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Influence of HIV-1 and/or HIV-2 infection and CD4 count on cervical HPV DNA detection in women from Senegal, West Africa

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Abstract

Background—HIV infection is associated with greater risk of precancerous lesions and cervical cancer in women. However, several factors remain unclarified regarding the association between HIV infection and HPV detection, especially among those with HIV type 2 versus type 1 infection and severely immunocompromised persons.

Objectives—To evaluate HPV overall and type-specific detection among HIV-infected and uninfected women in Senegal.

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Competing interests

None declared.

Ethical approval

This study was approved by the Human Subjects Committees of the University of Washington and the Université Cheikh Anta Diop, Dakar/Ministry of Health.

Study Design—Detection of HPV DNA for 38 genotypes in cervical swabs using PCR-based methods was evaluated in HIV-positive (n=467) and HIV-negative (n=2139) women participating in studies in Senegal. Among HIV-1 and/or HIV-2 positive women, CD4 counts were assessed. Adjusted multivariable prevalence ratios (PR) were calculated.

Results—The prevalence of any HPV DNA and multiple HPV types was greater among HIV-infected individuals (78.2% and 62.3%, respectively) compared with HIV-negative women (27.1% and 11.6%). This trend was also seen for HPV types 16 and 18 (13.1% and 10.9%) compared to HIV-negative women (2.2% and 1.7%). HIV-infected women with CD4 cell counts less than 200 cells/μl had a higher likelihood of any HPV detection (PR_a 1.30; 95% CI 1.07–1.59), multiple HPV types (PR_a 1.52; 95% CI 1.14–2.01), and HPV-16 (PR_a 9.00; 95% CI 1.66–48.67), but not HPV-18 (PR_a 1.20, 95% CI 0.45–3.24) compared to those with CD4 counts 500 cells/μl or above.

Conclusion—HIV-infected women, especially those most severely immunocompromised, are more likely to harbor HPV. Measures to prevent initial HPV infection and subsequent development of cervical cancer through focused screening efforts should be implemented in these high risk populations.

Background

Infection with high-risk human papillomavirus (HR-HPV) is a universally recognized risk factor for cervical cancer and for cervical intraepithelial neoplasia, its precursor lesions^{1–3}. Of the known oncogenic types, HPV types 16 and 18 are responsible for up to 70% of cancers^{4–6}. HPV detection is considerably more common among women infected with the human immunodeficiency virus (HIV) compared to uninfected women^{7–14}. Furthermore, women infected with HIV are known to be at increased risk of HPV-associated disease, including cervical intraepithelial neoplasia (CIN)^{15,16}. HIV-induced immunosuppression may limit the immune system's ability to effectively eliminate HPV infection, leaving an individual at greater risk of developing CIN or cancer⁹. However, the exact etiologic pathway between HIV-induced immunosuppression, HPV infection, and its clinical sequelae has yet to be clearly established.

CD4 lymphocyte count is an important prognostic marker of risk for AIDS-associated clinical events and death, and CD4 cell counts of less than 200 cells per μl indicate severe immuno-suppression¹⁷. It is hypothesized that HIV-induced immunosuppression, through the lowering of CD4 T-cells, may increase the risk of HPV detection, HPV persistence, and subsequent development of cervical neoplasia^{18–21}. Limited data exist to confirm the relationship between measurement of CD4 count and HPV detection, however, and the information that does exist has not been entirely corroborative^{10,18,22–25}. In addition, little is known concerning the effect of CD4 count on HPV type-specific detection, including the most commonly-detected oncogenic types, HPV-16 and HPV-18.

Objectives

Our objective was to investigate the relationship between overall and type-specific HPV detection and HIV infection, with special focus on the effect of CD4 count on HPV detection among HIV-infected individuals.

