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High Prevalence of Anal Human Papillomavirus–Associated Cancer Precursors in a Contemporary Cohort of Asymptomatic HIV-Infected Women

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Background. Although human immunodeficiency virus (HIV)-infected women are at high risk for anal cancer, few data have been published on prevalence of and risk factors for anal precancer and potential screening strategies in this risk group.

Methods. A cross-sectional anal screening study was nested in a gynecological cohort of HIV-infected women. Anal swab specimens were collected for cytology and human papillomavirus (HPV) testing. High-resolution anoscopy, with biopsy when indicated, was systematically performed.

Results. Among the 171 enrolled women, median age was 47.3 years and 98% were receiving combination antiretroviral therapy. Median $CD4^+$ count was 655 cells/μL and HIV load was <50 copies/mL in 89% of subjects. High-grade anal intraepithelial neoplasia or worse (HG-AIN+) was diagnosed in 12.9% (n = 21). In multivariable analysis, a history of cervical squamous intraepithelial lesion (odds ratio [OR], 4.2; 95% confidence interval [CI], 1.1–16.4) and anal HPV-16 infection (OR, 16.1; 95% CI, 5.4–48.3) was associated with increased risk of HG-AIN+. Abnormal anal cytology and HPV-16 infection performed best as a screening strategy for HG-AIN+ histology, with positive likelihood ratios of 3.4 (95% CI, 2.3–5.1) and 4.7 (95% CI, 2.5–8.7) and negative likelihood ratios of 0.2 (95% CI, .07–.8) and 0.4 (95% CI, .2–.9), respectively.

Conclusions. HIV-infected women with a history of HPV-associated cervical disease are at increased risk for HG-AIN+ and should be offered anal cancer screening. Anal cytology and HPV-16 genotyping had the best screening performance. Anal cytology is easy to perform routinely; it may be the best candidate for screening for HG-AIN among HIV-infected women.

Keywords. anal cancer screening; HIV; women; anal intraepithelial neoplasia; human papillomavirus.

The incidence of anal cancer is increasing in the general population in both sexes [1]. Among women, previous human papillomavirus (HPV)-associated genital precancers or cancer is a known risk factor for anal intraepithelial neoplasia (AIN) and cancer [2]. Many studies have now documented that people living with human immunodeficiency virus (HIV)/AIDS, mainly men who have sex with men (MSM), but also heterosexual men and women, have an increased risk for anal cancer [3]. In HIV-infected women, the risk for anal cancer is approximately 14 times higher than among HIV-positive women diagnosed with AIDS [4], with the anal cancer rate estimated at 30–36 per 100 000 person-years [3, 5]. Despite the introduction of combination antiretroviral

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therapy (cART), there is no evidence of a declining incidence of anal cancer [3].

Among HIV-infected women, several studies have documented the course of HPV-associated cervical disease; however, few data are available for anal disease [6]. Rates of abnormal anal cytology ranging between 10% and 42% have been reported in recent studies [7, 8]. Poorly controlled HIV and concurrent cervical lesions were reported as risk factors for high-grade anal lesions [9–11]. Hessol et al observed that HPV was more prevalent in the anus than in the cervix, and that there was little correlation between severity of anal and cervical disease [11]. This suggests that natural history might not be identical at these anatomical sites.

Effective screening for and treatment of cervical lesions have dramatically decreased cervical cancer mortality [12]. Routine screening for anal cancer is not yet recommended in HIV-infected individuals [13]. Performances of cytology, high-resolution anoscopy (HRA), and HPV testing have been evaluated primarily among men [14].

The present study aimed to determine the prevalence of anal HPV infection and related lesions and to assess the risk factors for anal high-grade AIN or invasive cancer (HG-AIN+) in a prospective cohort of HIV-infected women previously enrolled in a cervical cancer screening study and subsequently followed for at least 4 years. We also estimated the performance of available screening tests.

