Utility of extended HPV genotyping as primary cervical screen in an unscreened population with high HIV co-infection rate

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ABSTRACT

Objective: Screening with primary human papillomavirus (HPV) testing has been evaluated in highly pre-screened populations with lower HPV and HIV prevalence than what is the case in South Africa. High prevalence of HPV and underlying precancer in women living with HIV (WLWH) affect the clinical performance of screening tests significantly. This study investigates the utility and performance of an extended genotyping HPV test in detection of precancer in a population with a high coinfection rate with HIV.

Methods: A total of 1,001 women aged 25 to 65 years with no cervical cancer screening in the preceding 5 years were tested with cytology and primary extended genotyping HPV testing. The cohort of 1,001 women included 430 WLWH (43.0%) and 564 HIV-negative (56.3%) women.

Results: Abnormal cytology (atypical squamous cells of undetermined significance or higher) was significantly higher in WLWH (37.2% vs 15.9%) and high-grade squamous intraepithelial lesion or above (23.5% vs 5.2%). The WLWH also tested positive more often for any HPV type (44.3% vs 19.6%; $p < .0001$) The specificity for cervical intraepithelial neoplasia 2+ at 91.2% of a combination of HPV types, 16/18/45 (very high risk) and 31/33/58/52 (moderate risk), performed better than cytology or any HPV-positive result to predict cervical intraepithelial neoplasia 3+ on histology. The additional genotype information supports direct referral to treatment or colposcopy in a larger proportion of the screen-positive population.

Conclusions: The potential contribution of extended genotyping is demonstrated. The ideal choice of sensitivity and specificity ultimately depends on the health budget. More information will allow a screening algorithm, guiding management according to risk.

Key Words: cervical cancer, extended genotyping, primary human papillomavirus screening

Cervical cancer remains the leading cause of cancer deaths in South Africa and causes more than 4,000 deaths per year. This is particularly regretful when the elimination of disease is possible through widely available primary and secondary preventative strategies. Primary prevention through human papillomavirus (HPV) vaccination is clearly very important to future generations, but older women need effective screening with sensitive and specific tests followed by timely treatment of the precancers detected in the process. Primary HPV screening and treatment of lesions will reduce cancer and is in keeping with the World Health Organization global call for action in 2018 to eliminate cervical cancer.[1]

Screening strategies with primary HPV testing have mostly been evaluated in highly pre-screened populations with lower HPV and HIV prevalence than what is the case in South Africa. Human immunodeficiency virus coinfection changes the epidemiology of HPV infections, cervical precancer, and cancer.[2] High prevalence of HPV detection and underlying precancer in women living with HIV (WLWH) will affect the clinical performance of screening tests significantly. It is important that implementation studies are performed in geographies with high prevalence of people living with HIV.

In South Africa, conventional cervical cytology has been the standard screening tool for precancer and cancer. This has changed in the last decade to include liquid-based cytology (LBC) and, more recently, HPV testing. The most recent cancer control policy published by the national Department of Health states that "LBC- and HPV-based screening will be phased in based on resource availability."[3]

The World Health Organization call to action identified the 90-70-90 targets: 90% of girls fully vaccinated, 70% of women screened using a high-performance test, and treatment of 90% of women with precancer and invasive cancer.1 In low-and-middle income-countries (LMIC), there is a shortage of specialized clinical services like colposcopy. With limited capacity for the treatment of precancer, it is imperative to correctly identify those individuals with a true risk for cancer accurately to limit the number of referrals to colposcopy. This will in turn reduce waiting times and hopefully increase the proportion of women with precancers who receive effective treatment.

Some triage strategies such as HPV-DNA screening, with colposcopy triage of all those testing positive for high-risk HPV (hrHPV) other than types 16/18/45, may increase referrals to colposcopy clinics in 2040 4-fold.[4] When a primary screening test includes a built-in triage to stratify referral and treatment according to risk, it may reduce the number of visits of the client to the health service and increase compliance.

