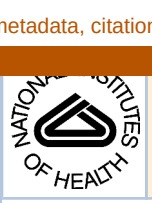

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Men's circumcision status and women's risk of HIV acquisition in Zimbabwe and Uganda

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Keywords

male circumcision; women; HIV; Zimbabwe; Uganda; misclassification

INTRODUCTION

Three randomized trials indicate that male circumcision (MC) lowers men's HIV risk [1-3]. The subsequent influence of MC on HIV risk in men's female sex partners has not been well-characterized.

The few existing studies on this topic have yielded mixed results. Compared to women with uncircumcised partners, those with circumcised partners have been found to have lower [4-10], higher [11], and approximately equal HIV risk [12]. A prospective study of urban Tanzanian women from family planning (FP) clinics [4] and prospective couples' studies in rural Uganda [5,9,10] found that women with circumcised partners had reduced HIV risk. Three cross-sectional studies agree, conducted among Kenyan FP clinic patients [6], urban Ugandan couples seeking HIV counseling and testing [7], and Brazilian serodiscordant couples [8]. Conversely, a cross-sectional study among childbearing Rwandan women found that MC was not associated with women's HIV prevalence [12], whereas HIV prevalence among pregnant Rwandan women seeking antenatal care was *higher* among women with circumcised partners [11]. Many of these studies presented only crude estimates of the effect of MC [8,9,11,12].

Several biologic mechanisms have been proposed through which MC may alter women's HIV risk. Uncircumcised men may have a higher efficiency of transmitting HIV, because the foreskin is a repository for shed cells and a hospitable environment for microorganism growth [13]. The foreskin may be more susceptible to HIV infection because of increased concentrations of HIV target cells: one study found that adult foreskin mucosa had higher mean proportions $CD4^+$ T cells, macrophages, and Langerhans' cells than pediatric foreskin or cervical mucosa. The same authors reported that, following *ex vivo* HIV infection of foreskin and cervical biopsies, adult foreskin mucosa had more rapid uptake of HIV than either cervical

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mucosa or the external surface of the foreskin tissue [14]. Several studies indicate that uncircumcised men have substantially increased rates of genital ulcer disease (GUD) [15], and presence of ulcers is a known cofactor increasing HIV transmissibility [16,17]. Finally, MC may have no direct effect on the transmissibility of HIV from infected men to susceptible women, but if circumcision reduces men's HIV risk, women partnered with circumcised men may be less likely to be exposed to HIV.

METHODS

We examined the effect of MC on women's HIV risk through secondary data analysis of the Hormonal Contraception and the Risk of HIV Acquisition (HC-HIV) study, a multi-site, prospective cohort study assessing the effect of hormonal contraception on HIV acquisition among women. Detailed methods have been published previously [18].

Study setting and population

The HC-HIV study recruited women from 1999-2002 in Uganda, Zimbabwe, and Thailand. Thai women were excluded from this analysis because of very low HIV incidence.

Eligible women were 18-35 years of age; HIV-seronegative; sexually active (≥ three acts in the past three months); and using either combined oral contraceptive pills (COCs), injectable depot medroxyprogesterone acetate (DMPA), or a non-hormonal or no contraceptive method. All Zimbabwean and most Ugandan participants were recruited from FP and maternal-child health clinics. Owing to low initial HIV incidence among Ugandan participants, recruitment in Uganda was expanded to include referrals from “high-risk” populations, such as sexually transmitted disease clinic patients, sex workers and military wives.

Data collection

We restricted the analysis to women in Zimbabwe and Uganda who completed at least one follow-up visit with valid HIV results and provided information about their primary partner's circumcision status (see below). Follow-up officially ended at the first visit following 24 months. We censored follow-up time after 28 months for a small number of women with extended follow-up.

At enrollment and each follow-up visit, women received structured interviews about their reproductive, contraceptive and sexual behavior and physical exams with specimen collection. Visits were conducted approximately every 12 weeks.

At enrollment, participants answered several questions about their primary partner, including his circumcision status. At subsequent visits, women were asked whether their primary partner had changed. Participants with new primary partners were asked if that partner was circumcised, and therefore MC was time-varying in this analysis. For a woman reporting a new primary partner with a different circumcision status than the previous partner, the switch in exposure status was assumed to have occurred at the start of the interval about which she was reporting. We did not collect MC data for non-primary partners.

Women were considered HIV-infected if positive on a combination of two enzyme-linked immunosorbent assays (ELISA) (Recombigen HIV-1/HIV-2 (Cambridge Biotech), Organon Vironostika (Organon Teknika), Abbott Murex (Abbott), or Sanofi (Sanofi Diagnostics Pasteur)) or rapid tests (HIV SAV1 or SAV2 (Savyon Diagnostics), Capillus HIV-1/HIV-2 (Trinity Biotech USA) or Determine (Abbott)). Positive results were confirmed by Western Blot (BioRad) or HIV polymerase chain reaction (PCR) (Amplicor HIV-1 DNA test, version 1.5 (Roche Diagnostics)). We conducted serial testing on stored specimens using PCR to accurately date incident HIV infections.

Statistical analyses

Statistical analyses were performed using SAS (Version 9.1.3, SAS Institute, Cary, NC).

