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Male circumcision is associated with a lower prevalence of human papillomavirus-associated penile lesions among Kenyan men

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Abstract

Human papillomavirus (HPV)-associated penile lesions in men may increase the risk of HPV transmission to their female partners. Risk factor data on HPV-associated penile lesions are needed from regions with a high burden of cervical cancer. Visual inspection of the penis was conducted using a colposcope at the 24-month visit among participants in a randomized controlled trial of male circumcision in Kenya, from May 2006 to October 2007. All photos were read independently by two observers for quality control. Penile exfoliated cells sampled from the glans/coronal sulcus and the shaft were tested for HPV DNA using GP5+/6+ PCR and for HPV16, 18 and 31 viral loads using a real time PCR assay. Of 275 men, 151 were circumcised and 124 uncircumcised. The median age was 22 years. Circumcised men had a lower prevalence of flat penile lesions (0.7%) versus uncircumcised (26.0%); adjusted odds ratio [OR]=0.02; 95% confidence interval [CI]: 0.003–0.1). Compared to men who were HPV-negative, men who were HPV DNA positive (OR=6.5; 95%CI: 2.4–17.5) or who had high HPV16/18/31 viral load (OR=5.2; 95%CI: 1.1–24.4) had higher odds of flat penile lesions. Among men with flat penile lesions, HPV56 (29.0%) and 16 (25.8%) were the most common types. Flat penile lesions are much more frequent in uncircumcised men, and associated with higher prevalence of HPV and higher viral loads. This study suggests that circumcision reduces the prevalence of HPV-associated flat lesions and may ultimately reduce male to female HPV transmission.

Keywords

Human papillomavirus; Penile lesions; Men; Circumcision; Kenya

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INTRODUCTION

Human papillomavirus (HPV) infection is the central cause of cervical cancer in women and plays an important role in other anogenital cancers in men and women[1–4]. Interventions that reduce HPV-associated penile lesions could be important to both men and women, because HPV-associated penile lesions may increase HPV transmission to their sexual partners[5].

Flat penile lesions are flat or slightly elevated, well demarcated, acetowhite lesions in which a capillary pattern can be observed[6]. They are commonly found among male partners of women with cervical intraepithelial neoplasia (CIN), but often go unnoticed without the application of acetic acid[6–8]. Positive associations have been found between flat penile lesions, lack of condom use, HPV positivity and high HPV viral load[6,9,10]. More data, however are needed to determine the type-specific distribution of HPV infection and whether other risk factors are associated with penile lesions. Other common penile lesions, including papular lesions and pearly penile papules, have not been associated with HPV infection[6,11]. While circumcision has been previously associated with a lower point-prevalence of HPV infection[12–15] and a decreased incidence of high-risk HPV[16], it is unknown whether circumcision reduces the prevalence of flat penile lesions. It is also unclear whether risk factors other than HPV infection differ between flat penile lesions, papular lesions and pearly penile papules.

The primary aim of this study was to determine the association between male circumcision status and HPV-associated flat penile lesions among men from Kenya. We also sought to investigate risk factors for penile lesions, including HPV, type-specificity and viral load of the HPV infection.

MATERIALS AND METHODS

Study Population and Enrollment

Uncircumcised men were screened between February 4, 2002 and September 6, 2005 in Kisumu, Kenya to participate in a randomized controlled trial (RCT) of male circumcision registered with ClinicalTrials.gov (NCT00059371)[17]. The primary aim of the RCT was to determine the effectiveness of male circumcision in reducing human immunodeficiency virus (HIV) incidence. Inclusion criteria included being uncircumcised, aged 18–24 years, HIV seronegative, sexually active, and having blood hemoglobin ≥9.0 g/dL. Study participants were recruited from sexually transmitted infection (STI) clinics, workplaces, and community organizations. For men in the intervention group, circumcision was normally performed within a few days of randomization and these men were counseled to abstain from sexually activity for at least 30 days after surgery.

Beginning May 5, 2006, RCT participants were invited to participate in a visual inspection examination of the penis with 3% acetic acid (VIA) at their 24-month visit. Of 1,398 men enrolled in the RCT with a 24-month visit after May 5, 2006, 275 (20%) consented to the VIA exam and were included in this sub-study. The study protocol was approved by the Institutional Review Boards of the Universities of Illinois at Chicago, Manitoba, Nairobi, and North Carolina; RTI International; and the VU University Medical Center.

Questionnaire and Specimen Collection

After undergoing informed consent, participants were administered a standardized questionnaire on sociodemographic characteristics and sexual behavior by a trained male interviewer at baseline and the 24-month visit[17]. Penile exfoliated cells were collected for HPV DNA detection at baseline prior to circumcision and at the 24-month visit from two anatomical sites: i) shaft and external foreskin tissue (shaft specimen) and ii) glans, coronal

sulcus and inner foreskin tissue (glans specimen), using pre-wetted Type 3 Dacron swabs in separate conical tubes[18].

Penile cell samples were placed in individual 15-mL centrifuge tubes containing 2-mL of 0.01 mol/L Tris-HCl, 7.4 pH buffer, and processed on the day of collection at the Universities of Nairobi, Illinois, and Manitoba (UNIM) clinic laboratory in Kisumu by centrifugation at high speed (maximum, 3000g) for 10 minutes. Excess Tris-HCl buffer was discarded using a Pasteur pipette, and the remaining cell pellet was resuspended in the same volume of 0.01 mol/L Tris-HCl buffer, and vortexed. Diluted cell pellets were then frozen at −75°C. Samples were sent using a liquid nitrogen dry shipper to the Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands, for HPV DNA testing.

