Sexually Transmitted Infections

Prevention strategies for sexually transmitted infections, HIV, and viral hepatitis in Europe

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Summary

The current prevention efforts for STIs, HIV and viral hepatitis in the WHO European Region, especially in the Central and Eastern subregions, are hindered by healthcare disparities, data gaps, and limited resources. In this comprehensive narrative review, we aim to highlight both achievements and persisting challenges while also exploring new developments that could significantly impact the prevention of these infections in the near future. While pre-exposure prophylaxis (PrEP) for HIV has been broadly approved and implemented in 38 out of 53 countries in the region, challenges remain, including cost, limited licensing, and incomplete adherence. We explore innovative approaches like on-demand PrEP, long-acting injectable cabotegravir, and intravaginal rings that have shown promising results, alongside the use of six-monthly lenacapavir, the outcomes of which are pending. Additionally, the potential of doxycycline post-exposure prophylaxis has been discussed, revealing efficacy in reducing chlamydia and syphilis risk, but effectiveness against gonorrhoea being contingent on tetracycline resistance rates, and the need of further data to determine potential resistance development in other bacteria and its impact on the gut microbiome. We examine successful vaccination campaigns against HBV and HPV, the ongoing development of vaccines for chlamydia, syphilis, herpesvirus, and gonorrhoea, and challenges in HIV vaccine research, including lines of research with significant potential like sequential immunization, T-cell responses, and mRNA technology. This review underscores the research endeavors that pave the way for a more resilient and robust approach to combating STIs, HIV, and viral hepatitis in the region.

Keywords: Pre-exposure prophylaxis; Post-exposure prophylaxis; Prevention vaccine; HIV; Gonorrhea; Syphilis; Chlamydia; Hepatitis B or C; HPV; sexually transmitted infections

Introduction

The transmission of HIV and sexually transmitted infections (STIs) are a pressing health issue in the European Region of the World Health Organization (WHO), which includes 53 countries in 3 sub-regions (Fig. 1).[1,2] Although reported cases of newly diagnosed HIV have declined by 24% in 2021 compared to 2019, there are variations across sub-regions. The highest numbers and incidence are in the East (78% of the overall number and 32.4 per 100,000 population,

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Key messages

Overview of HIV and STI prevention

- In Europe, although HIV combination prevention has reduced transmission, the region falls short of the UNAIDS 90-90-90 goals for 2020, with late HIV diagnosis remaining a challenge in all sub-regions, and is likely to experience a major challenge in reaching the 95-95-95 for 2025.
- Healthcare disparities, data gaps, and limited resources hinder prevention efforts in Europe, especially in Central and Eastern subregions, limiting the potential of strategies such as combination prevention or pre-exposure prophylaxis (PrEP) for HIV.

Successful interventions

- Successful implementation of PrEP within the context of combination prevention approach resulted in significant reductions in new HIV diagnoses in France and the United Kingdom.
- Ukraine has achieved significant progress in HIV prevention through strong government and community support which has led to a reduction in new infections, although progress is threatened by the ongoing war with Russia.
- The Netherlands implemented a comprehensive action plan for sexual health, and Sweden's chlamydia action plan with a change in the testing strategy resulted in a decline in reported infections.

PrEP and PEP for HIV

- The evidence showing the effectiveness of daily and on-demand PrEP with emtricitabine and tenofovir disoproxil fumarate (TDF-FTC) resulted in broad approval, implementation, and a reduction in HIV incidence. In 2022, it was rolled out in 38/55 countries in the WHO European region, with 130,000 people receiving PrEP prescriptions.
- PrEP availability and implementation face regional disparities and inequalities, especially in Central and Eastern Europe, due to challenges such as cost, limited licensing and lack of national guidelines, incomplete adherence, and low self-perceived risk levels.
- Innovative strategies such as long-acting cabotegravir injectables (every 2 months), have shown superior efficacy compared to daily TDF/FTC. Other new alternatives include dapivirine intravaginal rings, with reported lower efficacy compared to TDF/FTC, and lenacapavir subcutaneous injection (every 6 months) with pending results of ongoing trials.
- Post-exposure prophylaxis for HIV has been available since 1997 in most European countries for occupational and non-occupational exposure, but barriers include cost, awareness, side effects, and stigma, especially for non-occupational exposure.

PrEP and PEP with doxycycline for bacterial STIs

- Doxycycline post-exposure prophylaxis (PEP) reduces chlamydia and syphilis risk in men who have sex with men, but effectiveness against gonorrhea depends on tetracycline resistance rates in the population. Concerns include potential resistance development in other bacteria and impact on the gut microbiome.
- Ongoing trials assess doxycycline PEP efficacy and safety for other key populations, including women, and therefore addressing equity concerns.

Vaccines

- Hepatitis B virus vaccination effectively prevents transmission, cirrhosis, and liver cancer, with high coverage in Europe.
- Human papillomavirus (HPV) vaccines effectively prevent cervical lesions and anogenital warts, and are included in most country vaccination programs, except for some Central and Eastern European countries.
- Ongoing vaccine development targets chlamydia infection, syphilis, herpesvirus, and gonorrhoea. Chlamydia and syphilis vaccines are in the early phase of development. Prophylactic and therapeutic candidates for herpesvirus, and the efficacy of serogroup B meningococcal vaccines against gonorrhoea are currently being investigated in clinical trials.
- The genetic diversity and immune evasion mechanisms of HIV hamper vaccine development, with 7 out of 8 trials failing to show protective effects, while the RV144 trial demonstrated reduced HIV acquisition. Current research focuses on sequential immunization, T-cell help/responses and use of mRNA technology.

Fig. 1), while the lowest numbers but the fastest increase (41% increase in 2021 compared to 2020) are observed in the Centre sub-region.[1] Late HIV diagnosis, which is associated with poor outcomes such as severe disease and death, and an increased risk of ongoing transmission remains a challenge with 54% of people living with HIV being diagnosed late in Europe in 2021.[1] By 2021, the overall performance of the WHO European region for the global 90-90-90 targets set by The Joint United Nations Programme on HIV/AIDS (UNAIDS) for 2020 was 82-85-92, which falls short of the overall target of 73% of all people living with HIV being virally suppressed. There were significant differences between sub-regions and lower rates in the East and Centre sub-regions compared to the West.[3] Significant gaps in each pillar of the cascade such as the low testing rates reported for several key populations, and the challenges in accessing antiretroviral treatment and HIV care among specific groups such as mobile populations, people who inject drugs,

