

13. HIV-1 infection

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This review is intended to provide a fundamental perspective on the dynamic interplay between HIV-1 and the immune system, an essential aspect in defining the pathogenesis and treatment of AIDS. HIV-1 infection, the cause of AIDS, is a worldwide pandemic with enormous adverse health and economic implications, particularly in the developing world. This blood-borne and sexually transmitted disease, which evolved from simian immunodeficiency virus, infects and replicates in helper T cells and macrophages and utilizes CD4 and a chemokine coreceptor for entry. Immune deficiency occurs as a result of virally induced attrition of CD4 T cells, resulting in the development of opportunistic infections and malignancy. Prophylaxis against opportunistic infections is required according to the extent of immune deficiency. HIV-specific immunity can control viral replication and delay disease progression but does not clear infection. Antiretroviral treatment consists of inhibitors that target for viral entry, reverse transcriptase, and viral protease. Therapy can control viral replication, restore immunity, and delay disease progression, but it cannot eliminate infection. Thus chronic infection persists even in treated patients. Antiretroviral drugs have been highly effective in preventing mother-to-child transmission and for postexposure prophylaxis. Several novel vaccines in development hold promise for either effective infection prevention or attenuation of disease progression. (J Allergy Clin Immunol 2003;111:S582-92.)

Key words: HIV-1, AIDS, CD4 helper T cells, opportunistic infections, cytotoxic T lymphocytes, chemokine coreceptor, antiretroviral vaccine

THE GLOBAL HIV EPIDEMIC

During the past 20 years HIV-1 infection and acquired immunodeficiency syndrome have become a worldwide pandemic, with political and economic implications that transcend public health. In the developing world, where the epidemic is most rampant, the disease's adverse social and economic impact should not be underestimated.¹ According to the World Health Organization's assessment, more than 40 million people worldwide are currently infected, and AIDS has caused more than 20 million deaths. The prevalence of HIV-1 is increasing most rapidly in sub-Saharan Africa, where an estimated 4 million new infections occurred in 2001. The incidence

Abbreviations used

ART: Antiretroviral therapy
CTL: Cytotoxic T lymphocyte
gp: Glycoprotein
NNRTI: Nonnucleoside reverse transcriptase inhibitor
NRTI: Nucleoside reverse transcriptase inhibitor
PCP: *Pneumocystis carinii* pneumonia
PI: Protease inhibitor
RT: Reverse transcriptase
SIV: Simian immunodeficiency virus

of infection is also increasing at an alarming rate in southern and eastern Asia, where more than a million new infections are expected this year. In general, the virus is spreading most rapidly in geographic regions where the infrastructure to prevent and treat infection is most limited. AIDS is the leading cause of death in Africa and the fourth leading cause of death worldwide. An important aspect of the epidemic is its impact on families and social structure. Infection has a disproportionate impact on young adults and children, resulting in the loss through illness or death of those persons who can make the greatest contribution to the social support systems and economic vitality of their regions.^{2,3}

HIV-1 is a bloodborne and sexually transmitted disease. Transmission is primarily through insertive or receptive sexual intercourse, vertical transmission from mother to child, or exposure to contaminated blood or blood products.⁴ Persons who are at highest risk include people with infected sexual partners, infants born to HIV-infected mothers, intravenous drug users who share HIV-contaminated needles, and persons who receive inadequately screened blood products.⁵ AIDS was first recognized in the United States in a cluster of homosexual men who acquired opportunistic infections, principally *Pneumocystis carinii* pneumonia (PCP).⁶ Previously, PCP was most commonly associated with children with severe combined immune deficiency and patients with cancer, in whom immunity was compromised by chemotherapy. Unfortunately, many of the social stigma associated with the disease played a role in slowing the ability of public health agencies in the United States to aggressively screen at-risk populations early on in the epidemic.^{7,8}

Origin of HIV-1

HIV-1 is a lentivirus that most likely evolved from simian immunodeficiency virus (SIV), crossing from its predominant hosts (chimpanzees) to human beings sometime during the second half of the 20th century.^{9,10} Lentiviruses infect many different species, with varying virulence. SIV has multiple genetic variants and infects

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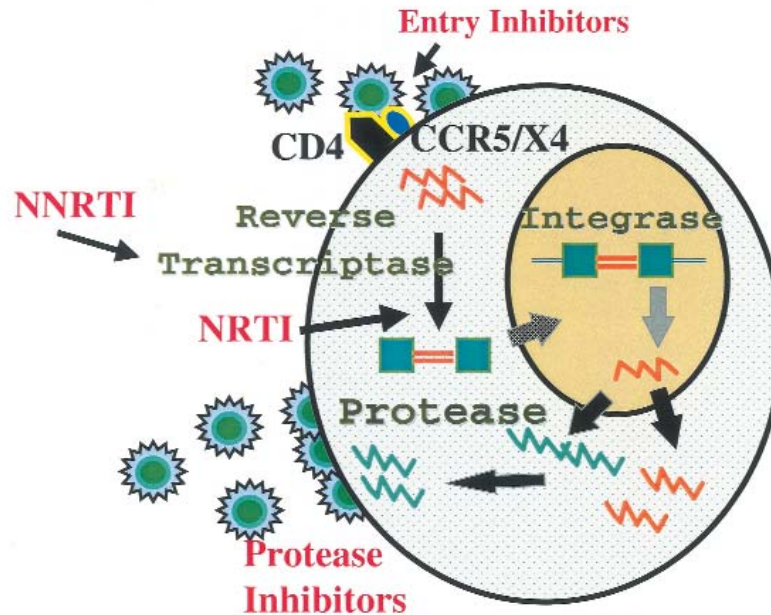


