MAJOR ARTICLE

Rates of HIV-1 Transmission per Coital Act, by Stage of HIV-1 Infection, in Rakai, Uganda

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Background. We estimated rates of human immunodeficiency virus (HIV)–1 transmission per coital act in HIV-discordant couples by stage of infection in the index partner.

Methods. We retrospectively identified 235 monogamous, HIV-discordant couples in a Ugandan population-based cohort. HIV transmission within pairs was confirmed by sequence analysis. Rates of transmission per coital act were estimated by the index partner's stage of infection (recent seroconversion or prevalent or late-stage infection). The adjusted rate ratio of transmission per coital act was estimated by multivariate Poisson regression.

Results. The average rate of HIV transmission was 0.0082/coital act (95% confidence interval [CI], 0.0039–0.0150) within ~2.5 months after seroconversion of the index partner; 0.0015/coital act within 6–15 months after seroconversion of the index partner (95% CI, 0.0002–0.0055); 0.0007/coital act (95% CI, 0.0005–0.0010) among HIV-prevalent index partners; and 0.0028/coital act (95% CI, 0.0015–0.0041) 6–25 months before the death of the index partner. In adjusted models, early- and late-stage infection, higher HIV load, genital ulcer disease, and younger age of the index partner were significantly associated with higher rates of transmission.

Conclusions. The rate of HIV transmission per coital act was highest during early-stage infection. This has implications for HIV prevention and for projecting the effects of antiretroviral treatment on HIV transmission.

Model estimates suggest that the rate of heterosexual HIV-1 transmission per coital act follows a U-shaped curve, being highest during the postseroconversion period, lower during latency, and increasing with advancing disease [1–4]. This is supported by findings that blood HIV load, which is higher during the postseroconversion period and during advanced disease, is the principal predictor of heterosexual transmission [5–8]. However, empirical data on heterosexual HIV infectivity by stage of disease are limited. We report the rate of HIV transmission per coital act in 235 heterosexual, HIV-discordant couples, with one HIV-infected partner and one monogamous HIV-uninfected partner, who were identified retrospectively from a population-based cohort in Rakai, Uganda.

SUBJECTS AND METHODS

Between 1994 and 1999, we enrolled 15,127 adults into a community randomized trial of STD Control for AIDS Prevention, in Rakai District, Uganda. Study methods, described elsewhere [9, 10], are summarized briefly.

All consenting residents 15–59 years old, who lived in 56 rural villages, were surveyed in the home at 10-month intervals for up to 40 months. Trial participants were enrolled as individuals; provided written, informed consent; and were guaranteed confidentiality. Condoms and voluntary HIV counseling and testing, for individuals and for couples, were promoted and provided free

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of charge. Participants were encouraged to share their HIV results with their partners; however, Uganda Ministry of Health policy does not allow the involuntary disclosure of HIV results to third parties, including partners [11]. Data linkage to identify couples was conducted after completion of the trial. Antiretroviral therapy (ART) was not available in Uganda at the time of the study, but participants were offered free general health care and treatment for opportunistic infections. The study was approved by human subjects review boards at the Uganda Virus Research Institute, the AIDS Research Subcommittee of the Ugandan National Council for Science and Technology, Columbia University, and Johns Hopkins University.

At each 10-month survey visit, participants provided serological samples and were administered a sociodemographic, behavioral, and health interview, which included questions on numbers of partners and the respondent's relationship to each partner. Coital frequency was determined by asking, "When you have relationships with this partner, how frequently do you usually have intercourse per day, per week and per month?" The monthly frequency of intercourse was used to estimate the number of coital acts during the period of observation. Male and female partners reported similar coital frequency. In couples in which the woman was the HIV-infected index partner, women reported a mean of 9.7 acts/month, and men reported a mean of 9.8 coital acts/month. In couples in which the man was the HIV-infected index partner, women reported a mean of 8.8 coital acts/month, and men reported a mean of 8.3 coital acts/month [12].

