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Human papillomavirus incidence and clearance among HIV-positive and HIV-negative men in Rakai, Uganda

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Abstract

Objectives—High-risk human papillomavirus (HR-HPV) infection is the most common sexually transmitted infection. Penile and cervical cancer rates are highest in sub-Saharan Africa. However, little is known about the impact of HIV infection on HR-HPV acquisition and clearance among heterosexual men.

Design—HR-HPV incidence and clearance were evaluated in 999 men (776 HIV-negative and 223 HIV-positive) aged 15–49 who participated in male circumcision trials in Rakai, Uganda.

Methods—Penile swabs were tested for HR-HPV by Roche HPV Linear Array. A Poisson multivariable model was used to estimate adjusted incidence rate ratios (adjIRR) and clearance risk ratios (adjRR).

Results—HR-HPV incidence was 66.5/100 py in HIV-positive men and 32.9/100 py among HIV-negative men (IRR=2.0, 95%CI 1.7–2.4). Incidence was higher with non-marital status (adjIRR=1.7, 95%CI 1.2–2.5), and decreased with age (adjIRR=0.6, 95%CI 0.4–1.0) and male circumcision (adjIRR=0.7, 95%CI 0.6–0.9). HR-HPV clearance was 114.7/100 py for HIV-positive men and 170.2/100 py for HIV-negative men (RR=0.7, 95%CI 0.6–0.8). Clearance in HIV-negative men was increased with circumcision (adjRR=1.5, 95%CI 1.3–1.7), HSV-2 infection (adjRR=1.2, 95%CI 1.0–1.4), and symptoms of urethral discharge (adjRR=1.4, 95%CI 1.1–1.7).

Conclusions—HR-HPV is common among heterosexual Ugandan men, particularly the HIV-infected. HIV infection increases HR-HPV acquisition and reduces HR-HPV clearance. Promotion of male circumcision and HPV vaccination is critical in sub-Saharan Africa.

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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.

Author contributions

All authors contributed to the study design, data collection, data analysis, writing and reviewing the paper.

Keywords

Human papillomavirus (HPV); HIV; male circumcision; Uganda

Introduction

High risk human papillomavirus (HR-HPV) infection is the most common sexually transmitted infection, and persistent HR-HPV can cause oral, anal, penile, and cervical cancer [1–6].

Previous studies have evaluated factors associated with penile HR-HPV incidence and clearance among heterosexual HIV-negative men in Europe, Latin America and the United States [7–12]. However, little is known about penile HR-HPV acquisition in heterosexual men in Africa, or in African men infected with HIV, populations which have among the highest rates worldwide of penile and cervical cancers. Women infected with HIV have significantly higher rates of multiple HR-HPV infections, reduced clearance and more rapid progression to neoplasia [13–16], so it is likely that the HIV epidemic in Africa exacerbates the problem of HR-HPV-related neoplasia. However, the impact of HIV on HR-HPV acquisition and clearance among heterosexual men is not known.

With the roll out of male circumcision and HPV vaccination programs in Africa, it is important to understand the risk factors and natural history of HPV infection among men in Africa. Here we report risk factors for HR-HPV incidence and clearance among HIV-positive and HIV-negative men in Rakai, Uganda.

Materials and Methods

HR-HPV incidence and clearance were evaluated in 999 men aged 15–49 years who had amplifiable DNA of HPV swabs on sequential visits collected over a period of up to 2 years during two trials of male circumcision for HIV and STI prevention in Rakai District, Uganda [17–21]. Men who had contraindications for surgery (e.g., anemia, active genital infection) were treated, and if their medical condition resolved, they were re-screened and enrolled into the trial. Those with anatomical abnormalities (e.g., hypospadias), other medical contraindications or indications for surgery (e.g., severe phimosis) were excluded. HIV-positive men with CD4 counts <350 cells/mm³ or WHO stage 4 disease were excluded from the trials; HIV seroconverters were also excluded from the analysis reported here. Participants provided written informed consent prior to screening and at enrollment. Men were randomly assigned to receive immediate circumcision (intervention) or circumcision delayed for 24 months (control). Circumcision status was assessed at each visit, and this status determined how men were categorized for the preceding interval. Infectious disease testing (HPV, HIV, HSV-2, and syphilis), physical examinations, and interviews to ascertain sociodemographic characteristics and sexual risk behaviors were conducted at baseline and repeated at 6, 12 and 24 months follow-up. Serum and swab samples were stored at -80°C . All subjects were offered free HIV counseling and testing, health education and condoms at each visit. All participants found to be HIV-positive were referred for free care to the Rakai Health Sciences Program HIV care and treatment services funded by the President's Emergency Plan for AIDS Relief.

