Prevalence, Incidence, and Type-Specific Persistence of Human Papillomavirus in Human Immunodeficiency Virus (HIV)–Positive and HIV-Negative Women

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Human immunodeficiency virus (HIV) infection and related immunosuppression are associated with excess risk for cervical neoplasia and human papillomavirus (HPV) persistence. Type-specific HPV infection was assessed at 6-month intervals for HIV-positive and HIV-negative women (median follow-up, 2.5 and 2.9 years, respectively). The type-specific incidence of HPV infection was determined, and risk factors for HPV persistence were investigated by statistical methods that accounted for repeated measurements. HIV-positive women were 1.8, 2.1, and 2.7 times more likely to have high-, intermediate-, and low-risk HPV infections, respectively, compared with HIV-negative women. In multivariate analysis, high viral signal, but not viral risk category, was independently associated with persistence among HIV-positive subjects (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1–2.9). Furthermore, persistence was 1.9 (95% CI, 1.5–2.3) times greater if the subject had a CD4 cell count <200 cells/μL (vs. >500 cells/μL). Thus, HIV infection and immunosuppression play an important role in modulating the natural history of HPV infection.

Infection with human papillomavirus (HPV) is required for the development of cervical cancer [1–4]. Both the prevalence of HPV infection [5, 6] and the risk of cervical squamous intraepithelial lesions [7, 8] are increased among women who are infected with human immunodeficiency virus (HIV). In addition, the lesions associated with HPV among immunosuppressed HIV-positive women are relatively greater in size and number and are more likely to recur after treatment [9–11].

The persistence of HPV infection is an important risk factor for progression of disease. Ho et al. [12] found that the persistence of type-specific HPV was associated with the persistence of cervical dysplasia, particularly in association with high HPV load. In other studies, infections with a cancer-associated HPV, specifically HPV-16, were more likely to persist than were other HPV infections [13, 14]. More recently, Franco et al. [15] showed that the median interval for loss of HPV positivity was greater for oncogenic types (8.1 months) than for nononcogenic types (4.8 months) and that the persistence of HPV-16 infections was similar to that of other oncogenic types. Liaw et al. [16] found that the presence of HPV-16 was associated with some excess risk for acquisition of other HPV types but that its presence did not affect the persistence of such additional infections. In one recent study that examined the role of HIV infection in HPV persistence, Minkoff et al. [17] found that HIV-positive women were more likely than HIV-negative women to acquire new infections with cancer-associated HPV and were less likely to lose these infections. Sun et al. [18] found that HIV-positive women were also more likely to have persistent infection and that depressed immune function, as measured by CD4 cell count, was associated with greater persistence. Here, we describe the effect of HIV infection and various degrees of immunosuppression on the natural history of HPV infection among HIV-positive and high-risk HIV-negative participants studied prospectively in the HIV Epidemiology Research Study.

Methods

Study population and data collection. Participants were recruited at 4 sites (Johns Hopkins University School of Hygiene

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Written informed consent was obtained from all subjects, in accordance with protocols approved by local institutional review boards at the study sites and by the Centers for Disease Control and Prevention (CDC). Human experimentation guidelines of the US Department of Health and Human Services and of the authors' institutions were followed in the conduct of this research.

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and Public Health, Baltimore; Montefiore Medical Center, Bronx, NY; Brown University, Providence, RI; and Wayne State University School of Medicine, Detroit), as described elsewhere [19]. In brief, 871 HIV-positive women who did not have AIDS-defining clinical conditions and 439 HIV-negative women with histories of sexual or drug abuse risk behavior were recruited between 1993 and 1995. A variety of recruitment modalities were used, including posted notices in community gathering places and community newspapers, letters to physicians, information meetings with staff members at drug treatment centers, invitations to participants in other studies, and word of mouth. HIV-negative and HIV-positive participants were recruited over the same period and by the same techniques [19].

At recruitment and in subsequent follow-up visits at 6-month intervals, participants answered questions in a structured interview, underwent a physical examination, and provided biologic specimens. Pap smears, collected with a cytobrush and Ayre's spatula, were read at a single cytologic laboratory (Kyto Diagnostics, New York, NY) by cytotechnologists who were unaware of the participants' HIV serostatus. Smears were evaluated according to predefined criteria (an expansion of the Bethesda scoring system for cervical cytology). A senior pathologist reread all abnormal tests, and 10% of those read as normal [20].

