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Comparable performance of conventional and liquid-based cytology in diagnosing anal intraepithelial neoplasia in HIV-infected and -uninfected Thai men who have sex with men

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Abstract

Background—Anal cytology has increasingly been used to screen for anal intraepithelial neoplasia (AIN) among men who have sex with men (MSM) at increased risk for anal cancer. Use of liquid-based cytology has been reported to reduce fecal and bacterial contamination and air-drying artifact compared to conventional cytology. Costs associated with liquid-based cytology, however, may limit its use in resource-limited settings.

Methods—Anal swab samples were collected from MSM participants and used to prepare conventional and liquid-based cytology slides. Abnormal conventional cytology results triggered referral for high-resolution anoscopy (HRA) and biopsy. Agreement between the two cytology techniques and the positive predictive value (PPV) ratios of histology confirmed AIN were calculated.

Results—Among 173 MSM, abnormal anal cytology was identified in 46.2% of conventional and 32.4% of liquid-based slides. The results agreed in 62.4% of cases with a kappa (κ) value of 0.49 ($P < 0.001$). HIV-infected MSM had a 3.6-fold increased odds of having discordant anal cytology results (95% CI 1.6–7.8, $p = 0.001$) compared with HIV-uninfected MSM. Histological AIN 2 and 3 were identified in 20 MSM. The PPV ratios and 95% CI indicated no difference between the two techniques.

Conclusions—Conventional anal cytology may be a preferred option for resource-limited settings given comparable performances to liquid-based cytology for the detection of AIN, although the agreement between the two techniques was lower among HIV-infected MSM. Due to high prevalence of abnormal anal cytology and AIN, health systems should prepare adequate infrastructure for HRA services and AIN treatment.

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Keywords

anal cytology; conventional; liquid-based; MSM

Introduction

Men who have sex with men (MSM) are at high risk of having anal pre-cancerous lesions and anal cancer from persistent human papillomavirus (HPV) infection.^{1–5} Human immunodeficiency virus (HIV) further accentuates these risks.^{1–7} An estimated incidence rate of anal cancer is 35 per 100,000 person-years among HIV-uninfected MSM compared to 70–100 per 100,000 person-years among HIV-infected MSM.^{8, 9} Similar to the use of cervical cytology to screen for cervical pre-cancerous lesions, anal cytology has increasingly been used to screen for anal pre-cancerous lesions among at-risk populations.^{10, 11}

Low cellularity, air-drying artifact, and obscuring bacteria and fecal material are common factors which hinder adequate evaluation of anal cytologic preparations and may result in false-negative diagnoses.^{12, 13} Use of liquid-based cytology techniques has been reported to reduce fecal and bacterial contamination and air-drying artifact in anal cytology slides compared to slides prepared by conventional techniques.¹²

In resource-limited settings, use of liquid-based smears for anal cytology is limited mainly by its related cost, therefore, conventional smears are generally the standard technique used.^{14–16} The purpose of this study was to compare anal cytology results from slides prepared by a conventional technique to those prepared by a liquid-based technique. Anal samples were collected from HIV-infected and -uninfected MSM who received clinical evaluations at the Thai Red Cross AIDS Research Centre in Bangkok, Thailand.

Methods

Data for the analyses in this publication were planned as part of a larger study to evaluate the use of multidisciplinary, MSM-targeted services to enhance HIV testing and linkage to care among MSM (*MSM VCT Study*, clinicaltrials.gov identification NCT01637324), which enrolled HIV-infected and -uninfected MSM at the Thai Red Cross AIDS Research Centre in Bangkok, Thailand. Anal histologic findings from some study participants who co-enrolled in another study (*Biomarkers to Detect Anal Intraepithelial Neoplasia (AIN) in Thai MSM*, NCT01637298) were also included in the analyses. Both studies were approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University in Bangkok, Thailand.

Enrollment and follow-up of study participants

Thai men 18 years or older who had a history of anal sex with men, lived in or near Bangkok, and had documented HIV status were enrolled into the two cohorts described above. All participants gave informed consent.