Visual Inspection Exams

After genital sampling for HPV DNA, consenting study participants were screened for penile lesions at the 24-month visit by visual inspection aided by a colposcope for magnification. The first visual inspection exam was conducted before the application of 3% acetic acid. A second exam was performed 2–3 minutes after acetic acid application to identify HPV-associated flat penile lesions. Acetic acid was applied with saturated gauze to the penile shaft, glans, coronal sulcus, frenulum, and outer and inner foreskin tissue for uncircumcised men.

Penile lesions were categorized as follows: i) flat lesions (flat or slightly elevated, well demarcated, acetowhite lesions in which a capillary pattern can be seen); ii) condylomata acuminata, or genital warts (exophytic lesions with an irregular surface); iii) papular lesions (small exophytic papules usually located near the frenulum with a smooth surface on which a hyperkeratinized layer could be present)[6]; and iv) pearly penile papules (small exophytic papules located around the corona, presenting in 1 to 4 rows)[11]. The VIA exams were performed by male medical doctors who were trained intensively by experienced medical doctors who had performed VIA in over 500 men. Both practical experience and a manual with multiple examples were used during this training.

The lesion type and anatomical site were recorded on standardized forms. Digital photographs were taken of ventral and dorsal sides of the glans/coronal sulcus with penile foreskin retracted for uncircumcised men before and after acetic acid application. All photographs were double read in Amsterdam without knowing HPV data, and in case of discrepancies (<10%), a consensus diagnosis was made after discussing the findings with the medical doctors who performed the VIA exams.

HPV DNA, HPV Viral Load and STI Testing

DNA was isolated from penile exfoliated cell samples using NucleoSpin 96 Tissue kit (Macherey-Nagel, Germany) and a Microlab Star robotic system (Hamilton, Germany). Presence of human DNA was evaluated by β-globin specific PCR, followed by agarose gel electrophoresis. HPV positivity was assessed by GP5+/6+ PCR followed by hybridisation of PCR products using an enzyme immunoassay readout with two HPV oligoprobe cocktails that, together, detect 44 HPV types (high-risk: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; low-risk: HPV6, 11, 26, 30, 32, 34, 40, 42, 43, 44, 53, 54, 55, 57, 61, 64, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, cand85, 86, cand89, JC9710). Subsequent HPV genotyping was performed by reverse line blot (RLB) hybridisation of PCR products[19,20]. Primers and probe sequences, as well as cycling and staining conditions have been detailed previously[19,20]. HPV16, 18 and 31 viral loads were subsequently determined using a real time PCR assay and LightCycler instrument (Roche Diagnostics, Basel, Switzerland)[21].

High HPV DNA viral load was defined as positive when HPV16, 18 or 31 specimen viral load was >250 copies per scrape in either glans or shaft specimens[7]. All other specimens containing HPV16, 18 or 31 DNA were considered to have low HPV16/18/31 viral load.

HPV types detected by enzyme immunoassay but not by RLB genotyping were designated as HPVX, indicating a type, sub-type or variant not detectable with probes used for RLB hybridization. HPV infections with multiple HPV types were considered high-risk if ≥1 high-risk HPV type was detected. Men with HPVX infections were excluded from high and low-risk HPV categorizations unless a high-risk HPV type was detected.

Urine samples were tested in the UNIM laboratory in Kisumu, and at the Department of Medical Microbiology laboratory, University of Nairobi in Nairobi, for *N. gonorrhoeae* and *C. trachomatis* infections by PCR-based methods (Roche Diagnostics, Basel, Switzerland). Serum specimens were tested for herpes simplex virus type 2 (HSV-2) antibody (Kalon Biological Ltd, Aldershot, United Kingdom) and for HIV antibody using two rapid tests (Determine, Abbott Diagnostic Division, Hoofddorp, Netherlands; and Unigold, Trinity Biotech, Wicklow, Ireland), confirmed by double ELISA (Adaltis Inc, Montreal, Canada; Trinity Biotech, Wicklow, Ireland) at the University of Nairobi.

Statistical Methods

Pearson's χ^2 and Fisher's exact tests were used to assess differences in baseline risk factors between men in the VIA sub-study and all other RCT participants. An adjusted odds ratio (OR) and corresponding 95% confidence interval (CI) measuring the association between flat penile lesions and male circumcision status was estimated via a multivariate logistic regression model adjusted for age and baseline variables significantly associated with participation in the VIA sub-study. Multivariate logistic regression models adjusted for age and male circumcision status were used to estimate ORs for flat penile lesions and other potential risk factors assessed at the 24-month visit. Analyses were repeated for papular lesions and pearly penile papule outcomes. Due to the limited number of condyloma acuminata diagnosed among the VIA participants (n=2), risk factor analyses could not conducted for this lesion type.

