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Anal Cancer Screening in Men Who Have Sex With Men in the Multicenter AIDS Cohort Study

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Objective: To evaluate the prevalence of anal cytology (ACyt) abnormalities among HIV-infected and HIV-uninfected men who have sex with men (MSM).

Design: Multicenter cohort study of 723 HIV-infected and 788 HIV-uninfected MSM with ACyt, with a second ACyt collected 2 years later. A referral for high-resolution anoscopy was suggested for abnormal ACyt.

Methods: ACyt samples were collected using a polyester swab and liquid cytology media and read in a central laboratory.

Results: Prevalence of any abnormal ACyt was 25% in HIV-uninfected MSM and increased to 38%, 41%, and 47% among HIV-infected MSM with current $CD4^+$ T-cell counts $\geq$500, 350–499, and $<$350 cells/mm^3 ($P < 0.001$), respectively. Anal HPV16 DNA was also more common in HIV-infected than HIV-uninfected MSM (25% versus 16%, $P < 0.001$). Abnormal baseline ACyt together with prevalent HPV16 DNA detection was present in only 7% of HIV-uninfected MSM compared to 18% of HIV-infected MSM with current CD4 < 350, $P < 0.001$. Among HIV-infected men, 56% of the men with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions ASCs-US/LSILs and 81% of men with atypical squamous cells cannot exclude high-grade (ASC-H/)/high-grade squamous intraepithelial lesions (HSIL) had lower grade ACyt findings 18–30 months later ("regressed"). However, 19% of untreated HIV-infected men with ASC-H/HSIL cytology maintained that same grade of cytology in their second test approximately 2 years later, and 15% with ASC-US/LSIL "progressed" to ASC-H/HSIL. Abnormal ACyt had high sensitivity (96%) but low specificity (17%) for biopsy-proven HSIL.

Conclusions: Prevalence of abnormal ACyt remains elevated in HIV-infected men during the current antiretroviral therapy era.

Key Words: anal dysplasia, screening, anal cytology, MSM, HIV, MACS, anal cancer, HPV

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INTRODUCTION

Although anal cancer is rare in the general U.S. population (1.8 per 100,000),[1] its incidence has been increasing since the 1960s.[2] Most anal cancers are squamous cell carcinomas causally related to high-risk types of human

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papillomavirus (HPV), which is most prevalent in populations which practice receptive anal intercourse, such as men who have sex with men (MSM).[3] Compared with the general U.S. population, anal cancer risk is 32 times higher in HIV-uninfected MSM and 52 times higher in HIV-infected MSM.[4] Between 2001 and 2005, almost one-third of anal cancers in men in the U.S. were diagnosed in HIV-infected individuals.[4]

Although current anal cancer rates in MSM are comparable with cervical cancer rates in women before the introduction of routine screening in the 1950s, anal cancer screening and prevention efforts remain limited. Using similar methods to cervical screening, initial studies suggest that anal cytology (ACyt) can detect anal squamous intraepithelial lesions (SILs) with similar sensitivity and specificity to that seen for cervical cytology.[5–7] High levels of abnormal ACyt have been uniformly reported among unscreened HIV-uninfected (12%–32%) and HIV-infected (34%–58%) MSM.[8–11] In these studies, most abnormalities detected were atypical squamous cells of undetermined significance (ASCs-US) or low-grade SIL (LSIL). Although high-grade SIL (HSIL) cytology most likely accurately predicts the presence of true precancer, its prevalence has been lower (≤5%) in both HIV-infected and uninfected MSM,[8–11] studies suggest that because of its limited sensitivity,[12] ACyt likely underestimates HSIL prevalence.[9]