Using extended Cox proportional hazards models, we estimated unadjusted and adjusted hazard ratios (HRs) and 95% CIs to describe the effect of primary partner's circumcision status on women's time to HIV infection. Person-time was calculated as time from enrollment to either the visit date at which HIV was detected or the last visit date for women remaining uninfected.

To evaluate heterogeneity of the MC effect among population subgroups (women recruited from FP clinics in Uganda *vs*. higher-risk settings in Uganda *vs*. FP clinics in Zimbabwe), we examined the significance of a product-interaction term between MC and population; an interaction term with $P<0.10$ led to inclusion in multivariable models [19]. We also examined participants' demographic characteristics, reproductive factors, and sexual behavior for their confounding influence on the MC effect measure. We included in preliminary multivariate models those variables that were associated with MC or HIV acquisition in simple Cox models.

We used a manual, backward elimination, change-in-estimate strategy to remove, one at a time, those variables that did not confound the association between MC and women's HIV risk [20]. Covariates were not retained if removal changed the MC association by less than 10% overall or in any stratum of population [21,22]. Women who did not know their partner's circumcision status were excluded from multivariable models.

To best characterize the relationship between MC and women's HIV risk, we present both the overall association between MC and women's HIV risk in the full cohort and associations between MC and women's HIV risk in each population subgroup.

Sensitivity analysis—We examined the robustness of the observed association between MC and women's HIV risk using sensitivity analysis (comparable to the methods of Lash and Silliman [23]). Specifically, because MC status was reported by women, we assessed the influence of misclassification of men's circumcision status on the observed HRs.

Using three reports of the sensitivity and specificity with which women classify MC (94% sensitivity with 89% specificity [24], 95% sensitivity with 92% specificity [25] and 92% sensitivity with 97% specificity (Ron Gray, unpublished data)), we corrected our estimates of the association between MC and women's HIV risk. Women who did not know their partners' circumcision status were excluded.

We carried out corrections in two steps, separately for each sensitivity-specificity pair. We first computed the two probabilities that a participant's report about her partner was inaccurate: that a man was truly circumcised, although his partner reported he was uncircumcised, or that he was truly uncircumcised, although his partner reported he was circumcised. Using these probabilities, we then randomly reclassified participants' partner's circumcision status 2,500 times to create 2,500 corrected datasets. From each reclassified dataset, we computed corrected unadjusted and adjusted HRs. We interpreted the median HR from the 2,500 simulations as the corrected HR and the 2.5^{th} and 97.5^{th} percentiles as the corrected 95% CI.

Ethical approval—All participants provided written informed consent prior to study entry. The HC-HIV study was approved by ethics committees at collaborating institutions.

RESULTS

The HC-HIV study enrolled 4,531 participants from Uganda and Zimbabwe. We excluded 114 women: 80 did not return for follow-up; 14 first returned 28 months or longer after enrollment, and were therefore censored; 12 used exclusively non-study contraceptive methods, and 8 were missing MC data at every follow-up visit. (Thirteen women missing MC at baseline, but with valid MC data later in follow-up, were excluded from Tables 1 and 2 but included in longitudinal analyses. All 13 women reported an uncircumcised partner later in follow-up). This analysis includes 4,417 women (393 “high-risk” Ugandans (9%), 1,793 “low-risk” Ugandans (41%), and 2,231 Zimbabweans (50%)).

Median follow-up time was 23 months and the median interval between visits was 3 months.

Baseline population characteristics (Tables 1 and 2)

Among 4,404 women providing the MC status of their primary partner at baseline, most (n=3,249, 74%) had uncircumcised partners, whereas 22% (n= 989) had circumcised partners and 4% (n=166) did not know their partner's circumcision status (Table 1). Circumcision was more common among partners of Ugandan (36%) than Zimbabwean women (9%). Zimbabwean women accounted for 98% of those who did not know whether their partner was circumcised.

Users of COCs, DMPA, and non-hormonal methods were roughly balanced among circumcised and uncircumcised groups. Ever use of male condoms was high: approximately four-fifths of women reported ever using male condoms, regardless of partner circumcision status (P=0.62). Sexually transmitted infections (STIs), including clinician-identified GUD, were present in few women, with no substantial differences by circumcision status of the primary partner. Women with circumcised partners had a lower mean age at coital debut (16.8 *vs*. 17.7 years, P<0.001), a higher mean number of lifetime sex partners (4.8 *vs*. 2.7 partners, P<0.001), and a higher mean number of nights the primary partner was away from home in the last month (9.1 *vs*. 6.1 nights, P<0.001) (Table 1).

To further explore differences in participant characteristics by circumcision status of the primary partner, we also examined baseline factors by population subgroup (low-risk Uganda *vs*. high-risk Uganda *vs*. Zimbabwe) (Table 2). Women from the high-risk Uganda stratum generally reported riskier behavior at baseline: these women were more likely to have ever engaged in sex work, to report two or more partners in the last three months, and to have a higher mean number of lifetime sex partners than women from either the low-risk Uganda or Zimbabwe strata (Table 2).

Follow-up

During follow-up, participants with partners who were circumcised, uncircumcised, and of unknown circumcision status contributed 1,674 PY, 5,636 PY, and 256 PY, respectively. Changes in partnerships where the new partner had a different circumcision status than the previous partner were reported by 243 women (6%) at some point during follow-up.

