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Female-to-Male Infectivity of HIV-1 among Circumcised and Uncircumcised Kenyan Men

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Background. A lack of male circumcision has been associated with increased risk of human immunodeficiency virus type 1 (HIV-1) acquisition in a number of studies, but questions remain as to whether confounding by behavioral practices explains these results. The objective of the present study was to model per–sex act probabilities of female-to-male HIV-1 transmission (i.e., infectivity) for circumcised and uncircumcised men, by use of detailed accounts of sexual behavior in a population with multiple partnerships.

Methods. Data were collected as part of a prospective cohort study of HIV-1 acquisition among 745 Kenyan truck drivers. Sexual behavior with wives, casual partners, and prostitutes was recorded at quarterly follow-up visits. Published HIV-1 seroprevalence estimates among Kenyan women were used to model HIV-1 per–sex act transmission probabilities.

Results. The overall probability of HIV-1 acquisition per sex act was 0.0063 (95% confidence interval, 0.0035–0.0091). Female-to-male infectivity was significantly higher for uncircumcised men than for circumcised men (0.0128 vs. 0.0051; $P = .04$). The effect of circumcision was robust in subgroup analyses and across a wide range of HIV-1 prevalence estimates for sex partners.

Conclusions. After accounting for sexual behavior, we found that uncircumcised men were at a >2-fold increased risk of acquiring HIV-1 per sex act, compared with circumcised men. Moreover, female-to-male infectivity of HIV-1 in the context of multiple partnerships may be considerably higher than that estimated from studies of HIV-1–serodiscordant couples. These results may explain the rapid spread of the HIV-1 epidemic in settings, found throughout much of Africa, in which multiple partnerships and a lack of male circumcision are common.

Heterosexual transmission is responsible for the vast majority of new HIV-1 infections, particularly in sub-Saharan Africa, where the HIV-1 pandemic already has had the greatest impact [1]. The spread of HIV-1 has not been uniform across Africa [2], and, although many biological and behavioral factors likely contribute to country-by-country variation, ecological and large-survey studies suggest that one principal explanation may be differences in the frequency of male circumcision [3, 4]. In addition, >30 cross-sectional and prospective studies have found that being uncircumcised is associated with increased individual-level risk of HIV-1 acquisition [5–7]. In spite of the consistency of these findings, questions remain as to whether residual confounding, especially by differences in sexual behavior, may be responsible for this apparent increased risk of HIV-1 acquisition for uncircumcised men.

The probability of HIV-1 transmission per sex act, or infectivity, has been calculated from several studies of HIV-1–serodiscordant couples from whom detailed information on sexual frequency over time was collected [8]. In these studies, the probability of female-to-male HIV-1 transmission for a single act of penile-vaginal intercourse was estimated to be on the order of 0.001 or less. A small number of studies have estimated female-to-male HIV-1 transmission risk in more transient partnerships—specifically, prostitute contacts—and these studies generated infectivity estimates >30-fold

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higher (0.03–0.08) [9, 10]. No study has estimated per-contact infectivity in the context of multiple partner types, although such partnerships are common in areas where HIV-1 transmission risk is greatest. Accurate estimates of HIV-1 infectivity are important for understanding sexual transmission of HIV-1 and are essential for modeling the effect of interventions aimed at controlling the HIV-1 pandemic [11].

From 1993 to 1997, we conducted a prospective cohort study of risk factors for HIV-1 acquisition among male trucking-company employees in Mombasa, Kenya [12, 13]. At regular follow-up visits, information on sexual encounters and condom use with different partner types was collected. This detailed accounting of sexual behavior allowed us to estimate per-contact risk of HIV-1 acquisition in this population in which multiple, concurrent partnerships are common. We previously reported that being uncircumcised was associated with a significantly increased risk of HIV-1 acquisition in this cohort [13], and here we report the effect of circumcision status on per–sex act HIV-1 transmission probability.

