ORIGINAL CONTRIBUTION

Prevalence of Anal Intraepithelial Neoplasia Defined by Anal Cytology Screening and High-Resolution Anoscopy in a Primary Care Population of HIV-Infected Men and Women

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BACKGROUND: Prevalence of high-grade anal intraepithelial neoplasia, the human papillomavirus-associated putative anal cancer precursor, is high in HIV-infected men who have sex with men, but less is known about its prevalence in other HIV-infected subgroups. Similarly, the prevalence of abnormal cytology, used as a screen, is not well-defined in these subgroups.

OBJECTIVE: This study aimed to estimate the prevalence of abnormal cytology and anal intraepithelial neoplasia in a primary care HIV-infected population.

DESIGN: This investigation was designed as a cross-sectional study.

SETTING: This study took place at a Ryan White–funded clinic.

PATIENTS: Included in the study were all (n = 779) HIV-infected patients receiving primary care services between March 2006 and March 2008.

MAIN OUTCOME MEASURES: The main outcome measures were anal cytology and high-resolution anoscopy results.

RESULTS: The prevalence of abnormal cytology was 43%: 62% in men who reported receptive anal intercourse, 39% in women who reported receptive anal intercourse, and 25% in all others (*P* trend <.0001). High-grade anal intraepithelial neoplasia prevalence was 27%: 44% in men who reported receptive anal intercourse, 26% in women who reported receptive anal intercourse, and 10% in all others (*P* trend <.0001). Two patients had squamous-cell cancer. Independent predictors of dysplasia were CD4 at screening, receptive anal intercourse, sexual orientation, and history of human papillomavirus disease. Anal cytology and histology findings were not well correlated.

LIMITATIONS: The study population may not be representative of the general HIV-infected population, there were differences between screened and unscreened patients and between patients with abnormal cytology who had high-resolution anoscopy and those who did not, only patients with abnormal cytology had high-resolution anoscopy, and there were possible misclassification errors and uncontrolled possible confounders.

CONCLUSIONS: High-grade anal intraepithelial neoplasia is relatively common in HIV-infected patients regardless of sexual practice. Although risk increases with receptive anal intercourse, patient-provided information on this sexual practice should not be used as a determining factor for screening. Strategies to prevent anal cancer are necessary for all HIV-infected patients.

KEY WORDS: Anal intraepithelial neoplasia; Dysplasia; Human immunodeficiency virus; Human papillomavirus.

Funding/Support: Clinic activities funded by North Central Texas HIV Planning Council.

Financial Disclosures: None reported.

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Dis Colon Rectum 2011; 54: 433–441
DOI: 10.1007/DCR.0b013e318207039a

Human papillomavirus (HPV) is a common viral infection that is even more prevalent among those coinfected with HIV.[1–4] HPV infections cause a variety of illnesses that progress more rapidly, are more severe, and can be more difficult to eradicate among HIV-infected compared with individuals not infected with HIV; those who are coinfected with HIV and HPV have higher levels of HPV, are often infected with multiple HPV types concurrently, and may be more likely to have persistence of HPV infection.[2,5–10]

Infection with specific subtypes of HPV, in particular, HPV 16 and 18, has been associated with the development of anogenital neoplasias.[11–12] There is well-documented evidence linking HPV infection to increased risk of cervical intraepithelial neoplasia, a precursor to cervical cancer.[13,14] There is evidence for a similar association between HPV and anal intraepithelial neoplasia (AIN) and anal cancer.[15–17] The incidence of anal cancer is increasing among men, in particular, among HIV-infected men who have sex with men (MSM).[15–18] Screening of persons at high risk for AIN is recommended; however, the outcome of screening is unknown.[19,20]

In response to an observed high incidence of HPV-related anal diseases in patients receiving care for HIV at the Tarrant County Health Preventive Medicine Clinic, routine screening for HPV disease was implemented. In this article we report findings from the anal cytology surveillance program at the Preventive Medicine Clinic.

METHODS

The study population was a prospective cohort of all patients receiving primary care services at the Preventive Medicine Clinic at Tarrant County Public Health from March 2006 to March 2008. The clinic provides medical and social services for HIV-infected patients living in North Texas who meet the Ryan White financial criteria; ie, uninsured or underinsured with income less than 3 times the federal poverty level. The study was approved by the institutional review board of the University of North Texas Health Science Center at Fort Worth Medical Center.