FIG 1. HIV-1 viral life cycle. The first step in the viral life cycle is attachment of gp120 to CD4 on the surface of helper T cells or macrophages, followed by binding to the viral coreceptor, either CCR5 or CXCR4. Entry inhibitors are designed to block viral attachment. After attachment, viral RNA enters the cell and is transcribed into double-stranded DNA by RT. NNRTIs bind directly to the enzyme to inhibit its function, whereas NRTIs compete for endogenous nucleotides to terminate the DNA strand. After reverse transcription, proviral DNA enters the nucleus and is integrated into the host DNA through the action of viral enzyme integrase. Viral replication begins by transcription of proviral DNA into either genomic RNA or mRNA, which is translated into viral proteins. HIV protease cleaves the viral polyprotein into functional peptides during the process of viral packaging and budding. PIs block this cleavage, resulting in nonviable virions.

multiple simian species. Similarly, there are currently two recognized strains of HIV, HIV-1 and HIV-2. HIV-2 is more closely related to SIV-1, less common, and less pathogenic than HIV-1, the principal cause of AIDS worldwide.¹¹ There are multiple HIV-1 groups and subtypes, with distinct geographic distributions according to their origins. Group M and its subtypes A to J are most prevalent worldwide, but recently two new groups, N and O, have been identified in Africa and eastern Europe.¹² The most common subtypes in group M are: B; which is the predominant subtype in North America, Europe, parts of South America and India, C; which is predominantly found in sub-Saharan Africa, and E; which is predominantly found in southeastern Asia. Each subtype is epidemiologically and antigenically distinct, a finding that may have implications for future vaccine initiatives.

HIV-1 VIROLOGY

HIV-1 virion and genetic organization

Knowledge of the viral life cycle and its genetic regulation is essential to an understanding of the natural history of HIV-1 infection and for the development of strategies to attenuate disease. A summary of the viral life cycle and the steps in its replication that are targets for antiretroviral therapy (ART) is shown in Fig 1. The basic structure of HIV-1 is similar to that of other retroviruses.

The virus particle consists of a host-derived lipid envelope, in which the highly glycosylated viral envelope protein, glycoprotein (gp) 120, protrudes from the surface, anchored by gp41, which spans the lipid membrane. Within the virus, structural proteins surround an inner core that contains enzymes and proteins required for viral replication, as well as the viral genome composed of two identical linear copies of RNA. The genome is approximately 10,000 nucleotides (10 kb) in size and consists of the prototypic genes *gag*, *pol*, and *env*, which are characteristic of all retroviruses.¹³ The *gag* gene encodes the core structural proteins, *env* contains the envelope proteins gp120 and gp41, essential for viral attachment and entry, and *pol* encodes the viral enzymes reverse transcriptase (RT), integrase, and protease. Two other genes essential for viral replication are *tat*, the major transactivator of the viral promoter within the long terminal repeats, and *rev*, which acts to facilitate gene transcription. In addition, accessory genes *nef*, *vpu*, *vpr*, and *vif*, although not essential to viral replication in vitro, contribute to the capacity to replicate in vivo. These accessory genes are unique to lentiviruses and do not appear in the genomes of the oncogenic retroviruses.¹⁴

Viral entry

HIV-1 uses two different types of receptors for cellular attachment and viral entry.¹⁵ Initial viral attachment occurs through the binding of the envelope protein gp120

to the CD4 molecule expressed predominantly on the surface of helper T lymphocytes and macrophages. Viral binding to CD4 is necessary but insufficient to mediate viral entry. Interaction between CD4 and gp120 increases the affinity of virus for coreceptor molecules, which are seven transmembrane, G-protein-coupled chemokine receptors that normally participate in cell migration to sites of inflammation. The two principal HIV-1 coreceptors, CCR5 and CXCR4, are differentially expressed on subpopulations of CD4-expressing cells, including T lymphocytes, thymocytes, macrophages, and dendritic cells. Viruses differ in ability to attach to different coreceptors and can be defined by coreceptor use.¹⁶ CCR5-using viruses enter macrophages and a subset of memory CD4 T lymphocytes. Viruses that use CXCR4 can infect most CD4 T lymphocytes, macrophages, and transformed T-cell or monocytic lines in culture.¹⁷ Genetic variation in HIV-1 envelope domains results in differences among viruses with respect to coreceptor use. Alternatively, genetic polymorphisms or deletions within CCR5 diminish or abrogate viral binding to receptor, which leads to a lower susceptibility to infection and slower disease progression in persons carrying these mutations.¹⁸ CXCR4-using viruses are generally more pathogenic than are CCR5-using viruses. However, most viruses transmitted from one person to another, either by sexual transmission or maternal transmission, use CCR5, even when infected persons have both viral types circulating in the blood.

