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Effect of Human Immunodeficiency Virus Infection on the Prevalence and Incidence of Vaginal Intraepithelial Neoplasia

L. Stewart Massad, M.D.,
Washington University School of Medicine, St. Louis, MO

Xianhong Xie, Ph.D.,
Albert Einstein College of Medicine, Bronx, NY

Ruth M. Greenblatt, M.D.,
University of California, San Francisco, CA

Howard Minkoff, M.D.,
Maimonides Medical Center, State University of New York, Downstate, Brooklyn, NY

Lorraine Sanchez-Keeland, M.D.,
Keck School of Medicine, University of Southern California, Los Angeles, CA

D. Heather Watts,
Eunice K. Shriver National Institute of Child Health and Human Development, Bethesda, MD

Rodney L. Wright, M.D.,
Albert Einstein College of Medicine, Bronx, NY

Gypsyamber D'Souza, Ph.D.,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Daniel Merenstein, M.D., and
Georgetown University School of Medicine, Washington, DC

Howard Strickler, M.D., M.P.H.
Albert Einstein College of Medicine, Bronx, NY

Abstract

Objective—To estimate the prevalence, incidence, and clearance of abnormal vaginal cytology and vaginal intraepithelial neoplasia in human immunodeficiency virus (HIV)-seropositive women.

Methods—Pap tests were done semiannually for 335 HIV-seropositive and 75 HIV-seronegative women with prior hysterectomy in the prospective Women's Interagency HIV Study cohort. Endpoints included abnormal Pap tests after hysterectomy and vaginal intraepithelial neoplasia regardless of hysterectomy.

Results—Over a median of 5.6 years of follow-up, vaginal Pap tests were abnormal at 1,076 (29%, 95% C.I. 25%, 33%) of 3,700 visits among HIV seropositive vs. 31 (4%, 95% C.I. 2%, 8%) of 763 visits among seronegative women (P < 0.001). Abnormal Pap tests included 641 atypical

Contact Dr. Massad at: Division of Gynecologic Oncology, Washington University School of Medicine, 4911 Barnes-Jewish Hospital Plaza, St. Louis, MO 63110 Tel: 314-362-3181, Fax: 314-362-2893, massadl@wudosis.wustl.edu.

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squamous cells of undetermined significance (ASC-US), 425 low-grade squamous intraepithelial lesions (LSIL), and 10 high-grade squamous intraepithelial lesions in HIV-seropositive women, and 28 ASC-US and three LSIL in HIV-seronegative women. The incidence of abnormal Pap tests after hysterectomy was 14/100 person-years among HIV-seropositive and 2/100 person-years among HIV-seronegative women ($P < 0.001$) and remained stable across time. The 5-year clearance rate of abnormal Pap tests was 34/100 person-years for HIV-seropositive and 116/100 person-years for HIV-seronegative women ($P < 0.001$). In multivariate regression models, women with lower CD4 counts were more likely to have and less likely to clear abnormal cytology when it occurred. The incidence of vaginal intraepithelial neoplasia 2+ was 0.2 and 0.01 per 100 person-years for HIV-seropositive and HIV-seronegative women ($P = 0.001$). Two HIV-seropositive women developed Stage II cancers, with remission after radiotherapy.

Conclusion—Vaginal Pap tests are often abnormal in HIV-seropositive women. Though more common than in HIV-seronegative women, vaginal intraepithelial neoplasia 2+ and especially vaginal cancers are infrequent.

Introduction

Infection with carcinogenic types of human papillomavirus (HPV) and consequent cervical intraepithelial neoplasia (CIN) are common in women with HIV (1, 2). CIN may require hysterectomy to prevent progression to cancer and is the most common reason for hysterectomy in women with HIV, underlying 42% of all hysterectomies (3).

The course of HPV-related disease after hysterectomy is unclear. HPV can infect the vagina as well as the cervix, and oncogenic HPVs can cause vaginal intraepithelial neoplasia (VAIN) and vaginal cancer (4). We have found oncogenic HPV in a high percentage of cervicovaginal lavage specimens from women with HIV who had undergone hysterectomy (5). Although vaginal intraepithelial neoplasia (VAIN) has been reported in 10% of women with HIV who were investigated in studies of global lower genital tract neoplasia, its presentation among HIV seropositive women has not been explored in detail (6).

