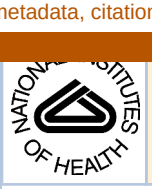

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Male circumcision and women's risk of incident chlamydial, gonococcal and trichomonal infections

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INTRODUCTION

Three randomized trials indicate that circumcised men have lower risk of acquisition of human immunodeficiency virus (HIV) than uncircumcised men,[1-3] and prevention interventions focusing on male circumcision (MC) are being introduced worldwide. Whether MC is associated with *women's* risk of acquisition of HIV or other sexually transmitted infections (STIs), however, has not been well-studied. (The only exception is women's risk of cervical cancer – of which sexually transmitted human papillomavirus (HPV) is a necessary cause – which is significantly lower in women with circumcised male partners.[4]) We found only two studies describing the association between MC and women's risk of *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (Ct), or *Trichomonas vaginalis* (Tv). In a large community cohort study in Rakai, Uganda, women with circumcised partners had reduced Tv risk but equal risks of GC and Ct when compared to women with uncircumcised partners.[5] MC was strongly associated with decreased odds of Ct seropositivity in female partners among controls recruited for a case-control couples' study of cervical cancer.[6]

MC could affect STI risk in women if it reduced men's risk of initial STI acquisition, and/or subsequently decreased the probability of future STI transmission to susceptible female partners. However, epidemiologic evidence regarding the association between MC and men's risk of GC, Ct and Tv is mixed, and findings in several studies have been compromised by small sample sizes, poor study designs, selection bias, uncontrolled confounding and other validity concerns. For gonococcal infection, many studies found no association between MC and men's GC risk,[7-19] although circumcised men had lower GC risk in some.[20-24] A preponderance of evidence suggests no association between MC and men's infection with Ct

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[8, 9, 11, 13-16, 18-21, 25-27] with few exceptions.[22, 28] A recent meta-analysis of MC and men's STI risk similarly concluded that there was no difference in men's risk of GC or Ct by circumcision status.[29] MC and Tv infection in men has not been investigated thoroughly. The two existing studies (one cross-sectional[30] and one ecologic[18]) both noted no association.

Because MC appears to be a promising disease prevention strategy, we analyzed whether MC was associated with women's STI risk. Using data from a multi-site, prospective cohort study conducted in Uganda, Zimbabwe and Thailand, we examined the effect of MC on women's risk of acquisition of Ct, GC and Tv.

MATERIALS AND METHODS

The Hormonal Contraception and Risk of HIV Acquisition (HC-HIV) study is a prospective cohort study with a primary objective to assess the effect of hormonal contraception on women's risk of HIV acquisition. Detailed methods have been described elsewhere.[31] We used the HC-HIV data to evaluate the association between MC and women's STI risk.

Study setting and population

The HC-HIV study enrolled and followed women from 1999-2004. Eligible women were 18-35 years of age; HIV-negative; sexually active; not pregnant or planning a pregnancy; and using oral contraceptive pills, injectable depot medroxyprogesterone acetate, or a non-hormonal or no contraceptive method. Women were recruited from three sites in Kampala, Uganda; four sites in Harare and Chitungwiza, Zimbabwe; and seven sites in Chiang Mai, Hat Yai, Khon Kaen, and Bangkok, Thailand.

All Zimbabwean and most Ugandan and Thai participants were recruited from family planning and maternal-child health (FP/MCH) clinics. Owing to low initial HIV incidence rates among Ugandan and Thai women, recruitment in these countries was expanded to include referrals from “higher-risk” populations, such as sexually transmitted disease clinics, sex workers and military wives.

Data collection

Participants reported their reproductive and sexual behavior during face-to-face interviews conducted at enrollment and during follow-up visits (every 3 months for approximately 24 months). Women also reported the circumcision status and other characteristics of their primary partner. Each participant was asked at every visit whether she had the same primary partner as at her previous visit; the circumcision status of any new primary partner was recorded.

At each visit we collected a single endocervical swab for polymerase chain reaction (PCR) identification of both gonococcal and chlamydial infection (AMPLICOR® Ct/NG Test, Roche Diagnostics, Somerville, NJ, USA). For Ct, optical density (OD) >0.8 was considered positive, and for GC, OD>2.5 was positive. Negative results were indicated for OD <0.2 for both Ct and GC. Testing was repeated if the results fell in the “gray zone” (for Ct: OD of 0.2–0.8; for GC, OD of 0.2–2.5). *Trichomonas vaginalis* was diagnosed using wet mount with examination under low (10×) and high (40-45×) magnification. Identification of motile flagellated trichomonads indicated positive Tv infection.

