NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.

HIV and AIDS

Authors

Helena M. Swinkels[1]; Andrew D. Nguyen[2]; Peter G. Gulick[3].

Affiliations

[1] University of British Columbia
[2] University of Queensland
[3] Michigan State University

Last Update: July 27, 2024.

Continuing Education Activity

Clinical prevention of HIV and **AIDS** is the cornerstone of controlling the global HIV pandemic, which has claimed over 40.4 million lives worldwide, including 1.5 million children. Although a cure remains out of reach, HIV is a chronic illness due to the effectiveness of antiretroviral therapy. Combined with significant advancements in prevention, the goal of halting the global HIV pandemic is now feasible. Current interventions acknowledge the complexity of clinical management, considering socio-economic factors, patient-centered care, continuous quality improvement, and the importance of social and regulatory environments to achieve optimal patient and population outcomes.

This activity comprehensively reviews HIV transmission, pathophysiology, clinical presentations, evaluation, up-to-date treatment, reporting, and implementation considerations for specific population groups to prevent the diagnosis of **AIDS**. Clinicians increase their knowledge, skills, and competence in managing HIV, improving patient outcomes, reducing transmissions, and contributing to global efforts of disease eradication. The role of the interprofessional team is highlighted, emphasizing collaboration among clinical, public health, and interdisciplinary team members.

Objectives:

- Determine the stage of HIV and related comorbidities to ensure timely diagnosis and treatment for patients.
- Apply the principles of antiretroviral therapy and prophylaxis for opportunistic infections to prevent and manage adverse effects.
- Interpret HIV treatment guidelines to ensure cultural sensitivity and maintain confidentiality for individual patients and affected populations.
- Collaborate with interprofessional team members to ensure continuity of care, improve patient outcomes for HIV prevention and treatment, and mitigate the risk of **AIDS**.

Access free multiple choice questions on this topic.

Introduction

HIV was first identified in 1983 and has since claimed approximately 40.4 million lives worldwide as of 2022. This number is staggering, and if left unchecked, HIV could become a global health crisis. However, the research, development, and widespread availability of highly active antiretroviral therapies (ARTs) have helped control the HIV pandemic. Likewise, advances in the treatment of HIV and opportunistic infections have rendered the disease a manageable chronic illness. Patients with HIV can live long and healthy lives. Preventing chronic diseases is a top health priority for this population due to the underlying **immunodeficiency**.

Adequate resources and advances in prevention, treatment, and implementation science make the United Nations General Assembly's 95-95-95 goals attainable. By 2025, the goal is to ensure that 95% of patients with HIV are diagnosed, 95% of diagnosed patients receive ART, and 95% of those prescribed ART achieve viral load suppression. [WHO. Global Health Sector HIV Strategies 2022] Globally, HIV and mortality rates show a steady decrease.

However, some countries report an uptrend in the rate of infections, mostly where political or other turmoil is occurring or where HIV is highly stigmatized.[UNAIDS. Global Report 2023] With improvements in treatment, the number of patients with HIV is also increasing, with approximately 37.7 million patients diagnosed in 2020 and 39 million patients diagnosed in 2022—two-thirds of whom live in Africa.

HIV imposes high costs on both patients and the healthcare system. Infection with HIV increases the risk of chronic disease, particularly cardiac and neurological. Although ART delays disease progress, treatment does not cure HIV, causes adverse effects, and requires consistent, prolonged connection to the healthcare system. Several barriers to universal treatment exist, including public- and self-stigma, lack of adequate access to care, inappropriate care, and costs. Using local clinical guidelines for managing HIV improves patient outcomes and prevents HIV transmission. Clinical guidelines promote quality programming for prompt diagnosis, treatment, and connection to care for patients with or at risk of acquiring HIV. Increasing the involvement of community-led organizations in HIV testing and treatment and integrating medical services for related health issues extend the reach of precise services, improve linkage to care, and improve overall health. Supportive social and policy environments regarding access to services, screening, reporting test results, and discrimination can safeguard patients and the community.

This clinical reference focuses primarily on HIV-1 and is designed to review the pathophysiology, clinical manifestations, and recommended treatment options for patients with HIV, providing clinicians with concise and up-to-date guidance for managing HIV. The optimal social and policy environments to support the HIV response, as recommended by the World Health Organization (WHO), the Joint United Nations Programme for HIV/**AIDS** (UNAIDS), the United States Centers for Disease Control (CDC), and state legislatures, with Florida legislation provided as an example, are discussed. Please see StatPearls' companion resource, "HIV-2 Infection," for more information.[1]

Etiology

HIV is part of the Retroviridae family in the *Lentivirus* genus. The virus mainly targets CD4+ T-lymphocyte helper cells, leading to extreme immune suppression with a continuous loss of cells. This suppression weakens the immune system and causes many clinical manifestations. Untreated HIV eventually progresses to **AIDS**. At this stage, the immune system cannot prevent infections, resulting in death due to opportunistic infections. Two main types of HIV include HIV-1 and HIV-2. Although their genomes are structurally similar, they diverge significantly at the amino acid level. The 2 viruses result from 2 different zoonotic transmissions of simian **immunodeficiency** viruses and, as a result, have substantial differences in their severity, transmissibility, and prognosis. Note that HIV-1 and HIV-2 are only 60% identical at the amino acid level and have a mere 48% identity similarity at the nucleotide level.

HIV-1 and HIV-2 particles comprise a lipid membrane surrounding a protein capsid. The capsid holds a nucleoprotein complex or core consisting of 2 identical copies of RNA and nucleocapsid, integrase, and reverse transcriptase proteins. The capsid protein organizes into a lattice structure, giving the capsid a characteristic conical shape. HIV is transmitted through various body fluids, such as blood, amniotic fluid, breast milk, semen, pre-ejaculate, rectal fluids, and vaginal fluids. HIV can be transmitted through sexual contact, during pregnancy and delivery, and through fomites, such as reusable medical equipment or syringes. Please see StatPearls' companion resource, "HIV Prevention," for more information.[1][2]

Epidemiology

HIV is a significant public health issue worldwide. HIV-1 causes most infections, with HIV-2 accounting for only 1 to 2 million infections. The prevalence of HIV-2 exceeds 1% of infections only in West Africa, although infections occur less commonly on all continents, particularly in cases with colonial or other ties to the area. According to the WHO HIV factsheet, there were 39 million patients with HIV at the end of 2022, with the majority (25.6 million) living in Sub-Saharan Africa.[WHO. HIV Data and Statistics 2023.] In 2022, 1.3 million new cases of HIV were reported worldwide, with 630,000 deaths related to HIV in the same year.

Although some countries report an increase in new infections, the overall global trend in HIV incidence has decreased. In particular, significant gains prevent and treat HIV in eastern and southern Africa, where the virus is most prevalent. From 2010 to 2022, 57% fewer new infections and 58% fewer **AIDS**-related deaths occurred in the region. Progress is slower in other areas, mainly where marked inequities and low prioritization of the HIV response

exist. A study of global trends in HIV among adolescents and young adults showed a decrease in incidence from 34.5 per 100,000 population in 1990 to 22.7 per 100,000 population in 2019. However, between 2010 and 2022 in Asia and the Pacific, a quarter of new infections affected people aged between 15 and 24 and their partners, with some countries reporting nearly half of all new infections in this population. In total, new HIV cases have decreased by only 14% in the region.

HIV incidence is increasing in some regions. The WHO Middle East and North African regions had a 61% increase in the incidence of HIV between 2010 and 2022, the largest in the world. Due to the low prevalence of HIV in this region, the number of people infected (about 16,000 people in 2022) is small relative to the 160,000 people estimated to be infected in Eastern Europe and Central Asia in 2022. New HIV cases in this region increased by 49% between 2010 and 2022. Challenging legal environments, human rights violations, and military conflicts have hindered the HIV response.

HIV diagnosis, treatment, and viral suppression rates vary across and within countries and regions. Globally, women accounted for 65.8% of new HIV cases in 2019. However, diagnosis, treatment, and viral suppression rates are lower among adolescent and adult men. For example, a phylogenetic study in Uganda estimated that men are 1.5 to 1 times less likely to be virally suppressed compared to women. Interventions that increase viral suppression rates among men similar to women close the gender disparity in incident HIV cases. UNAIDS and WHO identify 5 key populations who are disproportionately affected by HIV and warrant specific care and support to reduce global transmissions—men who have sex with men, sex workers, people in prisons and other closed settings, people who inject drugs, and transgender and gender-diverse people.[UNAIDS. Global Report 2023.]

The vast majority of new HIV cases worldwide occur from sexual contact. Most of these infections are transmitted through heterosexual contact due to the high number of infections in Africa, where this mode of transmission is dominant. Most new HIV diagnoses in most other regions of the world occur in men who have sex with men. [WHO. HIV Data and Statistics 2023.] In the United States, in 2021, 70% of all new infections were in men who have sex with men, whereas only 22% occurred through heterosexual contact.[CDC. Basic Statistics 2023.] Drug use is another significant risk factor for HIV. According to a meta-analysis from 2008, approximately 3 million people who inject drugs are living with HIV worldwide. According to the CDC HIV Factsheet, 1 in 10 new HIV cases in the United States can be attributed to injection drug use either alone or in men who have sex with men who report injection drug use. A systematic review evaluating the effectiveness of needle and syringe exchange programs reported that adequate needle and syringe exchange programs are effective in reducing the sharing and reuse of needles and syringes and HIV transmission among people who inject drugs. Please see StatPearls' companion resource, "HIV Prevention," for more information.[4][5][6][7][8]

Pathophysiology

The Retroviridae family is unique among viruses, with the RNA viral genome reverse-transcribed into DNA before being integrated into the host DNA, resulting in lifelong infection. The pathophysiological process is best known for HIV-1, with more recent research contributing to the understanding of differences in HIV-2 and HTLV viral replication and biology. As the primary host cellular receptor for HIV-1 and HIV-2 is the CD4+ antigen, T cells and macrophages that express CD4+ are the primary viral targets. Envelope glycoprotein on the surface of the viral particle facilitates viral entry into the host cell. Chemokine coreceptors 5 (CCR5) and 4 (CXCR4) on the host cell surface trigger a conformational change in the envelop protein, which results in the fusion of the viral and host cellular membranes. The viral capsid is released into the host cell when membrane fusion occurs.

The HIV-1 capsid remains intact or nearly intact until reaching the nuclear pore complexes on the nuclear envelope of the host cell. Previously believed to occur in the cytoplasm, reverse transcription is now believed to occur during or shortly after the capsid is imported into the nucleus; the nuclear capsid is essential in the efficiency of reverse transcription. The precise location and mechanism of reverse transcription and the role of the capsid have not been fully elucidated. Some molecular studies suggest uncoating and reverse transcription begins in the nucleus. In contrast, others suggest a partial uncoating of the viral capsid at the nuclear pore complexes, with early stages of viral DNA production occurring near the nuclear envelope of the host cell.

The viral reverse transcriptase enzyme initiates reverse transcription using host transfer RNA as primers, which bind at the 5' ends of the 2 identical RNA strands and progress in a 5' to 3' direction. Negative-sense single-stranded DNA

is initially produced, with doubling of the strand beginning part way along the viral genome. Elongation continues to the end of the genome, after which each strand is synthesized using the other as a template. The viral integrase protein then somewhat randomly integrates the double-stranded DNA into the host DNA. When viral particles are formed, they can infect other host cells to propagate the infection. Within 2 days of the initial mucosal exposure, HIV can be detected in the regional lymph node tissue. From here, the virus only requires 3 days to be detected in the plasma.

Genomic diversification is an important aspect of the pathogenesis of HIV, leading to changes in the severity of the disease and the response to ART. One of the primary driving factors for HIV-1 mutagenesis is the error rate of the reverse transcriptase encoded by the virus. According to results from several studies, the error rate of HIV-1 group M reverse transcriptase (subtype B) is 100 to 1000 times higher than that of the cellular DNA polymerases. These errors are incorporated into the viral genome and contribute to viral diversification. Other intrinsic and extrinsic factors, such as recombination errors, host restriction factors, and depletion of host deoxynucleoside triphosphates, can lead to viral mutagenesis and diversification, leading to ART failure.[1]

In the initial phase of the infection, viral replication is rampant, with an exponential increase in the plasma HIV RNA level due to the large population of susceptible CD4+ T cells without any host immune response. Subsequently, a significant decline from the peak viremia level occurs due to the HIV-specific immune response from the cytotoxic CD8+ T cells. After this decline, the HIV replication settles when replication and infection continue, but the initial intense immune response with associated symptoms resolves. The exact mechanisms involving the failure of humoral immunity are not fully understood. T cells within B-cell follicles, particularly the follicular T-helper cells and follicular regulatory T cells, are believed to be involved in poor humoral immunity and HIV persistence in patients treated with ART. In addition, follicular CD8+ cytotoxic T cells are relatively less abundant compared to their extrafollicular counterparts in patients with HIV, likewise believed to contribute to disrupted immunogenesis.[2][3]

Histopathology

Lymphadenopathy exhibiting distinctive morphological changes is evident in patients with HIV. In untreated cases, pronounced follicular hyperplasia emerges initially, marked by enlarged, irregularly shaped follicles that occupy a substantial portion of the lymph node's cross-sectional area. The mantle cell zones are absent or dramatically decreased. Centroblasts are the dominant cell types; the germinal centers have a starry-sky appearance. Follicle lysis or fragmentation is present when small lymphocytes infiltrate the follicle. Sinusoidal monocytoid B-cell hyperplasia is also present. Mixed follicular hyperplasia is the intermediate stage between florid and follicular involution. Here, the interfollicular area is relatively large compared to florid follicular hyperplasia, and the follicles and interfollicular area are more cellular compared to those observed in follicular involution.

