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Multitype infections with human papillomavirus: Impact of HIV coinfection

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Abstract

Background—Human immunodeficiency virus (HIV) infection predisposes women to genital coinfection with human papillomaviruses. Concurrent infection with multiple HPV types has been documented, but its frequency, correlates, and impact on development of precancer are poorly defined in HIV seropositive women.

Methods—HIV seropositive women and seronegative comparison women were enrolled in a cohort study and followed every six months 1994–2006. Cervicovaginal lavage samples were tested for HPV types using polymerase chain reaction amplification with MY09/MY11 consensus

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primers followed by hybridization with consensus and HPV type-specific probes. Analyses were performed using generalized estimating equations.

Results—Multitype HPV infections were found in 594/2543 (23%) HIV seropositive women and 49/895 seronegative women (5%, P < 0.0001). Compared to HPV uninfected women, those with multiple concurrent HPV infections were more likely to be younger, nonwhite, and current smokers, with lower CD4 counts and HIV RNA levels. The average proportion of women with multitype HPV infections across visits was 21% in HIV seropositive women and 3% in seronegative women (P <0.0001). Compared to infection with one oncogenic HPV type, multitype concurrent infection with at least one other HPV type at baseline did not measurably increase the risk of ever having CIN3+ detected during follow-up (O.R. 0.80, 95% C.I. 0.32, 2.03, P = 0.65).

Conclusion—Concurrent multitype HPV infection is common in HIV seropositive women and frequency rises as CD4 count declines, but multitype infection does not increase precancer risk.

Short summary

Compared to women seronegative for human immunodeficiency virus (HIV), HIV seropositive women have more concurrent multitype coinfections with human papillomavirus but multitype infection does not increase risk for cervical precancer.

Keywords

human immunodeficiency virus; human papillomavirus; cervical intraepithelial neoplasia

Introduction

Genital infections with human papillomaviruses (HPVs) are dynamic, usually occurring soon after acquisition of a new sexual partner and regressing after immune recognition yet occasionally persisting for years. Infection with a specific HPV type may reappear after becoming undetectable despite sexual abstinence (1). HPVs are categorized into types based on DNA sequence homology, and some women harbor multiple concurrent HPV types.

Multitype HPV infections may act synergistically to promote cervical oncogenesis (2). However, other studies indicate that the HPV types involved in multitype infections have similar rates of persistence (3), which appears to be a critical factor in the development of cervical cancer (4). HPV types do not appear to exhibit clustering; this suggests that multitype infections result from independent events (5). Multitype HPV infection has been associated with increased risk of subsequent acquisition of additional HPV of another type, although it is not clear how immune defects or immunogenetic or sexual risk factors contribute to this (6). Thus, multitype HPV infection may be a biomarker of a general susceptibility to infection by genital HPV.

Among women with the human immunodeficiency virus-1 (HIV), HPV coinfections are common and closely linked to risk for high grade cervical disease. How concurrent multitype HPV infections modulate risk for cervical intraepithelial neoplasia (CIN) is less well studied. HIV seropositive women are more likely than seronegative women to carry multitype HPV infections, more than a third of prevalent HPV infections have been reported

to involve multiple HPV types, and HIV seropositive women with more than 10 individual HPV types have been reported (7). Almost 60% of HIV seropositive African women have detectible concurrent multitype infections (8).

Different HPV types do not appear to infect the same cells. When analyzed using laser capture microdissection (LCM), most individual HPV lesions including essentially all high grade lesions appear to result from infections with single HPV types within a clonal population, even in women with multiple concurrent HPV infections (9, 10). In contrast, de Vuyst compared exfoliated cervical samples to biopsies showing CIN2 or CIN3 (CIN2+) and found that many cervical lesions in HIV seropositive women with HPV16/18 infections also contained other types; their study did not include LCM or longitudinal results describing longer-term CIN2+ risk (11).

