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Male Circumcision Reduces Human Papillomavirus Transmission to HIV-Negative Female Partners: A Randomized Trial in Rakai, Uganda

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Abstract

Background—Randomized trials show that medical male circumcision (MC) reduces high-risk human papillomavirus (HR-HPV) infection in men. We assessed the efficacy of MC to reduce HR-HPV in female partners.

Methods—HIV-negative men were randomized to immediate MC (intervention) or MC delayed for 24 months (control). HIV-uninfected female partners of married men (648 intervention and 597 control arm) were simultaneously enrolled and provided interview information and self-collected vaginal swabs at baseline, 12 and 24 months. Female HPV infection was a secondary trial end point. Vaginal swabs were evaluated for HR-HPV by Roche HPV Linear Array. An intention-to-treat analysis estimated prevalence risk and incident rate ratios (PRR and IRR) and 95% confidence intervals (95%CI) of HR-HPV by Poisson multiple regression. In women with

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Contributors

MJW, DS, and RHG oversaw the design and conduct of the trial, participated in all data analyses and writing the report. AART and PG oversaw the HPV assays, provided laboratory quality control, and participated in all data analyses and writing the report. GK was responsible for study conduct in the field. SW supervised the trial surgeons and assisted in interpretation of data. FN, FM, VS, and NKS participated in study implementation, data analysis and interpretation. XK and MC participated in statistical analysis and data management. SJR and TCQ provided technical assistance with laboratory procedures and interpretation of results. AO and KE performed the laboratory assays and quality control. All authors contributed to the preparation of the paper and approved the final version. The corresponding author had full access to all data in the study and final responsibility for the preparation and submission of the results for publication.

Conflicts of Interest

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.

pre-existing HR-HPV, we estimated the risk ratio (RR) of cleared infection (i.e., loss of detection). The trials were registered with ClinicalTrials.gov, NCT00425984 and NCT00124878.)

Findings—Female characteristics and HPV prevalence were similar between arms at enrollment. Two year retention rates were 84.7% (549/648) in intervention arm and 84.1% (502/597) in control arm spouses. Year 2 female HR-HPV prevalence was 27.8% (151/544) in the intervention and 38.7% (189/488) in the control arm (PRR=0.72, 95%CI 0.60–0.85, p=0.001). HR-HPV incidence was 20.7/100py in the intervention arm and 26.9/100py in the control arm wives (IRR=0.77, 95%CI 0.63-0.93, p=0.008). HR-HPV incidence was lower in intervention than control arm wives for 13 of 14 (92.9%) HR-HPV genotypes and in most demographic/behavioral subgroups. Genotype specific HR-HPV clearance was higher in the wives of men in the intervention arm (66.2%, 376/568) than the control arm (59.2%, 339/573, RR=1.12, 95%CI 1.02-1.22).

Interpretation—MC reduces the prevalence and incidence and increases clearance of HR-HPV infections in female partners.

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Keywords

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

Introduction

Human papillomavirus (HPV) is common in sexually active individuals, especially in developing nations.[1] HPV infection can cause genital warts, and high-risk HPV (HR-HPV) genotypes cause penile and anal cancer in men, as well as cervical cancer.[1-2] Cervical cancer is the third most common cancer in women worldwide.[3] Greater than 85% of the disease burden is in developing countries, and cervical cancer is the leading cause of cancer mortality in women in Eastern Africa.[3]

Three randomized trials conducted in South Africa, Kenya and Uganda, demonstrated that male circumcision (MC) significantly decreased HIV acquisition in men.[4-6] Two trials also reported that MC reduced the prevalence of penile HR-HPV infection by approximately 35%,[7-8] reduced the acquisition of new HR-HPV infections, and increased clearance of pre-existing HR-HPV infection in HIV-negative men.[9] We also previously reported that female partners of men randomized to MC had decreased rates of genital ulcer disease, *Trichomonas vaginalis*, and bacterial vaginosis.[10] However, MC did not reduce the rate of HIV transmission from infected men to their female spouses[11]

Several observational studies have reported that female partners of circumcised men had a significantly reduced risk of cervical neoplasia,[12-14] but the findings are not consistent.[15-16] Many of these observational studies had limited power, were vulnerable to confounding by sexual behaviors in men and women, and evaluated MC status by self-report or the female partner's report. Moreover, the long latent interval between initial HR-HPV infection and the development of cervical neoplasia complicates causal inferences from retrospective data on prior exposures. Since HR-HPV infection is a necessary precondition for cervical neoplasia,[17] the potential efficacy of MC for the prevention of cervical neoplasia can best be assessed in randomized controlled trials of MC which measure HR-HPV incidence, prevalence and clearance in female partners of the randomized men. We utilized data from a

randomized controlled trial of MC in Rakai, Uganda, to assess the efficacy of the procedure in reducing HPV rates in female partners.

