This policy brief focuses on the use of and the differences between HPV DNA-based and HPV mRNA-based molecular NAATs.

Cervical cancer is a leading cause of mortality among women. In 2020, an estimated 604,000 women were diagnosed with cervical cancer worldwide and about 342,000 women died from the disease. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the leading cause of cancer death in 36 countries. The vast majority of these countries are in sub-Saharan Africa, Melanesia, South America and South-Eastern Asia (1).

In 2018, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), issued a call to action for the elimination of cervical cancer. In November 2020, WHO launched the Global Strategy to accelerate the elimination of cervical cancer as a public health problem, with targets for 2030 (see below). Cervical cancer prevention plays an integral role in reaching the Sustainable Development Goals (SDGs) – not only the SDG for health and well-being (SDG 3), but also several others (SDGs 1, 2, 4, 5, 8 and 10).1

2030 targets to accelerate the elimination of cervical cancer as a public health problem

**VACCINATION**

90% of girls fully vaccinated with HPV vaccine by age 15

**SCREENING**

70% of women screened with a high-performance test by age 35 and again by age 45

**TREATMENT**

90% of women identified with cervical disease (pre-cancer or invasive cancer) receive treatment and care

Source: WHO, 2020 (2).

1 Details available at: [https://sdgs.un.org/goals](https://sdgs.un.org/goals)
WHO recommendations on screening and treatment to prevent cervical cancer

In 2019, WHO began the process of developing updated recommendations for the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition to support countries to reach the 2030 screening and treatment targets. To update the recommendations, reviews of the latest evidence were conducted to evaluate the benefits and harms of different screening tests for cervical pre-cancer lesions, and different screening and treatment approaches. The acceptability, feasibility, costs/resources and equity implications were also assessed. Fifty-three experts from all WHO regions reviewed the evidence and contributed to determining the new and updated recommendations for the general population of women and for women living with HIV.

These new guidelines focus mainly on formulating algorithms for screening and treatment, using HPV nucleic acid amplification tests (NAATs) for primary screening (3,4).

HPV NAATs refer to molecular tests for the detection of high-risk (i.e. cancer-causing or oncogenic) HPV types, including the following two types of test:
- HPV DNA-based molecular NAATs
- HPV mRNA-based molecular NAATs.

WHO recommendations, by population, on HPV NAATs for cervical screening to prevent cervical cancer

For the general population of women, HPV DNA NAATs are the recommended* primary screening test, but HPV mRNA detection may also be used. Both can be used in a “screen-and-treat” or “screen, triage and treat” approach, starting at age 30 and with a screening interval of 5–10 years when using HPV DNA tests and 5 years when using HPV mRNA tests.

Remark: Choosing HPV mRNA testing implies having the capacity to provide follow-up screening at 5-year intervals, and having health-care providers take the samples.

For the population of women living with HIV, HPV DNA NAATs are the recommended* primary screening test. It is suggested* that these tests be used in a “screen, triage and treat” approach rather than in a “screen-and-treat” approach, starting at age 25 and with a screening interval of 3–5 years.

Note: No recommendation was made for the use of HPV mRNA NAATs for women living with HIV because no applicable evidence was identified.

* “Recommended” = strong recommendation; “suggested” = conditional recommendation.

- HPV DNA NAATs detect the presence of the virus by detecting the viral DNA, whereas HPV mRNA NAATs detect transcripts of the viral E6 and E7 oncoproteins, which are responsible for the HPV-mediated oncogenic transformation of epithelial cells.
- HPV NAATs are rapidly evolving, with new products and additional data anticipated in the next few years.

Programmatic implications

Using an HPV NAAT as the primary screening test prevents more cervical cancers and saves more lives than using visual inspection with acetic acid (VIA) or cytology (conventional Pap smear and liquid-based cytology) as the primary screening test (see the comparison data on the next page).

Therefore, WHO encourages existing programmes with quality-assured cytology as the primary screening test to continue only until HPV NAAT testing is operational, and encourages existing programmes using VIA as the primary screening test to transition rapidly because of the inherent challenges with performance and quality assurance when using VIA.
Comparison of HPV NAATs: HPV DNA and HPV mRNA

When transitioning to HPV NAATs, these tables may help countries decide which HPV NAAT to choose.

