Executive summary

Background

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.

In May 2018, Dr Tedros Adhanom Ghebreyesus, World Health Organization (WHO) Director-General, issued a call to action for the elimination of cervical cancer. In November 2020, the Director-General launched the Global strategy to accelerate the elimination of cervical cancer, including the following targets for each of the three pillars for 2030: 90% human papillomavirus (HPV) vaccination coverage of eligible girls, 70% screening coverage with a high-performance test and 90% of women with a positive screening test or a cervical lesion managed appropriately. Following the launch of the global strategy, a large panel of experts met to define the key areas of focus to increase access to screening and treatment to reach the 2030 targets. One of the agreed areas of focus was to update the existing WHO recommendations for screening and treatment to prevent cervical cancer, and to simplify the algorithms.

Methods

This updated guideline for screening and treatment to prevent cervical cancer was developed in three steps:

1. Review the current guidelines and identify recommendations to update or to develop de novo.
2. Develop questions based on population **(P)**, intervention **(I)**, comparator **(C)** and outcomes **(O) (PICO questions)** for the recommendations and conduct new systematic reviews or update those conducted for the previous guideline, and model outcomes when primary research was not available.
3. Apply the **Grading of Recommendations Assessment, Development and Evaluation (GRADE)** methodology to assess the certainty of evidence and to develop recommendations using evidence-to-decision (EtD) tables.

The Guideline Development Group (GDG) for this guideline was formed in early 2019, and the GDG, WHO Secretariat, methodologists and technical groups (see *Annex 1*) met several times to establish the PICO questions, methodology and timeline. The WHO Secretariat led and coordinated the whole process to ensure recommendations were developed in line with the *WHO handbook for guideline development, second edition* (2014). The methods for evidence synthesis and mathematical modelling were used as applied in the previous edition of the guideline, *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention*. Based on clinical expertise, research and knowledge of tests in development, the Guideline Development Group (GDG) initially identified the screening tests and clinical algorithms for screening and treatment that could be evaluated. The GDG prioritized seven algorithms for evaluation, and these informed the systematic reviews. In 2020, the systematic review teams performed the systematic reviews for each of the PICO questions and, in parallel, the systematic reviews that had been prepared for the International Agency for Research on Cancer's *IARC handbooks of cancer prevention: cervical cancer screening, Vol. 18* (2021) were integrated for the development of these recommendations.

When relevant evidence was not available in primary research, a mathematical model was used to estimate the risk of important outcomes (e.g. recurrence of high-grade cervical intraepithelial neoplasia [CIN], cervical cancer) associated with the use of different screening and treatment strategies. In addition, a modelling group was created to evaluate the impact and cost–effectiveness of the different screening and treatment algorithms. Furthermore, we searched the published literature for studies providing information on acceptability, feasibility and costing aspects of these algorithms, and conducted a survey on feasibility and values and preferences of people using these services. GDG meetings took place on a weekly basis between August 2020 and November 2020 to review and assess the evidence and agree on the final new and updated recommendations and good practice statements presented in this guideline.

Screening and treatment approaches

- In the **"screen-and-treat approach"**, the decision to treat is based on a positive primary screening test only.
- In the **"screen, triage and treat approach"**, the decision to treat is based on a positive primary screening test followed by a positive second test (a "triage" test), with or without histologically confirmed diagnosis.

Summary of screening and treatment recommendations to prevent cervical cancer

In this present publication, there is a total of 23 recommendations and 7 good practice statements.

- Among the 23 recommendations, 6 are identical for both the general population of women and for women living with HIV and 12 are different and specific for each population.
- Among the 7 good practice statements, 3 are identical for both the general population of women and for women living with HIV and 2 are different and specific for each population.

In Table 1 below we have grouped the recommendations and good practice statements in two columns for the general population of women (left column, nos. 1–14) and for women living with HIV (right column, nos. 21–34), while in Table 2, the populations are not separated (nos. 41 and 42).[1]

There are currently 11 recommendations and 3 good practice statements for each population in Table 1, and an additional recommendation and good practice statement for both populations in Table 2.

[1] There are gaps in these numbers because WHO intends to issue additional recommendations soon on screening tests and implementation, which will be numbered as needed (expected to be 15–20 for the general population of women and 35–40 for women living with HIV).

