The Epidemiology of AIDS

Expression, Occurrence, and Control of Human Immunodeficiency Virus Type 1 Infection

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To Leanne, Karen and the rest of our families, for their encouragement and patience, and to the countless afflicted who sacrificed their precious time and privacy in the hope of sparing those who follow them.

Preface

No other subject of medical or scientific inquiry has ever stimulated such a profusion of published information so rapidly as AIDS. By the latter half of 1988 the number of articles catalogued in the National Library of Medicine AIDS Bibliography reached nearly 500 per month. Fortunately, exponentially accumulating information has been an extremely effective weapon in the war against this infectious disease. As we considered preparing this volume, we sensed that the new knowledge had carried us at least to "the end of the beginning" of our victory over the human immunodeficiency virus. That seemed to be an appropriate time to assemble the available information on the epidemiology of the infection into a coherent framework, comprehensible by the largest possible number of professionals engaged in health sciences and health care and by interested persons outside the field of health. We viewed the book then—and still view it—simply as another opportunity to focus attention on the peril of AIDS and on the potential for enlightened human responses to it.

December 1988

R.A.K.
D.P.F.

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I

BIOLOGIC AND CLINICAL EXPRESSION

1

The Biology of Human Immunodeficiency Viruses

PATRICIA FULTZ

The causative agent of the acquired immunodeficiency syndrome (AIDS) has been shown unequivocally to be a retrovirus termed human immunodeficiency virus (HIV) (Barre-Sinoussi et al., 1983; Gallo et al., 1984; Levy et al., 1984). Since 1983, when the virus was identified, much has been learned about its molecular structure and biologic properties. The genomes of several isolates of HIV from different areas of the world have been sequenced, proteins encoded in the viral genome have been identified, and their individual functions have been studied. Epidemiologic data and clinical observations on immunologic abnormalities in AIDS patients helped to identify the primary target cells for HIV as $CD4^+$ lymphocytes and cells of monocytic origin, with the CD4 molecule itself serving as the virus receptor (Klatzmann et al., 1984b; Dalgleish et al., 1984; McDougal et al., 1986). HIV has been shown to be cytopathic for some cells in which it replicates, particularly $CD4^+$ T cells. These findings led to a reasonable hypothesis to explain the severe immunodeficiency in persons infected with HIV. This chapter summarizes virus–host interactions and biologic properties of HIV that may influence infection and play a role in disease progression.

THE RETROVIRUS FAMILY

The retrovirus family of human and animal viruses consists of subfamilies—Oncovirinae, Spumavirinae, and Lentivirinae—examples of which are listed in Table 1.1. The oncoviruses historically are classified by morphology, as seen by electron microscopy, into type A, B, C, or D. Spumaviruses have a distinctive morphology, which is similar but not identical to that of type C oncoviruses in its prominent surface projections. Although lentiviruses resemble type D oncoviruses morphologically, the two classes can be distinguished, because intracisternal A-type particles are observed in type D- but not lentivirus-infected cells.

The retrovirus subfamilies can also be categorized by the arrangement of specific genes in their single-stranded RNA genomes. Although all retroviruses possess *gag*, *pol*, and *env* genes that code for core proteins, reverse transcriptase and protease enzymes, and viral envelope proteins, respectively, the lentiviruses appear to

Table 1.1. The Retrovirus Family

Subfamily	Morphologic Type	Specific Viruses
Oncovirinae	A	Intracisternal immature particles (not infectious)
	B	Mouse mammary tumor virus (endogenous)
	C	Simian and Moloney sarcoma; gibbon ape, murine, feline, and bovine leukemia viruses; human and simian T-lymphotropic viruses types 1 and 2
	D	Mason-Pfizer monkey virus, SAIDS retroviruses types 1 and 2 (SRV-1, SRV-2)
Spumavirinae	—	Simian and human foamy viruses
Lentivirinae	—	Maedi/visna, caprine arthritis encephalitis, and equine infectious anemia viruses; simian, bovine and feline immunodeficiency viruses; human immunodeficiency viruses types 1 and 2

Classification is based on morphology, pathogenesis, restriction enzyme maps, gene sequences, and serology.

have a more complex genome organization than other retroviruses. The additional genes, some of which are regulatory, may play a role in the pathogenesis of lentiviruses, which are associated with slowly progressive diseases that often affect the central nervous system. The proviral forms of all retroviruses contain, at both ends of the genomic DNA, direct repeat sequences called long terminal repeats (LTRs), which encode regulatory elements that control virus expression.

