Pathogenesis of HIV Disease: Opportunities for New Prevention Interventions

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Current efforts to prevent human immunodeficiency virus (HIV) disease, which largely focus on altering human behavior, have had some notable successes yet have failed to halt the spread of the acquired immunodeficiency syndrome pandemic. A greater understanding of the pathogenesis of HIV disease is providing us with the scientific rationale for additional approaches to prevention. Some of the approaches discussed in this article are available now. For example, we have the means to screen for and treat other sexually transmitted diseases that increase vulnerability to HIV, adult male circumcision is readily available in most properly equipped hospitals, and antiretroviral agents that decrease the viral load help prevent transmission from pregnant women to their infants. Other approaches discussed are under investigation. For instance, numerous topical microbicides are in various stages of development, incremental progress is being made toward creation of an HIV vaccine designed to prevent HIV transmission or slow the course of disease in people who become infected, and studies are under way to evaluate the risks and benefits of prophylactic antiretroviral therapy in individuals at high risk for HIV disease.

Despite rigorous and multifaceted approaches to the prevention of HIV infection, ~40,000 new infections occur annually in the United States, a number that has not changed significantly in >15 years [1]. Globally, the picture is even more disturbing, with ~4.3 million new cases of HIV infection in 2006, exceeding the total in 2004 by 400,000 [2]. It is imperative that we address these dismal statistics.

Prevention methods that have been successful in certain populations need to be adapted in order to target other groups and must be provided to more people. Worldwide, <20% of individuals who are at risk of becoming infected with HIV have access to basic prevention services, which, even when available, are confounded by complex societal and cultural issues [2]. Increased public education efforts and attempts to

modify behavior, more-widespread use of condoms, programs for treatment of substance abuse, and efforts to make clean syringes available are vital. Opt-out testing for HIV infection, discussed elsewhere in this supplement [3], is expected to have a major impact on detection and, therefore, transmission.

Concomitantly, it is important to pursue prevention approaches that are based on our growing understanding of the pathogenic mechanisms of HIV disease. Such strategies include the identification and treatment of coinfections, including sexually transmitted infections; the use of topical microbicides; the circumcision of men; the use of antiretroviral drugs for preexposure prophylaxis; the reduction of the viral load in order to decrease transmission rates; and the development of vaccines (table 1). These modalities focus on the pathogenesis of HIV disease, in the sense that they involve preventing the initial entry of HIV into the body, blocking the spread of infection, or slowing the progression of disease once infection is established.

EARLY PATHOGENIC EVENTS: A WINDOW OF OPPORTUNITY

The early events in HIV disease take place rapidly, and once they occur infection is permanently established

Table 1. Behavior-based and pathogenesis-associated approaches to preventing HIV infection.

Behavior
  Increased implementation of education programs and attempts
    to modify behavior
  Use of condoms and other barrier methods
  Treatment and prevention of drug and alcohol abuse
  Clean syringes (i.e., needle-exchange programs)
Pathogenesis
  Interruption of transmission from mother to child
  Use of topical microbicides
  Performance of male circumcision
  Use of prophylactic antiretroviral therapy
  Treatment of sexually transmitted diseases and other
    coinfections
  Creation and uptake of a vaccine

[4]. The events associated with primary HIV infection are likely critical determinants of the subsequent course of HIV disease. Preventing or interfering with these early events is an important goal of all prevention efforts that focus on pathogenic events.

Worldwide, HIV is most often transmitted during sexual activity, and dendritic cells at or near the mucosal surface of the involved sites play an important role in the initiation of HIV infection [4, 5]. These cells bind with high affinity to the HIV envelope glycoprotein gp120 and can retain infectious particles for days, thus facilitating the presentation of the virus to susceptible cells. The replication cycle of HIV in its target cell begins with the binding of viral gp120 to the CD4 molecule, its receptor on the host-cell surface. Once gp120 binds to CD4, the glycoprotein undergoes a conformational change that facilitates its binding to a cellular coreceptor. Fusion with the host cell membrane follows, and infection is established. An early burst of viremia and rapid dissemination of virus to lymphoid organs, particularly the gut-associated lymphoid tissue, are major factors in the establishment of the chronic and persistent infection that is a hallmark of HIV disease (figure 1) [6–8]. Despite the vigorous cellular and humoral immune responses seen during primary HIV infection, the virus succeeds in escaping immune-mediated clearance. Hence, once infection is established, it is never eliminated completely from the body [6].

