Title

Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples

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Decreased incidence of syphilis in both men and women associated with male circumcision: a prospective study among HIV-1 serodiscordant heterosexual African couples

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Abstract

Background—Male circumcision is a primary HIV-1 prevention intervention for men. It is uncertain whether male circumcision reduces the risk of syphilis among men and their female partners.

Methods—Using data from a prospective study among HIV-1 serodiscordant heterosexual couples from Kenya and Uganda, we assessed whether male circumcision was associated with incident syphilis in men and in their female partners. Multivariate Andersen-Gill survival methods were used, adjusted for age, sexual behavior, and plasma HIV-1 RNA levels of the HIV-1 infected partner.

Findings—4716 HIV-1 serodiscordant couples (37·5% with an HIV-1 infected male) were followed for a median of 2·75 years. At enrollment, 1575 (53·5%) HIV-1 uninfected and 560 (32·4%) HIV-1 infected men were circumcised; an additional 69 (4·2%) HIV-1 infected and 132 (4·8%) HIV-1 uninfected men became circumcised during study follow up. 221 incident syphilis infections were observed: 46 among HIV-1 infected men (incidence 1·10 per 100 person-years),

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JP, JMB, and RH designed the study. JP led the data analysis. LM, CC, AR, NM, AM, CC, EW, EB and JK reviewed the analysis and supported development of the manuscript. JP, JMB, RH prepared the first draft of the manuscript with input from all authors, and all authors contributed to subsequent drafts. All authors approved the final draft of the report.

Declaration of interests

We declare that we have no competing interests.

76 among HIV-1 uninfected men (1·09 per 100 person-years), 54 among HIV-1 infected women (0·77 per 100 person-years) and 45 among HIV-1 uninfected women (1·11 per 100 person-years). Male circumcision was associated with a 42% reduction in incident syphilis in men (adjusted hazard ratio [aHR] 0.58 95% CI 0·37–0·91) including a 62% reduction among HIV-1 infected men (aHR 0·38, 95% CI 0·18–0·81) and a non-significant reduction in incident syphilis among HIV-1 uninfected men (aHR 0·64, 95% CI 0·36–1·11). Among women, circumcision of their male partners was associated with a 59% reduction in incident syphilis (aHR 0.41 95% CI 0.25–0.69), including a 75% reduction among HIV-1 uninfected women (aHR 0·25, 95% CI 0·08–0·76) and a 48% reduction among HIV-1 infected women (aHR 0·52, 95% CI 0·27–0·97).

Interpretation—In this large prospective cohort study among HIV-1 serodiscordant couples, male circumcision was associated with decreased risk of incident syphilis in men and women. If confirmed, these results suggest that medical male circumcision could substantially reduce incidence of syphilis and its sequelae.

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Background

Over 40 studies, including three randomized controlled trials, have demonstrated that male circumcision provides at least 60% protection against HIV-1 acquisition for heterosexual men. [1–4] The consistently high efficacy observed in the three randomized clinical trials was the impetus for WHO-UNAIDS recommendations in 2007 that medical male circumcision be a priority HIV-1 prevention strategy and implemented in settings with low prevalence of male circumcision and high prevalence of HIV-1. [5] Multiple observational studies also support a preventive role for male circumcision for other sexually transmitted infections (STIs), including human papillomavirus (HPV), herpes simplex virus type 2 (HSV-2), *Trichomonas vaginalis*, chancroid, *Mycoplasma genitalium*, and genital ulcer disease (GUD) among heterosexual men. [6–13] Although a meta-analysis of randomized and observational studies concluded that there was no association between male circumcision and HIV-1 risk in women (summary relative risk 0·80, 95% CI 0·53–1·36, heterogeneity p=0.05), [14] a protective benefit of male circumcision on STI transmission to female partners for has been reported. Data from randomized trials have demonstrated reduced risk for HPV, genital ulcers, HSV-2, bacterial vaginosis, and *T. vaginalis* in women whose partners are circumcised while other observational studies found no association with bacterial vaginosis, *T. vaginalis*, and *Chlamydia trachomatis*. [15–21]