HPV identification. All participants who had cervicovaginal lavage specimens collected and tested for HPV infection were included in these analyses. Cervicovaginal lavage specimens were collected as described by Burk et al. [21] and were aliquotted and frozen at −70°C until testing. Polymerase chain reactions (PCRs) were done on all collected specimens by use of MY09/MY11/HMB01 L1 consensus primers, as described by Hildescheim et al. [14]. Primers for β-globin amplification were included in the same reaction mixture. The amplification products were identified in a dot blot format with biotinylated probes (type-specific probes for >25 HPVs, generic HPV probe, and β-globin probe) by a chemiluminescence system (Amersham). Specimens negative for β-globin ($n = 62$) were considered to be unsatisfactory and were excluded from analysis. There was no difference in the proportion of specimens found to be negative for β-globin according to HIV infection ($P = .14$). The intensity of the PCR signal among HPV-positive specimens was graded 1 to 4: 1 or 2 was classified as "low," and 3 or 4 was classified as "high." The positive controls were cells from SiHa and CD4-II cell lines containing HPV-16 and HPV-18 genomes, respectively. Cells equivalent to 25 and 250 genome copies were tested for each cell line.

The HPV-positive specimens were reported by specific type and were grouped in risk categories [1] as high: 16, 18, 31, and 45; intermediate: 33, 35, 39, 51, 52, 56, 58, 59, and 68; and low: 6, 11, 26, 40, 42, 53, 54, 55, 66, 73, 82, 83, and 84. Specimens positive by the generic probe but negative with type-specific probes were included as a fourth risk category (untyped) for analysis. A specimen with multiple HPV types was assigned the category of its highest risk type.

Statistical analyses. The cumulative prevalence, incidence, and persistence of HPV infection were analyzed by using baseline HIV serostatus and baseline CD4 cell count (cells/μL) as the primary covariates of interest. Three groups of HIV-positive women were characterized by using CD4 cell count cut off points of 200 and 500 cells/μL.

The proportion of women who were infected with HPV was calculated at baseline and at consecutive 6-month intervals. For this analysis, HPV infection was defined as the presence of any HPV DNA, as determined by the generic probe. Only women who contributed cervicovaginal lavage samples at a particular visit were included in the denominator for calculating the prevalence rate for that visit.

HPV type-specific incidence rates were computed among HIV-positive and HIV-negative women and were defined as the number of participants with an incident infection during follow-up divided by the person-years of follow-up from baseline to the initial type-specific infection. To maximize the informative value of the longitudinal data available during 3 years of follow-up, we modeled type-specific HPV persistence by using pairs of cervicovaginal lavage measurements. This approach is particularly suited for the investigation of factors associated with changes within a person over time [22]. In our application, each pair consisted of an index measurement (visit v) and a follow-up measurement (e.g., visit v + 1, visit v + 2, visit v + 3, and so forth), and such pairs were the unit of our analysis. Each measurement contributed at each visit could be an index and/or a follow-up measurement for a pair. We assessed all possible pairs of measurements (i.e., for consecutive visits 6, 12, 18, 24, 30, or 36 months apart) in which the first measurement was HPV positive. Pairs were categorized as HPV persistent or HPV nonpersistent, with HPV persistent defined as the repeated detection of the same HPV type at consecutive visits 6–36 months apart.

Figure 1 illustrates the construction of pairs and the definition of HPV persistence. Persistence at 6 months was defined as being positive at visit v + 1 for an HPV type when the participant was also positive for that HPV type at visit v. Persistence at 12 months was defined as being positive at visit v + 2 for an HPV type when the participant was also positive for that HPV type at visit v. Persistence at 18, 24, 30, and 36 months was defined similarly. For example, a participant whose HPV profile for 4 consecutive visits was (+, −, −, and −) would contribute a total of 3 pairs in which the initial HPV measurement was positive: (+ and −) at 6 months, (+ and −) at 12 months, and (+ and −) at 18 months. Likewise, a participant whose HPV profile for 4 consecutive visits was (+, +, −, and −) would contribute a total of 5 pairs in which the initial HPV measurement was positive: (+ and +) and (+ and −) at 6 months, (+ and −) and (+ and −) at 12 months, and (+ and −) at 18 months. Women who tested negative throughout follow-up did not contribute any data.

We determined the proportion of pairs that were persistent (i.e., +

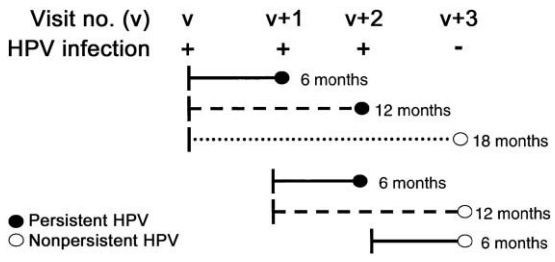

Figure 1. Hypothetical examples for definition of persistence and nonpersistence of human papillomavirus (HPV) infection.

Table 1. Number (%) of women, by baseline human immunodeficiency virus (HIV) status.

