A Europe free of AIDS, TB and viral hepatitis - and no one left behind

CSF Online Meeting

HPV and related cancers among people living with HIV and key populations

July 10 from 14:00 to 15:30 CET

Agenda

Time	Topic & Presenter
14:00 – 14:15	**HPV-related cancers among PLHIV and key populations: why do we need to pay special attention to these groups? /** Viatcheslav Grankov, WHO
14:15 – 14:30	**WHO recommendations on HPV vaccination and Regional Roadmap to accelerate the elimination of cervical cancer as a public health problem in the WHO European Region 2022-2030** /Liudmila Mosina, WHO
14:30 – 14:45	**Cervical cancer: control and prevention and WHO tools/** Vitaly Smelov, Isabelle Heard, WHO
14:45 – 15:00	**EACS guidelines vs. Implementation of HPV vaccination,** Konstantinos Protopapas, EACS Standard of Care
15:00 – 15:30	**Q&A and Discussion**

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Meeting Report

The CSF online meeting began with opening remarks from Nina Tumanyan (CSF Secretariat), welcoming participants, introducing the Agenda and emphasizing the significance of discussing HPV among people living with HIV and other key populations in the WHO European region.

HPV-related cancers among PLHIV and key populations: why do we need to pay special attention to these groups?

Viatcheslav Grankov from the WHO Regional Office for Europe emphasized the need for special attention to HPV-related cancers among people living with HIV (PLHIV) and other key populations. In his presentation, Grankov highlighted the epidemiology of HPV among these groups, the prevalence of rates of high-risk HPV types and their association with various cancers.

Findings from scientific studies:

- The global prevalence of HPV (all types) among adult women with normal cytological findings is estimated at 12%, with Eastern Europe showing a slightly higher prevalence of 14%.
- Women living with HIV have a higher prevalence of HPV compared to HIV-negative women. However, those on antiretroviral therapy (ART) show a lower prevalence of high-risk HPV compared to those not on ART.
- Among men who have sex with men (MSM), HPV infections are notably common: 78% in the anal area, 36% in the penile area, 17% in the oral area, and 15% in the urethral area. MSM living with HIV exhibit the highest prevalence of anal HPV and HPV16, regardless of type.
- Female sex workers (FSWs) globally have a pooled HPV prevalence of 39.5%, nearly four times higher than that of the general female population, with notable regional and country-specific variations.

- Data on HPV prevalence among transgender people is limited. However, it has been demonstrated that transgender men do not access preventive cervical screening at the same level as non-transgender female patients.

Grankov concluded that PLHIV and key populations are disproportionately affected by HPV, underscoring the need for targeted interventions and special attention. He also presented relevant WHO guidelines.

WHO recommendations on HPV vaccination and Regional Roadmap to accelerate the elimination of cervical cancer as a public health problem in the WHO European Region 2022-2030

Liudmila Mosina from the WHO Regional Office for Europe explored the WHO recommendations on HPV vaccination and the Regional Roadmap to accelerate the elimination of cervical cancer as a public health problem in the WHO European Region for 2022-2030. Her presentation covered both the global and regional strategies to combat cervical cancer through vaccination and integrated healthcare approaches.

WHO Recommendations on HPV Vaccination

The prevalence of cervical cancer in the WHO European Region:

- Cervical cancer remains a significant public health threat, with over 60,000 new cases and more than 30,000 deaths in 2020, according to Globocan estimates.
- Higher incidence and mortality rates in low and middle-income countries.
- Cervical cancer is preventable with the prophylactic HPV vaccine available since 2016.

HPV vaccines that are available from 2016:

- **Bivalent**: Cervarix (GlaxoSmithKline), Cecolin (Xiamen Innovax Biotech), Walrinvax (Yuxi Zerun)
- **Quadrivalent**: Gardasil (Merck & Co), Cervavax (Serum Institute of India)
- **Nonavalent**: Gardasil 9 (Merck & Co)

All these vaccines offer protection against two high-risk oncogenic HPV types responsible for 84-90% of cervical cancer cases. They have demonstrated high safety and efficacy.

Vaccination strategies and target groups

Mosina presented the vaccination strategies and target groups as defined by the WHO. The primary target group as considered by the WHO are teenage girls before they become sexually active. Additional target groups to be considered are boys, older males, and men who have sex with men. PLHIV should be prioritized for vaccination as part of public health programs.

An optimal vaccination schedule is a 2-dose schedule with a 12-month interval. An alternative schedule is an off-label single-dose schedule for girls and boys aged 9-20 years (for Cervarix, Gardasil, and Gardasil 9). However, immunocompromised individuals or those living with HIV should receive at least two doses, and where possible, three doses.

By 2025, nearly all countries in the WHO Europe region are expected to have introduced HPV vaccination into their national immunization programs.

Safety of HPV vaccines

The WHO Global Advisory Committee on Vaccine Safety (GACVS) last reviewed the safety of HPV vaccines in 2017, confirming their excellent safety profile with no new adverse reactions identified.

