Chapter 3
HIV/AIDS Global Epidemic

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Glossary

Acquired immunodeficiency syndrome (AIDS)	A clinical syndrome caused by the human immunodeficiency virus (HIV). Its pathogenesis is related to a qualitative and quantitative impairment of the immune system, particularly a reduction of the CD4+ helper T lymphocyte cell count (surrogate marker of the disease). After an average of 10 years, if untreated, HIV + individuals can develop opportunistic diseases (i.e., infections and cancers rarely detected in people with normal immune systems). The natural history of the disease can be dramatically modified with administration of combination therapy composed of antiretroviral (ARV) drugs.
CCR-5	A cell membrane protein expressed on several cell types including peripheral blood-derived dendritic cells, CD34+ hematopoietic progenitor cells, and certain activated/memory Th1 lymphocytes. This receptor is well defined as a major coreceptor in conjunction with CD4+, implicated in susceptibility to HIV-1 infection.

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CD4+	A large glycoprotein that is found on the surface of helper T lymphocyte cells, regulatory T cells, monocytes, and dendritic cells. Its natural function is as a coreceptor that assists the T cell receptor (TCR) to activate its T cell following an interaction with an antigen-presenting cell. CD4+ is a primary receptor used by HIV-1 to gain entry into host T cells.
CD4+ T cell	An immune cell, lymphocyte (white blood cell) characterized by the CD4+ antigen (protein) on its surface. This is a T lymphocyte considered to have a "helper" function to enhance the cellular immune response. The CD4+ is the primary receptor for the HIV virus, and upon infection, the virus can destroy the CD4+ cell. In HIV-infected people, the drop in CD4+ T lymphocyte cells is a major determinant of the progression of HIV infection to AIDS.
Coreceptor (CCR-5 or CXCR-4)	Protein molecules on the surface of lymphocytes or monocytes that bind to the gp120 protein of HIV and facilitate, with CD4, binding, fusion, and entry of the virus into the susceptible cell.
CXCR-4	An alpha-chemokine receptor specific for stromal-derived factor-1 (SDF-1 also called CXCL12), a molecule endowed with potent chemotactic activity for lymphocytes. This coreceptor is one of several chemokine receptors that HIV isolates can use to specifically infect CD4+ T cells.
DNA (deoxyribonucleic acid)	A nucleic acid that contains the molecular basis of heredity for all known living organisms and some viruses and is found in the nuclei and mitochondria of eukaryotes. Chemically, DNA consists of two polymer strands of units called nucleotides made up of one of four possible bases plus sugar and phosphate groups. The polymers are joined at the bases by hydrogen bonds to form a double helix structure.
Fusion of virus and cell membranes	A merging of cell and virus membranes that permits HIV proteins and nucleic acids to enter the host cell.
Fusion/entry inhibitors	A class of ART drugs that interferes with the virus' ability to fuse with the target cell's outer membrane, thereby blocking entry of the HIV into the host cell.
gp120	The major HIV envelope glycoprotein having a molecular weight of 120 that protrudes from the

	outer surface of the virion. This glycoprotein binds to a CD4+ receptor on a T cell to facilitate entry of the virus into the cell.
Human immunodeficiency virus (HIV)	The virus that causes acquired immunodeficiency syndrome (AIDS). It is a lentivirus belonging to *Retroviridae* family and was discovered in 1983 by Robert Gallo and Luc Montagnier. HIV infects and destroys helper T cells of the immune system causing a marked reduction in their numbers. Loss of CD4 cells leads to generalized failure of the immune system and susceptibility to life-threatening opportunistic infections. It is transmitted mainly through sexual intercourse, exchange of contaminated syringes among intravenous drug users, and contaminated blood transfusion. HIV-1 is the HIV type most frequently detected HIV worldwide and responsible for the global pandemic.
HIV-1 subtypes or clades	Genetically related HIV strains that are essentially phylogenetically equidistant, generating a starlike phylogeny. Subtypes A, B, C, D, F, G, H, J, and K are currently known subtypes A, B, C, and D are highly prevalent others have low prevalence and limited geographic distributions.
HIV-2	The second HIV virus discovered in West Africa in 1984, the virus is more closely related to the simian immunodeficiency virus of primates. Although HIV-2 can cause AIDS, it has a distinct epidemiology, lower rate of transmission, and slower progression to disease.
Incidence	Rate describing the number of new cases of disease occurring within a given time period, expressed as new cases per person-time.
Integrase	An enzyme found in retroviruses including HIV that permits the reverse transcribed viral DNA to be integrated into the infected cell's DNA. Integrase is an enzyme encoded by the polymerase gene of HIV.
Integrase inhibitors	A class of ART drugs that blocks the viral integrase the enzyme HIV uses to integrate its genetic material into its target host cell DNA.
Nucleus	A membrane-enclosed central compartment of a cell that functions to contain the genomic DNA and to regulate gene expression.

Prevalence	Number of cases of disease in a defined population at a specific point in time it is often expressed as a percentage.
Protease	An enzyme that hydrolyzes or cleaves the polyproteins into proteins and is important in the final steps of HIV maturation. In HIV, the protease enzyme is encoded by the *polymerase* gene.
Protease inhibitors	A class of ART drugs that interferes with the viral protease enzyme of HIV by inhibiting the viral polyproteins from being cleaved, which would allow the individual viral proteins to produce infectious viral particles.
Reverse transcriptase	An enzyme found in HIV that creates double-stranded DNA using viral RNA as a template and host tRNA as primers. The reverse transcriptase enzyme is encoded by the *polymerase* gene of HIV.
Reverse transcriptase (RT) inhibitors	A class of ART drugs that interfere with the reverse transcription step during the HIV life cycle. During this step, the HIV enzyme RT converts HIV RNA to HIV DNA. There are two main classes of RT inhibitors that are used as ART drugs. Nucleoside/nucleotide RT inhibitors (NRTI) are faulty DNA building blocks. When these faulty pieces are incorporated into the HIV DNA (during the process when HIV RNA is converted to HIV DNA), the DNA chain cannot be completed, thereby blocking HIV from replicating in a cell. Nonnucleoside RT inhibitors (NNRTI) bind to RT, interfering with its ability to convert the HIV RNA into HIV DNA.
RNA (ribonucleic acid)	A universal form of genetic material typically transcribed from DNA, it differs from DNA in that it contains ribose and uracil as structural components. In retroviruses like HIV, RNA is their primary genetic material and is found in a mature virus particle.
T-lymphotropic	A characteristic of a virus that infects and replicates in T lymphocytes, a type of immune cell. This was the descriptor of the human T cell leukemia virus (HTLV), a human retrovirus that causes T cell leukemia and lymphoma and is T-lymphotropic like HIV. HIV was originally called human T-lymphotropic virus type III (HTLV-III) by Gallo and colleagues.

Tuberculosis	The infectious disease caused by *Mycobacterium tuberculosis*. It usually involves the lungs (pulmonary tuberculosis) but can also affect other organs (i.e., kidneys, central nervous system, lymph nodes, bones, etc.; extrapulmonary tuberculosis). Pulmonary tuberculosis, which is the most frequent clinical form, can be classified as smear positive or smear negative according to the result of the sputum bacteriological examination. The former is a major public health problem being highly contagious. Only a few individuals develop tuberculosis after a mycobacterial infection, and most of them soon after infection: it is estimated that the lifetime risk is 5–10% in HIV negatives and 5–15% yearly in HIV positives.
Virion	A single and complete extracellular infective form of a virus that consists of an RNA or DNA core and in the case of HIV with a glycoprotein coat or "envelope."

