seroconversion until death (assumed to occur after 10 years [3]). However, many HIV-infected individuals will have additional sex partners during the course of their infection, and this significantly alters the pattern. The black bars in figure 1 show the other extreme, in which the seroconverter has the same coital frequency but all sexual contacts are susceptible. This might approximate the situation among sex workers in a relatively low-prevalence setting. In this case, only 23% of secondary infections are attributable to early-stage infection, 46% to the asymptomatic period, and 30% to late-stage infection.

Second, the Rakai studies have demonstrated the importance of biological cofactors such as genital ulcer disease (GUD), which substantially enhance the risk of transmission per coital act. Detailed analyses have shown that prevalences of sexually transmitted infections (STIs) in Ugandan cohorts were relatively low during the period of the studies [4]. In settings with higher STI rates, particularly where GUD is common, the low HIV transmission rate during the asymptomatic period is likely to increase significantly, as is illustrated in figure 1B of the editorial commentary by Cohen and Pilcher [2], along with the proportion of HIV transmission events.

Third, the relative importance of different stages of infection will evolve during the course of an HIV epidemic. In a concentrated or early epidemic, most infections may occur among high-risk groups with many sex partners, so that the black bars in figure 1 may be closer to the truth, although, initially, few HIV-infected subjects will have reached late-stage infection. Later in a generalized epidemic, more infections may occur among individuals with few partners, and the pattern will change to more closely resemble that shown by the white bars in figure 1. In a contracting epidemic, as is currently seen in Uganda, the number of incident infections is small in comparison with the number of prevalent infections, so that, even if most couples are monogamous, most new infections will be attributable to the later stages of infection. In the Rakai study [1], for example, only 10 (15%) of 68 seroconversions were attributable to transmission by acutely infected individuals (during the first 5 months of infection), and not one-half of them, as is suggested in the commentary.

In summary, HIV-negative partners of acutely infected individuals are clearly at very high risk, but the population-level effects of interventions targeted at acutely infected individuals will depend on the sexual behavior of HIV-infected individuals, the stage and extent of the HIV epidemic, and the prevalence of STIs and other biological cofactors.

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References
4. Orroth K, Koromump E, White R, et al. Higher STI rates, particularly among individuals who had seroconverted ≤1 year earlier [3]. Herpes simplex virus type 2 (HSV-2) represents the most common STI associated with GUD in Rakai [4]. HSV-2 seroprevalence in Rakai is high and is equivalent to rates in other African rural populations [5], and >60% of the partners in these HIV-discordant couples were HSV-2 seropositive. The role of HSV-2 in HIV transmission dynamics is related both to recurrent ulceration and to HSV-2 effects on HIV load [3, 6, 7]. Regardless of etiology, GUD occurring at high rates will increase transmission at all stages of HIV infection and, depending on patterns of sexual partnerships, may alter the relative potential epidemiological implications of our findings of increased risk of HIV transmission per coital act during early and late infection. We agree with their observation that the contribution of early infections to overall HIV transmission in a given population will be highly dependent on sexual behaviors, including, as indicated in our article [2], the numbers of partners, coital frequency, and the structure of sexual networks” (p. 1408). In a population in which HIV-positive individuals acquire new partners throughout the average 10-year course of infection, the proportion of transmissions contributed by persons with latent HIV infection may be considerable. Our analysis, which included only married couples, was not designed to directly assess population-level effects, although the data provide a valid basis for modeling HIV dynamics in communities.

We also agree that sexually transmitted infections (STIs) and, in particular, genital ulcer disease (GUD) increase the risk of HIV transmission at all stages of HIV infection. In our analyses, after adjustment for stage of HIV infection and HIV load, the risk of HIV transmission was 2-fold higher if the HIV-positive index partner reported GUD, and episodes of GUD were reported in 11.6% of follow-up intervals [2]. (In a separate Rakai study, GUD was reported by 17.3% of recently HIV-infected individuals, compared with 11.6% of individuals who had seroconverted ≤1 year earlier [3].) Herpes simplex virus type 2 (HSV-2) represents the most common STI associated with GUD in Rakai [4].
contribution of each stage to population-level HIV incidence.

Finally, it is true that, in the data we presented, only 10 (15%) of 68 seroconversions were attributable to transmission by acutely infected individuals. However, this proportion represents an artifact of the study design, since couples were included regardless of the stage of infection in the index partner. As was noted by Cohen and Pilcher [8], in our analyses, 43% of the 23 recent seroconverters transmitted HIV to their partner within the first 5 months. Thus, had we been able to follow all couples from the time of the initial index seroconversion, we would expect that ~40% would have become concordant HIV positive within a short time frame. The 212 couples who entered the study with an HIV-prevalent or late-stage index partner represent a subgroup of “survivors,” in which the HIV-negative partner evaded HIV acquisition during the early stage of the partner’s infection. The Rakai study cohort includes >300 concordant HIV-positive couples, many of which are likely to have become concordantly infected during the index partner’s acute/early infection, which occurred before the period of observation.

We thank Hayes and White for their insightful comments and agree that the behavioral and epidemiological context must be considered in any extrapolation of our findings to other populations.

References


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