We set out to update results on the prevalence and frequency of multitype HPV infections and the biologic susceptibility this represents among HIV seropositive and comparison seronegative women in a U.S. cohort study beyond what can be accounted for by CD4 count and HIV RNA levels. We also attempted to assess the impact of multitype infection on CIN3+ risk among HIV seropositive women; we focused on those with normal cervicovaginal cytology to assess risk for incident rather than prevalent lesions.

Materials and Methods

The Women's Interagency HIV Study (WIHS) is a U.S. multicenter cohort study of health outcomes among HIV seropositive women. WIHS also enrolled HIV seronegative comparison women. Enrollment began on October 1, 1994 at six study consortia and over time has enrolled 4,068 women, including those enrolled during an expansions from 2001–2002. Follow-up continued through March 31, 2006. The study was designed to ensure that the cohort reflected the evolving HIV epidemic in U.S. women (12, 13). At each site, human subjects committees reviewed and approved the study, and all participants gave written informed consent.

Women were followed for the development of CIN using single-slide conventional Pap smears obtained every six months using spatula and brush. Slides were read centrally according to the 1991 Bethesda System for cervicovaginal diagnosis. Colposcopy was required by study protocol for any epithelial cytologic abnormality, including those read as atypical squamous cells of undetermined significance (ASCUS). HPV testing was not used in clinical management. Biopsy results were interpreted at local sites and were not centrally reviewed. Abnormal results were categorized as CIN1, CIN2, CIN3, adenocarcinoma in situ (AIS), or cancer; the composite outcome CIN3+ incorporated CIN3, AIS, and cancer. Post-colposcopy histology results, such as those from loop excision or hysterectomy, were abstracted from medical records.

At each visit, the cervix and vagina were lavaged with 10 ml of saline, and an aliquot was assayed for HPV using described protocols (7). Briefly, MY09/MY11 consensus primers polymerase chain reaction (PCR) amplification was followed by hybridization with consensus and HPV type-specific probes able to detect more than 40 different individual

HPV types. Successful amplification of the β-globin gene during PCR was used to assess specimen adequacy; β-globin negative specimens were excluded. Results were classified as defined by the International Association for Research on Cancer, including any oncogenic HPV type (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), for any type, and negative for HPV.

The baseline visit was the first with adequate HPV results. Demographic, behavioral, and clinical variables at baseline were compared using Pearson's Chi-square tests. The association of HIV/CD4+ cell counts with the probability of having multiple HPV infections was assessed with generalized estimation equation (GEE) models for the binary outcome accounting for repeated observations over time. Both unadjusted and adjusted models were fitted, with covariates including age, race, smoking, number of male sexual partners in the six months before testing, recruitment period, and antiretroviral therapy (ART) in the six months before testing. The average number of HPV types over all person-visits was compared between the HIV+ and HIV seronegative participants with the GEE model for continuous outcomes. We also studied the association of CIN3+ risk among women with initial negative cervicovaginal cytology with various combinations of multiple HPV infections at baseline, including any two nononcogenic, any oncogenic HPV with at least one other any HPV, any two oncogenic, HPV16 with any other HPV, and HPV16 with any other oncogenic HPV. The proportionalities of the Cox models were checked. Unadjusted and adjusted models were fitted for the Cox models and the proportionality assumption of the Cox models was assessed. All the statistical tests were two-sided. $P = 0.05$ was used as the significance level. SAS 9.3 was used for all analyses.

Results

Table 1 shows the demographic and HIV-related medical characteristics of the 895 HIV seronegative and 2543 seropositive women included at the time of their first visit with HPV results. Compared to HPV uninfected women, those with multiple concurrent HPV infections were more likely to be younger, nonwhite, current smokers, and from the earlier recruitment cohort but not more likely to have more recent sexual partners. They also had lower CD4 counts and HIV RNA levels. Similar associations were found when women with multitype HPV infections were compared to those with single HPV infections. Median follow-up was 8.4 years.

