HIV infection

The right clinical information, right where it's needed
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HIV infection

Definition

HIV infection is a pandemic infectious disease whose impact on societies is without precedent. It is caused by a retrovirus that infects and replicates in human lymphocytes and macrophages, eroding the integrity of the human immune system over a number of years, culminating in immune deficiency and a susceptibility to a series of opportunistic and other infections as well as the development of certain malignancies.

At the initial consultation with the medical practitioner, an infected patient may be at any stage of the natural history from acute to chronic infection, ranging from asymptomatic through to severely ill. The initial assessment is key for prognosis and formulation of short- to long-term management plans.

AIDS (a syndrome of a constellation of infections, conditions, or malignancies) occurs as a result of HIV infection, and usually develops over 10-15 years (median 11 years).[1] [2]

Epidemiology

Globally, there were 37.9 million people living with HIV worldwide at the end of 2018, with approximately 1.7 million becoming newly infected in 2018. Approximately 70% of people living with HIV are in sub-Saharan Africa.[10] New cases peaked in 1999 (3.16 million) and have gradually decreased since then.[11] Approximately 80% of new HIV infections are from people who do not know they are infected or who are not receiving regular care. The transmission rate was zero in patients taking antiretroviral therapy who were virally suppressed.[12]

In the US, there were an estimated 38,281 diagnoses of HIV infection in 2017. The majority of diagnoses among males were in men who have sex with men (MSM). MSM accounted for 67% of all diagnoses in the US in 2017, while heterosexual contact accounted for 24%, and injection drug use accounted for 6%.[13] The number of new infections in the US was highest in the 25-29 year old age group in 2017.[13] Between 2010 and 2016, infection rates remained stable in MSM, decreased by approximately 17% in heterosexual men and women, and decreased by approximately 30% in people who inject drugs. However, infection rates have increased among certain demographics, including Latino MSM and black MSM aged 25-34 years.[14]

In the World Health Organization European Region (consisting of 53 countries, and including data for the Russian Federation), there were 159,420 newly reported cases in 2017 (20 new infections in 100,000 population). Transmission among homosexuals was the largest single route of infection, accounting for 49.4% of newly diagnosed cases. A total of 21.2% of new infections were attributed to MSM, and 13% to injecting drug use.[15] The number of new infections was highest in the 30-39 year old age group (36%).[15] In the UK, new diagnoses decreased by 6% in 2018 (compared with 2017) to 4484 cases (with 1908 of those in gay and bisexual men).[16] The overall number of people living with HIV in the UK was estimated to be 103,800 in 2018 (an estimated 6700 people were living with undiagnosed HIV infection).[17] The incidence in MSM is falling in some countries.[18]

Survey data underscore the disproportionate impact of the AIDS epidemic on women, especially in sub-Saharan Africa. Globally, 52% of adults living with HIV infection are women.[10] In the US, women accounted for 19% of estimated HIV diagnoses in 2017, with 86% acquired through heterosexual transmission.[13]

Globally, mortality peaked in 2006 with 1.95 million deaths, and has since decreased to 0.95 million deaths in 2017.[11] This figure dropped to 770,000 in 2018.[10]
Overall, globally, the HIV incidence rate is believed to have peaked in the late 1990s and to have stabilized subsequently, notwithstanding increasing incidence in a number of countries. Changes in incidence along with rising AIDS mortality have caused global HIV prevalence to level off. However, the numbers of people living with HIV have continued to rise, due to population growth and, more recently, the life-prolonging effects of antiretroviral therapy. In sub-Saharan Africa, the region with the largest burden of the AIDS epidemic, data also indicate that the HIV incidence rate has peaked and is starting to plateau in most countries. However, the epidemics in this region are highly diverse and especially severe in southern Africa, where some of the epidemics are still expanding.

**Etiology**

HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages. HIV can be transmitted via blood, blood products, sexual fluids, other fluids containing blood, and breast milk. Most individuals are infected with HIV through sexual contact, before birth or during delivery, during breast-feeding, or when sharing contaminated needles and syringes (intravenous drug users). Sexual intercourse is the most common, albeit inefficient, mode of HIV transmission. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative STIs, high HIV viral load in the host, and lack of antiretroviral therapy.[19]

**Pathophysiology**

The virus gains entry to the cells by attaching to the CD4 receptor and a coreceptor (CCR5 or CXCR4) via its envelope glycoproteins. It is called a retrovirus because it encodes the enzyme reverse transcriptase, allowing a DNA copy to be made from viral RNA. The reverse transcriptase enzyme is inherently error-prone, resulting in a high rate of HIV mutation, which can rapidly lead to viral resistance in those on treatment.[20]

Once integrated into the cellular DNA the provirus resides in the nucleus of infected cells and can remain quiescent for extended periods of time. Alternatively it can become transcriptionally active (especially where immune activity is occurring) and can use the human host cell machinery to replicate itself. Viral RNA is then spliced singly or multiply to make a variety of structural and regulatory and accessory proteins. Viral proteases further process proteins and mature viral particles are formed when the virus buds through the host cell membrane.

Within a few weeks of infection there is a high level of viral replication in the blood that can exceed 10 million viral particles per microliter of plasma. There is a concomitant decline in CD4 T cells. However, an immune response to HIV develops that curtails viral replication, resulting in a decrease in viral load and a return of CD4 T-cell numbers to near normal levels. The immune control is thought to be dependent on killer T cells and neutralizing antibodies. Depending on how effective this control is, the viral load is known as the set point and this is thought to be prognostic of natural history outcomes for the infected person.[21]

Research suggests that the host's initial response to HIV infection is critical and genetically determined. A small number of patients show unusually slow or no immune damage. These long-term controllers are being carefully studied with the hope of developing immune-based therapies for HIV.

**Classification**

HIV belongs to the genus *Lentivirus* of the family *Retroviridae* and has been divided into 2 types:

- HIV type 1 (HIV 1) is the virus responsible for the global epidemic. There are 3 major groups within HIV 1: group M (major, which includes clades A, B, C, D, and L), N (non-M and non-O), and O (outlier). Clade B is the commonly occurring virus in Europe and the US. Clades A, C, and D predominate in Africa, clades B and AE (a circulating recombinant form) in Asia, and clade B in South America.[3] Globally, subtype C accounted for 46.6% of all HIV infections between 2010 and 2015, followed by subtype B (12.1%), subtype A (10.3%), subtype CRF02_AG (7.7%), subtype CRF01_AE (5.3%), subtype G (4.6%), subtype D (2.7%), and subtypes F, H, J, and K (0.9% combined).[6] Subtype L was discovered in 2019 from samples taken in the Democratic Republic of the Congo in 2001.[7]
- HIV type 2 (HIV 2) is less pathogenic and restricted in the most part to West Africa.[3] [8]

Primary HIV infection refers to the first 6 months following HIV acquisition and is associated with an evolving HIV antibody response and high-level plasma viremia.[9]

AIDS occurs as a result of HIV infection, and usually develops over 10-15 years (median 11 years).[1] [2] It is a syndrome of a constellation of infections, conditions, or malignancies (based on criteria set by the Centers for Disease Control and Prevention and World Health Organization) that occur as a result of the increasing immune depletion that HIV infection incurs over time.[4]
Primary prevention

Condoms

The most widely available tool for prevention of HIV infection during sexual intercourse is the male condom. Male condoms afford a high degree of protection: consistent and correct male condom use reduces HIV transmission by 80% to 97%. Numerous studies have shown that the female condom is an acceptable method for many women and men, and is a valuable alternative for women whose partners refuse to use male condoms. Unlike the male condom, the female condom can be inserted some time before sex, and does not depend on the same degree of male cooperation for its successful use.

Pre-exposure prophylaxis (PrEP)

Studies have shown the effectiveness of daily oral antiretroviral therapy (ART), known as PrEP, in reducing the risk of HIV infection in adults who are at high risk for HIV acquisition. Evidence shows that oral tenofovir and emtricitabine prophylaxis is highly effective in reducing the risk of HIV acquisition and is considered safe, with minimal adverse effects.[32] There are also data that provide reassurance that resistance is unlikely to occur in patients taking PrEP.[33] As a consequence, it is increasingly being incorporated into international guidelines.[34]

- The Centers for Disease Control and Prevention recommends PrEP with tenofovir and emtricitabine as one prevention option for: adult sexually active men who have sex with men (MSM) who are at substantial risk for HIV acquisition; adult heterosexually active men and women at substantial risk for HIV acquisition; and adult injection drug users at substantial risk for HIV acquisition.[35] Furthermore, PrEP should be discussed with adult heterosexually active men and women whose partners are known to be infected with HIV (serodiscordant couples).[35]
- The US Preventive Services Task Force also recommends PrEP (with tenofovir alone or tenofovir plus emtricitabine) in high-risk people, including: sexually active MSM who have a serodiscordant partner, inconsistently use condoms, or have had gonorrhea, chlamydia, or syphilis in the past 6 months; sexually-active heterosexual people who have a serodiscordant partner, inconsistently use condoms with a high-risk partner whose HIV status is unknown, or have had gonorrhea or syphilis recently; and people who inject drugs and either share equipment or who are at risk of sexual acquisition.[36]
- World Health Organization guidelines strongly recommend offering PrEP containing tenofovir to HIV-negative individuals who are at substantial risk of HIV infection as part of combination prevention approaches.[37]

However, it should be noted that there has been a case report of tenofovir-susceptible, emtricitabine-resistant HIV acquisition despite high adherence to PrEP.[38] [39] New treatments for PrEP are currently in development.[40] Emtricitabine and tenofovir (as either the alafenamide or disoproxil fumarate salts) are available in a combination formulations specifically approved for PrEP.

Pericoital PrEP

Pericoital (on-demand) PrEP may be considered instead of daily PrEP in MSM who have infrequent sexual exposures.[41] On-demand PrEP has been found to be effective in MSM who are at a high risk of HIV infection. However, a post-hoc analysis of the ANRS IPERGAY trial found that on-demand PrEP was also effective in MSM who were at a lower risk of HIV infection (i.e., periods of less frequent sexual intercourse defined as 5 episodes per month), with a 100% relative reduction of HIV incidence reported compared with placebo.[42] In Australia, use of PrEP by MSM has been associated with a rapid decline in new HIV infections among MSM.[43] However, a rapid increase in the use of PrEP also resulted in an equally rapid decrease in consistent condom use.[44] Use of PrEP has increased in MSM from 6% in 2014 to 35% in 2017. Use increased in almost all demographic subgroups, but remains lower among black and Hispanic MSM.[45]

Treatment as prevention
ART may be used to prevent HIV transmission. This is commonly known as undetectable-untransmittable (or U=U). Several large studies have shown that ART prevents HIV transmission in both heterosexual couples and MSM who maintain an undetectable viral load.[46] [47] [48] [49] [50] [51] In light of this evidence, US guidelines recommend that physicians should inform patients that maintaining a HIV RNA level <200 copies/mL with ART prevents transmission to sexual partners. Another form of prevention should be used for the first 6 months of ART until an HIV RNA level of <200 copies/mL has been documented, with some experts recommending that sustained suppression is confirmed before assuming there is no risk of transmission.[52] The Prevention Access Campaign has also released a consensus statement stating that the risk of HIV transmission from a person living with HIV who is on ART and has achieved undetectable viral load in their blood for at least 6 months is negligible to nonexistent. [Prevention Access Campaign: consensus statement] Immediate initiation of ART is recommended for the HIV-positive partner of HIV-serodiscordant couples, to prevent HIV transmission.[46] [52]

Circumcision

The role of male circumcision in the prevention of HIV and STI acquisition has been shown in a number of cross-sectional studies and randomized controlled trials from different parts of Africa, with evidence suggesting reduction in HIV acquisition in circumcised men.[53] [54] [55] [56] [57] [58]

Other harm reduction methods

.Convincing evidence exists for the benefit of needle exchange and clean syringes in the setting of methadone clinics, termed “harm reduction,” where HIV transmission risk is related to shared intravenous drug use equipment. In addition, the supply of HIV-free blood and blood products, as well as sterile needles and syringes for injections and universal precautions in hospitals, has much reduced nosocomial transmission of HIV.[59]

Vaccines

Despite a great amount of research and clinical trials, an effective vaccine for the prevention and control of HIV has yet to be discovered.[60] [61] Long-acting injectable PrEP is undergoing clinical trials and may address issues with adherence, and could be an important prevention intervention for certain HIV populations.[62]

Screening

HIV screening

HIV testing is indicated:

- When someone requests a test
- When someone has a condition that indicates possible HIV infection
- When someone believes that they are at risk of infection through unprotected sexual activity, needle stick injury, or unsafe injection drug use
- In all pregnant women
- For public health and infection control (e.g., blood product safety)
- When required by, for example, life insurers.

