Amplified HIV Transmission and New Approaches to HIV Prevention

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(See the article by Wawer et al., on pages 1403–9.)

HIV has infected 40,000,000 people, killed >6,000,000 people, and devastated whole sectors of societies [1]. HIV infection is rightly considered by the United Nations to be a major threat to global security and economy [2]. Prevention of the spread of HIV demands precise knowledge of the biology and epidemiology of transmission [3], a challenge that even now has not been completely met. Although several studies of HIV epidemiology (reviewed in [4]) have described heterosexual transmission as occurring in ∼1/1000 coital acts, this number seems far too low to explain the magnitude of the HIV pandemic.

In this issue of the Journal of Infectious Diseases, Wawer et al. [5] provide a new and important understanding of the transmission of HIV. Between 1994 and 1999, the investigators enrolled 15,127 subjects from 56 villages in the Rakai District of Uganda in a trial designed to determine whether intermittent mass therapy directed against sexually transmitted infections (STIs) could reduce the spread of HIV. Although this intervention did not reduce the incidence of HIV infection [6], meticulous and extensive collection of demographic, clinical, and historical data on the participants has led to a steady and compelling stream of analysis [7–9].

In their earlier work [8], the investigators demonstrated that the risk of HIV transmission correlated strongly with blood viral burden and the incidence of genital ulcer disease [9]. In their current work, Wawer et al. [5] make another critically important observation: nearly one-half of the HIV transmission events observed could be ascribed to a sex partner with newly acquired HIV infection.

Although several “couples studies” of HIV transmission [10, 11] have been undertaken in the past, such studies depend on the identification of an index patient with established HIV infection. However, the Rakai investigators retrospectively “constructed” couples from the entire study population based on the subjects’ histories and (more recently) viral genetics [12]. This approach allowed them to detect the transmission of HIV within couples even when both partners were HIV seronegative at the beginning of the study. The authors identified 235 couples for study. On the basis of the number of coital acts reported by both partners, they estimated the probability of HIV transmission from a subject with early infection (an average of 2.5 months after seroconversion) as 8.2 cases/1000 coital acts, with established infection as 7–15 cases/10,000 coital acts, and with advanced (unrestrained and untreated) infection as 2.8 cases/1000 coital acts. Furthermore, the risk ascribed to patients with early infection is likely an underestimate, given that the data collected did not allow for the detection of subjects with (prerseroconversion) acute HIV infection, who are likely to have the highest blood and genital-tract HIV burden [13] and who may have STIs as well [9, 14, 15]. The authors estimate that the risk for HIV transmission from patients with acute infection might be as high as 1 case/50 coital acts—greater than the transmission risk associated with deep needlestick injuries [16].

These results strongly support earlier modeling predictions. Using blood and semen samples harvested from patients at different stages of disease, Chakraborty et al. [4] constructed a probabilistic model of HIV transmission. According to this model, the very high viral burden in semen that has been demonstrated in patients with acute HIV infection should result in an 8–10-fold increase in the risk of male-to-female transmission [13] (figure 1A). Coinfection with “classic” STI pathogens [17, 18] and high-risk behavior in acutely infected patients [19] would also amplify transmission in sexual networks [20] (figure 1B). As early as 1994, Koopman et al. [20] and Jacquez et al. [21] used population modeling to argue that the spread of HIV from patients with early,
transient hyperinfectiousness could contribute disproportionately to the epidemic.

When investigators have searched for people with acute HIV infection, they have been found. Rosenberg et al. [22] reported that 1.0% of patients with negative tests for Epstein-Barr virus infectious mononucleosis had serological results consistent with acute HIV infection. Pincus et al. [23] found that 1.0% of patients with “any viral symptoms” in a Boston urgent-care center had unsuspected acute HIV infection. In a Malawi STI clinic, 2.8% of all male clients with acute STIs had acute HIV infection [18]. However, acute retroviral symptoms occur in only one-half of patients, and the signs and symptoms are nonspecific [24]. Furthermore, the clinical diagnosis of acute HIV has relied on tests (HIV p24 antigen or nucleic-acid amplification tests) that add significantly to the costs of testing and have been dogged by concerns with specificity. Recent innovations in high-throughput group testing for HIV RNA in antibody-negative specimens allow more efficient identification of people with acute infection, regardless of clinical presentation [25, 26]. Not surprisingly, such patients are most often detected in STI clinics [27], which supports the importance of cotransmission of HIV and STIs.

If patients with acute HIV infections can be more readily detected, the opportunities for novel care and prevention are considerable. The results of clinical trials have suggested that very early antiretroviral therapy and/or immune-based therapy may benefit the acutely HIV-infected patient [28–30]. In addition, aggressive attempts to reduce the size of the latent HIV pool in these patients are likely to be forthcoming [31].

Prevention of HIV transmission is of paramount importance. Historically, HIV prevention efforts have focused on HIV-uninfected subjects, whereas prevention directed at infected subjects has only gained attention very recently [32, 33]. To respond adequately to the threat of amplified HIV transmission, HIV prevention strategies must use complementary diagnostic, behavioral, and biological tools. Unique partner notification, counseling and referral services [34], and novel biological interventions should be developed specifically for people with acute HIV infection. Wawer et al. [5] have confirmed the remarkable threat of HIV transmission posed by people with newly acquired HIV infection. The challenge now is to waste no time in finding the most creative strategies to incorporate these results into global HIV prevention efforts.

References

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