Given the high anal cancer risk in MSM, effective screening strategies are greatly needed. Prospective studies have demonstrated progression from normal anal epithelium or LSIL to HSIL over 2–4 years. Subsequent studies have also shown presence of high rates of HSIL—the putative anal cancer precursor—particularly among unscreened HIV-infected MSM.[8] It had previously been generally accepted that most biopsy-proven HSIL ($_b$HSIL) would persist and eventually progress to cancer if not treated; however, recent research has shown that some $_b$HSIL may regress without treatment.[13] In HIV-infected individuals with HSIL ACyt, there is an estimated 5-year progression rate to invasive anal cancer of 1.7%.[14]

Anal cancer screening is not widely implemented, even among the highest risk groups. This is likely because of several issues including limitations in research, clinical expertise, and practice guidelines. The efficacy of ACyt screening with linkage to treatment of $_b$HSIL to reduce anal cancer rates has not yet been tested in a randomized trial, although such a study is now underway. In addition, there are not enough clinicians trained in high-resolution anoscopy (HRA), a procedure analogous to cervical colposcopy that is needed to evaluate, diagnose, and treat $_b$HSIL. Finally, there are no consistent clinical recommendations on how MSM should be screened, either by ACyt or by proceeding directly to HRA. Although some U.S. experts currently recommend ACyt for all MSM, others call for a closer examination of relative harms and benefits before treating all $_b$HSIL.[15–18]

We conducted a study within a longitudinal cohort of HIV-infected and uninfected MSM to better understand the prevalence of abnormal ACyt and anal $_b$HSIL.

METHODS

Study Design and Population

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective study of HIV-infected and uninfected MSM, across 4 sites (Baltimore, Chicago, Pittsburgh, and Los Angeles) over 4 enrollment periods (1984–1985, 1987–1991, 2001–2003, and 2010–12). All MACS participants who attended any MACS study visits between June 2010 and July 2011 were eligible to participate in the Anal Health Study (AHS) and were offered a free ACyt test by study staff. Men with an inadequate ACyt were offered another ACyt at their next study visit 6 months later. The study protocol called for all men who enrolled to have a second ACyt 2 years later (with additional annual sampling in HIV-infected men, not presented here). The AHS was approved by the institutional review boards of each participating site. Biological and behavioral covariates of interest are routinely collected every 6 months in the MACS and were available for this analysis.

ACyt Collection

ACyt samples were collected by MACS clinicians who were trained in proper collection technique. Briefly, a water moistened polyester swab was blindly inserted into the anus to approximately 5 cm proximal to the anal verge and rotated in a spiral motion as it was withdrawn over 10–30 seconds.[6,19–21] After removal, the swab was placed into PreservCyt (Cytyc Corp., Marlborough, MA) liquid cytology media and vigorously agitated to remove cells. ACyt specimens were stored at room temperature until shipped to the laboratory for analysis.

ACyt Testing

Within 2 days of receipt, all samples were centrally processed by TriCore Reference Laboratories, Albuquerque, NM. Samples were processed as per manufacturer's protocol on a Hologic T-2000 instrument (Hologic, Bedford, MA) using a nongynecologic specimen filter and rehydrated using PreservCyt to the standard volume. A monolayer of cells was placed onto a slide using an automated system and Papanicolau staining was applied to slides before cells were visualized using microscopy. Specimens were initially screened for abnormalities by certified cytotechnologists and each was examined by a board-certified cytopathologist.

Results were reported using the Bethesda 2001 system for grading cervical cytology as follows: (1) Each sample was coded as adequate (sufficient nucleated squamous epithelial cells present) or inadequate for evaluation and (2) Adequate specimens were classified as negative (normal) or abnormal, ASC-US, or LSIL, and atypical squamous cells cannot exclude HSIL (ASC-H) or HSIL. Among 235 men whose baseline ACyt was inadequate, 161 men had a second adequate ACyt sample, a median of 11 months later; the results for these second ACyt samples were normal (76%), ASC-US (16%), LSIL (4%), and ASC-H/HSIL (3%).

