Risk of Cervical Precancer and Cancer Among HIV-Infected Women With Normal Cervical Cytology and No Evidence of Oncogenic HPV Infection

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Context US cervical cancer screening guidelines for human immunodeficiency virus (HIV)–uninfected women 30 years or older have recently been revised, increasing the suggested interval between Papanicolaou (Pap) tests from 3 years to 5 years among those with normal cervical cytology (Pap test) results who test negative for oncogenic human papillomavirus (HPV). Whether a 3-year or 5-year screening interval could be used in HIV-infected women who are cytologically normal and oncogenic HPV–negative is unknown.

Objective To determine the risk of cervical precancer or cancer defined cytologically (high-grade squamous intraepithelial lesions or greater [HSIL+]) or histologically (cervical intraepithelial neoplasia 2 or greater [CIN-2+]), as 2 separate end points, in HIV-infected women and HIV-uninfected women who at baseline had a normal Pap test result and were negative for oncogenic HPV.

Design, Setting, and Participants Participants included 420 HIV-infected women and 279 HIV-uninfected women with normal cervical cytology at their enrollment in a multi-institutional US cohort of the Women's Interagency HIV Study, between October 1, 2001, and September 30, 2002, with follow-up through April 30, 2011. Semiannual visits at 6 clinical sites included Pap testing and, if indicated, cervical biopsy. Cervicovaginal lavage specimens from enrollment were tested for HPV DNA using polymerase chain reaction. The primary analysis was truncated at 5 years of follow-up.

Main Outcome Measure Five-year cumulative incidence of cervical precancer and cancer.

Results No oncogenic HPV was detected in 369 (88% [95% CI, 84%-91%]) HIV-infected women and 255 (91% [95% CI, 88%-94%]) HIV-uninfected women with normal cervical cytology at enrollment. Among these oncogenic HPV–negative women, 2 cases of HSIL+ were observed; an HIV-uninfected woman and an HIV-infected woman with a CD4 cell count of 500 cells/μL or greater. Histologic data were obtained from 4 of the 6 clinical sites. There were 6 cases of CIN-2+ in 145 HIV-uninfected women (cumulative incidence, 5% [95% CI, 1%-8%]) and 9 cases in 219 HIV-infected women (cumulative incidence, 5% [95% CI, 2%-8%]). This included 1 case of CIN-2+ in 44 oncogenic HPV–negative HIV-infected women with CD4 cell count less than 350 cells/μL (cumulative incidence, 2% [95% CI, 0%-7%]), 1 case in 47 women with CD4 cell count of 350 to 499 cells/μL (cumulative incidence, 2% [95% CI, 0%-7%]), and 7 cases in 128 women with CD4 cell count of 500 cells/μL or greater (cumulative incidence, 6% [95% CI, 2%-10%]). One HIV-infected and 1 HIV-uninfected woman had CIN-3, but none had cancer.

Conclusion The 5-year cumulative incidence of HSIL+ and CIN-2+ was similar in HIV-infected women and HIV-uninfected women who were cytologically normal and oncogenic HPV–negative at enrollment.

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In an approach termed human papillomavirus (HPV) co-testing, cervical cancer screening guidelines in the United States endorse the use of oncogenic HPV DNA testing concurrent with cervical cytology in human immunodeficiency virus (HIV)–uninfected women 30 years or older.[1,2] According to these guidelines, women with a normal Papanicolaou (Pap) test result who test positive for oncogenic HPV should be rescreened in 1 year, whereas the recommended interval for rescreening in those who are oncogenic HPV–negative was recently increased from 3 years[3] to 5 years.[1,2] These recommendations reflect the low risk of cervical precancer and cancer observed in cytologically normal, oncogenic HPV–negative women during long-term follow-up studies (as recently reviewed by Whitlock et al,[4] 2011) and modeling studies that found that HPV co-testing at 3- and 5-year intervals provided out-

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comes similar to those provided by annual conventional Pap tests.[5]

However, HPV co-testing is not currently recommended as part of cervical cancer screening in HIV-infected women,[6] nor was this issue addressed in the updated screening guidelines.[1,2] Current recommendations are for HIV-infected women who have initiated sexual intercourse to have 2 Pap tests at 6-month intervals in the first year following diagnosis of HIV infection and, if results of the Pap tests are normal, then on an annual basis.[6] To our knowledge, only 1 study in HIV-infected women prospectively examined the risk of incident cervical precancer and cancer following a normal Pap test result and a negative oncogenic HPV DNA test result. That study in the Women's Interagency HIV Study (WIHS), a large prospective cohort of HIV-infected women and HIV-uninfected women, measured the cumulative incidence of any squamous intraepithelial lesion (SIL) and of high-grade SIL or greater (HSIL+), according to baseline HPV DNA results. No cases of HSIL+ were observed through 3 years of follow-up, and no cancers were diagnosed for up to 7 years among 412 cytologically normal, HPV-negative, HIV-infected women.[7]