SUBJECTS AND METHODS

Participants and procedures. Between March 1993 and June 1997, we enrolled HIV-1–seronegative employees of 6 trucking companies in Mombasa, Kenya, in the cohort. Study procedures have been detailed elsewhere [12, 13]. Briefly, all male employees were invited to attend a mobile research clinic that visited each company weekly. One thousand five hundred men underwent HIV-1 pretest counseling. Of 1233 HIV-1–seronegative men (82% of those tested), 999 (81%) returned for their results and were offered study enrollment. Demographic, employment, and sexual history characteristics were recorded, and circumcision status was verified by physical examination. At quarterly follow-up visits, data were collected on sexual behavior during the prior 3 months, including the number of sex partners, the number of sex acts with each of 3 different partner types (wives, casual partners, and prostitutes), and the number of sex acts in which condoms were used with each partner type. A physical examination was conducted to identify symptoms of sexually transmitted diseases (STDs)—specifically, urethral discharge and genital ulcers. Men were asked whether they had had similar STD signs during the interval since their last clinic visit. At each visit, blood was tested for HIV-1 antibodies by use of serial ELISAs (Enzygnost [Behring], followed, if results were positive, with Recombigen [Cambridge Biotech]). HIV-1 seroconversions were confirmed by Western blot (Cambridge Biotech). Individualized, confidential risk-reduction counseling was performed at each visit, and free condoms were provided. STDs were treated according to Kenya Ministry of Health guidelines. Informed consent was obtained from participants, and study procedures were approved by the ethical review committees of the University of Washington and the University of Nairobi.

Statistical analysis. Data were analyzed using SPSS version 10.0 and S-Plus 2000 (MathSoft). Comparisons of categorical variables were conducted using χ^2 tests, and comparisons of continuous variables were conducted using Mann-Whitney *U* tests.

Per–sex act transmission probability estimates were obtained using an extension of a model summarized by Allard [14]. In this model, the probability that subject i escaped infection by N_{ij} sex partner(s) of type j is represented by $\{1 - P_j[1 - (1 - \lambda)^{C_{ij}}]\}^{N_{ij}}$, where P_j represents the prevalence of HIV-1 infection among partners of type j, C_{ij} represents the average number of unprotected sex acts that subject i had with each partner of type j, and λ represents the per–sex act probability of infection (infectivity). Maximum-likelihood estimation was used to obtain infectivity estimates, and the likelihood-ratio test was used for hypothesis testing. Confidence intervals were calculated using the bootstrap method. Stratified analyses were performed to assess the effect of potential confounding factors, as has been done in other studies of HIV-1 transmission probabilities [10, 15].

We used self-reported data on sexual behavior, collected at quarterly study visits, to calculate each participant's total number of sex partners and sex acts during the study follow-up period. Data were categorized by partner type (wives, casual partners, or prostitutes). When >3 months had elapsed since the last clinic visit, numbers of sex partners and sex acts during the period not covered by our questionnaire were interpolated on the basis of the 3-month data reported at the next visit. Detailed information about specific partnerships was not collected, and repeated encounters with individual partners could not be verified over time. Thus, men who reported sexual contact with a wife or wives at multiple visits were assumed to be referring to the same partner(s). In contrast, casual-partner and prostitute contacts reported at multiple visits were assumed to be with independent partners. To test this assumption, we also performed infectivity calculations under the assumption that casual-partner reports from multiple visits were with the same partner(s), since these likely comprised a mixture of single-episode encounters and repeated encounters with more-stable partners, such as girlfriends. We felt that it was unlikely that sex acts with prostitutes reported at different visits were with the same partner. For men reporting >1 partner of any type (wife, casual partner, or prostitute), we calculated the average number of sex acts per partner, under the assumption that contacts were divided equally among all partners of each type. For sexual encounters in which condoms were used, we assumed that transmission risk would be reduced by 85% [16]. We also performed calculations under the assumption of no protective effect of condoms. Men were censored at their last follow-up visit or, for men who experienced seroconversion to HIV-1, at the midpoint between their last HIV-1–seronegative and first HIV-1–seropositive visits.

