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Challenges and Solutions to STI Control in the Era of HIV and STI Prophylaxis

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Abstract

Purpose of Review This article reviews current efforts to control bacterial sexually transmitted infections (STIs) among HIV pre-exposure prophylaxis (PrEP) users and outlines the opportunities and challenges to controlling STIs within HIV PrEP programs.

Recent Findings The incidence of STIs continues to rise globally especially among HIV PrEP users, with an estimated 1 in 4 PrEP users having a curable bacterial STI. STIs and HIV comprise a syndemic needing dual interventions. The majority of STIs are asymptomatic, and when testing is available, many STIs occur in extragenital sites that are missed when relying on urine testing or genital swabs. Optimal testing and treatment, including testing for antimicrobial resistance, pose difficulties in high income countries and is essentially non-existent in most low- and middle-income countries. Novel STI primary prevention strategies, like doxycycline post-exposure prophylaxis (PEP) for STI prevention, have proven to be highly efficacious in some populations. A few jurisdictions have issued normative guidelines and position statements for doxycycline PEP; however, clinical standards for implementation and data on public health impact are limited.

Summary STI incidence rates are high and rising in sexually active populations. Sexual health programs should leverage the expansion of HIV PrEP delivery services to integrate STI testing, surveillance, and novel STI prevention services.

Keywords Sexually transmitted infections (STIs) · HIV · PrEP · Prophylaxis

Introduction

Sexually transmitted infections (STIs) are a significant public health challenge worldwide with more than a million new cases of curable STIs, chlamydia, gonorrhea, trichomoniasis, and syphilis, reported daily globally [1]. Untreated STIs can lead to sequelae, such as infertility, neurological injury, or chronic pain, which contribute to significant disability-adjusted life years lost, especially among cisgender women [2, 3]. The prevalence and incidence of STIs are especially high among people who are having condomless sex, many of whom are already using HIV pre-exposure prophylaxis (PrEP), which provides protection against HIV but offers no protection against bacterial STIs [4–6]. A recent systematic review and metanalysis of studies among PrEP users from high income (HIC) and low-and-middle income countries (LMIC) reporting a combined outcome of chlamydia, gonorrhea, or syphilis reported a prevalence of 23.9% and an incidence of 72.2 per 100 person years [7].

A resurgence of syphilis has also been reported across HICs and LMICs since the introduction of anti-retroviral therapy [8]. In HICs, the resurgence is mainly concentrated among specific populations such as men who have sex with men (MSM), transgender women (TGW), and sex workers. There has also been a spike in syphilis cases among people who are unstably housed or in-housed in the US and increase of up to 300% in congenital syphilis in several places in countries like the US, Japan, and Brazil [9–12]. In LMICs, syphilis is still endemic in the general population, and the true burden may not be fully known as most data come from research conducted among women attending antenatal care [8, 13].

The World Health Organization (WHO) has recognized the rising burden of STIs and called for integration of STI treatment and prevention services into HIV PrEP programs [14]. When PrEP was first made available for use by people at risk

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of acquiring HIV, there were concerns that there would be an accompanying increase in the frequency of condomless sex and the number of sex partners (or "sexual liberalization") which would then lead to an increase in exposure to HIV and other STIs [15]. Early studies conducted after the roll-out of HIV PrEP suggested that HIV PrEP use was not associated with an increase in the number of condomless sex acts or increase in STI prevalence and incidence [5, 16]. Subsequent studies have, however, demonstrated a decrease in the use of condoms, an increase in the number of sex partners, and a high prevalence of bacterial STIs among people using PrEP [17–20]. It is also known that the prevalence and incidence of STIs were already on the rise before the advent of HIV PrEP, [21–25] and the high burden of STIs may not be fully accounted for by the introduction of HIV PrEP. Regardless of STI trends prior to or after introduction of HIV PrEP, it is clear that recommending condom use was insufficient HIV prevention strategy, and that people seeking PrEP face a high burden of STIs worldwide. The merits of HIV PrEP are now well established, and it is also unsurprising that there is a high prevalence of STIs among PrEP users, considering that a significant number of them rely on PrEP due to a lack of condom usage.

