Current HIV/AIDS Reports (2019) 16:244–256
https://doi.org/10.1007/s11904-019-00446-5

THE SCIENCE OF PREVENTION (JD STEKLER AND JM BAETEN, SECTION EDITORS)

Confronting Rising STIs in the Era of PrEP and Treatment as Prevention

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Published online: 10 June 2019

Abstract

Purpose of Review This study aims to review the epidemiology of sexually transmitted infections (STIs) among men who have sex with men (MSM) and suggest control measures.

Recent Findings Despite declines in new HIV diagnosis, bacterial STIs among MSM have dramatically risen since the late 1990s. This increase occurred concurrent with introduction of effective antiretroviral therapy, the advent of electronic mechanisms for meeting sex partners and population-level changes in sexual behavior, including decreased condom use. HIV pre-exposure prophylaxis (PrEP) is now further diminishing condom use, though its impact on STIs is uncertain. A plan to confront the MSM STI epidemic should include increased HIV/STI testing promoted through expanded public health clinical infrastructure, health care system reform to improve the care of gender and sexual minorities and promote low-barrier care, re-invigorated condom promotion, and scientific innovation.

Summary There is an urgent need to implement new STI control measures while continuing to expand PrEP use.

Keywords Sexually transmitted infections (STIs) · Pre-exposure prophylaxis (PrEP) · Men who have sex with men (MSM)

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that there are almost one million people living with HIV in the USA, with ~38,000 new cases of HIV diagnosed each year [1]. Over 70% of new diagnoses occur in the roughly 2% of the US population composed of men who have sex with men (MSM) [2]. The country has made remarkable progress in confronting the HIV epidemic. The advent of effective antiretroviral therapy (ARV) caused HIV-associated mortality to plummet in the late 1990s and early 2000s, and the overall incidence of HIV is declining. That decline, initially observed primarily in women and persons who inject drugs, is now ongoing in MSM [1], though significant disparities in HIV prevention success among MSM persist [3, 4]. Encouraged by recent trends and scientific advances, many states and cities have developed ambitious plans to "End AIDS" [5] or "Getting to Zero" [6], and in February of 2019, the US Department of Health and Human Services announced a new initiative to end the HIV epidemic in the USA [7, 8]. HIV pre-exposure prophylaxis (PrEP) is a central component of these plans [9].

HIV is the most important sexually transmitted infection (STI), and our progress in controlling HIV is a tremendous achievement. However, it seems to have come with a price: rates of bacterial STIs among MSM are now at unprecedented levels and continue to climb upwards. In this review, we discuss epidemiologic trends in bacterial STIs, factors that may have influenced those trends, and measures that clinicians, health care systems, and departments of public health can take to confront the STI epidemic. Although STIs are a problem affecting diverse populations, in this paper, we concentrate on the STI epidemic in MSM.

Epidemiology of Bacterial STIs in MSM

STI surveillance data in the USA do not include consistent information on the gender of cases' sex partners, limiting the

This article is part of the Topical Collection on *The Science of Prevention*

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availability of long-term data on STI trends in MSM. Despite this limitation, evidence suggests that rates of bacterial STIs among MSM dramatically declined in the 1980s following the onset of the HIV epidemic but began to climb in the late 1990s and early 2000s, a trend that has now persisted for almost two decades.

In many high- and middle-income nations, the upward trend in STIs is clearest for syphilis. Syphilis rates precipitously declined following the end of World War II and the introduction of penicillin (Fig. 1a). They then increased from the late 1950s to early 1990s, declined dramatically in the 1990s, and then rose—almost exclusively among men—between the early 2000s and the present. These data conflate epidemics occurring in MSM and heterosexuals. However, the excess rate of syphilis in men (i.e., the rate in men minus the rate in women) is an indirect method for evaluating STI epidemiology in MSM (Fig. 1b). This excess rate peaked in 1982, around the time that the first cases of HIV were reported, then dropped dramatically before starting to increase again around 2000. Data from King County, Washington (WA), where public health staff have collected data on the gender of sex partners among persons with STIs for many years, confirm the national epidemiologic picture described (Fig. 2). Investigators in San Francisco, California and Melbourne, Australia have reported similar long-term trends, and cities in North America and Europe have likewise reported rising STI rates in MSM over shorter, more variable periods of time [10, 11, 12••]. CDC estimates that 58% of all early syphilis cases in 2017 occurred in MSM [13], while in King County, WA the estimated annual rate of syphilis among

