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THE BIOLOGY AND EVOLUTION OF HIV

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■ **Abstract** This review examines the current state of knowledge about HIV/AIDS in terms of its origins, pathogenesis, genetic variation, and evolutionary biology. The HIV virus damages the host's immune system, resulting in AIDS, which is characterized by immunodeficiency, opportunistic infections, neoplasms, and neurological problems. HIV is a complex retrovirus with a high mutation rate. This mutation rate allows the virus to evade host immune responses, and evidence indicates that selection favors more virulent strains with rapid replication. While a number of controversial theories attempt to explain the origin of HIV/AIDS, phylogenetic evidence suggests a zoonotic transmission of HIV to humans and implicates the chimpanzee (*Pan troglodytes troglodytes*) as the source of HIV-1 infection and the sooty mangabey as the source of HIV-2 infection in human populations. New therapies provide hope for increased longevity among people living with AIDS, but the biology of HIV presents significant obstacles to finding a cure and/or vaccine. HIV continues to be a threat to the global population because of its fast mutation rate, recombinogenic effect, and its use of human defenses to replicate itself.

INTRODUCTION

This review examines the current state of knowledge on the biology of HIV in terms of protein synthesis, genetic variation, mutation rate, and recombinogenic effect. An understanding of the genetics of HIV provides a context for understanding the short- and long-term impact of HIV on the physiology of the human body in terms of the pathogenesis of HIV disease, and associated cofactors that eventually produce AIDS. Examination of HIV's genomic variation also provides clues concerning selective pressures and temporal changes in the evolution of the virus.

A number of controversial theories to explain the origin of HIV/AIDS are considered. These theories include biological warfare, human experimentation gone wrong, and the most controversial idea that AIDS does not exist. Although these theories are considered, a more likely explanation examined involves zoonotic transmission from nonhuman primates to human populations.

Finally, implications for drug therapies and the future spread of HIV/AIDS are considered in relation to HIV's fast mutation rate, recombinogenic effect, and its use of human defenses to replicate itself. New therapies promise hope for increased longevity among people living with AIDS, but the death toll continues to rise. Examination of the biology, genetics, and evolution of HIV disease indicates that HIV/AIDS is a continual threat to the human population.

In order to understand the biology and evolution of HIV/AIDS, we must first have a working definition of the disease and understand its modes of transmission. The ensuing discussion defines HIV/AIDS in children and adults and gives the distinguishing characteristics of HIV and AIDS, and identifies its modes of transmission.

HIV/AIDS DEFINED

Acquired immune deficiency syndrome (AIDS) is characterized by progressive loss of the $CD4^+$ helper/inducer subset of T lymphocytes. Loss of T cells leads to severe impairment of immune function, constitutional diseases, opportunistic infections, neurological complications (AIDS dementia complex), and neoplasms that seldom occur in persons with intact immune function (Ho et al 1987; Fauci 1988, 1993; Greene 1993; Levy 1993; Weiss 1993; Natl. Inst. Allergy Infect. Dis. 1995; Clavel et al 1986; Fisher et al 1988; Price et al 1988). While the precise mechanisms that result in destruction of the immune system are not completely understood, an abundance of epidemiologic, virologic, and immunologic data support the conclusion that infection with HIV (human immunodeficiency virus) is the underlying cause of AIDS (Ho et al 1987; Fauci 1988, 1993; Greene 1993; Levy 1993; Weiss 1993; Natl. Inst. Allergy Infect. Dis. 1995; Darby et al 1995).

HIV was originally designated human T lymphotropic virus (HTLV)-III, lymphadenopathy-associated virus (LAV), or AIDS-associated retrovirus (ARV) (Fauci 1988). AIDS is induced by the HIV virus. Therefore, it is specifically referred to as HIV/AIDS because other factors such as corticosteroids, cancer chemotherapy, and alkylating agents can also produce AIDS-like symptoms (Stine 2000).

The Centers for Disease Control (CDC) provides criteria for defining HIV/AIDS in adults, children, and in developing countries. The CDC currently defines AIDS in an adult or adolescent age 13 years or older as HIV infection with a $CD4^+$ T cell count less than 200 cells per cubic millimeter of blood and/or HIV infection and the presence of one of 25 AIDS-indicator conditions, such as Kaposi's sarcoma, *Pneumocystic carinii* pneumonia, or disseminated *Mycobacterium avium* (MAC) (CDC 1987a). In children younger than 13 years, the definition of HIV/AIDS is similar to that in adults and adolescents, except that lymphoid interstitial pneumonitis and recurrent bacterial infections are included in the AIDS-indicator list (CDC 1987b). In developing countries, where diagnostic facilities could be limited, a case definition based on the presence of certain clinical symptoms

associated with immunosuppression and the exclusion of other known causes of immune deficiency such as malnutrition or cancer are used in AIDS surveillance (Ryder & Mugewrwa 1994, Davachi 1994).

LENTIVIRUSES

HIV is a member of the lentivirus subfamily of retroviruses that produces chronic infection in the host and gradually damages the host's immune system (Dimmock & Primrose 1987, Hu et al 1996, Fauci 1988, Hahn et al 2000, De Cock et al 1993, Clavel et al 1986, Grez et al 1994, Beer et al 1999). Three major types of lentiviruses have been characterized in primates: simian immunodeficiency virus (SIV) and among humans, HIV-1, the predominant type in the world, and HIV-2, primarily found in West Africa and India (De Cock et al 1993, Clavel et al 1986, Grez et al 1994, Beer et al 1999).