Because HIV transmission risk reduction is an objective of the Preventive Medicine Clinic, data collected included psychosocial evaluations, histories of sexual practices and alcohol, tobacco, and recreational drug use, and laboratory parameters. In addition, complete physical examinations were conducted. Laboratory data were collected and then routinely repeated at 3-month intervals. Medical records were obtained from prior sources of medical care.

After examination of the perianus and confirmation of risk behaviors, the anal canal was sampled by inserting a tap water-moistened Dacron swab into the rectum; by use of the external anal sphincter as a fulcrum, the swab was rotated in a cone-shaped arc against the anal canal wall for approximately 30 seconds while being removed from the anal canal.[21] The swab was then immediately shaken vigorously in liquid fixative transport medium (PreservCyt, Cytyc Corporation). Specimens were processed in a commercial laboratory (Quest Diagnostics) by cytologists using the ThinPrep system (Cytyc Corporation). A conventional cytological assessment of stained cellular material was performed by experienced pathologists (Quest Diagnostics) and was categorized as normal, atypical squamous cells of undetermined significance (ASCUS); atypical squamous cells cannot rule out a high-grade lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL) by use of the Bethesda criteria.[22] Because there are no evidence-based guidelines for anal cytology screening, and because the sensitivity of cytology to detect AIN is low, a second cytological assessment was made in patients for whom the results of the initial cytological assessment was normal.

High-resolution anoscopy (HRA) was recommended to patients with abnormal anal cytology and was performed as previously described by Jay et al[23] on consenting patients. In brief, 5% lidocaine cream was applied to the anal canal during the digital anal examination. A disposable anoscope coated with a mixture of surgical lubricant and 5% lidocaine cream was used to introduce an applicator stick wrapped in gauze soaked in 5% acetic acid into the anal canal. After this was left in place for at least 1 minute, a colposcope was used to view the walls of the anal canal under magnification. Additional 5% acetic acid was applied to the areas being examined during the procedure and the most abnormal acetowhite areas suspicious for AIN were biopsied. Biopsy specimens were immediately placed in 10% formalin solution and sent for routine histopathologic examination by university-associated pathologists (Dermpath Diagnostics Cockerell & Associates). Results were categorized as normal anal epithelium, condyloma, AIN-1, AIN-2, AIN-3, or squamous-cell cancer.[24] Biopsy results were categorized as the most severe if multiple biopsies were performed. Patients who had AIN-2, AIN-3, or symptomatic condyloma were recommended to have infrared coagulation for treatment.

Definitions

Patients evaluated within 12 months of HIV seropositivity were categorized as newly diagnosed. CD4 at screening was the CD4 count obtained most proximate to the date of anal cytology collection. A history of previous HPV disease included patients who gave a history of genital or anal warts or abnormal cervical Papanicolaou test that required treatment. Sexual orientation was self-reported and was coded as "heterosexual," "MSM," "women who have sex with women," "bisexual," or "transsexual." For analysis, sexual