No. of clinic visits	HIV status[a]		Total
	Negative	Positive	
1	48 (11.4)	75 (8.7)	123 (9.6)
2	31 (7.3)	39 (4.5)	70 (5.5)
3	20 (4.7)	60 (7.0)	80 (6.2)
4	31 (7.3)	96 (11.1)	127 (9.9)
5	80 (19.0)	164 (19.0)	244 (19.0)
6	111 (26.3)	226 (26.2)	337 (26.2)
7	101 (23.9)	202 (23.4)	303 (23.6)
Total	422 (100)	862 (100)	1284 (100)

[a] Twelve women became seropositive during the study and were excluded from analysis. The percentages may not total 100% because of rounding.

and +) by viral factors (viral signal, number of HPV infections in a specimen, HPV risk category, and Pap smear results) and by host factors (HIV status, baseline CD4 cell count, and age at recruitment). We then applied multivariate models for correlated data, to determine which factors were independently associated with persistence. In addition, we did a subanalysis limited to incident HPV infections only. Robust methods for logistic regression with an exchangeable correlation structure were used to provide SEs, adjusted by multiple observations on individuals [23]. We used SAS software (version 6.12; SAS Institute) for all statistical analyses.

Results

Median follow-up for HIV-positive and HIV-negative women was 2.5 years (interquartile range [IQR], 2.0–2.9 years) and 2.9 years (IQR, 2.4–3.0 years), respectively. About two-thirds of participants (68.7%, HIV positive; 69.2%, HIV negative) had data for ⩾5 visits (table 1). At baseline, there were no differences in number of HIV-positive and HIV-negative women who currently smoked, but HIV-positive women were older (median age, 34.6 years) than HIV-negative women (median age, 32.4 years; $P = .004$; data not shown). There were no significant differences between HIV-positive and HIV-negative participants with regard to race (overall, 61.0% black), recent injection drug use at baseline (overall, 26.1%), or education (less than high school education, 55.6%). HIV-positive participants were more likely to have HPV infection at baseline and to have multiple HPV infections. HIV-positive women reported significantly fewer recent male sex partners at baseline and at all follow-up visits. In addition, HIV-positive women with lower CD4 cell counts reported significantly fewer partners than their immunocompetent HIV-positive counterparts.

HPV cumulative prevalence. The cumulative prevalence of HPV infection was clearly associated with both HIV infection and, among HIV-positive women, level of immunosuppression ($P < .01$) at all time periods (figure 2). Among HIV-negative women, the cumulative HPV prevalence increased from 28.1% at baseline to 54.0% at 36 months; the comparable cumulative HPV prevalences for HIV-positive women with CD4 cell counts ⩽200 cells/μL were 73.4% and 90.2%.

Type-specific HPV incidence and persistence. For each of the major risk categories of HPV infection (high, intermediate, and low), the risk of an incident case was greater for HIV-positive than for HIV-negative women (table 2). HIV-positive women were 1.8, 2.1, and 2.7 times more likely to have a high-risk, intermediate-risk, or low-risk HPV infection, respectively, compared with HIV-negative women.

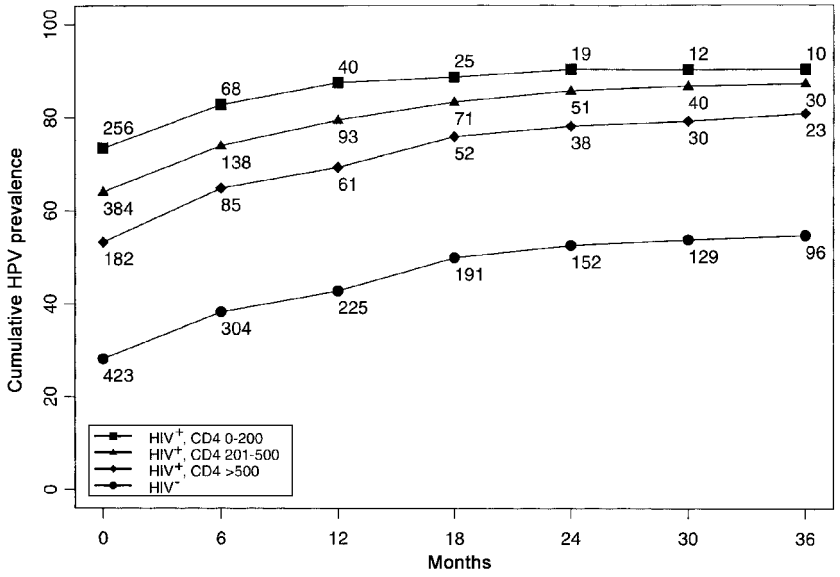

Figure 2. Cumulative prevalence of human papillomavirus (HPV) infection, by human immunodeficiency virus (HIV) status and CD4 cell count. Nos. along graph lines indicate women at risk for initial HPV infection and under observation. Differences between groups were statistically significant ($P < .01$) at all time periods.