We estimated the prevalence, incidence, and clearance of abnormal vaginal cytology and the risk of VAIN and vaginal cancer in HIV seropositive women and comparison seronegative women in a long term U.S. prospective cohort.

Methods

The Women's Interagency HIV Study (WIHS) is an ongoing multicenter U.S. cohort study of HIV infection and related health conditions begun October 1, 1994, with 2054 HIV seropositive and 569 seronegative comparison women and expanded in 2001–2002 with 737 HIV seropositive and 406 seronegative women. The protocols, recruitment processes, procedures, baseline results, expansion enrollment, and retention efforts of the WIHS have been previously described (7–9). Written informed consent for study was obtained following approval from institutional review boards of the collaborating institutions and agencies. Follow up continues, but this study includes information obtained through September 30, 2008.

Every six months, participants had histories taken by trained interviewers, followed by a physical examination that included a gynecologic exam and conventional Pap smear on a glass slide. Pap smears were read centrally and results were reported according to the 1991 Bethesda System (10), with high grade squamous intraepithelial lesions (HSIL) subcategorized as consistent with either moderate or severe dysplasia/carcinoma in situ, with modifications incorporating the 2001 Bethesda system in 2002. Colposcopy was prescribed by protocol for all women with abnormal cytology, defined as atypical squamous cells of

undetermined significance (ASCUS) or a more severe lesion. Histology results were interpreted locally and were not centrally reviewed; women with VAIN that was not graded were included in analysis of “any VAIN” but not VAIN2+. HIV status was confirmed by Western blot. Women who seroconverted during follow-up were excluded. Highly active antiretroviral therapies (HAART) were defined according to DHS/Kaiser guidelines (11).

We focused on two endpoints. First, we identified all women with abnormal vaginal cytology after hysterectomy. For women without a self-reported history, hysterectomy was assumed if no cervix was reported at two consecutive examinations. Contingency tables of demographic characteristics were constructed using data at the first visit after hysterectomy. Characteristics of HIV seropositive and seronegative women were compared using Pearson’s chi-square tests or Fisher’s exact tests.

The second endpoint was histologically confirmed VAIN, regardless of prior hysterectomy. We included VAIN documented by biopsy at a WIHS visit or at another institution. Since VAIN1 is considered to be a reflection of HPV infection of marginal oncogenic risk, we combined biopsies read as condyloma or koilocytosis with VAIN1. For analyses of VAIN by grade, each woman contributed only once, classifying her according to the highest grade of VAIN she had identified during study. Women were considered to have prevalent VAIN if it was diagnosed after one or more consecutive abnormal Pap tests beginning with enrollment. The prevalence of cytologic or histologic vaginal abnormality was compared between HIV seropositive and seronegative women using the Pearson’s chi-square test. Univariate and multivariable analyses that incorporated data from multiple visits were conducted using generalized estimating equation (GEE) models for binary data, as previously described (12), which adjusted for repeated observations of cytologic or histologic abnormalities in the same women over time. Temporal trends in prevalence over time were examined using a GEE model by incorporating visit number as a variable.

Incident cytologic abnormality was assessed in women who had undergone hysterectomy, since they received routine semi-annual vaginal Pap testing. Incident VAIN was VAIN identified after one or more negative Pap results, regardless of hysterectomy. Each woman could contribute only a single incident cytologic or histologic abnormality, analyzed as separate events. A chi-square test with one degree of freedom was used to compare differences in incidence rates between HIV seropositive and seronegative women during a single year or all years pooled; the statistic was based on the normal approximation to the binomial distribution, using the number of cases in the HIV seropositive group as the binomial random variable (13).