Similar to baseline findings, women partnered with circumcised men reported somewhat riskier sexual behavior during follow-up. Women with circumcised partners were more likely to self-report an STI (6% *vs*. 4% of follow-up intervals, P<0.001) or STI symptoms (26% *vs*. 20% of follow-up intervals, P<0.001), and to have a risky sexual partner – a man with STI symptoms, other sex partners, or who was HIV-positive – (23% *vs*. 14% of follow-up intervals, P<0.001). Although more women with circumcised partners reported never using condoms since the last visit (64% *vs*. 50% of follow-up intervals, P<0.001), they had a lower mean number of

unprotected acts (8.6 *vs*. 9.3 acts per month, $P<0.001$) than women with uncircumcised partners.

HIV acquisition

HIV infection occurred in 210 women during follow-up (34, 167 and 9 HIV seroconversions in women with partners who were circumcised, uncircumcised, and of unknown circumcision status, respectively) (Table 3). For the full cohort, unadjusted HIV incidence rates (IRs) were 2.03 per 100 PY (95% CI: 1.41-2.84) among those with circumcised partners, 2.96 per 100 PY (95% CI: 2.53-3.45) in women with uncircumcised partners, and 3.51 per 100 PY (95% CI: 1.61-6.67) in women who did not know their partner's circumcision status. When examining IRs by population subgroup, Zimbabwean women had the highest unadjusted rates of HIV acquisition, both overall and in each category of partner circumcision status. High-risk Ugandans with circumcised partners had the lowest rate of HIV acquisition of any subgroup (Table 3).

Unadjusted and adjusted multivariate models

We first examined associations between MC and HIV risk among all women in the cohort. The unadjusted Cox proportional hazard model indicated that women with circumcised partners had reduced HIV risk compared to women with uncircumcised partners (HR: 0.69, 95% CI: 0.48-0.99) (Table 4). The Kaplan-Meier plot shows similar results (P=0.06, Figure 1A).

After adjustment for age, age at coital debut, contraceptive method, husband's employment status, education level, and number of sex partners in the previous three months, the protective effect of MC weakened (HR: 0.78, 95% CI: 0.53-1.14 (Table 4)). After further adjustment for population subgroup, the association disappeared (HR: 1.03, 95% CI: 0.69, 1.53 (Table 4)).

We next examined the effect of MC on women's HIV risk within each population subgroup (Figures 1B, 1C and 1D). HIV-free survival time for women with circumcised and uncircumcised partners was similar for both the low-risk Ugandan and Zimbabwean subgroups (P=0.39 and P=0.62, respectively). For the high-risk Ugandan cohort, women with circumcised partners had longer HIV-free survival than women with uncircumcised partners (P=0.05).

In both unadjusted and adjusted multivariable models, MC status was not significantly associated with women's risk of HIV acquisition in any subgroup, although the point estimates varied widely (Table 4). The unadjusted estimate for high-risk Ugandans suggested protection, but was not statistically significant (HR: 0.26, 95% CI: 0.06-1.16), whereas there was little to no effect of MC on women's HIV risk among low-risk Ugandans (HR: 1.28, 95% CI: 0.69-2.35) or Zimbabweans (HR: 1.10, 95% CI: 0.64-1.87). Estimates were similar following adjustment (Table 4).

Some women acquired STIs (*Chlamydia trachomatis* (Ct), *Neisseria gonorrhoeae* (GC), *Trichomonas vaginalis* (Tv), herpes simplex virus type 2, or GUD) during follow-up. In order to better understand the influence of STIs, in preliminary analyses we examined the effect of controlling for STI status in multivariable models in several ways. Neither inclusion of baseline STI status, STI at the last visit, nor STI at the current visit meaningfully changed our estimates of the effect of MC on women's HIV risk. In addition, depending on the timing of infection, women's STI status could be affected by MC (*i.e*., may lie on the causal pathway between MC and women's HIV risk) [26]. For these reasons we did not adjust for confounding by STI in the final multivariate models. Removing from the analysis dataset those observations where women reported multiple partnerships also did not change the observed measures of effect (data not shown).

Sensitivity analyses

Under three sensitivity-specificity scenarios, associations between MC and women's HIV risk were generally robust to misclassification of MC status. In particular, misclassification of MC was not influential for low-risk Ugandans or Zimbabweans, for whom the original estimates fell within the 2.5th and 97.5th percentiles of the corrected HRs under all three misclassification scenarios. Possible misclassification of MC was more influential among high-risk Ugandan women. Under all three sensitivity-specificity scenarios, the median corrected HR for this group weakened considerably (though remained protective) (table available upon request).

DISCUSSION

Recent findings [1-3] indicate that MC is protective against HIV in men. We undertook these analyses to determine whether the protective effect of MC also extended to women in this cohort.

Although our unadjusted analysis agreed with earlier prospective studies reporting a significant protective effect of MC on women's HIV risk [4,5,9,10], after adjustment, we did not observe a significant protective effect of MC overall or for any subgroup. For a small group referred through high-risk settings, we found a suggestion of lower HIV risk for women with circumcised partners. The non-significant association in this subgroup is based on few HIV infections (19 total infections, and only two among women with circumcised partners, Table 3), and therefore, the suggestion that MC may be protective for these high-risk women must be interpreted very tentatively.

