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Long-term cumulative detection of human papillomavirus among HIV seropositive women

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Abstract

Objective—To estimate the effects of infection by human immunodeficiency virus (HIV) on the type-specific cumulative detection of cervicovaginal infection by human papillomavirus (HPV).

Design—Retrospective assessment of prospectively collected data in a multicenter U.S. cohort.

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Methods—HIV seropositive and at-risk seronegative participants in the Women's Interagency HIV Study were followed semiannually for up to 11 years. HPV typing was determined from cervicovaginal lavage specimens by polymerase chain reaction; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 were considered carcinogenic.

Results—Among 3438 women enrolled, (2543 HIV seropositive, 895 seronegative), the cumulative detection of any HPV infection rose among HIV seropositive women from 53% at baseline to 92% at 8 years and among seronegative women from 22% to 66% ($P < 0.0001$ for HIV seropositive vs seronegative women). The 8-year cumulative detection of carcinogenic and noncarcinogenic HPV was 67% and 89% among HIV seropositive and 36% and 56% among seronegative women ($P = 0.001$ for both carcinogenic and noncarcinogenic HPV). The 8-year cumulative detection of HPV16 and HPV 18 was 15.2% and 15.0% in HIV seropositive and 6.7% and 6.1% in HIV seronegative women ($P < 0.0001$ for both). In multivariable regression analyses, lower CD4 count, age under 30 years, and smoking but not number of lifetime sexual partners were significant correlates of cumulative HPV detection.

Conclusion—More than 90% of HIV seropositive women have HPV detected during long follow-up. Rates are lower among at-risk HIV seronegative women, though most also develop HPV infections.

Keywords

Human papillomavirus; HIV in women; immunodeficiency

Introduction

Genital infection with human papillomaviruses (HPVs) can lead to cervical, vulvar, vaginal, anal, and other cancers (1). Co-infection with the human immunodeficiency virus (HIV) amplifies the burden of HPV infection. HPV prevalence and short-term persistence are high among women with HIV (2-6). Further, women with HIV have a 77% cumulative risk of abnormal cervical cytology after up to 10 years of observation (7). Long-term cumulative HPV detection in women with HIV may be substantially higher, since many HPV infections do not result in abnormal cytology, but long-term surveillance studies have not been reported. Long-term type-specific infection rates are unknown.

The main purpose of this analysis was to estimate the cumulative detection of HPV infection in a cohort of HIV seropositive women and at-risk comparison HIV seronegative women. While prevalence and short-term incidence data have been published previously, we have not assessed long-term cumulative detection. In addition, this analysis included women recruited during a second enrollment round, with follow-up extended up to 8 years.

Materials and Methods

This study was part of the Women's Interagency HIV Study (WIHS), an ongoing observational multicenter cohort study of the health of HIV seropositive women and at-risk HIV-uninfected comparison women. Enrollment was initially conducted between October 1994 and November 1995 (2055 HIV seropositive, 569 seronegative women), and a second cohort was similarly enrolled during 2002 (738 HIV seropositive, 406 seronegative women).

(8, 9). After local human subjects committees' reviewed and approved the study, all participants gave written informed consent for data collection. Follow up continues, but this analysis includes information obtained between October 1, 1994 and March 30, 2005.

Every six months, participants had a physical examination that included cervicovaginal lavage (CVL) with 10 ml of saline. The current data reflect HPV DNA testing of over 34,000 CVL specimens conducted to assess the natural history of HPV infection in HIV seropositive and seronegative women; after which more targeted testing was conducted focused on the development of severe cervical neoplasia. Briefly, in the Natural History Study, routine testing of all available samples from all WIHS women enrolled during 1994-1995 continued through 8.5 years of follow- up (>27,000 CVLs), and then continued in a random sample of 300 women up to 12 years. For those enrolled during 2001-2002, testing in all samples from all women continued for 3.5 years with a random sample of 200 through 5 years. The number of women who contributed data to each time point by HIV status is shown in Figure 1.

