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MAJOR ARTICLE

Prevalence of and Risk Factors for Anal High-grade Squamous Intraepithelial Lesions in Women Living with Human Immunodeficiency Virus

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Background. Women living with human immunodeficiency virus (WLHIV) have disproportionately high rates of squamous cell carcinoma of the anus compared with the general population of women. Anal high-grade squamous intraepithelial lesions (HSILs) precede anal cancer, and accurate studies of HSIL prevalence among WLHIV in the United States are lacking.

Methods. The AIDS Malignancy Consortium 084 study was a multicenter national trial to evaluate the prevalence of and risk factors for anal HSIL in a US cohort. Eligible participants were WLHIV aged ≥18 years with no history of anal HSIL. Study participants had an examination including collection of cervical/vaginal and anal specimens, followed by high-resolution anoscopy with biopsy.

Results. We enrolled 256 women with evaluable anal pathology. The mean age was 49.4 years, 64% women were non-Hispanic black, 67% were former or current smokers, and 56% reported ever having anal sex with a man. The median CD4 T-cell count was 664 cells/μL. The prevalence of anal histologic HSIL (hHSIL) was 27% (95% confidence interval [CI], 22%–33%). There was a strong concordance (240/254) between local and consensus pathologists for hHSIL vs less than hHSIL (κ = 0.86 [95% CI, .79–.93]). Current CD4 count of ≤200 cells/μL was the strongest predictor of consensus anal hHSIL diagnosis (adjusted odds ratio [aOR], 10.34 [95% CI, 3.47–30.87]). History of anoreceptive intercourse was also associated with hHSIL (aOR, 2.44 [95% CI, 1.22–4.76]).

Conclusions. The prevalence of anal hHSIL in WLHIV in the United States was 27% in this study where all participants received high-resolution anoscopy and biopsy.

Keywords. HIV; HPV; HSIL; women's health; epidemiology.

Women living with human immunodeficiency virus (WLHIV) have a >10-fold higher risk of developing squamous cell carcinoma of the anus (SCCA) compared with the general population of women [1, 2]. There are pathophysiological similarities between cervical and anal cancer, including an etiologic association of persistent human papillomavirus (HPV) infection leading to the development of cancer precursor lesions, known as high-grade squamous intraepithelial lesions (HSILs) of the anus [3]. Strategies for SCCA prevention, inferred from the cervical cancer screening protocols, use anal cytology followed by diagnostic high-resolution anoscopy (HRA) for anal HSIL detection and subsequent treatment to prevent progression to SCCA.

Based largely on expert opinion, screening WLHIV for SCCA has been recommended by major national organizations, including the American Cancer Society [4], the Infectious Diseases Society of America [5], and the American Society of Colon and Rectal Surgeons [6]. To inform evidence-based optimal screening algorithms, it is critical to determine accurate estimates of the prevalence of and risk factors for anal HSIL. Current screening recommendations for women are based on prevalence estimates of histological HSIL (hHSIL) in human immunodeficiency virus (HIV)–infected men who have sex with men from large cohort studies where the prevalences have

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ranged from 29% to 52% [7–10]. There are no known unbiased estimates of anal hHSIL prevalence among WLHIV in the United States obtained by performing HRA on the entire cohort by rigorously certified providers. The majority of studies have relied on HRA-directed biopsies from women referred with an abnormal anal screening test or triage, thus potentially missing/underestimating the prevalence among WLHIV.

The AIDS Malignancy Consortium (AMC) 084 study, "Screening HIV-Positive Women for Anal Cancer Precursors," was a multicenter national trial to evaluate the prevalence, risk factors, and incidence of anal HSIL in a cohort of WLHIV in the United States. To assure the accuracy of anal HSIL detection, every study participant underwent HRA with directed or random biopsies and consensus pathology review confirmed the diagnosis of anal hHSIL. In this article, we report the prevalence of and clinical risk factors, not including anal cytology or anal HPV (to better assess which WLHIV should be screened with those modalities), for anal hHSIL in a cohort of WLHIV in the United States.