In these analyses, population (high-risk Ugandans *vs*. low-risk Ugandans *vs*. Zimbabweans) was very influential in characterizing the association between MC and women's HIV risk, both as a confounder in overall analyses and as a modifier leading to subgroup estimates of the effect of MC on women's HIV risk. We believe that population captured otherwise unmeasured differences in participants' risk of HIV. Population-level factors – *e.g*., prevalence of HIV and other STIs, density and complexity of sexual networks, availability of antiretroviral medications, and many other factors – play essential contextual roles in individual-level risk of exposure to HIV. For example, the likelihood of exposure to an HIV-infected sex partner was probably quite different for women in the two countries: HIV prevalence among women screened for HC-HIV in Zimbabwe was 38%, compared to 16% in Uganda [18].

First, population had a strong confounding influence. The unadjusted model indicated that MC was protective against women's acquisition of HIV; when population was included in the multivariate models, the protective effect of MC disappeared. This is because Zimbabwean women, comprising the largest segment of the full cohort, were less likely to have circumcised partners but more likely to become HIV-infected during follow-up [18]; thus the apparent protective effect of MC in the unadjusted estimate was actually due to the confounding influence of population.

Second, we detected substantial heterogeneity of the MC effect according to population. After adjustment for sexual behavior and demographic factors, the suggested protective effect of MC was limited to the subgroup of women reporting riskier behavior (those in Uganda referred from higher risk settings), whereas women in both countries from FP clinic populations saw no benefit from having a circumcised partner. Our finding of protection among the high-risk subgroup agrees with earlier observational studies among men, conducted prior to the recent randomized trials, suggesting that the protection granted by MC to men is greater for those with riskier behavior [5,27-30].

Wawer *et al*. hypothesize that the greater protection for high-risk men is due to induction of a mucosal immune response in the presence of repeated exposure to HIV [31]. Why might a protective effect of MC be more apparent in high-risk *women*? Even if MC reduces the per-act probability of transmission from infected men to susceptible women, it is still likely to be greater than 0. A woman with low-risk behavior who is nonetheless repeatedly exposed to the same infected man will (for example, her husband) will probably ultimately seroconvert, regardless of his circumcision status. On the other hand, the effect of MC may be more readily seen in women with multiple partners or frequent new partners, because the number of acts with a given partner over time would be fewer, and any reduced probability of infection due to circumcision more directly apparent.

Our analysis has a number of limitations. The HC-HIV study was not designed to evaluate the role of MC on women's HIV risk, and therefore we did not have some information that could have strengthened the analysis. For example, we did not ask about women's or partners' religion [32]. However, adjustment for ethnicity, a proxy for religion, had no substantial effect on the parameter estimates. In addition, because religion and ethnicity do not affect HIV risk directly but are themselves proxies for behavioral characteristics related to disease acquisition, and we measured these behaviors directly, we expect any bias to be minimal.

Women's sexual behavior, as well as MC, were self-reported, and may suffer from recall and courtesy biases. We attempted to account for misclassification of MC using sensitivity analyses, and we found that errors in reporting partners' circumcision status are unlikely to have obscured the association between MC and women's HIV risk. We note that our sensitivity analyses corrected the HRs only for MC misclassification of the primary partner. Some women, particularly those referred from higher-risk settings, may have been exposed to other men with unknown circumcision status. However, women reported multiple sex partners at only 2% visits (3% of visits contributed by low-risk Ugandan women, 7% of visits by high-risk Ugandan women, and <1% of visits from Zimbabwean women). If this is an accurate report, bias resulting from exposure to other partners is likely to be minimal; we also note that when we removed from the dataset those observations where women reported multiple partnerships, the observed measures of effect did not change. Alternatively, if 2% is a substantial underreport, the HRs may reflect a mixture of the effects of primary and non-primary partners' circumcision status on women's HIV risk.

MC may permit a man to avoid initial infection, breaking a link in the disease transmission chain and thereby reducing or eliminating the risk of infection in his partners, or it may reduce the transmissibility of HIV from infected men to susceptible women (or both). Our analysis captures the summary effects of these pathways. Ultimately a quantification of the distinct components of any effect of MC on women's HIV risk is needed, and a prospective, HIV-serodiscordant couples study (HIV-positive men and HIV-negative women) is a superior design to parse these effects (such a study is currently underway in Rakai, Uganda). We asked women about the HIV status of their partners, and attempted to conduct a subanalysis of the effect of MC on women's HIV risk just among women with HIV-positive partners, but we had insufficient sample size to characterize this association.

Men appear to gain substantial protection from MC [1-3]. However, we saw little influence of MC on HIV risk for most women in our cohort. The suggestion of protection among women recruited from high-risk settings warrants further investigation.

