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Publication Date

DOI

Peer reviewed

Association of cervical precancer with human papillomavirus types other than 16 among HIV co-infected women

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Abstract

Background—HIV-seropositive women face high risk for infection with oncogenic human papillomavirus (oncHPV) types, abnormal Pap test results, and precancer, but cervical cancer risk is only modestly increased. Human papillomavirus (HPV)16 is highly oncogenic but only weakly associated with HIV status and immunosuppression, suggesting HPV16 may have a greater innate ability to evade host immune surveillance than other oncHPV types, which in turn should result in a greater relative increase in the prevalence of other oncHPV types among women with cervical precancer.

Objective—We sought to assess whether the underrepresentation of HPV16 among HIV-seropositive relative to HIV-seronegative women remains among those with cervical precancers.

Study Design—HIV-seropositive and HIV-seronegative women in the Women's Interagency HIV Study were screened for cervical intraepithelial neoplasia (CIN) grade 3 (CIN3+). DNA from >40 HPV types was detected by polymerase chain reaction in cervicovaginal lavage specimens obtained at the visit at which CIN3+ was diagnosed.

Results—HPV16 was detected in 13 (62%) of 21 HIV-seronegative women with CIN3+ but only 44 (29%) of 154 HIV-seropositive women with CIN3+ ($P = .01$). The lower prevalence of HPV16 in CIN3+ among HIV-seropositive women persisted after controlling for covariates (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.08–0.78). The prevalence of other members of the

HPV16-related alpha-9 oncHPV clade as a group was similar in HIV-infected and uninfected women with CIN3^{+} (OR, 1.02; 95% CI, 0.53–1.94). The prevalence of non-alpha-9 oncHPV types was increased in HIV-seropositive vs HIV-seronegative women with CIN3^{+} (OR, 3.9; 95% CI, 1.3–11.8).

Conclusion—The previously demonstrated increase in CIN3^{+} incidence among HIV-seropositive women is associated with lower HPV16 and higher non-alpha-9 oncHPV prevalence. This is consistent with prior reports that HIV has a weak effect on infection by HPV16 relative to other oncHPV and supports use of nonavalent HPV vaccine in HIV-seropositive women.

Keywords

Introduction

Compared with HIV-seronegative women, HIV-seropositive women face dramatically increased risks of infection with human papillomaviruses (HPVs), including oncogenic HPV (oncHPV) types.[1] They also have a higher risk of abnormal Pap test results and precancer.[2,3] However, cervical cancer risk is only modestly increased by HIV infection,[4] and the incidence of cancer after 10 years of follow-up in a US national cohort of HIV-seropositive women was not significantly higher than that in HIV-seronegative women or US women of similar age.[5]

The reasons for this discrepancy are unclear. Screening may reduce cancer risk among women in study cohorts by eliminating precursors, but treatment of cervical precancers in HIV-seropositive women often fails to result in clearance.[6] An additional possibility is that many of the abnormal Pap test findings and cervical dysplasias found in HIV-seropositive women may reflect HPV infections of moderate oncogenic potential, with relatively few related to the highly oncHPV16.

HPV16 accounts for more than half of invasive cervical cancers in the general population, as well as a marginally smaller percentage of precancers.[7] HPV16 is also more common than many less oncHPV types in HIV-seronegative but not HIV-seropositive women.[1] Using data from 2 large, independent cohort studies of HIV infection, we observed that the prevalence of HPV16 had the weakest association of any oncHPV type with HIV status and immunosuppression, as measured by CD4 count.[8] Our group and others[8,9] interpreted this relative independence of HPV16 infection from host immune status as evidence that HPV16 may have a greater innate ability to evade host immune surveillance than other oncHPV types. If correct, this innate immunoevasiveness might partly account for the high prevalence of HPV16 in the general population. Moreover, the observed modest increase in cervical cancer risk among HIV-seropositive women may be explained at least in part if HPV16, the major etiologic risk factor for cervical cancer, is less strongly released by HIV-related immunosuppression than less oncHPV types.

If HPV16 has a greater innate ability than other oncHPV types to avoid the effects of immune surveillance, then HIV-related immunosuppression should result in a greater

relative increase in the prevalence of other oncHPV types among women with cervical precancer, and the prevalence of HPV16 positivity in precancers should be lower on a relative scale. On the other hand, if non-16 oncHPV types are more common in HIV-seropositive women but HPV16 remains the driver for most oncogenic events, then the prevalence of HPV16 in precancers found in HIV-seropositive women should remain high.