<table>
<thead>
<tr>
<th>HPV DNA NAATs</th>
<th>HPV mRNA NAATs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong>* as the preferred primary screening test in both “screen-and-treat” and “screen, triage and treat” strategies to prevent cervical cancer in the general population, starting at age 30</td>
<td>Suggested* as an alternative primary screening test in both “screen-and-treat” and “screen, triage and treat” strategies to prevent cervical cancer in the general population, starting at age 30</td>
</tr>
<tr>
<td><strong>Recommended</strong>* as the preferred primary screening test and suggested* for use within a “screen, triage and treat” strategy to prevent cervical cancer in women living with HIV, starting at age 25</td>
<td>No recommendation for use in women living with HIV because no applicable evidence was identified</td>
</tr>
<tr>
<td>5- to 10-year screening intervals suggested* in the general population, and 3–5 years in women living with HIV</td>
<td>5-year screening intervals suggested* in the general population</td>
</tr>
<tr>
<td>Samples taken by health-care provider OR self-collected</td>
<td>Samples taken by health-care provider ONLY</td>
</tr>
</tbody>
</table>

* “Recommended” = strong recommendation; “suggested” = conditional recommendation.

Comparison of public health impact

| HPV DNA may result in 8–12% lower incidence of cervical cancer than HPV mRNA |
| HPV DNA may lead to 6–8% lower incidence of cervical cancer mortality than HPV mRNA |
| HPV DNA may require 27–33% more pre-cancer treatments than HPV mRNA |

Comparison of resource requirements and availability of tests

**Resource requirements:**

- Overall costs over a lifetime may be 6–10% higher with HPV DNA testing than with HPV mRNA testing
- Costs of tests are expected to be similar
- Longer screening intervals are possible with HPV DNA testing (when used in the general population of women – see above) than with mRNA testing, which may result in the use of fewer resources (e.g. tests)
- Training needs are similar
- Equipment required is similar

**Availability:**

- Many HPV DNA tests are available, whereas currently the choice of commercial HPV mRNA tests is limited
- Rapid point-of-care tests for HPV DNA are at advanced stages in the pipeline and may soon become commercially available

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2 The estimates in this table are based on statistical modelling; the methods and details of the evidence are presented in the web annex available at: [https://www.who.int/publications/i/item/9789240040434](https://www.who.int/publications/i/item/9789240040434)

3 For further information, see the WHO Regulation and Prequalification Department website: [https://extranet.who.int/pqweb/in-vitro-diagnostics](https://extranet.who.int/pqweb/in-vitro-diagnostics)
Screening and treatment: two approaches

Policy-makers, programme managers, programme officers and other professionals in the health sector have the responsibility to choose strategies for cervical cancer prevention, at the country, regional and district levels. In the updated second edition of the recommendations on screening and treatment for cervical cancer prevention (3), two populations of women are referred to: women living with HIV and the general population of women; the latter refers to women who are confirmed HIV-negative or presumed to be HIV-negative when HIV status is unknown.4

SCREEN-AND-TREAT APPROACH

A. **When the primary screening test (HPV NAAT) is positive**, the decision to proceed with treatment is made without triage (i.e. no second screening test and no histopathological diagnosis).

B. **After a positive primary screening result with an HPV NAAT**:
   - Patients who are eligible for ablative treatment⁵ should receive this treatment, at the same visit after screening tests are performed (the single-visit approach), or at a second visit to the same or a different facility (the multiple-visit approach).
   - Patients who are not eligible for ablation can have excisional treatment on the same day, if they are eligible and if the clinic has the capacity for large-loop excision of the transformation zone (LLETZ).⁶ If LLETZ is not available on-site, women need to be referred for the excisional treatment.
   - Patients who are not eligible for ablation or LLETZ should be referred for further evaluation.

C. **After treatment**, women need to be followed up at one year, according to the recommendations (for the general population of women and for women living with HIV) (3,4).

SCREEN, TRIAGE AND TREAT APPROACH

A. **When the primary screening test (HPV NAAT) is positive**, the decision to proceed with treatment is based on the result of a second/triage test (i.e. HPV 16/18 genotyping, VIA, colposcopy, or cytology followed by colposcopy).

B. **After a positive primary screening result with an HPV NAAT but a negative triage test result**, women do not need treatment, but they do need appropriate follow-up evaluation at a specified date according to the recommendations (at two years for the general population of women, and at one year for women living with HIV) (3,4).

