

How Does HIV Cause AIDS?

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Many questions have been posed about acquired immunodeficiency syndrome (AIDS) pathogenesis. Is human immunodeficiency virus (HIV) both necessary and sufficient to cause AIDS? Is AIDS essentially an autoimmune disease, triggering apoptosis, or is virus infection the cause of T helper lymphocyte depletion? What is the significance of HIV tropism and the role of macrophages and dendritic cells in AIDS? Is there viral latency and why is there usually a long period between infection and AIDS? Is HIV variation a crucial aspect of its pathogenesis and, if so, do virulent strains emerge? Although this article provides few definitive answers, it aims to focus commentary on salient points. Overall, it is increasingly evident that both the tropism and burden of HIV infection correlate closely with the manifestations of disease.

Acquired immunodeficiency syndrome (AIDS) is the end-stage disease of human immunodeficiency virus (HIV) infection. The key to understanding its pathogenesis lies in elucidating the course of infection and the virus-host relation in the years preceding terminal illness. Figure 1 depicts the progression from initial infection to AIDS. Ever since its first description AIDS has been related to depletion of CD4⁺, T helper lymphocytes in the blood (1). We now know that other cells, especially tissue macrophages, become infected by HIV and that there is a considerable viral load in the lymph nodes. HIV infection may cause disease by one or more of a variety of direct and indirect means. However, early in infection, the cellular and humoral immune responses to HIV appear to be effective in limiting viral replication in peripheral blood cells.

Why, then, does AIDS finally develop, and why does it take a long and variable time to do so? There is no dearth of hypotheses to explain HIV pathogenesis. By and large they are not mutually exclusive but require critical examination before being weighted in importance, supported, or discarded. Moreover, there are lessons to be learned from lentivirus infections of animals that raise further questions regarding human disease. Why, for instance, do some horses permanently recover from equine infectious anemia when the virus evolves immune escape variants as readily as HIV? Can the wasting syndrome and brain disease of sheep infected with visna-maedi virus be equated to human AIDS without CD4 depletion?

This article is not intended to provide a detailed description of HIV pathogenesis. A comprehensive review has recently appeared (2). Here I wish to highlight the

emerging consensus on progressive HIV infection and to pose some of the questions that remain to be answered about HIV infection and AIDS in the hope that this may help to sharpen our thinking and to focus further research on important topics.

Is HIV Sufficient to Cause AIDS?

Our lack of understanding of how HIV causes AIDS has led some commentators to query whether HIV infection is sufficient to cause AIDS or whether HIV may be essentially harmless in the absence of other cofactors (3). Indeed, one retrovirologist has concluded that HIV infection is too silent to be the etiologic agent of AIDS at all (4). However, the overwhelming view is that HIV infection is active enough to be directly pathogenic, as I shall argue here, and that the epidemiological evidence for a causal relation between HIV and AIDS is compelling (5).

Some cases of severe unexplained im-

mune deficiency have come to light in persons who test negative for HIV-1 and HIV-2 even by sensitive polymerase chain reaction (PCR) methods for amplifying viral genomes. These rare and sporadic cases must have a different etiology (6), but that does not negate the role of HIV in the global pandemic any more than the existence of hepatitis C virus casts doubt on hepatitis B virus as a pathogen. Besides, AIDS is not a well-known old disease redefined; an outlying HIV⁺ case observed long before AIDS was recognized puzzled his doctors greatly (7).

In any illness that takes years to become manifest in severe form, cofactors would be expected to influence the rate at which disease develops. The other known human retroviral pathogen, human T cell leukemia virus-type I (HTLV-I), causes adult T cell leukemia or tropical spastic paraparesis in fewer than 6% of infected people during lifelong infection. Diseases associated with Epstein-Barr virus are even rarer, but few doubt the role of the virus. It seems curious, therefore, that so much emphasis has been placed on the importance of infectious cofactors for AIDS such as drugs and other infections (3), when more than 50% of HIV-infected people progress to AIDS. Proponents of the idea that *Mycoplasma penetrans* is a potential cofactor have elicited the most fuss in the lay press but its link with AIDS remains controversial (8). Cytomegalovirus (9) and other persistent virus infections (3) are just as likely candidates. Thus there is no strong indication that the