Another opportunity for triage is to extend genotyping information in routine screening and use genotyping to predict the risk to develop precancer and cancer. This enables referral for direct treatment those with very high risk, to offer colposcopy to those at moderate risk, and to rescreen those with low risk at an earlier interval. In very low-risk women, increased intervals between screening can be safely implemented.

In a study published by Schiffman and colleagues,[5] 4 management strategies (action bands) were suggested according to the HPV results. The management strategies were based on the risk for development of cervical intraepithelial neoplasia (CIN) 3+ within 3 years. Very high risk (VHR) of CIN3 mandating consideration of excision treatment if colposcopy did not reveal invasive cancer was associated with types 16, 18, or 45. Moderate risk (MR) was associated with HPV types 31, 33, 58, and 52, justifying colposcopy and directed biopsy. A low risk (LR) was associated with types 51, 35, 39, 68, 56, 59, and 66 and can be managed by intensified follow-up to permit HPV clearance or identify persistence. A sample that tested negative for all the HPV types in this test was associated with very low risk (VLR) allowing for return to routine screening with a long interval in between.[5]

The Onclarity assay (Becton Dickinson and company, Franklin Lakes, NJ) is an extended genotyping HPV testing platform where 14 hrHPV types can be detected.

The assay performs well in the laboratory and results have been found to be reproducible and reliable in a large quality control study. [6] The test performance was good, independent of sample collection before or after cytology aliquoting. The test performed well in different cytology preservation media.[7,8] In a study from Denmark, the assay had clinical sensitivity and specificity at least matching Hybrid Capture 2 (Qiagen, Germantown, MD) and linear array.[9]

The assay may be used as a primary screening tool but also as a triage for cytology.[10] The sensitivity and specificity of the test and its different channels in a population with a high background HIV infection rate has not been sufficiently explored to support the development of locally relevant treatment algorithms. In this study, the performance of this test to predict the outcome of histology-confirmed cervical lesions of different severity will be described and compared with the performance of cervical cytology.

OBJECTIVE

Investigate the utility and performance of an extended genotyping HPV test in detection of precancer in cervical cancer screening in a population with a high coinfection rate with HIV.

METHODS AND STUDY POPULATION

This report forms part of a larger screening study for the Vaccine and Cervical Cancer Screen (VACCS).A total of 1,001 women aged 25 to 65 years with no cervical cancer screening in the preceding 5 years were invited to take part in the study. Recruitment and enrolment occurred at 3 study sites in metropolitan areas of South Africa. One of the study sites was an HIV treatment clinic. The cohort of 1,001 women included 430 WLWH (43.0%) and 564 HIV-negative (56.3%) women. For another 7 women, the HIV status was unknown, and they were excluded from the analysis. Health care workers collected LBC samples on which cervical cytology was performed. The remaining LBC samples were subsequently tested with the Onclarity assay.

The original intention of the study was to perform a biopsy on all women with a positive HPV or cytology result. A proportion of women with abnormal cytology or HPV test (4%) was lost to follow-up and did not undergo a biopsy. A proportion of women with negative HPV and negative for intraepithelial lesion or malignancy (NILM) cytology was also biopsied.

Of the 1,001 Onclarity tests, 102 (10.2%) delivered an invalid result and were excluded from the performance analyses. The first 500 samples were tested together and, in this cohort, only had 22 (4.4%) invalid tests, which is similar to the rate observed in other published work.[11] The high rate of invalid results in the remaining samples was difficult to explain. Each invalid test was repeated and despite the repetition, the rate stayed higher than expected. This observed invalid rate is much higher than that found in other studies using the same test and platforms and may be due to issues like samples storage and transport.