Table 1. Screening and treatment recommendations and good practice statements for the general population of women and women living with HIV

Recommendations for the general population of women[a]	***Strength of recommendation and level of evidence***	**Recommendations for women living with HIV**[a]	***Strength of recommendation and level of evidence***
1. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate-certainty evidence	21. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. *Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.*	Strong recommendation, moderate certainty of evidence
2. WHO suggests using an HPV DNA primary screening test either **with triage or without triage** to prevent cervical cancer among the general population of women.	Conditional recommendation, moderate-certainty evidence	22. WHO suggests using an HPV DNA primary screening test **with triage** rather than without triage to prevent cervical cancer among women living with HIV.	Conditional recommendation, moderate certainty of evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
3a. **In a screen-and-treat approach** using HPV DNA detection as the primary screening test, WHO suggests treating women who test positive for HPV DNA among the general population of women. 3b. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among the general population of women, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (*Annex 4*). *Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).*	Conditional recommendation, moderate-certainty evidence	23. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among women living with HIV, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (*Annex 4*). *Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).*	Conditional recommendation, moderate-certainty evidence
4. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence	24. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence
5. WHO recommends starting regular cervical cancer screening at the **age of 30 years** among the general population of women.	Strong recommendation, moderate-certainty evidence	25. WHO suggests starting regular cervical cancer screening at the **age of 25 years** among women living with HIV. *Remarks: Low-certainty evidence found that there are likely to be small numbers of women living with HIV with cervical cancer who are below the age of 25. This recommendation applies to women living with HIV regardless of when they first tested positive for HIV.*	Conditional recommendation, low-certainty evidence

Recommendations for the general population of women[a]	***Strength of recommendation and level of evidence***	**Recommendations for women living with HIV[a]**	***Strength of recommendation and level of evidence***
6. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV. *Remarks: Neither VIA nor ablative treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.*	Conditional recommendation, low-certainty evidence	26. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV. *Remarks: Neither VIA nor ablative treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.*	Conditional recommendation, very low-certainty evidence
7. Priority should be given to screening women **aged 30–49 years** in the general population of women. When tools are available to manage women aged 50–65 years, those in that age bracket who have never been screened should also be prioritized.	Good practice statement	27. Priority should be given to screening women living with HIV **aged 25–49 years**. When tools are available to manage women living with HIV aged 50–65 years, those in that age bracket who have never been screened should also be prioritized.	Good practice statement
8. WHO suggests a regular screening interval of **every 5 to 10 years** when using HPV DNA detection as the primary screening test among the general population of women.	Conditional recommendation, low-certainty evidence	28. WHO suggests a regular screening interval of **every 3 to 5 years** when using HPV DNA detection as the primary screening test among women living with HIV.	Conditional recommendation, low-certainty evidence
9. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test, among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence	29. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test, among both the general population of women and women living with HIV.	Conditional recommendation, low-certainty evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
10. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.	Good practice statement	30. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.	Good practice statement
11. WHO suggests that the general population of women who have screened positive on an HPV DNA primary screening test and then negative on a triage test are retested with HPV DNA testing **at 24 months** and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	31. WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test, are retested with HPV DNA testing **at 12 months** and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence
12. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	32. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence
13. WHO suggests that women from the general population who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are **retested at 12 months** with HPV DNA testing when available, rather than with cytology or VIA or co-testing, and, if negative, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence	33. WHO suggests that women living with HIV who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are **retested at 12 months** with HPV DNA testing when available, rather than with cytology or VIA or co-testing, and, if negative, are **retested again at 12 month**s and, if negative again, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Recommendations for the general population of women[a]	*Strength of recommendation and level of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and level of evidence*
14. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.	Good practice statement	34. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.	Good practice statement

Table 2. Recommendation and good practice statement for treatment not covered in previous guidelines

For both the general population and women living with HIV	*Strength of recommendation and certainty of evidence*
41. Once a decision to treat a woman is made – whether from the general population of women or women living with HIV – it is good practice to treat as soon as possible within six months to reduce the risk of loss to follow-up. However, in women who are pregnant, good practice includes deferral until after pregnancy. In circumstances when treatment is not provided within this time frame, it is good practice to re-evaluate the woman before treatment.	Good practice statement
42. WHO suggests large-loop excision of the transformation zone (LLETZ) or cold knife conization (CKC) for women from the general population and women living with HIV who have histologically confirmed adenocarcinoma in situ (AIS). *Remarks: Loop excision may be preferred in women of reproductive age, in settings with greater availability of LLETZ and by providers with greater expertise performing LLETZ. CKC may be preferred when interpretation of the margins of the histological specimen is imperative.*	Conditional recommendation, low-certainty evidence

HPV: human papillomavirus; VIA: visual inspection with acetic acid.

[a] Rows shaded in blue indicate that the recommendation or good practice statement is identical for both the general population of women (left column) and women living with HIV (right column). In other rows, the wording of the recommendations differs for each population.

Summary recommendation for the general population of women

WHO suggests using either of the following strategies for cervical cancer prevention among the general population of women:

- HPV DNA detection in a screen-and-treat approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.
- HPV DNA detection in a screen, triage and treat approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.

Summary recommendation for women living with HIV

WHO suggests using the following strategy for cervical cancer prevention among women living with HIV:

- HPV DNA detection in a screen, triage and treat approach starting at the **age of 25 years** with regular screening **every 3 to 5 years**.