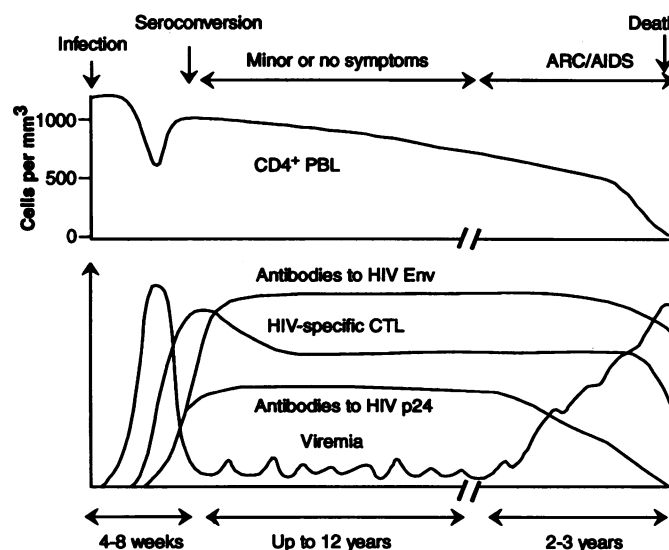


Fig. 1. Schematic course of HIV infection.

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development of AIDS necessarily involves a specific, infecting microorganism besides HIV, although in theoretical model systems the cumulative exposure to infections accelerates the rate of progression to AIDS (10) and may exacerbate disease late in the course of HIV infection.

The various opportunistic infections and opportunistic neoplasms that occur in AIDS are bound to depend on prior or current exposure to the proximate agent, and certain markers of AIDS may indeed depend on independent factors; in other words, HIV acts as the cofactor and not the underlying cause of that symptom. For example, the risk of Kaposi's sarcoma (KS) in Western countries is much greater among HIV⁺ male homosexuals than among HIV⁺ intravenous drug users or hemophiliacs (11). That and other observations argue for a specific, sexually transmitted etiologic agent for KS in which immune suppression (both in AIDS and in transplant patients) is the dominant cofactor for subsequent disease.

Emphasis on cofactors should not obscure the fact that population groups with different lifestyles have similar rates of progression to AIDS. Figure 2 shows that the development of AIDS in homosexual and hemophilic men in the West is indistinguishable, with a mean time from HIV seroconversion to disease development of approximately 9 years. It is thought that AIDS occurs more rapidly in Africa although insufficient cohort data are available to be sure (12). Perinatally infected infants also appear to have a faster rate of progression. Figure 2 also indicates there is a delay in the onset of AIDS in hemophilic patients who acquired HIV at a younger age relative to older individuals. The lag period is followed by a similar rate of progression to AIDS which may result from younger persons having greater CD4 lymphocyte reserves and precursors for renewal.

It is often assumed that there is something special about long-term survivors of HIV infection, and conversely, about those who succumb to AIDS relatively soon after infection. Yet the rates of progression depicted in Fig. 2 are also consistent with a stochastic, random occurrence of AIDS after HIV infection. "Long-term" survival could be pure luck. Nevertheless, I would expect genetic, behavioral, and environmental factors to influence the rate of progression to AIDS among individuals even if HIV is the sole etiologic pathogen. Predisposing and delaying factors are likely to relate both to the infecting HIV strain (see below) and to host traits. For instance, some combinations of major histocompatibility complex (MHC) antigens predispose to earlier AIDS (13); MHC-linked genetic determinants may be an important cofactor in HIV pathogenesis.

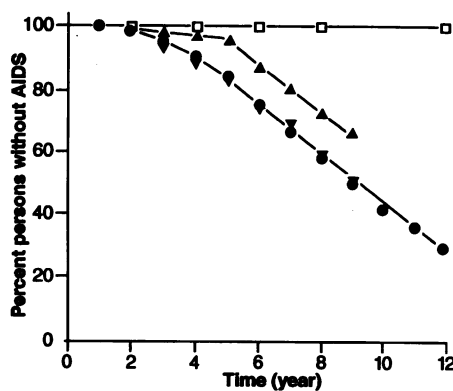


Fig. 2. Proportion of individuals surviving without AIDS plotted with data combined from several U.S. and United Kingdom cohorts (5, 62). ●, HIV⁺ homosexual men; ▼, HIV⁺ hemophilic men who were >20–25 years of age at time of infection; ▲, HIV⁺ hemophilic men who were <20 years of age at time of infection; and □, HIV⁻ hemophiliacs and homosexuals.

Is AIDS an Autoimmune Disease?

A virus can damage its target tissue in at least four ways: (i) Infection can be cytopathic; in other words, the virus kills the cells it infects. (ii) The immune response to infected cells leads to their destruction; for example, the pathogenesis of lymphocytic choriomeningitis virus in mice and of hepatitis B virus in humans is largely a consequence of specific cytotoxic T cells destroying virus-infected cells. (iii) The function of infected cells may be affected without cell death; in the immune system this could result in aberrant signaling via cytokines and cell-to-cell contacts. (iv) The virus may trigger autoimmune destruction through molecular mimicry of cellular antigens to which the host is normally tolerant. In HIV infection the first three mechanisms act in concert to cause AIDS. Although the effect of HIV on the immune system resembles autoimmune disease, it is driven by persistent, active viral expression.

