Editorial

Sexually Transmitted Diseases and Human Immunodeficiency Virus Infection: Cause, Effect, or Both?

Myron S. Cohen, MD;* and William C. Miller, MD, PhD, MPH*

The infectiousness of the index case and the susceptibility of the exposed host mediate the sexual transmission of human immunodeficiency virus (HIV). Infectiousness of the index case is determined by the inoculum of HIV and viral factors that favor transmission.[1] Persons with primary infection, late stage disease, or low CD4 counts appear to transmit HIV with greater efficiency, presumably through increased viral burden in genital secretions.[1-6] Susceptibility to HIV infection is determined by hereditary resistance factors, acquired immunity, site of exposure to the virus, and integrity of local barriers (e.g., vaginal epithelium).[7] Hereditary resistance factors, such as cell surface receptors required for transmission of some viral variants, have been identified in studies of exposed, but uninfected persons.[8] Acquired immunity, including protective cytotoxic T lymphocyte or antibody responses, may be important in persons repeatedly exposed to HIV who do not become infected.[9] Sexual practices also affect susceptibility, with receptive anal intercourse having the highest risk, followed by vaginal intercourse and fellatio.[2] Similarly, women are more susceptible to infection than men, through vaginal intercourse.[10] In general, any factor affecting excretion of HIV or the number of receptive cells can be expected to affect the efficiency of transmission.[10,11]

Classic sexually transmitted diseases (STD) that cause ulceration or mucosal inflammation appear to be powerful cofactors for transmission of HIV,[12,13] and may increase infectiousness, susceptibility, or both. The potential for increased infectiousness has been shown in recent studies documenting increased concentrations of HIV in secretions of men and women with coexisting STDs.[14-19]

Inflammation associated with an STD could also lead to excretion of more infectious HIV variants. Sexually transmitted diseases also are believed to increase susceptibility to HIV infection. Genital ulcers are assumed to disrupt the mucosal barrier, thereby increasing susceptibility.[13] Endocervical inflammation is associated with recruitment of cells receptive to HIV.[20]

Despite the large number of studies demonstrating a relation between STDs and HIV infection, some uncertainty regarding a causal role for STDs remains. Many studies examining HIV and STDs have been cross-sectional—determining HIV and STD status simultaneously.[21-26] Interpretation of these studies is problematic, because the timing of the relation between the STD and the acquisition of HIV is not known. Concurrent ulcerative STDs and HIV infection may simply represent increased susceptibility to the STD in an immunocompromised HIV-infected host. Prevalent STDs among HIV-infected persons, particularly mucosal STDs, such as gonorrhea, chlamydia, and trichomoniasis, are unlikely to be related to the acquisition of HIV infection, unless the observed HIV infection is acute. In many studies, inflammatory and ulcerative STDs most clearly represent sexual risk-taking behavior consistent with acquisition of HIV.

Cohort or longitudinal studies are necessary to examine directly the relation between STDs and HIV infection more precisely. Genital ulcer disease has been associated with increased incidence of HIV infection in men and women.[27-29] Urethritis in men and cervicitis in women have been associated with increased risk for acquiring HIV infection.[29] Gonorrhea, chlamydial infection, or trichomoniasis have been reported to increase the risk for HIV infection in women.[30] However, these studies are difficult to perform. Demonstration of a possible causal linkage for susceptibility requires demonstration of the presence of an STD followed in short temporal sequence by HIV seroconversion. With many STDs, the risk period for HIV acquisition is short, because symptoms will lead infected persons to seek treatment. Furthermore, it is difficult to discern whether an STD is associated with increased infectiousness and is cotransmitted by the index case, or if the STD is prevalent in the secondary case and increases susceptibility.

Studies using couples discordant for HIV infection represent a novel way to study the relation of HIV infection and STDs. Several studies of discordant couples have

been published that allow the assessment of particular risk factors that influence HIV transmission, because incident infections in the seronegative partner are likely to be transmitted from the seropositive partner.[31-43] Resistance factors also can be assessed in these studies. Many of these studies have shown a relation between immunosuppression or advanced disease and HIV transmission.[31-37] An increased viral burden also has been associated with increased risk of transmission.[39,40,43] One study identified receptive anal intercourse by women as a risk factor for increased susceptibility for HIV infection.[38] In this same study, STDs, especially ulcerative STDs, were associated with an increased risk that did not attain statistical significance.[38]

In this issue of the *International Journal of Infectious Diseases*, Perez and coworkers report on the effects of STDs on transmission of HIV in a large study of discordant couples.[44] In an effort to examine factors promoting transmission, a cohort of 224 heterosexual couples in stable partnerships was recruited from 1990 to 1995.[45,46] However, transmission proved to be a rare event. Since the couples were aggressively counseled about HIV prevention, prevention of transmission in the cohort can be considered a great success, albeit at the cost of the initial study design.