Testing and Treatment of STIs Within HIV PrEP Programs

Traditional strategies for control of STIs primarily rely on testing and treatment, [26] which requires sensitive diagnostics for both symptomatic and asymptomatic STIs followed by timely treatment.

STI testing is, however, largely unavailable—or inaccessible due to costs—in LMICs where the burden of STIs is greatest. In LMICs, symptom-based diagnosis and treatment of STIs (i.e., syndromic management) is currently the standard of care. This strategy misses asymptomatic infections, or approximately 70% of women with *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. [27] In addition, most women with vaginal discharge have no *C. trachomatis* or *N. gonorrhoeae* infection, [28, 29] and up to 30% of men with urethral discharge have no *C. trachomatis* or *N. gonorrhoeae*. [26] Incorporating risk scores and basic laboratory procedures to clinical evaluation has had negligible impact on the predictive value of vaginal discharge for *C. trachomatis* and *N. gonorrhoeae* infections [27, 30, 31]. For syphilis, many cases are asymptomatic repeat infections detected only by a four-fold rise in titers when using non-treponemal tests [32, 33]. This may prove difficult to detect especially in resource-limited settings relying on non-treponemal rapid point of care tests such as dual kits. Rapid tests which combine both treponemal and non-treponemal tests for active syphilis diagnosis in a single cartridge are now available and have the potential to improve diagnosis of active syphilis infection [34].

In resource-rich settings, quarterly molecular testing (and treatment) is the mainstay of chlamydia and gonorrhea control among people using PrEP [34]. An empirical study among MSM using PrEP has shown that implementing quarterly STI screening could effectively reduce the risk of asymptomatic STI exposure for a significant number of partners, leading to a decrease in transmission [35••]. However, there have also been concerns from modeling studies about the cost-effectiveness of quarterly testing due to the high costs of molecular tests especially for chlamydia and gonorrhea (particularly for cisgender MSM who experience fewer serious complications with less frequent testing) [36••]. There are also scientific implications like antibiotic resistance associated with more frequent use of antibiotics [37]. Importantly, the test and treat strategy faces the crucial problem of being reactive and inadequate in preventing the transmission of STIs, especially in populations with robust sexual networks.

Another important component of STI testing is to screen for STIs in extragenital sites, as STIs in such sites are often asymptomatic, difficult to treat, and can serve as reservoirs for uninterrupted transmission [38–40]. In LMICs, extragenital testing is rarely done as it is not part of routine care and the true burden of this is therefore not well known [41]. Detection of STIs at any site has been associated with increased chances of HIV acquisition [42, 43]. Screening for extragenital STIs regardless of symptoms should therefore be considered as part of routine STI testing. However, as there are non-pathogenic commensal *Neisseria* species present in extragenital sites such as the pharynx which can cross-react with some *N. gonorrhoeae* tests, it is important to consider confirmatory NAAT testing with more specific targets or tests with high (> 90%) positive predictive values [41, 44].

Primary STI Prevention

Primary STI prevention strategies have previously included recommendations like abstinence and consistent condom use. When utilized correctly and consistently, condoms provide high protection (more than 90%) against numerous STIs [45]. In real-world settings, condoms have proven to be ineffective, stigmatizing, and for some people, non-negotiable [46, 47].

Novel STI Prevention Strategies

Doxycycline Post-exposure Prophylaxis

Doxycycline post-exposure prophylaxis is gaining prominence as a potential primary STI prevention strategy [48, 49]. Doxycycline is an inexpensive and widely available antibiotic with a strong safety profile. Doxycycline

is first-line treatment for *C. trachomatis* and second-line treatment for syphilis; additionally, doxycycline has activity against *N. gonorrhoeae* in settings where tetracycline resistance is low.