Published surveillance data collected at the same time as our study were used to estimate HIV-1 prevalences among wives, casual partners, and prostitutes. Between 1993 and 1997, HIV-1 prevalence among pregnant women in Mombasa was 12%–17% [17]. Because all men in our study were initially HIV-1 uninfected, we estimated that HIV-1 prevalence among their wives would be slightly lower than this general population prevalence, and, thus, we assumed a prevalence of 10% for wife partners. To account for uncertainty in this estimation, we calculated additional models using HIV-1 prevalences of 5% and 15% among wives. We assumed that HIV-1 prevalence among casual partners would be between that found in the general population and that found in women attending STD clinics in urban Kenya, among whom HIV-1 prevalence between 1993 and 1997 was ~30% [17]. Thus, we estimated a prevalence of 25% for casual partners. We calculated additional models, using prevalences of 15% and 35%. To estimate HIV-1 prevalence among prostitutes, we used data collected in various locations in Kenya, to account for sexual activity during long-distance trucking jobs. In Mombasa, HIV-1 prevalence among prostitutes was ~55% between 1993 and 1997 [18]. However, many prostitutes in Mombasa work at nightclubs serving upper-class Kenyans and foreign tourists, and the prevalence among women who work in bars frequented by working-class Kenyan men has consistently been 60%–65% (L.L., unpublished data). In other parts of Kenya, especially along trucking routes, HIV-1 prevalence among prostitutes was often higher during this period [17]. We estimated a prevalence of 65% for prostitutes for the present study and calculated additional models using prevalences of 55% and 75%. Because our study cohort did not include both circumcised and uncircumcised participants who became infected with HIV-1 and reported sex acts exclusively with each partner type, there was insufficient information to model separate infectivity parameters for wives, casual partners, and prostitutes.

RESULTS

Nine hundred ninety-two HIV-1–seronegative men (99% of those returning for HIV-1 test results) were enrolled in the cohort, of whom 76% returned for at least 1 follow-up visit. As detailed elsewhere [12, 13], men who did and did not return for follow-up were generally similar with respect to age, marital status, religion, history of sex with prostitutes, history of condom use, and circumcision status. We excluded 6 men who were partially circumcised, 1 man whose circumcision status was not recorded, 1 man who provided no sexual behavior information during follow-up, and 3 men who had no HIV-1 testing performed after enrollment. Thus, this analysis included data from 745 men, of whom 95 (13%) were uncircumcised. Two men subsequently underwent circumcision, and data collected after their last uncircumcised visits were excluded.

The median duration of follow-up was 630 days (interquartile range [IQR], 273–1171 days). The median number of follow-up visits was 4 (IQR, 2–8), and visits were spaced at a median of 98 days (IQR, 91–140 days). There were no significant differences in duration or timing of follow-up by circumcision status ($P > .2$). Forty-three men (11 uncircumcised; 32 circumcised) experienced seroconversion to HIV-1 during follow-up, at an incidence of 3.0 cases/100 person-years.

At enrollment, the majority of men were married, although extramarital sexual activity was common overall and was practiced by the majority of married men (table 1). Circumcised men were older and more likely to be Muslim. They were more likely to report a history of condom use, and, if married, to report extramarital sex, which may reflect that they were more commonly occupied as drivers or driver's assistants and thus spent more days per month on the road than did uncircumcised men. Only 5 men (<1%) reported ever having had anal sex with a woman.

