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Accuracy of Visual Inspection with Acetic Acid to detect Cervical Cancer Precursors Among HIV-infected Women in Kenya

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Abstract

Visual Inspection with Acetic Acid (VIA) is becoming a more widely recommended and implemented screening tool for cervical cancer prevention programs in low-resource settings. Many of these settings have a high prevalence of HIV-infected women. We carried out a cross-sectional validation study to define the sensitivity, specificity and predictive values of VIA among HIV-infected women. Women enrolled in HIV-care at the Family AIDS Care and Education Services clinic in Kisumu, Kenya were recruited for participation. All participants underwent VIA followed by colposcopy performed by a second, blinded clinician. At colposcopy, lesions suspicious for cervical intraepithelial neoplasia 2 or greater (CIN2+) were biopsied. Disease status was determined by final histopathologic diagnosis in women who underwent biopsies. A satisfactory colposcopy with no lesions was considered a negative result. From October 2010 to June 2012, 1432 women underwent VIA and colposcopy. Five hundred and fourteen (35.7%) women had a positive VIA, and 179 (12.2%) had CIN2+ confirmed by colposcopically directed biopsy. Sensitivity, specificity, positive and negative predictive value of VIA for CIN2+ were 86.6%, 71.6%, 30.3% and 97.4%. Specificity, but not sensitivity, increased with older age. Among older women, sensitivity was affected by CD4+ count and use of antiretroviral therapy. Although they are impacted by age and immune status, test characteristics for VIA among HIV-infected women are similar to what has been reported for general populations. Recommendations to use VIA as a screening tool should not vary by HIV status.

Keywords

Visual Inspection with Acetic Acid; HIV-infection; Kenya; Cervical Cancer Screening

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Introduction

The high burden of cervical cancer combined with the lack of infrastructure and financial resources for cytology based screening programs has led to the search for alternative strategies for cervical cancer prevention in low-resource settings.[1] The most widely implemented low-cost screening technique is visual inspection with 3-5% acetic acid (VIA).[2] Over the past decade, several large studies have validated VIA as an inexpensive and effective detection method with the potential to decrease cervical cancer incidence and mortality.[3-5] In general populations, VIA has been shown to have a similar sensitivity (60-86%) and specificity (64-94%) to human papillomavirus (HPV) testing and cervical cytology. [6-9] VIA has commonly been paired directly with cryotherapy, either at a referral site, or within the same visit for a “see-&-treat” protocol that does not include diagnostic confirmation.[10] As a result of its low-cost, ease-of-use and potential to be used as part of a single-visit strategy, VIA has been recommended by the World Health Organization (WHO) as the screening method of choice for low-resource settings.[11, 12]

The countries with the highest burden of cervical cancer are often those more impacted by the HIV epidemic, especially in sub-Saharan Africa.[13] HIV significantly increases a woman's risk for development of cervical dysplasia and cancer.[14] Until recently, however, HIV and AIDS-related mortality outweighed the risk of dying from cervical cancer in these countries. Over the past five years, expansion of the healthcare infrastructure and improved access to highly active antiretroviral therapy (HAART) has substantially decreased AIDS-related mortality.[15] This means that women are living longer and at higher risk for cervical disease in places without the resources to implement cervical cancer prevention programs. Cervical cancer screening among HIV-infected women in resource-limited countries may therefore have a substantial, positive impact on health. It is essential that HIV status be taken into account when developing screening and treatment programs in these settings.

In contrast to cervical cytology and HPV testing, which have both been validated against colposcopy and histopathologic specimens in HIV-infected women in multiple, well-designed studies,[16-22] many of the studies validating VIA in HIV-infected women have been limited by either small sample sizes [23] or use of a non-histologic reference standard.[24-26] Recent well-powered studies of VIA among HIV-positive women that use colposcopy or histology as the gold standard show a range of values for VIA positivity (15-45%), sensitivity (63%-84%) and specificity (66%-89%), suggesting that population and provider factors are important determinants of test performance.[27-30] Some authors suggest that HIV may increase the likelihood of finding inflammation and aceto-white lesions on colposcopic exam, leading to both decreased specificity and sensitivity for cervical intraepithelial neoplasia (CIN) 2/3.[18, 19] Additionally, inflammation, which may render VIA interpretation less specific, is found more frequently in cytology from HIV-infected women than uninfected women.[31, 32] These findings suggest that there may be HIV-related factors that impact both the specificity and sensitivity of VIA among HIV-infected women. As this screening method is increasingly coupled with treatment in the absence of confirmatory diagnosis, we sought to measure the sensitivity and specificity of VIA among HIV-infected women against a reference standard of colposcopy in an adequately powered study in an HIV-primary care setting in western Kenya.