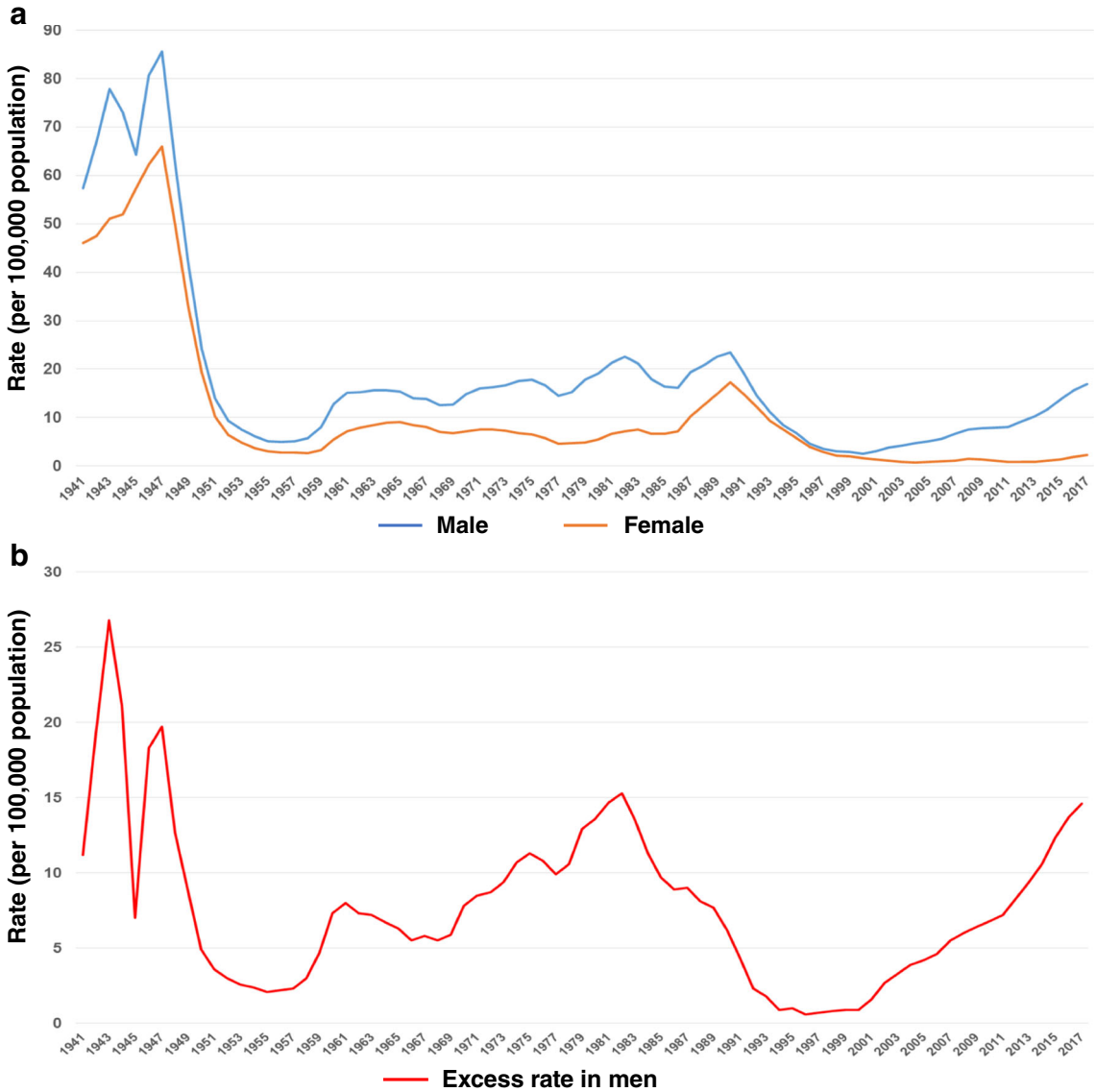

Fig. 1 **a** Rates of primary and secondary syphilis among men and women in the USA between 1941 and 2017. **b** The excess rate of primary and secondary syphilis in men (rate in men minus the rate in women) from 1941 to 2017

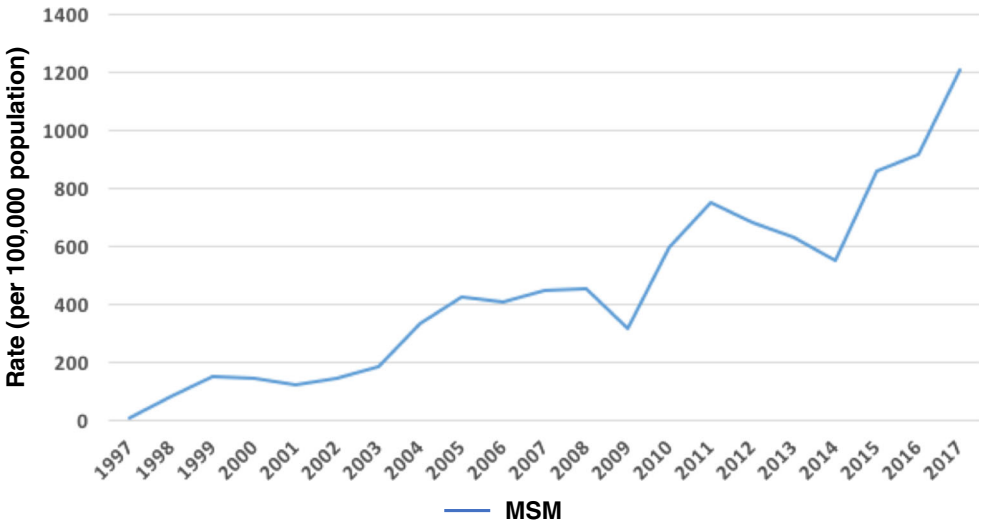

Fig. 2 King County, WA rates of early syphilis from 1997 to 2017 for MSM

MSM in 2017 was 1.2% (1208/100,000), with a rate of 4.8% (4791/100,000) among HIV-positive men.

