Cervicovaginal Human Papillomavirus Infection in Human Immunodeficiency Virus-1 (HIV)-Positive and High-Risk HIV-Negative Women

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Background: **Human papillomavirus (HPV) infection is associated with precancerous cervical squamous intraepithelial lesions commonly seen among women infected with human immunodeficiency virus-1 (HIV). We characterized HPV infection in a large cohort of HIV-positive and HIV-negative women participating in the Women's Interagency HIV Study to determine the prevalence of and risk factors for cervicovaginal HPV infection in HIV-positive women.** ***Methods:*** **HIV-positive (n = 1778) and HIV-negative (n = 500) women were tested at enrollment for the presence of HPV DNA in a cervicovaginal lavage specimen. Blood samples were tested for HIV antibody status, level of CD4-positive T cells, and HIV RNA load (copies/mL). An interview detailing risk factors was conducted. Univariate and multivariate analyses were performed.** ***Results:*** **Compared with HIV-negative women, HIV-positive women with a $CD4^+$ cell count of less than 200/mm^3 were at the highest risk of HPV infection, regardless of HIV RNA load (odds ratio [OR] = 10.13; 95% confidence interval [CI] = 7.32–14.04), followed by women with a $CD4^+$ count greater than 200/mm^3 and an HIV RNA load greater than 20 000 copies/mL (OR = 5.78; 95% CI = 4.17–8.08) and women with a $CD4^+$ count greater than 200/mm^3 and an HIV RNA load less than 20 000 copies/mL (OR = 3.12; 95% CI = 2.36–4.12), after adjustment for other factors. Other risk factors among HIV-positive women included racial/ethnic background (African-American versus Caucasian, OR = 1.64; 95% CI = 1.19–2.28), current smoking (yes versus no; OR = 1.55; 95% CI = 1.20–1.99), and younger age (age <30 years versus ⩾40 years; OR = 1.75; 95% CI = 1.23–2.49).** ***Conclusions:*** **Although the strongest risk factors of HPV infection among HIV-positive women were indicators of more advanced HIV-related disease, other factors commonly found in studies of HIV-negative women, including racial/ethnic background, current smoking, and age, were important in HIV-positive women as well. [J Natl Cancer Inst 1999;91:226–36]**

In 1993, the Centers for Disease Control and Prevention expanded the acquired immunodeficiency syndrome (AIDS) case definition to include invasive cervical cancer *(1)*. Human papillomavirus (HPV) infection is known to be etiologically associated with cervical cancer and with its precursor, cervical squamous intraepithelial lesions (SIL) *(2–4)*. Several studies have shown that the prevalence of SIL and of multifocal HPV-related lesions *(5,6)* are higher among human immunodeficiency virus-1 (HIV)-positive women than in HIV-negative women *(7–16)*. SIL may be more difficult to treat in HIV-positive women than in HIV-negative women *(13,17,18)*, and if cervical cancer does develop in an HIV-positive woman, it may be more aggressive and less responsive to treatment than in HIV-negative women *(9,19)*. Therefore, an understanding of the prevalence of and risk factors for HPV infection in HIV-positive women is of great importance.

Several earlier studies have characterized HPV infection in HIV-positive women. However, these studies included only small numbers of women and were usually performed at one study site with a relatively homogeneous study group with respect to ethnicity and HIV risk factors *(20–25)*. In addition, previous studies *(16,20,21,23,24)* characterized only a limited number of HPV types. Consequently, relatively little is known about the prevalence of HPV infection in HIV-positive women of different racial/ethnic backgrounds and HIV risk categories, the range of HPV types present, or the risk factors for HPV infection in these women. Although several previous studies have shown an association between HPV infection and reduced number of CD4 positive T cells, no studies have yet reported the association between HPV infection and HIV viral RNA load.

The Women's Interagency HIV Study (WIHS) is a prospective cohort study of 2056 HIV-positive and 569 HIV-negative women at six sites around the United States. The study began enrollment in October 1994. The aim of the WIHS is to characterize the natural history and pathogenesis of HIV infection and its complications in a large, geographically and ethnically diverse population of HIV-positive women when compared with a group of age-matched and risk-matched HIV-negative control subjects. The WIHS study population has been shown to accurately reflect demographic, social, and biologic characteristics of women infected with HIV in the United States *(26)*. The aim of

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See ''Notes'' following ''References.''

the present study was to characterize cervicovaginal HPV infection in the WIHS participants using cervicovaginal lavage specimens collected at enrollment. The prevalence of 29 different individual HPV types was determined along with the risk factors for HPV infection, including medical and sexual history, substance use, HIV status, blood levels of CD4 -positive T cells, and plasma HIV viral RNA load.

METHODS

Cross-sectional analysis of cervicovaginal HPV infection was conducted using baseline data obtained from 1778 HIV-positive and 500 HIV-negative women with assessable HPV results enrolled in the WIHS study in Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC. A description of the entire WIHS cohort and recruitment methods is published elsewhere *(26)*. The study was performed with the approval of review boards of each participating institution in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services. After informed consent was obtained, each woman underwent an extensive interview detailing her medical and psychosocial history, including symptoms related to HIV, prescription drug use, and hospitalizations. Subjects were also queried about past and current sexual practices, smoking, alcohol, and recreational drug use. HIV-negative women were matched to the HIV-positive women for age, drug use, and number of sexual partners. A complete physical examination and gynecologic examination were performed, followed by performance of a cervicovaginal lavage using 10 mL of normal saline (0.85% sodium chloride) *(27)*.

