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Negative Predictive Value of Pap Testing: Implications for Screening Intervals for Women With Human Immunodeficiency Virus

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Abstract

Objective—To estimate the accuracy of Pap testing for women who are human immunodeficiency virus (HIV)-seropositive, with a focus on negative predictive value.

Methods—Participants in the Women's Interagency HIV Study were followed with conventional Pap smears every 6 months. After excluding those with abnormal Pap tests before study, cervical disease, or hysterectomy, women with negative enrollment Pap results were followed for development within 15 or within 39 months of precancer, defined as a Pap read as high grade squamous intraepithelial lesion, atypical glandular cells favor neoplasia, or adenocarcinoma in

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situ, or a cervical biopsy read as cervical intraepithelial neoplasia 2+. Correlations between one or more consecutive negative Pap results and subsequent precancer were assessed using Cox proportional hazards models.

Results—Among 942 HIV infected women with negative baseline Pap tests, 8 (1%) developed precancer within 15 months and 40 (4%) within 39 months. After three consecutive negative Pap tests, precancer was rare, with no cases within 15 months and 10/539 (2%) within 39 months. No women developed precancer or cancer within 39 months after 10 consecutive negative Pap tests. Risks for precancer within 15 months after negative Pap included current smoking (aHR 1.5, 95% CI 1.2, 2.0 vs nonsmokers), younger age (aHR=1.5, 95% CI 1.1, 2.1 for women aged younger than 31 years vs older than 45 years) and lower CD4 count (aHR 11.8, 95% CI 1.3, 2.3 for CD4 200–500, aHR 2.2, 95% CI 1.6, 2.9 for CD4 <200/cmm, vs CD4 >500/cmm).

Conclusion—Annual Pap testing appears safe for women infected with HIV; for those with serial negative tests, longer intervals are appropriate.

Introduction

Women with HIV face a higher risk for cervical cancer than of the general population (1), That risk has remained elevated despite the widespread adoption of antiretroviral therapy (2). Nevertheless, most cervical cancers are preventable, even in women with HIV. With frequent Pap test surveillance and treatment of precursors, HIV infected and uninfected women have similar cervical cancer risk (3). The Centers for Disease Control and Prevention (CDC) recommends two Pap tests in the first year after HIV diagnosis, with annual Paps thereafter (4). This recommendation is based on expert opinion and has not been validated.

Cervical cancer prevention guidelines for the general U.S. population have been amended recently to recommend longer intervals between Pap tests (5). Under these guidelines, women should be screened only every 3 years. Cotesting with Pap and an assay for human papillomavirus (HPV) allows five-year screening intervals, but HPV screening may not be suitable for women with HIV, who have a high burden of HPV. More frequent testing is cost-ineffective: since cervical cancer is uncommon in the general population, many positive test results will reflect self-limited infection with HPVs conveying minimal oncogenic risk; shortening screening intervals from three years to one leads to cervical cancer in about 3/100,000 women screened (6).

The cumulative risk of abnormal Pap testing among women who are HIV seropositive is as high as 77% (7). The 2-year negative predictive value (NPV) of HPV testing for SIL Pap results ranged from 91–96%, depending on CD4 count (8). Pap tests may have a similarly high NPV for cervical precancer.

The aims of this analysis of Pap tests obtained at 6-month intervals in a large cohort of women who are HIV seropositive were to estimate the one-year and three-year NPV of Pap testing, to compare these results to those from HIV seronegative women, to estimate the accuracy of Pap testing, and to confirm or recommend adjusting CDC Pap test screening recommendations for women who are HIV seropositive.

Methods

This study was part of the WIHS, an ongoing multicenter cohort study of HIV-related disease among women who are HIV seropositive and at-risk seronegative comparison women (9). Enrollment began October 1, 1994 at 6 study consortia and over time enrolled 3,766 women, including an expansion during 2001–2002 (10). Follow up continues, but this

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analysis includes information obtained before October 1, 2010. Written informed consent for study was obtained after local human subjects committees approved protocols.