Reverse transcription

After attachment, the next step in the infectious process is viral penetration. The viral lipid envelope with trimeric complexes of gp120-gp41 fuses with the lipid membrane of the target cell, which permits entry of the viral core, containing proteins, enzymes, and genomic RNA, into the cytoplasm of the cell. Within the cytoplasm, viral RNA is reverse-transcribed into double-stranded DNA with endogenous cellular nucleotides by the unique retroviral enzyme RT. Ribonuclease H activity associated with RT degrades the RNA genome so that a single double-stranded DNA provirus is synthesized. Lentiviruses, particularly HIV-1, display extensive genetic variability among viral genomes as a result of errors introduced by RT. Nucleotide substitutions occur as frequently as 1 per 10,000 nucleotides, which can introduce new genetic changes with each cycle of viral replication. Selective pressures on viral viability and host interactions modulate the extent and location of variability within the genome. As a result of substitutions, deletions, duplications, and recombination, HIV-1 within an infected person is a "quasispecies" of genetically related virions.^{19,20}

Entry inhibitors

Conceptually, the use of agents to block viral entry is an attractive modality in the treatment of HIV-1 infection.²¹ Unfortunately, agents designed to block binding of gp120 to CD4 have had limited success. Chemokine receptor antagonists that block viral attachment to the CCR5 coreceptor are currently in development and have

had promising in vitro results indicating effective blockade of viral entry. CCR5 antagonists are unlikely to adversely affect immunity, because persons with genetic deletions of CCR5 appear to have normal immune function. After viral binding to its cellular receptors, HIV gp41 "harpoons" target cells to allow viral fusions and insertion. Fusion inhibitors, such as T20, are peptides that block fusion by directly binding to gp41.²² Such agents are in advanced stages of clinical development.

RT inhibitors

After viral attachment and entry, reverse transcription can be targeted by antiretroviral agents. These inhibitors fall into two classes, the nucleoside and nucleotide RT inhibitors (NRTIs) and the nonnucleoside RT inhibitors (NNRTIs). NRTIs, which were the first anti-HIV drugs used clinically, require intracellular phosphorylation for activation and compete with endogenous nucleotides for incorporation into the growing viral DNA strand. NRTIs lack a 3' hydroxy terminal, so when an NRTI is incorporated into DNA the next phosphodiester bond is not formed, and the DNA strand is terminated. In contrast, NNRTIs bind directly to HIV-1 RT, require no intracellular phosphorylation, and have limited impact on other cellular enzymes. The NNRTI class of drugs is highly effective in controlling viral replication and is the backbone of many combination antiretroviral regimens.²³

Viral integration

Once the DNA form of the virus has been synthesized, a preintegration complex, including viral DNA, proteins, and enzymes, is transported to the nucleus. Activity of the virally encoded integrase enzyme is essential for integration, which involves covalent linkage between long terminal repeat elements that flank the linear viral DNA and host chromosomal DNA. Integration into the host DNA appears more or less random, with no particular chromosomal site, although conformation or nucleotide composition of host DNA may provide preferential sites for viral integration. HIV-1 integrase provides yet another target for drug activity, and development of integrase inhibitors is ongoing.²⁴

Viral replication and assembly

Genetic organization of the integrated proviral form of HIV-1 DNA is colinear with viral RNA. As an integral component of the host cell genetic material, viral DNA is expressed as RNA by the normal RNA polymerase II-dependent transcriptional machinery of the host cell. Regulation of viral gene expression is controlled by the long terminal repeats, which are approximately 650 nucleotides and composed of a number of transcriptional regulatory elements common to eukaryotic cells.²⁵

Viral mRNA transcripts are initially spliced and transported to the cytoplasm for translation of Tat, Rev, Nef, and other regulatory proteins. Subsequently, full-length genomic transcripts, which serve as mRNA for Gag polyproteins matrix [p17^{MA}], capsid [p24^{CA}], nucleocapsid [p7^{NC}], p6, or viral enzymes [RT, protease, and inte-

grase], and spliced transcripts that encode envelope glycoproteins are all transported and translated. Viral structural proteins complex with full-length viral RNA and with envelope glycoproteins and assemble at the cytoplasmic membrane by virtue of a myristylation modification at the amino terminus of Gag p17^{MA}. Virus particles bud from the surface of infected cells and are enveloped by the host cell membrane.

To become infectious, newly budded virions undergo subsequent maturation, a process involving systematic cleavage of Gag polyproteins and enzymes by the activity of the virus-encoded protease. HIV-1 protease is a homodimeric aspartic protease composed of 99 amino acid monomers. Protease functions as a molecular scissors to cleave Gag and Gag-Pol polyproteins in an ordered process during viral maturation. The active site of protease contains two catalytic aspartic acid residues, which cleave the bond between two amino acids in a substrate. When substrate binds in the active site, the enzyme undergoes conformational change, and flaps close over the bound substrate. After catalysis, the flaps open, cleaved proteins disassociate, and the enzyme is poised for another round of activity.

