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ORIGINAL RESEARCH

# Visual inspection using naked eye and colposcopy as a predictor of high-grade lesions on final histology in HIV-positive and -negative South African women

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**Background:** Although potentially preventable, cervical cancer is the fourth most common cancer among women globally and a leading cause of cancer-related deaths. Women living in resource-limited countries are especially at risk due to poor access to cervical cancer screening and treatment. Alternative cervical cancer screening methodologies have been investigated where cytology-based screening is not feasible. This study aimed to assess the test performance of naked eye visual inspection analysis, in addition to the comparative performance of physician/colposcopist clinical impression to Reid's colposcopic index (RCI) grading system for histopathology, in the South African setting.

**Methods:** Women living with HIV (WLWH) and HIV-negative women aged 25 to 65 were recruited from three sites in South Africa. A cross-sectional study which assessed visual inspection with acetic acid (VIA), visual inspection with lugols iodine (VILI), colposcopic impression and RCI for the detection of histologically confirmed CIN2+ and CIN3+ was performed. Test positivity rates, sensitivity, specificity, and predictive values were calculated.

**Results:** Three hundred and forty-four WLWH and 409 HIV-negative women, with a median age of 40 years, were included in this analysis. Histologically confirmed CIN2+ was present in 38.51% and CIN3+ in 18.99%. Overall, positive test rates for VIA were 42.76%; VILI were 45.68%, colposcopic impression were 48.26% and RCI were 46.65%. Overall sensitivities/specificities for VIA and VILI for CIN3+ were 76.92/65.25% and 75.52/61.31%, respectively. The sensitivities however increased for WLWH (VIA 82.61%; VILI 80.43%) and decreased in HIV-negative women (VIA 66.67%; VILI 66.67%). Colposcopic impression/RCI performed better in WLWH (PPV 37.96/37.74%) than in HIV-negative women (PPV 25.63/26.80%).

**Conclusion:** The current study demonstrates that visual inspection methods perform better in WLWH than in HIV-negative women. VIA and VILI performed similarly within each sub-population, as did colposcopic impression and RCI. The use of visual inspection methods in cervical cancer screening in WLWH is warranted.

**Keywords:** cervical cancer, visual inspection with acetic acid, VIA, visual inspection with lugols iodine, VILI, colposcopic impression, Reid's colposcopic index, RCI

## Background

Cervical cancer is the fourth most frequently diagnosed cancer among women globally and the fourth leading cause of death. The GLOBOCAN estimates for 2020 indicate that approximately 604 127 women are diagnosed with cervical cancer annually, while 341 831 die from the disease.[1] The highest regional incidence and mortality is in sub-Saharan Africa, with rates elevated in Eastern Africa, Southern Africa, and Middle Africa. In South Africa, cervical cancer is the second most common cancer diagnosed among women and the commonest cancer among women in the reproductive age group 15 to 49 years.[2] Estimates for 2020 were reported at 12 333 incident cases (age-standardised incidence rate 36.4/100 000) and 6 867 deaths (age-standardised incidence rate 20.6/100 000). These alarming figures are particularly tragic, given cervical cancer is a potentially preventable disease. Successfully organised national cervical cancer prevention programmes have not yet been implemented in most developing countries due to reasons such as poverty, competing funding priorities, low prioritisation of cervical cancer and cultural practices.[3,4]

South Africa launched a national screening programme for cervical cancer prevention in 2000, offering three Papanicolaou (Pap) smears per lifetime starting after the age of 30, with 10-year intervals for HIV-negative women and three-year intervals for women living with HIV (WLWH). This national screening programme, however, has not been implemented widely in the public sector. Screening programmes based on Pap smears require technical capabilities and systems for training, effective communication, follow-up visits and transportation that are sometimes beyond the capacity of healthcare infrastructure in parts of South Africa. While cytology has reduced cervical cancer incidence, cases of cervical cancer still occur due to the wide variability of the sensitivity of the screening method.[5,6] Consequently, over referrals and over treatment often occur. Thus, other methods of cervical-cancer screening provision have been investigated.