Every six months, participants had a physical examination that included a conventional Pap smear. Slides were interpreted centrally according to the 1991 Bethesda system for classification of cervicovaginal cytology and were classified as negative for squamous abnormality, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells (AGC), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), adenocarcinoma in situ (AIS), and cancer (11); a later modification included atypical squamous cells, cannot exclude high grade lesion (ASC-H).

Women with Pap test results available from study entry were identified. We excluded those with documented or self-reported prior abnormal Pap tests, cervical cancer, or cervical disease treatments such as cryotherapy or loop excision. We also excluded women with prior hysterectomy.

Since cervical cancer is rare in our cohort (3), the primary study endpoint was cervical precancer, defined for this study as a composite of cervical cytology read as HSIL, AGC favor neoplasia or AIS, or cancer, as well as cervical biopsies read as grade 2 or 3 cervical intraepithelial neoplasia (CIN), or AIS(CIN2+). Pap tests read as ASC-US or LSIL but not precancer were considered abnormal but not precancer. Colposcopy was prescribed by protocol for women with any cytologic abnormality or visible condylomata, later modified to allow annual colposcopy for women with persistent ASCUS but negative colposcopy. Decisions about biopsy were made by site colposcopists and study participants, although conization was recommended for most patients with precancer. The proportion of women with precancer diagnosed within 15 and within 39 months after one, three, or 10 consecutive negative Paps was assessed to estimate NPV; these intervals were selected to allow for 12 and 36 months of additional surveillance, plus 3 further months for work-up of abnormalities. When interval Paps were missing, we imputed negative tests for single missing results between two consecutive negatives but left them as missing values when two or more consecutive Paps were missing. NPV was further estimated for subgroups stratified by HIV status and age.

Longitudinal analysis of predictors of precancer was performed using Cox proportional hazards models with time-updated covariates for current Pap test results, age, current tobacco use, current CD4 count, and current use of highly active antiretroviral therapy (HAART), as well as race. Models were run lagging risk factors both 15 and 39 months from the current Pap test or biopsy test. HAART use was defined as previously described (12). Risk factors for pre-cancer were modeled among all women, as well as when restricted to only women who are HIV seropositive. Adjusted hazard rations (aHR) and 95% confidence intervals are reported.

Results

Of 3729 women in WIHS with at least one satisfactory Pap result, we excluded 1736; women with one or more reasons for exclusion included 136 with precancer at the initial visit, 138 with a prior history of cervical disease or treatment, 131 with a self-reported prior history of cervical cancer, 348 with prior hysterectomy, and 1426 with a self-reported history of prior abnormal Pap. We also excluded 182 women with no follow-up, leaving 1811 women (1225 HIV seropositive and 586 seronegative) with no prior precancer and an available baseline Pap test for this analysis. Among these, 1462 women (942 HIV seropositive, 520 seronegative) had a negative baseline Pap test.

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The baseline demographic and medical characteristics of the women with negative initial Pap tests are presented in Table 1. For the analysis of outcomes after 15 months among these women with negative baseline Pap tests, we had 1153 person-years of follow-up among women who are HIV seropositive and 634 person-years of observation among women who are seronegative. For analysis of outcomes after 39 months, women who are HIV seropositive contributed 2818, and women who are seronegative contributed 1,556 person-years of follow-up.

The distribution of cytologic and histologic results is shown in Table 2; most women had precancer identified at a visit when cytology was only ASC or LSIL. Only 14 of the 40 women with Pap test results that proved to be falsely negative during 39 months of observation (i.e., women with baseline negative Pap results who developed precancer) had biopsy-confirmed CIN3. This represents only 1% of the 942 women at risk. No cancers were found in these women. One woman developed VAIN2 after hysterectomy within the 39 month window but had been censored because of the hysterectomy.