ROLE OF IMMUNE ACTIVATION

Paradoxically, HIV seems to thrive on immune activation. Indeed, chronic immune activation is a hallmark of HIV disease and results in increased viral replication and immune cell depletion, immune cell dysfunction, and aberrant lymphocyte turnover [6]. In addition to endogenous factors, such as the effects of proinflammatory cytokines, exogenous factors, including the direct interaction between the HIV envelope and

various cell types and the effects of other infecting microbes, are associated with heightened cellular activation and thus may have important effects on HIV disease pathogenesis [6]. Treating coinfections that potentially increase immune activation and provide a permissive environment for HIV replication is a promising, pathogenesis-associated approach to preventing HIV disease. In particular, there is considerable epidemiologic evidence for a link between the presence of other sexually transmitted diseases, particularly genital-ulcer diseases, and the risk of HIV transmission [9]. Recent studies have strengthened the evidence for this association. For example, in a 7-year prospective cohort study of acute HIV infection in Pune, India, Reynolds et al. [10] reported that subjects with recent or incident syphilis had a >4-fold increased risk for HIV acquisition. This increased risk was strong after controlling for other sexual risk behaviors. In an earlier study in Pune, this team found that recent incident herpes simplex virus–2 (HSV-2) infection was associated with a ~4-fold increased risk of HIV acquisition [11]. Interestingly, in this study, the risk of HIV infection was increased for individuals who were asymptomatic for HSV-2 infection (i.e., persons who did not have clinically apparent or self-reported genital ulcers), as well as for individuals with symptomatic HSV-2 infection. It had been assumed that the biologic mechanism for an increased risk of HIV infection in individuals with sexually transmitted diseases (STDs) was the impaired integrity of the mucosa. This and other studies suggest that additional mechanisms, such as immune activation, also may play a role. The prevention and treatment of STDs—both ulcerative and nonulcerative—offers promise as a strategy for preventing HIV infection [9].

Increasing evidence links other infections (e.g., helminthic infections, tuberculosis, and malaria) with increased susceptibility to HIV infection or worsening progression of HIV disease [12, 13]. Bentwich and colleagues [13, 14] have postulated that chronic infections, particularly helminthic infections, increase the risk of HIV transmission by causing chronic immune activation that results in increased plasma viral load. Helminthic infections also may increase susceptibility to HIV; for example, our laboratory collaborated with other laboratories to show that filariasis, an extracellular parasitic disease, increases the susceptibility of human peripheral blood mononuclear cells to HIV infection in vitro [15]. Although studies of antihelminthic treatment in HIV-infected individuals have had conflicting results with regard to viral load reduction [16], the inherent benefits of "deworming," in addition to the possible benefits for preventing HIV infection and managing HIV disease, argue for larger-scale testing of this approach [14].

The prevention and treatment of tuberculosis and malaria also may have an important role in preventing HIV infection [12]. Immune activation by *Mycobacterium tuberculosis* increases HIV plasma viremia and quasi-species diversity in coin-
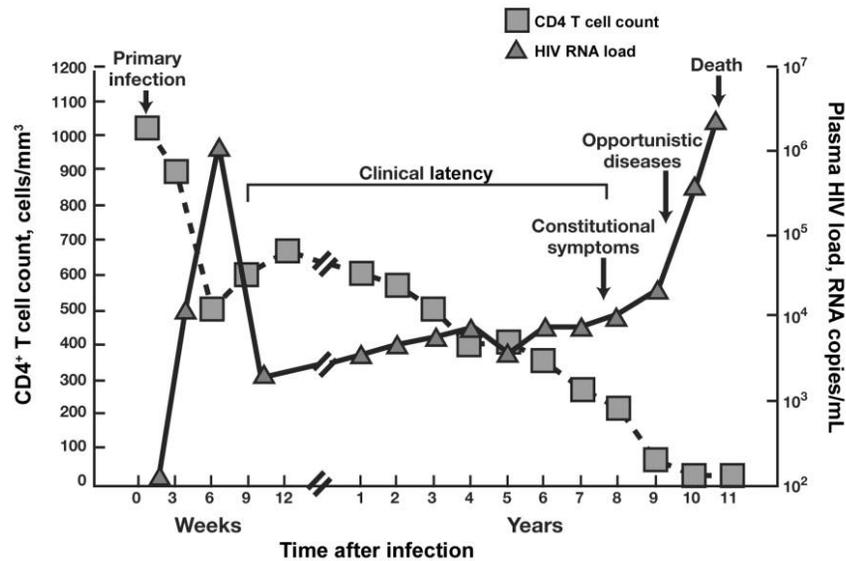
Figure 1. The typical course of HIV infection without intervention. The events associated with primary HIV infection are likely critical determinants of the subsequent course of HIV disease. Adapted from the following article with permission from the American College of Physicians: Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med 1996;124:654–63.