TRANSMISSION

The clustering of AIDS cases and the occurrence of cases in diverse groups can only be explained by transmission of a virus, HIV, in a manner similar to hepatitis B virus: by sexual contact, by inoculation with blood or blood products, and by perinatal transmission from mother to newborn infant (Quinn 1987; Francis et al 1983; Curran et al 1984; CDC 1982, Fauci 1988). Exchange of fluids is necessary for transmission. Preliminary evidence suggests selective transmission of certain maternal HIV-1 variants for mother-infant pairs. That is, only a minor subset of maternal strains is transmitted to infants (Wolinsky et al 1992, Wike et al 1992). Also, mother-to-infant transmission rates are lower for HIV-2 than HIV-1 (Andreasson et al 1993).

HIV is not transmitted through contact with inanimate objects, through vectors, or through daily contact with infected people. Kissing is low risk for HIV infection (one documented case). Antibodies have been detected in saliva, suggesting that these antibodies neutralize HIV to produce HIV seronegative status (Stine 2000).

THE BIOLOGY OF HIV

The HIV virus is roughly spherical and about one ten-thousandth of a millimeter across. Its outer envelope or coat is composed of a double layer of lipid envelope that bears numerous spikes. Each spike is composed of four molecules of gp120 and the same number of gp41 embedded in the membrane. Beneath the envelope is a layer of matrix protein that surrounds the core (capsid). The capsid has a hollow, truncated cone shape and is composed of another protein, p24, that contains the genetic material of the HIV virus. Two strands of RNA consisting of about 9200

nucleotide bases, integrase, a protease, ribonuclease, and two other proteins, p6 and p7, fit inside the viral core (Greene 1993, Stine 2000, Fauci 1988).

Retroviruses like HIV reverse the usual direction of genetic information within the host cell to produce protein. The process of protein synthesis in regular gene expression results from the DNA being copied into RNA and the RNA being translated into specific proteins. With retroviruses the RNA is copied using its reverse transcriptase (RT) enzyme. In the cytoplasm RT migrates along the RNA to produce a complementary strand of DNA. After completion of the first DNA strand the RT begins constructing a second strand, using the first one as a template (Dimmock & Primrose 1987, Stine 2000, Greene 1993, Fauci 1988).

The double-stranded retroviral HIV DNA moves into the nucleus, where it inserts into the host DNA and becomes a provirus. Infection of the cell is then permanent. The provirus can remain dormant for a long time. Its genes cannot be expressed until RNA copies are made by the host cell's transcription machinery. Transcription starts when genetic switches at the ends of the provirus' long terminal repeats (LTRs) activate the cell's RNA polymerase II. Regulatory proteins known as NF-kB/Rel (in almost all human cells) bind with the LTRs at the ends of the provirus to activate the cell's RNA polymerase and thereby cause transcription of the provirus to RNA. NF-kB/Rel regulatory proteins increase in production when the cell is exposed to foreign proteins or by hormones that control the immune system (Dimmock & Primrose 1987, Stine 2000, Greene 1993, Fauci 1988). One member of this family, c-Rel, actually hinders HIV transcription, but it is produced more slowly than the ones that stimulate transcription (Greene 1993).

There are two phases of transcription after infection of a cell by HIV. After proviral DNA makes complementary copies of RNA strands some of the strands are cut into segments by cellular enzymes and spliced into a length of RNA appropriate for protein synthesis. These RNA strands become messenger RNA, producing regulatory proteins necessary for the production of HIV. By the time they migrate out of the nucleus to the cytoplasm they are about 2000 nucleotides long. The first phase lasts about 24 hours. In the second phase unspliced RNA transcripts become new viral strands (genome RNA or structural genes) and migrate out of the nucleus into the cytoplasm. Two new size classes of RNA are produced in this phase: long-unspliced strands of 9749 bases that comprise the genome RNA and medium-length (singly spliced) transcripts of about 4500 bases (virion assembly) that encode HIV's structural and enzymatic proteins. This material is enclosed within the viral core protein to become new viruses that migrate out of the cell (Greene 1993, Stine 2000).

THE GENETICS OF HIV

All retroviruses have a somewhat homogeneous structure and contain the same three genes, *gag*, *pol*, and *env*, encoding the structural proteins and enzymes used in the replication cycle (Dimmock & Primrose 1987, Stine 2000, Greene 1993,

Fauci 1988). HIV and SIV are different from other retroviruses in having more genes with complex interactions. The common and assumed ancestral genetic structure for primate lentiviruses, HIV and SIV, is *LTR-gag-pol-vif-vpr-tat-rev-env-nef-LTR* (Beer et al 1999, Stine 2000, Greene 1993). The function of each gene is not fully understood, but the gag gene codes for the manufacture of the dense cylindrical core proteins, the viral nucleocapsid. The *Gag* gene can direct the creation of virus-like particles in the absence of *pol* and *env*, and when it is nonfunctional HIV loses its ability to migrate out of the host cell (Dimmock & Primrose 1987, Wills & Craven 1991). The *pol* gene codes for reverse transcriptase, protease, ribonuclease, and integrase, which cuts the cell's DNA and inserts the HIV DNA (Dimmock & Pimrose 1987, Greene 1993). The *env* gene codes for the two envelope proteins gp120 and gp41, the transmembrane that binds gp120 with the exterior of HIV (Dimmock & Primrose 1987, Stine 2000). The *tat* gene produces a regulatory protein that increases transcription of the HIV provirus. *Nef* may modify the cell to make it able to manufacture HIV virions later. *Rev* appears to be responsible for switching the processing of viral RNA transcripts to the pattern that dominates after the cell has been infected for over 24 hours (when two new size classes of RNA are created) (Greene 1993, Rosen 1991). The long terminal repeats are not part of the 9749 bases of the HIV genome but contain sequences that help the regulatory genes control *gag-pol-env* gene expression. *Vif* is required for complete reverse transcription of viral RNA into HIV DNA. *Vpu* helps HIV bud out of the cell by destroying the CD4 protein within T4 lymphocytes, and *vpr* is related to the transmission of cytoplasmic viral DNA into the nucleus (Dimmock & Primrose 1987, Stine 2000).