In those women with valid HPV test results (n = 899), 265/276 (96.0%), with any HPV type positive, had histology results available. Three hundred twenty-one of 564 (56.9%) women who screened negative for HPV and had NILM/uncertain on cytology also received random cervical biopsies. Fifty-eight of 59 (98.3%) women who screened negative for HPV but had atypical squamous cells of undetermined

significance (ASCUS) or above on cytology had valid histology results. This cohort of 644 women with histology was used for direct analysis.

As a result of the selective follow-up testing, verification bias was present in the crude data. To mimic a more realistic description of the entire population and assessment of test characteristics, simulation modelling was performed of missing histology using data from the available biopsies. Multiple imputations were made to estimate the histology results of non-biopsied women. A second analysis was performed using this histology end point simulation in addition to the confirmed histology results. This is called the verification bias-adjusted analysis.

All women with an abnormality on a screening test were referred to the colposcopy clinic for appropriate assessment treatment, when needed.

The study was approved by the Health Research Ethics committees of Pretoria (196/2014) and Stellenbosch Universities (reciprocal approval 2015).

RESULTS

There were some differences in the age distribution between the WLWH and HIV-negative cohorts; however, most of the women in the cohort were aged between 30 and 45 years, which is the most important screening age to detect and treat precancer lesions. (Details in Supplemental Table 1)

Any abnormal cytology (ASCUS+) was significantly higher in WLWH (37.2%, 160/430 vs 15.9%, 90/564) and high-grade squamous intraepithelial lesion (HSIL) or above (23.5%, 101/430 vs 5.2%, 29/564) (Table 1). In WLWH, 9/430 (2.1%) had cytology suggestive of malignancy.

TABLE 1. Cytology Results According to HIV Status

	WLWH (n=430)		HIV negative (n=564)		P value
	n	%	n	%	
Cytology NILM	259	60.2	473	83.8	*< 0.0001*
Cytology Ascus+	160	37.2	90	15.9	*0.0004*
Cytology HSIL +	101	23.5	29	5.2	*< 0.0001*
Cytology malignant	9	2.0	0	0	
NILM with any HPV +	52	20.1	39	8.2	*0.1177*

Cytology categories overlap and totals are more than n and 100%, respectively.

When the cytology results were analyzed in conjunction with the HPV results, WLWH had a much higher rate of any HPV+ (20.1%) when the cytology was reported as NILM when compared with HIV-negative women (8.2%), p = 0.1177. This likely indicates increased cancer risk in the WLWH NILM population when measured by HPV positivity rate.

In the 644 women with confirmed histology, 13 cases of invasive cancer were reported. These were equally distributed between HIV groups. However, there were significant differences in CIN2+ and

CIN3+ groups, with higher rates detected in WLWH. The WLWH had an extremely high rate of CIN2+ (50.5%), but even in the HIV-negative cohort, there was a high rate of CIN2+ of 32.4%. The CIN2 histology results were not reviewed or tested with p16 because this was a "real-world" screening study. It is important to note that the participants for study inclusion had no screening in the last 5 years or never. (See Supplemental Table 2).

A total of 899 valid HPV results were available for this cohort. There was clearly more HPV detected in WLWH. This was true for any HPV type (44.3%vs 19.6%; p < .0001) and for all the other types (Table 2). In the WLWH cohort, 55.7% tested negative for any hrHPV, whereas 80.4% of women in the HIV-negative cohort had a negative HPV test. Overall, 69.3% of participants tested negative for any of the oncogenic strains in the assay.

TABLE 2. HPV Results Reported According to Oncogenic Types and Risk-Stratified Action Bands

	WLWH (n=404)		HIV neg (n=495)		P value	Total (n=899)	
	n	%	n	%		n	%
Any hrHPV positive	179	44.3	96	19.6	*<0.0001*	276	30.7
HPV 16	40	9.9	24	4.9	*0.0038*	64	7.1
HPV 18/45	41	10.1	15	3.1	*<0.0001*	56	6.2
HPV 16/18/45 (VHR)	79	19.6	38	7.8	*<0.0001*	117	13.0
HPV 31/33/58/52 (MR)	55	13.6	34	6.8	*0.0007*	89	9.9
HPV 51/35/39/68/56/59/66 (LR)	45	11.1	25	5.0	*0.0007*	70	7.9
hrHPV negative (VLR)	225	55.7	393	80.4	*< 0.0001*	623	69.3

At a threshold of HSIL on cytology, sensitivity in the HIV-negative group is low at 17.7% for CIN2+ and 32.8% for CIN3+ (Table 3).

