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Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women

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Abstract

Objectives—To study anal intraepithelial neoplasia (AIN) and its associations with anal and cervical human papillomavirus (HPV), cervical neoplasia, host immune status, and demographic and behavioral risk factors in women with and at risk for HIV infection.

Design—Point-prevalence analysis nested within a prospective study of women seen at three clinical centers of the Women's Interagency HIV Study.

Methods—In 2001–2003 participants were interviewed, received a gynecological examination, anal and cervical cytology testing and, if abnormal, colposcopy or anoscopy-guided biopsy of visible lesions. Exfoliated cervical and anal specimens were assessed for HPV using PCR and type-specific HPV probing. Logistic regression analyses were performed and odds ratios (OR) estimated risks for AIN.

Results—470 HIV-infected and 185 HIV-uninfected women were enrolled. Low-grade AIN (LGAIN) was present in 12% of HIV-infected and 5% of HIV-uninfected women. High-grade AIN (HGAIN) was present in 9% of HIV-infected and 1% of HIV-uninfected women. In adjusted analyses among HIV-infected women, the risk factors for LGAIN were younger age (OR=0.59, 95% CI=0.36–0.97), history of receptive anal intercourse (OR=3.2, 95% CI=1.5–6.8), anal HPV (oncogenic types only OR=11, 95% CI=1.2–103; oncogenic and non-oncogenic types OR=11, 95% CI=1.3–96), and cervical HPV (oncogenic and non-oncogenic types OR=3.5, 95% CI=1.1–11). In multivariable analyses among HIV-infected women, the only significant risk factor for HGAIN was anal HPV infection (oncogenic and non-oncogenic types OR=7.6, 95% CI=1.5–38).

Conclusions—Even in the era of highly active antiviral therapy, the prevalence of AIN was 16% in HIV-infected women. After controlling for potential confounders, several risk factors for LGAIN differed from risk factors for HGAIN.

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Keywords

anal intraepithelial neoplasia; HIV-infection; human papillomavirus; women

Introduction

The incidence of anal cancer is increasing among several important subgroups of the United States (US) population, in particular among people with HIV/AIDS. The incidence of anal cancer is 10-50 times greater in men who have sex with men (MSM) and adults with AIDS than in the general population [1-8]. Among women with HIV/AIDS, the incidence of invasive anal cancer is 7-28 times greater than in the general population [9,10]. Risk factors for the development of anal cancer include sexual practices that increase exposure to anal human papillomavirus (HPV) such as receptive anal intercourse, history of anal warts and cigarette smoking [11-13].

Most invasive anal cancers, like cervical cancers, are squamous cell carcinomas and are associated with HPV infection. The natural history of squamous cell carcinomas of the anus (SCCA) is similar to other neoplasms where HPV plays an etiological role [14]. A small percentage of high-grade anal intraepithelial neoplasias (HGAIN) will become malignant, with invasion into the subjacent stroma. However, the natural history of AIN is not as well defined as that of cervical intraepithelial neoplasia (CIN) and most of the research on AIN has been done in men, particularly MSM.

The prevalence of anal HPV infection is higher in HIV-infected MSM (85-95%)[15-17] than in HIV-uninfected MSM (66%)[15] but is high in both groups compared with heterosexual men (24%) [18]. HIV-infected MSM are more likely to have multiple HPV types (61%) and oncogenic HPV types (65%) than are HIV-infected injection drug users or heterosexual men (26% and 44%, respectively) [16,18]. The risk factors for the detection of anal HPV in MSM include HIV infection, low CD4+ cell counts, presence of anal warts, and history of receptive anal intercourse [15]. The established risk factors for developing AIN are HIV infection, low CD4+ cell counts, persistent anal HPV infection, and infection with oncogenic HPV genotypes [19]. Less is known about the risk factors for anal HPV infection and AIN in women, either with or without HIV infection, although the sparse existing data indicate that the risk factors are similar to those in men [20,21].

Anal cancer remains one of the few carcinomas of the gastrointestinal tract that can be successfully treated with a combination of chemotherapy and radiation therapy, with or without surgery [22]. However, such treatment is often accompanied by substantial morbidity due to the radiation therapy and treatment failure is more likely with advanced disease. An understanding of the risk factors for AIN is important since detection and treatment of precancerous lesions such as HGAIN may prevent SCCA, similar to treatment of high-grade CIN to prevent cervical cancer.