HIV-infected cells contain from 400,000 to 2,500,000 copies of viral RNA per cell. Viral RNA can use as much as 40% of total protein synthesis for the production of gag viral protein, and there are high levels of viral RNA and protein synthesis prior to cell death. HIV produces viral RNAs at a level that has the potential to inhibit or compete for host protein synthesis (Somasundaran & Robinson 1988).

HIV GENOMIC VARIATION AND EVOLUTION

Mutations

Within a single cell HIV could make thousands of copies and some of them will be mistakes—mutations. Whereas some of these mutants may be inactive copies, others will be HIV mutants with enhanced survival and/or replication abilities. Both mutant and parent HIV replicate in the same manner, but over time as mutants are transmitted to other individuals and undergo more mutations these variants could evolve into a new viral strain such as HIV 3 (Stine 2000).

HIV has a high mutation rate (Dimmock & Primrose 1987, Ho et al 1995, Preston et al 1988, Vartanian et al 1992, Dougherty & Temin 1988, Hahn et al 1986, Saag et al 1988, Nowak 1990), but the mechanisms for producing HIV mutations are not completely understood. According to Levy (1988), new RNA

strands accumulate in the host-cell cytoplasm, where they exchange parts with each other to produce new varieties of HIV (recombination). Another theory posits that HIV variants are the product of error-prone RT enzymes of HIV (Preston et al 1988, Nowak 1990). RT makes 1–10 errors on average during the replication of the HIV genome (Nowak 1990, Dougherty & Temin 1988, Preston et al 1988). In other words, there is a nucelotide mistransmission such as substitution, addition, and deletion when RT composes proviral DNA. Other ways to create HIV genetic diversity involve any steps in the reproductive cycle (Stine 2000). Vartanian and associates (1992) reported that each HIV-infected cell carries mutant HIV that is genetically unique, causing high genetic diversity among isolates of HIV.

Mutation rates and selection rates vary for different components of the HIV genome. *Gag* and *pol* genes are less variable than the *env* gene. Within the *env* gene there are five hypervariable regions, V1 to V5. The V3 region, about 30 amino acids within the envelope protein gp120, is highly mutable, and changes of one amino acid in this region can restrict recognition by neutralizing antibodies (Looney et al 1988, Nowak 1990, Shaper & Mullins 1993, Kliks et al 1993).

Collections of genetically distinct HIV variants can evolve from the initial infection. Populations of these closely related genomes, called quasispecies (Shioda et al 1991), vary increasingly over time (Hahn et al 1986) and are the products of mutation and selection (Bonhoeffer et al 1995). Different mutants within these quasispecies can exhibit very different biological properties such as cell tropisms (affinity), cytopathic properties, surface antigen traits, and replication rates (Shioda et al 1991). Quasispecies can migrate into new cellular populations by acquiring mutations that facilitate adaptation (Doms & Moore 1997). That is, some mutants may be able to infect previously uninfected tissues.

The genetic diversity of the HIV virus results in drug resistance and evasion from immune responses and makes development of a vaccine a challenge (Bonhoeffer et al 1995, Korber et al 1998). For example, some HIV mutants can evade the immune response and thrive (Stine 2000). As such, the immune response is a major force in positive selection pressure generating genetic diversity (Nowak 1990). The high mutation rate also results in the production of viral strands that are not susceptible to drug therapy. This process explains why drugs such as AZT are efficacious only temporarily (Greene 1993, Korber et al 1998) and why some HIV-1 strains are not reliably detected by all antibody screening tests currently in use (Loussert-Ajaka et al 1994, Schable et al 1994). Drug therapies, therefore, are also a force in positive selection and in creating genetic diversity in HIV. This genetic diversity makes it extremely difficult to develop a drug that can kill all HIV viruses.

Recombination

Because HIV is diploid (carries 2 RNA molecules), there can be genetic recombination (exchange of parts) between these strands and other strands in the area (Stine 2000, Levy 1988). HIV is highly recombinogenic, but recombination can

only take place between genomes packaged within the same virion (Robertson et al 1997). Recombination in HIV is facilitated by coinfection with different subtypes of HIV and/or in cells with different susceptibilities for various subtypes and by geographic intermixing of subtypes (Laurence 1997). Recombination is probably involved in genetic diversity and selection pressures at every level, although it is only detected when distinct strains are present, for example two distinct strains in the same person (Korber et al 1998).

