PREVENTION AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS (STIs) IN THE ERA OF ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP) FOR HIV

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ACRONYMS AND ABBREVIATIONS

3TC  lamivudine
AMR  antimicrobial resistance
ART  antiretroviral therapy
EGASP Enhanced Gonococcal Antimicrobial Surveillance Programme
FTC  emtricitabine
GASP WHO Global Gonococcal Antimicrobial Surveillance Programme
GUD  genital ulcer disease
HAV  hepatitis A virus
HBV  hepatitis B virus
HCV  hepatitis C virus
HPV  human papillomavirus
HSV  herpes simplex virus
LMICs low- and middle-income countries
MSM  men who have sex with men
NAAT nucleic acid amplification testing
PEP  post-exposure prophylaxis
POC  point-of-care (test)
PrEP  pre-exposure prophylaxis
SRHS sexual and reproductive health services
STI  sexually transmitted infection
TDF  tenofovir disoproxil fumarate
XDR  extensively drug-resistant
After years of neglect, greater global attention is being paid to the increasing incidence of sexually transmitted infections (STIs). A recently published WHO report highlights that, annually, there are an estimated 376 million new cases of four curable STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis.

The need for greater focus on STIs has also been highlighted in the context of expanded use of pre-exposure prophylaxis (PrEP) for HIV prevention, where high STI prevalence at baseline and incidence during PrEP use have been observed. The epidemiological situation demands a call to action to ensure that these STIs are addressed, and that populations at risk have access to comprehensive STI prevention and care.

Integration of STI services and PrEP has challenges, but it also provides an opportunity not only to induce much-needed progress in STI control, but also to optimize broader sexual and reproductive health services for key, underserved and overlooked populations.

Figure 1. Existing and future interventions for improving STI prevention and control by leveraging PrEP scale-up
INTRODUCTION

Every day, more than 1 million new cases of four common curable STIs (chlamydia, gonorrhoea, syphilis and trichomoniasis) occur among people aged 15–49 years (1) (Box 1). These four STIs are also associated with an increased risk of acquiring and transmitting HIV. However, most cases are asymptomatic, meaning that people may not be aware they have an infection prior to testing.

WHY OTHER STIS, BEYOND HIV, MATTER FOR PUBLIC HEALTH

The consequences of sexually transmitted infections (STIs), including HIV, on both individual health and public health can be severe.

The World Health Organization (WHO) has outlined key global targets towards ending STI epidemics as public health concerns by 2030, including a 90% reduction globally in the incidence of syphilis and gonorrhoea, caused by the organisms *Treponema pallidum* and *Neisseria gonorrhoeae*, respectively (2). Strategies to achieve this should include better diagnosis, treatment and partner services for populations at high and ongoing risk of acquiring STIs.

STIs, including HIV, can also be transmitted from mother to child. Transmission of STIs to the fetus during pregnancy can lead to adverse outcomes for infants. For example, in 2016, syphilis alone caused an estimated 200 000 stillbirths and newborn deaths, making it one of the leading causes of preventable neonatal mortality worldwide.

Box 1. Key public health issues of STIs

- Worldwide, more than 1 million STIs are acquired every day.
- The incidence of STIs is disproportionately high among key populations, including men who have sex with men, sex workers, transgender people as well as adolescents and young adults.
- In 2016, there were an estimated 376 million new cases of four curable STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis.
- More than 500 million people are estimated to have genital herpes simplex virus (HSV) infection.
- More than 290 million women are infected with human papillomavirus (HPV), a cause of cervical cancer.
- Most STIs have no symptoms or only mild symptoms that may not be recognized as being due to an STI.
- STIs can increase the risk of HIV acquisition.
- In 2016, 988 000 pregnant women were infected with syphilis, resulting in over 200 000 stillbirths and newborn deaths.
- In some cases, STIs can have serious sexual and reproductive health complications (e.g. infertility in men and women; adverse pregnancy outcomes; newborn and congenital infections).
- Antimicrobial drug resistance, especially in *N. gonorrhoeae*, is a major public health threat.

For women, STIs can have serious reproductive health consequences beyond the immediate impact of the infection itself, including ectopic pregnancy and infertility. More than 290 million women have HPV infection, which can cause cervical cancer.