Materials and Methods

Study Design and Participants

Two parallel but independent trials of MC for HIV/STI prevention were conducted in Rakai, Uganda, as previously described.[4, 7, 10-11, 18] The trials initiated enrollment of participants in 2003. One trial, supported by NIH, enrolled 4996 HIV-negative uncircumcised men aged 15-49, with the pre-specified primary goal of assessing MC efficacy for HIV prevention in men, and with prespecified secondary goals to assess sexually transmitted infections (STI) including HPV. This trial was closed in December 2006 following an interim analysis which demonstrated efficacy of male circumcision for HIV prevention in men. The second trial, supported by The Bill and Melinda Gates Foundation, enrolled 922 HIV-positive men and 600 HIV-negative men aged 15-49, as well as female spouses of male participants in both trials, with the pre-specified primary goal of assessing MC efficacy for the prevention of HIV transmission to female partners.[10-11] The effects of MC on female STIs including HPV were secondary trial outcomes. In December 2006, it was calculated that the conditional power to detect 60% efficacy against HIV, as specified in the study protocol, was only 4.9% and enrollment was closed.[11] Female follow-up was completed in December 2007.

Briefly, 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. 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,[4, 11] using computer-generated random numbers prepared by the study statistician at Johns Hopkins University who had no contact with participants. Participants selected one out of 20 opaque envelopes containing the random assignments. Clinical officers (equivalent to a physician's assistant) consented and enrolled participants, administered the randomization process, and conducted follow-up visits. MC was performed using the sleeve procedure, which was found to be safe with all moderate and severe surgically-related adverse events resolving with treatment.[4, 19]

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. After providing written informed consent, women were enrolled and followed annually over two years. The consent described study procedures, risks and benefits and the voluntary nature of participation. Women received $1.50 per visit as compensation for their time and effort. Assessment of the effects of MC on female partner's HPV infection was a secondary trial end point.

The objective of this analysis is to assess the efficacy of MC for HPV prevention in concordantly HIV-negative female spouses of HIV-negative male trial participants. We excluded men or women who were HIV-infected at enrollment or who acquired HIV during the trial because HIV-positive individuals have high rates of persistent HPV infections.[20] Since there were more male HIV seroconverters in the control than in the intervention arm of the trials,[4] including HIV-seroconverters could potentially bias the HPV results.

The trial profile is given in Figure 1. Of the 2786 HIV-negative intervention arm men at enrollment, 1357 (48.7%) reported being married or in consensual union with 1463 women (mean=1.08 wives per married man). Of the 2810 HIV-negative control arm men at enrollment, 1349 (48.0%) reported being married or in consensual union with 1429 women

(mean=1.06 wives per married man). The number of enrolled women exceeded the number of enrolled men because of polygynous relationships among males. In order to ascertain the women's baseline HPV status immediately prior to their male partner's MC, and to avoid potential bias by arm, the analysis was restricted to female partners who enrolled at the same time as their husbands. There were 305 women in the intervention arm and 294 women in the control arm who did not have an enrollment vaginal swab collected due to a temporary stock outage of HPV Digene swabs and sample transport media which affected both arms simultaneously and equally. There were 648 concurrently enrolled HIV-negative female spouses who provided an enrollment vaginal swab in the intervention arm, and 597 in the control arm. The female retention rates at the year one follow-up visit were 86.6% (561/648) in the intervention arm and 86.3% (515/597) in the control arm. At the second year follow up, female retention rates were 84.7% (549/648) in the intervention group and 84.1% (502/597) in the control group.

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.[21] 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.[22-23] The specimens were maintained in a cold box <6 h until they were frozen at −80C.

All participants were offered free voluntary HIV counseling and testing as individuals and as couples, were provided with HIV/STI prevention education and offered free condoms.

The trials were approved by four institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the HIV subcommittee of the National Council for Research and Technology (Kampala, 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). The Gates-funded trial, which supported all women participants in this analysis, was overseen by an independent Data and Safety Monitoring Board (DSMB). The NIH-funded trial of HIV-negative men was overseen by the NIH Vaccine and Prevention DSMB. A Community Advisory Board provided suggestions on the conduct of the trials and recommended the level of compensation per study visit. The trials were registered with Clinical.Trials.Gov numbers NCT00425984 and NCT00124878.