HPV testing was performed using polymerase chain reaction (PCR) with L1 consensus primers as described previously *(28)*. Amplification of β-globin DNA was performed as a positive control for the presence of amplifiable DNA in the specimen. Testing was performed in two different laboratories (Chicago, Los Angeles, and San Francisco sites by J. Palefsky and Bronx/Manhattan, Brooklyn, and Washington, DC, sites by R. Burk). Duplicate testing of 129 randomly chosen samples was performed to measure interlaboratory variability. There was agreement in 110 (85%) of the samples overall with respect to the presence or absence of HPV, and when samples (n = 25) classified as equivocally positive by either of the laboratories were excluded, there was 94% agreement. Among the 41 samples tested by both laboratories in which both reported specific HPV types, there was agreement for at least one HPV type in 39 (95%) samples. Among cases in which both laboratories reported one or two HPV types, Palefsky detected 78% of the specific types detected by Burk, and Burk detected 80% of the types detected by Palefsky. Among samples reported by both laboratories to have three or more specific HPV types, Palefsky detected 59% of the specific types detected by Burk, and Burk detected 56% of the types detected by JP.

Briefly, 1 mL of cervicovaginal lavage material was removed for PCR analysis after vortexing the aspirated cervicovaginal lavage material. Cellular sediment (40–80 μL) was added to 100 μL of digestion solution containing 400 μg/mL of proteinase K (Boehringer Mannheim GmbH, Mannheim, Germany) in 100-m*M* Tris–HCl, 2 m*M* EDTA, and 2% Laureth 12. After two hours at 55 °C, the proteinase K was inactivated by heating tubes to 95 °C for 10 minutes. The tubes were then stored at −20 °C until PCR analysis was performed. To perform PCR, 2–10 μL of the digest was removed and added to tubes containing 10 m*M* Tris–HCl; 50 m*M* KCl; 4 m*M* $MgCl_2$; 200 μ*M* of each deoxyribonucleotide triphosphate; 2.5 U *Taq* DNA polymerase; 0.5 μ*M* of HPV primers MY09 and MY11 and the HPV 51 HMB01 primer; as well as β-globin primers GH20 and PC04 as described *(29)*.

The presence or absence of HPV and β-globin DNA was determined using DNA hybridization. Negative controls for each blot consisted of amplification of DNA of HuH7 or BJAB cells and tubes containing all reaction components except target DNA. Positive controls consisted of amplification of DNA from 100 SiHa cells as well as amplified DNA from the individual HPV types being sought. Five percent of the samples were amplified in duplicate. PCR amplification mixtures (2–6 μL) were applied to dot blots and the DNA was fixed on the membrane. To detect HPV DNA, the membranes were pretreated in 0.1× sodium chloride–sodium phosphate–EDTA (SSPE) and 0.5% sodium dodecyl sulfate for 30 minutes at 65 °C. Probes consisting of amplified biotinylated DNA from HPV16, HPV18, HPV11, and HPV51 were denatured and added in the presence of 2 mg/mL sheared salmon sperm DNA to the hybridization buffer and hybridized at 55 °C for at least 1.5 hours. After washing, streptavidin–horseradish peroxidase (Vector Laboratories, Inc., Burlingame, CA) was added to the blots at a concentration of 30 ng/mL in 250 mL of wash solution and binding allowed to occur with gentle agitation for 15 minutes at room temperature. After vigorous washing, detection of HPV types was performed using Enhanced ChemiLuminescent detection (Amersham Life Science Inc., Arlington Heights, IL) according to the manufacturer's instructions. Type-specific probing was performed using biotinylated oligonucleotide probes at a final concentration of 0.5 pmol/mL for the following HPV types individually: 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 69, 70, 73, Pap 155, Pap 291, and AE2. A sample was considered HPV positive when it was positive with the consensus probes. Specimens positive with the consensus probes but negative with the individual type probes were considered to have one or more ''other'' types. Specimens negative for β-globin gene amplification were excluded from analysis.

For some analyses, selected HPV types were classified according to oncogenic risk. High-risk types included types 16, 18, 31, or 45. Medium- to high-risk HPV types included high-risk types as well as HPV types 33, 35, 39, 51, 52, 56, 58, 59, 68, and 73. Low HPV risk types included 6, 11, 53, 54, 55, 66, Pap 155, and Pap 291. If a woman had HPV types from more than one group, the result was assigned to the highest risk category.

Blood was obtained for HIV testing, to determine HIV viral RNA load, and to determine CD4 level at the same time at which cervicovaginal lavages were collected. HIV testing was performed using enzyme-linked immunosorbent assay and all positive results were confirmed by western blot analysis. CD4 levels were measured using standardized two- or three-color fluoresence methods and HIV viral load was measured using a nucleic acid sequence-based amplification assay (NASBA) (Organon Teknika, Oklahoma City, OK) *(26)*.

Statistical Analysis

Prevalences of HPV or of specific HPV types were expressed as percentages within subgroups and were compared in univariate analysis using Pearson's chi-squared test, Fisher's exact test or the Mantel extension trend test for ordered categorical covariates *(30,31)*. CD4 count and HIV plasma viral load cut points were chosen *a priori* using conventional clinical categories for CD4 and approximate quartiles for HIV viral load. However, since the first quartile was below the limit of detection for the NASBA assay (4000 copies/mL), 4000 copies/mL were used for the first cut point. Subgroups formed by the cross-classification of HIV status, plasma HIV viral load, and CD4 count that had similar HPV prevalences were combined *a posteriori*, leaving four strata with a gradation of HPV risks. This stratification provided the basis for adjusting the univariate comparisons simultaneously for HIV, viral load, and CD4 level using stratified Mantel–Haenzel procedures *(30,32)*. Covariates with *P* values <.15 in this adjusted analysis were considered further in multivariate analyses of the HIV-infected cohort using logistic regression models *(33)*. The resulting model was then fit in the HIV-negative cohort and both are presented. Formal comparisons of race/ethnic groups were restricted to the three dominant groups: Hispanic, Caucasian, and African-American. All *P* values were two-sided and were not adjusted for multiple comparisons.

RESULTS

Of the 1935 samples from HIV-positive women tested, 157 (8%) were negative for β-globin amplification and were excluded from analysis. Of the 542 samples from HIV-negative women tested, 42 (8%) were negative for β-globin amplification and were excluded from analysis. Therefore, HPV results from cervicovaginal samples were available from 1778 HIV-positive and 500 HIV-negative women.