TABLE 3. Test Performance for Cytology at HSIL Threshold

Test characteristics Cytology HSIL	WLWH (n=430) %	HIV neg (n=571) %	Total (n=1001) %
Sensitivity for CIN2+	46.8	17.7	34.5
Sensitivity for CIN3+	63.9	32.8	51.9
Specificity for CIN 2+	94.4	99.0	97.4
Specificity for CIN 3+	87.9	98.2	94.2
PPV for CIN 2+	87.1	86.2	86.9
PPV for CIN3+	61.4	69.0	63.1
NPV for CIN 2+	68.6	78.6	74.8
NPV for CIN3+	89.0	92.4	91.1

NPV indicates negative predictive value; PPV, positive predictive value.

If the threshold for cytology is lowered to ASCUS+, the sensitivity for the HIV-negative group improves to 41.8% for CIN2+ and 57.4% in CIN3+, but 15.9% would need to be referred to colposcopy (See Supplemental Table 2). For WLWH, the referral rate at the ASCUS+ threshold would be 37.2%.

If any HPV is detected (Table 4), the sensitivity and specificity are similar to cytology at a threshold of ASCUS+ in WLWH, HIV negative, and in the combined groups. However, it would refer 44.3% of WLHW, 19.6% of HIV-negative, and 30.7% overall women to further investigation.

TABLE 4. Test Performance for Any hrHPV Detected

Test characteristics any hrHPV	WLWH (n=404) %	HIV negative (n=495) %	Total (n=899) %
Sensitivity for CIN2+	73.0	42.4	60.3
Sensitivity for CIN3+	80.8	63.8	74.5
Specificity for CIN 2+	79.9	88.7	85.4
Specificity for CIN 3+	67.5	82.3	78.6
PPV for CIN 2+	75.4	57.7	69.2
PPV for CIN3+	44.7	38.1	42.4
NPV for CIN 2+	77.8	80.9	79.8
NPV for CIN3+	91.6	94.7	93.6

The excellent specificity of the VHR positive results for CIN2+ in both subgroups (95.4% for WLWH and 97.0 for HIV negative) and overall (96.4%) (Table 5), supports the action of direct referral for treatment.

TABLE 5. Test Performance for VHR HPV-Positive (VHR Group 16/18/45)

Test characteristics VHR	WLWH (n=404) %	HIV negative (n=495) %	Total (n=899) %
Sensitivity for CIN2+	37.3	20.5	30.3
Sensitivity for CIN3+	41.4	31.0	37.6
Specificity for CIN 2+	95.4	97.0	96.4
Specificity for CIN 3+	87.4	95.4	92.2
PPV for CIN 2+	87.3	71.1	82.0
PPV for CIN3+	51.9	47.4	50.4
NPV for CIN 2+	64.3	77.0	71.7
NPV for CIN3+	82.2	91.3	87.5

The overall specificity for CIN2+ remains high at 91.2% when VHR and MR are combined (Table 6). That would support colposcopy referral as an action for this group.