HPV and HIV Detection

HPV genotyping was performed using the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN) as previously described.[24] HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered the primary HR-HPV genotypes. Detection of the beta-globin gene was used to determine the presence of cellular DNA from desquamated vaginal epithelium in order to assess adequacy of sample collection. Swabs without amplifiable cellular or viral DNA were considered to be insufficient for HR-HPV detection, and only those vaginal samples with detectable beta-globin and/or detectable HPV were included in the primary analysis.

HIV status was determined using two separate ELISAs, and discordant results were confirmed by HIV-1 Western Blot as previously described.[4]

Statistical Analysis

Enrollment and follow-up characteristics, sexual risk behaviors and STI symptoms were tabulated by study arm and differences assessed by chi-square tests.

The primary assessment of the efficacy of MC for reduction of HPV infection in women used an intention-to-treat analysis. An as-treated analysis was also carried out, in which intervention arm crossovers were classified as uncircumcised if the male partner failed to accept surgery. 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 samples positive for one or more HPV genotypes among samples with amplifiable cellular or viral DNA. HPV prevalence was tabulated at each visit, and the prevalence risk ratios (PRR) and 95% confidence intervals (95%CI) of HPV in the intervention relative to the control arm were estimated.

Incident HPV was defined as a newly 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 follow-up interval during which the new infection was detected. New HPV detection during the follow-up intervals used an individual participant as the unit of observation, and each woman with a newly detected HPV genotype was counted only once per follow-up interval, irrespective of whether a single HPV genotype or multiple HPV genotypes were newly detected. Incidence was classified as single or multiple (two or more) new HPV genotype-specific infections. The incidence of genotype-specific HR-HPV was assessed using women-intervals as the unit of observation, and the population at-risk was women without that genotype at a prior study visit, irrespective of co-infection with other HR-HPV genotypes. HR-HPV incidence in each arm was assessed by baseline sociodemographic and behavioral covariates at enrollment. Incidence rate ratios (IRR) and 95% confidence intervals (95%CI) of new HR-HPV detection in the intervention versus control arm at 12 and 24 months were estimated using Poisson log-linear regression with the logarithm of person-years as the offset. Since some of the male partners were polygynous, Poisson regression with GEE [25] exchangeable correlation structure was used to model the incidence rate ratio accounting for the potential correlation between women sharing 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 pre-existing HR-HPV genotype-specific infections which were negative for that genotype at a subsequent 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 estimated using a log binomial model with robust variance estimates based on GEE to account for multiple clearance events in women with more than one initial HR-HPV infection.

For incidence and clearance, potential confounders were examined in univariate analyses, and covariates found to be associated at $\alpha < 0.20$, or suspected confounders based on biological reasoning or prior studies, were included in multivariate regression analyses.

All p-values are 2-sided. Analyses were performed using R 2.8.1 and SAS 9.2 (Cary, NC).

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

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 had previously received voluntary counseling and testing (p=0.008) and more men in the control arm consumed alcohol prior to sexual intercourse (p=0.045) (Table 1). The female enrollment characteristics were comparable between study arms for all enrollment covariates examined. At enrollment, the prevalence of HR-HPV was 35.2% (228/648) in the women married to intervention arm men and 37.1% (221/595) in the women married to control arm men (PRR 0.95, 95%CI 0.82-1.10, p =0.479) (Table 2).

Throughout the duration of the study, 14 vaginal samples (0.8%, 14/1,758) tested in intervention arm women and 26 (1.6%, 26/1,614) tested in control arm women were excluded from the analyses because of the absence of detectable beta-globin and HPV DNA (Figure 1). This difference in DNA detection was statistically significant (p=0.04). There were 34 male intervention arm crossovers who did not accept surgery by one year after randomization. There were 7 male control arm crossovers at year one and 11 male control arm crossovers at year two who received MC from other sources.

In the primary intention-to-treat analyses, the prevalence of female HR-HPV infection at year two was 27.8% (151/544) in the intervention arm and 38.7% (189/488) in the control arm (PRR = 0.72, 95% CI 0.60-0.85, p=0.001) (Table 2). In an as treated analysis, the prevalence of any HR-HPV infections at year two was 28.4% (148/521) in spouses of circumcised men and 37.8% (192/508) in spouses of uncircumcised men (PRR = 0.75, 95% CI 0.63-0.90, p= 0.002) (Table 3). HR-HPV declined from 35.2% (228/648) at enrollment to 27.8% (151/544) at year 2 (Δ −7.4%, p=0.006) in female partners of men in the intervention arm but remained unchanged in female partners of men in the control arm (Δ +1.6%, p=0.59).

