Cervical Cancer Screening Guidelines for South Africa

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BACKGROUND

Epidemiology

Cervical cancer is almost completely preventable through effective primary (prophylactic HPV vaccine) and secondary prevention (screening) but it remains a major public health problem in South Africa. The age-standardised incidence rate in 2020 was estimated at 35.3 per 100 000 South African women, almost three times the global average of 13.3 per 100 000 women.[1] Estimates show that, in South Africa, currently more than 10 000 new cervical cancer cases are diagnosed each year and it was the leading cause of female cancer deaths in 15 to 44-year-olds in with a mortality rate of 19.6 per 100 000 women in 2020.[1] Many factors contribute to the high cancer rates including historic and persistent wealth disparities (SA has one of the highest Gini indices in the world), a high rate of people living with HIV and competing health priorities.

Primary prevention through HPV vaccination

The lack of progress in cervical cancer prevention is particularly concerning in an era when effective primary and secondary preventative strategies are available. Primary prevention through school-based HPV vaccination was introduced in 2014 and initially, relatively high rates of coverage were achieved for the first dose with a significant drop off with a second dose.[2] Only girls are vaccinated in the SA school-based program and the coverage has decreased dramatically during the COVID pandemic with only 3% of the target population receiving the vaccine in 2020.[3] HPV vaccination coverage to achieve herd protection must remain the most important focus. Increasing the cohorts for vaccination (all genders and more age cohorts) provides the best hope for reducing new cervical cancer cases. Other primary preventative strategies including controlling the HIV pandemic and reduction in smoking are also extremely important priorities. Vaccination of all young people against oncogenic HPV types must remain a high priority.

HPV, HIV & prevalence

Persistent viral infection with high-risk human papillomavirus (hrHPV) genotypes causes nearly all cervical cancers.[4] Data from South Africa estimate that 64.2% of invasive cervical cancers can be attributed to HPV16 or HPV18, and 3.2% of women with normal cytology test positive for HPV16/18.[1,5] Like in most other geographies, HPV 16 and 18 are the most important oncogenic strains detected in invasive cervical cancer in SA, which means that all the currently available vaccines will be effective in preventing cervical cancer caused by these types and many high-grade precancerous lesions. Besides protecting against HPV 16 and HPV 18 there is also a vaccine that protects against HPV types 16, 18, 31, 33, 45, 52 and 58 that would provide wider protection.[6]

Women living with human immunodeficiency virus (HIV) (WLWH) have a six-fold increased risk of developing pre-cancerous cervical lesions and cervical cancer, as well as a higher probability of early-age disease compared to HIV-negative women.[7] Women in South Africa have high rates of HIV and HPV infection resulting in high rates of precancer with low screening coverage.[8] Current estimates are that nearly 25% of South African women in their reproductive age (15–49 years) are living with HIV.[9]

World Health Organisation Call to Action

In May 2018 the World Health Organization (WHO) announced a global strategy, the "Call to action to eliminate cervical cancer as a public health problem". All regions of the world are encouraged to reach an incidence rate of below 4 per 100,000 women per year. There are three pillars of action.

- Vaccination of 90% of girls by the age of 15 with an effective HPV vaccine
- Screening of women with a high-performance test by the age of 35 years and again at 45 years
- To achieve treatment of 90% of women with pre-cancer or invasive cancer

Following the announcement of this global strategy, a panel of experts published an updated WHO Guideline for Screening and Treatment of Cervical pre-cancer lesions for Cervical Cancer Prevention.[10] These guidelines recommend HPV DNA detection as the most preferred method of screening rather than cervical cytology or visual inspection methods. The WHO also recommends the adoption of self-sampling; however, the exact methodology is not yet defined. The guidelines recommend different strategies for screening a low-risk population and for at-risk populations

living with HIV. There is a strong recommendation for screen-and-treat approaches in the general population; however, in people living with HIV the guidelines suggest a screen, triage, and treat approach. The South African HPV board used these guidelines as a departure point to refine a guideline document for use in our setting.

Current SA policy, screening uptake

The national cervical cancer prevention policy of 2017 allowed for three cervical cytology tests at ten-yearly intervals for low-risk women, commencing at the age of 30 years.[11] For women in the high-risk group, including WLWH, cervical cytology screening start at diagnosis and is repeated at shorter intervals. According to the present policy, HPV-based screening is to be phased in based on resource availability.