TABLE 6. Test Performance for VHR and/or MR Groups Combined (VHR 16/18/45 and/or MR 31/33/58/52)

Test characteristics VHR and MR	WLWH (n=404) %	HIV negative (n=495) %	Total (n=899) %
Sensitivity for CIN2+	59.4	34.1	48.9
Sensitivity for CIN3+	78.0	90.9	85.6
Specificity for CIN 2+	89.0	92.6	91.2
Specificity for CIN 3+	75.5	86.7	81.7
PPV for CIN 2+	82.1	62.5	75.2
PPV for CIN3+	67.7	55.2	63.1
NPV for CIN 2+	72.2	79.4	76.6
NPV for CIN3+	88.1	93.9	91.6

DISCUSSION

Cervical cytology has been the cornerstone of screening programs internationally for decades and reduced the incidence and mortality of cancer in many developed countries. There is, however, a very large burden of disease in LMIC with little hope to successfully implement cytology-based programs that need multiple samplings, relatively complex infrastructure, and a well-organized primary health care system. [12] In addition, the sensitivity of a single cytology result is lower than HPV testing, with many important lesions missed.[13] In a study from Argentina, with a similar economic environment as South Africa, "HPV testing increases detection of CIN2+ lesions and allows for improvement of programmatic indicators."[14] The HIV disease increases the diagnosis of cytological abnormalities and reduces the long-term efficacy of ablative or excisional treatments for precancer.[15] In this study, cytology at a low referral threshold of ASCUS+ performed like pooled HPV results but performed less well at higher thresholds. Our findings support the move to primary HPV testing in South Africa as proposed by the Cancer Control Policy of 2017.[3] Stratified HPV results with a focus on VHR and MR types improved specificity to approximately 90% or higher.

Cytology-based screening is less efficient in vaccinated populations because abnormal cytology disproportionately identifies minor abnormalities resulting from HPV types that are associated with lower cancer risk.[16,17] This is likely also true for WLWH where there is a high rate of infection with non-oncogenic strains of HPV.[18]

Multiple international studies reported HPV detection in screening populations with NILM cytology and how this triage strategy improved sensitivity of cytology and accurate diagnosis of CIN2+. In a large cohort study from the United States, where almost 34,000 women were screened with the Onclarity assay, Stoler and colleagues reported that Onclarity "was clinically validated for co-testing in NILM women."[19] The extended genotyping stratified women at greater CIN3 or higher risk. In this cohort, there was a significant proportion of NILM cytology that tested positive for HPV. The WLWH had a high rate of any HPV+ (20.1%) compared with HIV-negative women (8.2%; p = 0.1177). Cytology likely underestimates the risk for cancer in these women.

Women living with HIV have a higher risk for the acquisition, persistence, and progression of hrHPV and its negative effects, including precancer or cervical cancer. Two large meta-analyses found that cervical cancer incidence remains approximately 6 times higher in WLWH compared with the general

population or HIV-negative women.[20] In our cohort, there were significantly more abnormal cytology findings in the WLWH group compared with the HIV-negative group. The HSIL cytology was detected in 23% of WLWH compared with 5% HIV-negative ($p < 0.0001$).

Like other studies of WLWH, our cohort also demonstrated significantly more HPV detection in WLWH (44.3% vs 19.6%; $p < 0.0001$). In a systematic review by Liu and colleagues, HIV-positive women had higher HPV acquisition (relative risk = 2.64; 95% concluded CI = 2.04–3.42) and lower HPV clearance (hazard ratio = 0.72; 95% CI = 0.62–0.84) than HIV-negative women.[21]

Even in the HIV-negative cohort of this study, a relatively high number of hrHPV infections were found at 19.6%. This is in keeping with other reports from South Africa.[22,23] This finding impacts the clinical performance of HPV screening test and makes larger, population-based screening studies of utmost importance.

The histology results again demonstrated the higher prevalence of precancer (CIN2+) in WLWH (50.5% vs 32.4%; $p < 0.0001$) The overall rate of CIN2+ histology was 41.3%. This rate is high because of the selection bias toward participants with a screening abnormality.

A negative HPV test has been shown to have excellent negative predictive value for future development of precancer and cancer. [24] In the WLWH cohort, 55.7% tested negative for any hrHPV. Although this was much lower than the 80.4% in HIV-negative women, the clinical significance of this finding is important. The high negative predictive value means that, even in WLWH, more than half can be reassured after a negative screen and be discharged from increased cervical cancer surveillance (which is the norm in cytology-based screening programs).