Anal sample collection for anal cytology

Anal sample collection was performed at enrollment by trained study physicians and study nurses. A pre-moistened, non-lubricated Dacron swab (Solon™, Solon Manufacturing Company, Rhinelander, WI) was gently inserted approximately 5–8 cm into the anal canal until it reached the transformation zone. The swab was then removed with a twirling motion, while applying gentle pressure on the walls of the anal canal to maximize cellular yield. A conventional anal cytology slide was prepared by rolling the swab directly onto a glass slide.

The glass slide was immediately fixed in 95% ethanol. The swab was then put in a liquid-based cytology fluid (Liqui-PREP™, LGM International, Inc., Melbourne, FL), which was stored at 4°C until processed within 1 week after sample collection. To prepare the second slide, Liqui-PREP™ Cleaning Solution was added to the fluid to remove non-cellular debris before centrifugation at 1,000 g for 10 minutes. Liqui-PREP™ Cellular Base Solution was added to the cell pellet to encapsulate and facilitate cell adherence. A 50 µl aliquot of well mixed, homogenous suspension was then placed on a glass slide using a pipette and dried, resulting in a 1.5–2.0 cm diameter circle.

Anal cytology reading

Slides prepared by conventional and liquid-based techniques were stained with Papanicolaou stain. Anal cytology slides were read by cytotechnicians, blinded to the result of the slide prepared by the other technique, at the Cyto-pathological Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University in Bangkok, Thailand. The results of all anal cytology slides were confirmed by one highly experienced cytopathologist (ST). Satisfactory slides were defined as an estimated minimum of 8,000–12,000 well-preserved and well-visualized squamous epithelial cells if prepared by the conventional technique and an estimated minimum of 5,000 cells if prepared by the liquid-based technique. Presence or absence of rectal columnar, blood, and inflammatory cells in each slide were also documented. Anal cytology results were classified using the 2001 Bethesda system¹⁷ as normal, atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or carcinoma.

High resolution anoscopy and biopsy

Participants who had abnormal anal cytology results from ASC-US and above from conventional method in the *MSM VCT Study* had high resolution anoscopy (HRA) performed within 3 months of their enrollment visits. Participants who were enrolled in the *Biomarkers to Detect AIN in Thai MSM* study had HRA performed at their visits, regardless of anal cytology results. Acetic acid solution and Lugol's solution were used to aid visualization of abnormal anal tissue for biopsy. Histology results were read by pathologists, specializing in anal tissue pathology, at the Department of Pathology, Faculty of Medicine, Chulalongkorn University in Bangkok, Thailand. The highest histologic grades reported for each participant were used for data analyses.

Statistical Analysis

Statistical analysis was conducted with Stata version 11.2 (Statacorp, College Station, Tx, USA). Baseline characteristics of HIV-infected and HIV-uninfected participants were compared using Fisher's exact test, Mann-Whitney U test, or Chi-square test as appropriate.

Anal cytology and anal histology results were evaluated for correlation when samples from the same participants were available. Logistic regression was used to identify potential variables associated with discordant anal cytology results. The kappa statistic was calculated to identify the level of agreement between the conventional and liquid-based cytology tests, and a weighted kappa was calculated to assess the overall ordinal pairwise grading of the cytological results, weighting a disagreement by one diagnostic category by 0.67 and by 2 diagnostic categories by 0.33. The analysis was done on the same population, and thus prevalence is shared in the positive predictive value (PPV) calculations, and for this reason, we used PPV ratios to make inferences about differences in specificity between the two cytology tests. Confidence intervals (CI) around the ratios were calculated according to a binomial distribution.

Results

Participant characteristics

Between 18 May – 30 July 2011, we enrolled 179 MSM participants. Three participants were excluded from the analyses because they had another anal sample collection just prior to the Dacron swab collection for cytology (Figure 1). Another three participants were excluded because the duration between the initial Pap smears and histological follow-up exceeded 3 months. Among 173 participants included in the analyses, 118 were HIV-infected MSM and 55 were HIV-uninfected MSM (Table 1). Median age at first sex was 18 (interquartile range, IQR 15–20) years. Median number of sex partners within the past month was 1 (IQR 1–3), and 38.2% had receptive anal sex in the past month. Consistent condom use in the last month was reported by 43.9%. HIV-infected MSM were older than HIV-uninfected MSM (median age 35.5 vs 32 years, $P = 0.02$). Of HIV-infected MSM, 44.3% were currently on highly active antiretroviral therapy (HAART). Median CD4⁺ cell count (CD4 count) was 391 (312–549) cells/mm³ and median plasma HIV RNA was 1.60 (1.60 – 4.15) log₁₀ copies/ml.