Participants found to be Ct-infected at baseline or during follow-up were usually treated with doxycycline (100 mg twice daily for 7 days, oral), though azithromycin (1 g, oral) was also used occasionally in both Uganda and Thailand; pregnant women with Ct received erythromycin (500 mg four times daily for 7 days, oral). Women with GC in Zimbabwe were treated with kanamycin (2 g, intramuscular) or norfloxacin (800 mg, oral), whereas

ciprofloxacin (400 mg, oral) was used in Uganda and ceftriaxone (125 mg, intramuscular) in Thailand. Tv was treated with metronidazole (2 g, oral) in all three countries.

Statistical analyses

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

We estimated unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of primary partner's circumcision status on women's time to first infection with 1) Ct; 2) GC; 3) Tv; and 4) any STI (Ct, GC or Tv). We used extended Cox proportional hazards models to account for both time-independent and time-varying covariates.[32]

Our outcome was the first incident infection with each of the STIs under investigation. An infection was considered the first incident infection if the participant had tested negative for that STI at all previous follow-up visits. Women testing positive at baseline were treated and entered the at-risk pool for this analysis after receiving a negative result. Person-time preceding a missing STI outcome was excluded.

We restricted the analysis to women who completed at least one follow-up visit with valid STI results and non-missing MC status of the primary sexual partner. Because of HC-HIV's primary objective, women's follow-up time was censored at the visit they were found to be HIV-infected; women who used exclusively non-study contraceptive methods for their full follow-up were also excluded. Follow-up was scheduled to end at 24 months, but a small group of participants returned for their final visit much later. For these women (n=101) we censored follow-up time after 28 months.

The HC-HIV study enrolled 6,109 participants. For these analyses, we excluded 184 women: 149 never returned after enrollment; 9 returned for the first time after 28 months; 12 were missing the circumcision status of their primary partner at every follow-up visit; and 14 were missing results for Ct, GC and Tv at every follow-up visit. We separately analyzed each outcome from this starting pool of 5,925 women. Person-time contributed by women remaining infection-free for the full study duration was calculated as the number of months from enrollment to the last study visit. For women who acquired an STI during follow-up, person-time was calculated as the time from enrollment to first infection with the specific STI under investigation. For the combined analysis of all three STIs, women were censored after their first diagnosis with any one of the three infections.

Multivariable models were constructed as described elsewhere.[33] Briefly, we examined participants' demographic characteristics, reproductive factors and sexual behavior; we included in preliminary multivariable models all variables associated with MC or incident STI. We evaluated the proportional hazards assumption (PHA) using Cox tests and through visual inspection of log -log plots.[34] For any variable violating the PHA, we created product-interaction variables with time to include in preliminary multivariable models.

To construct final models, we used a manual, backward elimination, change-in-estimate strategy.[35] One at a time, we removed covariates from the preliminary, full model; if removal changed the MC-STI association by less than 10% overall or in any stratum of any interacting variable, a given covariate was not retained. We designated models as "final" when the remaining covariates confounded the MC-STI association or were retained for *a priori* considerations (age and contraceptive method).

Any covariate surviving the manual backward elimination procedure for at least one of the four MC-STI associations was included in the adjustment set for all other analyses.

Missing data—Fifty-six women (0.9%) were missing the circumcision status of their primary partners at baseline, but subsequently provided this information during follow-up. These women are excluded from descriptions of participant characteristics by baseline male circumcision status but included in multivariate models, which permit partner circumcision status to change if women change primary partners.

At any follow-up visit, women missing Ct, GC or Tv results were coded as missing for the "any STI" analysis. Therefore, more women and more follow-up time are included in analyses of individual STIs than in the analysis of the three infections combined.

Sensitivity analysis

Our main analyses evaluated the effect of circumcision status of the primary partner on women's risk of acquisition of three STIs. Because some women reported multiple sexual partnerships during follow-up, our observed associations may reflect a mixture of the effects of primary and non-primary partners' circumcision status. We conducted a simple sensitivity analysis by removing from the analysis all follow-up time where women reported multiple sexual partners. We then refit the unadjusted and adjusted models (using the same set of adjustment variables as in the main analysis) to determine whether the associations between MC and women's STI risk changed.

Ethical approval

All women enrolled in the HC-HIV study gave written informed consent prior to participating, and ethics committees at collaborating institutions gave approval for the study. The Institutional Review Board at the University of North Carolina at Chapel Hill approved this analysis.