During follow-up, sexual activity with a wife was reported by 573 men (77%), with a casual partner by 474 men (64%), and with a prostitute by 182 men (24%). Twenty-eight men (4%) reported sex acts with >1 wife. Nearly 25% of men (136/573) who reported sexual contact with a wife during follow-up were not married at enrollment. The median total number of sex acts per month was 4.0 (IQR, 1.9–7.3), of which 3.8 (IQR, 1.3–6.8) were unprotected by condoms. Among men who had sexual contact with any of the 3 partner types, unprotected sex was common with wives (99%; 569/573), casual partners (85%; 405/474), and prostitutes (71%; 129/182), although the median percentage of sex acts without condoms was lower for prostitute than for wife or casual contacts (58% vs. 100% and 91%, respectively). Sex acts with wives accounted for the vast majority of sex acts (84% vs. 15% for casual partners and 1.5% for prostitutes). Sexual behavior did not differ significantly by circumcision status ($P > .1$ for all comparisons, detailed elsewhere [13]). No participants reported sexual activity with men.

Per-contact infectivity of HIV-1. Overall, the probability of female-to-male HIV-1 transmission for a single act of penile-vaginal intercourse was estimated to be 0.0063 (95% CI, 0.0035–0.0091). Infectivity for uncircumcised men was significantly higher than for circumcised men (0.0128 vs. 0.0051; $P = .04$). Overall transmission probability estimates ranged from 0.0038 to 0.0122 when different HIV-1 prevalences among sex partners were assumed, and a ~2–3-fold greater infectivity was seen for uncircumcised men compared with circumcised men, across all HIV-1 prevalences (table 2).

Some have suggested that the protective effect of circumci-

Table 1. Population characteristics at enrollment.

Characteristic	Value among: All men ($n = 745$)	Uncircumcised men ($n = 95$)	Circumcised men ($n = 650$)	P for uncircumcised vs. circumcised men
Age, median (IQR), years	29 (24–34)	26 (23–34)	29 (25–34)	.01
Married	466 (63)	53 (56)	413 (64)	.2
Religion				<.001
Protestant	295 (40)	48 (50)	247 (38)	
Catholic	249 (33)	43 (45)	206 (32)	
Muslim	160 (22)	1 (1)	159 (25)	
Other	41 (6)	3 (3)	38 (6)	
Education, median (IQR), years	9 (7–12)	9 (8–12)	9 (7–12)	1.0
Employment, median (IQR), years	4 (1–8)	3 (1–8)	4 (1–8)	.3
Occupation				<.001
Driver	83 (11)	3 (3)	80 (12)	
Driver's assistant	146 (20)	9 (10)	137 (21)	
Mechanic	226 (30)	32 (34)	194 (30)	
Other	290 (39)	51 (54)	239 (37)	
Time on road per month				.009
0 days	426 (57)	65 (68)	361 (56)	
1–14 days	161 (22)	21 (22)	140 (22)	
>14 days	158 (21)	9 (10)	149 (23)	
Age at first sexual intercourse, median (IQR), years	15 (14–18)	15 (14–18)	15 (14–18)	.4
Has ever used condoms	403 (54)	41 (43)	362 (56)	.02
Has history of sex with prostitute	421 (57)	49 (52)	372 (57)	.3
Sex partners during past year, median (IQR), no.	2 (1–3)	2 (1–3)	2 (1–3)	.5
Had extramarital sex during past year				
Married men ($n = 466$)	258 (55)	21 (40)	237 (57)	.01
Unmarried men ($n = 279$)	256 (92)	40 (95)	216 (91)	.4

NOTE. Data are no. (%) of individuals, unless otherwise indicated. IQR, interquartile range.

sion on HIV-1 acquisition found in previous studies was confounded by cultural characteristics of Muslim men, among whom the prevalence of circumcision approaches 100% [19]. To explore this hypothesis, we calculated HIV-1 transmission probabilities with Muslim men excluded (table 3). In this analysis, the magnitude of our estimates changed relatively little and remained higher for uncircumcised men than for circumcised men (0.0129 vs. 0.0062; $P = .1$). Because only 1 Muslim man in our study was uncircumcised, we were unable to compare the effect of circumcision on HIV-1 infectivity among subjects in this subgroup. However, among those who were circumcised, HIV-1 infectivity was lower among Muslim than among non-Muslim men (0.0020 vs. 0.0062; $P = .05$).