Table 2. Incidence of type-specific human papillomavirus (HPV) infection (per 100 person-years), by baseline human immunodeficiency virus (HIV) status.

HPV risk category, HPV type	HIV negative			HIV positive			Relative risk (95% confidence interval)
	Incident cases	Person-years at risk	Incidence rate	Incident cases	Person-years at risk	Incidence rate	
High							
16	15	896	1.67	45	1737	2.59	1.5 (0.8–3.0)
18	11	925	1.19	45	1726	2.61	2.2 (1.1–4.7)
31	13	908	1.43	29	1767	1.64	1.1 (0.6–2.4)
45	7	937	0.75	43	1761	2.44	3.3 (1.5–8.6)
Any	37	837	4.42	114	1416	8.05	1.8 (1.3–2.7)
Intermediate							
33	5	936	0.53	34	1752	1.94	3.6 (1.4–11.9)
35	4	936	0.43	41	1802	2.28	5.3 (1.9–20.5)
39	3	945	0.32	11	1879	0.59	1.8 (0.5–10.3)
51	10	935	1.07	66	1746	3.78	3.5 (1.8–7.7)
52	9	933	0.96	67	1735	3.86	4.0 (2.0–9.1)
56	9	937	0.96	40	1775	2.25	2.3 (1.1–5.5)
58	7	916	0.76	44	1721	2.56	3.3 (1.5–8.8)
59	3	933	0.32	14	1854	0.76	2.4 (0.7–12.8)
68	7	942	0.74	37	1813	2.04	2.7 (1.2–7.3)
Any	57	1058	5.39	170	1172	14.5	2.1 (1.5–2.9)
Low							
06	2	940	0.21	32	1787	1.79	8.4 (2.1–72.4)
11	2	951	0.21	15	1853	0.81	3.5 (0.9–34.7)
26	0	951	0	13	1859	0.70	—
40	1	950	0.11	12	1864	0.64	6.1 (0.9–261.5)
42	0	951	0	0	1893	0	—
53	21	910	2.31	98	1573	6.23	2.7 (1.7–4.6)
54	17	909	1.87	59	1743	3.39	1.8 (1.0–3.3)
55	3	944	0.32	35	1838	1.90	6.0 (1.9–30.4)
57	0	951	0	0	1893	0	—
66	12	929	1.29	41	1773	2.31	1.8 (0.9–3.7)
73	1	949	0.11	35	1821	1.92	18.2 (3.1–740.9)
82	0	946	0	20	1859	1.08	—
83	18	903	1.99	62	1674	3.70	1.9 (1.1–3.3)
84	10	932	1.07	64	1752	3.65	3.4 (1.7–7.4)
Any	59	797	7.4	209	1056	19.8	2.7 (2.0–3.6)
Untyped	86	780	11.03	210	1426	14.73	1.3 (1.0–1.7)

NOTE. Dashes indicate that values were not calculated, because there were no incident cases among HIV-negative participants.

HIV-positive and HIV-negative women contributed 5730 and 405 pairs of persistent pairs, respectively, to the HPV persistence analysis. Among HIV-positive women, 540, 501, 451, 390, 321, and 164 women contributed persistent pairs at 6, 12, 18, 24, 30, and 36 months, respectively. The analogous numbers of HIV-negative participants were 132, 116, 108, 86, 72, and 41. Analyses were done at the level of individual pairs rather than of individual women. Intermittent detection of HPV infection was relatively uncommon. Among HPV-positive women who contributed 7 specimens and had ≥ 2 HPV-positive specimens ($n = 369$), only 13.0% had ≥ 2 intervening negative measurements.

HIV positivity was highly associated with type-specific HPV persistence at each follow-up period (6, 12, 18, 24, 30, and 36 months; table 3 and figure 3). At 6 months, 67.7% and 47.4% of pairs contributed by HIV-positive and HIV-negative participants, respectively, were persistent. Discrimination according to HIV status remained for as long as 36 months (the duration of follow-up for this analysis) past the index measurement. Even at 36 months after detection of an initial HPV infection, 45.2% of pairs from HIV-positive participants exhibited type-specific persistence, compared with only 14.8% of pairs from HIV-negative participants. The impact of HIV infection on HPV persistence was associated with immunosuppression, as illustrated in figure 4. For example, 24 months after the index HPV measurement, 70% of pairs contributed by HIV-positive women with CD4 cell counts ≤ 200 cells/μL had persistent HPV infection, compared with only 20% of pairs contributed by HIV-negative women.

