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## COMPARISON OF TWO ANAL CYTOLOGY PROTOCOLS TO PREDICT HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA

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## INTRODUCTION

Invasive anal squamous cell cancer (IAC) is a health crisis for gay, bisexual, and other men who have sex with men (MSM), and for male-to-female transgendered women who have had sex with men (TWSM), especially within the context of HIV-coinfection where risk for

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### Conflicts of Interest:

Dr. Wiley has received grants and payment for lectures including service on speakers bureaus from Merck & Co., Inc. Dr. Young is as an Advisory Board Member for Roche Molecular Systems and Quidel Corporation. None were declared for the remaining authors.

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invasive malignancy is greatest (1-6). Currently, experts recommend using the Dacron swab for anal cytology (Pap test) specimen collection at annual and semi-annual intervals for HIV-infected and -uninfected MSM, respectively (7, 8). Dacron-swab anal cytology poorly correlates with histological evaluation of disease (9) and while cervical-cytology sampling has informed anal-cytology specimen collection, cervical screening tools may not be appropriate for analcancer screening. For example, cytobrushes with and without spatulas, cytopicks; and cotton, Dacron, rayon, and nylon-flocked (NF)-swab have been evaluated in genital sampling for pathogens, including HPV, and for cervical cytology (10-14). Cytobrushes improved cervical sampling over cotton swabs by 58-76% for detecting endocervical cells in a sample of >800 adult females >29 years of age (14) and are shown superior to Ayers spatulas (10). One report suggests the cytobrush may be effective in anal cytology,(15) but may be uncomfortable in blind sampling (16). The NF-swab is evaluated extensively for respiratory-pathogen and -cytology sampling, yielding more cells and pathogens than other collection protocols (17-20). For example, Daley et al. report >2-fold cell yield of respiratory epithelial cells using NF-over Dacron swabs, and Krech et al. report a 5-fold greater yield of *Chlamydia trachomatis*, as well as greater HPV yield using NF-over rayon-wrapped swabs in cervicovaginal tissues (17, 21). Further, unsatisfactory cervical cytology findings range from 0.3-10.9% and 0.17-2.7% for specimens preserved using PreservCyt® (Hologic, Inc., Marlborough, Massachusetts) and SurePath™ (TriPath Imaging, Inc., Burlington, N.C.) preservatives, respectively (22-25), whereas the prevalence of unsatisfactory anal cytology specimens may range from 1% to upwards of 14% (26-33).

The cervix and the anal canal are distinct anatomical targets that might easily require different sampling tools. The cervix is firm and sampling is more akin to hitting the *bullseye* on a target while the anal canal is soft and folds much like the surface of a deflated balloon. Cervical cytology uses a speculum to visually guide sample collection and the *transformation zone* (TZ) of the cervix closely approximates the cervical os. The *dentate line* lies approximately ~5 centimeters proximal to the anal verge, and the *anal TZ* immediately adjoins it about ~0.5-1 cm, just cephalad (34). Current anal cytology recommendations are to blindly insert a Dacron swab through the anal verge ~5 cm, approximate it to the anal wall, and rotate the swab using lateral pressure to sample the canal circumferentially as it is withdrawn over 10-20 seconds and stored in liquid preservative for laboratory examination (35).

Although experts suggest screening in high-risk populations is important and data show it is cost-effective, there is no current national consensus for screening methods or frequency for anal cancer screening using Papanicolaou staining (Pap test) (8, 36-38). To date, no large studies evaluate the risks or benefits of early detection and treatment for preventing anal cancer and general reluctance among clinicians for anal cytology screening may be due to the imprecision of the test, the rarity of malignancy, and the limited success of available treatments, especially within the context of HIV infection where there is poor control over HPV infections (39-41). Developing a screening strategy with modest-to-high sensitivity and specificity for anal precancers, high-grade anal intraepithelial neoplasia (HG-AIN), is an important public health goal. Thus, to evaluate the sensitivity and specificity for two cytology collection procedures and compare their efficacy for predicting HG-AIN, we evaluated a protocol using an NF-swab (Copan Diagnostics Inc., Murrieta, CA) and the Dacron swab (Thermo Fisher Scientific, Miami, OK), each with preservative, for anal cytology.

