Overview of HIV

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This article provides an overview and reviews the HIV pandemic, the basic biology and immunology of the virus (e.g., genetic diversity of HIV and the viral life cycle), the phases of disease progression, modes of HIV transmission, HIV testing, immune response to the infection, and current therapeutic strategies. HIV is occurring in epidemic proportions, especially in Sub-Saharan Africa. In the US, men who have sex with men account for over half of AIDS diagnoses; racial and ethnic minorities are disproportionally affected. Factors influencing the progression and severity of HIV infection include type of immune response, coinfection (e.g., another sexually transmitted infection, including hepatitis B or C), age and behavioral and psychosocial factors. Antiretroviral therapies can achieve reduction in blood levels of the HIV virus below the limits of detection by current technology. However, effective treatment requires adherence to therapy. Patient failure to adhere to treatment regimens results in detectible circulating virus and in HIV disease progression, and is the primary cause of drug resistance. In addition to research on the immunology and virology of the disease, other studies focus on behavioral and psychosocial factors that may affect medication adherence and risk behaviors. **Key words:** HIV/AIDS, disease progression, immune response, treatment.

CDC = Centers for Disease Control and Prevention; **PCP** = *Pneumocystis carinii* pneumonia; **HCV** = hepatitis C virus; **ART** = antiretroviral treatment; **HAART** = highly active antiretroviral therapy.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by a chronic infection with the HIV. The official start of the epidemic occurred in the summer of 1981 when the US Centers for Disease Control and Prevention (CDC) reported on a cluster of *Pneumocystis carinii* pneumonia (PCP) in five homosexual men (1). However, there is substantial evidence that HIV first crossed the simian-human species barrier much earlier, possibly in Cameroon in West Africa (2). There is also evidence that HIV found its way to the Caribbean before the 1980s (3). From 1981, approximately 1.7 million people have been infected with HIV in the United States, >550,000 have subsequently died, and 1.2 million are currently living with HIV/AIDS (4). Despite improved HIV medications and lower morbidity and death rates in the past decade, there is still great variability in HIV disease progression (5). This article will briefly review and provide an overview of the phases of disease progression, the HIV pandemic, genetic diversity of HIV, the basic biology of the virus (e.g., the viral life cycle), modes of HIV transmission, HIV testing, immune response to the infection, and current therapeutic strategies.

Phases of HIV Disease Progression

Over two and a half decades of research has informed our understanding of this virus. We know much about the impact of the infection on immune function as well as the dynamics of the acute and chronic infection. During the first few weeks of infection, the patient often suffers from a flu-like illness and a rash, an illness termed acute HIV-1 infection syndrome (6). This initial phase of HIV infection is followed by a gradual deterioration of the immune function. HIV has the ability to infect $CD4^+$ lymphocytes and a variety of other cells in the body, including monocytes and thymocytes (5,7). The virus enters target cells via cell surface molecules, including CD4 and chemokine coreceptors (CXCR4, CCR5) (8). $CD4^+$ cells, also called "T-helper cells," play a central role in the immune response, signaling other cells such as the cytotoxic T cell and the B cells to perform their functions (9). Normally, a healthy person has a $CD4^+$ count of 800 to 1200 $CD4^+$ T cells per cubic millimeter (mm^3) of blood. As $CD4^+$ cells are destroyed by HIV and as these cells decrease in number, holes develop in the immune repertoire (5). Once the $CD4^+$ count falls <500 mm^3, half of the immune reserve has been destroyed and minor infections including cold sores (herpes simplex), condyloma (warts) and fungal infections, thrush and vaginal candidiasis, may occur (Table 1, Category B). These infections are troublesome but not life threatening. However, as the $CD4^+$count falls <200 cells/mm^3, the patient becomes particularly vulnerable to the serious opportunistic infections and cancers that typify AIDS, the end stage of HIV disease. As shown in the shaded parts of Table 1, AIDS is defined as a $CD4^+$count of <200 cells/mm^3 (Category 3), or the presence of a serious infection, such as PCP, toxoplasmosis, cytomegalovirus infections of the eye or intestine, as well as debilitating weight loss, diarrhea, HIV dementia and cancers, Kaposi's sarcoma and lymphomas (Category C) (10).