The trials were approved by the HIV Subcommittee of the Ugandan National Council for Research and Technology (Kampala, Uganda), and by three institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the Johns Hopkins University Bloomberg School of Public Health IRB (Baltimore, MD,

USA), and the Western Institutional Review Board (Olympia, WA, USA). The trials were overseen by independent Data Safety Monitoring Boards [18–19], and were registered with ClinicalTrials.gov numbers NCT00425984 and NCT00124878.

HPV, HSV-2, HIV and Syphilis Detection

Moistened Dacron swabs were rotated around the full circumference of the penis at the coronal sulcus and glans, and were stored in Digene specimen transport media at -80°C until assay. HPV genotyping was performed using the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN) [22]. HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered the primary HR-HPV genotypes. A total of 5141 samples from 1692 men were tested. 924 swabs (18.0%) with no detectable cellular beta-globin and/or detectable HPV were not included in this analysis, since the adequacy of the sample collection could not be ensured. There were 999 men (776 HIV-negative and 223 HIV-positive) with sequential visits with amplifiable viral or cellular DNA (3120 samples total) who were assessed in this study.

HSV-2 infection was determined by HSV-2 ELISA (Kalon Biological Ltd, Guilford, UK), as previously described [19, 23]. An HSV-2 seroconversion was defined as a negative enrollment serology followed by a positive follow up serology with confirmation by Euroimmun Western blot (Euroimmun, Lubeck, Germany) [24–25].

HIV status was determined using two separate ELISAs and confirmed by HIV-1 Western Blot, as previously described [18]. Active *T. pallidum* infection was determined by a positive rapid plasma reagin (RPR) followed by a positive *Treponema pallidum* particle agglutination assay (TPPA) [19].

Statistical Analysis

Incident HR-HPV was defined as a newly detected genotype identified in a man who was initially negative for any HR-HPV at the prior study visit, or a man who was previously HR-HPV positive but had one or more newly detected HR-HPV genotype(s) during the follow-up interval. HR-HPV incidence rates per 100 person-years (/100 py) were estimated assuming that the new HR-HPV infection was acquired at the mid-point of the sequential follow-up interval. The unit of analysis for HR-HPV incidence risk factors was an individual participant interval, and each man was counted only once per follow-up interval, irrespective of whether he acquired a single or multiple HR-HPV genotypes. Incidence was also assessed for each HR-HPV genotype, irrespective of the number of HR-HPV infections per individual, and all genotype-specific incident events were summed to provide global estimates. Incidence rate ratios (IRR) and 95% confidence intervals (95%CI) of HR-HPV acquisition were estimated using Poisson regression. Associations with fixed covariates such as baseline age, marital status, and education at enrollment, and by time-varying covariates such as sexual risk behaviors (e.g., number of partners, non-marital relationships, condom use, and alcohol use with sex) reported during follow up visits were assessed. Risk factors with a p-value <0.15 in univariate analysis were entered into a Poisson multivariable model to estimate adjusted incidence rate ratios (adjIRRs) and 95% confidence intervals (95%CI) of HR-HPV incidence.

Clearance (i.e., loss of detection) of any HR-HPV was estimated among men with pre-existing HR-HPV genotype-specific infections; each specific HR-HPV genotype was the unit of observation. Clearance was expressed as the rate of cleared HR-HPV genotypes per 100 person-years of observation among individuals with those pre-existing HR-HPV genotypes at the prior study visit. Clearance was assessed for each HR-HPV genotype, irrespective of the number of HR-HPV infections per individual, 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 Poisson regression with robust variance estimated based on generalized estimating equations to account for multiple clearance events in the same individual. Potential confounders were examined in univariate analyses and covariates found to be associated at p -value <0.15 were entered into a Poisson multivariable model to estimate adjusted risk ratios. Analyses were performed using Stata software (version 11, StataCorp, College Station, TX) and SAS software (version 9.2, SAS Institute, Cary, NC).

Results

There were 999 men (776 HIV-negative and 223 HIV-positive) with sequential visits and amplifiable viral or cellular DNA who contributed 1227.25 person years observation. The univariate associations of HR-HPV acquisition stratified by enrollment HIV status are shown in Table 1. The HR-HPV incidence rate was 32.94 /100 py (319 cases / 968.5 py) for HIV-negative men and 66.47 /100 py (172 cases / 258.75 py) for HIV-positive men (IRR=2.02, 95%CI 1.67–2.44, $p <0.0001$). In addition, the incidence of multiple (two or more) HR-HPV genotypes was significantly higher among HIV-positive men (27.93 / 100 py, 72 cases / 257.75 py) compared to HIV-negative men (9.39 / 100 py, 91 cases / 968.75 py), (IRR=2.97, 95%CI 2.15–4.10, $p <0.0001$).