Cytology (with an HSIL threshold) as a screening option in this population had a low sensitivity for diagnosing CIN2+ (34.5%). The sensitivity improves if the cytology threshold is taken at ASCUS + (54.2%) but at a cost for reduced specificity (97.4% vs 87.4%).

Any HPV positivity had an overall sensitivity of 60.3%to detect CIN2+ at specificity of 85.4%. This demonstrates that sensitivity of HPV testing in this cohort was superior to that of cytology, even at a low threshold of ASCUS+. The VHR action band achieves a high specificity of 96.4%, which supports immediate treatment of these abnormal results. The proportion that would be referred directly for treatment, using VHR positivity, would be 12.9% (116/899). The proportion rereferred for colposcopy (MR) and biopsy would be only 9.9%, which would be manageable in terms of health care resources. If the 2 action bands VHR and MR of the HPV test are used together, the sensitivity is at 48.9%, but specificity is still at a high level of 91.2%.

The different sensitivities and specificities of the HPV test at different cut-offs of estimated risk for current and future precancer lesions clearly demonstrate the contribution of extended genotyping in the study population. Combining the highest risk types into a strategy of see-and-treat has obvious programmatic benefits. The ideal choice of sensitivity and specificity ultimately depends on the health budget, priority granted to the prevention program and resources. Results according to these genotyping channels will allow a screening algorithm guiding management according to risk and based on the chosen test sensitivity and specificity.

Persistent, type-specific, HPV infection increases the risk for future development of precancer and cancer. In those women with positive HPV tests that do not qualify for immediate treatment, a potential use of more extensive HPV typing is in follow-up of individual patients. Full genotyping is not available for clinical use anywhere in the world, and having more HPV-type bands can be useful when monitoring

whether a given woman has a persistent or new infection.[25] This may also be a useful "test of cure" after treatment.

STRENGTHS AND LIMITATIONS

This population was purposefully selected to include a significant number of WLWH not only to evaluate the differences between HIV-affected and nonaffected women but also to inform the clinician about the validity of screening tests in a population with a high HIV and HPV burden. This is both a strength and a limitation. It provides valuable insights about screening WLWH and how tests may perform differently.

A limitation is that the results may not be generalizable to a "general screening population". The performance characteristics of the reported screening tests, and in particular sensitivity and specificity, may not reflect real-life performance due to the relatively small cohorts for a screening study and the high incidence of positive screening results and abnormal histology. Both the WLWH and HIV-negative cohorts reported here had much higher disease prevalence than the usual published well-screened, low-risk populations, and comparing results directly is therefore not valid.

A strength of the study is the high number of biopsy-proven histology results including a significant portion of women with negative screening tests.

CONCLUSIONS

The ideal screening tool for cervical cancer must be sensitive enough to diagnose most of true precancers and cancers, particularly in programs where screening opportunities are few. Most women in LMIC may only get 1 chance to be screened per lifetime. At the same time, the test should ideally identify only those with true precancers and cancers; therefore, be specific enough. In this high-prevalence population, cytology, when abnormal, performed well for specificity but was not sensitive enough. The HPV testing was more sensitive, and the specificity of the highest risk types allows for direct treatment without further testing. Extended genotyping information also allows the development of risk-based guidelines for the further management of women positive for non-16/18/45 hrHPV types.

This study highlights the urgent need to perform large, population-based screening studies in LMIC, particularly in geographies with a high rate of people living with HIV.

REFERENCES

1. WHO. Cervical cancer elimination initiative. Available from: https://www.who.int/initiatives/cervical-cancer-elimination-initiative. Accessed July 20, 2022.

