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Population and Individual-Level Effects of Human Immunodeficiency Virus Preexposure Prophylaxis on Sexually Transmitted Infection Epidemics Among Men Who Have Sex With Men

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Human immunodeficiency virus (HIV) preexposure prophylaxis (HIV PrEP)¹ provides substantial individual-level HIV risk reduction and may confer a population-level decrease in HIV incidence among gay, bisexual, and other men who have sex with men (MSM) when high HIV PrEP coverage is obtained.² Unfortunately, the effect of HIV PrEP on sexually transmitted infection (STI) epidemics among MSM is less clear. We review recent trends in reported STIs among MSM in the United States, discuss the mechanisms by which HIV PrEP may impact STI rates, and consider the resulting population and individual-level effects of HIV PrEP on STI epidemics.

STI BURDEN AMONG MSM IN THE UNITED STATES

Rates of reported STIs have increased in recent years among MSM in the United States. The rate of reported gonorrhea among men increased 19.3% during 2013 to 2017, with over 300,000 cases reported in 2017.³ Data on sex of sex partners for reported gonorrhea and chlamydia cases are not consistently collected by all jurisdictions. However, data from enhanced surveillance in select jurisdictions suggest that there are dual gonorrhea epidemics, with an estimated 42% of reported cases occurring among MSM and 58% among men who have sex with women only (MSW) and women.³ Additionally, rates of gonorrhea appear to be increasing more rapidly among MSM compared with heterosexuals; during 2010 to 2017, rates increased 283% among MSM (1368.6 to 5241.8 per 100,000), 54% among MSW (84.3 to 143.7 per 100,000), and 88% among women (102.7 to 187.6 per 100,000).³ Similar data for chlamydial infection are not available, so no national population-level estimates of chlamydial infection among MSM exist.

Syphilis is much less common than gonorrhea in the United States, with only 26,885 cases of primary and secondary (P&S) syphilis (the most infectious stages) reported among men in 2017.³ Given the lower burden, it is easier for local jurisdictions to interview most P&S

syphilis cases and collect information on sex of sex partners. Therefore, we know that most (58%) P&S syphilis cases in 2017 were diagnosed among MSM and that during the past 10 years, the annual number of cases among MSM increased steadily.³ In contrast, the burden of P&S syphilis is much lower among heterosexuals and appears to occur more often among high-risk subgroups, such as those who use methamphetamines or inject drugs.^{4,5} However, there have been recent increases in syphilis diagnoses among heterosexuals in the past 5 years, with concurrent increases in congenital syphilis.³

POTENTIAL RELATIONSHIPS BETWEEN HIV PREP AND STI TRENDS AMONG MSM

Interpreting observed increases in reported cases of STIs among MSM is difficult. Reported cases reflect only those that were both diagnosed and reported. Such cases include both incident and prevalent infections, and this distinction cannot be ascertained for most STIs. Furthermore, each case represents an infection rather than a person, so 1 person who has multiple infections in a single year may contribute multiple cases for that year and persons concurrently diagnosed with infections at multiple anatomic sites will be reported as a single case. Additionally, the ability to categorize cases by sex and sex of sex partners requires patient disclosure of sexual behaviors to provider and/or public health investigators; changes over time in disclosure could impact reported rates independent of changes in incidence (e.g., if more MSM disclose same sex behaviors, reported rates among MSM will increase). Trends in diagnosed cases are, therefore, a function of changes in incidence of initial infection, identification of symptomatic infections through symptom recognition and care seeking, identification of asymptomatic infections through screening, and rates of reinfection. Thus, there are at least 3 ways that HIV PrEP may affect STI case detection rates: increased case detection (e.g., increased screening), risk compensation (e.g., less condom use or increased number of partners), and increases and greater frequency of repeat infections.