Temporal Changes in HIV Genotype

Variation in the rate of HIV evolution may be determined by differences in host-mediated selection pressures (Wolinsky et al 1996, Nowak et al 1995). For instance, upon infection, the individual has a homogeneous viral population (Bonhoeffer et al 1995, Wolinsky et al 1996, Nowak 1995). Stable viral population equilibrium is found when the initial virus is relatively fit and replicating in a relatively constant environment. In this environment a particular genetic variant, regardless of its pathogenic ability, would be preferentially increased (Wolinsky et al 1996). Early in the infection the immune response reacts quickly and strongly against common viral variants (Boyd et al 1993). As HIV infects different cells and tissues, rare mutants escape surveillance (the immune response) and increase in frequency (Wolinsky et al 1996). This provides strong selection pressure for HIV viral diversification (Boyd et al 1993, Bonhoeffer et al 1995, Saag et al 1988). HIV variants can evolve rapidly in parallel and coexist during chronic infection (Delwart et al 1993, Stine 2000).

After the virus generates many variants with specific cell tropism (affinity) there is a decline of the immune response and selection pressures are weaker (Boyd et al 1993, Bonhoeffer et al 1995). Individuals who progress to AIDS usually have a more homogeneous viral population. Slow evolution may represent the apparent predominance of an optimally adapted variant (Wolinsky et al 1996).

Mathematical models of the interaction between $CD4^+$ cells and HIV-1 indicate that selection favors more virulent strains (Anderson 1989, 1991), and more virulent strains appear later in the asymptomatic or incubation period (Levy 1990, Fenyo et al 1989). HIV-1 isolates from asymptomatic individuals grow slowly and have low titers of reverse transcriptase activity, whereas isolates from patients with AIDS grow rapidly, show high reverse transcriptase activity, and induce cell death more often (Fenyo et al 1989, Nowak et al 1991).

HIV Subtypes/Clades

Based on phylogenetic relationships, HIV-1 viruses can be divided into three major subtypes or clades: M, N, and O (Simon et al 1998, Gao et al 1999, Louwagie et al 1993, Leitner et al 1997, Sharp et al 1994). The predominant M group consists of 11 clades denoted subtypes A through K (Los Alamos Natl. Lab. 1998). Multiple strains are found in many countries, but in the United States the

majority of isolates have been subtype B. The occasional presence of HIV-2 and HIV-1 subtypes other than B indicates multiple HIV introductions to North America (Hu et al 1996, Delwart et al 1993). Subtypes from Africa belong to four clades (A–D). Subtype C is found mainly along the south and east coast of Africa and the west coast of India (Delwart et al 1993, Stine 2000). E, B, and C are found in Southeast Asia (Louwagie et al 1993). One, subtype E, almost exclusively infects heterosexuals in northern Thailand, whereas both genotypes B and E are found in injection drug users in Bangkok (Moore & Anderson 1994, Kunanusont et al 1995).

Clines were shown for three of the genotypes. For instance, genotypes A and D were found in an east-to-west belt across sub-Saharan Africa from Senegal to Kenya. A north-to-south pattern was found for genotype C in Africa (Louwagie et al 1993).

Consideration of N and O groups reveals that nucleoside sequencing of the N group is restricted to Cameroon (Simon et al 1998). HIV-1 variants outside the M and N groups have been provisionally categorized as group O (De Leys et al 1990, Gurtler et al 1994). Within group O strains may differ as much from each other as the variants within group M subtypes differ from each other (Sharp et al 1994). Group O is primarily found in Cameroon (DeLeys et al 1990, Gurtler et al 1994), but it accounts for less than 10% of HIV infections (Gurtler et al 1994).

It must be recognized that the subtypes identified for HIV are provisional and reflect those isolates that have been collected and characterized (Hu et al 1996). Coinfection (Pieniazek et al 1995) and genetic recombination between different viral strains (Hu & Temin 1990) complicate identifying HIV variants. It is possible that difficult-to-detect divergent HIV strains have entered human populations (Hu et al 1996).

A major fraction of HIV-1 strains are intersubtype recombinants (Robertson et al 1997). For instance, a subtype from Cyprus, I, appears to be a recombinant of at least three subtypes, A, G, and I (it is not known if it originated in Africa or Cyprus) (Kostrikis et al 1995). Some exchanges may not be viable because certain combinations may not survive at either the RNA level or after translation of the RNA product (Robertson et al 1997).

HIV-2 comprises six distinct phylogenetic lineages, subtypes A through F (Los Alamos Natl. Lab. 1998, Gao et al 1994). HIV-2 predominates in West Africa and is also found in India (Hu et al 1996, Clavel et al 1986). HIV-1 and HIV-2 share about 60% nucleotide homology for *gag* and *pol* genes but much less for *env* and the other viral genes (Shaper & Mullins 1993).

Recombinant viruses are also found among HIV-2 strains (Gao et al 1994) and among SIVs (Chen et al 1996). So far, no viruses are known to be the product of recombinants of two highly divergent major groups of HIV-1, nor have recombinants of HIV-1 and HIV-2 been found in individuals dually infected with HIV-1 groups M and O (Takehisa et al 1997) or both HIV-1 and HIV-2 (Grez et al 1994).

HIV AND THE IMMUNE SYSTEM

Basic Immunology

HIV infects several cell types in the human body, but the more important cells are in the immune system. The immune system fights foreign substances, removes dead and damaged cells, and destroys mutant and cancerous cells. The human immune system is able to fight foreign entities never seen before because of the number of different kinds of cells called lymphocytes. The two types of lymphocytes are B and T cells that recognize foreign substances or nonself. B cells produce and secrete antibodies in response to an antigen (Pantaleo et al 1993a, Stine 2000). The three major types of T cells are cytotoxic or killer T cells, suppressor T cells, and helper T cells. Killer T cells eliminate virus-infected cells and are responsible for recovery from a viral infection. T suppressor/cytotoxic cells suppress the immune response after the foreign substance is eliminated. Helper T cells alert the immune system to antigens and signal other cells in the system to attack it. T4 cells do not kill cells but interact with B cells and killer T cells to help them attack foreign particles (Dimmock & Primrose 1987, Stine 2000).

