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Comparing Papanicolau smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy

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Abstract

Background—A rigorous comparison of cervical cancer screening methods utilizing data on immune status, antiretroviral therapy (ART) and colposcopy-directed biopsy has not been performed among HIV-positive women.

Methods—Between June and November 2009, 500 HIV-positive women were enrolled at an HIV treatment clinic in Nairobi, Kenya, and underwent Papanicolau (Pap) smear, visual inspection with acetic acid (VIA), human papillomavirus (HPV) and colposcopy-directed biopsy (gold standard). Positive Pap smear (ASCUS+, LSIL+, HSIL+), VIA, HPV and their combinations were compared with CIN2/3+. Sensitivity, specificity and AUC (sensitivity and 1–specificity) were

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Conflicts of interest
None of the authors has a major conflict of interest in this study.

compared using pairwise tests and multivariate logistic regression models that included age, $CD4^+$ cell count and ART duration.

Results—Of 500 enrolled, 498 samples were collected. On histology, there were 172 (35%) normal, 186 (37%) CIN1, 66 (13%) CIN2, 47 (9%) CIN3 and 27 (5%) indeterminate. Pap (ASCUS+) was the most sensitive screening method (92.7%), combination of both Pap (HSIL+) and VIA positive was the most specific (99.1%) and Pap (HSIL+) had the highest AUC (0.85). In multivariate analyses, $CD4^+$ cell count of 350 cells/μl or less was associated with decreased HPV specificity ($P = 0.002$); ART duration of less than 2 years was associated with decreased HPV ($P = 0.01$) and VIA ($P = 0.03$) specificity; and age less than 40 years was associated with increased VIA sensitivity ($P < 0.001$) and decreased HPV specificity ($P = 0.005$).

Conclusion—Pap smear is a robust test among HIV-positive women regardless of immune status or ART duration. Results should be cautiously interpreted when using HPV among those younger, immunosuppressed or on ART less than 2 years, and when using VIA among those aged 40 years or more.

Keywords

cervical cancer screening; HIV-1; human papillomavirus; Papanicolau smear; visual inspection with acetic acid

Introduction

Cervical cancer is the second most frequently diagnosed cancer among women worldwide with the highest incidence taking place in resource-limited countries, particularly in sub-Saharan Africa where approximately 75 000 new cases occur each year [1]. Sub-Saharan Africa is also home to 22.9 million HIV-infected people [2]. The proximity of these two diseases highlights the need to understand how HIV infection and its treatment may interact with the detection of cervical cancer.

There are several common cervical cancer screening methods available to HIV-positive women in resource-limited settings including the Papanicolaou test (Pap smear), visual inspection of the cervix with acetic acid (VIA) and human papillomavirus (HPV) testing. Among HIV-positive women, these methods have not been compared together and in combination against the gold standard of colposcopy-directed biopsy while examining an association with immunodeficiency or use of antiretroviral therapy (ART). Given the relationship between HIV and HPV infection, HPV and the duration of ART use, and the development of cervical intraepithelial neoplasia (CIN) and AIDS [3–7], it is reasonable to hypothesize that the test characteristics of these methods may vary according to immune status and length of ART exposure.

A rigorous comparison between these cervical screening methods is relevant in sub-Saharan Africa where large-scale HIV treatment programmes provide chronic medical care for an expanding number of HIV-positive women. As antiretroviral treatment programmes in this region are successfully rolled out and extending the lives of HIV-positive women, cervical cancer screening is being considered as an effective measure to reduce unnecessary morbidity and mortality in the population [8]. An important question for many of these

donor-funded HIV programmes is what cervical cancer screening method or combination of methods should be implemented and how should results be interpreted in relation to immunodeficiency or ART use.

Using data on histology from colposcopy-directed biopsy, $CD4^+$ cell count and duration of ART exposure, the objective of this study was to determine the sensitivity, specificity and positive predictive value (PPV) and negative predictive value (NPV) of Pap smear, VIA, HPV and their combinations among HIV-positive women.

Materials and methods

Study setting

The trial was conducted at the Cope Hope Center for Infectious Diseases in Nairobi, Kenya, between June and November, 2009. Funded by the President's Emergency Plan for AIDS Relief (PEPFAR), the Hope Center provides free ART to HIV-positive adults and children [9] and is administered by the Coptic Orthodox Mission with support from the University of Washington [10]. HIV-positive women enrolled at the Hope Center were seen during routine medical follow-up and referred to an adjacent research clinic for information on cervical cancer screening. Five hundred HIV-positive women were invited to participate and were eligible if they were between 18 and 55 years of age, had an intact cervix, were HIV-positive and never had cervical treatment for cancerous or pre-cancerous lesions. The study protocol was reviewed and approved by the institutional review boards at the University of Washington (Seattle, Washington, USA), Kenyatta National Hospital (Nairobi, Kenya) and the International Agency for Research on Cancer (IARC; Lyon, France).

