

HIV / AIDS

Background and Epidemiology

Human immunodeficiency virus (HIV) is a Lentivirus in the Retroviridae family that is the causative agent for acquired immunodeficiency syndrome (AIDS). AIDS case definitions include all HIV-infected persons with severe immunosuppression (less than 200 CD4+ T-lymphocytes/ μ L or a CD4+ T-lymphocyte percentage of total lymphocytes of less than 14). Alternatively, a diagnosis can be made using clinical conditions that include cancers or serious opportunistic infections associated with AIDS in HIV-infected patients.^{1,2}

In 2007, it was estimated that 33 million individuals were living with HIV infection worldwide.³ HIV / AIDS prevalence varies widely with geographical region: 2007 estimates of adult prevalence by region ranged from 0.1% to 5%. Sub-Saharan Africa, where AIDS remains a leading cause of death, is the most seriously affected region.³ In some sub-Saharan African countries, prevalence is as high as 33% among adults (15–49 years).³

In the US, the prevalence in adults aged 18 to 49 years was 0.47%. US prevalence also varies by gender and ethnicity (Table 1), with African Americans at a higher risk.⁴ The Centers for Disease Control and Prevention (CDC) estimates that 25% to 27% of the approximately 1 million HIV-infected individuals in the US are unaware of their condition and are likely to have transmitted the disease unknowingly. Individuals who are unaware of their HIV status have a transmission rate that is 3.5 times greater than those who are aware of their infection.⁶ Data show that

awareness of infection can decrease transmission risk by 3- to 5-fold.⁷

To reduce the risk of HIV transmission by people unaware of their infection, and to identify individuals who could benefit from earlier intervention, the CDC published revised recommendations for HIV screening in 2006. Major revisions include a move from screening only high-risk patients to universal opt-out screening (testing is performed unless the patient declines either verbally or in writing) for all persons between the ages of 13 and 64 presenting in a healthcare setting. For pregnant women, the new guidelines state that HIV screening should be included in the routine panel of prenatal screening tests. Repeat screening of high-risk patients at least annually, is also recommended (Table 2).^{7,8} The World Health Organization (WHO) endorses an opt-out approach to testing. This approach recommends testing for all patients whose clinical presentation is consistent with HIV infection, as a part of standard care for all patients in areas where HIV is a

generalized epidemic and selectively for patients where HIV is concentrated in a particular subpopulation.⁹ Since treatment is effective at decreasing morbidity and mortality, it is important that patients are diagnosed as infected as early as possible.

Table 2. Common risk factors that should trigger HIV testing.¹⁰

- Men who have sex with men
- Injection drug users
- Persons with multiple sex partners
- Sex workers
- Sexual contact with a known infected or at-risk person
- Sexually transmitted disease
- AIDS-defining illness*
- Oral candidiasis
- Tuberculosis
- Occupational exposure
- Sexual assault

*See Table 4

Table 1. Prevalence of HIV infection from National Health and Nutrition Examination Surveys (NHANES) 1999–2006, by age, gender, and race / ethnicity.⁴

	Percent Positive	95% Confidence Interval
Total ^a	0.47	0.34–0.64
Males	0.72 ^c	0.49–1.06
Non-Hispanic African American	2.64 ^d	1.88–3.70
All other race / ethnic groups ^b	0.48 ^d	0.26–0.86
Females	0.22 ^c	0.14–0.36
Non-Hispanic African American	1.49 ^e	0.91–2.43
All other race / ethnic groups ^b	0.03 ^e	0.01–0.13
Age ^a		
18–29 years	0.25 ^f	0.13–0.48
30–39 years	0.55	0.32–0.94
40–49 years	0.61 ^f	0.38–0.98
Race / Ethnicity		
Non-Hispanic Caucasian	0.23 ^g	0.11–0.48
Non-Hispanic African American	2.01 ^{g,h}	1.50–2.69
Mexican American	0.30 ^h	0.13–0.69

^aTotals differ from the sum for the non-Hispanic Caucasian, non-Hispanic African American, and Mexican American populations because those in the other race / ethnic category are included in the totals.