Protease inhibitors (PIs) compete with normal substrates for binding to the active site. Once bound, PIs do not dissociate from the enzyme, and there is paralysis of protease activity and blockade of virion maturation. The impact of PIs is exerted on viral infectivity of virions rather than on inhibition of virus production.²⁶

THE HIV-1 INFECTIOUS PROCESS IN VIVO

Acute infection in adults

The most common route of infection is through sexual transmission, when virus crosses mucosal surfaces to infect susceptible cells, such as CD4-expressing macrophages and T cells. On the basis of studies that used intravaginal inoculation of SIV, several possible scenarios have been determined to occur during the early phase of acute infection. Virus can attach to dendritic cells through binding of gp120 to an adhesion molecular complex called *dendritic cell-specific, intercellular adhesion molecule-grabbing nonintegrin* (DC-SIGN).²⁷ Though not productively infected, these cells migrate to regional lymph nodes, where infection of CD4 T cells occurs through direct cell-to-cell contact. Alternatively, submucosal macrophages and CD4 T cells become infected through contact with free virus or passenger-infected cells transmitted within the secretions of the infected partner.²⁸ Local epithelial barriers are effective in protection against infection, because only about 1 in 400 persons exposed to HIV-1 through sexual contact becomes infected. The risk of infection through heterosexual intercourse is estimated to be higher for women than for men.²⁹ Coinfections that lead to mucosal ulcerations, as seen in herpes simplex virus infection or bacterial infection, enhance the likelihood of infection through sexual transmission.³⁰ Breaks in the mucosal barrier allow HIV-1 to more easily cross

squamous epithelium, and local inflammation results in higher levels of T-cell activation, which enhances viral integration and replication.

Dendritic cells, macrophages, and CD4 T cells harboring virus migrate to the regional lymphoid tissues during the course of 3 to 5 days. Direct contact between virus-harboring cells and susceptible macrophages or CD4 T cells within the lymph node germinal centers leads to a brisk increase in viral replication within 14 days after exposure.²⁸ Virally induced local inflammatory responses actually facilitate viral replication and development of an acute phase of viremia, leading to dissemination of infection to other lymphoid tissues and organs. The clinical signs of acute retroviral syndrome in patients range from complete absence of symptoms to severe acute illness involving fever, malaise, rash, and encephalitis and lasting as long as 2 weeks. Only a third of HIV-infected patients exhibit symptoms of acute retroviral syndrome, defined as a mononucleosis-like illness with fever for longer than 3 days that occurs within 6 months of exposure to HIV-1.³¹ During the phase of acute viremia, ongoing viral replication reaches high levels, often higher than 10⁶ copies/mL plasma. HIV-specific antibody responses and cytotoxic T lymphocyte (CTL) responses have not yet developed, and virus is unchecked. Even though the commonly used antibody-based assays to diagnose infection may yield negative results during acute retroviral syndrome, patients are highly infectious and may display laboratory abnormalities, including atypical lymphocytosis, mildly elevated liver enzymes, hypergammaglobulinemia, elevated serum acute-phase reactants, leukopenia, thrombocytopenia, and inversion of the CD4 to CD8 T-cell ratio.³⁰

Perinatal infection

HIV infection in children primarily occurs through transmission of the virus from mother to child. In the absence of ART targeted to interrupt transmission, approximately 20% to 30% percent of infants born to HIV-infected women become infected.³² This percentage is higher in regions where breast-feeding is common. Infants born to HIV-infected mothers may become infected through transplacental transmission to the fetus, perinatal infection that occurs near the time of birth, or postnatal infection by breast-feeding.^{33,34} Approximately 20% of infected infants acquire infection in utero. In general, these infants have a more fulminant clinical course, with most having progression to AIDS within the first 2 years of life.³⁵ Compared with infants infected perinatally, they exhibit higher peak levels of viremia and demonstrate sustained elevation of viral burden during infancy.³⁶ Perinatal acquisition is the most common, accounting for 60% to 70% of infected infants.³⁷ Transmission is thought to occur by exposure to virus within maternal blood or by aspiration of infected maternal secretions.³⁹ Perinatally infected children have lower early levels of viral replication, slower attrition of CD4 T cells, and delayed clinical disease progression, with an estimated rate of progression to AIDS of 8% per year.⁴⁰

An additional 15% to 20% of infection is through ingestion of virus-laden maternal breast milk. Although it is uncommon in the developed countries where infant formula provides an alternative to breast-feeding, this route of infection is a significant additional source of infection in developing countries, where options for infant nutrition are limited, and may contribute to more than 15% of all pediatric HIV-1 infection.⁴¹

HIV-specific immunity

The first HIV-specific immune response during acute viremia is the emergence of CTLs, followed by the appearance of HIV antibodies, usually by 6 to 8 weeks after exposure.⁴² Clinical symptoms subside, and plasma viral levels decrease with the emergence of an HIV-specific immune response. HIV-specific CTLs provide the most effective control of viral replication.⁴³ Antigenic viral epitopes that serve as CTL targets are most commonly located within *env*, *gag*, *pol*, and *nef* peptides.⁴⁴ One of the great paradoxes of HIV-1 infection is the apparent inability of antibody to attenuate or protect against infection.⁴² Maternal antibody fails to protect the fetus from infection, and the capacity of antibody to control viral replication and delay disease progression is controversial.⁴⁵⁻⁴⁸ However, recent studies with simian-based animal model systems and high-affinity monoclonal or polyclonal anti-SIV antibodies indicate that neutralizing antibody can be effective in preventing maternal and sexual transmission.^{49,50} The development of vaccines that induce high levels of neutralizing antibodies has become a major focus of the HIV immunization strategy.⁵¹

Antibody responses are directed toward multiple HIV-1 peptides, forming the basis of the ELISA and Western blot diagnostic assay used to detect and confirm HIV-1 infection in adults. This test cannot be used as a diagnostic tool for infants infected through maternal transmission because of the presence of passively acquired maternal antibody. HIV antibody can be detected in the blood within days to weeks after acute infection, although in rare cases antibody production is delayed for several months. Persons exposed to HIV-1 should be closely monitored for seroconversion during the initial year after viral exposure.⁵²

