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The association between cervical HPV infection and HIV acquisition among women in Zimbabwe

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Abstract

Background—The prevalence of HPV is higher among HIV+ women, but the prevalence of HPV prior to HIV acquisition has not been carefully evaluated.

Objective—This study evaluated whether HPV infection is independently associated with heterosexual HIV acquisition in a cohort of Zimbabwean women.

Design—Case-control study nested within a large multi-center cohort study (HC-HIV).

Methods—Cases consisted of Zimbabwean women with incident HIV infection observed during follow-up (n=145). HIV-uninfected controls were selected and matched to cases (n=446). The prevalence of cervical HPV infections was compared at the visit prior to HIV infection in the cases and at the same follow-up visit in the matched controls.

Results—The odds of acquiring HIV were 2.4 times higher in women with prior cervical HPV infection after adjustment for behavioral and biologic risk factors. There was no statistically significant difference in the risk of HIV acquisition between women infected with high versus low risk HPV types. Loss of detection of at least one HPV DNA type was significantly associated with HIV acquisition (OR =5.4 [95%CI, 2.9–9.9] (p<.0001).

Conclusion—Cervical HPV infection is associated with HIV acquisition among women residing in a region with a high prevalence of both infections. Further studies are required to evaluate whether the observed association is causal.

Keywords

HPV; heterosexual HIV transmission; HIV prevention; cervical HPV; STI

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Introduction

Human papillomavirus (HPV) infection is one of the most prevalent sexually transmitted infections (STIs) worldwide. More than 100 types of HPV have been identified, with more than 40 known to infect the genital tract. Studies have conclusively shown that infection of the cervix, anus, and penis with certain types of HPV (high risk, or oncogenic types) is associated with development of epithelial lesions and cancers of the female and male anogenital tract [1–4].

HIV co-infection has been shown to increase the detection and persistence of HPV infection and the severity of its associated cervical lesions [5–8] but little is known about the effect of HPV infection on HIV acquisition. A recent study conducted among men who have sex with men found that having an anal infection with at least two HPV types was associated with HIV seroconversion HR=3.5, [95% CI, 1.2–10.6] (p = 0.002) [9]. These observations are consistent with a large literature which consistently demonstrates an association between other sexually transmitted infections (STIs) and HIV acquisition [10–12].

Cervical HPV infection could theoretically enhance HIV acquisition among uninfected women by recruiting an increased number of HIV target cells to the genital mucosa. Although HPV does not produce ulcerative genital lesions or exudates, eventual recruitment of T lymphocytes to the genital epithelium is required to clear the infection. One study found that HPV-associated dysplastic cervical lesions are associated with an increased number of CD4 + T cells when compared to normal cervical epithelium [13], though few studies have examined the CD4+ T-cell infiltrate in non-neoplastic, HPV-infected tissues. Because HPV, like most other intracellular viral infections, requires activated T-cells to elicit an effective cell-mediated immune response, it is biologically plausible that HPV infection enhances a woman's susceptibility to HIV acquisition by exposing target cells to HIV in male ejaculate.

Both HIV and HPV infections are highly prevalent in Zimbabwe. In 2008 the WHO estimated that 18% of adults living in Zimbabwe are infected with HIV nationwide, with estimates as high as 35% for urban centers and 57% for the highest risk populations (e.g. female sex workers) [14]. It is estimated that 53% of HIV-infected Zimbabweans are women. Among Zimbabwean women, cervical cancer is the most common malignancy, with an incidence of 40–50 per 100 000 [15]. For women 25 to 55 years old attending primary-care clinics in the Harare region, the prevalence of HPV was estimated to be 47.2%. Of women screened in that study, 53% were HIV seropositive. The prevalence of HPV was higher in HIV positive than HIV negative women (64.3% vs. 27.6% ($p<0.001$)) [16].

This study examines whether pre-existing cervical HPV infection is independently associated with HIV acquisition infection among Zimbabwean women participating in the Hormonal Contraception and Risk of HIV Acquisition (HC-HIV) Study.

