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High Rates of Anal High-Grade Squamous Intraepithelial Lesions in HIV-Infected Women Who Do Not Meet Screening Guidelines

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Background. Human immunodeficiency virus (HIV)–infected women have a higher burden of anal high-grade squamous intraepithelial lesions (HSIL) and anal cancer (AC) compared with HIV-uninfected women. Guidelines for AC screening in this population are heterogeneous. Here we report outcomes and risk factors for anal HSIL following implementation of universal AC screening offered to all HIV-infected women.

Methods. Data from women who underwent AC screening with anal cytology from April 2009 to July 2014 were analyzed. Routine clinical data included anal and cervical cytology, demographic/behavioral data, and high-resolution anoscopy (HRA) results. We evaluated the association of cytology with HRA results, and predictors of HSIL pathology, and compared rates of HSIL pathology among women meeting screening guidelines to those who did not.

Results. Seven hundred forty-five HIV-infected women were screened with anal cytology. Thirty-nine percent had abnormal anal cytology on initial screen and 15% on secondary screen; 208 women underwent HRA following abnormal anal cytology. HSIL was found in 26% and 18% of anal biopsies following initial and secondary screening, respectively. One woman had AC. Cigarette smoking more than doubled HSIL risk. Among women who underwent AC screening despite not meeting existing guideline criteria, 21% and 10%, respectively, were found to have HSIL on biopsy. Neither meeting criteria for screening nor history of receptive anal sex was significantly associated with HSIL.

Conclusions. Anal HSIL is common in HIV-infected women. Substantial numbers of HSIL would have been missed by strictly adhering to existing AC screening guidelines. These results support routine screening of all HIV-infected women regardless of human papillomavirus history or sexual practices.

Keywords. HIV; HPV; HSIL; anal cancer; women.

Persistent infection of the anal squamous mucosa by high-risk human papillomavirus (HPV) is thought to cause anal high-grade squamous intraepithelial lesions (HSIL), the putative precursors to invasive anal squamous cell carcinoma (ASCC) [1]. ASCC is a rare malignancy in the general population with a predilection for older women. The risk of ASCC, however, is increased significantly in persons living with the human immunodeficiency virus (HIV). This has been shown extensively for HIV-infected men who have sex with men (MSM), but is also true for HIV-infected women in whom unadjusted ASCC incidence rates of 30 per 100 000 person-years have been reported; this is 15 times the rate observed in women in the general population [2].

In contrast to other HIV-associated malignancies, improved immunologic and virologic control by means of effective antiretroviral therapy (ART) has not led to a decrease in the incidence of ASCC [3, 4]. Increased longevity of HIV-infected persons on ART decreases the impact of competing risks of death and may allow more time for the malignant transformation of the anal mucosa, accounting for rising ASCC incidence rates in the more recent ART era.

ASCC shares many pathophysiologic similarities with cervical cancer. Cervical cytology screening followed by colposcopy and ablation of cervical HSIL has led to substantial reduction in cervical cancer rates and is a widely accepted preventive management tool. Similar strategies have been proposed for screening for and treating anal HSIL to prevent ASCC using an algorithm that consists of anal cytology followed by high-resolution anoscopy (HRA) and targeted destruction of anal HSIL [5, 6].

Several studies have demonstrated a variety of risk factors for prevalent anal high-risk HPV infection in women including receptive anal intercourse (RAI), concomitant cervical HPV infection, cigarette smoking, presence of perianal condylomata,

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and CD4$^+$ T-cell counts <200 cells/mL [7–10]. The overall prevalence of HPV in the anus has been shown to be as high as 85%, which is higher than that of the cervix [11].

As a result, in 2007 the New York State Department of Health's (NYSDOH) AIDS Institute recommended annual anal cytology screening for HIV-infected MSM, HIV-infected persons with a history of anogenital condylomata, and HIV-infected women with abnormal cervical/vulvar histology [12]. In 2013, the HIV Medical Association (HIVMA) of the Infectious Diseases Society of America (IDSA) endorsed and updated those guidelines to also include a recommendation for annual anal cytology screening in HIV-infected women with a history of RAI [13]. These guidelines may underestimate the burden of HSIL in HIV-infected women as they do not reflect the higher prevalence of anal HPV infection compared with cervical infection [11] and non-RAI modes of HPV transmission [10, 11, 14].