METHODS

The AMC 084 trial was conducted at 12 AMC clinical trial sites in the United States. Participants were recruited between 2014 and 2016. The clinicians responsible for performing HRA at each AMC clinical site were certified as per the rigorous standards developed by the AMC HPV Working Group [6]. The certification process included each clinician's assembling a log of 50 HRA procedures with concurrent anal cytology and histology results as well as having a site visit by an expert HRA provider who observed the clinicians' HRA skills. The protocol was approved by the Cancer Therapy Evaluation Program of the National Cancer Institute and by the institutional review board of each participating institution.

Study Designs

AMC-084 was a longitudinal multisite study of prevalent and incident anal hHSIL through 2 years. Potential subjects were screened using a standardized questionnaire and medical records review. At baseline, all women were evaluated with collection of specimens for cervical/vaginal and anal assessments and by HRA with directed biopsies. If a study participant was diagnosed with anal hHSIL at any visit (the primary endpoint), the patient was then exited from the study.

Study Participants

Eligible women were 18 years or older, with HIV infection, having no history of anal HSIL by cytology or histology, and having laboratory test results within the past 120 days showing absolute neutrophil >750 cells/μL and platelet count ≥75 000 cells/μL. Women with a history of pelvic radiation, anal or perianal cancer, treatment for anal or perianal condyloma, or low-grade squamous intraepithelial lesion (hLSIL) within 4 months of study entry were ineligible. Women with previous hysterectomy were not excluded. Supplementary Figure 1 demonstrates the enrollment schema.

Study Procedures

Clinical charts were reviewed and study participants queried for HIV information (date of diagnosis, current and nadir $CD4^+$ T-cell counts, HIV loads, and antiretroviral therapy history) and HPV-related information (past history of HPV-related anogenital diseases, including warts and abnormal cytology and colposcopy results). A baseline questionnaire was administered to the study participant by research staff to determine her smoking status and recent sexual history. Absolute neutrophil and platelet counts, HIV viral load, and CD4 counts were required within 120 days of study enrollment, and if not available from clinical chart review, blood samples for these tests were collected.

All participants underwent a targeted physical examination. The vulva was examined for signs of HPV-related lesions. Additional evaluations of the vagina/cervix, anus and perianus are described in the following sections.

Cervical/Vaginal Specimen Collection

Two cervical/vaginal specimens were collected through a vaginal speculum for (1) cytology and (2) HPV testing. Cervical cytology was collected using standard procedures and reagents of local sites using cervical broom and/or cytobrush and/or spatula. The cytology specimen was preserved using either PreservCyt (Hologic, Marlborough, Massachusetts) or SurePath (Becton Dickinson, Franklin Lakes, New Jersey) as per local site standard. The specimen for HPV testing was collected similarly into PreservCyt. HPV testing utilized the Hybrid Capture 2 test (Qiagen, Gaithersburg, Maryland) a high-risk HPV DNA probe that detects 13 genotypes of HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

Anal Cytology Collection

The anal specimens were collected in a standard fashion using a Dacron swab moistened in tap water and inserted a minimum of 3 cm into the anus. Applying lateral pressure, the swab was rotated in a circular fashion for approximately 20 seconds as it was slowly removed from the canal, then immersed in the liquid-based cytology media required for local processing at each local institution (PreservCyt or SurePath) and agitated vigorously for 20–30 seconds to disperse the cells.

Site-specific pathology departments and cytopathologists processed the cervical and anal cytology specimens and evaluated the cytology using the Bethesda classification system [11]. Specimens were evaluated as negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells where high-grade squamous intraepithelial lesion could not be excluded (ASC-H), LSIL, and HSIL.