METHODS

The data presented are the results of a nested substudy, *icube*, within the VIHGY cohort, a multicenter study of HIV-infected women conducted in 5 sites within France, aimed at providing longitudinal data on cervical HPV infection and related lesions.

Women were recruited for this substudy during their first VIHGY visit in 2012 at 3 of the VIHGY hospital sites: Paris-Pitié-Salpétrière, Colombes-Louis-Mourier, and Marseille-Sainte Marguerite. Women were eligible if they had no history of anal cancer, and were invited to participate in a 2-step study: (1) anal HPV specimen collection during the gynecological visit and (2) to undergo an HRA at specialized anal dysplasia clinics. The *icube* protocol and consent form were approved by the institutional review board of Ile-de-France VI. Informed written consent was obtained before anal HPV specimen collection and before HRA. Previous medical history, the most recent CD4 cell count, viral load, and current cART status were obtained from the women's medical record. Anal HPV samples were collected prior to collection of the cervical specimen. Swabs were placed into PreservCyt collection medium (Hologic).

To identify specific HPV genotypes, samples were tested using HPV Linear Array (Roche Molecular Systems) according to the manufacturer's instructions. Linear Array allows detection of high-risk HPV (HR-HPV) types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 64, 66, 67, 68, 69, 70, 73, 82, and IS39 and low-risk types 6, 11, 40, 42, 54, 55, 61, 62, 71, 72, 81, 83, 84, and CP6108.

Women attending HRA were asked to complete a short questionnaire regarding anal disease history and sexual behavior. Anal swab specimens were collected for cytology before the physical examination, which included a digital anorectal examination.

Two experienced clinicians (I. E. and A.-C. L.) had received formal training at the University of California, San Francisco Anal Neoplasia Clinic and trained the other anoscopists. HRA was performed without knowledge of the cytology and HPV results. Acetowhite areas were biopsied and processed for histological examination.

Cervical cytology was read centrally. Anal cytology and biopsies were read in local laboratories, blinded to the HPV result, and then reviewed centrally (T. M. D.). Anal and cervical cytology results were categorized according to the 2001 Bethesda System terminology: negative; atypical squamous cells of undetermined significance (ASC-US); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL); atypical squamous cells, cannot exclude HSIL (ASC-H); and cancer. Anal histology was reported as benign, low-grade AIN (AIN1 and condyloma), HG-AIN (AIN2, AIN3), or invasive cancer according to the most recent lower anogenital squamous terminology recommendations [15]. If no biopsy was taken, histology was considered to be benign, provided that the HRA was normal.

Statistical Analysis

Baseline characteristics of the study population were described and compared according to acceptance to undergo HRA, using the χ^2 test for categorical variables and the rank-sum test for continuous variables. The reproducibility of anal cytology diagnoses was assessed after classification in 2 categories: negative or minor cytological abnormalities (negative, ASC-US, or LSIL) vs significant cytological abnormalities (ASC-H, HSIL, or invasive cancer). The agreement between cytologists was calculated using κ with 95% confidence interval (CI). The κ values were interpreted using Altman thresholds [16].

For the analyses of factors associated with HG-AIN+, a composite endpoint of the most severe diagnosis on cytology or histology was used. In the absence of histology, the grade was based on cytology alone. If the anal cytology was unsatisfactory, and the HRA was normal, those who were HPV negative were categorized as benign. Women with unsatisfactory cytology and no biopsy were excluded from the analyses if HR-HPV was positive. HG-AIN+ was defined as histological HG-AIN+ or HSIL on cytology, in the absence of biopsy.

Univariable and multivariable logistic regression models were used for analysis of factors associated with HG-AIN+.

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The following factors were assessed: age, sub-Saharan origin, tobacco smoking, total number of sexual partners, history of anal sex, anal sex in the last year, current CD4 cell count, nadir CD4 cell count, history of cervical LSIL or worse (LSIL+), history of cervical HSIL or worse, concurrent cervical cytology result, concurrent cervical HPV-16 infection, history of anal condyloma, and concurrent anal infection with HPV-16 or with HR-HPV excluding HPV-16. Variables with $P < .15$ in the univariable analysis were considered for inclusion in the final backward multivariable model in which $P < .05$ was considered as significant. HR-HPV types were defined according to the 2009 International Agency for Research on Cancer classification of types, which were at least "probably carcinogenic to humans"—that is, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 [17].

Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of anal HR-HPV, HPV-16, cytological result, and cytology combined with HPV-16 testing were calculated for detection of HG-AIN+ histology. Statistical analyses were performed using SAS software version 9 (SAS Institute, Cary, North Carolina).

RESULTS

Participant Characteristics

Of the 352 women who had at least 1 VIHGY study visit in 2012, 319 (90.6%) accepted the invitation to the anal HPV screening *icube* substudy. Of these 319 women, 171 (54%) attended the HRA examination. The median time between HPV testing and anal cytology/HRA was 48 days (interquartile range, 20–130 days). These 171 women were significantly older (47.3 vs 43.1 years; $P = .0004$) than the 148 remaining women who did not attend HRA. The 171 women also had a significantly higher median $CD4^+$ cell count (655 vs 561; $P = .005$), more received cART and had a viral load <50 copies/mL (89.3% vs 78.9%; $P = .01$), and had a longer time since HIV diagnosis (17 years vs 14; $P = .03$). Approximately one-third (36.8%) of the 171 women were born in sub-Saharan Africa (Table 1).

Interrater Agreement

All 171 anal cytologies were reviewed centrally. The rate of unsatisfactory cytology was 5.8% at the local laboratories and 12.3% with the central pathology reader ($\kappa = 0.61$ [95% CI, .41–.82]). Table 2 shows the comparison of the anal cytology results by the cytopathologists at local laboratories vs central reader for those considered adequate for evaluation by the central reviewer. The κ was 0.61 (95% CI, .39–.83). The central cytopathologist was more likely to interpret the cytology as ASC-H or more severe.

Prevalence of Anal HPV–Associated Disease

The prevalence of HR-HPV infection was 57.9%. Infection with multiple HPV types was found in 81 of 99 (81.8%) women who were infected with an HR-HPV type. HPV-16 was detected in 17.0%.

According to the centrally reviewed anal cytology, 29.3% were abnormal, with ASC-US or LSIL in 28 (18.7%) women, ASC-H or HSIL in 15 (10.0%) women, and anal carcinoma in 1 woman (0.6%) (Table 3). Of the 169 HRAs performed, no lesions were detected in 100 women (59.2%); acetowhite areas were biopsied in the remaining 69 women. Biopsy-proven low-grade AIN was found in 18 women (28.1%), HG-AIN in 10 women (15.6%), and cancer in 1 woman. Patients were treated according to clinical practice at each center, which included surgical excision, infrared coagulation, and electrocautery. The woman with anal squamous cell carcinoma was a 48-year-old woman born in Africa. She received chemotherapy with 5-fluorouracil, mitomycin, and pelvic irradiation of 45 Gy with complete disappearance of the primary anal mass and inguinal lymph node. Her disease has now been controlled for 2 years.

Risk Factors for HG-AIN+

The results of anal cytology, HRA, histology, and HPV testing are shown in Table 4. Low-grade AIN was detected in 33 of the 163 women (20.2%; 16 histologically confirmed results and 17 LSIL cytology alone) and HG-AIN+ in 21 (12.9%; 11 histologically confirmed results and 10 HSIL cytology alone). Results of univariable and multivariable analyses of factors associated with HG-AIN+ are presented in Table 5. In the multivariable analysis, histories of cervical LSIL+ (odds ratio [OR], 4.2 [95% CI, 1.1–16.4]) and concurrent anal HPV-16 infection (OR, 16.1 [95% CI, 5.4–48.3]) were independently associated with HG-AIN+. Number of sexual partners, history of anal sex, anal sex in the last year, current CD4 count, and nadir CD4 count <350 cells/μL were not significant.