Women in this earlier study, however, were enrolled during 1994-1995, prior to the widespread use of highly active antiretroviral therapy (HAART), which began in late 1996, and most remained naive to HAART for the first several years of the study. Approximately 20% had a CD4 cell count less than 200 cells/μL. Further, that study was limited by the absence of histologic results, the major clinical criteria used to determine the need for cervical treatment. Therefore, the current investigation examined the 3-year and 5-year risk of cervical precancer and cancer defined by cytology (ie, HSIL+) and histology (cervical intraepithelial neoplasia 2 or greater [CIN-2+]), each as its own end point, in a separate cohort of HIV-infected women and HIV-uninfected women enrolled in the WIHS during 2001-2002. The HIV-infected women in the 2001-2002 cohort were shown to be representative of US women with HIV/AIDS.[8]

METHODS

Participants and Specimens

The WIHS is an ongoing, geographically and ethnically diverse prospective cohort study of HIV-infected women and HIV-uninfected women enrolled through similar clinical and outreach sources at each of 6 clinical consortia located in the Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC.[9] The initial enrollment was conducted between October 1, 1994, and November 15, 1995 (n = 2059 HIV-infected women and n = 569 HIV-uninfected women), and a second enrollment was separately conducted between October 1, 2001, and September 30, 2002 (n = 737 HIV-infected women and n = 406 HIV-uninfected women).[8,9]

Interviewer-administered questionnaires are completed at each semiannual visit and include information regarding age, race/ethnicity (ie, black, white, Hispanic, other), additional demographic variables, medical history, and risk behaviors. The HIV-infected women in the 2001-2002 cohort were shown to be similar to women with AIDS among US women nationwide reported by the Centers for Disease Control and Prevention (CDC) in 2001, in terms of their racial distribution, other demographic factors, and CDC-defined HIV exposure category.[8]

At all semiannual visits participants received a Pap test and a cervicovaginal lavage for HPV DNA testing. Pap tests were interpreted centrally according to the 2001 Bethesda System.[10] Colposcopy is recommended for a cytologic diagnosis of atypical squamous cells of undetermined significance (ASC-US) or greater. Cytologic data for the current study were obtained from all WIHS sites, whereas colposcopic and histologic data were obtained from 4 designated WIHS sites (Brooklyn, Chicago, Los Angeles, San Francisco), chosen based on their facilities and clinician training. Written informed consent was obtained from all participants, and the study was approved by each local institutional review board. Data were available through April 30, 2011.

Laboratory Testing

Human papillomavirus DNA was detected with L1 consensus primer MY09/MY11/HMB01 polymerase chain reaction assays. Primer set PC04/GH20, which amplifies a 268–base-pair cellular β-globin DNA fragment, was included in each assay as an internal control to assess the adequacy of amplification. Details of these methods have been previously reported,[11,12] and the results were shown to have high sensitivity and specificity.[13-15] Within the WIHS, these assays have been shown to have high interlaboratory reproducibility.[13] Briefly, after proteinase K digestion, 2 to 10 μL of each cell digest was used in reaction mixtures containing 10mM Tris-HCl, 50mM KCl, 4mM $MgCl_2$, all 4 deoxyribonucleotide triphosphates (each at 200μM), 2.5 U of AmpliTaq DNA polymerase, and 0.5μM solutions of each primer. There were 35 amplification cycles (95°C for 20 seconds, 55°C for 30 seconds, and 72°C for 30 seconds), with a 5-minute extension period at 72°C on the last cycle. Amplification products were probed for the presence of any HPV DNA with a generic probe mixture and probed for HPV DNA with filters individually hybridized with type-specific biotinylated oligonucleotide probes for more than 40 individual HPV types.[11,12] The HPV types defined as oncogenic were 16/18/31/33/35/39/45/51/52/56/58/59/68/73, and other HPV types were considered nononcogenic.[16,17]

Statistical Methods

Initial descriptive analyses contrasted the characteristics of the HIV-infected women and HIV-uninfected women in this study, using the *t* test (means), Wilcoxon test (medians), or Pearson χ^2 test (proportions). For the oncogenic HPV-negative women, standard life-table methods were used to estimate the cumulative incidence of SIL and CIN of any grade, with 95% confi-

dence intervals (a measure of the precision of each estimate) calculated based on the life-table estimator under a normal approximation assumption. The CD4 cell count was used to stratify HIV-infected participants in preference to HIV viral load, because CD4 cell count but not HIV viral load has been associated with risk of incident invasive cervical cancer.[18,19]