Table 2 further explores the relationship of immune status and HPV infection using baseline data. Of 2543 HIV seropositive women who met inclusion criteria, 1210 (48%) had no detectable HPV and 1333 (52%) had at least one HPV infection, with oncogenic HPV infections in 716 (28% of all participants) and only non-oncogenic infections in 617 (24%). Of 895 HIV seronegative women included in the study, 93 (10%) had oncogenic HPV infections and 106 (12%) had non-oncogenic HPV. Thus, 199 (22%) had at least one HPV infection, and 696 (78%) had no HPV ($P < 0.0001$ vs HIV seropositive women). The proportion of women with oncogenic HPV at baseline increased with lower CD4 counts ($P_{trend} < 0.0001$).

Table 2 also shows that multitype HPV infections were more common among HIV seropositive women, found in 95 (12%) with CD4 >500 cells/cmm, 247 (23%) with CD4 200–500 cells/cmm, and 252 (42%) with CD4 <200/cmm. Furthermore, GEE multivariate models, showed that after adjustment for age, ethnicity, smoking, number of recent sexual partners, and recruitment cohort, HIV infection and CD4 stratum remained significant correlates of concurrent infection with two or more HPV types. (Table 3). Results from a model including only HIV seropositive women found that controlling for HAART use had no meaningful impact on these associations (Supplemental Table 1).

Clinicians may know only that an HPV test result is positive without knowing the number of types present. Among HIV seronegative women with at least one HPV type detected, the prevalence of at least one additional type was 17% (95% CI 15%, 20%). This prevalence increased with HIV co-infection and declining CD4 count: for CD4 count >500, multitype HPV infection among those with HPV was 30% (0.28, 0.33), for CD4 count 200–500 was 41% (39%, 44%), and for CD4 <200 was 55% (53%, 58%). Among these women with at least one HPV infection, this association of multitype concurrent infection with HIV status and declining CD4 count persisted after adjustment for other correlates. Compared to HIV seronegative women with at least one HPV infection, the odds ratio for multitype concurrent infection among HIV seropositive women with CD4 counts >500/cmm was 2.3 (95% C.I. 1.8, 2.8, P < 0.0001), among those with CD4 counts 200–500/cmm was 3.7 (95% C.I. 2.9–4.6, P < 0.0001), and among those with CD4 counts <200/cmm was 6.7 (95% C.I. 5.3, 8.4, P < 0.0001).

We also examined whether baseline infection with HPV was a risk factor (i.e., biomarker) of greater risk for subsequent incident “new detection” of additional HPV types, independent of host immune status and other cofactors. Specifically, we used Cox models that incorporated the presence of HPV(s) at baseline (i.e., 0, 1, 2, 3+ types) as the primary exposure variable and optimally controlled for the combined effects of CD4 and HIV RNA levels (i.e., 13 separate levels), as well as other covariates as above. As hypothesized, the data showed a higher risk of incident detection of a new HPV type amongst women with at least one pre-existing HPV infection (hazard ratio [HR] = 1.6 (95% C.I. 1.4, 1.8) p<0.0001), although the risk did not increase with the number of pre-existing HPV

The primary significance of HPV infection is the risk for cervical cancer and precancer that follows infection with oncogenic HPV types. Compared to infection with one oncogenic HPV type, multitype concurrent infection with at least one other HPV type at baseline did not measurably increase the risk of ever having CIN3+ detected during follow-up (O.R. 0.80, 95% C.I. 0.32, 2.03, P = 0.65). Similarly, concomitant baseline infection with two oncogenic HPV types did not increase CIN3+ risk (O.R. 1.06, 95% C.I. 0.35, 3.24, P = 0.91 for the comparison with infection with any one oncogenic HPV infection). Further, concomitant infection with other oncogenic types did not appear to modify the CIN3+ risk associated with infection by HPV 16, the most oncogenic type, regardless of the oncogenicity of the coinfecting type (for HPV16 infection with at least one other HPV type H.R. 0.32, 95% C.I. 0.05, 1.93, P = 0.21 and for HPV16 infection with any other oncogenic type 0.34, 95% C.I. 0.04, 3.04, P = 0.33). In a Cox model adjusting for other risk factors,

concurrent multitype oncogenic HPV infection was not associated with higher risk for CIN3+ than single oncogenic HPV infection (H.R. 0.84, 95% C.I. 0.23, 3.04, P = 0.79).