Circumcision status in this analysis was defined as actual circumcision status at the 24-month visit. Of 151 circumcised men who consented to VIA exams, 8 (5.3%) were originally assigned to the control arm but crossed over before the 24-month visit, and were subsequently circumcised. Results were similar with their exclusion from analyses (data not shown). β-globin positivity was 86.2% in the glans and 73.8% in the shaft specimens among circumcised men and 89.2% in the glans and 73.3% in the shaft among uncircumcised men. The effect of male circumcision on penile lesions and HPV type prevalence results did not differ substantially when analyses were restricted to β-globin positive samples, and thus reported analyses utilized HPV DNA data from all penile exfoliated cell specimens regardless of β-globin positivity.

RESULTS

At baseline, men who participated in the VIA exam (N=275) were more likely to live with their female sexual partner (p=0.01) and have ≥2 sex partners during the past 12 months (p<0.001), compared to all other RCT participants (N=2,509) (Table 1). All other baseline risk factors assessed were similar between men who did and did not participate in the VIA study.

Of the 275 participants, 151 (54.9%) men were circumcised and 124 (45.1%) uncircumcised at the 24-month visit. Baseline risk factors assessed, including HPV DNA positivity

(p=0.88), condom use (p=0.81) and the number of sexual partners within the last year (p=0.54), did not differ between the circumcised and uncircumcised groups (Table 2). The median age of all participants at the 24-month visit was 22 years (range 20–26). One participant was HIV seropositive (0.36%), while 28 were HSV-2 seropositive (14.6%) at the 24-month visit. Less than 2% of men had laboratory-diagnosed *N. gonorrhoeae* or *C. trachomatis* infections, or reported having had a sexually transmitted disease within the last 6 months. The median number of female sexual partners in the previous 12 months was 2 women (range 0–14). No men reported having a male sexual partner in their lifetime.

Prevalence of Penile Lesions

A total of 33 (12.0%) men had flat penile lesions detected after acetic acid application. The foreskin (or foreskin remnant among circumcised men) was the most common site for flat lesions (9.9%), followed by the frenulum (3.3%) and glans (2.6%). No flat lesions were detected on the penile shaft of any participant. Two uncircumcised participants were diagnosed with genital warts. Papular lesions (n=133; 48.4%) and pearly penile papules (n=187; 68.0%) were commonly present in both circumcised and uncircumcised men.

Association of Male Circumcision and Penile Lesions

Circumcised men were much less likely than uncircumcised men to have flat lesions (0.7% versus 26.0%, crude OR=0.02; 95%CI: 0.003–0.1). The strong association between circumcision and flat penile lesions remained after controlling for age, baseline marital status and the number of female sexual partners in the 12 months prior to enrolling in the RCT (OR=0.02; 95%CI: 0.003–0.1) (Table 3). The adjusted OR was similar when the analysis was restricted β-globin positive samples (OR=0.02; 95%CI: 0.003–0.02).

Circumcised men were more likely to have papular lesions (OR=3.0; 95%CI: 1.8–5.1 vs. uncircumcised) after controlling for age, baseline marital status and partners in the past 12 months. Male circumcision was also positively associated with pearly penile papules in the adjusted model (OR=1.9; 95%CI: 1.1–3.2) (Table 3).

Risk Factors for Flat Penile Lesions Other than Male Circumcision

Flat penile lesions were more common among HPV-positive men (21.2%, vs. 4.6% in HPV-negative men; OR=6.5; 95%CI: 2.4–17.5). A strong association was also found between flat lesions and men with high-risk HPV types vs. men who were HPV-negative (OR=8.3; 95%CI: 3.0–22.8). Both HPV DNA detected in the glans (OR=5.4; 95%CI: 2.1–14.0) and shaft (OR=5.1; 95%CI: 2.1–12.9) were strongly associated with flat penile lesions (Table 4).

Compared to men who were HPV-negative, participants with high HPV16/18/31 viral load were more likely to have flat penile lesions (OR=5.2; 95%CI: 1.1–24.4) (Table 4). Even men with low viral load were more likely to have flat lesions compared to HPV-negative men (OR=4.3; 95%CI: 1.0–18.1). Compared to men who were HPV-negative, a particularly strong association was found between high HPV16/18/31 viral load in the glans and the presence of flat penile lesions (OR=8.0; 95%CI: 1.5–41.8), with a weaker association found in the shaft (OR=3.8; 95%CI: 0.5–29.4) (data not shown).

Other risk factors assessed including education, condom use in the last 6 months, number of female sexual partners in the past 12 months and years of sexual activity were not significantly associated with flat lesion prevalence (Table 4).

Risk Factors for Papular Lesions and Pearly Penile Papules

HPV DNA positivity was not associated with papular lesions (OR=0.8, 95%CI: 0.5–1.3 vs. HPV-negative), nor with pearly penile papules (OR=0.8; 95%CI: 0.5–1.4), after controlling

for age and circumcision status (Table 4). Papular lesions and pearly penile papules were also not associated with other risk factors assessed such as HPV16/18/31 viral load, education, and the number of female sexual partners in the past 12 months.