In univariate analysis, high signal intensity in the index specimen was significantly associated with HPV persistence in HIV-positive women at all follow-up points; for HIV-negative women, the association held through 18 months (table 3). The presence of multiple infections in the index specimen was strongly associated with HPV persistence, but only among HIV-positive women (at 6–30 months). HPV risk category was not associated with persistence in either HIV-positive or HIV-negative women. Pap smear abnormality (atypical squamous cells of uncertain significance or more-severe lesions) in the index

Table 3. Correlates of type-specific human papillomavirus (HPV) persistence among human immunodeficiency virus (HIV)–negative and HIV-positive women.

Characteristic	No. (%) of persistent pairs, by months of follow-up					
	6	12	18	24	30	36
HIV negative						
Overall	167 (47.4)	104 (35.3)	64 (26.7)	34 (19.5)	27 (20.8)	9 (14.8)
Viral signal						
Low	50 (37.0)[a]	28 (24.8)[a]	15 (16.5)[a]	9 (13.2)	7 (13.5)	2 (7.7)
High	117 (53.9)[a]	76 (41.8)[a]	49 (32.9)[a]	25 (23.6)	20 (25.6)	7 (20.0)
No. of infections among HPV infections that were typed						
1	107 (49.1)	65 (35.3)	35 (25.7)	20 (19.6)	18 (25.7)	6 (21.4)
2–3	52 (46.4)	27 (30.7)	27 (28.1)	13 (20.0)	9 (18.0)	3 (12.0)
⩾4	8 (36.4)	12 (52.2)	2 (25.0)	1 (14.3)	0	0
HPV risk category						
Low	59 (46.1)	39 (35.8)	21 (23.6)	13 (21.0)	10 (22.2)	3 (12.5)
Intermediate	57 (47.9)	34 (35.8)	24 (31.6)	13 (22.8)	9 (22.0)	4 (25.0)
High	51 (48.6)	31 (34.1)	19 (25.3)	8 (14.6)	8 (18.2)	2 (9.5)
Pap smear						
Normal	114 (45.6)	67 (33.2)	36 (22.4)	15 (14.3)[b]	12 (16.7)	4 (11.4)
ASCUS or more severe	47 (54.7)	30 (40.0)	22 (34.9)	15 (27.3)[b]	10 (23.3)	4 (28.6)
Age, years						
<35	104 (46.2)	61 (30.4)[a]	32 (19.6)[a]	14 (12.0)[a]	12 (13.5)[a]	6 (13.6)
⩾35	63 (49.6)	43 (45.7)[a]	32 (41.6)[a]	20 (35.1)[a]	15 (36.6)[a]	3 (17.7)
HIV positive						
Overall	2098 (67.7)	1472 (60.3)	1000 (54.9)	641 (51.4)	377 (45.7)	142 (45.2)
Viral signal						
Low	432 (47.2)[a]	290 (39.6)[a]	212 (39.0)[a]	151 (39.3)[a]	90 (33.6)[a]	39 (36.1)[b]
High	1666 (76.3)[a]	1182 (69.2)[a]	788 (61.7)[a]	490 (56.7)[a]	287 (51.5)[a]	103 (50.0)[b]
No. of infections among HPV infections that were typed						
1	607 (59.3)[a]	436 (52.3)[a]	290 (48.3)[a]	172 (45.4)[a]	95 (40.3)[a]	31 (38.8)
2–3	974 (70.2)[a]	657 (61.5)[a]	477 (54.9)[a]	293 (49.8)[a]	188 (44.7)[a]	77 (45.0)
⩾4	517 (74.9)[a]	379 (70.5)[a]	233 (66.2)[a]	176 (62.6)[a]	94 (56.0)[a]	34 (54.0)
HPV risk category						
Low	884 (66.6)	627 (59.5)	447 (56.3)	291 (53.1)	168 (46.9)	69 (46.0)
Intermediate	778 (67.6)	526 (58.9)	333 (51.3)	216 (48.4)	121 (40.9)	42 (40.4)
High	436 (70.1)	319 (64.6)	220 (58.1)	134 (52.8)	88 (51.5)	31 (51.7)
Pap smear						
Normal	1041 (62.7)[a]	764 (56.3)[a]	540 (50.5)[a]	382 (50.4)	209 (43.3)	87 (45.6)
ASCUS or more severe	892 (74.2)[a]	602 (65.7)[a]	383 (61.5)[a]	225 (54.4)	144 (50.0)	52 (44.8)
Age, years						
<35	1049 (65.0)[a]	736 (57.5)[a]	494 (52.2)[b]	324 (49.6)	196 (45.3)	69 (42.3)
⩾35	1049 (70.5)[a]	736 (63.5)[a]	506 (57.8)[b]	317 (53.3)	181 (46.2)	73 (48.3)
CD4 cell count, cells/μL						
>500	271 (52.7)[a]	190 (46.3)[a]	130 (38.2)[a]	103 (38.2)[a]	59 (33.3)[a]	24 (41.4)[a]
201–500	958 (67.3)[a]	689 (58.1)[a]	485 (53.1)[a]	297 (49.8)[a]	183 (43.2)[a]	61 (37.2)[a]
⩽200	780 (74.9)[a]	530 (69.8)[a]	349 (68.6)[a]	223 (64.1)[a]	122 (60.4)[a]	48 (61.5)[a]

