conditions. InSTIs may also cause more weight gain than PIs or NNRTIs, with the greatest weight gain with bictegravir and dolutegravir.[62,63] InSTIs should be used with caution in advanced hepatic insufficiency. Multiple mutations have been identified conferring resistance to InSTIs, including cross-resistance as mutations accrue. Bictegravir and dolutegravir have a higher genetic barrier to resistance compared with elvitegravir and raltegravir.[58]

Capsid inhibitors interfere with multiple steps in the HIV replication cycle including migration of HIV-1 proviral DNA into the nucleus, viral assembly and release, and capsid core maturation. The capsid inhibitor lenacapavir is extremely potent (EC_{50} 30-190 pM) with a long plasma elimination half-life (11 days) making it suitable for long-acting formulations. Lenacapavir is available as a long-acting subcutaneous injection given every 26 weeks in conjunction with an oral loading dose. This medication is approved with an optimized background regimen for heavily-treatment experienced persons and is also under study as combination therapy for treatment naive individuals, as well as pre-exposure prophylaxis as a single agent. Lenacapavir is a substrate of PgP, UGT1A1, and CYP3A4 and is contraindicated with strong CYP3A4 inducers such as rifamycins and certain antiepileptics. It is a moderate CYP3A4 inhibitor, requiring caution with concomitant CYP3A4 substrates with narrow therapeutic indices. The main adverse effects with lenacapavir were mild to moderate injection site reactions. including pain, erythema, swelling, nodule,induration, pruritus, and rarely extravasation and mass. Nodules were typicallypalpable but not visible and may persist for months or longer. Several lenacapavir-associated resistance mutations were observed in clinical trials including single mutations conferring reduced activity, indicating a relatively low genetic barrier to resistance.

Novel antiviral agents in the classes listed above and agents in new drug classes that exploit other steps in the HIV life cycle (see Fig. 148-1) are in development, with a focus on long-lasting activity and/or high activity against drug-resistant virus.[64] Islatravir is a potent nucleoside analog reverse transcriptase/translocation inhibitor (translocation is the repositioning of reverse transcriptase after incorporating a nucleotide so it is ready to accept the next incoming nucleotide). Islatravir is being studied in long-acting formulations for up to six months duration as well. Long-acting antiretroviral therapy is emerging as a new treatment paradigm.

Drug Interactions

6 Medical use of antiretroviral agents is complicated by clinically significant drug-drug interactions that can occur with many of these agents.[38,65] Some interactions are beneficial and used purposely (eg, ritonavir and cobicistat as pharmacokinetic enhancers); others may be harmful, leading to dangerously elevated (eg, toxic) or inadequate drug concentrations (non-suppressive). Clinicians involved in the pharmacotherapy of HIV must understand the mechanistic basis for these interactions and maintain a current knowledge of drug interactions for these reasons.

Antiretroviral-associated drug interactions encompass a variety of mechanisms, including but not limited to: CYP3A-associated first-pass metabolism,

efflux and uptake drug transporters, and systemic clearance. The newer HIV PIs, NNRTIs (doravirine, etravirine, and rilpivirine), the CCR5 antagonist maraviroc, and the InSTI elvitegravir are extensively metabolized by CYP3A. In general, efavirenz, etravirine, and nevirapine are inducers of CYP3A, whereas the PIs and their pharmacoenhancers inhibit CYP3A. Ritonavir is a potent mechanism-based inhibitor of CYP3A-mediated metabolism and is now used exclusively at lower doses as a pharmacokinetic enhancer of other HIV PIs. Similarly, cobicistat, which is an analog of ritonavir without antiretroviral activity, is also a potent mechanism-based inhibitor of CYP3A activity and is used in a similar fashion. However, the interaction profiles for ritonavir and cobicistat differ and thus when switching between these agents, similar interactions cannot be assumed.[66] PIs and pharmacoenhancers also inhibit efflux (eg, P-glycoprotein and breast cancer resistance protein [BCRP]) and uptake transporters (eg, organic anion transporting polypeptide [OATP]), which contributes to the overall drug-drug interaction profile including certain statins (eg, rosuvastatin)[67] and the direct oral anticoagulant, dabigatran etexilate.[68] Some PIs including ritonavir induce transporters, making drug-drug interactions difficult to predict.

Darunavir and lopinavir must be taken with ritonavir or cobicistat to achieve optimal plasma concentrations. Atazanavir is also primarily used with ritonavir or cobicistat for the same reason, though it can be used without a pharmacoenhancer if dose adjusted. Many potential concomitant drugs on the market are substrates for CYP3A and drug transporters, and are therefore susceptible to clinically relevant drug interactions with lenacapavir, HIV PIs, NNRTIs, and pharmacoenhancers. Agents with narrow therapeutic indices and/or that exhibit major changes in pharmacokinetics with inhibitors or inducers of enzymes and/or transporters for which they are substrates are most important in this regard. Examples include, but are not limited to, simvastatin, lovastatin, corticosteroids (including inhaled, intranasal, and intraarticular), ergot derivatives, some antiarrhythmics, some erectile dysfunction drugs, some anticoagulants, and some anti-cancer agents.

The drug interaction potential of antimycobacterium agents, specifically the rifamycins, are particularly relevant, given the high potential for such infections in persons with HIV.[65] Rifampin and rifapentine, potent inducers of CYP3A metabolism and conjugation enzymes, are contraindicated with lenacapavir, HIV PIs, most NNRTIs, bictegravir, cabotegravir (oral and injectable), elvitegravir, and maraviroc because antiretroviral concentrations are reduced substantially even with ritonavir enhancement. Efavirenz should be administered as a 600 mg dose with rifampin; the 400 mg dose should not be used.[38] The usual dose of efavirenz can be used with rifapentine; dose adjustment is not required, which may be due in part to the concomitant use of isoniazid.[69] Raltegravir and dolutegravir doses should be increased in the presence of rifampin, with raltegravir dosing doubled and dolutegravir being administered twice daily. Dolutegravir and raltegravir do not require dose adjustment with once-weekly rifapentine, but should not be coadministered if rifapentine is administered once daily. The use of tenofovir alafenamide, a P-gp substrate, with rifamycins is also discouraged unless benefits outweigh risks and virologic response is closely monitored.[38,70,71] Tenofovir disoproxil fumarate does not require dose adjustment and may be a suitable alternative in these cases. Ritonavir enhancement generally allows coadministration of HIV PIs with rifabutin.[38,65] In such cases, the rifabutin dose will require adjustment, given its CYP3A-mediated clearance. Similarly, the herbal product St. John's wort (*Hypericum perforatum*) is a potent inducer of metabolism and is contraindicated with lenacapavir, PIs, NNRTIs, INSTIs, tenofovir alafenamide, and maraviroc.[38] The pharmacology of CYP3A interactions may be complicated by simultaneous induction/inhibition of drug transporter–mediated (eg, P-glycoprotein) bioavailability or clearance and/or other phase I (eg, CYP 2B6 for RTV) or phase II enzymes.

Some antiretroviral drugs require acidic environments for optimal absorption leading to interactions with antacids, particularly proton-pump inhibitors (eg, atazanavir, rilpivirine). On the other hand, some antiretroviral agents chelate polyvalent cations in antacids or mineral supplements, reducing absorption following coadministration (eg, InSTIs). Other potential mechanisms for drug interactions include inhibition of renal tubule secretion (eg, tenofovir and OAT inhibitors; inhibition of MATE and/or OCT2 by dolutegravir, bictegravir, and cobicistat), and antagonistic phosphorylation for NRTIs of the same nucleobase (eg, lamivudine and emtricitabine). This list of drug interactions and mechanisms for drug interactions is not complete. Clinicians who treat HIV must monitor for, and stay abreast of, antiretroviral drug interaction data. Websites are available that catalog and regularly update HIV drug-interaction information (http://www.hiv-druginteractions.org/), and the DHHS guidelines for antiretroviral use provide, and regularly update, excellent summaries of known clinically relevant drug interactions.[38]

Landmarks in the Evolution of Antiretroviral Therapy

7 ART has undergone major changes over the past decades. Illustrating these changes is important for a thorough understanding of current treatment strategies. The first landmark in this evolution was the availability of zidovudine, the first antiretroviral agent, which conferred a survival benefit in persons with AIDS, when given as monotherapy. A combination of two NRTIs was superior to zidovudine monotherapy in immunologic and virologic parameters, as well as survival benefit. Later, triple therapy (two NRTIs with an HIV PI or NNRTI) was associated with reduced incidence of OIs and improved survival, establishing the current paradigm of ART. Triple drug therapy has since evolved to include new drug classes (eg, INSTI),

coformulations, and better tolerated agents. This has in turn led to improvements in convenience, tolerability, safety, and virologic efficacy—enabling two drug therapy in some circumstances.

7 Taken together, these landmarks established that HIV should not be treated with single or dual NRTIs alone. Recommendations for initial treatment of most people with HIV now advocate a minimum of two active antiretroviral agents provided at least one in the regimen has a high barrier to resistance (eg, dolutegravir or boosted darunavir). Recommended initial regimens for most people with HIV comprise an InSTI with 1 to 2 NRTIs, and include bictegravir with tenofovir alafenamide plus emtricitabine; dolutegravir with tenofovir (as either tenofovir disoproxil fumarate or tenofovir alafenamide) plus emtricitabine; dolutegravir plus abacavir/lamivudine (abacavir can only be used in patients who are HLA-B*5701 negative); and dolutegravir with lamivudine (except in persons with baseline HIV viral loads >500,000 copies/mL (500×10^6/L), hepatitis B coinfection, or when antiretroviral therapy is to be initiated prior to the availability of hepatitis B serologic testing or HIV genotypic resistance testing). Multiple alternative regimens are also safe and effective, but have some disadvantages compared with those recommended for most persons with HIV such as dosing convenience (eg, the use of multiple tablets or twice daily administration), drug-drug interactions, weaker virologic responses with high viral loads, lower tolerability, or greater risk of long-term toxicities. Recommended antiretroviral regimens for initial therapy are listed in Table 148-2. Recommended first-line ART regimens constantly evolve and clinical controversies may emerge as data and clinical experience accrue and new strategies come under consideration, thus it is always advised to review the DHHS guidelines for the most updated ART recommendations.