We also considered whether ethnicity influenced our results. In Kenya, large differences in HIV-1 regional prevalence exist, with the highest prevalence found among members of the Luo ethnic group, who traditionally do not practice circumcision [20]. Some have suggested that studies of circumcision and HIV-1 risk involving Luo men may be confounded by differences between Luo and non-Luo men in HIV-1 prevalence among sex partners or in sexual practices [21]. In our study, Luo men were predominately uncircumcised (79/100; 79%). However, when we repeated our analyses with Luo men excluded, we found that per-act probability of HIV-1 transmission remained significantly higher for uncircumcised men than for circumcised men (0.0510 vs. 0.0051; $P = .008$). Among Luo men, infectivity was also higher for uncircumcised men than for circumcised men, although the difference was not statistically significant (0.0095 vs. 0.0051; $P = .6$).

In our previous study of this cohort, occupation and extramarital sex were found to be associated with HIV-1 seroconversion [13]. We performed subgroup analyses to examine these factors, as well as STDs and age, since these were associated with HIV-1 infectivity in other studies [15]. In all models, infectivity was higher among uncircumcised men than among circumcised men. Drivers/assistants had higher infectivity estimates than did men employed as mechanics or in other occupations ($P < .001$); they were also more likely to report prostitute contacts (32% vs. 21%, respectively; $P = .001$). Genital ulcer disease and urethritis were associated with slightly increased infectivity estimates, although the differences were not statistically significant. Since the number of days of travel per month and a history of condom use differed by circumcision status at study enrollment, we also conducted subgroup analyses based on these characteristics. Both of these characteristics were associated with higher infectivity estimates and were also sig-

Table 2. Female-to-male per-contact HIV-1 infectivity, by estimated HIV-1 prevalences among female partners.

HIV-1 prevalence, %, among			Per-contact infectivity among			Infectivity ratio (uncircumcised/ circumcised)	*P* for uncircumcised vs. circumcised men
Wives	Casual partners	Prostitutes	All men	Uncircumcised men	Circumcised men		
5	15	55	0.0122	0.0204	0.0104	1.96	.1
5	15	65	0.0116	0.0189	0.0100	1.90	.1
5	15	75	0.0110	0.0177	0.0095	1.85	.1
5	25	55	0.0085	0.0150	0.0072	2.08	.07
5	25	65	0.0082	0.0142	0.0070	2.03	.08
5	25	75	0.0079	0.0135	0.0068	1.98	.09
5	35	55	0.0065	0.0118	0.0055	2.13	.06
5	35	65	0.0064	0.0114	0.0054	2.09	.07
5	35	75	0.0062	0.0109	0.0053	2.05	.07
10	15	55	0.0091	0.0185	0.0073	2.53	.04
10	15	65	0.0087	0.0172	0.0070	2.44	.05
10	15	75	0.0083	0.0160	0.0068	2.37	.05
10	25	55	0.0065	0.0135	0.0053	2.57	.03
10	25	65	0.0063	0.0128	0.0051	2.49	.04
10	25	75	0.0061	0.0122	0.0050	2.43	.04
10	35	55	0.0051	0.0107	0.0042	2.53	.03
10	35	65	0.0050	0.0103	0.0041	2.48	.03
10	35	75	0.0049	0.0099	0.0041	2.42	.04
15	15	55	0.0064	0.0165	0.0048	3.42	.01
15	15	65	0.0061	0.0153	0.0047	3.26	.01
15	15	75	0.0059	0.0143	0.0046	3.13	.02
15	25	55	0.0048	0.0120	0.0038	3.17	.01
15	25	65	0.0047	0.0114	0.0037	3.06	.02
15	25	75	0.0046	0.0109	0.0037	2.96	.02
15	35	55	0.0040	0.0095	0.0032	2.97	.02
15	35	65	0.0039	0.0091	0.0032	2.89	.02
15	35	75	0.0038	0.0088	0.0031	2.82	.02

nificantly more common among drivers/assistants, likely reflecting higher-risk sexual behavior. Both characteristics also demonstrated higher infectivity for uncircumcised men than for circumcised men.