High-resolution Anoscopy and Biopsy

Following anal cytology specimen collection, a digital anal/rectal examination was performed followed by HRA using a plastic anoscope with 5% acetic acid and Lugol solution as previously described by Jay et al [12]. During the HRA, each study participant had at least 2 biopsies. Biopsies were taken of anal lesions most suspicious for anal hHSIL from 2 different quadrants of the anus. If <2 anal lesions were noted, 1–2 random biopsies were performed such that there were at least 2 anal biopsies from at least 2 different quadrants of the anal canal. After evaluation of the anal canal, 5% acetic acid was applied to the perianus, and the perianus was then examined under colposcopic guidance for any abnormalities. Biopsies were performed of any perianal abnormalities.

Anal Histology

The study outcome of interest was anal hHSIL (vs less than hHSIL) as determined by consensus pathology review. Biopsy specimens were evaluated using terminology and classifications (including recommendations for p16 staining) from the Lower Anogenital Squamous Terminology Project [3].

Central pathology review was submitted to a central pathologist. If there was a disagreement between the local and the central pathologist, then a third pathologist reviewed the slide and consensus for 2 of 3 pathologists was required. When several biopsies were taken from the same patient, the most severe histological grade was used for the analysis. In one case where the central and adjudicating pathologist interpreted the read as "favor HSIL" and no p16 immunostain was available for review, hHSIL diagnosis was assigned. In this study, anal hHSIL diagnosis refers to the consensus histologic diagnosis; a composite anal HSIL diagnosis of anal cytology and histology results was not used for this analysis.

Statistical Analysis

Prevalence was calculated as the overall proportion of participants with anal hHSIL and according to each group defined by participant characteristic. We computed 95% confidence intervals (CIs) using exact binomial calculations. The κ statistic was calculated to assess the agreement between local and central pathology results at the participant level. Univariate comparisons were made using χ^2 or Fisher exact tests. Investigating patient characteristics with $P < .15$ in univariate analyses, a multivariable logistic regression model was fit and the final model was determined using stepwise variable selection method with both variable entry and exit criteria based on a cutoff $P < .15$. Results of anal cytology were not considered in the model as our goal was to determine clinical predictors of anal HSIL using available clinical information excluding anal screening results. Results with P values <.05 were deemed statistically significant.

RESULTS

Most screened HIV-infected women were included in the baseline analyses (93% [256/276]). The women's mean age was 49.4 (standard deviation, 8.5) years of age, non-Hispanic black (64%), and former or current smokers (67%). The median CD4 T-cell count was 664 cells/μL (interquartile range [IQR], 444–881 cells/μL), 50% reported a nadir CD4 T-cell count of ≤200 cells/μL, and 95% of participants reported using antiretroviral therapy. Risk factors for HPV infection were common: 56% reported receptive anal intercourse with at least 1 partner, 55% showed history of abnormal cervical cytology, and 26% reported prior external anogenital wart diagnoses. Nearly 48% reported a history of sexual assault (Table 1).

The prevalence of anal hHSIL among participants was 27% (69/256; 95% CI, 22%–33%). The proportion with anal hHSIL according to concurrent anal cytology was 88% (15/17) HSIL; 40% (2/5) ASC-H; 45% (21/47) LSIL; 20% (16/81) ASC-US; and 12% (12/98) NILM ($P < .001$; Table 2). Most study participants with anal hHSIL had ASC-US or LSIL anal cytology (56% [95% CI, 43%–68%]). Only 26% (95% CI, 16%–38%) of anal hHSIL was found in women with concurrent ASC-H/HSIL anal cytology.

Anal hHSIL was associated with race and ethnicity, current and historical immunity, the number of anoreceptive intercourse partners, and history of abnormal cervical cytology/colposcopy (Table 1) and with concurrent cervical/vaginal cytology and cervical HPV infection (Table 2). Non-Hispanic white women, followed by Hispanic females and non-Hispanic blacks, showed 42%, 33%, and 21% prevalence of hHSIL, respectively ($P = .024$; Table 1). Current CD4 T-cell count of <200 cells/μL (67%) was associated with the highest prevalence of anal hHSIL compared to those with 201–350 cells/μL (39%) and >350 cells/μL (22%) ($P < .001$). Women reporting ≥2 male anoreceptive partners over their lifetimes were more likely to have hHSIL than those with 1 or no similar partners: 34%, 28%, and 17%, respectively ($P = .026$). Nearly 64% (7/11) of women with ASC-H/HSIL on concurrently performed cervicovaginal cytology showed anal hHSIL, whereas women with ASC-US or LSIL (28%) and NILM (25%) cervicovaginal cytology similarly showed hHSIL ($P = .021$; Table 2). The prevalence of hHSIL varied by site; of sites with at least 10 participants (excluding 1 site with only 1 participant), the median prevalence across sites was 19% (IQR, 18%–44%). Smoking, income, marital status, current combination antiretroviral therapy use, and history of genital warts were not associated with hHSIL.