The potential association between male circumcision and syphilis was first described in the mid-1850s in a medical report of patients with syphilis and *Neisseria gonorrhoeae* in which a greater proportion of non-Jewish men had syphilis compared with Jewish men, who were presumed to be circumcised due to religious practices. [22] Several more recent studies, including one meta-analysis, have suggested that circumcised heterosexual men are at lower risk of syphilis. [9] However, few studies have assessed the relationship between male circumcision and incident syphilis status among men with HIV-1 infection, and no studies to date have investigated the effect of male circumcision in HIV-1 infected or uninfected men on syphilis acquisition among women. A protective effect of male circumcision on the risk

of incident syphilis for HIV-1 infected and uninfected men and women would have important public health implications. Syphilis can lead to irreversible neurological and cardiovascular damage and syphilis during pregnancy can cause numerous adverse pregnancy and birth outcomes. [23] Male circumcision is currently being implemented as a medical procedure in settings of sub-Saharan Africa with high HIV-1 burden, [24] and in those settings syphilis prevalence is also often high. Evidence of additional benefits against syphilis may enhance current medical male circumcision programs. We aimed to investigate the relationship of male circumcision and the incidence of syphilis in a large prospective cohort of HIV-1 infected and uninfected African men and their female partners.

Methods

Study design & participants

Participants in this prospective study were members of Kenyan and Ugandan HIV-1 serodiscordant heterosexual couples enrolled in a randomized safety and efficacy clinical trial of pre-exposure prophylaxis (PrEP) for HIV-1 prevention (the Partners PrEP Study). [25,26] Trial recruitment, eligibility and exclusion criteria, and follow-up procedures have been previously described. [25] All couples received a comprehensive package of HIV-1 prevention services, including individual and couples risk-reduction counseling, screening and treatment for STIs, condoms, and referral for medical male circumcision and post-exposure prophylaxis according to national policies. At enrollment into the trial, HIV-1 infected partners were not eligible for antiretroviral therapy (ART) under the national ART guidelines during the study; they were referred for initiation of ART when they became eligible.

At an interim review, the trial's independent data safety and monitoring board recommended that the placebo arm be discontinued early due to clear demonstration of PrEP efficacy for HIV-1 prevention. [25] All participants were informed of the outcome and continued on active PrEP thereafter. Data through study completion (between 2008 and 2013) were included in this prospective analysis of male circumcision and incident syphilis.

Data collection

HIV-1 uninfected participants attended monthly and HIV-1 infected partners attended quarterly visits for up to 36 months. Follow up visits included standardized interviews about sexual behavior in the last 30 days, medical history, and assessment of clinical and laboratory safety. Male circumcision status was determined by physical examination at the time of study enrollment and each annual follow up visit and reported as fully circumcised, partially circumcised or not circumcised. HIV-1 uninfected partners underwent HIV-1 testing and were dispensed study medication. For HIV-1 infected partners, CD4 counts were quantified every 6 months using standard flow cytometry and plasma HIV-1 RNA levels were quantified using the COBAS Ampliprep/COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN), with a lower limit of quantification of 240 copies/mL.

Syphilis testing

Detailed descriptions of the Partners PrEP Study STI diagnostic testing are provided elsewhere. [26] Prevalent syphilis infection at enrollment was determined by a positive Rapid Plasma Reagin (RPR, Immutrep RPR [Omega Diagnostics], BD Macro-Vue RPR [BD diagnostics], or Human RPR [Human Diagnostics]) titer and confirmed with a positive *Treponema pallidum* hemagglutination (TPHA, Immutrep TPHA [Omega Diagnostics], Randox TPHA [Randox Laboratories], Human TPHA Liquid [Human Diagnostics], or Hexagon [Human Diagnostics]) assay result. Syphilis serology testing was conducted annually during follow up visits and if clinically indicated during other study visits. Study participants with syphilis at enrollment were considered to have a new incident infection during follow up if the RPR titer increased by 4-fold or more from the prior visit. For study participants with a negative RPR at enrollment, a positive RPR with a confirmatory positive TPHA assay at a follow-up visit was defined as an incident syphilis infection; and subsequent infections were deemed to be incident if a 4-fold-increase in RPR titer had occurred. Only incident non-persistent syphilis infections detected through serologic testing were included in the final analysis.

