# 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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## Summary

**Background** Male circumcision is a primary HIV-1 prevention intervention for men, but whether the procedure reduces the risk of syphilis among men and their female partners is uncertain. We aimed to assess whether male circumcision was associated with incident syphilis in men and in their female partners.

**Methods** In this large prospective cohort study, participants were members of Kenyan and Ugandan HIV-1 serodiscordant heterosexual couples enrolled in a randomised safety and efficacy clinical trial of pre-exposure prophylaxis for HIV-1 prevention (the Partners PrEP Study). Participants attended monthly or quarterly follow-up visits for up to 36 months. Annually, syphilis serology testing was done and male circumcision status was assessed. We used multivariate Andersen-Gill survival methods, adjusted for age, sexual behaviour, and plasma HIV RNA levels of the HIV-infected partner.

**Findings** 4716 HIV-1 serodiscordant couples (38%) with a man with HIV were followed for a median of 2·75 years. At enrolment, 1575 (53%) men with HIV and 560 (32%) men without HIV were circumcised; an additional 69 (4%) men with HIV and 132 (5%) men without HIV were circumcised during study follow-up. 221 incident syphilis infections were reported: 46 (21%) in men with HIV (incidence 1·10 per 100 person-years), 76 (34%) in men without HIV (1·09), 54 (24%) in women with HIV (0·77), and 45 (24%) in women without HIV (1·11). 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 in men with HIV (0·38, 0·18–0·81), and a non-significant reduction in incident syphilis in men without HIV (0·64, 0·36–1·11). In 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 in women without HIV (0·25, 0·08–0·76) and a 48% reduction in women with HIV (0·52, 0·27–0·97).

**Interpretation** 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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## Introduction

Data from more than 40 studies, including three randomised controlled trials, have shown that male circumcision provides at least 60% protection against acquisition of HIV-1 for heterosexual men.[1–4] The consistently high efficacy noted in the three randomised clinical trials was the impetus for WHO-UNAIDS recommendations in 2007 that medical male circumcision be a priority strategy for prevention of HIV and should be implemented in settings with low prevalence of male circumcision and high prevalence of HIV.[5] Several observational studies also support a preventive role for male circumcision for other sexually transmitted infections (STIs), including human papillomavirus, herpes simplex virus type 2, *Trichomonas vaginalis*, chancroid, *Mycoplasma genitalium*, and genital ulcer disease in heterosexual men.[6–13] Although a meta-analysis of randomised and observational studies concluded that there was no association between male circumcision and risk of HIV 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 has been reported. Data from randomised trials have shown reduced risk of human papillomavirus, genital ulcers, herpes simplex virus type 2, bacterial vaginosis, and *T vaginalis* in women whose partners are circumcised, whereas other observational studies did not show an 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*

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*gonorrhoeae* in which a greater proportion of non-Jewish men had syphilis compared with Jewish men, who were presumed to be circumcised because of religious practices.[22] Several recent studies, including one meta-analysis, have suggested that circumcised heterosexual men are at reduced risk of syphilis.[9] However, few studies have assessed the relation between male circumcision and incident syphilis status in men with HIV, and no studies to date have investigated the effect of male circumcision in HIV-infected or HIV-uninfected men on syphilis acquisition in women. A protective effect of male circumcision on the risk of incident syphilis for HIV-infected and HIV-uninfected men and women could 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 burden,[24] and in those settings syphilis prevalence is also often high. Evidence of additional benefits against syphilis could enhance present medical male circumcision programmes. We aimed to investigate the association between male circumcision and incidence of syphilis in a HIV-infected and HIV-uninfected African men and their female partners.

## Methods

### Study design and participants

In this large prospective cohort study, participants were members of Kenyan and Ugandan HIV serodiscordant heterosexual couples enrolled in a randomised 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 prevention services, including individual and couples risk-reduction counselling, screening and treatment for STIs, condoms, and referral for medical male circumcision and post-exposure prophylaxis according to national policies. At enrolment into the trial, HIV-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 group be discontinued early because of clear demonstration of PrEP efficacy for HIV 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.