Protocols for 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. All β-globin negative specimens were excluded, and rates were calculated based on the number of β-globin positive results to avoid positive bias in cumulative prevalence estimates. Results were classified as defined by the International Association for Research on Cancer, including any carcinogenic type (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), for any type, and negative for HPV. These investigational results were not used in patient management.

We defined the baseline visit for any individual as the first visit with an adequate (i.e., β-globin positive) HPV result, regardless of the time of entry to WIHS or chronological date. We excluded women with no interpretable HPV results, HIV seronegative women who seroconverted during follow-up, and those who reported a prior hysterectomy at their baseline visit. Women were not censored at the time of cervical disease treatment, since they remained at risk for new or recurrent cervical HPV infection; however, they were censored if they had a hysterectomy during follow-up.

Contingency tables were generated to assess baseline patient characteristics by HIV serostatus. Pearson's chi-squared tests were used to compare baseline characteristics between HIV seropositive and seronegative women, including baseline HPV prevalence. Mantel-Haenszel chi-square tests were used to compare HPV prevalence at baseline across HIV/CD4 strata. Wilcoxon rank-sum tests were used to compare medians. We assessed the cumulative detection of HPV across visits, defined as the proportion of women ever positive for any HPV or for a given HPV type. Cumulative detection of HPV across sequential midvisit times was estimated using the Kaplan-Meier method (1 – proportion surviving free of HPV); results for women with and without HIV were compared. Normal approximations to the log ratio of two cumulative detections were used to obtain 95% confidence intervals for each HPV type and for all HPV types. P-values based on the same approximations were given for overall cumulative detections. To assess how annual detection changed with age,

we charted annual HPV cumulative detection across age strata for all HPV types and for HPV 16/non16 carcinogenic types/noncarcinogenic types. Generalized estimating equation (GEE) models with logit link were used to study the multivariable association of risk factors with cumulative detection of HPV. These models focused on 5-year cumulative prevalence, the mid-point of the 10-year follow-up period, and the last time for which point data were available from both the 199-95 and 2002 subcohorts. All tests were two-sided with significance set at $P < 0.05$.

Results

Among all the 3766 women in WIHS (2791 HIV seropositive, 975 seronegative), 22 HIV seroconverters were excluded; 249 women (206 HIV seropositive, 43 seronegative) were excluded due to hysterectomy prior to their baseline visits; 57 women (42 HIV seropositive, 15 seronegative) were excluded because they had no HPV results from any visit. The number of women eligible for analysis of prevalence and cumulative detection was thus 3438 (2543 HIV seronegative, 895 seronegative). Median follow-up up in those enrolled during 1994-1995 was 6.8 years among HIV seropositive and 6.9 among HIV seronegatives, where as it was 2.4 years for HIV seropositive and seronegative women enrolled during 2002. Overall, the mean (median/minimum) percent (%) of: (i) WIHS women who had a cervicovaginal lavage (CVL) obtained was 95% (95%/91%); (ii) Women with a CVL who were HPV tested at each visit was 95% (97%/76%); (iii) HPV tests that were adequate at each visit was 96% (96%/92%).

The characteristics of women included in this study group at their first visits with valid HPV test results are shown in Table 1. The median age of HIV seropositive women was 35 years, while that of seronegative women was 32 years ($P < 0.0001$). Although the distribution of lifetime number of sex partners in HIV seropositive and seronegative women differed, there was no linear pattern to this and the median number was 10 in both groups ($P = 0.25$). The number of sex partners in the last six months, however, was greater in HIV seronegative than HIV seropositive women. Compared to HIV seronegative women, seropositive women were less likely to smoke but more likely to have ever used intravenous drugs. The low rate of use of highly active antiretroviral therapy (HAART) by HIV seropositive women reflects treatment standards at the time of enrollment (0.4% in those recruited in 1994-5; it has increased with time (10).