RESULTS

Baseline characteristics

The study population was comprised of women from Uganda (36.8%), Zimbabwe (37.6%) and Thailand (25.6%). High-risk participants from Uganda and Thailand made up 14.2% of the overall cohort (Table 1).

At baseline, 18.6% of participants reported a circumcised primary partner, 70.8% had an uncircumcised partner, and 9.7% said they did not know whether their partner was circumcised (Table 1). Circumcision was more common among partners of Ugandan women (35.7%) than among partners of women from Zimbabwe (9.4%) or Thailand (7.4%). Although the circumcision prevalence varied substantially by country, it did not vary by referral population within Uganda or Thailand. Of 575 participants reporting that they did not know whether their primary partners were circumcised, 409 (71.1%) were Thai, 163 (28.3%) were Zimbabwean and 3 (0.5%) were Ugandan. Participants' age did not vary substantially by circumcision status (median: 25 years for women with circumcised and uncircumcised partners and 26 years among women who did not know whether their partners were circumcised). The median level of education for all women, regardless of partner circumcision status, was 9 years. Most women (87.2%) cohabitated with their primary partner.

Women with circumcised partners reported somewhat riskier sexual behavior at baseline than women with uncircumcised partners or those who did not know whether their partners were circumcised. Participants with circumcised partners had a lower median age at coital debut (17 years *vs.* 18 for women with uncircumcised partners and 19 for women who did not know their partners' circumcision status). Although the median number of sex partners in the last 3 months was the same for all groups (1 partner), women with circumcised partners had a higher mean

number of partners (1.9 *vs.* 1.3 and 1.5 partners for women with uncircumcised partners and partners of unknown circumcision status, respectively). Similarly, each group reported a median of 0 nights that the primary partner was away from home in the last month, but women with circumcised partners had a higher mean number of nights when the partner was away (mean: 8.7 nights *vs.* 5.4 nights for women with uncircumcised partners and 3.8 nights for women who did not know whether their partners were circumcised). The majority of women (71.7% overall) reported ever using male condoms, including a higher proportion of women with circumcised partners (78.0%) than uncircumcised partners (71.5%). Fewer women who did not know whether their partner was circumcised reported ever using male condoms (58.1%).

Prevalent STI at baseline was relatively rare (Table 1), and did not vary substantially by baseline MC status of the primary partner. At the enrollment visit, 3.5% of participants were diagnosed with Ct (3.7%, 3.2% and 5.4% of women with partners who were circumcised, uncircumcised, and of unknown circumcision status, respectively), 1.6% with GC (2.3%, 1.5% and 1.2%, respectively), and 2.6% with Tv (2.5%, 2.7% and 2.1%, respectively).

Unadjusted and adjusted multivariable models

Chlamydial infection—Ct was the most common incident STI in this cohort, with 408 women acquiring a new Ct infection during follow-up. The unadjusted incidence rate (IR) among women with circumcised partners was 4.5/100 person-years (PY), compared to 3.9/100 PY for participants with uncircumcised partners and 5.1/100 PY among those who did not know whether their partners were circumcised (Table 2).

Time to Ct infection was similar for women with circumcised *vs.* uncircumcised partners After adjustment for contraceptive method, age, age at coital debut, and country, the adjusted HR was 1.25 (95% CI: 0.96 to 1.63) (Table 3).

Gonococcal infection—The unadjusted IR for GC among participants with circumcised primary partners was 3.8/100 PY, compared to 3.0/100 PY for those with uncircumcised partners and 1.7/100 PY for women whose partners' circumcision status was unknown (Table 2).

The adjusted HR comparing time to initial GC for women with circumcised partners to those with uncircumcised partners was 0.99 (95% CI: 0.74 to 1.31) (Table 3).

Trichomonal infection—The unadjusted IRs for *T. vaginalis* were 4.5/100 PY for women reporting circumcised primary partners, 3.8/100 PY for participants with uncircumcised partners, and 1.2/100 PY for women who did not know whether their partners were circumcised (Table 2).

The adjusted HR for Tv comparing women with circumcised partners to those with uncircumcised partners was 1.05, 95% CI: 0.80 to 1.36) (Table 3).

Any STI: Ct, GC or Tv—Ct, GC or Tv was diagnosed in 887 women over the follow-up period: women with circumcised partners had an IR of 10.3/100 PY; participants with uncircumcised partners had an IR of 9.5/100 PY; and women who did not know whether their partners were circumcised had an IR of 7.2/100 PY (Table 2).