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REFERENCES

1. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005;2:e298. [PubMed: 16231970]
2. Bailey RC, Moses S, Parker CP, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007;369:643–656. [PubMed: 17321310]
3. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet 2007;369:657–666. [PubMed: 17321311]
4. Kapiga SH, Lyamuya EF, Lwihula GK, Hunter DJ. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. Aids 1998;12:75–84. [PubMed: 9456257]
5. Gray RH, Kiwanuka N, Quinn TC, et al. Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. Rakai Project Team. Aids 2000;14:2371–2381. [PubMed: 11089626]
6. Hunter DJ, Maggwa BN, Mati JK, Tukei PM, Mbugua S. Sexual behavior, sexually transmitted diseases, male circumcision and risk of HIV infection among women in Nairobi, Kenya. Aids 1994;8:93–99. [PubMed: 8011242]
7. Malamba SS, Mermin JH, Bunnell R, et al. Couples at risk: HIV-1 concordance and discordance among sexual partners receiving voluntary counseling and testing in Uganda. J Acquir Immune Defic Syndr 2005;39:576–580. [PubMed: 16044010]
8. Guimaraes, M.; Castilho, E.; Ramos Filho, C. Heterosexual transmission of HIV-1 : a multicenter study in Rio de Janeiro, Brazil (abstract #ThC573).. VII International Conference on AIDS.; Florence, Italy. 1991; al. e
9. Gray, R.; Wawer, M.; Thoma, M., et al. Male circumcision and the risks of female HIV and sexually transmitted infections acquisition in Rakai, Uganda (abstract #128).. 13th Conference on Retroviruses and Opportunistic Infections.; Denver, CO. 2006;
10. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 2000;342:921–929. [PubMed: 10738050]
11. Chao A, Bulterys M, Musanganire F, et al. Risk factors associated with prevalent HIV-1 infection among pregnant women in Rwanda. National University of Rwanda-Johns Hopkins University AIDS Research Team. Int J Epidemiol 1994;23:371–380. [PubMed: 8082965]
12. Allen S, Lindan C, Serufilira A, et al. Human immunodeficiency virus infection in urban Rwanda. Demographic and behavioral correlates in a representative sample of childbearing women. Jama 1991;266:1657–1663. [PubMed: 1886188]
13. Alanis MC, Lucidi RS. Neonatal circumcision: a review of the world's oldest and most controversial operation. Obstet Gynecol Surv 2004;59:379–395. [PubMed: 15097799]
14. Patterson BK, Landay A, Siegel JN, et al. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. Am J Pathol 2002;161:867–873. [PubMed: 12213715]
15. Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. Sex Transm Infect 2006;82:101–109. discussion 110. [PubMed: 16581731]
16. Hayes RJ, Schulz KF, Plummer FA. The cofactor effect of genital ulcers on the per-exposure risk of HIV transmission in sub-Saharan Africa. J Trop Med Hyg 1995;98:1–8. [PubMed: 7861474]
17. Wald A. Synergistic interactions between herpes simplex virus type-2 and human immunodeficiency virus epidemics. Herpes 2004;11:70–76. [PubMed: 15960904]
18. Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. Aids 2007;21:85–95. [PubMed: 17148972]
19. Selvin, S. Statistical analysis of epidemiologic data. 3rd ed.. Oxford University Press; Oxford ; New York: 2004.

20. Kleinbaum, DG.; Klein, M. Survival analysis : a self-learning text. 2nd ed.. Springer; New York, N.Y.: 2005.
21. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–137. [PubMed: 2910056]
22. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923–936. [PubMed: 8256780]
23. Lash TL, Silliman RA. A sensitivity analysis to separate bias due to confounding from bias due to predicting misclassification by a variable that does both. Epidemiology 2000;11:544–549. [PubMed: 10955407]
24. Seed J, Allen S, Mertens T, et al. Male circumcision, sexually transmitted disease, and risk of HIV. J Acquir Immune Defic Syndr Hum Retrovirol 1995;8:83–90. [PubMed: 8548351]
25. Stern E, Lachenbruch PA. Circumcision information in a cancer detection center population. J Chronic Dis 1968;21:117–124. [PubMed: 5658579]
26. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37–48. [PubMed: 9888278]
27. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. Aids 2000;14:2361–2370. [PubMed: 11089625]
28. Reynolds SJ, Shepherd ME, Risbud AR, et al. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. Lancet 2004;363:1039–1040. [PubMed: 15051285]
29. Lavreys L, Rakwar JP, Thompson ML, et al. Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya. J Infect Dis 1999;180:330–336. [PubMed: 10395846]
30. Baeten JM, Richardson BA, Lavreys L, et al. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. J Infect Dis 2005;191:546–553. [PubMed: 15655778]
31. Wawer MJ, Reynolds SJ, Serwadda D, Kigozi G, Kiwanuka N, Gray RH. Might male circumcision be more protective against HIV in the highly exposed? An immunological hypothesis. Aids 2005;19:2181–2182. [PubMed: 16284475]
32. Bailey RC, Plummer FA, Moses S. Male circumcision and HIV prevention: current knowledge and future research directions. Lancet Infect Dis 2001;1:223–231. [PubMed: 11871509]

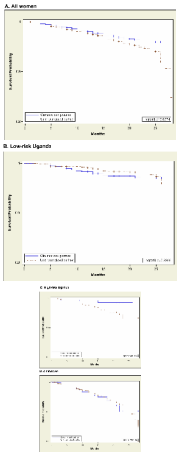

Figure 1.

Unadjusted Kaplan-Meier curve comparing HIV-free survival time for women partnered with circumcised men to women partnered with uncircumcised men, by population

A. All women

B. Low-risk Uganda

C. High-risk Uganda

D. Zimbabwe

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TABLE 1

Selected characteristics of participants at enrollment, by circumcision status of the primary partner, Uganda and Zimbabwe, 1999-2002.