In keeping with cervical cancer screening guidelines, our main analyses examined both 3-year and 5-year cumulative incidence. Participants who had had a hysterectomy or who reported cervical treatment were censored at the visit before their procedure. In life-table analysis, censoring is assumed to occur uniformly throughout each interval.[20] Therefore, to determine the overall follow-up rate in HPV-negative women at 5 years of observation, the effective sample size (the numerator) was calculated based on the number of women entering year 5 (which reflects all attrition that came before that final year) minus half of those who during that last year were censored. Cases were not considered censored and were included in the numerator. The overall follow-up rate was then this numerator divided by the number of women at the start of the study.[20] Given the low event rate, the main analyses used all available data and assumed that disease status did not change during intervals of missing data. To assess this assumption, however, in additional analyses, participants who for any reason had missing data for more than 1 year were censored at the time of the last visit at which they had complete data. Because this affected less than an average of 1.6% of participants annually and did not alter the findings, we elected to report herein the life-table results calculated without this additional censoring. The results censored for missing data are reported in eTable 1 and eTable 2, available at http://www.jama.com. The extent of missing data is shown in the footnotes of the life tables. Statistical significance was defined as $P<.05$, determined using 2-sided tests. All analyses were conducted using SAS version 9.1.3 (SAS Institute Inc), except where indicated.

Table 1. Baseline Characteristics of HIV-Infected and HIV-Uninfected Women Who Had Normal Cervical Cytology at Enrollment During 2001-2002 in the Women's Interagency HIV Study (WIHS)

Characteristic	HIV-Infected (n = 420)	HIV-Uninfected (n = 279)	*P* Value[a]
Age, y			
Mean (SD)	34 (7)	30 (8)	<.001
Median (IQR)	33 (28-38)	29 (23-36)	<.001
Race/ethnicity, No. (%)			
Black	222 (53)	159 (57)	.04
Hispanic	150 (36)	75 (27)	
White	31 (7)	33 (12)	
Other	17 (4)	12 (4)	
Smoking, No. (%)[b]			
Never	215 (51)	103 (37)	<.001
Former	58 (14)	35 (13)	
Current	146 (35)	141 (51)	
Alcohol use, No. (%)[b]			
None	249 (60)	113 (41)	<.001
Light (<3 drinks/wk)	119 (29)	84 (30)	
Moderate (3-13 drinks/wk)	32 (8)	53 (19)	
Heavy (≥14 drinks/wk)	17 (4)	28 (10)	
Injected drugs in the last 6 mo, No. (%)[b]			
Yes	3 (1)	7 (3)	.05
No	416 (99)	272 (97)	
Sexually active in the last 6 mo, No. (%)[b]			
Yes	335 (80)	243 (87)	.01
No	84 (20)	36 (13)	
HPV DNA test results, No. (%)			
Negative	287 (68)	218 (78)	.02
Nononcogenic	82 (20)	37 (13)	
Oncogenic	51 (12)	24 (9)	
CD4 cell count, cells/μL, No. (%)			
<200	23 (5)		
200-349	65 (15)		
350-499	98 (23)		
≥500	234 (56)		
HIV RNA, copies/mL, No. (%)[b]			
≤80	161 (39)		
>81-10 000	174 (42)		
10 001-100 000	68 (16)		
>100 000	10 (2)		
HAART use in past 6 mo, No. (%)			
Yes	199 (47)		
No	221 (53)		

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; IQR, interquartile range.
[a] From 2-sided *t* test (means), Wilcoxon test (medians), or Pearson χ^2 test (proportions) comparing HIV-infected and HIV-uninfected women.
[b] Some women were missing data (smoking [1 HIV-infected], alcohol use [3 HIV-infected and 1 HIV-uninfected], injection drug use [1 HIV-infected], sexual activity [1 HIV-infected], and HIV RNA [7 HIV-infected]).

RESULTS

Study Participants

There were 505 HIV-infected women and 345 HIV-uninfected women with normal cervical cytology at enrollment. Women were excluded from analysis if (1) their baseline HPV or CD4 cell count data were missing (n=52 HIV-infected women and n=31 HIV-uninfected women); (2) the cervix had been removed prior to enrollment (n=15 and n=7); (3) follow-up data were unavailable (n=18 and

n=27); or (4) HIV seroconversion occurred during follow-up (n=1).