The incidence of new HPV infections is shown in Table 4. Over the two-year follow-up, the incidence of HR-HPV was 20.7/100 py in intervention arm wives and 26.9/100 py in control arm wives (IRR= 0.77, 95% CI 0.63-0.93, p=0.008). The incidence of low-risk HPV (LR-HPV) was also reduced among the wives of circumcised men (IRR=0.83, 95% CI 0.69-1.00, p=0.05). New detection of multiple HR-HPV genotypes (IRR= 0.71, 95% CI 0.53-0.95, p=0.02) and multiple LR-HPV genotypes (IRR= 0.65, 95%CI 0.49-0.87, p=0.003) was lower among women married to men in the intervention arm. Although the incidence of single HR-HPV infections in female partners of intervention arm men was lower compared with partners of control arm men, the difference was not statistically significant.

The incidence of genotype-specific HR-HPV infection (including HPV 16) over 24 months was lower in the wives of intervention than control arm men for all HR-HPV genotypes examined, except for HPV 39 (Table 5). However, only HPV 33, 35 and 58 genotype-specific differentials were statistically significant. The incidence of LR-HPV genotype 6 and 11 was also assessed since these two genotypes are associated with genital warts, and MC

significantly reduced HPV 11 in female partners (IRR 0.20, 95% CI 0.06-0.72, p=0.006), but had no effect on HPV 6 in female partners (IRR 1.04, 95% CI 0.65-1.67, p=0.87), as shown in Supplemental Table 1.

The two-year cumulative rates of new HR-HPV detection per 100 person-years by sociodemographic and sexual behavioral characteristics and symptoms of sexually transmitted infections are shown in Table 6. The incidence of HR-HPV infection in female partners of men in the intervention arm was lower than in the wives of control arm men in all sociodemographic/behavioral subgroups, except for women reporting non-marital relationships and symptoms of dysuria. After adjustment for enrollment characteristics (age, condom use, alcohol consumption with sex, and number of sex partners during the past year), and controlling for correlation due to polygynous unions, the adjusted IRR of any new HR-HPV detection in female partners of intervention relative to control men was IRR=0.77 (95%CI 0.65-0.92, p=0.004).

As shown in Table 7, the cumulative probability of genotype-specific HR-HPV clearance (i.e., loss of detection) among women who were prevalent positive at enrollment was higher among the wives of men in the intervention arm (66.2%, 376/568) than wives of control arm men (59.2%, 339/573, RR=1.12, 95% CI 1.02-1.22, p=0.014). The proportion of genotype-specific cleared infections was higher in the intervention arm women for 10 of the 14 (71.4%) HR-HPV genotypes (Table 7). However, clearance of HPV16 was not increased. After adjustment for baseline age, education, number of sex partners, alcohol consumption with sex, condom use, and accounting for possible correlation of one woman clearing multiple genotypes, the HR-HPV clearance risk ratio in female partners of men in the intervention relative to the control arm was 1.10 (95% CI 1.03-1.20, p =0.003). The clearance probability at year two among women who acquired HR-HPV genotypes during the first year of the trial was also higher among intervention arm wives (82.1%, 124/151) compared to control arm wives (70.2%, 127/181, RR=1.17, 95%CI 1.04-1.32, p=0.014). Results were similar for genotype-specific LR-HPV clearance (Supplemental Table 2).

Self-reported rates of female partners' sexual practices and STI symptoms were assessed by the male partner's circumcision status (Supplemental Table 3). At year one, there were no differences in behaviors or STI symptoms between the two arms. At year two, the rate of female self-reported GUD was significantly lower in the female partners of intervention arm men (12.8%, 70/549) compared to women with control arm partners (17.1%, 86/502, p=0.046). In addition, the proportion of women reporting inconsistent condom use during the second year of follow-up was higher in the control than intervention arm (p=0.022). There were no differences in the reported number of sexual partners, non-marital relationships, vaginal discharge, or dysuria between the women in the two study arms at either year one or year two. Among the male partners, there were no reported differences in the number of sexual partners, non-marital relationships or condom use between study arms at enrollment and during follow-up.

Discussion

MC of adolescent and adult men in a rural Ugandan population significantly reduced both LR-HPV and HR-HPV prevalence and incidence and increased clearance of HR-HPV infection in female partners. The efficacy of MC for reducing HR-HPV prevalence in female partners over two years was 28%. These findings are compatible with observational studies of reduced cervical cancer associated with MC.[12-14] In conjunction with prior trial results in men,[7-8] these findings indicate that MC should now be accepted as an efficacious intervention for reducing heterosexually acquired HR-HPV and LR-HPV in HIV-negative

men and in their female partners. However it must be emphasized that protection was only partial, and it is critical to promote the practice of safe sex.