The observed increase in rates of syphilis is part of a larger increase in rates of bacterial STIs among MSM. In six areas participating in the CDC STD Surveillance Network, the estimated rate of gonococcal infection among MSM increased from 1369 to 3435 cases per 100,000 between 2010 and 2015 [14]. Similarly, between 2007 and 2016, the number of gonorrhea diagnoses among UK MSM increased over 400% [15]. While some of this increase could be a consequence of increased STI screening, particularly for extragenital infections, King County, WA data showed a dramatic increase in urethral gonorrhea, which is almost always symptomatic, suggesting that observed trends are not a consequence of increased STI screening alone [16]. Enteric bacterial infections, which are sometimes sexually transmitted among MSM, as well as sexually transmitted HCV have also increased [17–20]. Thus, we confront a MSM STI epidemic which is persistent, ever growing, and includes a wide diversity of pathogens.

Behavioral Epidemiology and Factors Driving Rising Rates of STIs in MSM

The broad changes in STI epidemiology observed among MSM over the last 30 years reflect population-level changes in sexual behavior and mixing patterns. MSM changed their behavior in response to the onset of the HIV epidemic in the 1980s, reducing their numbers of partners, particularly anal sex partners, and increasing condom use [21]. As early as the mid-1990s, it became clear that many men were choosing sex partners, using condoms and varying their sexual repertoire based on their partners' HIV status, a practice that was initially termed "negotiated safety" and subsequently renamed "seroadaptive behaviors" [22, 23]. Serosorting in particular—the practice of preferentially having sex, particularly condomless anal intercourse (CAI), with persons of known concordant HIV status—became increasingly widespread over the first decade of the twenty-first century [24, 25], and among HIV-positive men was associated with a decline in condom use [26]. The practice offered partial protection from HIV but was not associated with a diminished risk of bacterial STIs relative to condomless sex regardless of HIV status [25, 26]. At least in King County, WA, in recent years, the frequency of serosorting among HIV-positive MSM has declined, with a concurrent increase in CAI with HIV-uninfected or unknown-status partners [27]. This pattern of mixing may have facilitated the dissemination of the syphilis epidemic from its longstanding concentration among HIV-positive MSM into the larger population of HIV-negative MSM [12••, 16], an epidemiologic trend observed in San Francisco, Seattle, New York, and Los Angeles [28••].

The factors driving population level changes in sexual behavior and associated changes in rates of STIs are not entirely clear. However, two interrelated factors stand out as likely critical: effective ARV and the use of electronic mechanisms of communication, particularly the internet and geospatial social networking applications (GSN Apps), to find sex partners. The introduction of effective ARVs in 1996 was associated with a dramatic decline in HIV-associated mortality and ushered in an era of "treatment optimism" [29, 30•, 31–35]. Treatment optimism is the idea that MSM have adopted riskier sexual behaviors as treatment has improved and the consequences of HIV infection have become less dire. This idea was initially controversial and early studies reported mixed results. Some studies failed to associate treatment optimism with risk [36, 37] and others reported such an association in at least some populations [31, 38]. There is no question that the medical consequences of HIV have grown ever less severe over the last 20 years, and that fact has likely contributed to the population's assessment of HIV risk. Definitive evidence that virally suppressed persons with HIV have no risk of transmitting their infection [39] has probably further influenced the

population's sexual behavior, promoting practices such as viral load serosorting and perhaps contributing to declining levels of condom use, which may foster STI transmission even when they pose little or no risk of HIV transmission [40•, 41, 42].

How people meet sex partners has also radically changed over the last three decades [43, 44]. Public health authorities first became widely aware of the Internet's potential to act as a means to foster the spread of STIs after a syphilis outbreak among MSM in San Francisco in the late 1990s [45]. By 2008, more than 50% of MSM with syphilis in San Francisco reported meeting partners over the Internet [12••]. More recently, GSN Apps have supplanted Internet sites as the most common way for men to meet sex partners. Among San Francisco MSM receiving partner services for syphilis in 2016, almost half reported meeting a partner using an App [12••]. Similarly, almost half of all MSM receiving medical care at the Los Angeles LGBTQ Clinic in 2015–2016 and of those surveyed in Melbourne Australia in 2014 had met partners using an App [46, 47]. App-using men have higher numbers of sex partners [48], higher rates of substance use [49], and higher rates of gonorrhea and chlamydia (but not HIV or syphilis) [50] than those who do not use GSN Apps. It is uncertain whether or how much of a causal role the Internet and GSN Apps have played in fostering HIV or STI risk among MSM.