Across all visits, the average proportion of women with multitype HPV infections at each visit was 21% in HIV seropositive women and 3% in seronegative women (P <0.0001). Fig. 1 shows how the number of HPV types found per woman varied across type by severity of HIV infection. In multivariable analyses using GEE, differences among various CD4 strata were significant (P < 0.0001). The number of HPV types fell across time in all strata, including in HIV seronegative women (slope −0.009, 95% C.I. −0.012, −0.005, P < 0.0001). The slope of decline was similar for women with CD4 counts >500/cmm but declined more sharply for HIV seropositive women with CD4 counts <200/cmm and those with counts 200–500/cmm, who began with much higher average numbers of HPV types detected. Later visit number remained negatively associated with number of HPV types detected after further adjustment for age, ethnicity, smoking, and number of recent sexual partners. To address the possibility that improving CD4 levels within each CD4 stratum (e.g., moving closer to 200 CD4 cells/cmm in the CD4<200 stratum) over time might explain these findings, we further adjusted for CD4 count as a continuous variable within each CD4 stratum, and showed this had no impact on the results.

Discussion

Concurrent multitype HPV infections are present in 15–20% of HIV seropositive. The frequency of multitype HPV infections rises as HIV-related immunosuppression becomes more severe; among women with CD4 counts <200/cmm, multitype HPV infections are present in more than 40% and multiple oncogenic HPV types are found in 20%. Other demographic factors did not appear to impact risk for multitype HPV infection after controlling for immunosuppression.

Among women infected with high risk HPV types, most notably HPV16, coinfection with lower risk types did not modify risk for CIN3+ in women with normal baseline Pap results. The hierarchy of oncogenicity observed across cases of HPV infection, with HPV16 the most oncogenic type, appears to pertain when multiple concurrent infections are present. This reinforces the finding that most HPV lesions appear to result from infections with single HPV types (9, 10). Although having multiple HPV types and so multiple independent lesion might be expected to raise CIN3+ risk simply by increasing the number of independent lesions, our results confirm that type-specific oncogenicity rather than number of infections determines CIN3+ risk.

Women with at least one baselineHPV infection have a higher risk of subsequent incident detection of additional new HPV types, although risk did not increase further with a more pre-existing HPV types. This suggests that the presence of one or more HPV types is a biomarker for individual susceptibility to HPV, and possibly for the social and sexual behaviors that influence population-level viral mixing behaviors. These findings might be expected if a single HPV adequately characterizes the associations between HPV and host immune genes and sexual risk factors.

After controlling for CD4 count and other factors, we did not find that HAART use altered risk for multitype HPV infection. This does not indicate that antiretroviral therapy has no effect but rather that any impact of HAART is likely mediated through its beneficial impact on CD4 count.

Multitype infections have been associated with multiple lesions, only some of which are high grade. The accuracy of colposcopy in precise lesion grading has been questioned (14). Because they are more likely to harbor concurrent multitype infections, HIV seropositive women undergoing colposcopy may need more biopsies to identify high grade lesions. However, the number of HPV infections per woman in this study declined across time, and declines were steeper in women with more severe immunocompromise, as reflected by lower CD4 count. This likely reflects the effects of screening for and treatment of HPV-related lesions, though we cannot exclude the possibility of residual confounding due to age and aspects of immune status not beyond HIV RNA and CD4 levels.