## MATERIALS AND METHODS

### Subjects and Sampling

Fifty-eight adult MSM provided written informed consent for an IRB-approved study (University of California, Los Angeles, Medical IRB2 #11-000668) and all were enrolled in 1 of 4 Multicenter AIDS Cohort Study groups. Prior to examination, examiners collected a self-reported history for HIV infection, AIDS-defining conditions, anal treatments, and presence of recent anal bleeding, discharge, or pain. Men lay in the left lateral position for the exam, with legs flexed, and the anogenital region exposed. External genitalia were examined.

### Cytology specimens

were collected in order so that the swab procedures could be compared without biasing cytology findings for specimens collected using Dacron swab (42). Briefly, a Dacron swab was lightly moistened with water, inserted blindly beyond the anal verge ~5 cm, firmly approximated to the anal wall and circularly rotated while being withdrawn over ~30 seconds; thereafter, the swab was deposited into PreservCyt® (Dacron-protocol). Early experience showed the NF swab had a larger diameter that was difficult to pass through the verge unaided. Accordingly, the protocol was amended to use a disposable anoscope (CooperSurgical, Inc., Trumbull, CT) with water-soluble lubricant lightly applied to the leading edge, allowing for comfortable passage of the instrument. Once inserted just beyond the verge, the obturator was removed, and the internal aspect of the anoscope was cleared of residual lubricant using a dry Scopette swab (Owens & Minor, Mechanicsville, VA). Thereafter, an NF-swab passed through the anoscope was approximated to the anal wall ~5 cm beyond the verge close to the anal *dentate line*, circularly rotated, using lateral pressure during withdrawal, over 20-30 seconds using a standard procedure (35). The NF-swab specimen was placed into SurePath™ preservative and the anoscope was removed (NF-protocol). For both swab protocols, swabs were agitated several minutes in the specimen containers to dislodge the collected material.

### Following cytology specimen collection

high-resolution anoscopy (HRA) was performed. First, a 4X4-gauze-padded swab soaked with 3-5% acetic acid was passed through an anoscope, the anoscope was withdrawn, and the gauze was left in place one minute before being withdrawn. The anoscope was reintroduced using water-soluble lubricant, and the anal canal was examined using a colposcope for magnification and bright light. Biopsy was performed where acetowhite lesions showed punctation, friability, or highly vascularized appearances. Where hemorrhoids were significant and obstructed the ability of the examiner to evaluate the tissue, a 2% lidocaine/1:100,000 epinephrine solution was distributed evenly, with <0.5cc in each of four quadrants, using a 25-30 gauge needle. Biopsies were performed using Tischler (Sklar, West Chester, PA) or endoscopic (Pentax Corporation, Montvale, NJ) forceps and hemostasis was achieved using Monsel's solution (ferric subsulfate; CooperSurgical, Inc., Trumbull, CT) as needed.

### Board-certified cyto- and histo-pathologists

in one CLIA-certified laboratory used standard procedures to evaluate cytology and biopsy specimens, blinded to clinical examination findings. The Bethesda Classification System (43, 44) and the International Classification of Diseases for Oncology (45) were used to evaluate cytology and histology specimens, respectively. Cytology specimens were classified as negative for intra-epithelial lesion (NIL); atypical squamous cells, either of unknown significance (ASC-US) or favoring high-grade dysplasia (ASC-H); or low- or

high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively). PreservCyt®/Dacron-swab specimens showing fewer than 1-2 nucleated squames/high-power field (hpf) and SurePath™/NF-swab specimens showing fewer than 3-6 nucleated squames/hpf were evaluated as insufficient and reported as *unsatisfactory* (46). Histology was classified as negative for specimens showing keratosis, and benign hyperplasia, acute inflammation or reactive changes in the absence of dysplasia; low-grade anal intraepithelial neoplasia or mild dysplasia (LG-AIN); and HG-AIN for AIN 2/moderate dysplasia, AIN 2- 3/moderate-to-severe dysplasia, or AIN 3/severe dysplasia. For these analyses, the histology outcome is the most severe of findings where multiple biopsy specimens were evaluated. The sensitivity and specificity for cytology to predict HG-AIN was evaluated first excluding unsatisfactory cytology and then classified.