Several other screening tests are currently available for detecting pre-invasive cervical lesions. The most recent option is the direct detection of the human papillomavirus (HPV) in cervical specimens by target DNA amplification using polymerase chain reaction (PCR). The known cause of cervical pre-cancer and cancer is persistent infection with HPV.[7] HPV is one of the most prevalent sexually transmitted infections (STIs) worldwide, with infection with at least one strain of HPV occurring in approximately 70–80% of sexually active women during their lifetime.[8]

HPV DNA testing is the most sensitive test for cervical cancer screening and has a negative predictive value (NPV) approaching 100%, allowing for an increase in the screening interval for negative tests. As a result, fewer follow-up visits and additional tests are required, making it more cost effective than cytological testing.[9] The use of HPV DNA testing as a primary screening method, however, requires the use of a triage test to identify women with clinically relevant infections, as many of the detected infections are transient, and only a minority are associated with cervical abnormalities. HPV DNA testing in isolation may therefore not be clinically meaningful.[10]

In South Africa, HPV testing is only offered in the private sector and is not yet widely available in the public sector as part of the national screening programme. This method of screening also requires specialised equipment.[5] Women who test positive for HPV16 and HPV18 (often referred to as highest-risk HPV) are referred for a colposcopy and biopsy. Women who test positive for "non-highest-risk" HPV or a non-discriminate test are considered medium or intermediate risk. A test is thus needed to determine the need for referral to colposcopy or other follow-up procedures.[11]

Another screening option involves searching visually for macroscopic cervical pre-cancerous lesions with the application of diluted acetic acid (3–5%) (VIA) and/or lugol's iodine (VILI). The purpose of this screening technique is to identify acetowhite areas for VIA and areas of iodine non-uptake (non-staining) (areas in the form of pale or yellowish-white areas, particularly in the transformation zone, close to the squamocolumnar junction) for VILI, which may indicate tissue undergoing pre-cancerous changes. Screening with VIA and/or VILI is advantageous given the procedure is inexpensive, relatively straightforward, can be performed by non-physician healthcare workers and results are available immediately, allowing for the implementation of a screen-and-treat approach. It is, however, important to note that VIA and/or VILI may require rigorous, standardised training and continuous quality assurance, since it is subjective and dependent on expertise. While many researchers question the relevance of visual inspection in the cervical cancer screening paradigm, the South African Cervical Cancer Prevention and Control Policy proposes to offer VIA as the screening approach in resource-constrained regions, pending the national scale-up of liquid-based cytology and the rollout of HPV testing.[5] Additionally, many non-governmental organisations and governments around the world continue to support VIA and/or VILI, because of the low cost and low technological demand and the fact that results are available immediately, making screen-and-treat possible.[12-14]

A large cluster-randomised trial by Sankaranarayanan et al., assessing the effect of visual screening on cervical cancer incidence and mortality in India, reported a significant 25% reduction in cervical cancer incidence (hazard ratio 0.75 [95% CI 0.55–0.95]) and a significant 35% reduction in cervical cancer mortality (hazard ratio 0.65 [0.47–0.89]) in 49 311 women screened with a single round of VIA. Their findings indicate that VIA is a simple, feasible, and effective method to prevent cervical cancer and death among deprived populations in developing and developed countries.[15]

Colposcopy is an advanced method of visual inspection that allows a detailed assessment of the cervix, following a positive screening test result. As described in the manual for Colposcopy and Treatment by the International Agency for Research on Cancer (IARC), a colposcopic examination includes: i) the assessment of the cervix with low- and high magnification of at least 6–15 × ii) the assessment with acetic acid and/or lugol's iodine and iii) the assessment with white and/or green light. Various quantitative scoring systems are available. For the purpose of this study, we chose to evaluate colposcopic impression and the Reid's colposcopic index (RCI). The RCI is a systematic, objective method of colposcopically grading the severity of premalignant cervical lesions. The index considers four colposcopic signs: lesion margin, colour of acetowhitening, blood vessels, and iodine staining.[16]

This study aimed to assess the test performance of naked eye visual inspection analysis in the South African setting where data is limited, in addition to the comparative performance of physician/colposcopist clinical impression to the RCI grading system for histopathology.