Given that HIV infects and perturbs cells of the immune system, it is hardly surprising that some autoimmune signs are frequently seen in the course of infection (2, 14). AIDS has been likened to a chronic graft-versus-host type of disease (15). The fact that the HIV envelope binds to CD4 and might have small regions of similarity to MHC antigen has led to the idea that the viral envelope stimulates the T cell receptor complex in a manner similar to allogeneic (genetically nonidentical) MHC. In this respect it might act like a superantigen to activate or delete T cells in an antigen-independent manner (15), and those patients with inappropriate MHC haplotypes and T cell receptor repertoires would progress more rapidly to AIDS. As activated lymphocytes are more permissive to HIV replication, alloactivation

would act synergistically with more direct cytopathic effects of the virus. However, the evidence for alloactivation is weak.

Another intriguing finding with HIV-infected asymptomatic persons is that the lymphocytes are primed to undergo programmed cell death (apoptosis) when stimulated in culture (16). Apoptosis in the thymus is a natural process that eliminates autoreactive T lymphocytes to establish self-tolerance. Ameisen and Capron (16) have postulated that apoptosis is a marker of immune cell dysfunction; HIV infection leads to early priming of lymphocytes for suicide upon further stimulation. They argue that if apoptosis also occurs in vivo to a higher degree than normal, it could account for helper T cell depletion. However, a major fraction of peripheral blood lymphocytes (PBLs) from HIV⁺ persons that undergo apoptosis surprisingly appear to be uninfected CD8⁺ lymphocytes (17), and apoptosis may be triggered by HIV associated with antigen-presenting cells. The overall significance of the sensitivity of T lymphocytes to apoptosis *ex vivo* has yet to be clarified.

Which Cell Types and Tissues Become Infected by HIV in Vivo?

The CD4 differentiation antigen of the T lymphocyte serves as the major cell surface receptor for HIV, which helps to explain the depletion of CD4⁺ T helper lymphocytes in AIDS (18). Even during the asymptomatic phase, many HIV⁺ individuals show a selective defect in T cell response to recall antigens (19). Memory T helper cells (which are poised to respond to secondary exposure to antigen) may be preferentially infected over naïve cells, and different T helper subsets respond in complex ways to different stimuli at different stages of HIV infection (20). The other major cell type that becomes infected by HIV is the macrophage (2, 21). Tissues such as the lung and brain harbor HIV mainly in macrophage-type cells (alveolar macrophages and microglia, respectively).

Both T lymphocytes and macrophages become infected via CD4, as shown by the ability of monoclonal antibodies to CD4 to block HIV entry into these cells in culture (2, 21). However, Fc and complement receptors may also be involved in macrophage infection by opsonized virus, as most of the plasma virus particles in seropositive individuals will have bound antibodies. Several CD4⁻ cell types can be infected by HIV *in vitro*, including epithelial and endothelial cells as well as astroglial, oligodendroglial, and neuronal cells from the central nervous system (CNS) in which galactocerebroside acts as an HIV receptor. Infection of these cell types *in vivo* remains

controversial (2, 21). Blood dendritic cells and their counterparts in the skin and mucous membranes, the Langerhans cells, have been reported to support HIV replication (22), but this has been questioned by Steinman's group (23), which failed to confirm HIV replication in dendritic cells.

It has long been known from electron microscope and immunofluorescence studies (24) that HIV is found in massive amounts in the lymph nodes, even in the asymptomatic phase of infection. In addition to helper T lymphocytes and macrophages, virus particles are frequently associated with follicular dendritic cells (FDC), which have a distinct lineage from blood dendritic cells. These findings have recently been confirmed by molecular techniques (25). Thus active HIV replication is evident in lymph nodes at all stages of infection.

As proviral DNA is not detectable in FDC (25), it seems likely that the FDC entrap HIV particles and activate B lymphocytes, as previously suggested (26). Similarly, antigen-presenting cells derived from blood dendritic cells may capture and present HIV particles to clusters of helper T cells in lymph nodes, whereupon viral replication in the lymphocytes leads to their depletion *in situ* by viral cytopathicity and apoptosis (23, 27).

Is There a Latent State of HIV Infection?