Correlation of anal cytology results from slides prepared by conventional versus liquid-based techniques

Combining data from HIV-infected and -uninfected MSM, there was no unsatisfactory slide among those prepared by conventional technique, while 3 (1.7%) slides prepared by liquid-based technique were considered unsatisfactory (Table 2). Abnormal anal cytology from ASC-US and above was identified in 80 of 173 cases (46.2%) from conventional slides and in 56 (32.4%) from liquid-based slides. Rectal columnar epithelia were presented in 83 (48.0%) of conventional slides and 75 (43.4%) of liquid-based slides ($P = 0.136$). Squamous intraepithelial lesions were diagnosed in 16.9% of slides where rectal columnar cells were present and in 13.1% of slides without rectal columnar cells.

Anal cytology diagnosis using conventional and liquid-based slides agreed in 108 of 173 cases (62.4%), with a kappa (κ) value of 0.49 ($P < 0.001$). Excluding 3 indeterminate liquid-based slides, diagnosis within one and two diagnostic categories of each other was identified in another 51 (30%) and 11 (6.5%) of slides, giving a weighted κ of 0.45, $P < 0.001$ and an agreement of 85.7%. When data were compared using a weighted κ between HIV-infected and uninfected MSM, the cytology tests showed an overall lower agreement in HIV-infected participants (agreement = 82.1%, $\kappa = 0.39$, $P < 0.001$) than HIV-uninfected participants (agreement = 93.2%, $\kappa = 0.58$, $P < 0.001$).

Three cases of HSIL diagnosed from conventional slides were diagnosed as ASC-US (1), LSIL (1), and HSIL (1) by liquid-based slides. From liquid-based slides, 9 cases of HSIL diagnosed were read as ASC-US (2), LSIL (6), and HSIL (1) from conventional slides. Agreement between conventional and liquid-based slides for abnormal results from ASC-US and above was 75.1% ($\kappa = 48.7$, $P < 0.001$), 69.5% ($\kappa = 40.3$, $P < 0.001$) for HIV-infected MSM and 87.3% for HIV-uninfected MSM ($\kappa = 65.8$, $P < 0.001$). For abnormal results from LSIL and above, agreement between both techniques was 88.4% ($\kappa = 46.4$, $P < 0.001$), 85.6% for HIV-infected MSM ($\kappa = 46.4$, $P < 0.001$) and 94.6% for HIV-uninfected MSM ($\kappa = 37.3$, $P = 0.0024$). Agreement was 94.2% ($\kappa = 14.4$, $P = 0.01$) when results were read as HSIL and above, 92.4% for HIV-infected MSM ($\kappa = 15.0$, $P = 0.03$). There was no HSIL cases read from conventional cytology among HIV-uninfected MSM.

Being HIV-infected MSM was the only factor that was correlated with a higher risk for discordant anal cytology results by univariate analysis (OR 3.6, 95% CI 1.6–7.8, $p = 0.001$). Amongst the socio-demographic and behavioral characteristics presented in Table 1, there were no association with discordant anal cytology results. Within the HIV-infected MSM,

CD4 count, plasma HIV RNA levels and being on antiretroviral therapy were also not associated with discordant anal cytology results.

Detection of histologically confirmed AIN by abnormal conventional and liquid-based anal cytology results

Of 173 participants, 96 (55.5%) had HRA and 69 (40.0%) had biopsies performed (Table 3). By histology, AIN 1 was identified in 33 cases (47.8% of 69 participants who had biopsy performed) and AIN 2 and AIN 3 were identified in 20 (29.0%). The remaining (23.2%) had normal or benign histologic diagnoses. Of 20 AIN 2 and AIN 3 cases, 1 AIN 2 case and 6 AIN 3 cases had HSIL diagnosis by either conventional or liquid-based slides. ASC-US or higher-grade cytologic diagnoses could detect 17 AIN 2 and AIN 3 cases by conventional technique and 14 AIN 2 and AIN 3 cases by liquid-based technique (Table 4).