In women, anogenital HPV infection is likely to be multicentric and cervical HPV infection may serve as a reservoir and source of anal HPV infection or vice versa. Studies in HIV-infected women have found that the prevalence of HPV infection and disease was higher in the anus than in the cervix [20,23,24]. Because AIN may progress to invasive cancer, an understanding of the biology of AIN in high-risk groups of women is important to the design of anal cancer prevention efforts in these women. The goal of this investigation was to determine the prevalence of and risk factors for AIN in a representative cohort study of US women with HIV and at risk for HIV infection.

Methods

These results are from a study nested within the Women's Interagency HIV Study (WIHS), a prospective study of HIV-1 infection in women conducted in five locations within the US. The WIHS methods and baseline cohort characteristics have been described previously [25]. Briefly, between October 1994 and November 1995, 2056 HIV-1 infected and 569 uninfected women were enrolled. A second enrollment between October 2001 and September 2002, added 737 HIV-infected and 406 HIV-uninfected women. The HIV-infected women in the WIHS cohort reflect the ethnicity, exposure status, and ages of the national AIDS cases among US women [26].

Every six months, WIHS participants were interviewed and received a physical examination. Multiple gynecologic and blood specimens were collected at each visit. Interviewers assessed self-reported antiretroviral therapy (ART) use during the period prior to the study visit. ART medications were identified by photo-medication cards and recorded by both brand and generic drug names. The physical examinations included a pelvic exam with cervical Pap testing and cervicovaginal lavage (CVL) fluid collection.

For this WIHS anal sub-study, women were recruited in years 2001 to 2003 from the Brooklyn, Chicago, and San Francisco Bay Area WIHS sites. Women were eligible if they had no history of HGAIN or anal cancer. In addition to the WIHS interview, physical examination and specimen collection, women enrolled in the anal sub-study were administered a short questionnaire containing questions specific to anal disease. Participants also received an external anal examination for the presence of visible warts, hemorrhoids, discharge or ulcerations. Anal swab specimens were collected for anal cytology (ThinPrep™) and anal HPV testing. Among HIV-infected women, blood collected at the baseline anal study visit was tested for CD4+ lymphocytes and HIV RNA. Women with abnormal anal cytology were referred for high-resolution anoscopy (HRA) and biopsy of visible disease at a separate visit, as described previously [21]. Women enrolled in this sub-study were followed every six months through April 2006. The data analyzed in this report are from the baseline visit of the anal sub-study. Study protocols were reviewed and approved by the institutional review boards and informed consent was obtained from the participants.

Exfoliated cells for HPV DNA testing were obtained using CVL and by anal swabs, as previously described [27,28]. HPV DNA was detected with L1 consensus primer MY09/MY11/HMB01 polymerase chain reaction assays. Primer set PC04/GH20 that 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. Specimens that were negative for β -globulin amplification were considered inadequate, and their HPV DNA data were considered as missing. Details of these laboratory methods have been published previously [29], and the results were shown to have high reproducibility, sensitivity, and specificity [28,30,31]. 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 oncogenic HPV (types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59 and 66) and non-oncogenic HPV (types 6, 11, 13, 26, 32, 34, 40, 42, 53, 54, 55, 57, 61, 62, 64, 67, 68, 69, 70, 71 (AE8), 72, 73 (PAP238A), 81 (AE7), 82 (W13B and AE2), 83 (PAP291), 84 (PAP155), 85 (AE5), 89 (AE6), AE9, and AE10)[29,30].

Both anal and cervical cytology results were categorized according to the Bethesda system: normal; atypical squamous cells (atypia); low-grade squamous intraepithelial lesions (LSIL); and high-grade squamous intraepithelial lesions (HSIL). Women with unsatisfactory cervical or anal cytology due to insufficient cellularity were excluded from cytology classification. Anal and cervical histological results were categorized as benign, atypia, condyloma, AIN 1/CIN1,

AIN 2/CIN 2 and AIN 3/CIN 3. For this analysis, we defined the grade of the lesion as the more advanced diagnosis on cytology or histology when both were available. In the absence of histological data, grade was based on cytology alone. We hereafter refer to this combined categorization as 'cytology/histology'.

After the results from the anal and cervical cytology testing were available, participants with abnormal results were contacted and asked to return for anoscopy and/or colposcopy. Among the 148 women with abnormal anal cytology results, 50% had anoscopy and 41% had a biopsy for histological evaluation. Among the 166 women with abnormal cervical cytology results, 72% had colposcopy and 55% had a biopsy for histological evaluation. The main reason for lack of histological confirmation of the abnormal cytology results was failure of participants to return for anoscopy and colposcopy within six months after their baseline visit (74 women with abnormal anal cytology and 43 women with abnormal cervical cytology). The other reason was that no lesions were found on visual inspection (13 women with anoscopy and 32 women with colposcopy).