fected people, potentially increasing both the rate at which HIV disease progresses and the risk of HIV transmission to others [17]. In one study, our laboratory measured the plasma viral load in HIV-infected individuals before, during, and after the development of tuberculosis and found a 5–160-fold increase in viral replication during the active phase of tuberculosis [18]. These and subsequent data highlight the importance of prophylactic tuberculosis therapy in HIV-infected individuals with latent *M. tuberculosis* infection, which not only may control the spread of tuberculosis but also may decrease the rate of viral replication and thereby decrease the risk of HIV transmission. Episodes of acute malaria also have been associated with increases in HIV load that might accelerate HIV disease progression and facilitate transmission [19]. Such studies of HIV-infected individuals coinfected with "tropical diseases" may not pertain directly to the United States, where malaria, tuberculosis, and parasitic diseases are relatively rare, but they build on abundant in vitro data that aberrant immune activation facilitates replication of HIV [13, 14]. Treatment of HIV coinfections—and, ultimately, the creation and use of vaccines to prevent coinfections—is a possible HIV disease prevention modality being intensively studied by many research groups [12–14].

TOPICAL MICROBICIDES

It is clear that use of topical microbicides would be an especially important method of prevention for women who are otherwise dependent on male-controlled modalities of protection, such as use of a male condom or allowing the use of a female con-

dom. There is significant activity in this field: a recent survey found 14 candidate microbicides in clinical development, several of which are being evaluated in phase 2, phase 2B, or phase 3 effectiveness trials. In addition, nearly 36 products were in preclinical development [20]. These compounds have varying mechanisms of action, but the activities of all of the compounds focus on early mucosal events in pathogenesis. Candidate topical microbicides may serve as physical barriers, inhibit uptake by or infection of dendritic cells, neutralize or inhibit HIV at the mucosal surface, inhibit viral replication in infected cells, or enhance vaginal defenses (e.g., by maintaining a pH that is inhospitable to HIV and other pathogens) [5, 21]. Because many of the compounds under investigation are not microbicidal, they are sometimes referred to as "topical prevention" strategies.

MALE CIRCUMCISION

Observational studies found that the relative risk of HIV acquisition among circumcised males was 40%–80% less than that for uncircumcised males, but until recently, data from randomized, controlled trials were lacking [22]. Two major clinical trials recently found that medically performed adult male circumcision significantly reduced a man's risk of acquiring HIV through heterosexual intercourse [23, 24]. In a study of 2784 HIV-negative men in Kisumu, Kenya, investigators noted a 53% reduction in the incidence of HIV acquisition in circumcised men, compared with uncircumcised men [23]; a trial involving 4996 men in Rakai, Uganda, revealed a 51% reduction [24]. These studies confirm findings from an

earlier randomized, controlled study conducted in South Africa that found a 60% reduction in the incidence of HIV acquisition for men who were circumcised as adults [25].

There are several ways in which male circumcision likely protects against HIV acquisition [26, 27]. The highly vascularized inner foreskin tissue contains a high density of Langerhans' cells as well as increased numbers of CD4$^+$ T cells, macrophages, and other cellular targets for HIV. In contrast to the dry environment of the keratinized area on the outer surface of the foreskin, the moist environment under the foreskin may promote the presence or persistence of microbial flora, which, via inflammatory changes, may lead to even higher concentrations of target cells for HIV in the foreskin and a higher density of HIV-susceptible cells. The inner mucosa of the foreskin is more susceptible to microabrasion, providing a portal of entry for HIV, and the higher rates of ulcerative STDs in uncircumcised men may also increase susceptibility to HIV infection. Hence, eliminating the foreskin diminishes some of the targets for the virus, and allows for a more protective skin surface barrier against HIV. Adult male circumcision, though not completely protective against HIV, is a promising preventive tool that will likely have an important role as part of a comprehensive HIV disease prevention strategy [27].