### Sexual, behavioral, and other laboratory data

are part of the Multicenter AIDS Cohort Study repository, and in the case of one subject, by self-report. Demographic, health and illness events, and laboratory data, including HIV infection characteristics, are collected semi-annually using standardized instruments. However, to control for the effects of immune and disease characteristics, adjusted analyses were limited to HIV-infection (versus not) and chronological age at the time of the examination, evaluated as a continuous variable.

### Statistical Analysis

Descriptive and tabular analyses evaluated associations between the two protocols and cytology findings to predict risk for HG-AIN. Kappa statistics, sensitivity and specificity were estimated using SAS PROC FREQ (47). To evaluate sensitivity and specificity, cytology specimens showing ASC-US, ASC-H, LSIL or HSIL (ASC-US) were compared to findings of NIL, excluding unsatisfactory cytology from the analyses. A series of logistic regression models, using SAS PROC LOGISTIC, (48) examined the crude and adjusted odds of HG-AIN for NF- and Dacron-protocols individually, controlling for the effects of HIV-infection and age. Last, receiver operating characteristic (ROC) curves and the corresponding area under each curve ( $AUC_{ROC}$ ) were estimated for logistic regression analyses to evaluate the accuracy of Dacron- and NF-protocol cytology methods to predict HG-AIN, adjusting for the effect of age and HIV-infection (49). The  $AUC_{ROC}$  globally evaluates test accuracy, estimating the mean specificity across the range of possible sensitivity estimates for the models (49). Model fits were evaluated using the deviance statistic and were rejected or not using a 0.05 level of significance.

## RESULTS

The study sample is best described as white, HIV-infected, and older MSM (Table 1). Most participants were Caucasian (85%, 49/58), 5% (3/58) were Black, and 10% (6/58) reported “other” race groupings; 5% (3/58) reported Hispanic ethnicity. The mean age was 57.9 (+6.6) years, ranging 39.5-72 years, not varying significantly for HIV-infected/-uninfected men. Overall, 36% (21/58) showed HG-AIN by HRA and biopsy, and although estimates did not reach statistical significance, the prevalence of HG-AIN was 62% higher among HIV-infected than uninfected men (Table 1). Older and younger men were equally likely to show HG-AIN (OR=0.9,  $p=0.2$ ). For 40 of 42 HIV-infected men, infection duration could be estimated, and the average duration was 25.7 (+8.37) years, including estimated values for prevalent positive men (50). Among HIV-infected men, most reported no prior AIDS-defining conditions (79%, 33/40), and for the 36 whose data were complete, CD4+ count showed a downward trend before combined antiretroviral therapy (CART):  $\mu=-340.9$  (+/-208.8) cells/mm<sup>3</sup>/year; however, following CART, CD4+ cell counts trended positively, increasing by 284.7 (+/-171.1) cells/mm<sup>3</sup>/year.

### The prevalence of unsatisfactory cytology specimens

was 15% (9/58), where one or both specimens were independently evaluated as insufficient. Of these, 33% (3/9) showed unsatisfactory results for both specimens. Half as many NF- as Dacron-protocol cytology specimens were evaluated as unsatisfactory by experts: 7% (4/58) versus 14% (8/58).

### Agreement between NF- and Dacron protocol cytology

findings was poor to modestly poor (Table 2). Including those evaluated as unsatisfactory, 23 of 58 specimens agreed using either protocol procedure. The simple *Kappa* statistic, including 3 of 9 unsatisfactory specimens that were so classified by both procedures, was 16% (-1-33%). When values for unsatisfactory specimens were omitted from the analysis, agreement shifted somewhat; the simple and weighted *Kappa* statistics were 11% (-8-30%) and 24% (3-46%), respectively.

### Sensitivity and specificity

NF-protocol cytology showed 56% greater sensitivity for detecting HG-AIN and 26% greater specificity than did Dacron-protocol cytology (Table 3). Specifically, sensitivity and specificity for NF-protocol cytology ASC-US was 81% (58-95%) and 73% (50-89%), while Dacron protocol specimens showed 52% (30-74%) and 58% (34-80%) sensitivity and specificity, respectively.