Cervical screening uptake in South Africa however remains low in the public healthcare sector.[12,13,14] Data from the National Health Laboratory Network show that cervical cytology screening coverage in WLWH was well below 50%.[15] In the private health sector, opportunistic screening where the patient or her doctor takes initiative for regular screening visits, is common practice. Opportunistic screening can lead to some patients being overserviced while others remain inadequately screened.[16]

Self-sampling

The validity and feasibility of HPV testing on cervico-vaginal specimens collected by the patient has been accepted world-wide.[17,18] The WHO included self-sampling as part of cervical cancer screening in the latest guidelines.[10] Self-sampling has been shown to be preferable in terms of privacy, convenience, ease of use, physical and emotional comfort.[19] Self-sample specimens are stable, do not require a cold chain after collection, and can be effective in reaching under-screened populations. At the time of writing, there is no standardised way of managing the pre-analytical pathways and resulting of self-sampling and is therefore not widely used or recommended by most laboratory services. Moving towards self-collection in the near future is possible and may increase the uptake of screening significantly.[20]

Alternative screening options

Cytology is not an ideal screening tool in South Africa any longer due to the multistep process and relative lack of laboratory capacity. Turnaround times are problematic in the public sector. Sensitivity of a single cytology test is not adequate when infrequent screening opportunities exist.[21]Visual Inspection with Acetic acid (VIA) and other visual options are not sensitive or specific enough.

Treatment options for cervical pre-cancer

Treatment options for pre-cancer must be scalable in a country with huge healthcare disparities between urban and rural environments and should include ablative options like thermal ablation or cryotherapy. Limited data on the long-term cure rate in people living with HIV, especially following ablative therapies, is of concern. There is a need for prospective research to provide better evidence on which to base follow-up guidelines. Strengthening of policy, programs, treatment capacity and adequate training of healthcare workers are all integral to the success of secondary prevention of cervical cancer.

Methodology for generating these guidelines

The South African HPV Advisory Board was launched in 2010 in response to new diagnostic tests for HPV becoming available as a screening tool for cervical cancer, to provide guidance to clinicians and industry. The first clinical guidelines on screening and testing using HPV technology were published in 2010.[22] Soon after, HPV vaccines became available, and the Board was tasked to advise also on HPV vaccination as primary prevention tool. After its inception, leadership decided to become totally independent from individual industry sponsors and all guidelines have been developed based on the opinions of Board members only and not influenced by the pharmaceutical and diagnostic industries. Now renamed as the South African HPV Board to reflect the independent nature, membership includes clinicians and scientists working as gynecological oncologists, public health specialists, pathologists, virologists and program specialists. The Board and its working groups are multidisciplinary in nature, and works in collaboration with and supported by the South African Society of Obstetricians and Gynaecologists (SASOG) and the South African Society of Gynaecologic Oncology (SASGO).

These guidelines were developed and workshopped during an in-person meeting where there was representation from the national Department of Health, SASOG and SASGO. Methods for screening and treatment of pre-cancer lesions have evolved rapidly over the last two decades and current global and local literature was reviewed. A comprehensive list of literature consulted is not included in this document; special attention was paid to the WHO 2021 updated guidelines[9] and recent evidence of disease prevalence and screening test performance among the South African population.[22,23,24] All members of the Board gave input into the final document, which is the fourth updated guideline from the group.[25,26,27] These guidelines should not be used as official policy document from the Department of Health, but rather as a simplified practice guide for clinicians in public and private sector healthcare environments, working in a middle-income country with high rates of HPV and HIV.

Guidelines for screening

Target population

The age at initiation of screening is set at 25 years due to the high background risk of HIV infection, the resultant higher risk for oncogenic HPV infection and rapid progression to precancer in the South African population. In low-risk sub-populations first screening at age of 30 may be more appropriate and will reduce false positive screen results and overtreatment. Screening of women younger than 25 years is generally not recommended except for individuals with a particular risk, in which case cervical cytology is the preferred method for screening.

Age at exit of screening depends on previous screening history. All unscreened women older than 25 years should be offered at least one screening test. If an individual had three negative screening tests, screening can be stopped at 50 years of age. In individuals with any previous abnormal results, screening should continue until 60 years of age.

Primary screening test

Screening guidelines for South Africa have promised the phasing in of HPV as primary screening test for more than a decade. Now, for the first time, cervical cytology is not