Tests Characteristics for the Detection of HG-AIN+ Histology

As shown in Table 6, anal HR-HPV testing and anal cytology combined with HPV-16 testing had the highest sensitivity for detecting HG-AIN+ histology (91%). HPV-16 genotyping and anal cytology (abnormal cytology being defined as ASC-US or more severe) had sensitivities of 64% and 82%, respectively, with no significant differences between the tests. HPV-16 testing had the highest specificity (86%). Detection of HPV-16, anal cytology, and anal cytology combined with HPV-16 testing had similar ability to detect HG-AIN+ histology with a PLR of 4.7 for HPV-16, 3.4 for cytology, and 3.1 for anal cytology combined with HPV-16 testing, and NLR of 0.4, 0.2, and 0.1, respectively.

DISCUSSION

In this contemporary cohort of HIV-infected women receiving effective cART and with regular gynecological follow-up, the prevalence of any anal lesions was 33.1%, with low-grade AIN

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Table 1. Characteristics of the 171 Women Undergoing High-Resolution Anoscopy

Characteristic	No HRA (n = 148)		HRA (n = 171)		Total No.	*P* Value
	No.	%	No.	%		
Age, y, median (IQR)	43.1 (37.2–49.3)		47.3 (41.3–51.2)			.0004
Transmission group						
Heterosexual	123	83.1	138	80.7	261	.56
Intravenous drug users	12	8.1	22	12.9	34	
Other	4	2.7	3	1.7	7	
Missing	9	6.1	8	4.7	17	
Geographic origin						
Sub-Saharan Africa	70	47.3	63	36.8	133	.06
Other	78	52.7	108	63.2	186	
Behavioral characteristics						
Cigarette smoker at baseline	44	30.6	54	33.3	98	
Missing	4		9		13	
Total No. of sexual partners						
1–4	79	53.4	66	38.8	145	.009
≥5	69	46.6	104	61.2	173	
Missing	0		1		1	
History of anal sex			60	36.1	60	
Missing			5		5	
Anal sex in the last year			13	7.6	13	
Missing			5		5	
HIV clinical characteristics						
Prior diagnosis of AIDS	31	20.9	37	21.6	68	.88
Current cART use						
cART and HIV load <50 copies/mL	116	78.9	151	89.3	267	.02
cART and HIV load >50 copies/mL	24	16.3	15	8.9	39	
Missing	1		2		3	
$CD4^+$ cell count						
Median (IQR) cells/μL	561 (410–760)		655 (476–844)			.005
Nadir $CD4^+$ count						
Median (IQR) cells/μL	186 (92–289)		222 (110–320)			.10
Gynecological clinical characteristics						
History of treatment of LSIL+	28	18.9	52	30.4	80	.01
History of LSIL+	65	43.9	94	55.0	159	.05
Concurrent cervical Pap test result						
Normal	119	81.0	142	83.5	261	.40
ASC-US/LSIL	23	15.6	26	15.3	49	
ASC-H/HSIL	5	3.4	2	1.2	7	
Missing	1		1		2	
Anal clinical characteristics						
Concurrent anal HPV-16 infection	13	8.8	29	17.0	42	.03
History of anal condyloma			21	12.4	21	
Missing			1		1	
History of anal cytologic screening			19	11.1	19	

Abbreviations: ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; LSIL, low-grade squamous intraepithelial lesion; LSIL+, cervical low-grade or high-grade squamous intraepithelial lesion or invasive cancer.

in 20.2% and HG-AIN or cancer in 12.9%. Factors associated with HG-AIN+ in multivariable analysis were a history of cervical lesion (LSIL+) and concurrent anal HPV-16 infection. Anal cytology, HPV-16 detection, and cytology combined with HPV-16 testing were the best methods to identify women with HG-AIN+ histology.