Enrolment and study procedures

Upon enrolment in the study and after informed consent, participants had blood drawn for $CD4^+$ cell count (FACSCount; Becton Dickinson, Franklin Lakes, New Jersey, USA) and provided information on sociodemographic and clinical characteristics. Further data regarding the participant's HIV medical and ART history were obtained from Hope Center medical records. During the subsequent pelvic examination, a Pap smear was performed in which a Cervex brush was inserted into the endocervical canal, smeared on a glass slide and fixed (Andwin Scientific Safetex NO-TOUCH Pap kit; Addison, Illinois, USA). The same Cervex brush was then stirred in PreservCyt media (Hologic, Marlborough, Massachusetts, USA) that was later analysed for HPV.

VIA was subsequently performed by the study nurse who had received over 2 weeks of hands-on training in VIA and had over 6 months of work experience conducting VIA prior to study initiation. After the application of 5% acetic acid to the cervix for 2 min, VIA was considered positive if there was a well-defined, distinct acetowhite lesion close to the squamocolumnar junction. The examination was considered unsatisfactory if the squamocolumnar junction could not be fully visualized. After VIA, all women underwent colposcopy by the study doctor who took a single biopsy at the site of any visualized lesion or at 12 o'clock on the cervix if no lesion was seen, and placed the specimen in 10%

buffered formalin. The study doctor who performed the colposcopy was blinded to the VIA results obtained by the study nurse.

Pap smears and biopsies were prepared and processed by laboratory technologists and read by the study pathologist from Aga Khan Medical University, who reported cytology results according to the Bethesda 1991 revised classification scheme and histology results according to the Richart CIN staging system [11,12]. Samples prepared for reading had all identifying information removed and were given unique numbering systems by laboratory assistants that blinded the study pathologist to the identities of the participants and their samples. Pap smear and biopsy samples were read by the study pathologist at times separated by at least 2 days and each had their own separate numbering systems that could not be matched by the pathologist. Histology results based on colposcopy-directed biopsy provided the gold standard final diagnosis in this study.

Participants who were diagnosed as having CIN2 or CIN3 on biopsy were offered cryotherapy treatment. Those who were ineligible to receive cryotherapy were referred for subsidized care at a neighbouring government medical facility where they were treated with loop electrosurgical excision procedure (LEEP).

Laboratory methods

PreservCyt media was stored in Nairobi at ambient temperatures of 25°C or less before being shipped to the IARC in Lyon, France, and from there to Vrije Universiteit (VU) Medical Center in Amsterdam, the Netherlands. At the VU Department of Pathology, HPV DNA testing was performed on exfoliated cells [13]. Beta-globin PCR analysis was performed in order to assess the quality of the HPV DNA, and DNA was determined using general primer GP5+/6+-mediated PCR [14]. PCR products were hybridized using an enzyme immunoassay (EIA) that included an oligoprobe for high-risk HPV types. The high-risk HPV types included 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Samples that were positive on EIA for high-risk HPV types were considered HPV positive [7].

Statistical methods

Sociodemographic and clinical data were collected and recorded on paper forms that were scanned into a computer database using TeleForm software (Autonomy Cardiff, Vista, California, USA). Sensitivity, specificity, PPV, NPV and area under the curve (AUC) for sensitivity and 1-specificity were calculated using colposcopy-directed biopsy histology results as the gold standard. Test positivity was calculated by taking the number of positive results for each screening method and dividing by the total number of samples tested. Sensitivity, specificity and AUC were formally compared pairwise using McNemar's test and DeLong's test of AUC [15]. Comparisons of sensitivity and specificity were further stratified by age (<40 years and ≥40 years), duration of ART use (none, ART <2 years and ART ≥2 years) and $CD4^+$ cell count (≤350 and >350 cells/μl), and were compared using chi-square tests and logistic regression. Sensitivity and specificity found to be statistically significantly different for varying strata of age, $CD4^+$ cell count or duration on ARTon a univariate basis were further assessed in multivariate logistic regression models that included all three of these covariates.

Cytology results were presented using three different definitions of positive results: ASCUS +, which included ASCUS (atypical squamous cells +of undetermined significance), LSIL (low-grade squamous intraepithelial lesions), HSIL (high-grade squamous intraepithelial lesions) and AGC (atypical glandular cells); LSIL+, which included LSIL, HSIL and AGC; and HSIL+, which included HSIL and AGC. Positive histology results were defined as CIN2/3, which contained CIN2 or more severe findings.