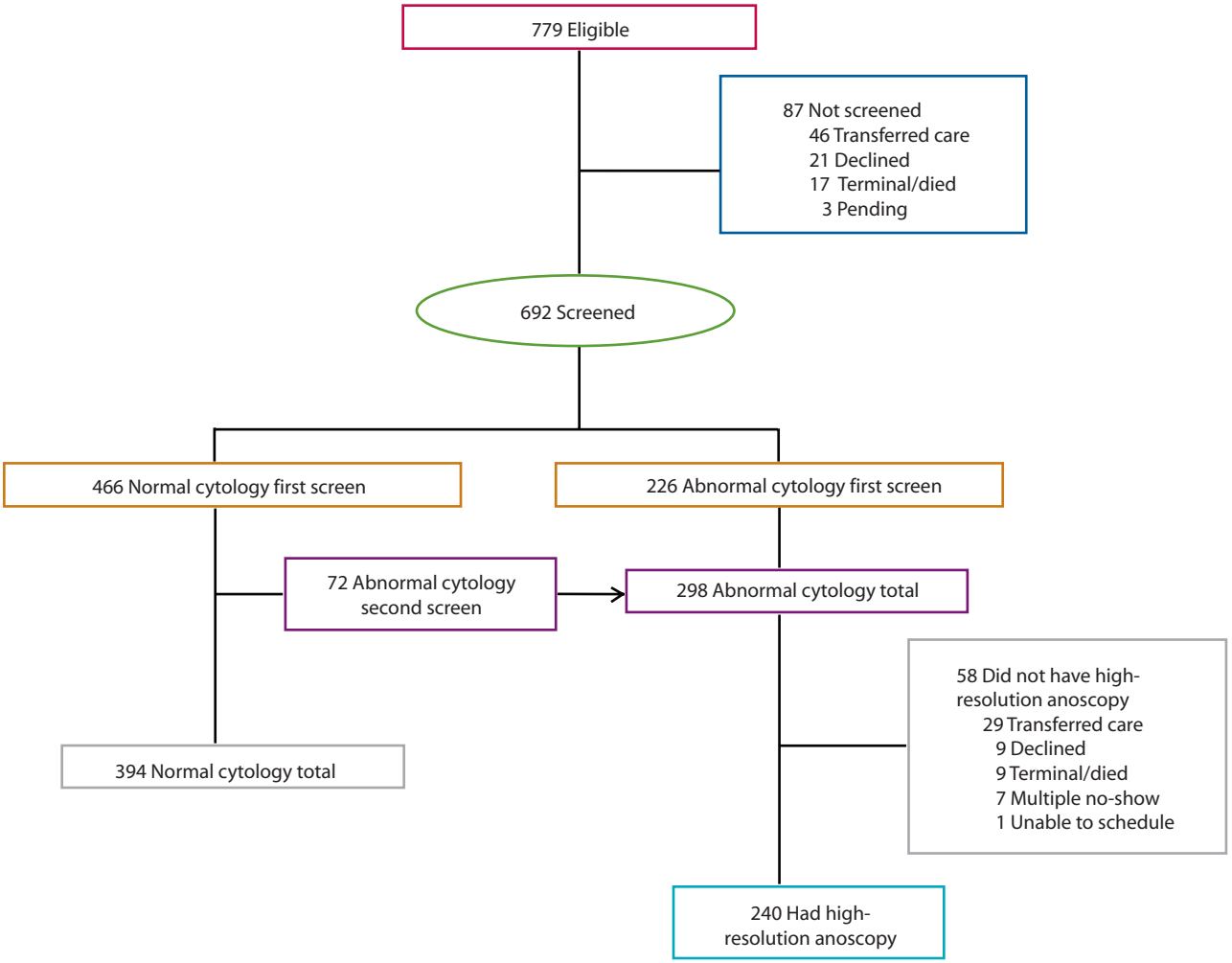

FIGURE 1. Patient flowchart.

orientation was dichotomized as "heterosexual" or "non-heterosexual." Smokers were patients who smoked tobacco at the time of their initial clinical evaluation.

For analysis, persons with 2 negative cytological screenings were assumed to not have dysplasia. There was a single ASC-H lesion cytology and this was included with HSIL. Low-grade AIN included condyloma and AIN-1. High-grade AIN included AIN-2 and AIN-3. Patients who had HRA with biopsies for reasons other than abnormal anal cytology were excluded.

Statistical Analysis

Descriptive statistics were generally stratified on gender and history of receptive anal intercourse. Comparisons between groups on frequencies were done using Fisher exact probability tests or χ^2 tests of association. The Spearman correlation coefficient (r_s) was used to evaluate the correlation between ordinal variables. Maximum likelihood estimates of ORs and 95% CIs were calculated by use of logistic regression analysis. A posteriori trend tests of "sexual practice" were conducted by coding this variable as 0, 1, or 2 based on the observed data. With use of a forward stepwise approach, multivariable ordinal logistic regression analysis was used to evaluate independent predictors of 3 levels of dysplasia (normal, low-grade, and high-grade); the proportional odds assumption was tested using the score test. Patients with missing data relevant to a given analysis were excluded from that analysis. All tests were 2-sided with .05 significance levels. Analyses were done using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Study Population

Of 779 patients who received care at the Preventive Medicine Clinic during the study period, 692 (89%) were screened with anal cytology (Fig. 1); patient characteristics are shown in Table 1. Screened patients were significantly younger than unscreened patients (mean (SD) age = 40 (10) vs 43 (10) y, $P = .007$) and were more

likely to be a race other than white (65% vs 44%, $P = .0002$) and to have recently received a diagnosis of HIV (15% vs 5%, $P = .007$).