HPV genotype for our analysis was grouped into oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and non-oncogenic types (6, 11, 26, 32, 40, 53, 54, 55, 61, 68, 70, 73, 82, 83, and 84 plus all those HPV types that hybridized only with the consensus probe) [32]. In addition, anal and cervical HPV infection was categorized into the following mutually exclusive groups: 1) only oncogenic HPV types; 2) only non-oncogenic HPV types; 3) both oncogenic and non-oncogenic HPV types; or 4) no HPV infection (the reference group).

Contingency table analyses were conducted to compare the distribution of participant characteristics by HIV serostatus. Cochran-Armitage Trend test analyses were conducted to assess the association between cigarette smoking and grade of anal disease. Logistic regression analyses were done to compute unadjusted odds ratios (OR, hereafter referred to as risk), 95% confidence intervals (95% CI), and *p*-values to estimate the relationship between each factor and risk of anal abnormalities. For the regression analyses, women with normal anal cytology/histology were the reference group and they were compared to those with low-grade (LG) AIN (LSIL, condyloma, AIN 1) or high-grade (HG) AIN (HSIL, AIN 2, and AIN 3). We then performed multivariable logistic regression analysis, including those characteristics that were significantly associated with anal disease in the unadjusted analyses. Since abnormal cervical cytology/histology and cervical HPV infection were highly correlated with each other, only cervical HPV infection (the stronger predictor variable) was included in the multivariable models. All multivariable models also included those variables that have been found to be associated with AIN, regardless of their statistical significance in our data set. These included HIV status, age, cigarette smoking status, highly active antiretroviral therapy (HAART) use, HIV RNA level, and CD4+ cell count. In the case of quasi-complete separation of data points for the anal HPV dummy variables, we employed a dispersion matrix algorithm to identify null response patterns in our logistic regression models to obtain convergent maximum likelihood model estimates [33,34]. *P*-values ≤ 0.05 were considered to be statistically significant. All analyses were performed using SAS/STAT® software version 9.1 [35].

Results

A total of 655 women, 470 HIV-infected and 185 HIV-uninfected, were enrolled in this study (Table 1). Because of missing data for some study variables, the sample size varied for each analysis. HIV-infected women were older, more likely to be widowed, divorced, or separated, reported lower household incomes, were less likely to be employed, drank less alcohol, and were more likely to have injected drugs than HIV-uninfected women.

The proportion of women reporting anal intercourse was high among both HIV-infected (47%) and HIV-uninfected women (46%) and was not statistically different between the two groups. However, women with HIV infection were significantly more likely to have abnormal anal cytology/histology (31%) compared with the HIV-uninfected women (9%), $p < 0.001$ (Table 1). Similarly HIV-infected women were more likely to have abnormal cervical cytology/histology (34%) compared with the HIV-uninfected women (19%), $p = 0.003$. HIV-infected women were more likely than HIV-uninfected women to have anal, cervical, and both anal and cervical HPV infection $p < 0.001$.

Among the women who had both anal cytologic and histologic evaluation, 20 women had atypia on anal cytology and eight (40%) were upgraded to more severe disease based on histological evaluation and 28 women had LSIL on anal cytology and five (18%) were upgraded to more severe disease based on histological evaluation. Among the women who had both cervical cytologic and histologic evaluation, 63 women had atypia on cervical cytology and 46 (73%) were upgraded to more severe disease based on histological evaluation and 25 women had LSIL on cervical cytology and eight (32%) were upgraded to more severe disease based on histological evaluation (not shown in table).

When cigarette smoking was evaluated by grade of anal disease among all women, current cigarette smokers were more likely to have higher-grade anal disease: 52% of women with normal cytology/histology were smokers, 57% of women with atypia, 63% of women with LGAIN, and 64% of women with HGAIN, one-sided trend test p -value 0.02 (not shown in tables). Similar results were seen when these analyses were restricted only to the HIV-infected women: 51% of women with normal cytology/histology were smokers, 58% of women with atypia, 65% of women with LGAIN, and 65% of women with HGAIN, one-sided trend test p -value 0.02.

