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use of mRNA tests for human papillomavirus (HPV)

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WEB ANNEX. EVIDENCE-TO-DECISION FRAMEWORK FOR mRNA TESTING FOR HPV

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Acronyms and abbreviations

AIS	adenocarcinoma in situ
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
DOI	declaration of interest
ERG	External Review Group
EtD	evidence-to-decision
GDG	Guideline Development Group
GRC	Guidelines Review Committee
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPV	human papillomavirus
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
IARC	International Agency for Research on Cancer
LEEP	loop electrosurgical excision procedure (also known as LLETZ)
LLETZ	large-loop excision of the transformation zone (also known as LEEP)
mRNA	messenger ribonucleic acid (referring to HPV E6/E7 messenger RNA)
NAAT	nucleic acid amplification test
PEPFAR	The United States President's Emergency Plan for AIDS Relief
PICO	population (P), intervention (I), comparator (C), outcome (O)
SDG	Sustainable Development Goal
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VIA	visual inspection with acetic acid
WHO	World Health Organization

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, Director-General of the World Health Organization (WHO), 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.

It was decided that the updated guideline and recommendations would be developed in four phases. The output of the first phase was a large set of recommendations on screening and treatment and the clinical algorithms for the most commonly used screening and triage strategies (with a focus on HPV DNA-based screening tests) for both the general population of women (i.e. women who are presumed or confirmed to be HIV-negative) and those living with HIV. This output was recently published in the *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition* (2021).[1] This current guideline delivers the initial output of the second phase of the guideline update: recommendations for the use of HPV mRNA (messenger ribonucleic acid) tests for screening to detect cervical pre-cancer and prevent cervical cancer.

Two approaches to screening and treatment are distinguished:

- 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.

1 Available at: https://www.who.int/publications/i/item/9789240030824

Human papillomavirus (HPV) E6/E7 messenger RNA detection (mRNA) is an alternative method to HPV DNA tests for HPV detection. The mRNA technologies involve detection of mRNA of E6/E7 oncoproteins that are responsible for HPV-mediated oncogenic transformation of epithelial cells. HPV E6/E7 mRNA detection could be more specific than detection of the viral HPV DNA because HPV mRNA tests correlate with actual virus replication, which is further down the HPV pathway toward development of pre-cancer changes. Most HPV DNA tests target the 13–14 most oncogenic HPV types. The HPV mRNA tests vary; one test targets all 14 of the most oncogenic types, while others target fewer oncogenic types.

Methods

The guideline has been developed according to the *WHO handbook for guideline development, second edition* (2014). The Guideline Development Group (GDG) for this guideline was formed in early 2019 and, based on their clinical expertise, research, and knowledge of tests in development, initially identified 13 clinical algorithms (involving several different screening tests) for screening and treatment that could be evaluated. In the first iteration of the updated guideline,[1] seven algorithms were prioritized for evaluation, and four more algorithms are addressed in this current guideline publication.

The GDG, WHO Steering Group and WHO Secretariat, methodologists and technical groups (see *Annex 1*) met several times to discuss the evidence pertaining to the previously established PICO (population, intervention, comparator, outcome) questions related to the priority algorithms using HPV mRNA testing. A systematic review and meta-analysis were conducted to evaluate cross-sectional and longitudinal accuracy of HPV mRNA testing in screening and treatment algorithms. We used the methods for evidence synthesis and mathematical modelling as applied in the published guideline for the first phase of this guideline update: when relevant evidence was not available in primary research, a mathematical disease model was used to estimate the risk of important outcomes (e.g. recurrence of high-grade cervical intraepithelial neoplasia [CIN], and cervical cancer) associated with the use of different screening and treatment strategies. In addition, modelling evaluated the impact and cost-effectiveness of the different screening and treatment algorithms. Systematic literature reviews were previously conducted (during the first phase of the guideline update) on acceptability, feasibility, resources and equity aspects of the use of different screening tests. Surveys were also previously conducted on the feasibility of implementation (among GDG members), and on the acceptability and values and preferences of people using these services. These existing reports were also drawn upon for the purposes of this phase of the guideline update because most reports targeted HPV tests in general and did not distinguish between HPV DNA and HPV mRNA tests. GDG meetings took place to review and assess the evidence and determine the final recommendations presented in this guideline, applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Summary of recommendations for the use of HPV mRNA testing to prevent cervical cancer

In this present publication, only recommendations for the use of HPV mRNA testing are presented. For other recommendations, please refer to the July 2021 publication of the *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition*.

In the general population of women, HPV DNA is the recommended primary screening test, but HPV mRNA detection may also be used.

When providing HPV mRNA testing, WHO suggests:

- **providing it with or without triage;**
- **using samples taken by the health-care provider; and**
- **5-year screening intervals.**

This is a conditional recommendation, based on low-certainty evidence.

Remarks:

- HPV DNA is the recommended screening test. Choosing the alternative option of HPV mRNA testing implies having the capacity to provide follow-up screening at 5-year intervals.

RECOMMENDATION:

WHO suggests that HPV mRNA detection using samples taken by the health-care provider may be used as a primary screening test, either with or without triage, to prevent cervical cancer in the general population of women with regular screening every 5 years.

Note: No recommendation was made for using HPV mRNA in women living with HIV because evidence on the outcomes of using HPV mRNA detection applicable to this population was not identified.

1. Introduction

1.1 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 *(1)*.

In May 2018, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), issued a call to action for the elimination of cervical cancer. A WHO Global Strategy to accelerate the elimination of cervical cancer as a public health problem was presented and unanimously endorsed by the Seventy-third World Health Assembly in August 2020. Subsequently, WHO officially launched the Global Strategy to accelerate the elimination of cervical cancer on 17 November 2020.[2]

The targets of the Global Strategy are to achieve, by 2030:

- **90% of girls fully vaccinated with human papillomavirus (HPV) vaccine by age 15 years**
- **70% of women screened with a high-performance test by 35 years of age and again by 45 years of age**
- **90% of women identified with cervical disease receive treatment (90% of women with pre-cancer treated, and 90% of women with invasive cancer managed) *(2)*.**

In the context of this Global Strategy, countries are updating their protocols for the prevention of cervical cancer and for the care and treatment of affected women. Cervical cancer prevention also plays an integral role in reaching the Sustainable Development Goals (SDGs), both for health (SDG 3) and gender equality (SDG 5).

To prevent cervical cancer, women can be screened using various tests to identify those who have or are at risk of cervical pre-cancer (see *Table 1.1*). Cervical intraepithelial neoplasia (CIN) is characterized by cellular changes in the transformation zone of the cervix. CIN is typically caused by infections with HPV, especially the high-risk HPV types such as strains 16 and 18 (these two strains cause more than 70% of cervical cancers) *(3, 4)*. CIN1 lesions – also referred to as low-grade squamous intraepithelial lesions – are morphological correlates of HPV infections. CIN2/3 lesions – also referred to as high-grade squamous intraepithelial lesions – are correlates of cervical pre-cancers that, if left untreated, may progress into cervical cancer (for further details, refer to Chapter 1 of WHO's *Comprehensive cervical cancer control guidance [5]*).

[2] Launch page: *https://www.who.int/news-room/events/detail/2020/11/17/default-calendar/launch-of-the-global-strategy-to-accelerate-the-elimination-of-cervical-cancer*

Table 1.1 Three approaches to cervical cancer screening and future tests

Molecular	Cytologic	Visual inspection
Nucleic acid amplification tests (NAAT)[a] » high-risk HPV DNA/ NAAT » mRNA **DNA methylation[b]** **Protein biomarkers[b]** » HPV antibodies » oncoproteins	**Conventional Pap smear[a]** **Liquid-based cytology (LBC)[a]** **Dual staining to identify p16 and Ki-67[a]**	**Visual inspection with acetic acid or with Lugol's iodine (VIA/VILI)[a]** » naked eye » magnified by colposcope or camera **Automated visual evaluation of digital images[b]**

[a] Current tests
[b] Tests under evaluation (future tests).

The traditional method to screen women for cervical cancer has been cytology (the Papanicolaou test, also known as the Pap smear or smear test). When cytology results are positive, the diagnosis is confirmed by colposcopy, and appropriate treatment is informed by biopsy of suspicious lesions for histological diagnosis.

Newer screening tests introduced in the last 15 years include visual inspection with acetic acid (VIA), and molecular tests, mainly high-risk HPV DNA-based tests,[3] which are suitable for use in all settings (Table 1.1). More recently, even newer tests and techniques have been developed: (i) other molecular tests such as those based on HPV mRNA, oncoprotein detection or DNA methylation; (ii) more objective tests performed on cytological samples such as p16/Ki-67 dual staining; and (iii) more advanced visual inspection tests based on artificial intelligence/machine learning platforms (e.g. automated visual evaluation of digital images) *(6–9)*.

[3] In this guideline, "an HPV DNA test" refers to a high-risk HPV DNA test, and "an HPV mRNA test" refers to an HPV E6/E7 messenger RNA test. Both of these tests are nucleic acid amplification tests (NAATs).

1.2 HPV mRNA technology and interpretation of test results

The focus of this edition of the updated guideline is the use of HPV mRNA tests (HPV E6/E7 messenger RNA detection) for HPV detection as an alternative method to HPV DNA tests for HPV detection. The virus infecting the basal cell layer of the cervical epithelium is comprised of a double-stranded DNA at its core and a protein coat (capsid). The DNA tests detect either the viral DNA through hybridization technique or a highly conserved region of the L1 capsid protein or of the E genes using polymerase chain reaction (PCR). Hence, HPV DNA tests detect the presence of the virus by detecting the viral DNA. The HPV mRNA tests detect transcripts of the viral E6 and E7 oncoproteins, which are responsible for HPV-mediated oncogenic transformation of epithelial cells.

Persistent infection from any of the high-risk types of HPV is essential for cervical oncogenesis. The process of carcinogenesis starts with the virus particles entering the basal layer of the cervical epithelium and integration of their DNA with the host cellular DNA. As the carcinogenic process advances, the E6 and E7 oncoproteins are expressed, and these proteins are primarily responsible for neoplastic transformation. The E7 protein can bind and degrade retinoblastoma (pRb) tumour suppressor protein, which initiates uncontrolled activation of the cell cycle. The E6 protein degrades p53 (another tumour suppressor protein), inhibiting apoptosis (programmed cell death), and upregulating telomerase activity. Degradation of the key tumour suppression proteins leads to cell cycle deregulation and cellular immortalization, thus kickstarting the process of carcinogenesis. The level of E6 and E7 expression of high-risk HPV types increases as the grade of cervical intraepithelial neoplasia worsens. Since these changes in HPV mRNA expression of E6/E7 oncoproteins directly underlie the neoplastic phenotype (i.e. HPV mRNA tests correlate with actual virus replication, which is further down the HPV pathway towards development of pre-cancer changes), detection of HPV E6/E7 mRNA of these two oncoproteins could be more specific than detection of the HPV viral DNA.