### Cytology using NF-protocol better predicted HG-AIN on histology than did the Dacron protocol cytology

Overall, 81% (17/21) of men with ASC-US cytology on NF-protocol showed histological evidence of HG-AIN, while 52% (11/21) of Dacron-protocol cytology specimens tested similarly positive (Table 3). Put another way, findings from NF-protocol cytology would result in 50% (29/58) of men evaluated being referred for diagnostic follow-up as compared to 41% (24/58) of men showing ASC-US using Dacron protocol. However, among those that would be referred for diagnostic follow-up, a higher proportion of HG-AIN-affected men would be detected using the NF-protocol procedure over Dacron: 59% (17/29) versus 46% (11/24), respectively. Conservatively, Dacron-protocol cytology misclassified men more often as *unaffected* when compared to NF-protocol findings, i.e., cytology showed NIL and histology showed LG- or HG-AIN: 58% (15/26) vs. 36% (9/25), respectively. HIV-infection and age alone did not predict HG-AIN well in this small sample using either Dacron or NF-protocol (Table 4, Unadjusted Analyses). For example, in unadjusted analyses, HIV-infected men showed 10% greater odds of HG-AIN than did uninfected men, and each additional year in age increased the odds of HG-AIN 10% (OR=1.1 and OR=1.1, respectively, p-values>0.05, Table 4).

The **multivariate analyses** suggests that after controlling for the effects of age and HIV infection, men who show ASC-US cytology using the NF-protocol have 3-fold greater odds for HG-AIN over men showing NIL (adjusted OR=3.0 (1.5, 6.2), Table 4). However, men showing ASC-US using the Dacron-procedure showed no statistically significantly greater odds of HG-AIN than men showing NIL on (Dacron) cytology (adjusted OR=2.0 (1.0, 4.0), Table 4). In both adjusted analyses, age and HIV-infection did not independently predict HG-AIN. Last, the AUC<sub>ROC</sub> analysis suggested the accuracy of NF-cytology showing ASC-US to predict HG-AIN was 21% greater than was Dacron cytology showing similar findings: C-statistics 0.776 vs. 0.643, respectively (Fig. 1).



## DISCUSSION

Analyses showed HG-AIN was commonly detected among HIV-infected and –uninfected MSM screened using two anal cancer screening protocols. Currently, a blindly-passed Dacron swab is customary for anal cytology specimen collection (35, 51). However, sensitivity and specificity for detecting HG-AIN were higher for NF- than Dacron-protocol specimens: 81% vs. 52%, albeit confidence intervals overlapped. Sensitivity and specificity of Dacron cytology were within published ranges: 42-98% and 32-96%, respectively (9, 28, 44, 52-56). Comparatively, sensitivity and specificity of cervical cytology for detecting high-grade cervical intraepithelial neoplasia ranges 11-99% and 14-97%, respectively (57). Experts currently recommend HRA and biopsy for anal cytology > ASC-US (27, 58). Poor specificity, even in high-risk populations, makes the predictive value of positive cytology poor and escalates healthcare costs associated with unnecessary diagnostic follow-up. Nonetheless, even relatively costly strategies can improve screening-test specificity enough to provide significant overall cost-savings. For example, the addition of molecular HPV testing or repeat cytology improves the test performance of cervical cytology two-fold when compared to immediate colposcopy referral for ASC-US cytology (59). Future efforts are best directed toward developing adjunctive or alternative screening strategies that improve specificity for anal cytology, so as to assure that additional diagnostic follow-up and healthcare costs are offset by improved performance of screening tests.

This study compares two instruments and procedures for cytology collection. The NF-procedure described herein uses a small plastic anoscope to open the verge for comfortable passage of the NF-swab with larger surface area. We found no statistically significantly greater odds of HG-AIN for men showing ASC-US on Dacron cytology, but found a 3-fold greater odds of HG-AIN for NF-cytology ASC-US when compared to otherwise similar men showing NIL. Nonetheless, our sample population is small, the Dacron-procedure was systematically collected first, and some findings vary from published works. For example, Vajdic et al. report first-collected and blindly passed Dacron anal cytology was superior to anoscope-guided and second-collected Dacron specimens in a sample of 151 MSM, 63% of whom were HIV-infected (29). Conversely, Gage et al. reported no significant difference in the mean number of detectable anal epithelial cells using an endogenous retrovirus biomarker, when first-collected NF- and Dacron anal cytology specimens were compared (60). However, authors showed higher (log) cell counts for second-drawn NF- (over Dacron-swab) specimens and in the overall comparison:  $\mu=8.1$  vs.  $7.1$  ( $p=0.03$ ) and  $8.3$  vs.  $7.8$  ( $p=0.03$ ), respectively (60). Herein, the NF-protocol more precisely predicted HG-AIN and yielded half as many unsatisfactory cytology specimens despite that Dacron cytology sampling was performed first.