Screening methods were compared with histology individually and in combination with each other. Dual combinations included VIA with HPV, VIA with Pap smear and Pap smear with HPV. In dual combinations, a positive result was defined as both tests ('plus') being positive or either test ('or') being positive.

All statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, New York, USA) and STATA version 12.1 (StataCorp LP, College Station, Texas, USA).

Results

Study population

Of the 500 women enrolled in the study, 498 underwent successful sample collection. The median age of the study population was 38 years and 45% were between the ages of 30 and 39 years (Table 1). Nearly half (43%) of the participants were married, and 51% had at least a secondary school education. Most women (77%) were employed, none reported any smoking history and 25% reported having three or more lifetime sexual partners.

The median $CD4^+$ cell count at the time of cervical cancer screening was 371 cells/μl [interquartile range (IQR), 245–533] and the median weight was 65 kg (IQR, 57–74). Two hundred and twenty-nine women (46%) had a $CD4^+$ cell count of 350 cells/μl or less. Three hundred and seventy-seven women (75%) were on ART at the time of cervical screening, and 182 (48%) of these women had been on ART for at least 2 years. Those on ART had been taking medications for a median duration of 797 days (IQR, 330–1210).

Cervical cancer screening results by method

On the basis of colposcopy-directed biopsy, 172 (35%) of the participants were classified as normal, 186 (37%) had CIN1, 66 (13%) CIN2, 47 (9%) CIN3 and 27 (5%) were indeterminate (Table 2). There were no invasive cancers noted on biopsy among the 498 HIV-positive women screened. On Pap smear, 187 (38%) were normal, 77 (15%) had ASCUS, 121 (24%) LSIL, 92 (18%) HSIL, 2 (0.4%) AGC and 19 (4%) were indeterminate. On VIA, 296 (59%) were negative, 197 (40%) were positive and 5 (1%) were indeterminate. On HPV, 234 (47%) were negative and 264 (53%) were positive.

Sensitivity, specificity and area under the curve

Individually, the most sensitive test was Pap (ASCUS+) (92.7%), which was significantly more sensitive than VIA (62.7%; $P < 0.001$), Pap (HSIL+) (71.8%; $P < 0.001$) and HPV (83.6%; $P = 0.04$) (Table 3). HPV was significantly more sensitive than VIA ($P < 0.001$) and Pap (HSIL+) ($P = 0.04$). Pap (HSIL+) (97.1%) was significantly more specific than VIA (65.9%; $P < 0.001$) and HPV (55.7%; $P < 0.001$), and VIA was more specific than HPV (*P*

= 0.006). The cervical screening method with the highest AUC was Pap (HSIL+) (0.85), which was significantly greater than VIA (0.64; $P < 0.001$), HPV (0.70; $P < 0.001$), Pap (ASCUS+) (0.71; $P < 0.001$) and Pap (LSIL+) (0.76; $P < 0.001$) (Table 3).

Combining cervical screening methods did not significantly improve test sensitivity over using Pap (ASCUS+) alone. However, combining VIA and Pap (HSIL+) to confirm positive test results had greater specificity than Pap (HSIL+) alone (99.1 vs. 97.1%; $P < 0.001$). Combining tests to confirm positive test results with Pap (HSIL+) improved the AUC of VIA and HPV but was not significantly greater than using Pap (HSIL+) alone (Table 3). Using VIA as a general screening tool followed by a confirmatory Pap (HSIL+) or HPV of all VIA positives ('both test positive') significantly increased the AUC of using VIA from 0.64 to 0.75 ($P < 0.001$) and 0.71 ($P < 0.001$), respectively. HPV followed by confirmatory positive Pap (HSIL+) increased AUC from 0.70 to 0.81 ($P < 0.001$); however, combining HPV and VIA made no significant difference compared with HPV alone (0.70 vs. 0.71; $P = 0.6$).

Association with immune status, duration of antiretroviral exposure and age

The specificity of HPV was significantly decreased at younger ages, lower $CD4^+$ cell counts and after little or no ART exposure (Table 4). The specificity of HPV at $CD4^+$ cell counts of 350 cells/μl or less was significantly less than at $CD4^+$ cell counts of more than 350 cells/μl (45.7 vs. 63.5%; $P < 0.001$) and among women less than 40 years of age compared to at least 40 years of age (50.0 vs. 65.1%; $P = 0.006$) (Table 4). Compared with women with at least 2 years of ART exposure, those women with no ART (66.2 vs. 51.5%, $P = 0.03$) and those with less than 2 years of ART (66.2 vs. 45.5%, $P < 0.001$) had lower HPV specificity (Tables 4 and 5). In multivariate analysis, age less than 40 years ($P = 0.005$), $CD4^+$ cell count of 350 cells/μl or less ($P = 0.002$) and ART less than 2 years ($P = 0.01$) remained significantly associated with decreased HPV specificity suggesting the independent effects of these covariates (Table 5).