Anal Cytology Screening

Anal cytology screening results are shown in Table 2. Abnormal anal cytology was observed in 298 (43%) screened patients and was significantly more likely in men than in women (48% vs 31%, $P < .0001$). The most common abnormality was ASCUS (60%) followed by LSIL (34%) and HSIL (6%); this distribution was similar in both men and women.

The presence of abnormal cytology was 62% among men who reported receptive anal intercourse, 39% among women who reported receptive anal intercourse, and 25% among men and women combined who reported no receptive anal intercourse (P trend $<.0001$); prevalence did not significantly differ by gender among patients in the latter group. Cytology results among patients who reported receptive anal intercourse were similar in men and women, but these results significantly differed from patients who reported no receptive anal intercourse ($P = .001$); namely, the latter group was more likely to be ASCUS vs LSIL or HSIL.

Histology

Histology results from HRA are shown in Table 2. Of 298 patients with abnormal anal cytology, 240 (81%) had HRA with a biopsy of either the transition zone, anal canal, or perianus (Fig. 1). Compared with the 58 patients who did not have HRA-directed biopsies, biopsied patients were more likely to identify as MSM or women who have sex with women vs heterosexual or bi- or transsexual ($P = .02$), to have histories of receptive anal intercourse ($P = .03$) or prior HPV disease ($P = .02$), and to have higher CD4 counts at screening ($P = .01$).

High-grade AIN was observed in 171 patients, or 71% (73% of men, 67% of women) of patients who had HRA for abnormal cytology. Prevalence was 27% among all patients combined (31% in men, 18% in women; $P = .0006$): 44% among men who reported receptive anal intercourse, 26% among women who reported receptive anal intercourse, and 10% among men and women who reported no receptive anal intercourse (P trend $<.0001$). There were 2 cases, one man and one woman, of squamous-cell cancer; both had histories of receptive anal intercourse. Only 3 patients with abnormal anal cytology who had HRA-directed biopsies were found to have normal anal epithelium.

The degree of anal cytology abnormality did not correlate well with histological abnormality ($r_s = 0.15$; Table 3); specifically, among subjects with ASCUS anal cytology, 67% had an HRA finding of high-grade dysplasia and both patients with squamous-cell cancer had ASCUS anal cytology.

TABLE 1. Characteristics of screened patients (N = 692)

Characteristic	*n (%)*
Sex	
No. of males (%)	488 (70.5)
No. of females (%)	204 (29.5)
Age (yrs)	
n	692
Mean (SD)	40.0 (10.4)
Median (range)	40.5 (14.0–79.0)
US born	
No. no (%)	185 (26.7)
No. yes (%)	507 (73.3)
Race	
No. white (%)	245 (35.4)
No. black (%)	213 (30.8)
No. Hispanic (%)	170 (24.6)
No. African (%)	56 (8.1)
No. other (%)	8 (1.2)
Sexual orientation	
No. heterosexual (%)	369 (53.3)
No. not heterosexual (%)	323 (46.7)
Smoker	
No. no (%)	316 (46.0)
No. yes (%)	371 (54.0)
Unknown	5
IV drug user	
No. no (%)	566 (81.8)
No. yes (%)	126 (18.2)
Newly HIV diagnosed	
No. no (%)	586 (84.7)
No. yes (%)	106 (15.3)
Years since HIV diagnosis	
n	691
Mean (SD)	7.9 (5.7)
Median (range)	7.2 (0.1–25.1)
CD4 at diagnosis	
No. <100 (%)	23 (3.3)
No. 100–199 (%)	133 (19.2)
No. 200–399 (%)	207 (29.9)
No. ≥400 (%)	329 (47.5)
Receptive anal sex	
No. no (%)	299 (43.3)
No. yes (%)	392 (56.7)
Unknown	1
Age at first receptive anal sex (y)	
n	376
Mean (SD)	19.5 (7.7)
Median (range)	18 (4–52)
Age at first vaginal sex (y)	
n	549
Mean (SD)	16.4 (3.5)
Median (range)	16 (4–36)
No. of sex partners	
≤5	138 (20.4)
6–20	242 (35.7)
21–0	128 (18.9)
>50	169 (25.0)
Unknown	15
HPV history	
No. no (%)	490 (70.8)
No. yes (%)	202 (29.2)

HPV = human papillomavirus; IV = intravenous.