Adherence

The simplest definition of adherence is the patient's follow-through on taking medication as directed. As with any chronic therapy, variable adherence to ART is common, and significantly impacts virologic response. Factors associated with poor adherence include major psychiatric illnesses, active substance use, unstable social circumstances, adverse events, and poor adherence with clinic visits.[38] Most, but not all, modern ART regimens consist of coformulations and long half-life drugs allowing for once-daily dosing (sometimes without food restrictions), which facilitates improved adherence compared with multiple dose units, multiple doses per day, and food restrictions with dosing. Average adherence rates are approximately 80% with antiretroviral regimens. Longer dosing "holidays" increase the risk of breakthrough viremia; however, newer regimens are more forgiving.[72] As clinicians, it is critical to establish a relationship of trust with the patient and to communicate to the patient the importance of proper medication taking. Education should be aimed at understanding the disease process, monitoring, goals of therapy, and consequences of poor adherence. An individual's "readiness" to take medications should be clearly established before treatment is initiated.[38] Help from caregivers, friends, and/or family members should be leveraged by the patient because social and psychological support are among the most important factors that influence adherence in this patient population. Strategies to encourage adherence, such as pill boxes, alarms, and setting a routine schedule should be discussed. Pharmacological approaches are among strategies being used to assess adherence objectively.[73]

Efficacy

Based on clinical trial data, more than 90% of patients will achieve undetectable viral loads with preferred and alternative ART regimens.[74-76] Given high efficacy across modern ART regimens, side effect profiles can help distinguish preferred versus alternative regimens. Starting with the nucleos(t)ide analog backbones, several studies have compared tenofovir alafenamide against tenofovir disoproxil fumarate, which have generally shown similar efficacy rates. Tenofovir disoproxil fumarate is associated with greater renal toxicity and bone demineralization, especially with the concomitant use of pharmacoenhancers,[77] whereas tenofovir alafenamide has been associated greater weight gain and lipid increases.[56] Abacavir–lamivudine combined with dolutegravir exhibits superior efficacy rates regardless of baseline viral load compared with efavirenz–tenofovir disoproxil fumarate–emtricitabine,[76] and similar efficacy rates to other InSTI combinations recommended for most people with HIV.[75] Together, these studies established recommendations for tenofovir disoproxil fumarate–emtricitabine or lamivudine, tenofovir alafenamide–emtricitabine, or abacavir–lamivudine as initial NRTI components of therapy. As mentioned above, if abacavir is to be used in any regimen, a test for the presence of HLA-B*5701 must be done as its presence has been strongly correlated with the development of abacavir hypersensitivity. Should this test be positive, an abacavir allergy should be added to the patient's medical record and abacavir should not be used in the patient, as the hypersensitivity reaction can be life-threatening.

The third active agent of ART regimens has also evolved based on large, randomized, controlled trials. Efavirenz and PIs maintained a long history as the recommended third active agent until comparative trials demonstrated poorer tolerability and more therapy discontinuations for efavirenz and PIs versus InSTIs.[76,78] Together, these and other studies support recommendations for InSTIs as third active agents for initial ART in most people with HIV.

Many agents are available for inclusion in regimens recommended in certain clinical situations, including NNRTIs (eg, doravirine, efavirenz, or rilpivirine) or PIs (darunavir and atazanavir boosted with either cobicistat or ritonavir).[38] Dual ART therapy may also be considered in situations where the use of tenofovir disoproxil fumarate, tenofovir alafenamide, or abacavir are not optimal choices. Dual ART regimens for initial therapy include more potent agents (dolutegravir plus lamivudine[79] and darunavir/ritonavir plus either lamivudine or raltegravir) and have evidence supporting their use in patients who are not ideal candidates for other recommended ART regimens. Clinicians are urged to consult the most recommended preferred and alternative regimens, as they are continuously updated with new studies and as longer-term follow-up data accrue.

Regimen Simplification and Long-Acting Therapies

Patients with sustained undetectable HIV-RNA taking out-of-date drug regimens may be candidates for simplification to one of the recommended regimens as previously described, or a more desirable alternative regimen based on past treatment history and other patient-specific factors. There are two additional dual antiretroviral combinations that may be considered in participants who are suppressed: dolutegravir with rilpivirine,[80] and long-acting intramuscular injectable cabotegravir with rilpivirine. As these drugs do not have activity against hepatitis B, they should be avoided in persons with HIV and hepatitis B coinfection. Screening for drug-drug interactions and avoiding use in individuals with resistance mutations to individual drug components is also critical to avoid therapeutic failure. Dolutegravir with rilpivirine is available as a coformulated tablet, and this regimen has shown high rates of continued virologic suppression following ART switch.

Cabotegravir with rilpivirine represents the first long-acting injectable combination approved for this indication. Studies with intramuscular cabotegravir/rilpivirine demonstrated noninferiority to oral ART.[81] This combination is only recommended in persons with HIV who have been suppressed and on stable ART for at least 3 to 6 months.[38] Cabotegravir with rilpivirine also cannot be used in pregnant or breastfeeding women until additional data supporting its use are available in this population. An oral lead-in period for 28 days is optional to ensure tolerability before starting the injections. The first intramuscular injection of cabotegravir with rilpivirine is given as a loading dose on the last day of oral therapy (600 mg [3 mL] of cabotegravir and 900 mg [3 mL] of rilpivirine), and then is administered as a maintenance dose (400 mg [2 mL] of cabotegravir and 600 mg [2 mL] of rilpivirine) every 4 weeks thereafter. Injections are administered intramuscularly into the gluteal muscle. Alternatively, 600 mg [3 mL] of cabotegravir and 900 mg [3 mL] can be given as a maintenance dose every 8 weeks. Every 2 months has been approved now and the oral lead-in is optional so made updates throughout to reflect this. A window period of 7 days is allowed around scheduled doses for unforeseen circumstances, but gaps beyond 7 days may require bridging with oral therapy to ensure that subtherapeutic exposures do not occur. The most common side effects are mild-moderate injection site reactions (>80%) that generally decrease over time. Despite the high rates of injection site reactions, over 90% of participants in clinical trials still preferred long-acting injectable options over daily oral ART. Other long-acting therapies in development such as lenacapavir (currently only approved for treatment-experienced persons) and islatravir hold great promise to further expand options for people living with HIV.[64]

Resistance

9 Regimen failure may be associated with antiretroviral resistance, and testing for such resistance is a useful clinical tool.[38,58] The two types of resistance tests available are phenotype and genotype. A phenotype test determines the concentration of antiretroviral agent necessary to inhibit replication of the patient's viral isolate by 50% (inhibitory concentration of 50% [IC_{50}]) in a recombinant in vitro viral assay. Results usually are expressed as a fold change in susceptibility (IC_{50}) compared with a wild-type laboratory strain virus. Generally, the fold-change in IC_{50} increases as HIV accumulates additional mutations that confer resistance to a particular drug. However, a single mutation may confer a high fold-change in IC_{50} for some drugs (eg, lamivudine, emtricitabine, efavirenz, nevirapine), rendering them ineffective after a single mutation. Although small-to-moderate increases in the fold change suggest reduced susceptibility to that antiretroviral agent, resistance may not be absolute, and partial susceptibility may remain. Theoretically, drug concentrations may be increased to overcome reduced susceptibility. The strength of phenotypic testing is to provide resistance information for complex mutation patterns, but it is also associated with higher cost, limited number of commercial providers, and slower turnaround time for results. Genotyping assesses genetic mutations and associated codon changes in gp41, reverse transcriptase, integrase, or protease in the patient's virus and compares it with the wild-type sequence. Certain mutations are known to confer resistance to specific drugs. An updated list of drug resistance mutations can be found at https://www.iasusa.org/resources/hiv-drug-resistance-mutations/, and the Stanford HIVdb Program also has useful tools for analyzing HIV drug resistance mutations: https://hivdb.stanford.edu/. Mutations are listed by the wild-type amino acid followed by the position in the protein or enzyme and end with the mutation found in the patient's virus. For example, a common mutation caused by lamivudine and emtricitabine is the M184V mutation: a substitution of valine (V) for methionine (M) at the 184 position of reverse transcriptase.

Mutations can confer varying degrees of antiretroviral drug resistance and in some cases, weighting algorithms have been developed to predict the relative impact of mutation combinations on antiretroviral activity. Algorithms have also been developed to predict a phenotype from a genotype test (ie, virtual phenotype). Resistance mutations may not be purely detrimental, for example, while M184V confers significant resistance to lamivudine and emtricitabine, it is also associated with a less fit virus. Interpretation of genotype resistance tests is complex; the reader is encouraged to obtain expert advice and consult the most recent guidelines on HIV resistance testing.

