ABSTRACT

Recent studies that have characterized the biology of HIV infection have suggested potential limitations of current approaches to HIV prevention, in addition to new strategies to interrupt transmission of the virus. The transmission of HIV is influenced by several factors related to the virus (eg, viral clade or viral load) and the host (eg, heritable mutations that confer resistance to HIV infection). The production of HIV is intermittently amplified in the genital tract, resulting in periods of increased infectivity. Accordingly, the likelihood of HIV transmission also is affected by coinfection with other sexually transmitted diseases and by the stage of illness, with the highest risk of transmission occurring during the earliest and latest phases of infection. The period of acute HIV infection is an especially important time of high viral production and low awareness of infection. RNA testing may help to identify individuals with early HIV infection who are not typically identified by conventional antibody screening. Antiretroviral therapy has been shown to reduce the amount of HIV in semen. In retrospective studies, antiretroviral agents have been associated with reduced likelihood of HIV transmission. Prospective studies to examine the effects of pharmacologic therapy on HIV transmission are in progress.

At least 80% of worldwide HIV infections are the result of sexual transmission. Recent advances in the biology of HIV infection have begun to suggest why current prevention approaches are often not effective, and to identify new strategies to prevent HIV infection. Semen can dwell in the vagina for several days and for an unknown period of time in the rectum, creating a relatively long period of time during which HIV transmission may occur. HIV is present in seminal plasma and seminal cells, although the relative importance of these 2 sources of HIV in the transmission of the virus is still uncertain. Nearly all transmitted HIV uses cell-surface receptors (eg, CD4 or CCR5) expressed on submucosal cells to infect HIV-free lymphocytes. Infection of receptive cells by HIV may occur in as little as 30 minutes, at least in exposed macaques (C Miller, Unpublished observations). The transmission of HIV depends on viral and host characteristics. The likelihood of infection is largely determined by the concentration of virus, but also is influenced by viral phenotypic factors. In the United States, HIV is primarily clade B, which is not as efficiently transmitted as clades A, C, and possibly E. Individuals who live in Africa are more likely to be exposed to viral clades that are more efficiently trans-
mitted. Hereditary resistance to viral infection by the host is conferred by CCR5 deletions, which result in reduced susceptibility to HIV infection among approximately 1% of the white population. Innate resistance may be conferred in women by vaginal flora, and conversely, women with bacterial vaginosis may be more susceptible to HIV. In relatively rare cases, individuals have exhibited acquired (immune) resistance to HIV infection and the absence of HIV infection despite repeated exposures. The understanding of the absence of HIV infection despite repeated exposures is especially important in the development of HIV vaccines.

**Probability of HIV Infection**

The probabilities of infection are well established for events, such as transfusion of infected blood (95 in 100), needle sharing by injection drug users (1 in 150), needle stick in the healthcare setting (approximately 1 in 2000 or 1 in 10 000 with zidovudine post-exposure prophylaxis), and transmission from mother to infant (1 in 4 without zidovudine treatment, or 1 in 10 with zidovudine). However, early estimates of the rate of sexual transmission, which suggested that transmission occurred in approximately 1 in 800 to 1 in 1000 episodes of sexual intercourse, are probably too low to account for the large number of individuals infected. It has been hypothesized that HIV transmission is intermittently amplified by increased genital tract shedding, and that sexual intercourse during this period of amplified transmission accounts for many cases of HIV infection. Amplified transmission of HIV may result in periods of increased infectiousness throughout the course of the disease but is especially important during the period of acute HIV infection before seroconversion. An individual who has recently acquired HIV and who has no anti-HIV antibodies demonstrates unrestrained HIV replication in the blood and genital tract. Coinfections, such as malaria, helminthic infections, or tuberculosis, also may increase levels of HIV.

Sexually transmitted diseases (STD) are especially important in increasing the transmission of HIV. STDs can cause inflammation, which may evoke more infectious HIV variants and increase the number of HIV receptor cells and the number of receptors per cell. By producing genital lesions, STDs also reduce the effectiveness of physical and mechanical barriers to HIV infection.