What we can say with confidence is that rates of bacterial STIs among MSM have dramatically increased over the last 20 years, likely due to multiple reasons. This increase occurred in the setting of population-level changes in sexual behavior, including decreased condom use, and was concurrent with the introduction of highly effective ARVs, which the population now correctly understands to be effective in preventing both HIV transmission and HIV-associated morbidity and mortality. During the same time period, the population adopted new technologies for meeting sex partners that may have substantially altered the sexual networks through which STIs are spread. In many areas, these changes were accompanied by declines in HIV transmission among MSM. The result is that trends in HIV and STIs are now substantially uncoupled. We seem to be enjoying great success combatting HIV infection even as our efforts to control bacterial STIs fail. This is the context into which PrEP is being widely introduced.

Has PrEP Increased Rates of STIs?

While PrEP has contributed to changes in sexual behavior in MSM, its impact on the incidence of STIs remains uncertain. Rising rates of bacterial STIs among MSM clearly antedate the widespread use of PrEP and PrEP did not cause the current STI epidemic. At the same time, the emergence of PrEP as an HIV-prevention strategy [51–54] has raised concerns that the intervention is exacerbating an already growing problem. Like "treatment optimism" in the late 1990s, PrEP could plausibly lead people to diminish their use of condoms, increase their number of sex partners, or change the partners with whom they have sex, altering sexual networks in ways that might facilitate STI transmission.

Early studies examining the impact of PrEP on sexual behavior did not consistently support the idea that PrEP would promote STI risk. The randomized controlled trials that established PrEP's efficacy, studies in which participants were blinded to whether or not they were receiving PrEP and uncertain about the intervention's efficacy, typically observed decreases in sexual risk behavior during follow-up [51, 52, 55–57]. An open-label extension trial of IPrEX found no evidence of risk compensation and no increase in STI rates among PrEP users [58]. However, a PrEP implementation study undertaken in San Francisco, Washington DC and Miami from 2012 to 2015 found that although sexual risk behavior and rates of STIs remained stable following PrEP initiation [59], condomless receptive anal sex increased among men in San Francisco. Studies surveying potential PrEP users regarding sexual behavior, including studies undertaken prior to widespread use of the intervention, reported variable results [60–63]. In some instances, these studies suggested that risk compensation would occur. For example, a study of 180 HIV-negative MSM in New York City found that 35% of likely PrEP users indicated that they would decrease their use of condoms once they were on PrEP, a finding also observed in Los Angeles [60, 61].

As PrEP use has become more common and knowledge of the intervention's efficacy more widespread, evidence suggests that many MSM decrease their use of condoms after initiating PrEP. The strongest evidence supporting this conclusion comes from the PROUD study, an open-label randomized trial of immediate vs. deferred PrEP initiation among MSM in England [54]. PrEP use was not associated with a higher number of anal sex partners, but men in the immediate PrEP arm were more likely to have > 10 condomless anal sex partners in the prior 90 days then men in the deferred PrEP arm (21 vs. 12%, $p = 0.03$). Cohort studies and a meta-analysis evaluating changes in sexual behavior following PrEP initiation have reported similar results, observing no changes in numbers of sex partners or episodes of anal sex but increases in CAI [64–67, 68•, 69, 70••].

The influence of PrEP on STI incidence is less certain. It is clear that MSM who take PrEP have a very high incidence of bacterial STIs, and a recent meta-analysis found that PrEP was associated with a 24% increase in the rate of STIs, and a 59% increase in the risk of rectal STIs [68•]. However, most studies reporting the impact of PrEP on STI incidence use results from secondary analysis, have not separately reported symptomatic and asymptomatic STIs, or adjusted for the frequency of screening [59, 65, 69, 71–73]. As a result, one cannot easily infer what influence, if any, PrEP might have on the incidence of STIs. Rectal and pharyngeal gonorrhea and chlamydia are common and almost always asymptomatic, and latent syphilis is likewise often diagnosed as a result of screening. Furthermore, PrEP users are tested for STIs more frequently