Demographics of the Study Population

The demographic characteristics of the HIV-positive and HIV-negative women with assessable HPV results are shown in Table 1. The demographic characteristics of these women were similar to those of the entire WIHS cohort *(26)*. The demographic characteristics of the HIV-positive women were similar to the HIV-negative women with the following exceptions: the HIV-positive women were older, a higher proportion had a history of an abnormal cervical cytology, and a lower proportion were current smokers.

Table 1. Demographic characteristics of Women's Interagency HIV Study (WIHS): HIV-positive and HIV-negative women characterized for the presence of human papillomavirus*

Characteristic	HIV positive, % (n = 1778)	HIV negative, % (n = 500)
Age, y		
<30	20	31
30–39	48	42
⩾40	32	28
Race/ethnicity		
Hispanic	24	27
African-American	56	54
Caucasian	18	16
Other	2	3
Annual household income <$12 000	63	64
Completed high school	63	63
History of abnormal cervical cytology	41	27
HIV risk category†		
Intravenous drug use	34	28
Heterosexual risk	42	25
Transfusion risk	4	3
No identified risk	21	44
Current smoker	55	63

*HIV = human immunodeficiency virus-1.

†HIV risk category was defined as follows: heterosexual risk was assigned to women who had sex with a male who used intravenous (IV) drugs, or was a hemophiliac, or was HIV positive, or who had sex with other men. Intravenous drug use (IVDU) risk was assigned to women with a history of IV drug use since 1985. Transfusion risk was assigned to women with a history of blood transfusion between 1975 and 1985. If more than one of these was present, IVDU overruled heterosexual risk which in turn overruled transfusion risk.

HPV Infection by HIV Status and Geographic Location

Overall, of 1127 (63%) of 1778 HIV-positive women and 149 (30%) of 500 HIV-negative women were positive for HPV DNA. Among the HIV-positive women, HPV infection was found in 226 (73%) of 310 Bronx women, in 184 (72%) of 257 Brooklyn women, in 175 (68%) of 256 Washington, DC, women, in 197 (63%) of 311 San Francisco women, in 132 (55%) of 240 Chicago women, and in 213 (53%) of 404 Los Angeles women. Among the HIV-negative women, HPV infection was found in 30 (30%) of 100 Bronx women, in 19 (29%) of 65 Brooklyn women, in 32 (36%) of 89 Washington, DC, women, in 29 (35%) of 84 San Francisco women, in six (12%) of 51 Chicago women, and in 33 (30%) of 111 Los Angeles women.

Relationship Between Detection of HPV and HIV status, CD4 Level, and Plasma HIV Viral Load

The relationship between plasma HIV viral load, CD4 level, and detection of HPV DNA among HIV-positive women is shown in Table 2. Detection of HPV DNA was associated with both lower CD4 level (P<.0001) and higher HIV viral load (*P*<.0001). Overall, the women with the highest prevalence of HPV DNA were those with a CD4 level of less than 200/mm^3, regardless of HIV viral load. At CD4 levels above 200/mm^3, a higher prevalence of HPV DNA was found among women with an HIV viral load of greater than 20 000 copies/mL compared with those with an HIV viral load of less than 20 000 copies/mL. The lowest prevalence of HPV DNA was found among those women with a CD4 level above 500/mm^3 and an HIV viral load of less than 4000 copies/mL.

Distribution of HPV Types Among HIV-Positive and High-Risk HIV-Negative Women

The distribution of HPV types in the overall study population is shown in Table 3. The spectrum of HPV types was similar between the HIV-positive and HIV-negative women and the range of HPV types was very broad. No individual HPV type was found in more than 9% of either the HIV-positive or HIV-negative women. HPV16 was detected in 5% and 2% of HIV-positive and HIV-negative women, respectively, and HPV18 was detected in 4% and 1%, respectively. As shown in Table 4, when the individual HPV types were grouped into high oncogenic risk, intermediate risk, and low risk, positivity with one or more HPV types in each of these categories was significantly more common among HIV-positive women than among HIV-negative women. In contrast to the results with the 29 individual HPV types tested, the proportion of HIV-positive and HIV-negative women with HPV types other than the 29 individual types was equivalent (18%) (Table 3).

Table 2. Human papillomavirus (HPV) prevalence in human immunodeficiency virus-1 (HIV)-positive women stratified by plasma HIV viral load and CD4 level*,†

	CD4 level/mm^3‡							
	⩾500		200–499		<200		Total§,†	
Plasma HIV RNA viral load (copies/mL)‡	No. positive/ total No.	%	No. positive/ total No.	%	No. positive/ total No.	%	No. positive/ total No.	%
<4000	101/230	44	132/225	59	29/37	78	275/509	54
4000–20 000	40/81	49	64/116	55	40/48	83	148/252	59
>20 000–100 000	42/66	64	124/185	67	95/122	78	269/385	70
>100 000	20/28	71	66/103	64	173/242	71	276/392	70
Total‖,†	220/454	48	459/735	62	393/517	76		

*Groups stratified by HIV viral load and CD4 level are bordered by lines with increasing thickness to denote higher HPV prevalence. *See* text.

†*P* values (two-sided) for trends in prevalences across HIV-1 RNA categories and across CD4 count categories are both <.0001.

‡Some women had missing HIV viral load or CD4 data.

§Total includes all women with HIV viral load data whether or not CD4 data were available.

‖Total includes all women with CD4+ data whether or not HIV viral load data were available.