^bIncludes non-Hispanic Caucasian, Mexican American, and other race / ethnicity

^c $P < 0.05$ for difference between gender

^d $P < 0.05$ for difference between non-Hispanic African American males and males in all other race / ethnic groups

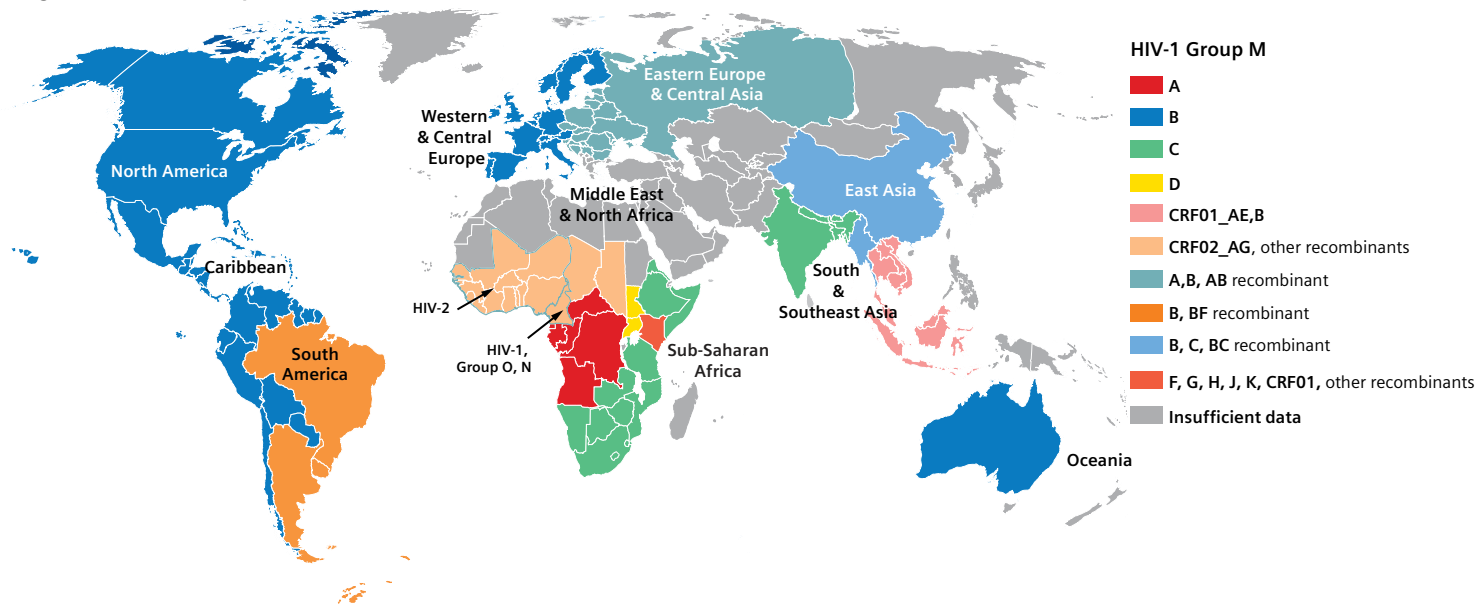
^e $P < 0.05$ for difference between non-Hispanic African American females and females in all other race / ethnic groups

^f $P < 0.05$ for difference between ages 18–29 and 40–49 years

^g $P < 0.05$ for difference between the non-Hispanic African American and non-Hispanic Caucasian populations

^h $P < 0.05$ for difference between the non-Hispanic African American and Mexican American populations

Figure 1. Global HIV prevalence and distribution.^{3,10}



Adults and children estimated to be living with HIV in 2007: total 33.2 million (range 30.6–36.1 million).⁵

	North America	Caribbean	South America	West & Central Europe	Mid East & N Africa	Sub-Saharan Africa	East Europe & Central Asia	East Asia	South & SE Asia	Oceania
Estimate (million)	1.3	0.23	1.6	0.76	0.38	22.5	1.6	0.8	4	0.075
Range (million)	0.48–1.90	0.21–0.27	1.4–1.9	0.6–1.1	0.27–0.50	20.9–24.3	1.2–2.1	0.62–0.96	3.3–5.1	0.053–0.120

*The ranges around the estimates define the boundaries within which the actual numbers lie, based on the best available information.