Figure 1 shows HPV cumulative prevalence at baseline and at each subsequent visit through the 8-year semiannual visit sequence. The prevalence of any HPV infection at the first visit sequence. The prevalence of any HPV infection at the first visit with HPV results was 1333/2543 (52%) among HIV seropositive women and 199/895 (22%) among seronegative women ($P < 0.0001$). When examined by CD4 stratum among HIV seropositive women, the prevalence of HPV of any type was 297/814 (36%) among women with CD4 counts >500/cmm, 559/1052 (53%) among women with CD4 counts between 200-500/cmm, and 434/604 (72%) among women with CD4 counts <200/cmm ($P < 0.0001$). The prevalence of carcinogenic HPV was 716/2543 (28%) among HIV seropositive women and 93/895 (10%) among seronegative women ($P < 0.0001$). Carcinogenic HPV types were found in 131/814 (16%) HIV seropositive women with CD4 counts >500/cmm, 299/1052 (28%) of those with

CD4 counts between 200-500/cmm, and 262/604 (43%) of those with CD4 counts <200/cmm (P < 0.0001). The prevalence of noncarcinogenic HPV was 1038/2543 (41%) among HIV seropositive women and 136/895 (15%) among seronegative women (P < 0.0001).

Cumulative HPV detection is shown in Fig. 1, censoring at loss to follow-up or hysterectomy, showing a progressive rise in cumulative detection both for any and for specifically carcinogenic HPV detection among both HIV seropositive and seronegative women. The cumulative incident detection of HPV among seronegative women lagged that of seropositive women by several years. Among HIV seropositive women, the cumulative detection of any HPV infection was 68% at one year but rose to 75% at two years, 86% at 5 years, and 92% at 8 years; similar rates in HIV seronegative women were 34%, 43%, 57%, and 66% (all P < 0.0001 vs HIV seropositive women. In HIV seropositive women, cumulative detection of carcinogenic HPV rose to 40% at one year, 47% at two years, 61% at 5 years, and 67% at 8 years; similar rates in HIV seronegative women were 16%, 20%, 20%, and 36% (again, all P < 0.0001 vs HIV seropositive women. Cumulative detection of noncarcinogenic HPV types is not shown in the figure but among HIV seropositive women was 59% at one year, 67% at two years, 82% at five years, and 89% at 8 years; similar cumulative detection rates among HIV seronegative women were 25%, 35%, 48%, and 56% (P < 0.0001).

We looked specifically at how the cumulative detection of HPV varied between HIV seropositive and seronegative women across hierarchical groupings of carcinogenicity. The ratio of 8-year cumulative detection of HPV 16 among HIV seropositive to seronegative women was 2.26 (95% C.I. 1.63, 3.14) and for HPV 18 was 2.44 (95% C.I. 1.69, 3.53). For non-16/18 carcinogenic HPV types, the ratio was 3.21 (95% C.I. 2.69, 3.73), higher than for HPV 16/18 (P = 0.03). The ratio was also higher, for noncarcinogenic types than for HPV 16/18, at the ratio was 4. (95% C.I. 3.62, 5.56) (P = 0.01).

In multivariable regression analyses, as shown in Table 2, enrollment characteristics correlated withs a higher cumulative detection of any HPV by five years included CD4 stratum among HIV seropositive women younger age, and enrollment cohort. Current smoking increased and former smoking decreased cumulative detection of HPV. Lifetime number of sexual partners was not associated with cumulative HPV detection. In a second analysis, we additionally assessed the impact of enrollment period on these findings by incorporating it as a covariate in our models. Although there was a small association between this enrollment period and cumulative prevalence (OR = 1.15; 95% C.I. 1.04, 1.26) its inclusion in the model had no discernable impact on other effect estimates in the model (data not shown), and enrollment period is not shown as a variable in Table 2.