First, HIV PrEP likely increases STI screening frequency and detection. Many bacterial STIs, particularly rectal and oropharyngeal gonococcal infections, are asymptomatic, and screening is needed to identify infection.⁶ Centers for Disease Control and Prevention STI screening guidelines recommend MSM be screened at least once per year at all exposed anatomic sites⁷; however, under current HIV PrEP guidelines, MSM on HIV PrEP should be screened as frequently as 4 times per year.¹ As a result, as HIV PrEP coverage expands, more STIs will be identified and treated independent of changes in incidence.⁸

Second, using HIV PrEP as a primary means for HIV prevention may change sexual behaviors in a way that facilitates STI transmission. For example, MSM on HIV PrEP may reduce condom use,^{9,10} which is the most effective way to prevent STIs. Furthermore, MSM on HIV PrEP may select partners differently, altering their sexual networks.⁹ If they select partners from networks with a higher prevalence of STIs, their risk of STI acquisition will increase independent of changes in condom use.¹¹ Additionally, MSM may change their number of partners as well as the type and frequency of sexual acts, each of which may

increase STI risk.⁹ Therefore, changes in behaviors related to HIV PrEP use may result in increased STI transmission.

Third, repeat infections for bacterial STIs are common, as diagnosed infections can be effectively treated with antibiotics and undiagnosed infections can self-resolve. Men who have sex with men on HIV PrEP will be screened more frequently than persons not on HIV PrEP and, as a result, may have higher rates of reinfection. Because each infection with an STI is reported as a new case, 1 individual may contribute multiple reported cases annually, and increased repeat infection will result in higher reported case rates. Men who have sex with men on HIV PrEP who are screened according to HIV PrEP guidelines,¹ may be diagnosed up to 4 times throughout the year if they are consistently reinfected after treatment.

IMPLICATIONS OF STI INCREASES AND REPEAT INFECTIONS FOR PREDOMINANTLY MSM SEXUAL NETWORKS

Regardless of the mechanism by which HIV PrEP increases reported STI case rates (either through increased case detection, increased incidence, or both), the implications of increases in STIs among MSM on HIV PrEP vary by whether we consider the benefit to the individual or to the population, as well as by the STI.

At the individual level, an untreated bacterial STI in a MSM may cause acute symptoms and can lead to serious complications, although they are rare. For example, the prevalence of neurologic complications among syphilis cases is estimated to be less than 2%^{12,13} and the prevalence of disseminated gonococcal infection among gonorrhea cases is not well known, but is estimated to be 0.5% to 3%.¹⁴ Additionally, bacterial STIs may facilitate HIV transmission and acquisition,^{15–17} but an incident STI is unlikely to negate fully the prophylactic benefit of HIV PrEP.^{18,19}

If diagnosed, all bacterial STIs are curable. Treatment of symptomatic infection eliminates acute symptoms. Even without symptoms, early identification of infection and prompt treatment shortens duration of a given infection. Although not well studied, reduction of time with an active infection may reduce the risk of complications. Furthermore, in the absence of repeat infection, the cumulative time spent in an infectious state is reduced which can halt ongoing transmission to partners.

The benefits of routine screening and treatment may be tempered in the presence of a repeat infection. With each repeat STI, the individual returns to the early stage of infection. The implications of this vary by STI. Syphilis is most infectious in the months after acquisition.²⁰ Because MSM may not recognize symptoms of recent infection (e.g., syphilitic chancres are typically painless and may occur in the throat and rectum, which may be less noticeable than genital chancres),²⁰ they may not seek treatment or change behaviors (e.g., reduce partner number or frequency of sexual acts). Consequently, repeat syphilitic infections may result in a longer cumulative period that the person is able to transmit the infection to their partners compared with a single, untreated infection of longer duration.

Within a network of individuals who are frequently screened, treated, and reinfected, this may lead to a more rapid spread and persistence of syphilis in a given sexual network.

For gonorrhea, the implications of repeat infections are not well understood. Persons with gonorrhea can transmit infection to partners throughout the course of their infection. Although it is unknown whether there is a constant probability of transmission, frequent screening should reduce time in the infectious period, reducing spread in the sexual network. This potential benefit is complicated by *Neisseria gonorrhoeae*'s ability to develop resistance to antimicrobials.¹⁴ It is hypothesized that untreated pharyngeal infections (which are usually asymptomatic) increase the likelihood of transfer of genes conferring resistance from other commensal bacteria.²¹ Routine screening and treatment could shorten the length of these infections, reducing the development of resistance. However, repeated treatment for gonorrhea, as well as treatment for other bacterial STIs, increases antibiotic pressure on the organism, possibly fueling development of resistance.²¹

