Perspective

HIV and Sexually Transmitted Diseases: Lethal Synergy

Sexually transmitted diseases (STDs) can increase risk for acquisition and transmission of HIV via a number of mechanisms, including breaching of mechanical barriers to infection, increased inflammation and higher levels of HIV cellular targets, and increased genital tract HIV levels. Studies in Malawi clinic populations indicate that treatment of STDs can reduce genital tract HIV levels. Work in Africa and India has indicated that genital herpes infection is associated with increased risk of acquisition of HIV and that presence of genital ulcer disease is associated with increased risk of transmission of HIV disease. Acute HIV infection has been found to be more frequent in individuals with active STDs, and cotransmission may be a common phenomenon. Acute HIV infection, which is not currently routinely diagnosed, is associated with increased risk of transmission. Greater efforts are needed in identifying acute HIV infection in STD clinics. This article summarizes a presentation by Myron S. Cohen, MD, at the International AIDS Society–USA course in Chicago in May.

Worldwide, approximately 85% of cases of HIV transmission occur through sex. HIV transmission depends on infectiousness and susceptibility.

Infectiousness and Susceptibility

HIV infectiousness is modulated by size of the inoculum of the infectious agent (ie, the concentration of virus) and phenotypic factors. With regard to phenotypic factors, there are many reasons to believe that the HIV clade B virus involved in infections in the United States, for example, is not as infectious as the clade C virus (Cohen, *New Eng J Med*, 2000) found in Africa or the recombinant BC virus found in China.

Susceptibility to infection is modulated by such factors as hereditary resistance, innate resistance, and acquired (immune) resistance (Buchacz et al, *AIDS*, 1998). An example of hereditary resistance is the CCR5 coreceptor deletion observed in a small percentage of the white population, which makes it more difficult for such individuals to acquire infection. A type of innate resistance is observed in the case of differences in vaginal flora: the typical vaginal flora in women in the United States, for example, is characterized as generally free of the factors associated with bacterial vaginosis and appears to confer some protection against HIV acquisition; the typical vaginal flora in Africa (occurring in some 70% of women) consists of few lactobacilli and a predominance of anaerobes and appears to be more conducive to HIV infection. An example of acquired resistance is observed among sex workers who have never acquired HIV infection despite what is likely to be repeated exposure to virus. The factor(s) responsible for this type of resistance remain elusive.

Ejaculate from an infected man contains cell-free and cellular HIV. Semen dwells in the vagina for 2 to 3 days, providing a long period of time for virus to penetrate barriers and find appropriate receptors in the submucosa. Epidemiologic studies have estimated the risk of HIV transmission to range from 5 in 10,000 to 26 in 10,000 penile/vaginal acts (Chakraborty et al, *AIDS*, 2001). The sense of rarity of transmission conveyed by such statistics is misleading, particularly when it is considered that many populations have very high prevalence rates of HIV infection occurring as a result of what must certainly be much lower numbers of sexual encounters. In fact, there are a number of factors that amplify risk of transmission and that need to be taken into account in efforts to prevent transmission. Factors that amplify the risk of HIV transmission include those that increase infectiousness, such as stage of HIV disease and presence of certain coinfections (eg, malaria, helminthic infections, tuberculosis), and those that can increase both infectiousness and susceptibility, such as other sexually transmitted diseases (STDs).

The risk of transmission correlates with the concentration of HIV in the ejaculate (Figure 1; Chakraborty, *AIDS*, 2001). Compared with a probability of transmission of roughly 1 in 1,000 at a viral concentration of 50,000 HIV RNA copies/mL, the estimated probability of transmission increases markedly with

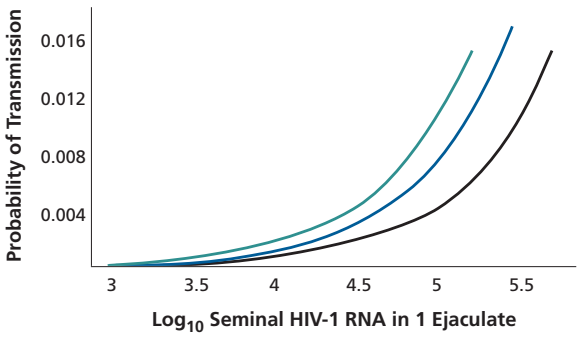

Figure **1.** Estimated probability of male-to-female HIV-1 transmission per sexual contact according to seminal HIV RNA level and cervical CCR5 receptor cell count. Three lines represent receptor cells/μL counts: 75th percentile (green), 50th percentile (blue), 25th percentile (black). Adapted from Chakraborty et al, *AIDS*, 2001.