The adjusted HR comparing time to initial STI for women with circumcised *vs.* uncircumcised partners was 1.02 (95% CI: 0.85 to 1.21) (Table 3).

Modeling results were largely unchanged when examining baseline (rather than time-varying) partner circumcision status. Because baseline condom use and baseline prevalence of GC and Tv was lower among Thai participants, we also examined whether restricting the analysis population to only African women affected our results; effect estimates were largely unchanged (data not shown).

Sensitivity analysis

When we excluded follow-up time where women reported multiple partnerships, our restricted datasets contained approximately 2.5% fewer person-years of follow-up. After restriction, nearly all effect estimates were unchanged (data not shown). The HRs for Ct, however, strengthened somewhat, particularly in the adjusted model (restricted HR: 1.37, 95% CI: 1.04 to 1.80).

DISCUSSION

In both unadjusted and adjusted analyses, women with circumcised partners had similar risk of chlamydial, gonococcal and trichomonal infections as women with uncircumcised partners.

Our findings largely agree with prior studies on MC and *men's* risk of these STIs. The literature on men's risk of Ct and Tv suggests no protective effect of circumcision (although the few studies of MC and Tv make overall conclusions difficult). Although the literature on MC and men's risk of GC is mixed, most reports suggest that MC is not associated with men's GC risk.

At least two mechanisms exist by which MC could affect women's STI risk. First, MC may change *men's* STI risk, and subsequently alter the probability that women will be exposed to infected men. However, as described above, no strong evidence supports a conclusively protective role for MC against men's acquisition of the three STIs evaluated here. Second, MC may change the probability of transmission from infected men to susceptible women - the absence of a foreskin may alter the efficiency of pathogen transmission. Although Ct, GC and Tv infections in men occur nearly exclusively in the urethra,[36] the foreskin is a repository for shed cells and secretions, and a moist, hospitable environment for pathogen growth. STI-infected, uncircumcised men may therefore expose their female partners to a higher pathogen burden than STI-infected circumcised men. Transient infectious organisms that do not ultimately adhere and infect exposed men may also have longer viability in uncircumcised men. We found no reports comparing pathogen burdens in circumcised *vs.* uncircumcised men.

Three clinical trials found a strong protective effect of MC against men's risk of HIV acquisition.[1-3] More than 50 cohort and cross-sectional studies found largely similar results. Few prospective evaluations have characterized the effect of MC on women's HIV risk, and the small number of existing studies have had mixed findings: an analysis of these HC-HIV data found no effect of MC on women's HIV risk in women from FP/MCH populations,[33] whereas three other prospective studies determined that women with circumcised partners had lower HIV risk than women with uncircumcised partners (in Tanzania[37] and Uganda[13, 38]). A more recent evaluation in Rakai, Uganda found reduced, but non-significant, reductions in HIV risk for women with circumcised partners.[5]

Our analysis has a number of limitations. First, because this is a secondary data analysis, some variables that may have contributed to the analysis were unmeasured (*e.g.*, potential confounders including women's or partners' religion).[39] In addition, an evaluation of MC and women's risk of syphilis or chancroid might have been informative, since MC has been associated with reduced risk of these two infections in men.[40] Unfortunately, we did not have incidence data on syphilis or chancroid in our cohort.

Second, women's sexual behavior, as well as MC, were self-reported, and may suffer from recall and social desirability biases. Misclassification of self-reported MC particularly has been noted as a limitation in previous studies,[39, 41] and several have attempted to characterize the accuracy with which men and their female partners can classify circumcision.[4, 16, 20, 21, 25, 42-50] If MC misclassification exists and is nondifferential (not associated with STI status), the observed effect of MC will be biased toward the null. In a previous analysis, using three data-driven scenarios (R. Gray, unpublished data)[48, 50] we examined the effect of MC misclassification on the observed association between MC and women's risk of HIV acquisition;[33] that sensitivity analysis resulted in little change in our findings for MC and women's HIV risk.[33] We expect bias to be similarly minimal in these analyses of women's STI risk.