Treatment of Special Populations

Pregnancy

Several considerations are relevant to the treatment of pregnant persons, including the health of the mother, prevention of HIV transmission to the fetus, potential for teratogenicity, and drug dosing issues based on pharmacokinetic changes during pregnancy. Treatment recommendations should be consulted to address the specific requirements for pregnant people with HIV and the prevention of vertical transmission.[19] Generally, pregnant people should be treated as would nonpregnant people, with the goal of maximally suppressing HIV-RNA. Pregnant people already on a suppressive regimen may remain on their current therapy unless there are known safety or efficacy concerns with the combination that they are taking. Preferred initial regimens for HIV treatment during pregnancy include a dual NRTI backbone (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine) with either an InSTI (dolutegravir or raltegravir) or boosted PI (atazanavir/ritonavir or darunavir/ritonavir). Alternative options include tenofovir alafenamide/emtricitabine or zidovudine/lamivudine for a dual NRTI backbone, and efavirenz or rilpivirine with one of the recommended NRTI backbones.

Efavirenz was historically avoided in persons planning to become pregnant due to concerns of neural tube defects, but a large-scale clinical study and ongoing monitoring of the Antiretroviral Pregnancy Registry (http://www.apregistry.com/HCP.aspx) have since shown no increased risk of birth defects with efavirenz in comparison to other ART options or background rates in pregnant people without HIV. Dolutegravir use at the time of conception was also associated with a higher rate of neural tube defects in infants in a preliminary analysis from the Tsepamo study. Long-term follow-up with additional women showed lower rates and the difference was no longer statistically significant, and other studies have not shown a signal.[19] Nonetheless, the potential risks and known benefits of dolutegravir treatment should be discussed with people of child-bearing potential. Cobicistat-containing regimens should be avoided in pregnancy as exposures to cobicistat and coformulated medications (ie, atazanavir, darunavir, and elvitegravir) are significantly reduced during pregnancy, which may increase the risk of treatment failure and perinatal HIV transmission.[19,82] If a person becomes pregnant while on one of these regimens, consideration should be given toward switching therapy, which may also carry its own risk of breakthrough, or more frequent viral load monitoring may be performed. Infants born to people with HIV require prophylaxis to prevent HIV transmission, and the exact recommendations vary depending on the maternal viral load, treatment history, and level of risk for transmission. Zidovudine is recommended intrapartum depending on the mother's viral load (more than 1,000 copies/mL [1×10^6/L] or unknown), based on early studies demonstrating clear prophylactic effectiveness as well as extensive familiarity with the side effect profile.[19] Infants considered low risk for perinatal HIV transmission (ie, maternal viral load suppressed at delivery and no adherence concerns) should receive zidovudine prophylaxis for 4 weeks after birth. Infants considered high risk (ie, mother received either no antepartum or intrapartum ART, only intrapartum ART, or antepartum ART but did not achieve viral suppression) should receive presumptive HIV treatment with zidovudine/lamivudine and either nevirapine or raltegravir from birth through 6 weeks of age. Perinatal HIV transmission has been reduced to less than 0.5% for pregnant people who are treated with ART and when infant prophylaxis is used. Breastfeeding is not recommended in the United States, but in resource-limited settings where lack of clean water makes breastfeeding a more favorable option, infants should receive additional prophylaxis.[49]

Preventing HIV Transmission

HIV treatment is a necessary component of reducing HIV-associated morbidity and mortality. However, it is also critical for preventing new HIV transmissions from occurring. There are several approaches for preventing new HIV transmissions as detailed in this section. Pharmacists play an important role in both treating and preventing HIV, and some states now allow pharmacists to prescribe and dispense HIV pre- and postexposure prophylaxis (PEP) in recognition of the critical role that pharmacists play in this cascade.

Undetectable Equals Untransmittable (U=U)

Undetectable equals untransmittable ("U=U," or Treatment as Prevention [TasP]) refers to the concept that people with HIV who achieve and maintain

suppressed or undetectable viral loads (meaning viral loads <200 copies/mL [200 × 10^3/L)) do not sexually transmit HIV to others.[6] This was demonstrated through multiple clinical studies that evaluated serodiscordant (ie, one partner with HIV and one without HIV) heterosexual and male-male couples. No linked HIV transmissions occurred between couples when the partner with HIV maintained a suppressed viral load. U=U requires persons with HIV to remain adherent to their prescribed ART and thus maintain suppression (exact length varies by duration of therapy and confirmation of viral suppression).[38,83] Individuals should be counseled on the need to remain adherent with routine viral load monitoring if solely following the U=U strategy and should still undergo routine STI screening. Partners without HIV should still be offered PrEP, particularly if unsure whether their partner's viral load is undetectable, if they have multiple sexual partners, or if they feel more comfortable taking PrEP. PEP should also be offered in cases where the partner with HIV has been inconsistently taking ART or is no longer suppressed. Condom use can help prevent other STIs. U=U does not cover other routes of HIV transmission, such as breastfeeding, sharing of drug injection equipment, or needlestick injuries.

Postexposure Prophylaxis (PEP)

Protection of people from potential HIV exposure is an important concern. The CDC has issued guidelines governing antiretroviral PEP of occupational (oPEP) and other non-occupational HIV exposures (nPEP) that should be consulted for updates as the knowledge in this field evolves.[13,16] Occupational exposures are those that happen in a work setting, most commonly needlestick injuries in healthcare workers, whereas non-occupational exposures occur outside of work, such as condomless intercourse or injection drug use. The principles are to assess the exposure risk and treat as soon as possible after high-risk exposures to prevent HIV infection. Assessing the exposure risk requires knowledge of the HIV-infection status of the source individual, which may be difficult to ascertain. The HIV status of the source should be determined as soon as possible with a rapid HIV test, whenever feasible. However, providers may have to rely on reasonable suspicion when this is not possible, so provider expertise is essential. PEP should not be delayed while waiting on the HIV status of the source if reasonable suspicion is present. PEP should be considered an urgent medical situation. The guidelines as of October 2021 recommend conventional ART regimens as summarized in Table 148-4, initiated as soon as possible and within a maximum of 72 hours of the potential exposure. Animal studies show reduced PEP efficacy when initiated 72 hours or more after the exposure.[16] The optimal duration of treatment is unknown, but at least 4 weeks of therapy is advocated. Expert consultation is needed when exposure to drug-resistant virus is suspected or confirmed to optimize the PEP regimen, but this should not delay initial initiation of PEP.

TABLE 148-4

Recommended Regimens for Occupational and Non-occupational Postexposure Prophylaxis

Population	Ranking	Regimen
Occupational postexposure prophylaxis (oPEP)		
Healthcare workers	Preferred	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg once daily + raltegravir 400 mg twice daily
	Alternative	Consult guidelines
Non-occupational postexposure prophylaxis (nPEP)		
Adults and adolescents ≥13 years, including pregnant persons, and normal renal function (CrCl ≥60 mL/min [1.0 mL/s])	Preferred	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg once daily + raltegravir 400 mg twice daily *OR* dolutegravir 50 mg once daily
	Alternative	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg once daily + darunavir 800 mg/ritonavir 100 mg once daily
Adults and adolescents ≥13 years, including pregnant persons, and renal dysfunction (CrCl <60 mL/min [1.0 mL/s])	Preferred	Zidovudine/lamivudine (dose-adjusted per CrCl) + raltegravir 400 mg twice daily *OR* dolutegravir 50 mg once daily
	Alternative	Zidovudine/lamivudine (dose-adjusted per CrCl) + darunavir 800 mg/ritonavir 100 mg once daily

Data from References 13 and 16.

Preexposure Prophylaxis (PrEP)

Preexposure prophylaxis (PrEP) involves the use of antiretroviral medications to prevent HIV. There are now three FDA-approved options for use in persons without HIV and at risk of HIV acquisition, to prevent infection should an HIV-exposure occur. These include oral emtricitabine with tenofovir (either in the form of tenofovir disoproxil fumarate or tenofovir alafenamide) and long-acting injectable cabotegravir. PrEP is effective in MSM, sero-discordant couples, and heterosexual men and women, including those who inject drugs, though the exact PrEP combinations that are approved in each of these populations vary based on available data (see Table 148-5).[36,84]

TABLE 148-5

Recommended Regimens for Preexposure Prophylaxis

PrEP Option	Emtricitabine with Tenofovir Disoproxil Fumarate	Emtricitabine with Tenofovir Alafenamide	Cabotegravir
Initial FDA approval	2012	2019	2021
Administration route	Oral	Oral	IM injection
Indication	Persons at risk through sex or injection drug use[a]	Persons weighing at least 35 kg (77 lb) who are at risk through sex, excluding people at risk through receptive vaginal sex.	Persons at-risk through sex
Dosing	Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg	Emtricitabine 200 mg/enofovir alafenamide fumarate 25 mg	Oral: 30 mg
			IM injection: 600 mg (3 mL)
	On-demand strategy also possible ("2-1-1")[b]	On-demand strategy not recommended (no data)	On-demand strategy not recommended (no data)
Dosing frequency	Once daily	Once daily	Oral lead-in: once daily
			IM injection: once monthly × first 2 months then every 2 months thereafter
HIV monitoring[c]	Every 3 months	Every 3 months	Month 1 visit and every 2 months thereafter
Safety monitoring	Renal[d]	Renal[d], lipids	None
	Optional: bone density	Optional: bone density	
Side effects	"Start-up syndrome" during 1st month; headache, abdominal pain, weight loss	"Start-up syndrome" during 1st month; diarrhea, weight gain	Injection site reactions, headache, fever, fatigue, myalgia, rash
Use in renal impairment	CrCl ≥60 mL/min (1.0 mL/s)	CrCl ≥30 mL/min (0.5 mL/s)	Can be used; no restrictions

[a]Only TDF has been studied in persons who inject drugs, but this population is expected to benefit from all systemic PrEP forms.

[b]Only MSM: 2 pills 2-24 hours before sex (closer to 24 hours preferred), 1 pill 24 hours after first dose, 1 pill 48 hours after first dose. If sex occurs the day after completing the 2-1-1 series, continue taking 1 pill daily until 48 hours after the last sexual event. If sex occurs <7 days from the last 2-1-1 dose, resume 1 pill daily. If sex occurs ≥7 days between the last pill and next sexual event, reinitiate with 2 pills.