To distinguish between these possibilities, we set out to assess the distribution and relative prevalence of individual HPV types among HIV-seropositive and HIV-seronegative women with cervical precancer and to assess the impact of age and other risk factors on the HPV type distribution in these women.

Materials and Methods

The Women's Interagency HIV Study (WIHS) is a US multicenter cohort study of health outcomes among HIV-seropositive women. WIHS also enrolled HIV-seronegative comparison women. Enrollment began on Oct. 3, 1994, at 6 study consortia and over time has enrolled 4068 women, including those enrolled during expansions from 2001 through 2002 and 2011 through 2012. The study was designed to ensure that the cohort reflected the evolving HIV epidemic in US women.[10,11] At each site, human subjects committees reviewed and approved the study, and all participants gave written informed consent. Follow-up continues, but this analysis includes information on histologic outcomes through March 31, 2012.

Single-slide conventional Pap smears were obtained every 6 months using spatula and brush and were read according to the 1991 Bethesda System for cervicovaginal diagnosis, with high-grade results subdivided as consistent either with moderate or with severe dysplasia. Colposcopy was required by study protocol for any epithelial cytologic abnormality, including those read as atypical squamous cells of undetermined significance. HPV testing was performed for research only and was not used in clinical management. Biopsy results were interpreted at local sites and were not centrally reviewed. Abnormal results were categorized as cervical intraepithelial neoplasia (CIN) grade 1, 2, or 3; adenocarcinoma in situ; or cancer. Postcolposcopy histology results, such as those from loop excision or hysterectomy, were abstracted from medical records.

At each visit, cervicovaginal lavage was conducted with 10 mL of saline. Protocols for semiannual HPV testing have been described previously.[2,3] Briefly, MY09/MY11 consensus primers polymerase chain reaction (PCR) amplification was followed by hybridization with consensus and HPV type-specific probes. 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 oncHPV type (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), for any type, and negative for HPV.

Preliminary data analysis examined the similarities and differences in characteristics between HIV-seropositive and HIV-seronegative cases of histologic CIN grade 3 (CIN3^{+}) at the time of diagnosis, using the *t* test to assess means, the Wilcoxon test for medians, or

the Pearson χ^2 test for proportions, as well as the Mantel extension test to assess ordinal data. Multivariate logistic regression models were used to explore the relative prevalence of each HPV type, or oncHPV phylogenetic species, by exposure factors such as HIV serostatus. These logistic regression models employed generalized estimating equation models to address multiple HPV types per woman.[12]

Results

Of the 2791 HIV-seropositive and 975 HIV-seronegative women enrolled in WIHS,CIN3^{+} was found in 154 (5.5%) HIV-seropositive and 21 (2.2%) HIV-seronegative women across all visits. Two women (both HIV seropositive) had invasive cancer; one was associated with HPV16 and HPV84, the other with HPV72 and HPV73. Table 1 presents the demographic characteristics at the time of diagnosis of CIN3^{+}. HIV-seropositive women were older (mean age 39.5 years) than HIV-seronegative women (mean age 32.8years, *P* = .0001). They also were enrolled earlier in the study and were more often current smokers.

Of the 175 CIN3^{+}, 173 (99%) had adequate HPV results, as assessed by beta-globin amplification, of which 171/173 (99%) were positive for at least 1 HPV type and 151/173 (87%) were positive for at least 1 oncHPV type. The detection rate for any oncHPV did not vary by HIV status or CD4 count (*P* = .53).

Table 2 shows how type-specific oncHPV prevalence differed between HIV-seropositive and HIV-seronegative women with adequate HPV data. Prevalence of HPV16 was 62% among the HIV-seronegative and 29% among HIV-seropositive women with CIN3^{+}, a statistically significant difference (*P* = .01) that was unaffected by adjustment for multiple covariates including age, enrollment period, smoking, lifetime number of sexual partners, and number of sex partners in the 6 months before CIN3^{+} diagnosis. After adjustment for these covariates, an apparent inverse association of HPV16 prevalence with CD4 strata using HIV-seronegative women as the referent was no longer significant. Similar results were obtained when we studied alternate endpoint definitions, which included CIN grade 2 (not shown) and cytologic high-grade squamous intraepithelial lesion subclassified as severe dysplasia (Table 3).