Definition of the Problem

The HIV/AIDS epidemic is now in its third decade since the discovery of the virus responsible for the disease in 1981. While the first cases of AIDS were first recognized in young men who have sex with men in the United States and Europe in the 1980s, it soon became clear that the virus could be spread through contaminated blood products and heterosexual sex. At the time of its discovery, acquired immunodeficiency syndrome (AIDS) was a new disease with high mortality, and the discovery of a new human virus as its cause in 1983 created new challenges for prevention, treatment, and vaccine efforts, many of which remain unmet today. Human immunodeficiency virus type 1 (HIV-1), as the causative agent of AIDS, has been the subject of intense research over the past three decades, in an effort to understand the biological properties of this new virus, its relatedness to other known retroviruses, characterize its epidemiology, and discover drugs and vaccines to control the epidemic.

In the early 1980s, it was recognized that HIV could be spread through blood, blood products, and sexual and perinatal transmission routes. High rates of HIV infection and its accompanying disease began to be recognized throughout the world in the late 1980s as the HIV/AIDS global pandemic became a frightening reality to the international community. The disproportionate burden of infection and disease first recognized in sub-Saharan Africa and then Asia with growing rates

of disease and mortality led to estimates of global infections growing in the tens of millions with no magic bullet to end the spread. While global estimates are necessarily fraught with numerous assumptions and subjected to poor reporting, UNAIDS revised down their global estimates in 2007 [1]. Nonetheless, at the end of 2009, an estimated 33.3 million people worldwide were living with HIV; 2.5 million of these were children, with almost two thirds of them in low- and middle-income countries [2]. While stunning in magnitude, these estimates now reflect a continued slowing of the growth trajectory of the pandemic, with lower rates of new infections and mortality, the latter being largely due to the continued scale-up of provision of antiretroviral therapy (ART) that began in 2004.

We are therefore at an important point in the time for the global HIV pandemic; the peak of infections in most countries occurred about a decade ago, and many high-burden countries are seeing a plateau or decrease in HIV prevalence rates. Large-scale treatment programs for low-income countries have succeeded in providing complex and relatively expensive ART drugs to almost one third of patients in need of these life-saving therapies; 5 million of the 15 million in need. Recent strides in identifying new and efficacious methods for prevention have been encouraging as the development of an effective vaccine is still awaited.

Introduction

AIDS was first recognized as a new and distinct clinical entity in 1981 [3–5]. The first cases were recognized because of an unusual clustering of diseases such as Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in young homosexual men. Although such syndromes were occasionally observed in distinct subgroups of the population – such as older men of Mediterranean origin in the case of Kaposi's sarcoma or severely immunosuppressed cancer patients in the case of *Pneumocystis carinii* pneumonia – the occurrence of these diseases in previously healthy young people was unprecedented. Since most of the first cases of this newly defined clinical syndrome involved homosexual men, lifestyle practices were first implicated as the cause of the disease.

AIDS cases were soon reported in other populations as well, including intravenous (IV) drug users [6] and hemophiliacs [7–9]. Hemophiliacs used clotting factor preparations which were prepared from the pooled blood of a huge number of donors, and IV drug users often used needles contaminated with small amounts of blood from previous users, thereby increasing their exposure to foreign tissue antigens. Asymptomatic hemophiliacs and intravenous drug users were often found to have abnormally low CD4 helper lymphocytes and higher than normal T suppressor cells, similar to the gay men with AIDS. The increase in T suppressor cells was presumably due to frequent antigenic stimulation; the decrease in CD4+ T helper cells was the more direct effect of the yet-to-be-discovered causative agent.

Three new categories of AIDS patients were soon observed: blood transfusion recipients [10, 11], adults from Central Africa [12–14], and infants born to mothers who themselves had AIDS or were IV drug users [15, 16]. The transfusion-associated

cases had received blood donated from an AIDS patient at least 3 years before they began showing symptoms [10, 11].

Based on the disparate populations afflicted with this new malady and the emerging epidemiology of the disease, the possible infectious etiology for AIDS was considered [17]. Multiple studies were initiated to determine the possible role of various microorganisms, especially viruses in causing AIDS. These studies measured and compared seroprevalence rates for suspect viruses in AIDS patients and controls. The short list of candidate viruses included cytomegalovirus (CMV), because it was already associated with immunosuppression in kidney transplant patients; Epstein-Barr virus (EBV), presumably because it was a lymphotropic virus; and hepatitis B (HBV), because infection with this virus was known to occur at elevated rates in both homosexual men and recipients of blood or blood products. However, based on the unique clinical syndrome and unusual epidemiology of AIDS, if the etiology was an already known virus, it would presumably have to be a newly mutated or recombinant genetic variant.

Max Essex [18, 19], Bob Gallo [20, 21], and Luc Montagnier, Francoise Barre-Sinoussi, and Jean-Claude Chermain [22] postulated that a variant T-lymphotropic retrovirus (HTLV) might be the etiologic agent of AIDS. Among the most compelling reasons for this hypothesis was that the human T-lymphotropic retrovirus (HTLV), discovered by Gallo and his colleagues [23] in 1980, was the only human virus known to infect T helper lymphocytes at that time. This fit with the new disease where T helper lymphocytes were selectively depleted by the causative agent [24–26]. AIDS patient blood samples were repeatedly cultured in an attempt to find a virus related to HTLV-I or HTLV-II [27]; however, these studies were only partially successful. Although antibodies cross-reactive with HTLV-I and HTLV-related genomic sequences were found in a minority of AIDS patients [18, 21, 22, 28], the reactivity was weak, suggesting either the coinfection of AIDS patients with an HTLV, or that a distant, weakly reactive virus was the causative agent. Proof that the disease was linked to a T-lymphotropic retrovirus was obtained by Gallo and his colleagues [29–31]. Further characterization of the agent – now termed human immunodeficiency virus type 1 (HIV-1) – revealed that it was the same as the isolate detected earlier by Montagnier and his colleagues [22]. Despite controversy over the names and identity of certain isolates, it is now clear that this new and unique human pathogen was not only a distant genetic relative of the known HTLV but also a virus that may have been more recently introduced into the humans from a primate reservoir.

A second HIV was discovered in 1984 based on antibodies from West African commercial sex workers that recognized proteins not only from the simian immunodeficiency virus (SIV) but also from HIV-1 [32, 33]. It is now known that HIV-1 is more closely related to SIVcpz, found mainly in the *Pan troglodytes troglodytes* chimpanzee species [34], while HIV-2 is related to SIVsm found in sooty mangabey monkeys (*Cercocebus atys*) [35]. HIV-2 is the second human immunodeficiency virus and constitutes the closest known human virus related to the prototype AIDS virus, HIV-1. HIV-2 shares many virologic and biologic features with HIV-1; however, its ability to transmit and cause disease is much lower [36–38].

HIV-2 infection is much less prevalent in the world; it is found primarily in West Africa and other parts of the globe with connections to West Africa, such as India, parts of South America, and urban centers with high rates of immigration from West Africa [39, 40].

Basic Virology of HIV

Human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) are members of the *Lentivirus* genus of the *Retroviridae* family of RNA viruses and are 50% similar at the genetic level. Retroviruses are enveloped viruses that infect a wide range of vertebrate hosts in a species-specific manner [41]. Steps in the HIV replication cycle (Fig. 3.1) include (1) recognition and binding of the virion to the host cell surface via specific primary and coreceptors and fusion to the host cell membrane; (2) uncoating of the virion and release of the HIV genetic material and other viral proteins including enzymes such as reverse transcriptase, integrase, and protease; (3) HIV RNA is reverse transcribed by the enzyme reverse transcriptase to make a double-stranded DNA copy; (4) HIV viral DNA is transported to the cell nucleus, where it integrates into the host cell's DNA, using the HIV viral integrase; (5) a new copy of the HIV viral RNA is produced which will become the genetic material for new HIV virions; (6) new viral RNA and proteins produced by the host cell move to the cell surface, and new, immature virions are packaged; and (7) the viral envelope proteins are inserted into the host cell membrane, and the virions bud from the cell surface, encapsulated by viral envelope, forming a mature HIV virion [42, 43].