In 2009, the Mount Sinai Medical Center implemented a program in which all HIV-infected patients are offered anal cytology screening regardless of risk and, if abnormal, are referred for HRA. Here we report rates and associated risk factors for anal HSIL among HIV-infected women after implementation of universal screening to determine whether current guidelines accurately identify women at risk for anal HSIL.

METHODS

This retrospective cohort study abstracted data from a longitudinal clinical database of HIV-infected women. Women were engaged in care at 1 of 3 clinical sites where they were offered anal cytology screening, regardless of whether they met the aforementioned guideline criteria, and subsequently referred for HRA if anal cytology was abnormal. Women with benign or inadequate anal cytology were not routinely referred for HRA and were not included in the analysis of HRA results. Approval for this retrospective review was obtained from the Icahn School of Medicine Institutional Review Board. The primary analytic sample included 208 individual women with abnormal anal cytology who underwent HRA between April 2009 and July 2014. Data on anal cytology results for all HIV-infected women during the study period was abstracted from the central clinical data warehouse to establish rates of abnormal cytology and HRA utilization in this cohort.

Sample Collection for Anal Cytology

The patients' primary HIV care or gynecologic provider collected anal cytology samples after receiving uniform instructions on sample collection. In brief, a moistened, nonlubricated cytobrush was inserted blindly 5–6 cm into the anal canal to collect cells from the anal verge to above the squamocolumnar junction. The cells were preserved in liquid-based cytology medium.

Results were reported in accordance with the Bethesda system for cervical cytology as benign; atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesion (LSIL); HSIL; or atypical squamous cells, cannot rule out HSIL (ASC-H) [15]. Patients with abnormal anal cytology were referred for HRA.

High-Resolution Anoscopy

All procedures were performed by a single provider (M. G.), an infectious disease specialist trained in HRA. HRA was performed using previously described techniques [16]. After treatment with 3% acetic acid and Lugol iodine, the squamocolumnar junction, the distal anal canal, and the anal margin were visualized under magnification to look for abnormal vascular patterns and other potential signs of HSIL or cancer, including ulceration, mass effect, and friability. Areas suspicious for HSIL or cancer were biopsied. Anal histology was reported according to severity of mucosal dysplasia as benign, LSIL, HSIL, and invasive carcinoma. If no lesion was seen, then no biopsy was taken and the patient was scored as having a "benign" examination. Random biopsies of normal-appearing tissue were not performed in this study.

Data Collection and Statistical Analysis

We reviewed all anal cytology data from our institution during the study period to determine the number of unique women who underwent anal cancer screening as well as the rates of abnormal cytology.

We then abstracted data for women who underwent HRA following their initial screening cytology. If initial anal cytology yielded benign or inadequate results, anal cytology was repeated within 12 months (secondary screen). Demographic data collected included age, race, history of RAI, history of anogenital condylomata, smoking history, history of abnormal cervical cytology, year of HIV diagnosis/duration of HIV infection, current CD4$^+$ T-cell count, nadir CD4$^+$ T-cell count, and HIV-1 plasma RNA load.

Demographics and clinical characteristics for subjects by HSIL diagnoses were compared using χ^2 tests for categorical variables and nonparametric tests for nonnormally distributed continuous variables. Comparisons of the distribution of anal cytology results for each histology result category (benign vs LSIL vs HSIL/cancer) were performed using the χ^2 test. To evaluate predictors of HSIL histology or invasive cancer, an adjusted logistic regression model was used, including factors that were significant in univariate analyses, as well as age and race/ethnicity. Less than 5% of the sample had missing data on smoking status and length of time with HIV; for the multivariable analysis, multiple imputation methods were used to impute missing data. For the HRA analytic cohort, it was determined which patients met clinical guidelines for anal cytology screening, and HSIL rates in patients who met screening criteria vs those

who did not were compared. All analyses were performed using Stata software version 13 (StataCorp, College Station, Texas).