Most HPV DNA tests target the 13–14 most oncogenic HPV types, whereas the HPV mRNA tests vary. At present there is only one technology commercially available and widely documented in the literature, called the Aptima™ mRNA assay, that can qualitatively detect the expression of HPV E6 and E7 mRNA from all 14 high-risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) through real-time amplification. This system can carry out up to 250 tests in approximately five hours. There are two other assays that target fewer oncogenic types, but information and use remains limited at this time.

HPV mRNA testing is based on pooled detection of HPV E6/E7 mRNA from high-risk types of HPV. The test is considered positive if HPV E6/E7 mRNA is above the detection threshold for any individual type or for multiple types. The Aptima™ mRNA assay does not separate out or give information on individual genotypes, such as HPV16/18/45. However, a separate assay is available that can be used to detect HPV16/18/45 among women testing positive on the pooled assay. It includes an internal control that monitors the presence of nucleic acid, and its processing and amplification. A result is considered negative when HPV mRNA in a sample is below the detection threshold and the internal control is positive. A result is considered positive when HPV mRNA in a sample is above the detection threshold, independent of the internal control result. Results are considered invalid when both HPV mRNA and the internal control are below the detection limit *(10)*.

1.3 Phased approach for development of updated recommendations and purpose of this guideline

Following the 2020 launch of the Global Strategy to accelerate the elimination of cervical cancer as a public health problem, 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 2013 *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention* (11), and to simplify the algorithms.

Guideline objective:

To improve national strategies for screening and treatment to prevent cervical cancer in all women, including women living with HIV.

It was decided that WHO's updated cervical cancer screening and treatment guidance would be developed in four phases:

Phase 1	Updated recommendations on screening and treatment and the clinical algorithms for the most commonly used primary screening tests and triage strategies (HPV DNA tests, cytology and VIA) for both women in general (i.e. women who are presumed or confirmed to be HIV-negative) and those living with HIV. Phase 1 also addresses routine screening programmes, the ages at which to initiate and stop screening, and the frequency of screening.
Phase 2	**Evaluate the evidence and develop recommendations for the clinical algorithms using (a) HPV mRNA tests and (b) dual-stain cytology for the general population of women and for women living with HIV.**
Phase 3	Develop recommendations for the implementation of these screening and treatment strategies.
Phase 4	Establish a consolidated "living guideline" for screening and treatment tests and algorithms (combining all the output from Phases 1–3), which will allow the recommendations to be updated as new evidence becomes available and is evaluated.

The output of Phase 1 was a guideline that was published and launched in July 2021, presenting a large set of recommendations and good practice statements, with a primary focus on the use of HPV DNA tests. For the rationale for the development of the new edition of recommendations for screening and treatment to prevent cervical cancer, please refer to section 1.3 of that guideline *(12)*.

Since the HPV mRNA test is in clinical use as a recognized option for HPV nucleic acid amplification testing (NAAT), the GDG prioritized evaluating the evidence on HPV mRNA testing to make recommendations for its use. The objective in this phase of the guideline update was therefore to develop recommendations for the use of HPV mRNA detection as a primary screening test for cervical cancer prevention – both in the general population of women and in women living with HIV. In addition to evidence gathered for this update process, this guideline is also supported by evidence compiled in the *IARC handbooks of cancer prevention: cervical cancer screening, Vol. 18*, which considers HPV mRNA as a NAAT that can be used for cervical cancer screening *(13, 14)*.

The clinical flowcharts for the algorithms presented in this guideline include HPV mRNA-based screening strategies and follow-up testing at 12 months post-treatment (see *Annex 4*). In the near future, the recommendations in this guideline will be integrated with the recommendations recently published in *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition (12)*, along with the outputs of the upcoming phase on dual-stain cytology screening and the forthcoming recommendations on implementation of screening and treatment strategies, to develop a full consolidated version of this guidance.

1.4 Previous and existing WHO recommendations for screening and treatment to prevent cervical cancer and definitions

In 2006, WHO published *Comprehensive cervical cancer control: a guide to essential practice* (C4GEP), which was updated in a second edition in 2014 *(15)*, consolidating all the recommendations for screening and treatment to prevent and treat cervical cancer up to that year. The consolidated C4GEP included the WHO recommendations for HPV vaccination, treatment of cervical cancer and pre-cancer lesions, and palliative care, as well as the recommendations from the previous edition (2013) of this guideline: *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention (11)*. In 2019, WHO published guidance on the use of thermal ablation for treatment of cervical pre-cancer lesions *(16)*, and in 2020, WHO published guidance documents to support the introduction and scale-up of screening and treatment interventions, specifically relating to HPV testing and relevant medical devices *(17)*.

In the updated second edition of the recommendations on screening and treatment for cervical cancer prevention, two populations of women are referred to: women living with HIV and the general population of women, which refers to women who are presumed or confirmed HIV-negative, but whose HIV status may be unknown. In addition, two approaches to screening and treatment are distinguished, the "screen-and-treat approach" and the "screen, triage and treat approach".

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.

In a **screen-and-treat approach**, treatment is provided based on a positive primary screening test alone, without triage (i.e. no second screening test and no histopathological diagnosis).

- When the patient is eligible for ablative treatment, this should ideally be done immediately, at the same visit as the screening test (the single-visit approach). At some facilities, this is not feasible and a second visit is needed (the multiple-visit approach).
- Women who are not eligible for ablation can have excisional treatment on the same day if the clinic has the capacity for large-loop excision of the transformation zone (LLETZ).[4] If LLETZ is not available on-site, women need to be referred for the excisional treatment or for further evaluation.

In a **screen, triage and treat approach**, the triage test is done if the primary screening test is positive, and the decision to treat is made when both the primary test and the triage test are positive.

- A positive triage test can lead to colposcopy with biopsy and histopathological examination for diagnosis to determine the appropriate treatment. The implementation of colposcopy and biopsy can be challenging, however, so this guideline also considers triage strategies that are not dependent on the availability of colposcopy.
- When the primary screening test is positive, and the triage test is negative, women need appropriate follow-up evaluation at a specified date according to the recommendations.

The publication of the output of Phase 1 of the update of the recommendations for screening and treatment to prevent cervical cancer (in July 2021) presented 23 recommendations and 7 good

[3] In this guideline, 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.

practice statements (12). Those recommendations focused mainly on the use of HPV DNA testing as the primary screening test. Table 1.2 provides a summary of the recommendations.

Table 1.2: Summary recommendations from the *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition:* HPV DNA tests

Summary recommendation for the general population of women	Summary recommendation for women living with HIV
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.	**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.

Source: WHO (2021) (12).

The full set of recommendations is provided in the 2021 publication, *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition* (12), and also in Annex 5 of this guideline.

1.5 Target audience

This document is intended primarily for policy-makers, programme managers, programme officers and other professionals in the health sector who have responsibility for choosing strategies for cervical cancer prevention, at country, regional and district levels. Health-care professionals – such as doctors, nurses and community health workers working in reproductive health programmes, antenatal and postnatal services, family planning services, HIV/AIDS control programmes and in clinics that care for women at the district and primary health care levels – may also consult this document to understand how recommendations are developed and why it is vitally important to select and implement evidence-based strategies to prevent cervical cancer.

This document will also be informative in an adapted form for women, girls and their families in making decisions about cervical cancer screening and treatment.

All individuals have the right to equality and non-discrimination in sexual and reproductive health care. In this guideline, we recognize that most of the available evidence on cervical cancer is based on study populations of cisgender women, and we also recognize that cisgender women, transgender men, non-binary, gender fluid and intersex individuals born with a female reproductive system require cervical cancer prevention services. However, to be concise and facilitate readability, we use the term "women" to refer to all gender diverse people at risk for cervical cancer. Sexual and reproductive health service providers and cervical cancer prevention services must consider the needs of – and provide equal care to – all individuals independently of gender identity or its expression.

2. Methods for development of recommendations on HPV mRNA testing

This updated guideline has been developed in accordance with the methods described in the *WHO handbook for guideline development, second edition* (18). More detailed methods are described in the recent publication of the outputs of the first phase of the guideline update (12). Information in this section focuses on methods specific to this phase of the guideline update: HPV mRNA testing.

2.1 Groups contributing to the guideline development process

Lists of all members of the Guideline Development Group (GDG), External Review Group (ERG), systematic review teams, modelling teams and other contributors are provided in Annex 1, with details of their expertise and affiliations. The WHO Secretariat consisted of staff from various relevant WHO departments, and staff from the International Agency for Research on Cancer (IARC). The Steering Group of the WHO Secretariat led the coordination of the development of this guideline. Members of the Secretariat who were not part of the Steering Group were kept informed of the guideline development process and participated in the discussions, in particular during meetings of the various teams.

For the evaluation of the evidence and formulation of recommendations relating to HPV mRNA testing, the GDG comprised 53 members (35 women, 18 men), from across all six WHO regions, including representatives from civil society organizations and women's groups, and women living with HIV. The members brought varied expertise on cervical screening and treatment. Two members acted as co-chairs and moderated the GDG meetings. An External Review Group (ERG) was also established to provide peer review for the guideline document. Its 18 members, none of whom was also a member of the GDG, had expertise in research, policy development, programme implementation and clinical care. Once the GDG had agreed on the recommendations, the ERG reviewed the full draft of the guideline and provided feedback.

Multiple teams prepared evidence relevant to HPV mRNA testing (see details in Annex 2).

- Two teams conducted evidence reviews relevant to HPV mRNA testing – one on test accuracy of HPV mRNA versus HPV DNA detection for CIN2+ and CIN3+, and one on longitudinal evidence for the use of HPV mRNA tests.
- One team developed the mathematical model relevant to HPV mRNA testing in the general population of women.
- One team ran a survey of the GDG members about the feasibility concerns relating to the priority screening algorithms (including but not limited to those involving HPV mRNA testing).

