Cervical cancer screening test performance for HIV-infected women:

A meta-analysis

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Abstract

Objectives: Screening for cervical intraepithelial neoplasia (CIN) in HIV-infected women is essential to prevent invasive cervical cancer. Visual inspection with acetic acid (VIA) and HPV DNA testing have been proposed as alternatives to traditional cytology (or Papanicolaou [Pap] smears) screening programs. This meta-analysis provides pooled data on test performance (i.e., sensitivity, specificity, positive predictive value, and negative predictive value) of Pap, VIA, and HPV DNA testing with the Hybrid Capture II in HIV-infected women for diagnosing CIN2 or worse (CIN2+).

Methods: A meta-analysis of cervical cancer screening test performance for HIV-infected women was conducted following the PRISMA guidelines using PubMed and EMBASE databases. Relevant data were extracted from the articles and analyzed using STATA 13.

Results: Six studies met the inclusion criteria and were selected for analysis. The pooled sensitivity of HPV DNA testing was 86.9% (95% CI, 58.3%-97.0%), VIA was 77.6% (95% CI, 73.5%-81.1%), Pap (at a low-grade squamous intraepithelial lesion [LSIL] threshold) 72.8% (95% CI, 41.1%-91.2%) and Pap (at a high-grade SIL [HSIL] threshold) 34.2% (95% CI, 8.7%-74.0%). The pooled specificities were 60.2% (95% CI, 40%-77.5%) for HPV DNA testing, 73.4% (95% CI, 50.5%-88.2%) for VIA, 72.9% (95% CI, 31.6%-94.0%) for Pap (LSIL threshold) and 94.5% (95% CI, 78.0%-98.8%) for Pap (HSIL threshold).

Conclusions: HPV DNA screening is a highly sensitive screening technique for HIV-infected women; however, there are still many barriers to its implementation in low-resource settings. VIA-based screening programs are a feasible alternative for HIV-infected women until the required resources (monetary resources and laboratory infrastructure) are committed for HPV DNA based screening programs.

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Background

Cervical cancer rates are decreasing in many western countries because there is now a clear understanding of the natural history of the disease,[1] which has allowed for development of effective prevention and treatment strategies.[2] Persistent high risk human papillomavirus (HPV) is well established as the inciting etiologic agent in the vast majority of pre-invasive cervical cancers, (also referred to as cervical intraepithelial neoplasia [CIN]) and invasive cervical cancers.[1] Approximately 5% of women with persistent, high-risk HPV infections will develop CIN grade 3 within a 10 year period.[3] National screening programs implemented in western countries detect early stage, pre-invasive disease (CIN grades 1, 2, and 3), preventing its progression to invasive cancer.[4] In the United States, for example, the age standardized incidence of cervical cancer has declined from 10.7 per 100,000 in 1990 (when organized Pap screening programs were introduced)[5] to 6.7 per 100,000 in 2010.[6] However, in regions without national screening programs, such as in sub-Saharan Africa, the rates of cervical cancer are still increasing.[7] Globally, there were an estimated 275,000 deaths from cervical cancer in 2008 and an estimated 529,000 new cases.[2] The majority (80%) of these deaths occurred in developing countries that also have the highest HIV rates.[7]

The Papanicolaou (Pap) smear is the traditional cytology screening test for secondary prevention of cervical cancer in high-resource countries. Cytology screening is used to detect SIL and has been extremely successful in reducing rates of cervical cancer. A 60% to 90% reduction was seen within three years of implementation in high-resource countries.[8] There are, however, several drawbacks to Pap screening that make it difficult to implement in low-resource settings. First, because of the need for sophisticated equipment and highly trained lab personal, the cost of Pap based screening programs is often prohibitive.[4,9] Second, a single round of Pap

screening has a low sensitivity (50%-70%), and repeat smears over the course of a woman's

lifetime are necessary to improve the performance of the test. Finally, women also need to come

back into the clinic to receive their results, increasing the likelihood of loss to follow-up.[4,9]

Visual inspection with acetic acid (VIA) had been proposed as an alternative to

traditional cytology screening programs.[10,11] VIA is a direct visual inspection technique in which

the practitioner applies 3–5% dilute acetic acid to the cervix and then examines the cervix using

a bright light. The identification of aceto-white areas on the cervix is considered a positive screen

because these areas are associated with CIN. An advantage of VIA, particularly in low-resources

settings, is that the screening results are immediate and women can be treated for CIN during the

same visit as the screening. This is known as the "screen-and-treat" approach. It minimizes the

risk of loss to follow-up after a positive screen that occurs with other screening methods such as

cytology or HPV DNA testing. It is also inexpensive,[11,12] as the materials needed for the

screening process are easy to obtain even in low-resource settings and VIA does not require any

laboratory equipment.[13,14] However, the drawback to VIA is that both the sensitivity and

specificity are lower that of HPV DNA testing.[13]