Like other retroviruses, HIV's genetic material becomes permanently integrated in the host cell's DNA, resulting in lifelong infection. The enzyme responsible for viral replication and encoded by the *polymerase* gene is the reverse transcriptase, which as an enzyme is error-prone, which results in considerable genetic variation. HIV enters susceptible cells via a primary receptor, the CD4+ on immune cells such as T lymphocytes. However, secondary coreceptors are also required for HIV's entry into a cell [44–47]. These are normal cellular membrane proteins, part of a seven-transmembrane spanning protein family, called chemokine receptors, and involved in the recruitment of chemokines for normal cellular function. CCR-5 and CXCR-4 are chemokine receptors that also serve as major coreceptors for the HIV virus. In conjunction with the primary receptor, CD4 molecule, they allow the virion to fuse with the susceptible host cell and allow virion entry. The CCR-5 coreceptor along with CD4 allows for HIV to infect CCR-5 bearing cells usually of the macrophage/monocyte lineage. The CXCR-4 coreceptor along with CD4 allows for HIV's fusion and entry into T cells [44, 48, 49].

The HIV genome, or genetic makeup, has been characterized and is 9.8 kilobases in length and contains nine different genes, which encode 15 proteins. There are three major classes of proteins: structural, regulatory, and

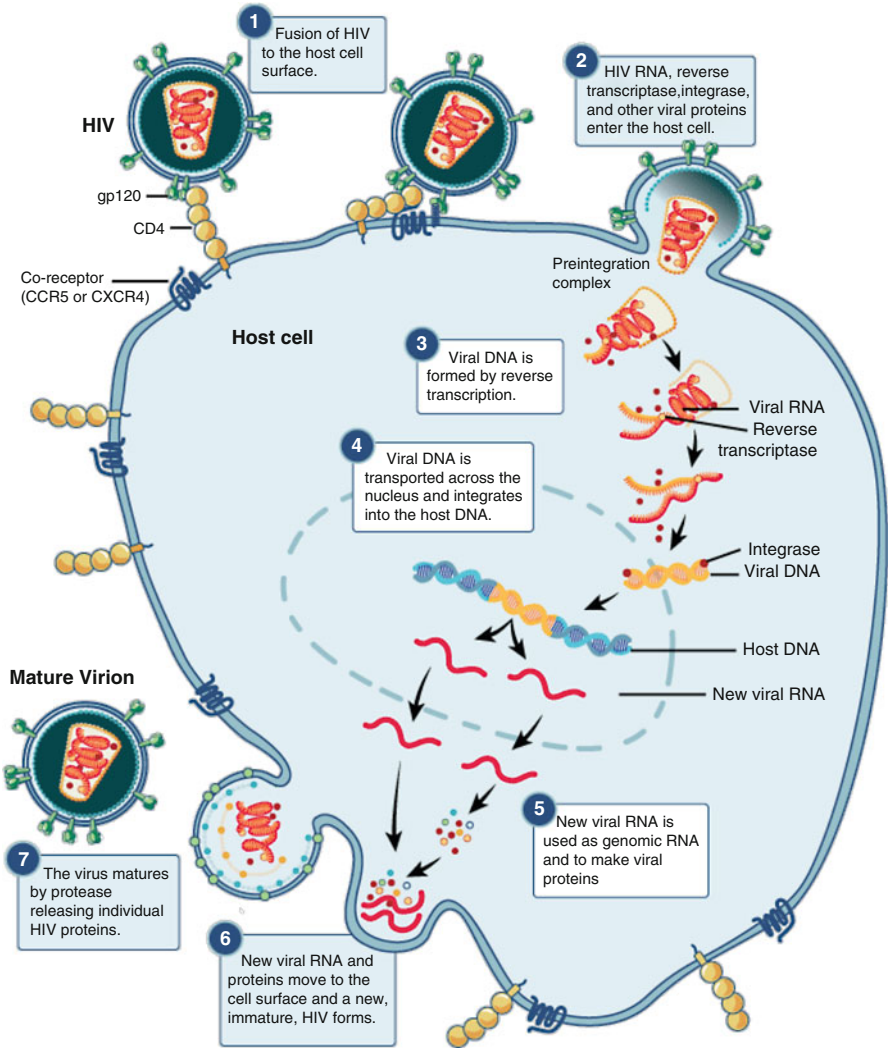

Fig. 3.1 HIV replication cycle [43]

accessory [42]. Three genes, *gag*, *pol*, and *env*, each encode multiple viral structural proteins. The *gag* (group-specific antigen) gene produces a 55-kd precursor protein, which is cleaved during viral maturation into the matrix (MA; p17), capsid (CA; p24), nucleocapsid (NC; p9), p1, p7, and p6 proteins. The *pol* gene (polymerase) encodes the enzymes including protease, reverse transcriptase (RT), and integrase, while the *env* gene (envelope) gives rise to the envelope proteins gp120 and gp41. The regulatory proteins are Tat and Rev, while the accessory proteins include Vpu, Vpr, Vif, and Nef [42].

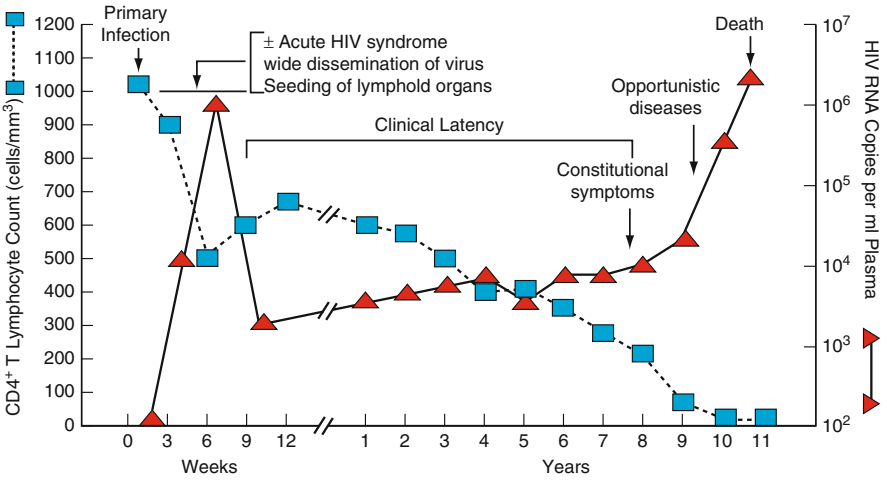

Fig. 3.2 Clinical progression of HIV infection [52]

HIV and the Cause of AIDS

HIV typically enters the body by blood, blood products, or through fluids exchanged in sex or childbirth. The virus infects a large number of CD4+ cells and replicates rapidly. During the acute phase of HIV infection, the blood carries a large number of HIV virus particles, which spread throughout the body, infecting various organs, particularly the lymphoid organs such as the thymus, spleen, and lymph nodes [50, 51]. During this phase, the virus may integrate and hide in the host cell's genetic material. Thus, evading the host's immune system, the virus may remain dormant for an extended period of time. In the acute phase of infection, a significant proportion of people may suffer flu-like symptoms [51, 52] (Fig. 3.2).

Weeks after exposure to the virus, the immune system responds with killer T cells (CD8+ T cells) and B cell–produced antibodies. At the same time, CD4+ T cell counts rebound. The virus levels may decrease at this point in time perhaps in response to the first host immune response. During this latency phase, a person infected with HIV may not experience HIV-related symptoms for several years despite the fact that the HIV continues to replicate [53]. It is this long course of dormancy that has given the lentiviruses ("lenti" – meaning slow) their name.

The immune system eventually deteriorates to the point that the human body is unable to fight off other infections; the timing and reasons for this are still subject to research. The level of HIV virus in the blood may dramatically increase, while the number of CD4+ T cells drops to dangerously low levels. An HIV-infected person is diagnosed with AIDS when he or she has one or more opportunistic infections, such as tuberculosis, and CD4+ T cells drop below 200 cells per cubic millimeter of blood, where the normal would be ~1,000 CD4+ T cells.