Classification

There are two major types of HIV: HIV-1 and HIV-2. HIV-1 is further subdivided into groups M, N, and O. HIV-1 group M is the predominant virus worldwide, accounting for about 90% of infections.^{8,11–13} Group M is further classified into several subtypes or clades of HIV. These are A to J and combinations of subtypes known as circulating recombinant forms (CRFs) and unique recombinant forms (URFs).⁸ HIV-1 group N is restricted to a few countries in Africa. HIV-1 group O is primarily limited to West Central Africa, although it is now seen outside that region. HIV-2 is predominately found in West Africa, but its presence is increasing in other areas (Figure 1).^{8,11}

Transmission and Pathophysiology

HIV is transmitted primarily via blood, semen, or vaginal fluids, although other body fluids such as colostrum and, more rarely, saliva can harbor infectious virus. Risk factors can vary by gender. In the US, male-to-male sexual contact is a leading cause of HIV transmission in men, while heterosexual contact poses the greatest risk for women (Figure 2). In highly endemic regions such as sub-Saharan Africa, heterosexual

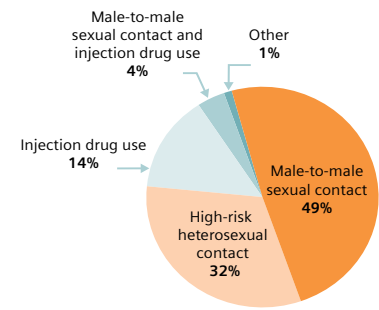
transmission is the leading risk factor for both men and women.

Viral binding to the host cell requires both the CD4 receptor and a coreceptor. Several coreceptors belonging to the chemokine receptor family have been identified. Two key coreceptors are CCR5 (present on a wide range of cells that include T-cells and macrophages) and CXCR4 (primarily found

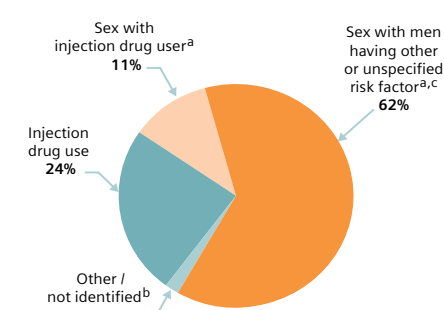
on CD4+ T-cells).^{15,16} Most patients are initially infected with HIV that preferentially binds to the CCR5 coreceptor (M-tropic, nonsyncytium-inducing). A shift in coreceptor usage from CCR5 to CXCR4 is associated with more rapid decline in CD4 cells, and a shift to a more aggressive disease state (T-tropic, syncytium-inducing).^{8,17} A small percentage of individuals carry a 32-base pair (32) deletion in the CCR5 gene.

Figure 2. Overall HIV or AIDS by transmission category.^{5,18}

Cases of HIV / AIDS among adults and adolescents of both sexes by transmission category, 2005, US (33 states).



Proportion of AIDS cases among female adults and adolescents by transmission category, 2006, US and dependent areas.



Note: Data have been adjusted for reporting delays, and cases without risk factor information were proportionally redistributed.

^aTransmission through high-risk heterosexual contact accounts for ~73% of AIDS cases in females. It includes heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

^bIncludes blood transfusion, prenatal exposure, and risk factor not reported or not identified

^cIncludes sex with a bisexual male, a person with hemophilia, and HIV-infected transfusion recipient, or an HIV-infected person with an unspecified risk factor

HIV / AIDS (continued)

Individuals homozygous for the 32 deletion appear to be highly resistant to HIV infection, while heterozygous individuals generally take longer for disease to develop.⁸

The eventual destruction of CD4+ cells weakens the patient's cellular and humoral immunity, leaving them vulnerable to life-threatening cancers and opportunistic infections.

Disease Progression

Acute HIV infection can be difficult to diagnose. Its signs and symptoms are nonspecific and can be easily mistaken for infectious mononucleosis, influenza, or other conditions. About 50% to 90% of those infected will exhibit acute symptoms. Acute symptoms generally start 4 to 28 days after initial infection and correspond to a peak in HIV viremia. These symptoms typically resolve within 4 weeks (Table 3).^{8,19} If the patient remains untreated, progression to AIDS will occur, on average, within 10 years.⁸ Patients with certain human leukocyte antigen (HLA) types may progress more rapidly to AIDS.²⁰

Table 3. Symptoms associated with acute HIV infections.^{8,19}

Symptom	Frequency (%)
Fever	>80–90
Malaise	>70–90
Myalgia or arthralgia	50–70
Night sweats	50
Headache	32–70
Lymphadenopathy	40–70
Pharyngitis	50–70
Nausea, vomiting, or diarrhea	30–60

Screening and Diagnosis

As mentioned previously, universal opt-out screening is now the recommended standard of care in the US, since awareness of HIV infection status can significantly reduce the risk of transmission. With the advent of highly active antiretroviral therapy (HAART), outcomes have dramatically improved. Timing of therapy is critical for optimal intervention, so early diagnosis is needed. Unfortunately, many patients are diagnosed late in the course of infection and subsequently develop AIDS within just one year of diagnosis.

