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PREVALENCE OF ANAL HPV AND ANAL DYSPLASIA IN HIV-INFECTED WOMEN FROM JOHANNESBURG, SOUTH AFRICA

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Abstract

BACKGROUND—Anal cancer is a relatively common cancer among HIV-infected populations. There are limited data on the prevalence of anal high-risk human papillomavirus (HR-HPV) infection and anal dysplasia in HIV-infected women from resource-constrained settings.

METHODS—A cross-sectional study of HIV-infected women age 25–65 recruited from an HIV clinic in Johannesburg, South Africa. Cervical and anal swabs were taken for conventional cytology and HR-HPV testing. Women with abnormal anal cytology and 20% of women with negative cytology were seen for high resolution anoscopy (HRA) with biopsy of visible lesions.

RESULTS—Two hundred women were enrolled. Anal HR-HPV was found in 43%. The anal cytology results were negative in 51 (26%); 97 (49%) had low-grade squamous intraepithelial lesions (SIL), 32 (16%) had atypical squamous cells of unknown significance and 19 (9.5%) had high-grade SIL or atypical squamous cells suggestive of high-grade SIL. On HRA, 71 (36%) had atypia or low-grade SIL on anal histology and 17 (8.5%) had high-grade SIL. Overall 31 (17.5%) had high-grade SIL present on anal cytology or histology. Abnormal cervical cytology was found in 70% and cervical HR-HPV in 41%.

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CONCLUSION—We found a significant burden of anal HR-HPV infection, abnormal anal cytology and high-grade SIL in our cohort. This is the first study of the prevalence of anal dysplasia in HIV-infected women from sub-Saharan Africa. Additional studies are needed to define the epidemiology of these conditions, as well as the incidence of anal cancer, in this population.

Keywords

Anal dysplasia; human papillomavirus; HIV infection; high resolution anoscopy; African Women

INTRODUCTION

As HIV-infected patients live longer due to effective combination antiretroviral therapy (cART), an increased risk for non-AIDS defining cancers is being reported.¹ HIV-infected individuals are at increased risk of virally-mediated cancers.^{1, 2} Anal cancer, which is caused by high-risk types of human papillomavirus (HR-HPV), is a relatively common cancer among men who have sex with men and HIV-infected men and women.^{3–5} The rates of anal cancer have risen significantly in HIV-infected women from very low rates during 1980–1989 to 11/100,000 person years during 1996–2004.⁶ A systematic review found that the anal cancer incidence among HIV-infected women ranged from 3.9 to 30/100,000 person years and the standardized incidence rate ranged from 3.2 to 41.2 compared to the general population.⁷

Sub-Saharan Africa has the largest population of HIV-infected people and over 50% are women.⁸ Although cervical cancer rates have declined to <10/100,000 person years in the USA, the rates in sub-Saharan Africa are 30–40/100,000 person years in the general population⁹ and are 3–5 times higher among HIV-infected women.^{10, 11} The prevalence of cervical HR-HPV infection is high among HIV-infected women from sub-Saharan Africa and multiple HR-HPV infections are often detected.^{12, 13} Cervical HR-HPV infection and dysplasia have been shown to be correlated with anal HR-HPV infection and dysplasia.^{14, 15} There is a 2–4 fold increase risk of anal high grade squamous intraepithelial lesions (HSIL) among HIV-infected women who have a history of cervical dysplasia.^{5, 16, 17} In sub-Saharan Africa, there are no data on the prevalence of anal HR-HPV infection and anal HSIL among HIV-infected women. Moreover, the rates of anal cancer have not been well described. We present data on anal HR-HPV infection and anal dysplasia in HIV-infected women recruited from an HIV treatment clinic located in Johannesburg, South Africa.

METHODS

Study Design

HIV-infected women aged 25–65 years were recruited from Themba Lethu Clinic (TLC), the HIV unit at Helen Joseph Hospital, Johannesburg, South Africa. Women were educated regarding the study and then signed informed consent. The University of Witwatersrand Human Research Ethics Committee, University of Cape Town Human Research Ethics Committee and the University of North Carolina Institutional Review Board (IRB) approved

this study. The research was conducted in accordance with the Declaration of Helsinki 1975, as revised in 2000.