Gonococcal antimicrobial resistance (AMR) may lead to a pandemic of extensively drug-resistant (XDR) *N. gonorrhoeae*, which can have major public health implications. In response, the WHO Global Gonococcal Antimicrobial Surveillance Programme (WHO GASP), a collaborative global network of regional and subregional reference laboratories, has been in place since 1990 to monitor gonococcal AMR worldwide (3).

Some viral infections that cause hepatitis can also be sexually transmitted. Transmission of hepatitis A virus (HAV) can occur from any oro-fecal contact due to sexual activity with an infected person. In adults, hepatitis B virus (HBV) is easily transmitted primarily through sexual activity among unvaccinated adults. Hepatitis C (HCV) has emerged in recent years as an STI among men who have sex with men (MSM), especially in those with HIV. HAV and HBV can be prevented with targeted vaccination. While there is currently no vaccine for HCV, curative treatment for HCV is becoming increasingly available.
Over 500 million people have genital HSV type 2 (HSV-2) or type 1 (HSV-1) infection, which is lifelong and incurable. Genital herpes can lead to recurrent genital ulcer disease (GUD) and, more rarely, can be transmitted to infants during delivery, resulting in neonatal herpes. Infection with HSV-2, as in the case of syphilis, gonorrhoea and chlamydia, increases the risk of acquiring and transmitting HIV infection.

**Box 2. Targets set out by the Global health sector strategy on STIs approved by the World Health Assembly**

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<th><strong>2030 targets (where we want to go)</strong></th>
<th><strong>Baseline (where we are)</strong></th>
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<td>90% reduction in the incidence of <em>Treponema pallidum</em> infection globally</td>
<td>6.3 million people newly infected with <em>Treponema pallidum</em> in 2016</td>
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<td>90% reduction in the incidence of <em>Neisseria gonorrhoeae</em> infection globally (2018 global baseline)</td>
<td>~87 million people newly infected with <em>Neisseria gonorrhoeae</em> in 2016</td>
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<td>50 or fewer cases of congenital syphilis per 100 000 live births in 80% of countries</td>
<td>473 congenital syphilis cases per 100 000 live births in 2016, a decline of 12% in 4 years</td>
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<td>Sustain 90% national coverage with the HPV vaccine and at least 80% in every district (or equivalent administrative unit) in the national immunization programmes in countries</td>
<td>Of 51 countries surveyed, 14 (27%) reported &gt;80% HPV vaccine coverage</td>
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**Box 3. The challenges that persist today**

- Untreated STIs are associated with long-term morbidity.
- STIs are often neglected programmatically and STI services are either not funded or underfunded.
- Condom use is on the decline in many countries.
- Syndromic management of STIs has limitations, particularly for women with vaginal infection and men with anorectal infection.
- Lack of available, affordable, accurate and easy-to-use point-of-care diagnostic tests for common STIs in low- and middle-income countries is a barrier to STI prevention and control.
- Partner notification services are underutilized.
- Surveillance systems for STIs are weak in many countries and disconnected from HIV surveillance.
ORAL PREP: OPPORTUNITY FOR REACHING PEOPLE AT HIGHEST HIV AND STI RISK, EXPANDING HIV PREVENTION AND OPTIMIZING STI SERVICES

Oral pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV acquisition. Where PrEP has been implemented alongside HIV testing and antiretroviral therapy (ART) services, population-level reductions in HIV incidence among MSM have been reported in high-income settings, including the United States, Australia and the United Kingdom (5–7). Similar trends, however, have yet to be observed in low- and middle-income countries (LMICs) and in populations other than MSM (e.g. young women) among whom PrEP is being introduced and has not reached coverage levels to result in population-level impacts.

WHO has recommended oral PrEP since 2015 for anyone at substantial risk for HIV infection (8). As of mid-2019, over 50 countries have national policies or guidelines recommending PrEP for populations at high risk of HIV acquisition (9). Since 2017, PrEP drugs (tenofovir/emtricitabine [TDF/FTC], and TDF/lamivudine [3TC]) have also been included in WHO’s Essential Medicines List (10).

In the “era” of PrEP, there is a concern that PrEP roll-out may be contributing to increasing rates of bacterial and other viral STIs being reported in countries (11). However, there is also recognition that the rates of STIs were increasing in countries prior to the introduction of PrEP. As people who could benefit from PrEP most are also likely to be at increased risk of STIs, PrEP can be an entry point for people to access more comprehensive sexual and reproductive health services (SRHS), of which STI screening and treatment is a critical element. To that effect, PrEP services could enhance global efforts to control STIs. Similarly, those accessing STI services may benefit from being offered PrEP.