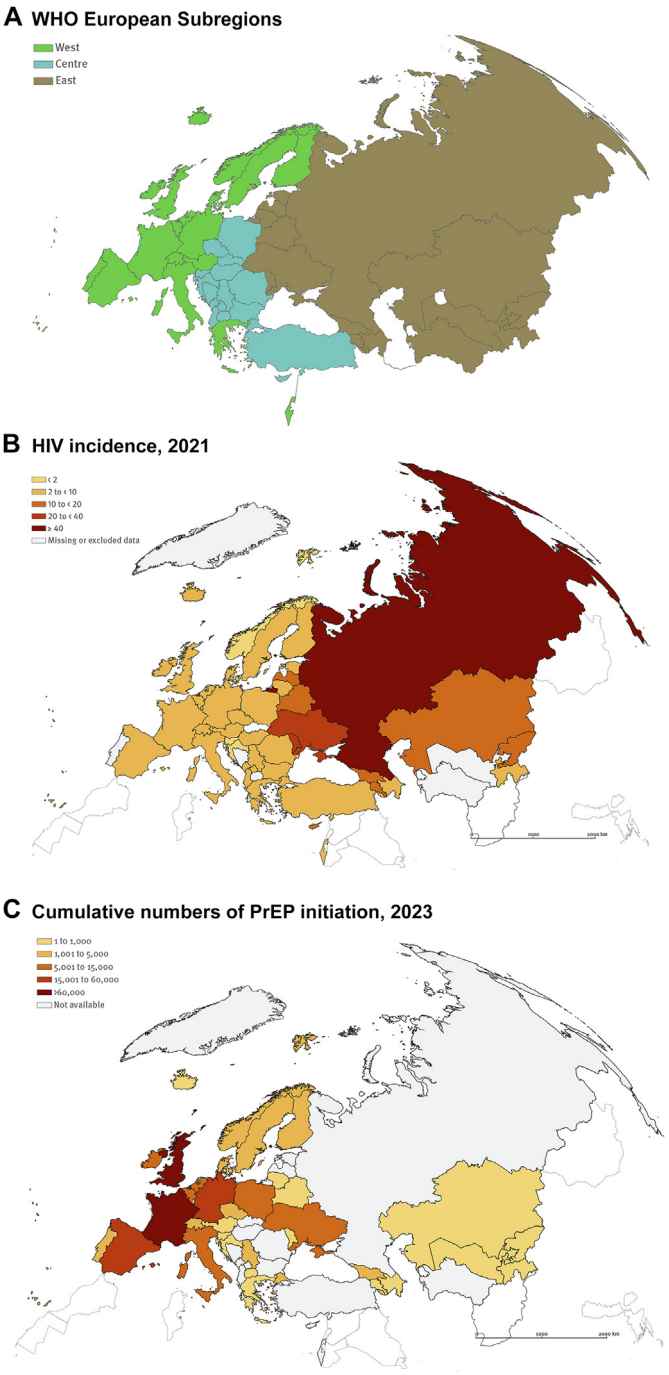

Fig. 1: Geographical areas, HIV incidence, and PrEP initiation in the WHO European Region. Legend: A. WHO European Region in accordance with the WHO HIV/AIDS surveillance report, which includes 53 countries categorized by sub-regions. The following list includes European Union (EU) members (marked with an asterisk) and non-EU countries. Western Europe (23 countries): Andorra, Austria*, Belgium*, Denmark*, Finland*, France*, Germany*, Greece*, Iceland, Ireland*, Israel, Italy*, Luxembourg*,Malta*, Monaco, Netherlands*, Norway, Portugal*, San Marino, Spain*, Sweden*, Switzerland, and United Kingdom. Central Europe (15 countries): Albania, Bosnia and Herzegovina, Bulgaria*, Croatia*, Cyprus*, the Czech Republic*, Hungary*, the former Yugoslav Republic (FYR) of Macedonia, Montenegro, Poland*, Romania*, Serbia, Slovak Republic*, Slovenia*, and Turkey. Eastern Europe (15 countries): Armenia, Azerbaijan, Belarus, Estonia*, Georgia, Kazakhstan, Kyrgyz Republic, Latvia*, Lithuania*, Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan. Data from: European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2009. Stockholm:European Centre for Disease Prevention and Control; 2010. B. HIV incidence in Europe in the year 2021. Incidence expressed as population per 100,000 persons-year. Data from: European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe. 2021–2020 data. Stockholm: ECDC; 2021. C. Cumulative numbers of PrEP initiation in European countries up to Q2 2023. Data from: https://data.prepwatch.org/.

incarcerated people, and people living in conflict regions, coupled with ongoing increase in new diagnoses in the Centre, and the persistently high rate of late presentations, suggest that Europe may experience a major challenge in reaching the 95-95-95 for 2025.[3]

Bacterial STIs, including *Chlamydia trachomatis* (chlamydia), *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea) infections, and lymphogranuloma venereum (LGV), have shown a rising trend since the 1990s, and increased significantly by 9%, 25%, 55%, and 75%, respectively, between 2015 and 2019 in the European Union (EU)/European Economic Area (EEA).[4] LGV is largely underdiagnosed in Europe due to the lack of appropriate diagnostic tools, particularly in countries in the WHO Central and Eastern Europe (CEE) regions.[5] Other STIs, including *Mycoplasma genitalium* and *Trichomonas vaginalis*, as well as emerging and re-emerging infectious diseases such as mpox, are becoming increasingly problematic in Europe. Data on STIs is very limited in non-EU regions of Europe and mostly in countries in CEE due to the heterogeneity in surveillance systems, underdiagnosis, and underreporting, lack of access to testing and treatment by key populations mentioned above who are most vulnerable to and disproportionately affected by STIs, and unavailability of modern testing technologies.[4,6] This surge in STIs has significantly impacted sexual and reproductive health laying a heavy burden on national health systems.[4,6]

HIV prevention is based on a combination approach that includes health promotion interventions such as condoms, needle and syringe programs (NSP), opioid substitution therapy (OST), sex education, and national HIV strategies/guidelines, as well as HIV testing, antiretroviral treatment (ART), and pre-exposure prophylaxis (PrEP), all of which can be delivered through the healthcare settings or through community-based organisations and should be tailored to the risk profile of the recipient.[7] While overall, 42/52 European countries could provide enough indicators of combination prevention, only five were categorised as having evidence of combination prevention implementation, 15 as having some evidence and 22 as having partial evidence.[7] In recent years, HIV prevention strategies in Europe have been strengthened contributing to a reduction on the acquisition risk at the population level.[7–9] UK reported that the number of new HIV diagnoses dropped by 39% in men who have sex with men and 24% in heterosexual men between 2015 and 2018.[8] However, STI prevention to date has mainly focused on improving diagnostic capacity, treatment access, and quality of care, but with significant disparities between countries, and only 23/52 European countries, the majority being EU members reported on STI testing coverage as an indicator of combination prevention.[7,10] Over the years, prevention interventions for STIs have faced numerous challenges, including limited testing opportunities, lack of effective treatment options for eliminating several viral STIs, inadequate condom use, and the increasing rates of antibiotic resistance to several bacterial pathogens. Moreover, testing and treatment coverage varies significantly between regions, countries and key populations resulting in inequitable access to preventive tools among key populations and among different regions, mainly CEE.