Nearly 20% (50/256) of women showed <2 areas suspicious for hHSIL at the time of HRA and underwent random biopsy. Of 73 random biopsies collected, 72 were evaluable. Abnormal histology was seldom found in random biopsy specimens: 86% (63/72) were normal, 8% (6/72) showed LSIL, and 4% (3/72)

Table 1. Participant Characteristics and Prevalence of Histologic Anal High-grade Squamous Intraepithelial Lesions at Baseline

Characteristic	Anal hHSIL Prevalence		Unadjusted OR	*P* Value[b]
	no./No.[a]	% (95% CI)		
Overall	69/256	27.0 (21.6–32.8)	…	
Demographic characteristics				
Age, y				.791
<40	8/30	26.7 (12.3–45.9)	0.81 (.44–1.49)	
40–49	21/86	24.4 (15.8–34.9)	0.91 (.37–2.21)	
≥50	40/140	28.6 (21.3–36.8)	Reference	
Race/ethnicity				.024
Non-Hispanic black	35/163	21.5 (15.4–28.6)	Reference	
Non-Hispanic white or other	17/42	40.5 (25.6–56.7)	2.49 (1.21–5.11)	
Hispanic	17/51	33.3 (20.8–47.9)	1.83 (.92–3.65)	
Smoking status				.130
Former/current	50/168	29.8 (23.0–37.3)	1.62 (.86–3.04)	
Never	17/82	20.7 (12.6–31.1)	Reference	
Education				.910
High school diploma or less	37/137	27.0 (19.8–35.3)	1.03 (.59–1.82)	
Some college or higher	29/110	26.4 (18.4–35.6)	Reference	
Annual income				.150
<$20 000	54/191	28.3 (22.0–35.2)	1.82 (.80–4.17)	
≥$20 000	8/45	17.8 (8.0–32.1)	Reference	
Marital status				.404
Married/not married, living with someone	12/55	21.8 (11.8–35.0)	0.74 (.36–1.51)	
Divorced/widowed/single	54/197	27.4 (21.3–34.2)	Reference	
HIV characteristics				
Current CD4 count, cells/μL				< .001
≤200	12/18	66.7 (41.0–86.7)	6.96 (2.48–19.51)	
201–350	9/23	39.1 (19.7–61.5)	2.24 (.91–5.48)	
>350	48/215	22.3 (16.9–28.5)	Reference	
VL suppressed (≤200 copies/μL)	56/218	25.7 (20.0–32.0)	0.69 (.32–1.47)	.337
VL unsuppressed (>200 copies/μL)	12/36	33.3 (18.6–51.0)	Reference	
Nadir CD4 count, cells/μL				.004
≤200	44/124	35.5 (27.1–44.6)	2.29 (1.29–4.08)	
>200	24/124	19.4 (12.8–27.4)	Reference	
Current cART user				.298
Yes	66/242	27.3 (21.8–33.4)	3.38 (.42–27.03)	
No/declined	1/10	10.0 (.0–44.5)	Reference	
Reported clinical history				
Lifetime male anal sex partners				.026
0	18/107	16.8 (10.3–25.3)	Reference	
1	20/71	28.2 (18.1–40.1)	1.94 (.94–4.00)	
≥2	23/67	34.3 (23.2–46.9)	2.59 (1.27–5.28)	
History of anogenital warts				.193
Yes	21/64	32.8 (21.6–45.7)	1.51 (.81–2.81)	
No	45/184	24.5 (18.4–31.3)	Reference	
History of abnormal cervical cytology				.004
Yes	47/140	33.6 (25.8–42.0)	2.42 (1.32–4.44)	
No	19/110	17.3 (10.7–25.7)	Reference	
Unsure/declined[c]	3/6	50.0 (11.8–88.2)	…	
History of colposcopy after abnormal cervical cytology				.004[c]
Yes	39/111	35.1 (26.3–44.8)	2.35 (1.18–4.68)	
No	25/132	18.9 (12.7–26.7)	Reference	
Unsure/declined[c]	5/13	38.5 (13.9–68.4)	…	
History of sexual assault				.379
Yes	36/122	29.5 (21.6–38.4)	1.28 (.74–2.23)	
No/declined	33/134	24.6 (17.6–32.8)	Reference	
Total	69/256	27.0 (21.6–32.8)	…	