Current screening and diagnostic tests rely on the detection of antibodies to HIV or viral ribonucleic acid (vRNA). Assays for the detection of HIV antibody in a variety of body fluids include automated immunoassays, microtiter-based tests, and manual point-of-care methods. It is important to note that assays are often designed differently, requiring an understanding of what individual assays might detect, or miss. Some HIV-1 assays have reduced detection of antibody to HIV-2 or HIV-1 group O, as they rely on cross-reactivity for recognition.

HIV-1 shares about 50% to 60% homology with HIV-2 in the more conserved regions, such as the *pol* and *gag* genes, but less in the envelope proteins often targeted for antibody detection.²¹ Some assays have been designed to specifically detect HIV-1, HIV-2, and HIV-1 group O, increasing the probability of reactivity to all main types of HIV-1 infection. Most currently available tests can reliably detect antibodies to HIV-1 and HIV-2. Newer assays can detect both IgM and IgG, reducing the potential for false negatives if the patient is in an early stage of seroconversion. Some tests are becoming available that detect both HIV antibodies and the p24 antigen. These antigen–antibody combination tests may facilitate slightly earlier detection of infection.

A reactive HIV antibody test should be confirmed with additional testing; supplemental tests include Western blot, the indirect fluorescent antibody (IFA) assay, and molecular tests. Western blot is currently a common method of confirmation. In the US, an HIV-1 Western blot is approved and commercially available. Many institutions follow CDC guidelines for Western blot interpretation, which require reactivity to at least two of the following antigens for a positive classification: p24, gp41, and gp120/160. A negative is the absence of all bands, although WHO suggests that results can still be reported as negative if there is a weak p17 band. An indeterminate classification is reported if there is reactivity to one or more antigens without meeting the criteria for positive.

Although the majority of HIV-2 infections will have antibody which cross-reacts with the HIV-1 antigens in the Western blot, there is an increased risk of an indeterminate or negative result with HIV-2 infections. Patients with a reactive immunoassay and a history consistent with HIV infection that do not confirm with a supplemental test

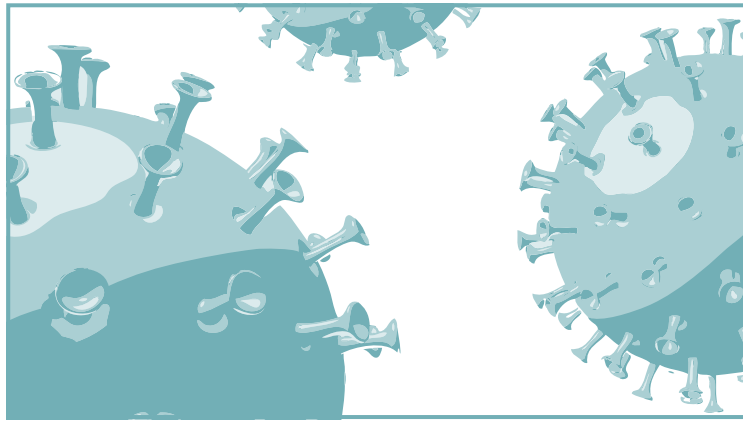
may benefit from further follow-up and additional testing.

In patients where the clinical suspicion for HIV infection is high and the antibody test is negative, a molecular test or repeat antibody test may be indicated.