Materials and Methods

Ethics Statement

This study was approved by the ethical review boards at the University of California, San Francisco and the Kenya Medical Research Institute. All women signed informed consent in English, Kiswahili or Dhluou prior to participation.

Study Design

We conducted a cross-sectional study to determine the specificity, sensitivity, positive and negative predictive value of VIA among HIV-infected women attending a cervical cancer screening program at the Family AIDS Care and Education Services (FACES) program in Kisumu, Kenya.[33] Women eligible for cervical cancer screening per the clinic screening protocol were recruited for participation in the study. Baseline eligibility criteria included women who were not pregnant, were 23 years or older, had not undergone previous screening in the FACES program, had no complaints of discharge or abnormal vaginal bleeding, and had an intact uterus and cervix. Final eligibility was confirmed by a satisfactory VIA with no evidence of cervical infection at the time of the exam (muco-purulent discharge or friability).

VIA and colposcopy were performed by study staff (one nurse and one clinical officer) who had been trained and certified to perform both exams independently and had each performed over 1500 VIAs and 300 colposcopies prior to study initiation. Clinician performance and adherence to outcome guidelines were reviewed by the study PI and co-investigators with extensive experience in VIA and colposcopy prior to study initiation. VIA was considered satisfactory if the entire squamocolumnar junction was identified. Positive VIA required identification of any well-defined aceto-white lesions at or near the squamocolumar junction. Immediately following the VIA, the clinician performing the exam left the room and colposcopy was performed by a second trained clinician who was blinded to the results of the VIA. Colposcopic assessment was done in four steps. Clinicians identified normal cervical anatomy before and after addition of acetic acid, through a green filter and after application of Lugol's Iodine. Colposcopy results were reported as normal, inflammation, probable CIN1, probable CIN2+ or suspicious for cancer. Women with normal colposcopic exams were determined to have no disease.[34] Women with unsatisfactory colposcopy or findings of probably CIN2+ on exam underwent cervical biopsy or curretage at the time of colposcopy.

Biopsy specimens were stored in 10% buffered formalin at room temperature, and sent to the Department of Human Pathology anatomical pathology lab at the University of Nairobi for interpretation. The laboratory is accredited by the Kenya National Accreditation Services (KENAS). Specimen processing services are automated, and quality assurance is ensured through weekly review of a randomly selected 10% of reported cases in a conference setting. For this study, specimens were read separately by two histopathologists who were blinded to the results of the VIA. Results were read using the Bethesda guidelines for cervical histo-pathology.[35] For specimens with more than one diagnosis (i.e. two biopsies were taken), the outcome was defined as the most severe diagnosis. Final diagnosis for discrepant results

from the same specimen was determined by consensus. Women with CIN2+ confirmed on biopsy were offered treatment with Loop Electrosurgical Excision Procedure (LEEP) in the clinic. Women with invasive cancer were offered LEEP in the clinic (Stage IA1) or referral to the provincial hospital for further staging and surgical or medical management.

Baseline demographic and clinical data was collected at the time of the visit, including age, marital status, education, reproductive history, last menstrual period, contraceptive use and current HAART regimen. The three-drug HAART regimens were those available at FACES, per the Kenya Ministry of Health Guidelines. First-line nucleoside reverse transcriptase (NRTI) based regimens contained zidovudine, stavudine or tenofivir plus lamivudine plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine or efavirenz. Second-line NRTI-based regimens included lopinavir/ritonavir, plus lamivudine or abacavir and an NRTI. Additional clinical variables were obtained from the paper file (reviewed at the time of the study visit) and the electronic medical record. These included verification of current and previous HAART regimens, WHO Stage, all documented CD4+ counts, time since HIV-diagnosis and duration of enrollment into HIV-care. CD4+ nadir has been shown to be an effective indicator of immune status as it relates to risk for cervical disease, so we defined the lowest CD4+ count measured while in care as a proxy for CD4+ nadir.

