

# Classical Sexually Transmitted Diseases Drive the Spread of HIV-1: Back to the Future

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(See the major article by Mlisana et al, on pages 6–14.)

The transmission of human immunodeficiency virus type 1 (HIV-1) depends on the infectiousness of the index case (ie, vector) and the susceptibility of the host [1]. The probability of the transmission event has been extensively studied [1–3], and the risk is often described as about 1 in 1000 coital events [4]. However, large numbers of exposures like these are often derived from studies of stable, heterosexual, discordant couples [4, 5]. By definition, the HIV-1–negative partners in these couples can be defined as “exposed and uninfected” at the time of enrollment. The transmission of HIV-1 is almost certainly often more efficient than reflected in studies of couples and is likely enhanced by amplifying factors [6].

Perhaps no other HIV transmission cofactor has attracted as much attention as sexually transmitted diseases (STDs). More than 20 years ago, Wasserheit and colleagues described the transparent and omnipresent relationship between classical STDs and HIV-1, coining this unfortunate marriage of pathogens “epidemiologic synergy” [7]. We subsequently showed that

infection with *Neisseria gonorrhoeae* greatly increased shedding of HIV-1 from the male genital tract in seminal plasma, offering a biological view of such synergy [8]. In recent years, however, interest in the relationship between STDs and HIV-1 has waned, primarily because it has proven nearly impossible to reduce the spread of HIV-1 through directed or empirical treatment of STDs [9].

In this issue of *The Journal of Infectious Diseases*, Mlisana et al [10] contribute to this consideration. Because of the limited laboratory infrastructure in low- and middle-income countries, treatment of STDs in women often depends on the recognition of signs and symptoms of vaginal discharge, leading to empirical treatment with antibiotics [11, 12]. Syndromic management is important but often suboptimal since a substantial number of people using this method are over- or undertreated [11, 12].

Mlisana and colleagues [10] have further expanded our concerns about syndromic management. Two-hundred forty-two women at risk for HIV-1 infection were enrolled in a prospective cohort. Four things were measured: the presence or absence of a vaginal discharge, detection of  $\geq 1$  STD pathogens, vaginal cytokine concentrations, and HIV-1 acquisition. The results offered a stark reality for HIV-1 prevention and demonstrate yet again that STDs represent a “hidden epidemic,” the title of a compelling Institute of Medicine report

published more than a decade ago [13]. Only 12.3% of women infected with a pathogen that might cause a vaginal discharge had signs or symptoms of infection. Women with STDs were  $>3$ -fold more likely to acquire HIV-1 than those who harbored no pathogens. Women with gonococcal infections, among the most inflammatory of the classical STD agents [14], had had an eye-opening 7-fold increased risk of HIV-1 acquisition, bringing us full circle to earlier reports [8]. Surprisingly, inflammatory cytokines were not significantly different in women with symptomatic STDs, compared with asymptomatic infections, although they were greater than in women with no STDs or with bacterial vaginosis. Passmore et al [15] have reported that some unique inflammatory cytokine profiles predict risk for HIV acquisition.

How can we fit these observations into sensible HIV-1 prevention strategies? Padian et al [9] have provided an exhaustive summary of interventions designed to prevent HIV-1 transmission, emphasizing the general lack of prevention benefit with treatment of classical STDs. The failure of this approach, in my opinion, is not because STDs are not critically important. Rather, we are simply unable to treat the right infections with the right drugs at the right times, and so the results of the interventions prove disappointing. Sadly, except for hepatitis B virus vaccine and HPV vaccine, STD vaccines are not available.

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Where do we go from here? Mlisana and colleagues argue for more frequent STD testing, using point-of-care assays where possible. This recommendation stems directly from our inability to know which women have an STD, as demonstrated in their report. The problem, of course, is that missing healthcare infrastructure and high relative costs for STD testing led to syndromic management of vaginal discharge in the first place, and these limitations have not been resolved. Mlisana et al also indicate that in the absence of some other strategy, the amplification of HIV-1 transmission by STDs—both infectiousness and acquisition—will continue unabated. Perhaps ironically, this past year was filled with great optimism in HIV-1 prevention, leading *The Economist* to focus on “The End of AIDS” [16] and Secretary of State Hillary Clinton to describe an “AIDS-Free Generation” [17]. But the “hidden epidemic” [13] of classical STDs is squarely blocking optimal prevention of HIV-1 transmission. These STDs—symptomatic or asymptomatic—simply cannot be ignored. As we commit to combination HIV-1 prevention, we must redouble our efforts to think of every possible way to recognize and treat classical STDs. Surely this problem is no more impossible to attack or less important than any other part of the HIV-1 pandemic.

## Note

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

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