Disease Burden

In 2007 worldwide, the number of adults and children living with HIV was estimated at 33.2 million, including 2.5 million children, with 2.5 million new cases that year, and 2.1 million AIDS deaths (11). HIV is among the leading causes of death worldwide and it causes more deaths than any other infectious diseases. Sub-Saharan Africa is disproportionally affected by HIV, comprising over two thirds (22.5 million) of the people living with HIV/AIDS worldwide and 76% of the AIDS deaths (12). By 2010, it is estimated that 18 million children will be orphaned due to losing parents in the epidemic in Sub-Saharan Africa, the region that has most of the world's AIDS orphans (13). Although there is a slight trend for a reduction in new HIV cases worldwide, it is estimated that the vast majority of AIDS deaths are due to inadequate access to HIV prevention and treatment (12).

In the United States, there are about 40,000 new HIV infections each year (14), with 1.2 million people living with

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TABLE 1. CDC Classification System for HIV-Infected Adults and Adolescents

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL[a]	B Symptomatic Conditions, Not A or C	C AIDS-Indicator Conditions
≥500 cells/mm^3	A1	B1	C1
200 to 499 cells/mm^3	A2	B2	C2
<200 cells/mm^3	A3	B3	C3

From the Centers for Disease Control and Prevention (10). Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm
[a]PGL = persistent generalized lymphadenopathy.

HIV/AIDS (4). The largest proportion of HIV/AIDS diagnoses in the US in 2005 was among men who have sex with men (accounting for 71% of all HIV infections among male adults and adolescents) (15). Recent surveillance data indicate an increase in HIV diagnoses among men (particularly Black men) who have sex with men. Blacks are also disproportionally affected by HIV, accounting for 49% of new HIV/AIDS diagnoses (14). Furthermore, the rate of AIDS diagnoses in 2005 for Blacks was 10 times that for Whites. Women are increasingly making up a larger part of the HIV epidemic. Females comprised 26% of the HIV/AIDS diagnoses in 2005; 64% of the women living with HIV/AIDS were Black, 19% were White, and 15% were Hispanic (16). Furthermore, HIV was the leading cause of death for Black women aged 25 to 34 years. HIV remains a disease of the young. Youth aged 15 to 24 years comprise about 40% of new HIV infections (17). The peak age of HIV diagnosis is between the ages of 25 and 44 years. The Kaiser Family Foundation estimated that, in 2007, in the United States, 42% to 50% of people with HIV/AIDS were not receiving care and 25% did not know they were HIV-infected (4).

Genetic Diversity of HIV

Two genetically distinct viral types of HIV have been identified (18). HIV-1 is the type associated with disease in the United States, Europe, central Africa, and most other parts of the world. HIV-2 has been found mainly in infected individuals in western Africa and is very similar to HIV-1 in that it has the same tropism for cells of the immune system and causes illness that results from immune deficiency. All HIV types and subtypes are thought to be derived from zoonotic introductions from nonhuman primates (19). HIV-1 variants are classified into three major groups: group M (main), group O (outlier), and group N (non-M/non-O). Group M, which is responsible for the majority of infections in the worldwide HIV-1 epidemic, can be further subdivided into 10 subtypes, or clades (A to K). Sub-subtypes and circulating recombinant forms (CRFs) have emerged over the past few decades (20). Genetic variation for HIV-1 is especially high, with rapid turnover of HIV-1 virions. Over 20 different CRFs have been defined within group M alone. The HIV-1 subtypes C and A account for the majority of HIV cases in the pandemic, but the other viral forms circulate globally. HIV-1 subtype B is predominant in North America, Western Europe, and Australia (21). Information garnered from the study of the biophysical, biochemical, and in vitro studies of the HIV-1 subtype B was used to develop the antiretroviral drugs we currently have available. However, subtype B only accounts for only a small portion of the virus subtypes comprising the HIV pandemic (20,21). The proliferation of these various viral forms has serious implications for the feasibility of vaccine development and will have a major impact on diagnostic testing, monitoring, and treatment.