HPV DNA testing is another alternative to cytology screening for CIN because of its

sensitivity and specificity are, higher than both Pap and VIA.[15] It also has the advantage of a

more simple sampling procedure that can be performed by either a practitioner or the women

herself.[16,17] The self-collected samples can reduce the number of visits required for testing. The

one disadvantage to the self-collect sample is that it has been shown to have more variability in

its sensitivity than the practitioner collected samples.[8] However, HPV DNA testing in general

requires higher technical abilities than VIA screening including the need for polymerase chain

reaction (PCR) equipment and staff trained in the equipment, making it difficult to implement in

low-resource settings.[15] HPV DNA testing is also more expensive than VIA which can be a limiting factor in low-resource settings where there are competing health priorities and limited funding.[8]

Cervical cancer screening programs are needed to prevent cervical cancer among all women. Screening programs are particularly important among high-risk populations such as HIV-infected women. HIV-infected women are at an increased risk for sexually transmitted diseases,[7,18] including HPV. This increased risk has been found in HIV-infected women with both low and high CD4 counts.[19,20] HIV-infected women are also less likely to clear an HPV infection, and more likely to have a persistent high-risk infection that progresses to pre-invasive or invasive cancer.[7]

The relative risk of HPV for HIV-infected compared to HIV-negative women does not vary greatly between populations but the risk of cervical cancer does because of the inequitable access and effectiveness of screening strategies, particularly in developing countries[21] In Africa, cervical cancer is the leading cause of cancer death for women. Within Africa, women in East and West Africa have 5 times the mortality rate from cervical cancer as women in North Africa.[22] Access to effective cervical cancer screening programs, particularly for high risk women (including HIV-infected women) has a great impact on the differences in cervical cancer burden between countries.

The cervical cancer health burden in HIV-infected women has also been impacted by the introduction of anti-retroviral medications. These life-saving medications have enabled HIV-infected women to live longer but because of the longer life span, they have also increased the risk of HIV-associated malignances, including cervical cancer.[23,24] Early diagnosis and

treatment of CIN through screening programs for HIV-infected women is essential in preventing morbidity and mortality from cervical cancer.

Significance:

Cytology screening programs have been shown to be effective in reducing the rates of cervical cancer in the developed world. However, traditional cytology screening programs are difficult to implement in low-resource settings that have the highest burden of cervical cancer and co-infection with HIV. [25] In order to reduce the burden of cervical cancer in HIV-infected women, effective strategies that can be implemented in developing countries[26] need to be studied. Visual inspection with acetic acid and HPV DNA testing have been proposed as alternatives to cytology screening.[13,25] A meta-analysis of screening test performance for these alternative tests in HIV-infected women has not been published and would fill a gap in the literature on cervical cancer screening.

We conducted a meta-analysis of cervical cancer screening test performance for HIV-infected women following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We used the PRISMA 27 steps and flow diagram (Figure 1) to organize the meta-analysis.[27]

Methods
Objectives

What is the test performance of Pap, VIA, and HPV DNA testing with the Hybrid Capture II (HC2) in HIV-infected women? What is the test sensitivity and specificity for diagnosing CIN2+?

Data Sources

We searched PubMed and EMBASE databases (2003 to present) for cervical cancer prevention studies that address the use of Pap, VIA, and HPV DNA testing in HIV-infected women. The last search was run on 8 August 2013. We used the following search terms for both searches: HIV; cervical cancer; cervical intraepithelial neoplasia; CIN; HPV; human papillomavirus; screening; VIA; visual inspection with acetic acid; DNA; Pap; Pap smear; Papanicolaou test; prevention. Additionally, the bibliographies of relevant articles were reviewed to determine if there were any other applicable studies that need to be included in the analysis. The results from each search including the date, time, and database searched were recorded using Microsoft Excel in order to ensure reproducibility of the results.

Eligibility Criteria

Studies were selected using the following inclusion criteria: 1) participating women were HIV-infected, 2) screening studies included cross-sectional, cohort, and experimental studies for Pap smear, VIA, and HPV DNA testing with HC2, 3) the gold standard for screening test statistic performance was histologically-proven disease, 4) the outcome measure was CIN2+. Studies were excluded if they were qualitative or participating women had a hysterectomy, previously tested positive for CIN2+, or previously had cervical cancer. Study validity was considered in the review based on the selection process for participants. Studies were reviewed and excluded by title and by abstract. Full studies were then selected for inclusion based on the above inclusion and exclusion criteria. Study exclusion and inclusion was then checked by a second independent reviewer to reduce reviewer bias.

Data Extraction

We created a data extraction sheet using Microsoft Excel specifically designed for this meta-analysis. Abstracted data included the characteristics of study participants, screening type, number of participants, outcome measure (severity of disease), gold standard for measuring test performance, the sensitivity and specificity with accompanying 95% confidence intervals and the true positive, true negative, false positive, and false negative for each screening test.

Statistical Analysis

The data were analyzed using STATA v13.0 (College Station, Texas) statistical software and graphed using Microsoft Excel (Redmond, Washington). The true positive, true negative, false positive, and false negative for each screening test by study was entered into STATA and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each of the studies was calculated. The results were then converted to the logit scale and pooled test statistics were calculated using metan, a meta-analysis procedure in STATA. The output was then back transformed to the probability scale. The heterogeneity was tested using Cochran's Q test ($p \leq 0.05$) and the effect of heterogeneity was calculated using the I^2 index, which indicates the percentage of variation between studies that is attributed to heterogeneity. Substantial heterogeneity was defined $I^2 \geq 75\%$.[28] If heterogeneity was identified, a random effects model was chosen for the meta-analysis. Forest plots of the sensitivity and specificity for each screening test were generated using Microsoft Excel.