Characteristic	Primary partner circumcision status						*P*	Total	
	Circumcised		Uncircumcised		Don't know				
	N=989	(%)*	N=3,249	(%)*	N=166	(%)*		N=4,404	(%)*
Population									
Uganda low-risk	639	(64.6)	1151	(35.4)	1	(0.6)		1791	(40.7)
Uganda high-risk	141	(14.3)	241	(7.4)	2	(1.2)	<0.001	384	(8.7)
Zimbabwe	209	(21.1)	1857	(57.2)	163	(98.2)		2229	(50.6)
Contraceptive method									
Low-dose combined oral contraceptive pills	348	(35.2)	1128	(34.7)	57	(34.3)		1533	(34.8)
Injectable depot medroxyprogesterone acetate	310	(31.3)	1149	(35.4)	49	(29.5)	0.05	1508	(34.2)
Non-hormonal or no contraceptive method	331	(33.5)	972	(29.9)	60	(36.1)		1363	(30.9)
Cohabitate with primary partner									
Yes	773	(78.2)	2770	(85.3)	140	(84.3)	<0.001	3683	(83.6)
No	216	(21.8)	479	(14.7)	26	(15.7)		721	(16.4)
Employed									
Yes	543	(54.9)	1637	(50.4)	70	(42.2)	0.003	2250	(51.1)
No	446	(45.1)	1612	(49.6)	96	(57.8)		2154	(48.9)
Male condom use ever									
Yes	795	(80.4)	2559	(78.8)	137	(82.5)	0.62	3491	(79.3)
No	194	(19.6)	689	(21.2)	29	(17.5)		912	(20.7)
Ever sex work									
Yes	13	(1.3)	27	(0.8)	2	(1.2)	0.37	42	(1.0)
No	976	(98.7)	3222	(99.2)	164	(98.8)		4362	(99.0)
New partner, last 3 months									
Yes	31	(3.1)	61	(1.9)	3	(1.8)		95	(2.2)
No	958	(96.9)	3186	(98.1)	163	(98.2)	0.17	4307	(97.8)
Missing/don't know	0	(0.0)	2	(0.1)	0	(0.0)		2	(0.1)
Number partners, last 3 months									
0 partners	0	(0.0)	3	(0.0)	0	(0.0)		3	(0.0)

AIDS. Author manuscript; available in PMC 2010 November 10.

Characteristic	Primary partner circumcision status						*P*	Total	
	Circumcised		Uncircumcised		Don't know				
	N=989	(%)*	N=3,249	(%)*	N=166	(%)*		N=4,404	(%)*
1 partner	932	(94.2)	3155	(97.1)	162	(97.6)	<0.001	4249	(96.5)
2 or more partners	57	(5.8)	91	(2.8)	4	(2.4)		152	(3.5)
Genital ulcer disease ‡									
Yes	7	(0.7)	28	(0.9)	2	(1.2)	0.78	37	(0.8)
No	982	(99.3)	3221	(99.1)	164	(98.8)		4367	(99.2)
***C. trachomatis* infection**									
Positive	34	(3.4)	86	(2.7)	8	(4.8)	0.28	128	(2.9)
Negative	946	(95.7)	3122	(96.1)	152	(91.6)		4220	(95.8)
Indeterminate/missing	9	(0.9)	41	(1.3)	6	(3.6)		56	(1.3)
***N. gonorrhoeae* infection**									
Positive	24	(2.4)	59	(1.8)	3	(1.8)		86	(2.0)
Negative	957	(96.8)	3148	(96.9)	156	(94.0)	0.41	4261	(96.8)
Indeterminate/missing	8	(0.8)	42	(1.3)	7	(4.2)		57	(1.3)
***T. vaginalis* infection**									
Positive	26	(2.6)	109	(3.4)	12	(7.2)		147	(3.3)
Negative	963	(97.4)	3136	(96.5)	153	(92.2)	0.007	4252	(96.5)
Indeterminate/missing	0	(0.0)	4	(0.1)	1	(0.6)		5	(0.1)

	Mean	(SD†)	Mean	(SD)	Mean	(SD)		Mean	(SD)
Age (years)	25.2	(4.5)	25.6	(4.5)	24.8	(4.3)	0.008	25.4	(4.5)
Education (years)	8.6	(3.3)	9.3	(2.9)	9.7	(2.1)	<0.001	9.1	(3.0)
Age at coital debut (years)	16.8	(2.4)	17.7	(2.6)	18.4	(2.3)	<0.001	17.5	(2.6)
Gravidity	2.7	(1.8)	2.4	(1.5)	1.9	(1.1)	<0.001	2.5	(1.6)
Number of sex partners, lifetime	4.8	(31.9)	2.7	(18.0)	1.7	(1.7)	<0.001	3.1	(21.7)
Number sex acts in last 30 days with primary partner	11.2	(9.6)	13.9	(11.2)	16.5	(14.4)	<0.001	13.4	(11.0)
Number of nights primary partner away in last 30 days	9.1	(12.2)	6.1	(10.3)	5.0	(8.6)	<0.001	6.7	(10.8)

*Because of missing data and rounding, not all categories total 100%.