In an alternative design, the investigators recruited 78 concordant couples (both partners HIV infected) for comparison.[44-46] In earlier work, these researchers reported on demographic, behavioral, and biologic factors that appear to separate concordant and discordant couples.[45,46] In these earlier studies, no differences in history of STDs were noted in concordant and discordant couples, but women in concordant couples were more likely to have inflammation or cervical dysplasia detected by Pap smear.[45]

The current analysis was undertaken to determine whether several different STDs might influence HIV transmission. Prior infections by herpes simplex virus type 2 (HSV-2), cytomegalovirus, syphilis, hepatitis B, *Chlamydia trachomatis*, and *Mycoplasma* species, including *M. genitalium*, *M. fermentans*, and *M. penetrans*, were determined by serum antibody status. The most important result was that seroprevalences of HSV-2 and *M. genitalium* were much higher in concordant couples than in discordant couples. Among couples with a male index case, the odds of HIV concordancy were approximately three times greater if both partners were seropositive for HSV-2 and two times greater for *M. genitalium*. No significant relation was observed for hepatitis B, cytomegalovirus, or syphilis. No increase in the prevalence of gonorrhea, chlamydia, or trichomoniasis (detected by culture or antigen detection) was detected in the concordant couples.

As noted by the authors, the cross-sectional study design limits interpretation of these results. The failure to observe a relation between the mucosal STDs, gonorrhea, chlamydia, and trichomoniasis, is likely due to evaluation of prevalent infections. The observed relation between

HSV-2 and HIV infection, as well as *M. genitalium* and HIV infection, may be explained in several ways. The most intriguing possibility is that these infections facilitated HIV transmission, by increasing either infectiousness or susceptibility, or both. Unfortunately, there is no way of knowing which infections came first. Thus, an alternative explanation is that couples with HIV infection could "share" STDs more readily, especially recognizing increased shedding of HSV-2 in genital secretions of patients with HIV.[47] Furthermore, the multivariable analysis was apparently limited to stage of HIV disease and infection status; although vaginal and anal intercourse did not account for the findings, the possibility remains that other factors could explain the observations.

Further elucidation of the relation between HIV infection and STDs, including HSV-2, *M. genitalium*, and other mucosal infections, is essential. If the hypotheses proposed by Perez are substantiated, these common infections may account for a significant proportion of heterosexual HIV transmission. From a population perspective, the importance of a risk factor is a function of both the relative risk of the factor and its prevalence in the population. Although syphilis and chancroid are believed to have high relative risks for HIV transmission, they are relatively uncommon infections in the United States. In contrast, the relatively common mucosal STDs, such as chlamydia, trichomoniasis, and gonorrhea, may play a major role in the sexual transmission of HIV infection because of their high prevalence. The data of Perez et al suggest that herpes simplex and *Mycoplasma* also should be added to the suspect list.[44] Herpes simplex virus-2 is a common infection, with an estimated prevalence of 22% in the United States.[48] The recognition that viral shedding occurs without an overt ulcer may also have important ramifications for HIV transmission. *Mycoplasma genitalium*, also a common infection, is found in both symptomatic and asymptomatic persons.[49]

Given the accumulated evidence for the relation between HIV and STDs, both behavioral and biologic strategies to prevent HIV transmission are warranted. In the absence of a vaccine, it is critical to reduce HIV infectiousness and susceptibility. Treatment of urethritis and cervicitis reduces excretion of HIV in the urethra,[16] semen,[14] and vaginal secretions.[17-19] Syndromic treatment of acute ulcerative and inflammatory STDs reduces the incidence of HIV.[50]

The work from Perez and co-workers suggests that treatment of HSV-2 and *M. genitalium* might also prevent HIV transmission.[44] Current therapeutic strategies for these infections would be insufficient for this purpose. Therapy for HSV-2 is used to suppress symptomatic vesicles or ulcers, but has not been used to reduce asymptomatic viral shedding, although this idea has recently gained considerable attention.[51] For *Mycoplasma* infections single-dose therapy is available.[52] However, asymptomatic infections are neither diagnosed nor treated.

Recommendations to alter approaches to STD management to prevent HIV infection cannot be made on the basis of the observations by Perez et al.[44] However, these results raise a number of intriguing possibilities that must be confirmed with more rigorous study designs. If confirmed, these results will have substantial implications for public health in the United States and elsewhere.

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