Results
Study Selection

The systematic search of the PubMed and EMBASE databases resulted in a total of 715 articles. Upon review of the references for the studies, an additional 41 articles were included for

review. 50 duplicated articles were eliminated. 659 articles were eliminated by title and abstract because they did not meet the eligibility criteria for the meta-analysis. An additional 34 articles were eliminated by full text with 6 studies meeting the inclusion criteria (5 from the database search and 1 from the references)[29–34] (Figure 1).

Figure 1. PRISMA Flow Diagram
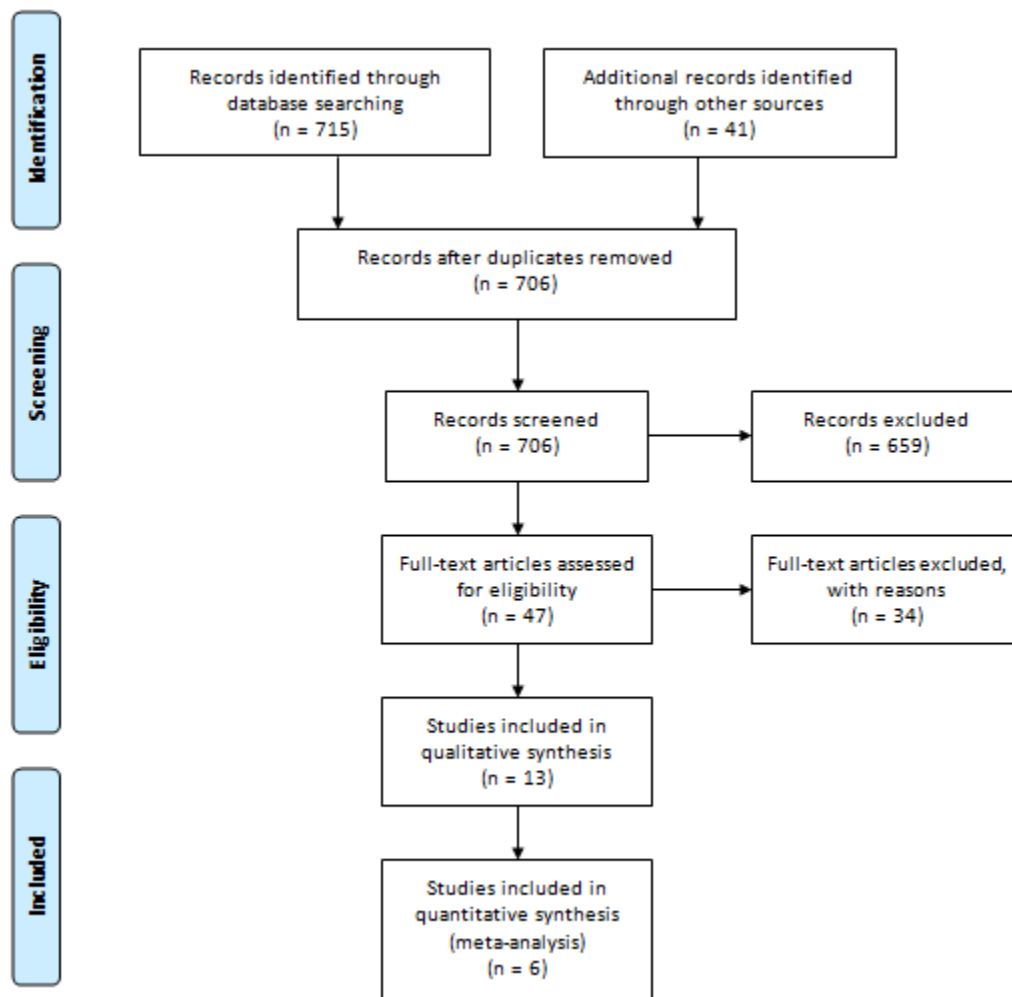
Study Characteristics

For each of the 6 eligible studies, study characteristics are included in Table 1. There were 4 cross-sectional and 2 cohort studies conducted in 5 different countries. 5 of the studies

addressed the test performance for Pap, 4 for VIA, and 4 for HPV DNA testing with HC2.

Individual study size ranged from 83 women in the smallest pilot study to 1128 women in the

largest cross-sectional study with a total of 2,804 women participating in cervical cancer

screening (2503 women tested by PAP, 2,507 by VIA and 2,449 by HPV DNA testing with

HC2). All women in included in the studies were HIV-infected and received at least one of the

three screening strategies. The gold standard for all of the studies was histology.