†SD=standard deviation.

‡Includes clinician-identified ulcer noted during physical exam on vulva, vaginal epithelium, cervical epithelium, perineum or perianal areas.

AIDS. Author manuscript; available in PMC 2010 November 10.

TABLE 2

Selected characteristics of participants at enrollment, by circumcision status of the primary partner and population subgroup, Uganda and Zimbabwe, 1999-2002.

	Low-risk Uganda* N=1791				High-risk Uganda* N=384				Zimbabwe N=2229					
	Circumcised		Uncircumcised		Circumcised		Uncircumcised		Circumcised		Uncircumcised		DK‡	
Primary partner circumcision status	N=639		N=1151		N=141		N=241		N=209		N=1857		N=163	
	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†
Contraceptive group														
COCs	239	(37.4)	349	(30.3)	39	(27.7)	73	(30.3)	70	(33.5)	706	(38.0)	57	(35.0)
DMPA	199	(31.1)	400	(34.8)	52	(36.9)	77	(32.0)	59	(28.2)	672	(36.2)	47	(28.8)
Non-hormonal or no method	201	(31.5)	402	(34.9)	50	(35.5)	91	(37.8)	80	(38.3)	479	(25.8)	59	(36.2)
Cohabitate with primary partner														
Yes	474	(74.2)	829	(72.0)	109	(77.3)	197	(81.7)	190	(90.9)	1744	(93.9)	137	(84.0)
No	165	(25.8)	322	(28.0)	32	(22.7)	44	(18.3)	19	(9.1)	113	(6.1)	26	(16.0)
Employed														
Yes	357	(55.9)	663	(57.6)	72	(51.1)	108	(44.8)	114	(54.5)	866	(46.6)	70	(42.9)
No	282	(44.1)	488	(42.4)	69	(48.9)	133	(55.2)	95	(45.5)	991	(53.4)	93	(57.1)
Male condom use ever														
Yes	511	(80.0)	941	(81.8)	114	(80.9)	202	(83.8)	170	(81.3)	1416	(76.3)	135	(82.8)
No	128	(20.0)	210	(18.2)	27	(19.1)	39	(16.2)	39	(18.7)	440	(23.7)	28	(17.2)
Missing/don't know	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Ever sex work														
Yes	3	(0.5)	4	(0.3)	8	(5.7)	8	(3.3)	2	(1.0)	15	(0.8)	2	(1.2)
No	636	(99.5)	1147	(99.7)	133	(94.3)	233	(96.7)	207	(99.0)	1842	(99.2)	161	(98.8)
New partner, last 3 months														
Yes	16	(2.5)	40	(3.5)	14	(9.9)	19	(7.9)	1	(0.5)	2	(0.1)	3	(1.8)
No	623	(97.5)	1110	(96.4)	127	(90.1)	222	(92.1)	208	(99.5)	1854	(99.8)	160	(98.2)
Missing/don't know	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Number partners, last 3 months														
0 partners	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)

	Low-risk Uganda* N=1791				High-risk Uganda* N=384				Zimbabwe N=2229					
	Circumcised		Uncircumcised		Circumcised		Uncircumcised		Circumcised		Uncircumcised		DK‡	
Primary partner circumcision status	N=639		N=1151		N=141		N=241		N=209		N=1857		N=163	
	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†	N	(%)†
1 partner	608	(95.1)	1092	(94.9)	117	(83.0)	213	(88.4)	207	(99.0)	1850	(99.6)	159	(97.5)
2+ partners	31	(4.9)	58	(5.0)	24	(17.0)	28	(11.6)	2	(1.0)	5	(0.3)	4	(2.5)
New partner, last 3 months														
Yes	16	(2.5)	40	(3.5)	14	(9.9)	19	(7.9)	1	(0.5)	2	(0.1)	3	(1.8)
No	623	(97.5)	1110	(96.4)	127	(90.1)	222	(92.1)	208	(99.5)	1854	(99.8)	160	(98.2)
Missing/don't know	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Genital ulcer disease§														
Yes	5	(0.8)	9	(0.8)	1	(0.7)	2	(0.8)	1	(0.5)	17	(0.9)	2	(1.2)
No	634	(99.2)	1142	(99.2)	140	(99.3)	239	(99.2)	208	(99.5)	1840	(99.1)	161	(98.8)
***C. trachomatis* infection**														
Positive	22	(3.4)	26	(2.3)	8	(5.7)	4	(1.7)	4	(1.9)	56	(3.0)	8	(4.9)
Negative	615	(96.2)	1124	(97.7)	133	(94.3)	237	(98.3)	198	(94.7)	1761	(94.8)	149	(91.4)
Indeterminate/missing	2	(0.3)	1	(0.1)	0	(0.0)	0	(0.0)	7	(3.3)	40	(2.2)	6	(3.7)
***N. gonorrhoeae* infection**														
Positive	13	(2.0)	15	(1.3)	5	(3.5)	4	(1.7)	6	(2.9)	40	(2.2)	3	(1.8)
Negative	624	(97.7)	1135	(98.6)	136	(96.5)	237	(98.3)	197	(94.3)	1776	(95.6)	153	(93.9)
Indeterminate/missing	2	(0.3)	1	(0.1)	0	(0.0)	0	(0.0)	6	(2.9)	41	(2.2)	7	(4.3)
***T. vaginalis* infection**														
Positive	13	(2.0)	32	(2.8)	5	(3.5)	5	(2.1)	8	(3.8)	72	(3.9)	12	(7.4)
Negative	626	(98.0)	1118	(97.1)	136	(96.5)	236	(97.9)	201	(96.2)	1782	(96.0)	150	(92.0)
Indeterminate/missing	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.2)	1	(0.6)