The UNAIDS and the Global Health Sector Strategies of the WHO on HIV, viral hepatitis, and STIs have set goals to be achieved by 2030 in Europe.[2,11] However, the implementation of these strategies remains challenging for several countries. First, economic, cultural, social, and political diversity between countries leads to significant inequalities.[3,12] Second, monitoring prevention strategies necessitates good quality epidemiological data and reporting, which is heterogeneous and inadequate or lacking in specific European regions, mainly CEE.[13] Third, coverage of sexual health services also varies due to differences in healthcare systems across countries.[4,13] Fourth, risk-based eligibility criteria for prevention interventions need careful consideration and assessment at the regional level. Fifth, barriers such as costs, limited public funding and reimbursement, adherence, and demand exceeding clinical capacity hinder the full potential of PrEP for HIV.[12,14,15] Sixth, effective vaccines for the primary prevention of HIV and bacterial STIs are not yet available. Finally, antimicrobial resistance and emerging STIs also pose new challenges to prevention and control efforts.[16] In addition, the 2022 mpox outbreak has represented a public health emergency of international concern, characterized by an unprecedented global spread of the infection in previously non-endemic countries, with transmission predominantly being through sexual contact among men who have sex with men, disproportionally affecting people living with HIV,[17,18] and severe presentations in people with low CD4 counts.[19] This recent outbreak highlights the global relevance of emerging and re-emerging infectious diseases with potential novel epidemiological and clinical characteristics, including new modes of transmission, as well as the importance of increasing surveillance and monitoring, strengthening prevention strategies, and investing in research of effective vaccines and broad-spectrum therapies.

The aim of this narrative review is to provide an overview of the current status of HIV and STI prevention in Europe, highlight successful interventions and case studies, identify existing gaps, and challenges, and explore new developments in the field that could significantly impact the prevention of new HIV and STI infections. This paper focuses on addressing the elements of HIV combination prevention, PrEP and PEP for HIV, PrEP and PEP with doxycycline for bacterial STIs, and vaccines for HIV and several STIs, and does not review the mechanism through which interventions are delivered. Other articles in the series cover

additional topics, such as the epidemiology of STIs and inequalities in access to sexual health services in the article on epidemiology,[20] the mitigation of antimicrobial resistance in *M. genitalium* and *N. gonorrhoeae* in the article on treatment,[21] and the screening for *T. vaginalis* and *C. trachomatis* in the article on asymptomatic screening.[22]

Key areas of successful interventions and case studies

Since 2015, significant progress has been made in prevention strategies for STIs including HIV and hepatitis in the WHO European region[23,24] with increased treatment coverage rates for HIV and HCV, and a higher rate of three-dose hepatitis B vaccination, with several countries already reaching the regional hepatitis B control targets.[25] In addition, efforts to achieve or maintain the elimination of vertical transmission (EVT) for HIV and syphilis have resulted in the official confirmation by the WHO of Belarus for EVT of both HIV and syphilis, and the confirmation of Armenia and the Republic of Moldova for EVT of HIV and syphilis, respectively.[26]

France became the first country to roll out PrEP in Europe in January 2016, following the successful ANRS IPERGAY study which had started in 2012.[27,28] Real-world data suggests a high adherence to HIV testing rates of over 81% among PrEP users, and a much lower estimated HIV incidence rate compared to non-users (incidence of 0.12 per 100 person-years compared to 1–2 per 100 person-years, respectively).[29] In the United Kingdom (UK), the PROUD PrEP trial for men who have sex with men also started in 2012 and demonstrated the effectiveness of PrEP.[30] The implementation of a combination prevention approach led to a 32% reduction in new HIV diagnoses among men who have sex with men attending selected sexual health clinics since 2013, compared to the previous year.[31] The UK reported a 53% decline in new HIV diagnoses between 2015 and 2021, while France reported a 20% decline between 2019 and 2021.[32–36]

Ukraine achieved significant progress in HIV prevention before the conflict with Russia, with full support from the government and the community, resulting in around 70% coverage of harm reduction programs and a 21% reduction in new infections over the past decade.[37,38] However, Russia's war in Ukraine since 2022 has severely impacted HIV services and jeopardized the progress made.[38]

In terms of STI prevention interventions in Europe, 15 out of 29 EU member countries had a national STI strategy in 2018, representing a 12% increase compared to 2012.[10] The Netherlands developed a national action plan for STI, HIV, and sexual health for the period 2018–2022. The plan was based on the consideration that sexuality is a positive human experience and had two main goals, ensuring citizens have adequate knowledge and make informed choices for safe and pleasing sex and providing access to appropriate and affordable healthcare, advice, support, and protection for sexual health.[10,39]

In 2006, Sweden developed a strategy to limit the transmission of HIV infection, other blood-borne infections and other STIs for the period 2006–2016.[40] The strategy included a universal surveillance system for chlamydia, with free testing, counselling, treatment, and partner notification as well as raising awareness on condom use and improving access to testing among young people, and improving sexual education in schools, which targeted to reduce the prevalence of *C. trachomatis* infection by 2014.[41] A new mutant variant generating false negative test results caused a sharp increase in chlamydia in 2007,[42] leading to the development of a chlamydia action plan for 2009–2014. This resulted in a decline in reported chlamydia infections and reduced the frequency of the new variant[43] being an excellent example of an effective response.

Despite the progress made, additional efforts are necessary to achieve the UNAIDS and WHO targets for HIV and STI. A WHO survey revealed that in 2019 more than 60% of reporting countries globally had a national STI strategy with the European region having the lowest rate at 37%. Elimination of vertical transmission strategies for HIV and syphilis was reported by 70% of countries globally with lower rates (48%) in Europe compared to other regions. However, Europe had a higher rate of HIV surveillance and the highest rate (82%) of *N. gonorrhoeae* antimicrobial resistance surveillance.[44]

PrEP and PEP for HIV

A sustained focus on HIV prevention is required to reach the Sustainable Development Goals (SDGs) by 2030.[45] PrEP and PEP are two key elements of the combination prevention strategy for HIV.[7]

Current strategies and regional uptake

The efficacy and safety of daily oral PrEP with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) for HIV prevention were established over a decade ago. However, it was not until 2015, following the results of two European studies that the full potential of PrEP was recognized leading to its broad approval and use with effectiveness as high as 97% when taken daily or on demand.[27,30,46] The WHO has recommended both daily and on-demand/event-driven PrEP with TDF-FTC since 2019.[24,47,48] Cisgender men, and trans and gender diverse people assigned male at birth, who are not taking exogenous estradiol-based hormones, may be offered oral on demand PrEP or daily oral PrEP as options. Cisgender women, trans and gender diverse people assigned female at birth, people with potential exposure through injecting practices, and people

taking exogenous estradiol-based hormones may use daily oral PrEP.