## Materials and methods

### *Design, setting and population*

The DiaVACCS study (ethics approval obtained) was a cross-sectional cohort study in which women between the ages of 25 and 65, unscreened in the preceding five years, were recruited from three sites in South Africa from December 2016 to March 2020. The study design, methodology and basic descriptive data have previously been described.[17] The aim of this study was to evaluate the performance of screening tests in general female and HIV-infected populations.

The current study comprised 753 women, of which 344 were HIV positive. Women were recruited from the general population, and from adult antiretroviral treatment (ART) clinics. All women were included in the VIA and VILI analysis. Of the 753 women, seven had missing colposcopy data and were excluded from the colposcopic impression and RCI analysis.

### *Visual inspection without magnification*

During the speculum exam, 3–5% acetic acid was applied to the cervix, using forceps and a cotton ball. After one minute, lesions were described based on size in quadrants, density of the acetowhite lesion and whether the transformation zone was

seen. The presence of other lesions, such as warts and ulcers was also noted. Sharp, distinct, and well-defined acetowhite areas were considered a test positive. Following acetic acid application, lugol's iodine was liberally and gently applied to the cervix using forceps and a cotton ball. Non-staining areas were considered a test positive.

### *Colposcopy*

A colposcopy was performed after the application of 3–5% acetic acid and before and after the application of lugol's iodine. The colposcopist recorded a clinical impression of the character of the lesion based on size in quadrant, acetowhitening, iodine uptake, vessels, and margin/surface of the lesion. The clinical impression was reported as either negative, low-grade, or high-grade, with both low-grade and high-grade considered test positives. The RCI was then formally calculated based on the character of the lesion. An RCI score of 5 and above was considered positive.

### *Biopsy and histology processing*

All visually detected lesions were biopsied. If no lesions were seen in a cervical quadrant, a random biopsy was obtained at the squamocolumnar junction in that quadrant. Two biopsies were obtained per participant. Histology examination was performed by an experienced histopathologist. In women who underwent large loop excision of the transformation zone (LLETZ) treatment, the worst histology between the biopsy and LLETZ was taken as final diagnosis.

### *Statistical analysis*

Microsoft Excel was used as the primary software for the data analysis process. VIA, VILI and colposcopy results were analysed by age group, HIV status and overall. The performance on the sensitivity, specificity, negative and positive predictive values were calculated with a gold standard of histology CIN2+ and CIN3+. Suitable values for missing histology were imputed using R programming language based on the participants age, HIV status, ARV use, and whether they screened positive or negative. Continuous variables were summarised using means and standard deviations. Categorical variables were summarised using percentages. Results were summarised in tables with two-sided confidence intervals calculated based on a 95% t-distribution. Significance level was set at 5%.

## Results

The median age of women was 40 years (IQR 34–48). A total of 344 (45.68%) were WLWH and 409 (54.32%) were HIV negative. CIN1+ was diagnosed in 504 (66.93%) women, CIN2+ in 290 (38.51%) women, CIN3+ in 143 (18.99%) women and 15 (2%) were screen-detect cervical cancers (Table I). Overall, the positivity rate for VIA was 322 (42.76%) and 344 (45.68%) for VILI. The positivity rates for both visual inspection screening tests were significantly higher in WLWH than in HIV-negative women ($p < 0.00001$), with the highest observed in VILI (62.21%). The rate of screen positives in WLWH was almost double that of HIV-negative women (Table II).