Table 1. Study Characteristics by Screening Test									
Title	Author	Year Published	Country	Study Design	Inclusion Criteria and Study Population	Exclusion criteria	Study Size	Gold Standard	Disease Threshold
Screening Test: PAP									
Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa	Firnhaber et al.	2013	South Africa	cross-sectional	Eligible following treatment of symptomatic STD, if menstruating at study enrollment asked to return within one to two weeks , HIV-positive	pregnant, previously undergone a hysterectomy/treatment for cervical neoplasia or cancer, severely ill, signs and/or symptoms suggestive of a STD	941	histology	CIN2+
Screening of cervical neoplasia in HIV-infected women in India.	Joshi et al.	2013	India	cross-sectional	HIV-infected women, 21 and 60 years, no debilitating illness, not pregnant at recruitment, intact uterus with no prolapse, and no previous history of cervical neoplasia		1081	histology	CIN2+
Comparison of conventional cervical cytology versus visual inspection with acetic acid among HIV-infected women in Western Kenya	Mabeya et al.	2012	Kenya	cross-sectional	Female, age 15–49 years, documented HIV infection, healthy, no debilitating disease	Current pregnancy or pregnancy in the last 6 months, history of or treatment for cervical cancer, total hysterectomy, dilatation and curettage in the last 6 months, current mucopurulent discharge, active vaginal bleeding, and diagnosis of STI in the last 3 weeks	135	histology	CIN2+
Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV- infected	Sahasrabuddhe et al.	2012	India	cohort study	consenting nonpregnant and previously unscreened HIV-infected women were enrolled in this study		266	histology	CIN2+

women in India									
HPV Prevalence and Cervical Intraepithelial Neoplasia among HIV-infected Women in Yunnan Province, China : A Pilot Study	Zhang et al.	2012	China	cross-sectional	HIV-positive, negative urine pregnancy test, no debilitating illness that may preclude a pelvic examination, no prior history of screening or treatment for cervical neoplasia, and hysterectomy		80	colposcopy /histology	CIN2+
Screening Test: VIA									
Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa	Firnhaber et al.	2013	South Africa	cross-sectional	Eligible following treatment of symptomatic STD, if menstruating at study enrollment asked to return within one to two weeks , HIV-positive	pregnant, previously undergone a hysterectomy/treatment for cervical neoplasia or cancer, severely ill, signs and/or symptoms suggestive of a STD	941	histology	CIN2+
Screening of cervical neoplasia in HIV-infected women in India.	Joshi et al.	2013	India	cross-sectional	HIV-infected women, 21 and 60 years, no debilitating illness, not pregnant at recruitment, intact uterus with no prolapse, and no previous history of cervical neoplasia		1128	histology	CIN2+
Comparison of conventional cervical cytology versus visual inspection with acetic acid among HIV-infected women in Western Kenya	Mabeya et al.	2012	Kenya	cross-sectional	Female, age 15–49 years, documented HIV infection, healthy, no debilitating disease	Current pregnancy or pregnancy in the last 6 months, history of or treatment for cervical cancer, total hysterectomy, dilatation and curettage in the last 6 months, current mucopurulent discharge, active vaginal bleeding, and diagnosis of STI in the last 3 weeks	135	histology	CIN2+
Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV- infected women in India	Sahasrabuddhe et al.	2012	India	cohort study	consenting nonpregnant and previously unscreened HIV-infected women were enrolled in this study		303	histology	CIN2+
Screening Test: HC2 HPV DNA									

Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa	Firnhaber et al.	2013	South Africa	cross-sectional	Eligible following treatment of symptomatic STD, if menstruating at study enrollment asked to return within one to two weeks , HIV-positive	pregnant, previously undergone a hysterectomy/treatment for cervical neoplasia or cancer, severely ill, signs and/or symptoms suggestive of a STD	941	histology	CIN2+
Screening of cervical neoplasia in HIV-infected women in India.	Joshi et al.	2013	India	cross-sectional	HIV-infected women, 21 and 60 years, no debilitating illness, not pregnant at recruitment, intact uterus with no prolapse, and no previous history of cervical neoplasia		1128	histology	CIN2+
Prevalence and predictors of colposcopic-histopathologically confirmed cervical intraepithelial neoplasia in HIV-infected women in India.	Sahasrabuddhe et al.	2010	India	cohort study	HIV-positive, negative urine pregnancy test, no debilitating illness that may preclude a pelvic examination, no prior history of screening or treatment for cervical neoplasia, and no prior hysterectomy	pregnancy or prior hysterectomy	297	histology	CIN2+
HPV Prevalence and Cervical Intraepithelial Neoplasia among HIV-infected Women in Yunnan Province, China : A Pilot Study	Zhang et al.	2012	China	cross-sectional	HIV-positive, negative urine pregnancy test, no debilitating illness that may preclude a pelvic examination, no prior history of screening or treatment for cervical neoplasia, and hysterectomy		83	colposcopy /histology	CIN2+

Heterogeneity Test:

Heterogeneity was detected between studies in the meta-analysis for all of the screening tests ($I^2 \geq 75\%$ and $p \leq 0.05$) except for VIA. In the case of VIA, homogeneity was found for test sensitivity ($I^2 = 0.0\%$ and $p = 0.65$) but not for test specificity ($I^2 = 98.2\%$ and $p = 0.0$). Therefore, a random effects model was used to calculate pooled test statistics for this meta-analysis.