HIV—The Virus

HIV belongs to a class of viruses called retroviruses and a subgroup of retroviruses known as lentiviruses or "slow" viruses (22). The course of infection with these viruses is characterized by a long interval between initial infection and the onset of serious symptoms. Like all viruses, HIV can replicate only inside cells, commandeering the cell's machinery to reproduce. Retroviruses have genes composed of ribonucleic acid (RNA) molecules whereas the genes of humans and most other organisms are made of a related molecule, deoxyribonucleic acid (DNA). However, once inside the cell, HIV and other retroviruses use the enzyme reverse transcriptase to convert their RNA into DNA, which can be incorporated into the human cell's genes (23).

The first step in viral replication (Figure 1) is the attachment of a viral particle to the $CD4^+$ receptor and a coreceptor (either CCR% or CXCR4) of the host cell (8). After the virus fuses with the host cell, the HIV virion enters the cell. Once bound, one of several coreceptors is necessary for the process of fusion and for the viral particle to disgorge its contents, i.e., two copies of the viral RNA. Once inside the cytoplasm of the cell, HIV reverse transcriptase converts the viral RNA into DNA, the nucleic acid form in which the cell carries its genes. A full-length copy of the DNA is made, and then degraded into a smaller functional piece (23,24).

The newly made HIV DNA moves to the cell's nucleus, where HIV integrase helps splice the viral DNA into the host's DNA. This integrated form of the virus is termed "provirus." Once the viral DNA has integrated into the host cell DNA, the cell, if activated, will go on to make viral proteins. In the current model of HIV pathogenesis, abnormal immune activation is viewed as the major factor in disease progression by creating the pool of activated $CD4^+$ T cells that can be targeted by HIV, leading to immune exhaustion (25). The degree of $CD8^+$ T-cell activation correlates positively with the risk of progression to AIDS (26). If the $CD4^+$ cell is not activated, it is possible for the virus to persist in a latent stage for many years (25). The ability of the virus to remain in latently infected cells has greatly complicated attempts to eradicate HIV. For this reason, patients who are HIV-positive must stay on antiviral therapy indefinitely (27). The activated