HR-HPV incidence was highest in younger men and decreased with age for both HIV-negative and HIV-positive men. Among HIV-negative men, HR-HPV incidence was higher for individuals who were unmarried, participated in non-marital relationships, had multiple sexual partners, and reported condom use. HR-HPV incidence was significantly lower among HIV-negative circumcised men. There were no associations between HR-HPV incidence and education, occupation, genital washing after sexual intercourse, self-reported symptoms of sexually transmitted infections (such as genital ulcer disease, urethral discharge and dysuria), enrollment syphilis status, and HSV-2 infection. Among HIV-positive men, both enrollment characteristics and risk behaviors for HR-HPV acquisition showed similar trends to the HIV-negative men, but associations were not statistically significant.

In multivariate Poisson regression (Table 2), the adjusted incidence rate ratios (adjIRRs) of HR-HPV acquisition for HIV-negative men were increased with non-marital status (adjIRR 1.73, 95%CI 1.19–2.52), and decreased with age (adjIRR for men >35 years, 0.64, 95%CI 0.43–0.95) and male circumcision (adjIRR 0.70, 95%CI 0.55–0.89). For HIV-positive men, HR-HPV acquisition decreased significantly with age. For HIV-negative and HIV-positive men, education, occupation, number of sexual partners, condom use, and urethral discharge were not associated with HR-HPV acquisition in multivariate analyses.

Table 3 shows the incidence rates for the 14 HR-HPV genotypes individually and combined, stratified by HIV status. Incident rates were not substantially different among HR-HPV genotypes. Among HIV-negative men, HR-HPV 66 had the highest incidence rate; in HIV-positive men, incidence was highest for HR-HPV 68. HIV-positive men were at significantly elevated risk of new genotype-specific HR-HPV infection compared to HIV-negative men (RR2.35, 95%CI 2.03–2.72). Stratifying by HIV serostatus, incidence was higher for 13 of 14 HR-HPV genotypes among HIV-positive men (with HR-HPV 59 as the only exception).

Table 4 shows the univariate associations of HR-HPV clearance stratified by enrollment HIV status. The HR-HPV clearance rate was 170.16 /100 py (593 cases / 348.5 py) for HIV-negative men and 114.73 /100 py (366 cases / 319.0 py) for HIV-positive men. This difference was statistically significant (RR 0.67, 95%CI 0.59–0.77, $p <0.0001$). Among

HIV-negative men, HR-HPV clearance was lower for unmarried men and increased for men who were circumcised, reported dysuria and urethral discharge, or were co-infected with syphilis or HSV-2. Clearance increased with older age, but this was of borderline statistical significance. There were no associations between HR-HPV clearance and number of sexual partners, condom use, alcohol use with sexual intercourse, washing genitals after sexual intercourse, and self-reported symptoms of genital ulcers. Among HIV-positive men, HR-HPV clearance was increased with older age, and the absence of self-reported genital ulcer disease.

In multivariate Poisson model (Table 5), the clearance rate of HR-HPV for HIV-negative men was increased among circumcised men (adjRR 1.48, 95% CI 1.26–1.74), men infected with HSV-2 (adjRR 1.20, 95% CI 1.01–1.44), and men reporting urethral discharge (adjRR 1.35, 95% CI 1.06–1.73). Clearance of HR-HPV was significantly lower for non-married men (adjRR 0.76, 95% CI 0.59–0.98) and men reporting dysuria (adjRR 0.68, 95% CI 0.49–0.96). There were no significant associations between HR-HPV clearance and age, occupation, and syphilis infection. For HIV-positive men, HR-HPV clearance was higher among men in non-marital relationships (adjRR 1.43, 95% CI 1.06–1.93), and there were no significant associations between HR-HPV clearance and age, occupation, those reporting genital ulcers, or HSV-2 infected men.