It is likely that some T cells harbor genuinely latent HIV genomes, that is, DNA proviruses that do not express viral RNA. However, viral latency does not occur in all infected cells, as is the case with varicella-zoster virus infection during the period between chicken pox and shingles. Resting CD4⁺ T cells in culture become abortively infected, resulting in arrested, incomplete proviruses, unless the cells are activated within a few days of infection (28). *In vivo*, however, latently infected PBL can be detected that carry complete, integrated provirus (29). These are probably memory cells that may have become infected while in an active state and that became quiescent before virus replication could be completed. In contrast, macrophages can become productively infected by HIV in a mature, nonproliferating, but immunologically active state (30). Notwithstanding the true latency of HIV in individual resting lymphocytes, the infection is not latent during the asymptomatic phase. Actively expressed HIV is found in lymph nodes and other lymphoid organs and in tissue macrophages at all stages of infection, indicating a much higher level of virus activity than in circulating T cells (24, 25). Plasma viremia also varies, showing transient small peaks and troughs (Fig. 1). In a recent study, in

which quantitative PCR was used, viremia was detected at all stages with highest virus particle titers before seroconversion and in AIDS-related complex (ARC) and AIDS (31). It will be important to determine whether the immune system is failing to clear virus replication or whether ongoing infection is regenerated from latent proviruses as T cells become activated.

The common usage of the term asymptomatic for patients without opportunistic infections, dementia, or severe weight loss does not mean that there are never signs of infection or relatively minor symptoms such as diarrhea and night sweats. Peripheral generalized lymphadenopathy syndrome (PGL or LAS) is a feature of HIV infection that was recognized early in the AIDS epidemic; hence the former name lymphadenopathy virus (LAV) for the first HIV isolate, which was made from a lymph node biopsy (32). Thus, there are signs of HIV activity throughout the course of the infection.

What Causes T Helper Cell Depletion?

This question has generated much debate and a plethora of explanations. The precise mechanism by which HIV kills cells may not matter in understanding how HIV causes AIDS, but it may be important for determining therapeutic strategy. Direct killing could be due to a cytolytic effect of the virus and to immune attack on virus-infected cells. Indirect killing of uninfected cells could be due to adsorption of shed gp120, cell fusion, interference with T helper and dendritic cell function, or induction of T suppressor cells.

HIV can cause direct cytopathic effects in activated CD4⁺ T cells in culture, either in single cells (33) or by syncytium induction (18, 21). Syncytia soon die in culture and would be expected to have an even shorter half-life in the blood, although they are sometimes seen in the brain and other tissues (2, 14). By incorporating noninfected cells into syncytia, a single gp160-expressing cell can eliminate many uninfected CD4⁺ cells, the so-called bystander effect. HIV-expressing cells will also be killed by HIV-specific cytotoxic T cell responses, which are the normal mechanism for eliminating virus-infected cells by cell-mediated immunity. Antibody-dependent, complement-mediated cytotoxicity and other humoral immune effects may also help to remove HIV-infected cells. Then there is the apoptotic phenomenon already alluded to, although its significance *in vivo* is not clear.

T cell precursors in the thymus or peripheral pools may be infected with HIV and therefore fail to proliferate and replenish the mature T helper lymphocyte popu-

lation. Defective antigen presentation (see below) will also inhibit T cell proliferation. During the asymptomatic period there is a fairly steady decline in numbers of circulating T helper lymphocytes (Fig. 1) often followed by a steeper decline in ARC and AIDS. Cell replenishment does not match cell loss.

Among the CD4⁺ T lymphocyte subsets, HIV appears to infect and affect the function of memory cells over naïve cells (20). Recent evidence also indicates that the effects of HIV on T cell responses during the asymptomatic stage reflects depletion or anergy of T_H1 (helping cellular immunity) in proportion to T_H2 (helping humoral immunity) as also seen in many parasitic infections (27). This may help to explain the persistent activation of B cells and the perturbation of T cell responses to antigen-presenting cells. The depletion of CD4⁺ T cells by HIV may affect the overall homeostasis of T cell populations, as recently reviewed by Stanley and Fauci (34).

What Role Do Macrophages and Dendritic Cells Play in AIDS?

Infected macrophages could be important reservoirs outside the blood and as carriers of HIV to different organs (the Trojan horse metaphor). These nonproliferating, mature cells can sustain HIV production *in vitro* for a considerable time without being killed by the virus. Cytokine secretion by infected macrophages is aberrant (35), which can lead to a cascade of secondary effects that are likely to be important in the wasting syndrome ("slim disease") and CNS disease seen in many AIDS patients. Indeed, the wasting and CNS attributes of human AIDS closely resemble the visna-maedi syndrome in sheep. Visna-maedi virus and equine infectious anemia virus are macrophage-tropic lentiviruses that do not induce severe depletion of CD4⁺ T cells (36). In a recent report (37) the wasting syndrome categorized by >10% weight loss was not correlated with falling CD4 T cell counts, but with interferon-mediated activation of macrophages as measured by urinary neopterin levels. Of course, the separation of T cell immune deficiency from wasting and CNS disease is a simplistic view that ignores the intricate relation between antigen-presenting cells and effector T lymphocytes. Nonetheless, it may be useful to think of the enteropathic, wasting, and brain diseases as being linked to macrophage infection and distinct from the severe immunodeficiency caused by T helper cell depletion.