For test performance calculations for the primary outcome, VIA results were categorized as negative or positive. Colposcopy results were categorized as presence or absence of biopsy-confirmed CIN2+. We based our sample size calculations on the CIN2+ prevalence of 7% in this clinic.[36] To determine VIA sensitivity between 70 and 80% with a two-sided alpha of 0.05, we needed to enroll 1400 women.[37] Sensitivity analysis was performed for each outcome including any CIN diagnosis at the time of colposcopy. Data cleaning and statistical analysis were performed using Stata12 (StataCorp, College Station, TX).

Results

Between October 2010 and June 2012, 1439 HIV-infected women were enrolled in this study and had satisfactory VIA. Of these, 1432 (98.8%) had complete colposcopy and biopsy results (Figure 1). The average age of participants was 34.3 years (± standard deviation 8.2), median CD4+ count was 488 (interquartile range 336-655 cells/dL) and 1055 (74.0%) were on antiretroviral therapy (Table 1).

Five hundred and fourteen (35.7%) women had a positive VIA. A total of 336 (23.3%) women underwent biopsy, 51/925 (5.5%) after a negative VIA and 285/514 (55.4%) after a positive VIA. Among all women with a satisfactory VIA and complete results, 179 (12.5%) had CIN2+ confirmed by colposcopically directed biopsy. The Cohen's Kappa for agreement between VIA and colposcopy impression was 0.54 (95% CI 0.50-0.59). The positive predictive value of VIA for confirmed CIN2+ was 30.3% and the negative predictive value was 97.4% (Table 2 and Appendix A). The sensitivity and specificity were 86.6% and 71.8%. Adjusting the outcome to include any CIN (sensitivity analysis 1) decreased the sensitivity while increasing the specificity and positive predictive value (Table 2). Excluding women with CIN1 (sensitivity analysis 2) increased the specificity and positive predictive value of VIA, without impacting sensitivity.

If treatment decisions were based on results at the time of VIA, 380 (26.4%) women would not have been managed appropriately. Three hundred fifty six (24.7%) of the screened women would have received unnecessary treatment for an cervix that appeared normal on colposcopy or biopsy. However, only 24 (1.7%) women would not have received treatment for an underlying CIN2+ diagnosed at colposcopy. Those 24 women represent 13.4% of women with underlying CIN2+.

When stratified by age, VIA had a significantly higher specificity for women > 35 years (77.2% vs 68.0%, chi-square p<0.001); no significant difference was found in regards to sensitivity (82.7% vs 88.2%, chi-square p=0.33). When the entire cohort was stratified by CD4+ count (< or ≥ 350 cells/mm^3), HAART status or HAART duration (< or ≥ 6 months), there was no difference in sensitivity or specificity (data not shown). However, when the cohort was stratified by age and immune status, sensitivity was affected by factors indicating immune status. Sensitivity was higher among women with a greater CD4+ count and non-HAART users in older women, but not in the younger women. (Table 3)

Discussion

This large, clinic-based study provides well-validated estimates of the sensitivity and specificity of VIA among HIV-infected women. In our cohort of almost 1500 women, VIA performed well as a screening test for CIN2+ among HIV-infected women, with similar sensitivity and specificity to that seen in general populations.[38] The VIA positivity, as well as the sensitivity and specificity estimates, were within the range of similar studies of HIV-infected women, adding to the existing body of literature and providing support for the performance of these tests by clinical officers and nurses.[27-30] In our cohort, test specificity increased with increasing age, without a significant drop in sensitivity. This differs from prior studies, perhaps because we had an overall younger cohort and used 35 as the age cut-off for stratification.[29] When the cohort was stratified by age, sensitivity and negative predictive value were higher among women with higher CD4+ counts and in non-HAART users in the >35 years age group, but not in younger women. This finding of improved sensitivity of VIA among women with a healthier immune status supports previous data.[30]

One of the main strengths of VIA is the immediate availability of results, which allows it to be coupled directly with treatment, either the same day or at a referral site. There is some concern that skipping histologic confirmation leads to overtreatment of women, resulting in increased costs, referral burden and potential for short- and long-term complications. The positive predictive value of VIA for CIN2+ is only 30%. If treatment decisions were based solely on VIA results in our cohort, 25% of women attending screening would have been treated unnecessarily. However, in the sensitivity analysis broadening the outcome to include CIN1, which may reflect transient infection with HPV, the positive predictive value of VIA was 67%. Although we are aware of the lack of precision introduced by the combined visual and histologic diagnosis of CIN, including it as a final outcome reduces the proportion of women with completely normal cervical exams to 11%. Further, in most low-resource settings, VIA has been coupled with cryotherapy, which also has extremely low rates of short- and long-term side effects, including HIV-shedding outcomes.[39, 40]