Several studies suggest that the transmission of HIV is greatest during the acute HIV infection stage. The strongest empirical support for this hypothesis is provided by a recent study by Wawer et al who examined early HIV transmission in Rakai, Uganda. These investigators found that 43% of all HIV transmission events occurred around the time of seroconversion, which most likely represents transmission by individuals with acute (pre-seroconversion) HIV infection. The rate of transmission was lower during the period of established HIV infection, and then increased again with the development of AIDS (Figure 1). Individuals who are developing AIDS symptoms but who are well enough to be sexually active represent a substantial proportion of cases of HIV transmission. Approximately 75% of all transmission in this study occurred in the earliest and latest stages of HIV infection.

Despite these patterns of HIV transmission, current prevention strategies focus primarily on the period of established chronic HIV infection, which represents the patient population that is most often seen in clinical practice. Because many cases of HIV transmission occur during acute HIV infection, it seems clear that more attention needs to be focused on prevention during this stage of disease; lack of attention to the patient groups with the highest transmission rates may be one reason why so little progress has been made in controlling HIV infection in the United States.

![Figure 1. HIV Transmission per Coital Act, and 95% Confidence Intervals, by Follow-up Interval](Reprinted with permission from Wawer et al. J Infect Dis. 2005;191:1403-1409.)

Incident index partners

Prevalent index partners

Late-stage index partners

Transmissions per 1000 coital acts

-5 6-15 16-25
-10 11-20 21-30
-20 21-40 31-40
-30 35-26 26-16
-40 15-5

Months after index partner seroconversion

Months of follow-up during prevalent infection

Months preceding death of index partner

An acute infection syndrome occurs in 50% or more of patients who are infected with HIV. This syndrome resembles mononucleosis and includes fever, fatigue, pharyngitis, weight loss, myalgia, and headache. The acute HIV infection syndrome is indistinguishable from acute infection symptoms caused by other common viral infections. As a result, in the entire world literature on HIV infection, fewer than 1000 patients have been described with this symptom pattern in association with early HIV infection. Because of the nonspecific nature of these symptoms, many individuals with acute infection do not recognize that they are infected with HIV and therefore do not seek medical attention. This suggests that better screening strategies are needed to identify these individuals.

HIV is generally detected in routine clinical practice using antibody testing. Although antibody tests continue to improve, several weeks are required for antibodies to develop to HIV, and a positive test result may identify an even larger number of cases of unrecognized HIV infection. Improved testing of this subset of persons who went to an STD clinic agreed to be tested for HIV. An alternative is the use of assays to detect HIV RNA, which is present near the first day of infection. The potential for RNA testing to identify cases of acute HIV infection was demonstrated in a recent study conducted in North Carolina. Antibody testing was performed for nearly 110,000 individuals over a period of 9 months, and 563 people with established HIV infection were identified. All HIV-negative specimens were then examined using HIV RNA testing, which identified an additional 23 people with (antibody-negative) acute HIV infection. Sixteen of 23 patients were detected in STD clinics, although less than 33% of people who went to an STD clinic agreed to be tested for HIV. Improved testing of this subset of persons may identify an even larger number of cases of unrecognized HIV. These results also emphasize that STDs and HIV are often found together and that patients with acute and established HIV are found in STD clinics. Identifying people with acute HIV infection in the STD clinic could provide an important opportunity for prevention. These patients are also likely to have much higher CD4 cell counts than those who come to an emergency room with Pneumocystis carinii pneumonia or another opportunistic infection.

In our studies in the United States, the median HIV viral load in blood of people with established HIV was approximately 29,000 copies per mL. The probability of transmission per coital act associated with this count is low, approximately 1 in 1000. Individuals with acute infection have more HIV in the blood, with a median concentration of approximately 210,000 copies per mL. The probability of transmission per coital act for these individuals is greater, or approximately 1 in 100 in the United States. Thus, there is an opportunity for reducing the transmission of HIV by 1 log unit by identifying people with acute infection and instituting effective prevention strategies.