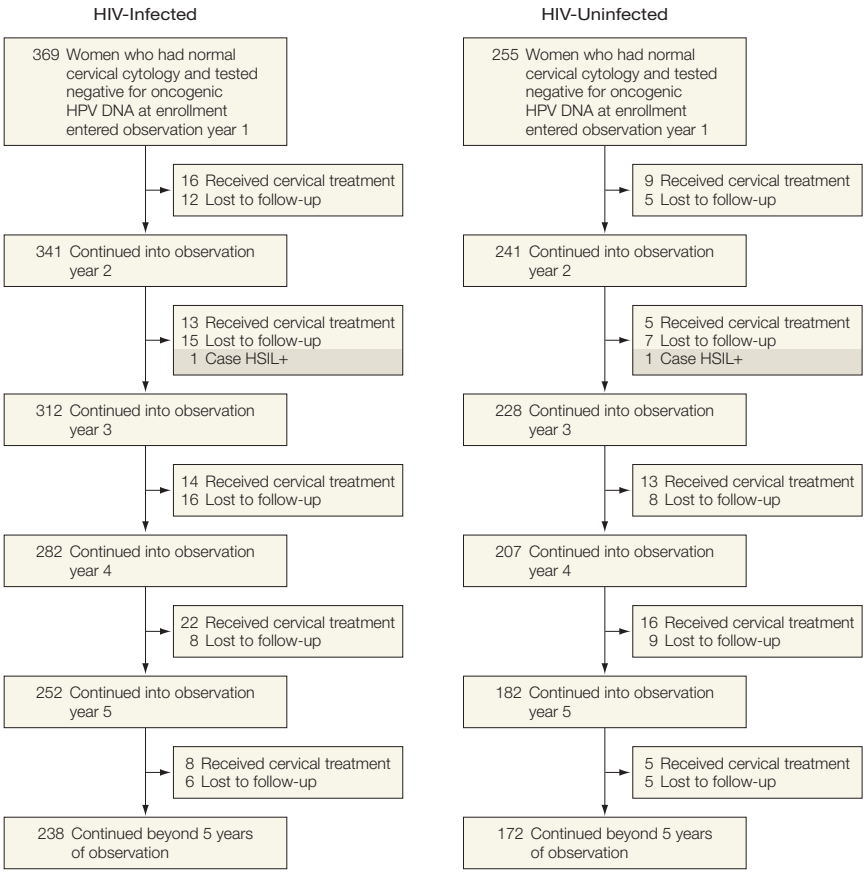
In total, 420 HIV-infected women and 279 HIV-uninfected women were included in the current analysis. TABLE 1 shows selected baseline characteristics of these women. The HIV-infected women were modestly older and more likely to be Hispanic than the HIV-uninfected women. Nearly half (47%) of the HIV-infected women were receiving HAART, and 56% had a CD4 cell count of 500 cells/μL or greater. Although HIV-infected women reported less recent sexual activity, they were more likely than HIV-uninfected women to test positive for any HPV DNA (32% vs 22%; $P=.02$). Among HIV-infected women, the prevalence of any HPV DNA and of oncogenic HPV DNA increased with decreasing CD4 cell count ($P \leq .004$ for trend for both); ie, the prevalence was 25% for any HPV and 8% for oncogenic HPV in HIV-infected women with CD4 cell count of 500 cells/μL or greater; 34% and 17%, respectively, for those with CD4 cell count of 350 to 499 cells/μL; and 47% and 18%, respectively, for those with CD4 cell count less than 350 cells/μL.

Overall, no oncogenic HPV was detected in 369 (88% [95% CI, 84%-91%]) of the HIV-infected women and 255 (91% [95% CI, 88%-94%]) of the HIV-uninfected women with normal cervical cytology at enrollment. We measured the cumulative incidence of cervical precancer and cancer in oncogenic HPV–negative women using cytology (HSIL+) and histology (CIN-2+) as separate end points.

Through the first 5 years of observation there were a total of 3281 person-visits of observation in HIV-infected women and 2242 person-visits in HIV-uninfected women, with a median follow-up time of 4.9 years. FIGURE 1 shows censoring because of treatment or loss to follow-up in these women, by year and HIV status. Six women who had undergone hysterectomy and 115 women who reported other cervical treatment (n=69 HIV-infected women and n=46 HIV-uninfected women) during follow-up were censored at the visit before their procedure. Loss to follow-up averaged 3.6% per year in HIV-infected women and 3.1% in HIV-uninfected women. In life-table analysis, all censoring is assumed to occur uniformly throughout each interval (see "Statistical Methods"). Overall, in the analysis of HSIL+, 70% (effective sample size, 177 noncases + 1 case) of the 255 HIV-uninfected women and 67% (effective sample size, 245 noncases + 1 case) of the 369 HIV-infected women contributed 5 years of observation. The corresponding rates of follow-up at 3 years of observation were 86% and 81%, respectively.