Within the infected person, a steady state develops between the capacity of infected CD4 T cells to produce new virus and elimination of infected cells by CTLs or clearance of virus by neutralizing antibody. The capacity of the cellular and humoral immune responses to control viral replication is the principal determinant in predicting the rate of disease progression. During infection, as much as 10% of the total CD8 T-cell population can be activated against HIV-1 antigens.⁵³ This aberrant degree of clonal expansion can overwhelm CTL immunity, resulting in T-cell anergy, skewing CD8 T-cell maturation, and leading to deletion of HIV-specific T-cell responses.⁴³ Virally induced T-cell deletion and clonal exhaustion of HIV-specific CTLs are similar to the pathogenesis observed in lymphocyte choriomeningitis virus infection in mice.⁵⁴ The failure of cytotoxic CD8 T cells to control viral replication occurs through several

mechanisms.⁵⁵ HIV *nef* gene product lowers expression of MHC class I, compromising CTL recognition of infected cells. Viral infection downwardly modulates critical T-cell signaling pathways, including the CD3-T-cell receptor pathway and the CD28 costimulatory pathway. Chronic expression of cell surface molecules associated with activation impairs lymphocyte homing by altering the normal expression of adhesion molecules involved in directing lymphoid cells to sites of viral replication.

A combination of viral replication under the selective pressure of the immune response and HIV-1 genetic variability leads to the rapid emergence of immune escape variants and further contributes to the development of chronic HIV-1 replication. HIV-1 can escape recognition by both cellular and humoral immunity through mutations within antigenic epitopes. In this case of CTLs, mutations alter antigenic peptide binding to MHC class I. Altered CTL epitopes can drive CTL proliferation without engaging effector mechanisms that induce cytolysis. As a result, there is an accumulation of HIV-specific memory CD8 T cells that fail to differentiate into effector CD8 T cells to elicit effective cytolysis of HIV targets.⁴³ Collectively, these mechanisms contribute to a chronic state of HIV replication that causes a global impairment of HIV-specific immunity. Recent studies have shown that viral escape mutants with altered MHC class I binding can be transmitted from one person to another, a finding that may have dire consequences for the development of future CTL-based vaccine strategies.⁵⁶

Viral dynamics and CD4 T-cell depletion

The causes that lead to the loss of CD4 T cells and the development of AIDS are multifactorial. The best conceptual description of HIV-1 immune pathogenesis has been the tap and drain model in which new T cells are produced from bone marrow and thymus, the tap, and CD4 T cells are deleted through viral induced attrition, the drain.⁵⁷ The dynamic equilibrium between the tap and drain determines both the rate and extent of immune deficiency. Steady-state viral load and clinical progression to AIDS reflect the capacity of the immune response to control viral replication by the elimination of free virus and the rate of production of new virus by productively infected cells. CD4 T-cell counts are a function of the capacity of the thymus to produce new T lymphocytes and the rate of virally induced CD4 T-lymphocyte attrition. After initial infection and peak viremia, the control of viral replication by the immune response results in establishment of a steady-state level of plasma virus, or set point. Higher set point values generally reflect poorer immune control of viral replication and predict more rapid CD4 T-cell depletion and faster disease progression to AIDS.⁵⁸ Most plasma virus (>95%) comes from newly infected CD4 T cells, with less plasma virus produced by macrophages and dendritic cells (<5%). Infected T cells have a short half-life of less than 20 hours to produce new virions before undergoing elimination by CTLs or virally induced apoptosis.⁵⁹ Free virus, which has a half-life in plasma of about 6 hours, is cleared through binding to

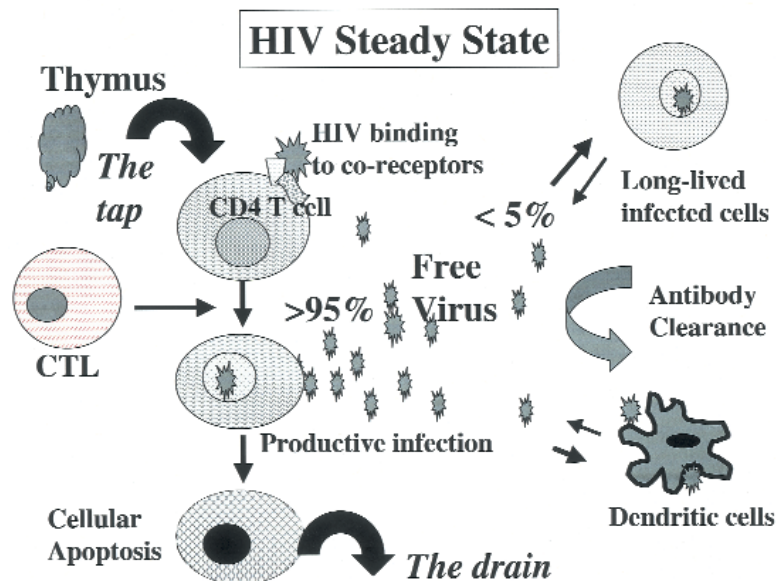


FIG 2. HIV steady state. In the tap and drain model of HIV-1, free virus binds to its receptors, CD4, and chemokine coreceptors. Productively infected CD4 T cells produce more than 95% of free virus in the plasma before they are either eliminated through cytolysis by HIV-specific CTLs or undergo cellular apoptosis. The half-life of an infected activated CD4 T cell is approximately 20 hours, and a free virion remains in the plasma for about 6 hours. Steady-state CD4 T-cell counts are maintained by the production of new T cells from the thymus, the tap, and the elimination of CD4 T cells by cytolysis or apoptosis, the drain. A minority, less than 5%, of free virus comes from infected macrophages, dendritic cells, and latently infected CD4 T cells. However, these long-lived latently infected cells can harbor virus for months to years and are not susceptible to ART.

new target cells or by antibody. The cellular dynamics of steady-state viral load are illustrated in Fig 2.