We also examined cumulative risk, including both prevalent and incident cases using Life Table method (14). Comparison between HIV seropositive and seronegative groups was conducted using the log-rank test. Multivariable Cox analysis was performed to examine time-to-event for incident abnormality (cytology or VAIN) with HIV status and CD4 count as our primary variables of interest, with adjustment for age, smoking, and number of sexual partners in past 6 months. The mid interval was used as the event time. Subjects were time censored at the last visit with available data if data were missing for two consecutive visits. Time to clearance of abnormality was also studied using life-table and Cox models. All statistical tests in our study were two-sides.

Results

After excluding 22 HIV seroconverters, 418 (11%, 95% C.I. 10%, 12%) of 3744 women in WIHS had reported prior hysterectomy (343 HIV seropositive, 75 seronegative), including 241 with hysterectomy before enrollment and 177 during follow-up. Of these, 410 (335 HIV

seropositive, 75 seronegative) contributed up to 28 vaginal Pap tests over a median of 5.6 years of follow-up after enrollment or hysterectomy, for a total of 4463 vaginal Pap test results (3,700 among HIV seropositive and 763 from seronegative women). Table 1 presents the demographic and medical characteristics of these women; except for a higher rate of smoking in women without HIV, HIV seropositive and seronegative women with hysterectomy were similar.

Pap tests were abnormal at 1076/3700 (29%, 95% C.I. 25%, 33%) visits among HIV seropositive women, but only 31/763 (4%, 95% C.I. 2%, 8%) visits among HIV seronegative women ($P < 0.001$), in analyses using GEE logistic regression. The distribution of Pap test results by HIV serostatus is shown in Table 2; women with HIV had more Pap test abnormalities, although most were ASCUS and LSIL, suggesting poorly controlled HPV infection rather than precancer. While HSIL Pap results were uncommon, they were more frequent in HIV seropositive (10/3700, 0.3%, 95% C.I. 0.1%, 0.6%) than in seronegative women (0/763, 95% C.I. 0%, 0%, $P = 0.0007$). The frequency of vaginal Pap test abnormality was similar for HIV seropositive women with hysterectomy before (698/2418 (29%, 95% C.I. 27%, 31%) smears) and after (378/1282 (29%, 95% C.I. 27%, 32%) smears) after study entry.

We have previously shown that visit-specific prevalence of cervical Pap test abnormality among all WIHS participants fell across time, presumably as treatments decreased the burden of cervical disease (8). In contrast, Fig. 1 shows no time trend in the prevalence of vaginal Pap test abnormality in either HIV seropositive or seronegative women ($P = 0.11$ for HIV seropositive women and 0.50 for seronegative women).

As shown in Table 3, multivariable analyses found that prevalent detection of any abnormal vaginal Pap test was more common in HIV seropositive women with increasing immunosuppression and current smokers but less likely among women with multiple sexual partners. CD4 count was also significantly associated with HSIL Pap test (P for trend < 0.001). As shown in Table 4, when analysis was repeated among only HIV seropositive women, CD4 lymphocyte count, HIV RNA level, use of HAART, and smoking were independently associated with vaginal Pap abnormality; age, ethnicity, number of sexual partners in the prior six months, and prevalent vs incident hysterectomy were not linked to a finding of abnormal Pap in these women. Similar results were obtained if analysis was restricted to any SIL (excluding ASC-US) and to prevalent Pap abnormalities (not shown).

We also analyzed the incidence of abnormal vaginal Pap tests. Among the 410 hysterectomized women, 136 (121 HIV seropositive, 15 seronegative) were excluded because of abnormal Pap tests at the time of hysterectomy (n = 108) or lack of follow-up (n = 28). Among the remaining 274 hysterectomized women, 114 (42%, 95% C.I. 38%, 46%) developed incident abnormal vaginal Pap tests while 160 (58%, 95% C.I. 52%, 64%) did not. The incidence of abnormal vaginal Pap tests after hysterectomy was 14/100 person-years among HIV seropositive and 2/100 person-years among seronegative women ($P < 0.001$).