The Centers for Disease Control and Prevention (CDC) recommends that all people 13-64 years of age be routinely tested for HIV, including annual screening for those determined to be at high risk.[73] More frequent screening can be considered for some asymptomatic men who have sex with men, based on individual risk factors, local epidemiology, and local policies.[74] Despite this recommendation, 37% of transgender men and women have never been tested for HIV.[75] Also, national surveillance data indicate that people who are at high risk of infection are not being retested as often as the CDC guidelines recommend.[76]
The US Preventive Services Task Force recommends screening in all people aged 15 to 65 years, younger and older adolescents and adults at increased risk of infection, and all pregnant women (including those who present in labor or at delivery whose HIV status is unknown). Repeat screening is considered reasonable in patients at higher risk of HIV infection, but there is insufficient evidence to recommend specific screening intervals.[77]

HIV testing is key to both effective primary and secondary preventive strategies and critical for implementation of a management plan for those who test positive. Testing has been shown to reduce risk behavior in people testing positive. Regular follow-up after positive test enables timely commencement of various prophylactic treatments to prevent opportunistic infections. In addition, timely testing before onset of advanced HIV enables adequate preparation for antiretroviral therapy.

Antibody-based tests or newer-generation HIV antibody/antigen combination assays are preferable as screening tests. Nucleic acid (HIV RNA) tests should be used if acute infection is suspected, or in neonates under 18 months of age (HIV DNA or RNA).

**Secondary prevention**

**Sexual contacts**

- Sexual contacts of the patient should be inquired about. HIV status may already be known. If not, disclosure should be discussed. Patients may not be able to do this immediately but should be encouraged, especially in a situation where disclosure is linked to being able to practice safer sex. Practitioners may also offer to assist with disclosure under these circumstances and offer immediate testing for partners. There may be local regulations, and physicians should refer to these where appropriate. Public health officers may be able to facilitate partner notification.

- Serodiscordant partners should be encouraged to be tested regularly,[158] and can be protected from infection by immediate initiation of antiretroviral therapy in the HIV-positive partner.[46] [47] [52] Tenofovir-based microbicide gel has reduced rates of HIV transmission to women.[159]

**Offspring**

- The physician should inquire whether the patient has children and how old they are. Their well-being and medical histories may give a clue to possible infection (if not already tested). If younger than 10 years of age and well and not previously tested, the physician may also advise having them tested. Children younger than 18 months of age may need a nucleic acid test (qualitative polymerase chain reaction). If still breast-feeding, advice against ongoing transmission risk should be given and consideration to weaning (if older than 6 months of age) or switching to bottle/formula feeding.[160]
Case history

Case history #1

A 32-year-old male taxi driver was found to be HIV-infected during a recent hospitalization for a pneumonic illness. Compatible chest x-ray findings and confirmatory sputum culture were positive for *Mycobacterium tuberculosis*, resulting in a diagnosis of pulmonary tuberculosis (TB). In consideration of this diagnosis, the patient had agreed to HIV testing in the hospital. HIV serology was positive by rapid HIV testing and this was confirmed on a second blood specimen. The patient was informed of the diagnosis and referred for outpatient care. In the outpatient clinic, a history obtained from the patient confirmed some months of deteriorating health. He had lost approximately 10 kg in weight and had experienced fevers, night sweats, loss of appetite, and intermittent bouts of diarrhea. In addition, 4 weeks prior to admission he had developed a productive cough and pleuritic chest pain. He had also noted a scaly skin condition at the hairline. His medical history is nonsignificant, but he nursed his mother with TB approximately 6 years ago. His current medication includes antituberculous therapy and pyridoxine. He has recently completed 1 week of topical mycostatin for oral candidiasis. On examination he is thin, with evidence of oral thrush and mild seborrheic dermatitis. He has mild bronchial breathing in his right upper chest, with mild tracheal deviation to the right. His neurologic, cardiovascular, and abdominal examinations are normal. A CD4 count performed while the patient was still in the hospital was 186 cells/ microliter. He was clinically staged, based on history and findings, as World Health Organization (WHO) stage 3. A baseline viral load, complete blood counts, and liver function tests are ordered prior to initiation of antiretroviral therapy. The patient discloses that he is married and has 3 children ages 6 years, 4 years, and 13 months. They are all well. Implications for testing the family for HIV are discussed with the patient.

Case history #2

A 26-year-old woman is 24 weeks pregnant and is offered an HIV rapid test as part of her prenatal care. Her test is positive and confirmed on a second rapid test. She is referred for general HIV care. At the HIV clinic she explains that she has been very well, with only pregnancy-related nausea and mild fatigue. This is her first pregnancy. On examination, she looks well, with mild generalized lymphadenopathy only. She has been married for 2 years and had only one sexual partner in the last 4 years. An HIV test taken at age 20 years was negative. A CD4 count is performed and she is staged as WHO stage 1. She receives counseling regarding risks to her unborn child and information about prevention of mother-to-child transmission. She has not yet disclosed her status to her partner and needs assistance with this, as well as further information about positive living and initiation of antiretroviral therapy.

Other presentations

The acute retroviral syndrome occurs in approximately half of patients following their infection with HIV. It is a symptom complex that ranges from mild, nonspecific influenza-like symptoms to a florid illness that may even require hospitalization. In the latter it may present with aseptic meningitis or meningoencephalitis, maculopapular rash, myalgia, arthralgia, fever, hepatosplenomegaly, diarrheal illness (gastroenteritis or colitis), and other neurologic findings such as peripheral neuropathy, Guillain-Barre syndrome, or facial palsy. Laboratory findings include lymphopenia, followed by lymphocytosis with atypical lymphocytes. In some cases, CD4 cell depletion may be severe, resulting in thrush or other infections such as *Pneumocystis jirovecii* pneumonia. During this time, serology may be negative or...
indeterminate, and diagnosis is most reliable by testing for HIV RNA viral load in plasma, although p24 antigen may also be positive at this time if the test is available.

Step-by-step diagnostic approach

Diagnosis and prevention of HIV are the responsibility of all healthcare practitioners. Providers should be sufficiently trained to diagnose infection and to manage the stage of positive living. Awareness of primary HIV infection (the first days to 6 months after HIV acquisition) in high-risk patient groups is critical to avoid missed diagnoses. Early recognition and prompt therapy can improve individual patient care and prevent further transmission.

Establishing the diagnosis

A person who feels they are at risk for being HIV positive or those who are getting routine HIV screening should receive pretest counseling. This should include determining actual risk factors and working through the process to follow with both a negative (risk-reduction counseling) and positive results. It may be prudent in cases where HIV is suspected to present the HIV test as an opt-out option among other diagnostics. Antibody tests, either enzyme-linked immunosorbent assay (ELISA) or rapid tests, are the most frequently used tests to diagnose HIV, but there has been a switch toward newer-generation HIV antibody/antigen-based assays.[63] A positive (reactive) result from an initial HIV antibody or combination antibody/antigen test is confirmed by a subsequent positive result from a supplemental molecular HIV test (typically HIV RNA or viral load) that differs from the initial test.[64] A quantitative HIV RNA polymerase chain reaction (PCR) must be used to diagnose acute retroviral syndrome.

Initial assessment

Initial assessment of a person newly diagnosed with HIV should be thorough and include a comprehensive and focused medical history and clinical examination, as well as appropriate laboratory tests, in order to assess the stage of HIV disease in the individual. Baseline laboratory investigations depend on available resources, and are used to define management goals and plans.

All patients should have: HIV antibody testing; a lymphocyte subset panel, including CD4 count; a hepatitis screen; a venereal disease research laboratory test; tuberculin skin test; and, ideally, complete blood count (CBC), chemistry profile, creatinine, liver function tests (LFTs), fasting blood glucose, serum lipids, and urinalysis. HIV viral load should also be performed at baseline in most developed countries. Drug resistance testing (genotype/phenotype) is recommended in settings where there are high levels of circulating resistant virus (e.g., the US).[52] Frequency and timing of testing vary for each investigation, and local guidance should be consulted.

At the end of the session a comprehensive management plan for future care should be made, including a plan for initiation of potent combination antiretroviral therapy (ART) and risk reduction counseling.[4] [52]

The patient may present at 1 of 4 stages:

- During the acute seroconversion illness
- During an asymptomatic period of clinical latency
- During a symptomatic period of immune dysregulation and milder immune deficiency before the development of AIDS
• With severe immunodeficiency and AIDS.

**History**

The clinician should elicit a history of common symptoms likely to be related to HIV, paying particular attention to those symptoms that would assist in staging the HIV disease by Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) classifications.[64] [65] These include fevers and night sweats, loss of weight, skin rashes, oral thrush or ulceration, diarrhea, headaches, and changes in mental status or neuropsychiatric function. Symptoms such as fever, sore throat, night sweats, fatigue, malaise, myalgia, diarrhea, and rash may all be associated with acute or primary HIV infection.[9]

All recent hospital admissions should be detailed as they may be related to HIV. Risk of tuberculosis (TB) and STIs should be assessed (symptoms and any known contact) and a vaccination history taken (particularly hepatitis A and B, pneumococcal, and tetanus). A note should be made of current medication and known allergies. All women should be asked about current and prior pregnancies and whether they have been pregnant since knowing their HIV status. The date of their latest Papanicolaou test should be confirmed.

Attention should be paid to risk factors for contracting HIV, such as intravenous drug use and sexual history, including sexual orientation and risks of further HIV transmission, number of partners, whether partners are aware of HIV status, use of condoms, and previous STIs (including viral hepatitis).[4] [66]

Social background and lifestyle issues should be discussed, including:[4] [66]

- Home environment: type of housing, how many people live there, water and electricity supply
- Children: ages and HIV status if known
- Disclosure of HIV status: to sexual partner, family, and/or friends
- Support structures: people who can provide emotional support for the patient
- Employment
- Smoking history
- Exercise
- Current and prior use of alcohol or other substance use.

In previously-treated patients who present to a new physician for an initial evaluation, a detailed history of previous ART, including resistance test results, should be obtained.

Disclosure to sexual partner(s) is important as that person will need to be assessed for risk of HIV infection and tested. Nondisclosure may indicate a reluctance to accept the diagnosis of HIV and can result in poor adherence to ART later.[66]

**Clinical examination**

In starting with the physician's general impression of the patient, it should be established if the patient is well or ill. The examination should be tailored to the extent of the patient's symptoms. Specific factors for evaluation include:

- Weight and height measurement
- Examination for generalized lymphadenopathy, noting site, size, and mobility of nodes
- Skin inspection for HIV-associated rashes and scars (including herpes zoster), papular pruritic eruptions, fungal infections, or Kaposi sarcoma
HIV infection

Diagnosis

- Examination of the mouth for oral thrush, oral hairy leukoplakia, Kaposi sarcoma, and periodontal disease
- Chest and cardiovascular examination for signs of, for example, pulmonic infection
- Abdominal examination to evaluate for hepatomegaly or splenomegaly
- Examination of the genitalia for signs of STIs (in all patients)
- Neurologic examination, including an assessment of mental status, meningismus, and peripheral neuropathy, and fundoscopy looking for retinal lesions[4] [64]
- Psychiatric assessment should include noting the patient's affect and orientation.

Anorexia and lymphadenopathy may be associated with acute or primary HIV infection.

HIV testing

Several laboratory tests are available and have various benefits and limitations:

- ELISA: the most established tests for detecting HIV infection rely on ELISA as an initial screening test. During or shortly after infection, IgM antibodies to HIV first appear. This is followed weeks to months later by IgG antibodies to Gag and Env, and then to viral enzymes and regulatory proteins. The time to first detectable IgG by ELISA takes a median of 3 to 4 weeks, with almost all newly infected people having detectable IgG levels by 6 months. During this time an ELISA test may be falsely negative, a period known as the window period. Fourth-generation ELISA tests reduce the window period to about 2 to 4 weeks, thereby reducing the number of false-negative results, especially in areas where incident infections are common. The ELISA is the preferred screening method in the developing world since it lends itself to high throughput, rapid testing, and automation
- Fourth-generation antibody (ELISA) and antigen (p24): the latest fourth-generation HIV tests incorporate the p24 antigen, meaning that obtaining a diagnosis of HIV during the window period is more likely, as the test examines both antibodies and the p24 antigen. This reduces the window period from 3 months to an average of 10 days; these tests may therefore be recommended for HIV confirmation.[63]
- Western blot: despite high specificity, the use of ELISA in populations where the prevalence of disease is low will lead to a high proportion of positive results being false. Thus, in the developed world, the protocol is to confirm positive or indeterminate ELISA results with a second test, the Western blot. Western blots require significant time and resources and so are not suited to many high-prevalence areas.
- Rapid test: this has worked well in resource-poor settings. Several have been endorsed by the US Food and Drug Administration and the WHO. These tests have higher than 99% sensitivity and specificity when combined with a confirmatory Western blot in the developed world and a second rapid test in the developing world.
- Other HIV screening tests: tests are available that detect the presence of HIV antibodies in fluids other than blood. Saliva has higher concentrations of IgA and IgG, and both ELISA and rapid tests exist for saliva.
- Nucleic acid testing (RNA or DNA): this provides the most sensitive test for HIV infection in the newborn, and can be used at 4 to 6 weeks of age. Placentally transferred maternal antibodies can persist in the neonate for up to 18 months, so antibody tests cannot be used to establish the diagnosis.
- Reverse-transcriptase PCR of viral RNA (viral load): this test measures active replication of HIV in blood and other body fluids, and is primarily used to assess activity of HIV and monitor the
response to ART. There is an ultrasensitive version of this test that can reliably measure viral RNA levels as low as 20 RNA copies/mL of plasma. This is also the most sensitive test for adults with acute HIV infection who might be in a window period without detectable antibody or antigen (p24).