During ongoing study monitoring, the frequency of technically inadequate ACyt results was greater than expected from that in previous studies.[22] To investigate and address

this, additional quality assurance steps were introduced including: (1) Monitoring and evaluation of the proportion of inadequate ACyt samples at each site; (2) Evaluation of whether switching the brand of polyester swab changed the proportion of samples deemed inadequate; (3) Comparing inadequate rates when sample was collected by the training physician (RDC) or by other MACS clinicians; (4) Comparison of ACyt results by individual MACS clinicians and by how frequently the clinicians collected anal swabs, and (5) Rereading of a subset of samples by an outside pathologist with expertise in ACyt interpretation (TMD).

Anal HPV Testing

The same sample used for ACyt was also used to test for anal HPV16 DNA using PCR by Tricore Reference Laboratory. In brief, DNA was extracted from 250 μL of the cytology sample using a Qiagen MinElute PCR Purification kit (Qiagen, Valencia, CA), 50 μL of sample was amplified using the PGMY09/11 primer system and hybridized using Linear Array (Roche Diagnostic Laboratories, Indianapolis, IN) for 37 different HPV types.

High-Resolution Anoscopy

Participants with an abnormal ACyt result were given an educational brochure about HRA with contact information for local HRA providers (the presence of at least one local HRA provider was a site activation requirement) and were referred to their primary care physician to discuss whether to have HRA. A referral thus assessed a more "real life" experience of follow-up for both abnormal ACyt and the engagement of an at-risk population, and was not a mandated study requirement. At each semiannual visit all AHS participants, regardless of their ACyt results, were asked whether they had an HRA examination and if so, copies of the HRA examination including anal biopsy were obtained.

Participants who had HRA performed for whom no biopsies were collected were considered to have had a finding of "no intraepithelial lesions" (NIL) on HRA examination. Biopsy confirmed the diagnosis of HSIL $_b$HSIL; also known as anal intraepithelial neoplasia 2+, and biopsy findings of LSIL (also known as AIN1) and no intraepithelial lesions were collected and reported using 2-tiered Lower Anogenital Squamous Terminology.[23] Participants who had abnormal ACyt and reported not having HRA were asked to answer a questionnaire to indicate the main reason why they did not have HRA from a list of options which include a text box for "other reason".

Statistical Analysis

Characteristics of enrolled participants were compared by HIV status and by ACyt results (normal versus abnormal, where abnormal was defined as ASC-US or higher) using χ^2 test for categorical and test of medians for continuous data. ACyt results were evaluated as adequate versus inadequate and the prevalence of each ACyt grade among adequate samples was reported. Cytological grade was compared in a subset of samples between the testing laboratory and a confirmatory second laboratory using percent agreement and Kappa statistic.

Serial cytology results were also evaluated among men who had ACyt within 18–30 months after their first adequate study ACyt and had not been treated for anal dysplasia during this time. We evaluated the proportion of men that "progressed" from any lower to higher cytological grade, "regressed" from any higher to lower cytological grade, or "maintained" the same cytological finding.

We explored the proportion of men with anal precancer (HSIL) or cancer diagnosed on biopsy ($_b$HSIL+) within the 3 years after the study baseline follow-up data were available to date. This was explored among 220 men who had at least one adequate ACyt sample, had no known history of $_b$HSIL before entry and who had at least one HRA at/after the first interpretable ACyt in study "entry." Cytological grade in the baseline ACyt was compared with HRA confirmed histology outcome (among 94 men who had HRA within less than 12 months of ACyt) and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported.

RESULTS

There were 1511 men who had ACyt testing as part of this study, including 723 HIV-infected and 788 HIV-uninfected men. At initial ACyt, the median age was 55 years (interquartile range = 49, 61), 72% were white, 21% were current smokers, and 36% of men had receptive anal intercourse in the past 6 months (Table 1). Median current CD4$^+$ T-cell count among HIV-infected men was 583 cells/mm^3. Only 6% (94/1511) of men had ever had an ACyt test before this study, and 1% (15/1511) had a previous confirmed diagnosis of invasive anal squamous cell cancer.

