Published in final edited form as:

Lancet Infect Dis. 2011 August ; 11(8): 604–612. doi:10.1016/S1473-3099(11)70038-X.

The Effect of Circumcision of HIV-Infected Men on Human Papillomavirus Infection in Female Partners: Analyses Using Data from a Randomized Trial in Rakai, Uganda

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Abstract

Background—Male circumcision (MC) reduces high-risk human papillomavirus (HR-HPV) in HIV-uninfected men and their female partners. We assessed whether MC of HIV-infected men reduces HR-HPV infection in their female partners.

Methods—Female partners of married HIV-infected men with CD4 counts >350 cells/mL randomized to immediate MC (intervention, n=211) and delayed MC (control, n=171) were evaluated for HR-HPV in vaginal swabs by Roche HPV Linear Array. Prevalence risk and incident rate ratios (PRR and IRR) and 95% confidence intervals (95%CI) of HR-HPV were estimated by Poisson multiple regression using an intention-to-treat analysis. In women with pre-existing HR-HPV, we estimated the risk ratio (RR) of clearance of infection (i.e., loss of detection). The trial was registered with ClinicalTrials.gov, NCT00124878.

Findings—Female characteristics and HPV prevalence were generally similar between arms at enrollment, except the intervention arm women were younger (p=0.04). Female HR-HPV prevalence at enrollment was 67.0% in intervention arm and 61.9% in control arm p=0.33. Two year female retention rates were 75.8% (160/211) in the intervention arm and 77.2% (132/171) in the control arm. Female HR-HPV prevalence at year two was 55.4% in intervention arm and 51.9% in control arm (PRR = 1.07, 95% CI 0.86–1.32, p=0.64). HR-HPV incidence over 2 years was 32.0/100py in intervention arm and 30.6/100py in control arm female partners (IRR=1.05,

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Contributors

All authors took part in the design, implementation, and analysis of this study and saw and approved the final version.

Conflict of interest statement

Dr. Gravitt received research funding from Roche Molecular Diagnostics who manufacture the HPV genotyping test used in this study. There are no other potential conflicts of interest relevant to this article.

95% CI 0.77–1.43, $p=0.78$). There was no difference in female genotype-specific HR-HPV clearance by study arm (RR=0.96, 95% CI 0.83–1.11, $p=0.61$).

Interpretation—Contrary to findings in HIV-negative men, male circumcision of HIV-infected men did not affect HR-HPV transmission to female partners.

Funding—Bill & Melinda Gates Foundation and National Institutes of Health.

Keywords

Male circumcision; transmission; female partners; human papillomavirus (HPV); cervical cancer; HIV; Uganda; sexually transmitted infections

Introduction

Human papillomavirus (HPV) infection can cause genital warts, and high-risk HPV (HR-HPV) genotypes cause cervical cancer, the third most common cancer in women worldwide.^{1–2} Greater than 85% of the cervical cancer burden is in developing countries.² Women with HIV have significantly higher rates of multiple HR-HPV infections and more rapid progression to neoplasia.^{3–6}

Three randomized trials conducted in South Africa, Kenya and Uganda, demonstrated that male circumcision (MC) significantly decreased HIV acquisition in men.^{7–9} The World Health Organization (WHO) now recommends that MC be provided as a component of HIV prevention programs.¹⁰ As MC is becoming widely available, HIV-infected men will inevitably request the procedure. WHO recommends that they should not be denied MC unless there are medical contraindications for surgery,¹⁰ even though one randomized trial of MC which was terminated early due to futility did not reduce the rate of HIV transmission from infected men to their female partners.¹¹

Two trials reported that MC reduced the prevalence of penile HR-HPV infection by approximately 35%^{12–13} by reducing acquisition of new HR-HPV infections in both HIV-uninfected and HIV-infected men.^{14–15} Several observational studies have reported that female partners of circumcised men had a significantly reduced risk of cervical neoplasia,^{16–18} but the findings are not consistent.^{19–20} In the Rakai randomized controlled trial of male circumcision, female partners of HIV-uninfected men randomized to MC had a 29% decrease in HR-HPV transmission from HIV-uninfected circumcised men.²¹

We utilized data from a randomized controlled trial of MC in HIV-infected men in Rakai, Uganda, to assess the efficacy of the procedure for reducing HR-HPV infection in female partners of HIV-infected men.

Materials and Methods

Participants, Study Design, and Randomization

There were 7274 men screened during the MC trials for HIV/STI prevention conducted by the Rakai Health Sciences Program (RHSP), in Rakai District, Uganda, as previously described.^{7, 11–12, 21–22} 922 HIV-infected men as well as female partners of male trial participants who were married or in long term consensual relationships were enrolled with the pre-specified primary goal of assessing MC efficacy on the prevention of HIV transmission to female partners.^{11, 23} The effects of MC on female STIs, including HPV, were secondary trial outcomes.