The life cycle of retroviruses begins with the binding of the virus to its receptor on the cell surface, followed by internalization and uncoating to reveal the genomic RNA. After viral RNA is converted into linear double-stranded DNA by the reverse transcriptase enzyme, the DNA enters the nucleus, where it circularizes and either remains free (lentiviruses and some oncoviruses) or integrates at random into the host cell's chromosomal DNA (all retroviruses). From its position in the host DNA, the retrovirus proviral DNA can either remain latent or be transcribed and translated into viral messenger RNA and proteins. The *gag* proteins and newly synthesized genomic RNA form immature core particles that move to the cell membrane, where they associate with *env* gene products inserted in the membrane. This complex buds from the cell, the core condenses, and the mature virion is formed. The long latency periods between initiation of retroviral infections and development of disease may be a consequence of insertion of viral DNA into host cell chromosomes, where the virus can remain dormant for extended periods.

THE HIV FAMILY

The HIV family of retroviruses includes not only the isolates originally associated with AIDS (lymphadenopathy-associated virus [LAV], human T-lymphotropic virus type III [HTLV-III], and AIDS-associated retrovirus [ARV]), now termed HIV-1, but also more recently isolated viruses of human (LAV or HIV type 2 [LAV-2, HIV-2] and SBL-6669) (Clavel et al., 1986; Albert et al., 1987) and simian (SIV) (Daniel et al., 1985; Fultz et al., 1986a; Murphey-Corb et al., 1986) origin. Isolates of HIV-2 and SIV are approximately 75 percent homologous to each other

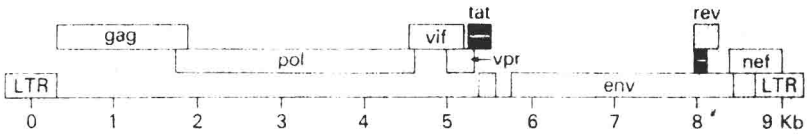


Figure 1.1. Genome organization of HIV-1 showing relative reading frames of individual genes. Both the *tat* and *rev* genes are encoded in two exons, in different reading frames, as indicated by identical shaded areas. The different genes and their functions are: *gag*, core proteins necessary for capsid formation; *pol*, enzymes required for virus replication; *env*, external glycoproteins; *vif* and *nef*, probably regulatory proteins; *tat* and *rev*, regulatory proteins essential for virus replication; *vpr*, unknown function. Kb, kilobases. (Source: Gallo et al., 1988.)

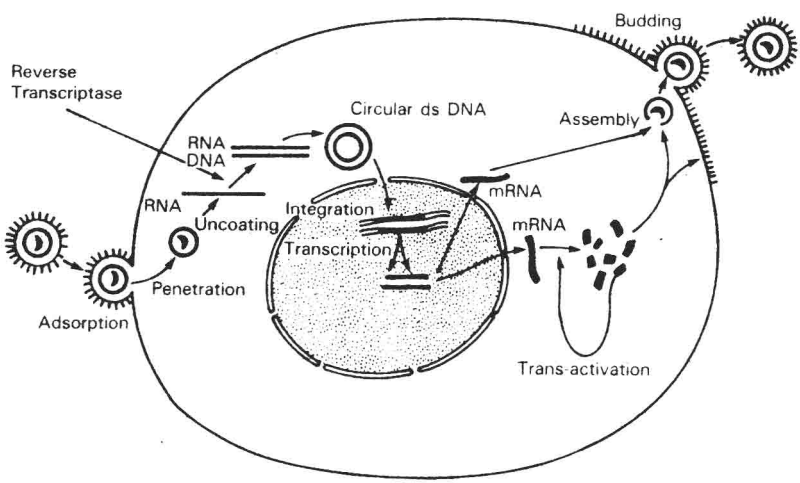
in nucleotide sequence, and both show only about 40 percent homology overall to HIV-1 (Guyader et al., 1987; Chakrabarti et al., 1987). The SIV_{agm} strain appears to be equally divergent from HIV-1, HIV-2, and SIV (Fukasawa et al., 1988). However, both HIV-2 and SIV can clearly cause AIDS or an AIDS-like disease in humans and simians, respectively (Clavel et al., 1987; Letvin et al., 1985; Fultz et al., unpublished data). Although the following discussion is based on studies with HIV-1, in general, the concepts should also be applicable to HIV-2, unless otherwise stated.