ACyt

At baseline, 28% (427/1511) of men had abnormal ACyt and in 16% (235/1511) of men the cytological specimen was inadequate (Table 1). Of the 1276 men with adequate baseline ACyt, 33% had abnormal ACyt. We did not identify any differences in the proportion of inadequate samples by provider characteristics (study sites, clinicians, and swab type used), or patient characteristics (HIV status, age), data not shown. Men with abnormal ACyt were more likely to be HIV-infected, to be current smokers, and to have more recent receptive anal intercourse partners, but were similar in terms of age and race, when compared to men with normal or inadequate ACyt results (Table 1; see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A776).

Among the 1437 men with an adequate ACyt (Fig. 1), abnormal ACyt was common (32%), and more frequent among HIV-infected (276/687, 40%) than in HIV-uninfected men (189/750, 25%; $P < 0.001$). The proportion of HIV-infected men with abnormal ACyt increased with lower CD4$^+$ T-cell count, with 38%, 41%, and 47% among men with current CD4$^+$ T-cell counts ≥500, 350–499, and <350 cells/mm^3, respectively ($P < 0.001$, Table 2). HSIL (1.5%) and ASC-H (2.4%) ACyt were uncommon overall. This difference was most notable for LSIL cytology, which was 3-fold more common in HIV-infected than in HIV-uninfected men (13.2% versus 4.5%, $P < 0.001$).

TABLE 1. Description of Study Population at Baseline AHS Visit, Stratified by Baseline ACyt Result

	Total (N = 1511)		Prevalence of ACyt result (by Row)			
	N	Col %	Normal (N = 849), %	Abnormal (N = 427), %	Inadequate (N = 235), %	*P*
HIV status						<0.001
HIV-uninfected	788	52%	62	21	17	
HIV-infected	723	48%	50	36	14	
Current ART use	723	91%	50	36	14	0.488
Race						0.138
White	1086	72%	58	27	14	
Black	271	18%	49	32	20	
Hispanic	127	8%	54	29	17	
Other	27	2%	63	22	15	
Center						0.013
Baltimore	359	24%	56	26	19	
Chicago	302	20%	54	34	12	
Pittsburgh	368	24%	61	27	12	
Los Angeles	482	32%	54	27	18	
Smoking Status						0.088
Never	410	28%	61	26	13	
Former	742	51%	56	28	15	
Current	298	21%	50	33	17	
Number of anal receptive partners in 6 mo before first ACyt						0.004
0	917	64%	58	26	16	
1	247	17%	55	30	15	
≥ 2	270	19%	51	37	12	
Before the baseline ACyt						
Ever had ACyt?						
No	1417	94%	56	28	16	0.89
Yes	94	6%	59	31	10	
Ever had HRA?	88	6%	47	45	8	<0.001
Ever diagnosed with invasive anal cancer?	15	1%	40	27	33	0.150
HIV viral lead, copies/mL (among HIV-infected)						0.148
Undetectable (≤40)	561	78%	51	34	15	
Detectable (>40)	161	22%	47	42	11	
	N	**Median**		**Median (IQR)**		
Age, yrs	1511	55	56 (50, 61)	55 (48, 60)	55 (49, 61)	0.162
Current CD4 T-cell count, cells/mm^3	723	583	595 (431, 769)	565 (401, 747)	599 (461, 808)	<0.001

IQR, interquartile range.

Anal HPV16 DNA was more common in HIV-infected than in HIV-uninfected men (25% versus 16%, $P < 0.001$). Ten percent of all men had both prevalent HPV16 DNA and abnormal ACyt at baseline (abnACyt/16+), and the frequency of this abnACyt/16+ profile increased significantly with HIV-infection and immunosuppression ($P < 0.001$, Table 2). Indeed, 18% of HIV-infected men with current CD4 < 350 had both abnormal ACyt and prevalent HPV16 DNA detected at baseline, compared with only 7% of HIV-uninfected men.