Men were eligible for enrollment if they were uncircumcised, aged 15–49, had no medical indications or contraindications for MC, and provided written informed consent.^{7, 11} Since the safety of surgery in HIV-infected men was unknown, HIV-infected men were excluded from enrollment if they had evidence of immunosuppression (CD4 cell count <350 cells/mL or WHO clinical stage 3 or stage 4 disease). Men were randomly assigned to receive immediate circumcision (intervention arm) or circumcision delayed for 24 months (control arm). Randomization was carried out in blocks of 20, stratified by community using computer-generated random numbers, as previously described.^{7, 11} All HIV-infected men and women were referred for management of their HIV disease by the Rakai Health Sciences Program's HIV care services, supported by PEPFAR. All HIV-infected individuals received a basic care package of trimethoprim-sulfamethoxazole prophylaxis, insecticide-treated bed nets, and hypochlorite water disinfection packets. Individuals found to have a CD4 cell count $\leq$ 250 cells/mL or WHO stage 4 disease at screening or during follow-up were referred for antiretroviral therapy, provided free of charge by the RHSP via PEPFAR funding.

Men who were married or in long-term consensual relationships were asked to identify their female partners; the latter were separately contacted and invited to participate in a follow-up study. Women were eligible for enrollment if their linked male partner was a trial participant and they were capable of providing informed consent, irrespective of the female partner's HIV status. The consent form described study procedures, risks, benefits, and the voluntary nature of participation. After providing written informed consent, women were enrolled and followed annually over two years. The trial initiated enrollment in 2003 and female follow-up was completed in December 2007.^{11, 21} All participants were offered free voluntary HIV counseling and testing as individuals and as couples, HIV/STI prevention education, and condoms. HPV results were not distributed to the participants since HPV status can change and testing was delayed by >36 months from sample collection due to lack of funding for the laboratory assays. The primary objective of this analysis was to assess the efficacy of MC of HIV-infected men on rates of HPV in female partners.

At each study visit, women were interviewed to ascertain sociodemographic characteristics, sexual risk behaviors and health status, including symptoms of genital tract infections (genital ulcer disease [GUD], vaginal discharge and dysuria). Symptomatic women were treated syndromically. At each visit, women were asked to provide self-administered vaginal swabs for HPV detection.²⁴ They were instructed to squat, insert a 20-cm Dacron or cotton-tipped swab and to rotate the swab high in the vaginal vault. After collection, the women handed the swab to a field worker who placed the swab in specimen transport medium (Digene Corporation, Gaithersburg, MD). This approach to specimen collection was well accepted, with compliance rates over 90% at the baseline and follow up visits. Studies have shown that self-collected vaginal swabs are comparable to physician collected cervical swabs for HPV detection.²⁵ The specimens were maintained at 4–10 °C for less than 6 hours until they were frozen at –80C.

The trial was approved by the Uganda National Council for Science and Technology, and by three institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the Committee for Human Research at Johns Hopkins University, Bloomberg School of Public Health (Baltimore, MD, USA), and the Western Institutional Review Board (Olympia, WA, USA), as previously described.¹¹ The trial was overseen by an independent Data and Safety Monitoring Board and was registered with Clinical.Trials.Gov (NCT00124878). A community advisory board provided suggestions on the conduct of the trials and recommended the amount of compensation per study visit.

HPV and HIV Detection

HPV genotyping was performed using the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN).²⁶ HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered the primary HR-HPV genotypes. To ensure adequacy of sample collection, only vaginal swabs with detectable cellular beta-globin and/or detectable HPV were included in the analysis.

HIV status was determined using two separate ELISAs, and discordant results were confirmed by HIV-1 Western Blot as previously described.¹¹

Statistical Analysis

Enrollment and follow-up characteristics, sexual risk behaviors and STI symptoms in men and their female partners were tabulated by study arm and differences assessed by chi-square tests. All p-values are 2-sided. Analyses were performed using R 2.8.1 and SAS 9.2 (Cary, NC).

The primary assessment of the efficacy of MC for prevention of female HPV infection used an intention-to-treat analysis. An as-treated analysis was also carried out, in which intervention arm crossovers were classified as uncircumcised during the previous 12 months if the male partner was uncircumcised at the study visit. Control arm crossovers who received MC from other sources were classified as circumcised during the follow-up interval in which the procedure was performed.

For prevalent HPV outcomes, we determined the proportion of women positive for one or more HPV genotypes. HPV prevalence was tabulated at each annual visit, and the prevalence risk ratio (PRR) of HPV in the intervention relative to the control arm was estimated.