In follicular involution, small, atrophic, and hypocellular follicles are observed. The germinal centers contain hyalinized follicular dendritic cell meshworks with few germinal center B cells. Hyalinized blood vessels are observed penetrating the follicles. Due to the scarcity of lymphocytes, the interfollicular area is expanded with a washed-out appearance. Histiocytes and polytypic plasma cells are abundantly present. Eventually, the lymph nodes enter the lymphocyte depletion stage, characterized by the loss of germinal centers and the near absence of lymphocytes. These lymph nodes contain medullary cords and sinusoids. The interfollicular area primarily consists of histiocytes, plasma cells, and a few immunoblasts. Focal hyaline deposits may be present with subcapsular and sinusoidal fibrosis.[4]

History and Physical

A medical history and physical examination include a review of systems indicated for patients with confirmed or suspected HIV. Attention to signs and symptoms rule out other conditions in the differential diagnosis that signal opportunistic infections or HIV-associated sequelae. The clinical presentation stages the HIV infection and ensures that any concurrent conditions are addressed. In addition to characterizing symptoms, the history identifies risk factors for HIV transmission in a nonjudgmental manner, including sexual contact and behavior, drug use, and blood transfusions. The sexual history should elucidate information regarding the number of partners, sexual practices, frequency and type of barrier protection, and previous history of sexually transmitted infections (STIs). Information about the HIV status of current and past partners should also be obtained.

The drug use history should include the type and frequency of substances used, means of administration, and source and sharing of equipment. A mental health assessment is essential for identifying conditions such as depression, other mental illnesses, or substance use that may result in barriers to care or contribute to the development of chronic diseases. Obtaining an immunization history is crucial to determine which vaccines could offer future protection against vaccine-preventable illnesses. For instance, *Streptococcus pneumoniae*, associated with adverse outcomes in HIV-positive individuals, and hepatitis B, linked to a heightened risk of hepatocellular carcinoma progression in patients with HIV, underscore the importance of such proactive measures.

Social history is an integral part of any medical evaluation. In the context of HIV and **AIDS**, this history provides insights into the patient's perceptions of and ability to adhere to treatment and potential barriers to connection to healthcare services. Identifying resources of support assesses living situation, income, insurance, social support, experiences of stigma, coping strategies, and exposure to sexual or other violence. The United States National Institutes of Health (NIH) describes 3 broad stages of HIV that develop over time—acute HIV, chronic or asymptomatic HIV, and **AIDS**.[NIH. Stages of HIV Fact Sheet 2021.] The CDC maintains a staging system based on CD4+ and **AIDS**-defining illnesses intended for surveillance.[10] The WHO has a staging system based on clinical presentation for clinical or surveillance purposes in areas with limited or no availability of CD4+ testing.[WHO. HIV Case Definitions 2007.][5][6][7]

Acute HIV

Approximately 90% of patients with acute HIV experience at least 1 symptom within the first 4 weeks after primary HIV infection. These symptoms are typically mild, nonspecific, and self-limited. Some patients present with more severe symptoms, known as acute retroviral **syndrome** or seroconversion illness. These symptoms are listed below in order of decreasing frequency.

- Fever
- Fatigue
- Muscle pain
- Skin rash
- Headache
- Sore throat
- Swollen lymph nodes
- Joint pain
- Night sweats
- Diarrhea

Symptom onset occurs acutely around 2 to 4 weeks (with a range of 4 days to 8 weeks) after viral infection, just before the peak of viremia. Lasting an average of 18 days, the resolution of symptoms coincides with the setting of a viral replication set-point approximately 30 days after the initial viremia. Without treatment, higher viral load and increased severity and duration of conversion illness are early predictors of a poor prognosis. Mucocutaneous ulceration is a characteristic feature of acute HIV characterized by shallow, sharply demarcated ulcers that have a white base surrounded by a thin area of erythema. Depending on the mode of transmission, ulcers may be located on the oral, anal, penile, or esophageal mucosa. Acute aseptic meningoencephalitis is reported as a clinical presentation of acute HIV-1.[2][8][9][10][11]

Chronic HIV

After HIV acquisition and subsequent setting of the viral set point, patients enter the chronic phase of the infection. Most patients with chronic HIV remain asymptomatic before developing **AIDS**. However, nonspecific fatigue may present, and persistent generalized lymphadenopathy is usual. Generalized lymphadenopathy is characterized by at least 2 noncontiguous sites other than inguinal nodes exhibiting enlarged lymph nodes for more than 3 to 6 months,

not explained by other lymphoproliferative or infectious causes.[4][12] Patients with chronic HIV without **AIDS** can develop oropharyngeal candidiasis, recurrent vulvovaginal candidiasis, oral hairy leukoplakia, disseminated cutaneous herpes simplex virus, and cervical dysplasia or cervical carcinoma in situ.[13][14][15] Cutaneous manifestations such as seborrheic dermatitis, bacillary angiomatosis, varicella-zoster virus reactivations, and molluscum contagiosum infections are common and tend to be severe in patients with HIV.[16][17][18]

AIDS

Eventually, HIV progresses to advanced disease, particularly if left untreated or inadequately treated. **AIDS** is diagnosed when specific **AIDS**-defining conditions are noted, regardless of the CD4+ count. These **AIDS**-defining conditions, outlined by the CDC, include:

- Candidiasis of the digestive tract (other than thrush)
- Candidiasis of the pulmonary tract
- Invasive cervical cancer
- Extrapulmonary or disseminated coccidioidomycosis, histoplasmosis, or cryptococcosis, including cryptococcal meningitis
- Chronic intestinal cryptosporidiosis or isosporiasis
- Cytomegalovirus retinitis
- Kaposi sarcoma
- HIV encephalitis and HIV-associated neurocognitive disorder
- Tuberculosis
- Primary lymphoma of the brain
- Non-Hodgkin lymphoma
- Burkitt lymphoma
- Mycobacterial infections
- *Pneumocystis jirovecii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia
- HIV-associated wasting **syndrome** [19]

These **AIDS**-defining illnesses tend to occur most frequently with low CD4+ counts <200 cells/mm^3, which correlates with untreated advanced HIV as the total lymphocyte count depletes over time.[20][21]

Evaluation

Testing is essential to confirm a diagnosis of HIV. Antibody, antigen-antibody, and nucleic acid amplification tests are available for screening or confirming HIV in symptomatic illness. No currently available testing technology can detect HIV during the initial viremic phase of the infection, known as the window or eclipse period, which lasts up to 20 days. The following tests are used to detect viral proteins:

- Nucleic acid amplification tests: Detects HIV RNA in the blood 6 to 8 days after infection, up to 33 days.
- Antigen tests: Detect viral proteins such as p24 antigen as early as 13 to 20 days after infection.
- Antigen-antibody tests: Detect viral proteins as with other antigen tests, plus anti-HIV immunoglobulin M (IgM) and IgG antibodies around 20 and 30 days, respectively, after infection.[CDC. HIV testing 2024.]

In clinical settings, combination antigen/antibody (Ag/Ab) tests are recommended to identify patients with HIV. These tests are available in most commercial laboratories and hospitals in developed nations and are increasingly available worldwide. Ideally, the Ag/Ab test should be a fourth-generation test capable of detecting HIV-1 and HIV-2 antibodies and the HIV-1 p24 antigen. If the initial positive test cannot cannot distinguish between HIV-1 and HIV-2 this distinction, a supplemental antibody immunoassay is required. All initial positive test results are followed by a second HIV test, preferably a test that is laboratory-based, to confirm a diagnosis of HIV. The false positive rate of third- and fourth-generation tests is very low.

If the combination assay result is negative, no further testing is indicated unless HIV exposure is too recent for detectable p24 antigen levels to have developed. If the initial Ag/Ab test result is negative and early HIV is suspected, an HIV-1 nucleic acid amplification test to detect HIV RNA should be performed. Specimens indeterminate on the initial Ag/Ab test or nonreactive or indeterminate with the HIV-1– and HIV-2–specific antibody assay are followed up with an HIV-1 nucleic acid amplification test.[24]

An acute HIV case is diagnosed with a positive nucleic acid amplification test result in the following settings:

- A recent negative screening immunoassay result
- A positive antigen-antibody immunoassay result, with a negative antibody-only immunoassay
- A nonreactive or indeterminate HIV-1– and HIV-2–specific antibody assay result following a positive screening assay

A negative HIV-1 nucleic acid amplification test result in the last settings indicates a false-positive HIV-1 test. When clinical suspicion for HIV is high and initial test results are negative, testing should be repeated in 1 to 3 weeks. Home-based, point-of-care, or rapid tests are essential to increase testing frequency or extend testing into populations that may otherwise not get tested. As with other HIV tests, positive results from point-of-care testing should be followed with standard laboratory, instrument-based immunoassays to confirm the diagnosis.[22]

When the diagnosis of HIV is established, a baseline laboratory evaluation facilitates the staging of HIV progression, selection of ART, and identification of comorbidities.[NIH. Guidelines for HIV 2023.]

- Quantitative CD4+ T-lymphocyte cell count
- Quantitative plasma HIV-1 RNA viral load
- Complete blood count, glucose, blood urea nitrogen, creatinine, liver enzymes, bilirubin, urinalysis, serum lipids, and serology for hepatitis A, B, and C
- HLAb*5701 test (if abacavir is being considered)
- Genotypic drug-resistance assessment focusing on genes for reverse transcriptase and protease in treatment-naive people, with the addition of integrase strand transfer inhibitor (INSTI) for patients who have been treated with ARTs
- Other tests may be indicated based on the history and physical examination, such as testing for sexually transmitted infections, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, syphilis serology, opportunistic infections, or cancer

Viral load is the most important indicator of initial and sustained response to ART and **aids** in ART selection. Some treatment regimes are ineffective in patients with high baseline viral loads. Viral load should be monitored at entry into care, initiation of therapy, and periodically afterward. CD4+ is the best indicator of immune function, disease progression, and survival and determines the need to start prophylaxis for opportunistic infections. Blood must be drawn for CD4+ testing before starting ART, but ART should not be delayed pending results. If CD4+ is unavailable, the WHO staging system should be used. Monitoring of other CD subsets is not recommended due to costs and lack of clinical utility. Routine testing for herpes simplex IgG, cytomegalovirus IgG, and toxoplasma IgG is not recommended, given that these tests do not delineate active disease versus previous exposure. Testing for serum cryptococcal antigen should be considered in patients with a CD4+ count of 100 cells/mm^3 or less. Please see StatPearls' companion resource, "HIV Testing," for more information.[23]

Treatment / Management

The goal of HIV-1 therapy with antiretroviral medications is to achieve sustained virologic suppression. According to current WHO and CDC guidelines, ART should begin after the diagnosis is confirmed and an initial assessment is completed for all patients with HIV, regardless of their immune status or clinical stage, unless a severe opportunistic infection is present.[NIH. HIV Guidelines 2023] Management of HIV must include identifying specific support required by the patient to maintain medication adherence, particularly for marginalized patients. Treatment choice is initiated based on patient preferences and ability to comply with a medication regimen.[WHO. Global HIV Strategies 2022.]

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), INSTIs, and protease inhibitors are used in treatment-naive patients. NRTIs inhibit viral replication by binding the viral reverse transcriptase and terminating DNA prolongation in HIV-1 and HIV-2 infections. NNRTIs block DNA prolongation by binding the viral reverse transcriptase at a separate site but are only active against HIV-1. INSTIs inhibit the transcribed viral DNA from integrating into the host genome. Protease inhibitors block the last step in the viral maturation process, rendering assembled viral particles immature and noninfectious. The most common drugs within each class in the initial treatment of HIV are listed below.[NIH. HIV Guidelines. 2023][23]

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

- Abacavir (contraindicated for patients who are HLA-B*5701 positive)
- Emtricitabine
- Lamivudine
- Tenofovir (tenofovir alafenamide or tenofovir disoproxil fumarate)
- Zidovudine

Non-Nucleoside Reverse Transcriptase Inhibitors

- Efavirenz
- Rilpivirine
- Doravirine
- Etravirine
- Nevirapine

Integrase Strand Transfer Inhibitors

- Raltegravir
- Elvitegravir with boosting agent cobicistat
- Dolutegravir
- Bictegravir
- Cabotegravir

Protease Inhibitors

- Atazanavir
- Darunavir
- Fosamprenavir
- Ritonavir-boosted lopinavir

- Nelfinavir
- Tipranavir

Other drug classes, such as CCR5 antagonists, fusion inhibitors, attachment inhibitors, capsid inhibitors, and post-attachment inhibitors, are reserved for patients with multidrug-resistant HIV.