The Partners PrEP Study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at all of the study sites.[25] All participants provided written informed consent in English or their local language.

### Procedures

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

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

### Statistical analysis

All couples in whom the circumcision status of the male partner was available were included in the statistical analysis for this study; a small number of couples with partially circumcised men were excluded. $\chi^2$ tests for proportions and Kruskal-Wallis tests for continuous measures were used to detect differences in demographic, behavioural, and medical characteristics between couples with circumcised versus uncircumcised male partners at enrolment.

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

We decided a priori to adjust our statistical models for age at enrolment, reported unprotected sex with the study partner in the past 30 days, and plasma HIV RNA concentration of the partner with HIV in the couple because of the known associations of these factors with male circumcision status or risk of STI or HIV transmission.[27–30] Unprotected sex and HIV RNA concentration were analysed as time-dependent variables

| | Couples with HIV-uninfected man (n=2946) | | | Couples with HIV-infected man (n=1770) | | |
|---|---|---|---|---|---|---|
| | Circumcised male partner (n=1575) | Uncircumcised male partner (n=1371) | p value | Circumcised male partner (n=574) | Uncircumcised male partner (n=1196) | 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) | <0·0001 | 8 (6–11) | 7 (4–9) | <0·0001 |
| Years of school completed, female partner | 8 (5–10) | 6 (3–6) | <0·0001 | 7 (5–10) | 5 (2–7) | <0·0001 |
| Enrolment site in Kenya (*vs* Uganda) | 1082 (69%) | 426 (31%) | <0·0001 | 350 (61%) | 228 (19%) | <0·0001 |
| **Couple characteristics‡** | | | | | | |
| Number of children together | 1 (0–3) | 2 (0–3) | 0·001 | 3 (1–4) | 3 (2–5) | <0·0001 |
| 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 behaviour within partnership‡** | | | | | | |
| Duration of sexual partnership (years) | 6 (2–11) | 6 (2–12) | 0·442 | 11 (5–17) | 12 (7–19) | <0·0001 |
| Coital frequency within couple, past month | 4 (3–8) | 4 (2–8) | 0·068 | 4 (2–8) | 2 (4–6) | <0·0001 |
| Reported unprotected sex with study partner, past month | 383 (24%) | 461 (34%) | <0·0001 | 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 characteristics** | | | | | | |
| CD4 cell count (cells per μL)§ | 454 (358–588) | 458 (351–598) | 0·783 | 523 (392–693) | 533 (399–716) | 0·167 |
| Plasma HIV-1 RNA ($log_{10}$ copies per mL)§ | 4·0 (3·2–4·6) | 4·2 (3·5–4·8) | <0·0001 | 3·7 (2·9–4·3) | 3·8 (3·2–4·4) | <0·0001 |
| ART use during study§ | 569 (36%) | 491 (36%) | 0·831 | 209 (36%) | 492 (41%) | 0·055 |
| Randomised to active PrEP group¶ | 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 enrolment | | | | | | |
| Male partner‖ | 97 (6%) | 67 (5%) | 0·149 | 19 (3%) | 29 (2%) | 0·300 |
| Female partner‖ | 149 (10%) | 178 (14%) | <0·0001 | 35 (6%) | 109 (10%) | 0·015 |

Data are median (IQR) or N (%). *Missing data not shown. †25 couples were excluded because the male partner was "partially" circumcised (11 couples with HIV-infected male partner and 14 couples with HIV uninfected male partner). ‡Couple sexual behaviour and demographic characteristics as reported by female partner. §Among HIV-infected male or female partners only. ¶Among HIV-uninfected male or female partners only. ‖Includes *Neisseria gonorrhoeae, Chlamydia trachomatis,* and *Trichomonas vaginalis.*