Serum, urine, and self-administered vaginal swab samples were collected from all participants at each 10-month survey visit. Serological testing was conducted for syphilis (Toluidine Red Unheated Serum Test [New Horizons], with confirmatory *Treponema pallidum* hemagglutination assay [Sera-Tek; Rujibero]) and for herpes simplex virus type 2 (HSV-2; HerpeSelect 2 ELISA IgG [Focus], with Western blot confirmation [13] of ELISA-positive samples). Urine samples were assayed for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (ligase chain reaction on urine samples [LCx Probe System; Abbott Laboratories]). In women, vaginal swabs were tested for *Trichomonas vaginalis* (InPouch TV culture; BioMed Diagnostics) and bacterial vaginosis (quantitative morphology of gram-stained slides). HIV serostatus was determined by use of 2 EIAs (Vironostika HIV-1; Organon Teknika and Cambridge Biotech). EIA-discordant samples and new HIV seroconversions were confirmed by Western blot (HIV-1 Western Blot; Bio-Merieux-Vitek). The serum HIV load in HIV-positive partners was determined by RNA reverse-transcription polymerase chain reaction (Amplicor HIV-1 Monitor 1.5 Assay; Roche Molecular Systems). HIV load was determined in the first serum sample available after HIV seroconversion (the incident index group), the first serum sample available after entry into observation (the prevalent index group), and the last serum sample available (the late-stage index group). HIV subtypes A, D, and A/D recombinants predominate in Rakai; however, in the present analysis, too few incident and late-stage index partners had A or A/D infections to allow an assessment of the effects of subtype by stage of infection.

After completion of the trial, analyses identified 414 HIV-discordant couples who subsequently received at least 1 follow-up visit that permitted the retrospective assessment of HIV transmission. In 239 of these couples, the HIV-uninfected partners reported that they were monogamous (defined as having only 1 sex partner during the period of observation). In 72 of 239 couples, the HIV-negative partner acquired HIV during follow-up. At the time of the retrospective analysis reported here, archival serum samples were available from both partners in 46 (64%) of 72 couples with seroconversion, which permitted the assessment of molecular linkage between the index partner's and the seroconverting partner's HIV-1 strains. Viral sequence data from the *gag* and gp41 regions [14] were compared in both partners on the basis of sequence distance and phylogenetic inferences, by use of bootstrap methods [8, 14–16]. Four (8.7%) of 46 couples had nonhomologous virus and were excluded from this analysis: 3 of these 4 couples were originally in the prevalent index group, and 1 was in the late-stage index group. In the remaining 26 couples in whom the HIV-uninfected partner seroconverted, there was insufficient remaining archival serum samples from 1 or both partners to assess molecular linkage. The behavioral and sociodemographic characteristics of the 26 couples and the HIV load distribution of the HIV-infected index partners were similar to those of the 46 couples in whom we examined molecular linkage. We would expect their rate of nonmarital HIV acquisition to be similar to the modest level observed in the couples with molecular assessment, resulting in ~2 misclassifications. We thus included these 26 couples in the present analysis, for a total of 235 couples for whom we present results.

In 23 couples, both partners were HIV uninfected at enrollment, and the index partner seroconverted during follow-up (incident index couples). In 161 couples, the index partner was HIV infected at enrollment and survived during follow-up (prevalent index couples), and, in 51 couples, the index partner was HIV infected at study entry and died during follow-up (late-stage index couples). None of the persons included in the analysis reported homosexual contact, anal intercourse, blood transfusion, or injection drug use during the period of observation.

For the 23 couples who entered as concordant HIV negative, the mean follow-up time was 17.3 months. In 10 of these couples, both members seroconverted during the same follow-up interval, and the partner who reported extramarital sexual contact was assumed to be the HIV-infected index partner. In the 161 couples with a HIV-infected prevalent index partner, the mean follow-up time was 30.6 months. In the 51 couples in which the HIV-

infected index partner died, the mean follow-up time was 26.9 months. Death was estimated to have occurred at the midpoint of the intersurvey period, ~5 months after the preceding interview, and HIV transmission was assessed for each of the 10-month intervals before the last data collection (i.e., 6–15 and 16–25 months before the death of the index partner). We were unable to assess transmission during the months immediately preceding death, because more than one-half of the surviving spouses moved away from the area shortly after their partner's death, before the next scheduled 10-month follow-up survey visit. Of the 13 spouses who were HIV uninfected at the time of the last interview before the partner's death and who remained in the community, none had seroconverted.