The inclusion criteria were documented HIV infection, age 25–65 and ability to give consent and participate in study related activities. Exclusion criteria were pregnancy, clinically active sexually transmitted infection (STI) (participation was allowed after the STI treatment was completed), prior hysterectomy with removal of the cervix, and significant medical/mental illness that would prevent the participant from completing the study. Participants completed a counselor-administered questionnaire on demographics, sexual history, and medical history specific to cervical and anal dysplasia. Participants underwent three anal swabs (one for conventional cytology and two for HR-HPV testing), and vaginal speculum examination for cytobroom collection for conventional cervical cytology and two cervical swabs for HR-HPV testing. Individual cervical and anal swabs were placed into vials of Digene specimen transport medium and PreservCyt. We used conventional cytology as liquid based cytology was not available within the South African public health sector at the time of this trial. Participants with an abnormal anal cytology defined as atypical squamous cells (ASC) or greater, and 20% of those with a negative cytology were asked to return for high resolution anoscopy (HRA) with biopsy of visible lesions. HRA was performed as described previously.¹⁸ Anoscopists were experienced cervical colposcopy providers and were trained in HRA by an experienced anoscopist. Ongoing quality assurance activities included quarterly reviews of digital HRA photographs and periodic in-person observation and mentoring of HRA procedures. HR-HPV testing was performed using Digene Hybrid Capture 2 (Qiagen Inc., Gaithersburg, MD, USA) on the Digene Specimen Transport Medium and Aptima HPV E6/E7 mRNA assay (Hologic Inc., San Diego, CA, USA) on a 1 mL aliquot of PreservCyt. These HR-HPV tests are not approved by the U.S. Food and Drug Administration for anal testing.

Pathology

Cervical and anal cytology was reported using the Bethesda system and were classified as negative, atypical squamous cells of uncertain significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), HSIL and atypical squamous cells of uncertain significance where a high-grade lesion could not be excluded (ASC-H) and squamous-cell carcinoma (SCC).¹⁹ A single pathologist (P.M.) interpreted all of the anal and cervical cytology results. HRA histology results were classified as normal, LSIL, and HSIL. Condyloma and atypia were considered LSIL for the purposes of analysis. Immunohistochemistry staining for p16 was not done routinely anal intraepithelial neoplasia grade 2 as recommended by the Lower Anogenital Screening Terminology standardization project (ref 19a). The pathologists were not blinded to the cytology results, but were blinded to the HR-HPV results. Histology specimens were interpreted by multiple pathologists from the South African National Health Laboratory Service in Johannesburg.

Statistical analysis

Baseline characteristics of this cohort and the prevalence of anal squamous intraepithelial lesions were summarized using descriptive statistics. If multiple anal biopsies were obtained, the most severe result was taken as the final diagnosis. Participants with inadequate biopsies

taken or were lost to follow up were removed from histology analyses. Student's t-test was used to compare log transformed Hybrid Capture 2 relative light units (RLU). Logistic regression was used to evaluate the relationship of various factors to the presence of anal HR-HPV DNA, anal E6/E7 mRNA and anal HSIL (defined as HSIL on cytology or histology or ASC-H on cytology). A single multivariable model was constructed for all 3 outcomes using all factors significant in one or more univariable models. All statistical analysis was conducted using SAS version 9.4 (Cary, NC).

RESULTS

Two hundred women were enrolled. Baseline characteristics of participants are described in Table 1. The median age was 38 years [IQR 33–44]. Participants had a median CD4 count of 430 cells/mm³ [IQR 311–600], and 89% had plasma HIV-1 RNA <400 copies/mL. Anal symptoms (pain, itching or bleeding) were reported by 37% of women.

Anal HR-HPV by either HPV DNA or E6/E7 mRNA was found in 85/199 (43%) of women. Cervical HR-HPV was found in 81/199 (41%). Anal and cervical HR-HPV test results were missing from one participant. The overall agreement between anal and cervical HR-HPV infection was 70%. The Cohen's kappa statistic is 0.38 (95% CI, 0.25–0.51) indicating modest agreement beyond chance.

Anal HR-HPV DNA results were available in 199 women and 82 (41%) had HR-HPV DNA detected. Anal E6/E7 mRNA results were available in 186 women and 30 (16%) had E6/E7 mRNA detected. HR-HPV DNA was detected in 27 of 30 (90%) with E6/E7 mRNA detected; 48 of 156 women (31%) without detection of anal E6/E7 mRNA had HR-HPV DNA detected. Women who had anal E6/E7 mRNA detected had greater amounts of HR-HPV DNA detected (5.1 vs. 2.4 log relative light units, $P<.0001$). Cervical HR-HPV DNA results were available in 199 women and 78 (39%) had HR-HPV DNA detected. Cervical E6/E7 mRNA results were available in 189 women and 52 (28%) had E6/E7 mRNA detected. HR-HPV DNA in the cervix was detected in 49 of 52 (94%) with E6/E7 mRNA detected; 24 of 136 women (18%) without detection of cervical E6/E7 mRNA had HR-HPV DNA detected.