HPV type distribution among men with and without flat penile lesions

Among men with flat penile lesions, 30 individual HPV types were detected at the 24-month visit, with high-risk HPV56 (29.0%) and 16 (25.8%) the most common types within single or multiple HPV infections (Figure 1). The next three most common HPV types were high-risk HPV52 (19.4%), 35 (12.9%) and 66 (12.9%). All other HPV types detected (n=25) had an HPV prevalence of less than 10%, including HPV18 (9.7%) and HPV6 (9.7%). HPV11 was not detected among any participant with flat penile lesions. At baseline, HPV prevalence among men with flat penile lesions was 53.3%. Of the 30 men with flat penile lesions who had HPV DNA data available from both the baseline and 24-month visit, 27 (90.0%) were HPV positive at one or more visit (data not shown).

A total of 40 HPV types were detected among men without flat penile lesions, with HPV16 the most common type (9.4%) within single or multiple infections. The next four most common types were HPV45 (3.9%), HPV66 (3.9%), HPV51 (3.4%), and HPV58 (3.4%). HPVX infections were found in 4.4% of men without flat lesions. All other HPV types detected (n=35) were found in ≤3% of participants, including HPV18 (2.6%), HPV6 (2.1%) and HPV11 (1.3%).

The prevalences of the 5 most common individual HPV types among men with flat penile lesions were all higher than the corresponding HPV prevalences among men without flat penile lesions (Figure 1). Multiple HPV types (defined as having ≥2 different high-risk or low-risk types) were more common among men with versus without flat penile lesions (67.7% vs. 19.6%, $p<0.001$).

DISCUSSION

Male circumcision was strongly associated with reduced odds of flat penile lesions. Men with HPV DNA detected had higher odds of flat penile lesions than men who were HPV-negative. High-risk HPV infection and high HPV16/18/31 viral load in the glans were particularly strong risk factors for flat penile lesions.

The prevalence of flat penile lesions among uncircumcised men in our study population (26%) was higher than that found among uncircumcised participants in a study (17%) of men in the Netherlands who self-reported no STI infections[7]. The prevalence of flat lesions among circumcised men in both studies was <1%. Higher flat lesion prevalence among uncircumcised men in our study could be due to the younger age of our study population.

Our results are consistent with previous studies that found associations between flat penile lesions and HPV using PCR or in situ hybridization methods[6,22]. HPV prevalence among men with flat lesions in our study (77%) was similar to that observed among 175 male sexual partners of women with CIN from the Netherlands (72%)[6]. Flat penile lesions were strongly associated with high-risk HPV infection and high HPV16/18/31 viral loads, especially in the glans, supporting findings from previous studies that HPV might play a role in their etiology[6,22–24]. These lesions could also be a useful parameter for evaluating efficacy of prophylactic HPV16/18 vaccines, given their common occurrence and strong associations with high-risk HPV and HPV16/18/31 viral loads. Due to their strong association with high HPV viral load, flat penile lesions may also increase transmission between sexual partners. Future studies on male-to-female HPV transmission are needed to confirm this hypothesis. Condom use was associated with both flat penile lesion regression

in a previous RCT of 100 male partners of women with CIN in the Netherlands,[9] and prevalence of flat penile lesions in this study, although our results were not statistically significant.

Although the relationship between genital warts and HPV has been well established, the observed prevalence of genital warts was too low to examine risk factors. The low prevalence of genital warts (1%) is in agreement with our study population's low prevalence of HPV6 (3%) and 11 (1%), the types which are commonly found in genital warts. The low prevalence of genital warts is comparable with prevalence data from other studies conducted in Africa, South America and Europe[6,8,25,26], especially among male partners of women without known HPV infection (i.e. 0–6%)[5].

Circumcision was associated with increased prevalence of papular lesions and pearly penile papules. Papular lesions and pearly penile papules are likely not sexually transmitted and were not associated with HPV infection in previous reports[6,11,27]. The association found between circumcision and papular lesions and pearly penile papules might be due to small mechanical traumas during intercourse or a tissue reaction following the circumcision procedure[28]. Alternatively, increased keratinization as a consequence of circumcision might lead to better visibility of papular lesions and pearly penile papules.

While previous studies have investigated HPV infection among men in Africa[29,30] to our knowledge, this is the first to investigate multiple risk factors for HPV-associated flat penile lesions among men from this region. Study advantages also include the use of a sensitive PCR assay and data on numerous potential risk factors. Additionally, all photos taken of penile lesions were double read in Amsterdam without knowledge of HPV status to reduce misclassification of penile lesions.

A study limitation is that penile lesions were diagnosed by colposcopy, and lesion diagnosis could have been misclassified due to observational bias. Acetic acid staining is not restricted to HPV-associated flat penile lesions. Other inflammatory conditions and traumatic micro-abrasions may react to the acetic acid test, but a different appearance and the absence of punctuation help to differentiate these features from true HPV-associated flat penile lesions. Penile lesions were also not directly swabbed for HPV DNA and taking biopsies of ascertained lesions was considered too invasive for this study population, in the context of an RCT. Therefore, another study limitation is that HPV infection was not detected directly from the lesion, and histological diagnosis of penile lesions was not possible. Previous reports of flat penile lesions indicate that these lesions usually represent hyperplasia or low grade penile intraepithelial neoplasia, although a minority of lesions may be high grade[5,6,8,22,27].

Only three HPV types were assessed for HPV DNA viral load in this study. Men categorized as having low HPV16/18/31 viral load may have had high viral loads for HPV types not assessed. Our sample was too small to restrict analyses to men with single HPV type infections. Additionally, viral load analyses were not normalized to cell equivalents. This may have contributed to variability in viral load assessment and to decreased specificity in categorizing specimens. Thus, viral load analyses should be interpreted with caution. Data on the baseline prevalence of flat penile lesions in this population were also not available, and thus limiting our analyses to cross-sectional associations.