Macrophages act as antigen-presenting cells particularly to memory T cells in the periphery. This interaction does not appear to be significantly impaired during the

asymptomatic phase of HIV infection. In contrast, Knight's group and others (22, 27) argue that the function of dendritic cells and macrophages in bringing and presenting antigen to naïve T cells in the lymph nodes is affected early in the course of HIV infection. Antigen-presenting cells would serve both as a reservoir of HIV and as an effector of immune dysfunction, inducing anergy of T_H1 and activation of T_H2 lymphocytes (27). Patients may survive on their memory T cell responses, but when these cells eventually become depleted, the lack of recruitment of new memory cells that should normally have occurred through the interaction of antigen-presenting cells with naïve T cells could contribute to immune deficiency.

Is Genetic Variation Important in Pathogenesis?

Lentiviruses are notoriously variable in genome sequence. Within one infected host, millions of genetic subtypes exist. This "swarm" of genomes is called a quasi-species (38), although I prefer the old-fashioned term "population polymorphism." Thus the genetic diversity of HIV *in vivo* is vast, and the population contains a large proportion of defective genomes. As soon as HIV is grown in culture there is bound to be selection for a smaller number of subtypes. On this account, Wain-Hobson and colleagues have stated that "to culture is to disturb" (38). While agreeing that this is undoubtedly the case, I would also say that "to culture is to discern"—the replication-competent viruses from genomic "noise."

There are three main aspects of genetic variation of HIV that could influence pathogenesis. (i) The development of tropisms for efficient replication in different cell types will affect the qualitative attributes of the syndrome—immune deficiency, wasting, enteropathic disease, and CNS disease. (ii) Antigenic variation can lead to escape from specific humoral and cell-mediated immune controls. (iii) Strains that differ in virulence may affect the pace and severity of disease.

In my opinion, too much emphasis has been placed on antigenic variation in isolation from considerations of viral titer, cell tropism, and virulence. For example, it is widely held that variation in the V3 loop sequence in gp120 is driven by escape from immune responses, which has been seen *in vitro* and *in vivo* (39). However, the V3 loop also contributes to the determination of lymphocyte versus macrophage tropism and, among T lymphotropic strains, to the emergence of highly cytopathic, syncytium-inducing variants (2, 14, 40). In primary HIV infection, before seroconversion, there is uniformity of genome sequences

within an infected individual (41), probably due to a small founder population and selection of the fastest growing virus. We do not yet know to what extent the ensuing variation is random for an expanding population, driven by immune escape, and driven by adaptation to new cell types.

The source of variation is the infidelity of reverse transcriptase, which has no editing mechanism for transcriptional errors (38). Once the quasi-species has established a degree of variability, however, genetic recombination (another attribute of retroviruses) may allow new combinations of mutations to be selected. For instance, one variant showing, for example, zidovudine resistance in the *pol* gene could recombine with one showing escape from neutralization in the *env* gene. Recombination may be particularly rapid with syncytium-inducing strains as cell fusion will permit reassortment of RNA genomes derived from different proviruses. Perhaps that is why these strains become resistant to zidovudine more rapidly. Recombination as a source of genetic variation merits further investigation.

What Is HIV Tropism?

Distinct substrains of HIV within the infected body differ in their tropisms for different cell types. Thus HIV isolates from the CNS including the cerebrospinal fluid (CSF) preferentially grow in macrophages in culture, whereas HIV isolates obtained from peripheral blood lymphocytes (PBL) that have been stimulated by phytohemagglutinin (PHA) and interleukin-2 (IL-2) propagate best in the same cell type (2). Such viruses are called macrophage-tropic and T cell-tropic, respectively. In reality, there is confusion about the terminology of HIV tropism, which, despite elegant molecular analysis of virus strains and recombinants, has tended to obscure our understanding of the way HIV propagates *in vivo*.

First, there is actually a broad spectrum of the relative efficiency of HIV replication between T lymphocytes and macrophages that is influenced by the cell type used for initial culture (42). Second, there is confusion between the capacity of HIV to grow in immortalized or leukemic T cell lines and replication in primary PHA + IL-2-stimulated PBL; only a minority of HIV isolates, which are adapted in the laboratory, grow in T cell lines, whereas nearly all isolates including macrophage-tropic strains grow in PBL. Third, primary isolates from PBL of asymptomatic persons tend to replicate slowly and attain lower final titers in culture, whereas isolates from AIDS patients often grow rapidly to high titers; they have been named slow-low and rapid-high strains (43). The latter are the viruses that most quickly adapt to growth in T cell lines.