Epidemiology of the Global HIV Pandemic

HIV and AIDS is a global pandemic. Although the means by which the virus can spread between people remains unchanged, the populations that are highly infected in different parts of the world are different. Transmission of the virus by blood and blood products for the treatment of various diseases such as hemophilia was recognized in the early 1980s. Ensuring that blood banks and blood products were free of HIV was accomplished relatively early in the pandemic in high-income countries, but is yet to be perfected in many low-income countries where screening of HIV and the high burden of disease pose distinct challenges to maintaining safe blood banks and blood products.

Spread of HIV infection through intravenous drug use was also recognized in high-income countries early in the epidemic. These often disenfranchised and stigmatized populations were difficult to identify to provide necessary diagnosis, care, and treatment. This continues to be a challenge for prevention efforts throughout the world, most significant in parts of Asia, where the spread of HIV through this mode of transmission is both prevalent and difficult to control.

Sexual transmission of HIV in most of the high-income countries remains a threat to men who have sex with men, where the virus and its disease were first recognized. In contrast, in most middle- and low-income countries, the risk of HIV transmission is predominantly through heterosexual sex. This means that the risk to women and their offspring is more significant in these geographic locations and represents a distinction in the epidemiology of HIV/AIDS in these settings. As a consequence, the risk of mother-to-child transmission in middle- and low- income countries was most severe in nations already burdened with high infant mortality. In 2009, 370,000 (230,000–510,000) children were infected with HIV through mother-to-child transmission [2]. This represents a decrease of 24% from 5 years earlier due to better methods of preventing transmission through identification of infected pregnant women and provision of more effective prophylaxis. Inadequate access to antenatal and postnatal services remains a barrier in providing these methods to all those in need [54].

UNAIDS has just completed their 2010 report which reports on HIV and AIDS statistics from around the globe ending in 2009 [2] (Table 3.1). Extensive analysis of these current rates and the trends from previous years allows for some cautious optimism on the status of the pandemic. This report continues to support the notion that the peak of new infections occurred in 1999 and rates of new infections continue to decline or plateau [55, 56]. In 2009, an estimated 2.6 million (2.3–2.8 million) people were newly infected with HIV. In 33 countries, most in sub-Saharan Africa, HIV incidence showed significant decreases compared to 2001 [2].

Globally, an estimated 33 million people are infected with HIV. In earlier years treatment was only provided in high-income countries; more recently local governments and international programs supporting antiretroviral therapy in low-income countries have had an impact on the annual death toll. A cumulative total of

Table 3.1 UNAIDS regional estimates for adults and children living with HIV (Adapted from [2])

	People living with HIV	
Geographic region	2009	2001
Sub-Saharan Africa	22,500,000	20,300,000
Middle East and North Africa	460,000	180,000
South and Southeast Asia	4,100,000	3,800,000
East Asia	770,000	350,000
Oceania	57,000	29,000
Central and South America	1,400,000	1,100,000
Caribbean	240,000	240,000
Eastern Europe and Central Asia	1,400,000	760,000
Western and Central Europe	820,000	630,000
North America	1,500,000	1,200,000

24 million people have died from AIDS between 1980 and 2007, and Bongaarts and colleagues project that this will reach 75 million by 2030 [56].

Regional HIV statistics for both 2009 and 2001 are provided in Table 3.1. These demonstrate the heterogeneity of the global pandemic. It is beyond the scope of this chapter to discuss each of the region's HIV epidemiology in depth. Summarized findings are therefore provided with more emphasis on sub-Saharan Africa where the highest burden of infection and disease is found.

Sub-Saharan Africa

Over 22 million people in sub-Saharan Africa are infected with HIV, although there is considerable variability among nations in rates of infection and disease [2] (Fig. 3.3). The countries of Southern Africa (Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe) have over 11 million people currently infected. Thus, this region of the continent alone represents over one third of the global pandemic in terms of adult HIV infections, new HIV infections, and deaths due to HIV. Swaziland, in 2009, reported a prevalence of 25.9%, representing the highest adult HIV prevalence rate for a given country [57]. In South Africa, where over five million people are living with HIV in 2009, AIDS is the major cause of maternal mortality and attributed to cause over one third of deaths in children under the age of 5 years old.

Other large countries, such as Nigeria with a population estimated at 150 million and Ethiopia with a population 82 million, have relatively low HIV prevalence rates below 4%, but still represent a significant portion of the global burden of disease because of their large populations. By contrast, many of the countries of Southern Africa are small, but with high prevalence rates. Thus, the distinct impact of the epidemics in such diverse settings can be appreciated.

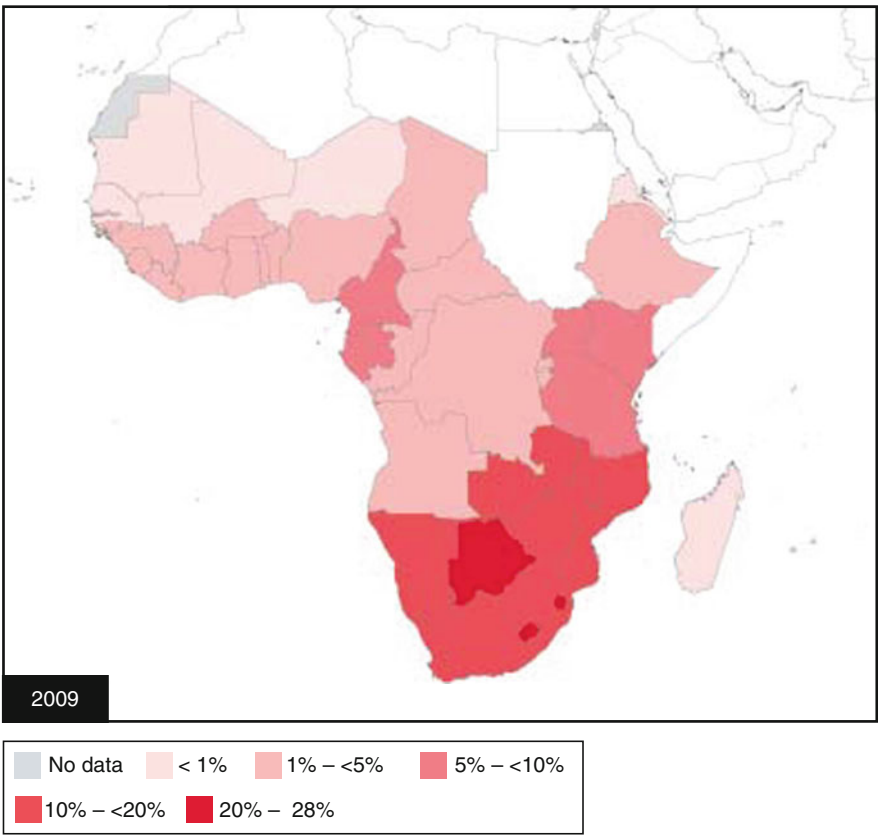

Fig. 3.3 HIV prevalence rates among adults aged 15–49 years old in sub-Saharan Africa, 2009 (Adapted from [2])

As of 2009, the rates of HIV infection in the countries of East Africa have been declining. Uganda's HIV prevalence has been stable in the 6–7% range since 2001. Kenya and Tanzania have shown declining prevalence rates, and Rwanda has been stable at 3% since 2005 [2].

In West and Central Africa, countries have maintained some of the lowest HIV infection rates of the continent. In 2009, 12 countries had rates below 2%; these included: Benin, Burkina Faso, Democratic Republic of the Congo, Gambia, Ghana, Guinea, Liberia, Mali, Mauritania, Niger, Senegal, and Sierra Leone. Nigeria's HIV infection rate has been declining for the past 6 years with the 2009 estimate at 3.6% (3.3–4.0%). The prevalence of HIV is highest in Cameroon at 5.3% (4.9–5.8%); Central African Republic, 4.7% (4.2–5.2%); Côte d'Ivoire, 3.4% (3.1–3.9%); and Gabon, 5.2% (4.2–6.2%) [2].