RESULTS

Seven hundred forty-five individual HIV-infected women were screened with anal cytology at least once during the study period. Thirty-nine percent of women had abnormal findings (defined as ASCUS or higher degree of abnormality) on initial screen. In an additional 15% of women, anal cytology was abnormal on secondary screen following an initial benign or inadequate screen. One hundred forty-seven (50%) and 61 (55%) women with abnormal anal cytology on initial and secondary screening, respectively, underwent HRA. Of the women who presented for HRA after initial screening, 32% had benign findings (defined as either benign HRA if no biopsies were taken or benign histology), 68% had dysplasia of any degree, and 26% had HSIL. One woman with a history of RAI and abnormal cervical cytology had superficially invasive, perianal squamous cell carcinoma (SCC) and was treated with wide local excision. Among women who presented for HRA following abnormal secondary screening, 54% had anal dysplasia of any degree and 18% had HSIL (Figure 1).

Baseline characteristics of women who underwent HRA are shown in Table 1 compared by HSIL diagnosis found on biopsy. Median age did not differ significantly between the 2 groups (P = .5). Most women who underwent HRA were either black or Hispanic, but race/ethnicity was not significantly different for women with HSIL compared to those without. Race/ethnicity and age did not appear to influence HRA utilization (both P = .2) (Table 2). There was no significant difference in rates of RAI (P = .1), preceding abnormal cervical cytology (P = .4), history of anogenital condylomata (P = .9), as well as immunologic (defined as most recent $CD4^+$ T-cell count) and virologic (defined as plasma HIV RNA <200 copies/mL) control between groups. Women who were found to have HSIL on biopsy were more likely to be active smokers (P = .03). Among women who underwent HRA, the most common abnormal cytology result was ASCUS found in 72% of women, followed by LSIL (20%). It should be noted that 8% of women had either ASC-H or HSIL cytology (data not otherwise shown).

Anal cytology did not appear to be a good predictor of histology results. While the likelihood of HSIL histology increased proportionally with the degree of abnormality on anal cytology, many women were found to have HSIL histology with underlying ASCUS or LSIL cytology. The woman with superficially invasive perianal SCC had concomitant ASCUS cytology and was found to have additional intra-anal HSIL histology. Eighty-three percent of women with HSIL cytology had HSIL or carcinoma on biopsy (Table 3). In an adjusted logistic regression model, only current cigarette smoking (odds ratio, 2.6 [95% confidence interval, 1.1–5.8]) was associated with a higher risk of HSIL histology or ASCC (Table 4).

In a separate analysis, the performance characteristics of existing anal cancer screening guidelines were examined. It is of particular interest that 24 (12%) HIV-infected women who underwent HRA following abnormal anal cytology did not meet criteria for anal cancer screening according to the NYSDOH AIDS Institute guidelines. Of those, 42% had anal dysplasia of any degree and 21% had HSIL histology. Similarly, 10 (5%) HIV-infected women who did not meet criteria for anal cancer screening according to HIVMA/IDSA guidelines had abnormal anal cytology requiring HRA. Of those, 38% had anal dysplasia of any degree and 10% had HSIL histology. The proportion of women with HSIL histology who met guideline-based anal cancer screening criteria did not differ significantly from that of women who did not meet these criteria (Table 5).