TABLE 2. Anal cytology and high-resolution anoscopy results by sex and sexual practice

	Men			*Women*			*All*	
	Anal sex (n = 313) n (%)	*Nonanal sex (n = 175) n (%)*	*All (n = 488) n (%)*	*Anal sex (n = 79) n (%)*	*Nonanal sex (n = 124) n (%)*	*All (n = 204) n (%)*	*Nonanal sex (n = 299) n (%)*	*Combined (n = 692) n (%)*
Cytology								
Normal[a]	120 (38.3)	134 (76.6)	254 (52.0)	48 (60.8)	91 (73.4)	140 (68.6)	225 (75.3)	394 (56.9)
ASCUS	104 (33.2)	31 (17.7)	135 (27.7)	18 (22.8)	25 (20.2)	43 (21.1)	56 (18.7)	178 (25.7)
LSIL	72 (23.0)	9 (5.1)	81 (16.6)	12 (15.2)	8 (6.5)	20 (9.8)	17 (5.7)	101 (14.6)
HSIL	17 (5.4)	1 (0.6)	18 (3.7)	1 (1.3)	0 (0.0)	1 (0.5)	1 (0.3)	19 (2.7)
HRA status (abnormal cytology only)								
Not done	32 (16.6)	13 (31.7)	45 (19.2)	5 (16.1)	8 (24.2)	13 (20.3)	21 (28.4)	58 (19.5)
Done	161 (83.4)	28 (68.3)	189 (80.8)	26 (83.9)	25 (75.8)	51 (79.7)	53 (71.6)	240 (80.5)
Cytology or histology[b]								
Normal cytology[a]	120 (42.7)	134 (82.7)	254 (57.3)	48 (64.9)	91 (78.4)	140 (73.3)	225 (80.9)	394 (62.1)
Histology = normal anal epithelium	1 (0.4)	1 (0.6)	2 (0.5)	0 (0.0)	1 (0.9)	1 (0.5)	2 (0.7)	3 (0.5)
Histology = low-grade dysplasia[a]	36 (12.8)	13 (8.0)	49 (11.1)	6 (8.1)	9 (7.8)	15 (7.9)	22 (7.9)	64 (10.1)
Histology = high-grade dysplasia[b] or squamous-cell cancer	124 (44.1)	14 (8.6)	138 (31.2)	20 (27.0)	15 (12.9)	35 (18.3)	29 (10.4)	173 (27.3)
Histology (abnormal cytology only)								
Normal anal epithelium	1 (0.6)	1 (3.6)	2 (1.1)	0 (0.0)	1 (4.0)	1 (2.0)	2 (3.8)	3 (1.3)
Low-grade dysplasia[c]	36 (22.4)	13 (46.4)	49 (25.9)	6 (23.1)	9 (36.0)	15 (29.4)	22 (41.5)	64 (26.7)
High-grade dysplasia[d] or squamous-cell cancer	124 (77.0)	14 (50.0)	138 (73.0)	20 (76.9)	15 (60.0)	35 (68.6)	29 (54.7)	173 (72.1)

"Anal" in box heads refers to reported history of receptive anal sex.
ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions; HRA = high-resolution anoscopy; AIN = anal intraepithelial neoplasia.
[a]Based on 2 cytological screenings.
[b]Categorization of entire study population because subjects with normal cytology did not have histology done. This section presents estimates of overall prevalence of each category.
[c]Condyloma or AIN-1.
[d]AIN-2 or AIN-3.

Predictors of Dysplasia

Of the variables shown in Table 1, all were significant univariable predictors of the level of dysplasia (normal cytology, low-grade dysplasia, high-grade dysplasia), with the exception of age, intravenous drug use, new HIV-diagnosis and age at first receptive anal intercourse. Multivariably, only CD4 at screening, receptive anal intercourse, sexual orientation, and HPV history were independently related to the level of dysplasia (Table 4).