Statistical methods

All couples in which the circumcision status of the male partner was available were included; a small number of couples with partially circumcised men were excluded. Chi-squared tests for proportions and Kruskal-Wallis tests for continuous measures were used to detect differences in demographic, behavioral and medical characteristics between couples with circumcised versus uncircumcised men at enrollment.

Differences in syphilis detected at enrollment among circumcised versus uncircumcised men (or women with exposure to circumcised versus uncircumcised men) were assessed using multivariate logistic regression. To assess incident syphilis during follow-up, Andersen-Gill survival models were used, to allow for multiple events per subject. Male circumcision status was analyzed as a time-dependent exposure variable, allowing for the inclusion of uncircumcised men who became circumcised during study follow up. Separate analyses were conducted to compare syphilis incidence rates among HIV-1 infected and uninfected men by their circumcision status and among HIV-1 infected and uninfected women by whether their male partner was circumcised or uncircumcised. Differences in the effect of male circumcision on syphilis incidence between HIV-1 infected and uninfected study participants were assessed using a likelihood ratio test of interaction within our Andersen-Gill survival models. HIV-1 uninfected participants at enrollment who became HIV-1 infected during study follow up were censored at seroconversion. HIV-1 infected participants were observed throughout study follow up regardless of partner's seroconversion status.

We determined *a priori* to adjust our statistical models for age at enrollment, reported unprotected sex with the study partner in the last 30 days, and the plasma HIV-1 RNA concentration of the HIV-1 infected partner in the couple due to the known associations of these factors with male circumcision status or risk of STI/HIV-1 transmission. [27–30] Unprotected sex and HIV-1 RNA concentration were analyzed as time-dependent variables

as reported at the follow up visit when syphilis testing was conducted. For HIV-1 uninfected participants, we included the HIV-1 RNA concentration of the HIV-1 infected partner. Additionally, we identified several demographic, behavioral, and medical characteristics to assess as potential confounders: pregnancy during follow up among female partners, marital status, cohabitation with study partner, number of children with study partner, reported sex with an outside partner, CD4 count of the HIV-1 infected partner, PrEP study arm assignment, HSV-2 status at enrollment, infection with a curable STI (*Neisseria gonorrhoeae*, *Chlamydia trachomatis* or *Trichomonas vaginalis*) at enrollment, and HIV-1 seroconversion of the HIV-1 uninfected partner during follow-up. None of these additional potential confounders were included in the final models because they did not substantially change the logistic regression model odds ratio or survival model hazard ratios (<10% change).

To examine the robustness of our Andersen-Gill models, we repeated the primary analysis using Poisson generalized estimating equations (GEE) regression models for interval-censored failure time data. [31] We also performed sensitivity analyses by 1) excluding cases with a subsequent 4-fold titer increase in RPR after previously detected incident syphilis to reduce potential misclassification due to treatment failure, 2) restricting the analysis to study participants whose partners had serologic evidence of syphilis infection to examine the effect of male circumcision on syphilis infections with the clearest evidence of linkage within the study partnerships and 3) restricting the analysis to men who became circumcised during follow up to examine the effect of the period immediately following the medical male circumcision procedure on syphilis acquisition and transmission. Data were analyzed using STATA 13.1/MP for Windows (Stata Corporation, College Station, TX).

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Results

Enrollment characteristics

A total of 4716 couples (99·3% of couples in the clinical trial) met criteria for inclusion in this analysis, in which the HIV-1 infected partner was female in 2946 couples and male in 1770 couples (Table 1); 31 were excluded due to missing data or having a “partial” male circumcision status. The median age at enrollment was 30 years (interquartile range [IQR] 25–36) for women and 36 (IQR 30–42) for men; most couples were married (98·2%) and had a median of 2 children (IQR 1–4) together. The median number of sex acts in the prior month was 4 (IQR 2–8) and 26·4% of couples reported unprotected sex. 13·9% of men and 0·8% of women reported having sex with an outside partner in the month prior to enrollment. The prevalence of other curable STIs was 4·5% among men and 10·0% among women (1.1% in men and 0.9% in women for *Chlamydia trachomatis*, 0.8% in men and 1.7% in women for *Neisseria gonorrhoeae, and* 2.8% in men and 8.5% in women for *Trichomonas vaginalis*).