In the incident index couples, the index partner's infection was assumed to have occurred at the midpoint of the intersurvey period, ~5 months after the previous survey visit. In the 10 couples in which both partners seroconverted during the same follow-up interval, transmission from the index partner to the initially uninfected partner was estimated to have occurred ~2.5 months after the seroconversion of the index partner—that is, at the midpoint of the estimated 5-month period during which the uninfected partner was exposed to HIV by the newly infected index partner. In the prevalent and late-stage index groups, transmission to the initially uninfected partner was estimated to have occurred at the midpoint of a given 10-month interval.

The average rate of HIV transmission per coital act for each exposure interval was estimated as the number of seroconversions divided by the total number of coital acts during an exposure interval. Rates of transmission per coital act were examined by use of the HIV-infected index partner's sociodemographic, behavioral, and health covariates. Symptoms of sexually transmitted infections (STIs)—including genital ulcer disease (GUD), discharge or dysuria, and symptoms potentially related to HIV/AIDS—were ascertained via interview; the presence of clinical signs was assessed by physical examination. For characteristics that changed over time (e.g., GUD or potential AIDS-related symptoms and condom use), time varying status, as reported for each follow-up period, was used in analyses.

Adjusted rate ratios (RRs) of transmission per coital act and 95% confidence intervals (95% CIs) were estimated by Poisson multiple regression by use of the natural logarithm of the total number of coital acts as an offset term. Robust SEs were estimated by generalized estimating equation methods, to adjust for correlated data. Covariates included in the Poisson model were those variables that were found to be significantly associated with transmission per coital act in univariate analyses. Because of the strong correlation between HIV load and probability of transmission, separate models were constructed with and without the HIV load covariate.

RESULTS

The mean coital frequency was 10.2 coital acts/month (median, 8.3 coital acts/month) among couples with an incident index partner and 10.0 coital acts/month (median, 8.3 coital acts/month) among couples with a prevalent index partner. Coital frequency decreased before the death of an index partner, from a mean of 8.7 coital acts/month (median, 8.0 coital acts/month) during the 16–25 months before death to a mean of 6.2 coital acts/month (median, 5.2 coital acts/month) during the 6–15 months before death.

Approximately 5 months after seroconversion of an index partner, the median serum HIV load was 30,000 copies/mL ($\log_{10}$HIV load, 4.48 copies/L; range, ⩽399 [undetectable]–3,100,000 copies/mL); by 15 months, the median HIV load had decreased to 2600 copies/mL. Among prevalent index partners, the median serum HIV load increased from 10,300 copies/mL ($\log_{10}$ HIV load, 4.01 copies/mL) at study entry to 15,000 copies ($\log_{10}$ HIV load, 4.18 copies/mL) after 30 months of follow-up. Among late-stage index partners, the median HIV load was 112,600 copies/mL ($\log_{10}$ HIV load, 5.05 copies/mL) at the date of the last test, which was conducted, on average, 5 months before death.

Table 1 shows the proportions of HIV-infected index partners who transmitted infection to their partners and the rate of transmission per coital act, by stage of HIV infection and by interval of follow-up. A total of 68 (28.9%) of 235 index partners transmitted HIV to their initially uninfected partners. The proportion of HIV-positive partners transmitting infection was highest among incident index partners, of whom 10 (43.4%) of 23 transmitted infection within ~2.5 months and 13 (56.5%) of 23 transmitted infection within ~35 months after their own seroconversion. Prevalent index partners transmitted infection at an average annual rate of 8.4% (range, 6.7%–10.9%). Among late-stage index partners, 19 (37.3%) of 51 transmitted infection during the ~6–35 months before death.

The overall rate of HIV transmission per coital act was 0.0012 (95% CI, 0.0009–0.0015). Transmission per act was highest in the interval immediately after the acquisition of HIV by the index partner (0.0082/coital act [95% CI, 0.0039–0.0150]), under the assumption of ~2.5 months of exposure for the HIV-negative partner (table 1 and figure 1). During the subsequent 10-month interval (~6–15 months after seroconversion by the index partner), the rate of transmission decreased to 0.0015/coital act (95% CI, 0.0002–0.0055), which was not significantly different from that observed among partners of prevalent index partners (0.0007/coital act [95% CI, 0.0006–0.0011]). Among late-stage index partners, the rate of transmission per coital act increased significantly during the last 2 follow-up intervals before death (6–25 months before death, 0.0036/coital act [95% CI, 0.0020–0.0059]).