**Table I:** Histology results amongst WLWH and HIV-negative women

| Histology | WLWH *n* = 344 | | HIV neg *n* = 409 | | Total *n* = 753 | | *p*-value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Negative | 95 | 28.02 | 141 | 36.53 | 236 | 31.34 | $p = 0.01309$ |
| CIN2+ | 170 | 50.15 | 120 | 31.09 | 290 | 38.51 | $p < 0.00001$ |
| CIN3+ | 92 | 27.14 | 51 | 13.21 | 143 | 18.99 | $p < 0.00001$ |
| Cervical cancer | 9 | 2.65 | 6 | 1.55 | 15 | 1.99 | $p = 0.25281$ |

**Table II:** Percentage screen positives for visual inspection cervical cancer screening methods

| Screening visual inspection method | WLWH *n* = 344 | | HIV neg *n* = 409 | | Total *n* = 753 | | *p*-value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| VIA | 204 | 59.30 | 118 | 28.85 | 322 | 42.76 | $p < 0.00001$ |
| VILI | 214 | 62.21 | 130 | 31.78 | 344 | 45.68 | $p < 0.00001$ |

Overall, positive test rates for colposcopic impression and RCI were 360 (48.26%) and 348 (46.65%), respectively. The highest observed positivity rates were in WLWH for both colposcopic impression and RCI. The positivity rate for RCI in WLWH was 24.56% higher in absolute terms in comparison to HIV-negative women (Table III).

**Table III:** Percentage abnormal colposcopic findings

| Diagnostic (visual inspection) method | WLWH *n* = 344 | | HIV neg *n* = 402 | | Total *n* = 753 | | *p*-value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Colposcopic impression | 210 | 61.05 | 150 | 37.31 | 360 | 47.81 | $p < 0.00001$ |
| RCI | 206 | 59.88 | 142 | 35.32 | 348 | 46.22 | $p < 0.00001$ |

The overall sensitivity, specificity, PPV and NPV of VIA for CIN2+ was 65.17%, 71.27%, 58.70% and 76.57%, respectively. Similarly, the overall sensitivity, specificity, PPV and NPV of VILI for CIN2+ was 64.48%, 66.09%, 54.36% and 74.82%, respectively. The sensitivity of VIA to detect CIN2+ was higher in WLWH compared to HIV-negative women; 76.47% and 49.17%, respectively. A similar trend was observed for the sensitivity of VILI to detect CIN2+ in WLWH (75.88%) and in HIV-negative women (48.33%).

Both visual screening methods performed equally within each sub-population and are thus equally suited methods for the detection of CIN3+. The sensitivity is above 75% overall. The sensitivity of VIA to detect CIN3+ was higher in WLWH compared to HIV-negative women; 82.61% and 66.67%, respectively (Table IV).

The lowest specificity was observed for VILI in WLWH (44.44%) and the highest for VIA in the HIV-negative cohort (76.54%). The lowest PPV was observed in the HIV-negative cohort, with VIA and VILI having comparative results, 28.81% and 26.15%, respectively (Table IV).

The overall PPV and NPV for colposcopic impression for CIN2+ were 57.45% and 80.22%, respectively. RCI performed similarly with a PPV of 58.08% and an NPV of 79.79%. Colposcopic

**Table IV:** Comparative performance of cervical cancer visual inspection screening tests for histologic outcome CIN3+

| | Characteristic | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|
| Total | VIA | 76.92 (69.96–83.89) | 65.25 (61.46–69.03) | 34.16 (28.96–39.36) | 92.34 (89.83–94.86) |
| | VILI | 75.52 (68.42–82.63) | 61.31 (57.44–65.18) | 31.40 (26.47–36.32) | 91.44 (88.72–94.16) |
| WLWH | VIA | 82.61 (74.76–90.46) | 49.21 (43.00–55.41) | 37.25 (30.58–43.93) | 88.57 (83.25–93.89) |
| | VILI | 80.43 (72.22–88.65) | 44.44 (38.28–50.61) | 34.58 (28.17–40.99) | 86.15 (80.16–92.15) |
| HIV neg | VIA | 66.67 (53.41–79.93) | 76.54 (72.13–80.94) | 28.81 (20.56–37.07) | 94.16 (91.45–96.86) |
| | VILI | 66.67 (53.41–79.93) | 73.18 (68.58–77.79) | 26.15 (18.53–33.78) | 93.91 (91.09–96.73) |

impression and RCI performed similarly in both sub-populations for CIN2+. The PPVs of both colposcopic tests for CIN2+ (colposcopic impression [64.81%]; RCI [64.62%]) in WLWH were significantly higher than for CIN3+ (colposcopic impression [37.96%]; RCI [37.74%]).