While selection bias appeared to be minimal when comparing the baseline characteristics of study participants to other men in the RCT, our findings should be interpreted with caution as this was a relatively small subset of men from the RCT. Participation was likely low in this sub-study because it was started relatively late, did not originally offer compensation unlike many other trial activities and required an additional exam at the end of the final, 24-

month visit in which photographs were taken. The prevalence of STIs other than HPV and HSV-2 infections was also low in our study population, and hence important associations between penile lesions and other STIs might have been missed. Additionally, our results may not be generalizable to other African cohorts due to the low prevalence of HIV (<1%) among our participants at the 24-month visit.

Male circumcision was strongly associated with reduced odds of flat penile lesions. Because flat penile lesions were also strongly associated with high-risk HPV infection and higher HPV16/18/31 viral load, circumcision may also reduce male-to-female high-risk HPV transmission[31,32]. Male circumcision has been found to be an acceptable and effective intervention to reduce HIV incidence among African men[17,33–35]. Since prophylactic HPV vaccines may not be readily available to men in many less developed countries and current HPV vaccines do not include all high-risk HPV types, circumcision may also provide a useful intervention to prevent HPV-associated penile lesions and ultimately invasive cervical cancer in developing countries.

Novelty and impact of the paper

To our knowledge, these data are the first to show that male circumcision reduces the prevalence of HPV-associated flat penile lesions. Given that flat penile lesions were also strongly associated with high-risk HPV infection and high HPV viral load, male circumcision may potentially reduce high-risk HPV transmission between sexual partners.

Abbreviations used

HPV	human papillomavirus
OR	odds ratio
CI	confidence interval
CIN	cervical intraepithelial neoplasia
RCT	randomized controlled trial
HIV	human immunodeficiency virus
STI	sexually transmitted infection
VIA	visual inspection with acetic acid
UNIM	Universities of Nairobi, Illinois and Manitoba
RLB	reverse line blot
HSV-2	herpes simplex virus type 2

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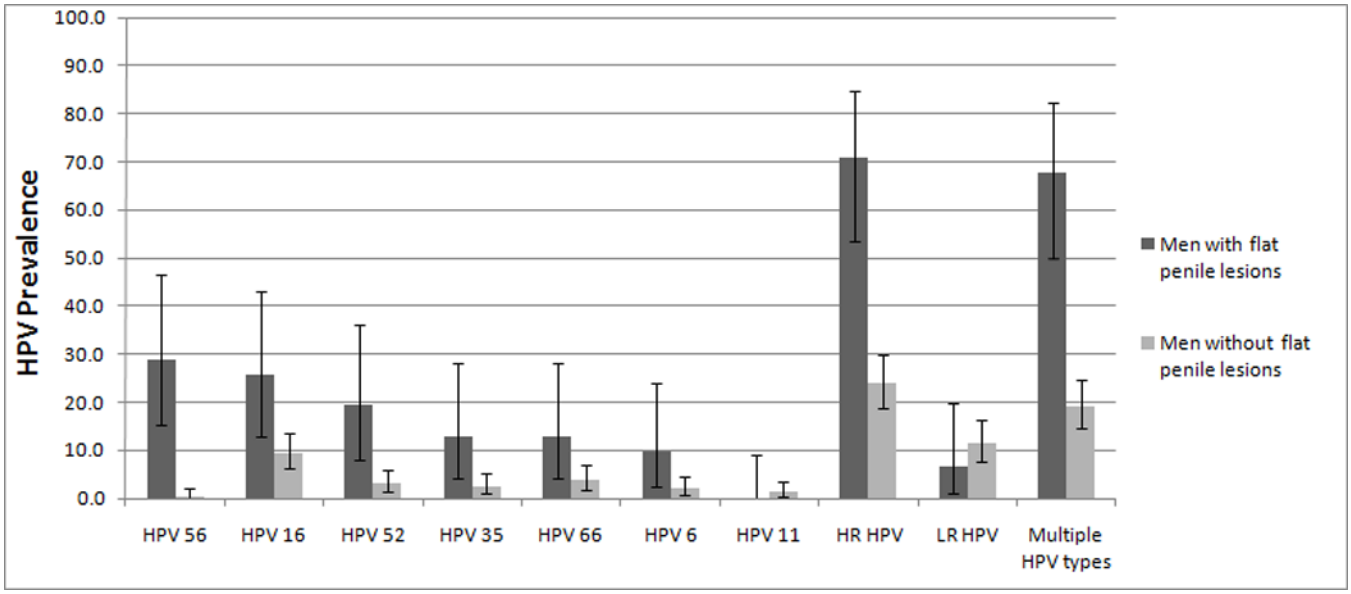

Figure 1.

Human papillomavirus (HPV) prevalence and 95% confidence intervals for the five most common HPV types, HPV6, HPV11 and HPV type groupings among men with flat penile lesions compared to men without flat penile lesions. HPV infections were considered high-risk (HR) if ≥1 HR HPV type was detected within single or multiple infections. Low-risk (LR) HPV infections were defined as the detection of ≥1 LR HPV type excluding co-infections with HR types or HPVX. A multiple infection was defined as >1HR or LR HPV type.