ACyt Interpretation Reproducibility

To evaluate the reproducibility of ACyt findings, a subset of selected ACyt samples (oversampled for inadequate and abnormal ACyt) was sent from the central testing laboratory for blinded reread at a second laboratory with ACyt expertise (TMD).[24] Agreement of classification of any abnormal ACyt between the 2 labs was 82%, Kappa = 0.61. Of those ACyt classified as negative (n = 59), LSIL (n = 20), HSIL/ASC-H (n = 24), and inadequate (n = 30) by the confirming laboratory and the percent agreement for ACyt grade read by the central testing laboratory was 70%, 60%, 67%, and 73%, respectively.

Comparison of ACyt 2 Years Apart

We compared the cytological classification of repeat ACyt among 447 HIV-infected and 409 HIV-uninfected men who had 2 adequate ACyt tests within 18–30 months and had

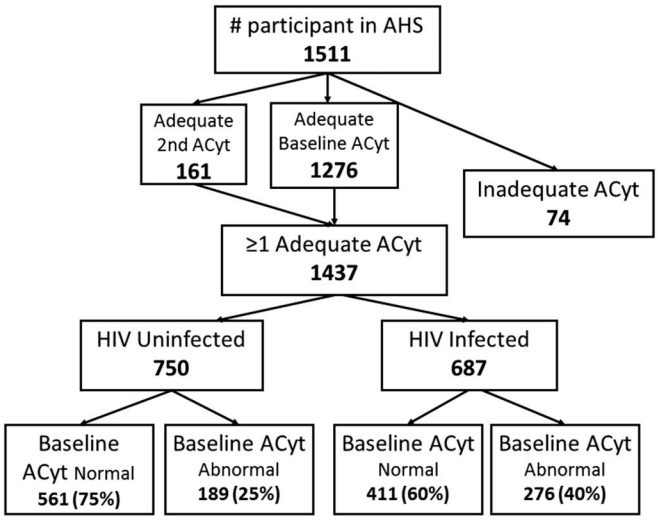

FIGURE 1. Study flowchart of the 1511 men enrolled in the MACS AHS, showing number of men with any adequate ACyt, and describing number with normal versus abnormal ACyt by HIV status.

no treatment of anal SIL during that time (Table 3). Among men with normal baseline cytology, 29% and 16% of subsequent ACyt specimens from HIV-infected and HIV-uninfected men, respectively, showed abnormalities of a higher grade (progressed) 18–30 months later (Table 3). Among men with baseline ASC-US/LSIL cytology, 61% regressed to normal cytology, whereas 15% of HIV-infected and 5% of HIV-uninfected men progressed to a higher-grade cytological classification.

Among HIV-infected men, 56% the men with ASC-US/LSIL and 81% of men with ASC-H/HSIL had lower-grade cytological findings 18–30 months later (regressed). However, 19% of untreated HIV-infected men with ASC-H/HSIL cytology maintained that same grade of cytology at their second test approximately 2 years later (Table 3), and 15% with ASC-US/LSIL progressed to ASC-H/HSIL. Among HIV-uninfected men, findings were similar but the proportion of men with ASC-US/LSIL who maintained the same cytological grade was 29% and only 5% progressed to ASC-H/HSIL (Table 3).

Identification of $_b$HSIL and Utility of Abnormal ACyt in Identifying Men With $_b$HSIL

Of the 1437 men in the AHS with adequate ACyt, 45 men were known to have had $_b$HSIL before their first ACyt, including 12 men with a history of invasive anal squamous cell cancer. Among the remaining 1392 men at risk for first $_b$HSIL diagnosis during the study, 16% (220/1392) elected to have evaluation using HRA and biopsy during study follow-up (June 2010–January 2015). Median time from baseline ACyt to first HRA in study was 0.5 years in those with abnormal ACyt and 2.4 years in those with normal ACyt.