There are both challenges and untapped opportunities to enhance STI prevention and control. In LMICs, expansion of STI services is hampered by high costs and limited availability of laboratory or point-of-care (POC) test kits. Optimizing STI services for prevention and control needs to prioritize diagnostic testing strategies (e.g. nucleic acid amplification testing [NAAT] and rapid diagnostic testing for screening), more effective treatment, targeted and increased HPV vaccine coverage, condom programming, strengthening human resource capacity and adequate funding. Syndromic management of STIs, the current approach in most LMICs, has significant limitations, given that most STIs are asymptomatic (12). Untreated STIs can lead to clinical consequences and sequelae in both men and women (e.g. for pregnant women and their infants).

Countries have to balance cost and feasibility in providing effective STI services with the goal of making PrEP widely accessible for maximum impact on HIV prevention. People taking PrEP are a core group for STI prevention and control and, therefore, should be prioritized. The increasing demand for PrEP presents an opportunity for STI and HIV service integration and the offer of targeted STI testing, treatment, vaccination, and other services for PrEP-eligible users.
KNOW YOUR STI EPIDEMICS: WHAT ARE THE STI EPIDEMIOLOGICAL TRENDS IN THE CONTEXT OF PREP USE? ?

Based on national surveillance reports, bacterial STI rates decreased in the 1980s (13). This was at a time when the HIV epidemic was growing rapidly, no treatment was available, and condoms were widely promoted among all populations as the only way to prevent HIV transmission. Since 2000, when effective HIV treatment has been available and knowledge of the prevention benefits of ART became clear (14), condom use, and focus and funding on condom programming, including condom social marketing, lessened.

WHO commissioned a systematic review in 2018 of the epidemiology of STIs among PrEP users (1). The review, which identified 88 studies, found that STI prevalence was high in people prior to starting PrEP – overall one in four PrEP users had an STI at baseline (24% had chlamydia, gonorrhoea and/or early syphilis). STI incidence patterns varied by setting and population included in the review; pooled STI incidence generally remained high during follow up when taking PrEP. Few studies disaggregated their STI findings by subpopulation. Although most studies were from high-income countries and among MSM populations, the available data from LMICs and among women also revealed a high STI prevalence at baseline. These data also showed that many of the infections among women were asymptomatic and routine STI testing revealed high levels of STI rates (e.g. chlamydia) in young women prior to PrEP initiation (15).

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PREVENTION AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS (STIs) IN THE ERA OF ORAL PRE-EXPOSURE PROPHYLAXIS (PREP) FOR HIV

IS ORAL PREP A RISK OR AN OPPORTUNITY FOR STI PREVENTION AND CONTROL?

There are concerns that PrEP introduction and scale up may pose risks, such as sexual behaviour change (e.g. decrease in condom use) in specific populations, and have an impact on the budget in already constrained health systems.

Despite condoms being highly effective in preventing HIV and other STIs, and global investment in condom programming, the reduction in condom utilization long preceded PrEP introduction in most countries. Therefore, public health measures for the prevention of HIV and other STIs need to be enhanced, not only by the promotion and provision of condoms, but also the prioritization of PrEP, coupled with more effective STI screening and treatment.

Where AMR data are limited, particularly in LMICs, introduction and scale up of PrEP can be leveraged to strengthen efforts around case detection of STIs and sentinel surveillance for AMR on Neisseria gonorrhoeae. In some sentinel countries (e.g. the Philippines and Thailand), WHO has initiated an Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP), which aims to collect standardized and quality-assured epidemiological and clinical information linked to microbiological and AMR data.

Nonetheless, PrEP uptake may provide an opportunity to decrease the incidence of both HIV and other STIs if better programmatic coordination is achieved. Modelling shows that more frequent testing in MSM PrEP users can result in a reduction in STI incidence – for gonorrhoea and chlamydia (16). Reframing PrEP, HIV treatment and STI control programmes as sexual health initiatives may lead to greater success in achieving 2030 targets than focusing on specific infections.