The sensitivity of VIA was significantly decreased among women at least 40 years of age compared with those less than 40 years of age (47.3 vs. 78.2%; $P < 0.001$), and this association was independent of $CD4^+$ cell count and duration of ART exposure ($P < 0.001$) (Tables 4 and 5). VIA specificity did not differ significantly between not being on ART and being on ART for at least 2 years ($P = 0.3$) (Table 5). However, VIA specificity was significantly decreased among those on ART for less than 2 years compared with those on ART for at least 2 years (57.3 vs. 72.5%; $P = 0.01$), and this association was independent of age and $CD4^+$ cell count ($P = 0.03$, Table 5).

Although the difference in Pap (HSIL+) specificity between women aged less than 40 years and at least 40 years was on the edge of statistical significance (98.6 vs. 94.6%; $P = 0.05$), it was not found to be statistically significant in a multivariate analysis that included $CD4^+$ cell count and duration of ART use ($P = 0.07$) (Tables 4 and 5).

Discussion

This study of HIV-positive women in Kenya compared three cervical cancer screening methods, Pap smear, VIA and HPV testing, with the gold standard of colposcopy-directed biopsy. In this comparison, Pap (ASCUS+) had the highest sensitivity, combination of both Pap (HSIL+) and VIA positive had the highest specificity and Pap (HSIL+) had the highest AUC. Immunosuppression and younger age were independently associated with decreased HPV specificity, while shorter exposure to ART was significantly associated with decreased HPV and VIA specificity. Finally, older age was significantly associated with decreased VIA sensitivity.

The high accuracy of Pap smear in this study confirms the utility of this standard test among HIV-positive women [16,17]. Given access to readings by experienced and highly trained pathologists, Pap (HSIL+) with its high AUC could be considered the best combination of sensitivity and specificity among the individual screening methods tested. Pap (HSIL+) was also the most specific test of the individual screening methods that were compared, whereas Pap (ASCUS+) was the most sensitive. The sensitivity and specificity of Pap smear remained unchanged regardless of immune status or duration of exposure to ART, suggesting the robustness of this test among HIV-positive women compared with HPV and VIA.

VIA has long been used as an economical alternative to Pap smear in a ‘see-and-treat’ approach with cryotherapy [18], and in this study, VIA among HIV-positive women had a sensitivity of 62.7% and a specificity of 65.9%. These results are comparable to the performance of VIA among HIV-negative women [19] and suggest that VIA may be a reasonable cervical cancer screening choice among HIV-positive women in resource-limited settings wherein cervical cancer screening is typically offered once in a lifetime and usually without affordable alternatives [20–22]. Another similarity to VIA among HIV-negative women is that the sensitivity of VIA was significantly decreased among HIV-positive women who were at least 40 years of age [23,24]. Decreased VIA sensitivity at older ages may reflect the reduced ability of visual inspection to detect changes in the transformation zone, which retreats into the endocervical canal among postmenopausal women [25].

The sensitivity and specificity of VIA did not significantly differ according to immune status. There was no significant difference in VIA sensitivity and specificity between women who had $CD4^+$ cell counts of 350 or less and more than 350 cells/μl. However, shorter duration of ART exposure was found to be associated with decreased VIA specificity. Although there was no significant difference between being off ART and on ART for at least 2 years, there was a significant difference in VIA specificity between being on ART for less than 2 years and on ART for at least 2 years, which was independent of age and immune status. The reason for this finding is not clear and merits further investigation, as this appears to be the first time this association has been reported in the literature.

Methods have recently been developed to batch test high-risk HPV types quickly and cheaply making cervical cancer screening with HPVa potentially feasible option in resource-limited settings in the near future [26,27]. Similar to results found among HIV-negative

women, HPV testing among HIV-positive women in this study was sensitive but less specific compared with other cervical cancer screening methods [28]. Therefore, the strength of HPV testing among HIV-positive women may be in its combined use with VIA or Pap smear. Confirming a positive VIA with HPV significantly increased the overall test effectiveness of using VIA alone. Similarly, confirming a positive HPV with Pap (HSIL+) significantly increased the overall test effectiveness of HPV alone.