The majority of sex acts were with wives, and wives could have been less likely to be chosen randomly with respect to HIV-1 status than were casual partners or prostitutes, which would bias our results if this was also associated with circumcision status. Thus, we performed an analysis excluding men who reported any sex acts with wives during the follow-up period. We found that uncircumcised men still had higher infectivity than did circumcised men (0.0356 vs. 0.0058; $P = .006$). Two hundred six men reported sexual activity only with wives during the follow-up period, 5 of whom experienced seroconversion to HIV-1. Infectivity among these men was lower than among the cohort as a whole (0.0038; 95% CI, <0.0001–0.6973). Only 24 of these men were uncircumcised, none of whom experienced seroconversion to HIV-1, so separate infectivity estimates could not be calculated by circumcision status.

We assessed whether our findings were robust when different assumptions were used for our statistical model. If we considered casual-partner reports from multiple visits as being with the same partners rather than as independent partnerships, HIV-1 infectivity was slightly higher than in our original model (0.0071; 95% CI, 0.0034–0.0108), and a significant effect was retained for uncircumcised compared with circumcised men (0.0148 vs. 0.0057; $P = .04$). To ascertain whether overreporting of condom use influenced our results, we calculated per–sex act HIV-1 infectivity under the assumption that all sexual contacts were unprotected by condoms. HIV-1 infectivity was reduced only slightly overall (0.0049; 95% CI, 0.0029–0.0070) and remained significantly higher among uncircumcised men than among circumcised men (0.0109 vs. 0.0040; $P = .02$). Finally, if interpolated sexual contacts were excluded, HIV-1 infectivity increased only slightly (0.0073; 95% CI, 0.0053–0.0135), remaining higher for uncircumcised men than for circumcised men (0.0173 vs. 0.0079; $P = .07$).

DISCUSSION

In this large prospective study of heterosexual African men, those who were uncircumcised had a >2-fold increased likelihood of HIV-1 acquisition per sex act, compared with those

Table 3. Per-contact HIV-1 transmission probabilities among all study participants and within subgroups.

Group	Per-contact infectivity among			Infectivity ratio (uncircumcised/ circumcised)	*P* for uncircumcised vs. circumcised men
	All men	Uncircumcised men	Circumcised men		
All men (n = 745)	0.0063	0.0128	0.0051	2.49	.04
Excluding Muslim men (n = 585)	0.0075	0.0129	0.0062	2.06	.1
Excluding Luo men (n = 645)	0.0058	0.0510	0.0051	9.91	.008
Driver/assistant (n = 229)	0.0135	0.0277	0.0120	2.32	.2
Mechanic/other occupation (n = 516)	0.0031	0.0090	0.0021	4.37	.02
Travel >14 days/month (n = 158)	0.0140	0.1370	0.0111	12.33	.004
Travel ⩽14 days/month (n = 587)	0.0043	0.0089	0.0033	2.67	.06
History of condom use at enrollment (n = 403)	0.0093	0.0233	0.0076	3.08	.04
No condom use at enrollment (n = 342)	0.0031	0.0067	0.0024	2.84	.2
Extramarital sex[a] (n = 510)	0.0065	0.0137	0.0051	2.67	.02
No sex acts with wives[a] (n = 172)	0.0105	0.0356	0.0058	6.19	.006
Genital ulcer disease[a] (n = 88)	0.0073	0.0175	0.0041	4.28	.04
Urethritis[a] (n = 190)	0.0061	0.0115	0.0046	2.53	.1
Age <30 years (n = 399)	0.0069	0.0123	0.0056	2.18	.1

NOTE. Probabilities were calculated using estimated HIV-1 prevalences of 10%, 25%, and 65% among wives, casual partners, and prostitutes, respectively.
[a] At any time during follow-up.

who were circumcised. This is the first study to estimate HIV-1 infectivity in a population with multiple, concurrent partnerships of different types. The overall probability of female-to-male HIV-1 transmission per sex act was 0.0063, several times higher than has been estimated from studies of HIV-1–serodiscordant couples [8].