**Table V:** Comparative performance of colposcopy to Reid Colposcopic Index for histologic outcome CIN3+

| | Characteristic | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|
| Total | Colposcopic impression | 32.71 (27.96–37.47) | 94.58 (92.26–96.90) |
| | RCI | 33.15 (28.31–38.00) | 94.23 (91.88–96.58) |
| WLWH | Colposcopic impression | 37.96 (31.45–44.47) | 92.19 (87.49 – 96.88) |
| | RCI | 37.74 (31.17–44.30) | 90.91 (85.96 – 95.86) |
| HIV neg | Colposcopic impression | 25.63 (18.81–32.44) | 95.98 (93.53 – 98.43) |
| | RCI | 26.80 (19.72–33.87) | 95.98 (93.53 – 98.43) |

Both methods performed equally within each sub-population. The PPVs of both colposcopic tests in WLWH were higher than for HIV-negative women. Expectably, a reverse trend was observed for the NPVs, with the strongest rule-in combinations performing slightly less well in ruling out disease. All testing combinations yielded NPVs above 90%.

## Discussion

### *Overall test positivity rates*

The current study evaluated the test performance of VIA and VILI *screening* methods and the *diagnostic* accuracy of colposcopic impression and RCI for CIN2+ and CIN3+ detection in South African women. Study findings were analysed overall and by HIV status.

Overall, we observed a notably high rate of positive test results including CIN2+ (38.51%), VIA (42.76%), VILI (45.68%), colposcopic impression (47.81%) and RCI (46.22%). Test positivity rates are consistent with findings in other studies conducted in South Africa and is potentially due to a high prevalence of HPV infection, high HIV burden and an unscreened general population.[18-20]

### *Overall performance of VIA and VILI as screening tools*

Overall, both VIA and VILI performed adequately at CIN2+. Performance improved at a higher disease threshold. Comparable sensitivities were observed for both tests at different disease thresholds. Our results are in line with several studies which demonstrate relatively high sensitivities, a range of specificities and low PPVs. A cross-sectional study conducted in Angola by Muwonge et al., evaluating the feasibility of cervical screening using VIA or VILI to detect and treat CIN found VILI to be more sensitive in detecting CIN2+ with a sensitivity and specificity of 88% (95% CI 78.4–94.4%) and 68.9% (95% CI 67.9–69.9%), respectively. The sensitivity of VIA was 70.7% (95% CI 59–80.6%) and specificity 94.5% (95% CI 94–95%).[21] The clinical significance of the screening tests can be described by evaluating the predictive values. The PPVs for both screening tests were approximately 20% higher for CIN2+ than CIN3+, meaning only 34.16% and 31.40% of women screened positive with VIA and VILI respectively, truly had a confirmed CIN3+ on histology. The high NPV for CIN3+ observed for both VIA and VILI means that 92.34% and 91.44% of women who screened negative with VIA and VILI respectively, in fact did not have a confirmed CIN3+.

### *Performance of VIA and VILI as screening tools in WLWH and HIV-negative women*

Positive test results were especially high in WLWH including 50.15% CIN2+, 27.14% CIN3+, 59.30% VIA, 62.21% VILI, 61.05% colposcopic impression and 59.88% RCI. Numerous studies have reported the association of HPV infection with increasing immunosuppression. WLWH have a high prevalence of HPV infection and are infected with a broader range of HPV genotypes than HIV-negative women, as described by Mbulawa et al., in which the prevalence of HPV in South African men and women according to age and HIV status was examined. The study included 486 women and demonstrated a high HPV prevalence of 74% (205/277; 95% CI 68.5–78.8%) among WLWH.[22] A prospective cohort study conducted in Cape Town by Zeier et al. found that immune restoration of WLWH by the initiation of combination antiretroviral therapy (cART) significantly reduced the risk for detection of HPV by 77% (OR 0.23, 95% CI 0.15–0.37).[23]