In 2022, PrEP was rolled out through the healthcare system in 38 out of 55 countries in the WHO European region, with approximately 130,000 people receiving a PrEP prescription that year.[15] Targeted and high-coverage PrEP implementation has led to a significant reduction in HIV incidence at the population level (Fig. 1B and C).[8,48]

PEP for HIV has been widely accepted and used since 1997 when evidence emerged supporting its effectiveness. A case–control study demonstrated an 81% reduction in the risk of HIV seroconversion when zidovudine was administered after needlestick exposure.[49] While limited evidence exists for PEP after sexual exposure or injection-drug use, its safety and feasibility have contributed to its widespread use and resulted in the recommendation of PEP in European guidelines for occupational and non-occupational exposure to HIV.[50] PEP availability is very high in most European countries, with the CEE reporting a 95.5% and 86.4% availability for both occupational and non-occupational exposure, respectively.[12]

Challenges

Despite the increasing number of European countries where PrEP is licensed, its utilization remains low. There are substantial inequalities and regional disparities in availability and implementation within Europe, such as much delayed introduction in CEE countries (Fig. 1C), lower access among people who inject drugs, migrant populations and women, and hesitancy of healthcare providers to offer PrEP.[12,15] As a result, overall coverage for people who are at the highest acquisition risk remains low. The 2017 European men who have sex with men Internet Survey (EMIS) revealed that 32% of participants had never heard of PrEP. In France, only 28% of men who have sex with men reported the use of PrEP for their last condomless anal intercourse with a casual partner.[51] A study in 2019 showed a significant gap of PrEP use in the Europe, where more than 500,000 (range 420.000–610.000) men who have sex with men who wanted and needed PrEP were not accessing it (overall gap 17.4%), with the largest gap for non-EU and/or CEE countries with rates up to 45%.[52] Barriers to scaling up PrEP in Europe include the cost of the drug itself and the associated costs of delivering PrEP in healthcare settings, lack of licensing and coverage, limited technical expertise, lack of national guidelines, incomplete adherence, and low levels of awareness and self-perceived risk.[12,53]

While most European countries fully reimburse occupational PEP (77.3% in CEE), only a few countries in Europe provide full reimbursement for non-occupational PEP (36.4% in CEE). The lack of cost coverage, limited awareness among healthcare workers and key populations, concerns about side effects, and stigma remain significant barriers to PEP uptake in Europe.[12]

New PrEP regimens

Medication adherence is a key determinant of PrEP efficacy and presents particular challenges in daily dosing regimens for some of the key populations, such as cis-gender and transgender women, young individuals, racially and ethnically minoritized communities, and people who inject drugs.[46] To address adherence challenges and offer more appealing regimens to all at-risk profiles, new PrEP agents are being developed, including novel oral agents, long-acting injectables, broadly neutralizing monoclonal antibodies (bNAbs), topical products, and new drug delivery systems like implants and transdermal devices.

One alternative to daily and on-demand PrEP is a daily combination of tenofovir alafenamide and FTC (TAF/FTC), which has demonstrated non-inferiority to TDF/FTC with an improvement in biomarkers of nephrotoxicity and bone mineral density loss.[54]

Long-acting agents and extended-release formulations show promise as novel PrEP options. The long-acting injectable cabotegravir (CAB-LA) is the first injectable ART approved for HIV PrEP in the United States (US) and several African countries.[55] CAB-LA has demonstrated safety and superior effectiveness compared to daily TDF-FTC for preventing HIV infection among men who have sex with men, trans-gender, and cis-gender women when administered as a single 600-mg intramuscular injection every 2 months.[56,57] While implementation challenges remain, CAB-LA is expected to increase PrEP uptake, adherence, and retention, and reduce stigma[58] and is currently being evaluated by the European Medicines Agency. Lenacapavir (LEN), another long-acting antiretroviral drug, from the new class of HIV capsid inhibitors, has been approved for the treatment of multi-drug resistant HIV-1 infection. It is also being assessed as an injectable PrEP agent, in phase III trials in men who have sex with men, trans- and cis-gender women, and people who inject drugs.[59] Long-acting LEN can be self-administered subcutaneously every 6 months and holds great potential for PrEP pending the results of effectiveness trials.

Long-acting bNAbs are another promising approach to preventing HIV acquisition. Two advanced and several early-stage clinical trials assessing bNAbs are underway.[60]

Topical agents or microbicides are other alternatives proposed as PrEP agents. Following mixed results from clinical trials with tenofovir vaginal gel, new topical products are under development, including vaginal rings, vaginal and rectal gels, and films.[61] In 2021, the WHO recommended a monthly dapivirine intravaginal ring for HIV prevention in cis-gender women, based on the results of two phase-III randomized placebo-

controlled clinical trials showing a 27% and 35% relative reduction in HIV incidence.[62,63]

Finally, innovative alternatives for PrEP include new drug delivery systems like subdermal implants and transdermal devices that could provide continuous protection from HIV over an extended period. Additionally, multipurpose prevention technologies are developed to offer combined prevention for HIV and other STIs, with or without contraception. Several of these products are at the early stages of development and/or entering early clinical trials.

Although these new PrEP agents have shown promise, some factors need to be considered before they can be routinely used. Some products may be associated with delays in HIV diagnosis and the emergence of HIV drug resistance. CAB-LA substantially alters the timing and patterns of HIV seroconversion, and although breakthrough infection is rare, diagnosis with antigen/antibody-based HIV tests can be delayed.[58] Moreover, cost and logistic challenges, such as higher drug cost, the requirement for additional staff time for intramuscular injections, and more frequent laboratory monitoring, can limit implementation and accessibility in low- and middle-income countries.