Table 3. Proportion of women with individual human papillomavirus (HPV) types stratified by human immunodeficiency virus-1 (HIV) status and CD4 count*,†,‡

HPV type	HIV status			CD4 count (among 1706 HIV-positive women)			
	HIV positive (n = 1778)	HIV negative (n = 500)	P§	<200 (n = 517)	200–499 (n = 735)	⩾500 (n = 454)	P§
6	3.1	0.4	.0001	5.6	2.6	1.3	.0001
11	2.4	0.4	.003	3.9	1.9	1.1	.004
16	5.2	2.0	.001	6.2	4.9	4.0	.11
18	4.2	1.2	.0006	6.6	3.8	1.8	.0002
26	0.7	0.2	.33	0.6	0.8	0.7	.87
31	3.5	0.2	<.0001	3.7	4.4	2.2	.24
32	2.0	0.4	.009	1.9	2.4	0.9	.25
33	3.6	0.4	<.0001	6.0	2.9	2.2	.001
35	2.1	0.4	.006	2.9	2.2	1.1	.05
39	0.9	0.0	.03	1.5	0.5	0.9	.26
40	1.2	0.0	.008	2.7	0.7	0.7	.004
45	3.7	0.4	<.0001	6.2	3.8	1.1	<.0001
51	3.1	1.0	.007	5.0	2.6	1.5	.001
52	4.0	1.2	.001	5.8	3.3	2.6	.01
53	8.5	1.6	<.0001	13.7	7.8	3.5	<.0001
54	4.0	0.0	<.0001	6.6	2.6	1.8	<.0001
55	0.7	0.2	.33	1.2	0.8	0.2	.10
56	4.7	0.8	<.0001	8.1	4.4	1.1	<.0001
58	7.1	2.4	<.0001	7.7	9.0	4.0	.03
59	3.9	0.8	.0002	6.0	3.9	1.1	<.0001
61	7.9	1.0	<.0001	9.5	8.2	5.3	.02
66	3.7	0.4	<.0001	4.8	3.8	2.0	.02
68	2.6	0.4	.001	5.6	1.6	0.9	<.0001
69	1.0	0.2	.15	1.4	0.8	0.4	.13
70	5.8	1.0	<.0001	8.7	4.9	3.7	.0008
73	3.4	0.2	<.0001	6.0	2.0	2.4	.001
Pap 155	4.4	0.2	<.0001	7.5	3.9	1.8	<.0001
Pap 291	5.7	1.4	<.0001	7.4	6.1	2.9	.003
AE2	1.2	0.2	.07	1.7	1.4	0.4	.07
Other	18.2	17.6	.79	17.4	18.6	17.8	.84

*Entries in body of table are percentages of number.

†Stratification by CD4 level includes HIV-positive women only.

‡72 HIV-positive women did not have CD4 levels available for analysis.

§Trend test, all *P* values are two-sided.

Table 4. Prevalence of human papillomavirus (HPV) types grouped by oncogenic risk, stratified by human immunodeficiency virus-1 (HIV) status and CD4 count*

Oncogenic risk†	HIV status				CD4 count (HIV-positive women only)				
	HIV positive (n = 1778)	HIV negative (n = 500)	OR	95% CI	⩾500 (n = 454)	200–499 (n = 735)	<200 (n = 517)	OR	95% CI
High	13.6%	3.0%	5.07	2.98–8.63	7.0%	13.3%	19.0%	2.03‡	1.34–3.08
								3.08§	2.02–4.70
Medium or high	30.9%	7.8%	5.29	3.76–7.45	18.7%	29.7%	42.6%	1.83‡	1.38–2.43
								3.22§	2.40–4.31
Low	9.2%	2.2%	4.49	2.42–8.33	6.8%	8.7%	11.6%	1.30‡	0.83–2.03
								1.79§	1.14–2.82
Unknown‖	23.3%	19.8%	1.23	0.96–1.57	22.9%	24.1%	21.9%	1.07‡	0.81–1.41
								0.94§	0.70–1.27

*Stratification by CD4 level includes HIV-positive women only. Seventy-two HIV-positive women did not have CD4 levels available for analysis. OR = odds ratio, CI = confidence interval.

†High-risk types included types 16, 18, 31, and 45. Medium or high risk included high-risk types and types 33, 35, 39, 51, 52, 56, 58, 59, and 73. Low-risk types included 6, 11, 53, 54, 55, 66, Pap 155, and Pap 291. If a woman had HPV types from more than one group, the result was assigned to the highest risk category. Results were only assigned to the low-risk category if the sample did not have any medium- or high-risk types.

‡OR for CD4 200–499 compared with the CD4 greater than or equal to 500 reference group.

§OR for CD4 <200 compared with the CD4 greater than or equal to 500 reference group.

‖Women who were HPV positive but negative for all high-, medium-, and low-risk types.

The distribution of individual HPV types was compared between different CD4 strata among the HIV-positive women and is shown in Table 3. Most of the individual HPV types tested were significantly more common among HIV-positive women in the lower CD4 strata (<200/mm^3 or between 200 and 500/mm^3), with the largest differences being the higher proportions of HPV types 6, 11, 18, 40, 45, 51, 53, 54, 55, 56, 59, 68, and Pap 155 among women with lower CD4 levels (range, 3.3-fold higher for

HPV51 among women with CD4 <200/mm^3 compared with women with CD4 >500/mm^3 to 7.4-fold higher for HPV56). In contrast, the proportion of HIV-positive women with other HPV types did not differ by CD4 strata (17.4% of women with CD4 <200/mm^3 and 17.8% of women with CD4 >500/mm^3 had other HPV types). Overall, HPV positivity in each of the oncogenic risk categories was increasingly common among those with lower CD4 levels (Table 4).

Table 5 shows that among all women who were HPV positive, the number of individual HPV types detected was higher among HIV-positive women than among HIV-negative women (P<.0001). Thirty-six percent of HIV-positive women with HPV infection were infected with two or more types compared with 12% of HIV-negative women with HPV infection (P<.0001). Among HIV-positive women with HPV infection, infection with multiple HPV types was most common among those with lower CD4 levels (P<.0001), and 28% of women with CD4 counts less than 200/mm^3 were infected with three or more HPV types.