We saw further evidence against MC misclassification when examining data from various sources, including the Demographic and Health surveys (DHS),[51-53] reporting that circumcision prevalence in Uganda is 25%, Zimbabwe is 10% and Thailand is 7%. Our measured MC prevalences in Zimbabwe (9%) and Thailand (7%) match the DHS estimates, but our estimate for Uganda (36%) is higher than expected given the DHS finding of 25%. This may be evidence of misclassification, though if women were uncertain, we expect that more of them would have reported not knowing their partners' circumcision status. Instead, only three participants in Uganda reported a partner with unknown MC status, compared to 163 in Zimbabwe and 409 in Thailand. The higher observed MC prevalence in Uganda may also be evidence of selection issues (*e.g.*, a higher than expected proportion of participants with Muslim partners) which could further be associated with behavioral differences; as indicated above, we did not collect data on women's or partner's religion, so we cannot explore this possible confounder. Finally, we note that in societies where MC is not traditionally practiced, men who seek out circumcision may do so to relieve genitourinary problems (*e.g.*, recurrent STIs or balanitis). Because we did not have information on women's partners' age at or reason for circumcision, we could not identify which partners chose circumcision for these reasons. These men may be at higher STI risk, and analyzing them in the same category as other circumcised men may have skewed the observed MC-STI associations.

We also did not know the STI status of women's partners. This information would have permitted various other informative analyses, including separate characterization of the effect of MC on men's initial STI risk and the effect of MC on the STI transmissibility from infected men to susceptible women. Instead, our measures of effect capture the overall, combined effect of these two pathways. In addition, the impact of MC on reducing STI transmission from men to women could be different by men's HIV status, if HIV-infected men had more frequent or severe episodes of STI, yet the HIV status of women's partners was also unmeasured.

As with any laboratory procedure, methods to diagnose Ct, GC and Tv are not always accurate. Microscopy (wet mount), the diagnostic method for trichomonas, has poor sensitivity (49%-67%) but nearly perfect specificity (often cited as 100%) compared to PCR.[54-57] A substudy conducted just among Zimbabwean participants at selected visits, which assessed Tv as a risk factor for HIV acquisition, compared wet mount with PCR for Tv diagnosis. This investigation concluded that the sensitivity and specificity for Tv diagnosis by microscopy was similar to published reports.[58] We anticipate that misclassification of Tv status would be nondifferential (not associated with MC), suggesting that the observed effect estimates may be biased toward the null. The AMPLICOR® CT/NG test, which has published sensitivity and specificity of 91.7% and 99.7%, respectively, for Ct[59] and 92.4% and 99.5%, respectively, for GC,[60] has been criticized for cross-reactivity with nonpathogenic *neisseriae* strains,[61-63] leading to higher false-positive rates than test characteristics would indicate. False-positive results are an issue of particular importance in a low-prevalence setting such as ours. In light of this problem, our outcome classification used the adjusted optical density parameters

described in the methods (B. Van der Pol, personal communication), but some women diagnosed with GC during follow-up may have been misclassified.

Because our main analysis evaluated only MC status of women's primary partner, for women with multiple partners, the observed associations mix the effect of MC status of primary and non-primary partners. To address this limitation we included a sensitivity analysis that excluded follow-up time where women reported multiple partnerships; this analysis confirmed a lack of association between MC and GC or Tv. However, in adjusted models, monogamous women with circumcised partners appeared to have a significantly increased risk of incident chlamydial infection compared to women with uncircumcised partners.

This finding disagrees with the only existing study of MC and women's Ct risk (Castellsague *et al*.),[6] which found significant protection against Ct seropositivity for women with circumcised partners (OR: 0.18, 95% CI: 0.05-0.58). However, both our study and that by Castellsague *et al*. were secondary data analyses using information originally captured to answer a different research question, and there are substantial differences between the two analyses that could have led to the contradicting results. These include design (prospective cohort *vs.* cross-sectional study), population (FP/MCH clinic attendees with a small proportion of higher-risk participants *vs.* general population and hospital-based controls recruited for a case-control study of cervical cancer in Colombia, Spain, Brazil, Thailand and the Philippines), total sample size (n=5,925 *vs.* n=300), number of Ct cases (n=408 *vs.* n=84) and method of outcome detection (PCR *vs.* microimmunofluorescence detection of Ct antibodies). Of note, when the data from Castellsague *et al*. are analyzed by individual country, the protective association between MC and Ct persists but is no longer statistically significant (Thailand, OR: 0.28, 95% CI: 0.03-2.99; Philippines, OR: 0.21, 95% CI: 0.04-1.21; presumably because of small cell sizes, individual ORs not calculated for Colombia, Spain and Brazil).[6]

MC has the potential to reduce HIV risk among millions of men, and intervention programs are being planned worldwide. The effect of MC on men's STI risk is not yet clear, and further research is warranted to determine whether MC also has direct or indirect effects on women's STI risk.