PREEXPOSURE AND POSTEXPOSURE CHEMOPROPHYLAXIS

Another important area of prevention research involves administering a daily dose of antiviral prophylaxis to individuals at risk for HIV infection [28]. Theoretically, if HIV replication could be inhibited immediately following exposure to the virus, permanent infection might be avoided. Such an approach would help to address the need for female-controlled prevention methods, which are a critical priority because ~50% of new infections globally are among women [2]. This approach, referred to as "preexposure prophylaxis," is a well-established tool for preventing other infectious diseases, such as malaria. Several lines of evidence suggest that preexposure prophylaxis against HIV infection may be feasible [29, 30]. For example, antiretroviral drugs have been used with great success to prevent HIV transmission from mother to infant. Multiple studies involving monkeys have shown that preexposure dosing with tenofovir with or without emtricitabine can prevent simian immunodeficiency virus infection, although protection in one study was overcome by multiple exposures to virus [30]. Tenofovir and emtricitabine have good safety profiles; in addition, they have a long half-life, suggesting that some protection may be afforded even if some doses are missed [31]. Of course, studies involving humans are essential, because findings from animal studies are not necessarily predictive of findings for people. Clinical trials of preexposure prophylaxis are ongoing; this will remain a promising but controversial area of research until these trials are completed [29, 30]. It is important to note that these trials will collect data on drug resistance in seroconverting persons, compliance, and the adverse impact, if any, of preexposure prophylaxis on risk behavior.

Prophylaxis soon after possible HIV exposure, known as "postexposure prophylaxis," also has a role in preventing HIV infection in nonoccupational and occupational settings. Data from animal studies and observational studies in humans suggest that antiretroviral therapy initiated no more than 48–72 hours after sexual exposure, injection-drug use, or occupational exposure and continued for 28 days reduces the likelihood of transmission [32, 33]. Federal guidelines recommend the prompt initiation of antiretroviral therapy when the exposure event presents a substantial risk for HIV transmission [32, 33].

REDUCING TRANSMISSION BY REDUCING VIRAL LOAD

Many pathogenesis-associated preventive measures focus on reducing the viral load as a means to render an HIV-infected person less infectious. The most direct approach is the treatment of infected individuals with combination antiretroviral treatment, which, in a majority of individuals, can reduce plasma levels of virus to undetectable levels [31]. Compelling evidence that reducing viral load reduces transmission comes from studies of maternal-fetal transmission. For example, in an analysis of transmission rates in the Women and Infants Transmission study, the rate of maternal-fetal transmission was 23.4% when the viral load of the mother was ⩾30,000 RNA copies/mL, compared with only 1% when her viral load was <400 RNA copies/mL (figure 2) [34]. Over a 10-year period, this study reported that the rate of transmission from mother to infant was 20% when the mother received no antenatal antiretroviral treatment, compared with a rate of only 1.2%
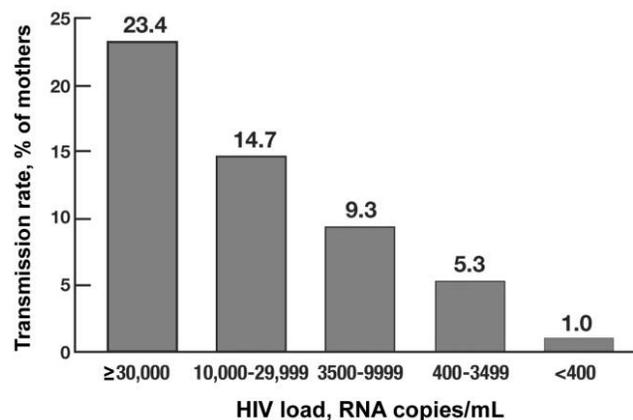

Figure 2. Association between maternal plasma HIV RNA levels at delivery and the risk of mother-to-child transmission of HIV. Data are from [34].
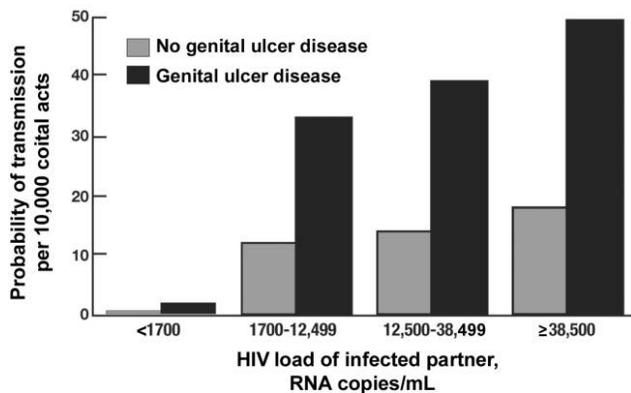
Figure 3. Probability of HIV transmission per coital act among monogamous, heterosexual HIV-discordant couples in Rakai, Uganda. Data are from [36].

when the mother received highly active combination antiretroviral therapy.

The relationship between viral load and transmissibility also has been demonstrated in relation to sexual transmission. For example, studies of monogamous, HIV-serodiscordant couples in Rakai, Uganda, have demonstrated a direct correlation between the infected partner's viral load and the probability of transmission (figure 3) [35, 36].