Table 1

Comparison of baseline characteristics for men enrolled in the randomized controlled trial of male circumcision who did and did not participate in the VIA sub-study

Risk Factor	Participated in VIA sub-study (N=275) n (%)[a]	Did not participate in VIA sub-study (N=2509) n (%)[a]	p-value[b]
Age (years)			
≤19	86 (31.2)	768 (30.6)	0.39
20–21	115 (41.8)	970 (38.7)	
≥22	74 (26.9)	771 (30.7)	
Randomization Assignment			
Uncircumcised	127 (46.2)	1266 (50.5)	0.18
Circumcised	148 (53.8)	1243 (49.5)	
HPV DNA positivity[c]			
Negative	124 (50.0)	980 (52.1)	0.68
LR-positive	27 (10.9)	219 (11.6)	
HR-positive	97 (39.1)	683 (36.3)	
Education			
Primary or none	100 (36.4)	847 (33.8)	0.39
Secondary or tertiary	175 (63.6)	1662 (66.2)	
Employment status			
No Income	95 (34.6)	896 (35.7)	0.70
Income	180 (65.4)	1613 (64.3)	
Condom use last 6 months			
Never	65 (25.8)	561 (26.1)	
≤50%	101 (40.1)	800 (37.3)	0.65
>50%	86 (34.1)	786 (36.6)	
Marital Status			
Not living with partner	250 (90.9)	2367 (94.8)	0.01
Living with partner	25 (9.1)	131 (5.2)	
Age at first intercourse (years)			
8–15	132 (49.6)	1167 (48.6)	0.75
16–21	134 (50.4)	1234 (51.4)	
Partners in last 12 months			
0–1	74 (27.2)	1009 (40.6)	<0.001
≥2	198 (72.8)	1477 (59.4)	
Lifetime # of female partners			
1–4	118 (47.4)	1281 (54.7)	0.08
5–7	63 (25.3)	533 (22.7)	
≥8	68 (27.3)	530 (22.6)	
Years of sexual activity			
0–3	78 (29.4)	788 (32.7)	0.37

Risk Factor	Participated in VIA sub-study (N=275) n (%)[a]	Did not participate in VIA sub-study (N=2509) n (%)[a]	p-value[b]
4–5	77 (29.1)	584 (24.3)	
6–7	60 (22.6)	564 (23.4)	
8–14	50 (18.9)	471 (19.6)	
HSV-2-seropositive			
No	189 (71.9)	1741 (72.2)	0.90
Yes	74 (28.1)	669 (27.8)	
N. gonorrhea			
Negative	262 (97.8)	2428 (98.1)	0.65[d]
Positive	6 (2.2)	48 (1.9)	
C. trachomatis			
Negative	252 (94.0)	2367 (95.6)	0.22[d]
Positive	16 (6.0)	108 (4.4)	
Self-reported STD[e]			
No	253 (92.0)	2339 (93.2)	0.45[d]
Yes	22 (8.0)	170 (6.8)	

NOTE. VIA: visual inspection with acetic acid; HPV: human papillomavirus; HSV-2: herpes virus type 2; STD: sexually transmitted disease

[a] Percentages do not include missing values

[b] P-value comparing men who did and did not participate in the VIA sub-study using Pearson's chi-square test unless otherwise noted.

[c] Men with HPVX infections were excluded from high and low-risk HPV categorizations unless a high-risk HPV type was detected.

[d] Fisher's exact test

[e] Sexually transmitted disease (current or within the last 6 months)

Table 2

Comparison of baseline characteristics for HIV seronegative, uncircumcised men participating in a VIA sub-study within a randomized controlled trial of male circumcision, stratified by circumcision status at the 24-month visit

Baseline Risk Factor	Circumcised at 24-month visit (N=151) n (%)[a]	Uncircumcised at 24-month visit (N=124) n (%)[a]	p-value[b]
Age (years)			
≤19	47 (31.3)	39 (31.5)	0.93
20–21	62 (42.7)	53 (42.7)	
≥22	42 (27.8)	32 (25.8)	
HPV DNA positivity[c]			
Negative	67 (49.3)	57 (50.9)	0.88
LR-positive	16 (11.8)	11 (9.8)	
HR-positive	53 (39.0)	44 (39.3)	
Education			
Primary or none	93 (61.6)	82 (66.1)	0.44
Secondary or tertiary	58 (38.4)	42 (33.9)	
Employment status			
No Income	102 (67.5)	78 (62.9)	0.42
Income	49 (32.5)	46 (37.1)	
Condom use last 6 months			
Never	36 (26.5)	29 (25.0)	0.81
≤50%	52 (38.2)	49 (42.2)	
>50%	48 (35.3)	38 (32.8	
Marital Status			
Not living with partner	138 (91.4)	112 (90.3)	0.83[d]
Living with partner	13 (8.6)	12 (9.7)	
Age at first intercourse (years)			
8–15	70 (48.6)	62 (50.8)	0.72
16–21	74 (51.4)	60 (49.2)	
Partners in last 12 months			
0–1	38 (25.7)	36 (29.0)	0.54
≥2	110 (74.3)	88 (71.0)	
Lifetime # of female partners			
1–4	68 (50.0)	50 (44.2)	0.50
5–7	35 (25.7)	28 (24.8)	
≥8	33 (24.3)	35 (31.0)	
Years of sexual activity			
0–3	45 (31.3)	33 (27.3)	0.26
4–5	39 (27.1)	38 (31.4)	
6–7	28 (19.4)	32 (26.4)	