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TABLE 1

Selected characteristics of participants (n=5,925) at screening/enrollment

Characteristic	Total	
	N	%
Country and referral population		
Uganda		
Family planning/maternal-child health clinics	1790	30.2
STD clinics, military wives, sex worker networks	390	6.6
Thailand		
Family planning/maternal-child health clinics	1065	18.0
STD clinics, military wives, sex worker networks	452	7.6
Zimbabwe	2228	37.6
Baseline circumcision status of the primary partner		
Circumcised	1100	18.6
Uncircumcised	4194	70.8
Don't know	575	9.7
Missing	56	0.9
Baseline contraceptive method		
Combined oral contraceptive pills	2003	33.8
Injectable depot medroxyprogesterone acetate	2075	35.0
Non-hormonal or no contraceptive method	1847	31.2
CT status at enrollment		
Positive	208	3.5
Negative	5645	95.3
Indeterminate	22	0.4
Missing	50	0.8
GC status at enrollment		
Positive	96	1.6
Negative	5757	97.2
Indeterminate	23	0.4
Missing	49	0.8
TV status at enrollment		
Positive	152	2.6
Negative	5766	97.3
Not done	7	0.1
Currently cohabitate with primary partner		
Yes	5169	87.2
No	756	12.8
Currently employed		
Yes	3382	57.1
No	2543	42.9
Husband currently employed		
Yes	5671	95.7

Characteristic	Total	
	N	%
No	201	3.4
Missing	53	0.9
Male condom use ever		
Yes	4246	71.7
No	1678	28.3
Don't know	1	0.02
Sex with men other than primary partner in last 3 months		
Yes	275	4.6
No	5649	95.3
Missing	1	0.02
Sex while intoxicated in last 3 months		
Yes	522	8.8
No	5402	91.2
Don't know	1	0.02
Ever exchanged sex for money or goods		
Yes	181	3.0
No	5744	97.0

	Median	IQR*
Age (years)	25	22 to 29
Education (years)	9	7 to 11
Age at coital debut (years)	18	16 to 19
Age of primary partner (years)	30	27 to 35
Number of pregnancies	2	1 to 3
Number of sex partners, last three months	1	1 to 1
Number sex acts in last 30 days with primary partner	9	4 to 16
Nights primary partner away in last 30 days	0	0 to 7

* IQR = interquartile range

TABLE 2

Unadjusted incidence rates and 95% confidence intervals for any STI, Ct, GC and Tv

Primary partner MC status			Circumcised			Uncircumcised			Unknown		
Outcome	**Total events**	**Total PY***	**Events**	**IR* per 100 PY***	**(95% CI*)**	**Events**	**IR per 100 PY**	**95% CI**	**Events**	**IR per 100 PY**	**95% CI**
Ct	408	9,899	80	4.46	(3.48, 5.44)	280	3.91	(3.45, 4.37)	48	5.06	(3.63, 6.49)
GC	305	10,016	68	3.77	(2.87, 4.66)	220	3.04	(2.64, 3.45)	17	1.73	(0.91, 2.56)
Tv	362	9,903	80	4.47	(3.49, 5.45)	270	3.78	(3.33, 4.24)	12	1.23	(0.53, 1.92)
Any STI†	887	9,440	175	10.28	(8.76, 11.81)	645	9.48	(8.75, 10.21)	67	7.19	(5.47, 8.91)

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

†If women were missing outcomes for any individual STI at a given visit, she received a missing value for ‘any STI.’ Consequently there are more missing outcomes for “any STI” than for individual STIs, and therefore the individual STIs do not sum to the “any STI” total of 895 cases.

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TABLE 3

Unadjusted and adjusted hazard ratios and 95% confidence intervals comparing STI risk for women with circumcised vs. uncircumcised primary partners.

Outcome	Events	HR	(95% CI)
Ct			
Unadjusted	408	1.14	(0.89, 1.45)
Adjusted*	408	1.25	(0.96, 1.63)
GC			
Unadjusted	305	1.24	(0.95, 1.63)
Adjusted*	305	0.99	(0.74, 1.31)
Tv			
Unadjusted	362	1.19	(0.93, 1.53)
Adjusted*	359	1.05	(0.80, 1.36)
Any STI			
Unadjusted	887	1.09	(0.92, 1.29)
Adjusted*	884	1.02	(0.85, 1.21)

*All adjusted models control for contraceptive method, age, age at coital debut, and country