The high rate of multitype infections among HIV seropositive women, especially those with CD4 counts <200/cmm, has clinical implications. Commercially available HPV assays do not provide information on individual types, reporting positivity for any of 12–14 high risk types or reporting separately infection with types 16, 18, and sometimes 45 versus a pooled other category. Women followed with HPV testing with these results may have clearance of one of the oncogenic types, spontaneously or after therapy, but may have persisting infections with other types. Typing beyond HPV types 16 and 18 does not appear to refine management. Nevertheless, repeated colposcopy may be required to assess HIV seropositive women with positive HPV tests, as CIN3+ lesions may be missed among multiple lesions linked to HPV types of lesser oncogenicity, such as exophytic condylomas and flat warts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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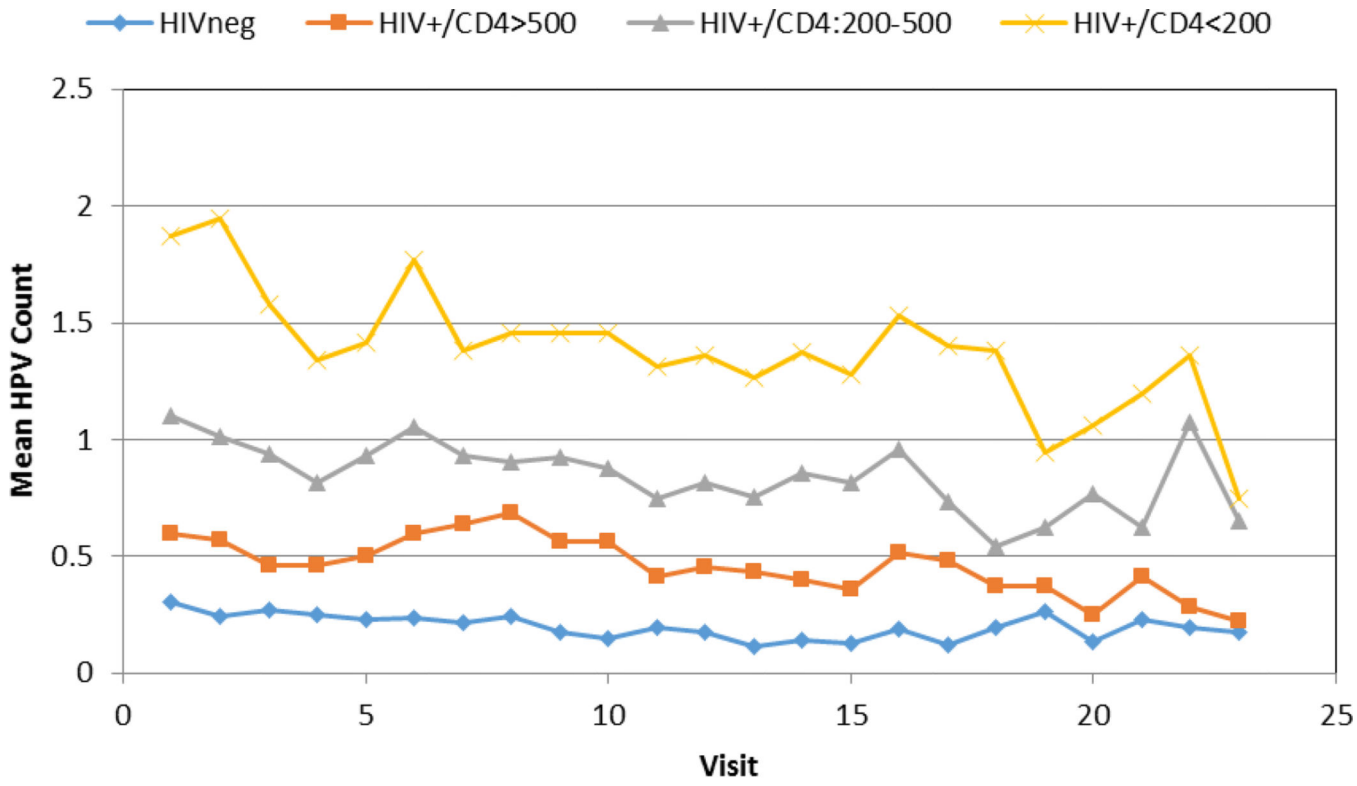