While this study did not assess cervical neoplasia, persistent HR-HPV infection is required for the development of cervical cancer.[17] Clearance of HR-HPV was greater in women married to intervention arm men, with the exception of HPV16 which is the most important genotype implicated in penile and cervical cancer.[1] However, decreased HR-HPV incidence and prevalence will likely reduce the long-term risk of cervical cancer in women with circumcised male partners.

The biological mechanism whereby MC could reduce HPV infection in female partners most likely involves a reduction of penile HPV carriage in men. Observational studies have demonstrated that HPV detection varies by anatomic site,[26-27] and that MC is associated with decreased HPV at the urethra, coronal sulcus, and shaft.[28] Two trials reported that MC reduced the prevalence of HR-HPV by 34% at the urethra and 35% at the coronal sulcus in HIV-negative men[7-8] due to reduced acquisition and increased clearance.[8] There is also a high degree of genotype-specific concordance within couples.[29] Thus, reduced male penile HR-HPV infection most likely leads to decreased female incidence and increased clearance probably as a result of reduced re-infection.

This study has limitations. About 20% of women in each arm did not have enrollment samples collected due to temporary stock outages, and this reduced the study sample size and power. However, the stock outages were not differential between study arms, so the missing data should not have biased the efficacy estimates. The HIV-negative women evaluated for HPV were all in stable partnerships with HIV-negative men enrolled into RCTs of MC, and they may represent a self-selected lower-risk population of more compliant participants in both arms. Thus, the findings may not be applicable to HIV-positive individuals or populations of women with a higher frequency of multiple sexual partners. In the minority of women who reported extramarital relationships, we did not observe a reduction in new HPV detection (Table 6). Since these external relationships may have occurred with men of different circumcision status, this could bias the estimate of efficacy towards the null. In addition, given the yearly follow-up intervals, incident infections that cleared prior to the subsequent follow-up visit would have been missed, and therefore, the precise timing of clearance cannot be estimated. There are also inherent difficulties in the interpretation of HPV epidemiology. Newly detected HPV infections may represent a combination of newly acquired infections, sampling variability, or possibly reactivation of prior latent infections below the limits of assay detection. If MC does not impact the risk of recurrence or reactivation, we may have underestimated the reduction of true new infections.

In summary, MC significantly reduced the prevalence and incidence of HR-HPV infections and modestly increased clearance of pre-existing HR-HPV among female partners of circumcised men. The 28% reduction in HR-HPV infections with circumcised partners suggests that MC could contribute to female HR-HPV and cervical neoplasia prevention in resource poor settings where vaccines are not available or in individuals with HR-HPV genotypes that are not covered by the vaccine. MC has now been shown to decrease HIV, HSV-2, and HPV infections and genital ulcer disease in men, as well as HPV, trichomoniasis, and bacterial vaginosis infection and genital ulcer disease in their female partners.[4-6, 30] Thus, MC reduces the risk of multiple STIs in both sexes, and these benefits should guide public health policies for neonatal, adolescent and adult MC programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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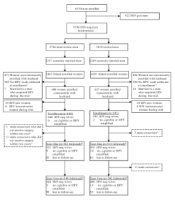

Figure 1.

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. Three women at year 2 were 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=598)	**Control group (n=561)**	**p-value**	**Intervention group (n=648)**	**Control group (n=597)**	**p-value**
Age (years)			0.596			0.458
15-19	8 (1.3%)	9 (1.6%)		80 (12.3%)	65 (10.9%)	
20-24	121 (20.2%)	118 (21.0%)		208 (32.1%)	208 (34.8%)	
25-29	173 (28.9%)	178 (31.7%)		178 (27.5%)	174 (29.1%)	
30-49	296 (49.5%)	256 (45.6%)		182 (28.1%)	150 (25.1%)	
Marital Status						0.184
Not married	1 (0.02%)	0 (0.0%)	0.206	1 (0.2%)	0 (0.0%)	
Monogamous	524 (87.6%)	506 (90.2%)		529 (81.6%)	506 (84.8%)	
Polygynous	73 (12.2%)	55 (9.8%)		118 (18.2%)	91 (15.2%)	
Religion						0.671
Catholic	384 (64.2%)	378 (67.4%)	0.624	391 (60.3%)	362 (60.6%)	
Protestant	172 (28.8%)	146 (26.0%)		186 (28.7%)	158 (26.5%)	
Saved/Pentecostal/other	38 (6.4%)	35 (6.2%)		57 (8.8%)	62 (10.4%)	
Muslim	4 (0.7%)	2 (0.4%)		14 (2.2%)	15 (2.5%)	
Education						0.556
No education	51 (8.5%)	50 (8.9%)	0.808	93 (14.4%)	78 (13.1%)	
Primary	437 (73.1%)	420 (74.9%)		464 (71.6%)	444 (74.4%)	
Secondary	84 (14.0%)	69 (12.3%)		80 (12.3%)	65 (10.9%)	
Post-secondary	26 (4.3%)	22 (3.9%)		11 (1.7%)	10 (1.7%)	
Number of sexual partners past year						0.489
0	0 (0.0%)	0 (0.0%)	0.305	0 (0.0%)	2 (0.3%)	
1	343 (57.4%)	305 (54.4%)		625 (96.5%)	573 (96.0%)	
2+	255 (42.6%)	256 (45.6%)		23 (3.5%)	22 (3.7%)	
Non-marital relationships in past year						0.267
No	497 (83.1%)	469 (83.6%)	0.823	641 (98.9%)	585 (98.0%)	
Yes	101 (16.9%)	92 (16.4%)		7 (1.1%)	12 (2.0%)	
Condom use in past year						