Recommended Therapy for Treatment-Naive Patients

Current guidelines recommend initiating INSTI-based therapy with a dual NRTI backbone before conducting further laboratory testing for most patients with HIV. In select cases where the HIV RNA level is <500,000 copies/mL, no coinfection with hepatitis B occurs, and no genotypic resistance is present, a 2-drug regimen with dolutegravir and lamivudine can be considered first-line. Tenofovir plus lamivudine or emtricitabine are the preferred NRTIs, and bictegravir and dolutegravir are the preferred INSTIs due to their effectiveness, adverse effect profiles, shorter duration to virological suppression, and lower propensity to develop resistance. INSTI-based regimens achieve faster viral suppression compared to protease inhibitor or NNRTI-containing regimens. The addition of other agents in the setting of advanced HIV on presentation does not improve clinical outcomes at the onset of treatment and is not recommended. Abacavir is no longer recommended as initial therapy due to the association with cardiovascular disease, the risk of hypersensitivity, and the need for HLA B*5701 testing. Antiretroviral treatment should be started regardless of the CD4+ count to reduce a combination of serious **AIDS**- and non–**AIDS**-related events and death from any cause if started at diagnosis compared to a deferred initiation of treatment.[24][25][26][27][28]

Comorbid conditions affect HIV ART selection due to contraindications or co-benefits of treatment, including the following:

- Hepatitis B virus coinfection: Tenofovir-containing ART regimens are preferred as tenofovir suppresses hepatitis B virus replication. ART regimens that use lamivudine or emtricitabine without tenofovir should be avoided as they can result in the rapid emergence of resistant hepatitis B virus.
- Renal dysfunction: Tenofovir disoproxil fumarate is associated with proximal tubular dysfunction and should be avoided in patients with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2. Tenofovir alafenamide can be used unless the patient has reduced renal function (estimated glomerular filtration rate <30 mL/min/1.73 m^2) and is not on dialysis, in which case no tenofovir formulation is indicated. The preferred regimen is dolutegravir plus lamivudine, adjusted for renal function. Atazanavir should also be avoided in patients with reduced kidney function.
- Osteoporosis: Tenofovir alafenamide is associated with less bone loss and is preferred over tenofovir disoproxil fumarate–containing regimens.
- Pregnancy: Bictegravir, doravirine, cabotegravir, dolutegravir/lamivudine combination, and dolutegravir/rilpivirine combination should not be initiated during pregnancy due to limited data to support their safety. Cobicistat-containing regimens should not be used during pregnancy due to inadequate drug levels. [NIH. HIV Guidelines 2023.]

When laboratory test results are available, the initial regime may be adjusted. A dual NRTI coformulation plus an antiretroviral from another class is prescribed for patients unable to take an INSTI-based regimen. For example, the protease inhibitor darunavir is boosted with cobicistat, ritonavir, or an NNRTI, either efavirenz or rilpivirine.[15]

Recommended Therapy for Treatment-Experienced Patients

Treatment-experienced patients require a wider range of antiviral options compared to initial treatment due to an increased probability of multidrug-resistant strains of HIV. Notably, the barrier to resistance is higher with combination antiretroviral therapy containing later-generation integrase inhibitors, including dolutegravir and bictegravir. However, emerging reports of increasing resistance to this class are apparent. Common resistance mutations identified at the initiation of antiretroviral therapy in treatment-experienced patients include M184V and KS65R with tenofovir, K103N/S in NNRTIs, and thymidine-analogue mutations in NRTIs.[29][30][31][32]

Initial therapy remains the same for treatment-naive patients with the goals of maintaining long-term virological suppression and limiting the progression of the disease. Patients still require 2 to 3 active agents against HIV to reduce the risk of virological failure and drug resistance. The regimens typically include an NRTI backbone with NNRTI and an integrase or protease inhibitor. The NADIA and REVAMP trials, among others, indicated that resistance to first-line antiretroviral agents did not indicate failures in virological suppression with second-line agents incorporating classes from the first-line agents, suggesting that drug-resistance assay may not always be required. However, given that these results were not primary endpoints, these findings should be interpreted cautiously, and drug-resistance assays may still yield better choices in well-resourced clinical settings. A genotypic drug-resistance assay is indicated when the patient is still taking the ART or as soon as possible after ART discontinuation.[24][33][34]

The challenge with antiretroviral agent resistance is that resistance may not predict clinical outcomes accurately.[35] In cases of complex drug resistance, phenotypic assays may be considered to test drug susceptibility against HIV.[36] When possible, drug resistance therapies can guide alternatives to first-line NNRTIs, integrase, or protease inhibitors. The therapies may include second-generation NNRTIs, capsid inhibitors, pharmacologically boosted protease inhibitors, and later-generation integrase inhibitors. Policies should be instituted nationally or regionally for presentations requiring third-line therapy. In cases of resistance to all available therapy, continuing the regimen that the patient best tolerates and maintains some level of virological suppression is important. Novel antiretroviral agents approved by the United States Food and Drug Administration, such as capsid or attachment inhibitors, may be considered when conventional treatment options result in virological and clinical failure. Future drugs based on monoclonal antibodies are being developed, informing treatment for treatment-experienced populations.[37][38][39][40][41]

Recommended Therapy for Patients on Preexposure Prophylaxis

Patients on preexposure prophylaxis with tenofovir alafenamide or tenofovir disoproxil fumarate with emtricitabine who subsequently acquire HIV require resistance testing before initiating therapy. They can be initiated on INSTI-containing regimens outlined above while genotype or resistance testing is pending. Patients who acquire HIV after receiving cabotegravir for preexposure prophylaxis require INSTI genotyping before beginning therapy with an INSTI-based regimen. Although the results are pending, a boosted protease inhibitor regimen containing darunavir and a tenofovir-based dual NRTI coformulation should be used. Please see StatPearls' companion resource, "Preexposure Prophylaxis for HIV Prevention," for more information.[24]

Therapy Considerations for Patients With HIV-2 Infections

Current recommendations for treating HIV-2 are primarily based on single-arm or observational studies, as most research and treatment efforts have focused on HIV-1. The initial regimen for managing HIV-2 should include 2 NRTIs plus a second-generation INSTI or a ritonavir-boosted protease inhibitor.[NIH. HIV Guidelines 2023.] Tenofovir disoproxil fumarate and emtricitabine are the preferred NRTIs. Dolutegravir is recommended as the preferred INSTI. Darunavir and lopinavir are more active against HIV-2 compared to other protease inhibitors and are the preferred agents. Two-drug regimens to treat HIV-1 and any regimen containing NNRTIs are ineffective against HIV-2 and should not be used in these infections.[42]

Drug-resistance assays for HIV-2 are limited to research laboratories, complicating the management of these infections. Current data suggest that HIV-2 is susceptible to NRTIs; however, HIV-2 is more likely to develop resistance compared to HIV-1. Patients with HIV-2 mutations may exhibit complex patterns of protease inhibitor cross-resistance, making sequential regimens ineffective for patients with this infection. In vitro studies report strong efficacy for INSTIs against HIV-2. Clinical data regarding mutations and efficacy of the most commonly used INSTI, such as dolutegravir, are limited, especially in those previously exposed to other INSTIs. Further research is needed to understand resistance patterns for antiretrovirals in patients with HIV-2.[43][44]

Opportunistic Infections

In addition to rapid ART initiation, prophylaxis for opportunistic infections should be started based on the level of immunosuppression.

- *Pneumocystis jirovecii* (previously *P carinii*): Prophylaxis is indicated for patients with thrush on presentation, a CD4+ count of less than 200 cells/mm^3 or a CD4+ count <14%.

- *Cryptococcus neoformans* and *Cryptococcus gattii*: Patients with a CD4+ count of less than 100 cells/mm^3 and a positive serum cryptococcal antigen result require prophylaxis.
- *Histoplasma capsulatum*: Prophylaxis is recommended in areas where histoplasmosis is endemic and the patient's CD4+ count is less than 150 cells/mm^3.
- *Mycobacterium avium* complex infection: If patients with HIV are rapidly initiated on ART, prophylaxis for *Mycobacterium avium* complex is not required. Patients with a CD4+ count of less than 50 cells/mm^3 without ART should receive prophylaxis.
- *Toxoplasma gondii*: Patients with CD4+ counts less than 100 cells/mm^3 who have positive test results for toxoplasma antibodies require chemoprophylaxis.[26]

In patients with a severe opportunistic infection, rapid initiation of ART can result in immune reconstitution inflammatory **syndrome**.[23] The opportunistic infection should be treated before initiating ART to decrease the risk. Initiate ART within two weeks of initiating treatment for most acute opportunistic infections, except acute cryptococcal meningitis.[45] Patients with cryptococcal meningitis may commence HIV therapy within 2 to 4 weeks of antifungal therapy. HIV treatment should be initiated within 2 weeks of tuberculosis treatment in patients who have active tuberculosis, especially if they have severe immunosuppression (CD4+ count <50 cells/mm^3); however, if evidence of tuberculous meningitis is detected, ART should be given with high-dose corticosteroid treatment.[24]

Recommended Therapy for Prophylaxis of Opportunistic Infections

Prophylaxis and treatment in HIV-infected patients with opportunistic infections is dependent on the level of immunosuppression for the patient and the isolation of any causative pathogens. Improving the underlying cause of the immunosuppression by treating HIV is recommended when managing opportunistic infections.[46] Given the high risk of *P jirovecii* with CD4+ counts <200 cells/mm^3 or CD4+ count <200 cells/μL or a CD4+ count <14%, low-dose trimethoprim/sulfamethoxazole (co-trimoxazole) prophylaxis is recommended, which protects against cerebral toxoplasmosis, bacterial infections, and malaria in endemic settings.[47][48] Alternatives for sulfur allergy where desensitization is not feasible include inhaled pentamidine, dapsone, or atovaquone.[49] Hypoglycemia must be monitored with the administration of pentamidine, whereas G6PD deficiency needs to be assessed before starting dapsone.[50][51] Atovaquone can be considered but may not be as efficacious. Prophylaxis is often discontinued after the CD4+ count returns to >200 CD4+ cells/mm^3 for 3 or more months in patients on antiretroviral therapy.[52][53]

For the treatment of *P jirovecii*, weight-based dosing of trimethoprim/sulfamethoxazole (co-trimoxazole) for 21 days is recommended in addition to high-dose steroids to manage the progressive respiratory complications of acute pneumonia and reduce mortality risk. Alternatives include primaquine with clindamycin and intravenous pentamidine for 21 days. Primary prophylaxis of toxoplasmosis, where the risk is greatest with a CD4+ count <100 cells/mm^3, is also covered by low trimethoprim/sulfamethoxazole (co-trimoxazole). Alternatives in the event of a non-severe allergy to sulfur include dapsone with pyrimethamine and calcium folinate. Discontinuation of primary prophylaxis may be considered if the CD4+ count is >200 cells/mm^3 for 3 or more months in individuals on antiretroviral therapy.[54][55][56][57] Vaccinations should be encouraged for patients with HIV, as these may reduce the risk of mortality from influenza, pneumococcal, and meningococcal pneumonia and reduce the risk of other blood-borne viral infections.[58][59][60][61] Given the higher risk of human papillomavirus–related cancers in patients with HIV, human papillomavirus vaccination is recommended.[62] Please see StatPearls' companion resource, "Prevention of Opportunistic Infections in HIV/**AIDS**," for more information.

Monitoring Following Initiation of Treatment

When treatment is initiated, the patient's HIV viral load should be evaluated in 2 to 4 weeks and no later than 8 weeks. The viral load can be rechecked every 4 to 8 weeks to ensure the levels decline. Virologic suppression to undetectable levels (defined as an HIV RNA level of <200 copies/mL) may take up to 24 weeks of continuous therapy. If the HIV RNA level has not declined by 2 log10 copies/mL within 12 weeks and adherence is confirmed, evaluation for resistance with genotype testing for the patient's regimen is recommended. Genotype resistance testing should also be obtained if virologic suppression is not achieved.[13] When viral suppression is established, the viral load should be monitored every 3 to 4 months.[7] An HIV RNA level that remains persistently below this lower limit of detection

demonstrates sustained virologic suppression—the primary goal of HIV therapy. Please see StatPearls' companion resource, "HIV Antiretroviral Therapy," for more information.

Inadequate Viral Suppression and Development of Resistance

When inadequate viral suppression occurs, the HIV viral load and selection pressure increase, inducing mutations favorable to resistance against active antiretroviral treatments. Virological failure occurs when HIV viral is above 1000 copies/mL on 2 separate and consecutive measurements over 3 months while on current antiretroviral treatment for 6 months or longer. This condition can result in clinical failure, described as a new event or recurrence of WHO stage 4 severe **immunodeficiency** after 6 months of current effective antiretroviral treatment. Clinical failure suggests concern for antiretroviral resistance while a patient adheres to effective antiretroviral treatment for 6 months or longer.[63] Given HIV has an RNA genome prone to mutations, selection pressure from active antiretroviral agents during reverse transcriptase can encourage drug-resistant mutants that lead to virological failure, clinical failure, and eventually immunological failure, defined as a CD4+ count of 250 cells/mm^3 or less.[64][65] Thus, while trials such as NADIA and REVAMP indicated treatment regimens incorporating antiretroviral agents with prior resistance is feasible, the theoretical basis of how HIV develops new mutations with inadequate viral suppression should be considered by the treating clinician in managing treatment-experienced patients.[33][34]

Immunological Recovery

In patients who had a baseline CD4+ count of 250 cells/mm^3 or less at diagnosis or immunological failure while on antiretroviral treatment but then subsequently recovered a CD4+ count at or above 500 cells/mm^3, immunological recovery constitutes only a minority of all patients on effective antiretroviral treatment. The reasons are often multifactorial, including adherence, baseline CD4+ count at diagnosis, the age and sex of the patient, the type of initial antiretroviral agents initiated at diagnosis and any delays, and the patient's baseline functional status.[66][67][68] When immunological recovery does occur, the timeline is typically over many months or years but depends on multiple factors, including the class of antiretroviral therapy, the baseline functional status of the patient, and treatment adherence. Conversely, inadequate immunological responses are associated with an increased risk of serious non-**AIDS** events and mortality in patients with HIV. Therefore, the treating clinician needs to monitor the CD4+ count in patients undergoing treatment with antiretroviral agents for potential sequelae.[69][70]

Differential Diagnosis

HIV should be considered in any patient with recurrent serious infections. Other conditions that may have similar effects on the patient's immune system include:

- Severe malnutrition
- Severe combined immune deficiency **syndrome**
- Chemotherapy-induced immunosuppression

The differential diagnosis in patients who present with acute HIV includes:

- Mononucleosis
- Toxoplasmosis
- Viral hepatitis
- Systemic lupus erythematosus

Toxicity and Adverse Effect Management

When prescribing antiretrovirals, a wide variety of potential drug-drug interactions, toxicities, and other adverse effects must be considered. Consultation with a pharmacologist is recommended. Some common reactions are listed below.[NIH. HIV Guidelines 2023.]