	Slope	SE	95% CI		P value
			LCL	UCL	
HIVneg	-0.009	0.002	-0.012	-0.005	<.0001
CD4>500	-0.010	0.003	-0.015	-0.004	0.0004
CD4:200-500	-0.017	0.004	-0.024	-0.009	<.0001
CD4<200	-0.031	0.007	-0.044	-0.018	<.0001

Fig. 1.

Mean number of HPV types identified across six-month visits 1994–2006. For differences among various CD4 strata, P < 0.0001) and for number of types across time including HIV seronegative women[1]

1

	Slope	SE	95% CI		P value
			LCL	UCL	
HIVneg	−0.009	0.002	−0.012	−0.005	<.0001

	Slope	SE	95% CI		P value
			LCL	UCL	
CD4>500	−0.010	0.003	−0.015	−0.004	0.0004
CD4:200–500	−0.017	0.004	−0.024	−0.009	<.0001
CD4<200	−0.031	0.007	−0.044	−0.018	<.0001

Table 1

Demographic characteristics at study baseline. N (%)

	Number of HPV Infections			P-values		
	0 (N = 1906)	**1 (N = 864)**	**2+ (N = 668)**	**Overall**	**2+ vs 0/1**	**2+ vs 0**
Age (years)				0.051	0.06	**0.03**
<30	547 (54)	255 (25)	209 (21)			
30–34	453 (55)	223 (27)	147 (18)			
35–39	426 (53)	201 (25)	177 (22)			
40–44	309 (61)	110 (22)	86 (17)			
>=45	171 (58)	75 (25)	49 (17)			
Ethnicity				**0.001**	**<.0001**	**0.0002**
White	301 (58)	149 (29)	72 (14)			
Hispanic	536 (57)	239 (26)	159 (17)			
Black	1006 (54)	449 (24)	410 (22)			
Others	63 (54)	27 (23)	27 (23)			
Smoking				**0.01**	**0.02**	**0.01**
Former/Never smoked	955 (58)	400 (24)	294 (18)			
Current smoker	947 (53)	460 (26)	373 (21)			
# of male sex partners past 6 mo				0.052	0.22	0.18
0	476 (52)	255 (28)	181 (20)			
1	1036 (56)	456 (25)	360 (19)			
2	194 (57)	71 (21)	75 (22)			
>=3	185 (60)	74 (24)	48 (16)			
Recruitment cohort				**<.0001**	**<.0001**	**<.0001**
1994–1995	1194 (51)	645 (27)	513 (22)			
2001–2002	712 (66)	219 (20)	155 (14)			
HIV/CD4+ count (cells/cmm)[1]				**<.0001**	**<.0001**	**<.0001**
HIV−	696 (78)	150 (17)	49 (5)			

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	Number of HPV Infections			P-values		
	0 (N = 1906)	**1 (N = 864)**	**2+ (N = 668)**	**Overall**	**2+ vs 0/1**	**2+ vs 0**
CD4>500	517 (64)	202 (25)	95 (12)			
CD4:200–500	493 (47)	312 (30)	247 (23)			
CD4<200	170 (28)	182 (30)	252 (42)			
HIV RNA level (copies/cmm)[1]				**<.0001**	**<.0001**	**<.0001**
HIV−	696 (78)	150 (17)	49 (5)			
<=4000	573 (60)	231 (24)	144 (15)			
4001–20,000	260 (50)	146 (28)	109 (21)			
20,001–100,000	206 (38)	177 (32)	166 (30)			
>100,000	145 (30)	149 (31)	191 (39)			
Antiretroviraluse past 6 mo[1]				0.19	0.24	0.47
No	1708 (55)	789 (26)	591 (19)			
Yes	198 (57)	75 (21)	76 (22)			

[1] Restricted to HIV seropositive women only.