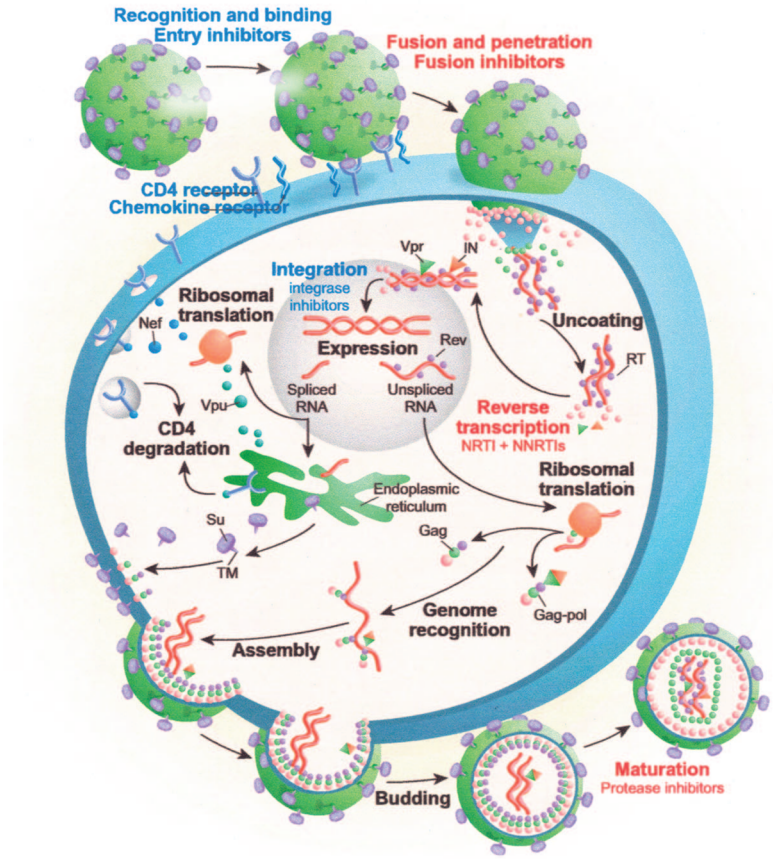

Figure 1. Viral life cycle of HIV. Reprinted with permission from Macmillan Publishers Ltd: Nature Medicine 2003;9:867–73. Twenty years of therapy for HIV-1 infection. Authors Roger J. Pomerantz and David L. Horn. Nature Medicine adapted the figure from the Journal of Molecular Biology, 1999;285:1–32. Structural Biology of HIV. Authors Brain G. Turner and Michael F. Summers. Reprint permission also granted from Elsevier.

cell makes viral proteins by copying the DNA back to RNA through a process called transcription. Transcription is controlled by both the host cell and the viral genes. The RNA transcribed from DNA, called messenger RNA (mRNA), is then transported from the nucleus of the cell to the cytoplasm.

Once in the cytoplasm, the mRNA of the virus takes over the usual protein-making apparatus of the cell and begins to make the proteins of the HIV virus, using the HIV mRNA as the template. This process is referred to as translation. The sequence of proteins in the mRNA molecules is translated into the RNA and proteins comprising the envelope and core of the virus. The gene products of the translation are much larger than those that make up the final virus and need to be spliced to smaller functional units. Viral protease cuts the gene products down to size. The HIV protease is highly specific for HIV and is the target of a class of drugs used to treat HIV. Once spliced, the viral envelope proteins come together within the host cell's membrane, with the core proteins, RNA and enzymes just inside the membrane. The virus then pinches off the cell and "buds" (23,24). A single cell can make thousands of infectious particles of HIV, either chronically, over weeks, or as a single burst resulting in cell death.

Factors That May Influence Viral Load and Disease Progression

Once HIV enters the body, it replicates very rapidly, producing a viral burst that infects many CD4 cells and involves all lymphatic tissue. Viral load in this early infection can reach millions of virions per ml of blood (one fifth of a teaspoon), increasing HIV transmission risk. There are a number of key factors that have an impact on the rate and severity of HIV infection including: type of immune response, coinfection with other sexually transmitted diseases, age, and behavioral variables (28–31). Long-term nonprogressors are patients who have had the virus for ≥10 years and yet are clinically healthy without treatment and have certain characteristics demonstrating a beneficial anti-HIV immune response (28,31). Coinfections may influence HIV disease progression. For example, among subjects who were adherent to antiretroviral treatment (ART), infection with hepatitis C virus (HCV) was associated with a lower CD4 cell count (32). In contrast, a large, urban cohort study produced no evidence that HCV infection substantially altered the risk of dying, developing AIDS, or responding immunologically to ART (33). In the absence of ART, older individuals have higher rates of pro-

gression than younger adults. A possible immunologic explanation could be that, as a person ages, there are fewer naïve cells and more memory CD4 cells—the preferred target of HIV infection. It is likely that either the memory cells are depleted more rapidly or the bone marrow, thymus, and extrathymic factors are less able to keep up with cell loss in the older population (29).

Disease progression in HIV is likely to be dependent on a number of physiological and psychosocial factors. Drug use, high-risk sex behaviors, and depression may interfere with the utilization of available HIV prevention and treatment resources (34). Behavioral factors, such as coping style and stressful life events, can have a critical impact on patient outcomes and are discussed in other papers in this issue (35–37).