- p24 antigen: this is a core HIV protein and is present during high viral replication and so is detectable in the blood during acute infection and again during late stages of infection. Its use, therefore, is as a supplementary test during the window period. This test becomes positive later than HIV RNA (viral load) during acute HIV infection, and this is why it is less sensitive during this stage of infection.

**CD4 count**

The CD4 cell count indicates the health of the host's immune system and assists in the initial assessment and ongoing monitoring of the patient. This is one of the most important tests to complete at entry into care as it establishes the patient's risk of developing HIV-associated complications, including AIDS-defining infections and malignancies. An average CD4 count for an HIV-negative adult is 800 cells/ microliter, and the average drop in CD4 count in HIV-positive patients is 75 cells/microliter/year. People with a CD4 count of >500 cells/microliter are usually asymptomatic, but still at an increased risk for general infections. A CD4 count of <350 cells/microliter implies substantial immune suppression. A CD4 count <200 cells/microliter defines an individual as having AIDS and places the patient at high risk for opportunistic infections (OIs), with *Pneumocystis jirovecii* pneumonia being the most common OI.

**Drug resistance testing**

Baseline antiretroviral drug resistance testing is important in settings where it is available to ensure the success of initial ART.[20] Estimates in the US are that the frequency of new infection with a virus with at least one major resistance mutation is around 10% to 25%.[20] The WHO reports ≥10% of adults starting antiretroviral therapy had a strain of HIV that was resistant to efavirenz or nevirapine in 12 of the 18 countries it surveyed between 2014 and 2018.[67]

Genotypic testing is cheaper and easier than phenotypic testing and is more commonly performed at baseline in the US due to increased transmission rates of genotype resistant virus.[68] Phenotypic testing may be preferable to assess resistance in patients who have failed several regimens (salvage) as the patient's genotypes may be difficult to interpret. However, with newer, more potent ART, including several regimens with a high genetic barrier to resistance and low failure rates, there is less drug resistance in the US.[69]

Genotypic testing is recommended at diagnosis to guide selection of initial ART. Treatment should not be delayed while awaiting results, as the regimen can be modified once results are received. Testing is also recommended when changing ART regimens in the following patient groups: patients with virologic failure and HIV RNA levels >1000 copies/mL, patients with HIV RNA levels >500 copies/mL and <1000 copies/mL, and patients with suboptimal viral load reduction.[52]

A Cochrane review found that drug resistance testing (genotypic or phenotypic) is likely to have little or no impact on mortality, progression to AIDS, or CD4 count. However, it may reduce the risk of virologic failure and viral load in patients who are experiencing treatment failure. It is unclear whether resistance testing provides any benefit for treatment-naive patients.[70]
Other tests

Pregnancy testing (urine beta human chorionic gonadotropin [beta-hCG]) should be done on all women of childbearing potential prior to starting ART, as some drugs are not recommended in pregnancy.

Hepatitis A, B, and C, STIs (gonorrhea, chlamydia, and syphilis), toxoplasma IgG, and human leukocyte antigen (HLA)-B*5701 testing should be performed in all individuals at their first clinic visit and prior to initiation of ART.

Tuberculin skin test should be performed, if deemed clinically necessary. A reaction of >5 mm may require TB prophylaxis.

A chest x-ray should be requested if there are symptoms of TB or pneumonia.[4]

Disease staging

Once the initial assessment and CD4 count is completed, the patient can be staged according to either the CDC or the WHO classification systems.[64] [65] Timing of follow-up and further management may depend on the classification, including any underlying or concurrent infections/malignancies; however, recommendations for initiation of ART should be advised at all stages of HIV infection. See Criteria section for detailed staging categories.

Baseline investigations prior to initiating ART

Before patients commence ART, the following tests should be done and monitored during the course of therapy:

- LFTs
- CBC with differential
- Electrolytes
- Serum creatinine (and calculated glomerular filtration rate) and U/A for proteinuria
- Random or fasting lipid profile
- Random or fasting plasma glucose
- Hepatitis B surface antigen
- STI (gonorrhea, chlamydia, syphilis) and hepatitis C screening
- HLA-B*5701 testing
- HIV RNA (viral load)
- Lymphocyte subset panel, including CD4 count
- HIV genotype resistance assay.

[VIDEO: Venepuncture and phlebotomy: animated demonstration ]

Risk factors

Strong

needle sharing with intravenous drug use

- 67 infections/10,000 exposures to an infected source who has a detectable viral load.[22]
unprotected receptive anal intercourse

- 50 infections/10,000 exposures to an infected source who has a detectable viral load.\[23\] \[24\]

unprotected receptive penile-vaginal sexual intercourse

- 10 infections/10,000 exposures to an infected source who has a detectable viral load.\[23\] \[24\]

percutaneous needle stick injury

- 30 infections/10,000 exposures to an infected source who has a detectable viral load.\[25\]

high maternal viral load (mother-to-child transmission)

- The level of HIV RNA at delivery is independently associated with risk of transmission.\[26\]

Weak use of progestin-only injectable contraceptives

- Evidence from studies evaluating the association between HIV acquisition and progestin-only injectable contraceptives, including depot medroxyprogesterone, suggests a possible increased risk of HIV acquisition in patients using these types of contraceptives, possibly due to hormonally-mediated changes in the vaginal epithelium. However, findings are inconsistent across studies.\[27\]
- The US Centers for Disease Control and Prevention (CDC) recommends that implants, progestin-only pills, and combined hormonal contraceptives can be used without restriction in women at high risk for HIV infection.\[28\] The CDC believes the benefits of depot medroxyprogesterone outweigh any theoretical or possible risks, and that women at a high risk for HIV should not be denied this treatment.\[28\]
- The World Health Organization recommends that women at a high risk of HIV can use all methods of contraception without restriction, including depot medroxyprogesterone. This recommendation is based on high-quality evidence from one randomized clinical trial that showed no statistically significant differences in HIV acquisition among women using intramuscular depot medroxyprogesterone acetate, copper IUDs, or levonorgestrel implants.\[29\]

herpes simplex virus type 2 (HSV-2) infection

- Evidence suggests that HSV-2 infection may increase the risk of HIV acquisition.\[30\] \[31\]

History & examination factors

Key diagnostic factors

fevers and night sweats (common)

- Unexplained fever and night sweats for more than 1 month (with no response to antibiotics) comprise a WHO stage 3 illness. These symptoms may indicate tuberculosis, which should be excluded. Malaria should be excluded in endemic areas.\[65\]

weight loss (common)

- Unexplained involuntary weight loss of less than 10% of body weight is a WHO stage 2 symptom. If more than 10% of body weight is lost or the BMI reduces to 18.5 this indicates more severe immunocompromise (WHO stage 3).\[65\] Loss of weight may result from malnutrition, tuberculosis infection, and HIV wasting syndrome.\[65\]
skin rashes and post-inflammatory scars (common)

- Rashes may occur throughout HIV disease and close attention should be paid to the skin. Rashes are the most common sign of WHO stage 2 disease: including herpes zoster (shingles), seborrheic dermatitis, pruritic papular eruptions, and fungal skin and nail infections (tinea corporis or unguium).[65]

oral ulcers, angular cheilitis, oral thrush, or oral hairy leukoplakia (common)

- The mouth should always be thoroughly examined. Both thrush and oral hairy leukoplakia indicate WHO stage 3 disease.
- Recurrent painful oral aphthous ulcers indicate WHO stage 2, as does angular cheilitis (cracking at the corners of the mouth due to a fungal infection).[65]

Fig-1

diarrhea (common)

- Unexplained diarrhea of more than 1 month in duration (with no pathogen diagnosed) indicates WHO stage 3 disease.[65]

wasting syndrome (common)

- Unexplained weight loss (more than 10% of body weight) or wasting together with either unexplained fever (lasting more than 1 month) or unexplained chronic diarrhea (for more than 1 month) comprise HIV wasting syndrome, an AIDS-defining illness (WHO stage 4).[65]

changes in mental status or neuropsychiatric function (common)

- Depression and anxiety are common in HIV-positive individuals. Change in mental status or cognition could be due to organic disease in late-stage HIV (WHO stage 4). Toxoplasmosis and cryptococcal disease should be excluded. In the absence of another condition to explain a drop-off in cognition or motor function, HIV encephalopathy may be diagnosed.[65]

recent hospital admissions (common)

- Recent admission for management of an infectious disease including bacterial infections (such as pneumonia, meningitis, bone or joint infection, severe pelvic inflammatory disease, septicemia), tuberculosis (TB), or fungal or viral infections should be elicited in the history.
- Bacterial infections and pulmonary TB are WHO stage 3-defining illnesses. Recurrent bacterial pneumonia is indicative of WHO stage 4 disease, as is a diagnosis of other pneumonias such as Pneumocystis jirovecii pneumonia and extrapulmonary TB.
- Fungal infections such as esophageal candidiasis and cryptococcal meningitis are WHO stage 4 illnesses, as are viral infections such as cytomegalovirus retinitis.[4] [65]

tuberculosis (TB) (common)

- The risk of TB increases with worsening immunosuppression. If a patient with HIV presents with symptoms of TB (e.g., cough, loss of weight, fever, and night sweats) and/or a history of a TB contact, TB should be excluded by sending 2 sputum samples for smear and direct microscopy and/or culture and examining a CXR (for infiltrates, cavitation, or effusion). In severe immunosuppression, TB may be present without a positive sputum (smear-negative TB).[4] [65]

medical comorbidities (common)
• Patients should be assessed for any other medical comorbidities that may impact on both disease progression and treatment decisions. For example, a patient with renal disease will require adjustment of antiretroviral doses. A patient with TB should have the TB treatment initiated as soon as possible, and those patients presenting with other opportunistic infections (OIs) should receive OI treatment along with antiretroviral therapy (ART). The timing of ART in the setting of OIs depends on the particular OI. Those with other chronic disease such as diabetes or heart disease will need to be managed in consultation with other specialty physicians. Consideration of drug interactions with ART and all medications should be given.

sexual activity (common)

• HIV is largely spread through sexual intercourse in all parts of the world. Because of this, ongoing assessments of sexual activity and risk for STIs should be done routinely for all patients with HIV.

generalized lymphadenopathy (common)

• Painless enlarged nodes, in 2 or more noncontiguous sites of >1 cm for more than 3 months.[65]

Kaposi sarcoma (common)

• Kaposi sarcoma may present as a pink or violaceous patch on the skin or in the mouth. It is an AIDS-defining condition.[65]

genital STIs (common)

• Chronic herpes infection - that is, progressive painful genital or anal ulceration for >1 month - is an AIDS-defining illness.[65] Other STIs associated with HIV infection include syphilis, chlamydia, and gonorrhea.

chronic vaginal candidiasis (common)

• Occurs in WHO stage 3 disease.[65] Rates of vaginal Candida colonization are higher in women with HIV infection.[71]

shingles (common)

• Occurs in WHO stage 2 disease.[65] Only an AIDS-defining illness if multidermatomal.

headaches (uncommon)

• Headaches may be indicative of central nervous system (CNS) disease. Headaches with focal CNS signs and symptoms may indicate toxoplasmosis infection (WHO stage 4). When accompanied by acute symptoms of meningism, headaches may indicate bacterial meningitis (WHO stage 3). Those with more low-grade chronic symptoms of meningism may indicate cryptococcal meningitis (WHO stage 4).[65] May also be associated with lymphoma.
• However, most cases of HIV-associated meningitis will be associated with headache without neck stiffness and with or without fever.

periodontal disease (uncommon)

• Poor oral hygiene with loosening of teeth, bleeding of gums, and bad odor indicates gingivitis or periodontitis, a WHO stage 3 condition.[65]

retinal lesions on fundoscopy (uncommon)

• Medical emergency and requires immediate referral for sight-saving intervention if cytomegalovirus retinitis.
shortness of breath on exertion, cyanosis on exertion, dry cough, silent chest on auscultation (uncommon)

- These are clinical features of *Pneumocystis jirovecii* pneumonia. This rarely occurs in patients with CD4 counts >200 cells/microliter. It presents with shortness of breath, with few clinical signs. Post-treatment will require ongoing secondary prophylaxis, or all patients with CD4 counts <200 cells/microliter or stage 3 or 4 illness should be offered prophylaxis with trimethoprim/sulfamethoxazole or dapsone.