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

- Abacavir is contraindicated for patients who are positive for the HLA-B*5701 allele due to the risk of hypersensitivity reactions. Pretesting is required before prescribing any regimen containing abacavir. Some studies have also demonstrated increased cardiovascular risk with abacavir.
- Tenofovir alafenamide is associated with higher lipid levels and weight gain but is associated with less renal toxicity compared to tenofovir disoproxil fumarate.
- Tenofovir disoproxil fumarate is associated with renal toxicity; proximal tubulopathies, such as Fanconi **syndrome**; and acute or chronic renal insufficiency, particularly when combined with boosters. Tubulopathy can cause osteomalacia, and tenofovir disoproxil fumarate can also cause decreased bone density.
- Emtricitabine has been associated with hyperpigmentation of the palms and soles.
- Didanosine and stavudine are no longer used due to severe adverse reactions and toxicity, such as fatal lactic acidosis, pancreatitis, and peripheral neuropathy. Lamivudine can rarely be associated with pancreatitis.[71][72][73][74]

Non-Nucleoside Reverse Transcriptase Inhibitors

- Doravirine, efavirenz, and rilpivirine have the potential for cytochrome P450 (CYP) enzyme drug interactions.
- Efavirenz can also cause dyslipidemia, rash, and QTc interval prolongations. The drug has the potential for short- and long-term psychiatric complications, suicidality, catatonia, and late-onset ataxia and encephalopathy.
- Rilpivirine can cause QTc interval prolongation but does not appear to be increased beyond 48 weeks compared to efavirenz. The drug is less commonly associated with depression, suicidality, and rash compared to efavirenz.[75][76][77][78][79]

Integrase Strand Transfer Inhibitors

- All drugs of this class can cause weight gain compared to other antiretroviral classes.
- Several drugs inhibit creatinine excretion without affecting glomerular filtration, including bictegravir, dolutegravir, and cobicistat.
- Bictegravir is a substrate for the enzymes CYP3A4 and UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1) and has the potential for drug-drug interactions. Examples include aluminum- and magnesium-based antacids, where bictegravir should be administered 2 hours before or 6 hours after, and rifampicin, a potent CYP3A inducer.
- Early studies suggested that dolutegravir exposure during conception may be associated with neural tube defects. However, a large cohort study of over 4 million pregnancies in the United States in 2023 did not identify an increased risk of neural tube defects among infants. Clinicians should discuss the current evidence when prescribing medications to people of childbearing potential.
- Raltegravir can increase creatinine kinase and less frequently cause myopathy and rhabdomyolysis. The drug is known to cause severe hypersensitivity reactions, including Stevens-Johnson **syndrome** and toxic epidermal necrosis. As a UGT1A1 substrate, the potential for drug-drug interactions is recognized. Rarely, raltegravir has been associated with depression and suicidal ideation in patients with preexisting psychiatric conditions.
- Cobicistat is an INSTI used exclusively as a pharmacokinetic enhancer of certain protease inhibitors and INSTIs. The drug strongly inhibits CYP3A4, resulting in significant potential for drug-drug interactions. Cobicistat must be discontinued in severe hepatic impairment. Similar to other INSTIs, the drug can increase creatinine excretion without impacting glomerular filtration.[80][81][82][83][84]

Protease Inhibitors

- Protease inhibitors other than atazanavir are associated with an increased risk of cardiovascular events.
- Atazanavir and darunavir are both CYP3A4 inhibitors and substrates with the potential for many drug interactions. Both are co-formulated with cobicistat or ritonavir due to their ability to boost therapeutic levels of atazanavir and darunavir.
- Atazanavir coformulations can cause indirect hyperbilirubinemia, nephrolithiasis, cholelithiasis, nephrotoxicity, and gastrointestinal adverse effects.
- Darunavir coformulations can cause skin rash, gastrointestinal adverse effects, and hepatotoxicity, particularly in patients with preexisting liver disease.[85][86][87][88]

CCR5 Inhibitor

Maraviroc adverse effects are uncommon, but when they occur, they are typically constitutional and include gastrointestinal upset and fever.[89]

Fusion Inhibitors

Enfurvitide, an injectable antiretroviral agent, can be associated with injection site reactions, including granuloma annulare and other symptomatic lesions.[90]

Capsid Inhibitors

The phase III clinical trial of lenacapavir involving 72 patients showed no serious adverse effects (grade 3 or above), with only injection site reactions and gastrointestinal symptoms identified. However, given the small numbers involved, post-marketing reports should be reviewed.[39]

Attachment Inhibitors

The phase III trial of fostemavir involving 371 patients showed mild gastrointestinal adverse effects that led to treatment discontinuation. However, given the small cohort, post-marketing reports should be reviewed. Various drug interaction tools exist online, allowing clinicians to access bedside information. When managing these potential adverse effects, the treating clinician should balance the competing priorities of maintaining virological suppression and reducing future antiretroviral class resistance with patient tolerance and concerns of long-term adverse effects. Considering the individual's circumstances strengthens the therapeutic relationship and encourages treatment adherence.[40][91]

Staging

Staging systems can be used for clinical or surveillance purposes to assess the rate of progression to more advanced stages, assist in monitoring the HIV burden at a population level, plan for prevention and care, and evaluate interventions. The CDC published the current definitions of HIV surveillance cases in 2014. The definitions of surveillance cases are not intended for clinical decision-making. HIV testing confirms the diagnosis and determines acute infection in stage 0, and the CD4+ count determines stages 1 to 3. All surveillance cases are assumed to be HIV-1 unless laboratory evidence indicates HIV-2. The criteria for stage 0 supersede and are independent of the criteria used for other stages.[19]

Confirmed HIV Case

For all adults, adolescents, and children aged 18 months and older:

- A second, different HIV test confirms a positive result from an initial HIV antibody or antibody-antigen test.
- Clinical criteria can be used where HIV test results have not been recorded, but other presumptive evidence exists, such as the history of therapy for HIV or an **AIDS**-defining illness.

Stage 0

This stage is defined by a positive test result within 180 days of:

- A negative or indeterminate test result
- A negative initial immunoassay result followed by a positive nucleic acid amplification test result to confirm acute infection
- A positive nucleic acid amplification test result following a positive antigen or antigen-antibody test result but unconfirmed by a second test

Stages 1 to 3

These stages are determined based on the CD4+ count for all people aged 6 and older (separate criteria exist for infants aged younger than 1 and children aged 1 to 5):

- Stage 1: 500 or more cells/μL
- Stage 2: 200 to 499 cells/μL
- Stage 3: less than 200 cells/μL

Globally, case definitions for HIV vary by country based on the testing technologies most appropriate for use in the local context. The WHO recommends test-based confirmation in adults and children aged 18 months or older to require a positive result from a rapid or laboratory-based HIV antibody, antigen, or virological test, confirmed by a second positive test result relying on different antigens or different test operating characteristics. Advanced HIV is confirmed by the diagnosis of a condition associated with advanced disease or a CD4+ count of less than 200 cells/mm^3 in an adult or child with HIV. The WHO's clinical staging for HIV can be used for clinical and surveillance purposes in resource-limited areas where CD4+ testing may be unavailable.[WHO. HIV Case Definition 2007.] Advanced disease is defined as stage 3 or 4.

Stage 0 or Primary HIV Infection

Patients have 1 or more symptoms associated with acute HIV or a constellation of symptoms consistent with acute retroviral **syndrome**.

Stage 1

In stage 1, patients are asymptomatic or have persistent generalized lymphadenopathy, defined as enlarged lymph nodes (>1 cm) in 2 or more non-contiguous sites (excluding inguinal nodes) not explained by any other cause.

Stage 2

In this stage, patients show unexplained weight loss (moderate degree, <10% of body weight), recurrent respiratory tract infections, herpes zoster exacerbations (mild-to-moderate severity), angular cheilitis, recurrent oral ulcerations, papular pruritic eruptions, seborrhoeic dermatitis, or fungal fingernail infections.

Stage 3

In stage 3, patients experience severe weight loss (>10% of body weight); unexplained chronic diarrhea; persistent fever; oral candidiasis; oral hairy leukoplakia; pulmonary tuberculosis; severe invasive bacterial infections, such as pneumonia, empyema, osteomyelitis, meningitis, and bacteremia; acute necrotizing ulcerative stomatitis; gingivitis or periodontitis; or unexplained anemia, neutropenia, or thrombocytopenia for more than 1 month.

Stage 4 or AIDS

In this stage, patients develop HIV wasting **syndrome**; pneumocystis pneumonia; chronic herpes simplex infection; esophageal candidiasis; extrapulmonary tuberculosis; Kaposi sarcoma; toxoplasmosis; HIV encephalopathy; extrapulmonary cryptococcosis infections; disseminated nontuberculous mycobacterial infections; progressive multifocal leukoencephalopathy; pulmonary candidiasis; cryptosporidiosis; isosporiasis; cytomegalovirus retinitis (or in an organ other than liver, spleen, or lymph nodes); disseminated mycoses, such as histoplasmosis, coccidioidomycosis, and penicilliosis; recurrent salmonella septicemia; lymphoma (cerebral or B-cell non-Hodgkin); invasive cervical carcinoma; or visceral leishmaniasis.

The WHO defines HIV wasting **syndrome** as the presence of unexplained weight loss greater than 10% of the body weight, with the presence of either unexplained chronic diarrhea or unexplained fever for 1 month or more. WHO clinical stage 4 and the CDC criteria for **AIDS** are almost identical.[13] A wide variety of studies in resource-limited settings have evaluated the utility of the WHO staging system for predicting immunological status defined by the CD4+ count. The findings indicate highly variable sensitivity and specificity across various CD4+ cut-off levels, questioning the utility for clinical decision-making. This issue underscores the importance of expanding the availability of CD4+ and viral load testing and the WHO and CDC recommendations to offer treatment to all patients who are HIV positive.[WHO. Global HIV Strategies 2022-2030.][16][14][15][35][43][44]

Prognosis

Without therapy, HIV infections are invariably fatal. However, effective ART with sustained virologic suppression dramatically improves the clinical outcomes for patients with HIV. According to a meta-analysis from 2017, life expectancy in high-income countries is estimated to be 43.3 years if ART begins at 20, and 32.2 years if ART begins at 35. In low- to middle-income countries, life expectancy is estimated to be 28.3 years and 25.6 years if ART starts at 20 and 35, respectively. In all regions, regardless of income, life expectancy after starting ART has improved, reflecting improvements in therapy and management such as improved ART regimens, earlier initiation of ART, and better socioeconomic and adherence support.[92]

Viral suppression is the key determinant of prognosis. Patients who achieve virologic suppression for at least 3 years without full immunologic recovery (CD4+ count <200 cells/mm^3) have 2.6 times greater all-cause mortality compared to those who achieve immunologic recovery (CD4+ >200 cells/mm^3). Treatment at diagnosis is associated with improved outcomes and better immune system recovery. Delaying ART until the patient's CD4+ count is less than 200 cells/mm^3 decreases the likelihood of the CD4+ count normalizing after multiple years of otherwise effective antiretroviral therapy, thereby increasing the patient's risk of **AIDS** and non-**AIDS**-related morbidity and mortality. Other factors correlating with poor immunologic recovery include older age, lower nadir CD4+ count, and extended ART initiation to viral suppression time. Hepatitis C, hepatitis B, and active injection drug use are identified as important factors contributing to higher morbidity and mortality among patients with HIV-1. For people who inject drugs, socioeconomic and adherence support should be offered, mainly if treatment is unavailable.[93][94][95]

Complications

Complications Related to HIV

The advent of ART has dramatically decreased the incidence of opportunistic infections and HIV-associated malignancies. However, progression to **AIDS** remains a significant complication of HIV. Screening and monitoring are warranted for **AIDS**-defining illnesses as appropriate to the patient's clinical status. In addition, screening and monitoring for specific HIV- and ART-related complications are listed below:

- HIV-associated neurocognitive disorders and psychiatric complications, with the use of efavirenz and, less frequently, rilpivirine and other INSTIs
- HIV-associated distal symmetric polyneuropathy
- HIV-associated lipodystrophy
- Mitochondrial toxicity of HIV NRTIs
- HIV-associated Kaposi sarcoma inflammatory cytokine **syndrome** and multicentric Castleman disease
- Hematological malignancies, including primary effusion, follicular, non-Hodgkin, Burkitt, and diffuse large B-cell lymphomas [96][97][98]

Please see StatPearls' companion resources, "**Acquired** Immune Deficiency **Syndrome**," "HIV Neurocognitive Disorders," and "HIV-Associated Lipodystrophy" for more information.