Baseline Risk Factor	Circumcised at 24-month visit (N=151) n (%)[a]	Uncircumcised at 24-month visit (N=124) n (%)[a]	p-value[b]
8–14	32 (22.2)	18 (27.3)	
HSV-2-seropositive			
No	107 (74.3)	82 (68.9)	0.33
Yes	37 (25.7)	37 (31.1)	
N. gonorrhea			
Negative	144 (98.6)	118 (96.7)	0.42[d]
Positive	2 (1.4)	4 (3.2)	
C. trachomatis			
Negative	139 (95.2)	113 (92.6)	0.44[d]
Positive	7 (4.8)	9 (7.4)	
Self-reported STD[e]			
No	138 (91.4)	115 (92.7)	0.82[d]
Yes	13 (8.6)	9 (7.3)	

NOTE. VIA: visual inspection with acetic acid; HPV: human papillomavirus; HSV-2: herpes virus type 2

[a] Percentages do not include missing values

[b] P-value comparing the intervention vs. control groups at baseline Pearson's chi-square test unless otherwise noted.

[c] Men with HPVX infections were excluded from high and low-risk HPV categorizations unless a high-risk HPV type was detected.

[d] Fisher's exact test

[e] Sexually transmitted disease (current or within the last 6 months)

Table 3

Adjusted odds ratios (ORs) for circumcision status at the 24-month visit and penile lesions among 275 Kenyan men

		Flat penile lesions[a]		Papular Lesions		Pearly Penile Papules	
Risk Factor	**N**	**n**	**OR (95% CI) [b]**	**N**	**OR (95% CI) [b]**	**n**	**OR (95% CI) [b]**
Circumcision status							
Uncircumcised	124	32	1.0 (Reference)	43	1.0 (Reference)	76	1.0 (Reference)
Circumcised	151	1	0.02 (0.003, 0.1)	90	3.0 (1.8, 5.1)	111	1.9 (1.1, 3.2)

NOTE. VIA: visual inspection with acetic acid; CI: confidence interval

[a] Visible after the application of 3% acetic acid

[b] Odds ratios adjusted for age at the 24-month visit (≥24, 22–23, ≤21 years), baseline marital status and number of sexual partners in the 12 months prior to randomization.

Table 4

Prevalence odds ratios (ORs) for risk factors of penile lesions among 275 Kenyan men at the 24-month visit, adjusted for age and circumcision status.

		Flat penile lesions[a] n=33; HPV%=77.4%		Papular Lesions n=133; HPV%=38.8%		Pearly Penile Papules n=187; HPV% = 40.8%	
Risk Factor	**N**	**n**	**OR (95% CI) [b]**	**n**	**OR (95% CI) [b]**	**n**	**OR (95% CI) [b]**
HPV DNA positivityc							
Negative	151	7	1.0 (Reference)	79	1.0 (Reference)	106	1.0 (Reference)
Positive	114	24	6.5 (2.4, 17.5)	50	0.8 (0.5, 1.3)	73	0.8 (0.5, 1.4)
LR-positive	28	2	2.3 (0.4, 13.8)	17	1.4 (0.6, 3.3)	18	0.7 (0.3, 1.7)
HR-positive	79	22	8.3 (3.0, 22.8)	28	0.6 (0.3,1.1)	49	0.8 (0.4, 1.4)
HPV16-positive	30	8	6.0 (1.8, 20.3)	11	0.7 (0.3, 1.5)	19	0.9 (0.4, 2.1)
HPV18-positive	9	3	7.3 (1.2, 45.5)	3	0.6 (0.1, 2.6)	5	0.7 (0.2, 3.1)
Multiple HPV-positive[d]	67	21	9.4 (3.5, 25.8)	28	0.8 (0.4, 1.4)	48	1.2 (0.6, 2.3)
HR- and LR-positive[e]	48	16	9.9 (3.3, 29.4)	16	0.5 (0.3, 1.1)	34	1.2 (0.6, 2.5)
HPV DNA positivity in glans[c]							
Negative	169	8	1.0 (Reference)	90	1.0 (Reference)	123	1.0 (Reference)
Positive	97	23	5.4 (2.1, 14.0)	40	0.8 (0.5, 1.3)	57	0.6 (0.3, 1.0)
LR-positive	29	3	2.3 (0.5, 10.5)	18	1.6 (0.7, 3.8)	18	0.6 (0.3, 1.4)
HR-positive	66	20	6.8 (2.6, 18.1)	21	0.5 (0.3, 1.0)	37	0.6 (0.3, 1.1)
HPV DNA positivity in shaft[c]							
Negative	195	16	1.0 (Reference)	98	1.0 (Reference)	131	1.0 (Reference)
Positive	70	15	5.1 (2.1, 12.9)	31	0.8 (0.4, 1.3)	48	1.1 (0.6, 2.0)
LR-positive	25	6	6.1 (1.6, 23.2)	11	0.7 (0.3, 1.7)	15	0.7 (0.3, 1.6)
HR-positive	40	9	5.5 (1.8, 17.1)	16	0.6 (0.3, 1.4)	29	1.5 (0.7, 3.2)
HPV 16/18/31 viral load[f]							
HPV negative	151	7	1.0 (Reference)	79	1.0 (Reference)	106	1.0 (Reference)
Low	23	4	4.3 (1.0, 18.1)	9	0.7 (0.3, 1.7)	15	0.9 (0.4, 2.3)
High	14	4	5.2 (1.1, 24.4)	4	0.5 (0.1, 1.7)	8	0.8 (0.2, 2.5)
Education[g]							
Primary or none	100	16	2.1 (0.9, 4.9)	49	1.0 (0.6, 1.6)	71	1.2 (0.7, 2.1)

