Probability of Heterosexual HIV-1 Transmission per Coital Act in Sub-Saharan Africa

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(See the article by Hughes et al, on pages 358–65.)

Estimating the probability of human immunodeficiency virus (HIV) infection per coital act has been the holy grail of HIV epidemiology for >2 decades. These estimates are needed for modeling the epidemic and for projecting the effects of preventive interventions. However, the estimates of the probability of transmission per sex act, largely derived from empirical studies and modeling based on HIV-discordant couples, have been troublingly heterogeneous, varying between low- and high-income countries, male-to-female versus female-to-male transmission, stage of HIV infection in the positive partner, the effects of sociodemographic and behavioral characteristics, and sexually transmitted infection cofactors [1–5]. An article by Hughes and colleagues in this issue of the *Journal* provides valuable new estimates of HIV transmission per coital act in sub-Saharan Africa [6]. This study of 3297 HIV-discordant couples enrolled in a randomized trial of acyclovir suppressive therapy in eastern and southern Africa has the advantage of large numbers, frequent follow-up with quarterly visits, and genetic linkage of the transmitted virus to the index HIV-positive partner so as to exclude infections acquired from external partners. The acyclovir intervention did not affect HIV acquisition [7], so this trial population provides an excellent observational study with which to estimate per coital HIV transmission. In addition, the investigators used rigorous statistical methods to estimate per coital act transmission probabilities and to assess the effects of covariates.

However, Hughes et al could only assess infectivity during latent stage disease, and were unable to measure transmission during early or late stages of HIV disease, which is associated with higher infectivity per coital act [1–3, 5, 8]. The investigators did not identify any acute or recent infections among the index positive partners in these stable HIV-discordant couples. Eligibility for enrollment into the randomized trial excluded HIV-infected partners with CD4 counts <250 cells/mL, and participants whose CD4 counts declined below that level were provided antiretroviral therapy. Also, the enrolled HIV-discordant couples who had accepted voluntary couples counseling and testing had very high rates of condom use (93% of sex acts were reported as protected), so generalizability to other sub-Saharan African settings with substantially lower couples-counseling rates and condom use is problematic [9].

Despite these caveats, the study provides important new information and confirms findings from prior investigations. Overall infectivity was 1–2 cases per 1000 per coital acts, similar to that reported during latency in low-income countries but higher than estimates from many industrialized countries [1, 2, 4, 5]. The HIV load in the index infected partner was the main driver of transmission, with a 2.9-fold adjusted risk of infection per $\log_{10}$ increment in viral load. This is somewhat higher than prior estimates of transmission risk associated with viral load [4, 10, 11], possibly because the short follow-up intervals and frequent viral load measurements allowed more precise estimates of the association between viral burden and infectivity. The male-to-female and female-to-male transmission rates per sex act were similar after adjustment for viral load, which is compatible with other studies from low-income populations that reported no gender-specific differentials in infectivity [1, 4], but is contrary to findings from high-income countries that suggest greater male than female infectivity [1]. Older age was associated with reduced transmission per sex act, as has been previously reported [2, 4], and male circumcision reduced female-to-male transmission by approximately 47%, an effect compatible with the efficacy reported in 3 randomized trials of circumcision for HIV prevention [12–14]. Herpes simplex virus type 2 infection and genital ulceration increased transmission between 2- and 2.7-fold, as reported in prior studies [1, 4, 15]. The

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estimated 78% protection afforded by condom use suggests a very high rate of consistent use [16], which is atypical for married couples in sub-Saharan Africa. In summary, it is reassuring that this large study by Hughes et al replicated findings from many prior studies; it also probably provides the most precise estimates of transmission per coital act during latent HIV disease.

There are many inherent difficulties in studying transmission per coital act in HIV-discordant couples. First, reporting of unprotected sex acts is subject to recall and reporting error and is likely to be imprecise. Second, HIV discordance is a transient state because intradyad transmission leads to concordant status, and couples who remain HIV discordant over time are likely to be selected survivors who may be at lower risk of transmission/acquisition. In addition, marital dissolution is common among HIV-discordant couples, particularly if the female is the infected partner [17], and this may lead to self-selection of intact partnerships remaining under observation.

There is much we still do not know about the complex host and viral factors affecting transmission risk. Transmission probabilities of 1–2 infections per 1000 coital acts during latent-stage HIV infection are too low to explain explosive heterosexual HIV epidemics [18]. Much higher transmission rates during acute and recent infection [3, 5, 7], particularly in combination with multiple concurrent partnerships, overlapping sexual networks, cofactors such as genital ulceration and possibly other sexually transmitted infections, and low rates of condom use, are thought to play major roles in HIV spread in populations [19], including the generalized epidemics in sub-Saharan Africa. In summary, the study by Hughes et al has added to our empirical knowledge, but much about transmission probabilities per sex act remains, in the words of Winston Churchill, "a riddle wrapped in a mystery inside an enigma."

Note

Potential conflicts of interest. All authors: No reported conflicts.

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