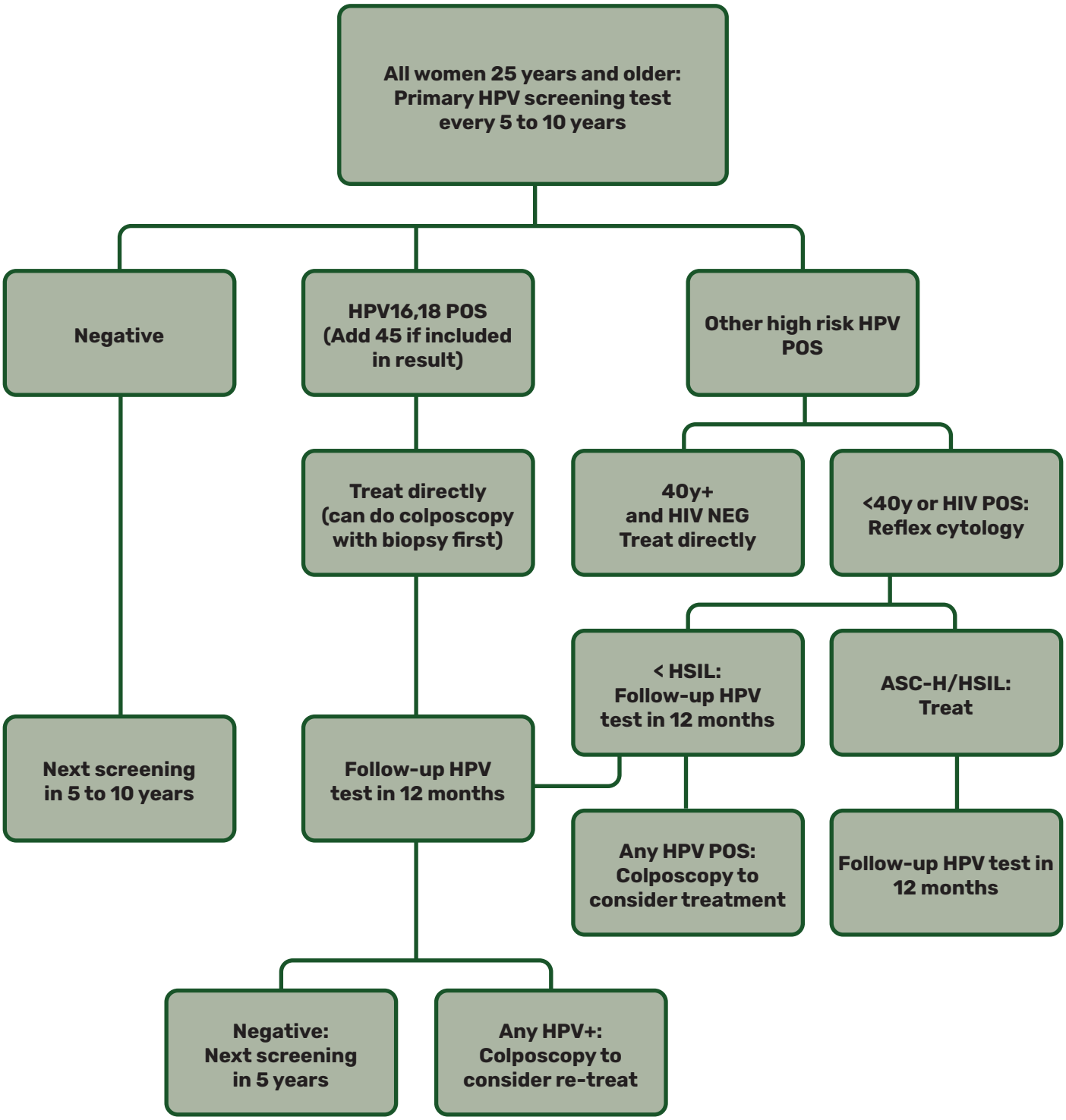
included any more as a preferred option. Due to the high rate of HIV infection in South Africa, possible stigmatisation, as well as practical and logistic considerations of different screening strategies, it was decided to recommend a universal screening strategy for women living with HIV and women at lower risk for cervical cancer. HPV-testing is the only universally appropriate screening test available at present.

These guidelines recommend a liquid-based collection from the cervical transformation zone taken by a health care worker as the most preferable. This makes HPV testing and reflex cytology, if needed, possible on one sample. The implementation of self-sampling in this screening algorithm is possible, which may improve uptake and coverage of screening. In that case a second visit is implied when cytology is needed for triage, which will increase loss-to-follow-up.

Screening interval

HPV-screening requires less frequent screening than cytology, and the recommended interval is stated as five to ten years. The frequency of screening can be varied within this window depending on the individual's risk profile, previous test results and available resources. HIV-positivity and previous HPV-positivity are the most important risk factors requiring a shorter screening interval.

Screening algorithm



Guidelines for treatment

Interpretation of screening results

Three different interpretations are possible: low-risk [negative for high-risk HPV types], intermediate-risk [positive for high-risk types but non-16/18(/45)] or high-risk [positive for HPV types 16/18 (45)].

- All women with "low-risk" results should return for the next round of screening at a routine (five to ten years according to cervical cancer risk group) interval.
- All women with "high-risk" results should be called for a treatment visit, ideally within six weeks, preferably earlier to prevent loss-of-follow-up.
- Women with an "intermediate-risk" result can be managed by an immediate second test (triage cytology test), can be followed at an earlier date for a repeat screening test (increased surveillance), or can directly be referred for a treatment visit based on existing risk factors.