Other diagnostic factors

current and prior use of other substances (common)

- Needle-sharing injection drug use with an infected source is a risk factor for HIV infection, and an obstacle to HIV treatment adherence.

peripheral neuropathy (common)

- May be related to HIV or some other medication or toxin. Important to try to find etiology since some antiretroviral therapy also causes peripheral neuropathy.

recurrent herpes simplex (common)

- Occurs in WHO stage 4 disease.[65]

hepatomegaly or splenomegaly (uncommon)

- May indicate acute HIV syndrome, opportunistic infection, or malignancy such as lymphoma.

meningeal signs (bacterial or viral meningitis) (uncommon)

- Vomiting, neck stiffness, and photophobia may indicate bacterial or viral meningitis; however, the finding of meningeal signs (meningism) is less likely in fungal meningitis. Most cases of HIV-associated meningitis will be associated with headache without neck stiffness and with or without fever.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serum HIV enzyme-linked immunosorbent assay (ELISA)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• ELISA should be ordered when HIV testing is indicated. False negatives may occur during window period immediately after infection before antibodies to HIV have occurred. A positive result should be confirmed with a Western blot or second ELISA. The window period can be reduced to 2 to 4 weeks by using fourth-generation tests and those that include IgM antibodies to HIV and/or HIV antigen (p24) assays.[63] [68]</td>
<td></td>
</tr>
<tr>
<td><strong>serum HIV rapid test</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• Point of care test. Staff should be trained to do the rapid test. Should be ordered when HIV testing is indicated. False-negatives may occur during window period immediately after infection before antibodies to HIV have occurred. A positive result should be confirmed with a second rapid test.</td>
<td></td>
</tr>
<tr>
<td><strong>HIV noninvasive tests</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• Most often used in surveillance. Most frequently sample buccal saliva. Both rapid and ELISA varieties are available.</td>
<td></td>
</tr>
<tr>
<td><strong>serum Western blot</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• Expensive, so most often used as a confirmatory test following a positive ELISA or rapid test. During the window period result may be falsely negative or indeterminate.</td>
<td></td>
</tr>
<tr>
<td><strong>serum p24 antigen</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• p24 protein is present during high viral replication and so is detectable in the blood during acute infection and again during late stages of infection. Its use, therefore, is as a supplementary test during the window period and is now part of newer fourth-generation assays indicated by the Centers for Disease Control and Prevention for routine HIV testing.[63]</td>
<td></td>
</tr>
<tr>
<td><strong>serum HIV DNA polymerase chain reaction (PCR)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• By HIV DNA PCR, qualitative proviral DNA in peripheral blood mononuclear cells can be used to make diagnosis of HIV especially during the window period. This is more costly than antibody-based diagnostic tests and is mainly used for HIV diagnosis in infants.</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 count</strong></td>
<td>CD4 count of &gt;500 cells/microliter: patients are usually asymptomatic; CD4 count of &lt;350 cells/microliter: implies substantial immune suppression; CD4 count &lt;200 cells/microliter: defines AIDS and places the patient at high risk of most opportunistic infections</td>
</tr>
<tr>
<td>• Indicates immune status and assists in the staging process.</td>
<td></td>
</tr>
</tbody>
</table>
### HIV Infection

#### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serum viral load (HIV RNA)</strong></td>
<td>recently infected people may attain levels in the millions of copies/mL; during control of infection, viral load may be controlled in the thousands or hundred of thousands; end stages of infection viral loads increase again into millions</td>
</tr>
</tbody>
</table>
|                                           | • An important test for establishing a baseline viral load before therapy and monitoring response to antiretroviral therapy. In developed countries, a baseline viral load followed by measurements at regular intervals is recommended, depending on the patient's response to therapy.[52] However, this is not common practice in resource-poor settings where testing for HIV RNA is less available.  
  • Quantitative viral RNA in plasma is used to confirm acute HIV, including acute retroviral syndrome (i.e., symptomatic patients before the HIV antibody test is positive). Detectable levels of <1000 copies/mL may indicate a false-positive result and should be repeated in 1 month, along with antibody tests. However, if the result is well >1000 copies/mL, then the diagnosis is confirmed. Quantitative viral RNA is not recommended as a diagnostic test in other clinical scenarios because it can be falsely positive. |
| **drug resistance testing**               | variable                                                                                                                                                                                                 |
|                                           | • Genotypic testing is recommended at diagnosis to guide selection of initial antiretroviral therapy. Treatment should not be delayed while awaiting results, as the regimen can be modified once results are received.[52]  
  • A Cochrane review found that drug resistance testing (genotypic or phenotypic) is likely to have little or no impact on mortality, progression to AIDS, or CD4 count. However, it may reduce the risk of virologic failure and viral load in patients who are experiencing treatment failure. It is unclear whether resistance testing provides any benefit for treatment-naive patients.[70] |
| **pregnancy test**                        | positive in pregnant women                                                                                                                                                                                                                   |
|                                           | • All women of childbearing potential should have a pregnancy test prior to starting antiretroviral therapy as some drugs are not recommended in pregnancy. Urine beta human chorionic gonadotropin (beta-hCG) is sufficient. |
| **serum hepatitis B serology**            | surface antigen positive in hepatitis B-infected patients                                                                                                                                                                                      |
|                                           | • Should be performed at baseline, before starting antiretroviral therapy, or if liver function is abnormal. Also recommended before starting direct-acting antiviral therapy for hepatitis C infection due to risk of hepatitis B reactivation.[52] |
| **serum hepatitis C serology**            | antibody positive in hepatitis C-infected patients                                                                                                                                                                                        |
|                                           | • Hepatitis C testing (hepatitis C virus antibody or RNA) should be tested in all patients at baseline and every 12 months in at-risk patients.[52]                                                                                                   |
| **serum venereal disease research laboratory test** | positive in patient with syphilis infection                                                                                                                                                                                            |
|                                           | • Nontreponemal antibodies will detect primary and early syphilis. Titer reduces with adequate treatment. Lack sensitivity in late stages of syphilis.                                                                                      |
| **Treponema pallidum hemagglutination test** | positive in patient with syphilis infection                                                                                                                                                                                            |
|                                           | • Good screening for all stages after primary syphilis. Remains positive after treatment.  
  • Follow-up tests are fluorescent treponemal antibody absorption test, rapid plasma reagin, or enzyme immunoassay. |

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**Notes:**
- This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Mar 04, 2020.
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### HIV Infection

#### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rapid plasma reagin</strong></td>
<td>positive in patient with syphilis infection</td>
</tr>
<tr>
<td>• Follow-up test.</td>
<td></td>
</tr>
<tr>
<td><strong>tuberculin skin test</strong></td>
<td>a reaction of more than 5 mm in a patient who has been screened for TB disease may require TB prophylaxis</td>
</tr>
<tr>
<td>• Indicated to establish evidence of exposure to and infection with tuberculosis (TB). False-negatives may occur in anergic patients (advanced HIV).</td>
<td></td>
</tr>
<tr>
<td><strong>CBC with differential</strong></td>
<td>may be normal or show anemia or thrombocytopenia</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>serum electrolytes</strong></td>
<td>may be normal or deranged</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>serum creatinine</strong></td>
<td>may be normal or elevated in coexisting renal disease</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>urinalysis</strong></td>
<td>may be normal or show proteinuria in renal disease or positive for leukocytes and nitrates in urinary tract infections</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy and monitored while on therapy.</td>
<td></td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>chest x-ray</td>
<td>Pneumocystis jirovecii pneumonia: interstitial to extensive alveolar shadowing; TB: many abnormalities possible including apical fibrosis/scarring, pleural effusion, hilar adenopathy, miliary pattern, lobar or patchy opacification; bacterial pneumonia: lobar or patchy opacification</td>
</tr>
<tr>
<td>• Should be requested if there are symptoms or signs of tuberculosis (TB). <em>P. jirovecii</em> pneumonia, or other pulmonary illness.</td>
<td></td>
</tr>
<tr>
<td>liver function tests (LFTs)</td>
<td>may be normal; baseline abnormal LFTs may reflect chronic hepatitis B, chronic hepatitis C, or alcoholism</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td>random or fasting lipid profile</td>
<td>cholesterol levels may be low at diagnosis; ART may be associated with rising levels</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy (ART) and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td>random or fasting plasma glucose</td>
<td>may be elevated in patients on ART</td>
</tr>
<tr>
<td>• Requested before initiation of antiretroviral therapy (ART) and monitored while on therapy.</td>
<td></td>
</tr>
<tr>
<td>hepatitis A serology (IgG)</td>
<td>may be negative or positive</td>
</tr>
<tr>
<td>• Should be performed in all patients. If the result is negative, the patient should be vaccinated against hepatitis A.</td>
<td></td>
</tr>
<tr>
<td>toxoplasma serology (IgG)</td>
<td>may be negative or positive</td>
</tr>
<tr>
<td>• Should be performed at baseline in all HIV-infected individuals, particularly those with a CD4 count of &lt;200 cells/microliter.</td>
<td></td>
</tr>
<tr>
<td>• If the result is positive and the CD4 count is &lt;50 cells/microliter, prophylactic therapy should be started.</td>
<td></td>
</tr>
<tr>
<td>gonorrhea and chlamydia testing</td>
<td>may be negative or positive</td>
</tr>
<tr>
<td>• Perform at baseline and every 3, 6, or 12 months depending on sexual activity risk.</td>
<td></td>
</tr>
<tr>
<td>• Urine/urethral swab, rectal swab, and throat swab should be taken for culture for nucleic amplification test. If test is positive, the patient should be treated with appropriate antibiotics.</td>
<td></td>
</tr>
<tr>
<td>human leukocyte antigen-B*5701 testing</td>
<td>may be negative or positive</td>
</tr>
<tr>
<td>• Should be ordered before initiation of antiretroviral therapy to assist with selecting the most suitable regimen. If positive, abacavir should be avoided.</td>
<td></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious mononucleosis</td>
<td>• Infection with Epstein-Barr virus (EBV) may resemble features of HIV acute seroconversion illness with fever, lymphadenopathy, pharyngitis, and maculopapular rash.</td>
<td>• EBV: IgM serology and Paul Bunnell positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Cytomegalovirus infection (CMV)</td>
<td>• May resemble HIV acute seroconversion illness with fever, lymphadenopathy, rash, and splenomegaly.</td>
<td>• CMV serology positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Influenza infection</td>
<td>• No specific differentiating signs; viral infections such as influenza may resemble acute seroconversion illness with fever, pharyngitis, and lymphadenopathy.</td>
<td>• Influenza viral culture or nucleic acid test (nasopharyngeal or respiratory sample) positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Common cold</td>
<td>• No specific differentiating signs; viral infections such as the common cold may resemble acute seroconversion illness with fever, pharyngitis, and lymphadenopathy.</td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>• Right upper quadrant abdominal pain, jaundice.</td>
<td>• Elevated liver function tests.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatitis B or C serology positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>• Fever, malaise, pharyngitis, lymphadenopathy, maculopapular rash. Condylomata lata on genital areas and oral ulcers. May have been preceded by painless genital chancre and inguinal lymphadenopathy (primary syphilis). Can coexist with HIV.</td>
<td>• Venereal disease research laboratory test positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treponema pallidum hemagglutination test positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HIV test negative.</td>
</tr>
<tr>
<td>Coronavirus disease 2019 (COVID-19)</td>
<td>• Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset.</td>
<td>• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA.</td>
</tr>
</tbody>
</table>
### Diagnostic criteria

#### World Health Organization staging[65]

**Stage 1**

- Acute seroconversion syndrome: there is no current case definition for acute seroconversion illness, although an acute viral syndrome in the early stages of HIV is well recognized. Primary infection usually presents within the first month of exposure to HIV and commonly presents with a fever and lymphadenopathy. Other clinical symptoms and signs might include pharyngitis, maculopapular rash, orogenital ulcers, or meningoencephalitis. Other opportunistic infections may occur, due to the transient lymphopenia. The CD4 count may drop profoundly. Diagnosis is made by observing the appearance of an HIV antibody (serial rapid tests or enzyme-linked immunosorbent assay [ELISA] or by noting the presence of HIV, using HIV-RNA or HIV-DNA and/or ultrasensitive HIV p24 antigen with an absent HIV antibody)[4] [21]
  - Persistent generalized lymphadenopathy (painless enlarged nodes, in 2 or more noncontiguous sites of more than 1 cm for more than 3 months)
  - Asymptomatic, that is, no symptoms reported that might be related to HIV/AIDS
  - Performance status 1 (fully active and asymptomatic).

**Stage 2**

- Weight loss of less than 10% of body weight
- Herpes zoster (shingles)
- Minor mucocutaneous manifestations
- Recurrent upper respiratory tract infections
- Performance status 2 (symptomatic but near fully active).

**Stage 3**

- Weight loss of more than 10% of body weight
- Chronic diarrhea for more than 1 month
- Prolonged fever for more than 1 month
- Oral candida, chronic vaginal candidiasis
- Oral hairy leukoplakia
- Severe bacterial infections
- Pulmonary tuberculosis (TB)
- Performance status 3 (in bed less than 50% of past month).