Transmission of HIV

HIV is a sexually transmitted disease. During sexual contact, the virus can cross the mucosal barrier of the vagina, vulva, penis, and rectum by first coming into contact with immune (dendritic) cells that carry the virus across the mucosa much like a Trojan horse (38). The dendritic cell picks up the virus on the exterior, crosses to the interior, and releases the infectious virus into the lymphatic tissues or directly into the lymph node. At that point, it is bound to a CD4 cell, travels to the lymphatic tissue, and begins the first cycle of infection. The risk of infection during intercourse is greatly increased by concurrent sexually transmitted diseases, rough sex, or a partner with a very high viral load such as that seen in primary infection and again in late-stage disease (39). Women are generally more likely than men to acquire HIV during heterosexual intercourse due to female physiological characteristics, such as the large amount of mucosal surface area that is exposed to seminal fluid (40). The risk of heterosexual transmission is greatly decreased with consistent and correct condom use. Regular condom use between heterosexual couples where one individual is HIV-positive and the other is uninfected leads to a very low risk of transmission (40). However, the only way to completely protect against the transmission of the virus is through practicing sexual abstinence. New chemical and biological agents, microbicides, which women could apply before sexual intercourse to protect themselves from HIV and other sexually transmitted infections, are currently being developed and tested (40). For example, a Phase 3, double-blind, randomized, placebo-controlled trial of a vaginal gel, 1.0% C31G (SAVVY), was done recently in Nigeria with 2153 HIV-negative women at high risk for HIV infection. This particular microbicide, SAVVY, did not reduce the incidence of HIV infection (41). The World Health Organization has recommended that male circumcision be recognized as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men (42).

HIV is also spread by contact with infected blood, most often through the practice of reusing or sharing syringes and needles with drugs (43). Needle exchange programs can reduce this risk (44). In the US, Canada, and Europe, the blood supply has been screened for HIV since 1985, and the risk of infection from blood products at this time is remote. However, people who received blood products in the 1980s should be screened for HIV infection (45).

There is a risk of transmitting HIV from a pregnant mother to the fetus or newborn either during pregnancy, during delivery, or by breast feeding. Optimal interventions, including ART, cesarean section, and formula feeding, have reduced the rate of mother-to-child transmission of HIV-1 from about 25% to 1% to 2% in developed nations. In developing countries, where ART may be unavailable and avoidance of breast-feeding is not an option, the overall risk of transmission at 18 to 24 months of age is as high as 15% to 25%. Of the estimated 700,000 children who were infected with HIV in 2003, about 315,000 were infected through breast-feeding (46).

Occupational risk to healthcare workers also exists, mainly through accidental needlestick or mucosal splash with contaminated blood. As of 2007, there were 57 documented cases of HIV seroconversion secondary to occupational exposure within the US (47). The risk for the occupational transmission of HIV varies based on the type and severity of the exposure. The average risk of HIV transmission among healthcare personnel is estimated to be 0.3% after a needlestick and 0.09% after mucous membrane exposure (48).

HIV Testing

Early HIV screening and detection are imperative for the long-term survival of patients with the virus and prevention of further transmission to sexual or injectable drug-sharing partners. In 1987, the United States Public Health Service issued guidelines which made HIV testing and counseling a primary prevention strategy for patients who were identified as practicing high-risk behaviors. Based on the 2006 HIV testing recommendations from the CDC, all patients in healthcare settings (regardless of risk factors) should be notified and then screened for HIV unless they decline testing (49). This approach to HIV testing is referred to as "opt-out screening." Routine screening for HIV is a crucial public health tool needed to identify the virus so that treatment can be offered before symptom development and also to reduce the likelihood of continued virus transmission.

