Cervical cancer is the fourth most common cancer among women in the world and is responsible for the highest number of cancer-related deaths among women in Sub-Saharan Africa (SSA), Southeast Asia, and Central America. In 2020, an estimated 604,000 persons were diagnosed with cervical cancer worldwide, with around 342,000 women dying from the disease. Social, economic, and structural inequities are significant drivers of cervical cancer incidence and mortality, with nearly 90% of cases occurring in low- and middle-income countries and twice as many women dying from the disease (60%) than in high-income countries.

Over 95% of cervical cancer cases are caused by the human papillomavirus (HPV), which is sexually transmitted and infects nearly all sexually active adults at least once in their lives, usually at a young age. In most cases, the infection is asymptomatic and resolves spontaneously within one to two years of infection. Yet, unlike the vaccine, natural infection provides only limited immunity, so reinfection remains possible. In addition, some of those infected are not able to fully recover, resulting in a chronic infection that may cause precancerous lesions to develop. It is critical to determine which women are at risk for such lesions, to screen them systematically, and to treat the lesions early, as untreated lesions can progress to life-threatening, invasive cancer.

Although HIV and HPV viruses are not medically linked, research shows important interactions between the two infections, leading the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and others to list cervical cancer as an “AIDS-defining illness” (i.e., the chronic presence of HPV is a marker for advanced HIV disease). Women living with HIV are at particularly high risk for cervical cancer. Compared with HIV-negative women, women living with HIV are twice as likely to become infected with HPV and are half as likely to be able to clear the virus once infected. They are more likely to have precancerous lesions, a lower chance of the lesions regressing, and a more rapid progression to cancer. Overall, women living with HIV are six times more likely to see an HPV infection develop into cervical cancer than HIV-negative women, often at a younger age. In addition, cervical cancer develops twice as quickly for women living with HIV who are not on antiretroviral therapy. HIV-positive women therefore require earlier and more frequent HPV screening. Women who have an HPV infection, in turn, are twice as likely to acquire HIV compared with those without HPV. All of these factors reinforce the need for integrated HIV and cervical cancer prevention, diagnosis, and treatment.

At the same time, the fact that cervical cancer is generally caused by a virus makes it one of the simplest cancers to prevent via vaccination. Additionally, if diagnosed in the early stages, cervical cancer is curable, especially if identified in the precancerous phase, including among women living with HIV. The discrepancy between the great potential for prevention and cure and the persistently high levels of disease and mortality are due to several factors, many of them related to socioeconomic inequities among and within countries. Such issues include delays in adopting the latest WHO guidelines on prevention and treatment; insufficient integration of cervical cancer care into HIV, primary, and sexual and reproductive health services; a lack of community awareness about preventing and treating cervical cancer; persistent stigma and misinformation about the disease; and insufficient prioritization among some governments and donors.

* Unlike HPV vaccines, which are administered intramuscularly and are highly immunogenic, resulting in long-term immunity against HPV, natural infection occurs via the mucosal site and generates limited immunity. People can be reinfected after a natural infection but not after vaccination.
Given the great potential to decrease the incidence and mortality of cervical cancer, WHO launched its global strategy to accelerate the elimination of cervical cancer in 2020 and updated its technical guidelines on prevention and treatment in July 2021 (see below). WHO’s strategy aims to eliminate cervical cancer by reaching and maintaining an incidence rate of less than 4/100,000 women in all countries. To fully eliminate cervical cancer within the next century, the strategy sets out the following “90:70:90 targets” for each country to achieve by 2030: (i) 90% of girls fully vaccinated with the HPV vaccine by the age of 15; (ii) 70% of women screened using a high-performance test by the age of 35 and again by the age of 45; and (iii) 90% of women with precancer treated and 90% of women with invasive cancer managed.

This policy brief will focus on the benefits of HPV DNA screening as a high-performance test and the best available form of screening for cervical cancer given its reliability, cost-effectiveness, and accessibility. If given sufficient community, political, and financial support, HPV DNA screening could radically improve the outcomes for women at risk of developing cervical cancer.