In Africa, the advantages to early identification may be even more dramatic. The University of North Carolina at Chapel Hill has conducted an HIV research program in the country of Malawi, a largely rural country of 10 million people in southern Africa since 1989. The total prevalence of HIV in Malawi is approximately 900,000 persons, and approximately 15% of the adult population is infected. Using the previously described strategy, we screened 1361 men for acute HIV infection in STD and dermatology clinics. HIV antibodies were detected in 47% of patients, indicating chronic established HIV infection. Of the antibody-negative patients, approximately 2% had acute HIV infection, indicated by the presence of HIV RNA in the blood. Acute HIV infection was more common among men with inguinal nodes (11.4% of patients screened), genital ulcers (7.8%), and among those patients who had been exposed to commercial sex workers (9.1%). In current worldwide practice, individuals with acute HIV infection are missed by HIV antibody testing alone, and they are being told that they are HIV negative. Examination of viral loads of the HIV-infected subjects in Malawi showed that in individuals with established clade C infection, the median concentration of virus is approximately 150,000 copies, with a transmission per coital act probability of approximately 1 in 100. Among individuals with acute HIV in Malawi, the median viral load is approximately 1 million copies, with viral load values as high as 2.5 billion copies. The probability of transmission per coital act from acute HIV in this population is approximately 1 in 50.

As noted previously, semen HIV concentration is a significant predictor of HIV infection risk. HIV RNA can first be detected in semen approximately 1 week after infection, at which time an RNA concentration of 100,000 copies per mL is detected. Over time, the concentration of HIV in the blood remains fairly constant, whereas the HIV concentration in semen decreases. The sexual transmission of HIV as a function of seminal HIV concentration is summarized in Figure 2. HIV RNA in semen increases during the acute infection period,
decreases during established chronic infection, and increases again during AIDS. The probability of transmission per coital act during the initial phase is probably as high as 1 in 30; during established HIV it decreases to 1 in 1000 to 10 000; and then increases again with the onset of AIDS to 1 in 100 to 1000. The incidence of HIV transmission per coital act over 16 weeks following infection is approximately 10-fold to 15-fold greater during the first 2 weeks of infection than at weeks 12 to 16.

Therefore, the goal of HIV detection efforts should be to find people during the early stages of HIV infection when infectivity is greatest. In addition, even in patients on antiviral therapy, infection with another STD causes enough inflammation for HIV to increase transiently, which may create an increased transmission probability.16

PREVENTION STRATEGIES

Many strategies have been proposed to help prevent HIV infection. STD control, behavior change, and condoms may work in some countries, but are not sufficient. Vaccines are being evaluated in clinical trials, but no vaccines are available that produce sterilizing immunity. The most that can be hoped for at present is that vaccination will induce sufficient preexposure immunity to reduce the amount of virus that is transmitted to the next person. Other potential strategies include treatment of bacterial vaginosis and the use of topical microbicides and diaphragms. Clinical trials are currently evaluating the effectiveness of male circumcision. Potential societal changes include finding ways to increase incentives for safer sex.

There are 3 ways in which antiretroviral therapy (ART) may be used to prevent HIV infection. Preexposure prophylaxis involves identification of individuals who are thought to be at such high risk of HIV infection that they should begin ART even before they are exposed. Tenofovir may be suited for this use, and several randomized controlled trials of tenofovir are in progress. The disadvantages of this approach are the cost of treatment and the toxicity of chronic ART for a patient who is not infected. It also is not clear whether tenofovir pretreatment increases the risk of HIV resistance to tenofovir should the individual become infected with HIV despite prophylaxis. In addition, tenofovir failed to protect macaques exposed to HIV through repeated low-dose rectal exposure.17

A second approach is the use of postexposure prophylaxis for sexual or nonsexual HIV exposure. Guidelines have been developed for postexposure prophylaxis for needle stick or other occupational exposures and for sexual exposure.18 These guidelines advocate the rapid initiation of prophylaxis in the case of possible HIV exposure. If there is any doubt about whether the patient has been exposed to HIV (eg, in a woman who has been sexually assaulted), prophylaxis should be initiated without delay because transmission

Figure 2. Prediction of the Efficiency of HIV Transmission According to HIV Burden in the Genital Tract