The cumulative risk of an abnormal Pap test, including baseline and follow-up, was high in both groups: after 12 years of observation, the risk of ever having abnormal vaginal cytology was 75%(95% C.I. 64%, 83%) in HIV seropositive and 42% (95% C.I. 2%, 66%) in seronegative women ($P = 0.13$). The risk of ever having a Pap read as HSIL or worse over 12 years of observation was 6.4% (95% C.I. 0.3%, 12.2%) for HIV seropositive women and 0.0% (95% C.I. 0%, 0%) for HIV seronegative women ($P = 0.03$).

Clearance of Pap abnormality was evaluated among all 193 women (177 HIV seropositive, 16 seronegative) with prevalent or incident Pap abnormalities. After excluding 25 women

without follow-up and 4 women who were treated (all excluded women were seropositive), the 193 women included 91 (84 HIV seropositive and 7 seronegative) women with prevalent Pap abnormalities and 102 (93 HIV seropositive, 9 seronegative) with incident abnormalities. Of these, 113 (64%, 95% C.I. 57%, 71%) of HIV seropositive and 13 (81%, 95% C.I. 57%, 93%) of seronegative women cleared their abnormality without treatment (P = 0.16) across all visits. The 5-year clearance rate was 34 cases/100 person-years for HIV seropositive women and 116/100 person-years for HIV seronegative women (P < 0.001). Clearance rates were higher for women with ASC-US (98, 72%, 95% C.I. 63%, 78%) than LSIL (28 (50%, 95% C.I. 37%, 63%, P = 0.004). In multivariable Cox analysis, clearance of any Pap abnormality was less likely among HIV seropositive women with lower CD4 counts (HR 0.79, 95% C.I. 0.37, 1.66 for CD4 >500/μl, 0.53, 95% C.I. 0.26, 1.1 for CD4 200–500/μl, and 0.36, 95% C.I. 0.16, 0.80, for CD4 <200/μl; P for trend = 0.002, compared to HIV seronegative women), or with LSIL vs ASC-US cytology (H.R. 0.52, 95% C.I. 0.32, 0.87, P = 0.01). Those with more than one sexual partner in the six months before abnormal Pap were more likely to clear Pap abnormalities (H.R. 2.34, 95% C.I. 1.19, 4.59, P = 0.01 vs no sexual partner). Age, ethnicity, smoking, parity, and incident vs prevalent hysterectomy were not linked to clearance of cytologic abnormality. In a separate model limited to HIV seropositive women, after adjusting for CD4 count, plasma HIV RNA level and HAART use were not associated with clearance.

We next assessed vaginal biopsy results, including women with and without prior hysterectomy. Biopsies were obtained from 269 women, including 255/2791 (9%, 95% C.I. 8%, 10%) HIV seropositive women and 14/953 (1%, 95% C.I. 1%, 2%) seronegative women (P < 0.001). Table 5 shows the highest grade VAIN for each woman, including results from women with multiple biopsies; although only HIV seropositive women had VAIN3, differences in the distribution of biopsy grade did not reach significance. Prevalent VAIN of any grade was found within six months of intake in 21/2791 (1%, 95% C.I. 0.7%, 1.4%) HIV seropositive women and no seronegative women (P = 0.01). Incident VAIN was found in 151 HIV seropositive and 7 seronegative women, and the incidence rate of VAIN was 0.8 per 100 person-years for HIV seropositive and 0.1 per 100 person-years for seronegative women (P < 0.001).

We found no prevalent cases of VAIN2+ in HIV seropositive or seronegative women, while incident VAIN2+ developed in 36 HIV seropositive women and one seronegative woman. The incidence of VAIN2+ was 0.2 per 100 person-years for HIV seropositive women and 0.01 per 100 person-years for HIV seronegative women (P = 0.001). Associations between VAIN and various risk factors are shown in Table 6. In multivariable Cox models, incident VAIN was associated with lower CD4 count, current smoking, and higher parity but not age, ethnicity, or number of recent sexual partners. In a separate model limited to HIV seropositive women, HIV RNA level in blood was not associated with incident VAIN after controlling for CD4 count. In another model incorporating HIV seropositive women that adjusted for multiple additional risk factors in addition to CD4 count and HIV RNA level, incident VAIN was linked to HAART use in the prior six months (HR 1.94, 95% CI 1.23, 3.05, P = 0.004) and current smoking (HR 2.04, 95% CI 1.19, 3.51, P = 0.01).