By univariate analyses (not shown), characteristics of index

Table 1. The proportion of HIV transmissions and HIV transmission rates per coital act by, stage of infection and by interval of follow-up, Rakai, Uganda, 1994–1999.

Characteristic	Transmissions/ no. of index partners (%)	Coital acts, no.	Rate of transmission per coital act (95% CI)
Incident index partner			0.0036 (0.0019–0.0062)
Time after index seroconversion, months			
0–5[a]	10/23 (43.5)	1221	0.0082 (0.0039–0.0150)
6–15	2/13 (15.4)	1313	0.0015 (0.0002–0.0055)
16–35[b]	1/7 (14.3)	1035	0.0010 (0.0000–0.0054)
All incident index partners combined	13/23 (56.5)	3569	0.0012 (0.0009–0.0015)
Prevalent index partner			
Follow-up interval, months			
0–10	14/161 (8.7)	15,728	0.0009 (0.0005–0.0015)
11–20	9/129 (7.0)	13,729	0.0007 (0.0003–0.0012)
21–30	10/92 (10.9)	10,630	0.0009 (0.0005–0.0017)
31–40	3/45 (6.7)	8438	0.0004 (0.0000–0.0010)
All prevalent index partners combined	36/161 (22.4)	48,525	0.0007 (0.0006–0.0011)
Late-stage index partner			
Time before index partner's death, months			
26–35	2/22 (9.1)	1432	0.0014 (0.0002–0.0050)
16–25	9/35 (25.7)	2792	0.0032 (0.0015–0.0061)
6–15	8/31 (25.8)	1878	0.0043 (0.0018–0.0084)
All late-stage index partners combined	19/51 (37.3)	6102	0.0031 (0.0020–0.0051)
All couples combined	68/235 (28.9)	58,196	0.0012 (0.0009–0.0015)

NOTE. CI, confidence interval.

[a] Based on ~2.5 months of partner exposure after the initial infection in the HIV-positive index partner.

[b] Two 10-month intervals were combined because of small numbers.

partners that were associated with a higher rate of HIV transmission per coital act were younger age (15–29 years), higher HIV load ($\geq$3.50 $\log_{10}$ copies/mL), and the presence of GUD. No significant association was seen with the sex of the index partner, circumcision status (in male index partners), AIDS-defining symptoms, symptoms of discharge or dysuria, or laboratory evidence of STIs. Forty-seven couples (19.6%) reported the occasional use of condoms, and no couple reported consistent use. There was no significant difference in the rate of HIV transmission per coital act with inconsistent condom use, compared with no reported use, at any stage of infection.

Table 2 shows unadjusted and adjusted RRs of HIV transmission per coital act by stage of HIV infection and by characteristics of index partners that were significant according to univariate analysis. In the adjusted model that included HIV load, younger age (<30 years; RR, 2.38), the presence of GUD (RR, 2.04), increasing quartiles of HIV load (RR, 7.06 for the highest quartile), and early- and late-stage HIV infection (RR, 4.98 and 3.49, respectively) remained significantly associated with a higher risk of transmission per coital act. The exclusion of HIV load from the model resulted in higher RRs for transmission risk during early-stage (RR, 7.23) and late-stage (RR, 5.81) infection.

DISCUSSION

The overall rate of HIV transmission observed in these discordant couples, 0.0012/coital act, is consistent with previous estimates from Rakai [12], Europe, and North America [3, 17]. The present analysis, however, provides the first empirical data on the substantial variation in transmission by stage of HIV-1 infection. After seroconversion of the index partner, the rate of transmission (0.0082/coital act) within the first 2.5 months was almost 12-fold higher than that observed in prevalent index couples (0.0007/coital act). The rate then increased significantly again ~2 years before the index partner's death (table 1 and figure 1). Risks of transmission per act remained significantly higher during early- and late-stage HIV infection, after adjustment for multiple covariates (table 2); this pattern is consistent with model estimates [1, 18, 19].