DISCUSSION

Using 2 anal cytologies for screening, we found that 27% of patients of a Ryan White primary care HIV clinic had high-grade AIN. This is the first report of the estimated prevalence of anal dysplasia in a primary care HIV population where screening was offered to men and women regardless of history of receptive anal sex. Although AIN and anal cancer are generally accepted to be more prevalent in HIV-infected patients, an estimate of the true prevalence of AIN has not been well defined because much of the data supporting the increased risk are from trials of highly selected groups.[2,9,25–29] Our findings indicate that HIV-infected patients are at high risk for high-grade AIN and squamous-cell cancer irrespective of their sexual practices, and this will require the development of screening and treatment strategies for prevention and early diagnosis of anal cancer among HIV-infected patients.

Although it has been established that high-grade AIN is common in HIV-infected MSM there is much less information available on the putative anal cancer precursor in HIV-infected non-MSMs.[2,9,25–29] We are aware of only a single study, reported by Piketty et al,[27] where non-MSM (HIV-infected) subjects, defined as heterosexual men who denied receptive anal intercourse, with cytological abnormalities had histological evaluation for degree of AIN. In that report of 50 subjects, 18 (36%) had abnormal cytology and 9 (18%) had high-grade AIN based on the most severe cytological or histological result.[26] We observed 41 abnormal cytologies among 175 HIV-infected men (23%) with no history of receptive anal intercourse (regardless of sexual orientation). Of the 28 (68%) of these men who had HRA-directed biopsies, 50% had high-grade AIN, which led to an overall prevalence of 9% among all HIV-infected men with no history of receptive anal intercourse. Our data, together with the data of Piketty et al[27] above, demonstrate that abnormal anal cytologies in HIV-infected non-MSMs are likely to result in high-grade AIN being identified at HRA.

To our knowledge, there is only one study, the

TABLE 3. High-resolution anoscopy results by abnormal cytology finding

High-resolution anoscopy result	*ASCUS (n = 140)* n (%)	*LSIL (n = 83)* n (%)	*HSIL (n = 17)* n (%)	*All (n = 240)* n (%)
Normal anal epithelium	3 (2.1)	0 (0.0)	0 (0.0)	3 (1.3)
Low-grade dysplasia[a]	43 (30.7)	19 (22.9)	2 (11.8)	64 (26.7)
High-grade dysplasia[b] or squamous-cell cancer[c]	94 (67.1)	64 (77.1)	15 (88.2)	173 (72.1)

ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions; AIN = anal intraepithelial neoplasia.
[a]Condyloma or AIN-1.
[b]AIN-2 or AIN-3.
[c]Two patients; both had ASCUS cytology.

Women's Interagency HIV Study (WIHS), that has reported results of screening HIV-infected women with histological evaluation of cytological abnormalities, as was done in our study. In WIHS, the subject population was recruited from drug treatment programs, street outreach, word-of-mouth referral, and clinics providing HIV care.[30] Subjects were screened with anal cytology and, if results were abnormal, HRA was recommended. Anal cytology was abnormal in 148 (31%) women and, of these, 41% underwent biopsies. The prevalence of high-grade AIN, defined as either an HSIL Papanicolaou test or an AIN-2 or -3 histology, in HIV-infected women overall was reported as 9%.[30] By comparison, in our study we identified abnormal cytology in 31% of HIV-infected women (same as WIHS), performed biopsies on 80% of the subjects, and observed high-grade AIN in 67% of those who underwent biopsies and in 18% overall. Thus, our data suggest that high-grade AIN may be more prevalent in HIV-infected women than previously reported, because we performed biopsies on a much higher percentage of women with abnormal cytology than was done in WIHS.

Receptive anal intercourse is accepted to be a mechanism for acquisition of anal HPV infection; however, multiple investigators have identified anal HPV infection in persons without a history of receptive anal intercourse.[27,31–33] Our data are also consistent with the concept that receptive anal intercourse is a mechanism for anal HPV infection. We observed, for receptive anal intercourse, a more than 2-fold multivariate increase in risk of increasing degrees of dysplasia (normal cytology, low-grade AIN, high-grade AIN). HIV-infected men who reported receptive anal intercourse were more likely to have

TABLE 4. Subject characteristics by cytology or histology result,[a] multivariable analysis