Regional Roadmap and Global Strategy for Cervical Cancer Elimination

WHO's global strategy to eliminate cervical cancer by 2030, which includes:

- Comprehensive vaccination coverage
- Organized screening programs:
- Equitable access to treatment

Mosina concluded that achieving the goals of the regional roadmap and the global strategy requires a coordinated effort to increase vaccination rates, improve screening, and ensure treatment access, particularly in underserved regions. This comprehensive approach aims to significantly reduce the burden of cervical cancer in the WHO European Region by 2030.

Cervical cancer: control and prevention and WHO tools

Vitaly Smelov from the WHO Regional Office for Europe provided an overview of several topics related to cervical cancer and HIV, including WHO tools for the elimination of cervical cancer, the Cervical Cancer Elimination Initiative (CCEI), and the commercial determinants of health.

Global and regional epidemiology

Cervical cancer is the fourth most common cancer among women globally. Within the European Region, it accounts for one-tenth of new cervical cancer cases. Despite ongoing efforts, the global burden of cervical cancer is anticipated to increase. By 2025, the global incidence is expected to rise by almost 40%, with a corresponding increase in mortality. In the European region, the incidence is expected to increase by 1.5%, but mortality is predicted to rise by 11%. Inequalities between countries in the European region are apparent, particularly when considering the overlap between incidence and mortality rates in lower-income countries.

Women living with HIV are six times more likely to develop cervical cancer compared to women without HIV. However, it's important to note that an HPV infection does not necessarily lead to cancer, as pre-cancerous lesions often regress over time.

Inequalities and cervical cancer

The disparities in cervical cancer outcomes stem from various factors, including risk factors such as HPV, HIV, and other sexually transmitted infections (STIs), as well as disparities in access to and utilization of services for vaccination, screening, treatment, and palliative care. These inequalities have significant cost implications: between 2005 and 2028, cancer incidence in the EU increased by 25%, cancer drug costs surged by 220%, and overall cancer care costs rose by 32%. The mortality rate from cervical cancer is closely linked to economic status, with wealthier women having a higher chance of survival.

The WHO Cervical Cancer Elimination Initiative

Pillar one: increased HPV vaccination

WHO has set ambitious targets for cervical cancer elimination: by 2030,

- 90% of girls should be vaccinated against HPV
- 70% of women should undergo high-performance testing by the age of 35 and again by 45
- 90% of women with cervical disease should receive appropriate treatment.

This aligns with the Sustainable Development Goal (SDG) 3.4, which targets a 30% reduction in mortality from non-communicable diseases (NCDs) by 2030.

Pillar two: screening and treatment of precancerous lesions

HPV testing

The WHO Prequalification Programme for in vitro diagnostics evaluates a range of HPV tests for use in public cervical cancer screening programs. The latest review in 2024 includes the following prequalified tests:

- **2017:** Xpert HPV
- **2018:** careHPV test
- **2019:** Abbott RealTime High Risk HPV
- **2023:** cobas HPV
- The transition to high-performance tests, such as HPV testing followed by treatment, is recommended over cytology-based screening. For women living with HIV, WHO recommends an HPV DNA detection strategy within a screen, triage, and treat approach, beginning at the

age of 25 with regular screenings every 3 to 5 years, with shorter intervals compared to the general population.

Screening and treatment strategies

Screening can be conducted using HPV DNA tests, including self-sampling methods. There is sufficient scientific evidence to recommend self-sampling. For example, during the COVID-19 Sweden pandemic implemented HPV self-testing.

Screening coverage

Screening coverage within the EU ranges from 41% to 83%. Across the broader WHO European region, coverage is less than 50% in many countries and falls below 30% in most Central Asian countries. Coverage is even lower among key populations, highlighting significant disparities in access.

Barriers to screening

Several barriers impede access to cervical cancer screening, including:

- Out-of-pocket costs
- Complex and difficult-to-navigate healthcare systems
- Geographic distance from services
- Stigma surrounding HPV
- Language barriers
- Attitudes and limited knowledge of healthcare providers

To address these challenges, screening must be integrated into a well-defined pathway that links organized screening efforts to the diagnosis of lesions, treatment, and ongoing monitoring.

WHO Europe Recommendations for enhancing screening:

- Establish programs with well-defined pathways and referral systems that address inequities in access.
- Behavioral and Cultural Insights: Use these insights to overcome barriers to participation in screening programs.
- Develop and implement strategies that effectively inform and engage target populations.
- Ensure healthcare providers are adequately trained in cervical cancer screening practices.
- Implement systems to maintain and improve the quality of screening processes.
- Ensure that screening is closely connected to prompt diagnostic and treatment services.

WHO resources

WHO's efforts in addressing cervical cancer have resulted in several key publications, including the "Pink Book," the "WHO Comprehensive Cancer Control: A Guide to Essential Practice" (2014), and the "WHO Planning and Implementing Palliative Care Services" (2016). In 2017, the World Health Assembly (WHA) passed a resolution on cancer prevention and control within an integrated approach. Since 2020, WHO has published various documents related to cervical cancer, including guidelines for screening and treatment, consolidated guidelines on HIV, viral hepatitis (VH), and STI prevention, treatment, and care, as well as handbooks and roadmaps aimed at accelerating cervical cancer elimination.