Both screening methods had sensitivities higher than 75% for both CIN2+ and CIN3+ in WLWH, with specificities ranging from 45% to 58%. Our HIV-positive sensitivity results appear consistent with other studies in Africa, with variable specificities reported. A study conducted in Kenya by Akinwuntan et al., assessing the correlation of cervical cytology and VIA in 150 WLWH, found VIA to have a sensitivity of 76% (95% CI 52–91%); specificity of 83% (95% CI 77–88%), PPV of 34% (95% CI 21–49%), and an NPV of 97% (95% CI 92– 99%).[24] In a randomised clinical trial by Kuhn et al., assessing two screen-and-treat strategies among 6 555 women in Cape Town, South Africa, among whom 956 were HIV-positive, the sensitivity of VIA was 63.9% (95% CI 46.2–79.2%) for CIN2+ and 58.3% (95% CI 27.7–84.8%) for CIN3+.[25]

### *Overall performance of colposcopic impression and RCI as diagnostic tools*

Both colposcopy methods had comparable PPVs for CIN2+ and CIN3+, with the highest observed PPVs for CIN2+. A study by Durdi et al., aimed at estimating the diagnostic efficacy of colposcopy and determining the strength of correlation between colposcopic impression using RCI and histopathology, found the PPV and NPV of colposcopy with CIN 1 as a disease threshold was 77% and 93.5% respectively and with CIN 2 as a disease threshold 95.8% and 98.3% respectively, quite high in comparison to our findings. No results were reported for CIN3. The degree of correlation between colposcopic impression using RCI and histopathology was substantial ($k = 0.73$).[26]

The difference observed in their study in comparison to ours could be explained by the disease prevalence of their population. As described by Power et al., PPVs and NPVs are attractive because they are clinically insightful. But, because they are dependent on prevalence, predictive values may not be applicable in practice.[27] As disease prevalence increases, the PPV of the test increases, and reciprocally, the NPV of the test decreases. As prevalence decreases, the opposite occurs: the NPV of the same test increases while the PPV decreases. Additionally, the design of our study differed in that all women in our study underwent colposcopy, regardless of screening test result.

### *Performance of colposcopic impression and RCI as diagnostic tools in WLWH and HIV-negative women*

The PPV of colposcopy for both disease thresholds were higher in WLWH than in HIV-negative women, which is expected given the disease prevalence of WLWH compared to that of HIV-negative women. Colposcopy has previously been demonstrated to correlate with histological diagnosis in WLWH in comparison to HIV-negative women. A study conducted in Cape Town by Batra et al., assessing the utilisation and outcomes of cervical cancer prevention services among HIV-infected women, found that in WLWH ($n = 897$), the PPV was 83%, and in HIV-negative women ($n = 537$) it was 81.1%.[28]

### *Strengths and limitations*

The current study reports cervical cancer screening among women in South Africa, a country with one of the highest HIV prevalence, and included a representative number of women attending adult ART clinics. The study included a high proportion of participants with confirmed histology.

## Conclusion

Cervical cancer screening strategies requiring multiple visits for diagnosis and treatment have proven difficult to implement in low-resourced and most medium-resourced countries. Visual screening methods as an alternative to cytology-based screening programmes are advantageous, given it is affordable with immediate results, can be performed by non-physician practitioners, allows for point-of-care testing, and allows for immediate treatment, meaning no loss to follow-up.

While the current study demonstrates that visual inspection methods could be useful in cervical cancer screening, particularly in WLWH, it is important to consider that in most studies, VIA and VILI demonstrate adequate sensitivity, only if intensive quality assurance is undertaken. This, however, may not always be possible to implement in non-academic environments and may result in over-treatment due to a relative lack of specificity.

The WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention recommends the rapid transition of existing screening programmes using VIA/VILI as a primary screening tool in the general population and in WLWH because of the inherent challenges with quality assurance. If VIA/VILI is the only screening tool feasible in the screening setting, it should be used in a screen-and-treat approach, with immediate treatment after a positive test result. In a screening paradigm where HPV DNA testing is available, VIA/VILI can be used as a triage tool in a screen, triage and treat approach.

Colposcopy, whether formally or informally scored, had a relatively poor PPV for CIN3+, regardless of HIV status, and for CIN2+ in HIV-negative women. The main finding is that clinician impression (of experienced colposcopists) did similar to RCI.

### *Conflict of interest*

The authors declare no conflict of interest.

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### *Ethical approval*

Ethical approval was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (ref no 196/2014).

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## Appendices

**Table A1:** Distribution of age (years) and percentage WLWH and HIV-negative women screened for cervical cancer

| Characteristic | No (%) |
|---|---|
| Age group, years | |
| 25–29 | 96 (12.75) |
| 30–34 | 110 (14.61) |
| 35–39 | 160 (21.25) |
| 40–44 | 137 (19.07) |
| 45–49 | 98 (18.19) |
| 50–54 | 86 (11.42) |
| 55–59 | 45 (5.98) |
| 60–64 | 21 (2.79) |
| HIV status | |
| HIV positive | 344 (45.68) |
| HIV negative | 409 (54.32) |

**Table A2:** Histology results amongst WLWH and HIV-negative women without imputation

| | WLWH *n* = 339 | | HIV neg *n* = 386 | | Total *n* = 725 | | *p*-value |
|---|---|---|---|---|---|---|---|
| Histology | *n* | % | *n* | % | *n* | % | |
| Negative | 95 | 28.02 | 141 | 36.53 | 236 | 32.55 | $p = 0.01309$ |
| CIN2+ | 169 | 49.85 | 114 | 29.53 | 283 | 39.03 | $p < 0.00001$ |
| CIN3+ | 91 | 26.84 | 50 | 12.95 | 141 | 19.45 | $p < 0.00001$ |
| Cervical cancer | 9 | 2.65 | 6 | 1.55 | 15 | 2.07 | $p = 0.25281$ |

**Table A3:** Comparison of screen positives for visual inspection cervical cancer screening methods among different age groups in WLWH and HIV-negative women

| Age groups | VIA *n* = 753 | | | | VILI *n* = 753 | | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | WLWH *n* = 344 | | HIV neg *n* = 409 | | WLWH *n* = 344 | | HIV neg *n* = 409 | | |
| | *n* | % | *n* | % | *n* | % | n | % | |
| 25–44 | 153 | 44.48 | 73 | 17.85 | 156 | 45.35 | 73 | 17.85 | $p < 0.00001$ |
| 45–64 | 51 | 14.83 | 45 | 11.00 | 58 | 16.86 | 57 | 13.94 | $p = 0.04904$ |

**Table A4:** Comparison of abnormal colposcopic findings among different age categories in WLWH and HIV-negative women

| Age groups | Colposcopic impression *n* = 746 | | | | RCI *n* = 746 | | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | WLWH *n* = 344 | | HIV neg *n* = 402 | | WLWH n = 344 | | HIV neg *n* = 402 | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | |
| 25–44 | 158 | 45.93 | 89 | 22.14 | 157 | 45.64 | 85 | 21.14 | $p < 0.00001$ |
| 45–64 | 52 | 15.12 | 61 | 15.17 | 49 | 14.24 | 57 | 14.18 | $p = 0.98697$ |