The unadjusted and adjusted analyses for risk of LGAIN among all women are shown in Table 2. In multivariable analysis, women with a history of receptive anal intercourse were 3.8 times more likely (95% CI 1.8-7.8) and women with anal HPV infection were 12-17 times more likely (95% CI 1.5-143) to have LGAIN than women with no history of receptive anal intercourse or anal HPV infection. Women with non-oncogenic cervical HPV infection or both oncogenic and non-oncogenic cervical HPV infection were 3.3-4.5 times more likely (95% CI 1.5-13) to have LGAIN than women with no cervical HPV infection.

When restricted to women with HIV infection and controlling for age, smoking status, HAART use, CD4+ cell count and viral load, the risk factors for LGAIN were younger age (OR=0.59, 95% CI=0.36-0.97), history of receptive anal intercourse (OR=3.2, 95% CI=1.5-6.8), anal HPV (oncogenic types only OR=11, 95% CI=1.2-103; oncogenic and non-oncogenic types OR=11, 95% CI=1.3-96), and cervical HPV (oncogenic and non-oncogenic types OR=3.5, 95% CI=1.1-11) (Table 3).

The unadjusted and adjusted analyses for risk of HGAIN among all women are shown in Table 4. Controlling for HIV infection, age and smoking status, women with oncogenic anal HPV infection only or both oncogenic and non-oncogenic anal HPV infection were 7-10 times more likely (95% CI 1.3-50) to have HGAIN than women with no anal HPV infection.

When restricted to women with HIV infection and controlling for age, smoking status, HAART use, CD4+ cell count and viral load, women with concomitant oncogenic and non-oncogenic anal HPV infection were 7.6 times more likely (95% CI 1.5-38) to have HGAIN than women with no anal HPV infection (Table 5).

To determine if the results of the logistic regression analyses varied if our outcome was based on cytology data alone, we also performed all of our logistic regression models using only the

cytology data. We found little to no difference in our estimated odds ratios and 95% confidence intervals (data not shown) compared with data using the combined cytology/histology results.

Discussion

Only a few studies have assessed the prevalence of AIN in HIV-infected women and even fewer had a comparison group of high-risk HIV-uninfected women. Our findings show that the prevalence of AIN among HIV-infected women is high and significantly increased above a comparison group of HIV-uninfected women.

Investigators from a smaller study of HIV-infected women in France reported the prevalence of HPV-related lesions to be 11.3%, with 4.6% for anal condyloma and 6.7% for AIN [36]. In an earlier study of the San Francisco WIHS participants, the prevalence among the HIV-infected women was 15% for anal atypia, 10% for LGAIN, and 1% for HGAIN [21]. This same study found that these rates were substantively higher than those of the HIV-uninfected women, 7%, 2% and 0%, respectively. We now report follow-up from that study using a larger sample size and a more recent time point. We found that the rates of atypia were lower than the prior rates but rates of HGAIN were higher than the prior rates. This was true for both the HIV-infected and HIV-uninfected women and may be the result of progression of dysplasia over time or due to the addition of histological evaluation (anal biopsies) that may have increased detection of higher-grade disease.

Consistent with our prior results [20], we also found a high prevalence of anal HPV infection among HIV-infected women (80%) and that the prevalence of anal HPV infection exceeded that of cervical HPV infection (45%), suggesting that HPV infection is either more common in the anus or is present at higher levels in the anus and is thus easier to detect.

We demonstrated that several of the risk factors for LGAIN and HGAIN in women differ. Most notably, having either oncogenic or non-oncogenic HPV types was strongly associated with LGAIN while having oncogenic HPV types was associated with HGAIN. These results are similar to what has been shown in the cervix with CIN [37,38] and in the anus with AIN [39, 40]. Additionally, we found that history of receptive anal intercourse was a risk factor for LGAIN but not for HGAIN. This was true when analyzed as a dichotomous variable (ever vs. never) or as a continuous variable (lifetime number of receptive anal intercourse acts). However, receptive anal intercourse is not necessary to acquire anal HPV infection or AIN. One study of anal HPV infection and AIN in HIV-infected men (50 heterosexual injection drug users and 67 MSM) found that anal HPV infection and AIN may be acquired in the absence of anal intercourse [16]. In women, HPV autoinoculation (e.g., HPV transmission from the cervicovaginal compartment to the anal mucosa) is certainly possible [20,41]. We also found that low CD4+ cell count, <200, had an increased (but not significant) OR for LGAIN but not HGAIN. Although few studies have analyzed LGAIN separately from HGAIN, our results are consistent with other studies in HIV-infected adults [17,36,40] and may explain why HIV-infected individuals with invasive anogenital disease (anal or cervical) have only moderate immunodeficiency at the time of diagnosis [9,42,43].