NOTE. ASCUS, abnormal squamous cells of uncertain significance.
[a] $P < .01$.
[b] $P < .05$.

specimen was associated with increased HPV persistence in HIV-positive participants through 18 months ($P < .01$). Participants >35 years old were more likely to have HPV persistence at all intervals for both HIV-negative and HIV-positive subjects, although levels of association were not always statistically significant. Finally, among HIV-positive women, immunosuppression level was strongly associated with HPV persistence at all follow-up intervals ($P < .01$). For example, at 6 months after the index visit, 74.9% of infections in women with CD4 cell counts ⩽200 cells/μL persisted, compared with 52.7% of infections among those with CD4 cell counts >500 cells/μL.

In multivariate analysis, high viral signal was independently associated with HPV persistence in both HIV-positive and HIV-negative women (table 4). The odds of persistence for women with high signal were 1.57 (95% confidence interval [CI], 0.96–2.58) and 2.51 (95% CI, 2.14–2.94) among HIV-negative and -positive women, respectively. Among HIV-positive women, level of immunosuppression remained significantly associated with type-specific persistence; the odds of persistence for women with CD4 cell counts ⩽200 cells/μL were 1.88 (95% CI, 1.52–2.33), compared with women with CD4 cell counts >500 cells/μL. Among HIV-positive women, older age (>35 years) was also associated with type-specific persistence (odds ratio [OR], 1.22; 95% CI, 1.00–1.49). Neither HPV risk category nor

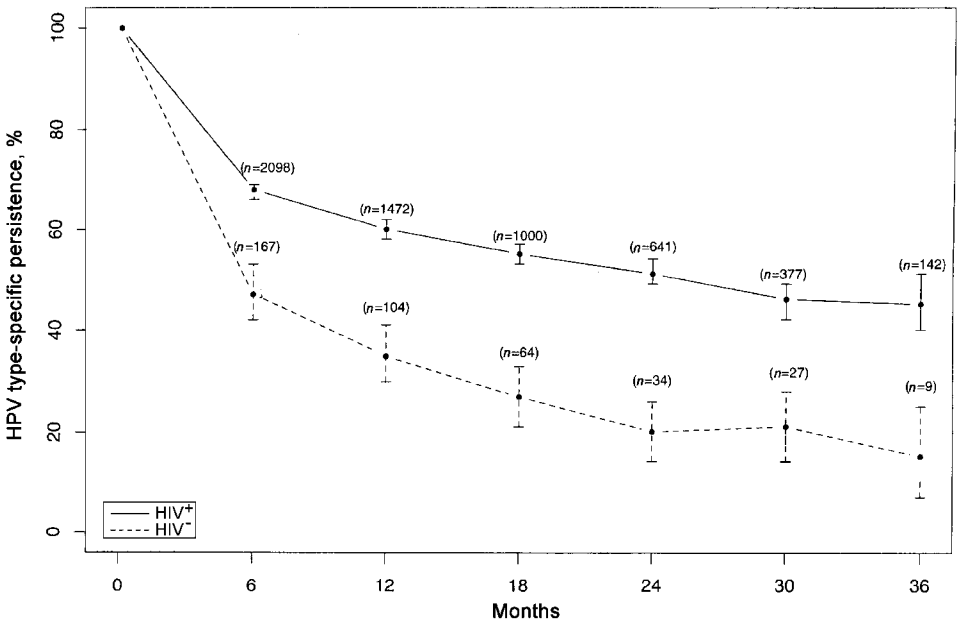

Figure 3. Persistence of human papillomavirus (HPV) after an initial infection, by human immunodeficiency virus (HIV) status. Nos. of persistent pairs at each follow-up period are shown *(n)*.

number of infections, however, remained predictive of persistence after adjustment for other covariates of interest.

When we limited the analysis of type-specific HPV persistence to incident infections, we found that, at each calendar period, pairs contributed by HIV-positive women were more likely to be persistent than were pairs contributed by HIV-negative women (e.g., 59.6% vs. 37.3% at 6 months, 45.7% vs. 26.4% at 12 months, and 42.5% vs. 19.2% at 18 months). As expected, the total number of pairs was reduced in this analysis. Among HIV-negative women, high viral signal was associated with persistence at 6, 12, and 18 months ($P < .05$). For HIV-positive women, trends were similar to those shown in table 3 (i.e., high viral signal, CD4 cell count, and Pap smear abnormalities were associated with persistence at 6, 12, and 18 months). Number of infections was not associated with persistence. The multivariate model for HIV-positive women indicated that high viral signal was independently associated with an OR of 2.04 (95% CI, 1.29–3.22). The association between CD4 cell count and type-specific persistence was also evident from this analysis (OR, 1.68; 95% CI, 0.97–2.91 [CD4 cell count ⩽200 cells/μL] and OR, 1.37; 95% CI, 0.91–2.07 [CD4 cell count 201–500 cells/μL] vs. CD4 cell count >500 cells/μL).