This well-powered study allowed us to evaluate the sensitivity and specificity of VIA among HIV-infected women with relative precision and to evaluate the impact of clinical and demographic factors on test performance. An additional strength of the study design includes the use of colposcopy with biopsy instead of cytology. Further, the clinicians performing the colposcopy were blinded to the VIA result in order to reduce verification bias. Although performing biopsy only for positive colposcopic findings is a common validation method for cervical cancer screening tests, especially those done in resource-limited settings, [27, 28, 30] the visual nature of both VIA and colposcopic assessment of the cervix to direct biopsies are intrinsically related, and likely result in overestimation of test sensitivity. In our study, although 55% of women with positive VIA had biopsies, only 23% of the entire cohort had a sample for histologic interpretation. The final estimation of sensitivity and specificity are likely overestimated in this study because we did not perform random cervical biopsies or endocervical curettage in all women with a negative colposcopy. Although this would have increased the accuracy of our outcome measure [41], it was our opinion that these additional procedures would have been unacceptable to many participants, to our community advisory board and to institutional review boards, with little additional yield in terms of clinical management of disease, as women are currently treated for diagnoses of CIN2 or CIN3.[42] Additionally, we limited our sample to women with satisfactory VIA, in order to have a dichotomour result for our calculations. This potentially would inflate the value of VIA, however in our setting, less than 1% of women had unsatisfactory VIA.

This study contributes to the ongoing evaluation of VIA for use in resource-limited settings, either in HIV-care and treatment clinics or in high HIV-prevalence areas. The test characteristics presented here will help with program planning, including protocol development and resource allocation. Our findings suggest that VIA performed favorably compared to estimates from studies including HIV-negative women or general populations. Based on these findings, HIV status should not alter recommendations for the use of VIA as a screening technique in low-resource settings or in populations with a significant proportion of HIV-infected individuals.

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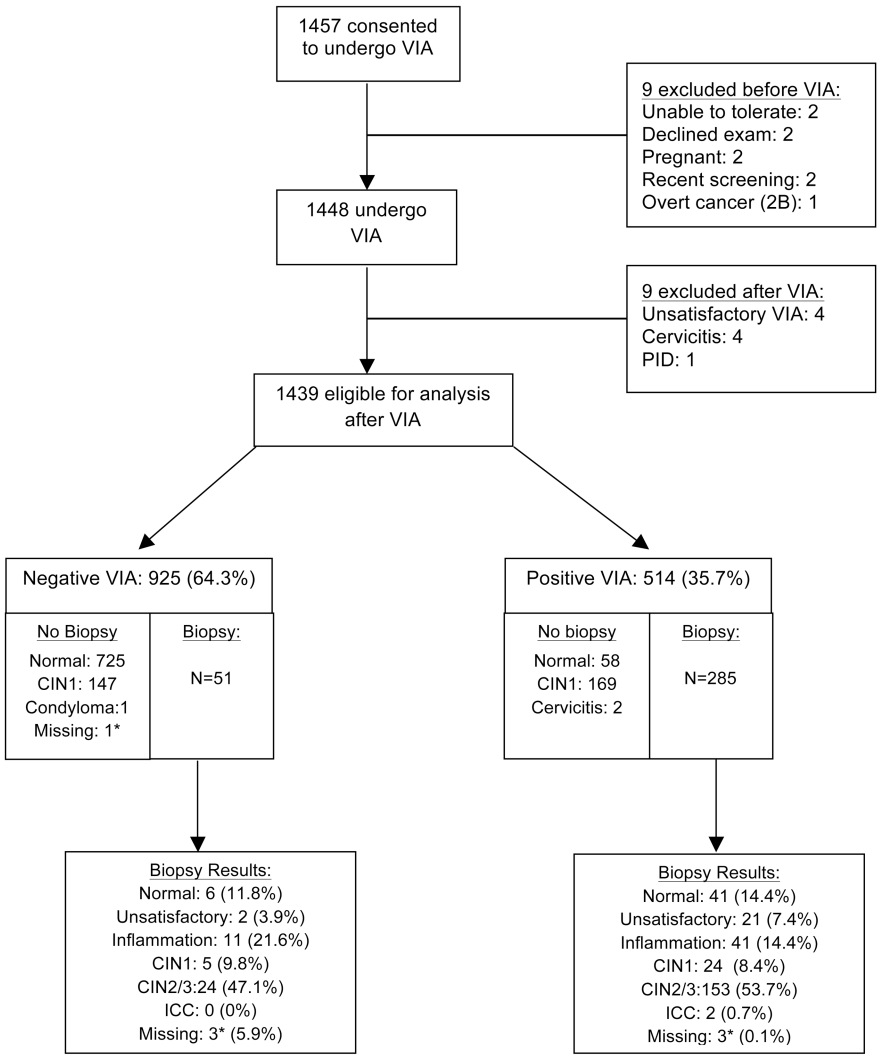
Abbreviations