Among HIV-infected women, in models adjusted for CD4+ cell count, neither HAART use nor plasma HIV RNA had independent effects on the risk of AIN. However, by adjusting for current CD4+ cell count we may be incorporating the beneficial effects of HAART. Longitudinal analyses are needed to adequately incorporate time-varying variables such as CD4+ cell count, HIV RNA, and HAART use and the risk of persistent AIN.

In trend test analyses, we found that current smoking was associated with a higher-grade of anal disease. However, in adjusted analyses we found no association with number of years of cigarette smoking and the risk of anal disease; this was true when we used current smoking

status (data not shown). A similar study of AIN in HIV-infected MSM also failed to find an association between smoking and any grade of AIN [17]. Our results may reflect our sample size or the different impact that smoking has on the anal mucosa versus the cervix and the risk of intraepithelial neoplasia. While several studies have reported an association between cigarette smoking and the risk of anal cancer [13,44,45], the results are not consistent [12] and in that regard differ from what has been reported in the cervix [46].

Although HIV infection was significant in unadjusted models for LGAIN and HGAIN, in adjusted analyses that included anal HPV infection the OR for HIV infection was increased but the 95% confidence interval spanned unity. This suggests that HIV infection may impact risk of neoplasia through its effect on immune suppression and persistence of anal HPV infection. Age also was included in all of our multivariable analyses but was found to be a significant risk factor for LGAIN only among HIV-infected women. Consistent with our findings, younger age has been found to be associated with anal HPV infection [20] and for AIN [21] among HIV-infected women.

In unadjusted analyses, both cervical HPV infection and cervical disease were associated with an increased risk of LGAIN and HGAIN. However, in analyses that adjusted for anal HPV infection, cervical HPV infection contributed only to LGAIN. The most likely explanation for this finding is that most women with cervical HPV infection or disease also have anal HPV infection. This finding warrants further investigation and may impact screening for anal HPV infection and disease in HIV-infected women.

The following limitations should be noted. Not all women with abnormal anal and cervical cytology had corresponding biopsy-based histological results. In addition, anal and cervical biopsies were performed only on participants with cytological abnormalities. Therefore the true prevalence of AIN and CIN is likely to be even higher than what we observed because some of the women with normal cytological findings may have had a false-negative cytology result [47]. Although this represents the largest group of HIV-infected women to be studied to date for AIN, in some of the subgroup analyses the samples sizes were small.

In summary, the high prevalence of anal and cervical HPV-related disease and anal HPV infection among the HIV-infected women is essential information that will help guide screening and treatment practices. Among all women, detection of anal oncogenic HPV types, either alone or in combination with non-oncogenic types, were the only significant risk factors associated with HGAIN. In contrast, LGAIN was significantly associated with both oncogenic and non-oncogenic HPV types, as is observed in studies of CIN. Other significant risk factors for LGAIN included history of receptive anal intercourse, cervical HPV and, among HIV-infected women, younger age.

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Table 1
 Characteristics of the 655 women from the San Francisco Bay Area, Chicago, and Brooklyn Women's Interagency HIV Study

Baseline characteristic	HIV-infected N=470	%	HIV-uninfected N=185	%	p-value
Study site					0.07
New York	163	35	61	33	
San Francisco	149	32	75	41	
Chicago	158	34	49	26	
Missing	0		0		
Age group, years					<0.001
≤ 30	80	17	73	39	
31-40	177	38	63	34	
41-50	159	34	39	21	
> 50	54	11	10	5	
Missing	0		0		
Race/ethnicity					0.59
White, non-Hispanic	63	13	23	12	
White, Hispanic	22	5	10	5	
Black, non-Hispanic	331	70	123	66	
Black, Hispanic	12	3	4	2	
Other, Hispanic	25	5	14	8	
Asian/Pacific Islander/Native American	6	1	6	3	
Other	11	2	5	3	
Missing	0		0		
Educational attainment					0.34
< High school	171	36	56	30	
High school	145	31	61	33	
> High school	153	33	67	36	
Missing	1		1		
Marital status					0.002
Married/living with partner	130	28	58	31	
Widowed/divorced/separated	146	31	32	17	
Never married/other	194	41	95	51	
Missing	0		0		
Household income, annual					0.02
≤ \$12,000	264	56	84	45	
\$12,001-24,000	109	23	44	24	
\$24,001-36,000	49	10	32	17	
> \$36,000	46	10	25	14	
Missing	2		0		
Currently employed					<0.001
No	337	72	90	49	
Yes	133	28	95	51	
Missing	0		0		
Anal sex, ever					0.80
No	249	53	100	54	
Yes	221	47	85	46	
Missing	0		0		
Current cigarette smoker (missing 0)					0.44
No	208	44	88	48	
Yes	262	56	97	52	
Missing	0		0		
Alcohol consumption per week					<0.001