PrEP and PEP with doxycycline for STIs

The use of doxycycline as prophylaxis (doxy-PEP and doxy-PrEP) for bacterial STIs is a relatively new concept with a historical background and has been assessed in studies involving individuals with high-risk sexual behavior. Doxycycline is generally well tolerated and approved for long-term use in acne treatment or primary prophylaxis against infectious diseases like malaria.[64] In a pilot trial involving 30 men who have sex with men with HIV and a history of syphilis, daily PrEP with 100 mg of doxycycline decreased the risk of acquiring bacterial STIs, including *T. pallidum*, *C. trachomatis* or *N. gonorrhoeae* infections, at week 48.[65]

Doxy-PEP in Europe was first used in the ANRS IPERGAY sub-study in France where 232 men who have sex with men on HIV PrEP were randomized in an open-label study to receive 200 mg of doxy-PEP 24–72 hours after sexual contact and a control group without PEP.[66] The doxy-PEP group showed a significant reduction in the risk of acquiring syphilis or chlamydia compared to the control group, but not for gonorrhea.[66] A US randomized trial assessing the same dosing regimen in 501 men who have sex with men on HIV PrEP or people living with HIV with a history of bacterial STI reported a significant reduction in all three bacterial STIs, including gonorrhea.[67] This difference in effectiveness may be attributed to the higher rate of tetracycline resistance of *N. gonorrhoeae* in France compared to the US.[67] Finally, the preliminary results of the DOXYVAC trial, which was presented very recently showed a strong reduction (70–80%) of chlamydia and syphilis incidence among 502 participants with a median follow up of 9 months.[68] While the data supporting the use of doxy-PEP for the prevention of bacterial STIs among men who have sex with men with the highest risk of STIs is promising and based on three large-scale, well-conducted randomized clinical trials, longer-term monitoring is still needed to weigh the risks and benefits. On the other hand, evidence on the efficacy of doxy-PrEP is very limited, based on a single small-scale study.

To date, no cases of resistance to doxycycline have been reported in *C. trachomatis* or *T. pallidum*,[69] although these organisms are not routinely tested for antimicrobial resistance. Resistance has been reported to occur with high selective pressure on *Chlamydia suis* in pigs. *T. pallidum* was able to develop high-level resistance to azithromycin in humans by means of a single point mutation on the 23S rRNA gene, and a point mutation in the 16S rRNA gene is a plausible mechanism for the development of doxycycline resistance.[70] Antibiotic resistance remains a major concern for *N. gonorrhoeae* and *M. genitalium*. The increase in doxycycline resistance rates after exposure in *N. gonorrhoeae* isolates is well-established. A study on PEP found a higher doxycycline resistance in *N. gonorrhoeae* isolates in the doxycycline group compared to the standard care group, but resistance testing in the cohort was limited; moreover, the number of doxycycline-resistant Staphylococcus *aureus* isolates increased.[67] On the other hand, doxycycline plays a role in the treatment of *M. genitalium*, for which antimicrobial resistance continues to increase, partly due to the extensive use of azithromycin for STI syndromes. Although doxycycline has limited efficacy for *M. genitalium*, with microbiological cure rates between 30 and 40%, it has the added benefit of decreasing the bacterial load.[71] Thus, current guidelines for the first-line treatment of *M. genitalium* recommend a 7-day regimen of doxycycline, followed by either an extended regimen of azithromycin or a 7-day regimen of moxifloxacin, for macrolide-susceptible and macrolide-resistant infections, respectively.[71] Moreover, there is also a significant concern about the potential negative effect of doxycycline on the gut microbiome.[67] A clinical trial is currently evaluating gut microbiota and *S. aureus* colonization in a cohort of doxycycline PrEP.[72] Guidelines exercise caution in endorsing doxy-PEP and recommend its use on a case-by-case basis.[73–76]

Studies have shown that individuals with high-risk sexual behavior and frequent STIs, have a strong interest in and willingness to take doxycycline prophylaxis. A US survey among men who have sex with men revealed that almost 70% would be willing to take doxycycline, preferably as a one-time dosing PEP (52%) compared to daily PrEP (40%).[77] Users of a gay social networking app have reported significant interest in trying doxy-PEP[78] as have participants in a study in Canada.[79] However, the

actual uptake of doxycycline prophylaxis varies among study cohorts ranging from 2.2% to 9.9%.[80–84]

Raising awareness among key populations about the risks and benefits of STI prophylaxis with doxycycline is crucial, and healthcare providers play a critical role in this respect. Currently, less than half of healthcare providers in the US report that they would be willing to prescribe doxycycline, but this percentage would rise to almost 90% upon recommendation by the Centers for Disease Control and Prevention (CDC).[77] Studies indicate that the interest in STI prophylaxis is high and some people are already using it off-label.[80,83,85]

Research on doxy-PEP/PrEP has primarily focused on men who have sex with men and people living with HIV due to their high STI risk and ease of enrollment. However, concerns about equity are raised since targeting only men who have sex with men may not address adverse outcomes that predominantly affect women, such as pelvic inflammatory disease and infertility.[64] Potential beneficiaries of STI prophylaxis include military recruits and officers, adolescents, female sex workers, ethnic minorities with limited sexual education, and people already taking HIV PrEP.[86,87] Doxycycline's efficacy in these populations and in cisgender women is being assessed in clinical trials. In a preliminary report, doxy-PEP was not effective in cisgender women, which was attributed to anatomical characteristics of the endocervical tissue, low adherence, or resistance.[88] A more recent analysis of the same study reported very low doxycycline levels in participants' hair samples (used to asses long term compliance) suggesting that poor adherence to doxycycline might have resulted in failure.[89] A computational model suggested a 10% reduction in new syphilis cases over a decade with 20% uptake and 80% adherence among men who have sex with men, but higher doxycycline doses would be needed to prevent STIs in other populations, such as heterosexuals with behaviorally bisexual men serving as a bridge population.[90,91]

The randomized trials on doxy-PEP provide good evidence for the prevention of the most common bacterial STIs among men who have sex with men with the highest risk of STIs. However, major concerns on the development of antibiotic resistance in sexually transmitted and other pathogens require additional data to define the potential public health risks and benefits to ensure its safe and effective use. Therefore, close monitoring of doxycycline users in this context is critical. Currently, the International Antiviral Society (IAS)-US Guidelines on HIV Treatment and Prevention recommends doxycycline PEP in men who have sex with men on HIV PrEP on a case-to-case basis and the California Department of Public Health has implemented the recommendation for men who have sex with men or transgender women.[92,93]

Vaccines

Vaccines are the ultimate game-changers in terms of infection prevention due to their potential to provide long-term and widespread protection in the community. The need for effective vaccines is underscored by the ongoing limitations of current efforts to control STIs which have proven inadequate in effectively reducing incident infections and associated morbidity as discussed in detail earlier. Consequently, developing effective vaccines is pivotal in the response to the HIV epidemic and to other STIs. This section includes working vaccines, which have proven to be highly effective in preventing STIs, and those that are in development and have a promising profile.

Working vaccines

To date, working vaccines for hepatitis A virus (HAV), hepatitis B virus (HBV), and human papillomavirus (HPV) have proved to be successful in decreasing the number of incident infections.