Studies of cisgender men who have sex with men (MSM) and transgender women (TGW) in the US and France demonstrated that doxycycline post-exposure prophylaxis (PEP) effectively reduced incident STIs (chlamydia, syphilis, and gonorrhea) [50, 51]. In the French study (ANRS-IPERGAY), for instance, doxycycline PEP reduced the incidence of chlamydia and syphilis from 35.4 to 5.6 cases per 100 person years [50]. A recent pharmacologic study has demonstrated that a single 200-mg dose of doxycycline attained levels greater than three to four times the minimum inhibitory concentration (MIC) for chlamydia and syphilis in vaginal tissue and six to nine times in rectal tissue, suggesting potential efficacy as PEP in both men and women [52••].

However, the only study of doxycycline PEP among cisgender women in Kenya with a high STI burden showed no significant reduction in incident STIs, [53••] a significant variation from the findings of studies among cisgender men and transgender women. Postulated explanations for these findings include differences in anatomy, in antibiotic resistance patterns, and sub-optimal adherence [53••]. More recent findings from the study indicate low detection of doxycycline in objective measures of use from a subset of participants [54]. These findings suggest low use of doxycycline as a likely explanation for null results. Further studies are needed to evaluate efficacy of doxycycline PEP for STI prevention among people assigned female sex at birth. Additionally, it is crucial to understand the reasons for missed doses and non-use to ensure that interventions are acceptable and accessible.

The results of the doxycycline PEP trials have led to issuance of normative guidelines and position statements in several countries and public health departments to guide conversations between healthcare providers and their clients [35, 36, 55, 56].

The main concern for doxycycline use as PEP rather than solely as treatment includes selection for antibiotic resistance in STIs and other pathogenic and non-pathogenic organisms. A recent study has reported that doxycycline PEP reduced *Staphylococcus aureus* colonization by 16% without a significant increase in doxycycline resistant *Staphylococcus aureus*. There is also concern about disruption of the microbiome of people who are highly sexually active and use doxycycline PEP frequently; however, evidence from use of daily doxycycline for acne and malaria indicate that while doxycycline lowers microbiome diversity, it is recoverable during follow up [57]. The impact of intermittent yet frequent dosing—rather than daily dosing—is unknown. More studies on the most appropriate candidates for doxycycline PEP, its acceptability by different populations, and the clinical and policy readiness for integrating this promising strategy into HIV PrEP programs are needed.

Meningococcal Vaccine for Prevention of Gonorrhea

N. gonorrhoeae and *Neisseria meningitidis* have genetic similarities, and data from recent studies suggest that a meningitis vaccine might reduce gonorrhea transmission [58••]. The DoxyVac study in France is prospectively evaluating impact of a meningococcal vaccine (4CMenB) on reducing incidence rates of *N. gonorrhoeae*, with ongoing analyses on the level of protection [59••]. A vaccine against *N. gonorrhoeae* would be an important addition in the face of rising incidence and antimicrobial resistance. A modeling study has shown that it would be cost-effective to use a gonorrhea vaccine with moderate efficacy if it is offered to individuals at high risk of STIs or those already diagnosed with gonorrhea [60]. This suggests that even with moderate efficacy, it could still be cost-effective to offer a gonorrhea vaccine to PrEP users as they have both high incident cases and are risk of future STI acquisition.

Other Bacterial STIs

Mycobacterium genitalium

Mycoplasma genitalium (*M. genitalium*) is still associated with non-gonococcal urethritis, cervicitis, pelvic inflammatory disease, and infertility though it is thought to be less symptomatic than other bacterial STIs and its severity is debated [61, 62]. Among people in Europe and the US, the pooled prevalence of *M. genitalium* is more than 16% [63••]. Notably, 82.6% of the *M. genitalium* infections were macrolide-resistant and 14.3% were resistant to a fluoroquinolone.