A

Risk of HIV transmission per coital act

1/50 – 1/1000 – 1/500 – 1/100 – 1/250 – 1/10 000 – 1/2000 – 1/1000

HIV RNA in semen, log_{10} copies/mL

Acute infection

Asymptomatic

infection

HIV progression

AIDS

B

HIV RNA in semen, log_{10} copies/mL

Acute infection

3 weeks

STI episode

STI episode

AIDS

| Expected distribution of viral burden in semen among men over time |
| Theoretical effect of a biological intervention designed to reduce viral excretion |
| A potential threshold for HIV transmission |

A. Probability of male-to-female HIV transmission per coital act, as a function of HIV disease stage in the index case. Transmission ease (3–5, 13). B. Determinants of high HIV transmission probability: acute infection, STI, and AIDS. STI = sexually transmitted infection.

may occur rapidly. Treatment can be discontinued if warranted on the basis of additional information. Therapy must be continued for 28 days. In laboratory studies, animals that have received less than 28 days of therapy have acquired HIV. Combination ART should be used with consideration to the resistance patterns that are present in the community and to treatment tolerability. It should be noted that it cannot be proven that postexposure prophylaxis is effective. A recent paper by Roland et al demonstrated 7 treatment failures among people who were committed to good postexposure prophylaxis.

A third use of ART is the actual effect of ART on transmission of HIV from an infected person to his or her sexual partner. This approach has great biological plausibility, as ART decreases the number of patients with detectable HIV in semen. Vernazza et al conducted a trial in which HIV RNA and DNA were examined in 114 men who received ART, in comparison to 55 drug-naïve, HIV-positive control subjects. After therapy, HIV could be recovered in seminal plasma from only 2 patients, compared to 67% of the untreated men. Cell-associated HIV also was detected in fewer treated patients than controls (Figure 3). It is not yet known whether HIV is transmitted by cells or by cell-free materials, and therefore, it is not possible to conclude that none of the individuals with suppressed RNA would develop HIV. However, it is clear that ART reduces the concentration of virus.

Several studies have attempted to demonstrate that ART can prevent HIV transmission. For example, modeling reports have suggested that the use of ART can prevent HIV transmission. Two retrospective clinical studies have found that transmission was reduced when antiviral therapy was introduced. Musicco et al, who studied a group of 436 monogamous seronegative female sexual partners of HIV-infected men, found that the rate of transmission was 50% lower among men who were using ART. In a more recent study, Castilla et al studied a cohort of 393 heterosexual couples in which one partner had been diagnosed with HIV infection in the pre-highly active antiretroviral therapy (HAART) era (1991–1995) or during the late HAART period (1999–2003). The transmission of HIV to the initially seronegative partner decreased from 10% of patients before the introduction of HAART to 1.9% of the group who were diagnosed after HAART was introduced. Several epidemiologic studies also have suggested that ART reduces HIV transmission. A study by Fang et al is especially interesting. These investigators examined HIV transmission for the entire island of Taiwan, where HIV is assessed by a national surveillance system and all HIV-positive individuals have received free treatment since 1997. After nationwide treatment was instituted, the rate of transmission of HIV decreased by 53%. Although all of these studies are suggestive, retrospective analyses alone cannot prove that ART reduces the risk of HIV transmission. The National Institutes of Health has chartered a large clinical trial of 1750 couples that are serodiscordant for HIV that will prospectively examine the effects of ART on HIV transmission. This is a difficult and expensive study to perform, and it will take another 5 to 6 years to complete. It is currently in its pilot phase, and approximately 50 couples have been enrolled.

**Conclusions**

Recent studies of the biology and epidemiology of HIV have added considerably to our understanding of how the virus is transmitted. These studies have suggested that it may be possible to improve the effectiveness of prevention by increasing the attention that we...
devote to patients who are most likely to be transmitting HIV. Several effective prevention strategies are currently available, and new approaches to prevention are being evaluated in large, randomized clinical trials. The use of antiretroviral agents in the prevention of HIV transmission will probably increase during the next several years.

REFERENCES