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Table 2. Interrater Agreement for Anal Cytology Interpretation in Adequate Specimens

	Central Pathology Review		
Local Laboratory	Negative or ASC-US or LSIL No. (%)	ASC-H or HSIL or ASCC No. (%)	Total No. (%)
Negative or ASC-US or LSIL, No.	131	7	138 (92.0)
ASC-H or HSIL or ASCC, No.	3	9	12 (8.0)
Total	134 (89.3)	16 (10.7)	150 (100)

Abbreviations: ASCC, anal squamous cell carcinoma; ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

To our knowledge, our study is the first to provide comprehensive data on HPV-associated anal disease among HIV-infected women, as all patients underwent cytology, HPV testing, and HRA to evaluate the prevalence and characteristics of anal HPV-associated lesions. Random biopsies of patients with normal HRA were not performed; thus, some lesions could have been missed [18]. Patients who agreed to participate in the HRA substudy differed significantly from women enrolled only in the anal HPV substudy. A history of cervical LSIL+ was more frequent among them, and anal HPV-16 was detected twice as frequently. Therefore, the prevalence of anal lesions in our study might be overestimated, whereas the power to detect risk factors and to evaluate the screening strategies was improved. Women who attended HRA also differed in terms of age and total number of sexual partners and had better HIV clinical characteristics. However, none of these factors were risk factors for HG-AIN+.

Table 3. Anal Cytology, High-Resolution Anoscopy, Anal Histology, and Human Papillomavirus Results in HIV-Infected Women (n = 171)

Characteristic	No.	%
Anal HPV (n = 171)		
HR-HPV infection	99	57.9
HPV-16 alone or with other genotypes	29	17.0
Infection with HR-HPV type other than 16	91	53.2
Multiple HPV infection[a]	81	47.4
Anal cytology (by central review) (n = 150)		
Negative	106	70.7
ASC-US/LSIL	28	18.7
ASC-H/HSIL	15	10.0
ASCC	1	0.6
Unsatisfactory specimen	21	
HRA (n = 169)		
Identification of acetowhite areas	69	40.8
Anal histology (n = 64)		
Benign	35	54.7
Low-grade AIN	18	28.1
High-grade AIN	10	15.6
ASCC	1	1.6

Abbreviations: AIN, anal intraepithelial neoplasia; ASCC, anal squamous cell carcinoma; ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; HIV, human immunodeficiency virus; HPV, human papillomavirus; HRA, high-resolution anoscopy; HR-HPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

[a] Multiple HPV infection: infection with at least 2 different genotypes including 1 HR-HPV type.

The overall prevalence of anal lesions was 33.1%, similar to what has been described in the Women's Interagency HIV Study [8]. Similar to others, we also found the prevalence of low-grade AIN to be twice as high as the prevalence of HG-AIN+ [7, 8, 19, 20]. Despite this, the prevalence of HG-AIN+ in our study population was lower than that of 30%–43% of patients reported among HIV-infected MSM [21].

Although anal cancer is a growing problem in women, there have been few studies evaluating anal cytology as a method of screening for the prevention of anal cancer in women, whether HIV infected or not. Interobserver agreement of anal cytology has been evaluated primarily in men [22, 23]. In the current study, when anal cytology was categorized as the clinically relevant categories of negative or minor cytological abnormalities vs significant cytological abnormality, we found good agreement between cytopathologists at local sites and central review with a κ at 0.61, similar to that previously reported in a study involving men [22]. The central review cytopathologist upgraded 7 cases to HSIL that had a local diagnosis of negative or LSIL. The κ value we report here for anal cytology is lower than that (0.82 [95% CI, .76–.87]) for agreement between 2 raters for liquid-based cervical cytology of samples collected among women participating in the VIHGY cohort [24]. The higher agreement observed with cervical samples might be related to much greater experience with sampling and interpreting cervical cytology compared with anal cytology [25].