Asia

HIV infection rates in 2009 for the region are similar to 2004, with an estimated 4.9 million (4.5–5.5 million) people are currently infected [2]. There is considerable heterogeneity of infection by countries, and some previously low-prevalence countries like Pakistan and Bangladesh are increasing, largely due to transmission in drug-injecting populations. Within countries, there is also considerable variation; for instance, five provinces of a total of 22 in China account for over half of the HIV infections of the country [58, 59]. The epidemic in this region of the world is largely due to significant subpopulations of injecting drug users and men who have sex with men, where rates remain high and often increasing.

Eastern Europe and Central Asia

The largest increases in new HIV infection rates are seen in this region of the world with a burden of 1.4 million people estimated to be living with the virus in 2009 [2]. HIV prevalence exceeds 1% in the Russian Federation and Ukraine. The epidemic is concentrated in high-risk populations that use injection drugs and are involved in sex work and their sexual partners [60].

Caribbean

This region of the world has a relatively low burden of people living with HIV (240,000), yet because of their small population size, their HIV prevalence of ~1% (0.9–1.1%) is still considered high for the region [2]. There is considerable variability between countries and within countries. Haiti has highly variable rates, including 12% in pregnant women from some urban settings [61, 62], whereas Cuba's prevalence is exceptionally low, at 0.1% (0.08–0.13%) [2]. Unprotected paid sex is considered the major mode of HIV transmission, and infection rates in women are over half of those infected with the virus.

Central and South America

The HIV epidemic appears stable in 2009 compared to previous years, and the number of children infected is declining with ~4,000 children newly infected in 2009 [2]. There are 1.4 million people living with the infection in this region, with concentrated infection rates in men who have sex with men and sex workers.

North America and Western and Central Europe

The burden of HIV infection is 2.3 million (2.0–2.7 million) in these higher-income countries, representing a 30% increase from 2001 [2]. It is believed that unprotected sex among men having sex with men is responsible for these disturbing increasing trends in Canada, the USA, and parts of Europe [63]. General decreases are seen in injecting drug user subpopulations overall, but certain countries continue to see this as a driver of the epidemic [64–66]. Immigrant populations and individuals acquiring HIV from more endemic regions are also contributing to the burden of infection particularly in urban centers [67].

Middle East and North Africa

This region of the world has historically had low rates of HIV infection, which may be due to inadequate reporting. In 2009, an estimated 460,000 people are living with HIV, which is a substantial increase from the 2001 reported statistics [2]. Transmission of the virus from contaminated drug-injection equipment is considered the major mode of transmission in the countries of this region.

Oceania

The burden of HIV infection in this region is small at 57,000 (50,000–64,000) but has increased from the 2001 statistics [2]. Papua New Guinea has the largest infection rates in this region, with a national adult HIV prevalence of 0.9% (0.8–1.0%). Unprotected heterosexual sex is more predominant in Papua New Guinea, whereas unprotected sex in men who have sex with men is more common in New Zealand and Australia [68].

Prevention

The optimal biomedical means of preventing infection with an infectious disease pathogen would be the use of an effective vaccine. As efforts to develop such a vaccine are still underway, public health officials around the world have resorted to other methods of preventing HIV transmission [69]. These revolve around the various types of HIV transmission such as men who have sex with men, sex workers, intravenous drug users, and heterosexual adults in places such as Africa. Education on risks of transmission, methods of prevention, and behavior change are at the core of all prevention programs spanning on populations at risk.

For many of these subpopulations, stigma, lack of access to services, or even legislation can diminish the potential of prevention programs and messages for behavior change.

Access to HIV testing and counseling is a foundation to all prevention methods, which provides access to comprehensive HIV care. Education and behavior change are critical components of prevention methods, and provision is often most effective when provided by community groups. In the early 1980s in the USA, pioneer groups such as the San Francisco AIDS Foundation, Gay Men's Crisis in New York, and AIDS Project Los Angeles demonstrated the role of education in promoting safer sex practices among gay and bisexual men [70]. Recent increases in new infections in young gay men in North America and Europe are of concern and suggest the need to enhance prevention efforts [2, 63].

Globally, HIV acquired through injecting drug use is estimated to represent 20% of the people living with HIV in 2009 [2]. Efforts to make injecting drug use safer through provision of clean needles have proven efficacy in lowering transmission through this route. UNAIDS reports in 2009 that in Eastern Europe and Central Asia where injecting drug use is a major driver of the HIV epidemic, five of nine countries report that more than 80% of people injecting drugs used sterile injecting equipment at their last injection. Eight of twelve countries in South and Southeast Asia reported the same [2]. However, the various governmental responses across the globe have often prevented the widespread adoption and support of such programs [65]. While provision of clean needles is inexpensive, it is believed that many programs provide inadequate numbers of clean needles to insure optimal prevention [66]. In addition, the substance abuse treatment programs, such as methadone programs, may help curtail the intravenous drug–using behavior and therefore eliminate the risk of the transmission [64].

Prevention methods directed at commercial sex work are needed worldwide and again represent a targeted high-risk population that is disenfranchised and difficult to reach through conventional health system structures. The prevention methods focus on HIV counseling and testing, safe sex through proper condom use, and concomitant diagnosis and treatment of sexually transmitted infections (STIs), which are known to facilitate HIV transmission [71]. A long-standing program for sex workers in Southern India, called Avahan, provided a combined prevention approach of community outreach, empowerment, condom programming, and STI and HIV testing services over an 8-year period with a decrease in HIV prevalence from 20% to 16% in these high-risk women [71, 72].

In many parts of the resource-limited countries, heterosexual transmission is the major risk factor for HIV acquisition. Testing and access to HIV care is again critical to these populations along with appropriate counseling on behavior change, proper condom use, and STI diagnosis and treatment. Proven prevention measures for this group would include abstinence, mutual monogamy, reduced number of sexual partners, and consistent condom use. For young people, abstinence and older age of sexual debut are considered part of prevention messages [69].

Since 2000, a number of epidemiologic surveys and studies considered the possible benefit of male circumcision (surgical removal of the foreskin) in

decreasing HIV transmission [73]. The penile foreskin is thought to be sensitive to epithelial tears, which carry a high density of CD4-bearing cells as targets for virus infection and subsequent replication [74]. In addition, uncircumcised men are at higher risk for STIs, which would facilitate HIV transmission [75–77]. In 2005–2006, randomized clinical trials conducted in South Africa, Kenya, and Uganda demonstrated a 55–76% lower HIV incidence compared to men still on the wait list of circumcision [78–80]. It is still unknown whether male circumcision will decrease male-to-female transmission of the virus, but these studies are underway [80]. There are other health benefits to male circumcision, but the surgical procedure is not without some risk, although serious complications are rare [76]. Nonetheless, for populations where men or boys are not circumcised, such as much of Southern and Eastern Africa, this becomes an important prevention tool [81].

Mother-to-child transmission of HIV is in large part responsible for the 2.5 million children living with HIV worldwide. Prevention of mother-to-child transmission (PMTCT) consists of identification of HIV infection in pregnant women and provision of a short course of antiretroviral drugs in a prophylactic manner (rather than treatment of the mother for her own disease to lower the viral burden in the mother and to decrease the risk of transmission to the baby). In resource-rich countries, most HIV-infected pregnant women would receive full ART (three drugs) as a means of preventing mother-to-child transmission; however, in most resource-limited settings, mono- or bi-therapy ART has been used due to cost and international recommendations at the time [82, 83]. In 2010, WHO revised their PMTCT guidelines based on clinical trial data from Africa, indicating that full ART could virtually eliminate mother-to-child transmission [84]. In settings where breast-feeding is judged to be the safest infant feeding option, ART prophylaxis continued to the mother and baby during this period could severely limit this mode of transmission [82–84]. While access to any PMTCT services remains a problem in a number of resource-limited countries and settings, only 54% access for sub-Saharan Africa, the potential for virtual elimination of mother-to-child transmission as these new guidelines are implemented becomes a real possibility [2, 82].