There are specialized receptors on the surface of T cells to identify one of many millions of possible antigens that may invade the body. Each T cell expresses a receptor that binds with the complementary antigen on the foreign particle to neutralize or destroy it. Killer and suppressor T cells carry the CD8 receptor (T suppressor cells are called T8 cell), and the helper T cells (T4 cell) carry the CD4 receptor. Collectively, T8 and T4 cells regulate the body's immune response to foreign antigens (Dimmock & Primrose 1987, Stine 2000).

HIV Infection and the Immune System

HIV-1 mainly targets $CD4^+$T lymphocytes and $CD4^+$ cells of monocyte/macrophage lineage (Dimmock & Primrose 1987, Connor & Ho 1994). T4 cells may be lost through a number of processes. For instance, defects in T4 cells caused by HIV infection may produce activation-induced cell death or apoptosis (normal cell death) (Pantaleo et al 1993a). HIV also may trick the immune system into attacking itself (Kion & Hoffmann 1991). Another method is syncytia formation, which involves the massing of healthy T cells around a single HIV-infected T4 cell resulting in loss of immune function (Stine 2000, Hoxie et al 1986, Sodroski et al 1986, Gelderbloom et al 1985). Death of cells could be due to direct membrane disruption involving calcium channels (Gupta & Vayuvegula 1987) and/or phospholipid synthesis (Lynn et al 1988). A buildup of unintegrated proviral copies of HIV DNA may cause cytopathology, because it is associated with cell death in other retroviral systems (Levy 1988). It is believed that depletion of T4 cells is insufficient to cause AIDS because not enough T4 cells are destroyed. Equally important may be T4 cell infection of monocytes and macrophages that engulf and destroy antigens (Bakker et al 1992).

HIV usually puts a portion of its virus on the surface of the cell that it infects. Killer cells, cytotoxic T lymphocytes, search out and destroy infected cells. However, HIV escapes detection by cytotoxic T lymphocytes because *Nef* gets cells to remove a protein that indicates to the killer cells that the T cell is infected. This makes it possible for HIV-infected cells to evade killer T cells (Cohen 1997).

HIV, Macrophages, and T cells

There is a temporal change in viral tropism during the course of HIV-1 infection. Early in infection macrophage tropic (M-tropic) HIV viruses have the ability to infect macrophages and are nonsyncytium-inducing (NSI) owing to their inability to form syncytia on T-cell lines (Connor et al 1993, Zhu et al 1993, Fenyo et al 1988, Schuitemaker et al 1992). Usually, about 4–5 years after infection virus strains evolve in some individuals (about 50%) that can infect T-cell lines in addition to primary T-cells (Tersmette et al 1989, Milich et al 1993, Shioda et al 1991). In this change in tropism the virus sometimes loses the ability to infect macrophages, but more often they retain this property and are referred to as dual tropic (Collman et al 1992). HIV-1 viruses that can infect T-cell lines are referred to as T-tropic and are syncytium-inducing (SI). Viruses that can grow on transformed cell lines by continual passage are called T-cell line adapted (TCLA) (Doms & Moore 1997). Others consider tropism as a range where, for example, macrophages are infected efficiently and T cell lines are less efficiently infected (Moore & Ho 1995, Sullivan et al 1995, Fenyo et al 1997). This switch may be related to colonization of different types of cells or a product of natural selection in which certain phenotypes are selected for and escape the immune response (Weiss 1996).

CD4 receptors alone are sufficient for binding HIV to T4 lymphocyte membranes, but coreceptors are required to mediate entry of HIV-1 into cells. The best-known HIV-1 coreceptors are CXCR4 and CCR5, members of the CXC and CC chemokine receptor subfamilies, respectively (the number of coreceptors used by SIV and HIV is now 14) (Doms & Moor 1997, Fenyo et al 1997, Dragic et al 1996). CCR5 is the primary coreceptor for HIV-1 isolates with the NSI phenotype (Fenyo et al 1997, Deng et al 1996, Dragic et al 1996), whereas SI phenotypes are associated with the use of CXCR4 alone or in conjunction with CCR5 (Simmons et al 1996, Zhang et al 1996, Fenyo et al 1997). Studies show that in the presence of CD4 and the appropriate coreceptor, both SI and NSI viruses can induce syncytium formation. Therefore, the terms SI and NSI are not absolute but are related to coreceptor expression levels on target cells (Fenyo et al 1997, Feng et al 1996). All HIV-1, HIV-2, and SIV strains use one or both of these main receptors (Dragic et al 1996).

CD8 T lymphocytes partly control HIV infection by the release of HIV-suppressive factors, beta chemokines, that are active on monocytes and lymphocytes. Beta chemokines MIP-1α, MIP-1β, and RANTES are most active against HIV-1 in combination and inhibit infection of $CD4^+$ T cells by primary, NSI HIV-strains at the virus entry stage. However, TCLA/SI HIV-1 strains are insensitive

to beta-chemokines. Therefore, some $CD4^+$ T-helper cells from HIV-1-exposed uninfected individuals resist infection with NSI strains (secrete high levels of beta chemokines) but are infected by TCLA/SI strains. It is unknown if high levels of these chemokines can delay HIV disease progression (Cocchi et al 1995).