The clearance rates for the 14 HR-HPV genotypes individually and combined, stratified by HIV status were evaluated (Supplemental Table 1). Clearance rates were not substantially different among HR-HPV genotypes. Among HIV-negative men, HR-HPV 58 was the most persistent while the clearance rate was highest for HR-HPV 31. Among HIV-positive men, HR-HPV 66 was the most persistent while the clearance rate was highest for HR-HPV 56. The clearance rate of genotype-specific HR-HPV was significantly lower for HIV-positive men compared to HIV-negative men (RR 0.67, 95% CI 0.59–0.77). Clearance was lower among HIV-positive men for 12 of 14 HR-HPV genotypes (with the exception of HR-HPV 35 and HR-HPV 56).

Discussion

HR-HPV incidence and clearance data in resource-poor settings are sparse and we believe this is the first study to evaluate risk factors for penile HR-HPV incidence and clearance in a rural African population of heterosexual men. The incidence of penile HR-HPV was high among both HIV-negative (32.94/100 person-years) and HIV-positive (66.47/100 person-years) men. Although comparisons across study populations are difficult, the incidence of HR-HPV is higher in this rural African population than among HIV-negative heterosexual men in the United States, Latin America, and Europe [9, 11]. The increased HR-HPV incidence in this study was associated with non-marital relationships and HIV infection, and HR-HPV incidence was reduced with older age and circumcision.

Studies in women have reported that HR-HPV prevalence and incidence are highest among women aged 25–35 years with a secondary peak among women more than 45 years [26], whereas U.S. studies in men found that the risk of acquiring HR-HPV was stable throughout their lifetime [11]. However, in this study, the HR-HPV acquisition rate decreased among men after age 30 years. This is plausible since men over 30 years old are more often in stable relationships, and may have acquired partial immunity from prior infections.

The effect of condom use on HR-HPV prevention in men is unclear. Some studies have not found a protective effect of condom use [27–29], while others have shown that consistent condom use is associated with lower HPV infection [30–31]. These studies differ by anatomic location of samples including areas such as the scrotum which are not protected by

a condom and by consistency of condom use. We found that condom use did not protect against HR-HPV infection on the penile coronal sulcus even when stratified by reported consistent and inconsistent condom use (data not shown). This finding may be due to the low rates of condom use or possible autoinfection of HR-HPV between genital sites [32].

Among HIV-negative men, HR-HPV clearance was higher in circumcised men, individuals reporting urethral discharge, and those co-infected with HSV-2. Among HIV-positive men, HR-HPV clearance was higher in those reporting non-marital relationships. It is possible that other genital tract infections create an inflammatory cytokine milieu which facilitates clearance of HPV infections. Overall, however, HIV-positive men had a significantly lower rate of HR-HPV clearance than HIV-negative men (RR 0.67, 95% CI 0.59–0.77).

We previously showed that male circumcision in HIV-negative men decreased HR-HPV prevalence and incidence, and increased clearance [19, 33–34]. Although male circumcision reduced HR-HPV prevalence and the incidence of multiple HR-HPV infections in HIV-positive men, there was no impact of circumcision on incidence of single HR-HPV infections or on clearance [35], as observed in the current analysis. The reduced acquisition and increased clearance of HR-HPV among circumcised men likely has benefits for both men with decreased penile lesions [36], and female partners with reduced HR-HPV prevalence [17] and lower rates of cervical cancer [37].

While all previous studies of HR-HPV risk factors among heterosexual men have focused on HIV-negative individuals, HIV infection was the strongest risk factor for HR-HPV incidence. Previous studies in HIV-positive women have shown an increased burden of HR-HPV through increased incidence and decreased clearance, and the effect was most marked with more severe immunodeficiency (lower CD4 T-cell counts and higher HIV viral load) [26]. In this study, CD4 count and HIV viral load were not available and could not be evaluated. However, all HIV-positive men had CD4 counts ≥ 350 and were free of AIDS symptoms at enrollment, so it is unlikely that they were severely immunodeficient.

While HSV-2 and syphilis were not associated with incident HR-HPV, HSV-2 was associated with a borderline increased clearance in HIV-negative men. Histological studies of genital warts suggest that a mucosal influx of CD4+ and CD8+ T-cells are required for clearance of HR-HPV infection [38–39], and HSV-2 infection is associated with increased CD4+ and CD8+ T cell densities in the foreskin mucosa [40]. Thus, it is biologically plausible that the association of HSV-2 with increased HR-HPV clearance is due to the increased recruitment of T-cells to the genital epithelium. HIV-negative men infected with syphilis had a higher rate of clearance, but this finding was not statistically significant. Urethral discharge, which may be indicative of an inflammatory process, was also associated with higher HR-HPV clearance.