- One team surveyed women about their values and preferences (relating to HPV testing in general, covering both HPV DNA and HPV mRNA).
- Two teams conducted a systematic review of qualitative literature on values, preferences, acceptability and feasibility, and a review of reviews on acceptability, feasibility, resources and equity for the use of different screening tests.

A guideline methodologist with experience of using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(19)* coordinated the presentation of evidence and decision-making processes that facilitated the development of the recommendations, as stipulated in the *WHO handbook for guideline development, second edition (18)*.

2.1.1 Declarations and management of conflicts of interest

Each invited GDG member completed a written declaration of interest (DOI) form (including those who had previously completed them prior to participation in the first phase of the guideline update). The DOIs were reviewed by two members of the WHO Secretariat and no conflicts of interest were identified (*Annex 3*). At the beginning of every GDG meeting, members were asked to declare any potential new conflicts of interest.

2.1.2 Confidentiality

Each GDG member also signed a confidentiality agreement at the beginning of the guideline development process, and the WHO Secretariat restated at the start of each GDG meeting that all discussions and draft recommendations were to remain confidential until publication.

2.2 Scoping review and appraisal of the existing recommendations

The questions for HPV mRNA are based on the scoping review and the prioritization of research questions and algorithms for screening and treatment that was performed by GDG members in 2019 at the start of the process of updating the WHO recommendations on this topic. The key questions relating to HPV mRNA tests (see *Table 2.1*) followed a similar format to those assessed for the recently published outputs of the first phase of the guideline update, referring to both the general population of women and women living with HIV.

Table 2.1. PICO questions for the recommendations in women

PICO 1	Should HPV mRNA versus HPV DNA or VIA or cytology in a screen-and-treat strategy be used in women?
PICO 2	Should HPV mRNA versus HPV DNA in a screen, triage and treat strategy be used in women?
PICO 3	Should women be followed up at 5 or 10 years after a negative or positive HPV mRNA result?

2.3 Priority algorithms

Since screening and treatment can be done using different primary screening and triage tests, there are numerous possible combinations or algorithms. In December 2019, GDG members were surveyed to prioritize the screening and/or triage tests and the treatments that should be evaluated. Following this prioritization exercise, a subgroup of GDG members met to review the results from the survey and to agree on the algorithms to be prioritized. They reached a consensus to address seven priority algorithms in the first phase of the guideline update (see Annex 4 in that guideline *[12]*), and to address the following four algorithms relevant to HPV mRNA testing for this phase of the guideline, as presented in *Table 2.2*. For detailed algorithms (clinical flowcharts) based on the recommendation in this guideline, see *Annex 4*.

Table 2.2. The four algorithms considered

Screen-and-treat approaches:	
1	**HPV mRNA** as the primary screening test, followed by treatment
Screen, triage and treat approaches:	
2	**HPV mRNA** as the primary screening test, followed by **VIA triage**, followed by treatment
3	**HPV mRNA** as the primary screening test, followed by **colposcopy triage**, followed by treatment
4	**HPV mRNA** as the primary screening test, followed by **cytology triage**, followed by colposcopy and treatment

2.4 Outcomes

The GDG agreed that the outcomes previously identified for the 2013 first edition of this guideline *(11)* and for the 2021 guideline which presented the output of the first phase of the guideline update continue to be the most relevant outcomes for the new PICO questions; they are listed in *Table 2.3*. Adverse events were defined as outcomes that were a direct consequence of pre-cancer treatment and were grouped as one category, with the exception of preterm birth, which was considered a critical outcome.

Table 2.3. Critical outcomes for the screening and treatment recommendations

Critical outcomes
Cervical cancer
Mortality
High-grade cervical intraepithelial neoplasia or worse (CIN2+)
HPV infection
Preterm birth
Pre-cancer treatments
Adverse events (direct consequence of pre-cancer treatment): – major infections or bleeding – procedure-associated pain – cervical stenosis – infertility – spontaneous abortion – perinatal deaths – premature rupture of membrane – unnecessary interventions – increased viral shedding in women living with HIV
Costs
Equity
Acceptability
Feasibility

Note: For additional details and definitions, see Annex 5 in the previous guideline providing the output of the first phase of the guideline update (WHO, 2021) *(12)*.

2.5 Syntheses of evidence

Evidence was synthesized for each PICO question according to the methods in the *WHO handbook for guideline development* (18), and the *Cochrane handbook for systematic reviews of interventions* (20). The literature review performed for the development of the *IARC handbook of cancer prevention: cervical cancer screening, Vol. 18* (13) was also part of the evidence synthesized for the development of this guideline – details of this review and its methods have been published (14).

A systematic review of the relative diagnostic accuracy of HPV mRNA tests compared with HPV DNA tests for detecting CIN2+ and CIN3+ was also performed and published (21). The literature search was conducted from 1994 up to August 2020 in PubMed/MEDLINE, Embase and Scopus, and the references of included studies were also searched for additional sources of evidence. A random effects meta-analysis of the relative clinical sensitivity and specificity of HPV mRNA tests compared with HPV DNA tests was conducted. Further details about the methods are provided in that publication.

The certainty of the evidence from the systematic reviews, modelling and surveys was assessed using the GRADE methodology. The four levels of certainty of evidence are summarized in *Table 2.4*.

Table 2.4. Interpretation of the GRADE levels of certainty of evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	We have limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Source: Schünemann et al., GRADE handbook (GRADEpro, 2013) (19).

2.5.1 Mathematical modelling

We used the Policy1-Cervix platform (developed by the Daffodil Centre, a joint venture between the University of Sydney and Cancer Council NSW, Australia), an extensively validated dynamic model of HPV transmission, vaccination, type-specific natural history, cancer survival, screening, diagnosis and treatment (22–30), to predict outcomes in women across all 78 low- and middle-income countries. The Policy1-Cervix model was one of three models used by the Cervical Cancer Elimination Modelling Consortium (CCEMC) to evaluate the impact of cervical cancer prevention interventions in 78 low- and middle-income countries (22, 23). For the baseline analysis, we assumed that 70% of women attended screening at each routine screening event and 90% of women complied with follow-up. Outcomes were assessed over the lifetime of birth cohorts eligible for screening in 2030 onwards and included cervical cancer incidence and mortality, pre-cancer treatments, additional preterm deliveries as a result of pre-cancer treatment and cost-effectiveness. A range of sensitivity analyses were considered, including a range of test performance assumptions for HPV mRNA tests. For the mRNA analysis, a specific validation exercise was performed to demonstrate that the Policy1-Cervix model predictions matched the available longitudinal information on the performance of HPV mRNA technology for cervical screening. Detailed methods for the mathematical modelling are presented in Supplementary material 13a, in *Web annex A: syntheses of evidence* (31).

2.5.2 Values and preferences

The results from the systematic review performed for the first phase of the guideline update that addressed, among other considerations, the values and preferences of end-users, health-care providers and other stakeholders were also used to address these considerations in this phase. The results of the literature review were compiled by study design and methodology, location and population, and presented to the GDG. The evidence was assessed using the GRADE-CERQual approach (Confidence in the Evidence from Reviews of Qualitative Research)[5] and confidence in the evidence was rated from very low to high in the summary of findings. This information was presented in evidence tables and in the evidence-to-decision (EtD) framework to inform the development of the recommendations by the GDG (see *Web annex: EtD framework for mRNA testing for HPV*), and the findings are also presented in Supplementary material 10, in *Web annex A: syntheses of evidence* (31).

For primary data, we also used the results of the voluntary and anonymous survey distributed via SurveyMonkey during the first phase of the guideline update. The survey was open to all women and girls aged 15 years and older, regardless of their prior cervical cancer screening or treatment status. The survey received approval from the WHO Ethics Review Committee and was run in English and French from 22 June to 18 September 2020. Awareness of the survey had been raised among a wide range of civil society groups through a webinar. The survey was also promoted through the Union for International Cancer Control and the WHO advisory group of women living with HIV, and shared through WHO regional focal points for Cervical Cancer Elimination Initiative.

[5] Further information is available at: www.cerqual.org

The responses from the 561 respondents, including their qualitative responses to open-ended questions, were analysed. The detailed methods and results are available in Supplementary material 9, in *Web annex A: syntheses of evidence (31)*.

Both the systematic review and the survey considered screening tests and HPV tests, but did not differentiate between HPV DNA and HPV mRNA tests as both are NAATs and the process from the client's perspective is similar. We therefore used this evidence to inform judgements for the recommendations for HPV mRNA testing.

2.5.3 Feasibility, acceptability, resources and equity considerations

Due to the paucity of data related to these considerations for HPV mRNA testing, evidence for HPV DNA testing was used to inform judgements, as both tests are NAATs. This evidence came from (i) a survey of the GDG members and (ii) a review of reviews.

The survey of GDG members was administered via SurveyMonkey to assess the implementation feasibility considerations for all of the priority algorithms. The survey was developed using the context and implementation of complex interventions (CICI) framework *(32)*. Each GDG member was asked about their level of concern about each algorithm being able to sustainably meet the large-scale goal of cervical cancer elimination. The following components of cervical cancer screening and management service delivery were queried separately according to the priority algorithm: demand generation, access to screening and the follow-up management of positives, workforce training, infrastructure development and maintenance, development and maintenance of the screening registry, and cost and integration with other priority health services. The considerations of the GDG members were assessed for the following eight stakeholder groups: health authorities at the national level, health authorities at the regional level, professional societies, providers at both the hospital and primary care levels, community health workers, clients (screened women) and the community. The detailed methods and results of the survey are provided in Supplementary material 11, in *Web annex A: syntheses of evidence (31)*.

A review of systematic reviews of the acceptability, feasibility, resources and equity considerations for the use of different screening tests included systematic reviews published since 2010 that synthesized results from studies with quantitative or qualitative design. Further information about the methods and findings are provided in Supplementary material 12, in *Web annex A: syntheses of evidence (31)*.

2.6 Development of the recommendations

All the GDG meetings that focused on formulation of recommendations were held virtually. Tables to facilitate decision-making for recommendations – evidence-to-decision (EtD) tables – were produced by the guideline methodologist for each recommendation and circulated to the GDG members before each meeting. These tables included a summary of the evidence (benefits and harms), relevant values and preferences information, and other issues, including use of resources and cost, feasibility, equity and acceptability.