[c]Consists of laboratory testing (antigen, antibody, and HIV-1 RNA [PCR]) and assess for signs/symptoms of acute HIV infection.

[d]Renal function should be assessed every 6 months for persons ≥50 years of age or with CrCl <90 mL/min (1.5 mL/s) and every 12 months in all other patients.

Data from References 36 and 103.

All sexually active adults and adolescents should be informed about PrEP. Prior to initiating PrEP, a negative HIV test should be documented, including negative symptoms of acute HIV infection. Reports of drug resistance from oral PrEP failures were mostly among individuals who initiated PrEP during acute HIV infection, in the window period before the rapid HIV test could detect infection. HIV acquisition during PrEP (especially for cabotegravir) can be challenging to diagnose because of prolonged HIV suppression and delayed antibody expression. HIV testing should be repeated at least every 3 months for those on oral PrEP, and for persons on cabotegravir, HIV testing is recommended at the month 1 visit (second injection) and then every 2 months thereafter (beginning with the third injection). Promotion of adherence and screening for potential drug-drug interactions is critical for PrEP effectiveness. It is also critical to continue routinely screening for STIs (all persons on PrEP) and hepatitis C virus (MSM, transgender women, and persons who inject drugs) as PrEP does not protect against these infections.

The most up-to-date PrEP guidelines should be consulted, as new PrEP strategies are under evaluation. Topical virucidal or antiretroviral drug formulations for use vaginally or rectally to prevent sexual transmission of HIV are in various phases of development. Use of a dapivirine ring resulted in a ~30% reduction in HIV acquisition, leading to review by the European Medicines Agency (EMA) for HIV prevention in women.[11]

EVALUATION OF THERAPEUTIC OUTCOMES

Two laboratory tests are used to evaluate response to ART: the plasma HIV-RNA and CD4 cell counts.[38] These tests should be performed at baseline, along with a medical history and physical, urinalysis, hematology, chemistries, serologies for coinfections, and patient education about HIV infection. An HIV resistance test is recommended upon initiation of care. After therapy is initiated, patients are generally monitored at 3-month intervals until HIV-RNA reaches undetectable levels. An assessment at 2 to 8 weeks is warranted to document early response. Monitoring may be increased to every 6 months in stabilized patients.

The two main indications for a change in therapy are significant toxicity and treatment failure. Should a single agent be responsible for an intolerable side effect that agent often can be singly changed out of the regimen. For example, the patient who experiences intolerable CNS disturbances during initiation of efavirenz can switch to a boosted PI or InSTI without changing the dual NRTI backbone. Maintaining virologic suppression is an important goal for switching therapy due to adverse events. Caution must be exercised when drugs in the regimen have overlapping toxicities, which makes changing a single agent problematic. Serious and life-threatening toxicities warrant cessation of the whole regimen before deciding upon a subsequent therapy.

As a general guide, the inability to achieve and maintain less than 200 copies/mL (200×10^3/L) of HIV-RNA represents treatment failure and should prompt consideration for changing therapy. This includes the inability to achieve less than 200 copies/mL (200×10^3/L) by 24 weeks of therapy initiation (repeat testing is suggested to confirm), or, after HIV-RNA suppression, repeated detection of greater than 200 copies/mL (200×10^3/L) of HIV-RNA.

Therapeutic Failure

The most important measure of therapeutic failure is suboptimal suppression of viral replication. Many reasons may underlie suboptimal suppression of viral replication such as pre-ART disease factors (eg, high viral load or preexisting drug resistance), nonadherence to medication, development of new drug resistance, intolerance to one or more medications, adverse drug-drug or drug-food interactions, or pharmacokinetic-pharmacodynamic variability.[38] In cases of suboptimal suppression of viral replication, these potential causes should be investigated and addressed, if possible. As a general rule, drug resistance develops for regimens that do not maximally suppress HIV replication. Drug resistance testing is recommended while the patient is undergoing the failing regimen or within 4 weeks after stopping the regimen as long as the HIV-RNA count is greater than 500 copies/mL (500×10^3/L), which is the threshold for most resistance assays (~500-1,000 copies/mL [$\sim 500 \times 10^3$–1.0×10^6/L]). Virus may revert to wild type if more than 4 to 6 weeks has elapsed between regimen discontinuation and the resistance test. Most clinicians use the genotype assay because it is less expensive and results typically are available sooner compared with the phenotype assay. Resistance results usually require expert interpretation.

Treating patients who have drug-resistant HIV utilizes the same general treatment approaches described for initial therapy above. Several

antiretroviral drugs are well-suited for drug-resistant HIV. The drugs in the newer classes (ie, InSTIs, entry inhibitors, capsid inhibitors) are also active against NRTI-, NNRTI-, and PI-resistant viruses in highly treatment-experienced patients in controlled trials.[38] Patients should be treated with at least two (preferably three) fully active antiretroviral drugs from different mechanistic classes based on medication history and resistance tests. The goal of therapy is to suppress HIV-RNA to undetectable levels. In cases when undetectable HIV-RNA cannot be attained, maintenance on the regimen is preferred over drug discontinuation so as to prevent rapid immunological and clinical decline.

Prior to the availability of new drugs and drug classes, other strategies were studied to help manage therapeutic failure including drug holidays, structured or strategic treatment interruptions, and structured intermittent therapy. The overall premise of these strategies was similar: stop all antiretrovirals to spare the patient from drug toxicities and to allow the virus to revert to wild type. Reinitiation of therapy was intended to reestablish control of viral replication, as wild-type virus would be expected to predominate, although it was known that resistant virus was archived in long-lived cells, so viral suppression was short lived. Patients randomized to episodic therapy (drug-sparing) guided by the CD4 experienced significantly increased risk of opportunistic disease or death from any cause, including non-AIDS causes.[85,86] Viral replication is damaging to the immune system and end organs and drug-sparing approaches are not advocated.

HIV CURE RESEARCH

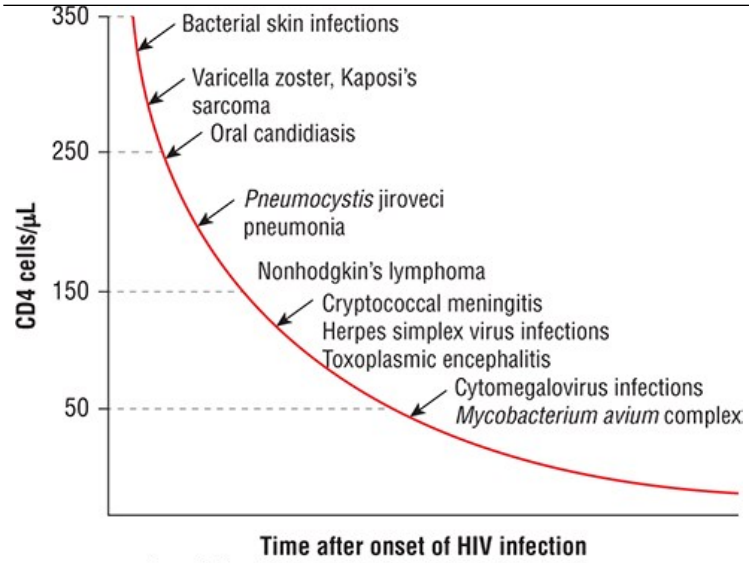
In 2007, the “Berlin patient,” a person with HIV and new-onset acute myeloid leukemia, underwent an allogeneic bone marrow transplant with homozygous CCR5delta32 stem cells.[87] Following a complicated clinical course, including graft versus host disease and second transplant, he was found to be free of HIV infection, as no virus could be detected in any sample tested in 2009. This was deemed a sterilizing cure and his case gave hope to researchers and patients alike for curing HIV infection. In 2019, a second person, the “London Patient,” has been reported as cured of HIV infection. Replicating these individuals’ treatment and clinical course, however, is not a practical or safe strategy for most persons living with HIV infection. Developing a cure will be particularly challenging because HIV integrates its genome into host cells, creating a latent reservoir. Thus, researchers have begun focusing on creating “functional cures,” where new treatments might allow patients to stop ART without disease progression. Ongoing clinical trials are evaluating such approaches.

COMPLICATIONS OF HIV INFECTION AND AIDS

In the pre-ART era, the major therapeutic focus was prevention and treatment of OIs associated with uncontrolled HIV replication and the steady decline in CD4 cells. Uncontrolled HIV is an insidious disease; persons often present with OIs, a consequence of the weakened immune system rather than HIV per se. Most OIs are caused by organisms that are common in the environment and often represent the reactivation of quiescent, hidden infections common in the population. The probability of developing specific OIs is closely related to CD4 count thresholds (Fig. 148-2). These CD4 thresholds serve as a basis for initiating primary OI chemoprevention.