	Men			Female Partners		
	Intervention group (n=598)	**Control group (n=561)**	**p-value**	**Intervention group (n=648)**	**Control group (n=597)**	**p-value**
None	398 (66.6%)	359 (64.0%)	0.638	554 (85.5%)	485 (81.2%)	0.153
Inconsistent use	193 (32.3%)	194 (34.6%)		92 (14.2%)	107 (17.9%)	
Consistent condom use	7 (1.2%)	8 (1.4%)		2 (0.3%)	3 (0.5%)	
Alcohol use with sex in past year	320 (53.5%)	333 (59.4%)	0.045	221 (34.1%)	196 (32.8%)	0.590
Transactional sexual intercourse in past year*	5 (0.8%)	8 (1.4%)	0.409	5 (0.8%)	3 (0.5%)	0.728
Prior receipt of voluntary counseling and testing	167 (27.9%)	119 (21.2%)	0.008	146 (22.5%)	117 (19.6%)	0.971
Self-reported symptoms of STDs in past year						
Genital ulcer disease	54 (9.0%)	51 (9.1%)	0.971	87 (13.4%)	83 (13.9%)	0.862
Urethral or vaginal discharge	25 (4.2%)	24 (4.3%)	0.934	298 (46.0%)	283 (47.4%)	0.637
Dysuria	33 (5.5%)	42 (7.5%)	0.173	126 (19.4%)	126 (21.1%)	0.501

Data are n (%). The number of men is less than the number of female partners enrolled due to polygynous unions. Condom use, the use of alcohol with sexual intercourse, and transactional sexual intercourse (defined as sexual intercourse in exchange for money or gifts) were evaluated only in sexually active subjects, although the percentages in these categories were calculated on the basis of the total number of subjects enrolled in each study group.

Table 2

Female HPV prevalence at enrollment, and at 12 and 24 months follow-up, by male circumcision study arm (intention-to-treat analysis).

	Intervention group		Control group		PRR (95% CI)
	HPV positive/ N*	Percent (%)	HPV positive/ N*	Percent (%)	
All genotypes					
Baseline	359/648	55.4%	334/595	56.1%	0.99 (0.89 - 1.09)
Year One	293/552	53.1%	302/505	59.8%	0.89 (0.80 - 0.99)
Year Two	251/544	46.1%	277/488	56.8%	0.81 (0.72 - 0.92)
Low-risk HPV					
Baseline	267/648	41.2%	249/595	41.8%	0.98 (0.86 - 1.12)
Year One	220/552	39.9%	222/505	44.0%	0.91 (0.79 - 1.05)
Year Two	180/544	33.1%	209/488	42.8%	0.77 (0.66 - 0.90)
High-risk HPV					
Baseline	228/648	35.2%	221/595	37.1%	0.95 (0.82 - 1.10)
Year One	187/552	33.9%	209/505	41.4%	0.82 (0.70 -0.96)
Year Two	151/544	27.8%	189/488	38.7%	0.72 (0.60 -0.85)

*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.

Table 3

Female HPV prevalence at enrollment, and at 12 and 24 months follow-up, by male circumcision status (as treated analysis).