During the meeting, the EtD tables and evidence were discussed with the GDG. Following the meeting, the methodologist, systematic reviewers, modellers and WHO Steering Group assessed the GDG input and used it to write the recommendations.

Agreement on the recommendations was made by consensus during the GDG meetings, and the final written recommendations were then approved electronically. The responses solicited via email were either to approve, approve "with the following remarks" or not approve. The GDG had agreed that, if consensus could not be reached, a majority vote of 51% would have been accepted to make recommendations – yet the group did reach a consensus on all the recommendations.

Strong recommendations (worded as "WHO recommends") were made when all the desirable consequences of the intervention **clearly** outweighed the undesirable consequences in most settings.

Conditional recommendations (worded as "WHO suggests") were made when the desirable consequences of the intervention **probably** outweighed the undesirable consequences in most settings

Table 2.5 describes how strong and conditional recommendations should be interpreted.

Table 2.5. Interpretation of strong and conditional recommendations

Implications	Strong recommendation (WHO recommends...)	Conditional recommendation (WHO suggests...)
For individuals	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but some may not.
For health-care providers	Most individuals should receive the recommended course of action. Adherence to this recommendation (when it aligns with national guidelines) could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices may be appropriate for different individuals and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require discussion and involvement of various stakeholders.

Source: Schünemann et al., GRADE handbook (GRADEpro, 2013) (19)

For information on important considerations for the recommendations, please refer to Chapter 3 of the published guideline which delivered the outputs of the first phase of the guideline update (12).

2.7 Management of the external peer review

The draft guideline document was circulated to the External Review Group (ERG) for comment. The WHO Secretariat prepared a summary table with all ERG responses and sorted the comments by topic or section. The WHO Secretariat then reviewed the comments, which were minor wording changes, without any implications for the substance of the recommendations themselves, and the guideline document was finalized.

3. Recommendations on HPV mRNA testing

In this present publication, only recommendations for the use of HPV mRNA testing are presented. For other recommendations, please refer to the July 2021 publication of the *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition (12)*, or to *Annex 5* of this guideline.

In the general population of women, HPV DNA is the recommended primary screening test, but HPV mRNA detection may also be used.

When providing HPV mRNA testing, WHO suggests:

- **providing it with or without triage;**
- **using samples taken by the health-care provider; and**
- **5-year screening intervals.**

This is a conditional recommendation, based on low-certainty evidence.

Remarks:

- HPV DNA is the recommended screening test. Choosing the alternative option of HPV mRNA testing implies having the capacity to provide follow-up screening at 5-year intervals.

RECOMMENDATION:

WHO suggests that HPV mRNA detection using samples taken by the health-care provider may be used as a primary screening test, either with or without triage, to prevent cervical cancer in the general population of women with regular screening every 5 years.

Note: No recommendation was made for using HPV mRNA in women living with HIV because evidence on the outcomes of using HPV mRNA detection applicable to this population was not identified.

For the detailed algorithms (clinical flowcharts) based on this recommendation, see *Annex 4*.

Justification

Despite the similar cross-sectional sensitivity and specificity of HPV mRNA testing compared with HPV DNA testing, a conditional recommendation was made for the use of HPV mRNA as a primary screening test because the longitudinal evidence on HPV mRNA test performance is uncertain. Modelling data suggest that there may be similar reductions in cervical cancer cases and deaths when using HPV mRNA testing with or without triage compared with HPV DNA testing with or without triage. In addition, there may be fewer treatments for pre-cancerous lesions when using HPV mRNA testing. However, the evidence from the mathematical model is uncertain, as the predicted reductions in cases and deaths when using HPV mRNA testing overlap with the uncertainty intervals for those with HPV DNA testing, and the model validation was performed against limited longitudinal data. Some longitudinal data with follow-up of more than five years and a model trial validation exercise (based on follow-up at 4–7 years) suggest that the incidence of CIN3+ may be higher in women who were negative for HPV mRNA compared with those who were negative for HPV DNA. There also do not appear to be other reasons related to feasibility or resources in favour of selecting HPV mRNA testing rather than HPV DNA testing.

The evidence available did not include women living with HIV, and data from the general population of women was not applicable to that population. Therefore, no recommendation was made for women living with HIV.

Summary of the evidence

The GDG considered evidence from cross-sectional and longitudinal studies, and from mathematical modelling of long-term outcomes. Well designed and implemented cross-sectional studies consistently found that compared with HPV DNA testing, the sensitivity of HPV mRNA is likely slightly lower and the specificity slightly higher at baseline: relative sensitivity and specificity for CIN2+ are 0.97 (95% CI: 0.95–1.00) and 1.03 (95% CI: 1.02–1.05), respectively, and for CIN3+ are 0.98 (95% CI: 0.95–1.02) and 1.03 (95% CI: 1.01–1.06), respectively (based on moderate-certainty evidence) *(21)*. Few studies measured the longitudinal performance and performance over repeat rounds of screening with HPV mRNA tests. Some of the available long-term data suggest that women who test negative for HPV mRNA may have a higher subsequent incidence of CIN3+ than those who test negative for HPV DNA, especially when using longer screening intervals (5+ years), but the data are sparse and the findings are also inconsistent across studies (low-certainty evidence) (see *Web annex: EtD framework for mRNA testing for HPV*).

The model used data extracted from the cross-sectional studies in the systematic review on sensitivity and specificity and was validated against the available longitudinal evidence. The findings – based on low-certainty evidence – suggest that when comparing the long-term effects of repeated rounds of HPV mRNA testing with HPV DNA testing, when implemented programmatically at 5-year screening intervals, there may be up to 8–12% higher relative cervical cancer incidence and 6–8% higher cervical cancer mortality for those screened with HPV mRNA compared with HPV DNA tests. However, after considering uncertainties in observed HPV mRNA test performance in a sensitivity analysis, the predicted reductions in cases and deaths with HPV mRNA testing overlap with the ranges of uncertainty for HPV DNA testing (for detailed results, see *Web annex: EtD framework for mRNA testing for HPV*). The modelling evidence also suggests that

the number of treatments for pre-cancer lesions may be lower than with HPV DNA testing strategies (27–33% fewer pre-cancer treatments), leading to lower costs (6–10% lower), although there are also uncertainties in these predictions, which are contingent on the available data.

When compared with VIA or cytology screening, HPV mRNA screening may result in greater reductions in cervical cancer incidence and mortality. There is very low-certainty evidence comparing samples taken by health-care providers with self-collected samples for HPV mRNA testing. Available data suggest that HPV mRNA testing performs worse with self-collected samples, and therefore the recommendation suggests samples taken by health-care providers (see *Web annex: EtD framework for mRNA testing for HPV*).

None of the studies reviewed contained information specifically for women living with HIV, and a separate analysis could not be performed. The GDG agreed that the agreed recommendation presented here does not apply to women living with HIV.

The GDG also considered whether there are advantages to using HPV mRNA testing over HPV DNA testing, and could not identify any advantages related to feasibility, acceptability, equity or resources, since implementation of HPV mRNA is similar to HPV DNA testing. The findings of the survey on values and preferences performed for the first phase of the guideline update were considered when formulating this recommendation. However, because collection of samples by health-care providers rather than self-sampling is suggested for HPV mRNA testing, the feasibility and acceptability of HPV mRNA testing may be different. The AptimaTM mRNA assay is the only HPV mRNA test that has been widely assessed to date. The prices of both HPV mRNA and HPV DNA testing are generally in the same range in high-income countries and both have similar equipment and training needs.

4. Research gaps and further considerations for HPV mRNA testing

For both the general population of women and women living with HIV, although cross-sectional data were available for the general population of women, and were used to inform the evidence on HPV mRNA tests presented in this guideline, the GDG noted that more longitudinal data on the impact of HPV mRNA tests in screening programmes are needed. This includes follow-up and assessment of outcomes beyond five years in women who have been screened using HPV mRNA testing. More studies are also needed on the test outcomes, with comparison between self-sampling and provider-collected samples, because it is important for programmes to provide more options for screening and treatment. In addition, there is an urgent need for different assays to be validated, using each of the specific transport media.

There is currently a complete absence of data on the use of HPV mRNA tests among women living with HIV. With the need for more frequent screening in women living with HIV due to higher rates of recurrence of cervical pre-cancer lesions, screening tests with higher specificity like HPV mRNA tests could have the additional benefits of decreasing the number of cervical cancer treatments needed in a screen-and-treat approach and lowering costs. Therefore, trials comparing the screen-and-treat approach with the screen, triage and treat approach using HPV mRNA testing for primary screening are important to further understanding of these dynamics and of HPV mRNA test performance among women living with HIV – particularly in low- and middle-income settings where diagnostic and treatment capacities may be different from high-income settings.

Comparative longitudinal studies comparing HPV mRNA and HPV DNA screening tests are needed, particularly those that will enable calculation of test performance (sensitivity, specificity, positive predictive value, negative predictive value) against a reference standard of histological confirmation. Furthermore, longitudinal studies that assess outcomes among women living with HIV over longer periods of time, including with different screening intervals and collection techniques, will be important to ascertain the long-term benefits and risks of different screening tests and strategies.

5. Dissemination and updating of the guideline

5.1 Guideline dissemination and impact

This recommendation will be integrated into a full consolidated version of *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition*, along with the outputs of the next phases of the guideline update, in the near future.

In brief, the outputs of each phase and the final consolidated second edition will be disseminated using WHO's worldwide network to make sure that the guideline reaches health-care providers and programme managers so that the most recent evidence is integrated and accessible for clinical decision-making to prevent cervical cancer. The full dissemination strategy was approved for the second edition and includes dissemination on the WHO website and in the next edition of HRP News, and printed copies will be disseminated upon request to health ministries, WHO country and regional offices, WHO collaborating centres on cervical cancer, and other cervical cancer collaborators and partners. Policy briefs and an app will also be produced. The guideline will be translated into the six WHO official languages.

Dissemination plans also include partners involved in the implementation and roll-out of cervical cancer screening and treatment programmes. These include other United Nations agencies, the United States President's Emergency Fund for AIDS Relief (PEPFAR), the Global Fund and Unitaid.

WHO headquarters will work with WHO regional offices and country offices to ensure that countries will be supported in the adoption, implementation and monitoring of the guideline. For this purpose, regional workshops and webinars in different languages will be organized to present, discuss and plan guideline adaptation and implementation, as well as to update current national guidelines.