Incident HPV was defined as a new detected genotype identified in women who were initially negative for any HPV at the prior study visit, or women who were previously HR-HPV positive but had one or more newly detected HPV genotype(s) during the next follow-up interval. HPV incidence rates per 100 person-years (/100 py) were estimated assuming that the new HPV infection was acquired at the mid-point of the sequential follow-up interval. HPV incidence used an individual participant as the unit of observation, and each woman was counted only once per follow-up interval, irrespective of whether she acquired a single or multiple HPV genotypes. Incidence rate ratios (IRR) and 95% confidence intervals (95%CI) of HR-HPV acquisition in the intervention versus control arm at 12 and 24 months were estimated using a Poisson log-linear regression model. Potential confounders were examined in univariate analyses, and covariates found to be associated with HPV and study arm at $\alpha < 0.15$ or covariates that have been reported as risk factors for HPV were included in multivariate analyses. Some women were in polygamous marriages with the same male partner, and a GEE²⁷ exchangeable correlation structure was used to model the incidence rate while accounting for the potential correlation between women with the same partner.

Clearance (i.e., loss of detection) of HR-HPV was estimated among women with pre-existing HR-HPV genotype-specific infections, and HR-HPV genotype was the unit of observation. Clearance was expressed as the proportion of women with pre-existing HR-HPV infections who were negative for that genotype at a subsequent sequential study visit. Clearance was assessed for each HR-HPV genotype, and all genotype-specific clearance events were summed to provide global estimates. The clearance risk ratio (RR) of any HR-HPV genotype infection was also estimated using log binomial regression with robust variance estimates to account for the correlation of multiple genotype infections within the same individual.

Role of the funding source

For the primary female HIV outcome, the Gates Foundation maintained oversight of trial progress, and participated in open data safety and monitoring board review and in the interpretation of data. For the secondary trial endpoint of HPV, no sponsors had a role in study design, data collection, or data analysis. The corresponding author had final responsibility for preparing and submitting results for publication.

Results

The trial profile is given in Figure 1. There were 7274 men who were screened and 922 HIV-infected men that were enrolled and randomized. Of the 474 HIV-infected intervention arm men at enrollment, 374 (78.9%) reported being married or in consensual union, and 291 (77.8%) had a female partner who consented to participate. Of the 448 HIV-infected control arm men at enrollment, 348 (77.6%) reported being married or in consensual union, and 239 (68.7%) had a female partner who consented to participate. The difference between arms in the proportions of female partners who consented to participation was statistically significant ($p=0.007$). There were 80 (27.5%) women in the intervention arm and 68 (28.5%) women in the control arm who did not have an enrollment vaginal swab collected due to a temporary stock outage of HPV Digene swabs which affected both arms simultaneously and equally. Thus, there were 211 (72.5%) concurrently enrolled female partners of HIV-infected men who provided an enrollment vaginal swab in the intervention arm, and 171 (71.5%) in the control arm. The number of women exceeded the number of enrolled men because of polygamous relationships, with 211 women in a consensual union with 193 men in the intervention arm (mean=1.09 female partners per married man) and 171 women in a consensual union with 155 men in the control arm (mean=1.10 female partners per married man).

The female retention rates at the year one follow-up visit were 88.2% (186/211) in the intervention arm and 86.5% (148/171) in the control arm. At the second year follow-up, female retention rates were 75.8% (160/211) in the intervention group and 77.2% (132/171) in the control group.

Male baseline sociodemographic characteristics, sexual behaviors, and symptoms of STIs were similar between male study arm participants, except that a greater proportion of men in the intervention arm did not use condoms ($p=0.03$) (Table 1). At enrollment, the male HR-HPV prevalence was 73.2% (134/183) in the intervention arm and 69.3% (104/150) in the control arm (PRR 1.06, 95%CI 0.92–1.21, $p=0.43$) (Table 1). The overall male HR-HPV prevalence was 71.5% (238/333) for any HR-HPV genotype and was 44.4% (148/333) for multiple HR-HPV genotypes.

The female enrollment characteristics were generally similar between study arms, except the intervention arm women were younger ($p=0.04$), more likely to be in a monogamous relationship ($p=0.09$), and reported lower condom use ($p=0.07$) (Table 1). HIV prevalence at enrollment was 64.0% among the female partners of intervention arm men and 62.0% among the female partners of the control arm men (Table 1). The prevalence of HR-HPV at enrollment was 67.0% in the women married to intervention arm men and 61.9% in the women married to control arm men (PRR 1.08, 95%CI 0.93–1.26, $p=0.64$) (Table 2).