We first assessed the accuracy of a single baseline cytology test among women who are HIV seropositive. Among the 1225 such women without a prior history of abnormal Pap test or cervical disease at study entry, 25 (2%) were diagnosed with precancer during 15 months of follow-up, and 17 of these 25 (68%) had initial abnormal Pap test results. Of 1200 women without precancer during 15 months of observation, 934 (78%) had negative Pap results at baseline. Thus, 8 (1%) of the women with negative cytology developed precancer within 15 months and 40 (4%) within 39 months. These results yield a sensitivity of Pap testing in women who are HIV seropositive of 68%, a specificity of 78%, and a positive predictive value of 6%. Table 3 shows how NPV varied by age, HIV serostatus, and number of prior negative Paps. Since NPV varies with prevalence, we modeled outcomes using the same sensitivity and specificity values while varying the prevalence of precancer varied from 1% to 6%; NPV in these models fell only from 99.6% (95%CI: 99.2%–100%) to 97.4% (95%CI: 96.4%–98.5%).

We next evaluated precancer risk among these same women with negative baseline Pap tests when followed longer. Among our 1225 HIV women who are seropositive, precancer developed in 71; 31 (44%) of these had abnormal Paps at baseline. Conversely, of 1154 women who did not develop precancer, 252 (22%) had abnormal Paps at baseline and 902 had negative Pap results. From these data we derived the sensitivity of a single Pap test for precancer within 39 months of 44%, a specificity of 78%, and a positive predictive value of 11%. When we evaluated the effect of varying 39-month precancer prevalence 1% to 6%, the NPV of cytology fell from 99.3% (95%CI: 98.7%–99.8%) to 95.6% (95%CI: 94.3%–96.9%).

We also compared precancer risk among women with HIV to that among HIV uninfected women. Risk was consistently higher for women who are HIV seropositive in all comparisons, both those at 15 and those at 39 months after one and three negative Pap tests (not shown).

We next attempted to estimate the NPV of serial negative Pap tests. After three consecutive negative Pap tests, including those from baseline and subsequently, none of 539 eligible women who are HIV seropositive developed precancer during the following 15 months, while 10 (2%) developed precancer within 39 months. Among 182 eligible women who are HIV seropositive with 10 consecutive negative Paps, none developed precancer within the next 39 months. These 182 HIV women who are seropositive with 10 consecutive negative Paps represented 55% of all women who are seropositive with 39 months of follow-up after

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10 Pap tests; the remaining 45% of women with adequate follow-up had one or more Pap abnormalities among the 10 specimens collected.

We estimated risk factors for precancer longitudinally among all WIHS participants with at least one Pap test, including those with Paps initially read as ASCUS or LSIL. In multivariate analysis (Table 4), women who are HIV seropositive had twice the risk of precancer at 15 months compared to seronegative women (adjusted HR 1.9, 95% CI 1.5, 2.5, P < 0.001). Other significant risk factors for precancer at 15 months included younger age (aHR 1.7 for age <31 years vs > 45 years, 95% C.I 1.3, 2.2, P < 0.001), current tobacco use (aHR 1.5, 95% C.I. 1.2, 1.9, P < 0.001), and abnormal Pap result during follow-up (aHR 11.9, 95% C.I. 9.6, 14.8,, P <0.001). Risk factors for pre-cancer within 39 months of a single negative Pap test were similar to those observed at 15 months (Table 4). Current oral contraceptive use and the number of male sexual partners in last 6 months were not associated with precancer risk within 15 or 39 months (data not shown). We also examined the effect of reporting a new sexual partner within the last six months on the subsequent incidence of precancer at 15 and 39 months. Having a new sexual partner was not a significant predictor of precancer in any of these models.

Risk factors for precancer were similar when restricted to women who are HIV seropositive only (Table 5). In that analysis, precancer during 15 months of follow-up was associated with any abnormal Pap (aHR 9.9, 95% C.I. 7.7, 12.6), current smoking (aHR 1.5, 95% C.I. 1.2, 2.0 vs nonsmokers), younger age (aHR 1.5, 95% C.I. 1.1, 2.1 for age younger than 31 years vs age older than 45, and lower CD4 count (aHR 1.8, 95% C.I. 1.3, 2.3 for CD4 200–500, aHR 2.2, 95% CI 1.6, 2.9 for CD4 <200, vs CD4 >500). Use of highly active antiretroviral therapy, age, and ethnicity were not associated with precancer risk within 15 months.