Study Design

Data collection

This study consisted of cross-sectional baseline data from women who participated in research studies in Dakar, Senegal between 2000 and 2010, and included women presenting to an outpatient primary care clinic (Pikine) considered at low risk for sexually transmitted infections including HIV (HIV prevalence below 1%) and an outpatient infectious disease clinic (Fann) serving high risk populations (HIV prevalence >10%)²⁶. The aims of these studies were to investigate the epidemiology of HPV and its association with HIV-associated immune responses, DNA methylation, and cancer control approaches, as described previously^{27,28}. All participants provided written informed consent upon enrollment, under approval of the Human Subjects Committees of the University of Washington and the Université Cheikh Anta Diop, Dakar/Ministry of Health. Subjects were older than 15 years of age, and were excluded from participation if they were pregnant or did not have an intact cervix. Upon enrollment, a structured interview soliciting demographic and medical information (including reproductive and sexual history) was given. Medical and gynecologic exams were carried out, and blood samples were collected to determine patients' HIV-1 and HIV-2 status, and for lymphocyte subset analysis. Cervical swab samples were obtained for HPV detection.

HIV Serology and Lymphocyte Analysis

Serologic assays for HIV-1 and HIV-2 were performed on patients' baseline blood samples using a two-test sequence, as previously described^{26,27,29,30}. First, serum samples were tested for the presence of either HIV-1 or HIV-2 antibodies (HIV 1/2 EIA; Sanofi Diagnostics Pasteur or Determine HIV 1/2; Abbott Laboratories, Abbott Park, IL). A second confirmatory immunoassay was then applied to distinguish HIV-1 and HIV-2 antibodies (Multispot, Genetic Systems; ImmunoComb BiSpot, Orgenics, Yavne, Israel). Blood samples were used to calculate CD4 lymphocyte data for HIV-positive participants, measured per microliter of blood (cells/ μ l). Cell counts were performed using the fluorescence activated cell sorter (FACS) Count analyzer (Becton-Dickinson Biosciences, San Jose, CA, USA).

HPV DNA Detection

Specimens were tested for HPV DNA with a polymerase-chain-reaction (PCR) assay using MY09 and MY11 L1 consensus primers, with amplification of the cellular β -globin gene as a control³¹. Genomic DNA was isolated from 200 μ l of the digested samples using QIAamp DNA blood mini kit according to the manufacturer's protocol (Qiagen, Valencia, CA) for most samples. DNA isolation was performed on 43 (1.6%) samples without the Qiagen assay due to protocol differences between studies. For these samples, digestion was performed with 20 μ g/ml proteinase K at 37°C for 1 h, and genomic DNA was ethanol precipitated from 200 μ l of the digested samples. The presence of HPV DNA was determined by PCR amplification followed by dot blot hybridization for all samples, and positive samples were subsequently genotyped for type-specific HPV. Of all samples, 16 (0.6%) were genotyped using the Roche line blot, which detected 27 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and

84)³². The vast majority of samples were tested using the Roche Linear array assay (2000–2005)³³ or a liquid bead microarray assay^{34,35} (2005–2010), which detected 37 types, with the addition of HPV types 61, 62, 64, 67, 69, 70, 71, 72, 81, IS39 (a subtype of HPV 82), and CP6108 (also known as HPV 89).

Statistical Analysis

We evaluated the association between HIV serostatus (positive versus negative) and overall and type-specific HPV detection (HPV types 16 and 18). Among HIV-positive women, the associations between HIV type (HIV-1 vs. HIV-2 vs. dual HIV-1/HIV-2), CD4 count, anti-retrovirus (ARV) treatment, and HPV detection were evaluated. Log binomial regression (with robust variance) was used for all analyses, and results were reported as prevalence ratios as HPV detection was common among women. Cervical HPV DNA types were classified according to their oncogenic potential, with HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 classified as high-risk types³⁴.