Among 220 men with HRA during study follow-up, 87 (40%) were confirmed to have $_b$HSIL+ during study follow-up (at/after first sufficient ACyt). The proportion of men confirmed to have $_b$HSIL+ was high among both HIV-infected (38/79; 48%) and HIV-uninfected (22/61; 36%) men with abnormal baseline ACyt. Only 80 men with normal baseline ACyt had HRA during follow-up, but among these men $_b$HSIL+ was diagnosed in HIV-infected (18/53, 34%) and HIV-uninfected (9/27, 33%) men.

Ninety-four men had HRA and anal biopsy within 12 months of baseline ACyt and we restricted the analysis of utility of ACyt in identifying men with $_b$HSIL to these men. Although there was a limited population with follow-up HRA and biopsy that was based on local standard of care, abnormal ACyt had high sensitivity (96%) but low specificity (17%) for $_b$HSIL (Table 4). The positive predictive value (PPV) of abnormal ACyt for $_b$HSIL was only 27% but the negative predictive value (NPV) was 92%. If all 220 men with HRA and anal biopsy were considered, sensitivity was lower at 67% and specificity was higher at 38%.

Follow-up for Abnormal ACyt

Interview follow-up data for men with abnormal cytology showed that many participants did not undergo diagnostic follow-up using HRA. Among 465 men with abnormal baseline cytology, 139 (30%) had HRA during the

TABLE 2. First Adequate ACyt Result Among 1437 Men With Adequate ACyt, by HIV Status and Current CD4+ T-Cell Count

	N (%)				
	HIV-Uninfected	HIV-Infected			Total
Baseline ACyt	N = 750	$CD4^+ \geq 500$ N = 421	$350 \leq CD4^+ < 500$ N = 151	$CD4^+ < 350$ N = 115	N = 1437
Normal ACyt	561 (75)	261 (62)	89 (59)	61 (53)	972 (68)
Abnormal ACyt	189 (25)	160 (38)	62 (41)	54 (47)	465 (32)
ASC-US/LSIL	165 (22)	140 (33)	54 (36)	50 (43)	409 (28)
ASC-H/HSIL	24 (3)	19 (5)	8 (5)	4 (3)	55 (4)
N positive (%)					
HPV16 DNA detected*	117 (16)	96 (23)	37 (25)	31 (27)	281 (20)
Abnormal ACyt and HPV16 detected	50 (7)	48 (12)	21 (14)	21 (18)	140 (10)

*Among 1423 participants consented to testing for HPV16 DNA.

TABLE 3. Comparison of First and Second Adequate ACyt Results in 856 Participants, Taken 18–30 Months Apart, Among HIV-Infected and HIV-Uninfected Men With No Anal Squamous Intraepithelial Lesion Treatment

	%							
	HIV-uninfected				HIV-infected			
Baseline ACyt	N	Lower Grade, %	Same Grade, %	Higher Grade, %	N	Lower Grade, %	Same Grade, %	Higher Grade, %	*P*
Normal	305	—	84	16	277	—	71	29	<0.001
ASC-US/LSIL	91	66	29	5	149	56	29	15	0.075
ASC-H/HSIL	13	92	8	0	21	81	19	0	0.364
Overall	409	18	69	13	447	23	54	23	<0.001

study, and 326 did not (of whom 68% [223/326] completed the follow-up survey). Thirty-seven percent of these men reported the primary reason for not undergoing HRA was that they were unaware that HRA was recommended or that they had insufficient information to act on the diagnostic follow-up recommendation. Another 22% stated no reason or reported not being interested in a diagnostic HRA, and 11% reported that they discussed it with their doctor who said HRA was not needed. Nearly 8% of men reported forgetting or being unaware of an abnormal ACyt finding. Additional reasons reported for not getting HRA included having had ≥1 normal previous cytology finding (4%), having had HRA previously (2%), deciding to have a follow-up cytology (3%) or colonoscopy (4%) instead of HRA, financial constraints (4%), and 5% reported other reasons, including not remembering whether they had HRA.