**Stage 4**

- Extrapulmonary TB
- *Pneumocystis jirovecii* pneumonia
- Cryptococcal meningitis
- Herpes simplex virus ulcer for more than 1 month
HIV infection

Diagnosis

• Esophageal or pulmonary candidiasis
• Toxoplasmosis
• Cryptosporidiosis
• Isosporiasis
• Cytomegalovirus
• HIV wasting syndrome
• HIV encephalopathy
• Kaposi sarcoma
• Progressive multifocal leukoencephalopathy
• Disseminated mycosis
• Atypical mycobacteriosis
• Nontyphoid salmonella bacteremia
• Lymphoma
• Recurrent pneumonia
• Invasive cervical carcinoma
• Performance status 4 (confined to bed more than 50% of the time).

Advanced HIV disease[72]

• CD4 cell count <200 cells/mm³, or stage 3 or 4 event at presentation in adults, adolescents, and children ≥5 years of age. All children <5 years of age should be considered as having advanced disease at presentation.
• Seriously ill adult or adolescent: respiratory rate ≥30 breaths per minute, heart rate ≥120 bpm, unable to walk unaided, or body temperature ≥102.2°F (≥39°C).
• Seriously ill child: lethargy or unconsciousness, convulsions, unable to drink/breastfeed, repeated vomiting, tachycardia or tachypnea, or body temperature ≥102.2°F (≥39°C).
• Severely immunosuppressed: CD4 cell count <50 cells/mm³.

Centers for Disease Control and Prevention case severity[64]

Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.

HIV infection, stage 0

• Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

HIV infection, stage 1 (≥6 years)

• Laboratory confirmation of HIV infection with no AIDS-defining condition, and
  • CD4+ T-lymphocyte count of ≥500 cells/microliter, or
  • CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

HIV infection, stage 2 (≥6 years)

• Laboratory confirmation of HIV infection with no AIDS-defining condition, and
HIV infection

- CD4+ T-lymphocyte count of 200 to 499 cells/microliter, or
- CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

HIV infection, stage 3 (AIDS; ≥6 years)

- Laboratory confirmation of HIV infection, and
  - CD4+ T-lymphocyte count of <200 cells/microliter, or
  - CD4+ T-lymphocyte percentage of total lymphocytes of <14% or
  - Documentation of an AIDS-defining condition.

Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/microliter and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

HIV infection, stage unknown

- Laboratory confirmation of HIV infection, and
  - No information on CD4+ T-lymphocyte count or percentage, and
  - No information on presence of AIDS-defining conditions.

Stage-3-defining opportunistic illnesses in HIV infection

- Bacterial infections, multiple or recurrent (only among children ages <6 years)
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive (only among adults, adolescents, and children ages ≥6 years)
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary (only among adults, adolescents, and children ages ≥6 years), disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent (only among adults, adolescents, and children ages ≥6 years)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
Profiles of disease progression

Rapid progressors: a small proportion of individuals develop AIDS within 1 to 2 years. This is associated with high levels of viral replication and a precipitous decline in CD4 numbers.

Long-term controllers: a small proportion of individuals are able to control HIV viral load without assistance of antiretroviral therapy. Many have low to undetectable viral loads and well-preserved CD4 counts for many years. This appears in part to be due to a robust immunity to HIV.
Step-by-step treatment approach

The most important issue to address in an adult with newly diagnosed HIV is adequate counseling and advice. The patient should then be staged and managed as clinically appropriate depending on stage of HIV disease and concurrent medical conditions. Potent combination antiretroviral therapy (ART) should be offered to all individuals with detectable HIV RNA regardless of CD4 cell count at the initial consultation. Immunization and prophylaxis for opportunistic infections should also be discussed and initiated as appropriate.

Guidelines suggest that, to optimize medication efficacy and quality of life, HIV primary care should be delivered by a clinician with HIV expertise, appropriate training, and experience, and who is also participating in an ongoing continuing education program. Referral to a physician or infectious disease specialist experienced in HIV management is preferable if the primary care physician does not have sufficient experience in managing patients on ART.

Treatment of pregnant women, postexposure prophylaxis, HIV-related opportunistic infections, dermatological conditions, and mental status changes are beyond the scope of this topic and are dealt with in separate topics. See Overview of HIV.

Initial care and counseling

Counseling and lifestyle advice, consideration of nutritional needs, and supplementation are recommended in all patients.

A package of interventions including screening (i.e., for tuberculosis [TB] and cryptococcal antigen), treatment and/or prophylaxis for major opportunistic infections (i.e., trimethoprim/sulfamethoxazole prophylaxis, TB preventive treatment, and fluconazole prophylaxis), rapid ART initiation, and intensified adherence support interventions (i.e., tailored counseling to ensure optimal adherence to the package, including home visits if feasible) should be offered to all patients presenting with advanced disease.[72]

Counseling:

- Risk reduction counseling in HIV-positive people has been shown to be effective in reducing further transmission of HIV. This is particularly important during acute or primary HIV infection when plasma HIV levels are high and the patient is highly infectious. More than one session of counseling may be needed to result in a change in high-risk sexual behavior. Referral should be made to appropriate counselor/support groups for ongoing counseling sessions.[19] [85]
- Counseling before initiating ART should focus on preparing the patient to commit to long-term ART.

Prevention and treatment of concomitant and opportunistic infections (OIs):

- Concomitant and opportunistic infections are common in HIV-infected patients.
- Primary prophylaxis against opportunistic infections including TB, Pneumocystis jirovecii, Mycobacterium avium complex, toxoplasmosis, and malaria (if required) is recommended.[86]
- Malnutrition is common in HIV disease, particularly in resource-poor areas. A cycle of opportunistic infection causing loss of weight and poor appetite, together with diarrhea and malabsorption, contributes to this malnutrition. Management would include ensuring an adequate balanced food source and early identification and management of OIs.[87] [88]
• If the patient has concurrent hepatitis B infection, appropriate treatment should be used as part of ART. All patients with hepatitis C and HIV co-infection require treatment according to the latest guidance.

Prevention of comorbidities:

• Routine primary prevention for chronic diseases of aging is recommended based on age and risk. This includes risk assessment, screening, and testing for age-appropriate conditions such as cardiovascular disease, liver disease, diabetes, cancers, and bone disease. Assessment of diet, physical activity, smoking status, alcohol abuse, and substance abuse should be included.

Micronutrient supplementation:

• There is limited evidence of consistent clinically important benefits with micronutrient supplementation; however, most practitioners add a multivitamin and mineral combination supplement containing vitamins A, B6, B12, C, D, E and folate, with calcium, magnesium, iron, zinc, and selenium.[89]

Vaccination:

• Vaccines should be given as early as possible in HIV infection or once the immune system has recovered on ART, as immune responses decrease with increased immunosuppression.
• Recommended vaccinations include pneumococcal (pneumonia), meningococcal, influenza, hepatitis B, human papillomavirus, and tetanus/diphtheria/pertussis (a tetanus/diphtheria booster is required every 10 years). Additional vaccinations may be recommended depending on the patient’s age, risk factors for a specific disease, and previous vaccination history. Current local immunization schedules should be consulted.[90]
• Other vaccines may be recommended in travelers depending on the risk of acquiring a given disease in the area of travel (e.g., Japanese B encephalitis, inactivated typhoid, yellow fever, inactivated polio).
• Live vaccines are generally contraindicated, particularly if immune compromise has already occurred. The measles-mumps-rubella (MMR) vaccine, varicella live vaccine, and herpes zoster live vaccine are contraindicated in patients with a CD4 count <200 cells/microliter. Other contraindicated vaccines include the Bacillus Calmette-Guérin (BCG), oral polio, typhoid, and yellow fever vaccines.

Starting antiretroviral therapy

ART is recommended for all HIV-infected patients, including those with acute or primary HIV infection, regardless of CD4 count; ART has been shown to reduce the risk of disease progression, decrease comorbid disease, and prevent HIV transmission.[52] The strength of this recommendation was reinforced by the Strategic Timing of AntiRetroviral Treatment (START) study, which found that the risk of developing serious illness or death was reduced by 53% among those in the early treatment group, compared with those in the deferred treatment group.[91] World Health Organization (WHO) guidelines support the recommendation to initiate ART in all patients living with HIV, regardless of CD4 count.[37]

ART should be started immediately (as soon as possible) after HIV diagnosis, including acute and recent infection, in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression, reduce the risk of transmission, and improve the rate of virologic suppression.[52] The WHO recommends that rapid ART initiation (i.e., within 7 days of diagnosis, preferably on the same
HIV infection

Treatment

day as diagnosis in patients who are willing and ready to start treatment and there is no clinical contraindication) should be offered to all people living with HIV following a confirmed diagnosis and clinical assessment.\[72\] One Cochrane review of seven randomized controlled trials (RCTs) with more than 18,000 adults found that rapid initiation (within 7 days of diagnosis) of ART probably results in greater viral suppression at 12 months compared with standard initiation in low- and middle-income settings.\[92\] Rapid initiation of ART may be difficult to achieve in resource-limited settings.

Although ART has long-term adverse effects, these are minimal compared with complications of untreated HIV infection.

**Choice of antiretrovirals**

The choice of effective drug combinations requires expertise, particularly in complex cases. Providers must be competent in managing medication adherence and ART adverse effects, and anticipating drug interactions between HIV and non-HIV medications. They must also be able to make drug and management modifications to maintain clinical benefits.

The classes of antiretrovirals that are currently in use include: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and pharmacokinetic enhancers or boosters (improve pharmacokinetic profiles of some antiretrovirals and increase their effectiveness, resulting in lower doses of the antiretroviral being needed). NRTIs, NNRTIs, and PIs are the antiretrovirals most commonly used and are the only classes available in regions such as southern Africa. INSTIs, while considered a first-line treatment in some countries, are generally only available in the developed world.

In most regions, a first-line ART regimen will generally consist of 2 NRTIs in combination with a third agent (usually an INSTI if available, or an NNRTI or boosted PI); however, guidelines and protocols may differ between countries and regions. Quadruple combination therapy has been found to be no more effective than triple combination therapy with currently available drugs.\[93\] \[94\] Local infectious disease specialists or HIV practitioners should be consulted and preferably patients referred to them for further management. Given the number of effective options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, and cost.\[52\]

Recommended initial regimens for most people with HIV (regimens have demonstrated durable virologic efficacy, good tolerability/toxicity profiles, and ease of use):\[52\]

- **INSTI-based regimens:**
  - Bictegravir plus tenofovir alafenamide plus emtricitabine
  - Dolutegravir plus abacavir plus lamivudine (only for human leukocyte antigen [HLA]-B*5701 negative patients)
  - Dolutegravir plus tenofovir plus lamivudine or emtricitabine
  - Raltegravir plus tenofovir plus lamivudine or emtricitabine.

Guidelines now also recommend a two-drug regimen of dolutegravir plus lamivudine (an INSTI plus an NRTI) as an initial regimen for most people with HIV, except in patients with pretreatment HIV RNA >500,000 copies/mL or active hepatitis B co-infection, or those who will initiate ART before results of HIV genotype testing or hepatitis B virus testing are available.\[52\] This recommendation is based on the results of two large, randomized controlled trials that showed that dolutegravir plus lamivudine was...
A combination formulation of dolutegravir/lamivudine has been approved in the US and Europe as a complete regimen for the treatment of HIV-1 infection in adults with no ART history.

Recommended initial regimens in certain clinical situations (these regimens are tolerable, but have some disadvantages compared with the first-line regimens above, or less supportive evidence):[52]

- **INSTI-based regimens:**
  - Elvitegravir plus cobicistat plus tenofovir plus emtricitabine
  - Raltegravir plus abacavir plus lamivudine or emtricitabine (only for patients who are HLA-B*5701 negative and HIV RNA <100,000 copies/mL).

- **PI-based regimens:**
  - Ritonavir- or cobicistat-boosted darunavir plus tenofovir plus lamivudine or emtricitabine
  - Ritonavir- or cobicistat-boosted atazanavir plus tenofovir plus lamivudine or emtricitabine
  - Ritonavir- or cobicistat-boosted darunavir plus abacavir plus lamivudine or emtricitabine (only for patients who are HLA-B*5701 negative).

- **NNRTI-based regimens:**
  - Doravirine plus tenofovir plus lamivudine or emtricitabine
  - Efavirenz plus tenofovir plus lamivudine or emtricitabine
  - Rilpivirine plus tenofovir plus lamivudine or emtricitabine (only for patients with HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/μl).

If ART is initiated before drug resistance testing and HLA B*5701 test results are available, one of the following regimens is recommended:[52]

- Bictegravir plus tenofovir alafenamide plus emtricitabine
- Dolutegravir plus tenofovir plus lamivudine
- Ritonavir- or cobicistat-boosted darunavir plus tenofovir plus lamivudine or emtricitabine.