In multivariable analysis, risk factors for HG-AIN+ included history of cervical lesion (low-grade or more severe, LSIL+) and concurrent anal HPV-16 infection. The mechanism underlying the relationship between a history of cervical LSIL+ and HG-AIN+ may reflect an initial HR-HPV infection of the cervix with autoinoculation from the cervicovaginal compartment to the anal canal, given the low rate of anal intercourse in our population. Having had a high-grade cervical lesion is a risk factor for anal cancer in the general population [26]. Only cervical LSIL+ was a risk factor in our study population, possibly due to the fact that the women were frequently screened for cervical lesions and that high-grade cervical lesions were previously treated. As observed in HIV-infected MSM [27], HPV-16 was associated with an increased risk of anal HG-AIN+. Similar to

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Table 4. Classification of the Presence of Either Histology or Cytology Lesion

	Abnormal HRA (n = 69)						
	Absence of Oncogenic HPV			Presence of Oncogenic HPV			
Anal cytology	Result of Anal Biopsy			Result of Anal Biopsy			Total
	No HG-AIN	HG-AIN+	Missing	No HG-AIN	HG-AIN+	Missing	
No HSIL	Absence of lesion, n = 16 Low-grade AIN, n = 4	HG-AIN+ n = 1	Absence of lesion, n = 1	Absence of lesion, n = 12 Low-grade AIN, n = 10	HG-AIN+ n = 4	Absence of lesion, n = 1 LSIL, n = 2	51
HSIL+	0	0	0	HSIL+, n = 5	HG-AIN+ n = 6	0	11
Unsatisfactory specimen	Absence of lesion, n = 3	0	0	Absence of lesion, n = 1 Low-grade AIN, n = 2	0	Unclassifiable, n = 1	7
Total	23	1	1	30	10	4	69
	Normal HRA, n = 100						
	Absence of Oncogenic HPV			Presence of Oncogenic HPV			
Anal Cytology	No Biopsy			No Biopsy			
No HSIL	Absence of lesion, n = 35 LSIL, n = 2			Absence of lesion, n = 32 LSIL, n = 12			81
HSIL+	HSIL+, n = 1			HSIL+, n = 4			5
Unsatisfactory specimen	Absence of lesion, n = 7			Unclassifiable, n = 7			14
Total	45			55			100
	Missing HRA, n = 2						
	Absence of Oncogenic HPV			Presence of Oncogenic HPV			
Anal Cytology	No Biopsy			No Biopsy			
No HSIL	Absence of lesion, n = 1 LSIL, n = 1			0			2
HSIL+	0			0			0
Total	2			0			2

Abbreviations: AIN, anal intraepithelial neoplasia; HG-AIN, anal high grade intraepithelial neoplasia, histology; HG-AIN+, high-grade anal intraepithelial neoplasia (AIN2 or AIN3) or anal squamous cell carcinoma; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion (cytology); HSIL+, high-grade squamous intraepithelial lesion, atypical squamous cells, cannot exclude HSIL, or anal squamous cell carcinoma; LSIL, low-grade squamous intraepithelial lesion (cytology).

what has been observed for the cervix [28], it is possible that HG-AIN+ associated with HPV-16 has a higher risk of progression to invasive carcinoma than those associated with non–HPV-16/-18 subtypes. Although earlier studies showed that CD4 count <200 cells/mL was a risk factor for anal cytological abnormalities in women, in our study population and in a recent article, neither CD4 count nor CD4 nadir was associated with composite cytohistology HG-AIN+ [8, 29, 30]. In fact, most of the prior studies were performed in the late 1990s, when the CD4 count threshold for starting cART was lower than at present (from <200 cells/μL in the early cART period to currently >350 cells/μL). It is possible that the women included in our study had less-severe immunodeficiency due to earlier access to cART (only 2 of them had a CD4 count <200 cells/μL at the time of the study) and that the repertoire of lymphocytes required to successfully control oncogenic HPV infection was less damaged [8]. It has also been shown that anal cancer occurs at all levels of immunosuppression [31]. As previously reported by others, we found that neither history of anal sex nor anal sex in the past year were risk factors for HG-AIN+ [8, 9]. In women, receptive anal intercourse may not be necessary to acquire anal HPV infection, as hypothesized above.