We also examined the effect of reporting a new sexual partner within six months of an index Pap on the subsequent incidence of precancer at 15 and 39 months. We used separate Cox models adjusting for Pap results, age, and HIV status among all women; for Pap result only for women with HIV; and for Pap result only among HIV seronegative women. Having a new sexual partner was not a significant predictor of precancer in any of these models.

Discussion

Current guidelines recommend that women infected with HIV obtain Pap tests at HIV diagnosis and six months later, with subsequent lifetime annual testing if both are negative (4). This guideline is based on expert opinion and the observations that the sensitivity of Pap testing is limited and women with HIV are at increased risk for cervical precancer. Harris and colleagues using data from the WIHS have shown that three-year screening intervals are safe for women who are HIV seropositive after a single combination Pap and high risk HPV DNA test (8).

Our results show that women who are HIV seropositive with negative Pap results and no history of Pap abnormalities have a low short-term risk for precancer and negligible risk for cancer. After HIV diagnosis, annual rather than semiannual Pap testing is safe for women with newly diagnosed HIV and no history of abnormal Pap tests.

Castle and associates have established guidance for cervical cancer prevention measures based on risk stratification for CIN3+, the most advanced marker for cancer risk (13). Given the slow rate of development of cervical precancer to cancer, they suggested routine screening intervals for women with a risk for CIN3+ of 2% or less over two to three years. Because the rate of progression from CIN to cancer may be accelerated in immunodeficient women, we used a more liberal definition of precancer than Castle and colleagues did,

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including CIN2 and unconfirmed HSIL Pap results. Three-year risk for precancer among women who are HIV seropositive in WIHS with three consecutive negative Pap results was only 2%; only 1% developed CIN3+ and none developed cancer within three years. These findings suggest that women who are HIV seropositive with negative Pap test histories can be screened at longer intervals than currently recommended.

Our finding that women with negative Paps are at relatively low risk of precancer and can be screened at intervals similar to those recommended for HIV seronegative women does not imply that women who are HIV seropositive are at low risk for precancer. Women with any Pap abnormalities require colposcopy to identify precancer and guide treatment that will interrupt oncogenesis, although management of abnormalities can follow current guidelines for HIV seronegative women (14, 15). Women with prior Pap test abnormalities and those with treated precancer, and cancer were not evaluated in this study and are not candidates for longer screening intervals. With intensive screening and follow-up women who are HIV seropositive are at very low risk for cancer (3).

Our study was limited by several factors. First, WIHS women were recruited from sites where some had received prior care, including Pap tests and treatment for cervical cancer precursors; initial study Paps may not be the first Paps after HIV diagnosis. However, the incidence of Pap abnormalities declined over time in WIHS, suggesting that intake screening identified many women with evolving cervical lesions (7). Further, exploratory analysis of our study group showed that Pap testing had a robustly high NPV for precancer across hypothetical populations with precancer risk as high as 6%. Second, WIHS women represent a self-selected group of women who are HIV seropositive. Our recommendations would be strengthened by validation at centers providing care for women who are HIV seropositive who have received less intensive surveillance. Third, we used 6-month rather than annual Pap intervals. However, women who have survived three years without a Pap abnormality should have lower precancer risk than those followed only 18 months, so our data on precancer risk should be considered a conservative estimate for women tested annually. Fourth, as this study population was restricted to women with no history of any abnormal Pap including the baseline study visit, clinicians may encounter a lower proportion of women who are HIV seropositive with three consecutive negative Paps. Fifth, many women in our cohort were recruited before the adoption of HAART; precancer risk for women on HAART may be lower. Finally, we used precancer rather than biopsy-confirmed CIN2+ as our endpoint as a conservative assumption since compliance with recommended colposcopy in WIHS is suboptimal. Since some HSIL Paps may reflect low grade disease and some CIN2 may regress, our results likely underestimate Pap's NPV, and longer screening intervals are probably safer than our results would indicate.

In conclusion, we suggest that after three negative annual Pap tests, women who are HIV seropositive can be screened at three year intervals. Alternatively, three-year intervals for women with three consecutive negative Paps may be restricted to women aged 40 and older, as these women had a risk of precancer in our study of less than 1%. Women with 10 or more consecutive Paps should defer screening for at least 3 years; further research may allow even longer screening intervals for these women.