However, both slow-low and rapid-high viruses grow to high titer in highly activated primary T lymphocytes, as in mixtures of cord-blood lymphocytes or PBL from two donors, when allogeneic activation occurs (43). Fourth, HIV isolates can be classified as syncytium-inducing (SI) and non-syncytium-inducing (NSI). SI isolates are obtained more frequently but not inevitably in patients with AIDS and ARC (44). Rapid-high isolates often have the SI phenotype or acquire it during early passage *in vitro*. The SI/NSI classification is now gaining general acceptance.

Nearly all types of HIV isolate propagate well in primary, stimulated PBL (42, 43). One real distinction is that most NSI and macrophage-tropic strains do not replicate in established T cell lines. Conversely, T cell line-adapted, SI isolates replicate poorly in macrophages, although Lazdins *et al.* (30) report that this restriction can be overcome by cultivating macrophages with transforming growth factor β .

Thus, the differential cellular tropisms of HIV are not as hard and fast as might be thought. The rapid-high SI virus strains often presage AIDS, appearing before the final, rapid depletion of CD4 lymphocytes in the circulation (44). Whether SI viruses are primarily a cause or a consequence of immune suppression, it is likely that they exacerbate AIDS once they take hold as the major virus population (45).

Animal models of lentivirus infection may help to elucidate viral tropism and pathogenesis, and I have already alluded to visna-maedi disease. The use of severe combined immunodeficient mice transplanted with human lymphoid cells or organs (Hu-SCID mice) may help to illuminate HIV pathogenesis (46), although I once queried whether Hu-SCID mice are more than expensive, furry culture flasks for PBL. It is now clear that these mice allow lymphoid development from implants such as human fetal thymus, and the system is susceptible to infection and depletion by HIV. However, the Hu-SCID model resembles primary, pre-seroconversion HIV infection rather than AIDS.

Simian immunodeficiency virus (SIV) infection of macaques provides an animal model that can aid our thinking on pathogenesis in relation to viral tropism, although there are differences, such as V3 being invariant in SIV (47). Narayan's group (48) demonstrated that if SIV recovered from a molecular clone with a T cell-tropic phenotype was inoculated into the brains of macaques, it did not result in infection. If, however, the virus was inoculated intravenously, infection of lymphocytes occurred. When macrophage-tropic variants appeared 3 months later, they were able to replicate in the brain upon inocula-

tion into naïve monkeys. Thus tropism variants analyzed and cloned *in vitro* do have significance *in vivo*.

As Daniel *et al.* (49) have recently shown, specific deletion of *nef* or other genes from SIV dramatically affects viral replication *in vivo* and protects the animals against challenge with a virulent strain. Studies of individual viral genes will help us to elucidate the process of pathogenesis, but it may be a misconception to think of one or the other of the HIV or SIV genes as a "pathogene," in the same sense as the oncogenes of acutely transforming retroviruses. Deletion of any viral gene that is required for efficient replication *in vivo* will surely lead to virus attenuation.

Does Antigenic Diversity Cause AIDS?

Considerable antigenic variation is evident in all lentivirus infections. With HIV, there is evidence for selection of escape mutants from neutralizing antibodies (39) and possibly for escape from CTL as well (50). Antigenic variation presents a considerable problem for vaccine development as it will be essential to induce broadly cross-protective immunity against the diverging strains as HIV spreads across the world. Antigenic variation is also postulated to account for HIV pathogenesis. Initially, the host raises excellent immune responses to HIV, and that leads to the long asymptomatic period upon seroconversion. Antigenic variation permits escape from immune responses, and the resurgence of sequential virus variants could lead to AIDS.

An interesting analysis of antigenic variation as a contributor to pathogenesis comes from the mathematical modeling of Nowak and May, based on antigenic diversity thresholds (51). Basically, they argue that the generation of antigenic variants causes an asymmetric interaction between immunological and viral diversity. While each virus strain impairs most immune responses by diminishing MHC-II-restricted T helper cells, strain-specific immune responses can only control specific virus variants. Eventually a diversity threshold is reached when the immune system fails to control the virus population. According to this model, HIV infection is an evolutionary process that determines the time scale from infection to disease.

Although Nowak and May can fit their model mathematically for all outcomes (acute disease, delayed disease, and no disease), I am wary of accepting this Panglossian view in which perturbations of group- and strain-specific immune responses yield quite different pathogenic consequences. The genetic diversity and load of SIV in asymptomatic African monkeys appears to

be similar to humans (52), yet only the latter develop AIDS. Chimpanzees can be infected with HIV-1 and immune escape mutants occur, but they have not yet developed disease. I therefore suspect that something besides a threshold of antigenic diversity leads to pathogenesis. Disease might be a consequence of sheer viral burden, host immunogenetics, or possibly allostimulation or APC dysfunction because PBL from infected chimpanzees do not exhibit apoptosis *ex vivo* (16, 53). This may also be true of other lentivirus infections; asymptotically infected sheep from Germany introduced visna-maedi virus into the relatively inbred Icelandic sheep with devastating effects. These considerations require discussion in terms of the evolution of virulence and tolerance in host-virus relations (51, 54).