Some exposed-uninfected individuals harbor identical mutations on both chromosomal copies of CC-chemokine receptor 5 (CCR-5) (Hill & Littman 1996, Samson et al 1996). A frameshift mutation, 32-base-pair deletion, generates a nonfunctional receptor that does not allow membrane fusion or infection by macrophage- and dual-tropic HIV-1 strains (Liu et al 1996, Samson et al 1996). This polymorphism has an allele frequency of 0.092–0.098 among whites but is absent among blacks from West and Central Africa and in Japanese populations. About 15–29% of whites are heterozygous, whereas about 1% are homozygous. The prevalence of heterozygotes was lower in an HIV-infected sample compared with the uninfected population. This indicates a possible partial protection from infection among individuals with a single copy of the mutant allele. However, both groups showed that those heterozygous for the CCR-5 mutation were susceptible to viral infection, although at reduced levels. It is not clear if transmission of HIV or progression to AIDS is affected by heterozygosity for the CCR-5 mutation (Samson et al 1996, Hill & Littman 1996).

PATHOGENESIS OF HIV/AIDS

Initial infection with HIV virus is followed by high viral replication with or without clinical symptoms (Daar et al 1991, Tindall & Cooper 1991, Ho et al 1989). In acute HIV infection there is typically a mild, flu-like illness with fever and muscle aches that lasts a few weeks (Greene 1993, Stine 2000, Fauci 1988). HIV antibodies are detected between 6–18 weeks after initial infection (Stine 2000). Then antibodies appear in the blood serum (seroconversion), after which it is difficult to isolate the virus. This asymptomatic period is distinguished by low viral replication interspersed with periods of increases in viremia (virus in blood) and by slow but constant decreasing numbers of $CD4^+$ cells (Tindall & Cooper 1991, Ho et al 1989, Fauci 1988, Fauci et al 1991).

Longitudinal studies of HIV-1-infected individuals indicate a long and variable incubation period (about 10 years) between infection and development of AIDS (Biggar 1990, Nowak et al 1991, Fauci et al 1991, Fauci 1988). A long asymptomatic period may be due to latent infection. During latent infection very little viral protein or RNA is produced (Rojko et al 1982). Research suggests that the *orf-B* gene of HIV is responsible for latency. This gene product interacts with cellular factors to slow down viral replication in a continuum that can proceed to latency (Levy 1988).

Another explanation for latency is related to the dichotomy between viral levels and viral replication in lymphoid organs versus peripheral blood. HIV is expressed in the lymphiod tissue throughout clinical latency even when there is minimal

viral activity in the blood (Pantaleo et al 1993b, Fauci 1993). Follicular dentritic cells in the lymph nodes are exposed to HIV early in infection, requiring the nodes to work hard to eliminate the virus. Latency may be due to the interplay between the envelope protein and immune system, where initially the lymph nodes contain the virus, but eventually the virus gains the upper hand when it evolves a variant that evades the immune system response (Dimmock & Primrose 1987, Fauci 1993). In AIDS collapsing nodes may no longer be able to remove the virus, allowing its escape into the bloodstream (Fauci 1993, Greene 1993, Embretson et al 1993). Latently infected lymphocytes and macrophages are reservoirs for immune depletion in AIDS (Embretson et al 1993).

In rare cases HIV-seropositive individuals become seronegative. In some of these individuals latent HIV in peripheral mononuclear cells were detected by polymerase chain reaction, but in others no HIV was detected (Farzadegan et al 1988). This suggests that HIV infection could be eliminated completely by the immune response, but more likely the virus is hiding at other sites in the body (Levy 1988, Farzadegan et al 1988).

AIDS is the end stage of a progressive and continuous pathogenic process involving profound immune deficiency, opportunistic infections, and neoplasms (Ho et al 1987; Fauci 1988, 1993; Weiss 1993; Natl. Inst. Allergy Infect. Dis. 1995). There is a slow and steady reduction in $CD4^+$ T-helper or inducer lymphocytes during this period in those who develop AIDS (Tindall & Cooper 1991; Fauci 1988, 1993; Nowak 1991). The number of T4 lymphocytes in the blood decreases during this chronic infection from 1000 per cubic millimeter to less than 100 (Ho et al 1989, Greene 1993).

Although the pathogenesis of HIV is similar in those with HIV-2 and HIV-1 (De Cock et al 1990, Le Guenno et al 1991), the immunologic deficiency is less severe and the disease progression is slower in HIV-2 (Le Guenno et al 1991, Whittle et al 1994, Marlink et al 1994). The virulence of HIV-2 is known to vary significantly and range from relative attenuation to great pathogenicity. Differences in clinical manifestations may be partly related to genetic differences among infecting viral strains (Gao et al 1994).