At enrollment, 45·6% of men were circumcised (574 [32·4%] of HIV-1 infected and 1575 [53·5%] of HIV-1 uninfected men, Table 1). Couples with circumcised men were more educated ($p<0.001$ for the education level of both members of couples with HIV-1 infected and uninfected men), more often from Kenya ($p<0·001$ for couples with HIV-1 uninfected and infected men), had more children ($p=0·001$ for couples with an HIV-1 uninfected man and $p<0·001$ for couples with an HIV-1 infected man), reported unprotected sex with the study partner less frequently in the past month ($p<0·001$ for couples with an HIV-1 uninfected man and $p=0·021$ for couples with an HIV-1 infected man), had male partners that reported sex with an additional partner less frequently ($p=0·002$ for couples with an HIV-1 uninfected man and $p=0·001$ for couples with an HIV-1 infected man), lower plasma HIV-1 RNA concentration of HIV-1 infected partners ($p<0·001$ for couples with HIV-1 uninfected and infected men), and lower prevalence of curable STIs among female partners.

Syphilis prevalence at enrollment and association with male circumcision status

Circumcised HIV-1 infected and uninfected men had a lower prevalence of syphilis at enrollment than those who were uncircumcised: for HIV-1 infected men, prevalence was 1·9% vs 7·3% among those circumcised and uncircumcised (adjusted odds ratio [aOR]=0·25, 95% confidence interval [CI] 0·17–0·36, Table 2) and for HIV-1 uninfected men, prevalence was 2·1% versus 4·8% among those circumcised and uncircumcised (aOR=0·51, 95% CI 0·40–0·66). This same pattern was observed in women: the prevalence of syphilis was 1·7% among HIV-1 infected women with circumcised male partners compared to 5·4% among those with uncircumcised male partners (aOR=0·35, 95% CI 0·27–0·46), and syphilis prevalence was 2·5% among HIV-1 uninfected women with circumcised male partners compared to 5·6% among those with uncircumcised male partners (aOR=0·45, 95% CI 0·37–0·64).

Incident syphilis during follow up and association with male circumcision status

A total of 1645 HIV-1 infected men, 2744 HIV-1 uninfected men, 1643 HIV-1 uninfected women, and 2773 HIV-1 infected women had complete information on male partner circumcision status, at least one syphilis serology result, and sexual behavior data during study follow up and were included in the final analysis of incident syphilis risk (Table 3). The median time that participants were in the study was 2·75 years (IQR 2·30–2·79). A total of 221 incident syphilis infections were observed: 46 among HIV-1 infected men (incidence 1·10 per 100 person-years), 76 among HIV-1 uninfected men (1·09 per 100 person-years), 54 among HIV-1 infected women (0·77 per 100 person-years) and 45 among HIV-1 uninfected women (1·11 per 100 person-years). A total of 21 individuals had more than one incident syphilis infection during follow up (9 women and 12 men).

Overall, male circumcision was associated with a 42% reduction in incident syphilis in men (Table 3) including a 62% reduction among HIV-1 infected men (adjusted hazard ratio [HR] 0·38, 95% CI 0·18–0·81) and a non-significant reduction in incident syphilis among HIV-1 uninfected men (adjusted HR 0·64, 95% CI 0·36–1·11). There was no statistically significant difference in the effect of male circumcision on syphilis incidence between HIV-1 infected and uninfected men (likelihood ratio $p_{interaction}=0·26$). Among women, circumcision of their male partners was associated with a 59% reduction in incident syphilis, including a 75%

reduction among HIV-1 uninfected women (adjusted HR 0·25, 95% CI 0·08–0·76) and a 48% reduction among HIV-1 infected women (adjusted HR 0·52, 95% CI 0·27–0·97). The effect of male circumcision on syphilis incidence between HIV-1 infected and uninfected women was not significantly different (likelihood ratio $p_{interaction}$=0·17). Analysis using Poisson GEE regression models for interval-censored failure time data produced results that were very similar to all Andersen-Gill models (data not shown).