than nonusers since PrEP follow-up involves STI screening. Studies that fail to standardize STI screening practices and/or separately report STIs based on the presence or absence of symptoms are subject to ascertainment bias. Focusing on urethral gonorrhea—which is almost always symptomatic—and primary and secondary syphilis may provide more accurate information on STI risk. Limited studies have assessed rates of urethral gonorrhea among PrEP users in STD clinics or clinics in which STI testing is commonly performed [70••, 74, 75, 76•]. The PROUD study did not observe a significant increase in STI incidence in MSM randomly assigned to immediate vs. deferred PrEP initiation [54], and a longitudinal study at the Los Angeles LGBT Center found no difference in urethral gonorrhea in participants before and after PrEP initiation [74]. In contrast, a cohort study evaluating STI incidence among PrEP users in a large health maintenance organization in California found the incidence of urethral gonorrhea increased following PrEP initiation [75]. While clinics in Montreal and Los Angeles observed no change in the risk of urethral gonorrhea following initiation of PrEP [74, 76•], these studies included gonorrhea cases diagnosed at PrEP initiation as occurring in the pre-PrEP period. It is common to initiate PrEP in persons presenting with a STI and inclusion of these STI events in the pre-PrEP period has the potential to bias the analysis against finding an increase in STI rates in PrEP users. To demonstrate this, a recent study conducted in King County, WA, found > 50% of individuals were diagnosed with a STI within 30 days of PrEP initiation visit [70••]. Excluding STI cases diagnosed at time of PrEP initiation, this study observed a slight increase in urethral gonorrhea, but a decline in primary or secondary syphilis, following PrEP initiation. This is the only study we have found in the literature that reports the incidence of symptomatic syphilis (primary or secondary) in PrEP users.

Taken together, existing data are insufficient to draw a definitive conclusion on whether MSM who initiate PrEP also increase their risk of STIs. The fact that condom use declines in PrEP users suggests that such a change in STI risk is likely, but definitive data are lacking. A mathematical modeling study found the increase in STI screening and treatment associated with PrEP could dramatically decrease the burden of gonorrhea and chlamydia at the population level [77]. In its base-case analysis, the model assumed that no MSM undergo extragenital STI screening in the absence of PrEP, and in a sensitivity analysis assumes that 20% of all men, regardless of risk, undergo such screening annually. These assumptions are not valid for some US cities where PrEP uptake is high—data from King County, WA suggest that 47% of all MSM and 62% of higher risk MSM test for STIs at least annually (Julia Hood, personal communication). High levels of STI testing in MSM also occur in Australian cities, especially among MSM with CAI with casual partners and high numbers of partners [78]. However, the assumptions may be true in some areas of the USA or in specific populations, highlighting how PrEP roll-out and enhanced STI control could be synergistic under some circumstances. However, it is difficult to disentangle the association between PrEP and incidence of STIs when individuals who seek PrEP often have higher than average STI risk and lower condom use.

Importance of Rising Rates of STIs

The ongoing epidemic of STIs among MSM has important implications for individual patients and for the public's health. Although bacterial STIs in men are seldom life threatening, they are morbid, costly, and likely play an important role in promoting HIV transmission. An estimated 3.5–8% of persons with early syphilis will have complicated infections, including neuro-, oto-, or ocular syphilis [79]. The number of cases of ocular syphilis has climbed concurrent with rising syphilis rates [80], in some instances leading to blindness [81], and a recent study reported that almost one third of patients had residual visual symptoms after curative treatment [80]. Otosyphilis may also be on the rise, and a recent study showed ~ 50% of persons with a new diagnosis of syphilis had evidence of hearing loss by portable audiometry [82]. Complicated syphilis is associated with significant costs and strain on the health care system due to need for additional workup and management, including IV penicillin administration [83]. In many areas of the USA, the resources needed to care for patients with complicated syphilis, particularly uninsured patients, are not available. In men, gonorrhea and chlamydial infection are less morbid infections than syphilis, but are associated with substantial cost [84], and these infections are responsible for an estimated one in seven new HIV infections in MSM [85, 86].

Increasing rates of STIs among MSM are unlikely to be restricted to MSM alone. The rate of primary and secondary syphilis in women increased 156% between 2013 and 2017, leading to 918 cases of congenital syphilis in 2017, including 64 stillbirths. This represents a 153% increase in congenital syphilis relative to 2013 [13]. During that same period, the rate of gonorrhea among US women increased 39%. Gonorrhea in women is frequently associated with major sequelae, including tubal factor infertility, ectopic pregnancy and chronic pelvic pain [87]. The extent to which rising rates of STIs in women are a consequence of rising rates of STIs in MSM is unknown. However, among MSM with syphilis, approximately 5% in King County, WA and 12% in North Carolina (Erika Samoff, personal communication) also report having sex with women, demonstrating that MSM and heterosexual sexual networks are not entirely distinct and suggesting that connections between these networks vary in ways that could promote regional and/or racial disparities.

Finally, the epidemic of STIs in MSM has implications in terms of antimicrobial resistance. The CDC has identified antimicrobial resistant *Neisseria gonorrhoeae* (AMR NG) as one of the US's three most urgent problems in the area of

drug-resistant bacteria, and gonococcal resistance is widely seen as a global public health threat [88–91]. Five percent of gonorrhea isolates among MSM already have reduced susceptibility to cefixime and 7% of isolates demonstrated a high rate of resistance to azithromycin in 2017 [13]. As overall gonorrhea rates rise, the potential for the development and dissemination of resistance also increases. Controlling AMR NG requires better gonorrhea control overall.