Methods

i. Study Subjects

We conducted a case-control study nested within a multi-center prospective cohort study, the HC-HIV study, conducted in Zimbabwe, Thailand and Uganda, described elsewhere in detail [17]. Here we included only participants from Zimbabwe. Briefly, between November 1999 and January 2004, women were enrolled and followed at four family planning and maternal and child health clinics in Chitungwiza and Harare—urban and peri-urban areas of Zimbabwe. Participants were sexually active women, ages 18–35 years, HIV-uninfected, with no history of injection drug use or blood transfusions within 3 months, and were not

pregnant. Participants had either used hormonal contraception, a non-hormonal method of contraception, or no contraceptive method for at least 3 months. At the screening visit, women received pretest HIV counseling and provided blood for HIV testing. Women returned within 15 days for test results and possible enrollment.

Of the 4692 women recruited in Zimbabwe, 2296 were enrolled. Of the remaining women, 1787 women were ineligible because they were HIV-infected. These women were counseled and referred for ongoing medical care.

ii. Study Design

Cases were the 154 Zimbabwean participants with incident HIV infections from the parent study. Controls included 479 HIV-negative participants. When possible, four controls were selected per case and matched on time in study, age group, and a composite STI/genital tract infection variable (some cases only had 2–3 controls that satisfied the matching criteria). The variable indicating time in study was defined as months between the enrollment visit and the index visit (t0) among the cases (i.e., the first HIV PCR-positive visit) +/− 2 months. The age groups were 18–20, 20–24, 25–29, and 30–35 years. The composite STI/genital tract infection variable was set to 1 if a participant was infected with *C. trachomatis, N. gonorrhoeae* or bacterial vaginosis (BV) at either the index visit or the previous visit. The composite STI variable was set to 0 for women negative for all three infections at both visits. Most women in this category were BV positive only. Prevalence of HPV infection at the visit preceding the index visit (t-1) among cases was compared between women who acquired HIV and matched controls.

iii. Data Collection Procedures

At enrollment, eligible women received a standardized interview in Shona (the local language) which included data on demographics, sexual behavior, contraceptive use, and reproductive health history. A standardized physical exam was conducted by study clinicians including a pelvic exam with collection of vaginal and cervical specimens. HIV risk reduction counseling including condom use, and free hormonal contraception and condoms were provided to participants. Vaginal infections diagnosed syndromically or by microscopy, and genital ulcers suspected to be syphilis or chancroid, were treated immediately on-site. Participants subsequently diagnosed with chlamydia, gonorrhea or syphilis by laboratory testing were recalled for treatment. Women found to have STIs including chlamydia, gonorrhea or syphilis were treated with antibiotic therapy, and offered partner treatment, according to the standard of care and WHO guidelines.

Standard follow-up visits were conducted every 12 weeks for 15–24 months. Mean follow-up was 21.9 months. Follow-up procedures were similar to those at enrollment including administration of a detailed interview, collection of blood specimens (for HIV-1, syphilis, and HSV-2), and a physical exam including collection of cervical and vaginal samples. Retention at study close was 88% [17].

This research was approved by the institutional review boards of the Medical Research Council of Zimbabwe, The University of California San Francisco, and Johns Hopkins University. All women provided written informed consent prior to participation.

iv. Laboratory Methods

All participants were HIV-uninfected at enrollment (determined by ELISA). Blood was collected for HIV testing at quarterly follow-up visits and positive ELISA or rapid tests were confirmed by Western blot or polymerase chain reaction (PCR). HIV DNA PCR was used as the final arbiter of infection status. For confirmed incident HIV infections, HIV PCR was

performed serially on banked specimens from previous visits. The visit at which HIV was first detected by HIV DNA PCR [17] is considered the index visit for this analysis.