Sensitivity analyses

To reduce potential misclassification of RPR titer increases representing syphilis treatment failure rather than new infections, we excluded cases with a subsequent 4-fold titer increase in RPR after previously detected incident syphilis. Results were similar to those from the full cohort: for HIV-1 infected men, the adjusted HR was 0·43, 95% CI 0·19–0·99 (36 events), for HIV-1 uninfected men, the adjusted HR was 0·58, 95% CI 0·58–1·04 (47 events), for HIV-1 infected women, the adjusted HR was 0·56, 95% CI 0·29–1·06 (38 events) and for HIV-1 uninfected women, the adjusted HR was 0·28, 95% CI 0·10–0·84 (32 events). To reduce potential misclassification of syphilis acquisition from outside partners, we restricted the cohort to study participants whose partners had serologic evidence of syphilis infection. Results were of similar magnitude to those from the full cohort, although power was limited: for HIV-1 infected men, the adjusted HR was 0·39, 95% CI 0·06–2·47 (9 events in 84 men), for HIV-1 uninfected men, the adjusted HR was 1·18, 95% CI 0·34–4·14 (19 events in 111 men), for HIV-1 infected women, the adjusted HR 0·73, 95% CI 0·24–2·23 (15 events in 115 women) and for HIV-1 uninfected women, the adjusted HR was 0·85, 95% CI 0·09–8·32 (10 events in 103 women).

Uptake of male circumcision and association with syphilis acquisition during follow-up

A total of 69 (4·2%) HIV-1 infected and 132 (4·8%) HIV-1 uninfected men became circumcised during study follow-up and there were no incident syphilis infections among their female partners. Two of 76 incident syphilis infections among HIV-1 uninfected men and two of 46 incident syphilis infections among HIV-1 infected men were among men who became circumcised during follow-up; all four syphilis infections were detected at the same annual visit when men were first documented to be circumcised. When we restricted our analysis to men who became circumcised during study follow up, the results were qualitatively similar to those of the primary analysis.

Discussion

In this large prospective study from East Africa, male circumcision was associated with a reduced risk of prevalent and incident syphilis for men and women. The magnitude of risk reduction associated with male circumcision ranged from ~40–75% and was statistically significant in all groups except for HIV-1 uninfected men where a trend towards a protective benefit was observed. There are very limited data assessing the relationship between male circumcision and incident syphilis risk for HIV-1 infected men and female partners of men with and without HIV-1 infection, and thus our findings provide important new information for the medical benefits of male circumcision.

There is a clear biological rationale for why male circumcision may protect against ulcerative STIs, such as syphilis. Uncircumcised men may be at increased risk due to penetration of pathogens through the inner surface of the foreskin and frenulum, or through micro-abrasions to the thinner epithelium lining the foreskin occurring during intercourse. [9] The warm, moist area under the foreskin may provide an environment which encourages replication of *Treponema pallidum* and other pathogens. Male circumcision may reduce transmissibility to female partners by reducing the surface area of the glans where spirochete-containing ulcers can form. At the population level, male circumcision could benefit women by reducing their risk of exposure to syphilis through reducing the risk of syphilis in their male partners. Current WHO guidelines recommend male circumcision programs for HIV-1 prevention among heterosexual men in settings with a high HIV/AIDS burden. [5,14] The effect of male circumcision programs in reducing syphilis incidence and secondary transmission, in addition to HIV-1 incidence among heterosexual men, could potentially have important public health implications and warrants future investigation.