Four of the 6 sites provided colposcopic and histologic data for the analysis of CIN-2+. The baseline characteristics of these women were similar to those of all cytologically normal participants in this study (eTable 3). Colposcopy results were obtained in 87% of HIV-infected women (85% ASC-US, 93% low-grade SIL, 100% HSIL)

Figure 1. Loss to Follow-up and Censoring for Cervical Treatment (Including Hysterectomy) Among Cytologically Normal, Oncogenic Human Papillomavirus–Negative Women in the Life-Table Analysis of HSIL+, by Year of Follow-up and HIV Status



In life-table analysis, all censoring is assumed to occur uniformly throughout each interval (see "Statistical Methods"). Therefore, to determine the follow-up rate, the effective sample size was calculated based on the number of women entering each year (which reflects all attrition that came before that year) minus half of those who during the previous year were censored plus the number of women who had events up to and including that year. For example, the effective sample size at year 5 for the analysis of high-grade squamous intraepithelial lesions or greater (HSIL+) in human immunodeficiency virus (HIV)–uninfected women is $182-(5+5)\div 2+1=177+1$. Thus, in the analysis of HSIL+, 70% (effective sample size, 177 noncases + 1 case) of the 255 HIV-uninfected women and 67% (effective sample size, 245 noncases + 1 case) of the 369 HIV-infected women contributed 5 years of observation. The corresponding rates of follow-up at 3 years of observation were 86% and 81%, respectively.

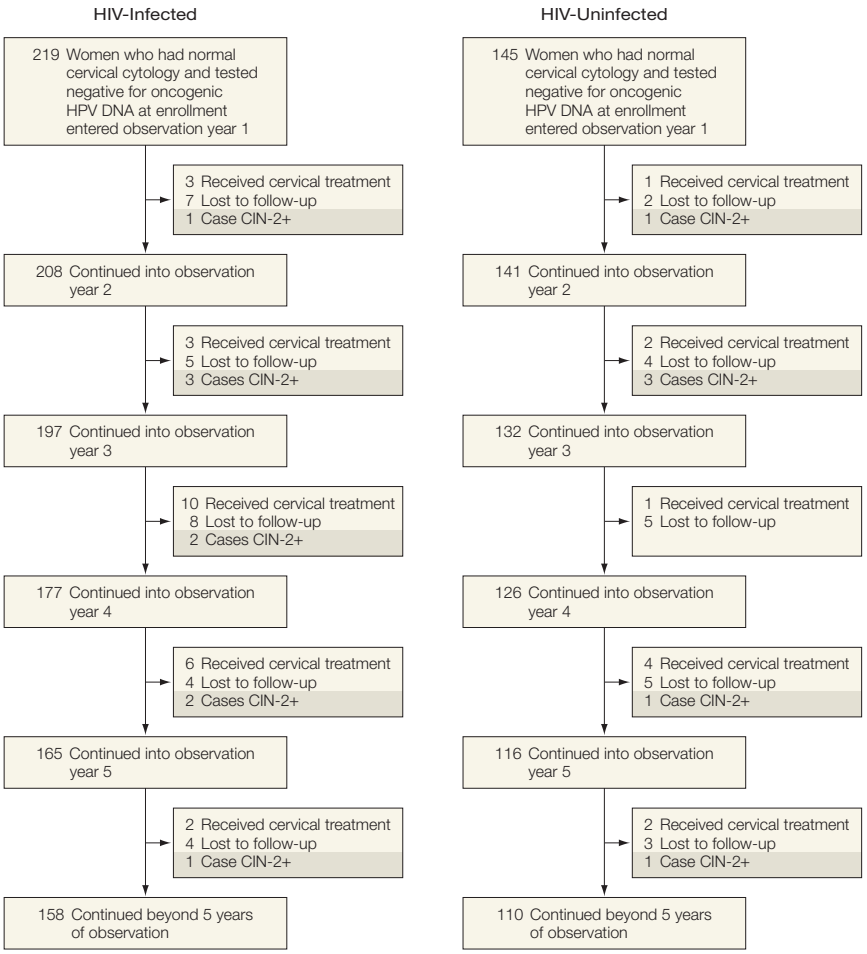
and 82% of HIV-uninfected women (83% ASC-US, 80% LSIL, 100% HSIL) with a subsequent abnormal Pap test result. Loss to follow-up, 2.9% per year in HIV-infected women and 2.9% in HIV-uninfected women, was similar to that reported above for all participants (FIGURE 2). In total, 83% (114 noncases + 6 cases) of 145 HIV-uninfected women and 78% (162 noncases + 9 cases) of 219 HIV-infected women contributed 5 years of observation to the analysis of CIN-2+. The corresponding rates of follow-up at 3 years of observation were 92% and 88%, respectively.