Few head-to-head trials have been performed and a large number of published anal cytology studies employ Dacron protocol, with few using cytobrush or other specimen collection instruments (9, 53, 55, 61-63). Since ~1950, comparative studies informed cervical cytology specimen collection and improved care, showing cervical cytobrush to be superior to swab and spatula specimen collection methods (64-70). Our experience and that of experts suggests cervical cytobrushes cause discomfort, making them ill-advised for care (16, 46). NF-swabs are designed to collect more cells and pathogens over the conventional Dacron swabs; however, PreservCyt® and SurePath™ preservatives may have differentially affected the number of insufficient cytology specimens. One large cervical cytology study showed fewer unsatisfactory cytology results attributable to SurePath™ over PreservCyt®, and that by reprocessing using SurePath™ converted 60% of insufficient specimens to satisfactory for interpretation, suggesting some differences herein may be due to specimen processing alone (22). Additionally, data show water-based lubricants are associated with higher rates of unsatisfactory cytology specimens and, in one randomized dose-response

controlled trial, showed an inverse association for one water-soluble lubricant (0.1-0.5g/vial) and cell counts/field using PreservCyt® specimens and an overall lower number of cells per field using a second (42). However, one trial showed no association between cytology findings and (0.5 mL) water-based lubricant added randomly to 1 of 2 paired PreservCyt® specimens (n=200); for ~8% discordant specimens, 8/15 showed cytology less severe in the lubricant-contaminated specimens, 5/15 showed vice versa, and 2/15 showed unsatisfactory results in one (71).

Additional, albeit modest, costs of NF-protocol sampling increase individual cytology costs. The NF-swab and anoscope add ~\$3.00 to the examination expense. However, some data show NF-swabs significantly improve the cell yield, while collecting comparable levels of nucleic acids, when compared to rayon swabs for respiratory sampling (17, 18). While an anoscope may be less comfortable than blind sampling with Dacron swab, men in this study voiced no complaints about the procedure. Thus, balancing cost, comfort, and yield of HG-AIN is an important public health goal. Herein, the NF-procedure netted a 31% greater yield of HG-AIN than Dacron-protocol but would result in 22% higher referral for diagnostic follow-up using current guidelines of ASCUS (30).

Few studies have evaluated anal cytology in older men. Our analyses showed age had little effect on risk for HG-AIN. Nonetheless, population data show men over 60 are at higher risk than younger men for invasive anal cancer,(3, 72) and that invasive malignancy may show slightly earlier onset among HIV-infected MSM than -uninfected men. For example, among the 219 anal cancer cases reported to the HIV/AIDS Cancer Match Study (N=263,254), the median age at diagnosis was ~3 years younger than expected: 42 versus 45 years (73).

A small sample size may limit these analyses and self-report data may contribute to misclassification of some characteristics. Systematic sampling may have introduced some bias; however, the ordered collection and choice of preservatives was based on randomized control trial findings that show water-soluble lubricants produce unpredictable artifacts and lower cell counts per field in PreservCyt®-preserved cytology specimens that are not seen with SurePath™(42, 71, 74). However, Dacron swab collection into PreservCyt® is the current standard for anal Pap test against which the NF-swab collection and SurePath™ were compared (35). Also, Scopette swabs removed lubricant from the internal wall of the anoscope, were not used to swab anal tissues, and facilitated unimpeded passage of the NF-swab. Albeit infrequent, some studies show wiping increases drying and crush artifact and more frequently noted limited cellularity by pathologist in cervical sampling (75, 76). Also, there may be residual confounding that is not controlled for solely by adjusting for age and HIV-infection in the multivariate analyses (77). Differences in unsatisfactory cytology specimens we measured cannot be attributed solely to the swab collection device. One meta-analysis of >2-million cervical cytology specimens analyzed in 42 studies shows the prevalence of unsatisfactory cytology was 0.3% and 1.3% for SurePath™ and PreservCyt® specimens, respectively, and three head-to-head comparisons show SurePath™ yields fewer unsatisfactory test results than does PreservCyt® (25). Last, samples were collected systematically, not randomly, as even small amounts of water-soluble lubricant might have irreparably disadvantaged the Dacron-collection procedure. Reports show first-collected Dacron cytology specimens more often detect HG-AIN over second-collected swabs, where specimens are discordant ( $p<0.001$ ) (29). Thus, if biased, our findings may conservatively estimate of the sensitivity and specificity of the NF-swab procedure.