Potential confounding factors were chosen *a priori*, and included age, age at first sexual intercourse, lifetime number of sexual partners (continuous) as well as smoking, study clinic, and use of Qiagen DNA purification (dichotomous)^{29,35}. To reduce the possibility of confounding, women who reported undertaking commercial sex work (n=108) were excluded from this analysis. Univariate and multivariable models were used to assess the relationship between HIV status, HIV type, CD4 count, ARV use, and HPV detection. STATA version 11.0 was used (STATA Corporation, College Station, TX).

Results

The median age of women was 43 years (range 15 to 84). Compared to HIV-uninfected women (n=2139), women with HIV-1 and/or HIV-2 infection (n=467) were more likely to be younger, be widowed or separated, initiated sex at a younger age, and had a greater number of lifetime sexual partners (Table 1).

HIV-infected women were more likely to have any HPV detected (78.2% vs. 27.1%, $p<0.001$), to have high-risk HPV detected (61.5% vs. 15.2%, $p<0.001$), and to have multiple types of HPV detected (62.3% vs. 11.6%, $p<0.001$) than HIV-uninfected women. The most common types of high-risk HPV detected among HIV-positive individuals were types 58 (18.8%), 52 (17.3%), 16 (13.1%), 18 (10.9%), 35 (9.6%), and 45 (9.6%) (Figure 1). Among HIV-negative women, the mostly commonly detected high-risk HPV types included types 58 (3.0%), 52 (2.3%), 16 (2.2%), 33 (2.0%), 31 (1.9%), and 18 (1.7%). After adjustment for confounders, HIV-positive women were more likely to have any HPV (PR_a : 2.28, 95% CI 2.01–2.58), high-risk HPV (PR_a : 3.17, 95% CI 2.66–3.79), and multiple HPV types (PR_a : 4.51, 95% CI 3.71–5.49) detected compared to HIV-negative women (Table 2). HIV-positive women were also more likely to have HPV type 16 and HPV type 18 (HPV-16 PR_a : 4.76, 95% CI 2.63–8.63; HPV-18 PR_a : 5.77, 95% CI 3.47–9.60). Upon stratification by age, similar patterns of HPV detection were observed in both younger (<35 years old) and older women, with HPV increased in those with HIV infection, although HPV prevalence was lower in women above age 35. Among all women with detectable HPV, those with HIV infection had a higher proportion of high risk types (78.6% vs 56.1%) and multiple types

(79.7% vs 42.8%) than HIV-negative women. Similarly, the proportion of HPV type 16 (16.7% versus 7.9%) and type 18 (14.0% versus 6.2%) was also higher among HIV-positive women than HIV-negative women with detectable HPV.

Of the 467 HIV-positive subjects included, 373 were infected with HIV-1, 78 with HIV-2, and 16 were dually infected with HIV-1 and HIV-2. Of those with HIV types -1, -2, and dual infection, the average (SD) CD4 count was 357.6 (291.0), 535.7 (337.9), and 268.4 (267.2) cells/ μ l, respectively. HIV-1 (79.6%), HIV-2 (70.5%) and dually (81.3%) infected women were similarly likely to have any HPV, multiple types of HPV, and HPV-16 detected (Table 3). HIV-2 infected women were less likely to be infected with high risk HPV (PR=0.69, 95% CI 0.54–0.90) and HPV-18 (PR=0.32, 95% CI 0.10–1.00) compared to HIV-1 infected women, although these differences were attenuated with adjustment for other covariates including age and CD4 count. Dually HIV-1 and HIV-2 infected women were similar to HIV-1 infected women with regards to HPV prevalence.