Hepatitis A vaccines have been available since the 1990s with well-documented effectiveness in the long-term and with the global decline in disease burden over the last three decades, they have become a tool to control the infection in endemic areas in specific key populations.[94] Men who have sex with men are particularly at risk as large outbreaks within this key population have been reported across all continents.[95] According to ECDC data, 22 EU/EEA countries have reported outbreak-confirmed cases in this group and specific HAV strains continue to spread.[96,97] The CDC recommends universal vaccination of men who have sex with men with the HAV vaccine given as a 2-dose schedule six months apart.[98]

The HBV vaccine is highly effective in preventing vertical transmission when given as a full 3- or 4-dose schedule at birth and in early infancy. Vaccination during later childhood and adulthood prevents onward transmission, liver cirrhosis, and hepatocellular carcinoma.[99,100] The current reduction in HBV-associated hepatocellular carcinoma rates is attributed to HBV vaccination.[101] Global efforts have led to an increase in HBV vaccination coverage among WHO member states, reaching an estimated global coverage of 83% by the end of 2020.[100] However, the coverage of birth dose vaccination varies significantly between regions from 6% to 84% with a global average of 42%.[100] Overall, the 3-dose vaccination rate among infants is high (91%) in Europe with a more than 10% increase compared to 2009.[100] The WHO's target for 2030 is to reduce the incidence of chronic HBV infections by 95% and HBV-associated deaths by 65%.[99]

The efficacy of HPV vaccination against cervical precancerous lesions is 96%.[102–104] It is also effective in preventing male anogenital warts, and precancerous lesions.[102–104] In countries where female vaccination coverage reached 50%, HPV vaccines were reported to

decrease HPV type 16/18 and HPV 31/33/45 infections by 68% and 28%, respectively, among 13–19-year-old girls.[105] Anogenital warts among boys aged <20 years decreased by 34% despite the unavailability of HPV vaccination for boys at the time of analysis, which strongly suggested a herd effect.[105] Long-term follow-up did not reveal any serious safety signals.[102] Despite the proven efficacy and safety of HPV vaccines, their uptake varies globally. By 2019, the majority of European countries had included HPV vaccines in their vaccination programs, initially targeting girls and later expanding the coverage to boys with some exceptions mainly from CEE.[106] Governments and healthcare providers have a pivotal role in including HPV vaccination in their countries' public health strategy and in boosting vaccine uptake. Table 1 includes the technical details of HBV and HPV vaccines and a summary of their efficacy.

Vaccines in development

Chlamydia trachomatis *vaccines*

As of the present date, no working vaccine for chlamydia has been presented since the early efforts in the 1960s. Early studies revealed that inactivated whole-cell immunization actually increased susceptibility to subsequent infection, which was attributed to the priming of regulatory T cells instead of effector T cells and tissue-resident memory T cell development.[112] However, there have been some promising advancements in vaccine development. For instance, combining UV-inactivated whole bacteria with the TLR7/8 agonist resiquimod and packing into charge-switching synthetic

Vaccine	Type & immunogen(s)	Adjuvant	Schedule	Efficacy
HPV yeast cell derived				
2-valent (Cervarix®)	Virus like particle HPV 16 L1 HPV 18 L1	aluminum hydroxide, 3-O-deacylated-4′–monophosphoryl lipid A	0-2-6	In women: 92.9% against CIN2, 80% against CIN3[107]
4-valent (Gardasil®)	Virus like particle HPV 6 L1 HPV 11 L1 HPV 16 L1 HPV 18 L1	aluminum hydroxyphosphate sulfate	0-2-6	In women: 100%, against HPV 16/18-related CIN 2/3 & AIS(96)
9-valent (Gardasil9®)	Virus like particle HPV 6 L1 HPV 8 L1 HPV 16 L1 HPV 18 L1 HPV 31 L1 HPV 33 L1 HPV 45 L1 HPV 52 L1 HPV 58 L1	aluminium hydroxyphosphate sulfate	ages 9–14: 0 & 6–12 months (2-dose) age >15.0 & 2 & 6 months (3-dose)	Similar efficacy with Gardasil 9 plus, induction of antibodies for 5 additional HPV strains In girls: 98.2% against HPV16/18-related CIN 2/3, AIS, Cervical Cancer 96% against HPV 6/11/16/18 related disease 88.7% against HPV 6/11/16/18 related persistent infection, genital warts, vulvar vaginal lesions In boys: 74.9% against HPV 6/11/16/18 related disease, 100% against penile/perineal/perianal intraepithelial neoplasia 89.3% against genital warts[102,108]
HBV Recombinant Yeast Derived[109]				
Recombivax®	Virus like particle Small S protein	aluminium hydroxyphosphate sulfate	0,1, 6 0,1,2,12	
Engerix B®	Virus like particle Small S protein	aluminium hydroxyphosphate		
Heplisav®	Virus Like particle Small S protein	cytidine phosphoguanosine (CpG) 1018 adjuvant	0,1	95.7% seroprotection vs 79.5% with Engerix B®[110] Effective in previous nonresponders[110]
HBV Recombinant Mammalian Cell Derived				
Gen Hevac B®	Virus like particle S protein, PreS2	aluminum hydroxide	0,1,6 (103)	
Sci-B-Vac®	Virus Like Particle Small S, Pre-S1, Pre S-2	aluminum hydroxide	0,1,6	Seroprotection against HBV was 91.4% vs 76.5% among EngerixB group Better protection in elderly, can also be considered as therapeutic vaccination, and effective in previous nonresponders[111]

Table 1: **Types, immunization schedules, and efficacy of HPV and HBV vaccines.**

particles, induced protective immunity.[112] To induce strong immune responses against chlamydia at mucosal sites may require developing mucosal adjuvants and delivery systems to direct the immune response towards mucosal tissues.[113,114] Both IFNγ-producing CD4+ T cells and chlamydia-targeted antibody responses are essential for achieving protective immunity. Certain subunits of *C. trachomatis* like major outer membrane proteins (MOMP) or polymorphic membrane proteins are promising vaccine candidates. For instance, the VD4 region of MOMP has demonstrated the ability to induce protective immunity in mice and pigs.[115,116] In a phase I trial, a combination of CTH522 with CAF01 liposomes as an adjuvant was reported to elicit a strong IgG and cell-mediated IFNγ response and was well tolerated.[117] However, chlamydia vaccines are still in the early phase of development.

Syphilis vaccines

Although immunization with 60 doses of inactivated *T. pallidum* was shown to protect against *T. pallidum* infection[118] in the rabbit model, multiple vaccine prototypes have failed to confer full protection. Factors such as the unavailability of culture, the paucity of outer membrane proteins (OMPs), and the intrinsic difficulties associated with OMP characterization have hindered the development of a syphilis vaccine.[118–120] In addition, *T. pallidum* employs several immune evasion mechanisms that can impede the development of protective antigen-specific immune responses.[121–126] While there is controversy, a few vaccine candidates such as TprK, TprC, and Tp0751 have shown encouraging results in accelerating lesion healing, reducing bacteria burden, or limiting spirochete dissemination.[127,128] Only a limited number of studies have tested multiple recombinant antigens simultaneously[129]; thus, it is plausible that multi-antigen vaccines can further improve protective outcomes. Advances in bioinformatic tools and *in vitro* culturing techniques may aid in overcoming the challenges of identifying and characterizing antigens, particularly OMPs.[119,130,131] The selected antigens should induce antibodies that promote opsonization and removal of bacteria by innate immune cells, and block bacteria dissemination to distant organs.[132] Type I interferon-γ-producing CD4+ T cells have the potential to enhance the phagocytic capability of macrophages,[132] contributing to this process. Consequently, surface-exposed antigens (i.e., OMPs) may be good vaccine candidates, as they can induce both opsonic antibodies and CD4+ T cell responses. An ideal syphilis vaccine should target several antigens to prevent *T. pallidum* infection, bacterial dissemination, disease progression, and/or transplacental invasion while covering bacterial genetic variability and protecting against possible reinfections with similar or different *T. pallidum* isolates.