IMPLICATIONS OF STI INCREASES AMONG MSM FOR PREDOMINANTLY HETEROSEXUAL SEXUAL NETWORKS

Although the networks of MSM and MSW/women are often described as distinct sexual networks, increases in STI burden among MSM may have implications for heterosexual STI epidemics. Evidence suggests that less than 10% of gonorrhea and syphilis cases are detected among men who have sex with both men and women (MSMW),^{3,22} suggesting that, although infrequent, bridging between networks does exist. Increasing STI burden in 1 sexual network composed predominantly of MSM may result in subsequent increases in predominantly heterosexual sexual networks, independent of increases in the number of MSMW who serve as bridges between the networks, although the impact of this will vary by STI. For gonorrhea, which currently is endemic to heterosexuals, increases among MSM will likely have a minimal impact on heterosexual transmission. Still, increased gonococcal infections in women may lead to increases in the severe reproductive health complications of an untreated infection, including pelvic inflammatory disease leading to chronic pelvic pain, infertility, and ectopic pregnancy.¹⁴

For syphilis, bridging may play a more significant role. Syphilis is currently increasing among heterosexuals, and the networks in which syphilis outbreaks occur likely have unique characteristics compared with the general population, including greater reported levels of sex work and injection drug use.^{4,5} The additional risk behaviors associated with heterosexual syphilis diagnoses may further facilitate the spread of infections. Thus, if bridging between these networks and MSM networks occurs, large increases in syphilis in MSM may result in subsequent increases among heterosexuals. Even small increases in heterosexual syphilis can have severe consequences as transmission from an untreated pregnant woman to her fetus is possible. Although congenital syphilis can be prevented through prenatal screening, women in these networks may have cooccurring conditions (e.g., homelessness, mental health concerns) that keep them from routine preventive care, elevating the risk of congenital syphilis.²³

Thus, the implications of expanding HIV PrEP coverage among MSM on STI epidemics are complicated. Increased routine syphilis and gonorrhea screening among MSM on HIV PrEP will benefit the individuals on HIV PrEP through prompt treatment for those infected, eliminating acute symptoms and possibly reducing sequelae and onward transmission to sex partners; however, new infections due to risk compensation (e.g., reduced condom use or increased number of partners), and frequent reinfections with related increases in highly infectious periods for syphilis, may lead to an increase of STIs in sexual networks, limiting the population-level benefit. A network-based mathematical model found that HIV PrEP implementation could avert 42% of gonococcal infections if 40% of MSM eligible for HIV PrEP received it.⁸ However, the same model found that with substantial risk compensation (e.g., significant reduction in condom use) and low HIV PrEP coverage, gonorrhea incidence could exceed reported rates before HIV PrEP implementation. Additionally, the population-level benefit of HIV PrEP on MSM STI epidemics may be diminished if it coincides with the development of antimicrobial-resistant gonorrhea or increased spread to heterosexual networks, where the consequences of untreated infections are more severe.

Although health benefits to the individual are an important consideration for patient management and care, public health programs need to focus on health benefits to the population. The above considerations suggest that there are a number of strategies that could align individual and population benefits of HIV PrEP for STI prevention and control. First, to reduce repeat STIs, public health programs and clinical providers could ensure MSM diagnosed with an STI understand the risks of repeat infections, have the resources needed to refer past sexual partners for treatment, and can negotiate risk reduction strategies with future sex partners, including discussing STI testing history before sexual activity, engaging in sexual behaviors that minimize exposure to STIs (e.g., mutual masturbation), and using condoms consistently and correctly. Second, to reduce delays in treatment, programs and providers could work to increase STI symptom recognition among MSM, regular screening, and ensure fast and easy access to quality STI sexual health services, such as express visit models.^{24,25} Third, STI prevention programs should prioritize syphilis investigations among women of reproductive age, ensuring timely treatment to reduce congenital syphilis incidence. Finally, further research is needed to determine the optimal STI screening frequency for MSM, regardless of HIV PrEP use, as a means to prevent and control STIs, as well as the potential benefit of STI PrEP (e.g., prophylactic doxycycline to prevent bacterial STIs) to reduce STIs among MSM.²⁶

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