HIV-positive study participants were evaluated by level of immune function, as measured by CD4 count. Amongst HIV-infected women, HPV DNA was detected in 67.1% of women with CD4 counts greater than or equal to 500 cells/ μ l, 68.7% of those with CD4 counts between 200 and 499 cells/ μ l, and 90.7% of women with CD4 counts less than 200 cells/ μ l. Compared to those with CD4 counts measuring 500 cells/ μ l or above, women with CD4 counts below 200 cells/ μ l were more likely to have any HPV (PR_a: 1.30, 95% CI 1.07–1.59), multiple HPV types (PR_a: 1.52, 95% CI 1.14–2.01), and high-risk HPV detected (PR_a: 1.67, 95% CI 1.25–2.25). Severely immunosuppressed women were also more likely to have HPV-16 (PR_a: 9.00, 95% CI 1.66–48.7) but not HPV-18 (PR_a: 1.20, 95% CI 0.45–3.24) DNA detected. Among all HIV-positive women with detectable HPV, those with CD4 less than 200 cells/ μ l had a higher proportion of high-risk HPV compared to those with CD4 levels at 500 cells/ μ l or above (87.2% versus 66.0%). Compared to women with CD4 counts 500 cells/ μ l, women who were moderately immunosuppressed (CD4 counts 200–499 cells/ μ l) were not at appreciably greater risk of any HPV, multiple HPV, or high-risk HPV detection. Compared to HIV-infected women who were not taking ARV at the time of study, and controlling for CD4 count and other potential confounders, those taking ARV showed no significant difference in HPV overall, high-risk, multiple, or HPV-16 or HPV-18 type-specific detection.

Discussion

Among our large sample of HIV-1 and/or HIV-2 positive and HIV-negative women, we observed positive associations between HIV infection and HPV DNA detection, multiple types, and high risk HPV types, especially HPV-16 and HPV-18. These results are comparable to findings from other African settings, and are likely due to increased exposure to HPV in occlusions after high-risk sexual activity, increased susceptibility to HPV due to HIV-associated immunosuppression, and the potential for re-activation of latent HPV virus due to immunosuppression^{12,33,36–40}. Moreover, among HIV-infected women in our sample, those with highest levels of immunosuppression (CD4 < 200 cells/ μ l) were most likely to have any, multiple, and high-risk types of HPV detected. This finding is consistent with most, although not all, of other studies evaluating this association^{10,18,22–25}.

HPV type 16 and 18 detection was more likely among HIV-positive compared to HIV-negative women in our sample. Further, we observed a higher proportion of HPV-16 infections among HIV-positive women with detectable HPV compared to HIV-negative women with detectable HPV. We also noted a greater likelihood of HPV-16 among HIV-infected women with lowest CD4 counts, although the broad confidence interval of this estimate limits any definitive interpretation. Another study has noted a similar trend between low CD4 count and HPV-16 detection⁴¹, although others have not^{23,24}. A study by Firnhaber *et al* conducted in South Africa found that, even among women with negative cytology, a significant association between CD4 count lower than 200 cells/μl and HPV-16 detection existed⁴¹. Firnhaber's finding among women with normal cytology may imply that the association between CD4 count and HPV-16 detection is present even after assuming that prevalent HPV-16 infections are likely to be over-represented in our cross-sectional design. This suggests that HIV-infected women, at least to some degree through the mechanism of CD4-cell depletion, are at increased risk of HPV infection, including the most oncogenic HPV types. One possible explanation for these findings is that reactivation of latent HPV viral infections occurs more frequently in the presence of HIV infection, especially with severe immunosuppression^{38,41}. From a biological perspective, HIV-mediated susceptibility to HPV infection may occur through several direct and indirect pathways, including the induction of pro-inflammatory cytokines leading to an interference of normal inflammatory responses to HPV⁴².

An increased risk of high-risk HPV infection may warn of a predisposition to adverse cervical events among HIV-infected women, especially those most immunocompromised. Indeed, HIV-positive women have been shown to have both higher rates of CIN prevalence and of low-grade lesion persistence^{43,44}. One recent report has even provided a biological mechanism for increased cervical carcinogenesis via HIV infection through the mediation of COX-2 expression, a molecule linked to cervical carcinogenesis⁴⁵.