PPVs of abnormal conventional and liquid-based anal cytology for detecting histologically confirmed AIN

By conventional cytology, ASC-US had 28.3% and LSIL had 39.1% PPVs in predicting histologic AIN2 and AIN 3, while HSIL had 50% PPV in predicting histologic AIN 2 and AIN 3 (Table 4). Using liquid-based cytology, ASC-US had 37.8% PPV, LSIL had 46.2% PPV, and HSIL had 66.7% PPV in predicting histologic AIN 2 and AIN 3. The 95% CI around the PPV ratios indicated that the PPVs of liquid-based versus conventional cytology were not significantly different.

For HIV-infected MSM, the PPVs were 29.4% for ASC-US, 38.1% for LSIL, and 50.0% for HSIL in predicting AIN 2 and AIN 3 by conventional cytology and were 40.0% for ASC-US, 41.7% for LSIL, and 62.5% for HSIL by liquid-based cytology. The PPVs were 22.2% for ASC-US and 50.0% for LSIL by conventional cytology and 28.6% for ASC-US, 100% for LSIL, and 100% for HSIL by liquid-based cytology to predict AIN 2 and AIN 3 among HIV-uninfected MSM. The 95% CI around the PPV ratios did not indicate significant differences between the two techniques when used either in HIV-infected or HIV-uninfected MSM.

Discussion

Our study demonstrated that anal cytology results read from slides prepared by a conventional technique had good correlation with those prepared using a liquid-based technique. In resource-limited settings, use of conventional Pap slides for cytology evaluations is more practical due to the high cost of liquid-based cytology fluid and associated equipments. The LiquiPrep™ solution used in the study provides an additional advantage over other liquid-based cytology fluids in terms of cost, because an automated slide preparation machine is not needed.

For cervical cytology, liquid-based cytology techniques have been shown to provide greater^{18–20} or at least equivalent diagnostic accuracy compared to the conventional smear.¹⁴ Studies on the use of liquid-based cytology techniques for anal cytology, however, are more limited. Use of ThinPrep® was shown to yield similar diagnostic results compared to conventional smears for anal cytology, although ThinPrep® provided additional benefits in reducing fecal and bacterial contamination and air-drying artifact.^{12, 13}

Previous studies have shown a wide range of unsatisfactory rates of anal cytology slides prepared by conventional techniques (17–24%)^{12, 13} and liquid-based techniques (7–17%).^{12, 13, 21} Rectal columnar cells, an indicator that the rectal transformation zone was adequately sampled, were found more frequently on liquid-based cytology slides than conventional slides in several studies.^{12, 13, 22} The presence of an adequate amount of well-

preserved and adequately fixed cells, however, may be as important as the presence of cells from the transformation zone when evaluating the sample quality of anal cytology slides.¹³ We found a very low unsatisfactory rate for both conventional (0%) and liquid-based slides (1.7%) for anal cytology, given that the presence of rectal columnar cells was not a requirement for our study.

We identified more abnormal anal cytology cases from conventional slides than from liquid-based slides, although more ASC-H and HSIL cases tended to be diagnosed from liquid-based slides. This is in contrast to previous findings which showed equal or higher detection rates of abnormal anal cytology with the use of liquid-based techniques because of reduction of fecal material, inflammation, bacteria, and air-drying artifact.^{12, 13} The detection rate of SILs from ThinPrep slides in one study was shown to be nearly eight times higher than conventional slides.¹³ This may be due to the different technique used for LiquiPrep™, as the smear was made manually using a pipette, which may not result in a thin, evenly dispersed monolayer of cells seen with semi-automated liquid-based slide preparation and the amount of cells obtained on the slides may be less. ThinPrep® and SurePath™ slides were prepared by a processor that mechanically disperses the cells, which are then drawn onto a filter by negative pressure and transferred onto a glass slide in a monolayer. In addition, the amount of cells available in our liquid-based cytology fluid may have been reduced by the antecedent preparation of the conventional anal cytology slide. However, this was not found to be an issue in a previous study.¹²