Discussion

Mounting evidence over the past 2 decades has led to a broad acceptance that HPV is the necessary etiologic agent for the development of invasive cervical cancer [3]. Although only a fraction of immunocompetent women infected with HPV develop cytologic abnormalities, immunocompromised HPV-positive women develop these abnormalities at greater frequencies [24]. In light of the escalation of the HIV epidemic in women and the observation that neoplasia in HIV-positive women is both more likely and more difficult to treat, understanding the reasons why immunosuppression in HIV-positive women confers excess risk is important. Several reports suggest that persistence of HPV infection may mediate the excess risk of disease [18, 25].

To further investigate this and related questions, we characterized several features of the natural history of HPV infection in a large cohort of HIV-positive and HIV-negative women studied at 4 US centers. Given the study's biannual collection of data on HIV infection and the levels of immunosuppression and HPV infection among participants, we were able to investigate the manner in which HIV modulates the course of HPV infection. Our findings support the conclusion that HIV infection and related immunosuppression are associated with high HPV prevalence, a higher risk of incident HPV infection, and an increased rate of type-specific persistence.

We found that cumulative prevalence of HPV infection after 3 years of follow-up was 54.6% among HIV-negative women, compared with 90.2% among HIV-positive women with CD4 cell counts ⩽200 cells/μL. The fact that 10% of the latter group of high-risk extremely immunosuppressed women did not shed HPV during follow-up suggests that there may be a degree of immunity to repeated HPV exposure. Further examination of factors associated with remaining HPV negative will be of interest. Also needed is continuing investigation of the reasons for high prevalence of HPV infection among immunosuppressed

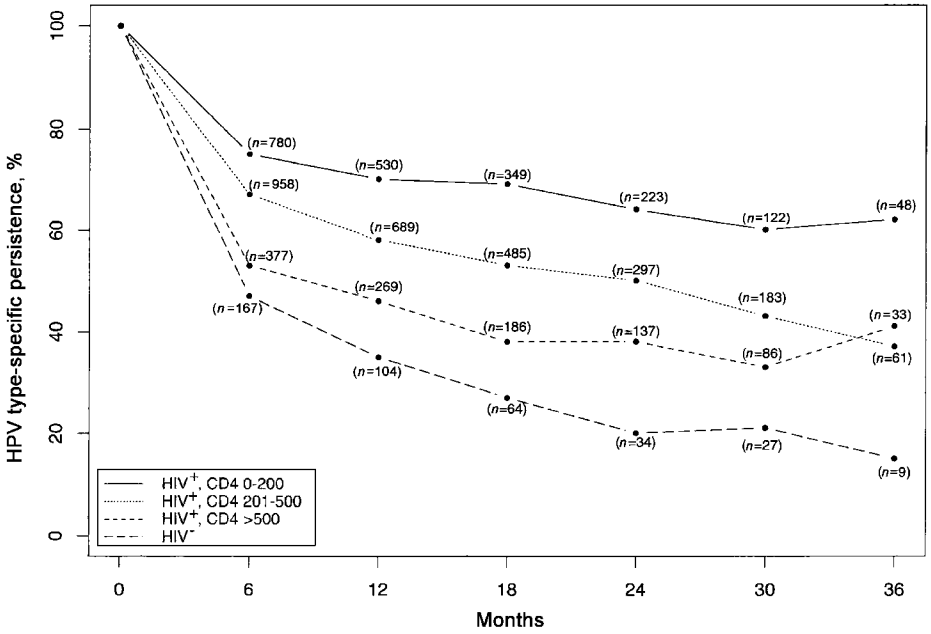

Figure 4. Persistence of human papillomavirus (HPV) after an initial infection, by human immunodeficiency virus (HIV) status and CD4 cell count. Nos. of persistent pairs at each follow-up period are shown *(n)*.

women. Explanations include increased incidence, a longer duration of infection (i.e., greater persistence), and increased likelihood of reactivation. An alternative explanation is intermittent shedding.