In the 46 couples with one seroconverting partner for whom we conducted molecular linkage, >91% of the seroconverting partners acquired a virus strain that was homologous to that found in the infected index partner: the 4 couples with non-homologous virus strains were excluded from the analysis. None of the partners reported anal intercourse during follow-up, consistent with the fact that we observe virtually no evidence of anal or rectal trauma compatible with anal intercourse in

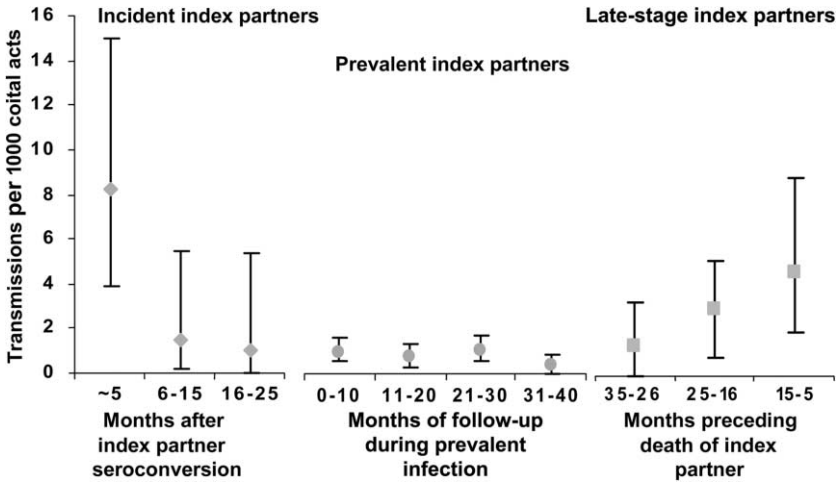

Figure 1. HIV transmission per coital act, and 95% confidence intervals, by follow-up interval

Rakai Program STD clinics. In addition, reported receipt of injections is not associated with the acquisition of HIV in this population [20]. The data thus reflect the effects of stage of HIV infection on heterosexual vaginal transmission.

We retained the 26 couples with proven transmission for whom we could not conduct molecular linkage (because of insufficient archival serum samples) in the analysis. Their characteristics did not differ from those of the 46 couples for whom linkage analysis was possible and for whom we observed a low rate (8.7%) of nonmarital HIV acquisition. It is thus possible that ~2 of 26 couples also acquired HIV from outside the marital union, but this degree of misclassification would have only a minimal effect on study results.

The 40-month maximum follow-up period in our analysis did not permit observation of any couples for the entire period between seroconversion of the index partner and death—a period of 8–10 years, on average, in rural Uganda [21, 22]. However, we were able to reconstruct the probable pattern of transmission rates during the course of infection. In 23 couples, the index partner seroconverted within a known 10-month period. Although the timing of index infection was not known in the 161 couples with a prevalent index partner, most of them were

Table 2. Unadjusted and Poisson-adjusted rate ratios (RRs) of HIV transmission per coital act, Rakai, Uganda, 1994–1999.

Characteristic of HIV-positive index partner	No. of index partners (or index partner follow-up intervals[a])	Unadjusted RR of HIV transmission (95% CI)	Adjusted RR of HIV transmission (95% CI) model with HIV load	Adjusted RR of HIV transmission (95% CI) model without HIV load
Age				
15–29 years	118	2.11 (1.2–3.95)	2.38 (1.30–4.38)	2.18 (1.19–4.00)
⩾30 years	117	1	1	1
GUD				
Yes	64[a]	2.19 (1.07–4.47)	2.04 (1.04–3.99)	2.05 (1.02–4.14)
No	489[a]	1	1	1
HIV load, quartile, $\log_{10}$				
⩾4.89	57	9.62 (3.00–30.84)	7.06 (2.29–21.81)	…
4.17–4.88	54	7.18 (2.30–22.38)	6.39 (2.10–19.42)	…
3.50–4.16	56	3.56 (1.07–11.81)	3.31 (1.01–10.80)	…
0–3.49	57	1	1	
Stage of HIV infection				
Incident[b]	23	8.25 (3.37–20.22)	4.98 (2.00–12.39)	7.25 (3.05–17.25)
Late stage[c]	161	5.45 (2.72–10.92)	3.49 (1.76–6.92)	5.81 (3.00–11.35)
Prevalent[d]	51	1	1	1

NOTE. CI, confidence interval; GUD, genital ulcer disease.