Risk Factors for HPV Infection in HIV-Positive and High-Risk HIV-Negative Women

Risk factors for HPV infection were examined in univariate analysis and are shown in Table 6, unadjusted and adjusted for HIV status, CD4 level, and HIV viral RNA load. The P values in this section refer to adjusted analyses. Among the demographic factors, younger age (P<.0001), single marital status (P = .004), and lower household income (P = .0004) were associated with HPV infection. History of intravenous drug use was not associated with increased risk of HPV infection (P = .28). Among the gynecologic factors, higher number of previous pregnancies was associated with HPV infection (P = .02) but not current pregnancy (P = .35) or menopausal status (P = .60). Among the self-reported sexually transmitted agents or diseases, history of genital warts (P=.004) and an abnormal Pap smear (P = .003) were both associated with detection of HPV, as were history of syphilis (P = .02) and pelvic inflammatory disease (P = .02). In contrast, self-reported history of chlamydia (P = .63), trichomonas vaginalis (P = .29), candida (P = .21), or bacterial vaginosis (P = .57) were not associated with HPV detection. Lifestyle habits, including smoking, alcohol use, and drug use, were assessed for association with HPV detection. Of these, current smoking (P = .0002) and ever smoking (P = .04) were each associated with increased risk of HPV detection, as were ever use of amphetamines and use of crack in the previous 6 months. However, pack-years among smokers (P = .69, data not shown), use of amphetamines (P = .34), or crack cocaine (P = .94) in the past 6 months and ever use of crack cocaine, cocaine, or heroin (P = .26) were not associated with HPV infection.

Time since first sexual intercourse was associated with HPV detection (P = .002). However, several other measures of sexual activity were not associated with HPV detection, including the total number of male sex partners in the past (P = .54) and the number of male sex partners in the past 5 years (P = .54). Several measures of recent sexual activity also were not associated with HPV infection, including the number of male sex partners in the past 6 months (P = .11) and the number of episodes of vaginal sex in the past 6 months (P = .56).

Since the women in the WIHS cohort were recruited between October 1994 and November 1995, very few HIV-positive women were on highly active antiretroviral therapy, including protease inhibitors, at the time the sample was obtained. However, a high proportion of HIV-positive women had a history of ever taking at least one antiretroviral agent (64%) or of taking at least one antiretroviral agent in the previous 6 months (36%). While both were strongly correlated with having a higher prevalence of HPV infection (P = .0001 and .0003, respectively), this association disappeared after adjustment for CD4 levels (P = .98 and .17, respectively). These data are indicative of confounding by indication for treatment.

A logistic regression model of risk factors for HPV infection among the HIV-positive women was constructed using factors shown to be significant in adjusted univariate analysis. These are shown in Table 7. To determine if the same factors were significant among HIV-negative women, a separate analysis of these women was performed using the same model. Among HIV-positive women, significant factors associated with HPV detection in the logistic regression model included the following: more advanced HIV disease as determined by CD4 count/HIV viral RNA load classification; WIHS site; race/ethnicity, with African-American women having the highest risk followed by Hispanic women; self-reported history of genital warts; history of an abnormal Pap smear; and current smoking. Protective factors included older age at enrollment; household income above $12 000 per year; and a higher number of prior pregnancies. When the same factors (without inclusion of CD4 count/HIV viral RNA load stratum) were analyzed among HIV-negative women, similar trends for most of the factors were noted with the exception of WIHS site and household income. However, many of these factors in HIV-negative women did not reach statistical significance.

Finally, the HIV-positive and -negative cohorts were combined to assess the role of HIV positivity and severity of HIV infection (as measured by CD4 count and HIV viral load) as risk

Table 5. Number of human papillomavirus (HPV) types among HPV-positive women stratified by human immunodeficiency virus-1 (HIV) status and by CD4 count*

No. of HPV types	HIV status				CD4 level/mm^3 (HIV-positive women only)					
	HIV positive		HIV negative		≥500		200–499		<200	
	No.	%	No.	%	No.	%	No.	%	No.	%
1	724	64	131	88	170	77	310	68	212	54
2	173	15	10	7	32	14	64	14	70	18
3–5	166	15	7	5	11	5	60	13	81	21
6–10	58	5	1	<1	7	3	24	5	25	6
>10	6	<1	0	0	0	0	1	<1	5	1

*Stratification by CD4 level includes HIV-positive women only.

Table 6. Unadjusted and adjusted analyses of selected risk factors for human papillomavirus (HPV) infection*