COFACTORS IN HIV INFECTION

HIV infection alone can cause immunodeficiency in the absence of other infections, but coinfection can hasten immune deficiency (Greene 1993) by aiding in the depletion of T4 cells. Concomitant viral infections with Epstein-Barr virus, cytomegalovarius, herpes simplex virus, hepatitis B infection (Jordan 1991, Cohen & Herbert 1996, Anderson 1995, Catania et al 1994, Walker et al 1989), infection with *Mycoplasma fermentans* (incognitus strain) (Lo et al 1991), respiratory infection such as tuberculosis (Zacarias et al 1994, Braun et al 1993, Snider et al 1991), and sexually transmitted diseases such as chancroid, gonorrhea, chlamydia, and syphilis (Baqi et al 1999, Levine et al 1998, Erbelding et al 2000, Lankoande

et al 1998, Ndinya et al 1997) are associated with HIV expression. Other cofactors including drugs used by injection-drug users such as heroin and other morphine-based derivatives (Walters & Simoni 1999, Reilley et al 2000, Eicher et al 2000), blood and blood products (Berkman 1984, Blumberg et al 1985), traumatic lacerations of the rectal mucosa (portal of entry for the virus) (Ratnam 1994), and stress, mental or physical (Siegel et al 1996, Puskar et al 1999, Wagner et al 1998, Cole et al 1996), can impair the immune system.

HIV, SIV, AND EVOLUTION

HIV-1 and HIV-2 represent cross-species (zoonotic) infections (Clavel et al 1986; Gao et al 1992, 1999; Ewald 1996; Hahn et al 2000; Dolittle 1989; Nzilambi et al 1988; Chakrabarti et al 1987). Five sources of evidence support a zoonotic transmission of primate lentiviruses, such as similarities in viral genome, phylogenetic relatedness, prevalence in the natural host, geographic coincidence, and plausible routes of transmission. HIV-1 and HIV-2 satisfy these criteria (Hahn et al 2000, Huet et al 1990, Hirsch et al 1989).

HIV-2 is closely related to SIVs isolated from macaques (SIV_{mac}) and sooty mangabeys (SIV_{sm}) (Clavel et al 1986, Gao et al 1992, Hahn et al 2000, Hirsch et al 1989). SIV_{sm} has been isolated from free-ranging and pet sooty mangabeys (*Cercocebus atys*) in West Africa (Chen et al 1996). However, no macaques in the wild in Asia and very few macaques in captivity are infected with SIV (Wu et al 1991). The close relationship between HIV-2 in humans and SIV_{sm} suggest that feral SIV-infected sooty mangabeys in West Africa are the natural source for HIV-2 infection in humans and macaque infection (Hirsch et al 1989; Gao et al 1992, 1999; Ewald 1996; Hahn et al 2000; Peeters et al 1989; Sharp et al 1994).

Examination of nucleotide sequence of HIV-2 and SIV indicate HIV-2 is more closely related to SIV_{sm} than it is to HIV-1 (Clavel et al 1986). For instance, HIV-2 and SIV_{sm} share an identical genomic structure (both have a protein, V_{px}, that is not found in any other primate lentiviruses) (Hirsch et al 1989) and the HIV-2 subtypes are not more closely related to one another than they are to SIV_{sm} (Chen et al 1996). Rather, SIV_{sm} and HIV-2 lineages are phylogenetically interspersed. This suggests that the different HIV-2 clades are not the result of a single mangabey-to-human transmission but are due to multiple independent cross-species transmission of SIV_{sm} into the human population (Hahn et al 2000). Transmission is possible because sooty managbeys are often hunted for food or kept as pets (Chen et al 1996, Marx et al 1991, Hahn et al 2000). SIV_{sm} has also been transmitted to humans after accidental exposure to monkey blood (Khabbaz et al 1994).

It is not known whether the chimpanzee is the natural reservoir for HIV-1, because only four animals tested SIV seropositive (Peeters et al 1989, Huet et al 1990, Janssens et al 1994, Vanden Haesevelde et al 1996). However, $SIV_{cpz\text{-}GAB}$ (Gabon), $SIV_{CPZ\text{-}GAB2}$ (Gabon), $SIV_{CPZ\text{-}ANT}$ (Zaire), and a new SIV_{cpz} sequence (SIV_{cpzUS}) (United States) indicate that SIV_{CPZ} and HIV-1 have the same genetic

organization containing a gene, V_{pu}, not present in other lentiviruses (Huet et al 1990; Peeters et al 1989, 1992; Gao et al 1992, 1999; Ewald 1996; Hahn et al 2000).

Gao et al (1999) found that two chimpanzee subspecies in Africa, the eastern *Pan troglodytes schweinfurthii* and *Pan troglodytes troglodytes*, harbor SIV_{cpz}, but that they form two highly divergent but supspecies-specific phylogenetic lineages. Such findings are consistent with the ancestor of SIV_{cpz} strains infecting the common ancestor of *P. troglodytes* followed by host-dependent viral diversification (Hahn et al 2000). HIV-1 strains known to infect humans, including the HIV-1 groups M, N, and O, are closely related to only the SIV_{cpz} lineage found in *P.t. troglodytes* (Gao et al 1999, Beer et al 1999, Hahn et al 2000, Huet et al 1990). Compared with SIV_{CPZ}, the three groups of HIV-1 are not each other's closest relatives, so they must have each arisen from a separate cross-species transmission (Simon et al 1998, Gao et al 1999). Also, it is only in this region that HIV-1 group M viruses show the greatest diversity (Nkengasong et al 1994). The natural range of *P.t. troglodytes* coincides with areas of HIV-1 groups M, N, and O endemicity, which suggests that *P.t. troglodytes* is the primary reservoir for HIV-1 and that it is the source of at least three independent introductions of SIV_{cpz} into the human population (Gao et al 1999, Beer et al 1999, Hahn et al 2000, Simon et al 1998, Peeter et al 1997). A possible route of transmission is hunting because chimpanzees are commonly hunted for food in Africa, especially in the west equatorial region (Gao et al 1999, Hahn et al 2000).