The incidence of VAIN remained higher among HIV seropositive women when only the 418 women with hysterectomy were evaluated. VAIN was found within six months of enrollment in 13 women, all HIV seropositive (4% of all seropositive women with hysterectomy, 95% C.I. 2%, 6%). In all, incident VAIN was found in 56 women (54 HIV seropositive, two seronegative). The incidence of VAIN was 2.9/100 person-years for HIV seropositive women and 0.4/100 person-years for seronegative women (P = 0.002). However, the incidence of VAIN2+ in women after hysterectomy was only 0.8/100 person-years for HIV seropositive and 0/100 person-years in HIV seronegative women (P = 0.05).

Treatment for VAIN was undertaken for 41 women (38 HIV seropositive, three seronegative). Only 12 women (11 HIV seropositive, one seronegative) required treatment for VAIN detected after hysterectomy, but Paps remained abnormal after treatment in 10 (9 HIV seropositive, one seronegative).

Two women, both HIV seropositive, developed vaginal cancer after prior hysterectomy. The first was diagnosed with stage II squamous cell carcinoma in 2000 and was treated with radiotherapy; she died 10 months later from substance abuse complications but with persistent vaginal cancer. Prior Paps tests had shown ASCUS or LSIL, but three vaginal biopsies prior to diagnosis showed only condyloma. The second patient had undergone hysterectomy in 1997 for cervical carcinoma in situ and a Pap test read as atypical glandular cells. No cancer was found then and no subsequent vaginal biopsies were done. She was diagnosed with a stage II adenosquamous carcinoma of the vagina in 2004 and was treated with excision and radiotherapy and was free of disease seven years after initial treatment.

Discussion

Although HPV-related disease can occur throughout the lower genital tract, vaginal precancers and cancers are uncommon. Our findings demonstrate that while HIV-related immunosuppression raises the risk for abnormal vaginal Pap tests and VAIN, HIV seropositive women remain at low absolute risk for vaginal precancer and cancer. The cumulative risk of abnormal Pap after up to 12 years of observation was 75% in HIV seropositive women after hysterectomy, but the risk of HSIL cytology among these women was only 6.4% over years of observation. Most HIV seropositive women with abnormal vaginal Paps cleared their abnormalities spontaneously, but more than a third did not; their likelihood of clearance was lower than that among seronegative women and the most severely immunosuppressed HIV seropositive women had the lowest likelihood of clearance. Treatments for VAIN after hysterectomy were relatively ineffective. Few abnormal Pap tests were associated with VAIN2+, and a lower proportion of HIV seropositive than seronegative women with abnormal vaginal Paps had VAIN2+, probably a reflection of opportunistic expression of HPV infections that are controlled in HIV seronegative women. In fact, In fact, among HIV seropositive women after hysterectomy, which is commonly performed for CIN (3), the incidence of VAIN2+ was only 0.8/100 person-years. Unfortunately, two cancers occurred in our cohort and were seen after only borderline cytology results.

Smoking, CD4 count, HIV RNA level, and HAART use were associated with higher risk for vaginal lesions. Future studies should explore whether smoking cessation and a rising CD4 cell count after HAART initiation lower risk for and speed clearance of abnormal vaginal Pap tests and VAIN. In the absence of prospective studies, these correlations may offer an additional incentive for smoking cessation and HAART adherence among women with these abnormalities.

Interpretation of our results is limited by several factors. We were unable to determine indications for prior hysterectomies in all cases, and the risk for abnormal Pap and VAIN may be lower among those undergoing hysterectomy for reasons other than CIN, such as bleeding or pain. Among immunocompetent women, Pap testing is not indicated after hysterectomy for benign disease, while women with a prior history of CIN or cancer merit long-term annual screening (15). Future research should determine whether HIV seropositive women with no history of prior CIN and women with multiple consecutive negative Pap tests benefit from continued Pap testing after hysterectomy.