Combining cervical screening methods may be useful in resource-limited settings such as sub-Saharan Africa where most screening programmes at HIV clinics require donor funding to provide these services to their catchment population. For example, in order to maximize the number of HIV-positive women screened effectively with a fixed amount of funding, an HIV treatment programme could consider offering inexpensive VIA to all women enrolled in the clinic and only offer more expensive Pap smear screening to the more limited number who are VIA positive. This would be less costly to the programme than offering Pap smear to all women, and the overall test effectiveness of combining these tests, as this study demonstrates, is better than VIA alone. Although conducting a comprehensive cost-effectiveness analysis is beyond the scope of this manuscript, our data contribute important information to future estimates of cost-effectiveness of cervical cancer screening among HIV-positive women [29–32].

There are several challenges to using HPV alone to screen HIV-positive women for cervical cancer. Immunodeficiency and shorter exposure to ART were each independently associated with decreased HPV specificity.

Although immunodeficiency is associated with increased detection of HPV and cervical dysplasia [7,33–35], our findings suggest that a significant amount of detectable HPV at lower $CD4^+$ cell counts is not associated with biopsy-proven disease. A reason may be the lag between the detection of HPV, which immunodeficiency may promote, and the development of CIN as represented by CIN2/3. The use of ART has been related to increased regression of CIN lesions [36–40] and may enhance HPV clearance from the cervix [7,41]. A recent study by Konopnicki *et al.* [6] found that sustained HIV viral suppression on ART was significantly associated with a decreased risk of persistent HPV infection that was independent of $CD4^+$ cell count. These results correlate with a positive association with ART exposure that was found in this study.

Decreased HPV specificity among HIV-positive women was also independently associated with age less than 40 years. This is consistent with the knowledge that the peak incidence of HPV infection occurs before 30 years of age and subsequently declines among HIV-negative women [42,43], whereas the peak of CIN occurs 5–15 years later [44]. For this reason, it is recommended in the United States to restrict HPV screening to women who are more than 30 years of age [45]. Our study suggests that similar age restrictions should apply to HIV-positive women.

In addition to having histology on all women as the gold standard comparison and a relatively large sample size of HIV-positive women, this study's strengths included detailed ART history and $CD4^+$ cell count data. However, there are several study weaknesses. The

Pap smears were read by a highly trained and experienced professor of pathology at a major urban university in Kenya, and had a sensitivity and specificity that was better than those found in similar studies among HIV-positive women in resource-limited settings [46–48]. As a result, our cytology results may be less replicable in many resource-limited countries and demonstrate the importance of good pathology training and laboratory support. The study was able to determine the association between test characteristics and the duration of ART exposure, and it did not include the duration of immunosuppression, HPV infection and cervical intraepithelial neoplastic disease. Consequently, some of these findings may not capture the interaction between examined covariates and the evolution of HPV infection and cervical disease over time.

A judicious interpretation of the findings from this cross-sectional study is required. Given the robust performance of Pap smear in this investigation, it is recommended that Pap smear be used among HIV-positive women when read in a well supported laboratory with good quality control. This study reinforces the use of Pap smear among HIV-positive women in resource-rich countries, but its results do not necessarily extrapolate to resource-constrained settings wherein laboratory facilities, training and support may be limited. The best results from HPV and VIA arise when they are used in combination with each other or with a good quality Pap smear, and these combinations could be used to help resource-constrained HIV treatment programmes screen a large patient population less expensively compared with offering Pap smears to all women. HPV is a highly sensitive test and a valuable objective screening tool, but positive results should be cautiously interpreted among HIV-positive women who are younger, immunocompromised or have been on little or no ART. Finally, the use of VIA among HIV-positive is similar to that among HIV-negative women and should be used in comparable situations when other screening alternatives are unavailable and/or unaffordable and among women less than 40 years of age [49].

Acknowledgments

M.C. designed and implemented the study, supervised the on-site data management, interpreted the data and wrote the article. N.M. helped implement the study and contributed to the study's design, analysis and writing. K.McK. implemented the study and helped interpret the data. H.DeV. supported and analysed the HPV information, interpreted the data and helped write the article. B.R. performed the statistical analysis and helped design the study and write the article. F.R. prepared, read and analysed the cytology and histology results, and helped interpret the data and write the article. R.P. helped collect and interpret the cytology and histology results. J.N. helped implement the study, collected data and conducted statistical analyses. E.N.-M. implemented the study. S.S. helped implement and design the study. G.J.-S. helped design the study, interpret the data and write the article.

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Table 1

Baseline characteristics.