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; hHSIL, histological high-grade squamous intraepithelial lesion; OR, odds ratio; VL, viral load.

[a]The denominators do not sum to 256 for some variables due to missing responses; variables with the most missing data are annual income (n = 20), lifetime male sex partners (n = 11), and education (n = 9).

[b]χ^2 or Fisher exact test.

[c]We did not include the unsure/declined group in the *P* value calculation as there were only 6 observations in the latter group.

Table 2. Prevalence of Histologic Anal High-grade Squamous Intraepithelial Lesions According to Baseline Cervical and Anal Cytology and Cervical Human Papillomavirus Results

Characteristic	Participants With Anal HSIL/Total Participants, No.	Prevalence of Anal HSIL, % (95% CI)	*P* Value[a]
Cervical cytology (n = 251)			.021
Negative	44/176	25.0 (18.8–32.1)	
ASC-US/LSIL	18/64	28.1 (17.6–40.8)	
ASC-H/HSIL	7/11	63.6 (30.8–89.1)	
Unevaluable (n = 3)	…	…	
Missing (n = 2)	…	…	
Cervix HPV HC2 (n = 251)			.019
HPV positive	26/72	36.1 (25.1–48.3)	
HPV negative	39/179	21.8 (16.0–28.6)	
Missing (n = 5)	…	…	
Anal cytology (n = 248)			< .001
Negative	12/98	12.2 (6.5–20.4)	
ASC-US/LSIL	37/128	28.9 (21.2–37.6)	
ASC-H/HSIL	17/22	77.3 (54.6–92.2)	
Unevaluable (n = 8)	…	…	

Abbreviations: ASC-H, atypical squamous cells, high-grade squamous intraepithelial lesion cannot be excluded; ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HC2, Hybrid Capture 2 test; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

[a]χ^2 test.

showed hHSIL. Overall, random biopsies detected only 3% (2/69) of women with anal hHSIL.

Table 3 shows that central pathology assessments strongly agreed with local evaluations of histology. At the study participant level, nearly 93% (64/69) of locally evaluated hHSIL was similarly diagnosed by expert central pathology assessment, and 95% (174/183) of locally evaluated less than hHSILs were similarly classified by central pathology. Nonetheless, 61% (60/99) of participants with anal biopsies classified as hLSIL by local pathologists were reclassified as benign by the central pathologists, resulting in lower agreement when considering 3 categories (hHSIL, hLSIL, and benign; weighted κ = 0.66 [95% CI, .59–.73]).

Multivariable analysis (Table 4) demonstrated that current low CD4 T-cell count was associated with hHSIL. Specifically, those with ≤200 cells/μL showed 10-fold higher odds of hHSIL (adjusted odds ratio [aOR], 10.34 [95% CI, 3.47–30.87]) compared with the reference CD4 count category of >350 cells/μL, and 201–350 cells/μL was associated to a lesser extent (aOR, 2.70 [95% CI, 1.02–7.15]). Similarly, having 1 or more lifetime anal sex partners was associated with anal hHSIL (aOR, 2.44 [95% CI, 1.22–4.76]) compared with those who never had an anal sex partner.