This study has limitations. The analysis was confined to a random sample of primarily married men, so we cannot fully assess the risk factors among single men. The six month and 12 month intervals between sample collection are long and may have underestimated the incidence and overestimated the duration of infection since individuals may have both acquired and cleared HR-HPV genotypes between study visits. We were conservative in our estimates of incidence and clearance, which were restricted to sequential samples with amplifiable cellular or viral DNA to ensure the adequacy of sample collection. We focused on penile HR-HPV detection at the coronal sulcus and did not estimate HR-HPV incidence or clearance at other genital sites. The findings are not applicable to all men with HIV since only men with CD4 cell counts ≥ 350 cells/mL and no evidence of AIDS-related illnesses were enrolled in the male circumcision trials. There are also inherent difficulties in the interpretation of HPV epidemiology. Incident HPV detection probably represents a

combination of true newly acquired infections and possible reactivation of prior latent infections. The increased incidence among HIV-positive men may be due to reactivated infections[15], and we were not able to distinguish between incidence and reactivation.

The highest burden of penile cancer is in sub-Saharan Africa, and HR-HPV is common among heterosexual Ugandan men, particularly the HIV-infected. The promotion of male circumcision and HPV vaccination is critical in sub-Saharan Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Risk factors for HR-HPV incident infection stratified by HIV status (univariate analysis).

	HIV-negative					HIV-positive				
	HR-HPV		HR-HPV Incidence		Unadjusted analysis		HR-HPV		HR-HPV Incidence	
	Incident Cases	py ^a	/100 py	IRR (95% CI)	P-value	Incident Cases	py ^a	/100 py	IRR (95% CI)	P-value
All participants	319	968.50	32.94			172	258.75	66.47		
Age (years)					0.005					0.013
15–24	101	268.00	37.69	1.00 (referent)		25	23.50	106.38	1.00 (referent)	
25–29	102	278.50	36.62	0.97 (0.74–1.28)		45	71.25	63.16	0.59 (0.36–0.97)	
30–35	73	234.00	31.20	0.83 (0.61–1.12)		62	80.75	76.78	0.72 (0.45–1.15)	
>35	43	188.00	22.87	0.61 (0.42–0.87)		40	83.25	48.05	0.45 (0.27–0.74)	
Education					0.54					0.10
No education or Primary	249	769.50	32.36	1.00 (referent)		141	223.25	63.16	1.00 (referent)	
Secondary or higher	70	199.00	35.18	1.09 (0.83–1.42)		31	35.50	87.32	1.38 (0.94–2.04)	
Occupation					0.27					0.09
Non-wage	204	647.75	31.49	1.00 (referent)		101	167.75	60.21	1.00 (referent)	
Wage	115	320.75	35.85	1.14 (0.91–1.43)		71	91.00	78.02	1.30 (0.96–1.75)	
Marital Status					0.002					0.61
Married	270	871.25	30.99	1.00 (referent)		138	211.50	65.25	1.00 (referent)	
Not Married	49	97.25	50.39	1.63 (1.20–2.20)		34	47.25	71.96	1.10 (0.76–1.61)	
Non-marital relationships					<0.0001					0.07
No	231	786.50	29.37	1.00 (referent)		127	204.75	62.03	1.00 (referent)	
Yes	88	182.00	48.35	1.65 (1.29–2.10)		45	53.00	84.91	1.37 (0.97–1.92)	
Number of sexual partners during past year					0.001					0.009
None	6	32.25	18.60	0.65 (0.29–1.46)		12	15.50	77.42	1.39 (0.76–2.53)	
1	174	604.50	28.78	1.00 (referent)		87	155.75	55.86	1.00 (referent)	
2+	139	331.75	41.90	1.46 (1.17–1.82)		73	86.50	84.39	1.51 (1.10–2.06)	
Condom use past year *					0.014					0.11
None	179	599.50	29.86	1.00 (referent)		59	104.50	56.46	1.00 (referent)	
Consistent or Inconsistent use	133	336.50	39.53	1.32 (1.06–1.66)		101	137.25	73.59	1.30 (0.94–1.80)	
	312	936								