The US Food and Drug Administration (FDA) has approved enzyme-linked immunoassay screening blood tests to be used by blood banks to detect antibody to both HIV-1 and HIV-2. A recent study was done to determine the ability of several FDA-licensed assays to detect anti-HIV in 240 human plasma specimens collected from two urban blood centers in Cameroon, where HIV genetic diversity and recombinant HIV strains are highly prevalent. The results indicated that the assays had high sensitivity for detection of emerging genetic variants (50). There are currently four rapid HIV tests that have been approved by the FDA. Two of these rapid HIV tests (OraQuick and Multispot) are able to screen for both HIV-1 and HIV-2, whereas the other two tests (Reveal and Uni-Gold

Recombigen) only screen for HIV-1 (51). Currently, none of the rapid tests are available over-the-counter.

Antiretroviral Therapies (ART)

There are currently 20 antiretroviral drugs that have been approved for use in the treatment of HIV (52). There are presently six classes of ART available that interrupt viral replication: a) nucleoside/nucleotide reverse transcriptase inhibitors, b) nonnucleoside reverse transcriptase inhibitors, c) protease inhibitors, d) fusion inhibitors, e) CCR5 antagonists, and f) integrase inhibitors (52). Each of these classes of drugs affects the HIV virus at a different stage in its life cycle. Current treatment consists of highly active antiretroviral therapy (HAART), that is, at least three drugs belonging to two classes of antiretroviral agents.

The decision of when to begin ART should be made on an individual basis. For those individuals whose $CD4^+$ count and clinical health assessment do not indicate a high risk of disease progression, initiating treatment may cause more harm than good because of the clinically significant rate of toxicities and side effects. A recent review of drug-induced side effects has been published (53). Side effects include immune reconstitution inflammatory syndrome, which results from the rebound in immune responses to a variety of occult infections and includes high fever, abdominal pain, and inflammatory masses. A fulminate flair of hepatitis B virus infection may occur as well as severe hypersensitivity drug reactions, cardiovascular complications, and exacerbation of underlying liver disease. An example of a common side effect is the development of lipodystrophy syndrome, characterized by fat redistribution dominated by peripheral fat loss and complex metabolic alterations including dyslipidemia and insulin resistance (54). According to current recommendations from the Panel on Antiretroviral Guidelines for Adults and Adolescents from the Department of Health and Human Services, patients who have not previously been treated (naïve patients) may be treated if their $CD4^+$ count falls <350 cells/mm^3 (52). Patients should be treated if they present with an AIDS-defining illness, or if the $CD4^+$ count is $<200/mm^3$ because they are at a greater risk of developing complications due to HIV infection. Treatment should be started with pregnant women, people with HIV-associated nephropathy, and with individuals coinfected with hepatitis B regardless of their $CD4^+$ count. In the US, it is now standard care to ask every pregnant woman to be HIV tested early in the pregnancy (52). Adherence is a key issue as multidrug resistance is a very real challenge. Psychosocial factors, which may create a barrier to patient adherence, should be addressed before the initiation of treatment (55).

Immune Reconstitution Post HAART

Adoption of treatment strategies recommended by the current National Institutes of Health guidelines has resulted in substantial reductions in HIV-related morbidity and mortality (52). The principles of therapy of HIV infection are based on our understanding of the immunologic damage caused by ongoing viral mutation from early in the infection process through late stages of the disease. Because the virus is highly mutable, every effort should be made to shut down viral replication completely. The goals of treatment are to suppress plasma viremia for as long as possible, to delay the selection of drug resistance mutations, and to preserve immune function. Studies show that HAART protects from death, and the data suggest that this occurs by increasing immune subset counts and decreasing viral load. Although HAART "maintains" immunocompetence, this may occur in conjunction with viral suppression itself having a direct beneficial effect on adaptive and innate parameters (56). The degree of improvement of the total CD4 count is, in part, a function of the initial degree of immune destruction. High baseline $CD4^+$ T-cell counts predicted a better virological outcome of HAART (57).