The most common high-risk genotypes among HIV-infected women in the present study were 58, 61, 52, 62 and 53, then 16. This finding is not unlike other studies in Africa, which note that non-16 and -18 HR-HPV types were most common among HIV-infected women^{10,13,46,47}. A meta-analysis by Clifford *et al* showed that HPV types 52 and 58 accounted for a high proportion of all HR-HPV infections among HIV-infected African women¹². Among HIV-negative women from our study, a number of HPV types including 54, 61, 58, 53, 62, 83, and 52 were detected more often than 16, a finding that is supported by another recent study in Senegal among HIV-negative women >35 years of age⁴⁸. As the currently available HPV vaccines only protect against types 16 and 18, a high prevalence of other high-risk types could infer an added risk of non-16 and -18 cervical carcinogenesis⁴⁹⁻⁵¹.

Few other studies have evaluated HPV overall and HPV type-specific detection by HIV type (1 versus 2)^{14,52}. Both HIV-1 and HIV-2, when compared to HIV-negative women, were associated with a greater likelihood of HPV detection in our study, as was also found by Langley *et al*⁵². HIV-2 infection is known to cause a slower loss of CD4 cells and lower risk of immunosuppression than HIV-1, and HIV-2 infected individuals generally demonstrate a more effective and sustained T-cell immunity²⁷. These biological differences may suggest

that a higher amount of circulating antiviral T-cells would help HIV-2 infected women to better control new or existing HPV infections, and in our study, the prevalence of high risk HPV types, including HPV-18, was lower in HIV-2 compared to HIV-1 infected women. However, after taking into account subject age and CD4 counts, HIV-1 and HIV-2 infected individuals were similar with respect to HPV prevalence.

Several limitations in our study should be noted. Information on ARV treatment was only available for a portion (39.6%) of subjects. This missingness was primarily due to protocol differences between studies contributing data to this analysis; ARV treatment information was not routinely collected for two of the four studies included. However, among women with known ARV status, and accounting for CD4 count, HPV detection was similar between those with and without ARV use. Furthermore, several recent studies have suggested that there is limited effect of ARV on HPV viral persistence^{36,41,53,54}, indicating that it is possible to interpret associations between HPV and HIV infection outside of the context of ARV. In addition, because HIV viral load data was not available for many of the HIV-infected women in this analysis, the influence of virologic suppression due to ART was not assessed. Finally, it was beyond the scope of our aims to evaluate the association between HIV, HPV, and cervical abnormalities identified by cytology in the current analysis.

Our most noteworthy findings are that HIV-positive women were more likely to have HPV DNA detected, including the most common high-risk types. Among HIV-infected women, those most severely immunosuppressed had the greatest likelihood of HPV detection and were most likely to have multiple HPV types detected. High risk HPV types, especially HPV-16, were detected in both HIV-1 and HIV-2 infected women with severe immunosuppression, most likely due to their increased persistence and/or rate of reactivation. Future studies among HIV-positive individuals could serve to clarify the impact of this increased HPV infection on the future development of cervical neoplasia and cancer. Further, the higher HPV prevalence and increased proportion of infections with multiple types among HIV-infected women does indicate that differential cervical cancer screening approaches may be warranted among HIV-infected women.

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Abbreviations

HPV	human papillomavirus
HIV	human immunodeficiency virus

HR-HPV	high-risk human papillomavirus
DNA	deoxyribonucleic acid
CIN	cervical intraepithelial neoplasia
ARV	antiretroviral

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Figure 1.

Type-specific prevalence of HPV among HIV-positive and HIV-negative women^a.

NOTE: Although this graphic contains a color, black-and-white reproduction is intended.