What Is to Be Done?

It seems unlikely that the behavioral trends that have contributed to increasing rates of STIs among MSM will reverse themselves. We need a strategy to confront the burgeoning STI epidemic. Our efforts should seek to advance three basic strategies: increasing STI testing, diagnosis, and treatment; increasing the use of condoms; and promoting scientific innovation. Here, we propose measures that government and health departments, health care organizations (HCOs) and medical providers, and members of affected communities can take to confront the rise in STIs (Table 1). These measures are designed to reiterate or complement actions steps proposed by the CDC and advocated in prior publications [92, 93••].

The CDC, local health departments, and other government agencies need to develop and promote clear guidelines advocating more frequent and complete STI screening among MSM and transgender persons, and fund the implementation of those guidelines. Higher risk MSM and transgender persons, including most persons on PrEP, should be screened for STIs quarterly, including HIV (if not already diagnosed with HIV). STI testing should include syphilis serological testing and testing for gonorrhea and chlamydial infection at all exposed anatomical sites. Current CDC guidelines do not clearly define high risk and suggest 3–6 month STI testing. Guidelines from Washington State, the UK and Australia are more specific and should either be adopted by medical providers and HCOs or serve as a starting point for local guidelines (Table 2) [94••, 95]. To assure that such guidelines can be implemented, elected officials and agencies with authority over insurance regulations should ensure that recommended STI testing is covered without insurance co-pays or deductibles.

We also need to change our healthcare system to better promote the medical care of gender and sexual minorities, including changes in the operation of both public and private HCOs and STD and sexual health clinics. We need these clinics more than ever if we are to succeed in controlling the STI epidemic and expand access to PrEP. However, there is room for improvement. Federal, state, and local authorities should allocate funds to increase the number of categorical sexual health clinics, improve the care they provide, align their work with public health objectives, and reorganize them to provide low barrier, rapid care. New York City has taken the lead in this area, investing $13 million annually to expand and improve their sexual health clinics. STD clinics in several other major metropolitan cities now also provide PrEP [59, 96], and many more plan to initiate such programs. Internationally, the Dean Street Express Clinic in London, England [97] is a model low barrier sexual health clinic. Patients receive rapid, walk-in PrEP care, STI testing and treatment. Using mobile technology and touchscreens, patients reserve time slots, check-in, and submit self-collected swabs for testing with results sent via text message. The clinic diagnosed approximately one-third of all cases of HIV in London MSM in 2017 [98], and an evaluation of the clinics found that the clinic averted STIs and reduced health care system costs [99].

Large HCOs also need to change. At present, gender and sexual minorities are typically invisible within the health care system. We cannot systematically implement guidelines promoting PrEP and HIV/STI testing to a population we cannot identify. HCOs need to consistently ask patients about their birth, current gender, gender of their sex partners and record information in searchable fields within electronic medical records. These data can be used to prompt clinicians to perform guideline recommended tests, offer patients PrEP, and monitor HCO care improvements. Re-organizing health care should also embrace the idea of low barrier care, allowing patients to test for HIV/STIs without seeing a medical provider or on a walk-in basis [100, 101]. The BREE collaborative in Washington State and the Fenway Institute in Boston have developed guidelines for improving aspects of the medical care of sexual and gender minorities [102, 103] which can help to educate and train health care professionals and guide HCOs as they alter the organization of care.

Our definition of the health care system needs a different model, one that embraces a wider spectrum of partners and sources of care. This includes working with pharmacies to expand access to PrEP and HIV/STI testing [104], patient navigation to facilitate more frequent STI testing and linkage and retention in PrEP [105], integration of PrEP linkage services into STD partner services [106–108], and perhaps the use of online services to increase STI testing with home delivery of STI testing kits.

Best practice clinical interventions should be widely implemented to increase STI testing. Medical providers should have access to nucleic acid amplification tests to perform extragenital testing for gonorrhea and chlamydial infection. Ideally, this would include use of self-collected swabs specimens, which have been used to expand STI testing while limiting impact on clinic flow and productivity [100, 101, 109]. Providers caring for MSM and transgender patients with HIV infection who are sexually active and not in monogamous relationships should routinely order syphilis serology with each blood draw. This has increased the diagnoses of asymptomatic syphilis infection among patients in Australia [110] and may help diminish syphilis transmission [111]. All sexual

Table 1 Measures that can be taken by government and health departments, medical providers, and health care organizations and the community to combat the increasing rates of STIs in MSM and transgender/nonbinary (TG/NB) population