In the primary intention-to-treat analyses, the prevalence of female HR-HPV infection at year two was 55.4% in the intervention arm and 51.9% in the control arm (PRR = 1.07, 95%CI 0.86–1.32, $p=0.64$) (Table 2). In an as-treated analysis, the prevalence of any HR-HPV infections at year two was 54.2% (78/144) in female partners of circumcised men and 54.3% (75/138) in female partners of uncircumcised men (PRR = 1.00, 95%CI 0.80–1.24,

$p=1.00$). There was also no difference in LR-HPV prevalence between the two arms (intervention 62.3%, control 61.1%, PRR=1.02, 95%CI 0.85–1.22, $p=0.90$) (Table 2).

Over the two-year follow-up, the incidence of HR-HPV was 32.0/100py in intervention arm female partners and 30.6/100py in control arm female partners (IRR= 1.05, 95%CI 0.77–1.43, $p=0.78$) (Table 3). After adjustment for female age, number of partners during the past year (single or multiple partners), and condom use (no use or some/always use), the adjusted IRR of any HR-HPV acquisition in female partners of intervention relative to control arm men was IRR=0.98 (95%CI 0.74–1.28, $p=0.86$). There also was no difference between the two arms in LR-HPV incidence over the two year follow-up (IRR=0.98, 95%CI 0.74–1.31, $p=0.90$) (Table 3). In a subgroup analysis of women who were negative for HR-HPV at enrollment, the incidence of HR-HPV over the two-year follow-up was 25.1/100py (26/103.5 py) in intervention arm female partners and 20.8/100py (20/96 py) in control arm female partners (IRR= 1.20, 95%CI 0.67–2.16, $p=0.53$).

In addition, there was no difference in genotype-specific HR-HPV clearance (i.e., loss of detection) among the female partners of men in the intervention arm (46.2%, 196/424) compared to female partners of control arm men (48.1%, 167/347, RR=0.96, 95%CI 0.83–1.12, $p=0.61$) (Table 4).

To further assess the lack of efficacy of MC to reduce HR-HPV in female partners of HIV-infected men, we conducted a sensitivity analysis based on the female HIV status. The overall prevalence of female HR-HPV at enrollment was higher among the HIV-infected women (74.5%, 178/239) compared to the HIV-uninfected women (47.8%, 66/138) ($p<0.001$). The prevalence of female HR-HPV among enrollment HIV-uninfected women at year two was 43.1% (25/58) in the intervention arm and 32.7% (18/55) in the control arm (PRR=1.32, 95%CI 0.81–2.13, $p=0.33$) (Table 5). The prevalence of female HR-HPV among enrollment HIV-infected women at year two was 62.4% (63/101) in the intervention arm and 65.8% (50/76) in the control arm (PRR=0.95, 95%CI 0.76–1.18, $p=0.75$) (Table 5). The effect of MC on HR-HPV incidence over the two year follow-up was similar for HIV-uninfected females (IRR=0.98, 95%CI 0.57–1.68, $p=0.93$) and HIV-infected females (IRR=1.07, 95%CI 0.73–1.56, $p=0.74$). The effect of MC on genotype-specific HR-HPV clearance among the HIV-uninfected female partners (RR=1.00, 95%CI 0.81–1.24, $p=1.00$) was similar to the HIV-infected female partners (RR=0.98, 95%CI 0.81–1.18, $p=0.80$).

Discussion

Circumcision of HIV-infected men did not reduce transmission of HR-HPV to their female partners. This is in contrast with previous findings that MC reduced HR-HPV prevalence and incidence among both HIV-uninfected and HIV-infected men,^{12, 14–15} and that MC reduced HR-HPV prevalence among female partners of HIV-uninfected men.²¹ Couples studies show that HIV/HPV coinfection is strongly associated with HPV-type specific concordance in sex partners.²⁸ HR-HPV prevalence (71.5%, 238/333) was significantly higher among the HIV-infected men than HIV-uninfected men in the Rakai male circumcision trials (37.5%, 321/857, $p<0.001$). Thus, male HR-HPV prevalence is so high in HIV-infected men, that it may overwhelm any secondary effect of MC on HR-HPV transmission to female partners. In addition, the intervention arm female HR-HPV genotype clearance (46.2%, 196/424) in this study is significantly lower than the clearance of HR-HPV among intervention arm females married to HIV-uninfected men (66.2%, 376/568, $P<0.001$).²¹ In this study population, there were more female HIV seroconverters among partners of intervention arm men and this may offset any potential benefit of MC for prevention of HR-HPV infection in female partners.^{29–30} multifactorial.