A recent meta-analysis concluded that circumcision was associated with a 50% reduced risk of HIV-1 acquisition [22]. Only 1 previous study examined per-contact transmission probabilities by circumcision status, although this may be the best method to avoid confounding by sexual behavior. Among men attending a Nairobi STD clinic, those who were uncircumcised had a higher probability of HIV-1 seroconversion after a single sexual encounter with a prostitute than did those who were circumcised (0.185 vs. 0.022, respectively), although these results were based on only 6 seroconversions, all among men with genital ulcer disease [9]. Infectivity by circumcision status could not be estimated in another study, among monogamous couples from the Rakai district of Uganda, because no circumcised men acquired HIV-1 [15]. Other infectivity studies have generally had homogeneous circumcision patterns among study participants [10]. The foreskin contains high densities of HIV-1 target cells, which suggests that a heightened HIV-1 risk in uncircumcised men is biologically plausible [23]. Our results suggest that the per-contact risk of female-to-male HIV-1 transmission for uncircumcised men in the context of multiple partnerships may exceed 1%, which is >10-fold higher than the typically estimated risk of sexual HIV-1 transmission [15].

Observational studies of the relationship between circumcision status and HIV-1 acquisition have been limited by potential confounding by behavioral practices [6, 7, 22]. Among circumcised men in our study, HIV-1 infectivity was lower among Muslims than among non-Muslims, potentially as a result of practices that could decrease HIV-1 infectivity, such as postcoital genital cleansing [19]. Additional research into the relationship between genital hygiene practices and HIV-1 transmission is warranted. However, our overall results changed little after Muslim men were excluded. Several studies have found more high-risk behavior among circumcised men than among uncircumcised men, suggesting that confounding by sexual behavior may actually underestimate the protective effect of circumcision [22]. In our study, circumcised men were more likely than uncircumcised men to be drivers or assistants, and these occupations, in turn, were associated with substantially higher infectivity. Randomized trials, which have begun in Africa, will best be able to control for differences in sexual behavior.

Most studies of HIV-1 infectivity have been conducted among HIV-1–serodiscordant couples from the United States or Europe [8]. In these studies, female-to-male per-contact probabilities of HIV-1 transmission ranged from 0.0001 to 0.0009. In the Rakai study, the estimated probability was 0.0013 [15]. In contrast, studies from Thailand and Kenya have estimated per-contact HIV-1 transmission probabilities ~30–80-fold higher (0.03–0.08) resulting from sexual encounters with prostitutes [9, 10]. In those studies, as in ours, HIV-1 prevalence among sex partners was inferred from surveillance data. The men in our study reported multiple partnerships, with wives, prostitutes, and casual partners, and we calculated HIV-1 infectivity estimates that were greater than those from studies of monogamous couples but lower than those from studies of prostitute contacts. Among men reporting sexual activity only with wives, HIV-1 infectivity was lower than among the rest of our study population, with a wide CI that overlapped HIV-1 transmission probabilities found in studies of HIV-1–serodiscordant couples. HIV-1 infectivity estimates have been used to model the effectiveness of interventions to prevent HIV-1 transmission, such as HIV-1 voluntary counseling and testing [24], STD treatment [25], provision of antiretroviral therapy [26, 27], and use of a partially effective HIV-1 vaccine [27]. Thus, the choice of infectivity estimates may affect policy decisions regarding strategies to combat the HIV-1 epidemic [28]. Our results indicate that HIV-1 infectivity in the context of multiple partnerships may be several-fold higher than that predicted by studies of HIV-1–serodiscordant couples.