Accuracy of Screening Tests:

The accuracy of the screening tests for CIN2+ detection in HIV-infected women was assessed using the sensitivity and specificity. The individual study results are presented in Table 2 with their respective 95% confidence intervals. Pooled estimates of performance were calculated for each screening test. The HPV DNA test had the highest pooled sensitivity at 86.9% (95% CI, 58.3%-97.0%) and VIA has the second highest pooled sensitivity at 77.6% (95% CI, 73.5%-81.1%). Pap sensitivity was measured at two thresholds: a low grade squamous intraepithelial lesion (LSIL) cutoff and a high grade squamous intraepithelial lesion (HSIL) cutoff. The pooled sensitivity for Pap was higher using the LSIL cutoff (72.8%; 95% CI, 41.1%-91.2%) than the HSIL cutoff (34.2%; 95% CI, 8.7%-74.0%) (Figure 2 – Forest Plots: Sensitivity for Screening Tests for CIN2+).

The HPV DNA and VIA screening tests had pooled specificities of 60.2% (95% CI, 40%-77.5%) and 73.4% (95% CI, 50.5%-88.2%), respectively. For Pap, the pooled specificity using the LSIL cutoff and the HSIL cutoff were 72.9% (95% CI, 31.6%-94.0%) and 94.5% (95% CI, 78.0%-98.8%), respectively (Figure 3 – Forest Plots: Specificity for Screening Tests for CIN2+).

The HPV DNA and VIA screening tests had pooled PPV of 24.5% (95% CI, 2.5%-42.5%) and 40.8% (95% CI, 31.0%-51.3%), respectively. The pooled PPV for Pap using an LSIL cutoff and Pap using an HSIL cutoff were 35.4% (95% CI, 29.9%-41.4%) and 58.9% (95% CI, 49.4%-67.8%), respectively. The pooled NPV were 96.6% (95% CI, 89.1%-99.0%) for HPV DNA testing, 93.2% (95% CI, 77.8%-98.1%) for VIA, 92.9% (95% CI, 82.4%-97.3%) for Pap using an LSIL cutoff and 88.4% (95% CI, 76.2%-94.7%) for Pap using an HSIL cutoff (Table 2. Cervical Cancer Screening Test Performance).
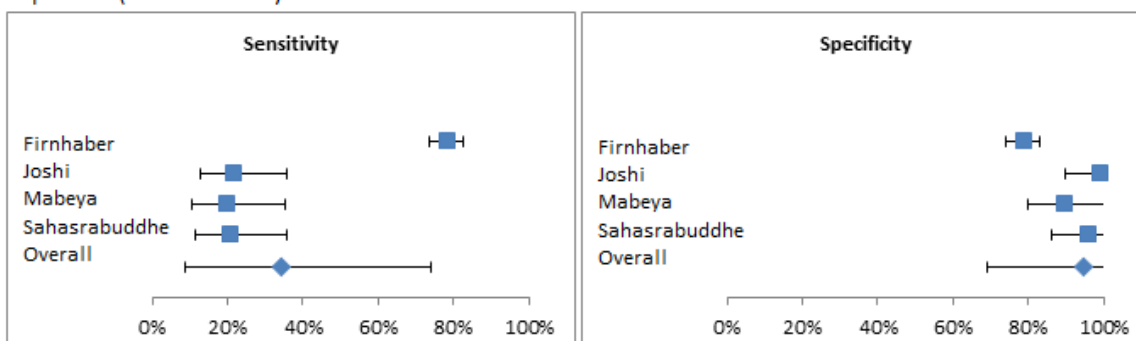
Figure 2. Forest Plots
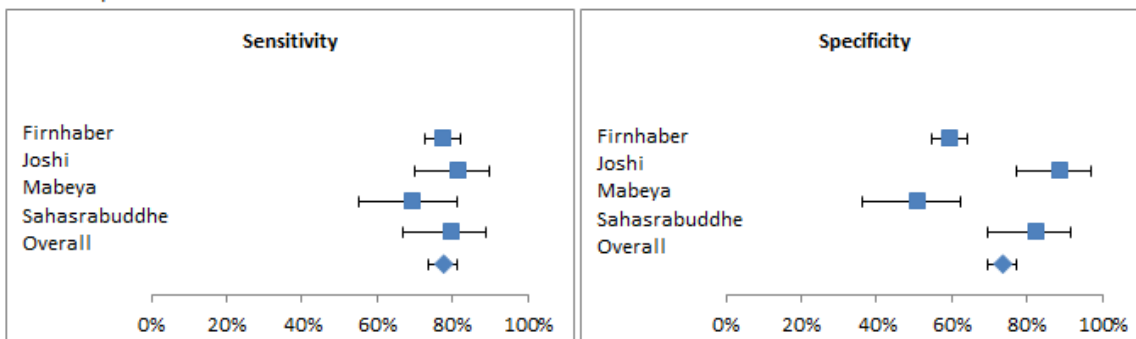
Screening Strategy I:
Pap smear (LSIL threshold)
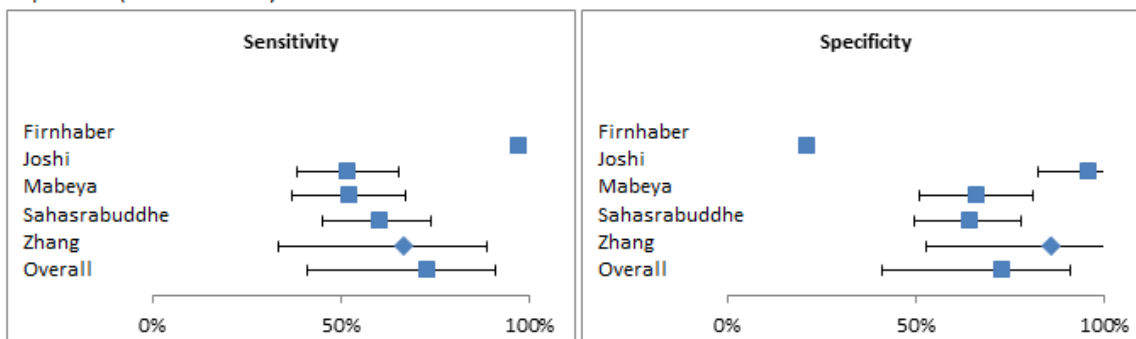
Pap smear (HSIL threshold)