The lower HPV16 prevalence in CIN3^{+} from HIV-seropositive vs HIV-seronegative women did not reflect an absolute decrease in HPV16-associated CIN3^{+} risk by HIV serostatus: HPV16^{+} CIN3^{+} was found in 13 (1.3%) of 975 HIV-seronegative women and 46 (1.6%) of 2791 HIV-seropositive women followed up in WIHS. Rather, there was a net increase in non-16 oncHPV[+] CIN3^{+}.

No additional type-specific differences by HIV serostatus reached statistical significance. In exploratory analyses, we used multivariate logistic regression to study whether analysis by larger phylogenetic groups might identify additional associations, as closely related HPV types might be similarly affected by host immune surveillance. In contrast to the lower HPV16 prevalence in HIV-seropositive vs HIV-seronegative women, the prevalence in CIN3^{+} of other HPV16-related alpha-9 oncHPV clade types showed no relation with HIV status (odds ratio [OR], 1.02; 95% confidence interval [CI], 0.53–1.94; *P* = .96), and HPV

types from clades other than alpha-9 had significantly higher prevalence in CIN3^{+} in HIV-seropositive vs HIV-seronegative women with CIN3^{+} (OR, 3.88; 95% CI, 1.28–11.78; *P* = .02). Limiting analysis of non-alpha-9 types to the other important carcinogenic clade, HPV18-related alpha-7 carcinogenic HPV types showed a similar positive but nonsignificant association with HIV seropositivity (OR, 3.14; 95% CI, 0.75–13.09; *P* = .12). The comparison of alpha-7 to all non-alpha-7 carcinogenic types was of borderline significance (OR, 4.08; 95% CI, 0.90–18.5; *P* = .07).

Comment

HIV-mediated immunosuppression is associated with a disproportionate increase in the prevalence of oncHPV types other than HPV16.[8] The current study reports that these more prevalent HPV types, which account for a minority of CIN3^{+} in HIV-seronegative women, are found in most CIN3^{+} in HIV-seropositive women. HPV16 was present in 62% of HIV-seronegative women with CIN3^{+}, while 71% of HIV-seropositive women with CIN3^{+} in HIV-seropositive women tested positive for only non-16 oncHPVs. This finding of a significantly lower prevalence of HPV16, the most important oncHPV type, in HIV-seropositive women with CIN3^{+} vs HIV-seronegative women had been predicted years earlier after studies showed that HPV16 infection itself was less affected by HIV status than other oncHPV. Specifically, our group and others[8,9] had hypothesized that the relative independence of HPV16 from the effects of HIV may reflect an innate ability to avoid host immune control and, as a corollary, that other oncHPV, being more affected by impaired immunity, would be more prevalent in HIV-seropositive than HIV-seronegative women with cervical precancer.

Consistent with this, although the proportion of CIN3^{+} associated with HPV16 was lower in HIV-seropositive than HIV-seronegative women, the absolute risk of HPV16-associated CIN3^{+} did not decline. Rather, other types less associated with CIN3^{+} in HIV-seronegative women emerged. CIN3^{+} risk is higher in HIV-seropositive than HIV-seronegative women.[3] Thus the decline in the proportion of CIN3^{+} associated with HPV16 detection reflects this increase in the burden of CIN3^{+} associated with non-HPV16 oncHPVs that HIV-seropositive women face rather than an HIV-HPV molecular interaction that reduces HPV16 oncogenicity.

The high prevalence of less carcinogenic oncHPVs in CIN3^{+} among HIV-seropositive women may contribute to the relatively low risk of cervical cancer in HIV-infected women compared with other virally associated AIDS-defining malignancies; ie, either because progression is less likely or because progression is delayed, allowing more time for screening to identify lesions prior to progression to cancer. Conversely, the modest impact of HIV on cervical HPV16 may help explain the modest effects of highly active antiretroviral therapy on cervical cancer rates in HIV-seropositive women. Reconstitution of immunocompetence by highly active antiretroviral therapy should at least partially reverse the effect of HIV on type-specific HPV prevalence. Since that effect was greatest for non-16 types and least for HPV16, immune reconstitution should similarly have the greatest impact on non-16 types and the least impact on HPV16.

Moreover, the diversity of oncHPV types found in CIN3+ among HIV-seropositive women suggests that the recently Food and Drug Administration–approved nanovalent HPV vaccine should be preferentially used in this population. The bivalent and quadrivalent HPV vaccines primarily target 2 oncHPV types, HPV16 and HPV18, although there may be some cross-protection. In HIV-seropositive women, this would likely protect against a minority of all CIN3+.