Characteristics	*N*	*N* or Median (% or IQR)
Age (years)	500	38 (3–43)
Age groups (years)	500	
18–29		62 (12%)
30–39		225 (45%)
40–49		177 (35%)
≥50		36 (7%)
$CD4^+$ cell count (cells/μl)	498	
≤200		81 (16%)
>200 and ≤350		148 (30%)
>350 and ≤500		128 (26%)
>500		141 (28%)
$CD4^+$ cell count (cells/μl)	498	371 (245–533)
Weight (kg)	493	65 (57–74)
BMI (kg/m^2)	482	
<18.5		13 (3%)
18.5–24.9		208 (43%)
25.0–29.9		165 (34%)
≥30		96 (20%)
WHO stage	496	
I		161 (33%)
II		138 (28%)
III		165 (33%)
IV		32 (6%)
Marital status	500	
Married		215 (43%)
Single		118 (24%
Divorced/separated		77 (15%)
Widowed		90 (18%)
Education level	500	
None		13 (2%)
Primary		94 (19%)
Secondary		254 (51%)
College		139 (28%)
Employment	500	
Employed		383 (77%)
Unemployed		117 (23%)
On ART	500	
Yes		377 (75%)
No		123 (25%)

Characteristics	*N*	*N* or Median (% or IQR)
Previous cervical screening	500	252 (50%)
Duration on ART (days)	377	797 (330–1210)
Smoking history	500	
No		500 (100%)
No. of lifetime sexual partners	387	
1		162 (42%)
2		130 (34%)
≥3		95 (25%)

ART, antiretroviral therapy;IQR, interquartile range.

Table 2

Papanicolaou smear, visual inspection with acetic acid and human papillomavirus testing of high-risk types compared with histology results from colposcopy-directed biopsy.

			Colposcopy-directed biopsy				
	N	(%)	Normal	CIN 1	CIN 2	CIN 3	Indeterminate
Pap							
No dysplasia	187	38%	140	31	5	3	8
ASCUS	77	15%	16	46	6	2	7
LSIL	121	24%	7	95	11	4	4
HSIL	92	18%	2	8	41	38	3
AGC	2	0.4%	1	1	0	0	0
Indeterminate	19	4%	6	5	3	0	5
Total	498	100%	172 (35%)	186 (37%)	66 (13%)	47 (9%)	27 (5%)
VIA							
Negative	296	59%	118	117	28	14	19
Positive	197	40%	54	65	38	33	7
Indeterminate	5	1%	0	4	0	0	1
Total	498	100%	172 (35%)	186 (37%)	66 (13%)	47 (9%)	27 (5%)
HPV							
Negative	234	47%	100	101	16	3	14
Positive	264	53%	72	85	50	44	13
Total	498	100%	172 (35%)	186 (37%)	66 (13%)	47 (9%)	27 (5%)

AGC, atypical glandular cells; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolau; VIA, visual inspection with acetic acid.

Table 3

Sensitivity, specificity, area under the curve of sensitivity and 1–specificity, positive predictive value, negative predictive value and test positivity of screening methods individually and in combination to detect CIN2/CIN3 (n = 453)[a].

	CIN2/CIN3	Sensitivity (95% CI)	Specificity (95% CI)	AUC	PPV (95% CI)	NPV (95% CI)	Test positivity
Pap							
ASCUS+	102	92.7 (86.3–96.3)	49.3 (44.0–54.5)	0.71	37.0 (31.5–42.8)	95.5 (91.3–97.7)	60.9
<ASCUS+	8						
Pap							
LSIL+	94	85.5 (77.7–90.8)	67.3 (62.2–72.1)	0.76	45.6 (39.0–52.5)	93.5 (89.7–96.0)	45.5
<LSIL+	16						
Pap							
HSIL+	79	71.8 (62.8–79.4)	97.1 (94.7–98.4)	0.85	88.8 (80.5–93.8)	91.5 (88.2–93.9)	19.6
<HSIL+	31						
VIA							
Positive	69	62.7 (53.4–71.2)	65.9 (60.7–70.7)	0.64	37.1 (30.5–44.2)	84.6 (79.8–88.5)	41.1
Negative	41						
HPV							
Positive	92	83.6 (75.6–89.4)	55.7 (50.4–60.9)	0.70	37.7 (31.9–43.9)	91.4 (86.8–94.5)	53.9
Negative	18						
VIA+HPV							
Positive	64	58.2 (48.8–67.0)	83.7 (79.4–87.2)	0.71	53.3 (44.4–62.0)	86.2 (82.1–89.5)	26.5
Negative	46						
VIA+Pap (ASCUS+)							
Positive	66	60.0 (50.7–68.7)	81.9 (77.5–85.6)	0.71	51.6 (43.0–60.1)	86.5 (82.3–89.8)	28.3
Negative	44						
VIA+Pap (LSIL+)							
Positive	64	58.2 (48.8–67.0)	88.0 (84.2–91.1)	0.73	61.0 (51.4–69.7)	86.8 (82.8–89.9)	23.2
Negative	46						
VIA+Pap (HSIL+)							
Positive	56	50.9 (41.7–60.1)	99.1 (97.5–99.7)	0.75	94.9 (86.1–98.3)	86.3 (82.5–89.3)	13.0
Negative	54						
HPV+Pap (ASCUS+)							
Positive	87	79.1 (70.6–85.6)	76.4 (71.6–80.6)	0.78	51.8 (44.3–59.2)	91.9 (88.2–94.6)	37.1
Negative	23						
HPV+Pap (LSIL+)							
Positive	81	73.6 (64.7–81.0)	84.3 (80.0–87.7)	0.79	60.0 (51.6–67.9)	90.9 (87.2–93.6)	29.8
Negative	29						
HPV+Pap (HSIL+)							
Positive	69	62.7 (53.4–71.2)	98.5 (96.6–99.4)	0.81	93.2 (85.1–97.1)	89.2 (85.7–91.9)	16.3
Negative	41						
VIA or HPV							