VIA	Visual Inspection with Acetic Acid
CIN2+	Cervical Intraepithelial Neoplasia 2+
FACES	Family AIDS Care and Education Services
HAART	Highly Active Antiretroviral Therapy
HPV	Human papillomavirus
LEEP	Loop Electrosurgical Excision Procedure
WHO	World Health Organization

Novelty and Impact

This large study of HIV-infected women provides precise estimates of the sensitivity, specificity, positive and negative predictive value of visual inspection with acetic acid. This builds on the current body of literature, in which quality and outcomes vary widely. These estimates will help planners determine the program needs, efficacy and wider impact of VIA, which is being more and more widely implemented in low-resource and high-HIV prevalence settings.



*Women with missing colposcopy or biopsy results were excluded from the final analysis, so the final number of women was 1432.

Figure 1. Flowsheet of study enrollment, eligibility and outcomes

Table 1
Baseline characteristics of women screened with VIA (n=1432)

Characteristic	Mean/median or n	SD, (IQR) or %[1]
Age (mean, yrs)	34.3	8.2
Relationship Status:		
Single	116	8.2%
Married	770	54.1%
Separated	149	10.5%
Widowed	388	27.3%
Number of current partners		
0	362	25.3%
1	1045	73.0%
>1	25	1.8%
Number of lifetime partners (median)	4.0	(3-5)
Employed	1418	99.2%
Reproductive History		
Gravida (median)	3.0	(2-4)
Parity (median)	3.0	(1-4)
Currently experiencing vaginal symptoms[2]	973	67.5%
Post-menopausal	128	8.8%
Had c-section	167	11.7%
Current Contraceptive Use		
Any contraception	536	37.3%
Hormonal contraception	423	29.5%
Contraception by Type:		
Oral contraceptives	58	4.0%
Injectable (Depo Provera™)	298	20.1%
Implant (Jadelle™ or Norplant)	68	4.7%
Intrauterine Device in-situ (Copper)	11	0.8%
Female Sterilization	74	5.1%
Condom only	27	1.9%
HIV-related Characteristics		
Time since first HIV-diagnosis (mean, mo)	39.0	26.2
Most Advanced WHO Stage		
1	444	31.0%
2	421	29.4%
3	442	30.9%
4	124	8.7%
CD4+ nadir, cells/dL[3]	510	259.5
200	140	9.8%
200 - 349	240	16.8%
350 - 499	354	24.7%

Characteristic	Mean/median or n	SD, (IQR) or %[1]
>=500	698	48.7%
On HAART	1055	74.0%
Duration on HAART (mo)	22.7	20.7
On HARRT >=6 months	783	74.2%
On first-line HAART regimen[4]	988	93.7%

[1] Mean with standard deviation was used to describe normally distributed variables. Median with IQR was used to describe non-normally distributed variables.

[2] Vaginal symptoms included abnormal discharge, itching or pain with intercourse

[3] Lowest documented CD4+count since enrollment into care

[4] First-line regimens included one nucleoside-reverse transciptase inhibitor (AZT, D4T or TDF) and two non-nucleoside reverse transcriptase inhibitors (NVP or EFV & 3TC). Second-line regimens contain a protease inhibitor (LPV/RTV) with one NRTI and one NNRTI.