There are several potential explanations for the differences in HIV-1 infectivity found in different studies. First, HIV-1–serodiscordant couples in prospective studies likely have some degree of resistance to transmission, simply because 1 partner had remained HIV-1 uninfected from the initiation of the partnership until study enrollment [8, 29]. Second, retrospective studies of couples suggest that the likelihood of HIV-1 transmission may be highest during the first sexual encounters of a partnership [30]. Thus, long-term studies of HIV-1–serodiscordant couples may not fully reflect HIV-1 transmission dynamics among the general public, where casual sexual contacts play a significant role in HIV-1 spread. Third, STDs could, in part, explain the high infectivity in the studies of prostitute contacts from Thailand and Kenya [9, 10], as well as our results. Although we did not observe any increase in HIV-1 infectivity for men who experienced genital ulcer disease or urethritis, we could not measure STDs among sex partners. The results of the earlier Kenyan study suggested that new genital ulcer disease, presumably acquired along with HIV-1 during the same sexual contact, increased HIV-1 infectivity from prostitutes [9]. In the Rakai study, genital ulcer disease in the infected partner was associated with increased infectivity [15]. Finally, since HIV-1 subtypes A, C, and D are found in Kenya and subtype B predominates in North America and Europe, transmission efficiency for different subtypes may, in part, explain our results.

We performed several analyses to assess the reliability of our statistical model. First, we assessed casual-partner encounters both as independent contacts and as contacts with the same partner. Second, we recalculated our estimates under the assumption of no condom use in the cohort. Third, we excluded interpolated sexual contacts. In all analyses, uncircumcised men had higher per-contact probability of HIV-1 acquisition than did circumcised men. In addition, our overall infectivity estimate remained several-fold higher than estimates from studies of HIV-1–serodiscordant couples. Finally, the reported sexual frequencies in our cohort are compatible with those in other studies from East Africa, suggesting that our data are reliable [31, 32].

The main weakness of our study is that the HIV-1 infection status and disease stage of sex partners was unknown. As in other studies that have modeled HIV-1 infectivity in the context of casual partnerships [9, 10], we used national HIV-1 surveillance figures to estimate HIV-1 prevalence among female partners. Our results were robust when we examined a wide range of potential HIV-1 prevalences for partners.

One potential concern for our study is the possibility that HIV-1 prevalence among sex partners differed for circumcised and uncircumcised men. Several pieces of evidence suggest that this possibility did not bias our results. First, uncircumcised men had higher infectivity than circumcised men in the analysis excluding men who reported sex acts with wives, since wives may have been less likely to have been chosen randomly with respect to HIV-1 status than were casual partners or prostitutes, potentially because of tribal or religious constraints on female sexual behavior that could be related to male circumcision practices. Second, our findings were reinforced after the exclusion of Luo men, who might have chosen sex partners along ethnic lines and whose partners, therefore, might have had high HIV-1 prevalence. Third, circumcised men were more likely to be drivers than were uncircumcised men and thus spent more time on the road, potentially putting them at greater risk of encountering HIV-1–infected casual partners or prostitutes [17]. This would make our results an underestimate of the difference in infectivity between uncircumcised and circumcised men.

Our results suggest that the probability of female-to-male sexual HIV-1 transmission might be >2-fold higher for uncircumcised men than for circumcised men. Moreover, HIV-1 infectivity in an African population with multiple partnerships may be substantially greater than previously estimated from studies of monogamous HIV-1–serodiscordant couples. Our models used detailed reports of sexual behavior that were collected as part of a prospective cohort study, diminishing the potential for uncontrolled confounding. The high probability of per-contact HIV-1 transmission seen in our study may explain the rapid spread of the HIV-1 epidemic in settings where multiple, concurrent partnerships are common. Moreover, our results strengthen the substantial body of evidence suggesting that variation in the prevalence of male circumcision may be a principal contributor to the spread of HIV-1 in Africa.

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