***Table 1:*** **Enrolment characteristics of serodiscordant couples with documented male circumcision status*†**

as reported at the follow-up visit when syphilis testing was done. For participants who did not have HIV, we included the HIV RNA concentration of the partner with HIV. Additionally, we identified several demographic, behavioural, and medical characteristics to assess as potential confounders: pregnancy during follow-up in female partners, marital status, cohabitation with study partner, number of children with study partner, reported sex with an outside partner, CD4 cell count of the partner with HIV, PrEP study group assignment, herpes simplex virus-2 status at enrolment, infection with a curable STI (*N gonorrhoeae, C trachomatis*, or *T vaginalis)* at enrolment, and HIV-1 seroconversion of the partner without HIV 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 with Poisson generalised estimating equation regression models for interval-censored failure time data.[31] We also did sensitivity analyses by excluding cases with a subsequent four-fold titre increase in rapid plasma reagin after previously detected incident syphilis to reduce potential misclassification due to treatment failure; by restricting the analysis to study participants whose partners had serological 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 by 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 analysed with STATA 13.1/MP for Windows (Stata Corporation, College Station, TX, USA).

### Role of the funding source

The funder had no involvement in the study design, data collection or analysis, interpretation of results, and writing of this report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication without involvement of the funding source.

## Results

4716 couples (99% of couples in the clinical trial) met criteria for inclusion in this analysis, of whom the HIV-infected partner was female in 2946 couples and male in 1770 couples (table 1); 31 were excluded because of missing data or for having a "partial" male circumcision status. The median age at enrolment was 30 years (IQR 25–36) for women and 36 years (30–42) for men; most (98%) couples were married and had a median of two children (IQR 1–4) together. The median number of sex acts in the previous month was four (IQR 2–8) and 1245 (26%) of couples reported unprotected sex. 655 (14%) of men and 37 (<1%) of women reported having sex with an outside partner in the month before enrolment. 212 (5%) men had other curable STIs and 471 (10%) of women (52 [1%] men and 37 [<1%] women had *C trachomatis*, 39 (<1%) men and 75 (2%) women had *N gonorrhoeae*, and 214 (5%) men and 381 (8%) women had *T vaginalis)*.

At enrolment, 2149 (46%) men were circumcised (574 [32%] had HIV and 1575 [54%] did not have HIV; table 1). Couples with circumcised men were more educated, more often from Kenya, had more children, reported unprotected sex with the study partner less frequently in the past month, had male partners that reported sex with an additional partner less frequently, had lower plasma HIV-1 RNA concentration of HIV-infected partners, and had a lower prevalence of curable STIs among female partners (table 1).

Circumcised men with and without HIV had a lower prevalence of syphilis at enrolment than those who were uncircumcised (table 2). This same pattern was noted in women.

1645 men with HIV, 2744 men without HIV, 1643 women without HIV, and 2773 women with HIV had complete information about male partner circumcision status, at least one syphilis serology result, and sexual behaviour 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

| | Total | Uncircumcised | Circumcised | Crude | | Adjusted* | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95% CI) | p value | OR (95% CI) | p value |
| All men (n=4682) | 196 (4%) | 152 (6%) | 44 (2%) | 0·33 (0·24–0·47) | <0·0001 | 0·37 (0·26–0·52) | <0·0001 |
| HIV-infected men (n=1759) | 98 (6%) | 87 (7%) | 11 (2%) | 0·25 (0·13–0·47) | <0·0001 | 0·25 (0·17–0·36) | <0·0001 |
| HIV-uninfected men (n=2923) | 98 (3%) | 65 (5%) | 33 (2%) | 0·42 (0·27–0·63) | <0·0001 | 0·51 (0·40–0·66) | <0·0001 |
| All women (n=4696) | 181 (4%) | 141 (5%) | 40 (2%) | 0·33 (0·23–0·47) | <0·0001 | 0·37 (0·26–0·53) | <0·0001 |
| HIV-infected women (n=2935) | 100 (3%) | 74 (5%) | 26 (2%) | 0·30 (0·19–0·47) | <0·0001 | 0·35 (0·27–0·46) | <0·0001 |
| HIV-uninfected women (n=1761) | 81 (5%) | 67 (6%) | 14 (3%) | 0·41 (0·23–0·74) | 0·003 | 0·45 (0·37–0·64) | <0·0001 |