These findings have implications for MC programs. WHO and UNAIDS recommend that MC should not be denied to HIV-infected men who request the procedure, unless there are medical contraindications.¹⁰ We agree with these recommendations since excluding HIV-infected men could result in stigmatization; HIV-infected men might seek surgery from potential unsafe sources to mask their serostatus, and circumcised HIV-uninfected men might use their MC status to negotiate unsafe sex. It has also been shown that safety of MC was comparable in HIV-infected and HIV-uninfected men,³¹ and MC of HIV-infected men reduces penile HR-HPV.¹⁵ The HR-HPV findings in this study, in conjunction with the findings that MC does not reduce transmission of HIV to female partners in one randomized controlled trial,¹¹ indicate the importance of strongly promoting consistent safe sexual practices when HIV-infected men receive MC.

This study has limitations. There are inherent difficulties in the interpretation of HPV epidemiology, particularly in HIV-infected individuals due to the complex relationship between HIV and HPV.^{29–30} A significantly higher proportion of female partners of men in the intervention arm (77.8%) compared to the control arm (68.7%) enrolled in this study ($p<0.001$), suggesting differential female motivation to participate, which could have introduced bias. However, apart from the younger age of the intervention group partners, female baseline characteristics did not differ significantly between study arms, and adjustment for the enrollment differentials did not materially affect the estimates of efficacy. The women evaluated for HPV were all in stable partnerships with HIV-infected men, and they may represent a self-selected population of more compliant participants in both arms. This may explain the non-significant decrease in HPV infection in female partners of both trial arms during the two year observation period (Table 2). We also cannot determine whether circumcision of men with CD4 cell counts <350 cells/mL or with AIDS-defining illnesses affects female HR-HPV carriage. Due to insufficient numbers on antiretroviral therapy, we were unable to assess the effects of HIV treatment on HPV transmission or acquisition. Also, given the yearly follow-up intervals, newly detected HR-HPV infections that cleared prior to the subsequent follow-up visit may have been missed, and the timing of clearance of pre-existing infections cannot be estimated.

Despite the benefits of MC for female partners of HIV-uninfected circumcised men such as reduced GUD, HR-HPV, trichomoniasis, and bacterial vaginosis,^{11, 21, 32} there is no efficacy of MC to reduce or increase HR-HPV among female partners of HIV-infected men. Whenever possible, MC should be offered in conjunction with HIV counseling services, condoms, and education on HIV prevention for men and women, to improve the health and safety of circumcised men and their partners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The trial was funded by the Bill and Melinda Gates Foundation (#22006.02). The Fogarty International Center (#5D43TW001508 and #2D43TW000010-19-AITRP) contributed to training. National Institute of Allergy and Infectious Diseases (NIAID), NIH grants U01-AI-068613 and 3U01-AI075115-03S1 and the NIAID Intramural Program provided laboratory support. A.A.R.T. was supported by the Johns Hopkins University Clinician Scientist Award.

We are most grateful to the study participants and the Rakai Community Advisory Board whose commitment and cooperation made this study possible. We wish to thank Dr. Edward M'bidde, Director, Uganda Virus Research Institute, for his ongoing support and Dr. Renee Ridzon of the Gates Foundation for her assistance with the trial.

References

1. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*. 2007 Jul; 7(7):453–459. [PubMed: 17597569]
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010 Jun 17.
3. Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA*. 2005 Mar 23; 293(12):1471–1476. [PubMed: 15784870]
4. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007 Sep 8; 370(9590):890–907. [PubMed: 17826171]
5. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005 Apr 20; 97(8):577–586. [PubMed: 15840880]
6. Clifford GM, Goncalves MA, Franceschi S. Group HPVvHS. Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 2006 Nov 28; 20(18):2337–2344. [PubMed: 17117020]
7. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*. 2007 Feb 24; 369(9562):657–666. [PubMed: 17321311]
8. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*. 2005 Nov.2(11):e298. [PubMed: 16231970]
9. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet*. 2007 Feb 24; 369(9562):643–656. [PubMed: 17321310]
10. UNAIDS. New data on male circumcision and HIV prevention: policy and programme implications. Montreux: UNAIDS. 2007
11. Wawer MJ, Makumbi F, Kigozi G, Serwadda D, Watya S, Nalugoda F, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet*. 2009 Jul 18; 374(9685):229–237. [PubMed: 19616720]
12. Tobian AA, Serwadda D, Quinn TC, Kigozi G, Gravitt PE, Laeyendecker O, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. 2009 Mar 26; 360(13):1298–1309. [PubMed: 19321868]
13. Auvert B, Sobngwi-Tambekou J, Cutler E, Nieuwoudt M, Lissouba P, Puren A, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in orange farm, South Africa. *J Infect Dis*. 2009 Jan 1; 199(1):14–19. [PubMed: 19086814]
14. Gray RH, Serwadda D, Kong X, Makumbi F, Kigozi G, Gravitt PE, et al. Male Circumcision Decreases Acquisition and Increases Clearance of High-Risk Human Papillomavirus in HIV-Negative Men: A Randomized Trial in Rakai, Uganda. *J Infect Dis*. 2010 Apr 6.
15. Serwadda D, Wawer MJ, Makumbi F, Kong X, Kigozi G, Gravitt P, et al. Circumcision of HIV-Infected Men: Effects on High-Risk Human Papillomavirus Infections in a Randomized Trial in Rakai, Uganda. *J Infect Dis*. 2010 Apr 6.
16. Drain PK, Halperin DT, Hughes JP, Klausner JD, Bailey RC. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. *BMC Infect Dis*. 2006; 6:172. [PubMed: 17137513]
17. Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med*. 2002 Apr 11; 346(15):1105–1112. [PubMed: 11948269]
18. Kjaer SK, de Villiers EM, Dahl C, Engholm G, Bock JE, Vestergaard BF, et al. Case-control study of risk factors for cervical neoplasia in Denmark. I: Role of the "male factor" in women with one lifetime sexual partner. *Int J Cancer*. 1991 Apr 22; 48(1):39–44. [PubMed: 2019457]