HR-HPV and HPV-16 detection had sensitivities of 91% and 64% and specificities of 44% and 86%, respectively, for detecting HG-AIN+ histology. In our study, the gynecologists, using a similar procedure as for the anal cytology, collected the anal

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Table 5. Factors Associated With the Risk of High-Grade Anal Intraepithelial Neoplasia or Worse in HIV-Infected Women

				Logistic Model					
		HG-AIN+		Univariable			Multivariable[a]		
Characteristics of Women	No.	No.	(%)	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Age at baseline									
18–39 y	30	4	(13.3)	1		.35			
40–49 y	84	8	(9.5)	0.7	(.2–2.5)				
≥50 y	49	9	(18.4)	1.5	(.4–5.2)				
Geographic origin									
Sub-Saharan Africa	60	5	(8.3)	1		.19			
Other	103	16	(15.5)	2.0	(.7–5.8)				
Cigarette smoker (8 missing)									
No	104	12	(11.5)	1		.30			
Yes	51	9	(17.6)	1.6	(.6–4.2)				
Total No. of sexual partners (1 missing)									
1–4	62	4	(6.5)	1		.06			
≥5	100	17	(17.0)	3.0	(1.0–9.3)				
History of anal sex (4 missing)									
No	101	10	(9.9)	1		.18			
Yes	58	10	(17.2)	1.9	(.7–4.9)				
Anal sex in the last year (4 missing)									
No	148	17	(11.5)	1		.14			
Yes	11	3	(27.3)	2.9	(.7–12.0)				
$CD4^+$ count									
≥500 cells/μL	115	13	(11.3)	1		.34			
350–500 cells/μL	35	5	(14.3)	1.3	(.4–4.1)				
<350 cells/μL	11	3	(27.3)	2.9	(.7–12.5)				
Nadir $CD4^+$ count									
≥350 cells/μL	32	2	(6.3)	1		.23			
<350 cells/μL	131	19	(14.5)	2.5	(.6–11.5)				
History of cervical lesion (LSIL+)									
No	74	3	(4.1)	1		.006	1		.04
Yes	89	18	(20.2)	6.0	(1.7–21.3)		4.2	(1.1–16.4)	
History of cervical lesion (HSIL+)									
No	117	13	(11.1)	1		.29			
Yes	46	8	(17.4)	1.7	(.6–4.4)				
Concurrent cervical Pap test result (1 missing)									
Negative	135	16	(11.9)	1		.38			
ASC-US/LSIL	25	3	(12.0)	1.0	(.3–3.8)				
ASC-H/HSIL/ICC	2	1	(50.0)	7.4	(.4–124.8)				
History of anal condyloma									
No	143	14	(9.8)	1		.003			
Yes	20	7	(35.0)	5.0	(1.7–14.5)				
Cervical HPV-16									
No	152	17	(11.2)	1		.03			
Yes	11	4	(36.4)	4.5	(1.2–17.1)				
Anal HPV-16									
No	136	7	(5.1)	1		<.0001	1		<.0001
Yes	27	14	(51.9)	19.8	(6.8–58.0)		16.1	(5.4–48.3)	

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Table 5 continued.

Characteristics of Women	No.	HG-AIN+ No.	HG-AIN+ (%)	Logistic Model Univariable OR	Univariable (95% CI)	Univariable *P* Value	Multivariable[a] OR	Multivariable (95% CI)	Multivariable *P* Value
Anal high-risk HPV infection other than HPV-16									
No	79	6	(7.6)	1		.06			
Yes	84	15	(17.9)	2.6	(1.0–7.2)				
Total	163	21	(12.9)						

Abbreviations: ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HG-AIN+, high-grade anal intraepithelial neoplasia or anal squamous cell carcinoma histology or HSIL cytology (composite cytology and histology endpoint); HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; HSIL+, HSIL, ASC-H, or ICC; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion; LSIL+, LSIL, HSIL, or ICC; OR, odds ratio.