Type-specific 8-year cumulative HPV detection rates are shown in Table 3. The most common HPV types in HIV seropositive women were noncarcinogenic: type 53 (25.3%), type 61 (24.2%), type 81 (20.9%), and type 62(20.7%). In contrast, the HPV types most commonly detected over 8 years of follow-up in HIV seronegative women Included the noncarcinogenic type 53 (9.0%) and type 81 (7.5%), but also the carcinogenic type 56 (7.7%). HPV 16 was detected over 8 years in 15.2% of HIV seropositive and 6.7% of

seronegative women, while HPV 18 was detected in 15.0% of HIV seropositive and 6.1% of seronegative women ($P < 0.0001$ for both). Other types were detected in 66.2% of HIV seropositive and 35.1% of seronegative women. Differences in cumulative HPV detection between HIV seropositive and seronegative women were significant at $P < 0.05$ for all types except type 69, 69.

Discussion

HPV acquisition is very common among sexually active women, and HIV seropositive women have among the highest HPV rates reported. These results expand upon our previous reports that HIV infection increases HPV detection (2, 3). With follow-up for some women now extending 8 years, cumulative HPV detection among HIV seropositive women surpassed 90%. Two-thirds of HIV seropositive women had carcinogenic HPV detected over 8 years.

Despite high cumulative HPV detection and a high frequency of abnormal Pap tests, prior work has shown that most abnormal Paps in HIV seropositive women are atypical or low grade (7). In registry studies, cervical cancer risk among these women is only modestly higher than that in the general population (11). In WIHS, which included aggressive screening and treatment of precursors and expert pathology review of reported cervical cancers, the increased risk of cervical cancer in HIV seropositive compared to seronegative women did not reach statistical significance (12).

Across time, almost 90% of HIV seropositive women in this study experienced noncarcinogenic HPV infections, significantly greater incidence detection than was observed for carcinogenic HPVs. Clifford and associates have reported in a meta-analysis that the noncarcinogenic HPV types 53, 61, and 83 were more common than carcinogenic types in North American women with HIV (13). They also reported that women with HIV and high grade Pap test abnormalities were more likely to have HPV types other than HPV 16. In the general population, HPV types 16 and 18 account for the majority of cancers and true precancers, while noncarcinogenic types do not increase cancer risk (14, 15).However, data in the WIHS has shown that the prevalence of HPV16 is the least affected by changes in immune status of any carcinogenic HPV among HIV seropositive women (4, 16). Most cervical cytologic lesions in HIV seropositive women who are in care and have regular Pap testing are atypical or low grade, while high grade lesions are not common and cancers are rare (7, 12). A high cumulative detection of noncarcinogenic HPV may contribute to this difference, although correlative studies linking individual cytology and HPV results are needed.

The cumulative detection of HPV in HIV seronegative women in our cohort lagged behind that among HIV seropositive women by several years yet still rose to 66% by 8 years, with carcinogenic HPV found in more than a third during the same period. The high rates of HPV detection in HIV seropositive women likely represent background HPV exposure rates in sexually active women. At-risk HIV seronegative women in WIHS reported more sexual activity and were more likely to report multiple partners than HIV seropositive women (17, 18), so lower exposure risk does not explain lower HPV detection in HIV seronegative

women. Higher HPV detection rates in HIV seropositive women reflect both more reactivation of prior infections acquired during more sexually active phases of their lives and ongoing sexual exposure. Conversely, lower HPV detection rates in HIV seronegative women likely reflect lower reactivation rates and similar HPV exposures that result in less detectable infection because host immune mechanisms either prevented infections or cleared them between HPV tests (3).

These high rates of cumulative HPV detection over time are consistent with prior reports, though our surveillance extends further. Despite excluding women with prevalent cervical disease, Sun et al found that cumulative detection of HPV after up to two years of observation was 83% in HIV infected women and 62% in uninfected women (5). Over three years of observation, Tornesello and associates found HPV in 39% of HIV infected and 14% of HIV uninfected women (19). Schneider and colleagues found a cumulative detection of HPV infection of 66% in presumably HIV uninfected young women despite five years of normal Pap results (20), while Winer and associates reported a 32% cumulative incidence in U.S. university students followed for two years (21).