Data are N (%), unless otherwise stated. OR=odds ratio. *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 2:*** **Prevalent syphilis—proportion of men and women with serological evidence of syphilis at enrolment and association with male partner circumcision status, by enrolment HIV serostatus**

| | Incident infections | Person-time (years) | Incidence per 100 person-years (95% CI) | Unadjusted | | Adjusted* | | $p_{interaction}$† |
|---|---|---|---|---|---|---|---|---|
| | | | | HR (95% CI) | p value | HR (95% CI) | p value | |
| 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 | .. | .. | .. | .. |
| Men with HIV (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 | .. | .. | .. | .. |
| Men without HIV (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) | .. | .. | .. | .. | .. |
| Women with HIV (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 | .. | .. | .. | .. |
| Women without HIV (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. *Adjusted model includes age, plasma HIV-1 RNA ($log_{10}$ copies per mL) of HIV-infected partner, and reported recent unprotected sex with study partner. †Likelihood ratio test assessed difference in the effect of male circumcision on syphilis incidence between HIV infected and uninfected study participants.

*Table 3:* **Incident syphilis—rate of syphilis during follow-up and risk estimates of male partner circumcision status, by enrolment HIV serostatus**

the study was 2·75 years (IQR 2·30–2·79). 221 incident syphilis infections were reported: 46 (21%) in men with HIV (incidence 1·10 per 100 person-years), 76 (34%) in men without HIV (1·09), 54 (24%) in women with HIV (0·77), and 45 (24%) in women without HIV (1·11). 21 individuals had more than one incident syphilis infection during follow-up (nine women and 12 men).

Overall, male circumcision was associated with a 42% reduction in incident syphilis in men (table 3), including a 62% reduction in men with HIV (aHR 0·38, 95% CI 0·18–0·81) and a non-significant reduction in incident syphilis in men without HIV (0·64, 0·36–1·11). No significant difference was noted between the effect of male circumcision on syphilis incidence between HIV-infected and HIV-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-uninfected women (aHR 0·25, 95% CI 0·08–0·76) and a 48% reduction among HIV-infected women (0·52, 0·27–0·97). The effect of male circumcision on syphilis incidence between HIV-infected and HIV-uninfected women was not significantly different (likelihood ratio $p_{interaction}$=0·17). Analysis with Poisson generalised estimating equations regression models for interval-censored failure time data produced results that were very similar to all Andersen-Gill models (data not shown).

To reduce potential misclassification of rapid plasma reagin titre increases representing syphilis treatment failure rather than new infections, we excluded cases with a subsequent four-fold titre increase in rapid plasma reagin after previously detected incident syphilis. Results were similar to those from the full cohort: for HIV-infected men, the adjusted HR was 0·43, 95% CI 0·19–0·99 (36 events) for HIV-uninfected men, the adjusted HR was 0·58, 95% CI 0·33–1·04 (47 events), for HIV-infected women, the adjusted HR was 0·56, 95% CI 0·29–1·06 (38 events) and for HIV-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 serological evidence of syphilis infection. Results were of similar magnitude to those from the full cohort, although power was restricted: for HIV-infected men, the adjusted HR was 0·39, 95% CI 0·06–2·47 (nine events in 84 men), for HIV-uninfected men, the adjusted HR was 1·18, 95% CI 0·34–4·14 (19 events in 111 men), for HIV-infected women, the adjusted HR was 0·73, 95% CI 0·24–2·23 (15 events in 115 women), and for HIV-uninfected women, the adjusted HR was 0·85, 95% CI 0·09–8·32 (ten events in 103 women).