Multiple studies have examined associations between male circumcision and the incidence of non-HIV-1 STIs. [32] A meta-analysis of studies reporting on the association of male circumcision and syphilis, essentially among HIV-1 uninfected men, reported a summary relative risk of 0·69, (95% CI 0·50–0·94) similar to our findings. [9] Two prior randomized trials have assessed the effect of male circumcision (versus delayed male circumcision) on syphilis acquisition among HIV-1 uninfected men; neither found a protective effect: adjusted HR 1·10, 95% CI 0·75–1·65 and risk ratio 1·23, 95% CI 0·41–3·65. [8,10] Both randomized trials excluded men who were HIV-1 or *T. pallidum*-infected at baseline and reported low detection of syphilis at follow up. Our study did not have these exclusion requirements, and thus our participants may have had greater syphilis exposure, permitting observation of the impact of male circumcision on syphilis risk that was not possible in the recent clinical trials.

This is the first study to our knowledge that has reported a statistically significant reduced risk of incident syphilis among female partners with circumcised male partners. Syphilis prevention in women continues to be an important goal. Several longitudinal studies and ongoing national-level surveys have established syphilis and HIV-1 comorbidity among women in sub-Saharan Africa. [33,34] Additionally, there are approximately 1 million new cases of congenital syphilis annually warranting further research on risk factors for syphilis among women and identification and implementation of effective interventions. [35] Efforts to promote medical male circumcision should emphasize the other reproductive health benefits to men and their female partners, including syphilis prevention, in addition to HIV-1 prevention.

Limitations of our study included the annual assessment of male circumcision status, which reduced our ability to precisely determine when initially uncircumcised men became circumcised. We tested for syphilis annually and when clinically indicated but generally had limited ability to detect all incident syphilis infections, especially infections that may have occurred between testing intervals, some of which were potentially treated by outside providers or indirectly treated with antibiotics prescribed for other medical conditions. Although our data are from couples, the one year interval between syphilis testing and

absence of laboratory testing to link syphilis infections complicates our ability to link syphilis infections within couples. Thus, there could be some misclassification in evaluation of male circumcision and incident syphilis if partners acquired syphilis from an outside partner whose male circumcision status was not known. Results from our sub-analyses restricted to study participants whose partners had prior evidence of syphilis infection were similar to those from our primary models although with limited power. Additionally, our study participants were mutually disclosed HIV-1 serodiscordant heterosexual African couples and therefore further data are needed to confirm our results in other populations.

In conclusion, we found a consistent protective effect of male circumcision on syphilis incidence among HIV-1 infected and uninfected men and women. Our results add to the body of evidence that male circumcision prevents STIs in populations beyond HIV-1 uninfected men. If confirmed, our results suggest that male circumcision could significantly reduce syphilis incidence and related sequelae in both men and their female partners. A reduction in syphilis infection for men and women via male circumcision could have important implications for syphilis control and enhancing the public health benefits of this effective intervention, particularly in settings with high HIV/AIDS comorbidity and where congenital syphilis persists as a public health problem.

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Panel: Research in Context

Systematic Review

We conducted a systematic search of the literature using PubMed with the terms “male circumcision”, “syphilis”, “acquisition”, “risk”, and “female partners”. We identified one meta-analysis synthesizing studies from 1950–2004 that reported a statistically significant summary measure demonstrating a protective effect of male circumcision on syphilis infection among men. [9] Two additional prospective studies published since this meta-analysis utilized randomized study designs to evaluate the relationship of male circumcision and syphilis acquisition among HIV-1 uninfected men. [8,10] These studies found no difference in the rate of syphilis incidence among HIV-1 uninfected men randomized to immediate versus delayed medical male circumcision. We did not identify any studies that investigated the relationship of male circumcision status and syphilis risk among HIV-1 infected men or the relationship of male circumcision status and syphilis risk among female partners.

Interpretation

In this large prospective study, male circumcision protected against syphilis acquisition in HIV-1 infected and uninfected men and women. If confirmed through other studies, our results suggest that male circumcision could play an important role for syphilis control and would enhance the public health benefits of this effective intervention, particularly in settings with high HIV/AIDS comorbidity and where congenital syphilis persists as a public health problem.