Anal cytology was unsatisfactory for one participant. Anal cytology showed no evidence of SIL or malignancy in 51/199 (26%). Abnormal anal cytology was found in 148/199 (74%): 32/199 (16%) had ASCUS, 97/199 (49%) had LSIL, and 19/199 (9.5%) had HSIL or ASC-H. Anal HR-HPV DNA was detected in 14/19 (74%) women with HSIL or ASC-H on anal cytology; E6/E7 mRNA was detected in 9 of 13 (69%) women with HSIL or ASC-H on anal cytology and mRNA results. Cervical cytology was unsatisfactory for two participants. Cervical cytology showed no evidence of SIL or malignancy in 60/198 (30%). Abnormal cervical cytology was found in 138/198 (70%): 11/198 (6%) had ASCUS, 98/198 (49%) had LSIL, and 29/198 (15%) had HSIL or ASC-H. Cervical HR-HPV DNA was detected in 27/29 (93%) of women with HSIL or ASC-H on cervical cytology; E6/E7 mRNA was detected in 20 of 24 (83%) women with HSIL or ASC-H on cervical cytology. Tables 2A and 2B show the cytological results according to HR-HPV status.

The HRA disposition is shown in Figure 1. One hundred forty-eight women with abnormal anal cytology were referred for HRA. Results are available on 140/148 (95%) women (4 did not return for HRA and 4 had biopsies obtained that did not yield a result). Seventeen women were diagnosed with anal HSIL on histology. Of the 51/199 (26%) women with normal anal cytology, 10 were referred for HRA and results are available for 9 women; one did not return for HRA. No woman with normal anal cytology was diagnosed with HSIL. LSIL or atypia was found on anal histology in 72 of 149 women (48%) with HRA results.

Thirty-one participants had anal HSIL (defined as HSIL detected by anal histology or cytology or ASC-H on anal cytology). Anal HR-HPV DNA detection had the following test characteristics for HSIL: sensitivity 77% (95% CI 59%–90%), specificity 65% (95% CI of 58% to 73%), and positive predictive value 29% (20% to 40%). E6/E7 mRNA had a sensitivity of 50% (95% CI 29%–71%), specificity of 89% (95% CI 83%–93%), and positive predictive value of 40% (95% 23%–59%).

We evaluated factors associated with anal HR-HPV DNA detection, HPV E6/E7 mRNA detection, and anal HSIL (Table 3). Anal HR-HPV DNA was independently associated with younger age, and anal condyloma with a statistically non-significant association for lower current CD4 counts, and less time on ART. Anal E6/E7mRNA was independently associated with anal condyloma only. Anal HSIL was independently associated with anal condyloma and anal symptoms.

DISCUSSION

These are the first data on the prevalence of anal HR-HPV infection and squamous intraepithelial lesions among HIV-infected women in sub-Saharan Africa. We found a high prevalence of these conditions, which is expected given the high rates of cervical HR-HPV, dysplasia and cancer that have been reported in this population. Biological similarities between anal and cervical cancer include HR-HPV infection as the etiologic agent and detectable HSIL as the precursor lesion to cancer. HPV types 16 and 18 have been isolated in about 70% of cervical and 80% of anal cancers.^{21, 22} Studies have shown a strong association between HIV infection and anal HR-HPV prevalence in both men and women.^{23, 24} Our study found a similar prevalence of anal and cervical HR-HPV infection, which is consistent with prior studies.^{16, 25}

Our estimate of anal HSIL is similar to prior studies of HIV-infected from the U.S., France and Brazil.^{5, 7, 16, 25} However, ours is likely an underestimate. Studies using expert HRA providers have found a higher prevalence of HSIL. A prior study in U.S. HIV-infected men who had sex with men found that 38% of those having abnormal cytology had HSIL detected on anal histology,²⁶ whereas we found that 17 of 140 women with abnormal cytology (12%) who underwent HRA had anal HSIL detected by histology. Baseline analyses of a cohort of HIV-infected women found that 72/225 (28%) had anal HSIL include 16% of women with normal anal cytology, 29% of women with ASCUS/LSIL cytology and 72% of women with HSIL/ASC-H.²⁷ In comparison, we found HSIL in no women with normal anal cytology, 9% of women with ASCUS/LSIL cytology and 33% of women with

HSIL/ASC-H (See Table 4). The prevalence of anal HR-HPV was similar in these studies 48% and 43%, respectively.