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increasing concentrations (eg, substantially greater than 1 in 100 at 1 million copies/mL). Figure 2 shows the relationship between viral load in semen and risk of transmission by disease stage. The high viral load present in semen during acute infection is associated with markedly increased risk of transmission. Although practices for diagnosing acute infection will change in the United States in the coming years, routine diagnosis depends on enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation; this approach misses acute infection at this stage, since antibody testing is not positive for a few weeks after infection. The mononucleosis-like symptoms of acute HIV infection (present in approximately half of cases) are often missed or overlooked. Data indicate that about half of all cases of HIV transmission may occur during the early phase of HIV (Wawer, 10th CROI, 2003). This important window of transmission requires increased attention in efforts to reduce spread of HIV disease.

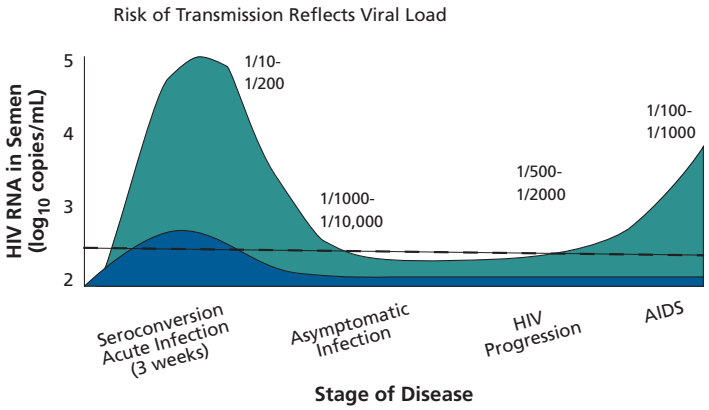

Figure **2**. Risk of HIV transmission by seminal HIV RNA concentration and disease stage. Adapted from Cohen et al, *Lancet*, 2001.

Effect of Other STDs on HIV Acquisition and Transmission

Other STDs can facilitate acquisition and transmission of HIV in a number of ways. On the susceptibility side, STDs can reduce physical and mechanical barriers of the virus (eg, by causing lesions in the mucosa), increase the numbers of receptor cells or density of their receptors (eg, by causing persistent inflammation), and produce a vaginal environment that is more conducive to transmission (eg, via presence of bacterial vaginosis and increased levels of anaerobes or amines). On the infectiousness side, STDs might evoke a more infectious HIV variant (Ping, *J Virol,* 2000) and can increase HIV concentrations in genital lesions, semen, or both (Cohen, *Lancet,* 1997). Cotransmission of HIV and another STD appears to be a common occurrence.

Numerous studies have shown a higher risk of acquiring HIV infection in the presence of STDs. Odds ratios for HIV seroconversion increase in the presence versus absence of chlamydia, gonorrhea, and trichomoniasis and in the presence versus absence of genital ulcers. The evidence for facilitated HIV acquisition in the presence of herpes simplex virus 2 (HSV-2) infection is very compelling (Wald and Link, *J Infect Dis*, 2002). HSV-2 is ubiquitous in the United States, with approximately 1 in 5 persons having the disease. Among African Americans, nearly 70% acquire HSV-2 by age 50 years. Of the approximately 50 million affected individuals, only 1 million have lesions, but all infected individuals intermittently shed the virus. As shown in Figure 3, a recent study in India showed an increased risk of HIV acquisition in individuals with HSV-2–seropositive status compared with seronegative status and a dramatically increased risk of HIV acquisition in those with recently acquired HSV-2 infection (Reynolds, *J Infect Dis*, 2003). A study of HIV acquisition in 174 HIV-serodiscordant monogamous couples in Rakai, Uganda (Gray, *Lancet*, 2001; Grosskurth et al, *Lancet*, 2000), showed that risk of HIV acquisition was higher in HSV-2–seropositive partners of HIV-infected individuals with the lowest HIV viral load than in HSV-2–seronegative partners of HIV-infected individuals with the highest HIV viral load. From the transmission perspective, study of this population in Rakai showed that the risk of HIV transmission was markedly elevated for individuals with genital ulcers versus those without genital ulcers at every level of plasma HIV viral load (Gray, *Lancet*, 2001). In general, data on the effects of STDs on HIV transmission are inadequate, partly because STD studies have focused on acquisition rather than transmission. Indeed, such focus is prevalent in HIV clinics throughout the world, and more attention needs to be given to viewing the individual with HIV infection not only as an individual who needs care for the disease, but as one who requires management to reduce the risk of transmitting the virus to others (*MMWR*, March 2003).