Cervical specimens were collected at each follow-up visit using a large swab provided in the Roche Amplicor sampling packet. Swabs were placed in the endocervix and rotated 3–5 times before being removed and vigorously agitated in the Amplicor specimen transport medium and then discarded. Specimens were processed for CT/NG testing (COBAS Amplicor, Roche Diagnostics, Indianapolis, IN) by addition of 1mL of Roche Amplicor specimen diluent. All residual material remaining after CT/NG testing was stored at −80°C. A 250 μl aliquot was removed for HPV testing and DNA was extracted using Qiagen Blood Kits on the MDx Biorobot (Qiagen, Germantown, MD). PCR; the PGMY 09/11 L1 consensus primer system was used for HPV detection (HPV Linear Array, Roche Diagnostics, Indianapolis, IN) [18]. Type specific infection was determined using hybridization with probes for 37 HPV types. High-risk HPV types were defined as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and low-risk HPV types were defined as 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 81, 82, 82 subtype (IS39), 83, 84, and 89 (CP6108). A human β-globin gene amplification was used as an internal control for DNA quality; samples negative for β-globin were classified as missing HPV data. Laboratory staff members were masked to the HIV status of the participant.

HPV testing was done at two time points; 1) at the visit in which HIV was first detected by HIV PCR (index visit) (t0), and 2) at the visit prior to the index visit (last visit where the case was HIV-negative by HIV PCR) (t-1).

Vaginal swabs were collected in saline for KOH whiff test and wet mount microscopy to identify yeast buds or pseudohyphae, motile trichomonads, or clue cells. Bacterial vaginosis was diagnosed based on Amsel criteria.

HSV-2 serostatus was determined by a type-specific serological IgG antibody enzyme-linked immunosorbent assay (ELISA; Focus Technologies, USA). Women were considered to be HSV-2 seropositive for this analysis if they were seropositive at the t-1 visit.

v. Behavioral Risk Measures

Based on the HC-HIV primary study analyses [17], several composite variables were created to represent highly correlated sexual behaviors. *Participant behavioral risk* consisted of 3 variables based on participant behavior during the previous 3 months: reporting either having multiple sex partners, a new sex partner, and/or engaging in commercial sex. For this analysis, these were combined into a composite dichotomous (yes/no) variable. *Primary partner risk* was defined as the participant reporting having a partner with HIV, urethral discharge, weight loss, nights spent away from home, and/or having sex with a female sex worker. Participants who responded “yes” to any of these questions were categorized as having primary partner risk. Additional measures of sexual behaviors during the previous three months included coital frequency and the percent of coital acts unprotected by a condom.

vi. Analysis

While this study is nested in a long-term cohort study, we are evaluating data from only one 3-month interval in the cohort (e.g., the visit prior to and at first HIV detection). We used data from the baseline survey for all time-independent variables. For time-varying variables, including contraceptive use, we used the updated data collected at the t-1 or t0 visit. Nine cases and 33 controls were excluded from the analysis due to missing data in one or more of the final model covariates, leaving an analytic dataset of 145 cases and 446 controls.

Detection of HPV DNA at the visit prior to HIV-infection (t-1) was evaluated as a risk factor for HIV acquisition by comparing HPV infection status between cases (HIV infected) and controls (HIV uninfected). Any HPV infection type at t-1 was the primary exposure of interest. In addition the 37 specific types of HPV were also considered.

We examined composite HPV exposure variables based on visits t-1: infection with at least one high risk HPV type, infection with any low risk HPV type but no high risk types, or no HPV infection (reference category). A three category variable based on infection status at t-1 and t0 was defined by the categories: loss of detection of any infection(s), only persistently detectable infection(s), and no HPV infection. Persistently detectable HPV infection was defined as positive with the same type-specific HPV(s) at the two consecutive visits (+/+). Loss of HPV detectability was defined as positive for a specific type at t-1 and negative for the same HPV type at t0 (+/−).

Univariate analyses comparing cases and controls were conducted for all covariates of interest. Multivariate analyses were done using a matched conditional logistic regression model adjusted for the presence of other STIs (HSV-2, syphilis, *T. vaginalis, N. gonorrhoeae* and *C. trachomatis*), other genital tract infections (bacterial vaginosis and candidiasis), condom use, hormonal contraceptive use, and composite measures of participant and participant's partner behavioral risk. Covariates that were considered *a priori* to be potential confounders and covariates that were associated with HIV ($p \leq 0.05$) in bivariable models were assessed for confounding by adding them to the multivariable model individually: if any of the HPV-HIV effect measures changed by 15% or more, the covariate was retained in the final multivariate model. Each HPV risk factor was then added individually as a single predictor to the model. All analyses were performed using SAS Version 9.1 (SAS Institute, Cary NC).