Postexposure prophylaxis (PEP) was the terminology frequently used to describe the use of short-course ART drugs given after an occupational setting exposure such as needle sticks with potentially HIV-infected blood. Similarly, PEP has been used in rape cases in settings where HIV infection is high and the potential for sexual transmission can be potentially decreased [85, 86]. Preexposure prophylaxis (PrEP) is the use of an ART drug administered to an HIV-negative individual prior to or at the time of the potential transmission event in an effort to decrease the viral inoculum and limit the potential for infection.

A recent study reported from South Africa this past year described the use of tenofovir-based gel as a microbicide to be used once 12 h before sex and again 12 h after sex as both safe and effective in reducing HIV transmission and STIs [87–89]. PrEP has also been successful in decreasing transmission in men who have sex with men and in heterosexual discordant couple studies [90, 91].

This paves the way for additional biomedical means of preventing infection, which can be coupled with other prevention methods depending on the setting and populations at risks [92, 93]. Further trials are underway to test this new and promising strategy to prevent HIV transmission.

Genetic Diversity of HIV

Early in the history of HIV research, it was recognized that each viral isolate varied from another in its nucleotide sequence, and multiple mechanisms for this genetic variation were considered [42, 94]. Part of the HIV replication cycle requires the reverse transcription of viral RNA by the virus' reverse transcriptase. This enzyme is error-prone, thereby generating approximately 1 error per 10^4 nucleotides, or viral genome. Estimates of HIV replication in people have suggested 10^{10}–10^{12} new viral particles produced per day [95, 96]. Thus, the potential for viral variation is significant even if the immune system, tissue compartmentalization, or antiretroviral therapy does not select for particular viral variants. Genetic variability between viral isolates from different patients [97, 98], frequently termed interisolate or interpatient variability, can vary by up to 5%. And in turn, this was also distinguishable from the genetic variation that was seen at the level of an individual patient, often termed intrapatient variability and variability up to 1% [99]. At the level of the individual patient, a swarm or quasispecies of highly related but distinguishable viral variants has been demonstrated throughout the course of HIV infection [100–102]. Thus, the genetic variation of HIV is hierarchical as depicted in the simplified schematic of subtype variation, interpatient variation, and intrapatient variation (Fig. 3.4).

Phylogenetic analyses of viruses from various geographic regions were used to identify three distinct groups M, N, and O within HIV-1 [34, 103, 104]. Most HIV-1 sequences belong to group M (major). A divergent subset of viruses identified in Cameroon in 1994, which did not cluster with group M viruses, were classified as group O (outlier) [105], and in 1998, another set of viruses which did not cluster with group M or O viruses were termed group N viruses [106]. A recent virus characterized from a gorilla has been designated group P [107]. It is thought that all virus groups were introduced by independent SIVcpz or SIVgor transmissions into the human population in the early part of the twentieth century [34, 104, 108].

The fruits of international HIV research have provided information of HIV viruses from different parts of the globe [109] (Fig. 3.5). The HIV-1 group M has been subdivided into genetic subtypes, defined originally on comparison of gag and env sequences of the virus and then later with full-length sequencing of the virus [110, 111]. Within a subtype, the average env genetic variation ranges from 5% to 15%, whereas the average env genetic variation between subtypes ranges from 20% to 30% [112, 113]. Remarkably, all the HIV-1s from the USA and Western Europe have been of a single subtype, B. Most of the diverse subtypes of HIV-1 including

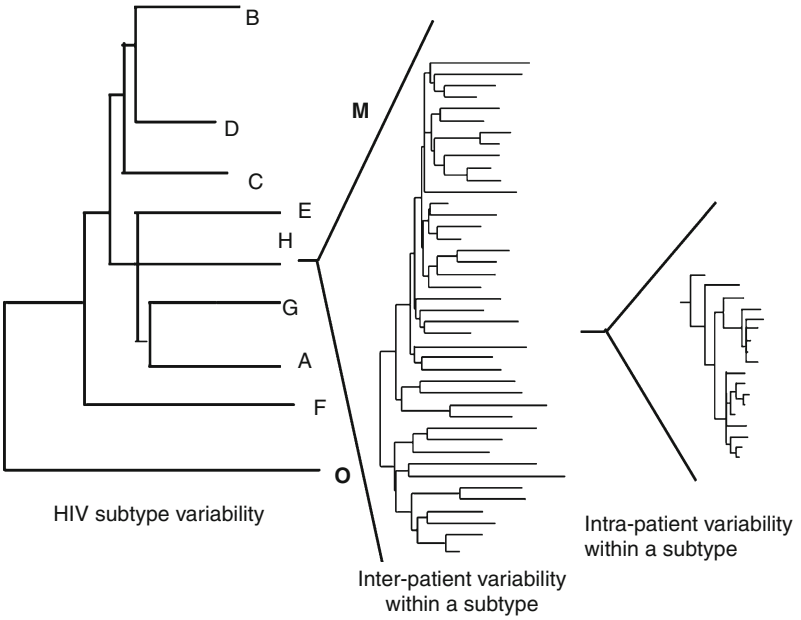

Fig. 3.4 Phylogenetic trees depict differences between HIV subtypes, variation between viruses from different patients, interpatient variability, and variation between viruses within the same patient, intrapatient variability

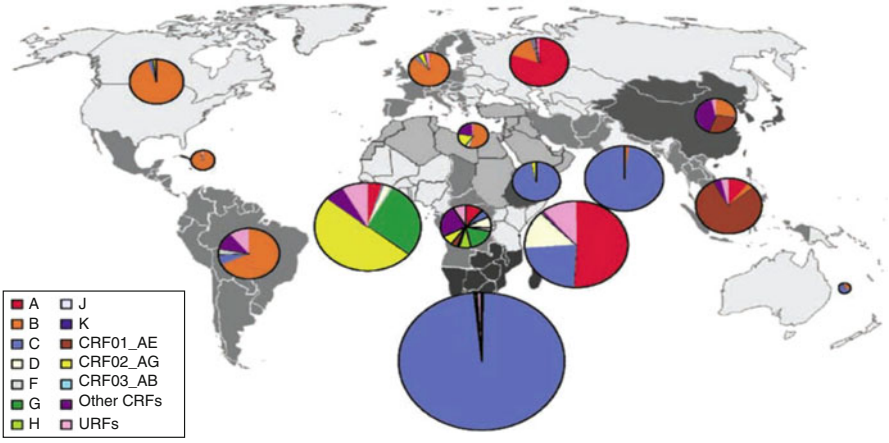

Fig. 3.5 Regional distribution of HIV-1 subtypes and recombinant viruses, 2004–2007. Fifteen regions of the world are depicted with *pie charts* representing the distribution of HIV-1 subtypes and recombinants from 2004 to 2007. The size of the pie charts corresponds to the relative numbers of people living with HIV in the region. *CRF* circulating recombinant form, *URF*, unique recombinant form (Adapted from [109])

circulating recombinant forms (CRFs) and unique recombinant forms (URFS) have been found in sub-Saharan Africa and, to a lesser degree, Asia, now accounting for 20% of the worldwide HIV viruses [109].

In Thailand, HIV-1 subtype B was detected in IV drug users during the mid-1980s. During the late 1980s, subtype E was first detected. By the early to mid-1990s, HIV-1 subtype E (CRF01_AE) had spread very rapidly throughout heterosexuals in Thailand, with the highest rates in the northern regions of the country [114]. Although apparently present earlier in the region, HIV-1 subtype B never spread to cause a major heterosexual epidemic, as did HIV-1 subtype E. Full-length sequencing of subtype E determined that it is actually a circulating recombinant form, consisting of subtypes A and E, now referred to as CRF01_AE [115, 116].