Drug Resistance

Effective sustained treatment with HAART is complicated by the prevalence of drug resistance. The highly mutable nature of HIV has led to a number of virus mutations that have decreased or negated the efficacy of some antiretroviral drugs. The primary cause of drug resistance is the lack of regimen adherence of patients who are on HAART. Genotypic assays are available to detect drug resistance mutations when present in HIV genes (58,59). Results can be reported within 1 to 2 weeks of sample collection. The International AIDS Society-USA maintains a list of significant resistance-associated mutations in the reverse transcriptase, protease, and envelope genes (60). Phenotypic assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. Phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is more complicated (52). Drug resistance testing is not advised for persons with viral load of <1000 copies/ml because amplification of the virus is unreliable (52). Resistance testing in a person with acute HIV infection is recommended. Performing drug resistance testing before initiation of ART in patients with chronic HIV infection is less straightforward. No prospective trial has addressed whether drug resistance testing before initiation of therapy confers benefit in this population. However, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed (61).

Resistance to some drugs may confer cross-resistance to other types of antiretrovirals, further complicating the selection of appropriate drug regimens. Resistant strains of HIV can be transferred from people who have been treated with antiretrovirals to treatment naïve individuals, so concerns about drug resistance are salient not only for the treatment exposed but also for the newly infected and for those who are new to drug therapy. The emergence of drug resistance in treated populations and the transmission of drug-resistant strains to newly infected individuals are important public health concerns in the prevention and control of HIV (62).

The influence of a number of psychosocial and behavioral factors has become a critical issue in relationship to drug

resistance (34). A patient's mood, stressful life events, and socioeconomic status can influence adherence to the very successful, though sometimes complex, three- and four-drug regimens. A highly motivated patient can dramatically influence his or her outcome, with regimens that require 95% adherence levels to prevent drug resistance. A missed weekend of medications can result in drug resistance. Unfortunately, adherence to these regimens is poor (63,64), and poor adherence translates into multiple drug-resistant strains of HIV and rapid progression (63). Even more recent once a day and twice a day regimens with low pill burdens have poor rates of adherence, with a recent Veterans Administration study showing a 76% refill rate to prescribed regimens (65).

Vaccine Development

Vaccine development has progressed slowly, due to the tremendous capacity of this virus to escape immune pressure as well as the number of strain variations. Nonetheless, with an improved understanding of effective host response to the infection and the ability to deliver viral antigens to the immune system in novel ways, vaccine development is being pursued vigorously (66). Since 1987, thousands of healthy human volunteers have participated in the testing of 30 candidate vaccines in >80 Phase I/II trials (67). A June 2005 study estimated that $682 million has been spent on AIDS vaccine research annually (68). A number of vaccine concepts are being pursued including live attenuated vaccines, subunit vaccines, and live recombinant vaccines. This essential research effort recently suffered a baffling setback. The first trial of a vaccine designed to elicit strong cellular immunity has shown no protection against infection. More alarmingly, the vaccine seemed to increase the rate of HIV infection in individuals with prior immunity against the adenovirus vector used in the vaccine (69). The field is still a long way from a testable vaccine that will induce neutralizing antibody responses. The degree of difficulty in developing an effective AIDS vaccine rivals that of sending humans to Mars and back to Earth again.

CONCLUSION

There have been outstanding advances in our knowledge of the immunopathogenesis of HIV-1 infection and AIDS since the discovery of the virus. Our understanding of the viral life cycle and the host response to infection is comprehensive. As a result, virus specific interventions have been developed that are highly active and that can contain viral replication. The damaged immune system can then be at least partially immune reconstituted, and even individuals presenting with late-stage infection now have an expectation of long-term survival if they have access to antiretrovirals and expert healthcare providers.

There has never before been a comparable increase in our scientific understanding of any disease process in so short a time. This extraordinary effort to understand and contain HIV-1 infection has enabled scientists to gain important new knowledge in virology, immunology, and oncology. The promise of these effective therapies rest, however, almost entirely on an individual's ability to adhere to sometimes complicated and often toxic regimens. Even with once a day pill regimens, adherence is often poor. Despite the advances in HIV treatment, there continues to be considerable variation in HIV disease progression. In addition to biological mechanisms, we need to consider behavioral and psychosocial factors such as depression, stress and coping that may affect adherence to medications as well as the immunology and virology of the disease.

