study design and methodology and suggest that the field must move forward without preconceived bias as to which results will be considered valid.

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Amplified HIV Transmission during Early-Stage Infection

To the Editor—Effective preventive interventions against heterosexual HIV transmission rely on an accurate understanding of HIV transmission dynamics. A key question is how the rate of transmission of HIV per coital act varies during the course of infection. Few empirical data have been published on this issue, and we are dependent mostly on the careful longitudinal studies performed in the Rakai district of Uganda.

In a recent issue of the Journal of Infectious Diseases, Wawer et al. [1] presented an elegant analysis of retrospective data on the Rakai study cohort. From 235 monogamous HIV-negative partners of HIV-infected index cases, they obtained estimates of the transmission rate per coital act according to stage of HIV infection. The highest transmission rate, 8/1000 coital acts, was observed during the first 5 months after seroconversion, falling to ~1/1000 coital acts during the long period of asymptomatic infection and increasing thereafter to 4/1000 coital acts during late-stage infection, from 6 to 15 months before the death of the index case. No estimates are presented for the last 5 months before death, although the authors suggest that coital frequency is likely to decrease during late-stage infection.

On the basis of these important data, commentators [2] pointed to the importance of early-stage infection for HIV transmission, stating that "nearly one-half of the HIV transmission events observed could be ascribed to a sex partner with newly acquired HIV infection" (p. 1391) and calling for interventions targeted at acute HIV infection. For 3 main reasons, we caution about overestimating the proportion of transmission events in sub-Saharan Africa that are attributable to acute infection.

First, the implications of these data for viral spread depend on the sexual behavior of HIV-infected individuals. The white bars in figure 1 show the proportion of HIV transmission events, based on the Rakai estimates, that occur during each stage of infection, under the assumption that the HIV seroconverter has only 1 subsequent HIV-negative sex partner. As many as 41% of transmission events would occur during the first 5 months after seroconversion; a further 44% would occur during the subsequent asymptomatic period, from 6 months to 8 years after seroconversion; and 14% would occur during late-stage infection, from 8 years after

Figure 1. Proportion of HIV transmission events according to time from infection, if the seroconverter is assumed to have only 1 subsequent sex partner (white bars) or if all subsequent sexual contacts are with susceptible individuals (black bars). Assumptions include that the time from infection to death is 10 years and that transmission does not occur during the 5 months before death.
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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Reply to Hayes and White

To the Editor—Hayes and White [1] raise a number of pertinent issues regarding the 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]. 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