Viruses in the HIV family are classified as lentiviruses based on morphology, genomic organization, percentage of nucleic acid identity to RNA (Gonda et al., 1985, 1986; Chiu et al., 1985), and cross-reactivity of antibodies to proteins (Montagnier et al., 1984a) of other lentiviruses. Mature lentivirus particles contain an eccentric, bar-shaped core that is formed after the virus buds from the cell membrane. The envelope glycoprotein of HIV has two properties in common with that of visna virus, the prototype lentivirus: its size, which is much larger than *env* gene products of type C oncoviruses, and a large number of potential glycosylation sites (Sonigo et al. 1985). These two viruses also have an open reading frame, *vif* (formerly designated *sor* or *Q* in HIV and *Q* in visna) between the *pol* and *env* genes (Wain-Hobson et al., 1985; Sonigo et al., 1985; Ratner et al., 1985) (see Fig. 1.1 and Gallo et al., 1988). HIV contains four additional genes not identified in other lentiviruses: *tat* (Arya et al., 1985; Sodroski et al., 1985), *rev* (formerly *trs/art*), (Sodroski et al., 1986b), *nef* (formerly *3'-orf* or *F*) (Franchini et al., 1986), and *vpr* (formerly *R*) (Wong-Staal et al., 1987). An additional open reading frame, termed *vpx* (formerly *X*) and not seen in isolates of HIV-1, was identifed in SIV and HIV-2 (Chakrabarti et al., 1987; Franchini et al., 1987; Guyader et al., 1987). In addition, SIV_{agm} has no *vpr* gene. The *tat* and *rev* genes code for proteins with regulatory functions that are essential for virus replication and probably act at both transcriptional and translational levels. The coding sequences for both of these genes are novel for retroviruses, because they are composed of multiple exons (Arya et al., 1985; Sodroski et al., 1985, 1986b). The functions of the *vif*, *nef*, and *vpr* gene products are not known, but the former two are thought to be regulatory. All of the proteins, including those with regulatory and those with unknown functions, are recognized by serum from some HIV-infected persons.

ROLE OF CELLULAR TROPISM IN PATHOGENESIS AND TRANSMISSION OF HIV

It is well established that HIV preferentially infects and replicates in T lymphocytes bearing the cell surface molecule CD4 (Klatzmann et al., 1984a; Dalgleish et al., 1984). The process by which HIV-1 integrates, replicates and establishes latency in the cell is depicted in Figure 1.2 Infection by HIV is not limited to $CD4^+$ T lymphocytes; infection of cells of monocytic/macrophage origin (Gartner et al., 1986; Ho et al., 1986; Nicholson et al., 1986), some B cells (Montagnier et al., 1984b), and colorectal cells (Adachi et al., 1987) also has been demonstrated. The ability of HIV to infect cells other than T lymphocytes is apparently related to the presence of the CD4 molecule (Maddon et al., 1986), which serves as the receptor for the virus and also plays a role in the cytopathic effects of HIV on $CD4^+$ cells (Lifson et al., 1986). The major surface glycoprotein, gp120, encoded by the *env* gene of HIV, appears to bind directly to CD4 (McDougal et al., 1986). This interaction between gp120 and CD4 not only allows entry of the virus into the cell but also is responsible for syncytia formation (Lifson et al., 1986; Sodroski et al., 1986a) and at least some cell death. Certain strains of HIV-2, including one isolated from a patient with an AIDS-like illness, do not cause cell fusion or typical cytopathic effects on $CD4^+$ cells (Evans et al., 1988; Kong et al., 1988). Direct cell-to-cell transfer of virus via fusion is one mechanism by which the virus may escape immune elimination, particularly by neutralizing antibodies. There is no evidence that other proteins encoded in the HIV genome play a role in cytopathic effects. (See Chapter 2.)