Clinical and laboratory findings in HIV-1 infection

HIV-1 infection impairs T-cell immunity, resulting in the development of opportunistic infections, increased risk of malignancy, and other conditions that are typical of patients who have defects in cell-mediated immunity. HIV-infected children and adults have an increased risk of malignancies, usually those associated with viral coinfection, such as human herpesvirus 8–associated Kaposi sarcoma and EBV-driven B-cell lymphoma. Virus can directly effect target organs, causing progressive multifocal leukoencephalopathy, cardiomyopathy, nephropathy, and chronic dysfunction within other organ systems. The Centers for Disease Control and Prevention classification systems for the clinical conditions associated with HIV-1 infection in children and adults are summarized in Table I.^{60,61}

Regularly monitored viral load and CD4 T-cell counts are the best prognostic measures to predict the development of HIV-associated conditions and progression to AIDS. Persons with high steady-state levels of viral replication (>35,000 copies/mL) have greater than 60% risk for the development of AIDS within 5 years of infection, whereas only 8% of infected persons who have steady-state viral loads of less than 5000 copies/mL have AIDS develop within the same time frame (Fig 3). Deter-

mination of the extent of immune suppression is based primarily on evaluation of CD4 T-cell counts.⁶⁰ There are age-related differences in total CD4 T-cell counts. Infants and children have higher total lymphocyte counts than do adults. Thus, an HIV-infected child who has normal CD4 T-cell counts according to adult parameters may be highly immune suppressed and susceptible to opportunistic infections. The relative percentages of CD4 T cells used to define mild, moderate, and severe immune suppression are constant across age groups. Infected persons with mild immune suppression (>25% CD4 T cells) are generally symptom free, although incidences of recurrent viral upper respiratory infections, allergic disease, mucocutaneous candidiasis, lymphadenopathy, and splenomegaly are frequently increased. Patients with moderate immune suppression, defined as CD4 T-cell counts between 15% to 24%, are at risk for pancytopenias, recurrent viral infections with herpes simplex and varicella zoster, and systemic bacterial infections. Severe immune suppression (CD4 T-cell count <15%) carries high risks of PCP, recurrent life-threatening bacterial infection, extrapulmonary cryptococcal infection and other systemic fungal infections, central nervous system toxoplasmosis, and disseminated mycobacterial infection. Long-term prophylaxis against opportunistic infections, particularly PCP, candidal, and mycobacterial infections, is warranted in HIV-infected persons with severe immune suppression.⁶²

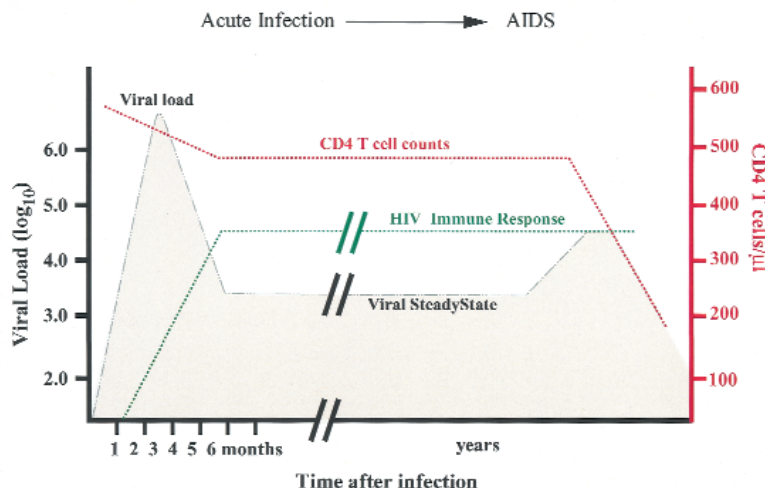


FIG 3. Natural history of HIV-1 infection. After initial infection there is an acute phase of viremia, as represented by the shaded area beneath the dotted line. Plasma viral load can reach greater than 6.0 log₁₀ viral copies/mL, peaking 6 to 12 weeks after exposure. During the acute infection, infected patients are highly infectious but have negative results of diagnostic tests that rely on the presence of anti-HIV antibodies such as the HIV ELISA and Western blot assays. Anti-HIV immunity is marked by the appearance of anti-HIV viral antibodies and CTL responses, as represented by the dotted line. Anti-HIV antibodies remain detectable throughout the course of infection. Viral levels fall as a result of the HIV immune response. The effectiveness of the immune response is the principal determinant of the level of steady-state viral replication. High steady-state levels lead to early fall in CD4 T-cell counts and progression to AIDS in less than 5 years, whereas lower steady-state levels result in slower disease progression. During the acute phase of infection there is evidence of T-cell activation and an increase in the number of circulating CD8 T cells, as evidenced by an inverted CD4 to CD8 ratio. AIDS results when virally induced CD4 T-cell attrition results in critically low cell levels and persons acquire opportunistic infections or other AIDS-defining illnesses.