The prevalence of anal and cervical HR-HPV infection was lower in those with longer duration of cART use. This relationship was seen for cervical HR-HPV infection in the Women's Interagency HIV Study.²⁸ The interplay between HIV and HR-HPV infection is complex and not well understood. In our cohort, we did not see a relationship between CD4 count and anal HSIL. This could be due to the possible ascertainment bias of HSIL, the relatively small sample size, or the relative high median CD4 count (430 [IQR 311–600] cells/mm³). The START study, which randomized cART-naïve, HIV-infected participants with CD4 over 500 cells/mm³ to immediate or deferred cART, found a 63% reduction in virally mediated cancers.²⁹ Hopefully, earlier initiation of cART, as recommended by the World Health Organization,³⁰ will result in a lower incidence of HPV-associated cancer.

The E6/E7 mRNA assay had lower sensitivity (50% vs. 77%) and a higher specificity for anal HSIL than did HR-HPV DNA (89% vs. 65%). Other studies have found that the sensitivity of E6/E7 mRNA for cervical HSIL was similar to HR-HPV DNA assays.^{31, 32} It is not clear why the sensitivity of E6/E7 mRNA for anal HSIL appeared lower in our study. Our estimated sensitivity was similar when considering HSIL on histology alone, HSIL on cytology or HSIL on either test (data not shown). It is possible that the swab order may have been a factor. The swab placed into PreservCyt was the third swab obtained, after cytology and HR-HPV DNA, and this may have resulted in less cellular material available for analysis. It is important to note that 15/199 (8%) did not have a valid result suggesting issues with the specimen quality. Additional studies are needed to clarify the utility of HPV mRNA assays for anal cancer screening.

We were unable to evaluate the role of receptive anal sex in this population as we asked about anal sex in the prior 6 months rather than lifetime history using an interviewer-administered questionnaire. Querying about lifetime history and use of computer assisted structured interviewing would have been a preferred approach. Although receptive anal sex has been shown to be a risk factor for anal HSIL, anal HSIL is commonly found among HIV-infected women who do not report that history.³³

In addition to limitations discussed above, HPV typing would have allowed for more detailed analyses of anal and cervical HR-HPV infections to elucidate the relationship between these infections. This study was a cross-sectional assessment. Longitudinal follow up would have allowed additional opportunities for diagnosis of anal HSIL. Although we did not identify anal HSIL among women with normal anal cytology, a more robust assessment of anal HSIL prevalence would have been possible if all women had undergone HRA.

We found a high prevalence of anal infection with HR-HPV and anal dysplasia among HIV-infected women in Johannesburg South Africa. Further studies are needed to define the incidence of anal cancer in this population. Prospective cohort studies to better understand the epidemiology of anal HSIL in this population should be considered. These data are needed before anal cancer screening can be considered in this region.

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Figure 1. High resolution anoscopy (HRA) disposition

This shows the referral of participants to high resolution anoscopy (HRA), number of procedures completed and HRA results. NILM=no evidence of intraepithelial lesions or malignancy; LSIL= low grade squamous intraepithelial lesions; HSIL=high grade squamous intraepithelial lesions.

Table 1

Baseline characteristics of 200 HIV-seropositive female participants in an anal cancer screening study from Johannesburg, South Africa

Characteristic	Median [IQR] or No. (%)
Age (years)	38 [33–44]
Current CD4 count, cells/mm ³	430 [311–600]
Nadir CD4 count, cells/mm ³	158 [74–227]
Current ART use	193 (97%)
Length of ART use (years)	3.0 [1.6–5.3]
Plasma HIV RNA <400 copies/mL	166 (89%)
One or more sex partners in prior 6 months	157 (79%)
Current tobacco use	5 (2.5%)
No prior cervical cytology	95 (48%)
History of anal condyloma	13 (6.5%)
Current anal symptoms (pain, itching or bleeding)	73 (37%)
Anal HPV DNA detected, Digene hc2 (n=199)	82 (41%)
Anal E6/E7 mRNA detected, Aptima (n=182)	30 (16%)
Abnormal anal cytology ^I (n=199)	148 (74%)
Cervical HPV DNA detected (n=199)	78 (39%)
Cervical E6/E7 mRNA detected (n=189)	52 (28%)
Abnormal cervical cytology ^I (n=198)	138 (70%)

ART=antiretroviral therapy; HPV=human papillomavirus; IQR=interquartile range; mRNA=messenger RNA

^I Abnormal cytology includes atypical squamous cells and squamous intraepithelial lesions.