69 (4%) men with HIV and 132 (5%) men without HIV were circumcised during study follow-up and no incident syphilis infections were reported in their female partners. Two of 76 incident syphilis infections among HIV-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 reduced prevalence and incidence of syphilis for men and women (panel). The magnitude of risk reduction associated with male circumcision ranged from 40% to 75% and was statistically significant in all groups except for HIV-uninfected men for whom a trend towards a protective benefit was noted. Data assessing the relation between male circumcision and incident syphilis risk for HIV-infected men and female partners of men with and without HIV infection are few, and thus our findings provide important new information about the medical benefits of male circumcision.

There is a clear biological rationale for why male circumcision could protect against ulcerative STIs, such as syphilis. Uncircumcised men could be at increased risk because of penetration of pathogens through the inner surface of the foreskin and frenulum, or through microabrasions to the thinner epithelium lining the foreskin occurring during intercourse.[9] The warm, moist area under the foreskin could provide an environment that encourages replication of *T pallidum* and other pathogens. Male circumcision might 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. Present WHO guidelines recommend male circumcision programmes for HIV prevention among heterosexual men in settings with a high HIV/AIDS burden.[5,14] The effect of male circumcision programmes in reducing syphilis incidence and secondary transmission, in addition to HIV incidence among heterosexual men, could potentially have important public health implications and warrants future investigation.

Several studies have examined associations between male circumcision and incidence of non-HIV STIs.[32] A meta-analysis of studies reporting on the association of male circumcision and syphilis, essentially among HIV-uninfected men, reported a summary relative risk of 0·69 (95% CI 0·50–0·94) similar to our findings.[9] Two previous randomised trials have assessed the effect of male circumcision (versus delayed male circumcision) on syphilis acquisition among HIV-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 randomised trials excluded men who were HIV-infected 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 could have had greater syphilis exposure, allowing observation of the effect 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 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 emphasise the other reproductive health benefits to men and their female partners, including syphilis prevention, in addition to HIV 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 restricted ability to detect all incident syphilis infections, especially infections that could 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 1-year interval between syphilis testing and absence of laboratory testing to link syphilis infections complicates

### *Panel*: Research in context

**Systematic review**

We searched PubMed with the terms "male circumcision", "syphilis", "acquisition", "risk", and "female partners", for articles published between Jan 1, 1950, and June 30, 2014. Only articles available in English through original publication or translation were included. We identified one meta-analysis synthesising studies between January, 1950, and April, 2004, that reported a significant summary measure showing a protective effect of male circumcision on syphilis infection in men.[9] Two additional prospective studies published since this meta-analysis used randomised study designs to assess the relation between male circumcision and syphilis acquisition in HIV-1 uninfected men.[8,10] These studies showed no difference in the rate of syphilis incidence in men without HIV who were randomised to immediate versus delayed medical male circumcision. We did not identify any studies that investigated the relation between male circumcision status and risk of syphilis in men with HIV or the relation between male circumcision status and risk of syphilis in female partners.

**Interpretation**

In this large prospective study, male circumcision protected against syphilis acquisition in HIV infected and uninfected men and women. If confirmed by other studies, our results suggest that male circumcision could play an important part in syphilis control and could 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.

our ability to link syphilis infections within couples. Thus, some misclassification could have occurred in assessment of male circumcision and incident syphilis if partners acquired syphilis from an outside partner whose male circumcision status was unknown. Results from our subanalyses restricted to study participants whose partners had previous evidence of syphilis infection were similar to those from our primary models although with limited power. Additionally, our study participants were mutually disclosed HIV-serodiscordant heterosexual African couples and therefore further data are needed to confirm our results in other populations.

In conclusion, we identified a consistent protective effect of male circumcision on syphilis incidence among HIV-infected and HIV-uninfected men and women. Our results add to the body of evidence that male circumcision prevents STIs in populations beyond HIV-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.

#### Contributors

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

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Data management was provided by DF/Net Research Inc. (Seattle, USA) and site laboratory oversight was provided by Contract Laboratory Services (University of the Witwatersrand, Johannesburg, South Africa).

#### Declaration of interests

We declare no competing interests.

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