Triage tests

A second test after an intermediate test result gives a further indication of risk. In comparison to treating all these women, it reduces overtreatment; and when compared to following them all, it improves program effectiveness. Immediate reflex to liquid based cytology is chosen here and can be performed only on health care worker collected specimens. Soon there may be molecular solutions for effective triage which can be done on self-collected samples, like extended genotyping or methylation markers.[21]

In these guidelines the recommendation is to selective triage of those who test positive for "other high-risk HPV" by immediately referring to treatment all HIV negative women who are 40 years and older, as this group has a significantly higher risk for disease and the risk of overtreatment is less. On the other hand, women either younger than 40 years, or HIV-positive are triaged by reflex cytology in the laboratory, and treated only if their cytology shows HSIL or more. If the triage test is negative, they return for screening in one year.

Choice of treatment method

At the treatment visit, the recommended option is to offer immediate treatment, called "screen-and-treat", because it enhances program effectiveness and risk reduction. For higher resource environments where colposcopy is available, clinically indicated, and follow-up is guaranteed, it may be used in conjunction with biopsy to confirm the screening results and to guide treatment.

Both types of treatment methods available to treat cervical cancer risk and pre-cursor lesions can be used for patients with positive screening tests. Excisional methods provide a histology sample and is suited for lesions suspicious of cancer or extending into the endocervical canal. Large loop excision of the transformation zone (LLETZ or LEEP) is widely offered and effective; cold knife cone should not be used routinely as it causes significant shortening of the cervix and reproductive failure. Ablative methods include cryotherapy and more widely available thermo-ablation which cause limited loss of cervical stroma but does not provide tissue for histology. These methods are not suited to treat lesions that are suspicious for invasion, very large (>2/3 or > three quadrants) or stretching into the canal. Treatment failure, using ablative therapies is common amongst the HIV positive population.[28] Follow-up after treatment is essential.

Follow-up after treatment

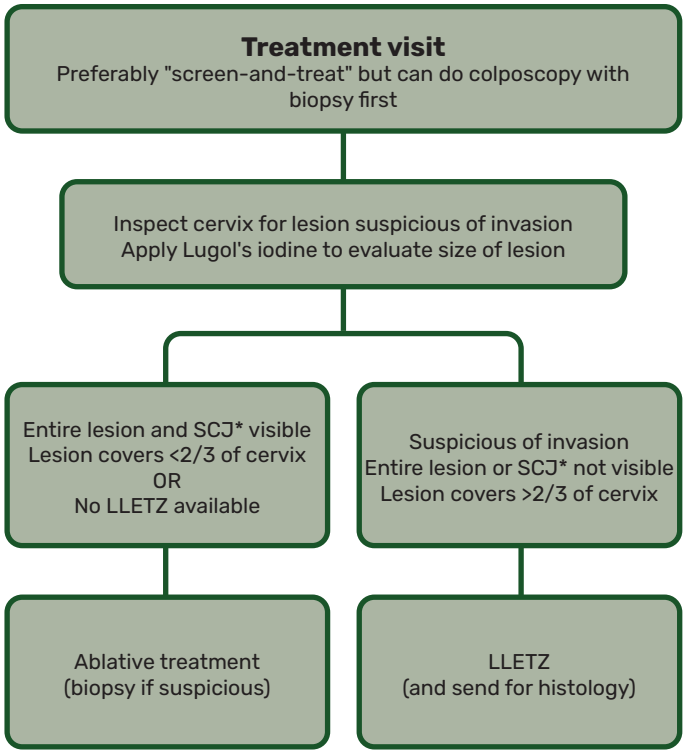
Follow up after excisional or ablative treatment for precancer is essential due to the risk of treatment failure and subsequent development of pre-cancer and cancer. Women who have a negative HPV-test during follow-up can return to the low-risk group with a longer interval. The management of individuals with repeated abnormalities after previous treatment should be Individualised and falls outside the scope of these guidelines.

Conclusion

We recommend a universal screening strategy for South Africa based on primary HPV-screening, with partial genotyping, starting from 25 years, varying screening interval between five and ten years based on risk and exiting at the age of 50 years only after three negative tests.

There is now sufficient evidence to recommend treatment for everyone with the highest risk HPV-types, and for all "other HPV-positive" women who are above the age of 40 years. Reflex cytology should be offered to increase the specificity of screening for women with non-16/18 HPV types who are HIV-positive or younger than 40 years.

We recommend nationwide development of screening facilities and wide implementation of thermo-ablation and LLETZ treatment on indication. After treatment, women need yearly follow-up until HPV-negative.



TREATMENT ALGORITHM

**Squamo-columnar junction of cervix*

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