A systematic review did not show significant differences in sensitivity and specificity of anal cytology to detect abnormal histologic diagnoses between conventional and liquid-based cytology techniques conducted across different studies.¹⁰ Although we could not comment on the absolute sensitivity and specificity in our study due to the lack of reference testing on every participant, we found the overall agreement between conventional and liquid-based cytology to be 62.4% and a κ value of 0.43, which showed moderate agreement between the two techniques. HIV-infected MSM had a 3.6-fold increased odds of having discordant anal cytology results. The overall agreement, as well as agreement when abnormal results from ASC-US and above were considered, were lower in HIV-infected than HIV-uninfected MSM. The PPV ratios demonstrated comparable performances of both techniques in detecting histologically confirmed AIN, both in HIV-infected and HIV-uninfected MSM.

Conventional cytology was able to accurately read only 1 out of 9 HSIL results on liquid-based cytology, while only 1 out of 3 HSIL results on conventional cytology was correctly read by liquid-based cytology. Of 20 cases who had histologically confirmed AIN 2 and AIN 3 in our study, if referral to HRA was triggered by HSIL alone, only 1 case would have been diagnosed on conventional cytology and 6 cases on liquid-based cytology. This is in accordance with previous findings which showed that the grade of disease on anal cytology did not correspond well to the histologic grade after biopsy,^{21, 23–26} and suggested that MSM with screening anal cytology results that are abnormal at any grade should be considered for HRA.²⁴ The high prevalence of abnormal anal cytology underlies the importance of the readiness of health systems for referral to HRA services. Setting up HRA services is challenging in both resource-rich and resource-limited settings due to the cost and the paucity of trained clinicians. Use of other tests such as HPV genotypes, E6/E7 mRNA, or abnormal cell cycle markers may be useful either as a primary screening or adjunctive screening method to anal cytology to detect high-grade AIN.^{27, 28} For this purpose, liquid-based cytology provides its advantage over conventional cytology as these adjunctive tests can be conducted from the same liquid-based cytology sample.

Our study had several limitations. We had limited statistical power to study agreement of the two cytology techniques among subset of MSM with high-grade AIN (AIN 2 and AIN 3), the putative anal precancerous lesions, since there were only 20 AIN 2 and AIN 3 cases. We also could not make definitive conclusions on the performance characteristics of anal cytology for the detection of high-grade AIN since HRA and biopsy was not performed among the majority of MSM with normal anal cytology in this study. In addition, the sequence of anal sample collection in our study could affect the amount of cells available for liquid-based cytology. Ideally, the sequence of anal sample collection could have been reversed for a subset of slides to overcome this limitation. Lastly, the reading of anal cytology and anal histology slides in our study were not performed by the same cytotechnician or pathologist. The interobserver agreement for anal cytology has been reported in other studies to be moderate with a weighted κ statistic ranging from 0.72 to 0.92.^{29, 30} All cytotechnicians and pathologists in our study have participated in quality control programs conducted during the course of the associated studies to minimize interobserver variances.

In summary, we demonstrated that anal cytology results using a conventional slide preparation technique were similar to those using a liquid-based technique, although the agreement between the two techniques was lower among HIV-infected MSM. With low agreement between anal cytology and histology diagnoses in general, programs which aim to screen for high-grade AIN would need to prepare adequate infrastructure for HRA services and treatment. The need for new biomarkers to detect high-grade AIN will become more apparent as more screening programs are established worldwide.

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Figure 1.

Flow diagram of the number of participants included in the study analyses, according to the STAndards for the Reporting of Diagnostic accuracy studies (STARD).