	Mean	(SD)‡	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	24.9	(4.5)	24.9	(4.5)	25.3	(4.6)	25.0	(4.3)	25.9	(4.5)	26.0	(4.4)	24.8	(4.3)
Education (years)	8.4	(3.6)	8.9	(3.9)	7.7	(3.2)	7.9	(3.4)	9.9	(1.8)	9.7	(1.8)	9.7	(2.0)
Age at coital debut (years)	16.3	(2.1)	16.8	(2.4)	16.1	(2.2)	16.4	(2.0)	18.7	(2.4)	18.5	(2.5)	18.4	(2.3)

	Mean	(SD)‡	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Gravidity	2.7	(2.0)	2.5	(1.9)	3.0	(1.8)	2.8	(1.8)	2.3	(1.3)	2.3	(1.2)	1.9	(1.0)
Number sex partners, lifetime	3.4	(3.9)	3.2	(3.3)	16.4	(83.4)	10.0	(65.2)	1.5	(1.4)	1.4	(1.9)	1.7	(1.7)
Sex acts in last 30 days with primary partner	9.5	(7.0)	9.9	(9.1)	10.9	(9.8)	10.4	(7.6)	16.9	(13.3)	16.7	(11.8)	16.8	(14.4)
Nights primary partner away from home, last month	10.7	(12.8)	10.4	(12.8)	11.0	(12.8)	8.2	(11.8)	3.0	(6.9)	3.1	(6.6)	4.7	(8.3)

*One woman in the low-risk Uganda subgroup and two women in the high-risk Uganda subgroup did not know whether their partner was circumcised; these women are excluded from totals.

†Because of missing data and rounding, not all categories total 100%.

‡DK = participant does not know partner circumcision status; SD=standard deviation

§Includes clinician-identified ulcer noted during physical exam on vulva, vaginal epithelium, cervical epithelium, perineum or perianal areas.

TABLE 3

Incident HIV infections, person-time and HIV incidence rates overall and by population subgroup, Uganda and Zimbabwe, HC-HIV Study, 1999-2004

	Events	PY*	IR*,†	95% CI*,†
Full cohort	210	7565.9	2.78	2.41 to 3.18
Circumcised partner	34	1673.6	2.03	1.41 to 2.84
Uncircumcised partner	167	5636.3	2.96	2.53 to 3.45
Partner MC status unknown	9	256.1	3.51	1.61 to 6.67
By population subgroup				
High-risk Uganda	19	703.8	2.70	1.63 to 4.22
Circumcised partner	2	237.0	0.84	0.10 to 3.05
Uncircumcised partner	15	464.3	3.23	1.81 to 5.33
Partner MC status unknown	2	2.5	80.0	9.69 to 288.99
Low-risk Uganda	43	3276.3	1.31	0.95 to 1.77
Circumcised partner	17	1108.1	1.53	0.89 to 2.46
Uncircumcised partner	26	2164.3	1.20	0.78 to 1.76
Partner MC status unknown	0	3.8	--	--
Zimbabwe	148	3585.9	4.13	3.49 to 4.85
Circumcised partner	15	328.5	4.57	2.56 to 7.53
Uncircumcised partner	126	3007.7	4.19	3.49 to 4.99
Partner MC status unknown	7	249.8	2.80	1.13 to 5.77

* PY = person-year; IR = incidence rate; CI = confidence interval.

† per 100 PY.

TABLE 4

Unadjusted and adjusted hazard ratios and 95% confidence intervals, comparing women with circumcised partners to women with uncircumcised partners, overall and by population subgroup, Uganda and Zimbabwe, HC-HIV Study, 1999-2004

	Events	HR*	95% CI*
Summary estimates			
Unadjusted	201	0.69	0.48-0.99
Adjusted (Model 1)†	197	0.78	0.53-1.14
Adjusted (Model 2)‡	197	1.03	0.69-1.53
By population subgroup			
Unadjusted			
High-risk Uganda	17	0.26	0.06-1.16
Low-risk Uganda	43	1.28	0.69-2.35
Zimbabwe	141	1.10	0.64-1.87
Adjusted (Model 1)†			
High-risk Uganda	14	0.16	0.02-1.25
Low-risk Uganda	43	1.33	0.72-2.47
Zimbabwe	140	1.12	0.65-1.91

*HR = hazard ratio; CI = confidence interval.

†Adjusted for age, age at coital debut, contraceptive method, husband's employment status, education, number of partners in the last three months, and a product-interaction term between time and number of partners in the last three months (to relax the proportional hazards assumption).

‡Adjusted for the same covariates as Model 1, and in addition, population and a product-interaction term between time and population (to relax the proportional hazards assumption). Model 2 is not relevant for the population-specific estimates, because these estimates were generated using a product-interaction term between circumcision and population