Characteristic	*Normal cytology[b] (n = 365)* n (%)	*Low-grade dysplasia[c] (n = 63)* n (%)	*High-grade dysplasia[d] (n = 165)* n (%)	*OR*	*(95% CI)*	*P*
CD4 at diagnosis						
No. <100 (%)	8 (2.2)	0 (0.0)	7 (4.2)	0.62	(0.50, 0.76)	<.0001
No. 100–199 (%)	48 (13.2)	10 (15.9)	45 (27.3)			
No. 200–399 (%)	115 (31.5)	18 (28.6)	52 (31.5)			
No. ≥400 (%)	194 (53.2)	35 (55.6)	61 (37.0)			
Receptive anal sex						
No. no (%)	214 (58.6)	22 (34.9)	29 (17.6)	2.58	(1.54, 4.33)	.0003
No. yes (%)	151 (41.4)	41 (65.1)	136 (82.4)			
Sexual orientation						
No. heterosexual (%)	253 (69.3)	28 (44.4)	46 (27.9)	2.52	(1.55, 4.09)	.0002
No. nonheterosexual (%)	112 (30.7)	35 (55.6)	119 (72.1)			
HPV history						
No. no (%)	285 (78.1)	41 (65.1)	94 (57.0)	1.96	(1.35, 2.85)	.0004
No. yes (%)	80 (21.9)	22 (34.9)	71 (43.0)			

Twenty-six subjects with normal cytology had histology done for other reasons and were therefore excluded. Fifty-eight subjects had abnormal cytology but unknown histology and were therefore also excluded. Only subjects with nonmissing data for all variables considered were included. ORs, CIs, and *P* values are from the multivariate model (ie, include all variables shown in table), arrived at via forward stepwise regression. For categorical variables (eg, CD4 at diagnosis), the category level was modeled as a continuous variable. Univariate ORs and 95% CIs for variables considered were: CD4 at diagnosis = 0.67 (0.56, 0.82), receptive anal sex = 5.09 (3.52, 7.38), sexual orientation = 4.77 (3.38, 6.75), HPV history = 2.43 (1.72, 3.46), male sex = 2.01 (1.38, 2.93), race (white vs all other races) = 2.20 (1.57, 3.07), smoker = 2.05 (1.47, 2.87), age at first vaginal sex (categorical) = 0.86 (0.73, 1.03), number of sexual partners (categorical) = 1.30 (1.12, 1.51), years since HIV diagnosis = 1.03 (1.00, 1.06), CD4 nadir (categorical) = 0.77 (0.64, 0.93), number of years on HAART (categorical) = 0.92 (0.75, 1.12).
AIN = anal intraepithelial neoplasia; HPV = human papillomavirus; HAART = highly active antiretroviral therapy.
[a]Subjects with normal cytology did not have histology done.
[b]Includes 3 subjects with histology that had normal anal epithelium.
[c]Subjects with histology = condyloma or AIN-1.
[d]Subjects with histology = AIN-2, AIN-3, or squamous-cell carcinoma.

abnormal anal cytology (62% vs 23%, $P < .0001$) and high-grade AIN (44% vs 9%, $P < .0001$) than were other HIV-infected men. Nonetheless, 50% of men with abnormal cytology who did not report receptive anal intercourse had high-grade AIN. Similarly, in HIV-infected women, those who reported receptive anal intercourse were more likely to have abnormal cytology (39% vs 27%, $P = .004$) and high-grade AIN (26% vs 13%, $P = .03$) than women who did not. Similar to the pattern observed in men, 60% of women with abnormal cytology who did not report anal receptive intercourse had high-grade AIN. This suggests that receptive anal intercourse may be a risk factor for high-grade AIN, but the absence of anal intercourse cannot be used to systematically exclude HIV-infected patients from screening.

Of the potential risk factors we included in our study, only receptive anal intercourse, anogenital HPV disease, sexual orientation, and immune status as measured by CD4 count were independently associated with the risk of dysplasia. Low CD4 count, receptive anal intercourse, and HPV infection are well-known risk factors.[25,30] Our observation that receptive anal intercourse and sexual orientation were independent risk factors suggests that there may be confounding (but uncontrolled) factors involved. For example, among subjects reporting receptive anal intercourse in our study, almost all heterosexual subjects were women and almost all nonheterosexual subjects were men; thus, it was not practical to test for an interaction between sex and orientation. But an uncontrolled factor that differed between heterosexual women and nonheterosexual men that was also associated with dysplasia risk, such as having unprotected receptive anal intercourse or frequency of receptive anal intercourse, may explain the association between sexual orientation and dysplasia risk that we observed.