A similar situation occurred in India, with HIV-1 subtypes B and C. While B appeared to be introduced earlier and it expanded among intravenous drug users, this subtype did not appear to spread as rapidly among heterosexuals as did HIV-1 C. Previously associated with the massive heterosexual epidemic in southeastern Africa, subtype C also caused a rapid heterosexual epidemic in Western India, apparently initially spreading from the Bombay region [114, 117]. The results in Africa and Asia suggest that HIV-1 subtypes A, C, D, and CRF01_AE are well adapted for heterosexual transmission compared to subtype B, perhaps due to differential ability to infect dendritic cells in the sexual mucosa [118].

Various studies have shown associations between viral genotype and biology [119]. There is some evidence suggesting a relationship between subtype and modes of transmission. Studies in Cape Town [120], Finland [121], Thailand [122, 123], and Australia [124] found that most subtype B strains were associated with homosexual transmission while non-B strains were associated with heterosexual transmission. Infection with certain subtypes has also been associated with increased risk of vertical transmission. A study conducted on mother-child pairs in Tanzania revealed that mothers infected with HIV-1 subtype A, subtype C, and intersubtype recombinant were more likely to transmit to their infants than mothers infected with subtype D [125]. In an earlier related study, Renjifo et al. [126] also found that in perinatally transmitted C/D recombinant viruses, the V3 regions (*env*) were always from subtype C and never from subtype D, suggesting that viruses containing subtype D-V3 have a reduced fitness as compared to those with subtype C-V3. Finally, a study of injection drug users in Thailand found a significantly higher transmission probability associated with subtype E (CRF_01 AE) as compared to subtype B [127].

Some studies have also demonstrated significant differences between subtypes with regards to disease progression. Kanki et al. [128] found that women infected with a non-A subtype were eight times more likely to develop AIDS than were those infected with subtype A. Similarly, Kaleebu et al. [129, 130] reported that subjects with subtype A had a slower progression to disease than those with subtype D. Clinical and immunological differences have also been found between subtypes. In Kenya, where subtypes A, C, and D were all cocirculating within the same population, Neilson et al. [131] found that high plasma RNA levels and low CD4

counts were significantly associated with subtype C infection. In a prospective study conducted at a methadone treatment clinic in Thailand, people infected with CRF01_AE were found to have higher viral loads in early infection than those infected with subtype B [132]. However, this difference decreased over time such that the viral loads were similar at 12, 18, and 24 months postseroconversion [132]. Similarly, a study in our laboratory indicated that women infected with CRF02_AG had a significantly higher viral load during the early stage of infection than women not infected with CRF02_AG [133]. Infection with multiple subtypes has also been associated with higher viral load and lower CD4+ T cell counts [134].

Complete sequence analysis of viruses from around the world has further characterized an HIV pandemic that is increasing in complexity with a higher prevalence of recombinant viruses, currently at 20% of all HIV viruses [109]. In West Africa, Asia, and South America, the predominant virus is a circulating recombinant form. The predominant virus of West Africa is CRF02_AG, which appears to represent a recombinant event that occurred early in the divergence of subtypes A and G. In contrast, the BC and BF recombinants of China and South America, respectively, are derived from more recent recombinants between contemporary parental virus lineages [135]. An understanding of the genetic diversity of predominant HIV-1 subtypes, sub-subtypes, and circulating recombinant forms in a given population may be important in designing effective HIV vaccines [136, 137]. Although the importance of matching a vaccine candidate to regional circulating strains is yet unclear, incorporation of local strains might maximize the efficacy of a potential vaccine candidate [137].

Treatment

Antiretroviral therapy (ART) drugs that block or reduce HIV virus replication in the infected patient are used for the treatment of AIDS. The first ART drug was put into use in 1986–1987: zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI) that because of its chemical similarity to the host's nucleoside, inhibited the growing DNA chain and served as a chain terminator such that virus replication could not occur. Other NRTIs act in a similar manner, but another class of ART drugs includes nonnucleoside reverse transcriptase inhibitors (NNRTI), which bind to the virus' reverse transcriptase enzyme in a specific position and manner, blocking the enzyme from completing the transcription. NRTI and NNRTIs are often used in combination as the typical first-line regimens for patients with AIDS [138–140]. Since AZT, there has been tremendous progress in developing improved and more efficacious ART drugs and combination regimens for treating AIDS patients in high-income regions of the world; however, the cost of many of these newer drugs has been prohibitive for most middle- and low-income countries despite their disproportionate share of the AIDS burden.

Currently, there are a total of five classes of FDA-approved ART drugs that act on different parts of the HIV virus life cycle: NRTIs and NNRTIs act on the reverse transcription; other drugs act by inhibiting the viral protease, the viral integrase, or blocking virus entry at the level of the coreceptor. ART is typically prescribed in combination with current recommendations requiring at least two active classes of drugs [138–140]. Side effects and toxicities for each of these drugs may be serious and result in significant complications, requiring the patient to switch drug regimens.

The error-prone reverse transcription of HIV replication and its viral dynamics suggest that every possible single point mutation in the HIV genome occurs between 10^4 and 10^5 times per day in an untreated HIV-1-infected individual [141]. Therefore, the propensity for development of drug resistance mutations is high and the reason that strict adherence to taking the prescribed drugs is necessary to maintain viral suppression. In an effort to improve adherence and decrease pill burden to the patients, fixed-dose combination pills are available for most of the typical first-line ART regimens, allowing all drugs to be included in a single pill.

By the late 1990s, treatment for AIDS was widely available in high-income countries, but the vast majority of patients in middle- and low-income countries could not access these expensive drugs. In 2000, at the United Nations Millennium Summit, Kofi Annan declared a call for action to address the gap in treatment and to promote prevention and research in response to the AIDS epidemic [142]. In 2001, the UN General Assembly adopted a Declaration of Commitment on HIV/AIDS, endorsing equitable access to care and treatment as a fundamental component of a comprehensive and effective global HIV response [143]. UNAIDS had reported at the end of 2002 that developing countries had ~300,000 AIDS patients receiving ART with an unmet need estimated at 5.5 million [144]. The international donor community moved toward addressing the goals of equitable access through initiation of large-scale treatment and care programs. The President's Emergency Plan for AIDS Relief (PEPFAR), a program launched in late 2003, authorized over $15 billion dollars in 15 target countries, the largest commitment to a single disease in the history of US government support [145]. Other programs such as the Global Fund to Fight AIDS, Tuberculosis and Malaria [146], the Bill & Melinda Gates Foundation [147], Clinton Foundation [148], World Bank [149], and Medecins Sans Frontieres [150], to name a few, supported this effort with advocacy to country governments, and the rapid scale-up of providing ART to patients in need moved from rhetoric to action.

UNAIDS reported at the end of 2009 that 5.2 million people in low- and middle-income countries received ART, a significant increase from 2008 and unimaginable in 2003 [2]. However, the pandemic has continued, and in these countries, this accomplishment only represents 36% of the 15 million AIDS patients in these countries in need. Children and patients coinfected with TB remain an ART priority in these settings. Many of the original ART drugs developed in the late 1980s went off patent and have now been manufactured in generic form and meet international standards [151]. The Clinton Foundation in mid-2000 helped negotiate important drug cost reductions so that first-line drug per patient approximated $350 per year,

rather than the $1,000 per month of the brand name drugs in 2000 [148]. However, the improvement in ART therapy in high-income countries was made possible through newer drugs and new classes of drugs like integrase inhibitors, or entry blockers, which are still cost-prohibited in most middle- and low-income country ART programs. Thus, although patients are receiving ART, the pharmacy of drugs available for toxicities or second- and third-line therapy remains limited in most low-income countries.