FIGURE 148-2

Natural history of opportunistic infections associated with human immunodeficiency virus infection. CD4 counts expressed as cells/μL can be converted into SI units by multiplying by 10^6/L.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

5 In the ART era, the main principle in the management of OIs is treating HIV infection to enable CD4 cell recovery and maintenance above protective levels.[65] Additional important principles regarding management of OIs are as follows:

1. Prevent exposure to opportunistic pathogens
2. Vaccinate to prevent first-episode disease (consult HIV-specific guidelines)
3. Use primary chemoprophylaxis at certain CD4 thresholds to prevent first-episode disease
4. Treat emergent OI
5. Use secondary chemoprophylaxis to prevent disease recurrence
6. Discontinue prophylaxes with sustained ART-associated immune recovery

Several considerations are required for the patient who presents with an OI and is simultaneously diagnosed with HIV and who thus needs both OI and ART treatment. Immediate initiation of ART is indicated for OIs that respond to CD4 recovery, such as cryptosporidiosis, progressive multifocal leukoencephalopathy (JC virus), and mild-to-moderate Kaposi's sarcoma (HHV8 virus). Rapid initiation of ART (within days to weeks) is also indicated in the setting of other OIs such as tuberculosis, *Mycobacterium avium* complex (MAC), and PCP, but several potential issues need consideration. First, drug-drug interactions and the complexity of adhering to concomitant ART and OI regimens can be daunting. Careful review of potential interactions and adherence support should be provided. Second, clinicians must be cognizant of potentially overlapping drug toxicities (eg, rash) that create problems when attempting to stop the perceived culprit drug. Third, an immune reconstitution inflammatory syndrome (IRIS) has been associated with initiation of ART in the presence of underlying OIs. IRIS is generally characterized by fever and worsening of OI manifestations in the first few weeks to months after initiating ART despite evidence of treatment efficacy. Risk factors for IRIS are a low CD4 count (eg, less than 50 cells/μL [0.050 × 10^9/L]) and a high antigenic burden. An ART-associated rapid-onset immune reconstitution against the smoldering OI infection, and resulting proinflammatory cytokine cascade, is the mechanism of IRIS. The most serious IRIS reactions involve neurological OIs such as cryptococcal meningitis, where IRIS can lead to increased morbidity and mortality. For cryptococcal meningitis, it may be prudent to delay ART until completion of the induction or induction/consolidation phase of antifungal therapy (up to 10 weeks). Generally, treatment of IRIS is supportive and may include corticosteroids and/or NSAIDs, depending on the OI. Expert consultation should be used in the management of ART initiation in patients with advanced HIV infection and OIs, and the most up-to-date guidelines should be consulted.

The epidemiology of specific OIs can depend upon geographical region.[49,65] For instance, TB is particularly endemic on the African continent and is considered a major OI in that region, but the incidence of TB is relatively uncommon in the United States. Major OIs in the United States include PCP,

toxoplasmosis, MAC, cytomegalovirus retinitis, and cryptococcal meningitis. All have decreased substantially in incidence with the advent of ART. Furthermore, primary and secondary chemoprophylaxis for specific OIs have contributed to the same decreases. Nevertheless, opportunistic diseases continue to be complications of HIV disease and occur at low CD4 lymphocyte counts in patients who are unaware of their HIV infection, or who have not responded to ART therapy or OI prophylaxis because of adherence issues or inadequate engagement with the healthcare system.

Selected OIs and recommended first-line regimens for OI treatment are given in Table 148-6. Recommended therapies for primary OI prophylaxis are given in Table 148-7.[65] These recommendations are representative and not as extensive as in the published guidelines, which include multiple additional treatment considerations and alternatives, as well as coverage of less common OIs. The following brief discussion of PCP provides a more in-depth overview of the epidemiology, diagnosis, clinical manifestations, and results of treatment and serves as an illustration for the principles discussed above.

TABLE 148-6

Selected Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals

Clinical Disease	Preferred Initial Therapies for Acute Infection in Adults (Strength of Recommendation in Parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
Fungi		
Candidiasis, oral	Fluconazole 100 mg orally for 7-14 days (AI) *Or* Nystatin 500,000 units oral swish (~5 mL) four times daily for 7-14 days (BII)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting Taste, patient acceptance
Candidiasis, esophageal	Fluconazole 100-400 mg orally or IV daily for 14-21 days (AI) *Or* Itraconazole 200 mg/day orally for 14-21 days (AI)	Same as above Elevated liver function tests, hepatotoxicity, nausea, and vomiting
Pneumocystis jirovecii pneumonia	*Moderate to severe episodes* Trimethoprim–sulfamethoxazole IV or orally 15-20 mg/kg/day as trimethoprim component in three to four divided doses for 21 days[a] (AI) moderate or severe therapy should be started IV *Mild-to-moderate episodes* Trimethoprim–sulfamethoxazole 15-20 mg/kg/day as trimethoprim component orally in three divided doses or trimethoprim–sulfamethoxazole double strength tablets, two tablets three times daily	Skin rash, fever, leucopenia Thrombocytopenia
Cryptococcal meningitis	Liposomal amphotericin B 3-4 mg/kg/day IV with flucytosine 100 mg/kg/day orally in four divided doses for a minimum of 2 weeks (AI) *followed by*	Nephrotoxicity, hypokalemia, anemia, fever, chills Bone marrow suppression
	Fluconazole 800 mg/day, orally for 8 weeks. (AI)[a] Doses can be reduced to 400 mg orally once daily in clinically stable patients with negative CSF cultures. (AIII)[a]	Same as above
Histoplasmosis	Liposomal amphotericin B 3 mg/kg/day IV for 2 weeks (AI) *followed by*	Same as above
	Itraconazole 200 mg orally thrice daily for 3 days then twice daily, for 12 months (AII)[a]	

Coccidioidomycosis	Amphotericin B deoxycholate 0.7-1.0 mg/kg IV daily (AII) or lipid formulation amphotericin B 4-6 mg/kg IV daily (AIII) until clinical improvement, then switch to an azole (BIII) *Or* Fluconazole 400-800 mg IV or PO once daily (meningeal disease) (AII)[a]	Same as above Same as above
Protozoa		
Toxoplasmic encephalitis	Pyrimethamine 200 mg orally once, followed by weight-based therapy: • If <60 kg, pyrimethamine 50 mg orally once daily • If >60 kg, pyrimethamine 75 mg orally once daily *Plus* • If <60 kg, sulfadiazine 1 g orally four times daily • If >60 kg, sulfadiazine 1.5 g orally four times daily *And* Leucovorin 10-25 mg orally daily for 6 weeks (AI)[a]	Bone marrow suppression Rash, drug fever
Isosporiasis	Trimethoprim and sulfamethoxazole: 160 mg trimethoprim and 800 mg sulfamethoxazole orally or IV four times daily for 10 days (AII)[a]	Same as above
Bacteria		
Mycobacterium avium complex	Clarithromycin 500 mg orally twice daily, *plus* ethambutol 15 mg/kg/day orally (AI) for at least 12 months	GI intolerance, optic neuritis, peripheral neuritis, elevated liver tests
Salmonella enterocolitis or bacteremia	Ciprofloxacin 500-750 mg orally (or 400 mg IV) twice daily for 14 days (longer duration for bacteremia or advanced HIV) (AIII)	GI intolerance, headache, dizziness
Campylobacter enterocolitis (mild to moderate)	Ciprofloxacin 500-750 mg orally (or 400 mg IV) twice daily for 7-10 days (or longer with bacteremia) (BIII)	Same as above
Shigella enterocolitis	Ciprofloxacin 500-750 mg orally (or 400 mg IV) twice daily for 7-10 days (*or* >14 days for bacteremia) (AIII)	Same as above
Viruses		
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg IV every 8 hr until lesions regress, then acyclovir 400 mg orally three times daily until complete healing (famciclovir or valacyclovir is alternative) (AIII)	GI intolerance, crystalluria
Primary varicella-zoster	Acyclovir 10-15 mg/kg every 8 hr IV for 7-10 days (severe cases), then switch to oral valacyclovir 1 g three times daily after defervescence if no evidence of visceral involvement (famciclovir or acyclovir is alternative) (AIII)	Obstructive nephropathy, CNS symptoms
Cytomegalovirus (retinitis)	Ganciclovir 5 mg/kg IV every 12 hr or valganciclovir 900 mg orally twice daily for 14-21 days (AI) with or without: Intravitreal ganciclovir (2 mg) or foscarnet (2.4 mg) for 1-4 doses over 7-10 days (for sight threatening lesions) *plus* valganciclovir 900 mg twice daily for 14-21 days then once daily until	Neutropenia, thrombocytopenia

	immune recovery from ART (AIII)[a]	
Cytomegalovirus esophagitis or colitis	Ganciclovir 5 mg/kg IV every 12 hr for 21-42 days; may switch to valganciclovir 900 mg orally every 12 hr when oral therapy can be tolerated (BI)	Same as above

[a]Maintenance therapy is recommended.

ART, antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

See Table 126-3 for levels of evidence-based recommendations.

Data from Reference 66.

TABLE 148-7

Therapies for Prophylaxis of Select First-Episode Opportunistic Diseases in Adults and Adolescents