	Government/Health Departments	Medical Providers and Health Care Organizations	Community
Increase STI screening frequency and completeness	1. Guidelines • Clear guidelines • Quarterly STI testing • Extragenital GC/CT testing in higher risk MSM and transgender patients* 2. Sexual health/STD clinics • Expand clinics • Improve appeal to MSM and transgender individuals • Facilitate rapid testing • Promote PrEP use* 3. Health insurance • Coverage of quarterly HIV/STI testing • Removal of co-pays or deductibles • Coverage of HIV/STI testing visits managed by nonlicensed providers (e.g. medical assistants and health educators)* 4. Outreach • Integrate STI screening into PrEP navigation*	1. Identify gender or sexual minority patients • Routinely ask patients about sex at birth, current sex, gender of sex partners • Record in searchable electronic medical records (EMR) data fields* 2. HIV/STI screening guidelines • Promote guideline adherence through EMR-based interventions, text message reminders 3. Low barrier models of STI care • Allow self STI testing without appointments or evaluation by medical providers* 4. Routine syphilis testing • Test HIV+ MSM and transgender patients for syphilis with each blood draw 5. Self-obtained specimen collection • Self-obtained specimens need lab validation and promotion in clinical settings* 6. PrEP follow-up • Simplify follow-up procedures that integrate quarterly STI testing*	1. Advocacy • Increase simplicity and accessibility of frequent HIV/STI testing 2. Community promotion of frequent HIV/STI testing 3. PrEP • Integrate STI screening into PrEP navigation* 4. Community driven STI care • Expand community HIV/STI testing*
	• Expand options to access care: Increase HIV/STI testing in outreach settings and nontraditional sources of care, such as pharmacies • Technology: Expand technology use to improve communication, provide patients with test results, remind patients and clients to seek HIV/STI testing*		
Increase Condom Use	• Access: Expand access to free condoms and evaluate the impact of expanded condom distribution and promotion. • Promotion: Clinicians, health departments and community-based organizations should discuss condoms with patients and clients, emphasizing that most MSM use condoms at least some of the time, and that increasing one's use of condoms can have prevention benefit.		
Improve syphilis care to minimize the morbidity associated with STIs	• Identify complicated cases: Integrate questions on ocular, oto- and neurosyphilis into clinical evaluations and partner services outreach investigations • Provide and promote prompt evaluations and treatment: Develop systems to ensure access to lumbar puncture, specialty evaluation, and intravenous therapy • Education: Promote community awareness of STI symptoms and complications*		
Integrate PrEP and STI services*	• Public Health Clinics: Use of partner services to integrate STI services with PrEP initiation and navigation within STI clinics • Community Settings: Promotion of STI testing within community PrEP programs, increase the use of case management or navigators to help individuals access both PrEP and STI services at no cost, education of health care providers to improve sexual health care. • Patient centric care: Use of technology, mobile applications on smartphones, self-obtained specimen collection, walk-in testing, low wait times		
Education*	• Providers: Increase awareness of guidelines, online curriculum and other resources for providers to learn about PrEP, STI care and care for minority populations • Patients: Expand education in the community of increasing STI rates, prevention, complications and resources for care		

*Interventions that are also key to expanding PrEP access and retention

Table 2 Comparison of screening guidelines for STI testing for MSM and transgender/nonbinary (TG/NB) persons from Washington State, USA, UK, and Australia

Population	Washington State, US	United Kingdom	Australia
Men who have sex with men (low risk)	At least annual HIV and STI screening on all sexually active MSM and TG/NB persons who have sex with men: - Serological testing for syphilis (i.e. RPR or other syphilis screening test) - Rectal nucleic acid amplification testing (NAAT) or culture for gonorrhea and chlamydial infection (MSM and TG/NB persons who report receptive anal sex only) - Pharyngeal NAAT or culture for gonorrhea - Urine testing for gonorrhea and chlamydial infection - HIV using a 4th generation serological test (if patient is not previously known to be HIV infected)	Annual STI testing including HIV testing should be recommended to all sexually active MSM (other than those with one long-term mutually exclusive partner^)	All of the STI tests listed in the table below should be offered to all MSM at least once a year: - Gonorrhea: ano-rectal swab and pharyngeal swab, urethral/urine testing is not recommended in asymptomatic men - Chlamydia: first pass urine, ano-rectal swab and pharyngeal swab - Syphilis - HIV
Men who have sex with men (high risk)	Testing every 3 months in MSM and TG/NP persons who have sex with men with any of the following risks: - Diagnosis of a bacterial STI in the prior year (gonorrhea, chlamydial infection or early syphilis) - Methamphetamine or popper (amyl nitrite) use in the prior year[#] - ≥10 sex partners (anal or oral) in the prior year - Condomless anal intercourse with a partner of unknown or discordant HIV status in the prior year - Persons taking HIV pre-exposure prophylaxis (PrEP)	Testing every 3 months in men with any of the following risk: - Diagnosis of syphilis, gonorrhea or rectal or urethral chlamydial infection - Drug use (methamphetamine, inhaled nitrites, GBL, ketamine, other new psychoactive substances) during sex in the last six months - >10 sexual partners in the last 12 months - Unprotected anal intercourse with partner(s) of unknown or serodiscordant HIV status in the last 12 months Multiple or anonymous partners since last test - Any unprotected sexual contact (oral, genital or anal) with a new partner since last tested	Testing up to four times a year in MSM with any of the following risks: - Any unprotected anal sex - More than 10 sexual partners in six months - Participation in group sex - Use recreational drugs during sex HIV-positive MSM: - syphilis testing at each occasion of CD4/VL monitoring - chlamydia/gonorrhea testing should be considered at each occasion of CD4/VL monitoring.