Do HIV Strains Differ in Virulence?

Until recently, variation in virulence has been largely an ignored parameter in the debate about HIV pathogenesis. Yet almost all pathogens produce virulent and more benign variants. With HIV and related lentiviruses, the quasispecies are so diverse that different grades of virulence could be generated within one individual.

The clearest evidence for lentivirus variants that heritably differ in their pathogenic effect comes from experimental SIV infections. The Pbj14 strain of SIV kills macaques in 10 to 14 days by causing a massive lymphoid infiltration of the gut that results in hemorrhagic diarrhea. When given rehydration therapy, however, the monkeys can survive to develop more conventional AIDS 3 to 4 months later. The point of the argument is not that the acute disease differs from AIDS but that it is a reproducible property of the virus, even of an infectious molecular clone (55). Other molecular clones of SIV also differ in virulence for inducing AIDS (49).

There are a few cases of fatal primary infections of HIV (56), but the virus has been insufficiently characterized to say whether this was a result of virulent strains or exceptionally susceptible hosts. Conversely, a cluster of long-surviving persons infected by HIV from a single source has been reported in Australia (57), raising the possibility that this virus is relatively apathogenic, or slow to cause disease. HIV-2 is thought to have a slower time course to AIDS than HIV-1 (2), and recently, SIV-like genomes were described in Liberians who maintain a very low load of unculturable virus and show no symptoms of disease (58).

I have already discussed the variation in disease spectrum that may reflect the balance of viral tropisms within the quasispe-

cies. It seems clear that variants can differ in virulence and in the type of disease they are capable of inducing. Roos *et al.* (59) found that NSI and, more seldom, SI viruses occur in primary infections from transmitters with both types of virus; their preliminary evidence suggests that the recipients with SI viruses may show a more rapid decline in CD4⁺ T cells.

One may ask whether and how the clock is reset each time HIV transmits from one person to another. The transmission of virulent subtypes of HIV, and of drug-resistant variants, will require further study. Given that we have only witnessed the beginning of the HIV pandemic, and that the scope for viral variation within and between humans is enormous, novel pathogenic HIV variants might emerge (60). One may also hope that when the rate of transmission slows, less virulent strains will predominate, as has been suggested for HIV-2 (54).

Synthesis

I have outlined several possible contributing factors in HIV pathogenesis: (i) other infections activate HIV by stimulating the lymphocytes that harbor the proviruses; (ii) the HIV envelope itself nonspecifically activates lymphocytes in a manner similar to an allogeneic reaction—this renders the cells sensitive to apoptosis; (iii) antigen-presenting cells (macrophages and dendritic cells) produce aberrant cytokine signals, causing changes in T cell responses including a switch from T_H1 to T_H2 activity; (iv) memory T lymphocytes are not replenished as fast as they are killed by HIV or immune responses to HIV antigens; (v) HIV develops sequential escape mutants to keep one step ahead of the immune response; (vi) cumulative antigenic diversity in the evolutionary dynamics of HIV overcomes the immune system; and (vii) virulent cytopathic HIV variants emerge. We need to devise experiments that would allow us to distinguish between some of the models. A common feature among them is that persistent HIV replication occurs. It generates conditions that promote its continued growth; in other words, HIV eventually becomes its own opportunistic infection.

Almost all the models involve unbalanced immune activation as a prelude to immune collapse. An exception may be the down-regulation of lymphocytes by affected antigen-presenting cells (22), but even here, differential effects on naïve and memory cells could lead to simultaneous activation and anergy in different T cell subsets (27). I have also postulated that severe immunosuppression resulting from a deficiency in T cells and the wasting/CNS disease may be two distinct attributes of AIDS. If that is the

case, distinctive therapeutic approaches might be sought. And if immune alloactivation by HIV is a significant factor, "therapeutic vaccination" with envelope-based immunogens might exacerbate the disease. An excellent review by Angela McLean on "the balance of power between HIV and the immune system" has just appeared (61), in which concepts similar to those reviewed here are placed within the context of a simple mathematical model.

In conclusion, the foregoing discussion illustrates the complexity of HIV infection and the many ideas on how the virus causes AIDS. There are enthusiasts for each of the different aspects, and it is too early in the epidemic and in research to be dogmatic about mechanism. Indeed many of the models of HIV pathogenesis are not mutually exclusive. We are like the blind men who encountered an elephant: Each of us had a different image of AIDS because we could not grasp the whole. The emerging view, however, is that a progressive HIV burden involving first activation and eventually destruction of the immune system is what lies behind AIDS.