Reversing STD Amplification of HIV Transmission and Acquisition Risk

Goals of research to determine how best to reduce the increased risk of HIV transmission and acquisition associated with other STDs include demonstrating reduced genital tract HIV levels with STD treatment and demonstrating

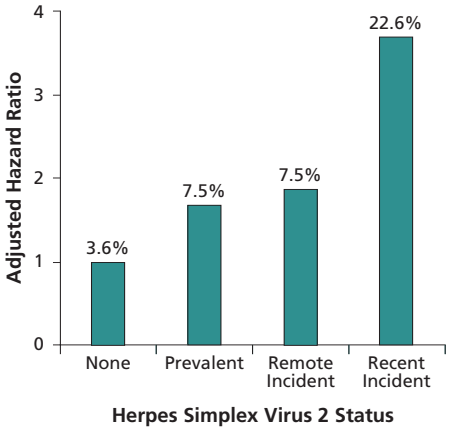

Figure **3.** Risk of acquiring HIV-1, by herpes simplex virus type 2 (HSV-2) infection status, in a cohort of patients at 3 sexually transmitted infection clinics and 1 reproductive tract infection clinic in Pune, India, May 1993 through April 2000. HIV-1 incidence per 100 person-years is given above each column. Adapted from Reynolds et al, *J Infect Dis*, 2003.

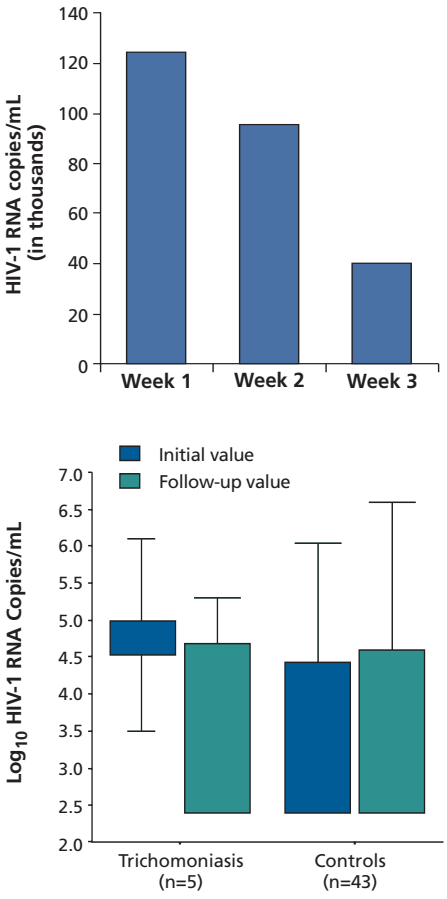

Figure **4.** Top: Effect of a single ceftriaxone injection in reducing seminal HIV level in 86 men with urethritis (median values). Adapted from Cohen, *Lancet*, 1997. Bottom: Effect of treatment for trichomoniasis on genital tract viral load in 5 patients compared with controls. Adapted from Price et al, *Sex Transm Dis*, 2003.

reduced acquisition of HIV with STD therapy for the HIV-infected index case or the HIV-uninfected susceptible host. The University of North Carolina project in Malawi has provided data indicating the benefits of STD treatment in reducing HIV risk. Malawi has a population of 10 million, 90% of which is rural, and a per capita income of US $190. Among the population, 900,000 are living with HIV disease; the disease prevalence is 15% in the adult population and 47% in the STD clinic population. In a study conducted in an STD clinic, a single injection of ceftriaxone for presumptive gonorrhea in 86 men with urethritis produced a reduction in median seminal HIV RNA concentration from approximately 120,000 copies/mL to 40,000 copies/mL over 3 weeks, with no change occurring in plasma viral load (Figure 4, top). Such findings indicate that the amplified transmission risk associated with high seminal HIV level can indeed be markedly reduced. Similarly, treatment for trichomoniasis in the STD clinic produced a reduction in genital tract viral load (Figure 4, bottom).

Findings in clinics in Lilongwe, Malawi, emphasize both the potential association of other STDs with HIV acquisition risk and the need to focus attention on acute HIV infection. Of 1361 men screened for HIV infection in STD and dermatology clinics (Pilcher et al, *AIDS,* 2004), 40.6% were HIV antibody-positive. An additional 24 (1.8%) were found to have acute infection by positive plasma HIV RNA assay and negative antibody results. Individuals with acute HIV infection accounted for 11.4% of individuals with affected inguinal lymph nodes, 7.8% of those with genital ulcer, and 9.1% of those who admitted to sex with a commercial sex worker. Cases of acute HIV infection were found only in men with another STD. Median plasma HIV RNA levels were approximately 100,000 copies/mL in men with chronic infection and 1 million copies/mL in those with acute infection (Figure 5); since viral loads in semen are likely similar to the plasma viral loads, the men with acute infection carry a substantially higher risk of transmitting virus in sexual encounters.