Our examination of type-specific infection determined that the incidence of infection for all categories of HPV was higher among HIV-positive women. Several explanations might be considered: first, higher rates of exposure; second, increased likelihood of reactivation of latent infections; or third, increased susceptibility to infection. We found that higher incidence rates could not be attributed to higher rates of exposure to HPV, as the reported number of recent sex partners was lower for HIV-positive women than for HIV-negative women. An increased likelihood of reactivation of latent infections acquired before recruitment seems to be more plausible. As for the third explanation, it is not known whether HIV infection increases the probability of HPV infection in an exposed woman. It is possible that HPV infection is more readily detectable in HIV-positive women because of a higher HPV load in the specimen.

An additional emphasis of our analysis was to identify viral factors at the index measurement that were associated with type-specific HPV persistence, defined here as the repeated detection of the same HPV DNA type at consecutive visits 6–36 months apart. Among HIV-positive women, immunosuppression and high viral signal both made persistence more likely. The latter observation is in keeping with findings from a recent nested case-control study in which cervical carcinoma in situ associated with HPV-16 was more common in women with high HPV-16 virus loads [26]. We found that number of infections and HPV risk category (high, intermediate, or low) were not associated with persistence. The latter results contrast with those of Hildescheim et al. [14], whose findings suggested that women infected with a cancer-associated HPV type at the index visit were more likely to be infected with the same type of HPV at the follow-up visit than were those with a non–cancer-associated type (45% vs. 24%; $P = .11$). Similarly, Ho et al. [13] found that the odds of HPV persistence for >6 months was associated with infection with a high-risk HPV type at the previous visit (adjusted OR, 1.5; $P = .03$).

We also found that age affected persistence among HIV-positive women: those >35 years old were more likely to demonstrate persistence for ⩽18 months ($P < .05$). In our multivariate analysis, however, the odds of persistence among older women had only borderline significance. These results are consistent with those of Hildesheim et al. [14], who found that women >30 years old were more likely to have persistent HPV than were those <24 years old (65% vs. 24%; $P = .02$). Findings by Ho et al. [13] also indicated that older age is associated with persistence.

Longitudinal studies of HPV infection with ongoing follow-up are important, to determine the correlates and outcomes associated with HPV persistence. It is in keeping with current models of carcinogenesis that persistent HPV infection would lead to increased genetic instability and favor the accumulation of cellular genetic mutations that precede the development of cancer. Several epidemiologic models that quantify such viral persistence have been proposed, and recent investigations have

Table 4. Multivariate model of type-specific persistence of human papillomavirus (HPV) in human immunodeficiency virus (HIV)–positive and HIV-negative participants.

	HIV negative		HIV positive	
Characteristic	OR	95% CI	OR	95% CI
Viral signal				
Low	1.0		1.0	
High	1.57	0.96–2.58	2.51	2.14–2.94
No. of infections[a]				
1			1.0	
2–3			0.98	0.85–1.14
⩾4			1.14	0.94–1.39
HPV risk category				
Low	1.0		1.0	
Intermediate	0.82	0.41–1.65	0.88	0.72–1.08
High	0.98	0.51–1.88	1.12	0.87–1.45
CD4 cell count, cells/μL				
>500			1.0	
201–500			1.37	1.14–1.63
⩽200			1.88	1.52–2.33
Age, years				
<35	1.0		1.0	
⩾35	0.87	0.52–1.47	1.22	1.00–1.49

NOTE. Separate models were fit for HIV-negative and HIV-positive women. Multivariate models were adjusted for all variables in the table and for time between measurements. CI, confidence interval; OR, odds ratio.

[a] Among HPV infections that were typed.

sought to gain a better understanding of viral persistence. These studies consistently demonstrated that HIV-positive women are more likely to have persistent infection than their HIV-negative counterparts. By use of various methods and definitions to quantify persistence, the studies have found that HIV infection and immunosuppression are important predictors of persistence. Sun et al. [18] defined a person as having persistent HPV if the same HPV type was detected in 2 consecutive measurements within 12 months. Ahdieh et al. [25] computed the percentage of HPV positivity among serial measurements (i.e., the ratio of HPV-positive measurements to total HPV measurements) and the duration of infection by using a time-to-event analysis. Wallin et al. [4] showed that patients with cervical cancer were significantly more likely to have type-specific persistent HPV than were control subjects.

In the present study, we used another approach to characterize persistence—the use of sequential pairs of measurements contributed by study participants. We were comfortable using this approach, given that intermittent viral shedding was rare, and we applied methods that accounted for the inherent correlation of repeated measurements. As such, we were able to maximize the informative value of the longitudinal HPV measurements that were carefully collected over a 3-year period.

In summary, this study documents the association of HIV infection and related immunosuppression with the prevalence and incidence of HPV infection and with type-specific HPV persistence. The extent to which persistence relates to significant cervical pathology among women who are infected with HIV requires further investigation. In addition, the extent to which highly active antiretroviral therapy can effectively reverse immunosuppression and decrease the progression of cervical disease remains to be established.

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