Screening Strategy II:
Visual inspection with acetic acid

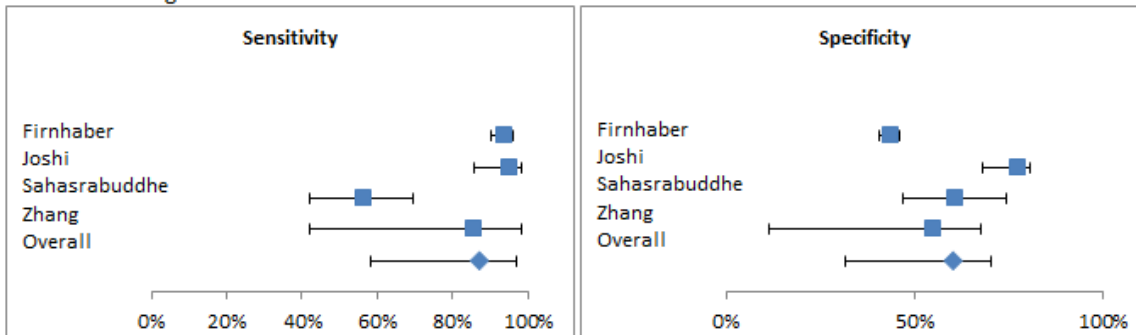Screening Strategy III:
HPV DNA testing with HC2

	Screening Type	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	PPV (95% confidence interval)	NPV (95% confidence interval)
Author					
Firnhaber et al.	PAP - LSIL	97.4% (94.9%-98.7%)	21.4% (18.4%-24.8)	37.8% (34.5%-41.3%)	94.4% (89.2%-97.2%)
Joshi et al.	PAP - LSIL	52.0% (38.3%-65.3%)	96.0% (94.6%-97.1%)	38.8% (28.0%-50.9%)	97.6% (96.5%-98.4%)
Mabeya et al.	PAP - LSIL	52.5% (37.2%-67.3%)	66.3% (56.3%-75.1%)	39.6% (27.5%-53.2%)	76.8% (66.5%-84.7%)
Sahasrabuddhe et al.	PAP - LSIL	60.5% (45.4%-73.8%)	64.6% (58.1%-70.6%)	24.8% (17.4%-33.9%)	89.4% (83.7%-93.3%)
Zhang et al.	PAP - LSIL	66.7% (33.3%-88.8%)	85.9% (75.8%-92.3%)	37.5% (17.9%-62.3%)	95.3% (86.5%-98.5%)
Total PAP LSIL		72.8% (41.1%-91.2%)	72.9% (31.6%-94.0%)	35.4% (29.9%-41.4%)	92.9% (82.4%-97.3%)
Firnhaber et al.	PAP - HSIL	78.4% (73.5%-82.6%)	78.8% (75.4%-81.8%)	64.5% (59.5%-69.1%)	88.1% (85.2%-90.5%)
Joshi et al.	PAP - HSIL	22.0% (12.6%-35.5%)	99.2% (98.5%-99.6%)	57.9% (35.6%-77.4%)	96.3% (95.0%-97.3%)
Mabeya et al.	PAP - HSIL	20.0% (10.3%-35.2%)	89.5% (81.5%-94.2%)	44.4% (24.0%-67.0%)	72.6% (63.9%-80.0%)
Sahasrabuddhe et al.	PAP - HSIL	20.9% (11.3%-35.6%)	96.0% (92.4%-97.9%)	50.0% (24.0%-67.0%)	86.3% (81.4%-90.0%)
Total PAP HSIL		34.2% (8.7%-74.0%)	94.5% (78.0%-98.8%)	58.9% (49.4%-67.8%)	88.4% (76.2%-94.7%)
Akinwuntan et al.	VIA	76.2% (54.0%-89.7%)	83.2% (77.0%-87.9%)	34.0% (22.0%-48.5%)	96.8% (92.6%-98.7%)
Firnhaber et al.	VIA	77.7% (72.8%-82.0%)	59.6% (55.7%-63.3%)	48.6% (44.2%-53.0%)	84.5% (80.8%-87.6%)
Joshi et al.	VIA	81.7% (69.8%-89.5%)	88.8% (86.7%-90.5%)	29.0% (22.7%-36.3%)	98.9% (97.9%-99.4%)
Mabeya et al.	VIA	69.6% (54.9%-81.1%)	51.0% (41.4%-60.4%)	38.6% (28.7%-49.3%)	79.1% (67.7%-87.2%)
Sahasrabuddhe et al.	VIA	80% (66.7%-88.9%)	82.6% (77.4%-86.8%)	47.6% (37.2%-58.2%)	95.4% (91.7%-97.5%)
Total VIA		77.6% (73.5%-81.1%)	73.4% (50.5%-88.2%)	40.8% (31.0%-51.3%)	93.2% (77.8%-98.1%)
Firnhaber et al.	HC2 HPV DNA	93.5% (90.2%-95.8%)	43.9% (40.1%-47.8%)	45% (41.2%-48.9%)	93.3% (89.8%-95.6%)
Joshi et al.	HC2 HPV DNA	95% (85.6%-98.4%)	77.4% (75%-79.8%)	19.1% (15.1%-24%)	99.6% (98.9%-99.9%)
Sahasrabuddhe et al.	HC2 HPV DNA	56.3% (42.1%-69.5%)	61% (54.8%-66%)	21.8% (15.4%-29.9%)	87.9% (82.1%-92.0%)
Zhang et al.	HC2 HPV DNA	85.7% (41.9%-98%)	55.3% (44%-66%)	15% (6.9%-29.6%)	97.7% (85.3%-99.7%)
Total HC2 HPV DNA		86.9% (58.3%-97%)	60.2% (40%-77.5%)	24.5% (12.5%-42.5%)	96.6% (89.1%-99.0%)