19. Brinton LA, Reeves WC, Brenes MM, Herrero R, Gaitan E, Tenorio F, et al. The male factor in the etiology of cervical cancer among sexually monogamous women. *Int J Cancer*. 1989 Aug 15; 44(2):199–203. [PubMed: 2547727]
20. Dickson NP, Ryding J, van Roode T, Paul C, Herbison P, Dillner J, et al. Male circumcision and serologically determined human papillomavirus infection in a birth cohort. *Cancer Epidemiol Biomarkers Prev*. 2009 Jan; 18(1):177–183. [PubMed: 19124496]
21. Wawer MJ, Tobian AA, Kigozi G, Kong X, Gravitt PE, Serwadda D, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. *Lancet*. 2011 Jan 6.
22. Tobian AA, Ssemijja V, Kigozi G, Oliver AE, Serwadda D, Makumbi F, et al. Incident HIV and herpes simplex virus type 2 infection among men in Rakai, Uganda. *AIDS*. 2009 Jul 31; 23(12): 1589–1594. [PubMed: 19474649]
23. Gray RH, Kigozi G, Serwadda D, Makumbi F, Nalugoda F, Watya S, et al. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol*. 2009 Oct 29; 200(1):42, e1–e7. [PubMed: 18976733]
24. Serwadda D, Wawer MJ, Shah KV, Sewankambo NK, Daniel R, Li C, et al. Use of a hybrid capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. *J Infect Dis*. 1999 Oct; 180(4):1316–1319. [PubMed: 10479163]
25. Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric M, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. *Sex Transm Infect*. 2005 Jun; 81(3): 207–212. [PubMed: 15923286]
26. Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. *J Clin Microbiol*. 1998 Oct; 36(10):3020–3027. [PubMed: 9738060]
27. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986; 73:13–22.
28. Mbulawa ZZ, Coetzee D, Marais DJ, Kamupira M, Zwane E, Allan B, et al. Genital human papillomavirus prevalence and human papillomavirus concordance in heterosexual couples are positively associated with human immunodeficiency virus coinfection. *J Infect Dis*. 2009 May 15; 199(10):1514–1524. [PubMed: 19392625]
29. Wang C, Wright TC, Denny L, Kuhn L. Rapid Rise in Detection of Human Papillomavirus (HPV) Infection Soon After Incident HIV Infection Among South African Women. *J Infect Dis*. 2011 Jan 7.
30. Nowak RG, Gravitt P, Morrison CS, Gange SJ, Kwok C, Oliver A, et al. Increases in human papillomavirus (HPV) detection during early HIV infection among women in Zimbabwe. *J Infect Dis*. 2011 In press.
31. Kigozi G, Gray RH, Wawer MJ, Serwadda D, Makumbi F, Watya S, et al. The Safety of Adult Male Circumcision in HIV-Infected and Uninfected Men in Rakai, Uganda. *PLoS Med*. 2008 Jun 3.5(6):e116. [PubMed: 18532873]
32. Tobian AA, Gray RH, Quinn TC. Male circumcision for the prevention of acquisition and transmission of sexually transmitted infections: the case for neonatal circumcision. *Arch Pediatr Adolesc Med*. 2010 Jan; 164(1):78–84. [PubMed: 20048246]

Figure 1.

Study profile.

#Due to HPV Digene swab stock outage which affected both arms simultaneously and equally.

*Some subjects were unavailable for follow-up in year 1 but were available for follow-up in year 2.

^The intention-to-treat analysis included all women who had detectable beta-globin and/or HPV. The male crossovers in dashed boxes were only relevant to the as-treated-analysis. Eight women (five associated with intervention arm and three associated with control arm) at year 2 were also excluded because their male partner's circumcision status could not be confirmed at that visit.