Results

The mean age of study participants at time of enrollment was 25 years. At enrollment, cases were more likely than controls to have 3 or more lifetime sexual partners, to have never married, to be polygamous, divorced or widowed and were less likely to be living with their primary partner (Table 1). At the t-1 visit cases were less likely than controls to be using hormonal contraception and were more likely than controls to have high primary partner risk. There were no statistically significant differences between cases and controls in our measures of participant behavioral risk, unprotected sex, or primary partner circumcision status at the t-1 visit. There was no baseline difference between cases and controls in years of education.

i. HPV Prevalence

The median number of days between the t0 and t-1 visit was 80 for cases and 81 days for controls. All 37 HPV types were found in the cohort. The prevalence of HPV at the t-1 visit (when all women were HIV negative) was 48.7% (63.4% and 44.4% among HIV-positive cases and HIV-negative controls, respectively). At t-1, the most prevalent HPV types were: HPV 16 (8.8%), 35 (6.3%), 51 (5.1%), 52 (5.4%) 58 (7.6%) and 68 (5.3%). All other types were found in <5% of the cohort at that visit. Among HPV positive women, the prevalence of multiple genotype infection was 43%, with a median number of types per positive sample of 2 (interquartile range 1–3).

ii. Association between HPV and HIV Acquisition

In multivariate analysis (Table 2), the odds ratio for HIV acquisition among women with any HPV infection (at t-1) was 2.4 [95% CI, 1.5 – 4.0] after controlling for behavioral and

biologic covariates. Also having at least 1 high risk HPV type, and having only low risk HPV type(s) at the t-1 visit, were both independently associated with HIV acquisition. Increased risk of subsequent HIV infection was also associated with infection with *C. trachomatis* or *T. vaginalis*, candidiasis and HSV2 at the t-1 visit.

Women with a single HPV infection have 1.8 [95% CI, 1.0–3.3] times the odds of acquiring HIV as those with no infections, which was only marginally significant. However we found strong evidence that having multiple HPV infections was independently associated with HIV acquisition: the odds of HIV acquisition among women with 2 HPV infections was 2.9 [95% CI, 1.4–5.9] while women with 4 or more infections had an OR of 5.6 [95% CI, 2.5–12.9] (Table 3). The mean number of infections for the controls was 2.0±1.5 (median 1.0 (1.0–8.0)) whereas the mean number of infections for cases was 2.7±2.3 (median 2.0 (1.0–12.0)).

Among women with any HPV infection at t-1, loss of detection of any HPV type was strongly associated with HIV acquisition compared to persistent detection of all types OR=5.4 [95% CI,2.9–9.9] after controlling for biologic and behavioral risk factors. Persistent detection of all HPV types, however, was not significantly associated with HIV acquisition (Table 4).

Discussion

In this study, cervical HPV infection was associated with a 2.4-fold increased risk of HIV acquisition. While these findings indicate that cervical HPV infection may increase susceptibility to sexual HIV acquisition, further studies will be required to determine causality.

The association between other sexually transmitted viral and bacterial infections and HIV acquisition has a history of interpretative difficulties [19]. By virtue of shared transmission risks, there are justifiable concerns that positive associations merely reflect residual confounding by unmeasured sexual risk behaviors. On the other hand, the ulcerative and highly inflammatory sequelae of these infections provide biologically plausible mechanisms supporting a true increased susceptibility to HIV among STI co-infected individuals. These same caveats also apply for understanding a potential causal association between HPV infection and HIV acquisition.

HIV-positive men are well-known to have a higher prevalence of anal and oral HPV infection [20]. In addition, recent data from our group confirms a statistically significant increase in prevalence of HPV infection in penile swabs from HIV-positive compared to HIV-negative men (74% and 62%, respectively), and a much higher rate of multiple genotype HPV infection [R. Gray, P. Gravitt, unpublished data], a risk factor for HIV acquisition in our analysis. While a per-sex-act transmission probability for HPV has not been estimated, natural history data suggest up to 40% probability of HPV transmission [21]. Compared to the 0.07 – 0.82% per-sex-act transmission of HIV [22] [23] [24], it is likely that men who are HPV and HIV co-infected will transmit the HPV infections more rapidly to a susceptible female partner. In relatively short term follow-up, this may be reflected by a higher cross-sectional prevalence of HPV among women who later acquire HIV from the same partner. Given that our study tested for HPV no earlier than 3 months prior to HIV acquisition, we cannot rule out the possibility of residual confounding as a possible explanation for our observations.