Diagnosis of acute (incident) HIV provides an opportunity for emergent prevention by identifying transmission chains. In North Carolina during 9 months in 2003 and 2004, routine assessment for HIV RNA in more than 100,000 samples collected in testing centers resulted in diagnosis of a substantial number of cases of acute infection and, through follow-up, permitted detection of an outbreak of HIV transmission in a college population. Routine identification of acute infection may also eventually provide greater opportunity for therapeutic intervention aimed at preventing the establishment of chronic infection, should such strategies ever prove to be feasible and effective. Finally, detection of acute HIV in STD clinics provides an opportunity for merging HIV and STD prevention efforts.

Antiviral Therapy to Prevent HIV Infection

A number of studies are under way to determine the logistics and effects of antiretroviral therapy or antiviral therapy for herpes simplex virus (HSV) infection in preventing HIV transmission. Five trials of preexposure prophylaxis are planned in which HIV-uninfected commercial sex workers will take tenofovir once daily to assess whether any effect on HIV acquisition can be ascertained. Studies of the logistics of postexposure antiretroviral prophylaxis are also being performed, in the absence of being able to sufficiently power a study to determine preventive effect. Two large-scale trials of antiviral

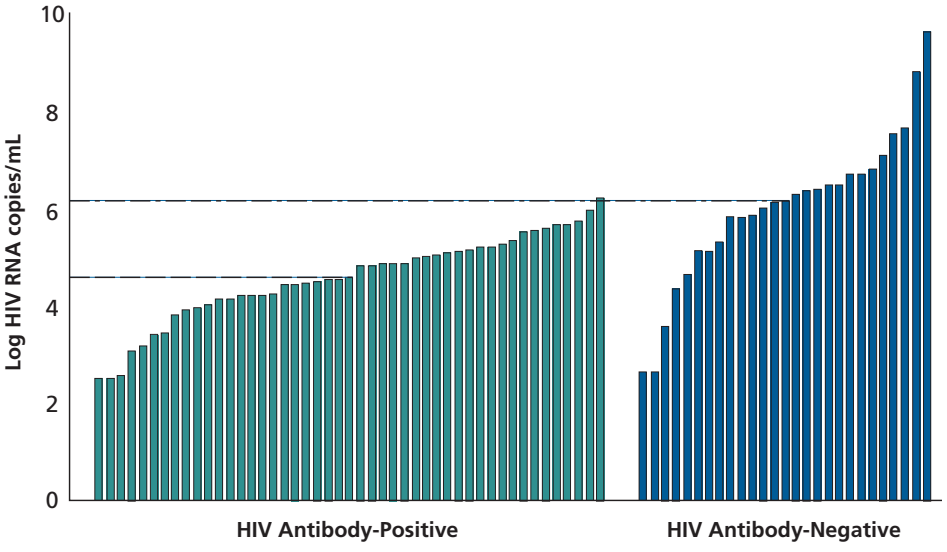

Figure **5.** Plasma HIV RNA levels in men in a clinic population in Malawi with chronic (HIV antibody-positive) or acute (HIV antibody-negative) HIV infection. Adapted from Pilcher et al, *AIDS*, 2004.

therapy for HSV infection have been designed. In the HIV Prevention Trials Network (PTN) 039 study, HIV-seronegative high-risk individuals who are HSV-2–seropositive will take acyclovir daily for 1 year to determine whether such suppressive therapy reduces acquisition of HIV infection. In a trial funded by the Gates Foundation, individuals with HSV-2 and HIV infection who have HIV-seronegative sex partners will take acyclovir to determine if rate of transmission to their partners is thereby reduced. The PTN 052 study is a randomized trial of antiretroviral therapy to prevent HIV transmission in HIV-serodiscordant couples. It has previously been shown that triple-drug potent antiretroviral therapy markedly reduces HIV RNA concentration in seminal plasma. In the PTN 052 study, 1750 HIV-serodiscordant couples with the HIV-infected partner having CD4+ cell count greater than 300/μL and less than 500/μL will be enrolled at 7 sites (2 in Malawi, 2 in India, and 1 each in Thailand, Zimbabwe, and Brazil) and randomized to triple-drug antiretroviral therapy or primary care. The study is scheduled to go on for 7 years, and has a 90% power to detect a 35% reduction in sexual transmission of HIV.

Summary

After 20 years, HIV detection still depends on voluntary counseling and testing or detection of AIDS, and there are clear limitations to such an approach. HIV and STDs are probably frequently cotransmitted, and acute HIV infection can and should be detected in STD clinics and in patients with STDs. Detection of acute HIV infection is of benefit to prevention efforts. Identification and treatment of other STDs can be effective in reducing risk of HIV acquisition and transmission. Reduction of HIV concentrations in genital secretions, by whatever means, is likely to be effective in reducing HIV transmission.

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