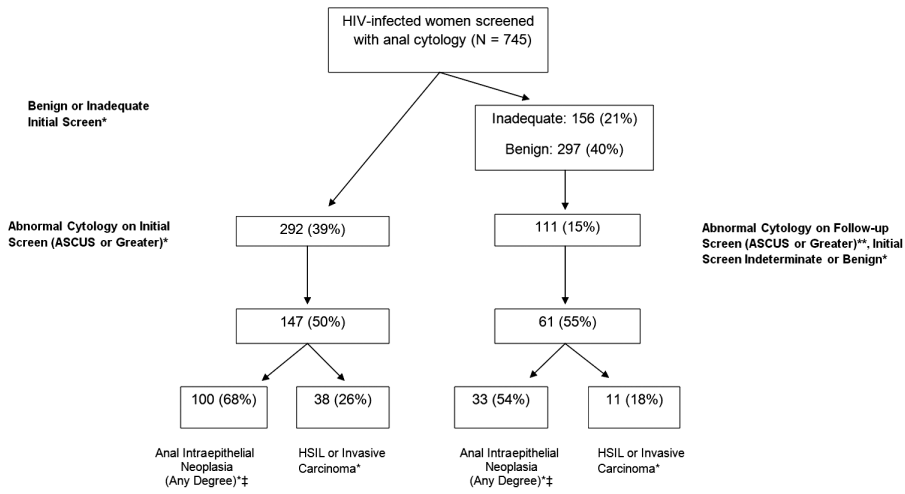

Figure 1. Study flow chart. *Percentages reflect proportion of preceding category; **Follow-up screen with 25% inadequate specimens; ‡includes HSIL and invasive carcinoma. Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion.

Table 1. Baseline Characteristics of Cohort by Anal High-Grade Squamous Intraepithelial Lesion Status

Characteristic	HSIL (n = 49)	No HSIL (n = 159)	*P* Value
Age, y, median (IQR)	48 (44–51)	47 (41–52)	.5
Race/ethnicity			.5
White	2 (4)	18 (11)	
African-American	25 (51)	76 (48)	
Hispanic	21 (43)	60 (38)	
Other	1 (2)	5 (3)	
Anal Pap result			<.001
ASCUS	31 (63)	118 (74)	
ASC-H	1 (2)	4 (3)	
LSIL	7 (14)	35 (22)	
HSIL	10 (20)	2 (1)	
Receptive anal sex	36 (74)	97 (62)	.1
Abnormal cervical Pap smear	44 (90)	136 (86)	.4
Smoking			.03
Never	10 (20)	54 (34)	
Former	11 (23)	47 (30)	
Current	28 (57)	57 (36)	
History of anogenital warts	17 (35)	54 (34)	.9
Most recent CD4 count, cells/μL, median (IQR)	513 (317–757)	522 (335–773)	.9
Most recent HIV plasma RNA <200 copies/mL	35 (71)	124 (78)	.3
Years since HIV diagnosis			.1
<5	3 (6)	6 (4)	
5–10	5 (10)	35 (22)	
11–15	11 (23)	45 (29)	
>15	29 (60)	70 (45)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ASC-H, atypical squamous cells, cannot rule out HSIL; ASCUS, atypical cells of undetermined significance; HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; LSIL, low-grade squamous intraepithelial lesion.

DISCUSSION

In this urban cohort of HIV-infected women who underwent anal cancer screening as part of a universal screening protocol, we sought to determine the rates of abnormal anal cytology and subsequent histology. We also evaluated potential predictors of HSIL as well as the performance of existing screening guidelines. We found high rates of abnormal anal cytology and HSIL histology in subjects referred for HRA based on abnormal anal cytology. In addition, these data demonstrate that not meeting criteria for anal cancer screening by existing guidelines was not a reliable predictor for the absence of HSIL in this patient population.

The prevalence of anal dysplasia in HIV-infected women is not well known, and there is little consistency across studies. Stier et al suggest [11] that the significant heterogeneity in prevalence rates and significance of risk factors for anal HSIL among women is due to varied populations studied and outcomes measured. Among HIV-infected women in the ART era, the overall prevalence of abnormal anal cytology in the literature is between 10% and 42% [9, 11, 17–19], whereas

Table 2. Baseline Characteristics for Subjects With Anal Cytology Abnormalities Who Underwent High-Resolution Anoscopy Compared to Those Who Did Not