Table 1

Baseline characteristics of 173 men who have sex with men enrolled at the Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Characteristics	Total n=173	HIV Status		P-value
		HIV-infected n=118	HIV-uninfected n=55	
MSM VCT Study (n) Biomarkers to Detect AIN in Thai MSM study (n)	153 20	108 10	45 10	
Age, years, median (IQR)	34 (28 – 40)	35.5 (29 – 41)	32 (25.5 – 37.5)	0.02
CD4 count, cells/mm³, median (IQR)	n/a	391 (312–544)	n/a	-
HIV RNA, log₁₀ copies/ml, median (IQR)	n/a	1.60 (1.60 – 4.15)	n/a	-
Current use of HAART, n (%)	n/a	78 (44.3)	n/a	
Education, n (%) Lower than Bachelor's Degree Bachelor's Degree Higher than Bachelor's Degree	76 (43.9) 76 (43.93) 21 (12.14)	57 (48.31) 46 (38.98) 15 (12.71)	19 (34.6) 30 (54.6) 6 (10.9)	0.15
Monthly income, USD, median (IQR)	360 (240 – 600)	360 (240 – 600)	390 (232.5 – 600)	0.72
Age at first sex, years, median (IQR)	18 (15 – 20)	18 (15 – 20.25)	18 (15.5 – 20)	0.59
Number of sex partners in the past month, median (IQR) 0 1 2–5 > 5 Do not want to answer	1 (1 – 3) 1 (0.6) 56 (32.4) 44 (25.4) 11 (6.36) 61 (35.3)	1.5 (1 – 3) 1 (0.9) 37 (31.4) 34 (28.8) 4 (3.4) 42 (35.6)	1 (1 – 4) 0 (0.0) 19 (34.6) 10 (18.2) 7 (12.7) 19 (34.6)	0.51 0.11
Receptive anal sex as sexual route in the past month, n (%) No Yes No sex in the past month Do not want to answer	41 (23.7) 66 (38.2) 3 (2.89) 61 (35.3)	25 (21.2) 48 (40.7) 3 (2.5) 42 (35.6)	16 (29.1) 18 (32.7) 2 (3.6) 19 (34.6)	0.61
Consistent condom use in the past month, n (%) Yes No Do not want to answer	76 (43.9) 36 (20.8) 61 (35.3)	54 (45.8) 22 (18.6) 42 (35.6)	22 (40.0) 14 (25.5) 19 (34.6)	0.57

IQR, interquartile range; n/a, not applicable; HAART, highly active antiretroviral therapy

Table 2

Anal cytology results from slides prepared by conventional versus liquid-based techniques, combined HIV-infected and -uninfected MSM and by HIV status

Combined HIV-infected and -uninfected MSM						
Conventional cytology	Liquid-based cytology					
	Unsatisfactory	Negative	ASC-US	LSIL	HSIL ^a	Total
Negative	3	81	9	1	0	96
ASC-US	0	26	23	1	2	52
LSIL	0	7	8	3	6	25
HSIL	0	0	1	1	1	3
Total	3	114	41	6	9	173
HIV-infected MSM						
Conventional cytology	Liquid-based cytology					
	Unsatisfactory	Negative	ASC-US	LSIL	HSIL	Total
Negative	2	44	7	1	0	54
ASC-US	0	22	16	0	2	40
LSIL	0	6	7	3	5	21
HSIL	0	0	1	1	1	3
Total	2	72	31	5	8	118
HIV-uninfected MSM						
Conventional cytology	Liquid-based cytology					
	Unsatisfactory	Negative	ASC-US	LSIL	HSIL	Total
Negative	1	37	2	0	0	40
ASC-US	0	4	7	1	0	12
LSIL	0	1	1	0	1	3
HSIL	0	0	0	0	0	0
Total	1	42	10	1	1	55

ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion

^aFive atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H) results among liquid-based slides were grouped with HSIL in this table. Of these 5 cases, 1 had ASC-US and 4 had LSIL read by conventional slides. There was no ASC-H result among the conventional slides.

Table 3

Anal cytology and histology results, combined HIV-infected and -uninfected MSM

Anal histology	Anal cytology					
	No HRA	Normal HRA, No Biopsy	Normal	AIN 1	AIN 2	AIN 3
Conventional cytology						
Normal	74	11	4	2	3	0
ASC-US	0	15	9	20	1	7
LSIL	2	1	2	11	4	4
HSIL	1	0	1	0	0	1
Liquid-based cytology						
Normal	61	21	11	15	4	2
ASC-US	12	5	4	12	2	6
LSIL	1	1	1	3	0	0
HSIL ^a	0	0	0	3	2	4
Inadequate	3	0	0	0	0	0
<i>Total</i>	<i>77 (44%)</i>	<i>27 (16%)</i>	<i>16 (9%)</i>	<i>33 (19%)</i>	<i>8 (5%)</i>	<i>12 (7%)</i>
						<i>173 (100%)</i>

AIN, anal intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion. Percentages are rounded and may not always add up to 100%.