Risk Factor	N	Flat penile lesions[a] n=33; HPV%=77.4% n	OR (95% CI) [b]	Papular Lesions n=133; HPV%=38.8% n	OR (95% CI) [b]	Pearly Penile Papules n=187; HPV% = 40.8% n	OR (95% CI) [b]
Secondary or tertiary	175	17	1.0 (Reference)	84	1.0 (Reference)	116	1.0 (Reference)
Employment status[g]							
No Income	180	20	1.0 (Reference)	88	1.0 (Reference)	124	1.0 (Reference)
Income	95	13	1.4 (0.6, 3.5)	45	1.0 (0.6, 1.7)	63	0.9 (0.5, 1.7)
Condom use last 6 months							
Never	58	11	2.3 (0.8, 6.4)	27	1.0 (0.5, 1.9)	36	0.8 (0.4, 1.6)
≤50%	68	4	0.7 (0.2, 2.4)	33	0.9 (0.5, 1.7)	47	1.0 (0.5, 1.9)
>50%	112	13	1.0 (Reference)	52	1.0 (Reference)	77	1.0 (Reference)
Marital Status							
Not living with partner	203	26	1.0 (Reference)	103	1.0 (Reference)	144	1.0 (Reference)
Living with partner	72	7	1.0 (0.4, 2.8)	30	0.6 (0.3, 1.1)	43	0.6 (0.3, 1.0)
Age at first intercourse (years)							
8–15	165	22	1.2 (0.5, 2.8)	78	0.8 (0.5, 1.4)	113	1.1 (0.6, 1.9)
16–21	96	11	1.0 (Reference)	50	1.0 (Reference)	64	1.0 (Reference)
Partners in last 12 months							
0–1	126	20	1.0 (Reference)	62	1.0 (Reference)	81	1.0 (Reference)
≥2	146	13	0.5 (0.2, 1.2)	69	0.8 (0.5, 1.3)	104	1.3 (0.8, 2.2)
HSV-2-seropositive							
No	164	21	1.0 (Reference)	84	1.0 (Reference)	114	1.0 (Reference)
Yes	28	2	0.4 (0.1, 1.8)	13	0.8 (0.4, 1.9)	19	0.8 (0.4, 2.0)
Lifetime # of female partners							
1–4	87	14	1.0 (Reference)	37	1.0 (Reference)	54	1.0 (Reference)
5–7	67	4	0.3 (0.1, 1.1)	37	1.6 (0.8, 3.1)	45	1.2 (0.6, 2.4)
≥8	86	14	0.9 (0.4, 2.2)	39	1.3 (0.7, 2.4)	61	1.8 (0.9, 3.4)
Years of sexual activity							
0–3	64	7	1.0 (Reference)	34	1.0 (Reference)	46	1.0 (Reference)
4–5	69	12	1.4 (0.5, 4.2)	30	0.8 (0.4, 1.7)	44	0.9 (0.4, 2.1)
6–7	73	7	1.1 (0.3, 4.0)	31	0.6 (0.3, 1.3)	52	1.0 (0.5, 2.2)

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Risk Factor	N	Flat penile lesions[a] n=33; HPV%=77.4% n	OR (95% CI) [b]	Papular Lesions n=133; HPV%=38.8% n	OR (95% CI) [b]	Pearly Penile Papules n=187; HPV% = 40.8% n	OR (95% CI) [b]
8–14	54	7	1.6 (0.4, 6.1)	32	1.7 (0.7, 3.9)	34	0.8 (0.3, 1.9)

NOTE. CI: confidence interval; HPV: human papillomavirus; HR: high-risk; LR: low-risk; HSV-2: herpes simplex virus type 2

[a] Visible after the application of 3% acetic acid; n=1 uncircumcised participant missing flat penile lesion status

[b] Odds ratios adjusted for age categorized as ≥24, 22–23 and ≤21 years and circumcision status at the 24-month visit

[c] HR HPV infections were defined as ≥1 HR detected. Men with HPVX infections were excluded from high and low-risk HPV categorizations unless a high-risk HPV type was detected. All other HPV infections were categorized as LR. n=1 missing a shaft HPV result.

[d] Defined as an HPV infection in which >1 HPV type was detected.

[e] Defined as a multiple HPV infection in which HR and LR HPV infections co-occur.

[f] High HPV viral load defined as HPV 16, 18 and/or 31 >250 copies/scrape in the glans or shaft HPV specimens. All other specimens containing HPV 16, 18 or 31 were considered to have low HPV16/18/31 viral load.

[g] Assessed at the baseline visit