Baseline characteristic	HIV-infected		HIV-uninfected		p-value
	N=470	%	N=185	%	
None	259	56	79	43	
< 3 drinks	129	28	66	36	
3-13 drinks	53	11	37	20	
>= 14 drinks	24	5	3	2	
Missing	5		0		
Ever infected drugs					0.01
No	308	66	140	76	
Yes	162	34	45	24	
Missing	0		0		
Anal cytology/histology					<0.001
Normal	305	66	157	91	
Atypia	43	10	4	2	
Condyloma	23	5	4	2	
AIN-1	31	7	5	3	
AIN-2	12	3	0	0	
AIN-3	25	6	2	1	
Inadequate specimen	28		12		
Missing	3		1		
Cervical cytology/histology					0.003
Normal	277	66	139	81	
Atypia	53	13	19	11	
Condyloma	24	6	6	3	
CIN-1	40	10	5	3	
CIN-2	2	<1	1	1	
CIN-3	21	5	2	1	
Squamous cell carcinoma	2	<1	0	0	
Inadequate specimen	1		0		
Missing	50		13		
Anal HPV infection					<0.001
No	86	20	82	50	
Yes	339	80	83	50	
Missing *	45		20		
Cervical HPV infection					<0.001
No	238	55	141	85	
Yes	191	45	25	15	
Missing *	41		19		
Both anal & cervical HPV					<0.001
No	223	58	138	92	
Yes	163	42	12	8	
Missing *	84		35		
Anal HPV					<0.001
No HPV infection	86	20	82	50	
Oncogenic HPV only	59	14	19	12	
Non-oncogenic HPV only	151	36	55	33	
Both oncogenic and non-oncogenic	129	30	9	5	
Missing *	45		20		
Cervical HPV					<0.001
No HPV infection	238	55	141	85	
Oncogenic HPV only	46	11	10	6	
Non-oncogenic HPV only	110	26	12	7	
Both oncogenic and non-oncogenic	35	8	3	2	

	HIV-infected	HIV-uninfected	p-value
Baseline characteristic	N=470	N=185	
Missing*	41	19	

* Includes specimens that were negative for β -globulin amplification.

Table 2

Unadjusted and adjusted odds ratios and 95% confidence intervals for risk of LGAIN (n=63) among the 525 women from the San Francisco Bay Area, Chicago, and Brooklyn Women's Interagency HIV Study

Variable	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
HIV status				
HIV-uninfected	1.0	Referent	1.0	Referent
HIV-infected	3.1	1.5-6.4	1.4	0.52-3.8
Site				
San Francisco	1.0	Referent		
Brooklyn	1.4	0.73-2.9		
Chicago	1.8	0.91-3.4		
Age, 10-year groups	1.1	0.84-1.4	0.94	0.62-1.4
Race/ethnicity				
Black or other, non-Hispanic	1.0	Referent		
Hispanic, all races	0.73	0.30-1.8		
White, non-Hispanic	1.4	0.69-2.9		
Educational attainment				
< High School	1.1	0.58-2.1		
High School	1.0	Referent		
> High School	1.0	0.53-2.0		
Marital Status				
Married or living with partner	1.0	Referent		
Not married or living with partner	0.81	0.46-1.4		
Household income				
>\$12,000	1.0	Referent		
<=\$12,000	1.2	0.68-2.0		
Employment				
Employed	1.0	Referent	1.0	Referent
Unemployed	2.2	1.2-4.0	1.3	0.61-2.9
History of receptive anal intercourse				
Never had receptive anal intercourse	1.0	Referent	1.0	Referent
Ever had receptive anal intercourse	2.6	1.5-4.5	3.8	1.8-7.8
Number of years smoked cigarettes	1.3	1.0-1.8	1.1	0.75-1.7
Alcohol use				
Currently drinks alcohol	1.0	Referent		
No current alcohol use	1.3	0.77-2.2		
History of injection drug use				
Never injected drugs	1.0	Referent		
Ever injected drugs	0.88	0.49-1.6		
Cervical cytology/histology**				
Normal	1.0	Referent		
Abnormal	3.3	1.9-5.7		
Anal HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	23	2.8-190	17	2.0-141
Non-oncogenic types only	22	2.9-162	12	1.5-95
Both types	55	7.3-412	17	2.1-143
Cervical HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	2.2	0.78-6.2	1.7	0.55-5.5
Non-oncogenic types only	4.6	2.4-9.0	3.3	1.5-7.4
Both types	10	4.2-24	4.5	1.6-13

* Adjusted for HIV infection, age, employment, history of receptive anal intercourse, number of years of cigarette smoking, anal HPV infection, and cervical HPV infection.