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Table 1

Demographic and Medical Characteristics of 1,462 Women Who Are Human Immunodeficiency Virus Seropositive and Seronegative With an Initial Negative Pap Test at Study Enrollment

	HIV+		HIV−		*P*
	n	%	n	%	
Number	942	64	520	36	
Age (years)					
Younger than 31	266	28	232	45	
31–45	570	61	255	49	<0.001
Older than 45	106	11	33	6	
Ethnicity					0.86
American African	533	56	296	57	
Hispanic	106	11	63	12	
Caucasian	128	14	63	12	
Other	175	19	98	19	
Cohort					<0.001
Original (1994/95)	652	69	292	56	
2001/02 recruit	290	31	228	44	
Smoking					0.006
Never smoked	334	36	159	30	
Current smoker	458	49	299	58	
Ever smoked	144	15	62	12	
Oral contraceptive use in last 6 months					0.002
No	902	96	479	92	
Yes	38	4	41	8	
Male sexual partners in last 6 months					<0.001
None	296	32	106	20	
1	510	55	259	50	

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	HIV+		HIV−		*P*
	n	**%**	**n**	**%**	
2 or more	125	13	154	30	
CD4 count					
Less than 200	131	14			
200–500	396	43			
Greater than 500	389	43			
AIDS					
No	800	85			
Yes	142	15			
On HAART					
No	805	85			
Yes	137	15			

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

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Table 2

Distribution of Subsequent Cytologic and Histologic Abnormalities Among 40 of 942 Women With Human Immunodeficiency Virus Who Developed Precancer When Followed for 39 Months After a Negative Pap Test at Study Enrollment

Pap Test Result*	Biopsy Results			
	No biopsy	CIN2[2]	CIN3	Total
Negative	0	3	0	3
ASC-US	0	8	5	13
ASC-H	0	0	1	1
LSIL	0	7	4	11
HSIL: CIN2	2	1	3	6
HSIL: CIN3	5	0	1	6
Total	7	19	14	40

Data are n.

*Pap results at the visit when precancer was detected.

CIN, cervical intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells, cannot rule out high-grade lesion; LSIL, low-grade squamous intraepithelial lesion;

HSIL:CIN2: high-grade squamous intraepithelial lesion, favor moderate dysplasia; HSIL:CIN3: high-grade squamous intraepithelial lesion, favor severe dysplasia or carcinoma in situ.

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Table 3

Negative Predictive Values for Precancer Among All Women and Women of Various Ages After One or More Consecutive Pap Test Results and Varying Follow-up Intervals, Stratified by Human Immunodeficiency Virus Serostatus

		All Women			HIV+		HIV−	
	Age (years)	**n**	**15 mo**	**39mo**	**15mo**	**39mo**	**15mo**	**39mo**
Number of initial negative Pap results								
1		1462	99.2 (98.7, 99.6)	96.4 (95.5, 97.4)	99.2 (98.6, 99.7)	95.8 (94.5, 97.0)	99.2 (98.5, 100)	97.7 (96.4, 99.0)
3		867	99.9 (99.7, 100)	98.5 (97.7, 99.3)	100	98.1 (97.0, 99.3)	99.7 (99.1, 100)	99.1 (98.1, 100)
10		331	100	100	100	100	100	100
One negative Pap								
	Younger than 31	498	99.2 (98.4, 100)	95.8 (94.0, 97.6)	98.9 (97.6, 100)	95.1 (92.5, 97.7)	99.6 (98.7, 100)	96.6 (94.2, 98.9)
	31–45	824	99.0 (98.4, 99.7)	96.6 (95.4, 97.8)	99.1 (98.4, 99.9)	95.8 (94.1, 97.4)	98.8 (97.5, 100)	98.4 (96.9, 100)
	Older than 45	139	100	97.8 (95.4, 100)	100	97.2 (94.0, 100)	100	100
Three negative Paps								
	Younger than 31	241	100	98.3 (96.7, 100)	100	98.3 (96.0, 100)	100	98.4 (96.1, 100)
	31–45	519	99.8 (99.4, 100)	98.5 (97.4, 99.5)	100	97.9 (96.4, 99.5)	99.5 (98.4, 100)	99.5 (98.4, 100)
	Older than 45	107	100	99.1 (97.2, 100)	100	98.8 (96.4, 100)	100	100
10 negative Paps								
	Younger than 31	48	100	100	100	100	100	100
	31–45	217	100	100	100	100	100	100
	Older than 45	66	100	100	100	100	100	100

Data are % (95% CI) unless otherwise specified.