	Male circumcised group		Male not circumcised group		PRR (95% CI)
	HPV positive/ N*	Percent (%)	HPV positive/ N*	Percent (%)	
All genotypes					
Baseline	359/648	55.4%	334/595	56.1%	0.99 (0.89 - 1.09)
Year One	278/528	52.7%	317/529	59.9%	0.88 (0.79 - 0.98)
Year Two	247/521	47.4%	279/508	54.9%	0.86 (0.77 - 0.97)
Low-risk HPV					
Baseline	267/648	41.2%	249/595	41.8%	0.98 (0.86 - 1.12)
Year One	213/528	40.3%	229/529	43.3%	0.93 (0.81 - 1.07)
Year Two	178/521	34.2%	209/508	41.1%	0.83 (0.71 - 0.97)
High-risk HPV					
Baseline	228/648	35.2%	221/595	37.1%	0.95 (0.82 - 1.10)
Year One	172/528	32.6%	224/529	42.3%	0.77 (0.66 -0.90)
Year Two	148/521	28.4%	192/508	37.8%	0.75 (0.63 -0.90)

*The total number of women (N) includes all those who had detectable beta-globin and/or HPV. Three women at year 2 were excluded because their male partner's circumcision status could not be confirmed at that visit. Subjects could be included in both the high-risk and the low-risk HPV categories if they had both HPV genotypes.

Table 4

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.

	Intervention group		Control group		IRR (95% CI)
	N / py	Incidence / 100 py	N / py	Incidence / 100 py	
Any LR HPV Infection					
0-1 year	143/480.5	29.8	151/428.5	35.2	0.84 (0.67-1.06)
1-2 year	103/428.5	24.0	125/355.5	35.2	0.68 (0.53-0.89)
Total 0-2 year	217/909	23.9	225/784	28.7	0.83 (0.69-1.00)
Single LR HPV Infection					
0-1 year	108/480.5	22.5	103/428.5	24.0	0.94 (0.71-1.22)
1-2 year	68/428.5	15.9	80/355.5	22.5	0.71 (0.51-0.97)
Total 0-2 year	133/909	14.6	114/784	14.5	1.01 (0.78-1.29)
Multiple LR HPV Infection					
0-1 year	35/480.5	7.3	48/428.5	11.2	0.65 (0.42-1.01)
1-2 year	35/428.5	8.2	45/355.5	12.7	0.65 (0.41 - 1.00)
Total 0-2 year	84/909	9.2	111/784	14.2	0.65 (0.49-0.87)
Any HR HPV Infection					
0-1 year	121/491.5	24.6	148/430	34.4	0.72 (0.56-0.91)
1-2 year	94/433	21.7	103/366.5	28.1	0.77 (0.58-1.02)
Total 0-2 year	191/924.5	20.7	214/796.5	26.9	0.77 (0.63-0.93)
Single HR HPV Infection					
0-1 year	88/491.5	17.9	101/430	23.5	0.76 (0.57-1.01)
1-2 year	58/433	13.4	61/366.5	16.6	0.80 (0.56-1.15)
Total 0-2 year	109/924.5	11.8	114/796.5	14.3	0.82 (0.63-1.07)
Multiple HR HPV Infection					
0-1 year	33/491.5	6.7	47/430	10.9	0.61 (0.39-0.96)
1-2 year	36/433	8.3	42/366.5	11.5	0.73 (0.46-1.13)
Total 0-2 year	82/924.5	8.9	100/796.5	12.6	0.71 (0.53-0.95)

Table 5

Genotype-specific female HR-HPV incidence over two years by study arm. N is the number of women with newly detected genotypes.

HR HPV Genotype	Intervention group		Control group		IRR (95% CI)
	N /py	Incidence / 100 py	N /py	Incidence / 100 py	
16	36/939	3.8	40/848	4.7	0.81 (0.52 - 1.28)
18	37/974.5	3.8	34/854	4.0	0.95 (0.60 - 1.52)
31	15/1000.5	1.5	17/890.5	1.9	0.79 (0.39 - 1.57)
33	8/1006	0.8	26/868	3.0	0.27 (0.12 - 0.59)
35	23/971.5	2.4	35/867.5	4.0	0.59 (0.35 - 0.99)
39	18/996	1.8	13/894.5	1.5	1.24 (0.61 - 2.54)
45	18/991	1.8	21/880.5	2.4	0.76 (0.41 - 1.43)
51	42/956	4.4	48/834	5.8	0.76 (0.50 - 1.15)
52	23/973.5	2.4	32/857	3.7	0.63 (0.37 - 1.08)
56	29/984.5	2.9	28/879	3.2	0.92 (0.55 - 1.55)
58	23/977.5	2.4	35/838.5	4.2	0.56 (0.33 - 0.95)
59	27/992.5	2.7	33/866.5	3.8	0.71 (0.43 - 1.19)
66	24/967	2.5	29/871.5	3.3	0.75 (0.43 - 1.28)
68	18/980	1.8	26/877	3.0	0.62 (0.34 - 1.13)

Table 6

Female HR-HPV incident infection and incidence rate ratios over two year follow-up by enrollment sociodemographic and behavioral characteristics and symptoms of sexually transmitted infection reported during the year prior to enrollment. N is the number of women with newly detected HR-HPV infections.