Herpesvirus vaccines

No licensed vaccine exists against herpes simplex virus (HSV) infections but several prophylactic or therapeutic vaccine candidates are in development.[133–135] (Table 2) Challenges in herpes vaccination include the absence of widely accepted endpoints for clinical trials, lack of industry interest, limited understanding of immunological correlates of prevention, and the modest effect of previous herpes exposure on vaccine effectiveness.[134]

Mpox vaccines

The recent mpox outbreak in humans represents a major global health problem, with a high predominance of men who have sex with men among affected individuals and frequency of genital lesions, implying the likelihood of sexual transmission. From January 1, 2022, to September 8, 2023, a total of 26,087 cases were reported from Europe, but the numbers have since declined which is attributed to combined measures such as timely diagnosis, isolation, partner notification, contact tracing, and vaccination.[136,137] Currently, three vaccines containing attenuated strains of the vaccinia virus are available, developed based on the high degree of sequence similarity between orthopoxviruses, and the wide range of antibody response to membrane and structural proteins.[138] (Table 3) Although preliminary studies have reported favorable outcomes, robust evidence is still lacking.[138,139]

HIV vaccines

The genetic diversity of HIV, both within and between individuals, makes it a challenging target for vaccine development. Moreover, its complex immune evasion

Vaccine	Type & immunogen(s)	Adjuvant	Schedule	Efficacy
Herpes simplex vaccine				
GEN-003	Recombinant insect cell HSV-s glycoprotein D2 + truncated form of infected cell polypeptide 4	Matrix M-2	0-3-6 weeks	Durable reductions in viral shedding among 60 μg antigen plus 50/75 μg adjuvant recipients[135]
HerpeVac	Glycoprotein D (gD)	Alum/3-deacylated form of Monophosphoryl Lipid A (MPL)	0, 1, 6 months	35% against HSV1 disease[133]

Table 2: **Characteristic of developing HSV vaccines.**

Vaccine	Type	Schedule	Use and efficacy	Recommended populations
ACAM2000® (US)	Second generation Replication-competent vaccinia virus	Single dose	Authorized for use against smallpox. Available for use against mpox by an FDA Expanded Access Investigational New Drug (EA-IND) protocol Level and duration of protective efficacy unknown.	Mass vaccination of the general population is not recommended Primary prevention: High risk groups including men who have sex with men, people with multiple partners, healthcare providers and laboratory staff at high risk. Post-exposure preventive vaccination: Close contacts of cases within four days of exposure
LC16m18® (Japan)	Third-generation Attenuated, minimally replication-competent vaccinia virus	Single dose		
Imvanex® (Europe) JYNNEOS® (US) Imvamune® (Canada)	Third-generation Replication-deficient modified vaccinia Ankara virus	Two doses 28 days apart	Authorized for use against smallpox and mpox. Effectiveness for mpox is 36%–86% for vaccination with a single dose and 66%–89% after two doses.	*ACAM2000 is not recommended for people for whom replicating vaccines are contraindicated (such as pregnant women, immunocompromised people, young children)

Table 3: **Characteristics of MPXV vaccines.**[136,138]

mechanisms and ability to integrate into host immune cells further augment its capacity to counteract immune responses.[140,141] To date, 7 out of 8 vaccine trials have failed to demonstrate a protective effect.[141] Only the RV144 trial (CRFAE_01 canarypox/gp120 vaccine) demonstrated a reduction in HIV acquisition and was associated with higher levels of HIV-1 variable loop 2 (V2) antibodies and lower levels of IgA type antibodies binding to the envelope protein.[142] In contrast, the HVTN 702 trial in Africa did not show any protective effect, despite participants developing higher anti-gp120 and gp140 antibodies, whereas the RV144 recipients had higher levels of V2-specific antibodies.[143] The HVTN706 Mosaico trial was stopped early after an interim analysis that showed no benefit of vaccination with AD26 vector carrying the 4-valent T cell mosaic genes.[144]

Current research is focused on sequential immunization with antigenically different immunogens and the induction of T-cell help/responses at specific time points.[141]

The success of mRNA technology in COVID-19 vaccines has encouraged researchers to develop an HIV vaccine using a similar platform. The eOD-GT8