[a] Denominator denotes no. of intervals in which GUD was present or absent.
[b] Based on the first 5 months after the index partner's seroconversion.
[c] Based on the 6–25 months before the index partner's death.
[d] Based on all available follow-up intervals (i.e., up to 40 months).

monitored for at least 3 10-month intervals, and the rate of transmission was relatively stable over time, providing an estimate of the average transmission rate per act during latent HIV infection. A total of 51 index partners died; the rate of HIV transmission per coital act ⩾2 years before death was not significantly different from that observed during latency or ⩾6 months after seroconversion of the index partner (table 1 and figure 1), which suggests overlap among the 3 groups.

We were unable to observe the magnitude or the duration of the peak viremia or the rate of HIV transmission per coital act during the weeks immediately after HIV acquisition in the index partner. Although the median serum HIV load observed ~5 months after seroconversion (30,000 copies/mL) was similar to levels observed in other populations at a comparable time point [23], recent data from Malawi have suggested a peak HIV load of 6.10 $\log_{10}$ copies/mL (>1 million RNA copies/mL) shortly after the acquisition of HIV [24]. The rate of transmission per coital act may thus be very high for a short period immediately after HIV infection. In Rakai couples, if the average length of exposure between infection of the index partner and HIV transmission was only 1 month (encompassing ~10 coital acts), rather than the 2.5 months that we estimated, the rate of transmission during this period could be as high as 0.02/coital act. In populations, the epidemiological effects of different magnitudes and durations of the peak rate of transmission would depend on the numbers of partners, coital frequency, and the structure of sexual networks [1, 25–27].

Because we could not observe the effect of short-term variations in HIV load on transmission, this may underestimate the effects of HIV load in the multivariate model (table 2). The model suggests, however, that HIV load may not explain all of the increased risk seen during early-stage disease. Potential contributing factors could include higher susceptibility in newly exposed, uninfected partners and the presence of GUD. In Rakai, we observed high rates of genital ulcers, particularly among HSV-2–seropositive persons, during early-stage HIV infection [28].

The likelihood of transmission within a partnership over time is likely to be heterogeneous and nonlinear [29]. Our data do not capture the effects of short-term variations in infectivity and susceptibility but describe the average transmission rate per coital act during different stages of HIV infection in the index partner. In couples with prevalent index partners, the rate of transmission per coital act remained relatively constant during each 10-month period of the 40-month follow-up, which suggests that the average infectivity rate per coital act was stable during this period.

Of all the 741 Rakai couples with HIV infection who were retrospectively identified between 1994 and 1999, 414 (55.9%) were HIV discordant and 327 (44.1%) were concordant HIV positive at enrollment. In the present study, only 13 (57%) of 23 of initially negative partners remained uninfected ~5 months after the index partner seroconverted. Couples in whom transmission did not occur during early infection, and those who remained persistently discordant over time, may represent a selected subgroup of "survivors" in whom either the index partners were less infectious and/or the seronegative partners were less susceptible [26]. We are undertaking additional studies to examine such potential factors.

The Rakai data were collected from stable heterosexual couples, whose primary risk was through vaginal intercourse, and additional studies are required to examine transmission by stage of HIV infection in other epidemic settings. Nonetheless, our data have a number of clinical and epidemiological implications.

The highest rate of transmission per coital act, as well as the highest proportion of transmissions, occurred during early-stage infection in index partners, a time when few seroconverters know their HIV status or receive ART. Although the rate was also higher during late-stage infection, the overall contribution of the latter to a heterosexual HIV epidemic is likely to be limited, because individuals with advanced HIV infection report less sexual intercourse and have fewer partners, and only a minority of couples remain discordant by this stage. Thus, ART, initiated relatively late during infection, under current guidelines [30], may have only a modest impact on HIV transmission [31]. Also, because most HIV transmissions occur before index cases are eligible to receive ART, the heterosexual spread of drug-resistant HIV may be modest in this population. Measures that prevent primary HIV infection or reduce early viremia (as may occur with HIV vaccines) are likely to have a greater effect than ART on the spread of HIV. Increased efforts to identify persons with early-stage HIV infection are also warranted, to promote safe behaviors, and, where appropriate, to provide ART [19, 30]. In conclusion, the empirical estimates of the rates of heterosexual HIV transmission per coital act, by stage of HIV infection in index partners, reported here show high rates of transmission during early- and late-stage disease, which may assist in epidemic modeling, in the design and evaluation of HIV prevention strategies, and in the assessment of the likely epidemiologic impact of ART.

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