	HIV-negative					HIV-positive				
	HR-HPV Incident Cases	py [^]	HR-HPV Incidence /100 py	Unadjusted analysis		HR-HPV Incident Cases	py [^]	HR-HPV Incidence /100 py	Unadjusted analysis	
				IRR (95% CI)	P-value				IRR (95% CI)	P-value
Alcohol use with sexual intercourse [*]					0.60					0.23
No	89	279.00	31.90	1.00 (referent)		27	50.00	54.00	1.00 (referent)	
Yes	224	657.25	34.08	1.07 (0.84–1.37)		133	191.25	69.54	1.29 (0.85–1.95)	
Wash genitals after sexual intercourse [*]					0.92					0.21
No	33	100.75	32.75	1.00 (referent)		12	12.75	91.12	1.00 (referent)	
Yes	279	835.25	33.40	1.02 (0.71–1.46)		148	229.50	64.49	0.69 (0.38–1.23)	
Genital ulcer disease (self-reported)					0.47					0.17
No	297	911.00	32.60	1.00 (referent)		136	214.00	63.55	1.00 (referent)	
Yes	22	57.50	38.26	1.17 (0.76–1.81)		36	43.75	82.29	1.29 (0.90–1.87)	
Urethral discharge (self-reported)					0.21					0.12
No	309	948.00	32.59	1.00 (referent)		159	245.00	64.90	1.00 (referent)	
Yes	10	20.50	48.78	1.50 (0.80–2.81)		13	12.75	101.96	1.57 (0.89–2.77)	
Dysuria (self-reported)					0.88					0.94
No	317	961.75	32.96	1.00 (referent)		167	250.50	66.67	1.00 (referent)	
Yes	2	6.75	29.63	0.90 (0.22–3.61)		5	7.25	68.97	1.03 (0.43–2.52)	
Circumcised					0.002					0.63
No	211	557.75	37.83	1.00 (referent)		105	152.75	68.74	1.00 (referent)	
Yes	108	410.75	26.29	0.70 (0.55–0.88)		67	105.00	63.81	0.93 (0.68–1.26)	
Enrollment syphilis status					0.43					0.17
Negative	301	923.00	32.61	1.00 (referent)		158	229.00	69.00	1.00 (referent)	
RPR and TPPA Positive	18	45.50	39.56	1.21 (0.75 – 1.95)		14	29.75	47.06	0.68 (0.39–1.18)	
HSV-2 status					0.38					0.16
Persistent Negative	139	456.50	30.45	1.00 (referent)		12	27.00	44.44	1.00 (referent)	
Enrollment Indeterminate	56	144.50	38.75	1.27 (0.93–1.74)		26	39.75	65.41	1.47 (0.74–2.91)	
Prevalent Positive or Seroconverter	124	367.50	33.74	1.11 (0.87–1.41)		134	192.00	69.79	1.57 (0.87–2.83)	

^{*} Only evaluated in sexually active individuals.

py represents person-years.

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Table 2

Adjusted incidence rate ratios for HPV infection

	HIV-negative		HIV-positive	
	adj IRR (95% CI)	P-value	adj IRR (95% CI)	P-value
Age (years)		0.02		0.022
15–24	1.00 (referent)		1.00 (referent)	
25–29	1.05 (0.78–1.42)		0.49 (0.29–0.85)	
30–35	0.87 (0.62–1.22)		0.64 (0.39–1.07)	
>35	0.64 (0.43–0.94)		0.40 (0.23–0.70)	
Education				0.23
No education or Primary	-----		1.00 (referent)	
Secondary or higher	-----		1.30 (0.85–1.99)	
Occupation				0.38
Non-wage	-----		1.00 (referent)	
Wage	-----		1.15 (0.84–1.59)	
Marital Status		0.005		
Married	1.00 (referent)		-----	
Not Married	1.73 (1.19–2.52)		-----	
Non-marital relationships		0.36		0.81
No	1.00 (referent)		1.00 (referent)	
Yes	1.16 (0.84–1.59)		1.05 (0.70–1.59)	
Number of sexual partners during past year		0.08		0.15
1	1.00 (referent)		1.00 (referent)	
2+	1.28 (0.97–1.70)		1.33 (0.91–1.95)	
Condom use past year [*]		0.94		0.68
None	1.00 (referent)		1.00 (referent)	
Consistent or Inconsistent use	1.01 (0.77–1.33)		1.08 (0.76–1.53)	
Urethral discharge (self-reported)				0.29
No	-----		1.00 (referent)	
Yes	-----		1.41 (0.74–2.69)	
Circumcised		0.003		
No	1.00 (referent)		-----	
Yes	0.70 (0.55–0.89)		-----	

^{*} Only evaluated in sexually active individuals.

Table 3

Type-specific HR-HPV incidence, stratified by HIV.