Glossary

apoptosis = cellular suicide, also known as programmed cell death. HIV may induce apoptosis in both infected and uninfected immune system cells.

B cells = white blood cells of the immune system that produce infection-fighting proteins called antibodies.

$CD4^+$ T cells = white blood cells that orchestrate the immune response, signaling other cells in the immune system to perform their special functions. Also known as T-helper cells, these cells are killed or disabled during HIV infection.

$CD8^+$ T cells = white blood cells that kill cells infected with HIV or other viruses, or transformed by cancer. These cells also secrete soluble molecules that may suppress HIV without killing infected cells directly.

Cytokines = proteins used for communication by cells of the immune system. Central to the normal regulation of the immune response.

Cytoplasm = living matter within a cell.

dendritic cells = immune system cells with long, tentacle-like branches. Some of these are specialized cells at the mucosa that may bind to HIV after sexual exposure and carry the virus from the site of infection to the lymph nodes. See also follicular dendritic cells.

Env = complex HIV protein; part of the virus that binds with the CD4 receptor to enter the host cell.

Enzyme = a protein that accelerates a specific chemical reaction without altering itself.

follicular dendritic cells (FDCs) = cells found in the germinal centers (B cell areas) of lymphoid organs. FDCs have thread-like tentacles that form a web-like network to trap invaders and present them to B cells, which then make antibodies to attack the invaders.

Germinal centers = structures within lymphoid tissues that contain FDCs and B cells, and in which immune responses are initiated.

Gp41 = glycoprotein 41, a protein embedded in the outer envelope of HIV; plays a key role in HIV's infection of $CD4^+$ T cells by facilitating the fusion of the viral and cell membranes.

Gp120 = glycoprotein 120, a protein that protrudes from the surface of HIV and binds to $CD4^+$ T cells.

Gp160 = glycoprotein 160, an HIV precursor protein that is cleaved by the HIV protease enzyme into gp41 and gp120.

integrase = an HIV enzyme used by the virus to integrate its genetic material into the host cell's DNA.

Kaposi's sarcoma = a type of cancer characterized by abnormal growths of blood vessels that develop into purplish or brown lesions.

killer T cells = see $CD8^+$ T cells.

lentivirus = "slow" virus characterized by a long interval between infection and the onset of symptoms. HIV is a lentivirus as is the simian immunodeficiency virus (SIV), which infects nonhuman primates.

LTR = long terminal repeat, the RNA sequences repeated at both ends of HIV's genetic material. These regulatory switches may help control viral transcription.

Lymphoid organs = tonsils, adenoids, lymph nodes, spleen and other tissues; act as the body's filtering system, trapping invaders and presenting them to squadrons of immune cells that congregate there.

Macrophage = a large immune system cell that devours invading pathogens and other intruders; stimulates other immune system cells by presenting them with small pieces of the invaders.

Monocyte = a circulating white blood cell that develops into a macrophage when it enters tissues.

opportunistic infection = an illness caused by an organism that usually does not cause disease in a person with a normal immune system. People with advanced HIV infection suffer opportunistic infections of the lungs, brain, eyes, and other organs.

Pathogenesis = the production or development of a disease; may be influenced by many factors, including the infecting microbe and the host's immune response.

PGL = persistent generalized lymphadenopathy.

protease = an HIV enzyme used to cut large HIV proteins into smaller ones needed for the assembly of an infectious virus particle.

provirus = DNA of a virus, such as HIV, that has been integrated into the genes of a host cell.

retrovirus = HIV and other viruses that carry their genetic material in the form of RNA and that have the enzyme reverse transcriptase.

reverse transcriptase = the enzyme produced by HIV and other retroviruses that allow them to synthesize DNA from their RNA.

syncytia = giant cells formed by the fusion of other cells.

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