	CIN2/CIN3	Sensitivity (95% CI)	Specificity (95% CI)	AUC	PPV (95% CI)	NPV (95% CI)	Test positivity
Positive	97	88.2 (80.8–93.0)	37.9 (32.9–43.1)	0.63	31.3 (26.4–36.7)	90.9 (85.1–94.6)	68.4
Negative	13						
VIA or Pap[b]							
Positive	92	83.6 (75.6–89.4)	63.8 (58.6–68.8)	0.74	42.6 (36.2–49.3)	92.4 (88.3–95.2)	47.7
Negative	18						
Pap[b] or HPV							
Positive	102	92.7 (86.3–96.3)	54.2 (48.9–59.4)	0.73	39.4 (33.6–45.4)	95.9 (92.1–97.9)	57.2
Negative	8						

ASCUS, atypical squamous cells of undetermined significance; AUC, area under the curve; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NPV, negative predictive value; Pap, Papanicolau; PPV, positive predictive value; VIA, visual inspection with acetic acid. '+' denotes both test positive is positive. 'or' denotes either test positive is positive.

[a]Only women with adequate results on all tests included.

[b]Positive Pap smear defined as HSIL+.

Table 4

Sensitivity and specificity of individual cervical cancer screening methods to detect CIN2/CIN3 compared by $CD4^+$ cell count, antiretroviral therapy duration and age (n = 453)[a].

	CD4+ cell count		
	≤350 cells/μl	>350 cells/μl	*P*
Sensitivity	**CIN2/CIN3 (*n* = 59)**	**CIN2/CIN3 (*n* = 51)**	
Pap (ASCUS+)	91.5	94.1	0.7[b]
Pap (LSIL+)	84.7	86.3	0.8
Pap (HSIL+)	71.2	72.5	0.9
VIA	69.5	54.9	0.1
HPV	86.4	80.4	0.4

Specificity	**≤CIN1 (*n* = 151)**	**≤CIN1 (*n* = 192)**	
Pap (ASCUS+)	47.0	51.0	0.5
Pap (LSIL+)	66.9	67.7	0.9
Pap (HSIL+)	95.4	98.4	0.1[b]
VIA	62.3	68.8	0.2
HPV	45.7	63.5	<0.001

	ART duration			
	Off ART	On ART <2 years	On ART ≥2 years	*P*
Sensitivity	**CIN2/CIN3 (*n* = 26)**	**CIN2/CIN3 (*n* = 44)**	**CIN2/CIN3 (*n* = 40)**	
Pap (ASCUS+)	92.3	95.5	90.0	0.6
Pap (LSIL+)	84.6	88.6	82.5	0.7
Pap (HSIL+)	65.4	79.5	67.5	0.3
VIA	61.5	68.2	57.5	0.4
HPV	92.3	81.8	80.0	0.4

Specificity	**≤CIN1 (*n* = 91)**	**≤CIN1 (*n* = 110)**	**≤CIN1 (*n* = 142)**	
Pap (ASCUS+)	54.9	48.2	46.5	0.4
Pap (LSIL+)	73.6	65.5	64.8	0.3
Pap (HSIL+)	97.8	97.3	96.5	0.8
VIA	65.9	57.3	72.5	0.04
HPV	51.6	45.5	66.2	0.003

	Age		
	<40 years	≥40 years	*P*
Sensitivity	CIN2/CIN3 (*n* = 55)	CIN2/CIN3 (*n* = 55)	
Pap (ASCUS+)	90.9	94.5	0.7[b]
Pap (LSIL+)	83.6	87.3	0.6
Pap (HSIL+)	72.7	70.9	0.8
VIA	78.2	47.3	<0.001

	Age		
	<40 years	**≥40 years**	***P***
HPV	83.6	83.6	1.0

Specificity	**≤CIN1 (*n* = 214)**	**≤CIN1 (*n* = 129)**	
Pap (ASCUS+)	48.1	51.2	0.6
Pap (LSIL+)	66.4	69.0	0.6
Pap (HSIL+)	98.6	94.6	0.05[b]
VIA	62.6	71.3	0.1
HPV	50.0	65.1	0.006

ART, antiretroviral therapy; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolau; VIA, visual inspection with acetic acid.