** Not included in multivariable model.

Table 3

Unadjusted and adjusted odds ratios and 95% confidence intervals for risk of LGAIN (n=54) among the 359 HIV-infected women from the San Francisco Bay Area, Chicago, and Brooklyn Women's Interagency HIV Study

Variable	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
Site				
San Francisco	1.0	Referent		
Brooklyn	1.8	0.82-3.7		
Chicago	1.7	0.80-3.7		
Age, 10-year groups	0.84	0.61-1.2	0.59	0.36-0.97
Race/ethnicity				
Black or other, non-Hispanic	1.0	Referent		
Hispanic, all races	0.77	0.29-2.1		
White, non-Hispanic	1.1	0.47-2.5		
Educational attainment				
< High School	1.4	0.67-2.8		
High School	1.0	Referent		
> High School	1.2	0.59-2.6		
Marital Status				
Married or living with partner	1.0	Referent		
Not married or living with partner	0.87	0.47-1.6		
Household income				
>\$12,000	1.0	Referent		
<=\$12,000	1.2	0.66-2.1		
Employment				
Employed	1.0	Referent		
Unemployed	2.0	0.95-4.1		
History of receptive anal intercourse				
Never had receptive anal intercourse	1.0	Referent	1.0	Referent
Ever had receptive anal intercourse	2.7	1.5-5.0	3.2	1.5-6.8
Number of years smoked cigarettes	1.3	0.94-1.7	1.3	0.80-2.0
Alcohol use				
Currently drinks alcohol	1.0	Referent		
No current alcohol use	1.0	0.57-1.8		
History of injection drug use				
Never injected drugs	1.0	Referent		
Ever injected drugs	0.85	0.46-1.6		
Current HAART use				
No	1.0	Referent	1.0	Referent
Yes	1.6	0.86-2.8	1.1	0.48-2.5
CD4+ cell count mm ³				
> 500	1.0	Referent	1.0	Referent
200-500	2.2	1.1-4.5	1.5	0.62-3.7
< 200	5.1	2.2-12	2.8	0.87-9.2
HIV RNA, copies				
< 500	1.0	Referent	1.0	Referent
500-4,000	1.1	0.46-2.5	0.49	0.15-1.6
> 4,000	1.6	0.82-2.9	0.64	0.25-1.7
Cervical cytology/histology**				
Normal	1.0	Referent		
Abnormal	3.0	1.6-5.5		
Anal HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	14	1.7-120	11	1.2-103
Non-oncogenic types only	11	1.5-88	7.2	0.88-60
Both types	28	3.7-215	11	1.3-96
Cervical HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	1.7	0.54-5.6	1.1	0.31-4.1
Non-oncogenic types only	4.0	1.9-8.3	2.4	0.99-6.0
Both types	8.1	3.2-20	3.5	1.1-11

* Adjusted for age, history of receptive anal intercourse, number of years of cigarette smoking, current HAART use, CD4+ cell count, HIV RNA, anal HPV infection, and cervical HPV infection.

** Not included in multivariable model.

Table 4

Unadjusted and adjusted odds ratios and 95% confidence intervals for risk of HGAIN (n=39) among 501 women from the San Francisco Bay Area, Chicago, and Brooklyn Women's Interagency HIV Study