Shigellosis

Shigellosis, a foodborne or waterborne infection endemic in LMICs, is also associated with sexually transmitted gastroenteritis with increasing prevalence among men who have sex with men (MSM), [64, 65] especially among people engaged in HIV care and HIV PrEP care [65, 66]. Among strains of *Shigella* in the US, Europe, and Asia, resistance to first line antibiotics for management and transcontinental spread has been reported [67]. As this spread is occurring among sexual networks with high prevalence of STIs such as chlamydia, syphilis, and gonorrhea, antibiotic treatment (and prophylaxis) for STIs is likely to exert selection pressure on strains of *Shigella* circulating in these sexual networks, threatening both individual clinical management and population level control [67].

Antimicrobial Resistance

In addition to rising rates of extreme drug resistant *M. genitalium* and *Shigella* spp., some strains of *N. gonorrhoeae* are now resistant to almost all classes of antibiotics including extended spectrum cephalosporins and azithromycin [39, 68]. This is a serious concern as *N. gonorrhoeae* is the second most common bacterial STI worldwide and its incidence is on an upward trajectory [63••]. Many NAAT tests do not detect AMR and there are no recommended tests for predicting treatment failure [69, 70]. Nonetheless, there are promising NAAT tests in development that can detect both *N. gonorrhoeae* and ciprofloxacin susceptibility, an important proof of concept [71]. New and cost effective antibiotics are also needed. Currently, there are new antimicrobial agents in phase III clinical trials with activity against *N. gonorrhoeae*, gepotidacin, and zoliflodacin [72–74]. Chlamydia and syphilis are still susceptible to their first-line therapies, even though concerns about development of antimicrobial resistance abound [75–77].

Opportunities for Integrating STI Prevention in HIV PrEP Programs

HIV PrEP delivery platforms still represent a unique opportunity for integrating and expanding STI prevention strategies alongside those for HIV prevention. People using HIV PrEP have already self-identified as being at risk of STIs and have made a step toward embracing prevention; hence, these platforms are natural settings to incorporate STI prevention services. The use of HIV PrEP involves navigating through side effects and adherence strategies, factors that can make strategies such as doxycycline PEP compatible among people with experience with HIV PrEP.

Renewed efforts are underway to expand the reach of HIV PrEP programs with the recent introduction of new HIV PrEP agents, such as the dapivirine vaginal ring and long-acting cabotegravir as well as the use of non-traditional HIV PrEP delivery platforms such as retail pharmacies, [78, 79] community settings [80–82], and telemedicine services to deliver HIV PrEP [83–85]. In recognition of barriers to accessing PrEP care, ongoing research is also being conducted on multi-purpose prevention tools (MPTs) [86]. MPTs simultaneously prevent HIV, other STIs, and/or unplanned pregnancy. All PrEP care models are opportune settings to improve access to interventions for sexual health with integrated STI testing, treatment, and prevention services.

Co-design and Participatory Community Research for HIV and STI Prevention

The incidence and prevalence of STIs varies widely among different populations even within similar geographical settings because of complex individual, social, and structural dynamics, such as access to education and healthcare, lack of trust in the healthcare system, socio-economic status, and racism [87–89]. It is therefore crucial that communities and populations that bear a disproportionate burden of STIs take part in designing interventions that are tailored to their unique circumstances [90].

Conclusion

The integration of STI prevention services within HIV PrEP delivery settings is inadequate given the rising rates of STIs. With STI prevention strategies like STI prophylaxis and novel HIV PrEP delivery models, integrated STI and HIV prevention is increasingly possible. As many STIs are asymptomatic and present in extra-genital sites, investment in multisite, asymptomatic STI testing (and antimicrobial resistance testing) is a crucial component of STI control. Primary prevention strategies, like doxycycline PEP and STI vaccines, represent potentially impactful and cost-effective strategies. Importantly, people working in the field of sexual health need to pro-actively adopt human-centered STI research designs to incorporate the priorities and preferences of the concerned communities.

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Declarations

Conflict of Interest Dr. Elizabeth Bukusi has received honoraria for speaker bureau/scientific advisory board from Merck and ViiV. The other authors declare competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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