Table 1

Baseline characteristics, risk behaviors, and symptoms of sexually transmitted infections of men and their female partners by study arm.

	Men			Female Partners		
	Intervention group (n=193)	Control group (n=155)	p-value	Intervention group (n=211)	Control group (n=171)	p-value
Age (years)			0.09			0.04
15–19	0 (0.0%)	0 (0.0%)		5 (2.4%)	9 (5.3%)	
20–24	7 (3.6%)	10 (6.5%)		49 (23.2%)	32 (18.7%)	
25–29	43 (22.3%)	22 (14.2%)		74 (35.1%)	44 (25.7%)	
30–49	143 (74.1%)	123 (79.4%)		83 (39.3%)	86 (50.3%)	
Marital Status						0.09
Not married	0 (0.0%)	1 (0.6%)	0.06	0 (0.0%)	2 (1.2%)	
Monogamous	174 (90.2%)	127 (81.9%)		179 (84.8%)	133 (77.8%)	
Polygynous	19 (9.8%)	27 (17.4%)		32 (15.2%)	36 (21.1%)	
Religion						0.48
Catholic	135 (69.9%)	117 (75.5%)	0.42	139 (65.9%)	119 (69.6%)	
Protestant	51 (26.4%)	32 (20.6%)		47 (22.3%)	39 (22.8%)	
Saved/Pentecostal/other	7 (3.6%)	5 (3.2%)		13 (6.2%)	5 (2.9%)	
Muslim	0 (0.0%)	1 (0.6%)		12 (5.7%)	8 (4.7%)	
Education						0.43
No education	12 (6.2%)	20 (12.9%)	0.18	29 (13.7%)	32 (18.7%)	
Primary	150 (77.7%)	111 (71.6%)		157 (74.4%)	125 (73.1%)	
Secondary	24 (12.4%)	17 (11.0%)		22 (10.4%)	12 (7.0%)	
Post-secondary	7 (3.6%)	7 (4.5%)		3 (1.4%)	2 (1.2%)	
Number of sexual partners past year (including spouse)						0.24
0	1 (0.5%)	0 (0.0%)	0.31	1 (0.5%)	4 (2.3%)	
1	97 (50.3%)	68 (43.9%)		198 (93.8%)	155 (90.6%)	
2+	95 (49.2%)	87 (56.1%)		12 (5.7%)	12 (7.0%)	
Condom use in past year						0.07
None	103 (53.4%)	61 (39.4%)	0.03	144 (68.2%)	101 (59.1%)	
Inconsistent use	81 (42.0%)	83 (53.5%)		60 (28.4%)	57 (33.3%)	
Consistent condom use	9 (4.7%)	11 (7.1%)		7 (3.3%)	13 (7.6%)	

	Men		Female Partners	
	Intervention group (n=193)	Control group (n=155)	Intervention group (n=211)	Control group (n=171)
Alcohol use with sex in past year	139 (72.0%)	118 (76.1%)	100 (47.4%)	69 (40.4%)
Transactional sexual intercourse in past year*	6 (3.1%)	3 (1.9%)	2 (0.9%)	1 (0.6%)
Self-reported symptoms of STDs in past year				
Genital ulcer disease	56 (29.0%)	39 (25.2%)	58 (27.5%)	49 (28.7%)
Urethral or vaginal discharge	22 (11.4%)	13 (8.4%)	111 (52.6%)	94 (55.0%)
Dysuria	32 (16.6%)	16 (10.3%)	50 (23.7%)	37 (21.6%)
HIV status				
Persistently HIV negative	0 (0.0%)	0 (0.0%)	61 (28.9%)	59 (34.5%)
HIV seroconversion during trial	0 (0.0%)	0 (0.0%)	15 (7.1%)	6 (3.5%)
Persistently HIV positive	193 (100.0%)	155 (100.0%)	135 (64.0%)	106 (62.0%)
High-risk HPV prevalence [#]	134 (73.2%)	104 (69.3%)	140 (67.0%)	104 (61.9%)
				0.31

Data are n (%). The number of men is less than the number of female partners enrolled due to polygynous unions.

* Transactional sexual intercourse was defined as sexual intercourse in exchange for money or gifts.

[#] There were only 183 men in the intervention arm, 150 men in the control arm, 209 women in the intervention arm, and 104 women in the control arm with available samples that had amplifiable DNA. The percentages were calculated using the denominator of individuals with amplifiable samples.