Variable	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
HIV status				
HIV-uninfected	1.0	Referent	1.0	Referent
HIV-infected	9.5	2.3-40	3.1	0.67-14
Site				
San Francisco	1.0	Referent		
Brooklyn	1.3	0.60-2.9		
Chicago	1.1	0.49-2.6		
Age, 10-year groups	1.5	1.1-2.1	1.3	0.80-2.1
Race/ethnicity				
Black or other, non-Hispanic	1.0	Referent		
Hispanic, all races	0.80	0.27-2.4		
White, non-Hispanic	1.5	0.62-3.5		
Educational attainment				
< High School	0.65	0.28-1.5		
High School	1.0	Referent		
> High School	1.0	0.47-2.2		
Marital Status				
Married or living with partner	1.0	Referent		
Not married or living with partner	1.0	0.50-2.1		
Household income				
>\$12,000	1.0	Referent		
≤\$12,000	0.92	0.48-1.8		
Employment				
Employed	1.0	Referent		
Unemployed	1.6	0.76-3.2		
History of receptive anal intercourse				
Never had receptive anal intercourse	1.0	Referent		
Ever had receptive anal intercourse	1.2	0.64-2.4		
Number of years smoked cigarettes	1.5	1.1-2.1	1.2	0.79-1.9
Alcohol use				
Currently drinks alcohol	1.0	Referent		
No current alcohol use	0.97	0.50-1.9		
History of injection drug use				
Never injected drugs	1.0	Referent		
Ever injected drugs	1.5	0.79-3.0		
Cervical cytology/histology**				
Normal	1.0	Referent		
Abnormal	2.7	1.3-5.6		
Anal HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	8.7	1.7-45	7.0	1.3-37
Non-oncogenic types only	4.6	0.98-22	2.2	0.42-11
Both types	22	5.1-97	10	2.0-50
Cervical HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	3.4	1.1-10	1.8	0.57-5.9
Non-oncogenic types only	4.1	1.8-9.3	1.9	0.73-4.8
Both types	6.4	2.1-20	2.0	0.56-7.3

* Adjusted for HIV infection, age, number of years of cigarette smoking, anal HPV infection, and cervical HPV infection.

** Not included in multivariable model.

Table 5

Unadjusted and adjusted odds ratios and 95% confidence intervals for risk of HGAIN (n=37) among 342 HIV-infected women from the San Francisco Bay Area, Chicago, and Brooklyn Women's Interagency HIV Study

Variable	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Site				
San Francisco	1.0	Referent		
Brooklyn	1.5	0.64-3.5		
Chicago	1.2	0.49-2.8		
Age, 10-year groups	1.2	0.86-1.7	1.1	0.65-1.9
Race/ethnicity				
Black or other, non-Hispanic	1.0	Referent		
Hispanic, all races	0.94	0.31-2.8		
White, non-Hispanic	1.2	0.48-3.2		
Educational attainment				
< High School	0.62	0.27-1.5		
High School	1.0	Referent		
> High School	0.90	0.40-2.0		
Marital Status				
Married or living with partner	1.0	Referent		
Not married or living with partner	1.1	0.50-2.3		
Household income				
>\$12,000	1.0	Referent		
≤\$12,000	0.92	0.46-1.8		
Employment				
Employed	1.0	Referent		
Unemployed	1.4	0.63-3.1		
History of receptive anal intercourse				
Never had receptive anal intercourse	1.0	Referent		
Ever had receptive anal intercourse	1.3	0.65-2.6		
Number of years smoked cigarettes	1.4	0.99-2.0	1.2	0.77-2.0
Alcohol use				
Currently drinks alcohol	1.0	Referent		
No current alcohol use	0.80	0.40-1.6		
History of injection drug use				
Never injected drugs	1.0	Referent		
Ever injected drugs	1.3	0.63-2.5		
Current HAART use				
No	1.0	Referent	1.0	Referent
Yes	2.5	1.2-5.3	2.2	0.87-5.8
CD4+ cell count mm ³				
> 500	1.0	Referent	1.0	Referent
200-500	1.5	0.67-3.2	1.2	0.48-3.1
< 200	3.4	1.3-9.2	1.3	0.36-4.7
HIV RNA, copies				
< 500	1.0	Referent	1.0	Referent
500-4,000	1.0	0.40-2.6	1.1	0.33-3.4
> 4,000	0.96	0.44-2.1	1.1	0.40-3.2
Cervical cytology/histology **				
Normal	1.0	Referent		
Abnormal	2.2	1.0-4.7		
Anal HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	5.1	0.94-27	5.0	0.88-29
Non-oncogenic types only	3.2	0.68-15	1.8	0.34-9.7
Both types	11	2.6-50	7.6	1.5-38
Cervical HPV Infection				
Neither type, no HPV infection	1.0	Referent	1.0	Referent
Oncogenic types only	2.2	0.65-7.2	1.3	0.34-4.8
Non-oncogenic types only	3.0	1.3-7.0	1.5	0.55-4.1
Both types	4.6	1.4-15	1.5	0.39-5.6

* Adjusted for age, number of years of cigarette smoking, current HAART use, CD4+ cell count, HIV RNA, anal HPV infection, and cervical HPV infection.

** Not included in multivariable model.