Table 2. Cervical Cancer Screening Test Performance

Discussion

Based on this meta-analysis of test performance of Pap, VIA, and HPV among HIV-infected women, HPV testing appears to have the highest sensitivity of 86.9% (95% CI, 58.3%-97.0%). This is ideal for women at high risk of pre-invasive and invasive cervical cancer (e.g.,

HIV-infected women) because HIV-infected women are more likely to have rapid progression of cancers[7,18] and a missed case could result in serious morbidity or mortality. The test also has specificity of 60.2% (95% CI, 40%-77.5%), a PPV of 24.5% (95% CI, 12.5%-42.5%) , and a NPV of 96.6% (95% CI, 89.1%-99.0%) . Despite its relatively favorable performance profile, several important barriers to wide-scale implementation remain, particularly in low-resources settings.

First, HPV DNA testing with HC2 is more expensive than VIA.[8] According to a cost analysis of cervical cancer screening techniques in South Africa by Goldie et al.[35] a single lifetime screening with HPV DNA testing (HC2) was associated with a cost of $118/years of life saved (YLS). A single lifetime screening program with VIA on the other hand was less expensive than not implementing a screening program. It may be possible to reduce the cost of HPV DNA testing if patient collected samples can be used instead of clinician collected samples. This reduced the cost effectiveness ratio for a single lifetime screening for HPV DNA testing to $26/YLS compared to no screening.[35] In addition, new rapid HPV DNA tests such as careHPV[TM] have the potential to decrease the screening cost to $50/YLS[36] for a single lifetime visit.

Second, HPV DNA testing with HC2 is technically complex.[15] Running HC2 HPV DNA test, detecting 13 high risk HPV genotypes with single amplification technology, requires sophisticated laboratories and training that may not be available in low-resources settings.[37] To address this issue, the careHPV[TM] screening test was developed as an alternative to HPV DNA testing with HC2 for low-resource settings.[37,38] It does not require refrigeration of the reagent, can be run by a healthcare worker with limited training, and only takes two and half hours to run the results.[37] The implementation of screening programs using careHPV[TM] may make national HPV screening programs a feasible option in low-resource settings.

Finally, HPV DNA testing is logistically complex, requiring multiple visits and a diagnostic test. HPV DNA testing requires multiple visits to a health facility because there are no commercially available point-of-care HPV tests.[8] In order to reduce the number of visits, researchers have looked into the efficacy of HPV DNA testing samples collected by the patient herself because the quality of the sample is less important in determining the sensitivity of HPV DNA testing than in cytology screening.[39] A meta-analysis by Ogilvie et al.[40] found that self-collected samples for HPV DNA testing has similar accuracy (sensitivity of 74% and a specificity of 88%) to provider collected samples;[28] however, there is limited data on self-collection in HIV-infected women.