Pathogen	Indication	First Choice (Strength of Recommendation in Parentheses)
Standard of care		
Pneumocystis jirovecii	$CD4^+$ count <200/mm^3 (<0.2 × 10^9/L) *or* oropharyngeal candidiasis	Trimethoprim–sulfamethoxazole, one double-strength tablet orally once daily (AI) or one single-strength tablet orally once daily (AI)
Histoplasma capsulatum	$CD4^+$ count <150/mm^3 (<0.15 × 10^9/L) endemic geographic area and high risk for exposures	Itraconazole 200 mg orally once daily (BI)
Mycobacterium tuberculosis		
Isoniazid-sensitive	(Active TB should be ruled out): positive test for latent TB infection with no prior TB treatment history (AI) *Or* negative test for latent TB infection, but close contact with case of active tuberculosis (AII)	Rifapentine (weight-based) orally plus isoniazid 900 mg orally plus pyridoxine 50 mg orally once weekly for 12 weeks (AII) Rifapentine Weekly Dose: • 32.1-49.9 kg: 750 mg • >50 kg: 900 mg *Or* Isoniazid 300 mg plus rifampin 600mg plus pyridoxine 25–50 mg orally daily for 3 months (AI) Rifapentine only recommended for persons receiving RAL-, EFV- or once daily DTG-based ART regimen
For exposure to drug-resistant TB	Consult public health authorities	
Toxoplasma gondii	Immunoglobulin G antibody to *Toxoplasma* and $CD4^+$ count <100/mm^3 (<0.1 × 10^9/L)	Trimethoprim–sulfamethoxazole one double-strength tablet orally once daily (AII)
Mycobacterium	$CD4^+$ count <50/mm^3 (<0.05 × 10^9/L)	Azithromycin 1,200 mg orally once weekly (AI) or 600 mg orally twice

avium complex		weekly (BIII) *Or* Clarithromycin 500 mg orally twice daily (AI)
Varicella zoster virus (VZV)	Preexposure: CD4 ≥200/mm^3 (≥0.2 × 10^9/L), no history of varicella vaccination or infection, or, if available, negative antibody to VZV Postexposure: Significant exposure to chicken pox or shingles for patients who have no history of vaccination or either condition or, if available, negative antibody to VZV	Varicella vaccination; two doses, 3 months apart (BIII) Varicella-zoster immune globulin, 125 IU per 10 kg (maximum of 625 IU) IM, as soon as possible and within 10 days after exposure (AIII)
Streptococcus pneumoniae	Any individual regardless of CD4 count	13-valent polysaccharide vaccine, 0.5 mL intramuscularly once (AI) followed by 23-valent polysaccharide vaccine 0.5 mL 8 weeks later (CIII) Re-vaccinate with PPV23 0.5 mL IM one time (BII) if the following: • Aged 19-64 years and >5 years since first PPV23 dose • Final dose to be given at >65 years, and if >5 years since the previous PPV23 dose • Typically, no more than 3 doses of PPV23 in a lifetime
Hepatitis B virus	All susceptible patients	HBV vaccine IM (Engerix-B 20 µg/mL or Recombivax HB 10 µg/mL), 0, 1, and 6 months (AII) Anti-HBs should be obtained 1 month after the vaccine series completion (BIII)
Influenza virus	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine (annual): 0.5 mL intramuscularly (AIII) (live-attenuated vaccine is contraindicated in all persons with HIV)
Hepatitis A virus	All susceptible (anti-hepatitis A virus–negative) patients at increased risk for hepatitis A infection (eg, chronic liver disease, injection drug users, men who have sex with men)	Hepatitis A vaccine: two doses at 0 and 6-12 months (AII) antibody response should be assessed 1 month after vaccination; with revaccination as needed when CD4 >200 cells/µL (>0.2 × 10^9/L)(BIII)
Human papillomavirus (HPV) infection	Target age for vaccination: 11-12 years (AIII) Vaccination through age 26 is recommended but vaccine effectiveness is lower if vaccination occurs after onset of sexual activity (BII)	HPV recombinantvaccine 9 valent intramuscularly at months 0, 1-2, and 6 (BIII)

See Table 126-3 for levels of evidence-based recommendations.

Data from Reference 66.

Pneumocystis jirovecii Pneumonia

Pneumocystis jirovecii (*carinii*) pneumonia (PCP) is the most common life-threatening OI in patients with AIDS.[88] *P. jirovecii* was formerly named *P. carinii*; the name change was made to distinguish the organism that infects humans (*P. jirovecii*) from the strain that infects rodents (*P. carinii*). Nevertheless, the acronym PCP is still used today. PCP was common early in the AIDS epidemic, but the incidence of PCP has fallen markedly since the advent of ART and effective prophylaxis for PCP. It still occurs in persons unaware of their HIV infection, and breakthrough PCP can occur in those with variable adherence to ART and/or prophylaxis.

P. jirovecii is a fungus that has protozoan characteristics as well.[88] Exposure to *P. jirovecii* is widespread; two-thirds of the population have developed serum antibodies by age 2 to 4 years. The organism resides without consequence in humans unless the host becomes immunologically impaired.[88] Disease associated with immunosuppression probably occurs from both new acquisition and reactivation. Ninety percent of PCP cases in AIDS patients occurred in those with CD4 counts less than 200 cells/mm^3 (0.2×10^9/L).[65] Other risk factors include oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and high-plasma HIV-RNA. Past episodes of PCP increase risk for future episodes, which provides the basis for secondary chemoprophylaxis, as described below.

The presentation of PCP in AIDS often is insidious.[88] Characteristic symptoms include fever and dyspnea. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur. Chest radiographs may show florid or subtle interstitial and bilateral infiltrates but occasionally are normal. Arterial blood gases may show minimal hypoxia (PaO_2, 80-95 mm Hg [10.6-12.6 kPa]) but in more advanced disease may be markedly abnormal. The diagnosis of PCP usually is made by identification of the organism in induced sputum or in specimens obtained from bronchoalveolar lavage. Less commonly, transbronchial or open lung biopsy is used to locate the organism. The stain used for organism identification affects the sensitivity and specificity of the respiratory samples. Many laboratories prefer direct immunofluorescent staining using monoclonal antibodies. PCR is an alternative diagnostic method that is highly sensitive and specific for detecting *Pneumocystis.* Unfortunately, PCR does not distinguish whether the presence of the organism is due to colonization or disease. 1,3-β-D-glucan is a component of *Pneumocystis* cell walls that is elevated in patients with PCP. The assay for 1,3-β-D-glucan has a high sensitivity for those with PCP and can therefore be used to rule out PCP, but it is nonspecific because elevation may also be due to various causes, including other fungal infections.[65]

Untreated PCP has a mortality rate of nearly 100%. Several potential treatments are available for PCP, but the treatment of choice is trimethoprim–sulfamethoxazole (also called cotrimoxazole), which is associated with a response rate of 60% to 100%.[65] Parenteral pentamidine is equally efficacious but significantly more toxic. Trimethoprim–sulfamethoxazole is also the regimen of choice for primary and secondary prophylaxis of PCP in patients with and without HIV.[65] Additional drugs, such as echinocandins, and vaccines are in development for PCP.[89]

When used for treatment of PCP, the dose of trimethoprim–sulfamethoxazole is 15 to 20 mg/kg/day (based on the trimethoprim component) as three to four divided doses. Treatment duration typically is 21 days but also must be based on clinical response. Trimethoprim–sulfamethoxazole is usually initiated by the IV route, although oral therapy may suffice in mildly ill and reliable outpatients or for completion of a course of therapy after a response has been achieved with IV administration.[65,89] Patients with moderate-to-severe PCP (eg, PaO_2 more than 70 mm Hg [9.3 kPa]) should be treated with corticosteroids as soon as possible after starting PCP therapy and certainly within 72 hours, in order to blunt the deterioration seen just after initiation of PCP therapy. Alternative regimens include primaquine with clindamycin or IV pentamidine for moderate-to-severe disease, and dapsone with trimethoprim, primaquine with clindamycin, or atovaquone for mild-to-moderate PCP.[65] Early initiation of ART (within 2 weeks) is recommended, keeping in mind the potential issues described earlier.

Adverse reactions to trimethoprim–sulfamethoxazole and pentamidine are common, occurring in 20% to 85% of patients in this setting.[65] The more common adverse reactions seen with trimethoprim–sulfamethoxazole are rash (rarely including Stevens–Johnson syndrome), fever, leukopenia, elevated serum transaminase levels, and thrombocytopenia. The incidence of these adverse reactions is higher in persons with HIV than in those not infected with HIV. Mild rashes should be watched closely for progression to more severe reactions but are not an absolute contraindication to continuing therapy. This highlights the need for thoughtful consideration of ART components because of overlapping toxicities with some antiretrovirals such as NNRTIs, which are also associated with rash and hypersensitivity, including life-threatening cases. Alternative treatments can have their own side effect profiles to consider. Dosage modification or pharmacokinetic monitoring can reduce the toxicity of trimethoprim–sulfamethoxazole. Early addition of adjunctive corticosteroid therapy to anti-PCP regimens decreases the risk of respiratory failure and improves survival. The adverse effects associated with corticosteroid use for this scenario are minimal, primarily an increased incidence of herpetic lesions, although some concerns exist about the potential for reactivation of tuberculosis or cytomegalovirus and/or long-term effects on bones.

Prevention of PCP is clearly a preferable treatment strategy. Primary prophylaxis is recommended for any person with HIV who has a CD4 lymphocyte count less than 200 cells/mm^3 (0.2×10^9/L) (or CD4 percentage of total lymphocytes less than 14% [0.14]) or a history of oropharyngeal candidiasis.[65,88] Secondary PCP prophylaxis is recommended for all persons with HIV who have had a previous episode of PCP. Trimethoprim–sulfamethoxazole is the most effective and least expensive agent and is the preferred therapy for both primary and secondary prophylaxis of PCP in adults and

adolescents.[65,88] It also confers cross-protection against toxoplasmosis and many bacterial infections. The recommended dose in adults and adolescents is one double-strength tablet daily, although other regimens, such as one double-strength tablet thrice weekly or one single-strength tablet daily and gradual dose escalation using liquid trimethoprim–sulfamethoxazole, have been used to reduce the incidence of adverse reactions and improve adherence. Alternative prophylactic regimens are available if trimethoprim–sulfamethoxazole cannot be tolerated.

In the ART era, the profound reduction in HIV replication and restoration in CD4 cell count to levels rarely associated with the development of OIs provides a basis for the discontinuation of primary and secondary prophylaxis.[65] For PCP, primary prophylaxis should be discontinued in patients receiving and responding to ART who have a CD4 cell count greater than 200 cells/mm^3 (0.2×10^9/L) sustained for at least 3 months, but should be reinstated if the CD4 count drops to less than 200 cells/mm^3 (0.2×10^9/L). The same criteria apply for both discontinuation and reinitiation of secondary prophylaxis of PCP. However, continued secondary prophylaxis should be considered when the original PCP episode occurred at a CD4 count greater than 200 cells/mm^3 (0.2×10^9/L).