Other two-drug regimens may be considered when abacavir or tenofovir cannot be used or are considered to be suboptimal:[52]

- Ritonavir-boosted darunavir plus raltegravir (only for patients with HIV RNA <100,000 copies/mL and CD4 count >200 cells/μl)
- Ritonavir-boosted darunavir plus lamivudine.

Other regimens for various clinical scenarios may be used; however, a specialist should be consulted when choosing other combinations. The above regimens are recommended by the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Other guidelines may recommend different regimens; however, most agree that second-generation INSTIs (bictegravir and dolutegravir) now offer the most advantages for the treatment of HIV and are generally a first-line option when available. The WHO supports the use of a dolutegravir-based regimen first-line, with efavirenz-based regimens recommended as a suitable alternative.[95]

Fixed-dose combination tablets that combine a number of drugs in 1 tablet are available, and can assist in improving medication compliance. Tenofovir is available as tenofovir disoproxil fumarate or the
oral prodrug tenofovir alafenamide. Tenofovir alafenamide is available only in fixed-dose combination formulations with other antiretroviral agents. The prodrug is associated with less renal toxicity and less of an effect on bone mineral density, while tenofovir disoproxil fumarate is associated with lower lipid levels.[52] [96]

Dolutegravir should be used with caution in women of childbearing potential and those who are trying to conceive. Data has shown an increased risk of neural tube defects with dolutegravir-containing regimens (0.3%) compared with ART that does not contain dolutegravir (0.1%). It is not known whether this is a drug class effect. Therefore, before starting treatment with an INSTI, a pregnancy test should be performed. The benefits and risks of using dolutegravir around the time of conception should be discussed with women of childbearing potential. Dolutegravir is an alternative, rather than a preferred, option in individuals who are trying to conceive, as well as individuals who are not trying to conceive but who are sexually active and not using contraception. Dolutegravir may be used in individuals who are using effective contraception.[52]

HIV RNA (viral load), CD4 counts, adherence, and adverse effects should be monitored to optimize and evaluate the efficacy of ART. For people with pretreatment drug resistance to NNRTIs, or people at high risk of pretreatment drug resistance to NNRTIs because of prior exposure to NNRTIs or from other risks, a non-NNRTI-containing regimen may be preferable. As individual level drug resistance testing isn’t available in most low- and middle-income countries, nationally representative data may be used.[97]

Once virologic suppression is achieved, regimen switching (within or between a class of drugs) may be considered in some patients, provided there is no evidence of viral resistance to the drugs in the new regimen. A regimen may be switched, for example, to simplify regimens, enhance tolerability, decrease toxicity, prevent drug interactions, and reduce costs. The aim is to maintain viral suppression without jeopardizing future treatment options. The patient’s ART history should be reviewed, and any past instances of treatment failure and drug resistance should be taken into account when selecting a new regimen. A three-drug regimen is usually recommended; however, there is emerging evidence that a two-drug regimen may also maintain virologic suppression. The Food and Drug Administration has approved dolutegravir/rilpivirine to treat adults with HIV-1 infection whose virus is currently suppressed on a stable regimen for at least 6 months, with no history of treatment failure and no known substitutions associated with resistance to the individual components. Monotherapy is not recommended. A specialist should be consulted before switching regimens.[52]

[FDA: HIV treatment information for adults]

**Failure of first-line regimen**

Virologic failure is defined as the inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.[52] Patients with virologic failure should be referred back to an HIV-experienced clinician or infectious disease specialist for further drug resistance testing, adherence assessment, and optimization of their treatment regimens based on drug resistance patterns.[98]

Immunologic failure is failure to achieve and maintain an adequate CD4 response despite virologic suppression.[99] These patients should also be referred to their specialist for assessment of current medications, untreated co-infections, and serious medical conditions.

If the initial regimen is not tolerated, a single drug switch within a drug class is an option, provided that the viral load is suppressed.
It is important to ensure and reassess medication compliance. This includes involvement of support structures such as a treatment partner and support groups. The patient should be counseled on the importance of adhering to the medication dosing and timing at each visit. In cases of drug toxicity, the causative drug can be replaced by another, less toxic option without having to change the rest of the regimen.

**Non-AIDS-defining comorbidities**

As the epidemic progresses, there is a greater recognition of the increases in non-AIDS comorbidities related to HIV disease. Such comorbidities include cardiovascular disease, renal disease, cancer, and bone and metabolic abnormalities.[100] [101] [102]

People living with HIV are at increased risk of cardiovascular disease, both prior to and while taking ART. They are also at increased risk of renal disease, particularly older patients and those in the later stages of infection. ART reduces the risk of progression of renal disease. HIV-positive individuals are at an increased risk of osteoporosis and osteopenia compared with those who are HIV-negative. Vitamin D levels are often low in HIV-positive individuals. Some antiretrovirals (e.g., tenofovir disoproxil fumarate) may worsen renal and bone health.

**Treatment details overview**

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: [see disclaimer](#)

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
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</table>
| newly confirmed infection | 1st start antiretroviral therapy  
plus select antiretroviral therapy regimen  
plus supportive care |

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Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
HIV infection

TREATMENT

Acute

newly confirmed infection

1st start antiretroviral therapy

» Antiretroviral therapy (ART) is recommended for all HIV-infected patients, including those with acute or primary HIV infection, regardless of CD4 count as it has been shown to reduce the risk of disease progression, decrease comorbid disease, and prevent HIV transmission.[52] The strength of this recommendation was reinforced by the Strategic Timing of AntiRetroviral Treatment (START) study, which found that the risk of developing serious illness or death was reduced by 53% among those in the early treatment group, compared with those in the deferred treatment group.[91] World Health Organization (WHO) guidelines support the recommendation to initiate ART in all patients living with HIV, regardless of CD4 count.[37]

» ART should be started immediately (as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression, reduce the risk of transmission, and improve the rate of virologic suppression.[52] The WHO recommends offering rapid ART initiation to all people living with HIV following a confirmed diagnosis and clinical assessment, in patients who are willing and ready to start treatment, and where there is no clinical contraindication.[72] Rapid ART initiation is defined as within 7 days of diagnosis, preferably on the same day as diagnosis. One Cochrane review of seven randomized controlled trials with more than 18,000 adults found that rapid initiation (within 7 days of diagnosis) of ART probably results in greater viral suppression at 12 months compared with standard initiation in low- and middle-income settings.[92] Rapid initiation of ART may be difficult to achieve in resource-limited settings.

» Although ART has long-term adverse effects, these are minimal compared with complications of untreated HIV infection.

plus select antiretroviral therapy regimen

Treatment recommended for ALL patients in selected patient group

Primary options

INSTI-based regimen

» bictegravir/emtricitabine/tenofovir alafenamide
HIV infection

Acute

OR

INSTI-based regimen

» dolutegravir
This regimen is recommended only for HLA-B*5701-negative patients.

-and-

» abacavir

-and-

» lamivudine

OR

INSTI-based regimen

» dolutegravir

--AND--

» tenofovir disoproxil

-or-

» tenofovir alafenamide
Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

--AND--

» lamivudine

-or-

» emtricitabine

OR

INSTI-based regimen

» raltegravir
Available in 400 mg and 600 mg tablet formulations. The 600 mg formulation is given once daily (1200 mg once daily), while the 400 mg formulation is given twice daily (400 mg twice daily).

--AND--

» tenofovir disoproxil

-or-

» tenofovir alafenamide
Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

--AND--

» lamivudine

-or-

» emtricitabine

OR

INSTI-based two-drug regimen

» dolutegravir/lamivudine
**Acute**

This regimen is not recommended in patients with pretreatment HIV RNA >500,000 copies/mL or active hepatitis B co-infection, or those who will initiate ART before results of HIV genotype testing or hepatitis B virus testing are available.

### Secondary options

#### INSTI-based regimen

- **elvitegravir**
  - **and**
    - **cobicistat**
  - **and**
    - **emtricitabine**

--AND--

- **tenofovir disoproxil**
- **or**
  - **tenofovir alafenamide**

Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

**OR**

#### INSTI-based regimen

- **raltegravir**

This regimen is recommended only for HLA-B*5701-negative patients and HIV RNA <100,000 copies/mL.

- **and**
  - **abacavir**

--AND--

- **lamivudine**
- **or**
  - **emtricitabine**

**OR**

#### PI-based regimen

- **darunavir**

--AND--

- **ritonavir**
- **or**
  - **cobicistat**

--AND--

- **tenofovir disoproxil**
- **or**
  - **tenofovir alafenamide**

Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

--AND--

- **lamivudine**
### Acute

- **or-**
  - emtricitabine

**OR**

**PI-based regimen**

- atazanavir

- **AND-**
  - ritonavir
  - **or-**
    - cobicistat

- **AND-**
  - tenofovir disoproxil

- **or-**
  - tenofovir alafenamide
  
  Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

- **AND-**
  - lamivudine
  - **or-**
    - emtricitabine

**OR**

**PI-based regimen**

- darunavir
  
  This regimen is recommended only for HLA-B*5701-negative patients.

- **AND-**
  - ritonavir
  - **or-**
    - cobicistat

- **AND-**
  - abacavir

- **AND-**
  - lamivudine
  - **or-**
    - emtricitabine

**OR**

**NNRTI-based regimen**

- doravirine

- **AND-**
  - tenofovir disoproxil

- **or-**
  - tenofovir alafenamide
  
  Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

- **AND-**
**Acute**

- lamivudine  
  -or-  
  - emtricitabine

**OR**

**NNRTI-based regimen**

- efavirenz

**--AND--**

- tenofovir disoproxil  
  -or-  
  - tenofovir alafenamide  
  Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

**--AND--**

- lamivudine  
  -or-  
  - emtricitabine

**OR**

**NNRTI-based regimen**

- rilpivirine  
  This regimen is recommended only for patients with pretreatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cell/µL.

**--AND--**

- tenofovir disoproxil  
  -or-  
  - tenofovir alafenamide  
  Tenofovir alafenamide (an oral prodrug of tenofovir) is only available in fixed-combination formulations for this indication.

**--AND--**

- lamivudine  
  -or-  
  - emtricitabine

- The choice of effective drug combinations requires expertise, particularly in complex cases. Treatment is best individualized by a clinician who is experienced in HIV management.

- In most regions, a first-line antiretroviral therapy regimen will generally consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third agent (usually an integrase strand transfer inhibitor [INSTI], or a nonnucleoside reverse transcriptase inhibitor [NNRTI] or boosted protease inhibitor [PI]).[52] [93] [94] Some guidelines now also recommend a two-drug regimen of an INSTI plus an NRTI (e.g., dolutegravir plus lamivudine) as
HIV infection

Acute

an initial regimen. Regimens recommended by the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents are detailed here. Other guidelines may recommend different regimens.

» Dolutegravir should be used with caution in women of childbearing potential and those who are trying to conceive. Data has shown an increased risk of neural tube defects with dolutegravir-containing regimens (0.3%) compared with ART that does not contain dolutegravir (0.1%). It is not known whether this is a drug class effect. Therefore, before starting treatment with an INSTI, a pregnancy test should be performed. The benefits and risks of using dolutegravir around the time of conception should be discussed with women of childbearing potential. Dolutegravir is an alternative, rather than a preferred, option in individuals who are trying to conceive, as well as individuals who are not trying to conceive but who are sexually active and not using contraception. Dolutegravir may be used in individuals who are using effective contraception.

» A specialist should be consulted for further guidance on regimens and doses. Regimens and doses may differ in children and adolescents, older people, patients with hepatic/renal impairment or other comorbidities, and pregnant/breastfeeding women and are beyond the scope of this topic.

» Patients must be ready to adhere to treatment, and their readiness should be established through counseling. Fixed-dose combination tablets that combine two or three classes of drugs in one tablet (or two drugs from the same class) are available, and can assist in improving medication compliance.

» Once virologic suppression is achieved, regimen switching (within or between a class of drugs) may be considered in some patients, provided there is no evidence of viral resistance to the drugs in the new regimen. A specialist should be consulted before switching regimens.

» [AIDSinfo: antiretroviral agents in HIV-1-infected adults and adolescents]

plus supportive care

Treatment recommended for ALL patients in selected patient group
Counseling: risk reduction counseling in HIV-positive people has been shown to be effective in reducing further transmission of HIV. More than one session of counseling may be needed. Referral should be made to appropriate counselor/support groups for ongoing counseling sessions.[19][85] Counseling before initiating antiretroviral therapy (ART) should focus on preparing the patient to commit to long-term ART.

Prophylaxis of opportunistic infections: primary prophylaxis against opportunistic infections including tuberculosis, *Pneumocystis jirovecii*, *Mycobacterium avium* complex, toxoplasmosis, and malaria (if required) is recommended.[86] Early identification and management of opportunistic infections is extremely important.

Other infections: patients with concomitant hepatitis B or C should be treated according to latest guidance.

Comorbidities: routine primary prevention for chronic diseases of aging is recommended based on age and risk (e.g., risk assessment, screening, and testing for age-appropriate conditions such as cardiovascular disease, liver disease, diabetes, cancers, and bone disease). Assessment of diet, physical activity, smoking status, alcohol abuse, and substance abuse should be included.