Table 2

Female HPV prevalence at enrollment, and at 12 and 24 months follow-up, by male circumcision study arm

	Intervention group		Control group		PRR (95% CI)
	HPV positive /N*	Percent (%)	HPV positive /N*	Percent (%)	
All genotypes					
Baseline	184/209	88.0%	141/168	83.9%	1.05 (0.97 – 1.14)
Year One	154/186	82.8%	118/148	79.7%	1.04 (0.94 – 1.15)
Year Two	123/159	77.4%	96/131	73.3%	1.06 (0.92 – 1.21)
Low-risk HPV					
Baseline	160/209	76.6%	118/168	70.2%	1.09 (0.96 – 1.23)
Year One	128/186	68.8%	90/148	60.8%	1.13 (0.96 – 1.33)
Year Two	99/159	62.3%	80/131	61.1%	1.02 (0.85 – 1.22)
High-risk HPV					
Baseline	140/209	67.0%	104/168	61.9%	1.08 (0.93 – 1.26)
Year One	113/186	60.8%	95/148	64.2%	0.95 (0.80 – 1.12)
Year Two	88/159	55.4%	68/131	51.9%	1.07 (0.86 – 1.32)

*. The total number of women (N) includes all those who had detectable beta-globin and/or HPV. Subjects were included in both the high-risk category and the low-risk category if they had both HPV genotypes.

Female HPV incidence by study arm and follow-up interval for participants with amplifiable cellular and/or viral DNA at sequential study visits. N is the number of women with newly detected HPV infections.

Table 3

	Intervention group		Control group		IRR (95% CI)
	N / py**	Incidence / 100 py**	N / py**	Incidence / 100 py**	
Low-risk HPV					
0–1 year	70/149	47.0	52/119	43.7	1.08 (0.75–1.54)
1–2 year	53/127.5	41.6	50/102	49.0	0.85 (0.58–1.25)
Total 0–2 years	102/276.5	36.9	83/221	37.6	0.98 (0.74–1.31)
High-risk HPV					
0–1 year	62/153	40.5	53/118.5	44.7	0.91 (0.63–1.31)
1–2 year	46/131	35.1	34/110	30.9	1.14 (0.73–1.77)
Total 0–2 years	91/284	32.0	70/228.5	30.6	1.05 (0.77–1.43)

**
py represents person-years.

Table 4

Clearance of pre-existing genotype-specific female HR-HPV infections by study arm. The denominators (N) are individuals with the specified genotype who had amplifiable cellular and/or viral DNA at both enrollment and follow-up, and were positive for the genotype at enrollment.

HR HPV Type	Intervention group		Control group		Rate Ratio (95% CI)
	Cleared / N	%	Cleared / N	%	
16	19/40	47.5%	21/42	50.0%	0.95 (0.61 – 1.48)
18	18/34	52.9%	13/27	48.1%	1.10 (0.66 – 1.82)
31	5/19	26.3%	6/16	37.5%	0.70 (0.26 – 1.88)
33	6/13	46.2%	5/12	41.7%	1.11 (0.45 – 2.70)
35	19/46	41.3%	18/33	54.5%	0.76 (0.48 – 1.20)
39	13/22	59.1%	6/19	31.6%	1.87 (0.89 – 3.95)
45	13/33	39.4%	9/24	37.5%	1.05 (0.54 – 2.05)
51	18/35	51.4%	19/36	52.8%	0.97 (0.62 – 1.52)
52	16/33	48.5%	13/22	59.1%	0.82 (0.50 – 1.35)
56	6/21	28.6%	6/8	75.0%	0.38 (0.17 – 0.84)
58	19/51	37.3%	14/37	37.8%	0.98 (0.57 – 1.70)
59	20/28	71.4%	16/23	69.6%	1.03 (0.72 – 1.47)
66	12/27	44.4%	13/25	52.0%	0.85 (0.49 – 1.50)
69	12/22	54.5%	8/23	34.8%	1.57 (0.80 – 3.09)
Total	196/424	46.2%	167/347	48.1%	0.96 (0.83 – 1.12)

Female HPV prevalence at enrollment, and at 12 and 24 months follow-up, by male circumcision study arm and stratified by female partner enrollment HIV status.

Table 5

	Intervention group		Control group		PRR (95% CI)
	HPV positive / N*	Percent (%)	HPV positive / N*	Percent (%)	
HIV-negative					
Baseline	38/75	50.7%	28/63	44.4%	1.14 (0.80 – 1.63)
Year One	27/69	39.1%	27/59	45.8%	0.86 (0.57 – 1.28)
Year Two	25/58	43.1%	18/55	32.7%	1.32 (0.81 – 2.13)
HIV-positive					
Baseline	102/134	76.1%	76/105	72.4%	1.05 (0.90 – 1.22)
Year One	86/117	73.5%	68/89	76.4%	0.96 (0.82 – 1.13)
Year Two	63/101	62.4%	50/76	65.8%	0.95 (0.76 – 1.18)

* The total number of women (N) includes all those who had detectable beta-globin and/or HPV. Subjects were included in both the high-risk category and the low-risk category if they had both HPV genotypes.