C. **After a positive primary screening result with both an HPV NAAT and with triage test(s)**:
   - Patients who are eligible for ablation should receive this treatment, at the same visit if feasible at the facility (i.e. immediately), or at a second visit to the same or a different facility.
   - Patients who are not eligible for ablation can have excisional treatment on the same day, if they are eligible and if the clinic has the capacity for LLETZ. If LLETZ is not available on-site, women need to be referred for the excisional treatment.
   - Patients who are not eligible for ablation or LLETZ should be referred for further evaluation.

D. **After treatment**, women need to be followed up at one year, according to the recommendations (for the general population of women and for women living with HIV) (3,4).

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4 Cervical cancer screening is also an opportunity to offer HIV screening services in high-HIV-prevalence countries.
5 Ablative treatment (or “ablation”) refers to cryotherapy and thermal ablation. For eligibility, see Annex 5, section 5.1 (3).
6 The term LLETZ is used to refer to excision of the transformation zone. In some countries, the term LEEP (loop electrosurgical excision procedure) is used, and the two terms are often used interchangeably.
Choosing between the “screen-and-treat” approach and the “screen, triage and treat” approach when using HPV NAATs for primary screening

IMPACT OF THE APPROACHES ON INCIDENCE AND MORTALITY

The impact of BOTH approaches is SIMILAR.

For women in the general population and women living with HIV, with either approach there will be a similar reduction in cervical cancer cases and deaths.

IMPACT OF THE APPROACHES ON THE HEALTH SYSTEM

In terms of resource needs (equipment, supplies and staff time), the addition of triage testing will be accompanied by an increased need for resources to provide the triage testing, but it will also be accompanied by a decreased need for resources due to fewer pre-cancer treatments being performed.

When using a triage test, treatments are reduced by half in both the general population of women and among women living with HIV. However, among women living with HIV, the total number of treatments avoided when using a triage test is much greater because of the higher number who initially screen positive with HPV NAATs.

The CHOICE between these two approaches can therefore be guided by consideration of the following CONTEXTUAL factors:

- the capacity of the health system to provide triage tests compared with the capacity to provide more treatments when not using triage;
- access to equipment, supplies and trained staff;
- HIV prevalence – the screen, triage and treat approach using HPV DNA NAATs is suggested for women living with HIV, rather than a screen-and-treat approach. Therefore, the HIV prevalence or burden must be taken into consideration when deciding which approach to apply: where HIV prevalence is recognized as being high in the general population or in specific regions of a given country, or where there are subpopulations with higher HIV prevalence or burden, the screen, triage and treat approach is suggested.

Transition to HPV NAATs-based screening programmes

When making the transition, the following key points should be kept in mind.

- Programmes should aim to reach all women with screening for cervical cancer (and treatment when needed).
- Continuing screening is crucial: existing programmes with quality-assured cytology or VIA as primary screening tests should be continued until HPV NAATs screening is operational.
- The transition to use of HPV NAATs should be done rapidly because of the inherent challenges with performance and quality assurance of other screening approaches, especially VIA.
- Priority should be given to screening women in the general population aged 30–49 years, and women living with HIV aged 25–49 years.
- Screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.
- Screening without treatment does not prevent cervical cancer. Health-care providers must ensure that women receive treatment and follow-up according to recommendations (3,4).

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7 There is no recommendation on the use of HPV mRNA NAATs in women living with HIV because no applicable evidence was identified in this population.
Research priorities

- Data are needed about the specificity and sensitivity of HPV NAATs (principally for HPV mRNA tests) among women living with HIV, including those on antiretroviral therapy (ART). More evidence is needed about the optimal timing for initiation of screening and frequency of screening among women living with HIV under 35 years of age, such as whether subgroups of women living HIV can commence screening later (e.g. those on ART with well controlled disease) or earlier (e.g. those with perinatally acquired HIV).

- More research and evidence are needed on the impact of using existing and new triage tests after primary screening with an HPV NAAT, particularly from populations in low- and middle-income countries.

- Evidence is urgently needed to determine the optimal timing for initiation of screening and frequency of screening among women in the general population and women living with HIV who have received HPV vaccination.

- More research is needed on self-collection of samples for HPV mRNA testing.

- Better longitudinal data are needed on the persistence and/or recurrence of HPV infection and on the recurrence of HPV-associated lesions after ablative or excisional treatment.

References