[a] Only women with adequate results on all tests included.

[b] Fisher's exact test.

Table 5

Univariate and multivariate logistic regression models of sensitivity of visual inspection with acetic acid, specificity of Pap (HSIL+), specificity of visual inspection with acetic acid and specificity of human papillomavirus.

	Univariate model		Multivariate model[a]	
Sensitivity of VIA	**OR for positive test among CIN2/CIN3 (95% CI)**	***P***	**OR for positive test among CIN2/CIN3 (95% CI)**	***P***
Age ≥40 years	1.0		1.0	
Age <40 years	4.00 (1.74–9.17)	<0.001	3.95 (1.70–9.22)	<0.001
$CD4^+$ cell count >350 cells/μl	1.0		1.0	
$CD4^+$ cell count ≤350 cells/μl	1.87 (0.86–4.09)	0.1	1.75 (0.73–4.20)	0.2
On ART ≥2 years	1.0		1.0	
Off ART	1.18 (0.43–3.24)	0.7	0.79 (0.26–2.40)	0.7
On ART <2 years	1.58 (0.65–3.86)	0.3	1.09 (0.40–2.98)	0.9

	Univariate model		Multivariate model[a]	
Specificity of Pap (HSIL+)	**OR for negative test among ≤CIN1 (95% CI)**	***P***	**OR for negative test among ≤CIN1 (95% CI)**	***P***
Age ≥40 years	1.0		1.0	
Age <40 years	4.04 (1.03–15.89)	0.05	3.56 (0.88–14.31)	0.07
$CD4^+$ cell count >350 cells/μl	1.0		1.0	
$CD4^+$ cell count ≤350 cells/μl	0.33 (0.08–1.29)	0.1	0.33 (0.08–1.37)	0.1
On ART ≥2 years	1.0		1.0	
Off ART	1.62 (0.31–8.56)	0.6	1.37 (0.25–7.49)	0.7
On ART <2 years	1.30 (0.30–5.57)	0.7	1.59 (0.35–7.16)	0.5

	Univariate model		Multivariate model[a]	
Specificity of VIA	**OR for negative test among ≤CIN1 (95% CI)**	***P***	**OR for negative test among ≤CIN1 (95% CI)**	***P***
Age ≥40 years	1.0		1.0	
Age <40 years	0.67 (0.42–1.08)	0.1	0.67 (0.41–1.08)	0.1
$CD4^+$ cell count >350 cells/μl	1.0		1.0	
$CD4^+$ cell count ≤350 cells/μl	0.75 (0.48–1.17)	0.2	0.80 (0.50–1.27)	0.3
On ART ≥2 years	1.0		1.0	
Off ART	0.73 (0.42–1.30)	0.3	0.80 (0.45–1.42)	0.8
On ART <2 years	0.51 (0.30–0.87)	0.01	0.55 (0.32–0.94)	0.03

	Univariate model		Multivariate model[a]	
Specificity of HPV	**OR for negative test among ≤CIN1 (95% CI)**	***P***	**OR for negative test among ≤CIN1 (95% CI)**	***P***
Age ≥40 years	1.0		1.0	
Age <40 years	0.54 (0.34–0.84)	0.006	0.51 (0.31–0.81)	0.005
$CD4^+$ cell count >350 cells/μl	1.0		1.0	

Specificity of HPV	Univariate model		Multivariate model[a]	
	OR for negative test among ≤CIN1 (95% CI)	*P*	OR for negative test among ≤CIN1 (95% CI)	*P*
$CD4^+$ cell count ≤350 cells/μl	0.48 (0.31–0.75)	<0.001	0.49 (0.31–0.77)	0.002
On ART ≥2 years	1.0		1.0	
Off ART	0.55 (0.32–0.94)	0.03	0.62 (0.36–1.09)	0.1
On ART <2 years	0.43 (0.26–0.71)	<0.001	0.51 (0.30–0.86)	0.01

ART, antiretroviral therapy; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; VIA, visual inspection with acetic acid.

[a] All covariates listed are included in the multivariate model.