If HPV DNA testing is used as the primary screening technique, a diagnostic test is essential to reduce overtreatment because of its modest specificity 60.2% (95%, CI 40%-77.5%), likely due to the large number of HIV-infected women that are infected with HPV DNA but do not exhibit lesions.[39] Colposcopy is recommended for all positive cases; however, due to the higher number of false positives with HPV DNA screening, a PPV of only 24.5% (95%, CI12.5%-42.5%), the number of women sent for a diagnostic test would increase, increasing the cost and case load at colposcopy clinics.[41] However, this meta-analysis demonstrated that HPV DNA testing has a high negative predictive value of 96.6% (95%, CI 89.1%-99.0%). Therefore, a HIV-infected woman that tests negative for HPV DNA is not likely to have cervical lesions and would not need follow-up diagnostic testing. HIV-infected women have a higher prevalence of HPV infection than HIV-negative women, therefore, for HPV DNA testing to be used as a primary screening technique there need to be local resources and personnel to provide the additional diagnostics to confirm the presence of lesions in HPV-positive women.[42] If no diagnostic test is available in a limited resource setting, triage tests with either VIA or Pap after

screening with HPV DNA testing has been proposed as an alternative,[42] particularly if they can be done at the same visit. This could be an alternative to expensive diagnostic tests; however, additional research is needed on this topic for HIV-infected women.

In many low-resource settings, VIA has been used to overcome the barriers associated with either cytology or HPV-based screening. For example prioritizing a screening test with high specificity rather than sensitivity would reduce the cost associated with the diagnostic test[41] and over-treatment, which may be associated with adverse pregnancy outcomes such as spontaneous abortion,[43] pre-term delivery,[44,45] and cervical stenosis.[45] While Pap with a HSIL threshold had the highest specificity at 94.5% (95%, CI 78.0%-98.8%), Pap smear screening programs are difficult to implement in low-resource settings because of the resources and personal required.[4,9] In addition, studies have found high false negative rates when screening with cytology in HIV-infected women.[39] VIA has a higher specificity than HPV DNA testing (73.4% compared to 60.2%) and a lower cost to implement, both in technical expertise and equipment.[8]

VIA can also be implemented using the screen-and-treat approach in which a women is screened and treated in the same visit without a confirmatory diagnostic test. This approach has already been implemented in several countries as an alternative to the traditional cervical screening method of conducting the screening test in the first visit and returning for a second visit for treatment.[46–49] The screen-and-treat approach can reduce the number of visits required for screening and treatment and reduces the risk of loss to follow-up.[45] It has also been determined to be safe in HIV-infected women[18,49] and is a feasible screening option for HIV-infected women in low-resource settings. Additional research could strengthen the argument for the use of the screen-and-treat approach in HIV-infected women because currently some studies

do not confirm their diagnosis with colposcopy directed biopsy[49,50] and therefore, over treatment or missed cases cannot be determined.

Strengths of the Study

This meta-analysis was conducted based on the PRISMA guidelines for meta-analyses and systematic reviews, reducing the risk of reporting bias in the results. All studies that met the inclusion and exclusion criteria for the review and had available data were included in the analysis. In addition, all efforts were made to contact the original authors of studies that were considered for inclusion but did not provide all of the necessary results in the published articles. Also, the pooled statistics were calculated taking into account variability across studies in screening test performance.

Limitations of the study

One of the main limitations of the meta-analysis was that for the pooled test performance, the patient populations, sample size, and screening methods were not exactly the same. There was an age range in the populations from 18 through 65 years. The differences in screening test performance were not broken down by age group in all of the studies. Also, studies had different sample sizes ranging from 83 to 1,128 which affected the power of the individual studies and the may have reduced reliability of the smaller study test statistics. The pooled test statistics calculated in the meta-analysis may have then been affected by the resultant variation in reliability. Furthermore, the training and practitioner for the screening methods were not standardized across studies. This is relevant to the current meta-analysis because VIA has been shown to be more accurate when an experienced nurse or doctor is performing the procedure.[29] All of these differences may have led to the high level of heterogeneity between the studies. There may have also been positive bias in the studies due to the use of colposcopy directed

biopsy to perform histology as the gold standard.[51–53] Colposcopy is not an exact test and may in fact miss the same CIN2+ lesions as the other screening tests for cervical cancer including those included in this meta-analysis, falsely increasing the sensitivity of the screening test.[53] Therefore, the sensitivities reported in the meta-analysis may be higher than the true test sensitivities.

Conclusion

This meta-analysis demonstrates that HPV DNA testing with HC2 is highly sensitive (86.9%; 95% CI, 58.3%-97%) for HIV-infected women. Because molecular testing is often more reliable, it is becoming the preferred global standard; however, there are still any barriers to implementing molecular screening programs in low-resources settings. These include the relatively high cost of the test, a need for a well-established, modern national laboratory services, and the logistical difficulties of asking women to return for test results and/or for additional diagnostic testing and treatment. While countries work towards establishing more complex HPV-based screening programs, VIA screening may be an acceptable, short-term alternative. The single-visit screen-and-treat approach is an important and attractive feature of VIA-based programs. VIA may also be easier to integrate into already existing HIV programs than HPV DNA testing because of the low cost and lack of technology required.[13,14] This meta-analysis combines the existing literation on cervical cancer screening modalities for HIV-infected women, demonstrating the current gaps in this field of study.

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