Integration of STI and PrEP programmes can be viewed bi-directionally (not only integrating STI services into PrEP services but also considering STI clients as people also at risk for HIV and therefore potentially eligible for PrEP). Such an approach fosters synergies and efficiencies from a public health perspective. However, there are many challenges to programmatic integration, including siloed funding streams and programmes, the availability and costs of expanded etiological STI testing (i.e. nucleic acid amplification test or NAAT), and gaps in capacity and training for STI management.

Box 4. The opportunities for optimizing STI prevention and control

- Build on the current momentum around these global health priorities:
  - Global action plan on AMR
  - HPV vaccination targets for adolescent girls for cervical cancer prevention: consider also vaccination to prevent anal and oropharyngeal cancer in MSM and transgender women
  - Viral hepatitis elimination goal: consider including HCV testing and HAV/HBV vaccination for PrEP users, and HCV and HBV treatment.
- Update national STI and PrEP guidelines.
- Integrate STI services into existing HIV services, including PrEP programmes (and vice versa).
- Move beyond the syndromic approach to diagnosing STIs and invest in diagnostic testing.
- Develop and implement training in provision of both STI and PrEP services for health-care providers.
- Capitalize on opportunities to provide comprehensive services more efficiently, as there is an overlap between the PrEP package and STI package of services.
- Support community engagement around greater advocacy to generate demand and service delivery for PrEP and STIs.
- Negotiate lower costs for NAAT assays, treatment and vaccines (e.g. HBV, HPV vaccines).
- Expand the use of multitesting platforms such as the dual HIV/syphilis test and POC test for gonorrhoea and chlamydia.
WHAT ACTIONS ARE NEEDED TO OPTIMIZE STI SERVICES IN THE CONTEXT OF ORAL PREP?

To promote better SHRH, the unmet need for appropriate STI screening and treatment for people at risk for HIV and other STIs should be filled, particularly in LMICs. The current state of STI interventions, both within PrEP and other HIV services and beyond, is inadequate to achieve the targets set in the *Global health sector strategy on STIs, 2016–2021*. As such, the following actions can accelerate progress towards those targets:

1. **Advocacy drive:** make stronger efforts to ensure that STIs are prioritized by ministries of health, donors and other stakeholders.

2. **Push for greater investment in:**
   - building capacity for screening and treatment of STIs (including support for key population-led services and community-based organizations);
   - additional research, from early product development to implementation research;
   - developing more affordable, accurate and easy-to-use POC STI testing to support countries in their STI responses;
   - vaccine development, such as for gonorrhea.

3. **Establish and maintain multipartner platforms** to consider how to optimize testing (including frequency of testing), treatment and prevention strategies for STIs, which include vaccinations and other multipurpose technologies.

4. **Aim for greater innovation in next-generation interventions and service delivery for STI control** (including digital health):
   - Current interventions under development and review include self-sampling/-testing, pooled sampling, antibiotics for PrEP/post-exposure prophylaxis (PEP). For example, review the evidence on the use of doxycycline to prevent chlamydia and/or syphilis acquisition (17), and the role of multipurpose technologies (e.g. that combine PrEP for HIV and other STIs/contraception into a single method) in short-term and long-term STI control efforts.
   - Review current models of service delivery and share and adapt effective models to the country, epidemiological and population context.
KEY MESSAGES

• The prevalence and incidence of STIs remain high worldwide, including in people who are taking PrEP.

• PrEP is highly effective in reducing the risk of acquiring HIV; the benefits of PrEP at the population level are starting to be reported (reduction in HIV incidence within a population/health jurisdiction).

• PrEP should be part of a broader package of services, which includes HIV testing services, assisted partner notification, provision of male and female condoms and lubricants, contraception choices, screening and treatment of STIs, and opportunities to vaccinate for viral hepatitis (HAV/HBV) and HPV. PrEP may engage key populations, such as MSM and transgender men and women, and cis-women, who may be at increased risk for STIs.

• STI services are often underprioritized and poorly funded nationally and by international donors; PrEP presents an opportunity to think strategically about how more comprehensive services can be supported by governments and other stakeholders.

• Challenges persist in STI diagnosis and treatment: missed opportunities for treatment, concerns regarding mistreatment and potential for overtreatment, including in PrEP users who do not have access to appropriate diagnostic testing.
  – It is time to move beyond the syndromic management of STIs, where possible, as many infections are missed with this approach.
  – Etiological STI testing/diagnosis and development of cheaper, effective POC diagnostics remains a high priority.
REFERENCES


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