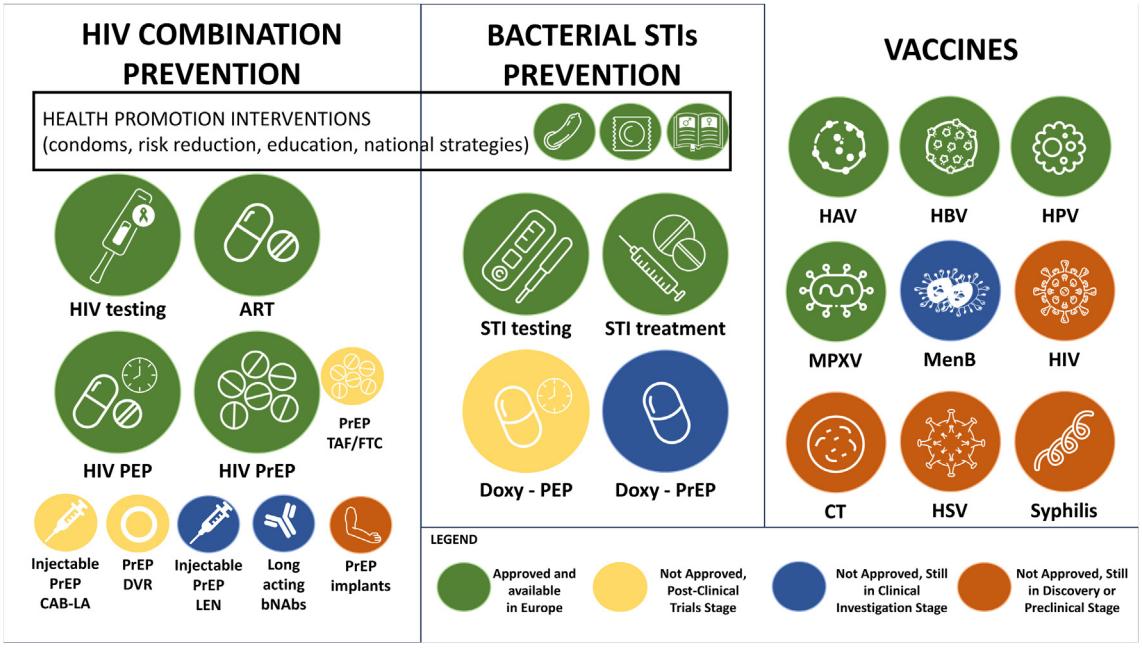

***Fig. 2*: Prevention strategies for STIs: HIV combination prevention, prevention for bacterial STIs and vaccines**. ART: antiretroviral treatment; bNAbs: broadly neutralizing antibodies; CAB-LA: long-acting cabotegravir; CT: *Chlamydia trachomatis*; Doxy: doxycycline; DVR: dapivirine vaginal ring; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; HPV: human papillomavirus; LEN: lenacapavir; MenB: serogroup B meningococcal vaccine; MPXV: monkeypox virus; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection; HSV: herpes simplex virus.

Search strategy and selection criteria

This is a non-systematic narrative review. We searched the PubMed for studies reporting PEP, PrEP and vaccines for HIV and STIs. Keywords used in the database search were ('pre-exposure prophylaxis' OR 'PrEP') OR ('post-exposure prophylaxis' OR 'PEP') OR ('prevention') OR ('vaccine' OR 'vaccines') AND ('HIV' OR 'human immunodeficiency virus' OR 'gonorrhea' OR 'syphilis' OR 'herpes simplex virus' OR 'HSV' OR 'STI' OR 'STIs' OR 'sexually transmitted infections' OR 'hepatitis B' OR 'HBV' OR 'human papillomavirus' OR 'HPV'). The publication year was limited to the latest fifteen years (from 6th February 2008 to 6th February 2023). Hand searching from the reference lists of the retrieved articles was also included and individual screenings were run for specific topics as required. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Only the articles published in English were included.

60mer mRNA vaccine (mRNA-1644) has recently been evaluated in a clinical trial (NCT05414786).[145]

Serogroup B meningococcal vaccine for gonorrhoea prevention

Developing a vaccine for *N. gonorrhoeae* has been challenging, mainly due to the high antigenic variability of the bacterial surface and a lack of suitable animal models. As of now, there is no effective gonorrhoea-specific vaccine available. However, observational studies have shown that serogroup B meningococcal vaccines, which are used to protect against *Neisseria meningitidis* infections, provide cross-protection against *N. gonorrhoeae*. In a retrospective case–control study, exposure to the outer membrane vesicle meningococcal B vaccine MeNZB was associated with a 31% reduction in gonorrhea diagnosis.[146] More recently, the broader spectrum four-component serogroup B meningococcal vaccine 4CMenB has shown efficacy ranging from 30 to 46% in preventing gonorrhea in four observational studies, two of them in adolescents and young adults.[147–150] Modelling studies have suggested that even a partially effective vaccine could reduce the population prevalence of gonorrhoea by 40–60% and the incidence by up to 25% over 70 years.[151–153]

The efficacy of serogroup B meningococcal vaccine to prevent *N. gonorrhoeae* infections is currently under investigation in several clinical trials (NCT04597424, NCT04350138, NCT04415424, NCT05766904, NCT05294588).

Conclusions and future perspective

There has been great progress in HIV and STI prevention over the past few years (Fig. 2). The combination approach for HIV prevention contributed to the population-level reduction in transmission, antiretroviral treatment and HIV PrEP coverage have increased in Europe, and successful vaccines for HBV and HPV have led to a reduction in incident infections with rising coverage rates. International bodies have supported countries to improve their national strategies for HIV and STI prevention. However, these strategies have not yet reached their full potential in curtailing the HIV and STI epidemic in Europe. One in five people living with HIV in the European region are still unaware of their status, and 54% are diagnosed late. Although relatively small, an alarming fraction of people living with HIV are not receiving HIV treatment, especially in the Centre and East sub-regions. As a result, a proportion of people living with HIV have not reached viral suppression, thus limiting the effects of 'treatment as prevention'. At each step of the HIV PrEP care continuum, several barriers persist that hinder the implementation of the new prevention strategies. Moreover, the increasing trend in bacterial STIs is ongoing. Prevention of STIs is a challenging issue considering that there is no consensus on a fully effective strategy to reduce the number of new infections. Antibiotic resistance in *N. gonorrhoeae* is becoming a major issue jeopardizing treatment success and whether or not the wider use of doxy-PEP will induce resistance in *N. gonorrhoeae* and *M. genitalium* isolates in the future is unknown.

STI prevention including HIV, is an evolving field that accommodates new strategies. Next-generation HIV PrEP agents show promise in terms of uptake, adherence, and persistence. New approaches for STI prevention such as doxy-PrEP and -PEP and the use of meningococcal vaccines are being explored with promising results. Although with no solid evidence yet for high efficacy, studies on vaccines for other STIs are ongoing.

Although we have all the necessary tools for the effective prevention of HIV and STIs, none of the above-mentioned strategies alone will be sufficient to change the game at the regional level. A more ambitious and holistic approach with multilevel interventions is still required to address individual, structural, social, and political barriers. To achieve this goal, we need to "scale up interventions to sufficient levels to have the necessary impact on HIV and STI incidence, considering the technical, social, economic, and political structures of each country and the specific needs of each population. Special attention must be given to awareness and education, expanding the scope of prevention interventions to all eligible individuals, developing and updating national guidelines, and providing easy and free-of-charge access to all prevention tools while eliminating the stigma associated with these infections, and involving the community at all intervention levels. A firm commitment from European countries to HIV and STI prevention and full support from international organizations is the key to reaching global targets in Europe.

Contributors

DG conceptualized the review, developed the methodology, and oversaw the preparation of the manuscript. AA and CB conducted the literature search. DG, TN, AA, CB, GL, AÇ, JC, GS, KK, and JMM wrote the original draft. DG, TN, and JMM contributed to the visualization elements. OM contributed to editing the final document. All authors reviewed and edited the final version and approved the final manuscript.

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Declaration of interests

Deniz Gökengin attends advisory board meetings for Gilead, GSK, and MSD, and receives grant from GSK. Jean Michel Molina reported receiving grants from Merck for a treatment trial funded by ANRS, payments for serving on advisory boards of ViiV, Gilead, and Merck, expert testimony payments from Merck and a payment from Aelix for participation on an advisory board. Geoffroy Liegeon has received drugs from Gilead Sciences and ViiV Healthcare for two academic-funded PrEP clinical trials.

The remaining authors have nothing to declare.

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