In addition, impact of the fully updated and consolidated second edition will be measured by developing and disseminating surveys for both health workers and clients, as was done during the guideline development on the topic of values and preferences. This will be done a year after release to assess any changes in country policies and national guidelines. This will also assess the reach of the guideline and ultimately its impact in changing practice.

Over the next year, WHO's *Comprehensive cervical cancer control: a guide to essential practice*, which was last published in 2014 (15), will be revised to provide an up-to-date and global consolidation of all recommendations to prevent cervical cancer.

5.2 Guideline update

Evidence for the sensitivity and specificity of the different tests addressed in the full updated guideline (including in this present guidance, focusing on HPV mRNA testing) and evidence on the impact of these tests on important outcomes is accumulating, and syntheses of this evidence are needed. These syntheses will be used in a continual process to develop new recommendations – as part of the "living guidelines" approach – in the final phase of the guideline update *(33)*.

The GDG will continue to work with the WHO Secretariat in an ad hoc manner, so that the research gaps identified during the process can be addressed. The GDG anticipates that as data and experience with new screening tests and modalities advance, new recommendations will be needed through a living guideline process that is able to rapidly respond and evolve.

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ANNEXES

Annex 1. Guideline groups

Guideline Development Group (GDG) members

WHO region	Last name	First name	Institution	Country
African Region	Achieng	Claire Judith Ikate	Uganda Cancer Society	Uganda
African Region	Awori	Ruth	Representative from communities of women living with HIV	Uganda
African Region	Chinula	Lameck	Kamuzu Central Hospital	Malawi
African Region	Chirenje	Z. Mike	University of Zimbabwe	Zimbabwe
African Region	Denny	Lynette	University of Cape Town	South Africa
African Region	Diop	Mamadou	Joliot Curie Cancer Institute	Senegal
African Region	Happy	Margaret	Advocacy for Quality Health Uganda	Uganda
African Region	Ingbian	Priscilla	Community health support and empowerment initiative	Nigeria
African Region	Motshedisi	Sebitloane	University of Kwazulu-Natal	South Africa
African Region	Mugo	Nelly	Kenya Medical Research Institute	Kenya
African Region	Muzingwani	Laura S.	I-TECH Namibia	Namibia
African Region	Obiri-Yeboah	Dorcas	University of Cape Coast	Ghana
African Region	Shiferaw	Netsanet	Pathfinder International	Ethiopia
Region of the Americas	Arrossi	Silvina	Centro de Estudios de Estado y Sociedad (CEDES)	Argentina
Region of the Americas	Barnabas	Ruanne	University of Washington	United States of America (USA)
Region of the Americas	Bento Claro	Itamar	National Cancer Institute José Alencar Gomes da Silva (INCA)	Brazil
Region of the Americas	Chung	Michael	University of Washington	USA
Region of the Americas	Correa	Flavia Miranda	Brazilian National Cancer Institute	Brazil
Region of the Americas	Cremer	Miriam	Basic Health International	USA
Region of the Americas	Darragh	Teresa	University of California San Francisco	USA

WHO region	Last name	First name	Institution	Country
Region of the Americas	Gage	Julia	National Cancer Institute	USA
Region of the Americas	Gravitt	Patti	University of Maryland School of Medicine	USA
Region of the Americas	Herrero	Rolando	Costa Rican Agency for Biomedical Research	USA
Region of the Americas	Johnson	Ebony	Representative from communities of women living with HIV	USA
Region of the Americas	Maza	Mauricio	Basic Health International, Salvador	El Salvador
Region of the Americas	Murillo	Raul	Hospital Universitario San Ignacio	Colombia
Region of the Americas	Moley	Kelle	Bill & Melinda Gates Foundation – Reproductive Health Technologies	USA
Region of the Americas	Ogilvie	Gina	BC Women's Hospital and Health Centre	Canada
Region of the Americas	Picconi	Maria Alejandra	HPV Reference Laboratory, National Institute for Infectious Diseases – ANLIS Dr Malbran	Argentina
Region of the Americas	Pinder	Leeya	University of Washington	USA
Region of the Americas	Reis	Veronica	Jhpiego	USA
Region of the Americas	Ross Quiroga	Gracia Violetta	Bolivian Network of People Living with HIV/AIDS	Bolivia
Region of the Americas	Sahasrabuddhe	Vikrant	National Cancer Institute	USA
Region of the Americas	Thomson	Kerry	PATH	USA
Region of the Americas	Wentzensen	Nicolas	National Cancer Institute	USA
Eastern Mediterranean Region	Atif Waqar	Muhammad	Aga Khan University Hospital	Pakistan
Eastern Mediterranean Region	Ghanbari -Motlagh	Ali	Ministry of Health	Iran
Eastern Mediterranean Region	Hashem	Tarek	Menofyia University	Egypt
European Region	Bruni	Laia	Catalan Institute of Oncology	Spain

WHO region	Last name	First name	Institution	Country
European Region	Boily	Marie-Claude	Imperial College London	United Kingdom of Great Britain and Northern Ireland (United Kingdom)
European Region	Cain	Joanna	International Federation of Obstetrics and Gynecology (FIGO)	United Kingdom
European Region	de Sanjose	Silvia	PATH	Spain
European Region	Kelly	Helen	London School of Hygiene and Tropical Medicine	United Kingdom
European Region	Mackie	Anne	Public Health England Screening and Screening Quality Assurance Service	United Kingdom
European Region	Petignat	Patrick	Hôpitaux Universitaires de Genève	Switzerland
European Region	Prendiville	Walter	International Agency for Research on Cancer (IARC)	France
European Region	Sasieni	Peter	King's College London	United Kingdom
European Region	Torode	Julie	Union for International Cancer Control (UICC)	Switzerland
South-East Asia Region	Bhatla	Neerja	All India Institute of Medical Sciences	India
South-East Asia Region	Eamratsameekool	Wachara	Phanomphrai Community Hospital	Thailand
South-East Asia Region	Nessa	Ashrafun	Bangabandhu Sheikh Mujib Medical University	Bangladesh
South-East Asia Region	Thinn	Myint Myint	Central Women's Hospital	Myanmar
Western Pacific Region	Luvsandorj	Bayarsaikhan	National Cancer Center of Mongolia	Mongolia
Western Pacific Region	Zhao	Fanghui	China Cancer Institute	China

GDG member representatives from United Nations agencies

WHO region	Last name	First name	Institution	Country
Region of the Americas	Engel	Danielle	United Nations Population Fund (UNFPA)	USA
European Region	Shakarishvili	Anna	Joint United Nations Programme on HIV/AIDS (UNAIDS)	Switzerland
European Region	Tenhoope-Bender	Petra	UNFPA Switzerland	Switzerland

External Review Group (ERG) members

WHO region	Last name	First name	Institution	Country
Region of the Americas	Meglioli	Alejandra	International Planned Parenthood Federation/Western Hemisphere Region	United Kingdom
Region of the Americas	Nogueira	Angélica	Federal University of Mina Gerais, Brazilian Society of Medical Oncology	Brazil
Region of the Americas	Schiffman	Mark	National Cancer Institute	USA
Region of the Americas	Teran	Carolina	Universidad Mayor, Real y Pontificia de San Francisco Xavier de Chuquisaca	Bolivia
Region of the Americas	Trimble	Ted	National Cancer Institute	USA
Region of the Americas	Venegas	Gino	Facultad de Medicina, Universidad de Piura	Perú
Region of the Americas	White	Heather	TogetHER for Health	USA
Eastern Mediterranean Region	Moawia	Mohammed	National Cancer Institute, University of Gezira	Sudan
Eastern Mediterranean Region	El Hanchi	Zaki	National Institute of Oncology, CHU	Morocco
European Region	Chowdhury	Raveena	MSI Reproductive Choices UK	United Kingdom
European Region	Cubie	Heather	University of Edinburgh	United Kingdom
South-East Asia Region	Ghimire	Sarita	Nepal Cancer Care Foundation	Nepal
South-East Asia Region	Shamsunder	Saritha	Safdarjung Hospital	India
South-East Asia Region	Suri	Vanita	Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research	India
Western Pacific Region	Garland	Suzanne	University of Melbourne	Australia
Western Pacific Region	In	Ha Hyeong	Center for Gynecologic Cancer, National Cancer Center	Republic of Korea
Western Pacific Region	Jin-Kyoung	Oh	Department of Cancer Control and Population Health Research, National Cancer Center	Republic of Korea
Western Pacific Region	Myong Cheol	Lim	Center for Gynecologic Cancer, National Cancer Center	Republic of Korea

Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist supporting guideline development

Nancy Santesso
Department of Health Research Methods, Evidence and Impact
McMaster University, Toronto, Canada
Area of expertise: guideline development, systematic reviews, clinical epidemiology

Systematic review teams

Last name	First name	Institution	Country
Arbyn	Marc	Unit Cancer Epidemiology – Belgian Cancer Centre – Sciensano	Belgium
Lauby-Secretan	Beatrice	IARC	France

Modelling team

The modelling team supported the development of this guideline for women in the general population and women living with HIV. The modelling work was performed by the team led by **Karen Canfell** at Cancer Council NSW, Sydney, Australia (now the Daffodil Centre, a joint venture between the University of Sydney and Cancer Council NSW) using the Policy1-Cervix platform. The team members are listed in the table below.

The modelling team gratefully acknowledges: **John Murray** from the University of New South Wales, Sydney, who was also involved in the development of the HIV/HPV model used for the evaluation of screening in women living with HIV; **Megan Smith** from Cancer Council NSW, who contributed to past model development and discussions about model validation for newly emergent technologies; and **Susan Yuill** from Cancer Council NSW, who contributed to the systematic review of the evidence on HPV triage strategies led by Marc Arbyn of the Belgian Cancer Centre (see Systematic review teams above), which was used to inform the modelling.