Table 1

Socio-demographic, sexual behavior and disease characteristics of Senegalese study population, by HIV status^a

	<u>HIV-1 and/or HIV-2 positive</u>	<u>HIV-negative</u>
	N (%)	N (%)
Total	467	2139
Clinic		
Pikine primary care clinic	16 (3.4)	1668 (78.0)
Fann ID clinic	451 (96.6)	471 (22.0)
Age (years)		
<35	179 (38.3)	411 (19.2)
35–39	82 (17.6)	297 (13.9)
40–44	85 (18.2)	370 (17.3)
45	121 (25.9)	1061 (49.6)
Marital status		
Monogamously married	139 (30.1)	850 (39.9)
Polygamously married	98 (21.2)	925 (43.4)
Never married	27 (5.8)	74 (3.5)
Separated/Divorced	74 (16)	145 (6.8)
Widowed	124 (26.8)	136 (6.4)
Alcohol use	10 (3.3)	21 (1.1)
Smoker	6 (1.9)	14 (0.8)
No contraceptive use	408 (88.7)	1752 (82.3)
Education		
None	261 (56.4)	1121 (52.8)
Primary	136 (29.4)	643 (30.3)
Secondary or above	66 (14.3)	361 (17.0)
Age at first sex (years)		
<15	157 (33.6)	579 (27.1)
16–20	215 (46.0)	1042 (48.7)
21	95 (20.3)	518 (24.2)
Lifetime partners		
1	205 (46.3)	1372 (65.3)
2–5	228 (51.5)	702 (33.4)
>5	10 (2.3)	26 (1.2)
HIV type		
HIV-1	373 (79.9)	---
HIV-2	78 (16.7)	---
HIV 1/2	16 (3.4)	---
CD4 count (cells/μl)		
500	79 (29.9)	---
200–499	99 (37.5)	---

	<u>HIV-1 and/or HIV-2 positive</u>	<u>HIV-negative</u>
	N (%)	N (%)
<200	86 (32.9)	---
ARV treatment	86 (81.9)	---

^aIncludes the following missing values: marital status (14), alcohol use (450), smoker (447), no contraceptive use (17), education (18), age at first sex (62), lifetime partners (63), CD4 count among HIV-infected women (203), and ARV treatment among HIV-infected women (282)

Table 2

Prevalence ratio (PR) estimates for the association of HIV-infection (HIV-1 and/or HIV-2 positive versus HIV-negative) with the detection of overall and type-specific HPV infections.

	HIV-1 and/or HIV-2 positive n (%)	HIV-negative n (%)	Univariable PR	95% CI	Multivariable PR ^a	95% CI
All women	N=467	N=2139				
Any HPV	365 (78.2)	579 (27.1)	2.89	2.65–3.14	2.28	2.01–2.58
High-risk HPV	287 (61.5)	325 (15.2)	4.04	3.58–4.58	3.17	2.66–3.79
Multiple HPV types	291 (62.3)	248 (11.6)	5.37	4.69–6.16	4.51	3.71–5.49
HPV 16	61 (13.1)	46 (2.2)	6.07	4.20–8.79	4.76	2.63–8.63
HPV 18	51 (10.9)	36 (1.7)	6.49	4.29–9.82	5.77	3.47–9.60
Among women <35 years	N=179	N=411				
Any HPV	166 (92.7)	125 (30.4)	3.04	2.57–3.59	2.43	1.97–2.99
High-risk HPV	131 (73.2)	73 (17.8)	4.10	3.24–5.20	3.25	2.45–4.31
Multiple HPV types	132 (73.7)	47 (11.4)	6.42	4.80–8.59	5.27	3.71–7.49
HPV 16	26 (14.5)	8 (1.9)	7.43	3.42–16.15	7.62	2.08–27.98
HPV 18	25 (14.0)	7 (1.7)	8.17	3.59–18.60	7.75	2.97–20.21
Among women ≥35 years	N=288	N=1728				
Any HPV	199 (69.1)	454 (26.3)	2.82	2.54–3.13	2.21	1.90–2.58
High-risk HPV	156 (54.2)	252 (14.6)	3.98	3.43–4.63	3.21	2.58–4.01
Multiple HPV types	159 (55.2)	201 (11.6)	5.09	4.33–5.98	4.11	3.24–5.22
HPV 16	35 (12.2)	38 (2.2)	5.93	3.82–9.20	4.15	2.02–9.05
HPV 18	26 (9.0)	29 (1.7)	5.77	3.45–9.63	5.17	2.74–9.76

^a Adjusted for age (continuous), age at first sex (continuous), lifetime sexual partners (continuous), use of qiaagen column for DNA processing, and study clinic.