		HPV positive		Unadjusted		Two-sided *P*	
	No.	No.	%	odds ratio	95% CI	Unadjusted	Adjusted
HIV status							
Negative	500	149	(29.8)	1.00		<.0001	
Positive	1778	1127	(63.4)	4.08	3.29–5.05		
CD4 level/mm^3 (HIV positive only)							
>500	454	220	(48.5)	1.00		<.0001	
200–500	735	459	(62.5)	1.77	1.40–2.24		
<200	517	393	(76.0)	3.37	2.57–4.43		
HIV plasma RNA copies/mL							
<4000	509	275	(54.0)	1.00		<.0001	
4000–20 000	252	148	(58.7)	1.21	0.89–1.64		
20 000–100 000	385	269	(69.9)	1.97	1.49–2.61		
>100 000	392	276	(70.4)	2.02	1.53–2.67		
Age, y							
⩾40	718	377	(52.5)	1.00		.04	<.0001
30–39	1035	592	(57.2)	1.21	1.00–1.46		
<30	512	297	(58.0)	1.25	0.99–1.57		
WIHS site							
Chicago	291	138	(47.4)	1.00		<.0001	<.0001
Bronx/Manhattan	410	256	(62.4)	1.84	1.36–2.50		
Brooklyn	322	203	(63.0)	1.89	1.37–2.61		
Washington DC	345	207	(60.0)	1.66	1.21–2.28		
Los Angeles	515	246	(47.8)	1.01	0.76–1.35		
San Francisco	395	226	(57.2)	1.48	1.09–2.01		
Race/ethnicity							
Caucasian	430	207	(48.1)	1.00		<.0001	.0002
Hispanic	557	301	(54.0)	1.27	0.98–1.63		
African-American	1229	733	(59.6)	1.59	1.28–1.99		
Other	49	25	(51.0)	1.12	0.62–2.03		
Married							
No	1776	1024	(57.7)	1.00		.004	.004
Yes	498	250	(50.2)	0.74	0.61–0.90		
Household income							
<$12 000	1370	804	(58.7)	1.0		.002	.0004
⩾$12 000	811	420	(51.8)	0.76	0.63–0.90		
Prior pregnancies							
0	229	137	(59.8)	1.00		.10	.02
1–3	1003	571	(56.9)	0.89	0.66–1.19		
⩾4	1040	566	(54.4)	0.80	0.60–1.07		
History of abnormal Pap‡							
No	1368	705	(51.5)	1.00		<.0001	.003
Yes	856	542	(63.3)	1.62	1.36–1.93		
History of gonorrhea§							
No	1487	801	(53.9)	1.00		.005	.08
Yes	766	461	(60.2)	1.29	1.08–1.55		
History of syphilis§							
No	1835	998	(54.4)	1.00		.0006	.02
Yes	418	266	(63.6)	1.47	1.18–1.83		
History of PID*							
No	1888	1031	(54.6)	1.00		.006	.02
Yes	346	217	(62.7)	1.40	1.10–1.77		
History of genital herpes§							
No	1778	966	(54.3)	1.00		.005	.22
Yes	479	295	(61.6)	1.35	1.10–1.66		
History of genital warts§							
No	1780	940	(52.8)	1.00		<.0001	.004
Yes	475	323	(68.0)	1.90	1.53–2.35		
Ever smoker							
No	622	335	(53.9)	1.00		.24	.04
Yes	1647	934	(56.7)	1.12	0.93–1.35		
Current smoker							
No	1004	538	(53.6)	1.00		.05	.0002
Yes	1266	732	(57.8)	1.19	1.00–1.40		

Table 6 (continued). Unadjusted and adjusted analyses of selected risk factors for human papillomavirus (HPV) infection*

		HPV positive		Unadjusted		Two-sided *P*	
	No.	No.	%	odds ratio	95% CI	Unadjusted	Adjusted
Ever amphetamines							
No	1607	930	(57.9)	1.00		.003	.02
Yes	660	337	(51.1)	0.76	0.63–0.91		
Crack: past 6 mo							
No	1830	1009	(55.1)	1.00		.12	.003
Yes	440	261	(59.3)	1.19	0.96–1.47		
Time since first sex, y							
<15	569	333	(58.5)	1.00		.18	.002
15–24	944	525	(55.6)	0.89	0.72–1.10		
⩾25	719	393	(54.7)	0.85	0.68–1.07		

*Number of subjects analyzed for each risk factor varies due to missing data. WHHS = Women's Interagency HIV Study.

†Adjusted for the following four strata: 1) human immunodeficiency virus-1 (HIV) negative; 2) HIV-positive CD4 greater than 200/mm^3, HIV viral load <20 000/mm^3; 3) HIV positive. CD4 greater than 200/mm^3, HIV viral load greater than 20 000; and 4) HIV-positive CD4 less than 200.

‡Pap smear.

§Self-report.

factors for HPV detection. The results in Table 8 show that adjustment for the factors in the logistic regression model from Table 7 had very little impact on the associations between HIV status, severity of HIV infection, and the risk of HPV. HIV positivity and more advanced HIV disease were among the strongest predictors of HPV infection and these associations were not confounded by other predictors, such as WIHS site, race, and age/ethnicity.

Discussion

This is the largest study reported to date examining the prevalence of and risk factors for HPV infection in HIV-positive and control high-risk HIV-negative women. The large number of women in this study provided us with statistical power to adequately assess a large number of potential risk factors. Furthermore, we were able to study women from a variety of ethnic/racial groups and geographic locations around the United States. The HPV detection technique used was capable of detecting at least 29 individual HPV types, permitting a detailed analysis of HPV types in HIV-positive women. Finally, this is the first study to examine the role of plasma HIV viral load as a risk factor for detection of HPV.

Our data confirm earlier observations *(15,34–37)* that HPV infection is significantly more common among HIV-positive women when compared with high-risk HIV-negative women. HIV infection and more advanced HIV disease as determined by lower CD4 level and higher HIV viral load were the strongest independent risk factors for HPV infection in logistic regression analysis, and these data are consistent with an important role for the immune response in controlling HPV infection. Combined with the absence of a significant role for sexual activity in the previous 6-month period, these data suggest that detection of HPV in HIV-positive women more likely reflects either reactivation or persistence of pre-existing HPV types rather than recent HPV acquisition. Consistent with this, history of an abnormal Pap smear and genital warts were also independent risk factors for HPV infection among HIV-positive women, likely reflecting past exposure to HPV.

Previous studies of the role of HIV infection in detection of HPV were limited to measures of CD4 count as an indicator of the stage of HIV disease. However, CD4 levels and HIV viral