ART-Related Complications

The advent of ART has also raised the risk of cardiovascular disease morbidity and mortality. Patients with HIV experience age-related comorbidities such as cardiovascular disease more frequently, and much of the long-term care for patients with HIV focuses on minimizing cardiovascular risks. Multiple different factors contribute to increased cardiovascular risk for patients with HIV, including:

- The prevalence of dyslipidemia among patients with HIV, with and without ART, is high.
- Glucose intolerance or diabetes frequently occurs in patients receiving ART; this may be due to specific ART drugs, such as earlier-generation protease inhibitors.
- Multiple ART regimens are associated with weight gain.

Weight gain is common among patients on ART and is 1 of the significant contributors to cardiovascular risk for patients with HIV. The exact mechanisms involved are unknown. Some ART agents contribute more to weight gain compared to others. INSTIs are associated with more weight gain compared to protease inhibitors or NNRTIs, and tenofovir alafenamide is associated with more weight gain compared to tenofovir disoproxil fumarate, abacavir, or zidovudine. Current guidelines recommend lifestyle modification counseling from the onset of ART to mitigate weight gain and metabolic complications. Routine screening for glucose intolerance, diabetes, and hyperlipidemia is recommended.[5][99]

Deterrence and Patient Education

Education, support, and counseling from the interdisciplinary care team are essential for patients with HIV. Patients can be referred to organizations such as the CDC or NIH, which offer freely accessible education.[NIH. Fact-sheets.]

HIV Treatment

Patients should be informed about the need for regular labwork and follow-up. They should also be encouraged to keep all medical appointments and speak freely and openly with their clinician to ensure that adverse effects, potential barriers to treatment, and other health concerns can be addressed effectively. Patients undergoing HIV treatment require consistent education and counseling to promote medication adherence, including the importance of starting ART as soon as possible after diagnosis and the need to take the prescribed medications in compliance.

Medication adherence is essential to achieve HIV viral load suppression. Viral load increases within weeks of stopping HIV medications and enhances the risk of developing resistant organisms, complications from HIV, and transmission. Overcoming the challenges with medication adherence includes seeking support through counseling, support groups, or consistent communication with the treating teams. Patients should be offered home nurse visits, blister packs, or automated reminders to support adherence.

Identifying the signs and symptoms that indicate toxicity from ART and the recommended next steps should be relayed when educating patients. Minor adverse effects, such as nausea upon initiation of therapy, can be managed with over-the-counter medications. Signs and symptoms of liver or kidney injury should lead patients to seek immediate medical care. Patients should be aware of the potential for drug-drug interactions and the importance of the pharmacist in managing their medications. They should be encouraged to document their medication regimen to maintain self-efficacy in treatment. Patients with HIV are at elevated risk of cardiac and metabolic complications, may face complications that affect nutrition, and may need to avoid certain foods due to the immunocompromised state. Lifestyle modifications to encourage healthy eating, regular exercise, and the management of other risk factors, such as smoking, are recommended.

Prevention of HIV Transmission

Patients with HIV are often highly motivated to prevent transmission to others, particularly when they have a partner who is not infected with HIV. Recent data in the United States reveal that every 10% increase in viral suppression on a population level is associated with a 4% decline in the incidence of HIV in the subsequent year. Clinical education and emphasis on undetectable equals untransmittable are crucial elements of HIV treatment, benefiting both the patient's health and that of their partner or partners. People of child-bearing age may be concerned about the transmission of HIV during pregnancy and should be aware of the options for treatment and the benefits of planning.

People with an undetectable viral load may continue to make proactive decisions to protect people within immediate contact. The person can correctly and consistently use condoms, choose sexual activities with lower risk, encourage their partners to take preexposure prophylaxis, and avoid sharing needles, syringes, and other drug injection equipment. People may be required to disclose their HIV or other communicable disease status, for example, to clinicians in jurisdictions with these requirements or to healthcare regulatory authorities if they provide healthcare services.[19]

Stigma, Discrimination, and Mental Health

Diagnosis with a chronic illness can be a significant source of stress for anyone, given the medical burden on lifestyle. The diagnosis can challenge one's sense of well-being or complicate existing mental health or other conditions. Individuals may feel sadness, hopelessness, or anger. In addition to the challenges of a new diagnosis of a serious chronic illness, patients with HIV face further difficulties due to stigma and discrimination, including self-stigma. Self-stigma occurs when patients with HIV internalize the negative opinions of others, such as believing only certain kinds of people acquire HIV or that they deserve to contract the disease of their behaviors.

The need to disclose HIV status to sexual or injection partners before sex or drug use can be uncomfortable and provoke anxiety, especially where punitive laws exist. Patients with HIV may have fears associated with protecting others, which limit their interactions with other people and lead to isolation. Referrals to a psychologist, social worker, specialized nurse, public health, other interdisciplinary team member, or support groups can assist patients in coping with social issues. Likewise, encouraging patients to share their HIV status with certain friends and family can lead to practical and emotional benefits. Please see StatPearls' companion resources, "HIV Antiretroviral Therapy," and "HIV Prevention," for more information.

Pearls and Other Issues

Clinicians must be aware of any rules and regulations regarding HIV screening, testing, reporting, and managing HIV in the jurisdiction where they practice. These rules and regulations vary widely. In some jurisdictions, rules and regulations may exist as public health acts and follow a progressive enforcement framework; in others, they may be incorporated into criminal law and carry significant penalties.

Relevant State Laws in the United States

Most states in the United States have defined guidelines in their administrative codes. For example, Florida Administrative Code Rule 64B8-13.005 states that every physician licensee must complete 1 hour of Category I American Medical Association CME that covers HIV and **AIDS** every 2 years. This requirement includes information regarding Florida State Law for HIV testing and test result reporting provided in statutes 381.004 and 384.25 mandating the following:

- Before HIV testing, the patient must be notified orally or in writing that the test is planned. The patient must be given the right to refuse testing, which is documented in the medical record.
- If the patient or their legal guardian signs a medical consent form for medical care in a healthcare setting, such as a clinic, emergency setting, or hospital, a separate consent form for an HIV test during the period in which the general consent is in effect is not required.
- In a nonhealthcare setting, such as community outreach programs, informed consent with the option to decline testing and information regarding sites that provide anonymous testing in the community must be obtained.
- In the event of a positive test result, the patient must receive appropriate care and medical support services, information on the importance of notifying partners who may have been exposed, and ways to prevent transmission.
- In the event of a negative test result, every effort should be made to notify the patient and provide information regarding ways to prevent the acquisition of HIV.

- In a healthcare setting, if the patient is discharged before the results are available, the county health department must notify the test subject to fulfill the responsibility after a positive test result.
- Preliminary (unconfirmed) tests that yield positive results can be revealed only when decisions about medical management cannot await confirmation, including the need to provide recommendations to the person tested. Results can be revealed only to specific people:
    - The person tested and clinicians responsible for the medical care and decision-making for the tested individual.
    - The person tested and clinicians responsible for the care and decision-making of a newborn who may be affected by these results.
    - Healthcare personnel subject to significant exposure from the person whose results were positive.
    - Individuals tested using rapid testing technologies under manufacturers' instructions approved by the United States Food and Drug Administration.
- Unconfirmed test results must not be presented to the patient as an HIV diagnosis. The rationale for releasing unconfirmed results must be documented in the chart. Confirmatory testing must be obtained, and the results must be communicated to the individual tested.
- Positive HIV test results, after confirmatory testing, may only be released to the tested individual or their designated legally authorized representative.
- Results must be reported to the State Health Department following rules for reporting and controlling disease. Results may also be shared with clinicians who use semen or body parts from an infected individual, health facility committees for purposes of program monitoring and evaluation, and authorized researchers and epidemiologists, as proscribed under appropriate statutes and procedures.
- The patient must provide written authorization for the release of such testing to any other individual or third-party payor for HIV test results to be released. In this scenario, consent beyond general consent is required to release medical records. A specific authorization for the release of HIV test results must be provided.
- If HIV testing is conducted due to medical personnel exposure, the occurrence should be documented and recorded only in the medical personnel's personnel records. In addition, the cost of the initial HIV test should be borne by the medical personnel or their employer.
- If the source of the exposure is unavailable or not voluntarily present for testing, the medical personnel or the employer may seek a court order for HIV testing from the source individual. The test results should be released to the source and the person who experienced the exposure.
- Clinicians, laboratories, and healthcare facilities that diagnose or treat individuals with HIV/**AIDS** must report the result no later than 2 weeks following the diagnosis or treatment as outlined above.
- Violation of these rules is subject to penalties, fines, and disciplinary actions.

Impact of Legislation on HIV Testing in the United States

Laws and regulations concerning HIV and **AIDS** are developed considering a variety of parameters that impact patients' willingness to test for HIV. For example, to provide patients with privacy, confidentiality, and dignity, the Florida legislature considered the need for informed consent and privacy in designing laws regarding HIV and other sexually transmitted diseases, including laws for reporting.

Informed consent

- Informed consent includes an explanation to the patient regarding confidentiality, mandatory reporting, and the opportunity for anonymous testing.

- This consent maintains that in a healthcare setting, a patient must be notified of a planned HIV test, and they have the right to refuse the test.
- Informed consent allows a legal guardian to provide informed consent if a person is incompetent, incapacitated, or a legal minor.

Confidentiality

- Confidentiality ensures information regarding a person's HIV status is kept confidential, except when:
    - The patient gives consent.
    - The data are provided for statistical purposes and exclude identifying information.
    - The clinician or facility must disclose the result for mandatory reporting to medical personnel, state agencies, or mandated court jurisdiction.
    - The information needs to be disclosed during a medical emergency; only relevant information for the patient's care can be disclosed.
- Consequences if confidentiality is violated include:
    - The person commits a misdemeanor of the first degree, which is punishable by a fine of up to $1000 and up to 1 year in prison.
    - A person who spreads information about a patient with HIV or another sexually transmitted disease for monetary gain or with malicious intent commits a felony in the third degree, which is punishable by a fine of up to $5,000 or imprisonment of up to 5 years.

Reporting

- Reporting ensures results are promptly and confidentially reported to the Florida Department of Health to allow for contact follow-up and other public health activities, such as surveillance. A positive test result or other diagnosis of HIV or **AIDS** must be reported within 2 weeks using the system developed by the CDC or an equivalent system to ensure confidentiality.
- The Department of Health may fine anyone who fails to report HIV or **AIDS** up to $500 for each offense, and a regulatory agency is informed of the violation.

Similar laws exist on these ethical principles in other settings worldwide, which are important to reference when treating 1 or more patients with HIV.

Enhancing Healthcare Team Outcomes

Almost 21 million lives have been saved with antiretroviral therapy worldwide. However, current prevention and treatment services miss or inadequately serve millions. Key indicators of the quality of HIV care for optimal patient and population health outcomes include the linkage of HIV-positive individuals to care, documentation of treatment by patients linked to care, and attainment of viral suppression among patients who are treated. For example, in the United States in 2021, 80% of patients with HIV were linked to care within 30 days of diagnosis, defined as at least 1 viral load or CD4+ test. However, of all people with an HIV diagnosis in 2021, only 54% were retained in care (defined as ≥2 viral loads or CD4+ tests ≥3 months apart in 2021), and only 66% were virally suppressed (defined as an HIV RNA level of <200 copies/mL).

Within countries, variability in key quality care indicators exists across populations. Although the disparities are greatest in low- and middle-income countries, significant inequities continue to exist in prevalence and incidence across population groups in countries with well-developed HIV responses. For example, compared to the general population in the United States, HIV disproportionately affects people who inject drugs, patients who live in the United States South, and patients who are Black, Hispanic, Latino, transgender, or men who have sex with men. Across the European Economic Area, migrants accounted for 44% of new HIV diagnoses in 2019.

A successful HIV response depends on multiple factors, including utilizing a team-based and patient-centered care approach, a focus on prevention in the community and healthcare settings, robust monitoring and surveillance systems, continuous program quality improvement, and supportive social and legal environments. An integrated interprofessional team including physicians, nurses, pharmacists, social workers, public health officials, and community partners is essential to improve clinical outcomes for patients with HIV, improve population health, and ultimately change the course of the global HIV pandemic.[24]

Patient-Centered, Team-Based Care

Patient-centered care facilitates the maximum benefit from prevention services, improving clinical and public health outcomes. As HIV is an epidemic that disproportionately affects marginalized populations, programming that places the individual at the center of care ensures equality, minimizes stigma, and overcomes socioeconomic barriers that limit care access. For example, patients with HIV or who are at risk for HIV acquisition and have underlying socioeconomic disadvantages or substance use disorders are at high risk for medical nonadherence. Physicians, nurse practitioners, and physician assistants all provide primary care to patients with HIV. Clinician use of current HIV guidelines, genotype resistance testing, and measures to support adherence to therapy ensures patients receive adequate medical treatment. Systematic monitoring for complications minimizes the risk and consequences of the disease and ART.