### The Benefits of HPV DNA Testing in Secondary Prevention of Cervical Cancer

As cervical cancer is largely caused by a virus, it is simpler to prevent and screen for than many other cancers. The first line of prevention—known as “primary prevention”—is a vaccine, which WHO recommends giving to girls between the ages of 9 and 14 years. But while the vaccine is now part of the national immunization schedules of 85% of high-income countries, it is part of regular vaccination programs for only 25% of low-income countries. Barriers to higher levels of vaccination include vaccine supply shortages and high costs, lack of awareness about cervical cancer and prevention techniques, and insufficient integration into ongoing vaccination campaigns, reducing availability and contributing to higher delivery costs.

With continued low rates of primary prevention in low- and middle-income countries, saving women’s lives requires the best possible methods of “secondary prevention” for cervical cancer, meaning early screening for and treatment of precancerous lesions. Traditionally, such screening has been carried out using visual inspection with acetic acid (VIA), in which a vinegar-like substance is placed on the cervix to expose precancerous lesions, or using cytology (a Pap smear or liquid cytology), in which cells from the cervix are sent to a laboratory to assess for abnormality. Cytology is not commonly used in lower-income settings, however, and where it is used, it suffers the disadvantages of long turnaround times due to insufficient infrastructure and too few trained cytopathologists. In addition, both of these methods rely on human subjectivity and are therefore highly dependent on the training and skills of the provider, leading to variable sensitivity.

#### Overview of HPV DNA Tests

Most HPV DNA tests available are laboratory-based and run on high-throughput molecular platforms—already available in countries for HIV, TB, hepatitis, SARS-CoV-2, and other pathogen testing—and form part of the menu offered by manufacturers under preferential pricing or Global Access Program conditions. This means that HPV DNA tests cost, on average, US$11.92 (EXW) per test and US$13.23 in-country with the addition of logistics, distributor margins, controls, and other procurement-related costs. Additional product prices provided by the Clinton Health Access Initiative (CHAI) are listed below, most of which have come down a further 25% to 50% following more recent price negotiations.

In addition to indicating whether someone is infected with HPV or not, the test result provides information on whether the HPV 16, 18, or other oncogenic types are present. Samples can be self-collected or collected by a health care provider, after which they can be preserved in liquid cytology media. Examples include PreservCyt Solution (Hologic), SurePath Preservative Fluid (TriPath Imaging), and Abbott Cervi-Collect Specimen Collection Kit.

WHO prequalified tests, which also have stringent regulatory authority approval, include the:

1. automated, high-throughput laboratory-based Abbott Realtime high-risk HPV assay run on the m2000 platform, priced at US$5.69 (EXW) per test, or US$7.99 (EXW) with the instrument included, in 33 countries in SSA;

2. and the POC Cepheid Xpert HPV assay run on the GeneXpert, priced at US$14.90 (EXW) per test in 145 low- and middle-income countries and as part of the all-inclusive GX 16 program.

Other automated, high-throughput laboratory-based tests with stringent regulatory approval (including US Food and Drug Administration approval and CE marking) and Global Access Programs include the:

1. Roche cobas HPV assay run on the cobas 4800/6800/8800 platforms, priced at US$7.90 (CPT) per test in 89 low- and middle-income countries;

2. and the Hologic Aptima HPV assay run on the Panther system, priced at US$9.00 (DAP), all-inclusive, per test in eight African countries and at US$11.28 (DAP) in 50 countries.

In addition to these existing tests, at least one additional POC option will come onto the global market within the next year or two with WHO prequalification and/or stringent regulatory approval. This option is expected to be as decentralized as Cepheid’s option, as well as cheaper. Additional work is planned to validate different sample collection devices and methods for self-collection to ensure an evidence-informed approach that meets the needs of both quality and convenience.

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* Shortages of the vaccine should be alleviated when WHO releases expected new guidelines calling for only one dose of the vaccine for the general population and two doses for adolescents living with HIV.
EGPAF’s support to cervical cancer programs: the case of Lesotho

EGPAF’s work on women’s sexual and reproductive health has long included cervical cancer in addition to its primary focus on HIV. EGPAF implements comprehensive cervical cancer programming at supported facilities in Eswatini, Kenya, Lesotho, Malawi, Mozambique, Tanzania, and Uganda, with additional programming across other countries in SSA. EGPAF teams help build national capacity by supporting the training, mentoring, and supervision of health care providers at supported sites, as well as the introduction and use of relevant technologies and equipment. Specifically, EGPAF trains health care workers on the screening, diagnosis, management, and prevention of cervical cancer and the integration into HIV programming infrastructure. EGPAF also introduces new and best-in-class tools to achieve these goals.