Table 1

Enrollment characteristics of serodiscordant couples with documented male circumcision status[1,2]

	Couples with HIV-1 uninfected man n=2946			Couples with HIV-1 infected man n=1770		
	Circumcised male partner n=1575	Uncircumcised male partner n=1371		Circumcised male partner n=574	Uncircumcised male partner n=1196	
	Median (IQR) or N (percentage)		p-value	Median (IQR) or N (percentage)		p-value
Demographic characteristics						
Age, male partner(years)	34 (29−40)	34 (28−41)	0·542	38 (33−44)	39 (34−45)	0·292
Age. female partner (years)	29 (24−34)	29 (24−35)	0·358	32 (27−37)	33 (28−39)	0·037
Years of school completed, male partner	8 (6−12)	7 (5−10)	<0·001	8 (6−11)	7 (4−9)	<0·001
Years of school completed, female partner	8 (5−10)	6 (3−6)	<0·001	7 (5−10)	5 (2−7)	<0·001
Enrollment site in Kenya (vs Uganda)	1082 (69%)	426 (31%)	<0·001	350 (61%)	228 (19%)	<0·001
Couple characteristics[3]						
Number of children together	1 (0−3)	2 (0−3)	0·001	3 (1−4)	3 (2−5)	<0·001
No children together	424 (23%)	364 (27%)	0·821	99 (17%)	162 (14%)	0·040
Married	1514 (96%)	1342 (98%)	0·006	564 (98%)	1182 (99%)	0·330
Cohabitating	1529 (97%)	1348 (98%)	0·026	566 (99%)	1176 (98%)	0·660
Sexual behavior within partnership[3]						
Duration of sexual partnership (years)	6 (2−11)	6 (2−12)	0·442	11 (5−17)	12 (7−19)	<0·001
Coital frequency within couple, past month	4 (3−8)	4 (2−8)	0·068	4 (2−8)	2 (4−6)	<0·001
Reported unprotected sex with study partner, past month	383 (24%)	461 (34%)	<0·001	111 (19%)	290 (24%)	0·021
Reported sex with an additional partner, past month, male partner	181 (11%)	212 (15%)	0·002	62 (11%)	200 (17%)	0·001
Reported sex with an additional partner, past month, female partner	13 (1%)	16 (1%)	0·349	4 (1%)	4 (1%)	0·287
HIV-1 characteristics						
CD4 cell count (cell/μl)[4]	454 (358−588)	458 (351−598)	0·783	523 (392−693)	533 (399−716)	0·167
Plasma HIV−1 RNA (log_{10} copies/ml)[4]	4·0 (3·2−4·6)	4·2 (3·5−4·8)	<0·001	3·7 (2·9−4·3)	3·8 (3·2−4·4)	<0·001

	Couples with HIV-1 uninfected man n=2946			Couples with HIV-1 infected man n=1770		
	Circumcised male partner n=1575	Uncircumcised male partner n=1371		Circumcised male partner n=574	Uncircumcised male partner n=1196	
	Median (IQR) or N (percentage)		p-value	Median (IQR) or N (percentage)		p-value
ART use during study[4]	569 (36%)	491 (36%)	0·831	209 (36%)	492 (41%)	0·055
Randomized to active PrEP arm[5]	1069 (68%)	918 (67%)	0·597	373 (65%)	781 (65%)	0·895
Medical characteristics						
Ever pregnant during study period	578 (37%)	529 (39%)	0·292	134 (23%)	261 (23%)	0·472
Curable STI at enrollment						
Curable STI, male partner[6]	97 (6%)	67 (5%)	0·149	19 (3%)	29 (2%)	0·300
Curable STI, female partner[6]	149 (10%)	178 (14%)	<0·001	35 (6%)	109 (10%)	0·015

[1] Missing data not shown

[2] 25 couples were excluded because the male partner was “partially” circumcised (11 couples with HIV-1 infected male partner and 14 couples with HIV-1 uninfected male partner)

[3] Couple sexual behavior and demographic characteristics as reported by female partner

[4] Among HIV-1 infected male or female partners only

[5] Among HIV-1 uninfected male or female partners only

[6] Includes *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*

Table 2

Prevalent syphilis: proportion of men and women with serologic evidence of syphilis at enrollment and association with male partner circumcision status, by enrollment HIV-1 serostatus