However, there are biologically plausible mechanisms to suggest that HPV infection could increase HIV susceptibility and our observations are consistent with at least one of these mechanisms. Although HPV has evolved elaborate mechanisms of immune evasion [24–26] these mechanisms merely delay, rather than prevent a rigorous immune response against

HPV infection. Histologic evidence from regressing warts has documented that a robust CD4+ and CD8+ T cell response, and a pro-inflammatory milieu, including upregulation of interferons, is necessary to clear HPV infections [25].

We thus reasoned that the influx of CD4+ lymphocytes (HIV target cells) prior to loss of HPV detection could transiently increase the risk for HIV acquisition, assuming that loss of HPV detection represents an immunologic response to the viral infection. Our data would support this hypothesis. HIV acquisition was significantly higher in women with HPV loss of detection in the interval concomitant with HIV acquisition, compared to women who were HPV positive at t-1 but with persistently detectable HPV infections during the same interval. Although this is certainly supportive of a potential causal association between HPV loss of detection and HIV acquisition, a possible mechanism of reverse causation cannot be ruled out. That is, it is not possible to differentiate whether loss of HPV detection preceded HIV acquisition or vice-versa. It is possible that the cytokine storm that occurs during acute HIV infection reverses HPV-induced immune anergy. The pro-inflammatory response to HIV infection could theoretically alter the cervical microenvironment to provide the necessary co-stimulatory molecules needed to facilitate immune mediated loss of detection of HPV infections. It is of interest that 45% of HPV infections that contribute to loss of detectability exposures during the interval of HIV acquisition ‘reappear’ within the next 6-month period (P. Gravitt, unpublished data). More work will be needed to fully understand the immunologic events proximal to HPV loss of detection and HIV acquisition.

A recent study suggested that having multiple anal HPV infections was associated with HIV acquisition among men who have sex with men [9]. Our study also demonstrated that multiple cervical HPV infections are an independent risk factor for female HIV acquisition. Chin-Hong, et al. suggested that the association with multiple, rather than single, HPV infections may reflect a higher number of anal lesions, which are friable and potentially increasing the accessibility of HIV to stromally located T-cells and macrophages [9]. Indeed, an elevated number of CD4+ cells have been demonstrated in high-grade cervical dysplasia [13]. Our study did not have reliable information regarding the prevalence of cervical lesions, although infection with multiple types could similarly be a marker for multiple lesions. Nevertheless, given that HPV loss of detection would be less likely than persistent detection to be associated with lesions, our data suggests that the association between HPV and HIV acquisition, if real, could occur in the absence of lesions as was recently demonstrated for HSV [26].

Our study had a number of strengths. First, the study population represents a general population of women, rather than a specific high-risk group, so the study is generalizable to larger populations of women. The study is prospective and thus considers the effect of pre-existing HPV infection on subsequent HIV infection. The use of HIV DNA PCR at serial visits in this study allowed for more precise identification of the timing of HIV acquisition.

There are also limitations to this study. The complexity of HPV biology makes the study of HPV and HIV acquisition challenging. The definition of HPV persistent detectability and loss of detectability in this study was dictated by the study visit intervals rather than by HPV biology, and therefore the exact temporal relationship between HPV loss of detectability and HIV acquisition cannot be established.