EGPAF’s program in Lesotho exemplifies what progress can be achieved when a government is strongly committed to improving its cervical cancer program. In the early 2000s, the government of Lesotho, which finances HPV vaccination and treatment for cervical cancer, became concerned by the high costs associated with late-stage cervical cancer diagnosis. It therefore decided in 2006 to look into improving prevention and early screening and treatment. Since 2011, it has worked with EGPAF and community leaders and organizations to ensure that all girls are vaccinated by age 14*, all women—those living both with and without HIV—are screened for cervical cancer in accordance with WHO guidelines, all women with precancer are quickly treated, and women with invasive cancer are given effective treatment and care. With EGPAF’s support and funding from Unitaid and the President’s Emergency Plan for AIDS Relief (PEPFAR), HPV DNA testing has been piloted in two districts and will soon be phased in countrywide, leveraging on the Cepheid GeneXpert machines already available in-country.

Together, the government of Lesotho and EGPAF established and continue to support a center of excellence and national training center in the capital city for cervical cancer prevention, screening, and treatment, alongside HIV and other sexual and reproductive health care services. At the same time, EGPAF’s training of physicians and nurses in screening and treatment of precancerous lesions has enabled women to access preventive care in facilities throughout the country. EGPAF in Lesotho also works closely with civil society organizations active at both facility and community levels to build knowledge, create demand, and encourage utilization of services among women, including campaigns specifically targeting women living with HIV and underserved populations, like sex workers and factory workers. EGPAF’s pioneering work in Lesotho has expanded across the countries that EGPAF supports, with cervical cancer prevention being integrated into HIV programs across SSA.

The benefits of HPV DNA testing

Fortunately, another form of screening for secondary prevention is now available: the HPV DNA test, a molecular test run on cells sampled from the vagina or cervix that determines if a woman is infected with the HPV, and, therefore, at higher risk of cervical cancer. The test detects all 14 high-risk or “oncogenic” HPV types and also simultaneously reports the specific detection of the particularly high-risk 16 and 18 types that cause the vast majority of cancer cases. As a lab test with no subjective assessment needed, it has greater reproducibility than the VIA or cytology tests, and, as it is a molecular test, is also highly sensitive and specific. It is therefore the most reliable way of identifying women with a high risk of developing cancer at the earliest possible stage.

If women test positive for HPV infection, they are further screened for precancerous lesions, which can be immediately treated through thermotherapy, cryotherapy (although thermotherapy is preferable), or, if necessary for larger lesions, Loop Electrosurgical Excision Procedure, usually leading to full remission. Precancerous lesions uncaught sufficiently early may progress to invasive cancer that requires treatment by radiation and chemotherapy, which are seldom available, accessible, or affordable in low-income countries. Effective early screening can therefore vastly improve a woman’s chance of survival in such settings, as it alerts health care workers to the potential presence of precancerous lesions before they can develop into life-threatening cancer.

HPV DNA test samples may be collected by nurses or other health care workers at primary health care, sexual and reproductive health clinics, or HIV clinics, meaning there is no need for women to travel to specialized facilities. Moreover, samples for HPV DNA testing can be taken by a woman herself via self-collection kits, either in a private room at a health care facility or in her own home. Community health workers can support the sample collection process by delivering sample kits to women, returning them quickly to clinics or laboratories, facilitating access to results, and encouraging women to seek treatment, if needed.

Fortunately, HPV DNA tests are compatible with existing molecular platforms currently used for HIV, TB, and other infections and diseases, both on high output laboratory equipment and near point-of-care (POC) machines. While laboratories and POC sites would need to manage additional demand for existing machines, the increased use of HPV DNA plus oncogenic type screening would reduce the need for labor-intensive cytology, saving money for pathology services and freeing up lab resources. Including HPV DNA tests should therefore be entirely manageable within an optimized and integrated diagnostics network approach that maximizes efficiency and clinical value across diseases.

* Note that HPV vaccination in Lesotho was stopped after about three years until it was reintroduced in 2022, with adequate provision to make it sustainable.