Cumulative Incidence of Precancer

TABLE 2 and TABLE 3 show the data for cytology and histology, respectively. Two cases of HSIL+ were observed during the 5 years of observation (Table 2), 1 among the HIV-uninfected women and 1 among the HIV-infected women with a CD4 cell count of 500 cells/μL or greater. Overall, the cumulative incidence of HSIL+ was 0.3% (95% CI, 0%-0.9%) in HIV-infected women and 0.4% (95% CI, 0%-1.3%) in HIV-uninfected women. Similarly, there were few cases of CIN-2+ (Table 3). Based on a total of 15 cases, the cumulative incidence of CIN-2+ over 5 years of follow-up was 2% (95% CI, 0%-7%) in HIV-infected women with CD4 cell count less than 350 cells/μL, 2% (95% CI, 0%-7%) in those with CD4 cell count of 350 to 499 cells/μL, 6% (95% CI, 2%-10%) in those women with CD4 cell count of 500 cells/μL or greater, and 5% (95% CI, 1%-8%) in HIV-uninfected women. Given the concordance of the findings across CD4 cell count strata, we combined the data among HIV-infected women. The overall 5-year cumulative incidence of CIN-2+ in HIV-infected women was 5% (95% CI, 2%-8%). Of the CIN-2+ cases, 2 were CIN-3 (an HIV-infected woman with a baseline CD4 cell count of 350-499 cells/μL, and an HIV-uninfected woman). The overall 5-year cumulative incidence of CIN-3+ was 0.5% (95% CI, 0%-2%) in HIV-infected women and 0.7% (95% CI, 0%-2%) in HIV-uninfected women. No cancers were observed.

Although the 5-year cumulative incidence rate of CIN-2+ was estimated to be 5% in HIV-infected women as well as HIV-uninfected women, we examined to what extent their true values could be different. Specifically, we calculated the upper and lower confidence limits for these data (estimated difference, 0% [95% CI, –4% to 5%]). A similar analysis was conducted for HSIL+. As reported above, the cumulative incidence of HSIL+ in HIV-infected women and HIV-uninfected women was 0.3% and 0.4%, respectively, and the calculated difference was –0.1% (95% CI, –0.9% to 0.9%). Interestingly, unlike with HSIL+, the cumulative incidence of any SIL differed by host immune status (Table 2). HIV-infected women with CD4 cell count

Figure 2. Loss to Follow-up and Censoring for Cervical Treatment (Including Hysterectomy) Among Cytologically Normal, Oncogenic Human Papillomavirus–Negative Women in the Life-Table Analysis of CIN-2+, by Year of Follow-up and HIV Status



In life-table analysis, all censoring is assumed to occur uniformly throughout each interval (see "Statistical Methods"). Therefore, to determine the follow-up rate, the effective sample size was calculated based on the number of women entering each year (which reflects all attrition that came before that year) minus half of those who during the previous year were censored plus the number of women who had events up to and including that year. For example, the effective sample size at year 5 for the analysis of cervical intraepithelial neoplasia 2 or greater (CIN-2+) in human immunodeficiency virus (HIV)–uninfected women is 116 – (2 + 3) ÷ 2 + 6 = 114 + 6. Thus, in the analysis of CIN-2+, 83% (114 noncases + 6 cases) of 145 HIV-uninfected women and 78% (162 noncases + 9 cases) of 219 HIV-infected women contributed 5 years of observation. The corresponding rates of follow-up at 3 years of observation were 92% and 88%, respectively.

less than 350 cells/μL had a 5-year cumulative incidence of any SIL of 25% (95% CI, 13%-34%), compared with 11% in each of the other 2 HIV-infected groups and 6% in HIV-uninfected women. The cumulative incidence of any CIN did not vary substantially by HIV serostatus or CD4 cell count (Table 3).

Data from follow-up visits beyond 5 years of observation are also of interest but need to be addressed conservatively, because there was continued incremental loss to follow-up—an average of 4.0% and 3.4% per year, respectively, for HSIL+ and CIN-2+ (eTables 4-7). Most notably, no cases of invasive cancer were detected during all 9 years of observation. There was 1 case of CIN-3 in an HIV-infected woman with a CD4 cell count of 500 cells/μL or greater, which occurred between 8 and 9 years of follow-up, and 1 case of HSIL involving an HIV-uninfected woman diagnosed between 6 and 7 years of follow-up. Of the 5 cases of CIN-2 observed after 5 years of follow-up, 3 occurred among HIV-infected women with CD4 cell count of 500 cells/μL or greater, 1 among those with CD4 cell count of 350 to 499 cells/μL, and 1 in an HIV-uninfected woman. Overall, the 7-year cumulative incidence of CIN-2+ was 6% (95% CI, 2%-9%) in HIV-infected women and 5% (95% CI, 1%-9%) in HIV-uninfected women, whereas it was 8% (95% CI, 3%-12%) and 5% (95% CI, 1%-9%), respectively, after 9 years of observation. For CIN-3+, the cumulative incidence rates were 2% (95% CI, 0%-4%) and 0.7% (95% CI, 0%-2%), respectively, after 9 years of observation.