In addition, a recent analysis found that the rate of transmission within the first 2.5 months after seroconversion of the index partner was almost 12-fold higher than that seen later in disease, a finding likely explained by the high viral burden during acute infection [37]. The rate of transmission increased significantly again ~2 years before the death of the index partner, an observation likely due to the higher viral load seen in late-stage HIV disease. The high rate of transmission during acute infection—when most people do not yet know they are HIV positive—supports the need for better screening, as proposed in the new CDC recommendation for opt-out testing.

AN HIV VACCINE: THE FINAL FRONTIER

Historically, vaccines have provided a safe, cost-effective, and efficient means of preventing illness, disability, and death due to infectious diseases. Successful vaccines are usually based on the assumption that the body can mount an effective immune response during natural infection and that the vaccine will mimic the natural response to infection. With most vaccine-preventable diseases (e.g., smallpox, polio, measles, and influenza), the body can clear the infectious agent and provide protection against future exposure. Unfortunately, this is not the case with HIV infection, because the natural immune response to HIV infection is unable to clear the virus from the body. Some of the factors that contribute to the problematic nature of development of a preventive HIV vaccine are the high

mutability of the virus, the fact that the infection can be transmitted by cell-free or cell-associated virus, the likely need for the development of effective mucosal immunity, and a lack of understanding of the precise correlates of immunity in HIV disease [38, 39]. Many promising HIV vaccines are in various stages of clinical development, and the ultimate goal of an HIV vaccine is to prevent infection. However, even a vaccine that does not prevent infection but significantly alters the course of disease or the infectivity of the individual could have a positive impact on not only the individual but also the spread of infection in the community. In this regard, a number of studies of vaccines that induced predominantly cellular (i.e., T cell) immune responses in monkeys showed that the vaccines did not protect the animals against infection but lowered the initial burst of viremia following acute infection and decreased the viral set point [38–40]. Because most sexually transmitted HIV infections occur during the acute phase of HIV infection, during the advanced stage of disease, or at other times when the viral load is high, such a vaccine could benefit infected individuals and their sex partners by limiting the initial burst of viremia during primary infection and decreasing the established viral set point. For example, in a comparison of plasma simian immunodeficiency virus concentrations in macaques vaccinated with an "imperfect" vaccine with those in unvaccinated animals, the vaccine did not prevent initial infection with SIVmac239 but blunted the initial burst of viremia and lowered the established viral set point (figure 4) [40]. Clinical trials using this strategy have been initiated.

CONCLUSION

Although classically not considered to be "prevention research," studies of the pathogenesis of HIV disease are providing us
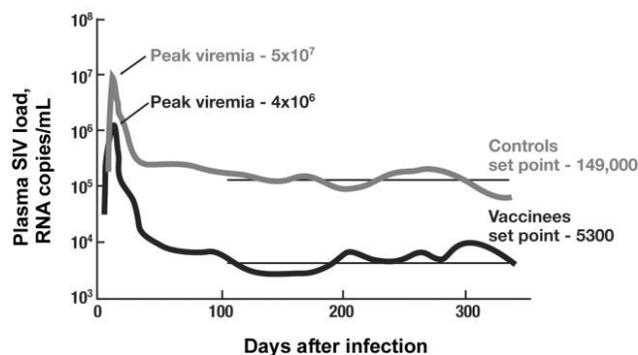

Figure 4. Comparison of plasma simian immunodeficiency virus (SIV) loads in macaques vaccinated with an "imperfect" vaccine with SIV loads in unvaccinated animals. Adapted from the following article with permission from the American Society for Microbiology: Wilson NA, Reed J, Napoe GS, et al. Vaccine-induced cellular immune responses reduce plasma viral concentration after repeated low-dose challenge with pathogenic simian immunodeficiency virus SIVmac239. J Virol 2006; 80:5875–85.

with important opportunities to develop novel preventive measures. It is likely that none of these measures will be 100% effective and, hence, will need to be used in combination as part of a multipronged prevention package that includes condom use and other proven methods.

We can anticipate that the treatment of sexually transmitted diseases and other coinfections will play an important role in a 21st-century "prevention cocktail" for HIV infection. Safe, effective, and aesthetically acceptable topical microbicides could, without the knowledge or consent of their partners, provide women the opportunity to protect themselves. Adult male circumcision shows significant promise. Despite potential drawbacks (e.g., the development of resistance), preexposure prophylaxis shows promise, and the global scale-up of antiretroviral treatment for all HIV-infected people who need it will benefit their health and reduce transmission at the population level. The success in screening for and treating HIV infection in pregnant women must be extended globally. Ultimately, an HIV vaccine, even an imperfect vaccine that does not prevent infection but slows disease progression and reduces transmission, will be critical to the effective control of HIV globally.

Acknowledgments

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