Micronutrient supplementation: there is limited evidence of consistent clinically important benefits with micronutrient supplementation; however, most practitioners add a multivitamin and mineral combination supplement containing vitamins A, B6, B12, C, D, E and folate, with calcium, magnesium, iron, zinc, and selenium.[89]

Vaccinations: recommended vaccinations include pneumococcal (pneumonia), meningococcal, influenza, hepatitis B, human papillomavirus, and tetanus/diphtheria/pertussis (a tetanus/diphtheria booster is required every 10 years).[90] Live vaccines are generally contraindicated.
HIV infection

Treatment

<table>
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1st reassessment of antiretroviral therapy

» Virologic failure is defined as the inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.[52]

» Patients with virologic failure should be referred back to an HIV-experienced clinician or infectious diseases specialist for further drug-resistance testing, adherence assessment, and optimization of their treatment regimens based on drug resistance patterns.[98]

» Immunologic failure is the failure to achieve and maintain an adequate CD4 response despite virologic suppression.[99] These patients should also be referred to their specialist for assessment of current medications, untreated co-infections, and serious medical conditions.

» If the initial regimen is not tolerated, a single drug switch within a drug class is an option, provided that the viral load is suppressed.
Emerging

Ibalizumab

Ibalizumab, an intravenous humanized monoclonal antibody fusion inhibitor that binds CD4, has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency for adults who are heavily treatment-experienced and who cannot be successfully treated with other currently available therapies (e.g., multidrug resistant HIV). In a phase III trial, 43% of patients achieved HIV RNA suppression after 25 weeks of treatment (in combination with other antiretroviral drugs).[103] Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for this drug.[52]

Long-acting injectable antiretroviral therapies

Long-acting injectable antiretroviral therapies (e.g., cabotegravir, rilpivirine) that are administered monthly or every other month have entered phase III clinical trials for both the prevention and treatment of HIV infection, and will potentially be available for clinical use for certain patient groups within the next few years. An injectable regimen of cabotegravir plus rilpivirine administered every 4 or 8 weeks was found to be as effective as oral cabotegravir plus abacavir/lamivudine at maintaining viral suppression for up to 96 weeks, and was well accepted and tolerated.[104]

PRO 140

PRO 140 (a humanized form of the PA14 antibody) is a monoclonal antibody targeted against the C-C chemokine receptor type 5 (CCR5) receptor on T-lymphocytes that has shown significant antiviral activity in 3 small trials but is still considered an investigational drug.[105]

Other antiviral therapies

Maraviroc (a CCR5 receptor antagonist) and enfuvirtide (a fusion inhibitor, which binds to the gp41 or chemokine receptors and inhibits entry of the virus into immune cells) are approved by the FDA for HIV infection; however, their exact place in therapy is yet to be determined and guidelines do not currently recommend their use. Other antiviral therapies currently under investigation include attachment inhibitors and maturation inhibitors.[106] [107] Fostemsavir is an investigational, first-in-class attachment inhibitor in development for the treatment of HIV-1 infection. It works by binding directly to the glycoprotein 120 (gp120) subunit on the surface of the virus. An application for approval has been submitted to the FDA.[108]
Recommendations

Monitoring

Clinical and laboratory monitoring

Postexposure monitoring in HIV-negative individuals:

- In occupational exposure, HIV testing should be offered at baseline, 6 weeks, 12 weeks, and 6 months.
- If a newer, fourth-generation, combination HIV p24 antigen-HIV antibody test is utilized for follow-up HIV testing of exposed individuals, HIV testing may be concluded 4 months after exposure.[153]
- If a newer testing platform is not available, follow-up HIV testing is typically concluded 6 months after HIV exposure.[153]
- In nonoccupational exposure, HIV testing should be offered at 4-6 weeks, 12 weeks, and 6 months.[154]

Virologic and immunologic monitoring:

- A patient with early HIV disease should be monitored every 3-6 months, whereas a patient with late HIV disease should be monitored every 2-3 months.
- At each visit patients should be assessed for opportunistic infection and their clinical stage updated.
- HIV RNA (viral load) should be measured at entry into care and immediately prior to commencing antiretroviral therapy (ART). While on ART, HIV RNA should be checked at 2-8 weeks after commencing therapy, every 3-4 months during the first 2 years of therapy, and every 6 months after 2 years of therapy with consistently suppressed viral load.[155]
- A CD4 count should be done at entry into care and prior to initiation of ART. While on ART, the CD4 count should be checked 3 months after the initiation of therapy, then every 3-6 months for the first 2 years of therapy or if viremia develops or the CD4 count drops to <300 cells/microliter. After 2 years, patients with a consistently suppressed HIV RNA (viral load) can have their CD4 count checked every 12 months if their CD4 count is 300-500 cells/microliter. Monitoring the CD4 count is optional in patients with a count of >500 cells/microliter.[155]

Patient instructions

- Good nutrition: wherever possible, a healthy balanced diet should be followed. Alcohol should be consumed only in moderation. A multivitamin that does not exceed the daily RDA value should be taken daily. Vitamin D supplementation should also be considered.
- Lifestyle: safer sex advice is critical. Even in couples where HIV infection is concordant it is necessary to practice safer sex (use condoms) to prevent super-infection with a resistant virus. Cessation of smoking, alcohol abuse, and substance abuse are also important for a healthy lifestyle. Individuals who inject drugs should be offered harm reduction programs, including needle exchange and opioid dependence therapies.
- Reproduction: couples should be advised on their options for reproduction. This will differ depending on concordance and treatment. The estimated risk for male-to-female HIV transmission is 8 per 10,000 episodes of unprotected vaginal sex. No cases of HIV transmission have been reported in studies of serodiscordant couples in which the infected partner was virologically suppressed with antiretroviral therapy (ART); however, HIV RNA has been detected in the semen of men taking ART who have undetectable levels in their blood. Whether this poses a risk for transmission is unknown.[156] Advice at this stage should be that reproduction is possible and that it can be made as safe as possible, but that reproduction intention needs to be discussed with the practitioner well before conception to ensure best and safest possible scenarios for both
HIV infection

Follow up

partners and the potential infant. For serodiscordant couples, the Centers for Disease Control and Prevention recommends autologous sperm intrauterine insemination if the woman is HIV-positive, or one of the following options if the man is HIV-positive: use sperm from an HIV-negative donor (the safest option); use ART to suppress infection in the man and have condomless sex near ovulation while the woman is using pre-exposure prophylaxis; or collect and "wash" the sperm to remove HIV-infected cells in conjunction with ART and pre-exposure prophylaxis.[157]

- Natural history: patients generally need a sense of what to expect. The information should be based on what is known to be the natural history of HIV in most patients, with a discussion about rapid and long-term controllers but also recognition that most patients fall into the category of slow progressors. Drawing out the relationship between viral activity and CD4 count is a very useful graphic way for patients to better understand the relationship between viral activity and the progression of disease. The message should be tempered by the much more optimistic outlook in the ART era, and patients should be given the understanding that HIV is now a chronic and manageable infectious disease. The need for program adherence needs to be raised with an ultimate aim of drug adherence when the time comes. Some patients will benefit from comparing HIV to other chronic conditions that require regular monitoring (e.g., diabetes or asthma).

- Disclosure: it should be discussed that lifelong care and management will require support from other people in the patient's life. It should be explored who those people may be and how they may be engaged early on so that this support may be forthcoming. Patients sometimes appreciate help with disclosure, especially to sexual partners. A facilitator in this situation can quickly resolve any concerns and fears a sexual partner may have and also assist in further management of the contacts.
## Complications

<table>
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>acute seroconversion</td>
<td>short term</td>
<td>medium</td>
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<tr>
<td>Acute HIV infection will occur in 50% of those infected, with a viral illness resembling infectious mononucleosis characterized by: fever, malaise, myalgia, pharyngitis, gastrointestinal disturbance, headache, generalized lymphadenopathy, and hepatosplenomegaly. A rash and aphthous ulceration is also suggestive of the diagnosis. Nervous system involvement can occur, for example, meningoencephalitis, Bell palsy, and Guillain-Barre syndrome. Viral load is extremely high due to the virus replicating before immune response has occurred. Management is largely supportive. Potent combination antiretroviral therapy with the same regimens used for treating established chronic infection should be initiated as soon as possible in the setting of acute seroconversion to reduce symptoms, decrease risk of transmission, preserve immune status, and potentially minimize the size of the latent HIV reservoir.</td>
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<tr>
<td>severe acute syndrome</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Present with symptoms for more than 2 weeks, high viral loads and immune depletion may result in opportunistic infections, for example, esophageal thrush or <em>Pneumocystis jirovecii</em> infection, and a poorer overall prognosis. Likely to be a rapid progressor and will require careful follow-up monitoring for immune depletion. Antiretroviral therapy should be initiated as soon as possible.</td>
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<tr>
<td>rapid progressors</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>A small proportion of individuals develop AIDS within 1 to 2 years. This is associated with high levels of viral replication and a precipitous decline in CD4 numbers, probably due to impairment in the hosts' initial responses to HIV infection. Incidence is likely to decrease given the current recommendations to initiate antiretroviral therapy in all HIV-infected patients.</td>
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<tr>
<td>AIDS</td>
<td>long term</td>
<td>high</td>
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<tr>
<td>AIDS occurs as a result of HIV infection, and usually develops over 10-15 years (median 11 years). May present with an AIDS-defining illness such as esophageal candida, extrapulmonary tuberculosis, cryptococcal meningitis, or <em>P jirovecii</em> pneumonia. CD4 count and viral load should be monitored closely and antiretroviral therapy initiated with timing depending on the presence of specific opportunistic infections.</td>
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<tr>
<td>HIV-associated hypotestosteronism</td>
<td>long term</td>
<td>medium</td>
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<tr>
<td>Up to 70% of HIV-infected men have testosterone deficiency and this problem persists despite successful ART. Hypogonadism is also expected to rise with the aging HIV population. Testosterone...</td>
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replacement therapy (TRT) is common in the setting of HIV and often done without proper evaluations or monitoring. Given studies suggesting TRT may increase the risk of cardiovascular events, thrombosis, and death, caution is needed when initiating TRT in the current ART era.[150]

A small proportion of individuals are able to control HIV viral load without assistance of antiretroviral therapy (ART). Many have low-to-undetectable viral loads and well-preserved CD4 counts for many years. This appears in part to be due to a robust immunity to HIV. However, even these individuals are likely to benefit from consistent and uninterrupted use of ART.[128]

People with HIV are twice as likely to develop cardiovascular disease. The global burden has tripled over the past 2 decades and is responsible for 2.6 million disability-adjusted life years.[130] The cumulative incidence is estimated to be 20.5% in men and 13.8% in women by the age of 60 years, compared with 12.8% (men) and 9.4% (women) in the US general population.[131]

HIV infection has also been associated with an increased risk of peripheral arterial disease; however, this risk appears to be highest in patients with a sustained CD4 count <200 cells/microliter.[132] May be related to HIV itself and/or to ART. Increased risk has been reported with cumulative use of protease inhibitors.[133] Patients with HIV and hepatitis C co-infection have an increased risk of cardiovascular disease compared with patients who have HIV infection alone.[134]

Cardiomyopathy, myositis, and congestive cardiac failure are common cardiovascular complications of untreated HIV infection. There is also an increased risk of ischemic heart disease due to the chronic inflammation associated with HIV infection among those on long-term, suppressive ART. Certain ART medications may worsen this risk by altering lipid metabolism and increasing hyperlipidemia.

The American Heart Association has released guidance on the prevention and management of cardiovascular disease in people living with HIV infection.[109]

The risk of venous thrombotic events is elevated in people with HIV. A retrospective cohort study found a crude incidence of 2.33 events per 1000 person-years, and an incidence of 2.50 events per 1000 person-years when standardized for age and sex. Factors associated with a higher risk of a venous thrombotic event included: CD4 count <200 cells/microliter; high viral load; and a history of (or current) opportunistic infection. There was no association between any specific ART and the risk of a venous thrombotic event. Primary prophylaxis is not routinely recommended.[135]

Acute and chronic renal disease can be seen, including worsening of existing renal disease (diabetic, hypertensive), as well as HIV-related disease. The most common cause of HIV-related chronic renal failure (GFR <60ml/min) is HIV-associated nephropathy. Most commonly occurs at lower CD4 counts; affects older patients and people of African descent.