Last name	First name	Institution	Country
Canfell	Karen	The Daffodil Centre, a joint venture between the University of Sydney and Cancer Council NSW	Australia
Caruana	Michael	The Daffodil Centre	Australia
Hall	Michaela	The Daffodil Centre	Australia
Keane	Adam	The Daffodil Centre	Australia
Killen	James	The Daffodil Centre	Australia
Lui	Gigi	The Daffodil Centre	Australia
Nguyen	Diep	The Daffodil Centre	Australia
Simms	Kate	The Daffodil Centre	Australia

Costing expertise

Last name	First name	Institution	Country
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Gauvreau	Cindy	Hospital for Sick Children/University of Toronto	Canada

Observers

Last name	First name	Institution	Country
Anderson	Benjamin	University of Washington	USA
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de Lussigny	Smiljka	Unitaid	Switzerland
Franco	Eduardo	Division of Cancer Epidemiology, McGill University	Canada
Huang	Lisa Pei-Ching	Expertise France	France
Jafa	Krishna	Bill & Melinda Gates Foundation	USA
Jeronimo	Jose	Cancer Consulting	USA
Kumar	Somesh	Jhpiego	USA
Lapidos-Salaiz	Ilana	United States Agency for International Development (USAID)	USA
Mesher	David	Public Health England, International Agency for Research on Cancer (IARC)	United Kingdom
Odayar	Jasantha	University of Cape Town	South Africa
Parham	Groesbeck	University of North Carolina	USA
Perez Casas	Carmen	Unitaid	Switzerland
Roitberg	Felipe	WHO	Switzerland

WHO Secretariat – headquarters members (Geneva, Switzerland)

Last name	First name	Departments
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Broutet	Nathalie	Department of Sexual and Reproductive Health and Research
Cortes	Myriam	Department of Sexual and Reproductive Health and Research
Dalal	Shona	Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
De Mello	Maeve	Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
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El Sheikh	Fayad	Department of Immunization, Vaccines and Biologicals
Fidarova	Elena	Department of Noncommunicable Diseases
Gottlieb	Sami	Department of Sexual and Reproductive Health and Research
Hutubessy	Raymond	Department of Immunization, Vaccines and Biologicals
Ilbawi	Andre	Department of Noncommunicable Diseases
Khosla	Rajat	Department of Sexual and Reproductive Health and Research
Kuku	Stephanie Yetunde	Department of Digital Health and Innovation
Narasimhan	Manjulaa	Department of Sexual and Reproductive Health and Research
Newman	Morkor	Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
Purnat	Tina	Department of Digital Health and Innovation
Rangaraj	Ajay	Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
Riley	Leanne Margaret	Department of Noncommunicable Diseases
Sands	Anita	Department of Regulation and Prequalification
Ströher	Ute	Department of Regulation and Prequalification
Velazquez Berumen	Adriana	Department of Health Product Policy and Standards
Vojnov	Lara	Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
Xu	Hongyi	Department of Noncommunicable Diseases

WHO Secretariat – regional advisers and International Agency for Research on Cancer (IARC) staff

WHO region	Last name	First name
African Region	Barango	Prebo
African Region	Dangou	Jean-Marie
African Region	Kapambwe	Sharon
African Region	Lago	Hugues
African Region	Ouedraogo	Leopold
African Region	Sebitloane	Tshidi
Region of the Americas	Ghidinelli	Massimo
Region of the Americas	Gómez Ponce de León	Rodolfo
Region of the Americas	Luciani	Silvana
Eastern Mediterranean Region	Gholbzouri	Karima
Eastern Mediterranean Region	Hermez	Joumana George
Eastern Mediterranean Region	Slama	Slim
European Region	Corbex	Marilys
European Region	Masoud	Dara
European Region	Smelov	Vitaly
South-East Asia Region	Dorji	Gampo
South-East Asia Region	Jayathilaka	Chandani Anoma
South-East Asia Region	Raina	Neena
South-East Asia Region	Sharma	Mukta
Western Pacific Region	Ishikawa	Naoko
Western Pacific Region	Mannava	Priya
Western Pacific Region	Narayan	Elick
Western Pacific Region	Shin	Hai-rim
Western Pacific Region	Sobel	Howard
Western Pacific Region	Tiko	Josaia
Western Pacific Region	Tran	Huong
IARC	Almonte Pacheco	Maribel
IARC	Basu	Partha
IARC	Clifford	Gary
IARC	Lauby-Secretan	Beatrice
IARC	Sauvaget	Catherine

Annex 2. Evidence-gathering teams and guideline task groups

Screen-and-treat **Screen, triage and treat** (follow-up studies)	**Screen-and-treat** **Screen, triage and treat** (diagnostic studies)
Lead: Beatrice Lauby-Secretan	**Lead: Marc Arbyn**
Véronique Bouvard Iciar Indave Isabel Mosquera **IARC handbook Working Group:** Marc Arbyn Hans Berkhof Karen Canfell Michael Chung Miriam Elfstrom Silvia de Sanjose Nicolas Wentzensen Fanghui Zhao	Karen Canfell Silvia de Sanjose

Values and preferences	**Feasibility and implementation**	**Clinical algorithms**
Lead: Ajay Rangaraj WHO Advisory Group of Women Living with HIV Nathalie Broutet Shona Dalal Linda Eckert Morkor Newman Nancy Santesso Julie Torode	**Leads: Patti Gravitt and Nancy Santesso** Prajakta Adsul Maribel Almonte André Carballo Lisa Huang José Jeronimo Somesh Kumar Najat Lahmi Kelly McCrystal Raul Murillo Jasantha Odayar Katayoun Taghavi	**Lead: Partha Basu** Maribel Almonte Silvina Arrossi Neerja Bhatla Nathalie Broutet Karen Canfell Z. Mike Chirenje Miriam Cremer Shona Dalal Lynette Denny Linda Eckert Jose Jeronimo Beatrice Lauby Raul Murillo Laura Muzingwani Groesbeck Parham Walter Prendiville Nancy Santesso Nicolas Wentzensen

Annex 3. Declarations of interests

WHO region	Last name	First name	Declaration of interests	Confidentiality agreement
African Region	Achieng	Claire Judith Ikate	No interests declared	Received
African Region	Awori	Ruth	No interests declared	Received
African Region	Chinula	Lameck	No interests declared	Received
African Region	Chirenje	Z. Mike	No interests declared	Received
African Region	Denny	Lynette	No interests declared	Received
African Region	Diop	Mamadou	No interests declared	Received
African Region	Happy	Margaret	No interests declared	Received
African Region	Ingbian	Priscilla	No interests declared	Received
African Region	Motshedisi	Sebitloane	No interests declared	Received
African Region	Mugo	Nelly	No interests declared	Received
African Region	Muzingwani	Laura S.	No interests declared	Received
African Region	Obiri-Yeboah	Dorcas	No interests declared	Received
African Region	Shiferaw	Netsanet	No interests declared	Received
Region of the Americas	Arrossi	Silvina	No interests declared	Received
Region of the Americas	Barnabas	Ruanne	No interests declared	Received
Region of the Americas	Bento Claro	Itamar	No interests declared	Received
Region of the Americas	Chung	Michael	No interests declared	Received
Region of the Americas	Correa	Flavia Miranda	No interests declared	Received
Region of the Americas	Cremer	Miriam	No interests declared	Received
Region of the Americas	Darragh	Teresa	No interests declared	Received
Region of the Americas	Gage	Julia	No interests declared	Received
Region of the Americas	Gravitt	Patti	No interests declared	Received
Region of the Americas	Herrero	Rolando	No interests declared	Received
Region of the Americas	Johnson	Ebony	No interests declared	Received
Region of the Americas	Maza	Mauricio	No interests declared	Received
Region of the Americas	Murillo	Raul	No interests declared	Received

WHO region	Last name	First name	Declaration of interests	Confidentiality agreement
Region of the Americas	Moley	Kelle	No interests declared	Received
Region of the Americas	Ogilvie	Gina	No interests declared	Received
Region of the Americas	Picconi	Maria Alejandra	No interests declared	Received
Region of the Americas	Pinder	Leeya	No interests declared	Received
Region of the Americas	Reis	Veronica	No interests declared	Received
Region of the Americas	Ross Quiroga	Gracia Violetta	No interests declared	Received
Region of the Americas	Sahasrabuddhe	Vikrant	No interests declared	Received
Region of the Americas	Thomson	Kerry	No interests declared	Received
Region of the Americas	Wentzensen	Nicolas	No interests declared	Received
Eastern Mediterranean Region	Atif Waqar	Muhammad	No interests declared	Received
Eastern Mediterranean Region	Ghanbari-Motlagh	Ali	No Interests declared	Received
Eastern Mediterranean Region	Hashem	Tarek	No interests declared	Received
European Region	Bruni	Laia	No interests declared	Received
European Region	Boily	Marie-Claude	No interests declared	Received
European Region	Cain	Joanna	No interests declared	Received
European Region	de Sanjose	Silvia	No interests declared	Received
European Region	Kelly	Helen	No interests declared	Received
European Region	Mackie	Anne	No interests declared	Received
European Region	Petignat	Patrick	No interests declared	Received
European Region	Prendiville	Walter	No interests declared	Received
European Region	Sasieni	Peter	No interests declared	Received
European Region	Torode	Julie	No interests declared	Received
South-East Asia Region	Bhatla	Neerja	No interests declared	Received
South-East Asia Region	Eamratsameekool	Wachara	No interests declared	Received
South-East Asia Region	Nessa	Ashrafun	No interests declared	Received
South-East Asia Region	Thinn	Myint Myint	No interests declared	Received
Western Pacific Region	Luvsandorj	Bayarsaikhan	No interests declared	Received
Western Pacific Region	Zhao	Fanghui	No interests declared	Received

Annex 4. Algorithms for use of HPV mRNA tests in the general population of women

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.