This study suggests that HPV may be a risk factor for HIV acquisition. If this relationship is found to be causal, given the high prevalence of HPV in countries like Zimbabwe, treatment and prevention of HPV could potentially impact HIV transmission rates. However, at present it is unknown whether excisional treatment of HPV mediated lesions (LEEP or cryotherapy), or even vaccination against HPV, can reduce HIV transmission. This study

suggests that while HPV infection may increase risk of HIV acquisition, the type of HPV was not important. This is in contrast to results from another recent study among a similar population of Zimbabwean women, which found that high- but not low risk HPV infection increased HIV risk [27] and a study among heterosexual men in South Africa which found an association between penile infection with high risk and not low risk HPV types and HIV infection [28]. Although the explanations for these discordant observations is not clear, if multiple high and low risk HPV types are risk factors for HIV acquisition, currently available vaccines would be insufficient to reduce HIV acquisition.

Additional research is needed to corroborate HPV as a risk factor for HIV acquisition before reaching conclusions about a causal relationship between HPV and HIV acquisition. However, if found to be true, in countries such as Zimbabwe with high HPV prevalence and high HIV incidence, decreasing the burden of HPV could potentially have a significant impact on HIV acquisition among women.

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Table 1

Univariate association of demographic and sexual behavior exposures between cases (women who acquired HIV) and controls (women who remained HIV negative) at enrollment (A) and at the visit prior to HIV infection (t-1) (B).

		Cases N(%) (N=145)	Controls N(%) (N=446)	OR (95% CI)
A				***
	Age (years)			
	18–19	14 (9.6%)	42 (9.4%)	
	20–24	62 (42.8%)	186 (41.7%)	
	25–29	44 (30.3%)	141 (31.6%)	
	30–36	25 (17.2%)	77 (17.3%)	
	Years of education			
	≤ 9 years	47 (32.4%)	150 (33.6%)	1.0
	> 9 (some secondary school)	98 (67.6%)	296 (66.4%)	0.98 [0.6–1.5]
	Marital status			
	Never married	8 (5.5%)	7 (1.6%)	4.1 [1.4–11.9]
	Monogamous marriage	109 (75.2%)	389 (87.2%)	1.0
	Polygamous marriage	14 (9.7%)	22 (4.9%)	2.1 [1.1–4.2]
	Separated/divorced/widowed	14 (9.7%)	28 (6.3%)	1.6 [0.8–3.2]
	Living with partner			
	Yes	120(82.8%)	410 (91.9%)	0.4[0.2–0.8]
	No	25 (17.2%)	36 (8.1%)	1.0
	Lifetime # sexual partners			
	≤3	122 (84.1%)	405 (90.8%)	1.0
	>3	23 (15.9%)	41 (9.2%)	2.0 [1.1–3.5]
B	**Use of hormonal contraception since last visit**			
	Yes	49 (33.8%)	107 (24.0%)	1.0
	No	96 (66.2%)	339 (76.0%)	1.8 [1.2–2.8]
	Participant risk behavior†			
	Low	139 (96.0%)	437 (98.0%)	1.0
	High	1 (0.7%)	4 (0.9%)	0.7 [0.1–7.4]
	Primary partner risk†			
	Low	48 (33.1%)	203 (45.5%)	1.0
	High	97 (66.9%)	243 (54.5%)	1.7 [1.2–2.6]
	Any unprotected sex with any partner			
	No	50 (34.5%)	121 (27.1%)	1.0
	Yes	95 (65.5%)	325 (72.9%)	0.7 [0.5–1.1]
	Primary partner circumcised			
	Yes	14 (9.7%)	31 (7.0%)	1.0
	No	122 (84.1%)	374 (83.6%)	1.5 [0.7–3.1]
	Don’t Know	7 (4.8%)	41(9.2%)	0.6 [0.2–1.3]

[***] These variables were used for matching cases and controls, so calculation of ORs would have been inappropriate.

[†] Several composite variables were created to represent highly correlated sexual behaviors. *Participant behavioral risk* consisted of 3 variables based on behavior during the previous 3 months: reporting either having multiple sex partners, or a new sex partner(s) or engaging in commercial sex. *Primary partner risk* was defined as the participant reporting having a partner with HIV, urethral discharge, weight loss, nights spent away from home, or having sex with a female sex worker.

Table 2

Univariate and adjusted odds ratios[†] for HIV acquisition by sexually transmitted infections or abnormal vaginal flora at the visit prior to HIV acquisition (t-1).