^aFive atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H) results among liquid-based slides were grouped with HSIL in this table. Of these 5 cases, 1 had ASC-US and 4 had LSIL read by conventional slides. There was no ASC-H result among the conventional slides.

Table 4

Positive predictive values of abnormal conventional and liquid-based anal cytology results for detecting histologically confirmed anal intraepithelial neoplasia

Combined HIV-infected and -uninfected MSM						
Cytology result	Histologic diagnosis	Conventional cytology		Liquid-based cytology		PPV ratio
		n	PPV, % (95% CI)	n	PPV, % (95% CI)	
		60		37		
ASC-US+ ^a	AIN 1+ ^b	48	80.0 (67.7–89.2)	32	86.5 (71.2–95.5)	1.08 (0.90–1.29)
	AIN 2+ ^c	17	28.3 (17.5–41.4)	14	37.8 (22.5–55.2)	1.34 (0.75–2.38)
		23		13		
LSIL+ ^d	AIN 1+ ^b	20	87.0 (66.4–97.2)	12	92.3 (64.0–99.8)	1.06 (0.85–1.33)
	AIN 2+ ^c	9	39.1 (19.7–61.5)	6	46.2 (19.2–74.9)	1.18 (0.54–2.57)
		2		9		
HSIL+ ^e	AIN 1+ ^b	1	50.0 (1.3–98.7)	9	100 (66.4–100)	2.00 (0.50–8.00)
	AIN 2+ ^c	1	50.0 (1.3–98.7)	6	66.7 (29.9–92.5)	1.33 (0.31–5.75)
HIV-infected MSM						
Cytology result	Histologic diagnosis	Conventional cytology		Liquid-based cytology		PPV ratio
		n	PPV, % (95% CI)	n	PPV, % (95% CI)	
		51		30		
ASC-US+ ^a	AIN 1+ ^b	40	78.4 (64.7–88.7)	25	83.3 (65.3–94.4)	1.06 (0.86–1.32)
	AIN 2+ ^c	15	29.4 (17.5–43.8)	12	40.0 (22.7–59.4)	1.36 (0.74–2.50)
		21		12		
LSIL+ ^d	AIN 1+ ^b	18	85.7 (63.7–97.0)	11	91.7 (61.5–99.8)	1.07 (0.84–1.37)
	AIN 2+ ^c	8	38.1(18.1–61.6)	5	41.7 (15.2–72.3)	1.09 (0.46–2.59)
		2		8		
HSIL+ ^e	AIN 1+ ^b	1	50.0 (1.3–98.7)	8	100 (63.1–100)	2.00 (0.50–8.00)
	AIN 2+ ^c	1	50.0 (1.3–98.7)	5	62.5 (24.5–91.5)	1.25 (0.28–5.53)
HIV-uninfected MSM						

Combined HIV-infected and -uninfected MSM						
Cytology result	Histologic diagnosis	Conventional cytology		Liquid-based cytology		PPV ratio
		n	PPV, % (95% CI)	n	PPV, % (95% CI)	
ASC-US+ ^a	AIN 1+ ^b	8	88.9 (51.8–99.7)	7	100 (59.0–100)	1.13 (0.89–1.42)
	AIN 2+ ^c	2	22.2 (2.8–60.0)	2	28.6 (3.7–71.0)	1.29 (0.24–6.99)
		2		1		
LSIL+ ^d	AIN 1+ ^b	2	100 (15.8–100)	1	100 (2.5–100)	1.00 (1.00–1.00)
	AIN 2+ ^c	1	50.0 (1.3–98.7)	1	100 (2.5–100)	2.00 (0.50–8.00)
		0		1		
HSIL+ ^e	AIN 1+ ^b	0	-	1	100 (2.5–100)	-
	AIN 2+ ^c	0	-	1	100 (2.5–100)	-

PPV, positive predictive value; CI, confidence interval; AIN, anal intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion

^a ASC-US+ includes ASC-US, LSIL, and HSIL.

^b AIN 1+ includes AIN 1, AIN 2, and AIN 3.

^c AIN 2+ includes AIN 2 and AIN 3.

^d LSIL+ includes LSIL and HSIL.

^e HSIL includes HSIL and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H).