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Scientific and Social Issues of Human Immunodeficiency Virus Vaccine Development

Barton F. Haynes

Development of a preventive immunogen for human immunodeficiency virus (HIV) infection is a national priority. The complexities associated with HIV host-virus interactions, coupled with the rapid progression of the HIV epidemic worldwide, have necessitated lowering expectations for an HIV vaccine that is 100 percent effective and have raised important scientific and nonscientific issues regarding development and use of preventive and therapeutic HIV vaccines.

HIV infection is preventable (1, 2). In spite of this, HIV is spreading worldwide at an alarming rate, and projections of the magnitude of the pandemic by the year 2000 are staggering (3). The development of a preventive HIV vaccine (an immunogen administered to HIV-uninfected individuals to prevent infection) is a national priority. Efforts have also begun to develop therapeutic HIV vaccines, whereby HIV-infected individuals would be treated with immunogens designed to boost salutary anti-HIV immune responses, decrease virus-infected cells, and either eradicate HIV or prolong the time until development of acquired immunodeficiency syndrome (AIDS) (4-6).

HIV Preventive Vaccine Development

The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use. What has been developed are (i) promising experimental immunogens and (ii) clear ideas of what the central questions are that should be asked in ongoing and planned human clinical trials (7). Whereas traditional non-HIV vaccine development tracks have led to successful killed or attenuated immunogens in spite of lack of

knowledge of pathogenic mechanisms or correlates of protective immunity (such as for the development of vaccines for smallpox or polio) (8), the emergent nature of the HIV pandemic, coupled with a plethora of critical unknowns, has forced investiga-

tors to pursue several vaccine tracks simultaneously in hope of the rapid development of a successful preventive HIV vaccine (9, 10) (Fig. 1).

Scientific Problems of HIV Preventive Vaccine Development

Although more is known about HIV than almost any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventive vaccine.

Optimal requirements for a preventive vaccine. A successful preventive HIV vaccine should be safe and effective for the prevention or quick eradication of initial HIV infection by multiple HIV strains, regardless of HIV exposure by mucosal or parenteral routes (9, 11-17). It is important to emphasize, however, that most vaccines prevent disease, not infection. Thus, a successful HIV vaccine may not prevent establishment of infection but still may prevent the development of AIDS. For the

Tracks For Vaccine Development

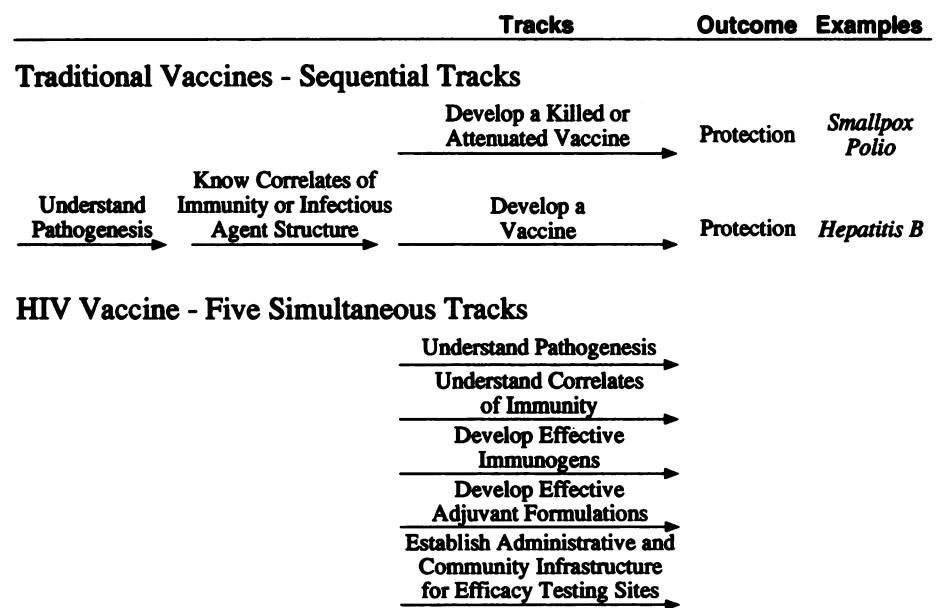


Fig. 1. Approaches to vaccine development. Traditional vaccines either use successful approaches without knowledge of pathogenesis or correlates of immunity (such as with the development of the smallpox and polio vaccines) or proceed in sequential tracks of understanding aspects of pathogenesis, correlates of immunity, or infectious agent structure before development of an effective immunogen (such as with the hepatitis B vaccine). In contrast, HIV vaccine development is proceeding along several simultaneous tracks to maximize the chances of rapidly developing a successful preventive vaccine.

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