Figure 1.2. Replication and establishment of latency of HIV-1 infection. (Adapted from De Clerq, 1986.)



PATHOGENESIS OF HIV

The pathogenesis of HIV infection is characterized by a long latent period during which CD4+ T-helper cells are gradually lost, resulting in severe immunodeficiency. Efforts to define more precisely the pathophysiology of HIV infections have focused on studies of the natural history of infection in defined high-risk populations and in animal models. The latter consist of HIV infection of chimpanzees (Alter et al., 1984; Fultz et al., 1986c) and, more recently, infection of macaque monkeys with the closely related simian immunodeficiency virus, SIV (Desrosiers and Letvin, 1987). These model systems may provide information on factors that influence progression to AIDS and on features of the immune response necessary for protection against infection and disease. They should also be valuable in the development of prophylactic and therapeutic drugs and vaccines.

To observe extensive replication and cell death in HIV-infected cultures of normal human lymphocytes, the cells must be activated (McDougal et al., 1985). Not all CD4+ lymphocytes will be activated at one time; therefore, this may be one explanation for the gradual loss of CD4+ cells in HIV-infected persons. The body probably fights to maintain a critical balance between loss of CD4+ cells through cytopathicity of HIV or lysis by immune destruction and regeneration of CD4+ cells. It may take multiple stimuli to activate different subsets and to destroy significant numbers of CD4+ helper cells. It is also possible that latent infection by HIV of not only T cells but also monocytes impairs normal cellular function to such an extent that the cells cannot effectively respond to invading pathogens.

Several groups (e.g., Ho et al., 1986; Nicholson et al., 1986) have demonstrated that, in general, HIV is not cytopathic for monocytes/macrophages and replicates to low, often undetectable, levels in in vitro cultures. However, infected monocytes readily transmit infectious virus to susceptible CD4+ cells. Thus, tropism for and cytopathic effect on CD4+ lymphocytes and replication and sequestration in intracytoplasmic vacuoles in macrophages, which serve as reservoirs of infectious virus (Gendelman et al., 1988), are properties of HIV that could account for the progressive loss of helper T cells and resulting immunodeficiency.

Latent infection of monocytes/macrophages by HIV might also provide an ideal mechanism for spread of infection to the central nervous system. HIV has been isolated from brain tissue and cerebrospinal fluid of AIDS patients (Levy et al., 1985a; Ho et al., 1985b), suggesting that the virus is neurotropic. Maddon et al. (1986) demonstrated that CD4 is present on cells in the brain. Most HIV RNA- or antigen-positive cells in brain tissue from infected persons appear to be of monocytic origin (Koenig et al., 1986), but some data suggest that on occasion neurons or glial cells may be infected (Wiley et al., 1986).

Several groups (e.g., Gendelman et al., 1986; Rando et al., 1987; Mosca et al., 1987) have recently shown in vitro that herpesviruses can activate the expression of genes under control of the HIV LTR. These data imply that, in persons infected with both HIV and a herpesvirus, the herpesvirus could activate HIV in latently infected cells, resulting in increased virus production. However, there is no evidence that activation occurs in vivo or that increased virus production results in progression to AIDS. Furthermore, there is no epidemiologic evidence that herpesviruses are cofactors in the development of AIDS.