Table 3
Prevalence ratio estimates for the association of HIV infection and detection of overall and type-specific HPV infection (n=467).

	Any HPV			Multiple HPV infections			High risk HPV			HPV16			HPV18		
	Univariable PR (95% CI)	Multivariable PR (95% CI)		Univariable PR (95% CI)	Multivariable PR (95% CI)		Univariable PR (95% CI)	Multivariable PR (95% CI)		Univariable PR (95% CI)	Multivariable PR (95% CI)		Univariable PR (95% CI)	Multivariable PR (95% CI)	
HIV type^a															
HIV-1	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
HIV-2	0.89 (0.76–1.03)	0.90 (0.70–1.16)		0.82 (0.66–1.03)	0.93 (0.66–1.31)		0.69 (0.54–0.90)	0.90 (0.63–1.30)		1.25 (0.69–2.24)	2.15 (0.81–5.73)		0.32 (0.10–1.00)	0.46 (0.06–3.61)	
Dual HIV-1/2	1.02 (0.80–1.30)	1.02 (0.75–1.39)		1.07 (0.76–1.51)	1.07 (0.75–1.53)		1.06 (0.76–1.49)	1.13 (0.79–1.63)		1.52 (0.53–4.37)	NA ^e		1.55 (0.54–4.47)	NA ^e	
CD4 count (cells/μl)^{b,c}															
500	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
200–499	1.02 (0.83–1.26)	1.00 (0.80–1.25)		1.17 (0.87–1.59)	1.06 (0.78–1.46)		1.23 (0.91–1.67)	1.27 (0.93–1.74)		1.60 (0.30–8.52)	0.82 (0.11–6.27)		0.77 (0.27–2.23)	0.93 (0.33–2.66)	
<200	1.35 (1.14–1.60)	1.30 (1.07–1.59)		1.79 (1.37–2.32)	1.52 (1.14–2.01)		1.78 (1.36–2.34)	1.67 (1.25–2.25)		8.73 (2.09–36.4)	9.00 (1.66–48.7)		1.20 (0.45–3.24)	1.53 (0.58–4.03)	
ARV treatment^d															
No	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Yes	1.06 (0.89–1.26)	0.97 (0.76–1.23)		1.35 (1.06–1.73)	1.09 (0.79–1.51)		1.31 (1.04–1.65)	1.10 (0.78–1.54)		1.92 (0.81–4.57)	1.10 (0.43–2.86)		1.14 (0.50–2.59)	1.26 (0.42–3.79)	

^a Adjusted for age (continuous), age at first sex (continuous), lifetime sexual partners (continuous), use of Qiagen column for DNA processing, CD4 count and study clinic. Excludes 203 missing values for CD4 count.

^b Adjusted for age (continuous), age at first sex (continuous), lifetime sexual partners (continuous), use of Qiagen column for DNA processing, and study clinic.

^c Wald test values for CD4 count trend in multivariable analysis: HPV-positive (p=0.005), HPV multiple infection (p=0.002), High risk HPV (p<0.001), HPV16 (p=0.005), HPV18 (p=0.599)

^d Adjusted for age (continuous), age at first sex (continuous), lifetime sexual partners (continuous), use of Qiagen column for DNA processing, study clinic, and CD4 count (continuous). Excludes 282 missing values for ARV treatment and 203 missing values for CD4 count.

^e Multivariable analysis not conducted due to small number of HPV type-specific infections in dual HIV-1/2 infected women