DISCUSSION

To our knowledge, this is the first study to report anal hHSIL prevalence in a cohort of WLHIV who all received high-resolution anoscopy and biopsy. We found that the prevalence of biopsy-proven anal HSIL among WLHIV was 27%, which is the highest reported prevalence of histologically confirmed anal HSIL to date among WLHIV in the United States. We also found that the risk for anal hHSIL was greater in women with lower current CD4 T-cell counts and in women with a history of anal intercourse, and prevalence of hHSIL varied by site (IQR, 18%–44%).

In our study, we also found 41% of study participants with anal hHSIL had concurrent NILM (negative) or ASC-US anal cytology. Thus, it is possible that prior studies reporting prevalence underdiagnosed anal hHSIL because these studies utilized

Table 3. Local Versus Central Pathology Assessment of Anal Biopsies, at the Participant Level

		Central Pathology Review[a]			
		Benign	LSIL	HSIL	Total
Local Pathology Interpretation[a]	Benign	81	0	1	82
	LSIL	60	35	4	99
	HSIL	5	4	64	73
	Unevaluable	2	0	0	2
	Total	146	39	69	256

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

[a]Most severe diagnosis at the participant level.

Table 4. Multivariable Logistic Regression Model Evaluating Predictors of Anal Histologic High-grade Squamous Intraepithelial Lesions (n = 245)[a]

Predictor	Adjusted Odds Ratio (95% CI)	*P* Value
Race		
Non-Hispanic black	Reference	.100
All others	1.72 (.90–3.23)	
Current CD4 count, cells/μL		
≤200	10.34 (3.47–30.87)	< .001
201–350	2.70 (1.02–7.15)	.045
>350	Reference	
No. of lifetime anal sex partners		
≥1	2.44 (1.22–4.76)	.012
0	Reference	

Abbreviation: CI, confidence interval.

[a]Model selected using stepwise method with criteria for entry and exit both being $P < .15$. Model initially considered variables that were significant in univariate analyses at $P < .15$: race, smoking status, baseline and nadir CD4 T-cell count, lifetime male anal sex partners, reported history of abnormal cervical cytology, and baseline cervical cytology. As a sensitivity analysis, the interaction between race and any history of anal sex ($P = .065$) was explored in an alternate model, but because the interaction was not significant, it was not included in the final model.

anal cytology prior to referring for HRA and biopsy. Heard et al [13] performed HRA on all patients and detected histologic HSIL in 6.4% (11/171) of their cohort. Studies of HIV-infected women in which only women with abnormal anal cytology underwent HRA found rates of anal hHSIL ranging from 4% to 9% [14–19]. The largest reported cohort by Gaisa et al found that of 795 HIV-infected women undergoing anal cancer screening with anal cytology, 39% of anal cytology specimens were abnormal; however, only 50% of the women with abnormal anal cytology underwent HRA [16]. Overall, 6.6% of the 795 women screened had anal hHSIL detected. Thus, we believe that most prior studies of anal hHSIL prevalence in women living with HIV underrepresented the true prevalence of hHSIL in this population because only individuals with abnormal anal cytology underwent HRA. Our study also had a very low rate of unevaluable anal cytology specimens (8/256 [3%]) compared with prior studies (12% in Heard et al [13]; 14% in de Pokomandy et al [20]; and 21% in Gaisa et al [16]).

Similar to prior studies, we found that abnormal anal cytology is more common than abnormal cervical cytology [15]. Cambou et al screened 863 HIV-infected women and found that 30.9% had abnormal anal cytology compared with 22.4% with abnormal cervical cytology [21]. De Pokomandy et al reported that in their Canadian cohort of 151 HIV-infected women, 36.7% had abnormal anal cytology, compared with 24.3% with abnormal cervical cytology [20]. Kojic et al, in a cohort study of 120 HIV-infected women in the United States, found that 38% had abnormal anal cytology compared with the 33% with abnormal cervical cytology [22]. In their cohort of HIV-infected women from Johannesburg, South Africa, Goeieman et al reported that 74% had abnormal anal cytology compared with 70% with abnormal cervical cytology [14].