TREATMENT AND PREVENTION OF HIV-1 INFECTION

Use of ART

Currently the best treatment for HIV-1 infection is the use of combination ART that targets multiple steps in the viral life cycle. Drug regimens that include combinations of an NRTI plus either a PI or an NNRTI can have significant impact in delaying progression to AIDS and preventing or reversing immune deficiency.^{63,64} As a result, HIV-1 infection in both adults and children has changed from a progressive disease that ultimately results in death from opportunistic infection or malignancy to a chronic condition with slow disease progression that requires lifelong therapy.⁶⁵ Early expectations that combination ART would eradicate infection have been unfulfilled, because virus can persist in latent reservoirs for many years despite effective therapy.^{66,67} In light of the reality that current treatments fail to achieve total viral clearance, clinicians have had to reassess the use of ART and consider the toxicity of treatment regimens, the burden of daily use of multiple drugs on quality of life, and the ability of most persons to adhere to complex lifelong treatment regimens. Drug-induced complications associated with antiretroviral treatment include development of lipodystrophy, hyperglycemia, and elevated triglyceride and cholesterol levels associated with the use of PIs; the development of metabolic abnormalities and cytopenias associated with RT

inhibitors; and the emergence of drug-resistant viruses requiring therapy cycling that ultimately limits the use of future drug combinations.^{68,69} Furthermore, the long-term benefits of combination therapy and the durability of treatment to maintain viral suppression are uncertain. Although the use of combination ART that suppresses viral replication to undetectable levels is still considered the optimal clinical management of HIV-1 infection, the newer guidelines that weigh the risk and benefits of treatment suggest that treatment can be delayed until viral levels are greater than 55,000 copies/mL or CD4 T-cell counts fall below 25% or 350 cells/μL.^{23,69}

ART containing a PI or NNRTI produces a first-phase logarithmic decline in viral burden within 2 weeks of treatment.^{57,70} A second-phase decline, at which time more than 80% of patients have undetectable viral levels, occurs by 8 to 12 weeks after treatment initiation.⁶⁷ PI- or NNRTI-based ART is most effective in achieving sustained and durable suppression of viral replication when administered during acute infection.⁷¹ If ART is initiated before development of chronic infection, HIV-specific immunity alone can maintain sustained suppression of viral replication even in the absence of treatment in some patients.⁷¹ This observation has led to application of structured treatment interruptions as a means to restimulate HIV-specific CTL responses in patients who have maintained undetectable levels of viral replication. This strategy appears to be most effective when initiated in persons who have had effective ART during acute infection.⁷¹

HIV-1 genetic variability is directly linked to rate of viral replication; thus, effective viral suppression through treatment slows the emergence of drug-resistant viral variants.²⁰ Unfortunately, not all HIV-infected persons who receive ART achieve or sustain undetectable plasma viral levels. Viral replication in the presence of suboptimal ART selects for variants with accumulation of amino acid substitutions in RT or protease (genotypic resistance) and reduced sensitivity to inhibitors (phenotypic resistance).⁷² In general, profiles of genotypic and phenotypic resistance are concordant, although the multiple combinations of amino acid mutations that can develop in persons with different therapies might require direct testing to ascertain levels of resistance. Resistance to one drug often confers some level of reduced sensitivity to other drugs of the same class, which dictates that genotypic resistance be evaluated before switching therapies.⁷²

When the selective pressure of drug is removed, the predominant replicating virus reverts to the pretherapy, drug-sensitive genotype and phenotype, indicating that wild-type virus has a replication advantage relative to drug-resistant variants. Some drug-resistant viruses replicating under the selective pressure of ART appear to have a lower pathogenic impact on immunity.⁷³ This may be due to a lower replication capacity within the thymus that preserves thymic output and allows for immune reconstitution, despite persistently high levels of viral replication.⁷⁴⁻⁷⁶

Immune reconstitution after ART

Reduction in viral load after ART reverses many of the adverse effects of HIV-1 infection on immune function. During the first few weeks of treatment, viral levels decline and lymphocytes recirculate from lymphoid tissues, as evidenced by a rapid increase in peripheral blood lymphocyte counts involving predominantly memory T cells and B cells.⁷⁷ During the subsequent weeks, both HIV-infected adults and children show a significant capacity to restore thymic output, reestablish diversity within the T-cell repertoire, and correct T-cell function.^{76,78,79} Declining viral burden is also associated with a decrease in T-cell activation markers and improved antigen-specific immunity by T cells.^{78,80,81} Several large clinical studies show that prophylaxis for PCP can be safely discontinued when CD4 T-cell counts are reconstituted after ART.⁶² Most significantly, decline in viral level restores HIV-1-specific immune responses that undoubtedly help to sustain the suppression of viral replication.^{43,82}

Preventing HIV-1 infection with ART

At present, chemoprophylaxis is the only effective means of preventing HIV-1 transmission from one person to another. The use of ART to prevent transmission has been most examined in the setting of maternal transmission. Zidovudine and other RT inhibitors given to HIV-infected women during pregnancy and labor, as well as short treatment courses for newborn infants, reduce the rate of perinatal infection by more than two thirds.⁸³ Studies of ART in the setting of maternal transmission form the basis of all treatment strategies for postexposure