We found that cumulative detection of HPV was not related to lifetime number of partners. While this may seem counterintuitive, since HPV is sexually transmitted, HPV incidence is more closely related to recent sexual activity, as even women with impaired immunity can clear HPV over time (3). Women with large numbers of lifetime partners who are too ill for sex are unlikely to acquire new HPV infections, while women with relatively few lifetime partners but recent new partners are likely to acquire new infections.

Our study was limited by several factors. At enrollment, most women were over age 30 years and so were beyond the age of highest risk for HPV acquisition, especially acquisition of types 16 and 18 (22, 23). In addition, we only tested for HPV at six-month intervals, while some infections might have been acquired and cleared between visits, and some women were lost to follow-up for variable intervals. Identification and treatment of lesions related to HPV types 16 and 18 prior to WIHS enrollment may have increased the proportion of non-16/18 carcinogenic HPV types detected during follow-up. We were unable to assess the impact of prior treatment on subsequent HPV detection, as this was captured only by self-report and appeared unreliable. We have previously shown that antiretroviral therapy reduces HPV infection, but mainly in women who are highly adherent (24); because of the complexity of assessing adherence, we did not explore the impact of antiretroviral therapy on cumulative detection. Women were censored from follow-up at hysterectomy because hysterectomy distorts the pattern of HPV infection, favoring noncarcinogenic types (25). Nevertheless, women might have continued to contribute after hysterectomy to cumulative HPV detection. Life-long cumulative HPV detection is likely to be even greater than our results indicate.

Persistence rather than incidence of HPV infection appears to determine cancer risk; additional work is needed to define which types are most persistent, how HIV-induced immunosuppression influences HPV persistence as well as incidence, and how persistent infections are correlated with development of precancer and cancer in immunocompromised women. We could not determine whether the higher rate of HPV detection in HIV

seropositive women was due to more persistent infections that were more likely to be detected at semiannual visits, to more frequent reactivation of previously acquired infections, or to greater susceptibility to HPV infection. Furthermore, condom use can decrease HPV acquisition and speed clearance (26, 27); because of limitations to our data on consistency of condom use across partners and time, we did not explore whether condom use alters HPV risk over time. Further studies should investigate the effectiveness of condoms in reducing HPV acquisition among HIV seropositive women.

The high cumulative detection of HPV in HIV seropositive women underscores the importance of education for these women and the clinicians who care for them. HPV-related cervical, vaginal, and vulvar lesions are common, often chronic problems in HIV seropositive women. The most commonly detected HPV types over time in HIV seropositive women were noncarcinogenic, potentially causing cytologic changes and cervical lesions but posing minimal risk for cancer. Balancing the importance of treatment for true cancer precursors against the discomfort and disruption of repeated colposcopy and cervical interventions will require a deeper understanding of the natural history of HPV in HIV seropositive women. Our group is exploring the links between HIV-related immunocompromise, HPV clearance and persistence, and their relationship to progression to cervical and other lower genital tract cancers.

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All co-authors were involved in conception and design and drafting and revision of the manuscript for important intellectual content. In addition, Dr. Xie did statistical calculations and help guide analyses. Dr. D'Souza helped focus analyses based on HPV expertise. Drs. Minkoff, Levine, Young, and Cohen are principal investigators for the WIHS and supervise the overall study. Dr. Watts performed critical executive functions for WIHS as a program representative from NICHD. Drs. Palefsky and Burk performed HPV testing and provided guidance about terminology and focused discussion. Ms. Keller provided patient care and oversaw local site gynecologic management and patient data acquisition critical to the conduct of the work and assisted in describing the relevance of findings to clinical care.