Our findings are similar to those of metaanalyses of HPV typing in cervical disease. These also showed lower relative prevalence of HPV16 compared to other types in HIV-seropositive women with high-grade cervical dysplasia, although HPV16 remained dominant in cervical cancers.[9,13,14] Contrary studies are from resource-limited countries and had limited sample size for conducting type-specific analyses. In the largest of these, Joshi et al[15] found that almost 60% of 53 cases of CIN grades 2 and 3 identified in HIV-seropositive Indian women contained HPV16 DNA, with an additional 11% containing HPV18. Among previously unscreened South African women, HPV16/18 accounted for 54% of CIN grade 3 but only 31% of CIN grade 2, while the distribution of HPV types was similar regardless of HIV serostatus.[16] Dominance of HPV16 in cancers but not precancers suggests that the oncogenic potential of non-16 oncHPVs in HIV-seropositive women may be limited. Our cohort had too few cancers to assess this possibility. Additional studies are needed to assess the impact of both antiretroviral and cervical lesion treatment on HPV type distribution and type-specific prognosis.

Strengths of this study include the large size and multisite character of the WIHS cohort and the use of validated PCR for HPV genotyping. Our study has some limitations. We studied CIN grade 3 and not invasive cancer, since in longitudinal cohorts studies of cancer cannot be conducted, given that all CIN grade 3 as well as all CIN grade 2 must be treated. The small number of CIN3+ in HIV-seronegative women and the limited prevalence of CIN3+ associated with some less common oncHPVs even in HIV-seropositive women limited the power of analyses. HPV16-related lesions are more visible colposcopically,[17] and the intensive cervical cancer screening regimen in WIHS may have resulted in preferential detection and eradication of HPV16 lesions. However, both HIV-seropositive and HIV-seronegative women in our study were subjected to the same surveillance schedule, and preferential removal of HPV16 lesions should have resulted in similar reductions regardless of HIV status. Our HIV-seropositive women were older than HIV-seronegative women; since HPV16 lesions tend to present earlier, this age difference might have introduced bias as their HPV16 lesions might have been detected and treated prior to study entry, but effects persisted after adjustment for age. We identified HPV from cervicovaginal lavage rather than performing microdissection to link types to individual CIN3+ lesions. However laser capture microdissection has shown that when multiple oncHPVs including HPV16 are present, CIN3+ lesions contain HPV16.[18]

In summary, HIV infection is associated with a relative decrease in the proportion of CIN3+ associated with HPV16, while oncHPVs outside the alpha-9 family are linked to the majority of CIN3+. The impact of HIV-mediated immunosuppression on alpha-9 oncHPVs other than HPV16 is unclear, with some types more and others less prevalent in HIV-

seropositive women. Molecular virologic research should explore determinants of immune identification and escape across HPV types.

These findings also have clinical relevance. The increased prevalence of non-16 HPV types in CIN3^{+} in HIV-seropositive women suggests that genotyping restricted to HPV16 may be less useful in triaging borderline cytology results, as many CIN3^{+} in HIV-seropositive women are not HPV16 associated. HPV genotyping may identify lesions in HIV-seropositive women that are less likely to progress and more suitable for observation, when appropriate criteria are met. HIV-seropositive women considering observation rather than treatment for lesser grades of CIN may be reassured by the finding that most precancers are not HPV16 associated and so might be less likely to progress during observation. HIV-seropositive girls should be immunized with the nonavalent HPV vaccine, as they are at risk for development of CIN3^{+} from a wide range of oncHPVs.

Acknowledgments

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Table 1

Demographic and medical characteristics of HIV-seropositive and HIV-seronegative women with cervical precancer (cervical intraepithelial neoplasia grade 3)

	HIV−, N = 25	HIV+, N = 166	
	N (%)		Pvalue[a]
Age, y			.001
<30	11 (44)	20(12)	
30–34	6(24)	33 (20)	
35–39	4(16)	42 (25)	
40–44	1(4)	30(18)	
45	3(12)	41 (25)	
Race			.08
White	3(12)	16(10)	
Hispanic	3(12)	41 (25)	
Black	16(64)	105(63)	
Others	3(12)	4(2)	
Enrollment period			.01
1994 through 1995	12(48)	126(76)	
2001 through 2002	13 (52)	39 (23)	
2010	0(0)	1(1)	
Smoking			.02
Never smoked	4(16)	35 (21)	
Former smoker	9(36)	22(13)	
Current smoker	12(48)	107(65)	
Lifetime no. of male sexual partners			.28
<5	2(8)	29(18)	
5–9	10(40)	40 (24)	
10–49	8(32)	49 (30)	
50	5(20)	46 (28)	
No. of male sexual partners past 6 mo			.08
0	6(24)	56 (34)	
1	13(52)	93 (57)	
2	2(8)	7(4)	
3	4(16)	7(4)	
CD4+ count, cells/cm			
>500		26(16)	
200–500		71 (43)	
<200		67(41)	
HIV viral load, copies/mL			
4000		76 (46)	