DISCUSSION

This report demonstrates a high prevalence of abnormal ACyt among MSM in a multisite U.S. study. Abnormal ACyt and anal HPV16 DNA were more common among HIV-infected than among HIV-uninfected MSM and increased with immunosuppression. Most ASC-US and LSIL ACyt were no longer detected (regressed) on ACyt 2 years later. $_{b}$HSIL was primarily detected among HIV-infected and HIV-uninfected men with abnormal ACyt, and was also detected in men with normal ACyt. Prevalence of abnormal ACyt remains elevated in HIV-infected men during the current antiretroviral therapy era, although this was primarily due in higher prevalence of LSIL cytology.

The prevalence of abnormal ACyt observed among MSM in this study was similar to previous reports of frequent cytological abnormality (ASC-US+ and 41%–68%) but low (≤5%) prevalence of HSIL ACyt,[10,25,26] although this is not consistent with some smaller older studies reporting higher prevalence of HSIL ACyt.[27–29] The high proportion of MSM tested who had anal $_{b}$HSIL in this study is comparable with another study on MSM which reported 16% 2-year cumulative incidence,[30] and supports the need for effective screening methods in this population.

Rates of cytological inadequacy vary by study, and despite investigation into potentially contributing variables, none were identified as causal. It should be noted that although the rate of inadequacy was higher than expected, there are reports with similar rates in the literature.[10,26] However, lower rates (<5% insufficiency) are also in the literature.[22,29] This has implications for the utility of ACyt testing, because a high insufficiency rate can decrease patient interest in testing because of the need for repetition and hence decrease screening efficacy. The interpretation of ACyt varies between cytopathologists and to enhance reporting uniformity, we elected to have all ACyt read centrally for men from all study sites over the duration of the study.

As HRA was not required as part of this study, this study provides information on a more "real life" clinical referral pathway where patient and provider factors contribute to HRA referral. Although only 15% of participants had HRA data available, these data include participants from each study site including some participants with negative ACyt who also underwent HRA. Sensitivity and specificity of any abnormal ACyt to detect $_{b}$HSIL in this study were comparable with that reported in previous ACyt studies,[5,22,31,32] and comparable with that of a single cervical cytology for cervical $_{b}$HSIL.[33,34] Only a small proportion of men with normal ACyt had HRA during this study, and this group is likely not representative.

This is one of the largest studies to describe ACyt prevalence among HIV-infected MSM in the recent anti-

TABLE 4. Comparison of First Adequate Anal Cytology Result With the Biopsy Result From Subsequent HRA, Among 94 Men Who Had HRA Within Less Than 12 Months After Anal Cytology

	HRA Outcome/Biopsy			
Cytology	No Intraepithelial Lesions	$_{b}$LSIL	$_{b}$HSIL	Total
Normal (negative)	8	4	1	13
ASC-US+	43	16	22	81
Total	51	20	23	94

Utility of Any Abnormal ACyt for $_{b}$HSIL	%	n/N
Sensitivity	96	22/23
Specificity	17	12/71
Positive Predictive Value	27	22/81
Negative Predictive Value	92	12/13

ASC-H/HSIL: Atypical squamous cells cannot exclude high-grade/high-grade intraepithelial lesion on anal cytology.

$_{b}$LSIL, Low-grade squamous intraepithelial lesion on biopsy; $_{b}$HSIL, High -grade squamous intraepithelial lesion on biopsy.

retroviral treatment era, and to compare prevalence with HIV-uninfected MSM. This study underscores the increased risk of anal disease among MSM in general and especially among HIV-infected MSM. Despite this risk, the research suggests that issues of inadequate ACyt samples and low specificity of ACyt may limit the utility of this method for anal cancer screening. This study contributes to our understanding of anal precancer risk among MSM. It is clear that MSM are at high and continuing risk of anal precancer and cancer. The challenge now is how to best screen for and manage precancer to reduce the progression to invasive disease.

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