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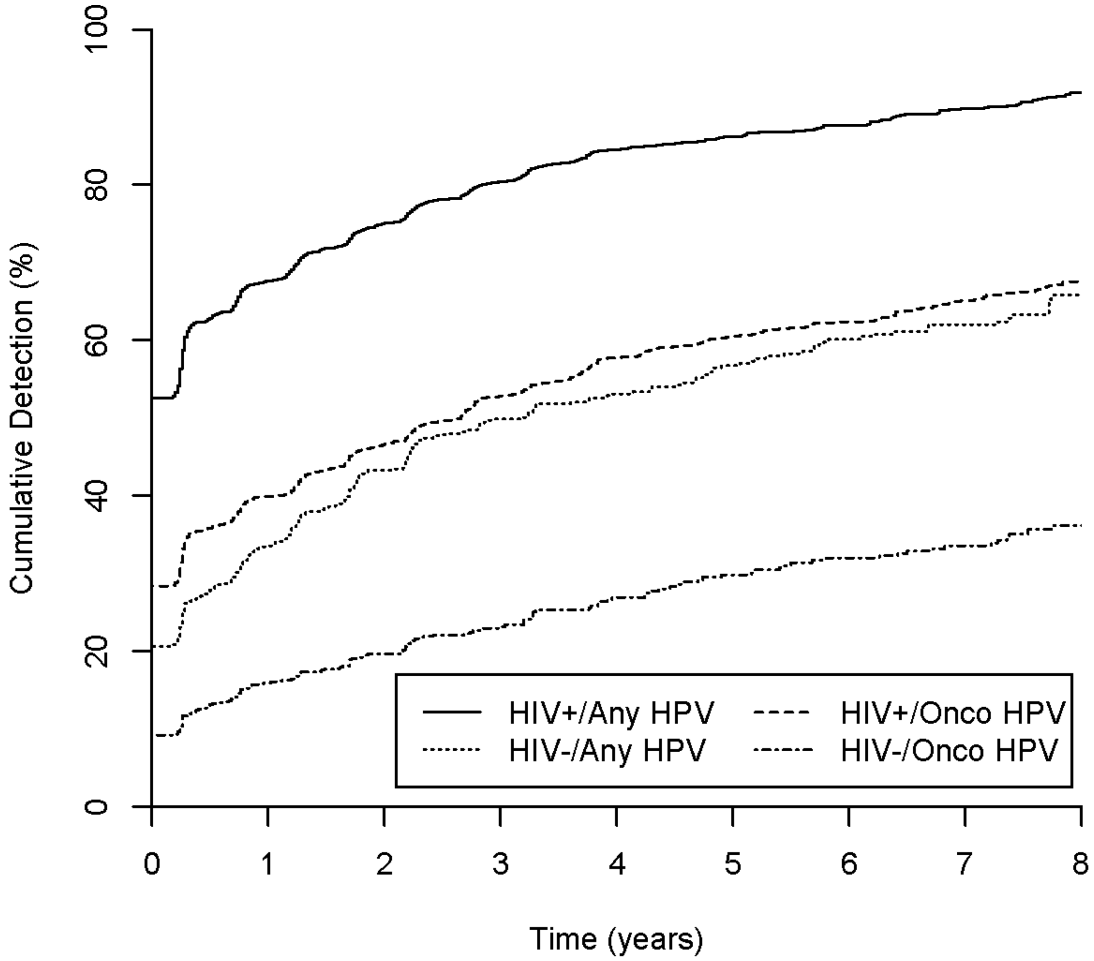

No. of women with HPV data at corresponding WIHS visit*

HIV+	2543	1747	1551	1269	1097	1007	952	854	651
HIV-	895	611	600	429	325	292	276	242	171

*Baseline is the first visit with adequate HPV test data for each individual. Shown is the number of women at baseline and each subsequent visit through the 8-year semiannual visit (i.e., 16 additional visits after baseline for each individual). The mean (median / minimum) percent (%) of: (i) WIHS women who had a cervicovaginal lavage (CVL) obtained at each visit was 95% (95% / 91%); (ii) Women with a CVL who were HPV tested at each visit was 95% (97% / 76%); (iii) HPV tests that were adequate at each visit was 96% (96% / 92%).