Future research should focus on improving anal cancer screening specificity to lower overall costs and improve the predictive value of positive screening tests. For example, molecular HPV testing to triage ASC-US cervical cytology for diagnostic colposcopy has significantly reduced the overall cost of mass cervical cancer screening and improved detection of HG-



disease (78). Finding similar effective adjunctive tests for anal cytology holds promise of improving care for individuals and minimizing healthcare expenditures.

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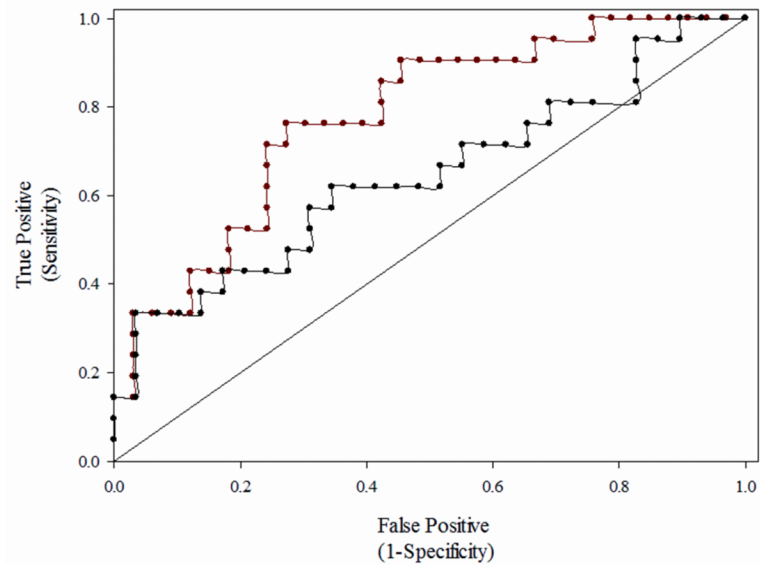
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**Figure 1.** Comparison of Receiver Operating Characteristic (ROC) Curves for Anal Cytology Showing > Atypical Squamous Cells of Unknown Significance (ASC-US) Using Dacron- (black) and NF-swab (red) Protocols to Predict High Grade Anal Intraepithelial Neoplasia, Adjusted for the Effect of Age and HIV-infection Among 58 MSM ( $C=0.643$  and  $C= 0.776$ , respectively).



**Table 1**

Sociodemographic (n=58) and HIV-infection Characteristics of Study Participants Evaluating NF- and Dacron-swab Anal Cytology Specimen Procedures

	Seropositives N (%)	Seronegatives N (%)
Total	42 (72)	16 (28)
Race <sup>a</sup>		
White	36 (86)	13 (81)
Black	3 (7)	0
Other	3 (7)	3 (19)
Hispanic ethnicity	3 (8)	0
Biopsy <sup>a</sup>		
NIL	18 (42.9)	7 (43.8)
LG-AIN	7 (16.7)	5 (31.3)
HG-AIN	17 (40.5)	4 (25.0)
	Mean (SD)	Mean (SD)
Age, years <sup>a</sup>	56.99 (5.7)	60.41 (8.2)
Range	41.2-66.1	39.5-72.0
HIV Infection Characteristics		
Years Duration: HIV infection	25.7 (8.4)	-
Range	0.5 – 34.0	-
Nadir CD4+ before HAART <sup>b,c</sup>	340.9 (208.8)	-
Range	1.0-819.0	-
Slope of CD4+ Counts before HAART	-30.84 (52.06)	-
Nadir CD4+ after HAART <sup>b,c</sup>	284.7 (171.1)	-
Range	10.0-835.0	-
Slope of CD4+ Counts after HAART	27.66 (64.77)	-
HIV-RNA peak after HAART <sup>c</sup>	4.9 (0.7)	-
HIV-RNA Set-Point before HAART <sup>c</sup>	3.8 (0.8)	-
AIDS-Diagnoses		
None	33 (79)	16 (100)
Kaposi's Sarcoma	1 (2)	-
Pneumocystis carinii Pneumonia	2 (4)	-
Cryptosporidiosis	1 (2)	-
Non-Hodgkin's Lymphoma	1 (2)	-
Candida Esophagitis	1 (2)	-
Wasting Syndrome	1 (2)	-
Pulmonary Tuberculosis	1 (2)	-
Multiple AIDS Diagnoses	1 (2)	-