Until those studies have been completed, all HIV seropositive women who have had a hysterectomy should be advised to continue annual Pap testing. Women facing hysterectomy for cervical disease should be counseled that while surgery may be lifesaving as a cervical cancer prevention measure, HPV is not eradicated and vaginal Pap tests will often be abnormal and must be followed up with colposcopy for all abnormalities, including ASCUS. Although HPV cannot be eradicated surgically and abnormal Paps often persist after therapy, VAIN2+ should be treated, and intravaginal use of 5-fluorouracil may improve disease control (refs). VAIN1 can be treated or followed depending on symptoms and treatment risk. With such careful surveillance and targeted intervention, women living with HIV can be reassured that abnormal Pap results and VAIN rarely presage vaginal cancer.

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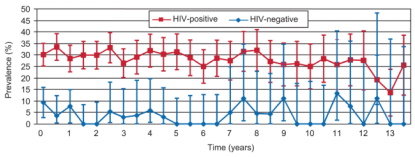

Fig. 1.
Prevalence of Pap abnormality across time among women with and without human immunodeficiency virus (HIV) infection after hysterectomy.

Table 1

Demographic and Medical Characteristics of 410 Women With Vaginal Pap Test Results After Hysterectomy

Characteristic	HIV Seropositive (n=335)	HIV Seronegative (n=75)	*P**
Hysterectomy			0.24
Before enrollment	199 (59)	39 (52)	
After enrollment	136 (41)	36 (48)	
Age group			0.30
34 or younger	28 (8)	2 (3)	
35–39	65 (19)	17 (23)	
40–44	103 (31)	27 (36)	
45 or older	139 (41)	29 (39)	
Race			0.41
White	41 (12)	14 (19)	
Hispanic	61 (18)	15 (20)	
Black	224 (67)	45 (60)	
Others	9 (3)	1 (1)	
Smoking			0.04
Never smoked	59 (18)	11 (15)	
Former smoker	94 (28)	12 (16)	
Current smoker	178 (54)	52 (69)	
Sexual partners in past 6 mo			0.72†
0	144 (45)	34 (47)	
1	146 (45)	29 (40)	
2	18 (6)	6 (8)	
3 or more	14 (4)	3 (4)	
Parity			0.27
0	56 (17)	15 (20)	
1	89 (27)	12 (16)	
2	68 (21)	16 (22)	
3 or more	116 (35)	31 (42)	
CD4+ T cell count (μl)			
Greater than 500	91 (28)		
200–500	155 (48)		
Less than 200	78 (24)		
HIV RNA level (copies/μl)			
4000 or less	142 (44)		
4001–20,000	56 (17)		
20,001–100,000	75 (23)		
Greater than 100,000	51 (16)		

Characteristic	HIV Seropositive (n=335)	HIV Seronegative (n=75)	*P*[*]
HAART use in past 6 mo			
No	246 (73)		
Yes	89 (27)		

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

Data are n (%) unless otherwise specified.

[*] By Pearson's chi-square test

[†] By Fisher's exact test

Table 2

Distribution of Posthysterectomy Vaginal Pap Test Results from 3,700 Person-Visits Among HIV Seropositive and 763 Visits Among HIV Seronegative Women

	HIV Seropositive	HIV Seronegative
Normal	2624 (70.9)	732 (95.9)
ASC-US*	641 (17.3)	28 (3.7)
LSIL†	425 (11.5)	3 (0.4)
HSIL‡	10 (0.2)	0 (0)

HIV, human immunodeficiency virus.

Data are n (%). $P < 0.001$ for differences in distribution by serostatus.