Fig. 1.

Cumulative detection of any and of carcinogenic (onco) human papillomavirus (HPV) among HIV seropositive (HIV+) and seronegative (HIV-) women. For all time points, risk of any and of carcinogenic HPV was higher among HIV seropositive women ($P < 0.0001$).

Table 1

Characteristics of study participants at the first visit with results of human papillomavirus testing. N (%)

Characteristic*	HIV+ (N = 2543)	HIV- (N = 895)	P-value
Age (years)			<.0001
<30	635 (25)	376 (42)	
30-34	639 (25)	184 (21)	
35-39	641 (25)	163 (18)	
40-44	391 (15)	114 (13)	
>=45	237 (9)	58 (6)	
Race/Ethnicity			0.49
White	396 (16)	126 (14)	
Hispanic	677 (27)	257 (29)	
Black	1386 (55)	479 (54)	
Others	84 (3)	33 (4)	
Smoking			0.004
Never smoked	853 (34)	278 (31)	
Former smoker	406 (16)	112 (13)	
Current smoker	1277 (50)	503 (56)	
Ever used intravenous drugs			0.03
No	1183 (71)	484 (75)	
Yes	489 (29)	159 (25)	
Lifetime number of male sexual partners			0.001
<5	616 (25)	180 (20)	
5-9	502 (20)	191 (22)	
10-49	784 (31)	330 (37)	
>50	593 (24)	182 (21)	
Number of male sexual partners in past 6 months			<.0001
0	745 (30)	167 (19)	
1	1414 (56)	438 (49)	
2	203 (8)	137 (15)	
>=3	158 (6)	149 (17)	
CD4+ T cells/cmm			
>500	814 (33)		
200-500	1052 (43)		
<200	604 (24)		
HIV viral load (copies/ml)			
<=4000	948 (38)		
4001-20,000	515 (21)		
20,001-100,000	549 (22)		

Characteristic*	HIV+ (N = 2543)	HIV- (N = 895)	P-value
>100,000	485 (19)		
Use of highly active antiretroviral therapy			
No	2193 (86)		
Yes	349 (14)		

*Certain data were missing for some women in some categories: smoking (7 HIV seropositives, 2 seronegative), ever used intravenous drugs (2 HIV seropositive), lifetime number of male sexual partner (48 HIV seropositive, 12 seronegative), number of male sexual partner in past 6 months (23 HIV seropositive, 4 seronegative), CD4+ T-cell count (73 HIV seropositive), HIV viral load (46 HIV seropositive), use of highly active antiretroviral therapy (1 HIV seropositive).

Table 2

Ratio of cumulative detection of any HPV type after five years of observation.

Characteristic		Cumulative Risk Ratio	95% CI[1]		P-value
			LCL[2]	UCL[3]	
HIV/CD4 count (cells/cmm)	HIV- (ref)	1	-	-	<.0001[4]
	CD4>500	1.80	1.58	2.06	<.0001
	CD4:200-500	3.03	2.69	3.41	<.0001
	CD4<200	5.76	5.07	6.55	<.0001
Age (years)	<30 (ref)	1	-	-	-
	30-34	0.75	0.67	0.84	<.0001
	35-39	0.77	0.69	0.87	<.0001
	40-44	0.63	0.55	0.73	<.0001
	>=45	0.69	0.59	0.81	<.0001
Smoking	Never (ref)	1	-	-	-
	Former	0.82	0.72	0.95	0.01
	Current	1.14	1.03	1.26	0.01
Life time number of male sexual partners	<5 (ref)	1	-	-	-
	5-9	1.05	0.93	1.20	0.43
	10-49	1.00	0.89	1.13	0.98
	>=50	1.09	0.96	1.23	0.21
Enrollment period	1994-95 (ref)	1	-	-	<.0001[4]
	2001-02	1.80	1.58	2.06	<.0001

[1] Confidence interval

[2] 95% lower confidence limit

[3] 95% upper confidence limit

[4] By test for trend

Table 3

Cumulative incidence detection of individual HPV types at 10 years (%).