Characteristic	HRA (n = 208)	No HRA (n = 200)	*P* Value
Age, y, median (IQR)	47 (42–52)	46 (39–54)	.2
Race/ethnicity, No. (%)			.2
White	20 (10)	15 (8)	
African-American	101 (49)	114 (57)	
Hispanic	81 (39)	69 (35)	
Other	6 (3)	2 (1)	

Abbreviations: HRA, high-resolution anoscopy; IQR, interquartile range.

the prevalence of anal HSIL histology ranges from 3% to 26% [11, 17, 19–22], with higher rates noted in women undergoing HRA based on abnormal screening cytology. The rate of abnormal anal cytology on initial screening in our cohort was 39% and is consistent with what has been reported in other studies. Similarly, the prevalence rates of HSIL histology among women who underwent HRA based on abnormal anal cytology (26%) are within the range reported in similar studies [11]. The rate of HRA completion among women with abnormal anal cytology in our cohort was relatively low at 50%, which compares favorably with other series most similar to ours in scope. Other studies, some analyzing much smaller cohorts, have reported HRA completion rates of 70%–80% [19, 23, 24], with the exception of Hessol et al [20], who also reported a rate of 50%.

An additional 15% of women developed abnormal anal cytology on secondary screening following initial benign or inadequate anal cytology. Among those, HRA utilization was slightly higher at 55% and yielded anal dysplasia of any degree in 54% and HSIL in 18%, which is lower than the rates observed in women who underwent HRA following initial screening. While the lower rates are partially explained by the fact that this group had been prescreened, the substantial numbers do illustrate the limitations of anal cytology. Our data re-demonstrate that correlation between anal cytology and histology is relatively poor and that a significant number of HSIL pathology is found even in the absence of HSIL cytology. Lee et al showed that among a

Table 3. Anal Cytology Results Preceding High-Resolution Anoscopy Evaluation Compared to High-Resolution Anoscopy Results

	Histology			
Cytology	Benign	LSIL/Condyloma	HSIL/Cancer	*P* Value
Whole cohort				<.001
ASCUS	70 (92)	48 (58)	31 (63)	
ASC-H	0 (0)	4 (5)	1 (2)	
LSIL	6 (8)	29 (35)	7 (14)	
HSIL	0 (0)	2 (2)	10 (21)	

Abbreviations: ASC-H, atypical squamous cells, cannot rule out HSIL; ASCUS, atypical cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Table 4. Unadjusted and Adjusted Logistic Regression Models Evaluating Predictors of High-Grade Squamous Intraepithelial Lesions

Characteristic	Unadjusted OR for HSIL	95% CI	Adjusted OR for HSIL	95% CI
Age	1.0	.9–1.0	1.0	.9–1.0
Receptive anal sex	1.7	.8–3.4	1.7	.8–3.5
Smoking				
Never	Ref	Ref	Ref	Ref
Former	1.3	.5–3.2	1.3	.5–3.4
Current	2.7	1.2–6.0	2.6	1.1–5.8
>10 years since HIV diagnosis	1.8	.8–4.1	2.0	.8–5.8

Abbreviations: CI, confidence interval, HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion; OR, odds ratio.

Table 5. Proportion of High-Grade Squamous Intraepithelial Lesion Diagnoses Meeting Screening Guidelines

Guideline	HSIL Diagnoses, No. (%)		*P* Value
	Met Screening Guidelines	Did Not Meet Screening Guidelines	
NYSDOH[a]	44 (24)	5 (21)	.7
IDSA[b]	48 (24)	1 (10)	.3

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; IDSA, Infectious Diseases Society of America; NYSDOH, New York State Department of Health.

[a]One hundred eighty-four subjects met New York State AIDS Institute screening guidelines, 24 did not.

[b]One hundred ninety-eight subjects met Infectious Diseases Society of America screening guidelines, 10 did not.

cohort of MSM at high risk for anal dysplasia, as many as 23% with benign anal cytology had HSIL pathology [25]. Because initial benign cytology does not reliably rule out the presence of HSIL, repeat screening in regular intervals is likely to increase yield. Conceivably, the addition of oncogenic HPV testing in populations with lower rates of anal high-risk HPV infection than MSM could increase the positive and negative predictive values of anal cytology.