Comprehensive recommendations are available for management of PCP and other OIs in the context of HIV infection, including prophylaxis, treatment, and removal of prophylaxis with the control of HIV infection.[65] Readers are advised that data continue to emerge on new OI therapies, the safety of stopping primary and secondary prophylaxis, as well as criteria for when to restart secondary prophylaxis. The most current guidelines should always be consulted. Similar OI guidelines specific to children have been developed and are updated regularly.[43]

The Aging HIV Population

9 Given the life-prolonging effects of ART, approximately half of persons with HIV are over 50 years of age in resource-rich countries.[90] Along with older age come higher rates of well-known chronic and acute illnesses such as osteoporosis and osteopenia, renal and hepatic insufficiency, metabolic syndrome, neurocognitive decline, atherosclerotic disease, frailty, and non-AIDS malignancies. Many of these illnesses occur at higher than expected rates in older persons with HIV in the ART era.[91,92] The cause(s) of these higher rates is the focus of intense study. Initially, adverse events from antiretroviral medications such as hyperlipidemia were thought to contribute significantly to these conditions but ongoing inflammation and viral persistence play a critical role. Therefore, ART generally protects against non-AIDS events and it is universally recommended to manage these emerging complications. Additionally, persons with HIV should adopt healthy habits to slow the aging process including healthy diets, regular exercise, and adequate sleep.

One-third of deaths in people living with HIV are attributed to cancer.[93] While contemporary ART has reduced the incidence of HIV-related cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma, other non-AIDS-related malignancies impact persons with HIV at significantly elevated rates such as Hodgkin's lymphoma and anal, lung, skin, and hepato-carcinoma. Part of this risk may be attributed to elevated exposures or susceptibilities to human papillomavirus (oral and anal cancer), smoking (lung carcinoma), and chronic hepatitis B and/or C coinfection (liver cancer), which are modifiable risk factors. For example, guidelines advocate HPV vaccination for younger persons with HIV, as well as increased screening for anal cancer in those with existing genital or anal warts.[65] Antiretroviral drugs may contribute directly to these increased cancer rates, as some agents have been associated with cancers in observational studies.[94] However, persisting immunosuppression may be an underlying cause of higher cancer rates in persons with HIV.[91] While the approach to treatment of non-AIDS-related malignancies in persons with HIV is similar to that in persons without HIV, treatment is complicated by drug-drug interactions or additive toxicities that may exist between the antiretrovirals and the oncolytics.[95]

Cardiovascular disease has also emerged as a major concern for persons with HIV. Persons with HIV are at higher risk of cardiovascular disease compared with persons without HIV, including persons with viral suppression.[91] This increased risk is similar in magnitude to other well-established risk factors such as hypertension and hyperlipidemia. Elevated systemic inflammation and its impact on endothelial structure and function and the clotting cascade is thought to underlie much of this risk, as elevations in circulating C-reactive protein and IL-6 correlate with clinical outcomes. Statins are beneficial in persons with HIV and dyslipidemia, in part because of their anti-inflammatory effects. In this population, pitavastatin reduced markers of arterial inflammation and immune system activation.[96] Antiretroviral drugs themselves may also contribute to cardiovascular risk, given the well-known relationships between PIs, efavirenz, and certain NRTIs with dyslipidemia (increased triglycerides and low-density lipoproteins [LDL] and decreased high-density lipoproteins [HDL]) and abnormal glucose homeostasis (insulin resistance and impaired glucose tolerance).[91] Retrospective studies have found an association between myocardial infarction and abacavir use, but other studies have not, so this association is controversial and highlights the difficulty in using observational and retrospective data to attribute risk to these emerging medical conditions. Tenofovir alafenamide

has been associated with lipid increases in comparison to tenofovir disoproxil,[56] though it is unclear whether tenofovir disoproxil has lipid-lowering properties or if tenofovir alafenamide is involved in mechanistically causing these increases.[91] Metabolic abnormalities in persons with HIV on ART, such as hyperlipidemia and hyperglycemia, should be reviewed with consideration given toward optimizing ART where possible to minimize side effects and avoid drug-drug interactions.

Another relevant problem for persons with HIV is body fat abnormalities. Older ART was associated with changes in body fat distribution[97] and newer ART options, such as InSTIs and tenofovir alafenamide, have been associated with weight gain. The thymidine analogs, particularly stavudine, were associated with lipoatrophy of the subcutaneous fat in the extremities and face, and these agents and older PIs were associated with hypertrophy of the deep abdominal fat depot. Collectively these fat abnormalities were termed HIV lipodystrophy. Newer agents are less associated with lipodystrophy compared with older agents, which provides a basis for switching therapy to newer regimens or initiating therapy with preferred regimens. The best management of body fat changes is prevention through initiation of preferred regimens less likely to cause such changes (see current recommendations for initial therapy, Table 148-2).[65] The weight gain with InSTIs and tenofovir alafenamide is a separate issue from lipodystrophy seen with older ARV medications. The greatest weight gain was with InSTIs (dolutegravir ~ bictegravir > raltegravir > elvitegravir), followed by PIs, and then NNRTIs.[62,63] Tenofovir alafenamide has also been associated with greater weight gain than tenofovir disoproxil fumarate,[56] and this effect is more pronounced when combined with dolutegravir. A clear underlying mechanism has not been established, and some studies have also failed to identify associations.

Functional declines of end organs such as kidney, liver, skeletal muscle (frailty), and brain (cognition) are other important considerations for older persons with HIV. These declines are expected with aging but are related with HIV itself.[91] However, certain drugs may also exacerbate these issues. The NNRTI efavirenz, for instance, is commonly associated with central nervous system perturbations including somnolence, attention deficits, and psychiatric issues. These effects exacerbate neurocognitive impairment, although this is controversial and difficult to disentangle from the effects of HIV. Similarly, integrase inhibitors have been associated with neuropsychiatric side effects, such as insomnia, worsening depression, and increased suicidality, particularly among those with preexisting psychiatric conditions. These effects have primarily been analyzed with dolutegravir, with risk factors including preexisting conditions, age over 60 years, female sex, and the concomitant use of abacavir.[98] The most important defense against HIV-associated neurocognitive decline is durable suppression of viral replication.[99]

HIV also causes a nephropathy (termed HIV-associated nephropathy, or HIVAN), most commonly a glomerulopathy that can lead to end-stage renal disease in the absence of ART.[100] The incidence of this condition has declined by approximately 60% in the ART era, demonstrating that ART is the most important intervention against HIVAN. Black people are more likely to experience HIVAN compared with White people. Some antiretroviral drugs impact renal health and these may exacerbate the effects of HIV. For example, atazanavir and lopinavir may crystallize in urine leading to obstruction, whereas tenofovir may injure the proximal tubule leading to Fanconi syndrome in rare cases.[101] The newer tenofovir alafenamide pro-drug is less likely to cause proximal tubulopathy because plasma concentrations of tenofovir are lower compared with tenofovir disoproxil.[74] Renal function should be monitored routinely in all persons with HIV, including consideration for more frequent monitoring for patients receiving the drugs mentioned above.[38]

Persons with HIV experience coinfection with hepatitis B (HBV) and hepatitis C virus (HCV) relatively commonly, and this can drive declines in hepatic function in this population.[65] For example, up to 30% of persons with HIV in the United States have HIV-HCV (~300,000 individuals) including as many as 90% of persons who use injection drugs and 90% of persons with hemophilia. HIV worsens the prognosis of HCV by reducing the chance of HCV clearance and accelerating HCV progression. With chronic HCV infection, progression to fibrosis, cirrhosis, and liver failure is several-fold faster in HIV-HCV patients versus HCV-monoinfected patients. ART reduces progression to hepatic decompensation and, among HIV-HCV coinfected population on ART, progression is faster in those who do not fully suppress HIV replication. For these reasons, ART is recommended for HIV-HCV coinfected persons and HCV therapy should be offered according to HCV guidelines.[102] The most important consideration for co-treatment is potential drug-drug interactions between ART and HCV therapies. Again, the most recent information should be consulted in reviewing potential interactions.[38,102]

The same general principles extend to HIV-HBV coinfected patients, who comprise approximately 10% of the HIV population.[65] However, two unique considerations are relevant for HIV-HBV coinfection. First, the ART regimen should include tenofovir (in the form of tenofovir disoproxil or alafenamide) plus either lamivudine or emtricitabine, given the HBV activity of these agents. Second, hepatic flares and decompensation has been reported when tenofovir-based therapy was interrupted or discontinued. If discontinuation is necessary, close monitoring of hepatic function is indicated.

Despite these issues in the contemporary ART era, the pharmacotherapy of HIV infection has steadily improved over the past 30 years, such that HIV is now a chronic but manageable condition. Whether the patient will ultimately mount a durable response to ART depends upon adherence, convenience/tolerability, and pharmacologic effectiveness. As discussed throughout this chapter, a large number of considerations go into choosing the optimal ART for a given patient. These factors include pre-ART disease characteristics (eg, resistance testing, viral load, and CD4 count), ART characteristics (eg, coformulations, food requirements, drug-drug interactions), comorbid conditions (eg, preexisting renal dysfunction), potential for pregnancy, HLA-B*5701 and/or tropism testing (if abacavir or maraviroc are being considered), and co infections (eg, TB infection). The clinician's knowledge and application of HIV pathophysiology and pharmacologic principles of ART will ultimately guide therapeutic success.