Table 7. Logistic regression model for human papillomavirus (HPV) prevalence

	HIV-positive cohort		HIV-negative cohort*	
Covariate	OR	95% CI	OR	95% CI
CD4 level/mm^3				
>500	1.00		Not applicable	
200–500	1.48	1.11–1.97		
<200	2.80	1.94–4.04		
HIV plasma RNA copies/mL				
<4000	1.00		Not applicable	
4000–20 000	1.24	0.88–1.75		
20 000–100 000	1.61	1.16–2.24		
>100 000	1.42	0.99–2.03		
WIHS site				
Chicago	1.00		1.00	
Bronx	2.16	1.39–3.37	3.45	1.25–9.52
Brooklyn	1.89	1.23–2.92	2.71	0.93–7.94
Washington, DC	1.63	1.04–2.55	3.89	1.41–10.74
Los Angeles	0.96	0.65–1.42	3.35	1.19–9.40
San Francisco	1.42	0.94–2.15	3.76	1.33–10.61
Race/ethnicity				
Caucasian	1.00		1.00	
Hispanic	1.30	0.90–1.90	1.05	0.51–2.16
African-American	1.64	1.19–2.28	1.47	0.77–2.82
Age, y				
⩾40	1.00		1.00	
30–39	1.41	1.07–1.85	1.13	0.63–2.03
<30	1.75	1.23–2.49	2.24	1.21–4.15
Household income >$12 000/y	0.68	0.53–0.88	1.05	0.64–1.71
Prior pregnancies				
0	1.00		1.00	
1–3	0.78	0.51–1.20	0.49	0.25–0.93
⩾4	0.61	0.39–0.95	0.56	0.29–1.09
History of genital warts†	1.44	1.07–1.93	1.66	0.83–3.34
History of abnormal Pap‡	1.30	1.01–1.67	1.38	0.84–2.26
Current smoker	1.55	1.20–1.99	1.05	0.65–1.71

*Model was developed in human immunodeficiency virus-1 (HIV)-positive cohort and applied to both HIV-positive and HIV-negative cohorts for comparison.

†Self-report.

‡Pap smear.

Table 8. Human papillomavirus virus (HPV) prevalence and odds ratios and 95% confidence intervals (CIs) for CD4 count/HIV viral RNA load strata compared with HIV-negative control subjects, unadjusted and adjusted for all covariates shown in Table 7

Covariate	No.	HPV positive		Odds ratio (95% CI)	
		No.	%	Unadjusted	Adjusted
HIV negative	500	149	29.8	1.00	1.00
HIV positive: CD4 >200/mm^3, RNA <20 000 copies/mL	652	337	51.7	2.52 (1.97–3.22)	3.12 (2.36–4.12)
HIV positive: CD4 >200/mm^3, RNA >20 000 copies/mL	382	252	66.0	4.57 (3.43–6.08)	5.78 (4.17–8.08)
HIV positive: CD4 <200/mm^3	517	393	76.0	7.47 (5.65–9.86)	10.13 (7.32–14.04)

load have been shown to be independent predictors of the course of HIV disease *(38)*. In this study we examined different risk strata for HPV using a combination of these two measures of HIV disease severity. Our data show that a combination of CD4 levels and HIV viral load, as shown in Tables 2 and 8, may be optimal in predicting the risk of HPV infection in HIV-positive women. The risk of HPV was highest at CD4 counts less than 200 cells/mm^3, regardless of HIV viral load, but was also uniformly high at a HIV viral load of greater than 20 000 copies/mL. Our data suggest that at their extremes, both factors may be important in activation of HPV replication and facilitation of subsequent HPV detection. Overall, HIV-positive women were at the lowest, intermediate, and highest risk of HPV infection, respectively, when they had a CD4 level greater than 200/mm^3 with an HIV viral load of less than 20 000 copies/mL, a CD4 level greater than 200/mm^3 with an HIV viral load of greater than 20 000 copies/mL, and a CD4 level less than 200/mm^3.

Ten of the 11 most prevalent HPV types among the HIV-positive and HIV-negative women were common to both cohorts. The spectrum of HPV types detected was thus similar among HIV positive and HIV-negative women, and no single HPV type was detected in more than 9% of the women in either group. HPV types representing the entire spectrum of oncogenic risk were found and there was no particular predilection for detection of the high-risk oncogenic HPV types, such as HPV 16 or 18, consistent with an earlier study *(37)*. However, among the HIV-positive women, certain HPV types were significantly more common among those with lower CD4 levels, and these also spanned the range of oncogenic risk. These included HPV 6, 11, 18, 40, 45, 51, 53, 54, 56, 59, 68, and Pap 155. Of interest, in a study of anal HPV infection in HIV-positive and HIV-negative men, the four HPV types shown to increase in prevalence with lower CD4 counts were HPV types 18, 45, 53, and 59, a subset of this group of HPV types detected more commonly among the more immunosuppressed women *(39)*. Of these types, HPV 18, 45, and 59 are closely related phylogenetically *(40)* and it is possible that these types share one or more epitopes that render them particularly sensitive to the loss of immune control as reflected by declining CD4 levels.

Most HIV-negative women reported to be HPV positive had only one HPV type detected at the time of sample collection. In our study, 12% of HIV-negative and HPV-positive women were infected with multiple types, while 36% of HIV-positive and HPV-positive women were infected with multiple types. These data likely represent an underestimate of the true number of HPV types, since our probes do not detect all HPV types. A clear trend was also seen between lower CD4 levels and detection of a higher number of HPV types. Like the overall prevalence of HPV positivity, the higher number of HPV types detected in women with lower CD4 levels reflects either persistence or activation of pre-existing HPV infections in the setting of declining immunity rather than recent acquisition. It is currently unknown if the presence of multiple HPV types potentiates the pathogenesis of SIL. However, in studies of anal HPV infection in HIV-positive and HIV-negative men, detection of multiple HPV types was common *(39)* and was associated both with concurrent anal lesions and progression of anal lesions to a higher grade over a 2-year follow-up period in both HIV-positive and HIV-negative men when compared with detection of a single type or no HPV infection *(41)*. Furthermore, multiple cervical HPV types were risk factors for persistent cervical HPV infection among young women, and persistent HPV infection was a risk factor for development of cervical lesions *(42,43)*.

In most earlier studies of HIV-positive women in which multivariate analyses were performed, HIV status and lower CD4 levels were dominant risk factors for HPV infection *(15,34–37)*. In part, this may have reflected inadequate power to detect more modest relative risks. Because of the relatively large number of study subjects, our study permitted us to explore risk factors that also play a role in detection of HPV as well as to compare risk factors between HIV-positive and HIV-negative women.