	Cases N(%) (N=145)	Controls N(%) (N=446)	OR (95% CI)	aOR[*] (95% CI)
HPV				
Negative	53 (36.6%)	248 (55.6%)	1.00	1.0
Any type positive	92 (63.4%)	198 (44.4%)	2.7 [1.7–4.1]	2.4 [1.5 – 4.0]
HPV				
Negative	53 (36.6%)	248 (55.6%)	1.00	1.0
Any HR-positive	71 (49.0%)	148 (33.2%)	2.7 [1.7–4.3]	2.3 [1.4 – 3.9]
Only LR-positive	21 (14.5%)	50 (11.2%)	2.5 [1.3–4.6]	2.8 [1.3 – 5.9]
N. gonorrheoae				
PCR Negative	129(89.0%)	428 (96.0%)	1.0	1.0
PCR Positive	16 (11.0%)	18 (4.0%)	2.9 [1.4–6.0]	2.3 [0.93 – 5.5]
C. trachomatis				
PCR Negative	134 (92.4%)	433 (97.1%)	1.0	1.0
PCR Positive	11 (7.6%)	13 (2.9%)	2.7 [1.1–6.3]	3.4 [1.2 – 9.5]
Candidiasis				
Negative	112 (77.2%)	385 (86.3%)	1.0	1.0
Positive	33 (22.8%)	61 (13.7%)	1.8 [1.1–2.9]	2.1 [1.2 – 3.8]
Bacterial vaginosis				
Negative	92 (63.4%)	295 (66.1%)	1.0	1.0
Positive	53 (36.6%)	151 (33.9%)	1.2 [0.8–1.9]	1.3 [0.8 – 2.4]
Trichomoniasis				
Negative	133 (91.7%)	436 (97.8%)	1.0	1.0
Positive	12 (8.3%)	10 (2.2%)	4.4 [1.7–11.5]	4.6 [1.6 – 13.6]
HSV-2 seropositive				
Negative	24 (16.6%)	208 (46.6%)	1.0	1.0
Positive	121 (83.4%)	238 (53.4%)	4.4 [2.7–7.2]	4.5 [2.7 – 7.8]

[†]Two HPV models were explored separately and are separated by double lines. Both models were developed using conditional logistic regression and were mutually adjusted for other STI covariates as well as the confounders listed below.

[*]Controlled for living with partner, primary partner risk, hormonal contraception and condom use

Table 3

Univariate and adjusted odds ratios for HIV acquisition by HPV multiple infection status at t-1.

	Cases N(%) (N=145)	Controls N(%) (N=446)	OR (95% CI)	aOR* (95% CI)
Number of HPV genotypes				
0	53 (36.6%)	248 (55.6%)	1.00	1.0
1	34 (23.4%)	104 (23.3%)	2.0 [1.2–3.3]	1.8 [1.0–3.3]
2	22 (15.2%)	49 (11.0%)	2.9 [1.5– 5.4]	2.9 [1.4–5.9]
3	12 (8.3%)	21 (4.7%)	3.0 [1.4–6.5]	2.5 [1.0–6.0]
≥4	24 (16.6%)	24 (5.4%)	5.9 [2.9–12.0]	5.6 [2.5–12.9]

*Controlled for living with partner, primary partner risk, hormonal contraception, condom use, HSV-2, Gonorrhoeae, Chlamydia, Trichomoniasis, BV, and Candida

Table 4

Adjusted odds ratios for HIV acquisition by HPV type-specific loss of detection or persistent detection from t-1 to t0.

	Cases N(%) (N=145)	Controls N(%) (N=446)	OR (95% CI)	aOR* (95% CI)
HPV negative	53 (36.8)	248 (56.2)	1.0	1.0
Loss of detection of any HPV type	70 (48.6)	84 (19.0)	5.3 [3.2–9.0]	5.4 [2.9–9.9]
Persistent detection of all HPV types	21 (14.6)	109 (24.7)	1.12 [0.6–2.0]	0.97 [0.51–1.85]

*Controlled for living with partner, primary partner risk, hormonal contraception, condom use, HSV-2, Gonorrhea, Chlamydia, Trichomoniasis, BV, and Candida