Table 2

A: Prevalence of cervical HPV, stratified by cervical cytology result					
	Normal (n=60)	ASCUS (n=11)	LSIL (n=98)	ASC-H/HSIL (n=29)	Total (n=197)
Cervical hc2 HPV+	11/60 (18%)	1/11 (9%)	38/97 (39%)	27/29 (93%)	77/197 (39%)
Aptima E6/E7 mRNA+	8/59 (15%)	2/11 (18%)	22/93 (24%)	20/24 (83%)	52/187 (28%)

B: Prevalence of anal HPV, stratified by anal cytology result					
	Normal (n=51)	ASCUS (n=32)	LSIL (n=97)	ASC-H/HSIL (n=19)	Total (n=198)
Anal hc2 HPV+	16/51 (31%)	11/32 (34%)	40/96 (42%)	14/19 (74%)	81/198 (41%)
Aptima E6/E7 mRNA+	5/50 (10%)	1/31 (3%)	15/91 (18%)	9/13 (69%)	30/185 (16%)

* Cervical cytology was missing from 2 participants, HPV hc2 results were missing from 1 participant, and Aptima E6/E7 mRNA results were missing from 11.

* Anal cytology was missing from 1 participant, HPV hc2 results were missing from 1 participant, and Aptima E6/E7 mRNA results were missing from 14 participants.

ASCUS=atypical squamous cells of undetermined significance; ASC-H=atypical squamous cells cannot exclude HSIL; HPV=human papillomavirus; HSIL=high grade squamous intraepithelial lesions; LSIL=low grade squamous intraepithelial lesions; mRNA=messenger RNA.

Table 3

Risk factors for anal HPV, anal HSIL, and cervical HPV, odds ratio (95%CI)

	Anal HSIL [/]		Anal HPV DNA detected		Anal E6/E7 mRNA detected	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age per 10 years	.65 (.38–1.1)	.67 (.37–1.3)	.49 (.33–.74)	.51 (.33–.79)	.81 (.48–1.4)	.76 (.43–1.4)
CD4 (per 100 cells/mm ³)	.87 (.71–1.05)	.89 (.71–1.1)	.82 (.71–.94)	.85 (.72–1.01)	.97 (.82–1.2)	.95 (.77–1.2)
Nadir CD4 (per 100 cells/mm ³)	.94 (.69–1.3)		.87 (.69–1.1)		1.0 (.76–1.4)	
Time on ART (per year)	.96 (.83–1.12)	1.01 (.86–1.2)	.84 (.75–.95)	.89 (.78–1.02)	1.1 (.92–1.2)	1.1 (.92–1.3)
Plasma HIV-1 RNA <200 copies/mL	.83 (.31–2.2)	--	0.56 (.27–1.2)		.43 (.17–1.1)	
Anal condyloma	5.5 (1.7–17.8)	5.1 (1.5–17)	8.9 (1.9–41)	10.7 (2.1–265)	16 (4.6–58)	16 (4.5–58)
Anal symptoms	2.5 (1.2–5.4)	2.2 (1.0–5.1)	1.5 (0.82–2.6)	1.2 (.62–2.2)	1.1 (.49–2.5)	.9 (.36–2.3)

[/] Anal HSIL was defined as HSIL on cytology or histology or atypical squamous cells, cannot exclude HSIL on cytology (n=31).

ART=antiretroviral therapy; HPV=human papillomavirus; mRNA=messenger RNA; HSIL=high grade squamous intraepithelial lesions.

Table 4

Prevalence of anal squamous intraepithelial lesions according to cytology results

	NILM	LSIL	HSIL	No HRA
NILM, n=9	3 (33%)	6 (67%)	0	42
ASCUS/LSIL, n=122	56 (46%)	55 (45%)	11 (9%)	7
HSIL/ASC-H, n=17	1 (6%)	11 (61%)	6 (33%)	2

ASCUS=atypical squamous cells of undetermined significance; ASC-H=atypical squamous cells cannot exclude HSIL; HSIL=high grade squamous intraepithelial lesions; HRA=high resolution anoscopy; LSIL=low grade squamous intraepithelial lesions; NILM=no evidence of intraepithelial lesion or malignancy.