Commercial determinants of health

Recommended reading:

- Eurohealth Special Issue on Commercial Determinants of Cancer Control (2022)
- Report on Commercial Determinants of NCDs in the WHO European Region (2023)

Vitaly Smelov concluded with the following **take-home messages:**

- Cervical cancer, a largely preventable disease, and controlled HIV infections continue to pose significant health burdens in Europe.
- Effective prevention and treatment strategies for both cervical cancer and HIV are crucial to maximizing health outcomes for women.
- Cervical cancer screening should be a standard component of HIV care for women living with HIV. Ensuring equitable access to these services is essential.
- Strong cross-referral systems should be established at all levels of the health system to link HIV and cervical cancer services. This will encourage women to return for necessary treatment and follow-up care.
- Stay vigilant against health inequalities and the influence of commercial determinants of health, which can exacerbate disparities.
- The WHO envisions the elimination of cervical cancer, including among key populations, through targeted and inclusive strategies.

EACS guidelines vs. Implementation of HPV vaccination and the Greek example

Presented by Konstantinos Protopapas, MD, a member of the EACS Standard of Care Scientific Committee.

EACS guidelines

The October 2023 version of the EACS guidelines recommends that people living with HIV (PLHIV) should be vaccinated with three doses of the HPV vaccine between the ages of 9 and 45. However, health insurance coverage for the vaccine varies across countries depending on factors such as age, sex, and sexual orientation. The guidelines also recommend using a 9-valent vaccine, if available. Individuals treated for high-grade dysplasia may benefit from a full course of vaccination as secondary prevention.

Scientific review

Konstantinos Protopapas presented a scientific review article on the efficacy and durability of the immune response to HPV vaccines in PLHIV, addressing frequently asked questions such as whether a 9-valent, 2-valent, or 4-valent HPV vaccine should be used. Based on the review, it can be concluded that the 9-valent vaccine is recommended because it protects against more HPV types. Another question addressed was whether an additional dose (a 4-dose regimen) is necessary, considering that studies show no significant difference in seropositivity or antibody levels with an additional dose. Given the high cost, this could pose a burden for low- and middle-income countries (LMICs).

Konstantinos Protopapas talked about possible **barriers** to HPV vaccination, such as:

- Cost
- Lack of full reimbursement
- Absence from national guidelines
- Fear of side effects
- General anti-vaccination attitudes
- Lack of encouragement from healthcare providers
- Inadequate dissemination of guidelines among those who would benefit
- Vaccine shortages and stockouts.

The management of STIs in Central and Eastern Europe

At the 2023 EACS Conference, a poster by Gokenkin et al. was presented on the management of sexually transmitted infections in Central and Eastern Europe, highlighting areas for improvement. The poster showed that the 9-valent HPV vaccine is available in 20 countries, but not in 4 others (all

non-EU). Kosovo, for instance, has no HPV vaccine available. The HPV vaccine is included in the national vaccination program for all children in 10 EU countries and 2 non-EU countries.

Notably, in Greece, the vaccine is included for all children, women**, men who have sex with men (MSM), and PLHIV**.

Vaccination strategies in Europe and the Greek example

Vaccination strategies vary across Europe; for example, in Italy, the vaccine is available at any age, while in many other countries, it is reimbursed only up to age 26 or 27. In the UK, the age limit is 45, and **Greece recently increased its age limit from 26 to 45.**

Greece's recent change to its national vaccination program is surprising, given that it is the second poorest country in Europe, according to Eurostat.

On the question of vaccine cost, Protopapas presented a study titled "Modeling Health Impact and Cost Effectiveness of Vaccination in HIV+ and HIV- MSM in Germany." The study suggests that vaccination is cost-effective for HIV-positive MSM, with approximately one-third of averted cases occurring in 5-6% of the MSM population, supporting the argument for including MSM up to age 45 in national vaccination programs.

Key Points summarized by Konstantinos Protopapas:

- HPV transmission from women to men is higher than from men to women.
- Indirect herd protection in men depends on maintaining high vaccination coverage in women.
- MSM are unlikely to benefit from herd protection through the vaccination of only women.
- Vaccination, regardless of gender, provides immediate protection for men.

Konstantinos Protopapas concluded by presenting the **recommendations of the European Cancer Organisation:**

- By 2025, all European cancer plans should include actions to achieve population-based and gender-neutral HPV vaccination.
- By 2030, gender-neutral HPV vaccination programs should be in place in all European countries.
- The target by 2030 is for 90% of all adolescents of both genders to complete the full course of vaccination.
- Consideration should be given to the needs of high-risk groups, including MSM, migrants, and sex workers, who may otherwise fall outside the age parameters of universal vaccination programs.
- Consideration should also be given to older age groups on a gender-neutral basis.