In a multivariate analysis, only being a current smoker was a significant risk factor for HSIL histology in our cohort. Smoking is a well-defined risk factor for many HPV-related malignancies, including anal cancer [26, 27]. A recent study of 803 HIV-positive MSM found that smokers, relative to nonsmokers, had significantly higher rates of developing anal HSIL (23% vs 17% at baseline, 40% vs 33% over a 10-year study period) [28]. Our study results support the association between smoking and HPV-related anal dysplasia, and extend this finding to HIV-infected women.

While a history of anogenital warts, cervical or vulvar dysplasia, and RAI are included as criteria in the HIVMA anal cancer screening recommendations, their strength as predictors of anal dysplasia is unclear. In the present study, none of these predictors was significantly associated with HSIL in adjusted analyses. In a recent review, Stier et al noted that RAI was not a consistently significant predictor of anal HSIL in HIV-infected women [11]. While a large study among HIV-infected women in Texas identified RAI as a significant risk factor for anal HSIL, 60% of women with abnormal cytology found to have HSIL on histology denied a history of RAI [19]. Thus, the predictive value of reported RAI for anal dysplasia remains unclear, and HIV-infected women who do not report a history of RAI may also be at risk for anal dysplasia. Associations between nonanal genital dysplasia in HIV-infected women and anal dysplasia are also unclear. Some studies have reported an association between HPV-related cervical/vulvar dysplasia and anal dysplasia in HIV-infected women [24, 29], while others do not [20]. With respect to anogenital warts, Abramowitz et al found that a history of anal condylomata among HIV-infected persons was significantly associated with anal dysplasia [30]. However, the authors note that many cases of anal condylomata were diagnosed 8 or more years prior to the study.

Our results do suggest that the prevalence of anal HSIL in HIV-infected women is high even among those who do not meet current anal cancer screening guidelines. Furthermore, the criteria used in existing guidelines, such as history of RAI, anogenital warts, and abnormal cervical/vulvar histology, were not significantly associated with anal HSIL histology in our cohort. Although the natural history of anal dysplasia might differ from that of cervical dysplasia, many algorithms pertaining to anal cancer screening have been extrapolated from the success of cervical cancer screening. While the natural history of anal HSIL is not as well characterized as that of cervical HSIL, we advocate that the comparable rates of cervical and anal dysplasia in the setting of similar cancer incidence rates favor expanding anal cancer screening to all HIV-infected women, much like universal cervical cancer screening is now the standard of practice [31–33].

Our study had several strengths. The study sample comes from a large HIV-infected cohort in an urban area. All HRAs were performed by a single provider, eliminating interoperator variability. Additionally, because screening was offered to all HIV-infected women, not just those who meet currently recommended anal cancer screening criteria, the prevalence rates found for abnormal cytology and HSIL are likely more representative of the true prevalence among HIV-infected women. Limitations include the retrospective nature of the study, lack of availability of oncogenic HPV testing during the complete study period, and suboptimal HRA completion rates. However, comparison of baseline characteristics suggests that women who did not undergo HRA did not differ significantly in anal cytology results. This implicates that our overall estimates of HSIL histology for the cohort are likely to be conservative.

As previously outlined and with all its weaknesses, anal cytology is the only currently available, realistic screening tool for

anal cancer. HRA appears to be an important method to detect anal HSIL and anal cancer, although the implementation of HRA into routine screening may be difficult at this time due to the paucity of trained providers.

Prospective studies evaluating the natural history of anal HSIL are necessary to better understand the progression and regression rates of anal dysplasia in the HIV-infected population. However, our data suggest that current anal cancer screening criteria may be too stringent, potentially leading to missed HSIL diagnoses, and that anal cytology screening should be offered to all HIV-infected women.

Note

Potential conflicts of interest. Authors certify no potential conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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