‡ Since 2020, WHO no longer recommends cryotherapy as a technique for treating precancerous lesions, as thermal ablation is lower cost and more effective.
Finally, HPV DNA tests are cost-effective relative to other screening tests. The price of HPV tests is currently between US$5.70 and US$9.00 for most tests used at high-throughput centers and US$14.90 for the Xpert (Cepheid) POC test run on the GeneXpert machine, versus around US$12.00 per Pap smear test. But even the assay run on the GeneXpert machine remains more cost-effective than cytology, as HPV DNA tests are conducted less frequently than cytology tests due to their much higher sensitivity. In addition, tests are conducted at POC sites, where results can be delivered while the patient waits, meaning lower costs per test result received than those requiring central laboratory processing, where monthslong turnaround times mean that many discouraged women never get results at all. The early identification and treatment of women will also reduce overall health care costs by limiting the need for costly cancer treatment and management. By identifying which women will not need any immediate follow-up services following a negative HPV DNA test result, the HPV DNA test can also decrease the volume of other types of screening tests previously used to free up health care workers’ time for treating precancerous lesions for those women who require it.

HPV DNA tests have proven so effective for secondary prevention that WHO now 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” as part of a “screen, triage, and treat approach.” Triage for women testing positive can then be carried out via partial genotyping (determining whether the oncogenic types 16 or 18 are present with the HPV DNA test), colposcopy, VIA (for women who test positive for HPV DNA with other high-risk types), or cytology. For those who test positive for HPV DNA but do not have a visible lesion following VIA, it is recommended that they be retested for HPV DNA positivity at one year for women living with HIV or at two years for women not living with HIV. If still HPV DNA positive (defined as chronic HPV infection), they should be offered treatment. WHO recommends that women should be screened every five to 10 years for the general population (from ages 30 to 49) and every three to five years for women living with HIV (for women aged 25–49), and supports such testing at clinics or via self-collection kits. The new guidelines will cut back on the amount of time-consuming cytology, colposcopy, and VIA testing, as these procedures will only be needed for triaging the small group of women who test positive for HPV DNA. In some cases, even these other triage options can be avoided, as the HPV DNA test result automatically generates the HPV 16 and 18 types for those testing positive, thereby already providing one of the recommended forms of triage (Figure 1).

§ Prices are especially competitive with other forms of screening after recent price reductions negotiated by CHAI.
Challenges and opportunities in scaling up the use of HPV DNA testing

Despite the numerous benefits of HPV DNA testing for lifesaving early screening outlined above, a number of barriers have restricted its rollout and scale-up to date. Many countries have not yet fully adopted or implemented the 2021 WHO guidelines, meaning that HPV DNA testing and the use of types 16 and 18 for triage have not yet been integrated into national guidelines. Nor have these countries integrated HPV DNA testing into the full range of entry points for women’s health, despite the enormous potential that such integration could have for improving health outcomes for women. Low political prioritization also means that budgets presented for domestic or foreign funding often do not include cervical cancer prevention and treatment.

Some donor funding is available for cervical cancer, including HPV DNA screening, but often just for women living with HIV. For example, PEPFAR provides funding for cervical cancer screening and treatment for women living with HIV in a limited number of countries through their Go Further partnership. Noting the potential benefits for reducing cervical cancer mortality, PEPFAR’s 2022 Country Operational Plan Guidance promotes the use of HPV DNA testing as part of the screen, triage, and treat process among women living with HIV. PEPFAR supports the use of self-sampling for HPV DNA testing, which also proved effective during COVID-19 restrictions, in addition to provider training for provider- and self-collected HPV DNA test sampling and systems to enhance client tracking and reduce HPV DNA test turnaround time to less than seven days. It also supports community-based organizations’ work on demand creation for screening, including using HPV DNA tests, and their efforts to tackle misinformation and stigma. Yet, PEPFAR’s funding for cervical cancer is usually only available in connection with HIV projects, limiting its access to HIV-negative women. And even among these projects, cervical cancer tends to receive lower prioritization within broader budgets, despite the great potential to reach women living with HIV through numerous entry points. The Global Fund also provides some funding for cervical cancer programs in relation to HIV coinfection budgets.

An additional challenge for scale-up is the lack of information available to women about the risks of cervical cancer and the few nonprofit organizations dedicated specifically to addressing this gap. In many cultures, there is a strong stigma about discussing and seeking medical care for a sexually transmitted infection, even one that nearly every adult will get unless immunized. The fact that women living with HIV are at higher risk for cervical cancer adds to the stigma, as the two conditions are confounded in the public’s view. Women in resource-limited settings also struggle to find the time and money to travel to health care clinics or hospitals and often prioritize raising money for their families over taking care of their own health. Given the stigma and the broader reluctance to seek medical care for sexual and reproductive health concerns, even women who test positive may fail to seek treatment. Peer support or other forms of psychosocial support could help such women.