Among the covariates in logistic regression analysis that could be compared between HIV-positive and HIV-negative women, some were found to be significant only among the HIV-positive women, including current smoking. Smoking may be a risk factor for the development of cervical intraepithelial neoplasia *(3)*. However, consistent with the lack of association among HIV-negative women in our study, most studies *(3,44–46)* of women have shown that smoking is not an independent risk factor for HPV detection. Since smoking may suppress immune response in HIV-positive individuals *(47)*, including local immune response through an effect on Langerhans cells *(48,49)*, it is possible that HIV-positive women may be uniquely susceptible to the effects of smoking.

Other risk factors studied in HIV-positive and HIV-negative women were found to be significant in both groups, including younger age. Epidemiologic studies *(44,50)* of younger women have shown that cervical HPV infection is acquired early after initiation of sexual activity. A large proportion of sexually active young women are HPV positive as detected by PCR, but the prevalence peaks in the late teens and early twenties and then declines *(51,52)*. Risk factors for HPV infection in young women have primarily been shown to reflect sexual activity including younger age, younger age at first intercourse, number of recent male sex partners, the male partner's sexual behavior, and race *(29,43,46,53–55)*. Although the mechanism of the age-related decline of HPV prevalence is not well understood, it may reflect acquisition of cell-mediated immunity. Since younger age was independent of HIV status and stage of HIV disease as a risk factor in this study, our data suggest that in this study population,

the protection afforded by older age may be due to mechanisms other than acquisition of immunity. However, even though the older women in our study had a lower prevalence of HPV infection than the younger women, they also had a remarkably high prevalence of HPV infection when compared with women in the general population of a similar age. Thus, the scenario of an infection that is acquired at an early age and then cleared or suppressed to the level at which it can no longer be detected among women in the general population is dramatically different among HIV-positive women, and to a lesser extent among high-risk HIV-negative women.

Higher number of prior pregnancies was another factor that was significant among both HIV-positive and HIV-negative women and showed a protective effect for HPV infection. These data are consistent with an earlier study of women at low risk of HPV infection that showed a higher risk of HPV infection with nulliparity *(46,55)* but differed from another in which pregnancy was positively associated with HPV infection *(45)*.

Several risk factors were significant among the HIV-positive women and showed a similar but not statistically significant trend among the HIV-negative women, possibly due to the smaller number of HIV-negative subjects. These include race or ethnicity, history of genital warts, and an abnormal Pap smear. Among the racial and ethnic groups studied, African-American women had the highest risk of HPV infection, consistent with earlier studies of HIV-negative women *(29,44)*. Certain major histocompatibility complex (MHC) class II haplotypes, such as DRB1*1501–DQB1*0602, have been associated with increased risk of cervical cancer among Hispanic women *(56)*. Among African-American women, the DQB1*0303 and DQB1*0604 haplotypes were associated with an increased risk of cervical cancer *(57)*. It is possible that African-American women may have a higher prevalence of MHC class II haplotypes that predispose to HPV infection, perhaps through impaired immune response.

The prevalence of HPV infection among HIV-positive women was higher in East Coast U.S. cities than in Chicago or West Coast cities. Although we cannot exclude confounding due to HPV testing being performed in two different laboratories, this is unlikely given the high interlaboratory agreement rate, which was comparable to that of another interlaboratory study (Burk R: personal communication). In addition, similar rates of HPV detection were noted in East and West Coast cities among the HIV-negative women. The lowest rate of HPV detection was found in HIV-negative women in Chicago, and this group was also found to have very low rates of cytologic abnormalities *(58)*. Since the HIV-negative women would be more likely to have lower HPV DNA copy numbers than the HIV-positive women, any artifacts introduced by differences in sensitivity of detection between the two laboratories should have been more apparent among the HIV-negative women. The geographic distribution of HPV prevalence did not reflect race or ethnicity of the women, since race/ethnicity were independently associated with HPV. HIV risk category was also unlikely to play a role, since there was no significant difference between women with a history of intravenous drug use and those who probably acquired HIV heterosexually.

The data in this study should be interpreted with caution, since they represent a cross-sectional analysis. Earlier studies of HIV-negative *(59,60)* and HIV-positive *(37)* women have shown that detection of specific HPV types may vary over time, even at short testing intervals. The significance of a ''one-time detection''; of different HPV types will become clearer with longitudinal studies using serial collection of cervicovaginal lavages from the same women, with establishment of the pattern of infection/reinfection with different HPV types. In addition, we were unable to assess the impact of antiretroviral treatment on HPV detection. Since enrollment in the WIHS ended in November 1995, before widespread use of protease inhibitors, there was very little use of highly active antiretroviral therapy in the WIHS cohort prior to baseline. Furthermore, because of confounding by indication for treatment, it was not possible to assess the impact of single- or double-agent antiretroviral therapy in the cohort. Finally, there were a large number of statistical tests in this analysis that increased the probability of type I error. Coupled with the large sample size, this means that some of the weaker observed associations should be interpreted with caution.

In summary, HIV-positive women had a higher prevalence of HPV infection than high-risk HIV-negative women. Since HPV infection is strongly associated with SIL, a high proportion of HIV-positive women are at risk for this disease. Compared with HIV-negative women, HIV-positive women had a higher number of HPV types per person but did not appear to be at increased risk of oncogenic HPV types relative to types with lower oncogenic risk. Many of the same risk factors for HPV infection were significant or showed similar trends between HIV-positive and high risk HIV-negative women, including younger age, fewer prior pregnancies, history of genital warts, and race/ethnicity. Risk factors unique to the HIV-positive women included lower household income, smoking, and measures of more advanced HIV disease. Our data point to a dominant, but not exclusive, role for HIV-related immunosuppression in explaining the difference in prevalence of HPV infection between HIV-positive and HIV-negative women. They also support the hypothesis that the higher prevalence of HPV infection among HIV-positive women reflects persistence or reactivation of previously acquired HPV types rather than recent acquisition of new HPV types.

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NOTES

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