Nurses are essential in achieving care and public health goals by supporting patients in understanding, for example, the risk of transmission, complications, and the need for medication adherence. Home-visiting nurses can help patients remain compliant with medical care and laboratory testing. According to a study from sub-Saharan Africa, immediate ART at the time of home-based positive test results increased clinical follow-up and linkage to care. Nurses and nutritionists can monitor weight and promote adequate nutrition and hydration to promote overall health, minimize cardiovascular risks, and minimize the risk of HIV wasting **syndrome**.

Pharmacists augment the patient's understanding by discussing potential adverse effects of therapy, ways to minimize drug interactions, and ensuring patients know when to seek help should any treatment complications occur. Measures such as blister-packed medications can ease the burden of setting up pills, minimize the risk of incorrect dosing, and improve medication adherence. Public health nurses and physicians are important in connecting and following up with contacts to prevent further transmission. They have a primary role in preventing HIV in the community, including identifying and responding rapidly to HIV outbreaks in the community. They also support the patient care team in unusual instances where patients are persistently unwilling or unable to follow recommendations to prevent transmission.

Community health, peer support, and social workers are vital in promoting patient well-being and improving linkage to care. Social workers can allocate resources for transportation and childcare support, provide assistance with mental health services, or make referrals to finance medications. Community health and peer support workers, for example, assist in the development of stigma-free services or increase the availability of home-based services. Please see StatPearls' companion resource, "HIV Antiretroviral Therapy," for more information.[10]

Community HIV Prevention

Primordial, primary, and secondary prevention are all important in the context of improving outcomes for HIV. The percentage of new transmissions and the number of HIV-positive people who are aware of their HIV status are key quality indicators for prevention efforts. Worldwide, 86% of the 39 million people estimated to be living with HIV knew their status in 2022. In the United States, 87% of the estimated 1.2 million people living with HIV knew their status in 2021. Primordial prevention includes addressing the determinants of health that lead to increased risks for acquiring HIV, including poverty, discrimination, stigma, or other mechanisms that marginalize groups of people. Beneficial social and policy environments are essential in primordial prevention and the prevention and care spectrum.

Primary prevention targets patients who have risk factors, including public awareness and education regarding safe sexual practices and ways to reduce the risk of HIV transmission among people who inject drugs. The promotion of safer sexual practices, treatment of opioid use disorder, and widespread access to clean syringe services and other harm reduction approaches are effective prevention strategies that should be implemented across the globe.

[19] Voluntary medical circumcision for heterosexual males is an effective prevention approach in southern and eastern areas of Africa where HIV is highly prevalent. Preexposure prophylaxis is a highly effective strategy for patients at high risk, for example, due to a sexual partner who is HIV positive, having multiple sexual partners without using condoms consistently, or the use of injectable drugs.

Developing cost-effective recommendations and education to screen for HIV is a critical component of prevention. For example, the United States Preventive Services Task Force (USPSTF) recommends that clinicians in the United States screen all pregnant women and at-risk persons aged 15 to 65, with particular emphasis on individuals at high risk of infection.[20] Maternal HIV screening has resulted in a significant decline in mother-to-child HIV transmission, preventing nearly 22,000 perinatal infections between 1994 and 2010.[21] Treatment as prevention recognizes that HIV is not sexually transmitted if the viral load is undetectable (defined as <200 copies of HIV-1 RNA/mL of plasma).[22][23] Otherwise known as undetectable=utransmittable or U=U, evidence is increasing of the effectiveness for those who share drug injection equipment. Emphasis on U=U is a strong motivator for patient adherence to medication. However, with undetectable viral loads, HIV transmission occurs perinatally and through breast milk. Please see StatPearls' companion resource, "Prevention of HIV," for more information.

HIV Prevention in Healthcare Settings

In the healthcare context, the use of rigorous infection prevention and control procedures has led to widespread decreases in occupationally and iatrogenically transmitted HIV. The elimination of the reuse of needles, syringes, and other medical equipment that can transmit HIV has been a global success story in many countries. The widespread implementation of standard precautions, previously called universal precautions, is another key preventive strategy. Initially developed to prevent HIV transmission, standard precautions are utilized to avoid the transmission of all infectious agents. The first line of defense to break the chain of transmission of infectious agents in healthcare settings is the application of standard precautions, irrespective of their known or suspected infection status. The type of infection control practice necessary is based on the level of anticipated contact with the patient and assumes that any patient's blood or body fluids may contain an infectious agent.

Hand hygiene is the most important measure to prevent transmission of disease, encompassing washing hands with soap and water for at least 40 to 60 seconds when visibly soiled, after restroom use, or potential exposure to spore-forming organisms. Alcohol-based hand rubs can otherwise be used. Clinicians should wash their hands between patients immediately after gloves are removed and before and after any direct patient contact or contact with invasive devices, blood or body fluids, secretions, mucous membranes, or nonintact skin if gloves are worn. Gloves, masks, goggles, eye visors, face shields, or gowns are used when blood, body fluids, secretions, or excretions could cause contamination. Needles and sharps should be discarded immediately in appropriate puncture-resistant containers.

Occupational post-exposure prophylaxis is crucial for preventing infections in healthcare settings, as it is challenging to avoid accidental exposures to potentially infectious body fluids. Post-exposure prophylaxis involves the provision of a minimum of 3 antiretroviral drugs for 28 days for all occupational exposures to HIV after the exposure and within 72 hours. Counseling, HIV testing at baseline and follow-up, and monitoring for toxicity are also provided. Using the post-exposure prophylaxis consultation service for clinicians is recommended in all cases. Please see StatPearls' companion resource, "Universal Precautions," for more information.[24][27]

Monitoring, Surveillance, and Continuous Quality Improvement

Collecting and using reliable, granular, and timely data are essential for improving team performance and population health. Using data means identifying at-risk clients, setting targets, and developing strategies. UNAIDS first proposed a set of global *90-90-90* HIV prevention targets for HIV in 2014 by countries of the United Nations General Assembly. Although these goals were not reached, many countries made significant progress. Setting *95-95-95* goals for 2025, the goals were updated in 2020 and adopted by the United Nations General Assembly in 2021 and include:

- 95% of all people with HIV who know their status
- 95% of all people who have HIV and receive antiretroviral therapy
- 95% of all patients on ART who achieve viral suppression

The projected impact is fewer than 370,000 people acquiring HIV and fewer than 250,000 people dying from HIV worldwide in 2025. The WHO and country and state disease control and prevention centers, such as the United States CDC, are primary data sources for monitoring HIV trends and progress toward goals. Behavioral and clinical characteristics of adults with HIV are followed in the United States by the Medical Monitoring Project. Instituted in 2005, this is a cross-sectional, nationally representative, complex sample survey. The CDC's AtlasPlus allows clinicians to explore national HIV, hepatitis, sexually transmitted infections, and tuberculosis data relevant to their population.[CDC. NCCHHSTP AtlasPlus 2023.] All data from 2020 and 2021 must be interpreted in the context of decreased case surveillance and services during the COVID-19 pandemic. Consequently, clinicians can improve care and contribute to population health improvements by completing required documentation, participating in initiatives to streamline surveillance, and engaging in continuous program quality improvement within their practice setting utilizing public health data.

Social and Policy Environments

Local legislative bodies, policy-making organizations, and institutions can improve patient-centered care and population health outcomes for patients with HIV by basing legislative and policy frameworks that influence the effectiveness of HIV and **AIDS** programming on recommendations developed by organizations such as the UNAIDS, WHO, and the NIH. The WHO recommends specific HIV policies that promote optimal HIV testing and care and track any country's progression. These recommendations include the use of preexposure prophylaxis, dual HIV and syphilis rapid diagnostic tests, self-testing, optimal first- and second-line treatments, routine viral load testing, and same-day ART initiation, amongst other measures, in national policies and guidelines. UNAIDS, WHO, and national HIV strategies outline key social, legal, and policy factors that lead to better patient and population health outcomes for HIV prevention and care.

Political commitment and adequate resources are fundamental building blocks for an adequate public health response. The setting of targets can garner political commitment. The United States National HIV/**AIDS** Strategy and the Ending the HIV Epidemic in the United States initiative aims to reduce new HIV transmissions in the United States by 90% by 2030, prioritizing the reduction of HIV-related health disparities and inequities and improving the well-being of patients with HIV.[CDC. Ending the HIV epidemic 2023.] A renewed global commitment to funding is necessary. The gap between actual and required funding is widening in low- and middle-income countries, mainly due to a decrease in the proportion of funding provided by high-income nations. Fully funded, resilient, integrated, and accessible public and community health systems lead to increased uptake of both HIV and other health services. Social and structural inequalities to HIV-related services, resources, and tools can be addressed through universal health care, shared service delivery models, and measures to improve access to medicines and health technologies for patients experiencing marginalization, including uninsured or underinsured individuals in the United States.

The removal, or at a minimum, the nonenforcement of harmful laws must be a priority. For example, laws criminalizing HIV exposure, non-disclosure, and transmission discourage people from getting tested, increasing transmission and creating a barrier to early treatment. Likewise, the criminalization of particular groups of people undermines an effective HIV response by discouraging sex workers, men who have sex with men, and those who are transgender or inject drugs from using prevention and treatment programs due to fear of arrest and prosecution. A 2015 study estimated that 33% to 46% of all new HIV cases over a decade could be avoided by decriminalizing sex work worldwide.

Many countries have amended laws to remove barriers to the HIV response, including decriminalizing vertical HIV transmission in Belize in 2023, sex work in Belgium in 2022, and same-sex sexual relations in several countries in 2022 and 2023. However, concerning setbacks occurred in many countries, including Indonesia. Strengthening laws, policies, and systems that realize and protect human rights is also necessary. For example, the promotion of gender equity and safe work environments leads to lower vulnerability for women and girls. Modeling studies from Canada and Kenya show that the elimination of violence by police, clients, and strangers could avert 17% to 20% of new HIV cases among women who are sex workers and their clients in a decade.

Strengthened policies and laws augment the education and community action necessary to address the stigma and discrimination that impact the health and well-being of patients with HIV. According to UNAIDS, 1 in 3 countries

reporting on HIV policies indicate that 10% of men who have sex with men and more than 50% of sex workers, people who inject drugs, and transgender individuals avoid healthcare due to fears of stigma, discrimination, or confidentiality. Stigma and discrimination, rooted in outdated fears of HIV from the 1980s, must be addressed through open discussion about HIV using non-stigmatizing language both within and outside of health care. Discrimination can manifest in healthcare settings as the refusal of service to patients with HIV, the use of stigmatizing language, or the absence of appropriate services, resources, or tools.

Review Questions

- Access free multiple choice questions on this topic.
- Click here for a simplified version.
- Comment on this article.

References

1. Meissner ME, Talledge N, Mansky LM. Molecular Biology and Diversification of Human Retroviruses. Front Virol. 2022;2 [PMC free article: PMC9242851] [PubMed: 35783361]
2. Kahn JO, Walker BD. Acute human **immunodeficiency** virus type 1 infection. N Engl J Med. 1998 Jul 02;339(1):33-9. [PubMed: 9647878]
3. Xu Y, Ollerton MT, Connick E. Follicular T-cell subsets in HIV infection: recent advances in pathogenesis research. Curr Opin HIV **AIDS**. 2019 Mar;14(2):71-76. [PMC free article: PMC6355349] [PubMed: 30585797]
4. Chadburn A, Abdul-Nabi AM, Teruya BS, Lo AA. Lymphoid proliferations associated with human **immunodeficiency** virus infection. Arch Pathol Lab Med. 2013 Mar;137(3):360-70. [PubMed: 23451747]
5. Thompson MA, Horberg MA, Agwu AL, Colasanti JA, Jain MK, Short WR, Singh T, Aberg JA. Primary Care Guidance for Persons With Human **Immunodeficiency** Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021 Dec 06;73(11):e3572-e3605. [PubMed: 33225349]
6. Thio CL, Seaberg EC, Skolasky R, Phair J, Visscher B, Muñoz A, Thomas DL., Multicenter **AIDS** Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002 Dec 14;360(9349):1921-6. [PubMed: 12493258]
7. Yin Z, Rice BD, Waight P, Miller E, George R, Brown AE, Smith RD, Slack M, Delpech VC. Invasive pneumococcal disease among HIV-positive individuals, 2000-2009. **AIDS**. 2012 Jan 02;26(1):87-94. [PubMed: 22008657]
8. Brew BJ, Garber JY. Neurologic sequelae of primary HIV infection. Handb Clin Neurol. 2018;152:65-74. [PubMed: 29604985]
9. Robb ML, Eller LA, Kibuuka H, Rono K, Maganga L, Nitayaphan S, Kroon E, Sawe FK, Sinei S, Sriplienchan S, Jagodzinski LL, Malia J, Manak M, de Souza MS, Tovanabutra S, Sanders-Buell E, Rolland M, Dorsey-Spitz J, Eller MA, Milazzo M, Li Q, Lewandowski A, Wu H, Swann E, O'Connell RJ, Peel S, Dawson P, Kim JH, Michael NL., RV 217 Study Team. Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand. N Engl J Med. 2016 Jun 02;374(22):2120-30. [PMC free article: PMC5111628] [PubMed: 27192360]
10. Lavreys L, Baeten JM, Chohan V, McClelland RS, Hassan WM, Richardson BA, Mandaliya K, Ndinya-Achola JO, Overbaugh J. Higher set point plasma viral load and more-severe acute HIV type 1 (HIV-1) illness predict mortality among high-risk HIV-1-infected African women. Clin Infect Dis. 2006 May 01;42(9):1333-9. [PubMed: 16586394]
11. Lapins J, Gaines H, Lindbäck S, Lidbrink P, Emtestam L. Skin and mucosal characteristics of symptomatic primary HIV-1 infection. **AIDS** Patient Care STDS. 1997 Apr;11(2):67-70. [PubMed: 11361765]
12. Osmond D, Chaisson R, Moss A, Bacchetti P, Krampf W. Lymphadenopathy in asymptomatic patients seropositive for HIV. N Engl J Med. 1987 Jul 23;317(4):246. [PubMed: 3474522]
13. Suryana K, Suharsono H, Antara IGPJ. Factors Associated with Oral Candidiasis in People Living with HIV/**AIDS**: A Case Control Study. HIV **AIDS** (Auckl). 2020;12:33-39. [PMC free article: PMC6969700] [PubMed: 32021484]
14. Apalata T, Longo-Mbenza B, Sturm A, Carr W, Moodley P. Factors Associated with Symptomatic Vulvovaginal Candidiasis: A Study among Women Attending a Primary Healthcare Clinic in Kwazulu-Natal, South Africa.