Screen-and-treat approaches:

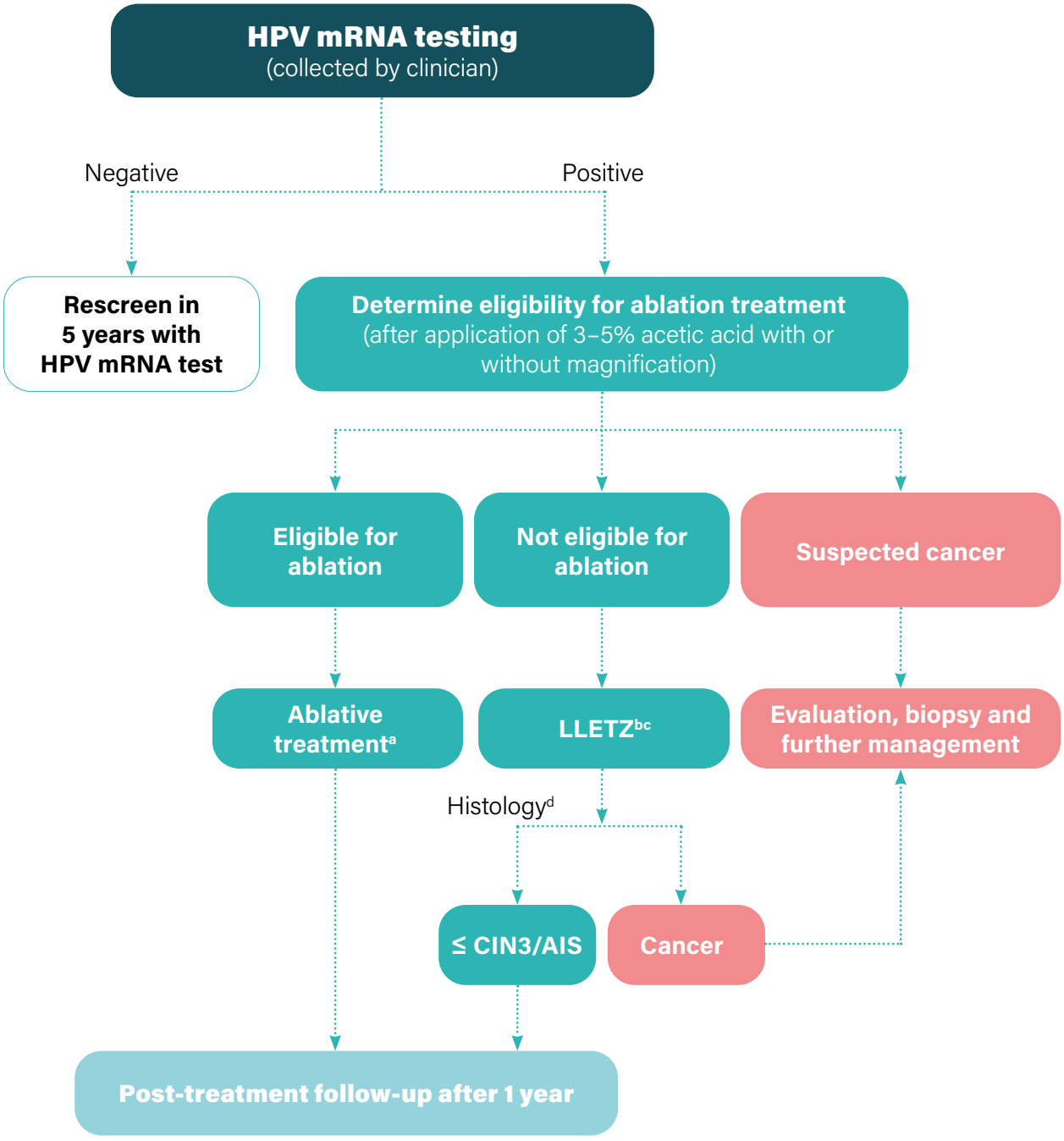
1. **HPV mRNA** as the primary screening test, followed by treatment

Screen, triage and treat approaches:

2. **HPV mRNA** as the primary screening test, followed by **VIA triage**, followed by treatment
3. **HPV mRNA** as the primary screening test, followed by **colposcopy triage**, followed by treatment
4. **HPV mRNA** as the primary screening test, followed by **cytology triage**, followed by **colposcopy** and treatment

ALGORITHM 1. PRIMARY HPV mRNA SCREENING (SCREEN-AND-TREAT APPROACH)

For the general population of women



[a] Ablative treatment includes cryotherapy and thermal ablation.
[b] Cold knife conization (CKC) if LLETZ not available.
[c] LLETZ and LEEP (loop electrosurgical excision procedure) indicate the same procedure.
[d] Histology may not be available in certain settings; women should be advised to attend follow-up after 1 year or to report earlier, if they have any of the symptoms of cervical cancer.
AIS: adenocarcinoma in situ; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; LLETZ: large-loop excision of the transformation zone.

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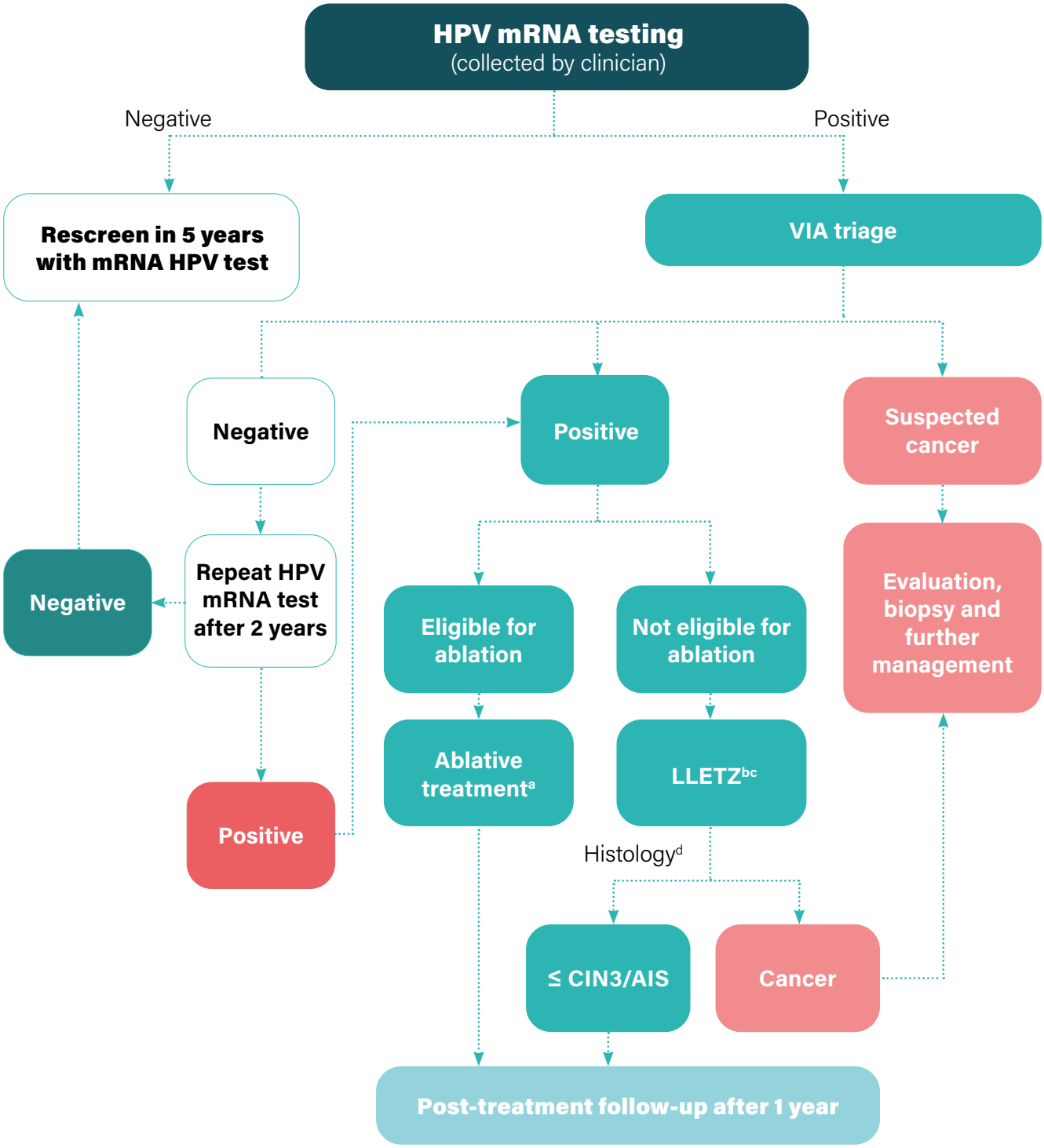
ALGORITHM 2. PRIMARY HPV mRNA SCREENING AND VIA TRIAGE (SCREEN, TRIAGE AND TREAT APPROACH)

For the general population of women



[a] Ablative treatment includes cryotherapy and thermal ablation.
[b] Cold knife conization (CKC) if LLETZ not available.
[c] LLETZ and LEEP (loop electrosurgical excision procedure) indicate the same procedure.
[d] Histology may not be available in certain settings; women should be advised to attend follow-up after 1 year or to report earlier, if they have any of the symptoms of cervical cancer.

AIS: adenocarcinoma in situ; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; LLETZ: large-loop excision of the transformation zone; VIA: visual inspection with acetic acid.