HIV, human immunodeficiency virus.

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Table 4

Multivariate Risk Factors for Precancer Within 15 (or 39) Months After Each Pap Test Obtained in Semiannual Sampling During Longitudinal Follow-up Among Human Immunodeficiency Virus (HIV)-seropositive and HIV-Seronegative Women's Interagency HIV Study Women

	Within 15 Months		Within 39 Months	
	Hazard Ratio (95%CI)	***P***	**Hazard Ratio (95%CI)**	***P***
Pap results				
Negative (ref)	1		1	
Abnormal	11.9 (9.6,14.8)	<.001	6.8 (6.0,7.8)	<0.001
HIV status				
Negative (ref)	1		1	
Positive	1.9 (1.5,2.5)	<.001	2.4 (2.0,2.9)	<.001
Age (in years)				
Younger than 31	1.7 (1.3,2.2)	<.001	1.6 (1.3,2.0)	<.001
31–45	1.0 (0.8,1.2)	0.74	1.0 (0.9,1.2)	0.78
Older than 45(ref)	1		1	
Smoking status				
Never smoked (ref)	1		1	
Current smoker	1.5 (1.2,1.9)	<.001	1.6 (1.4,1.9)	<.001
Ever smoked	0.9 (0.7,1.2)	0.53	1.1 (0.9,1.3)	0.51
Ethnicity				
American African (ref)	1		1	
Hispanic	1.2 (0.9,1.7)	0.27	1.2 (0.9,1.4)	0.20
Caucasian	1.1 (0.8,1.5)	0.41	0.9 (0.8,1.1)	0.51
Other race	1.1 (0.8,1.4)	0.54	0.9 (0.7,1.0)	0.07

CI, confidence interval; HIV, human immunodeficiency virus.

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Table 5

Multivariate Risk Factors for Precancer Among HIV-Seropositive Women Only Within 15 (or 39) Months After Each Pap Test Obtained in Semiannual Sampling During Longitudinal Follow-up

	Within 15 Months		Within 39 Months	
	Hazard Ratio(95%CI)	***P***	**Hazard Ratio (95%CI)**	***P***
Pap results				
Negative (ref)	1		1	
Abnormal	9.9 (7.7,12.6)	<.001	5.6 (4.8,6.5)	<.001
Age (years)				
Younger than 31	1.5 (1.1,2.1)	0.01	1.3 (1.1,1.6)	0.01
31–45	0.9 (0.7,1.2)	0.50	0.9 (0.8,1.1)	0.49
Older than 45(ref)	1		1	
Smoking status				
Never smoked (ref)	1		1	
Current smoker	1.5 (1.2,2.0)	<.001	1.7 (1.4,2.0)	<.001
Ever smoked	0.8 (0.5,1.1)	0.18	0.9 (0.7,1.2)	0.62
Ethnicity				
American African (ref)	1		1	
Hispanic	1.2 (0.8,1.7)	0.37	1.2 (1.0,1.6)	0.10
Caucasian	1.0 (0.7,1.4)	0.94	0.9 (0.7,1.1)	0.18
Other race	1.0 (0.8,1.3)	0.85	0.8 (0.7,1.0)	0.05
CD4 cell count				
Greater than 500 (ref)	1		1	
200–500	1.8 (1.3,2.3)	<.001	1.6 (1.3,1.9)	<.001
Less than 200	2.2 (1.6,2.9)	<.001	2.0 (1.6,2.4)	<.001
On HAART				
No (ref)	1		1	
Yes	1.1 (0.9,1.3)	0.42	0.9 (0.8,1.0)	0.16

CI, confidence interval; HAART, highly active antiretroviral therapy.