[a] In the multivariable model, all variables with $P < .15$ in univariable model were selected. Then a backward model with $P < .15$ was used.

sample for HPV testing. They found it easy to perform, and it was well accepted by participants (91% of women attending their gynecology consultation participated). Anal cytology had a high sensitivity (82%) for the identification of HG-AIN+ histology. A similar high sensitivity of anal cytology has also been found in other populations such as non-HIV-infected women with HPV-associated lesions of the lower genital tract and in HIV-infected men [14, 32]. The specificity of anal cytology was 76%, lower than what has been described in HIV-uninfected women (93%), but much higher than that reported in HIV-infected men (47% [95% CI, 24%–71%]), although the reasons are unclear [14]. Collection of a specimen for anal cytology is quite simple to do, fast and painless, usually performed in a doctor's office, and does not require the use of an anoscope. Finally, anal cytology and HPV-16 testing, with a high PLR and low NLR, are easy tests to perform and might therefore be the optimum screening strategy for detection of HG-AIN+ histology among HIV-infected women, although at a higher cost.

Unlike cervical cancer, there are no guidelines for screening and treatment of anal lesions. The success of screening programs depends on a number of fundamental principles, including that (1) the target disease should be a common form of cancer with high associated morbidity and mortality; (2) test procedures should be safe, acceptable, and relatively inexpensive; and (3) an effective treatment should be available [33]. Our findings of a high prevalence of anal HPV–associated

Table 6. Clinical Performance of Human Papillomavirus (HPV) Testing and Genotyping, Anal Cytology, and Cytology Combined With HPV Typing to Detect High-Grade Anal Intraepithelial Neoplasia or Worse Histology in HIV-Infected Women

Test	High-Grade AIN or Worse Histology Yes	High-Grade AIN or Worse Histology No	Total	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	PLR (95% CI)	NLR (95% CI)
HR-HPV positive	10	75	85	91 (62–98)	44 (36–52)	12 (7–20)	98 (91–99)	1.6 (1.3–2.0)	0.2 (.03–1.4)
HR-HPV negative	1	58	59						
HPV-16 positive	7	18	25	64 (35–85)	86 (80–91)	28 (14–48)	97 (92–99)	4.7 (2.5–8.7)	0.4 (.2–.9)
HPV-16 negative	4	115	119						
ASC-US or worse	9	32	41	82 (52–95)	76 (68–82)	22 (12–37)	98 (93–100)	3.4 (2.3–5.1)	0.2 (.07–.8)
Negative cytology	2	101	103						
ASC-US or worse or HPV-16 positive	10	39	49	91 (62–98)	71 (62–78)	20 (12–34)	99 (94–100)	3.1 (2.2–4.3)	0.1 (.02–.8)
Negative cytology and HPV-16 negative	1	94	95						

2 missing HRA; 4 abnormal HRA and no biopsy; 21 unsatisfactory cytology specimens.

Abbreviations: ASC-US or worse, atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion or high-grade squamous intraepithelial lesion or anal squamous cell carcinoma; CI, confidence interval; High-grade AIN or worse, high-grade anal intraepithelial lesion or anal squamous cell carcinoma; HRA, high-resolution anoscopy; HR-HPV, high-risk human papillomavirus; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

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disease in HIV-infected women support the need for enhanced screening efforts among these women, particularly as no decrease in the incidence of anal cancer has been observed, despite the availability of cART [5]. Because early diagnosis and treatment of high-grade lesions may prevent progression to anal cancer, all women diagnosed with HG-AIN+ should be considered for treatment or at least be followed closely, as recently proposed in men [31].

Anal cytology along with HPV-16 genotyping, having the best screening performance, might be a useful strategy for identification of anal lesions. Although the effectiveness of treatment of anal HG-AIN+ has not been fully established, anal cytology and HPV testing appear to be well accepted by both gynecologists and patients; these tests could readily be offered to HIV-infected women during their gynecological examination and may facilitate the early detection and treatment of anal cancer and its precursors.

Notes

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