2. Mbulawa ZZA, Marais DJ, Johnson LF, et al. Impact of human immunodeficiency virus on the natural history of human papillomavirus genital infection in South African men and women. J Infect Dis 2012;206:15–27.

3. National Department of Health. Cervical Cancer Prevention and Control Policy. 2017. Available from: https://www.health.gov.za/wp-content/uploads/2021/07/cervical-cancer-policy.pdf. Accessed July 20, 2022.

4. Van Schalkwyk C, Moodley J, Welte A, et al. Modelling the impact of prevention strategies on cervical cancer incidence in South Africa. Int J Cancer 2021;149:1564–75.

5. Schiffman M, Hyun N, Raine-Bennett TR, et al. A cohort study of cervical screening using partial HPV typing and cytology triage. Int J Cancer 2016; 139:2606–15.

6. Young S, Vaughan L, Yanson K, et al. Analytical and clinical sample performance characteristics of the Onclarity assay for the detection of human papillomavirus. J Clin Microbiol 2020;59, e02048-20.

7. Cuzick J, Ahmad AS, Austin J, et al. A comparison of different human papillomavirus tests in PreservCyt versus SurePath in a referral population-PREDICTORS 4. J Clin Virol 2016;82:145–51.

8. Cuzick J, Cadman L, Mesher D, et al. Comparing the performance of six human papillomavirus tests in a screening population. Br J Cancer 2013;108:908–13.

9. Ejegod DM, Junge J, Franzmann M, et al. Clinical and analytical performance of the BD Onclarity HPV assay for detection of CIN2+ lesions on SurePath samples. Papillomavirus Res 2016;2:31–7.

10. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24:102–31.

11. Botha MH, on behalf of Vaccine and Cervical Cancer Screen (VACCS) project. Primary HPV screening and cervical cytology in HIV-negative and HIV-positive South African women. Unpublished data: Oral presentation SASOG congress, March 2020, South Africa.

12. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020;395:591–603.

13. Mustafa RA, Santesso N, Khatib R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet 2016;132:259–65.

14. Arrossi S, Paolino M, Laudi R, et al. Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy Demonstration Project in Argentina: a population-based, before-and-after retrospective cohort study. Lancet Glob Health 2019;7:e772–83.

15. Zeier MD, Botha MH, van der Merwe FH, et al. Progression and persistence of low-grade cervical squamous intraepithelial lesions in women living with human immunodeficiency virus. J Low Genit Tract Dis 2012;16:243–50.

16. Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers 2016;2:16086.

17. Castle PE, Xie X, Xue X, et al. Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. Prev Med 2019;118:44–50.

18. Zeier MD, Botha MH, Engelbrecht S, et al. Combination antiretroviral therapy reduces the detection risk of cervical human papilloma virus infection in women living with HIV. AIDS 2015;29:59–66.

19. Stoler MH, Wright TC, Parvu V, et al. HPV testing with 16, 18, and 45 genotyping stratifies cancer risk for women with normal cytology. Am J Clin Pathol 2019;151:433–42.

20. Castle PE, Einstein MH, Sahasrabuddhe VV. Cervical cancer prevention and control in women living with human immunodeficiency virus. CA Cancer J Clin 2021;71:505–26.

21. Liu G, Sharma M, Tan N, et al. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS 2018;32:795–808.

22. Giuliano AR, Botha MH, Zeier M, et al. High HIV, HPV, and STI prevalence among young Western Cape, South African women: EVRI HIV prevention preparedness trial. J Acquir Immune Defic Syndr 2015;68:227–35.

23. Mbulawa ZZA, Somdyala NI, Mabunda SA, et al. High human papillomavirus prevalence among females attending high school in the Eastern Cape Province of South Africa. PloS One 2021;16:e0253074.

24. Dillner J, Rebolj M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ 2008;337:a1754.

25. Mariani L, Sandri MT, Preti M, et al. HPV-testing in follow-up of patients treated for CIN2+ lesions. J Cancer 2016;7:107–14.