Renal disease may also be related to certain ART medications. Renal toxicity can be minimized by using tenofovir alafenamide or abacavir instead of tenofovir disoproxil fumarate. Overall, endstage renal disease is about 3 times higher among individuals with HIV infection compared with those without infection.[136]
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tr>
<td>HIV- or ART-associated bone disease</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>Risk of osteoporosis and osteopenia is increased in HIV-positive patients, and vitamin D levels are often low. Bone disease may be related to certain ART medications such as tenofovir disoproxil fumarate. This toxicity can be minimized by using tenofovir alafenamide or abacavir instead of tenofovir disoproxil fumarate. Overall, HIV-infected individuals are at about a 4 times higher risk of osteoporosis compared with those without HIV.[137]</td>
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<tr>
<td>HIV-associated cancer</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) are declining in the ART era, but continue to occur at rates several times higher than in the general population. Those infected with HIV are experiencing a rising burden of non-AIDS defining cancers in the ART era. These include anal cancer, Hodgkin lymphoma, oropharyngeal cancers, lung cancer, skin cancer, and liver cancer. Cancer as a cause of death has increased from 11% to 22% in a survey of French patients with HIV. Age-appropriate cancer screening is important for this population.[138] [139] [140] [141] [142] [143]</td>
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<tr>
<td>HIV-associated liver disease</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>HIV-infected patients have high rates of end-stage liver disease (ESLD) mostly due to viral hepatitis co-infection. There has been little to no change in the rate of ESLD in the ART era, but this is expected to change with antiviral agents against hepatitis C virus. Appropriate liver cancer screening for those with viral hepatitis co-infection is important in this population.[145]</td>
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<tr>
<td>HIV-associated neurocognitive dysfunction</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>This disorder is characterized by memory and cognitive difficulties, and is highly prevalent at 15% to 20% among HIV-infected individuals on ART.[146]</td>
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<tr>
<td>Patients with HIV infection have substantially higher rates of depression compared with the general population. Antidepressant therapy may improve symptoms compared with placebo; however, the quality of evidence is low in HIV-infected people.[147]</td>
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<tr>
<td>HIV-associated diabetes</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>Prevalence of diabetes in HIV-infected people ranges from 2% to 14% depending on type of study, ascertainment of diabetes, and risk factors. There is conflicting evidence on whether HIV infection is an independent risk factor for diabetes. Age-appropriate diabetes screening is important for this population.[148]</td>
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<tr>
<td>Research is ongoing as to whether there is a causal association between diabetes in HIV-infected patients and ART.[149]</td>
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<tr>
<td>HIV-associated lung disease</td>
<td>long term</td>
<td>low</td>
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<tr>
<td>COPD is the most common chronic lung condition diagnosed among those with HIV with a prevalence of approximately 20% in different cohorts. Whether HIV infection is an independent risk factor beyond associations with smoking or bacterial lung infection is unclear.[151]</td>
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Current evidence suggests a high prevalence of hearing impairment in people living with HIV compared with those without HIV; however, the etiology is not understood.[152]

May present with signs of World Health Organization stage 2 or 3 symptoms, including shingles, oral thrush, loss of weight, or pulmonary tuberculosis. CD4 count and viral load should be reviewed.

In early disease, the CD4 count may be transiently depressed at the time of concomitant infection if the patient is having it monitored regularly. Patients with advanced HIV deteriorate more easily, and infections should be diagnosed and contained as soon as possible.

In some opportunistic infections, empiric, best-guess treatment is warranted, especially in patients with compromised immunity. A broad-spectrum antibiotic is probably most commonly prescribed where an acute bacterial infection is suspected.

In patients with very advanced disease, monitoring the patient for immune reconstitution inflammatory syndrome (IRIS) for the first 3 to 6 months after starting antiretroviral therapy is very important, and will reduce morbidity and mortality if treatment is instituted early. IRIS is more common in patients with very advanced disease and extensive burden of OIs.[129]

Prognosis

The majority of HIV-infected individuals are able to regulate viral replication for many years because of an effective immune response; however, in the current era of potent combination antiretroviral therapy (ART), the recommendation is to initiate ART in all HIV-infected people and not to monitor with serial blood testing and clinical assessments in patients who are off therapy. Without ART, there is a steady decline over time of CD4 numbers and slow destruction of immunity leading to gradual onset of constitutional symptoms followed by opportunistic infections and malignancies. Patients may progress through the stages consecutively, but in many cases may move to a stage, skipping a clinical stage in between. Individuals do not revert to a previous stage even if treated.

ART reduces HIV replication to levels that are undetectable by laboratory assays. This allows the restoration of even advanced immune deficiency to safe levels in the vast majority of treated persons and the restoration...
and maintenance of health in a previously progressive and uniformly fatal syndrome. ART can also reduce HIV transmission and prevent infection after blood or sexual exposure (postexposure prophylaxis). As long as appropriate ART is taken as prescribed without default, the benefits of the viral suppression will be sustained. Poor adherence is the most common cause for failure of a regimen due to development of drug resistance, leading to breakthrough replication and persistent immune damage. Under these circumstances, a new regimen must be found with nonresistant agents, which can then, if taken correctly, lead to viral suppression once more. The central goal of HIV therapy then is maximal suppression of viral replication sufficient to prevent the selection of viral resistance mutations, and long-term adherence without therapy interruptions remains the key to the efficacy of all HIV regimens.[121]

Most patients on ART achieve virologic suppression within 3 to 6 months. Viral rebound rates have decreased over the years, and the risk decreases with increasing duration of viral suppression. A UK-based cohort study of over 16,000 HIV-positive persons found that a substantial proportion of patients on ART will not experience viral rebound over their lifetime (approximately 1% of men who have sex with men aged 45 years and older experienced viral rebound per year).[122] Rates of viral suppression nearly tripled in the US from 32% in 1997 to 86% in 2015, mainly due to improvement in ART regimens over the years.[123]

Globally, mortality peaked in 2006 with 1.95 million deaths, and has since decreased to 0.95 million deaths in 2017.[11] This figure dropped to 770,000 in 2018.[10] The all-cause mortality rate in the first 3 years after starting ART is declining. The rate was lower for those who began treatment between the years 2008 and 2010 compared with those who began treatment from 2000-2003. This is likely to be due to factors including the availability of less toxic drugs, improved adherence to drug regimens, and better management of comorbidities. Life expectancy after starting ART has improved over time.[124] Life expectancy has increased to approximately 63-67 years of age (depending on country and sex) for patients aged 20 years who started therapy from 2008-2010; however, it is still lower than in the general population.[125] Cancer mortality among people with HIV infection is much higher than in the US general population. Approximately 10% of deaths are due to cancer, most commonly non-Hodgkin lymphoma, lung cancer, and liver cancer.[126]

A small proportion of individuals are able to control HIV viral load without assistance of ART. Many have low-to-undetectable viral loads and well-preserved CD4 counts for many years. This appears in part to be due to a robust immunity to HIV. However, even these individuals are likely to benefit from consistent and uninterrupted use of ART.

Two cases of remission have been reported in patients with HIV-1 infection after stem-cell transplantation with donor stem cells from individuals with a homozygous mutation in the HIV coreceptor CCR5. The latest case was reported in the UK in March 2019, ten years after the first case. The man has been in remission for 18 months after undergoing an allogeneic hematopoietic stem-cell transplant for Hodgkin lymphoma using cells from a CCR5delta32/delta32 donor and then stopping ART. While these cases help further HIV research, the clinical implications are currently unknown, but support the development of HIV remission strategies based on preventing CCR5 expression.[127]
### Diagnostic guidelines

#### International

**Guidelines for the use of antiretroviral agents in adults and adolescents with HIV** [52]

**Published by:** US Department of Health and Human Services  
**Last published:** 2019

**CDC health information for international travel (the Yellow Book): HIV infection** [78]

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2019

**Quick reference guide: recommended laboratory HIV testing algorithm for serum or plasma specimens** [79]

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2018

**HIV infection: detection, counseling, and referral. Sexually transmitted diseases treatment guidelines 2015** [80]

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

**Laboratory testing for the diagnosis of HIV infection: updated recommendations** [63]

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

**Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations** [81]

**Published by:** World Health Organization  
**Last published:** 2017

**Guidelines on HIV self-testing and partner notification** [82]

**Published by:** World Health Organization  
**Last published:** 2016

**Consolidated guidelines on HIV testing services** [83]

**Published by:** World Health Organization  
**Last published:** 2015
# Treatment guidelines

## International

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<th>Topic</th>
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<th>Last published</th>
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<tr>
<td>Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV [86]</td>
<td>Department of Health and Human Services</td>
<td>2019</td>
</tr>
<tr>
<td>Guidelines for the use of antiretroviral agents in adults and adolescents with HIV [52]</td>
<td>Department of Health and Human Services</td>
<td>2019</td>
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<tr>
<td>CDC health information for international travel (the Yellow Book): HIV infection [78]</td>
<td>Centers for Disease Control and Prevention</td>
<td>2019</td>
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<tr>
<td>Guidelines for the use of antiretroviral agents in pediatric HIV infection [110]</td>
<td>Department of Health and Human Services</td>
<td>2019</td>
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<tr>
<td>Guidance for non-HIV-specialized providers caring for persons with HIV who have been displaced by disasters (such as a hurricane) [111]</td>
<td>Department of Health and Human Services</td>
<td>2018</td>
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<tr>
<td>Antiretroviral drugs for treatment and prevention of HIV infection in adults [41]</td>
<td>International Antiviral Society-USA</td>
<td>2018</td>
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<tr>
<td>2017 HIVMA of IDSA clinical practice guideline for the management of chronic pain in patients living with HIV [112]</td>
<td>Infectious Diseases Society of America</td>
<td>2017</td>
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<tr>
<td>Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis [113]</td>
<td>CIHR Canadian HIV Trials Network</td>
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<tr>
<td>Recommendations for HIV prevention with adults and adolescents with HIV in</td>
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<tr>
<td>the United States, 2014 [114]</td>
<td>Published by: Centers for Disease Control and Prevention  Last published: 2014</td>
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<td>Contraceptive eligibility for women at high risk of HIV [29]</td>
<td>Published by: World Health Organization  Last published: 2019</td>
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<tr>
<td>Update of recommendations on first- and second-line antiretroviral regimens</td>
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<td>[115]</td>
<td>Published by: World Health Organization  Last published: 2019</td>
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<tr>
<td>Updated recommendations on first-line and second-line antiretroviral</td>
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<td>regimens and post-exposure prophylaxis and recommendations on early</td>
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<td>infant diagnosis of HIV [95]</td>
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<td>Consolidated guidelines on person-centred HIV patient monitoring and case</td>
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<td>surveillance [116]</td>
<td>Published by: World Health Organization  Last published: 2017</td>
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<tr>
<td>Guidelines for managing advanced HIV disease and rapid initiation of</td>
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<td>antiretroviral therapy [72]</td>
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<td>Guidelines on the public health response to pretreatment HIV drug resistance</td>
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<tr>
<td>[97]</td>
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<td>Consolidated guidelines on HIV prevention, diagnosis, treatment and care for</td>
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<td>key populations [81]</td>
<td>Published by: World Health Organization  Last published: 2017</td>
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<td>Integrating collaborative TB and HIV services within a comprehensive</td>
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<td>Guideline on when to start antiretroviral therapy and on pre-exposure</td>
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<td>prophylaxis for HIV [37]</td>
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### International

<table>
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<tr>
<th>Guidelines</th>
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<tr>
<td>European AIDS Clinical Society guidelines: version 10.0 [118]</td>
<td>European AIDS Clinical Society</td>
<td>2019</td>
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<tr>
<td>Adult antiretroviral therapy guideline 2017 [119]</td>
<td>Southern African HIV Clinicians Society</td>
<td>2017</td>
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</tbody>
</table>
### Online resources

1. **UNAIDS Data 2019** *(external link)*
2. **Prevention Access Campaign: consensus statement** *(external link)*
3. **FDA: HIV treatment information for adults** *(external link)*
4. **AIDSinfo: antiretroviral agents in HIV-1-infected adults and adolescents** *(external link)*
Key articles

- World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. September 2015 [internet publication]. Full text

- Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. July 2019 [internet publication]. Full text


- Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. October 2018 [internet publication]. Full text

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29. World Health Organization. Contraceptive eligibility for women at high risk of HIV: guidance statement - recommendations on contraceptive methods used by women at high risk of HIV. 2019 [internet publication].  Full text


37. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. September 2015 [internet publication]. [Full text]


50. PARTNER Study Group. HIV transmission risk through condomless sex in gay couples with suppressive ART: the PARTNER2 Study extended results in gay men. 2018 [internet publication]. Full text


52. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. July 2019 [internet publication]. Full text


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78. Centers for Disease Control and Prevention. CDC health information for international travel (the Yellow Book): HIV infection. June 2019 [internet publication]. Full text


82. World Health Organization. Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services. December 2016 [internet publication]. Full text


86. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. September 2019 [internet publication]. Full text


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|-------------------|--------------------------------------------------|
| 95. | World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. December 2018 [internet publication]. [Full text] |


111. US Department of Health and Human Services. Guidance for non-HIV-specialized providers caring for persons with HIV who have been displaced by disasters (such as hurricane). September 2018 [internet publication]. Full text


117. World Health Organization. Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs. 2016 [internet publication]. Full text


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<tr>
<td>155.</td>
<td>Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.</td>
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<td>158.</td>
<td>National Institute for Health and Care Excellence.</td>
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</table>
HIV infection

Images

Figure 1: Oral candidiasis in a patient with HIV

Public Health Image Library (PHIL)
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