[*] TG/NB: Transgender and Non-Binary

^The definition of long-term exclusive partner used is for more than two years, but there is no evidence on which to derive a threshold for reduced risk

[#] Cocaine use not prevalent in WA state but might be a risk factor for STIs in areas of high prevalence

contacts of persons diagnosed with an STI should be treated to prevent ongoing transmission and, in the case of syphilis, prevent the clinical progression of incubating, seronegative infections. Furthermore, in accordance with CDC guidelines, all persons with a STI should be re-tested 12 weeks following their initial treatment [83]. SMS texting reminders increase STI retesting rates and clinicians and HCOs should offer these to patients whenever possible [112]. At least in heterosexuals, the combination of home-testing with SMS reminders is better still [113], and at least one clinic in the UK is now routinely offering MSM the option of home testing using fingerstick blood specimens for HIV and syphilis [114]. When SMS reminders are unavailable, clinicians should schedule retesting in advance and ask patients to use reminder notifications on cellphone calendars.

We need to re-invigorate our efforts to promote condom use in all populations, including MSM. Most MSM use condoms. For example, among MSM seen in our STD clinic in King County, WA in 2016, less than 5% reported never using condoms, though fewer than 20% used them all of the time. The options to use condoms are not all or none. Clinicians, public health officials, and persons working with populations at high risk for HIV and STIs should increase their emphasis on condom use, presenting it as an option patients may want to use selectively but which they could also use more frequently. Many cities promote condom use through media campaigns, condom distribution programs outreach and online resources to help patients locate and access free condoms [115–117]. Such programs should be expanded but also better evaluated to assess whether they actually affect condom use at the population level.

While the measures described above can play an important role in combating the current epidemic, perhaps more than anything, we need scientific innovation. Several potential interventions and priority areas stand out. Studies of doxycycline STI pre- and post-exposure prophylaxis suggest that the intervention decreases rates of chlamydia and syphilis in high-risk MSM [118, 119], though concerns related to long-term safety and promotion of antimicrobial resistance require further investigation. More sensitive and rapid diagnostic tests for bacterial STIs are needed. Syphilis testing relies on serological tests that are insensitive in early infection, require blood draws and have a relatively long turnaround time. Ideally, we would have sensitive rapid tests that combine initial and confirmatory testing and can be integrated into home or outreach testing. Rapid point of care tests for syphilis exist or are in development, and further research into this field and widespread availability of these assays are needed for the complex diagnosis of this disease [120, 121]. Effective STI vaccines remain a priority. A recent case control study found that persons who received a Group B outer membrane vesicle meningococcal vaccine were less likely to be diagnosed with gonorrhea [122]. Additional data on this vaccine, including information on correlates of immunity is required. New STI treatments, including therapies for drug-resistant *N. gonorrhoeae* and complicated syphilis are needed. Finally, in order to capitalize on both technological advances and advances in health care and prevention delivery, we need implementation science research, broadly defining this term to include studies of population-level uptake and outcomes.

Conclusion

Countries around the world have made remarkable progress in confronting the HIV epidemic, including the epidemic among MSM. However, partially as a result of that success, we now face a global epidemic of STIs among MSM. That epidemic is associated with significant morbidity, contributes to ongoing HIV transmission and, if left unchecked, threatens to expand to other segments of the population. PrEP did not cause the epidemic of STIs among MSM. But it has the potential to make the epidemic worse. That conclusion should not dampen our commitment to ensuring that people at high-risk for HIV acquisition receive PrEP. As we continue to promote PrEP and expand its availability, we need a parallel effort to confront STIs, an effort that includes strengthening the public health STI clinical infrastructure, broad changes in the organization of health care to improve the care of gender and sexual minorities, deployment of defined best clinical practices, and scientific innovation. If these efforts are done correctly, our seemingly uncoupled epidemics of HIV and STIs can be confronted by a coordinated and synergistic clinical and public health response.

Funding Information Research reported in this publication was supported by NIAID, NCI, NIMH, NIDA, NICHD, NHLBI, NIA, NIGMS, and NIDDK of the National Institutes of Health under award number AI027757.

Compliance with Ethical Standards

Conflicts of Interest and Source of Funding MRG has research support from Hologic and GSK. Other authors report no conflict of interest.

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

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- • Of importance
- •• Of major importance

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