We detected anal hHSIL in 88% of study participants with anal cytologic HSIL. The 2016 International Guidelines for Practice Standards in the Detection of Anal Cancer Precursors proposes a quality assurance metric: >90% of patients with cytologic HSIL should have hHSIL detected on HRA [23]. In other studies, the proportion of study participants having hHSIL detected in association with cytology anal HSIL was 67% (73/109) in Machalek et al [24], 52% (11/21) (with ASC-H included as HSIL cytology) in Heard et al [13], and 35% (6/17) (with ASC-H included as HSIL cytology) in Goeieman et al [14]. In addition, we found that random biopsies of the anal canal in our cohort of HIV-infected women did not add significantly to the detection of anal hHSIL (2/69 [3%]). In comparison, the study from Silvera et al [25] reported that random biopsies resulted in an increased number of patients with anal hHSIL by 10% (13/132) in men.

Reported clinical risk factors for anal hHSIL in HIV-infected women have varied across studies. We found that current CD4 T-cell count ≤200 cells/μL was associated with increased risk of anal hHSIL. Gaisa et al [16] reported that the only risk factor for anal HSIL was current smoking; no association was found between history of anal sex and recent abnormal cervical cytology. Of note, Heard et al found that risk factors for anal HSIL included abnormal cervical cytology and anal HPV-16 whereas history of anal sex and smoking were unrelated in their cohort [13]. However, as we were mainly interested in clinical risk factors rather than biomarkers of hHSIL in this analysis, we did not include anal cytology or anal HPV detection in our model. Although we found that a history of anal intercourse was a risk factor for anal hHSIL, it is important to note that anal hHSIL was found in 17% of women without a history of anal intercourse. Similarly, Gaisa et al found that 26% of HIV-infected women with anal hHSIL denied a history of anal intercourse [16]. It has been proposed that the anus may well be a reservoir for genital HPV infections, given the close proximity of the anus to the cervix. Inoculation of the anus may occur by toilet wiping [26] or simply due to a field effect.

Strengths of our study include the large study size, thorough clinical questionnaire, expertise, and certification of the clinicians performing HRA, unbiased estimation of anal hHSIL performing HRA on all study participants, mandated biopsies on HRA, and central pathology review of biopsies. Limitations of the study include lack of central pathology review for anal cytology and the inability to distinguish current from former smokers on the baseline data evaluation. In addition, variability for anal hHSIL detection existed across AMC sites, possibly due to HRA clinician expertise or population characteristics.

In conclusion, it is likely that the prevalence of anal hHSIL in women living with HIV is much higher than previously estimated based on our study of WLHIV in the United States. We found that >60% of the women had abnormal anal cytology. The high prevalence of anal hHSIL and invasive anal cancer