	Total		Uncircumcised		Circumcised		Crude OR (95% CI)	p-value	Adjusted OR (95% CI)[1]	p-value
	No.	%	No.	%	No.	%				
All men (n=4682)	196	4·2%	152	6·0%	44	2·1%	0·33 (0·24−0·47)	<0·001	0·37 (0·26−0·52)	<0·001
HIV-1 infected men (n=1759)	98	5·6%	87	7·3%	11	1·9%	0·25 (0·13−0·47)	<0·001	0·25 (0·17−0·36)	<0·001
HIV-1 uninfected men (n=2923)	98	3·4%	65	4·8%	33	2·1%	0·42 (0·27−0·63)	<0·001	0·51 (0·40−0·66)	<0·001
All women (n=4696)	181	3·8%	141	5·5%	40	1·9%	0·33 (0·23−0·47)	<0·001	0·37 (0·26−0·53)	<0.001
HIV-1 infected women (n=2935)	100	3·4%	74	5·4%	26	1·7%	0·30 (0·19−0·47)	<0·001	0·35 (0·27−0·46)	<0·001
HIV-1 uninfected women (n=1761)	81	4·6%	67	5·6%	14	2·5%	0·41 (0·23−0·74)	0·003	0·45 (0·37−0·64)	<0·001

[1] Adjusted model includes: age, plasma HIV-1 RNA (log_{10} copies/ml) of HIV-infected partner, and reported recent unprotected sex with study partner

Table 3

Incident syphilis: rate of syphilis during follow-up and risk estimates of male partner circumcision status, by enrollment HIV-1 serostatus

	No. of incident infections	Person-time (years)	Incidence rate (per 100 person-years)	Unadjusted HR (95% CI)	p-value	Adjusted HR[1] (95% CI)	p-value	$p_{interaction}$[2]
All men (n=4389)	122	11153·8	1·09 (0·92−1·31)					
Circumcised	44	5514·6	0·80 (0·59−1·07)	0·57 (0·36−0·89)	0·012	0·58 (0·37−0·91)	0·017	0·26
Uncircumcised	78	5586·6	1·40 (1·12−1·74)	1·00				
HIV-1 infected men (n=1645)	46	4199·8	1·10 (0·82−1·46)					
Circumcised	8	1489·7	0·54 (0·27−1·07)	0·38 (0·18−0·81)	0·012	0·38 (0·18−0·81)	0·013	
Uncircumcised	38	2680·1	1·42 (1·03−1·95)	1·00				
HIV-1 uninfected men (n=2744)	76	6953·9	1·09 (0·87−1·37)					
Circumcised	36	4024·9	0·89 (0·65−1·24)	0·64 (0.37−1.12)	0·118	0·64 (0·36−1·11)	0·115	
Uncircumcised	40	2906·5	1·38 (1·01−1·88)	1·00				
All women (n=4416)	99	11132·0	0·89 (0·73−1·08)					
Circumcised male partners	28	5484·8	0·51 (0·35−0·74)	0·40 (0·24−0·68)	0·012	0·41 (0·25−0·69)	0·001	0·17
Uncircumcised male partners	71	5598·9	1·27 (1·00−1·60)					
HIV-1 infected women (n=2773)	54	7062·8	0·77 (0·59−1·00)					
Circumcised male partners	22	4075·1	0·54 (0·36−0·82)	0·50 (0·27−0·94)	0·033	0·52 (0·27−0·97)	0·040	
Uncircumcised male partners	32	2964·5	1·08 (0·76−1·53)	1·00				
HIV-1 uninfected women (n=1643)	45	4069·3	1·11 (0·82−1·48)					
Circumcised male partners	6	1409·7	0·43 (0·19−0·95)	0·29 (0·10−0·85)	0·024	0·25 (0.08−0.76)	0·014	
Uncircumcised male partners	39	2634·5	1·48 (1·08−2·03)	1·00				

HR: hazard ratio

[1] Adjusted model includes: age, plasma HIV-1 RNA (log10 copies/ml) of HIV-infected partner, reported recent unprotected sex with study partner

[2] Likelihood ratio test assessed difference in the effect of male circumcision on syphilis incidence between HIV-1 infected and uninfected study participants