ART is not just the provision of pills; the diagnosis of AIDS requires laboratory tests and the clinical management of an AIDS patient entails regular monitoring of immune function, diagnosis, and treatment of comorbidities and measurement of viral load (virus levels in the bloodstream) when possible [142]. These laboratory tests often require sophisticated lab equipment and costs per test that can be quite high, almost the same cost of annual drug costs. In many low-income settings, these diagnostic or monitoring tests were not even available; in some instances where patients were required to pay for clinical tests, the costs were prohibitive to the typical AIDS patient that already had significant economic burdens. In recent years, a major contribution of large-scale care and treatment support from PEPFAR and others has built the infrastructure and provided the training to perform these critical laboratory tests. Provision of laboratory equipment, insuring adequate clean water and electricity to run the equipment and laboratory test specific requirements for cold chain, and short expiration remain challenges for both start-up and sustainability. In some instances, the costs of the tests have been reduced, but there is a critical need for cheaper, efficient, and point-of-care tests that will increase their availability and use for patient management.

Further, the complexity of clinical management and care of HIV infection requires training, infrastructure building, and overall strengthening of the existing health-care system in most developing country settings. Again, the leadership in individual countries coupled with support from the international donor communities has provided the training necessary for the complex administration of HIV care and treatment. However, human resources in many countries are limiting, and further efforts to encourage task-shifting within the medical team and bolstering of the medical education system are important to achieving the provision of ART to the many patients that are still in need.

Vaccine

Since the discovery of the virus and its initial characterization in the early 1980s, the search for an effective vaccine has been the subject of intense research. HIV infection can occur via free virus and/or virus-infected cells. Once infection has occurred with integration of viral genetic material in the target host cell, elimination of the virus by the host's immune mechanisms is not possible. The approach to vaccine design has often sought to mimic the protective immune responses, often

identified in animal model systems or in individuals that have demonstrated protection [152, 153]. To date, the correlates of protective immunity from HIV have yet to be identified. Vaccine scientists therefore began with more conventional approaches of seeking to design vaccine candidates that would elicit strong virus-neutralizing antibodies or robust cell-mediated responses or both [154, 155]. The proof of principle has been shown for both of these approaches in nonhuman primate model [156, 157]. However, the model has not been predictive of HIV vaccine efficacy in humans; differences in routes of exposures, strains, and amount of virus are just some of the complexities of this model. Dozens of vaccine candidates have been developed, tested in nonhuman primate models and even early clinical trials in humans [157, 158].

AIDS vaccine candidates are evaluated in a stepwise manner in a series of clinical trials known as phases I, II, and III. Phase I and II trials generally involve a small number of volunteers and provide researchers with critical information about the safety and immunogenicity of the vaccine. The cost of phase III trials can be in hundreds of millions of dollars, and the enrollment for the trial is large, so the AIDS vaccine community moved to an intermediate "test of concept" trial where lower numbers of trial participants were needed; the statistical power of the trial design would allow evaluation of immunogenicity and low ranges of efficacy. It is not until phase III trials that the efficacy of the vaccine is truly assessed.

Candidate HIV vaccines that were tested in phase I and II trials over the past 20 years included inactivated whole virus, or virus particles, subunit HIV envelope vaccines delivered in novel adjuvant or delivery systems, DNA vaccines and live recombinant vector vaccines, and various combination approaches. The results of phase I and II trials indicated that they were safe but did not generate sufficient immune responses to warrant proceeding to phase III trials [157, 159–163].

By 2008, only four candidate HIV vaccines had proceeded to phase IIb and III efficacy trials. Two of the trials were subunit gp120 (envelope) vaccines tested by VaxGen in the USA, Canada, and the Netherlands with 5,400 volunteers, largely men who have sex with men [164]. A second trial was conducted in 2,545 intravenous drug users in Thailand, using recombinant envelope from subtype B and also CRF01_AE [165, 166]. Although neutralizing antibodies were induced by the vaccine, neither trial showed evidence of protection. Subsequently, two trials assessed vaccine candidates based on the premise that cellular immune responses would be protective; the viral antigens were delivered in an adenovirus 5 vector; in order to enhance the generation of the cellular responses, the candidates were tested in the "Step" and "Phambili" trials conducted by Merck [167–169]. Adenovirus 5 is considered a harmless virus, but it does infect humans, and many populations mount antibodies to this virus, frequently without any signs of disease. Some of the volunteers in the Step and Phambili trials did not have antibodies to adenovirus 5, and in those volunteers, the vaccine showed no effect. However, in volunteers with antibodies to adenovirus 5, the vaccinated group showed higher rates of HIV infection, and thus, the vaccine had increased rather than decreased the chances of HIV infection [167–170]. Both trials were interrupted as a result of these unexpected results.

In 2008, a Summit on HIV Vaccine Research and Development determined that research toward a vaccine needed to place greater emphasis on basic research and slowed the pace of candidates, moving toward expensive clinical trials in people [171, 172].

In late 2009, the results of the US military vaccine group's RV144 trial in Thailand were announced. A phase IIb trial was conducted with a recombinant vector approach using the ALVAC virus (an avian poxvirus) used to express HIV proteins to prime the immune response combined with recombinant gp120 protein; both of these entities alone had been tested in people and shown poor immunogenicity [173]. The RV144 trial conducted in 16,400 men and women in Thailand starting in 2003, nonetheless, showed a modest efficacy of 31% protection after 3.5 years of follow-up; there were 51 infected in the vaccine group compared with 74 in similarly sized placebo group [174]. Further analysis of those protected failed to show significant neutralizing antibodies or even CD8+ T cell responses although more had favorable CD4+ T cell responses. Thus, the trial, while giving some optimism for vaccines, has failed to clearly indicate what specific type of immunity was responsible for the protection seen; further analysis will continue to evaluate the trial in hopes of guiding more improved candidates for the future [175].

While the search for a vaccine continues, the research thus far has given not only the scientific community a deeper understanding of both the HIV virus but also the human immune system and its interaction with this unique virus [157]. This will not only inform vaccine efforts for other infectious diseases but also facilitate the use of novel immunomodulatory entities and delivery systems that have been developed and tested. The development of an effective HIV vaccine will be used in conjunction with the many established methods of prevention that have been described, and new modalities such as male circumcision and ART treatment as prevention, which show great promise for additional preventative benefits [176]. Advances in these areas have now merged the interventions of treatment, vaccine, and prevention, to form a future strategy of combined prevention [69].

Future Directions

Thirty years ago, a mysterious disease affecting men who have sex with men in the USA initiated the world's appreciation of a new human virus with disease-causing potential and global spread that was unprecedented. Since that time, it is estimated that 60 million people have been infected with HIV responsible for over 25 million deaths. The history of HIV's discovery is instructive to our overall outlook on infectious diseases in general. HIV originated in closely related viruses of primates with multiple variants that still resemble close relationship to the viruses of great apes. The virus and its many genetic variants showed distinct differences in its epidemiology based on geographic location, risk groups

affected, spread, and disease. In addition, the increasing complexity and higher prevalence of recombinant forms of the HIV epidemic suggests that more vigilant surveillance with improved technologies will be important. The marked dichotomy between the epidemics of high-income versus middle- and low-income countries has challenged public health efforts to address prevention and treatment needs. ART drugs and laboratory tests developed in high-income countries are high in cost and complexity of use; this continues to be a major obstacle to the largest number of people infected and suffering from HIV and AIDS. In the past decade, an international effort to provide equal access to prevention, care, and treatment has demonstrated that the gap in access can be narrowed. Newer and more efficacious regimens to prevent mother-to-child transmission have just been adopted in the 2010 WHO guidelines and hold the potential of eliminating transmission as the guidelines are rolled out [84]. WHO has also revised the 2010 ART guidelines, which will initiate treatment for patients with less severe disease, CD4+ cell counts below 350, rather than 200 cells per cubic milliliter of blood [177]. While the increased costs and actual implementation of these new guidelines will pose an obstacle for many poor countries of the world, the ultimate realization of these guidelines will further decrease the burden of people living with HIV and increase the longevity of those already on treatment.

The historic and unprecedented support and efforts from the international donor community have made major progress in scaling up prevention and treatment of HIV in areas of the world with the most need. They have begun the difficult task of encouraging national leadership, building up broken or nonexistent health systems, in order to address the pandemic, but the burden of disease is still significant, and efforts must be continued with a perspective of long-term sustainability.

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