	HIV⁻, N = 25	HIV⁺, N = 166	
		N (%)	*P*value[a]
4001–20,000		24 (15)	
20,001–100,000		34 (21)	
>100,000		30 (18)	
AIDS history			
No		94 (57)	
Yes		72 (43)	

[a]Comparing HIV seropositive with HIV-seronegative women.

Massad et al. HPV16 prevalence in cervical precancers of HIV⁺ women. Am J Obstet Gynecol 2015.

Table 2

Percentage of oncogenic human papillomavirus types among women with high-grade lesions

HPV type	Cases: HIV⁻ (N = 21)	Cases: HIV⁺ (N = 154)	Cases: CD4 >500 (N = 25)	Cases: CD4: 200–500 (N = 65)	Cases: CD4 <200 (N = 62)
16	61.9[a]	28.6	28.0	33.8	22.6[b]
18	0.0	11.7	8.0	10.8	14.5
31	0.0	13.0	16.0	12.3	12.9
33	4.8	12.3	8.0	9.2	17.7
35	14.3	15.6	12.0	16.9	14.5
39	4.8	7.8	0.0	9.2	9.7
45	0.0	4.5	12.0	3.1	3.2
51	4.8	7.1	4.0	6.2	9.7
52	23.8	11.0	16.0	1.5	17.7
56	0.0	12.3	8.0	10.8	16.1
58	14.3	12.3	4.0	15.4	12.9
59	0.0	2.6	0.0	3.1	3.2
68	4.8	8.4	4.0	10.8	8.1
73	0.0	7.1	0.0	7.7	9.7

Each woman contributed only once. Results sum to >100% because of multitype infections.

HPV, human papillomavirus.

[a] *P* value comparing HPV16 prevalence between HIV⁺ and HIV⁻ women = .002, other comparisons were nonsignificant;

[b] *P* trend for HPV16 prevalence over HIV/CD4⁺ groups (HIV⁻, CD4 >500, 200–500, <200) = .005, other comparisons were nonsignificant.

Massad et al. HPV16 prevalence in cervical precancers of HIV⁺ women. Am J Obstet Gynecol 2015.

Table 3

Percentage of oncogenic human papillomavirus types among women with cervical intraepithelial neoplasia grade ≥ 2 including cytologic severe high-grade squamous intraepithelial lesion

HPV type	Cases: HIV− (N = 33)	Cases: HIV+ (N = 234)	Cases: CD4 >500 (N = 46)	Cases: CD4: 200–500 (N = 89)	Cases: CD4 <200 (N = 97)
16	48.5	26.5[a]	21.7	30.3	24.7[b]
18	9.1	10.7	6.5	10.1	13.4
31	0.0	11.5	10.9	13.5	10.3
33	3.0	12.0	4.3	10.1	17.5
35	12.1	15.0	10.9	15.7	15.5
39	3.0	7.3	4.3	6.7	9.3
45	3.0	5.1	8.7	3.4	5.2
51	3.0	9.0	6.5	7.9	11.3
52	18.2	10.7	13.0	4.5	14.4
56	0.0	11.5	10.9	10.1	13.4
58	21.2	15.8	15.2	15.7	16.5
59	0.0	2.6	0.0	2.2	4.1
68	6.1	11.5	6.5	14.6	11.3
73	0.0	5.1	0.0	5.6	7.2

Each woman contributed only once. Results sum to >100% because of multitype infections.

HPV, human papillomavirus.

[a] *P* value for comparing HPV16 prevalence between HIV+ and HIV− women = .01, other comparisons were nonsignificant;

[b] *P* trend for HPV16 prevalence over HIV/CD4+ groups (HIV−, CD4 >500, 200–500, <200) = .07.

Massad et al. HPV16 prevalence in cervical precancers of HIV+ women. Am J Obstet Gynecol 2015.