HR-HPV Genotype	HIV-negative			HIV-positive			HIV+/HIV- Crude Incidence
	Incident Cases	Py [^]	Incidence Rate /100 py	Incident Cases	py [^]	Incidence Rate /100 py	
16	42	997.75	4.21	27	260.25	10.37	2.46 (1.52–4.00)
18	38	1026.25	3.70	22	276.25	7.96	2.15 (1.27–3.64)
31	18	1043.25	1.73	18	290.50	6.20	3.59 (1.87–6.90)
33	18	1046.75	1.72	16	290.50	5.51	3.20 (1.63–6.28)
35	29	1031.00	2.81	23	281.00	8.19	2.91 (1.68–5.03)
39	15	1048.00	1.43	17	295.00	5.76	4.03 (2.01–8.06)
45	17	1032.50	1.65	20	276.25	7.24	4.40 (2.30–8.39)
51	47	981.25	4.79	23	275.00	8.36	1.75 (1.06–2.88)
52	34	1019.75	3.33	20	284.75	7.02	2.10 (1.21–3.66)
56	14	1053.75	1.33	17	301.50	5.64	4.24 (2.09–8.61)
58	44	1006.00	4.37	24	270.75	8.86	2.03 (1.23–3.33)
59	44	1014.00	4.34	11	288.00	3.82	0.88 (0.45–1.70)
66	50	1005.75	4.97	20	278.75	7.17	1.44 (0.86–2.42)
68	37	1023.25	3.62	31	274.50	11.29	3.12 (1.94–5.03)
Any HR-HPV	447	14329.25	3.12	289	3943	7.33	2.35 (2.03–2.72)

[^] py represents person-years.

Table 4

Risk factors for HR-HPV clearance stratified by HIV status (univariate analysis).

	HIV-negative					HIV-positive				
	HR-HPV		HR-HPV Clearance		Unadjusted analysis		HR-HPV		HR-HPV Clearance	
	Cleared Cases	py ^a	/100 py	RR (95% CI)	P-value		Cleared Cases	py ^a	/100 py	RR (95% CI)
All participants	593	348.50	170.16				366	319.00	114.73	
Age (years)										
15-24	225	144.75	155.44	1.00 (referent)	0.03		44	43.50	101.15	1.00 (referent)
25-29	180	104.75	171.84	1.11 (0.90-1.35)			91	104.75	86.87	0.86 (0.57-1.31)
30-35	115	60.50	190.08	1.22 (0.99-1.51)			135	100.25	134.66	1.33 (0.91-1.95)
>35	73	38.50	189.61	1.22 (0.97-1.53)			96	70.50	136.17	1.35 (0.89-2.04)
Education										
No education or Primary	480	282.50	169.91	1.00 (referent)	0.95		308	274.50	112.20	1.00 (referent)
Secondary or higher	113	66.00	171.21	1.01 (0.80-1.27)			58	44.50	130.34	1.16 (0.84-1.61)
Occupation										
Non-wage	386	216.75	178.09	1.00 (referent)	0.14		224	175.75	127.45	1.00 (referent)
Wage	207	131.75	157.12	0.88 (0.75-1.05)			142	143.25	99.13	0.78 (0.59-1.02)
Marital Status										
Married	501	276.50	181.19	1.00 (referent)	0.001		286	251.75	113.61	1.00 (referent)
Not Married	92	72.00	127.78	0.71 (0.57-0.87)			80	67.25	118.96	1.05 (0.78-1.40)
Non-marital relationships										
No	412	241.00	170.95	1.00 (referent)	0.86		268	248.50	107.85	1.00 (referent)
Yes	181	107.50	168.37	0.98 (0.83-1.17)			98	70.50	139.01	1.29 (0.98-1.69)
Number of sexual partners during past year										
None	14	9.25	151.35	0.90 (0.63-1.28)	0.68		24	21.75	110.35	0.93 (0.55-1.57)
1	333	198.00	168.18	1.00 (referent)			201	169.75	118.41	1.00 (referent)
2+	246	141.25	174.16	1.04 (0.88-1.22)			141	127.50	110.59	0.93 (0.71-1.23)
Condom use past year [*]										
None	315	186.00	169.36	1.00 (referent)	0.84		143	114.00	125.44	1.00 (referent)
Consistent or Inconsistent use	264	153.25	172.27	1.02 (0.86-1.20)			199	182.75	108.89	0.87 (0.66-1.14)
Alcohol use with sexual intercourse [*]										