Table 2

Sensitivity, Specificity, Positive and Negative Predictive Values of VIA in primary and sensitivity analyses

VIA Test Performance, % (95% CI)	Base Case[1] n=1442		Sensitivity Analysis 1: Any CIN[2] n=1442		Sensitivity Analysis 2: Excluding CIN1[3] n=1088	
Sensitivity	86.6%	(80.7-91.2%)	66.3%	(62.0-70.3%)	86.6%	(81.1-91.6%)
Specificity	71.6%	(69.0-74.1%)	81.9%	(79.4-84.5%)	82.0%	(79.5-84.5%)
PPV	30.3%	(26.4-34.5%)	67.7%	(63.5-71.7%)	48.6%	(42.8-54.1%)
NPV	97.4%	(96.1-98.3%)	80.9%	(78.1-83.4%)	96.9%	(95.6-98.1%)
Test Positivity Rate	35.7%	(33.2-38.2%)	35.7%	(33.2-38.1%)	29.3%	(26.6-32.0%)
Prevalence	12.5%	(10.8-14.2%)	36.5%	(33.9-39.0%)	16.5%	(14.0-18.5%)
Likelihood Ratio +	3.05	(2.7-3.4)	3.66	(3.1-4.3)	4.80	(4.2-5.7)
Likelihood Ratio −	0.19	(0.13-0.27)	0.41	(0.36-0.47)	0.16	(0.11-0.23)
2 × 2 tables for Base Case and Sensitivity Analysis						
	CIN2+	Not CIN2+	CIN1+	Not CIN1+	CIN2+	Not CIN2+
Positive	155	356	346	165	155	164
Negative	24	897	176	745	24	745

[1] Base case analysis: true positives limited to biopsy-confirmed CIN2+. All other diagnoses were considered negative.

[2] Sensitivity Analysis 1: true positives included any biopsy confirmed or visual impression of CIN1.

[3] Sensitivity Analysis 2: true positives limited to biopsy-confirmed CIN2+, true negatives limited to negative colposcopy or negative biopsy. All other diagnoses excluded from analysis

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Table 3

Clinical performance of VIA and CIN2+ prevalence stratified by age and HIV-related characteristics.

35 years and younger (n=859)						
VIA Performance, % (95% CI)	**CD4<350 n=239**	**CD4>=350 n=620**	**p-value**	**Not on HAART n=259**	**On HAART n=600**	**p-value**
Sensitivity	91.4% (81.0-97.1)	85.5% (75.0-92.8)	0.31	89.8% (82.0-95.0)	89.9% (82.2-95.0)	0.31
Specificitiy	66.3% (58.9-73.1)	68.2% (64.2-72.1)	0.63	67.7% (63.4-71.8)	67.7% (63.5-71.8)	0.98
PPV	46.5% (37.1-56.1)	25.2%(19.8-31.3)	<0.01	35.2%(29.3-41.5)	35.2% (29.3-41.4)	0.06
NPV	96.0% (90.9-98.7)	97.4% (95.3-98.8)	0.42	97.1% (94.8-98.6)	97.2% (94.9-98.6)	0.88
Prevalence	24.3% (19.0-30.2)	11.1% (8.8-13.9)	<0.01	16.0% (13.0-19.5)	16.3% (13.0-19.5)	0.05
Test Positivity	47.7% (41.3-54.1)	37.7% (33.9-41.6)	0.008	41.7% (37.7-45.6)	41.7% (37.7-45.6)	0.29
Over 35 years (n=573)						
VIA Performance, % (95% CI)	**CD4<350 n=141**	**CD4>=350 n=432**	**p-value**	**Not on HAART n=118**	**On HAART n=455**	**p-value**
Sensitivity	68.2% (45.1-86.1)	93.3% (77.9-99.2)	0.03	100% (69.2-100.0)	78.6% (63.2-89.7)	<0.01
Specificitiy	73.7% (64.8-81.4)	77.9% (73.5 -81.9)	0.34	80.6% (71.8-87.5)	76.3% (71.6-80.1)	0.32
PPV	32.6% (19.5-48.0)	23.9% (16.5-32.7)	0.26	32.3% (16.7-51.4)	25.0% (17.9-33.3)	0.41
NPV	92.6% (85.3-97.0)	99.4% (97.8-99.9)	0.002	100% (95.8-100.0)	97.3% (94.8-98.7)	<0.01
Prevalence	15.7% (10.0-22.7)	6.9% (4.-9.7)	0.002	8.5% (4.1-15.0)	9.2% (6.7-12.3)	0.80
Test Positivity	32.6% (24.9-40.7)	27.0% (22.8-31.2)	0.18	26.3% (18.2-34.3)	29.0 (24.8-33.2)	0.56

p-values shown are for chi-square.