*Atypical squamous cells of undetermined significance

†Low- grade squamous intraepithelial lesions

‡High- grade squamous intraepithelial lesions

Table 3

Factors Associated With Finding Any Abnormal Vaginal Pap Result After Hysterectomy

Characteristic		Odds Ratio	95% Lower Confidence Limit*	95% Upper Confidence Limit	*P*
CD4 count (cells/μl)	HIV seronegative (ref)	1			<.001†
	Greater than 500	6.23	2.81	13.82	<.001
	200–500	11.01	5.05	24.01	<.001
	Less than 200	20.41	9.16	45.46	<.001
Hysterectomy	Prevalent (ref)	1			
	Incident	1.20	0.81	1.80	0.36
Age (years)	34 or younger (ref)	1			
	35–39	1.64	0.75	3.62	0.22
	40–44	1.25	0.53	2.95	0.61
	45 or older	1.22	0.52	2.87	0.64
Ethnicity	Black (ref)	1			
	White	0.65	0.35	1.20	0.17
	Hispanic	0.76	0.44	1.30	0.31
	Other	0.90	0.39	2.05	0.80
Smoking	Never (ref)	1			
	Former	1.65	0.91	2.99	0.10
	Current	2.20	1.24	3.91	0.01
Number of sexual partner in past 6 mo	0 (ref)	1			
	1	0.82	0.63	1.07	0.14
	2	0.56	0.32	0.96	0.03
	3 or more	0.54	0.29	1.03	0.06

HIV, human immunodeficiency virus.

*Confidence limit

†*P* for trend.

Table 4

Correlates of Any Vaginal Pap Abnormality Among HIV Seropositive Women

Characteristic		Odds Ratio	95% Lower Confidence Limit*	95% Upper Confidence Limit	*P*
CD4	Greater than 500 (ref)	1			<.001†
	200–500	1.80	1.30	2.47	0.003
	Less than 200	3.06	1.96	4.76	<.001
HIV RNA level (copies/μl)	Less than or equal to 4000 (ref)	1			0.02†
	4001–20,000	1.33	0.99	1.78	0.06
	20,001–100,000	1.40	1.00	1.96	0.0496
	Greater than 100,000	1.68	1.07	2.65	0.02
Smoking	Never (ref)	1			
	Former	1.73	0.91	3.28	0.09
	Current	2.52	1.35	4.70	0.004
HAART use in past 6 mo	No (ref)	1			
	Yes	1.94	1.45	2.59	<.0001

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

*Confidence limit

†*P* for trend.

Table 5

Highest Grade Vaginal Biopsy Result Among 269 HIV Seropositive and Seronegative Women Undergoing Biopsy

	HIV Seropositive	HIV Seronegative	Total
Normal or Benign	83 (33)	7 (50)	90
VAIN1	136 (53)	6 (43)	142
VAIN2	27 (11)	1 (7)	28
VAIN3	7 (3)	0	7
Cancer	2 (1)	0	2
Total	255	14	269

Data are n (%). $P = 0.68$ by Fisher's exact test for differences in distribution by serostatus.

VAIN, vaginal intraepithelial neoplasia.

Table 6

Factors Associated With Incident Vaginal Intraepithelial Neoplasia in Multivariable Analysis

Characteristic		Hazard Ratio	Lower 95% Confidence Limit*	Upper 95% Confidence Limit	*P*
CD4 count (per μl)	HIV seronegative (ref)	1			**<.0001**†
	Greater than 500	5.90	1.73	20.08	**0.005**
	200–500	14.48	4.52	46.43	**<.0001**
	Less than 200	22.50	6.89	73.49	**<.0001**
Age (years)	Less than or equal to 34 (ref)	1			
	35–39	0.83	0.46	1.48	0.53
	40–44	0.76	0.41	1.39	0.37
	Greater than or equal to 45	1.09	0.62	1.94	0.76
Ethnicity	Black (ref)	1			
	Hispanic	0.65	0.39	1.06	0.08
	Other	0.64	0.36	1.13	0.12
Smoking	Never (ref)	1			
	Former	1.33	0.72	2.47	0.36
	Current	1.90	1.13	3.21	**0.02**
No. of sexual partner in past 6 months	0 (ref)	1			
	1	0.91	0.60	1.37	0.64
	2 or more	0.71	0.34	1.50	0.37
Parity	0 (ref)	1			
	1	0.86	0.50	1.46	0.57
	2	0.39	0.20	0.74	**0.004**
	Greater than or equal to 3	0.64	0.38	1.05	0.08

*Confidence limit

†*P* for trend