Ann Med Health Sci Res. 2014 May;4(3):410-6. [PMC free article: PMC4071743] [PubMed: 24971218]
15. Ottria L, Lauritano D, Oberti L, Candotto V, Cura F, Tagliabue A, Tettamanti L. Prevalence of HIV-related oral manifestations and their association with HAART and CD4+ T cell count: a review. J Biol Regul Homeost Agents. 2018 Jan-Feb;32(2 Suppl. 1):51-59. [PubMed: 29460518]
16. Brown P, Elmasry S, Olagunju A, Garcia S, Sarihan M. A Case of Disseminated Cutaneous Herpes Simplex Virus-1 as the First Manifestation of Human **Immunodeficiency** Virus Infection. J Investig Med High Impact Case Rep. 2021 Jan-Dec;9:23247096211045245. [PMC free article: PMC8447091] [PubMed: 34521234]
17. Timoney MT, Atrio JM, McGowan JP, Fine SM, Vail R, Merrick ST, Radix A, Hoffmann CJ, Gonzalez CJ. Screening for Cervical Dysplasia and Cancer in Adults With HIV [Internet]. Johns Hopkins University; Baltimore (MD): Mar, 2022. [PubMed: 35467815]
18. Knight CL. Physical Examination in Human **Immunodeficiency** Virus Disease. Med Clin North Am. 2022 May;106(3):527-536. [PubMed: 35491072]
19. Centers for Disease Control and Prevention (CDC). Revised surveillance case definition for HIV infection--United States, 2014. MMWR Recomm Rep. 2014 Apr 11;63(RR-03):1-10. [PubMed: 24717910]
20. Damtie D, Yismaw G, Woldeyohannes D, Anagaw B. Common opportunistic infections and their CD4 cell correlates among HIV-infected patients attending at antiretroviral therapy clinic of Gondar University Hospital, Northwest Ethiopia. BMC Res Notes. 2013 Dec 14;6:534. [PMC free article: PMC3866565] [PubMed: 24330921]
21. Kumarasamy N, Vallabhaneni S, Flanigan TP, Mayer KH, Solomon S. Clinical profile of HIV in India. Indian J Med Res. 2005 Apr;121(4):377-94. [PubMed: 15817951]
22. Burudpakdee C, Near AM, Tse J, Faccone J, Rodriguez PL, Karichu JK, Cheng MM. Real-world HIV diagnostic testing patterns in the United States. Am J Manag Care. 2022 Feb 01;28(2):e42-e48. [PubMed: 35139295]
23. Goldschmidt R, Chu C. HIV Infection in Adults: Initial Management. Am Fam Physician. 2021 Apr 01;103(7):407-416. [PubMed: 33788514]
24. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, Lehmann C, Springer SA, Sax PE, Thompson MA, Benson CA, Buchbinder SP, Del Rio C, Eron JJ, Günthard HF, Molina JM, Jacobsen DM, Saag MS. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2023 Jan 03;329(1):63-84. [PubMed: 36454551]
25. Lévy Y, Lelièvre JD, Assoumou L, Aznar E, Pulido F, Tambussi G, Crespo M, Meybeck A, Molina JM, Delaugerre C, Izopet J, Peytavin G, Cardon F, Diallo A, Lancar R, Béniguel L, Costagliola D. Addition of Maraviroc Versus Placebo to Standard Antiretroviral Therapy for Initial Treatment of Advanced HIV Infection: A Randomized Trial. Ann Intern Med. 2020 Mar 03;172(5):297-305. [PubMed: 32040959]
26. Saag MS. HIV Infection - Screening, Diagnosis, and Treatment. N Engl J Med. 2021 Jun 03;384(22):2131-2143. [PubMed: 34077645]
27. Jacobson K, Ogbuagu O. Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naïve human **immunodeficiency** virus-infected patients compared to non-nucleoside and protease inhibitor-based regimens in a real-world clinical setting: A retrospective cohort study. Medicine (Baltimore). 2018 Oct;97(43):e13016. [PMC free article: PMC6221636] [PubMed: 30412140]
28. INSIGHT START Study Group. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G, Llibre JM, Molina JM, Munderi P, Schechter M, Wood R, Klingman KL, Collins S, Lane HC, Phillips AN, Neaton JD. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807. [PMC free article: PMC4569751] [PubMed: 26192873]
29. Diaz RS, Hunter JR, Camargo M, Dias D, Galinskas J, Nassar I, de Lima IB, Caldeira DB, Sucupira MC, Schechter M. Dolutegravir-associated resistance mutations after first-line treatment failure in Brazil. BMC Infect Dis. 2023 May 24;23(1):347. [PMC free article: PMC10210384] [PubMed: 37226112]
30. DeKoven S, Naccarato M, Brumme CJ, Tan DHS. Treatment-emergent reverse transcriptase resistance during antiretroviral therapy with bictegravir, tenofovir alafenamide, and emtricitabine: A case series. HIV Med. 2023 Nov;24(11):1137-1143. [PubMed: 37317505]
31. Wensing AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Günthard HF, Paredes R, Shafer RW, Richman DD. 2022 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2022 Oct;30(4):559-574. [PMC free article: PMC9681141] [PubMed: 36375130]
32.

Margot NA, Wong P, Kulkarni R, White K, Porter D, Abram ME, Callebaut C, Miller MD. Commonly Transmitted HIV-1 Drug Resistance Mutations in Reverse-Transcriptase and Protease in Antiretroviral Treatment-Naive Patients and Response to Regimens Containing Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide. J Infect Dis. 2017 Mar 15;215(6):920-927. [PubMed: 28453836]

33. Siedner MJ, Moosa MS, McCluskey S, Gilbert RF, Pillay S, Aturinda I, Ard K, Muyindike W, Musinguzi N, Masette G, Pillay M, Moodley P, Brijkumar J, Rautenberg T, George G, Gandhi RT, Johnson BA, Sunpath H, Bwana MB, Marconi VC. Resistance Testing for Management of HIV Virologic Failure in Sub-Saharan Africa : An Unblinded Randomized Controlled Trial. Ann Intern Med. 2021 Dec;174(12):1683-1692. [PMC free article: PMC8688215] [PubMed: 34698502]
34. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, Asienzo J, Kaimal A, Mirembe G, Lugemwa A, Ategeka G, Borok M, Mugerwa H, Siika A, Odongpiny ELA, Castelnuovo B, Kiragga A, Kambugu A., NADIA Trial Team. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022 Jun;9(6):e381-e393. [PubMed: 35460601]
35. Blanco JL, Marcelin AG, Katlama C, Martinez E. Dolutegravir resistance mutations: lessons from monotherapy studies. Curr Opin Infect Dis. 2018 Jun;31(3):237-245. [PubMed: 29634660]
36. Hanna GJ, D'Aquila RT. Clinical use of genotypic and phenotypic drug resistance testing to monitor antiretroviral chemotherapy. Clin Infect Dis. 2001 Mar 01;32(5):774-82. [PubMed: 11229846]
37. Patel DM, Moyo C, Bositis CM. A Review of the 2010 WHO Adult Antiretroviral Therapy Guidelines: Implications and Realities of These Changes for Zambia. Med J Zambia. 2010;37(2):118-124. [PMC free article: PMC3506379] [PubMed: 23193354]
38. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach: 2010 Revision. World Health Organization; Geneva: 2010. [PubMed: 23741771]
39. Segal-Maurer S, DeJesus E, Stellbrink HJ, Castagna A, Richmond GJ, Sinclair GI, Siripassorn K, Ruane PJ, Berhe M, Wang H, Margot NA, Dvory-Sobol H, Hyland RH, Brainard DM, Rhee MS, Baeten JM, Molina JM., CAPELLA Study Investigators. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2022 May 12;386(19):1793-1803. [PubMed: 35544387]
40. Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina JM, Grinsztejn B, Diaz R, Castagna A, Kumar P, Latiff G, DeJesus E, Gummel M, Gartland M, Pierce A, Ackerman P, Llamoso C, Lataillade M., BRIGHTE Trial Team. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2020 Mar 26;382(13):1232-1243. [PubMed: 32212519]
41. Blair HA. Ibalizumab: A Review in Multidrug-Resistant HIV-1 Infection. Drugs. 2020 Feb;80(2):189-196. [PubMed: 31970712]
42. Reeves I, Cromarty B, Deayton J, Dhairyawan R, Kidd M, Taylor C, Thornhill J, Tickell-Painter M, van Halsema C. British HIV Association guidelines for the management of HIV-2 2021. HIV Med. 2021 Dec;22 Suppl 4:1-29. [PubMed: 34927347]
43. Raugi DN, Smith RA, Ba S, Toure M, Traore F, Sall F, Pan C, Blankenship L, Montano A, Olson J, Dia Badiane NM, Mullins JI, Kiviat NB, Hawes SE, Sow PS, Gottlieb GS., University of Washington-Dakar HIV-2 Study Group. Complex patterns of protease inhibitor resistance among antiretroviral treatment-experienced HIV-2 patients from Senegal: implications for second-line therapy. Antimicrob Agents Chemother. 2013 Jun;57(6):2751-60. [PMC free article: PMC3716120] [PubMed: 23571535]
44. Smith RA, Raugi DN, Pan C, Sow PS, Seydi M, Mullins JI, Gottlieb GS., University of Washington-Dakar HIV-2 Study Group. In vitro activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. Retrovirology. 2015 Feb 05;12:10. [PMC free article: PMC4328052] [PubMed: 25808007]
45. Volberding PA. HIV Treatment and Prevention: An Overview of Recommendations From the IAS-USA Antiretroviral Guidelines Panel. Top Antivir Med. 2017 Feb/Mar;25(1):17-24. [PMC free article: PMC5677040] [PubMed: 28402930]
46. Soriano V, Dona C, Rodríguez-Rosado R, Barreiro P, González-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. **AIDS**. 2000 Mar 10;14(4):383-6. [PubMed: 10770540]
47. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. Arch Intern Med. 1996 Jan 22;156(2):177-88. [PubMed: 8546551]