Based on stored samples, humans in central Africa have been infected with HIV-1 group M viruses since 1959 (Zhu et al 1998). Multiple phylogenetic analyses authenticate the 1959 sample from the Democratic Republic of the Congo (formerly Zaire) as the oldest known HIV-1 infection. The initial zoonotic transmission is placed at the sequence very near the ancestral node of the B, D, and F clades of the M group. This suggests that diversity in these clades arose after 1959. Based on molecular clocks, with consideration of the peculiarities of HIV, the origin of zoonotic transmission to humans is placed at around 1930 (range 1910 to 1950) (Korber et al in Hahn et al 2000). The major-group viruses that dominate the AIDS pandemic shared a common ancestor in the 1940s or the early 1950s.

CONTROVERSIAL THEORIES ON THE ORIGIN OF HIV/AIDS

Since the inception of AIDS there have been a number of controversial theories about its origins. For example, one such theory suggests that AIDS was created by a biological warfare experiment that went wrong. It was suggested that researchers in the United States with Defense Department sponsors released a genetically engineered virus into Central Africa to study its impact on humans. A variant hypothesis is that it escaped from a laboratory where researchers tested the virus on prisoners who could increase their chances of parole by volunteering for the experiment.

When the prisoners were released, some became injection drug users and AIDS flourished (Adams 1989).

Gilks (1991) suggested zoonotic transmission in which the AIDS virus entered the human population through inoculation of prison volunteers with malaria-infected blood. Others suggested such transmission through grafts of simian testicles to humans in the early 1920s when some people believed it could delay or avert physical and mental disabilities (Gosden 1992), or that contaminated polio vaccine administered in the late 1950s in Africa was responsible for zoonotic transmission (Koprowski 1992). Another theory is that AIDS spread through reuse of unsterilized needles in vaccination programs. An offshoot of this hypothesis is that "inoculators" (used where people believe in the potency of injections over pills) sold injections in markets and bars and spread the virus. Other theories stated that AIDS was spread to the West by activities of international plasma dealers (Adams 1989), or that ritual scarification contributed to transmission (Pela & Platt 1989).

Early in the AIDS epidemic, because homosexual men comprised the initial population with AIDS in the United States, it was speculated that a homosexual lifestyle was the cause of the disease (Sonnabend et al 1983, Mavligit et al 1984). Peter Duesberg popularized this hypothesis. Duesberg, a molecular biologist at the University of California at Berkeley and a member of the National Academy of Sciences, put forth the most controversial hypothesis that HIV is a harmless passenger virus that does not cause AIDS (Duesberg 1989, 1994). Duesberg proposed a drug-AIDS hypothesis for the acquisition of AIDS. It predicts that (*a*) AIDS in the United States will be restricted to intravenous and oral users of recreational drugs and of AZT, (*b*) AIDS in the United States will predominantly affect adult males because they are the main users of recreational drugs and AZT, (*c*) US AIDS is new because the drug-use epidemic is new, (*d*) only the heaviest drug abusers will get AIDS, just like emphysema usually occurs among the heaviest smokers, (*e*) specific drugs cause group-specific AIDS disease (e.g. he says nitrites, used by homosexual men, are some of the best-known mutagens and carcinogens), and (*f*) most pediatric AIDS cases are caused by mothers who abuse drugs during pregnancy (Duesberg 1987, 1989, 1990, 1992, 1994, 1995). However, virologic, epidemiologic, and immunologic evidence supports the conclusion that HIV causes AIDS.

THE FUTURE OF HIV/AIDS

HIV may continue to be virulent because of its fast mutation rate, recombinogenic effect, and its use of human defenses to replicate itself. For instance, superinfection by viruses of different lineages has the potential for generating recombinant viruses with considerable genetic complexity. Such recombination could occur in humans to produce, for example, HIV-3 because biological mechanisms that usually constrain the evolution of viruses may not apply to HIV. That is, HIV may be evolutionarily free of constraints that could reduce its virulence.

Vaccine efficacy is strain or subtype specific (Hu et al 1996). As a result, developing a vaccine that protects 80% or more of those vaccinated has failed for pathogens that display extensive genetic variation both within and between hosts (Moore & Anderson 1994, Larder et al 1989, Larder & Kemp 1989). While researchers continually develop new drugs to attack the virus, HIV continually produces new variants that are already standing by to circumvent the drug. In addition, replacement of susceptible strains can occur rapidly (Wei et al 1995), and drug-resistant strains can be transmitted producing "primary" resistance in newly infected individuals (Erice et al 1993, Siegrist et al 1994). Therefore, immune system and drug-related selection may broaden the clinical expression of HIV/AIDS to include uncommon infections and constitutional diseases. Eventually, surveillance of drug-resistant HIV strains may be necessary, similar to surveillance of drug-resistant gonorrhea, malaria, and tuberculosis (Hu et al 1996).

While new therapies provide hope for increased longevity among people living with AIDS, the focus of drug therapies has not been in areas with the highest prevalence of HIV/AIDS. For instance, clinical trials for vaccines have been based on subtype B (found in the United States) and not on subtypes prevalent in the hardest hit countries such as those in Africa (Lurie et al 1994). In these areas and where multiple HIV strains are present, development of vaccines is problematic. However, in order to develop a vaccine and drug therapies, and to eventually end the HIV/AIDS pandemic, we must understand the biology and evolution of HIV.

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