TABLE I. Centers for Disease Control and Prevention clinical categories of pediatric, adolescent, and adult HIV disease

	Age
Category N (no symptoms)	
Confirmed infection	P
Category A (no [adult] or minimal [pediatric] symptoms)	
Lymphadenopathy or hepatosplenomegaly	B
Dermatitis	P
Parotitis	P
Recurrent upper respiratory tract infection	P
Constitutional symptoms (fever, diarrhea for >1 mo)	B
Pancytopenia	P
Idiopathic thrombocytopenia	A
Systemic bacterial illness	P
Bacillary angiomatosis	A
Oropharyngeal candidiasis	B
Persistent vulvovaginal candidiasis poorly responsive to therapy	A
Cervical dysplasia or cervical carcinoma in situ	A
Oral hairy leukoplakia	A
Pelvic inflammatory disease	A
Listeriosis	A
Category B (moderate symptoms)	
Cardiomyopathy	P
Neonatal cytomegalovirus	P
Chronic diarrhea	P
Herpes simplex virus stomatitis, pneumonia, esophagitis	P
Recurrent herpes zoster	B
Leiomyosarcoma	P
Lymphoid interstitial pneumonitis	P
Nephropathy	P
Nocardiosis	P
Peripheral neuropathy	A
Congenital toxoplasmosis	P
Disseminated varicella	P
Category C (severe symptoms, case definition of AIDS)	
Multiple bacterial infections	B
Recurrent pneumonia	B
Disseminated coccidiomycosis	B
Extrapulmonary cryptococcosis	B
Cryptosporidiosis diarrhea	B
Chronic isosporiasis diarrhea	B
Candidiasis of the esophagus, trachea, or lungs	B
Disseminated cytomegalovirus (other than liver, spleen, nodes)	B
Encephalopathy	B
Progressive multifocal leukoencephalopathy	B
Cervical carcinoma	A
Persistent herpes simplex virus	B
Disseminated histoplasmosis	B
Disseminated tuberculosis	B
Disseminated <i>Mycobacterium avium</i> complex	B
PCP	B
<i>Salmonella</i> sepsis	B
Central nervous system toxoplasmosis	B
Wasting syndrome	B
CD4 T-cell counts <200 cells/mL or <15%	A
HIV-associated malignancy	B
Kaposi sarcoma	
Central nervous system lymphoma	
B-cell lymphoma	
Immunoblastic lymphoma	

P, Pediatric condition; B, both pediatric condition and adolescent/adult condition; A, adolescent/adult condition.

prophylaxis.³² ART lowers the risk of transmission in two ways. First, the likelihood of exposure to virus is reduced by lowering viral load in blood and secretions. Second, and more importantly, susceptible cells are protected from infection.⁶⁸ In the setting of maternal transmission, zidovudine effectively protects fetal cells from infection even when maternal viral burden is high.⁸⁴ Potent NNRTIs, such as nevirapine, are highly effective in preventing infection even when treatment consists of a few doses given to mother and child at the time of birth.⁸⁵ In the setting of health care workers exposed to HIV-1-contaminated blood through needle sticks, postexposure prophylaxis with ART is recommended to prevent infection.⁵²

HIV-1 vaccines

The scope of the global HIV-1 epidemic has created an urgent need to implement effective vaccines that either protect against infection or prevent disease. Both HIV and SIV have unique attributes that pose special challenges for vaccine development.⁸⁶ Similar to infections with herpesviruses, after the acute infection and suppression by the immune response virus persists as latent infection. Unlike herpesviruses, HIV persistence eventually causes disease in all infected persons. Furthermore, RT errors result in rapid development of antigenic variation, leading to immune escape. Chronic infection contributes to the paradox of high levels of HIV-specific immunity in both cellular and humoral responses but continued viral replication leading to immune deficiency.⁸⁷ Most applications that have been based on adoptive transfer of antibody or immunization targeted toward enhancing mucosal immunity in animal models have not provided complete protection against viral challenge. Vaccine development has also been hampered by the lack of a clear identification of the immune components that best correlate with protection.

Currently, multiple strategies are moving forward in vaccine development, but the likelihood that traditional protein-based vaccines will provide effective immunity against infection is uncertain.⁸⁸ Vaccine strategies that are based on the principle that infection with live, nonpathogenic strains of HIV-1 generate immunity that protects against superinfection with wild-type strains.⁸⁹ However, studies that have used this approach in simian animal models have shown that attenuated virus can still cause disease.⁹⁰ Several candidate vaccines are in an advanced stage of clinical development, including vaccines that express HIV-1 antigenic peptides by modified, nonpathogenic vaccinia or pox viruses that are capable of generating CTL and antibody responses.⁹¹ DNA-based vaccines have been shown to be safe and capable of priming virus-specific CTL responses. These promising agents are in the early stages of clinical development.⁹² In simian models, DNA vaccines coupled with immune-based enhancement of CTL responses provide effective priming of virus-specific cell-mediated immunity. Vaccinated animals challenged with pathogenic virus are able to control viremia and prevent progression to clinical

AIDS.⁹³ This vaccine approach to attenuating disease rather than preventing infection may prove to be a more feasible strategy to address the growing worldwide epidemic. The recent progress made in the understanding of the immunopathogenesis of HIV-1 infection has contributed greatly to the potential for deployment of an effective vaccine in the near future.

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