48. Thera MA, Sehdev PS, Coulibaly D, Traore K, Garba MN, Cissoko Y, Kone A, Guindo A, Dicko A, Beavogui AH, Djimde AA, Lyke KE, Diallo DA, Doumbo OK, Plowe CV. Impact of trimethoprim-sulfamethoxazole prophylaxis on falciparum malaria infection and disease. J Infect Dis. 2005 Nov 15;192(10):1823-9. [PMC free article: PMC2740817] [PubMed: 16235184]
49. Bozzette SA, Finkelstein DM, Spector SA, Frame P, Powderly WG, He W, Phillips L, Craven D, van der Horst C, Feinberg J. A randomized trial of three antipneumocystis agents in patients with advanced human **immunodeficiency** virus infection. NIAID **AIDS** Clinical Trials Group. N Engl J Med. 1995 Mar 16;332(11):693-9. [PubMed: 7854375]
50. Stahl-Bayliss CM, Kalman CM, Laskin OL. Pentamidine-induced hypoglycemia in patients with the **acquired** immune deficiency **syndrome**. Clin Pharmacol Ther. 1986 Mar;39(3):271-5. [PubMed: 3485027]
51. Pamba A, Richardson ND, Carter N, Duparc S, Premji Z, Tiono AB, Luzzatto L. Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. Blood. 2012 Nov 15;120(20):4123-33. [PubMed: 22993389]
52. Hughes W, Leoung G, Kramer F, Bozzette SA, Safrin S, Frame P, Clumeck N, Masur H, Lancaster D, Chan C. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with **AIDS**. N Engl J Med. 1993 May 27;328(21):1521-7. [PubMed: 8479489]
53. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for Pneumocystis carinii pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet. 1999 Jan 16;353(9148):201-3. [PubMed: 9923876]
54. Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection. Cochrane Database Syst Rev. 2015 Apr 02;2015(4):CD006150. [PMC free article: PMC6472444] [PubMed: 25835432]
55. Smego RA, Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. Arch Intern Med. 2001 Jun 25;161(12):1529-33. [PubMed: 11427101]
56. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-Toxoplasma effects of dapsone alone and combined with pyrimethamine. Antimicrob Agents Chemother. 1991 Feb;35(2):252-5. [PMC free article: PMC244986] [PubMed: 2024957]
57. Miro JM, Lopez JC, Podzamczer D, Peña JM, Alberdi JC, Martínez E, Domingo P, Cosin J, Claramonte X, Arribas JR, Santín M, Ribera E., GESIDA 04/98 Study Group. Discontinuation of primary and secondary Toxoplasma gondii prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. Clin Infect Dis. 2006 Jul 01;43(1):79-89. [PubMed: 16758422]
58. Sheth AN, Althoff KN, Brooks JT. Influenza susceptibility, severity, and shedding in HIV-infected adults: a review of the literature. Clin Infect Dis. 2011 Jan 15;52(2):219-27. [PMC free article: PMC4990828] [PubMed: 21288848]
59. Cohen C, Moyes J, Tempia S, Groom M, Walaza S, Pretorius M, Dawood H, Chhagan M, Haffejee S, Variava E, Kahn K, Tshangela A, von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Severe influenza-associated respiratory infection in high HIV prevalence setting, South Africa, 2009-2011. Emerg Infect Dis. 2013 Nov;19(11):1766-74. [PMC free article: PMC3837669] [PubMed: 24209781]
60. Harris CM, Wu HM, Li J, Hall HI, Lee A, Zell E, Harrison LH, Petit S, Farley MM, Lynfield R, Miller L, Nichols M, Reingold A, Schaffner W, Thomas A, MacNeil JR, Clark TA, Cohn AC. Meningococcal Disease in Patients With Human **Immunodeficiency** Virus Infection: A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. Open Forum Infect Dis. 2016 Oct;3(4):ofw226. [PMC free article: PMC5170493] [PubMed: 28018927]
61. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, Zilmer K, Vella S, Kirk O, Lundgren JD., EuroSIDA Group. Hepatitis B and HIV: prevalence, **AIDS** progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. **AIDS**. 2005 Mar 24;19(6):593-601. [PubMed: 15802978]
62. Palefsky J. Human papillomavirus-related disease in people with HIV. Curr Opin HIV **AIDS**. 2009 Jan;4(1):52-6. [PMC free article: PMC2756707] [PubMed: 19339939]
63. Al-Omairi O, Elgalib A, Al Kindi H. HIV Drug Resistance among Patients Failing Therapy at a Tertiary Center in Oman: A Case Record Review. Oman Med J. 2019 Nov;34(6):490-495. [PMC free article: PMC6851064] [PubMed: 31745412]

64. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach [Internet]. World Health Organization; Geneva: Jul, 2021. [PubMed: 34370423]
65. Abram ME, Ferris AL, Das K, Quinoñes O, Shao W, Tuske S, Alvord WG, Arnold E, Hughes SH. Mutations in HIV-1 reverse transcriptase affect the errors made in a single cycle of viral replication. J Virol. 2014 Jul;88(13):7589-601. [PMC free article: PMC4054409] [PubMed: 24760888]
66. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. World Health Organization; Geneva: 2016. [PubMed: 27466667]
67. Demeke Bayou F, Nigussie Amare S. Time to Immunologic Recovery and Its Determinant Factors Among Adult HIV Patients Who Initiated Antiretroviral Treatment at Hiwot Fana Specialized University Hospital, Harar, Ethiopia. HIV **AIDS** (Auckl). 2021;13:1009-1014. [PMC free article: PMC8647166] [PubMed: 34880680]
68. Gunda DW, Kilonzo SB, Kamugisha E, Rauya EZ, Mpondo BC. Prevalence and risk factors of poor immune recovery among adult HIV patients attending care and treatment centre in northwestern Tanzania following the use of highly active antiretroviral therapy: a retrospective study. BMC Res Notes. 2017 Jun 08;10(1):197. [PMC free article: PMC5465538] [PubMed: 28595630]
69. Mendicino CCP, Moodie EEM, Guimarães MDC, Pádua CAM. Immune recovery after antiretroviral therapy initiation: a challenge for people living with HIV in Brazil. Cad Saude Publica. 2021;37(9):e00143520. [PubMed: 34669770]
70. Fan L, Li P, Yu A, Liu D, Wang Z, Wu Y, Zhang D, Zou M, Ma P. Prevalence of and prognosis for poor immunological recovery by virally suppressed and aged HIV-infected patients. Front Med (Lausanne). 2023;10:1259871. [PMC free article: PMC10625403] [PubMed: 37928477]
71. Dean L. Abacavir Therapy and *HLA-B*57:01* Genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. Medical Genetics Summaries [Internet]. National Center for Biotechnology Information (US); Bethesda (MD): Sep 1, 2015. [PubMed: 28520363]
72. Sabin CA, Ryom L, d'Arminio Monforte A, Hatleberg CI, Pradier C, El-Sadr W, Kirk O, Weber R, Phillips AN, Mocroft A, Bonnet F, Law M, de Wit S, Reiss P, Lundgren JD., D:A:D Study Group. Abacavir use and risk of recurrent myocardial infarction. **AIDS**. 2018 Jan 02;32(1):79-88. [PubMed: 29028664]
73. Nan C, Shaefer M, Urbaityte R, Oyee J, Hopking J, Ragone L, Perger T, Win B, Vangerow H, McCoig C, Vannappagari V. Abacavir Use and Risk for Myocardial Infarction and Cardiovascular Events: Pooled Analysis of Data From Clinical Trials. Open Forum Infect Dis. 2018 May;5(5):ofy086. [PMC free article: PMC5946856] [PubMed: 29766019]
74. Karris MY. Short Communication: Resolution of Tenofovir Disoproxil Fumarate Induced Fanconi **Syndrome** with Switch to Tenofovir Alafenamide Fumarate in a HIV-1 and Hepatitis B Coinfected Patient. **AIDS** Res Hum Retroviruses. 2017 Jul;33(7):718-722. [PMC free article: PMC5512307] [PubMed: 28403627]
75. Shirasaka T, Tadokoro T, Yamamoto Y, Fukutake K, Kato Y, Odawara T, Nakamura T, Ajisawa A, Negishi M. Investigation of emtricitabine-associated skin pigmentation and safety in HIV-1-infected Japanese patients. J Infect Chemother. 2011 Oct;17(5):602-8. [PubMed: 21369776]
76. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. Drugs. 1999 Nov;58(5):919-49. [PubMed: 10595868]
77. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. **AIDS** Read. 2003 Jul;13(7):344-8. [PubMed: 12889452]
78. Tuon FF, Guastini CM, Boulos MI. Acute pancreatitis associated with lamivudine therapy for chronic B hepatitis. Braz J Infect Dis. 2008 Aug;12(4):263. [PubMed: 19030723]
79. Dheda M. Efavirenz and neuropsychiatric effects. South Afr J HIV Med. 2017;18(1):741. [PMC free article: PMC5843229] [PubMed: 29568641]
80. Valenzuela-Rodriguez G, Diaz-Arocutipa C, Collins JA, Hernandez AV. Weight and Metabolic Outcomes in Naïve HIV Patients Treated with Integrase Inhibitor-Based Antiretroviral Therapy: A Systematic Review and Meta-Analysis. J Clin Med. 2023 May 24;12(11) [PMC free article: PMC10253862] [PubMed: 37297839]
81. Stader F, Battegay M, Marzolini C. Physiologically-Based Pharmacokinetic Modeling to Support the Clinical Management of Drug-Drug Interactions With Bictegravir. Clin Pharmacol Ther. 2021 Nov;110(5):1231-1239. [PMC free article: PMC8597021] [PubMed: 33626178]
82.

Kourtis AP, Zhu W, Lampe MA, Huang YA, Hoover KW. Dolutegravir and pregnancy outcomes including neural tube defects in the USA during 2008-20: a national cohort study. Lancet HIV. 2023 Sep;10(9):e588-e596. [PMC free article: PMC10614030] [PubMed: 37506721]

83. Calza L, Danese I, Colangeli V, Vandi G, Manfredi R, Girometti N, Borderi M, Appolloni L, Puggioli C, Viale P. Skeletal muscle toxicity in HIV-1-infected patients treated with a raltegravir-containing antiretroviral therapy: a cohort study. **AIDS** Res Hum Retroviruses. 2014 Dec;30(12):1162-9. [PubMed: 25369244]
84. Teppler H, Brown DD, Leavitt RY, Sklar P, Wan H, Xu X, Lievano F, Lehman HP, Mast TC, Nguyen BY. Long-term safety from the raltegravir clinical development program. Curr HIV Res. 2011 Jan;9(1):40-53. [PMC free article: PMC3267161] [PubMed: 21198432]
85. DAD Study Group. Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte Ad, El-Sadr W, Thiébaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007 Apr 26;356(17):1723-35. [PubMed: 17460226]
86. Marin RC, Behl T, Negrut N, Bungau S. Management of Antiretroviral Therapy with Boosted Protease Inhibitors-Darunavir/Ritonavir or Darunavir/Cobicistat. Biomedicines. 2021 Mar 18;9(3) [PMC free article: PMC8003312] [PubMed: 33803812]
87. Bissio E, Lopardo GD. Incidence of hyperbilirubinemia and jaundice due to atazanavir in a cohort of Hispanic patients. **AIDS** Res Hum Retroviruses. 2013 Mar;29(3):415-7. [PMC free article: PMC3581036] [PubMed: 23121190]
88. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda (MD): Jul 18, 2024. Darunavir. [PubMed: 31643326]
89. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, Nadler J, Clotet B, Karlsson A, Wohlfeiler M, Montana JB, McHale M, Sullivan J, Ridgway C, Felstead S, Dunne MW, van der Ryst E, Mayer H., MOTIVATE Study Teams. Maraviroc for previously treated patients with R5 HIV-1 infection. N Engl J Med. 2008 Oct 02;359(14):1429-41. [PMC free article: PMC3078519] [PubMed: 18832244]
90. Ball RA, Kinchelow T., ISR Substudy Group. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. J Am Acad Dermatol. 2003 Nov;49(5):826-31. [PubMed: 14576660]
91. Iacob SA, Iacob DG, Jugulete G. Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations. Front Pharmacol. 2017;8:831. [PMC free article: PMC5703840] [PubMed: 29218008]
92. Teeraananchai S, Kerr SJ, Amin J, Ruxrungtham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med. 2017 Apr;18(4):256-266. [PubMed: 27578404]
93. Engsig FN, Zangerle R, Katsarou O, Dabis F, Reiss P, Gill J, Porter K, Sabin C, Riordan A, Fätkenheuer G, Gutiérrez F, Raffi F, Kirk O, Mary-Krause M, Stephan C, de Olalla PG, Guest J, Samji H, Castagna A, d'Arminio Monforte A, Skaletz-Rorowski A, Ramos J, Lapadula G, Mussini C, Force L, Meyer L, Lampe F, Boufassa F, Bucher HC, De Wit S, Burkholder GA, Teira R, Justice AC, Sterling TR, M Crane H, Gerstoft J, Grarup J, May M, Chêne G, Ingle SM, Sterne J, Obel N., Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. Clin Infect Dis. 2014 May;58(9):1312-21. [PMC free article: PMC6276895] [PubMed: 24457342]
94. Kelley CF, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, Crane HM, Willig J, Mugavero M, Saag M, Martin JN, Deeks SG. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. Clin Infect Dis. 2009 Mar 15;48(6):787-94. [PMC free article: PMC2720023] [PubMed: 19193107]
95. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, Burgisser P, Erb P, Boggian K, Piffaretti JC, Hirschel B, Janin P, Francioli P, Flepp M, Telenti A. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet. 2000 Nov 25;356(9244):1800-5. [PubMed: 11117912]
96. Karass M, Grossniklaus E, Seoud T, Jain S, Goldstein DA. Kaposi Sarcoma Inflammatory Cytokine **Syndrome** (KICS): A Rare but Potentially Treatable Condition. Oncologist. 2017 May;22(5):623-625. [PMC free article: PMC5423516] [PubMed: 28424322]
97. Berhan A, Bayleyegn B, Getaneh Z. HIV/**AIDS** Associated Lymphoma: Review. Blood Lymphat Cancer. 2022;12:31-45. [PMC free article: PMC9063794] [PubMed: 35517869]

98. Vaccher E, Gloghini A, Carbone A. HIV-related lymphomas. Curr Opin Oncol. 2022 Sep 01;34(5):439-445. [PubMed: 35900752]
99. Sax PE, Erlandson KM, Lake JE, Mccomsey GA, Orkin C, Esser S, Brown TT, Rockstroh JK, Wei X, Carter CC, Zhong L, Brainard DM, Melbourne K, Das M, Stellbrink HJ, Post FA, Waters L, Koethe JR. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2020 Sep 12;71(6):1379-1389. [PMC free article: PMC7486849] [PubMed: 31606734]

Disclosure: Helena Swinkels declares no relevant financial relationships with ineligible companies.

Disclosure: Andrew Nguyen declares no relevant financial relationships with ineligible companies.

Disclosure: Peter Gulick declares no relevant financial relationships with ineligible companies.

Bookshelf ID: NBK534860 PMID: 30521281