among WLHIV suggests the need for anal cancer screening in this population. However, optimal screening strategies for anal cancer prevention among WLHIV with anal HSIL are not yet known. Prevention of anal cancer in women living with HIV should focus on identification of cost-effective strategies for screening and treatment of anal cancer precursors.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Colón-López V, Shiels MS, Machin M, et al. Anal cancer risk among people with HIV infection in the United States. J Clin Oncol **2018**; 36:68–75.
2. Silverberg MJ, Lau B, Achenbach CJ, et al; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. Ann Intern Med **2015**; 163:507–18.
3. Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med **2012**; 136:1266–97.
4. American Cancer Society. Can anal cancer be found early? Available at: www.cancer.org/content/cancer/en/cancer/anal-cancer/detection-diagnosis-staging/detection/. Accessed 27 October 2018.
5. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA; Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. Clin Infect Dis **2014**; 58:e1–34.
6. Stewart DB, Gaertner WB, Glasgow SC, Herzig DO, Feingold D, Steele SR; Prepared on Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). Dis Colon Rectum **2018**; 61:755–74.
7. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol **2012**; 13:487–500.
8. Machalek DA, Jin F, Poynten IM, et al; SPANC Study Team. Prevalence and risk factors associated with high-grade anal squamous intraepithelial lesions (HSIL)-AIN2 and HSIL-AIN3 in homosexual men. Papillomavirus Res **2016**; 2:97–105.
9. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS **2005**;19:1407–14.
10. Berry JM, Palefsky JM, Jay N, Cheng SC, Darragh TM, Chin-Hong PV. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. Dis Colon Rectum **2009**; 52:239–47.
11. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system: terminology for reporting results of cervical cytology. JAMA **2002**; 287:2114–9.
12. Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. Dis Colon Rectum **1997**; 40:919–28.
13. Heard I, Etienney I, Potard V, et al; ANRS-C017 VIHGY Study Group. High prevalence of anal human papillomavirus-associated cancer precursors in a contemporary cohort of asymptomatic HIV-infected women. Clin Infect Dis **2015**; 60:1559–68.
14. Goeieman BJ, Firnhaber CS, Jong E, et al. Prevalence of anal HPV and anal dysplasia in HIV-infected women from Johannesburg, South Africa. J Acquir Immune Defic Syndr **2017**; 75:e59–64.
15. Stier EA, Sebring MC, Mendez AE, Ba FS, Trimble DD, Chiao EY. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am J Obstet Gynecol **2015**; 213:278–309.
16. Gaisa M, Ita-Nagy F, Sigel K, et al. High rates of anal high-grade squamous intraepithelial lesions in HIV-infected women who do not meet screening guidelines. Clin Infect Dis **2017**; 64:289–94.
17. Gandra S, Azar A, Wessolossky M. Anal high-risk human papillomavirus infection and high-grade anal intraepithelial neoplasia detected in women and heterosexual men infected with human immunodeficiency virus. HIV AIDS **2015**; 7:29–34.
18. Tandon R, Baranoski AS, Huang F, et al. Abnormal anal cytology in HIV-infected women. Am J Obstet Gynecol **2010**; 203:21.e1–6.
19. Hessol NA, Holly EA, Efird JT, et al. Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women. AIDS **2009**; 23:59–70.
20. Cambou MC, Luz PM, Lake JE, et al. Anal human papillomavirus (HPV) prevalences and factors associated with abnormal anal cytology in HIV-infected women in an urban cohort from Rio de Janeiro, Brazil. AIDS Patient Care STDS **2015**; 29:4–12.
21. de Pokomandy A, Kaufman E, de Castro C, et al; EVVA Study Group. The EVVA cohort study: anal and cervical type-specific human papillomavirus prevalence, persistence, and cytologic findings in women living with HIV. J Infect Dis **2017**; 216:447–56.
22. Kojic EM, Cu-Uvin S, Conley L, et al. Human papillomavirus infection and cytologic abnormalities of the anus and cervix among HIV-infected women in the study to understand the natural history of HIV/AIDS in the era of effective therapy (the SUN study). Sex Transm Dis **2011**; 38:253–9.
23. Hillman RJ, Cuming T, Darragh T, et al. 2016 IANS international guidelines for practice standards in the detection of anal cancer precursors. J Low Genit Tract Dis **2016**; 20:283–91.
24. Machalek DA, Poynten IM, Jin F, et al; SPANC Study Team. A composite cytology-histology endpoint allows a more accurate estimate of anal high-grade squamous intraepithelial lesion prevalence. Cancer Epidemiol Biomarkers Prev **2016**; 25:1134–43.
25. Silvera R, Gaisa MM, Goldstone SE. Random biopsy during high-resolution anoscopy increases diagnosis of anal high-grade squamous intraepithelial lesions. J Acquir Immune Defic Syndr **2014**; 65:65–71.
26. Simpson S, Blomfield P, Dennis A, Tabrizi SN, Blizzard L, Turner R. Front-to-back wiping and dabbing behaviour wiping post-toilet significantly associated with anal neoplasia and HR-HPV carriage in a cohort of women with a history of an HPV-mediated gynaecological neoplasia. Cancer Epidemiol **2016**; 42:124–32.