<sup>a</sup>Non-significant (NS) between HIV groups

<sup>b</sup>T-lymphocytes/mm<sup>3</sup>

$c_{\log_{10}}$  transformation

**Table 2**

Comparison of Dacron- and NF-Swab Cytology Specimen Cytology Results for 58 MSM

	Dacron-swab Unsatisfactory	NIL	ASC-US	ASC-H	LG-SIL	HG-SIL	Total
Unsatisfactory	3	0	1	0	0	0	4
NIL	4	13	7	0	0	1	25
ASC-US	0	8	5	0	1	0	14
ASC-H	0	0	2	0	0	0	2
LG-SIL	1	4	1	1	1	1	9
HG-SIL	0	1	0	1	1	1	4
Total	8	26	16	2	3	3	58

Simple Kappa = 0.11 (−0.08, 0.30), and Weighted Kappa = 0.24 (0.03, 0.46). Including unsatisfactory cytology: Kappa = 0.16 (−0.01, 0.33)

**Table 3**

Comparison of Dacron- and NF-Protocol Cytology to Histology for 58 MSM Evaluated Using High-Resolution Anoscopy and Biopsy for Histology

Dacron-Swab Cytology	Histology				NF-Swab Cytology	Histology			
	Normal (Col %)	LG-AIN (Col %)	HG-AIN (Col %)	Total (Col %)		Normal (Col %)	LG-AIN (Col %)	HG-AIN (Col %)	Total (Col %)
Unsatisfactory	6(24)	2(17)	0	8 (14)	Unsatisfactory	3 (12)	1 (8)	0	4 (7)
NIL	11(44)	5(42)	10(48)	26 (45)	NIL	16 (64)	5(42)	4 (19)	25 (43)
ASC-US	7(28)	5(42)	4(19)	16 (28)	ASC-US	4 (16)	1 (8)	9 (43)	14 (24)
ASC-H	0	0	2 (10)	2 ( 3)	ASC-H	0	2 (17)	0	2 (3)
LG-SIL	1(4)	0	2(10)	3 ( 5)	LG-SIL	2 (8)	3 (25)	4 (19)	9 (16)
HG-SIL	0	0	3(14)	3 ( 5)	HG-SIL	0	0	4 (19)	4 (7)
Total (Row %)	25(43)	12(21)	21(36)	58(100)	Total (Row %)	25 (43)	12 (21)	21 (36)	58(100)

Sensitivity: 52% (Exact 95% Confidence Interval (CI): 30-74%). Specificity: 58% (CI: 34-80%)

Sensitivity: 81% (CI: 58-95%). Specificity: 73% (CI: 50-89%)

**Table 4**

Two Multivariate Analyses Evaluating Dacron- and NF-swab Procedures for Predicting HG-AIN on Histology for 58 MSM

Cytology	Unadjusted Analyses (95% Confidence Interval)		Adjusted Analyses <sup>a</sup> (95% Confidence Interval)	
	Dacron Swab <sup>b</sup>			
NIL	1		1	
ASCUS	2.0	(1.0, 4.0)	2.0	(0.9, 4.2)
Nylon-Flocked Swab <sup>b</sup>				
NIL	1		1	
ASCUS	2.7	(1.4, 5.3) <sup>b</sup>	3.0	(1.5, 6.2) <sup>c</sup>

<sup>a</sup> Adjusting for the effect of age and HIV infection (infected vs. not).

<sup>b</sup> 8 unsatisfactory Dacron-protocol cytology, n=50; and 4 unsatisfactory NF-protocol cytology, n=54.

<sup>c</sup>  $p < 0.05$