COMMENT

This study found similar risk of cervical precancer and cancer in HIV-infected women and HIV-uninfected women with normal cervical cytology and a negative test result for oncogenic HPV DNA at enrollment. Specifically, through 5 years of follow-up, we observed no meaningful differences in the cumulative incidence of HSIL+ or CIN-2+ between HIV-uninfected women and HIV-infected women, regardless of CD4 cell count in this cohort. Based on our analyses, few cases of cervical precancer would have gone undiagnosed had the HIV-infected women we studied not had any additional Pap tests for 5 years following enrollment and no more than in the HIV-uninfected women. The estimated cumulative incidence of CIN-2+ in HIV-infected women was 5% across the 5 years of observation, with an upper 95% confidence limit of 8%. Two HIV-infected women had CIN-3, representing a 5-year cumulative incidence of 0.5%. None had cancer through 9 years of follow-up.

These results are consistent with those of a prior study conducted by our research group in a separate cohort of women enrolled in the WIHS.[7] That study involved a much larger number of HIV-infected women with low CD4 cell count, consistent with the fact that the prior cohort was enrolled in 1994-1995, before the widespread use of HAART. Nonetheless, no cases of HSIL+ were detected in HIV-infected women within 3 years of their normal Pap test and negative HPV DNA results at study entry. Although differences in the 2 cohorts and the absence of histologic data from the earlier study make it inappropriate to combine their data, it is reassuring that both cohort investigations conducted to date found that HIV-infected women who were cytologically normal and oncogenic HPV–negative had similar risk of cervical pre-

Table 2. Cumulative Incidence of Any SIL and High-Grade SIL or Greater (HSIL+) in HIV-Infected Women and HIV-Uninfected Women Who Had Normal Cervical Cytology and Tested Negative for Oncogenic HPV DNA at Enrollment[a]

Baseline HIV Status and CD4 Cell Count	Year	No. at Start of Interval[b,c]	No. of Any New SIL	Any New SIL Cumulative Incidence (95% CI)[d]	No. of New HSIL+
HIV-infected					
CD4 cell count, cells/μL					
<350	1	72	4	6 (0-11)	0
	2	65	2	9 (2-15)	0
	3	60	6	18 (8-27)	0
	4	51	2	21 (11-31)	0
	5	47	2	25 (13-34)	0
350-499	1	81	0	0	0
	2	75	1	1 (0-4)	0
	3	69	2	4 (0-9)	0
	4	62	2	7 (1-14)	0
	5	58	2	11 (3-18)	0
≥500	1	216	4	2 (0-4)	0
	2	207	6	5 (2-8)	1
	3	193	3	6 (3-10)	0
	4	181	5	9 (5-13)	0
	5	169	3	11 (6-15)	0
HIV-uninfected	1	255	4	2 (0-3)	0
	2	245	4	3 (1-5)	1
	3	233	3	4 (2-7)	0
	4	224	2	5 (2-8)	0
	5	213	1	6 (3-9)	0

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL+, high-grade squamous intraepithelial lesion or greater; SIL, squamous intraepithelial lesion.

[a] Loss to follow-up averaged 3.6% per year in HIV-infected and 3.1% in HIV-uninfected women.

[b] Censoring because of treatment of cervical neoplasia involved 17 HIV-infected women with CD4 cell count less than 350 cells/μL, 21 with CD4 cell count of 350 to 499 cells/μL, 35 with CD4 cell count of 500 cells/μL or greater, and 48 HIV-uninfected women.

[c] Some participants had missing data. A mean of 5.5% each year had missing data among HIV-infected women with CD4 cell count less than 350 cells/μL, 5.7% with CD4 cell count of 350 to 499 cells/μL, and 5.3% with CD4 cell count of 500 cells/μL or greater; a mean of 6.1% of HIV-uninfected women were missing data.

[d] 95% confidence intervals calculated using standard life-table methods.

cancer and cancer as those who were HIV-uninfected.