HPV type	HIV- (N = 895)[1]	95% CIs for HIV-	HIV+ (N = 2543)[1]	95% CIs for HIV+	P-value
6	2.5	(1.4, 3.6)	7.4	(6.2, 8.6)	<.0001
11	0.9	(0.1, 1.6)	6.1	(4.9, 7.3)	<.0001
16	67	(4.6, 8.8)	15.2	(13.4, 16.9)	<.0001
18	6.1	(4.0, 8.3)	15.0	(13.2, 16.7)	<.0001
26	1.6	(0.3, 2.8)	3.7	(2.8, 4.7)	0.04
31	5.5	(3.5, 7.5)	11.5	(9.9, 13.1)	0.0003
32	1.8	(0.6, 3.0)	9.5	(7.9, 11.0)	<.000l
33	2.2	(0.9, 3.6)	11.0	(9.5, 12.6)	<.000l
35	2.1	(0.9, 3.3)	7.0	(5.7, 8.2)	0.0001
39	1.6	(0.7, 2.6)	6.2	(5.0, 7.4)	<.000l
40	0.7	(0.l, 1.3)	4.3	(3.3, 5.3)	0.0001
45	4.1	(2.3, 5.9)	11.0	(9.4 12.5)	<.000l
51	4.9	(3.0, 6.8)	15.3	(13.5, 17.2)	<.000l
52	4.5	(2.8, 6.3)	16.l	(142, 18.0)	<.000l
53	9.0	(6.5, 11.5)	25.3	(23.1, 27.5)	<.000l
54	2.2	(1.1, 3.2)	14.6	(12.8, 16.5)	<.000l
55	0.7	(0.l, 1.3)	4.7	(3.6, 5.8)	0.0001
56	77	(5.0, 10.5)	13.0	(11.3, 14.7)	0.01
58	5.2	(3.5, 6.9)	18.9	(16.9, 20.9)	<.000l
59	3.6	(1.6, 5.6)	9.2	(7.8, 10.5)	0.002
61	7.3	(4.7, 10.0)	24.2	(22.0, 26.4)	<.000l
62	6.2	(3.5, 8.9)	20.7	(17.7, 23.6)	<.000l
63	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)	NA
66	2.5	(1.2, 3.7)	13.5	(11.7, l5.4	<.000l
67	0.3	(0.0, 0.8)	3.7	(2.0, 5.4)	0.001
68	2.5	(1.3, 3.8)	10.1	(8.5, 11.6)	<.000l
69	2.5	(0.0, 5.2)	3.6	(2.2, 4.9)	0.53
70	7.1	(4.5, 9.8)	17.5	(15.6, 19.5)	<.0001
71	5.7	(3.1, 8.4)	16.1	(13.4, 18.7)	<.0001
72	4.2	(1.7, 6.7)	10.9	(8.6, 13.2)	0.003
73	2.3	(0.9, 3.7)	11.2	(9.6, 12.8)	<.0001
81	7.5	(4.5, 10.5)	20.9	(18.1, 23.7)	<.0001
82	1.1	(0.3, 1.9)	7.1	(5.7, 8.4)	<.0001
83	6.2	(4.0, 8.5)	20.1	(18.1, 22.2)	<.0001
84	2.3	(1.0, 3.5)	19.1	(17.0, 21.2)	<.0001
85	1.6	(0.1, 3.0)	6.6	(4.9, 8.3)	0.003
89	1.1	(0.0, 2.2)	60	(4.2, 7.7)	0.001
Other	35.1	(30.6, 39.6)	66.2	(63.2, 69.2)	<.0001

[1] Number of women at enrollment. The number of women contributing data at each time point is shown in Fig. 1.