Table 2

Distribution of HPV infections by HIV serostatus and CD4 lymphocyte count at baseline. N (%)

Variable	HIV− (N = 895)	HIV+				P-value 1[3]	P-value 2[4]
		Overall[1] (N = 2543)	CD4[2]>500 (N = 814)	CD4:200–500 (N = 1052)	CD4<200 (N = 604)		
HPV						**<.0001**	**<.0001**
Negative	696 (78)	1210 (48)	517 (64)	493 (47)	170 (28)		
Non-oncogenic	106 (12)	617 (24)	166 (20)	260 (25)	172 (28)		
Oncogenic	93 (10)	716 (28)	131 (16)	299 (28)	262 (43)		
# of any HPV types						**<.0001**	**<.0001**
0	696 (78)	1210 (48)	517 (64)	493 (47)	170 (28)		
1	150 (17)	714 (28)	202 (25)	312 (30)	182 (30)		
2	34 (4)	265 (10)	54 (7)	109 (10)	95 (16)		
3+	15 (2)	354 (14)	41 (5)	138 (13)	157 (26)		
# of oncogenic HPV types						**<.0001**	**<.0001**
0	802 (90)	1827 (72)	683 (84)	753 (72)	342 (57)		
1	76 (8)	467 (18)	107 (13)	204 (19)	144 (24)		
2	13 (1)	143 (6)	11 (1)	53 (5)	71 (12)		
3+	4 (0)	106 (4)	13 (2)	42 (4)	47 (8)		

[1] Because of missing CD4 count data at baseline, the overall number of HIV seropositive women is greater than the total number of women in the individual CD4 strata.

[2] Cells/cmm

[3] HIV seronegative vs all HIV seropositive (“overall”)

[4] Across three CD4 strata (>500, 200–500, <200 cells/cmm) among HIV seropositive women only.

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Table 3

Association of HIV/CD4+ cell counts on the relative odds of having multiple HPV infections[1]

Variable		OR[2]	95% CI[3]		P-value
			LCL[4]	UCL[4]	
HIV/CD4+ count (cells/cmm)	HIV− (ref)	1			**<.0001**[5]
	CD4>500	4.03	3.16	5.16	**<.0001**
	CD4:200–500	9.57	7.62	12.02	**<.0001**
	CD4<200	23.41	18.48	29.67	**<.0001**
Age (years)	<30 (ref)	1			
	30–34	0.68	0.57	0.81	<.0001
	35–39	0.64	0.53	0.77	<.0001
	40–44	0.56	0.45	0.68	<.0001
	>=45	0.51	0.40	0.64	<.0001
Race	White (ref)	1			
	Hispanic	1.14	0.90	1.45	0.28
	Black	1.78	1.44	2.19	<.0001
	Others	1.43	0.94	2.19	0.10
Smoking	Never smoked (ref)	1			
	Former smoker	0.90	0.74	1.11	0.33
	Current smoker	1.54	1.31	1.82	<.0001
# of sexual partners past 6 months	0 (ref)	1			
	1	1.25	1.10	1.41	0.001
	2	1.42	1.19	1.68	<.0001
	>=3	1.27	1.01	1.58	0.04
Recruitment cohort	Old (ref)	1			
	New	0.74	0.62	0.88	0.001

[1]Generalized estimating equation (GEE) logistic regression models were used to assess the relation of HIV and CD4+ cell count with the probability of having multiple concurrent HPV types; while accounting for other covariates, as well as repeated observations (repeated clinical visits and the multiplicity of HPV types at each visit).

[2]Odds ratio

[3] Confidence interval

[4] Lower confidence limit, upper confidence limit

[5] P-value for trend.