**Table A5:** Comparative performance of cervical cancer visual inspection screening tests for histologic outcome CIN2+

| | Characteristic | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|
| Total | VIA | 65.17 (59.67–70.68) | 71.27 (67.14–75.41) | 58.70 (53.30–64.09) | 76.57 (72.56–80.58) |
| | VILI | 64.48 (58.95–70.01) | 66.09 (61.77–70.41) | 54.36 (49.08–59.64) | 74.82 (70.21–79.42) |
| WLWH | VIA | 76.47 (70.05–82.89) | 57.47 (50.07–64.87) | 63.73 (57.09–70.36) | 71.43 (63.88–78.98) |
| | VILI | 75.88 (69.41–82.36) | 51.15 (43.67–58.63) | 60.28 (53.69–66.87) | 68.46 (62.20–74.72) |
| HIV neg | VIA | 49.17 (40.13–58.20) | 79.58 (74.92–84.25) | 50.00 (40.88–59.12) | 79.04 (74.34–83.73) |
| | VILI | 48.33 (39.30–57.37) | 75.09 (70.08–80.09) | 44.62 (35.99–53.24) | 77.78 (70.56–84.99) |

**Table A6:** Comparative performance of cervical cancer visual inspection screening tests for histologic outcome CIN2+ stratified by age

| Age group | Characteristic | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|
| 25–44 | VIA | 67.30 (60.93–73.67) | 71.23 (66.02–76.45) | 62.83 (56.50–69.17) | 75.09 (69.97–80.21) |
| | VILI | 65.88 (59.44–72.31) | 69.18 (63.86–74.50) | 60.70 (54.34–67.06) | 73.72 (67.99–79.45) |
| 45–65 | VIA | 59.49 (48.50–70.49) | 71.35 (64.52–78.17) | 48.96 (38.83–59.09) | 79.22 (72.76–85.68) |
| | VILI | 60.76 (49.82–71.70) | 60.82 (53.45–68.19) | 41.74 (32.63–50.85) | 77.04 (69.27–84.81) |

**Table A7:** Comparative performance of cervical cancer visual inspection screening tests for histologic outcome CIN3+ stratified by age

| Age group | Characteristic | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|
| 25–44 | VIA | 79.81 (72.00–87.61) | 64.16 (59.44–68.88) | 36.73 (30.41–43.04) | 92.42 (89.29–95.55) |
| | VILI | 78.85 (70.90–86.79) | 63.16 (58.41–67.91) | 35.81 (29.57–42.05) | 91.97 (88.74–95.20) |
| 45–65 | VIA | 69.23 (54.27–84.19) | 67.30 (60.93–73.67) | 28.13 (19.02–37.23) | 92.21 (87.94–96.48) |
| | VILI | 66.67 (51.39–81.95) | 57.82 (51.12–64.52) | 22.61 (14.88–30.34) | 90.37 (85.35–95.39) |

**Table A8:** Comparative performance of colposcopy to Reid colposcopic index for histologic outcome CIN2+

| | Characteristic | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|
| Total | Colposcopic impression | 57.45 (52.43–62.46) | 80.22 (76.18–84.26) |
| | RCI | 58.08 53.00–63.13) | 79.79 (75.66–83.92) |
| WLWH | Colposcopic impression | 64.81 (58.41–71.22) | 76.56 (70.88–82.24) |
| | RCI | 64.62 (58.15–71.10) | 75.00 (69.14–80.86) |
| HIV neg | Colposcopic impression | 47.50 (39.70–55.30) | 82.16 (76.18–88.14) |
| | RCI | 49.02 (41.03–57.00) | 82.33 (76.24–88.42) |

**Table A9:** Comparative performance of colposcopy to Reid colposcopic index for histologic outcome CIN2+ stratified by age category

| Age groups | Characteristic | CIN 2+ | |
|---|---|---|---|
| | | PPV, % (95% CI) | NPV, % (95% CI) |
| 25–44 | Colposcopic impression | 62.45 (56.55–68.35) | 80.17 (75.31–85.03) |
| | RCI | 63.28 (57.35–69.21) | 80.17 (75.26–85.07) |
| 45–65 | Colposcopic impression | 46.09 (36.88–55.30) | 80.30 (72.96–87.65) |
| | RCI | 45.87 (36.41–55.33) | 79.14 (71.42–86.85) |