Conclusion

The HPV DNA test represents a potentially game-changing development for women at risk of cervical cancer given its high sensitivity, cost-effectiveness, accessibility, and WHO’s recommendation for use among both HIV-positive and negative women. It saves women and health care workers time and money as it can be carried out less frequently due to its high performance and can be delivered with shorter turnaround times. Its higher sensitivity can save lives by providing early signals of the need for further investigation and treatment. The HPV DNA test is particularly useful in resource-limited settings, where the use of cytology screening is limited and effective treatment of invasive cancer is not accessible for most women. To enable this tool to save countless lives, it is now necessary to gain the full support of governments and donors, as well as high-level advocacy on the part of implementing partners in order to introduce and scale up HPV DNA screening programs and to improve awareness about its benefits for all women.

1 Since 2018, PEPFAR’s Go Further partnership has provided funding to eight SSA countries: Botswana, Eswatini, Lesotho, Malawi, Mozambique, Namibia, Zambia, and Zimbabwe.
Recommendations

In order to speed up the use of HPV DNA testing as the standard of practice in screening women for cervical cancer, the following steps should be taken as soon as possible:

**Governments should:**

- **Update national policies and plans on cervical cancer**
  - Rapidly align national policies on cervical cancer screening and treatment with the WHO recommendations from 2021 and any subsequent updates
  - Prioritize prevention, screening, and treatment of cervical cancer within national strategic health plans
  - Ensure that cervical cancer prevention, screening, and treatment are integrated into all relevant health care entry points, especially primary health care, sexual and reproductive health, and HIV services, and ensure proper training for health care workers in these settings

- **Secure funding**
  - Prioritize cervical cancer prevention, screening, and treatment in requests to donors, including related work by community-based organizations
  - In national budgets, incorporate cervical cancer prevention, screening, and treatment, including related work by community-based organizations
  - Provide free vaccinations, screening, and treatment for cervical cancer—with no out-of-pocket expenses for people living both with or without HIV—and support women in traveling to health care facilities

- **Scale up HPV DNA screening**
  - Ensure that HPV DNA testing, including via self-collected samples, is available to all women at the ages recommended by the WHO guidelines
  - Ensure that test results are delivered to all women in a timely manner, preferably during the same visit to enable immediate follow-up
  - Ensure that HPV DNA testing needs are included in central laboratories and that POC testing plans are within a diagnostic network optimization approach
  - Support community efforts to increase awareness of, demand for, and use of HPV DNA tests

**Donors should:**

- **Provide funding for cervical cancer, including HPV DNA testing**
  - Include funding for cervical cancer prevention, screening, and treatment within funding streams for universal health coverage and health systems strengthening, in addition to existing HIV program funding

- **Strengthen support for civil society and community-based organizations**
  - Support community-based organizations’ efforts to increase awareness of and demand for cervical cancer vaccination, screening, and treatment and to combat stigma and misconceptions around cervical cancer
  - Support community-based organizations’ efforts to facilitate women’s access to HPV DNA testing, including via self-collection kits

- **Push for prices of HPV DNA tests to come down**
  - Work with private industry, large procurement agencies and countries, and civil society to seek additional decreases in costs for HPV DNA assays, especially for POC tests, through such methods as encouraging additional products to enter the market, volume-based global price reductions across instrument menus, and pooled procurement

**Civil society should:**

- **Improve awareness about cervical cancer and scale up demand**
  - Inform women about the lifesaving benefits of early screening and treatment and the benefits of using HPV DNA screening
  - Provide community education about cervical cancer and address misconceptions

- **Support access to DNA testing and sample transportation in the community**
  - Facilitate women’s access to HPV DNA tests and inform women of the benefits of using self-collection kits
  - Provide support for timely sample transportation to diagnostic sites
  - Accompany women throughout the post-test process, including by encouraging them to find out their results and pursue treatment if needed

- **Call on governments to improve access to HPV DNA testing**
  - Call on governments to rapidly scale up HPV DNA screening and to devote greater resources to cancer treatment and management
  - Call on governments to ensure that women receive test results in a timely manner

By following these recommendations and strategies, the promise of a world without cervical cancer can be achieved.
References