	Intervention group		Control group		Incidence rate ratio (95% CI)
	N / py	HR-HPV incidence /100 py	N / py	HR-HPV incidence /100 py	
Age (years)					
15-19	21/101	20.8	29/75	38.7	0.54 (0.31-0.94)
20-24	68/294.5	23.1	73/263	27.8	0.83 (0.60-1.16)
25-29	48/260	18.5	66/236.5	27.9	0.66 (0.46-0.96)
30-49	54/269	20.1	46/222	20.7	0.97 (0.65-1.44)
Marital Status					
Not married	1/1.5	66.7	0/0	0.0	
Monogamous	153/754	20.3	176/672	26.2	0.77 (0.62-0.96)
Polygamous	37/169	21.9	38/124.5	30.5	0.72 (0.46-1.13)
Education					
None	27/144	18.8	26/108	24.1	0.78 (0.45-1.34)
Primary	142/648.5	21.9	159/592	26.9	0.82 (0.65-1.02)
Secondary or beyond	22/132	16.7	29/96.5	30.1	0.56 (0.32-0.97)
Number of sexual partners*					
1	183/903	20.3	204/771	26.5	0.77 (0.63-0.94)
2+	8/21.5	37.2	9/22	40.9	0.91 (0.35-2.36)
Non-marital relationships*					
No	188/915	20.5	211/785	26.9	0.76 (0.63-0.93)
Yes	3/9.5	31.6	2/8	25.0	1.26 (0.21-7.56)
Condom use past year*					
No	162/797.5	20.3	170/658	25.8	0.79 (0.63-0.98)
Yes	29/127	22.8	43/135	31.9	0.72 (0.45-1.15)
Alcohol use with sexual intercourse*					
No	115/598	19.2	148/538	27.5	0.70 (0.55-0.89)

	Intervention group		Control group		Incidence rate ratio (95% CI)
	N / py	HR-HPV incidence /100 py	N / py	HR-HPV incidence /100 py	
Yes	76/326.5	23.3	65/255	25.5	0.91 (0.66-1.27)
Genital ulceration					
No genital ulcers	160/800	20.0	182/684	26.6	0.75 (0.61-0.93)
Genital ulcers	31/124.5	24.9	32/112.5	28.4	0.88 (0.53-1.43)
Vaginal discharge					
No discharge	105/495	21.2	125/433	28.9	0.73 (0.57-0.95)
Discharge	86/429.5	20.0	89/363.5	24.5	0.82 (0.61-1.10)
Dysuria					
No dysuria	145/749	19.4	172/617.5	27.9	0.70 (0.56-0.87)
Dysuria	46/175.5	26.2	42/179	23.5	1.11 (0.74-1.70)

*Evaluated only in subjects who were sexually active. One woman per arm reported no sexual intercourse in the preceding year at the first annual follow-up, and 3 intervention arm women and 1 control arm woman reported no sexual intercourse at the second annual follow-up.

Table 7

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		Risk Ratio (95% CI)
	Cleared / N	%	Cleared / N	%	
16	39/75	52.0%	40/54	74.1%	0.70 (0.54 - 0.92)
18	35/39	89.7%	26/51	51.0%	1.76 (1.32 - 2.35)
31	14/24	58.3%	9/23	39.1%	1.49 (0.81 - 2.75)
33	15/22	68.2%	26/41	63.4%	1.08 (0.74 - 1.55)
35	33/49	67.3%	22/37	59.5%	1.13 (0.81 - 1.58)
39	17/27	63.0%	14/21	66.7%	0.94 (0.62 - 1.44)
45	20/32	62.5%	15/31	48.4%	1.29 (0.82 - 2.03)
51	34/55	61.8%	42/64	65.6%	0.94 (0.72 - 1.24)
52	35/ 47	74.5%	30/49	61.2%	1.22 (0.92 - 1.61)
56	24/33	72.7%	20/29	69.0%	1.05 (0.76 - 1.45)
58	28/43	65.1%	33/66	50.0%	1.30 (0.94 - 1.80)
59	22/26	84.6%	23/39	59.0%	1.43 (1.05 - 1.95)
66	39/53	73.6%	22/36	61.1%	1.20 (0.89 - 1.64)
68	21/43	48.8%	17/32	53.1%	0.92 (0.59 - 1.44)
Total	**376/568**	**66.2%**	**339/573**	**59.2%**	**1.12 (1.02 - 1.22)**