Once the patient is definitively diagnosed, HIV viral load and CD4+ cell levels and resistance testing should be performed to determine their baseline values where these tests are available.^{8,17} In countries where viral load and resistance testing are not widely available, WHO recommends, at a minimum, that a CD4+ count be taken at baseline.⁹ Patients should also be assessed for opportunistic infections and cancers, and treated appropriately. Ideally, therapy should not be initiated without baseline resistance testing; approximately 5% to 15% of newly diagnosed HIV-infected patients harbor drug-resistant virus (either by primary infection or superinfection with a resistant strain).²² The decision to start antiretroviral therapy is based on several factors including, but not limited to, HIV viral load, CD4+ T-cell count, and whether the patient has symptomatic HIV infection or any AIDS-defining condition (Table 4).¹⁷

Table 4. AIDS indicator conditions.⁸

- Candidiasis of the esophagus, bronchi, trachea, or lungs
- Invasive cervical cancer
- Coccidioidomycosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month)
- Cytomegalovirus (CMV) of any organ other than the liver, spleen, or nodes
- Encephalopathy, HIV-related
- Herpes simplex virus (HSV) with mucocutaneous ulcer (>1 month), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, extrapulmonary
- Isosporiasis, chronic intestinal (>1 month)
- Kaposi sarcoma
- Lymphoma: Burkitt's, immunoblastic, or primary central nervous system (CNS)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, extrapulmonary
- *Mycobacterium tuberculosis* infection, any site
- *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*)
- Pneumonia, recurrent bacterial (two or more episodes in 12 months)
- Salmonella septicemia, recurrent
- Toxoplasmosis, CNS
- Wasting syndrome from HIV



Antiretroviral Therapy

Antiretroviral therapy (ART) is typically administered as a combination of drugs. HAART is a combination of antiretroviral drugs from at least two drug classes.¹⁷ The main classes of drugs are the nucleoside / nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 inhibitors, and integrase inhibitors.¹⁷ While ART / HAART is highly effective, it is also associated with serious adverse effects such as myopathy, peripheral neuropathy, lipodystrophy, dyslipidemias, and increased risk for cardiovascular disease (Figure 3).¹⁷ Patients should be monitored closely for adverse effects and compliance.

ART / HAART effectiveness is commonly monitored by CD4+ cells, viral load, and presence or absence of AIDS-associated cancers or opportunistic infections.¹⁷ Patients with unstable disease or coinfections such as HCV may need to be monitored more frequently. Where viral load testing is available, a typical goal of therapy is to achieve an undetectable viral load. The viral load should be measured immediately before therapy, 2 to 8 weeks after initiation, and at routine intervals to monitor patient response.¹⁷

Resistance to therapy is determined by genotypic or phenotypic methods. Neither approach, however, is able to detect resistant strains that are less than 20% of the total viral load or that are latently

infecting memory CD4+ T-cells.¹⁷ A significant change in resistance pattern or increased viral load can signal the need to adjust therapy to better address the predominant strain. If the patient's viral load reduction is suboptimal ($<1.0 \log_{10}$ copies/mL) or starts to increase, resistance testing should be repeated.¹⁷ The results of the resistance testing are then used to guide therapy. Patients with unstable disease or coinfections, such as HCV, may need to be monitored more frequently.

Since viral load results obtained from different commercial assays can vary, comparisons should be interpreted with caution. Ideally, the patient should be monitored with the same viral load assay throughout the course of disease.

Conclusion

Early identification of individuals with antibody to HIV can improve outcomes and may lead to reduced transmission rates. As HIV lacks both an effective vaccine and is currently not curable, ART / HAART is essential for optimal patient outcome. Molecular tests are critical for optimal patient care. Viral loads coupled with CD4+ T-cell counts help define therapy timing as well as assess treatment efficacy. Resistance testing is central to treatment selection, guiding the healthcare provider both in the initial choice of therapy as well as in the response to changes in drug resistance profiles.

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Figure 3. Physical and metabolic adverse effects of antiretroviral therapy.¹⁷

Physical Signs		Metabolic Changes			
Fat Wasting	Fat Accumulation	Abnormal Lipids	Insulin Resistance	Bone Disease	Mitochondrial Toxicity
<ul style="list-style-type: none"> • Face • Limbs • Buttocks 	<ul style="list-style-type: none"> • Abdominal viscera • Buffalo hump • Gynecomastia 	<ul style="list-style-type: none"> ↑ Triglycerides ↑ LDL ↓ HDL 	<ul style="list-style-type: none"> • Diabetes 	<ul style="list-style-type: none"> • Avascular necrosis • Osteoporosis • Osteopenia 	<ul style="list-style-type: none"> • Neuropathy • Acidosis • Pancreatitis • Hepatitis