For women, an ASCUS cervical cytology result is considered an equivocal cytological abnormality. ASCUS cervical cytology identifies women who most commonly have HPV infection or low-grade cervical intraepithelial neoplasia but have a relatively low risk of having high-grade intraepithelial neoplasia.[34–35] In contrast, several reports have found that evaluation of ASCUS anal cytology from HIV-infected men is frequently associated with high-grade AIN.[28,36] In our study, ASCUS was the most common anal cytological abnormality (60% of abnormal cytology results) and 67% of those with ASCUS had an HRA-directed biopsy finding of high-grade AIN. Thus, it appears that ASCUS anal cytology abnormalities do not correlate well with HRA findings, which is in contrast to cervical cytology/histology comparisons.[28,36,37] There are several possible explanations for this; for example, anal cytology specimens are collected blindly and thus sampling error may be more common than in cervical cytology. Criteria for specimen adequacy and for interpretation of anal cytology may need revision for better risk stratification. Our data suggest that strategies recommended for managing cervical ASCUS cytology, such as repeated cytological screening, if applied to anal cytology are likely to result in delayed diagnosis of high-grade AIN or squamous-cell cancer. At present, our data, in combination with reports published previously, indicate that any abnormal anal cytology in an HIV-infected patient requires further investigation.

The prognosis of anal cancer is strongly associated with the stage of disease at diagnosis.[38,39] Anal cancer is often diagnosed late and approximately 25% of newly diagnosed anal canal carcinomas are larger than 5 cm in diameter and clinically node-positive.[40] We identified through screening 2 cases of anal squamous-cell cancer. Both patients were aware that they had enlarging anal lesions yet neither notified their clinician. One of the patients declined recommended anal evaluation because she believed she had hemorrhoids. The other patient had a history of anal warts and assumed they had returned. Both patients had visible disease that was easily palpable by anorectal examination. Therefore, it appears that delayed examination, and thus diagnosis, was the result of shame, denial, and rationalization that is often associated with diseases of the sexual or excretory organs.[41,42] Because survival and morbidity are correlated with the size of the primary anal cancer, and because of increased prevalence in HIV-infected patients, early diagnosis of anal cancer will require that clinicians incorporate periodic anal examination into HIV care and that patients overcome the typically negative feelings associated with anal examinations so that they will be accepted when recommended.

These data have several limitations. As a cross-sectional study conducted at a single geographical site, our study population may not be representative of the general HIV-infected population and thus our estimates of prevalence and risk may be biased. Screened patients were younger and were more likely than unscreened patients to have recently received diagnoses of HIV; both of these factors are likely to reduce the risk of AIN, thus resulting in downwardly biased prevalence estimates. Among patients who had abnormal cytology, those who had HRA-directed biopsy compared with those who did not were significantly different in terms of sexual orientation, history of receptive anal intercourse, CD4 at the time of screening, and prior HPV disease. The effects of these differences on our study findings are difficult to estimate, but we had a relatively high rate of HRA-directed biopsy (81%) among patients with abnormal cytology and thus any potential biases from these differences are likely to have been minimized. In addition, HRA was done only on patients with cytological abnormalities and this may have resulted in missing some cases of high-grade AIN. It is also possible that sensitive behaviors such as having receptive anal intercourse may have been underreported, which may have resulted in a misclassification error, but such an error is likely to be nondifferential (resulting in risk estimates biased toward

1.0). Finally, there may be confounding factors that were uncontrolled in our analysis.

Despite our study limitations, it is likely that our principal finding that high-grade AIN is common in all HIV-infected patients, regardless of having had receptive anal intercourse, is generalizable. Although the risk of high-grade AIN appears to increase with receptive anal intercourse, patient-provided information on this sexual practice should not be used as a determining factor for screening. These data suggest that strategies to prevent anal cancer are necessary for all HIV-infected patients.

ACKNOWLEDGMENTS

We acknowledge Vanessa Miller, DrPH, MSN, who recognized the importance of this issue and who obtained grant support for comprehensive HPV screening and treatment from the North Central Texas HIV Planning Council. In addition, we recognize the PMC Clinic Staff and Tarrant County Public Health Administration for their support without which this program could not have been successful. S. Robert Harla, D.O., edited the manuscript and provided valuable comments.

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