	HIV-negative					HIV-positive				
	HR-HPV Cleared Cases	py ^a	HR-HPV Clearance /100 py	Unadjusted analysis		HR-HPV Cleared Cases	py ^a	HR-HPV Clearance /100 py	Unadjusted analysis	
				RR (95% CI)	P-value				RR (95% CI)	P-value
No	180	108.25	166.28	1.00 (referent)	0.68	61	52.50	116.19	1.00 (referent)	0.95
Yes	399	231.00	172.73	1.04 (0.87–1.25)		280	243.25	115.11	0.99 (0.73–1.35)	
Wash genitals after sexual intercourse*										
No	52	30.00	173.33	1.00 (referent)	0.93	23	15.25	150.82	1.00 (referent)	0.23
Yes	527	309.25	170.41	0.98 (0.68–1.43)		319	282.00	113.12	0.75 (0.47–1.20)	
Genital ulcer disease (self-reported)										
No	537	316.25	169.80	1.00 (referent)	0.84	309	241.50	127.95	1.00 (referent)	0.002
Yes	56	32.25	173.64	1.02 (0.82–1.27)		57	77.50	73.55	0.57 (0.41–0.81)	
Urethral discharge (self-reported)										
No	575	340.00	169.12	1.00 (referent)	0.01	338	296.25	114.09	1.00 (referent)	0.78
Yes	18	8.50	211.77	1.25 (1.05–1.49)		28	22.75	123.08	1.08 (0.64–1.81)	
Dysuria (self-reported)										
No	588	346.00	169.94	1.00 (referent)	<0.0001	353	311.00	113.51	1.00 (referent)	0.44
Yes	5	2.50	200.00	1.18 (1.09–1.28)		13	8.00	162.50	1.43 (0.58–3.54)	
Circumcised										
No	356	243.25	146.35	1.00 (referent)	<0.0001	207	181.25	114.21	1.00 (referent)	0.94
Yes	237	105.25	225.18	1.54 (1.32–1.79)		159	137.75	115.43	1.01 (0.78–1.32)	
Enrollment syphilis status										
Negative	552	330.75	166.89	1.00 (referent)	0.01	332	289.25	114.78	1.00 (referent)	0.98
RPR and TPPA Positive	41	17.75	230.99	1.38 (1.08–1.78)		34	29.75	114.29	1.00 (0.64–1.55)	
HSV-2 status										
Persistent Negative	259	165.00	156.97	1.00 (referent)	0.004	48	32.25	148.84	1.00 (referent)	0.09
Enrollment Indeterminate	104	70.75	147.00	0.94 (0.75–1.16)		45	37.75	119.21	0.80 (0.50–1.28)	
Prevalent Positive or	230	112.75	203.99	1.30 (1.10–1.54)		273	249.00	109.64	0.74 (0.53–1.03)	

* Only evaluated in sexually active individuals.

^a py represents person-years.

Table 5

Adjusted risk of HR-HPV clearance

	HIV-negative		HIV-positive	
	adj RR (95% CI)	P-value	adj RR (95% CI)	P-value
Age (years)				
15–24	1.00 (referent)	0.86	1.00 (referent)	0.15
25–29	0.93 (0.76–1.13)		0.82 (0.57–1.19)	
30–35	1.05 (0.85–1.30)		1.19 (0.81–1.74)	
>35	0.97 (0.75–1.25)		1.17 (0.77–1.78)	
Occupation				
Non-wage	1.00 (referent)	0.37	1.00 (referent)	0.08
Wage	0.93 (0.79–1.09)		0.79 (0.61–1.03)	
Marital Status				
Married	1.00 (referent)	0.04	-----	
Not Married	0.76 (0.59–0.98)		-----	
Non-marital relationships				
No	-----		1.00 (referent)	0.02
Yes	-----		1.43 (1.06–1.92)	
Genital ulcer disease (self-reported)				
No	-----		1.00 (referent)	0.07
Yes	-----		0.71 (0.49–1.02)	
Urethral discharge (self-reported)				
No	1.00 (referent)	0.02	-----	
Yes	1.35 (1.06–1.73)		-----	
Dysuria (self-reported)				
No	1.00 (referent)	0.03	-----	
Yes	0.68 (0.49–0.96)		-----	
Circumcised				
No	1.00 (referent)	<0.0001	-----	
Yes	1.48 (1.26–1.74)		-----	
Enrollment syphilis status				
Negative	1.00 (referent)	0.37	-----	
RPR and TPPA Positive	1.14 (0.85–1.53)		-----	
HSV-2 status				
Persistent Negative	1.00 (referent)	0.06	1.00 (referent)	0.94
Enrollment Indeterminate	0.96 (0.78–1.18)		0.80 (0.48–1.34)	
Prevalent Positive or Seroconverter	1.20 (1.01–1.44)		0.94 (0.66–1.34)	