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CCR5	chemokine (C–C motif) receptor 5
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CXCR4	chemokine (C–X–C motif) receptor 4
CYP	cytochrome P450
DHHS	Department of Health and Human Services
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
gp	glycoprotein
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
IC_{50}	concentration of antiretroviral agent necessary to inhibit 50% of viral replication

Ig	immunoglobulin
InSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
LDL	low-density lipoprotein
LTR	long-terminal repeat
MAC	*Mycobacterium avium* complex
MSM	men who have sex with men
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OI	opportunistic infection
PCP	*Pneumocystis jirovecii* (*carinii*) pneumonia
PCR	polymerase chain reaction
PI	protease inhibitor
PEP	postexposure prophylaxis
PrEP	preexposure prophylaxis
RT-PCR	reverse-transcription polymerase chain reaction
SIV	simian immunodeficiency virus
TB	tuberculosis
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding the management of *Pneumocystis jirovecii* pneumonia is true?

   A. Untreated PCP has a mortality rate of approximately 20%.

   B. Sulfamethoxazole–trimethoprim is dosed based on the sulfamethoxazole component.

   C. Primary prophylaxis is recommended for patients with fewer than 100 CD4 cells/μL (0.1×10^9/L).

   D. Moderate-to-severe disease should be treated with adjunctive corticosteroids.

2. Which of the following regarding the molecular characteristics of HIV is false?

   A. HIV is a single-stranded RNA virus.

B. HIV-2 is the predominant type found in the United States.

C. There are multiple clades (subtypes) that further distinguish the HIV viruses.

D. HIV is believed to have originated from a cross-species transmission of a simian immunodeficiency virus from primates to humans.

3. Which of the following are AIDS-defining illnesses? (Select all that apply)

A. Esophageal candidiasis

B. *Mycobacterium tuberculosis*

C. Rhinovirus

D. Syphilis

4. Which of the following is false regarding the integrase strand transfer inhibitors (InSTI)?

A. They are relatively well-tolerated compared with other antiretroviral drugs.

B. Dolutegravir has a higher genetic barrier to resistance compared with elvitegravir and raltegravir.

C. They are mainly excreted as unchanged drug in urine.

D. They are recommended as part of first-line ART regimens.

5. Which of the following is not an accurate characterization of the HIV epidemic?

A. HIV infections are most concentrated in sub-Saharan Africa.

B. The main risk factor for females is heterosexual intercourse.

C. The main risk factor for HIV worldwide is men who have sex with men.

D. Approximately 38 million humans have HIV infection worldwide.

6. Which one of the following statements regarding HIV drug resistance is false?

A. A phenotype assay measures the in vitro drug concentration needed for inhibition of the patient's viral isolate.

B. A genotype assay measures the genetic makeup of the patient's virus and reports the important mutations found

C. Nonnucleoside analog reverse transcriptase inhibitors are susceptible to a single genetic mutation in HIV that extends cross-resistance to the class (except etravirine or doravirine).

D. The protease inhibitors class is susceptible to a single genetic mutation in HIV that extends cross-resistance to the class (low genetic barrier).

7. Which of the following statements regarding the transmission of HIV is false?

A. Receptive sexual intercourse carries higher risk for HIV acquisition compared with insertive intercourse.

B. Persons with HIV on ART with an undetectable HIV-RNA do not transmit HIV to others through sex (U=U).

C. Encouraging safer sex practices is a major component in preventing sexual transmission.

D. The presence of genital ulcers or sexually transmitted infections does not increase the risk for contracting HIV.

8. Which of the following is true regarding postexposure prophylaxis (PEP)?

A. PEP is available after both occupational and other non-occupational, high-risk HIV exposure.

B. PEP consists of two ART agents.

C. Two weeks of PEP therapy is advised following exposure.

D. PEP initiation should be delayed while waiting on the HIV status of the source.

9. Which is true regarding pre-exposure prophylaxis (PrEP)?

A. PrEP using 2:1:1 dosing should be recommended for all modes of HIV transmission.

B. PrEP consists of three drug regimens given for one month.

C. HIV acquisition during long-acting PrEP with cabotegravir may be associated with delayed seroconversion.

D. PrEP can be started while waiting for an HIV negative test.

10. Which of the following steps in the HIV life cycle establishes lifelong infection?

A. Adsorption and penetration

B. Reverse transcription

C. Viral maturation

D. Integration

11. Which of the following are true regarding the monitoring of therapeutic outcomes following ART initiation? (Select all that apply)

A. Plasma HIV-RNA and CD4 are the primary tests used to evaluate response.

B. If a single agent is responsible for toxicity, all agents in the regimen should be changed.

C. Treatment failure is generally defined as the inability to achieve and maintain virologic suppression.

D. Once a patient's immune system has been restored (increased CD4 cell count), ART may be held until the CD4 count is less than 250 cells/μL (0.25×10^9/L) without any long-term risk to the patient.

12. Which of the following is the most important drug-drug interaction issue specific to cobicistat or ritonavir?

A. Concomitant acid suppression with proton pump inhibitors

B. Concomitant drugs that undergo extensive CYP3A4 metabolism

C. Concomitant drugs that undergo extensive renal clearance via filtration

D. Concomitant drugs that undergo extensive glucuronidation via UGT1A1

13. Which of the following is false regarding ART use during pregnancy and lactation?

A. The goal is to suppress HIV replication to undetectable levels.

B. Pregnancy can be associated with altered antiretroviral drug pharmacokinetics.

C. Prophylaxis for the infant may be warranted.

D. Breastfeeding is recommended in the United States.

14. Which of the following characteristics is best representative of the nucleoside analog reverse transcriptase (NRTI) inhibitor class?

    A. Significant drug-drug interaction potential with cytochrome P450 (CYP450) substrates.

    B. A single mutation in HIV reverse transcriptase gene causes cross-resistance to the whole class.

    C. The drugs enter cells, become phosphorylated to the active triphosphate anabolite, and inhibit HIV reverse transcriptase.

    D. Most are extensively metabolized by the liver.

15. Which of the following is/are false regarding chronic illnesses that have emerged in the ART-era? (Select all that apply)

    A. HIV-related cancers have emerged as a leading cause of mortality and morbidity in the ART-era.

    B. Patients with HIV infection are at a lower risk for cardiovascular disease compared to HIV-negative individuals.

    C. As much as half of the HIV population is over 50 years old in resource-rich countries.

    D. Hepatitis C coinfection is rare and should not be treated in patients taking ART.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Adjunctive corticosteroids are recommended in moderate-to-severe disease. Untreated PCP has a mortality rate of nearly 100%, based on the trimethoprim component, and primary prophylaxis is indicated when the CD4 cell count is <200 cells/μL (0.2×10^9/L). See the "Pneumocystis jirovecii Pneumonia" section for additional information.

2. **B.** HIV-1 is the predominant type found in the United States. See the "Etiology" and "Detection of HIV and Surrogate Markers of Disease Progression" sections for more information.

3. **A, B.** Rhinovirus (C) causes the common cold and syphilis (D) is a sexually transmitted infection. Though both of these conditions can occur in persons with HIV, neither of these are AIDS-defining conditions. See Table 148-1 for a list of AIDS-defining conditions.

4. **C.** InSTIs are metabolized by CYP3A4 and/or UGT1A1. See the "Antiretroviral Agents" and "Drug Interactions" sections for more information.

5. **C.** Though MSM account for the majority of new HIV cases, this is subsequent to unprotected receptive anorectal intercourse. See the "Epidemiology"section for more information.

6. **D.** Protease inhibitors (notably atazanavir and darunavir) have higher genetic barriers to resistance and typically require multiple mutations to become ineffective. See the "Antiretroviral Agents" section for more information.

7. **D.** The presence of genital ulcers and other sexually transmitted diseases increases the risk of HIV transmission.

8. **A.** PEP consists of at least three antiretroviral medications, should be continued for 4 weeks, and should be initiated as soon as possible (within a maximum of 72 hours) after potential exposure. See the "Post-Exposure Prophylaxis" section for more information.

9. **C.** 2:1:1 Dosing is only recommended in MSM engaging in receptive anal sex. PrEP only consists of 1 to 2 antiretroviral drugs (either long-acting cabotegravir or emtricitabine/tenofovir in the form of either tenofovir alafenamide or tenofovir disoproxil fumarate), and should NOT be initiated until negative HIV infection is confirmed to prevent drug resistance mutations with subtherapeutic HIV therapy. See the "Pre-Exposure Prophylaxis" section for more information.

10. **D.** Integration refers to the insertion of reverse-transcribed, double-stranded HIV DNA by the HIV integrase enzyme into the host cell's genome. This is a key step in establishing lifelong HIV infection. See the "Pathogenesis" section for more information.

11. **A, C.** If a single agent is responsible for toxicity, then only the single agent needs to be changed, not the entire regimen. HIV requires lifelong therapy and should not be discontinued once the CD4 count increases – cessation of ART would result in viral load rebound and a CD4 count drop,

placing the individual at risk of increased HIV-associated morbidity and mortality. See the "General Approach to Treatment" section for more information.

12. **B.** Cobicistat and ritonavir are potent inhibitors of CYP3A4, and thus cause several drug-drug interactions through this pathway. See the "Drug Interactions" section for more information.

13. **D.** Breastfeeding is not recommended in the United States due to concerns over the risk of HIV transmission and availability of formula. See the "Pregnancy" section for more information.

14. **C.** This class of drugs has a low potential to cause or be susceptible to drug-drug interactions, and generally multiple mutations are required to make the entire class ineffective. N(t)RTIs are primarily renally eliminated unchanged (except for abacavir), and thus are not metabolized by the liver. See the "Antiretroviral Agents" and "Drug Interactions" sections for more information.

15. **A, B, D.** Non-HIV related cancers are more commonly encountered, persons with HIV are at higher risk of cardiovascular disease, and hepatitis C is a commonly encountered coinfection in persons with HIV that should be treated. See the "The Aging HIV Population" section for more information.