There are, however, limitations to the current study. Most importantly, the current findings are generalizable only to women who are similar to those in the WIHS—mainly HIV-infected women undergoing long-term follow-up. Second, testing of cervicovaginal lavage specimens may have lower sensitivity for detection of oncogenic HPV than does testing of cervical swabs or cytobrushes.[21,22] Our results are therefore likely conservative, because a small improvement in assay sensitivity would likely result in an improvement in the negative predictive value of HPV testing for CIN-2+ in cytologically normal HIV-infected women. The study used life-table analysis, which has unavoidable limitations. In particular, life-table methods assume noninformative censoring (ie, that the rate of disease in censored participants is similar to that in those not censored), and no statistical methods have been developed to estimate exact confidence intervals for cumulative incidence rates when events are rare, although for sample sizes and event rates in the range we studied, the normal approximation has been shown to provide accurate results.[23] It also must be noted that some women with an abnormal Pap test result did not follow investigators' recommendations to have colposcopy, and there was no centralized review of histologic specimens. Reassuringly, though, a recent review by an expert pathologist confirmed 25 of 27 cases of CIN-2+ diagnosed in other WIHS women by their local pathologists (personal communication, Teresa Darragh, MD, Professor of Clinical Pathology, University of California, San Francisco, written communication, October 21, 2011).

In summary, the results of this prospective study suggest that HIV-infected women undergoing long-term clinical follow-up who are cytologically normal and oncogenic HPV–negative have a risk of cervical precancer similar to that in HIV-uninfected women through 5 years of follow-up. Additional observational studies or a randomized clinical trial may be necessary before clinical guideline committees consider whether to expand current recommendations regarding HPV co-testing to HIV-infected women. More broadly, the current investigation highlights the potential for

Table 3. Cumulative Incidence of Any CIN and CIN-2+ in HIV-Infected Women and HIV-Uninfected Women Who Had Normal Cervical Cytology and Tested Negative for Oncogenic HPV DNA at Enrollment[a]

Baseline HIV Status and CD4 Cell Count	Year	No. at Start of Interval[b,c]	No. of Any New CIN	Cumulative Incidence, (95% CI)[d]	No. at Start of Interval[c,e]	No. of New CIN-2+	Cumulative Incidence (95% CI)[d]
HIV-infected							
CD4 cell count, cells/μL							
<350	1	44	0	0	44	0	0
	2	42	1	2 (0-7)	42	1	2 (0-7)
	3	40	2	8 (0-15)	40	0	2 (0-7)
	4	34	1	10 (0-19)	34	0	2 (0-7)
	5	32	2	16 (3-27)	33	0	2 (0-7)
350-499	1	47	1	2 (0-6)	47	0	0
	2	43	2	7 (0-14)	43	1	2 (0-7)
	3	39	2	12 (2-21)	39	0	2 (0-7)
	4	33	2	17 (5-29)	34	0	2 (0-7)
	5	28	2	23 (9-36)	30	0	2 (0-7)
≥500	1	128	5	4 (0-7)	128	1	1 (0-2)
	2	120	4	7 (3-12)	123	1	2 (0-4)
	3	114	4	11 (5-16)	118	2	3 (0-6)
	4	104	4	14 (8-20)	109	2	5 (1-9)
	5	96	3	17 (10-23)	102	1	6 (2-10)
HIV-uninfected	1	145	4	3 (0-5)	145	1	1 (0-2)
	2	138	9	9 (4-14)	141	3	3 (0-6)
	3	123	2	11 (5-16)	132	0	3 (0-6)
	4	115	1	12 (6-17)	126	1	4 (0-7)
	5	105	1	12 (7-18)	116	1	5 (1-8)

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN-2+, CIN-2 or greater; HIV, human immunodeficiency virus.
[a] The CIN analysis is limited to the 4 WIHS sites that contributed colposcopic and histologic data (see "Methods"). Loss to follow-up in these 4 clinical sites was similar to that among all cytologically normal women in the 2001-2002 cohort (see Table 2); that is, loss to follow-up was 2.9% per year in HIV-infected and 2.9% in HIV-uninfected women.
[b] In the analysis of any new CIN incidence, censoring because of treatment for cervical neoplasia involved 5 HIV-infected women with CD4 cell count less than 350 cells/μL, 3 with CD4 cell count of 350 to 499 cells/μL, 5 with CD4 cell count of 500 cells/μL or greater, and 9 HIV-uninfected women.
[c] Some participants had missing data. A mean of 5.6% each year had missing data among HIV-infected women with CD4 cell count less than 350 cells/μL, 6.5% with CD4 cell count of 350 to 499 cells/μL, and 4.5% with CD4 cell count of 500 cells/μL or greater; a mean of 5.6% of HIV-uninfected women were missing data.
[d] 95% confidence intervals calculated using standard life-table methods.
[e] In the analysis of CIN-2+ incidence, censoring because of treatment for cervical neoplasia involved 7 HIV-infected women with CD4 cell count less than 350 cells/μL, 7 with CD4 cell count of 350 to 499 cells/μL, 10 with CD4 cell count of 500 cells/μL or greater, and 10 HIV-uninfected women.

a new era of molecular testing, including HPV as well as other biomarkers, to improve cervical cancer screening in HIV-infected women.

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