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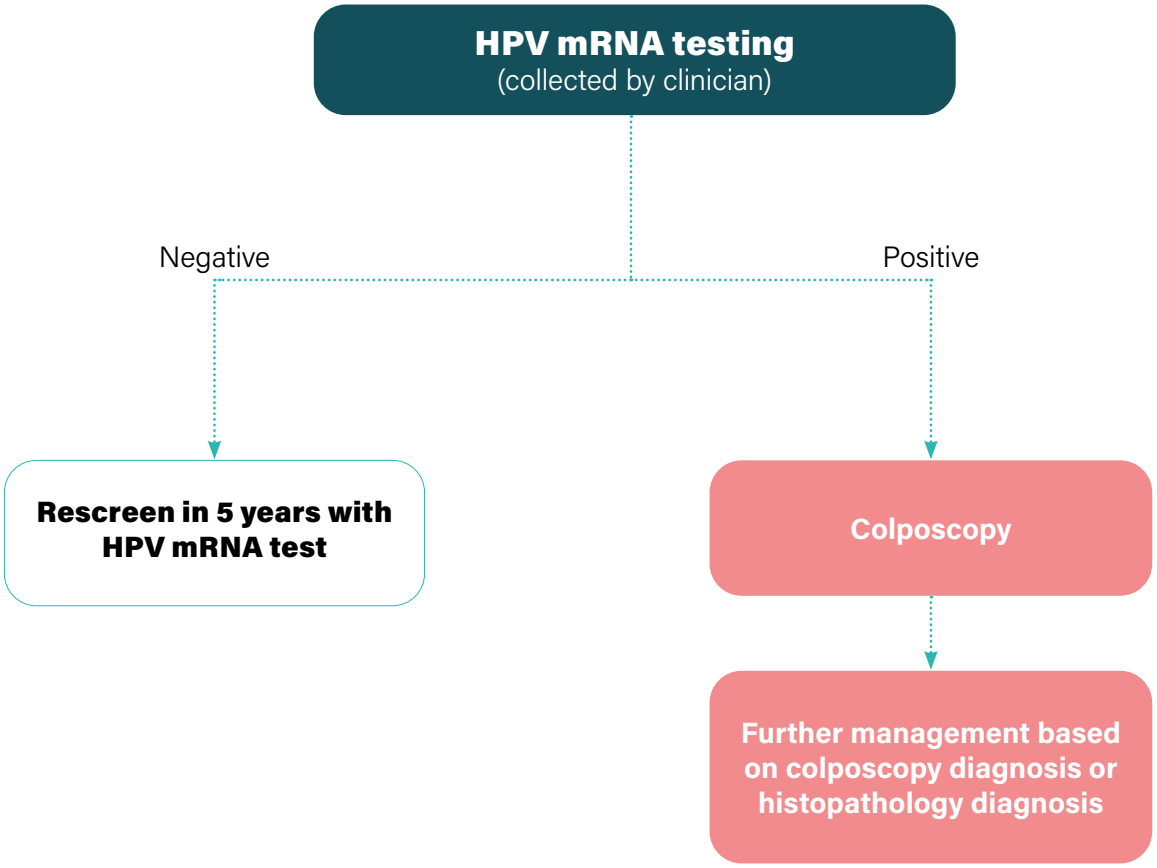
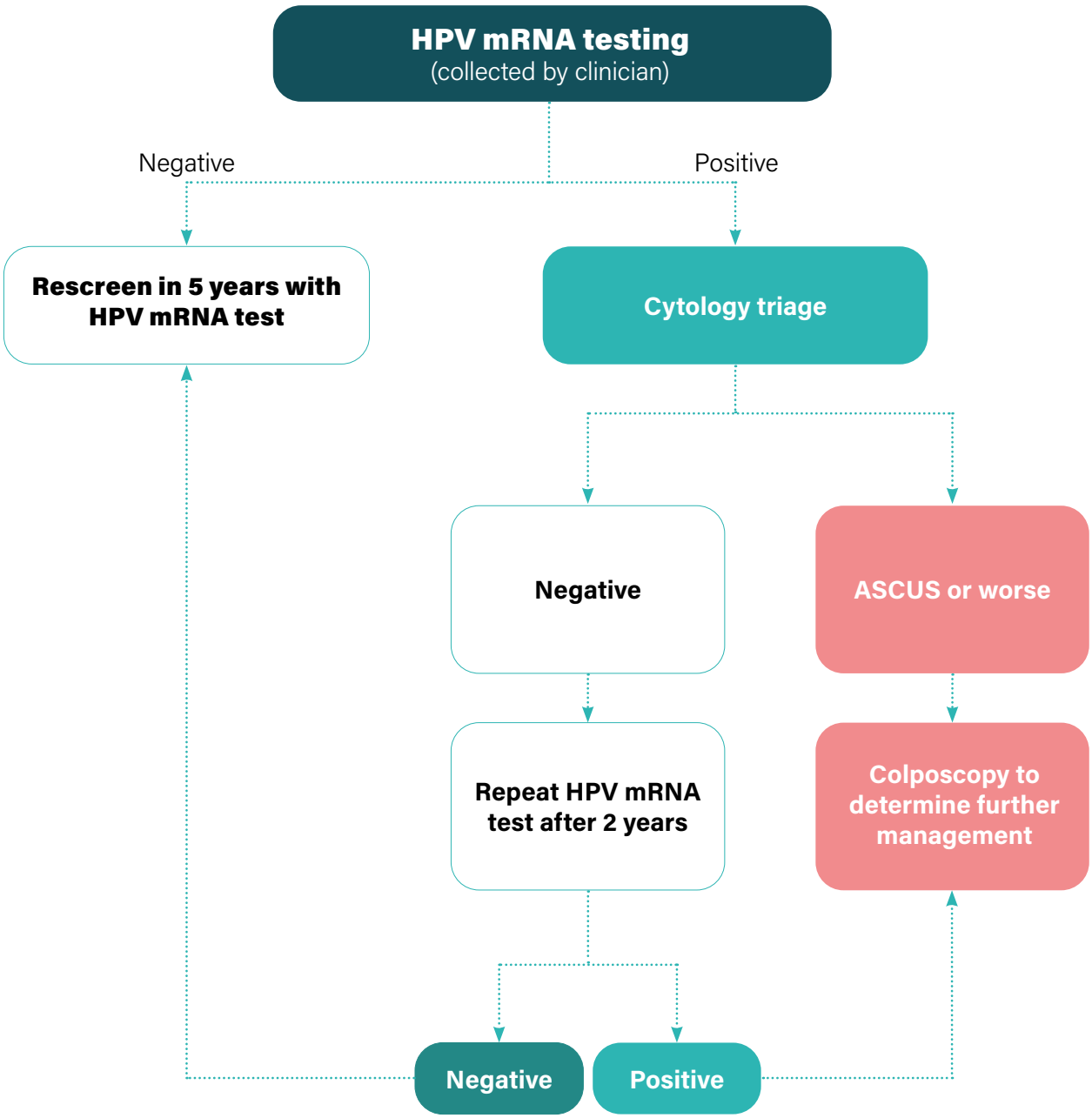
ALGORITHM 3. PRIMARY HPV mRNA SCREENING AND COLPOSCOPY TRIAGE (SCREEN, TRIAGE AND TREAT APPROACH)

For the general population of women



ALGORITHM 4. PRIMARY HPV mRNA SCREENING AND CYTOLOGY TRIAGE FOLLOWED BY COLPOSCOPY (SCREEN, TRIAGE AND TREAT APPROACH)

For the general population of women



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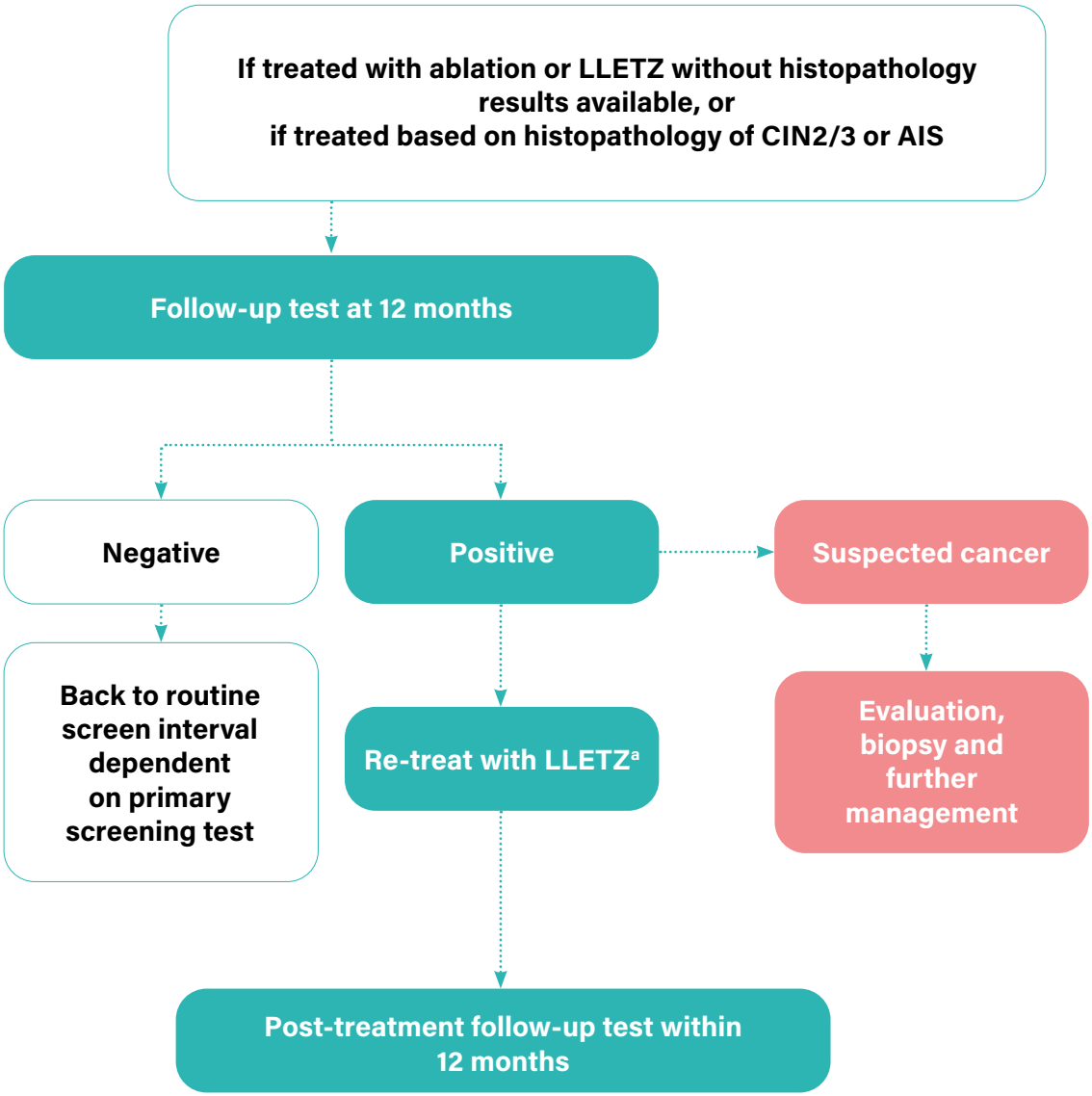
FOLLOW-UP TESTS AT 12 MONTHS POST-TREATMENT

For the general population of women



[a] In circumstances where LLETZ not available, use cryotherapy or thermal ablation for retreatment, if eligible.
AIS: adenocarcinoma in situ; CIN: cervical intraepithelial neoplasia; LLETZ: large-loop excision of the transformation zone.

Annex 5. Recommendations from Phase 1 of the guideline update: HPV DNA tests and other cervical screening methods[1]

[1] These recommendations and good practice statements were published in *WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition* (2021), available at: https://www.who.int/publications/i/item/9789240030824

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 certainty of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and certainty 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 pink 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 certainty of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and certainty 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

[a] Rows shaded in pink 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 certainty of evidence***	**Recommendations for women living with HIV**[a]	***Strength of recommendation and certainty 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

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Recommendations for the general population of women[a]	***Strength of recommendation and certainty of evidence***	**Recommendations for women living with HIV**[a]	***Strength of recommendation and certainty 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 months** and, if negative again, move to the recommended regular screening interval.	Conditional recommendation, low-certainty evidence

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Recommendations for the general population of women[a]	*Strength of recommendation and certainty of evidence*	Recommendations for women living with HIV[a]	*Strength of recommendation and certainty 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.

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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**.

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