Addressing the Sexually Transmitted Infection and HIV Syndemic

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The HIV and sexually transmitted infection (STI) epidemics, which have always been and will always be intertwined, are at an inflection point. Two scientific advancements over the last decade have substantially influenced the sexual health of people living with HIV and individuals at risk for HIV.

First, Undetectable equals Untransmittable (U = U) is an important public health campaign that supports the findings that individuals with a suppressed viral load do not transmit HIV despite condomless sex.[1] U = U builds on the findings of several large trials that have demonstrated the remarkable efficacy of HIV treatment as prevention.[1,2] U = U, in addition to promoting the power of HIV therapy to halt transmission, has the potential to decrease stigma and improve retention in care.[3] Second, pre-exposure prophylaxis (PrEP), with adequate adherence, provides high protection from HIV for persons at risk, even without condom use, providing the potential to significantly reduce the population-level burden of HIV.[4] Widespread and equitable provision of antiretroviral therapy, as well as PrEP, will be critical components of addressing the HIV epidemic.[5]

There are some concerns that these biomedical prevention strategies, especially PrEP for men who have sex with men (MSM), will lead to changes in sexual behavior, such as decreased condom use and a greater number of partners.[6] These changes in sexual behavior could exacerbate the STI epidemic. PrEP care guidelines worldwide recommend frequent testing for STIs, typically at quarterly intervals. Distinguishing an increased incidence of STIs due to changes in behavior vs ascertainment bias from an increased rate of STI testing among persons taking PrEP requires a unique study setting.

In this issue of *JAMA,* Traeger and colleagues[7] describe changes in bacterial STI incidence that occurred among 2981 participants who enrolled in the PrEP Expanded (PrEPX) Study, a PrEP demonstration project with the goal of examining the effects of broad PrEP rollout on population-level HIV incidence in the state of Victoria, Australia. The study focused on a subpopulation of participants in PrEPX (n = 1378 [32%]) who had STI testing data available prior to enrollment in the trial. The availability of preenrollment testing data is important because PrEPX participants, as part of comprehensive PrEP care in the demonstration project, were offered quarterly STI testing. This led most participants to receive more frequent STI testing during the demonstration project than prior to their enrollment. Because the majority of STIs are asymptomatic, increased testing will diagnose more asymptomatic STIs that would have otherwise gone undetected by patients and public health systems.

In the subpopulation in this study (n = 1378), the unadjusted incidence of any STI increased significantly (incidence rate ratio, 1.41 [95% CI, 1.29-1.56]) during PrEPX, from 69.5 per 100 person-years in the preenrollment period to 98.4 per 100 person-years during follow-up. However, when the authors adjusted for increased testing frequency among participants, STI incidence attenuated to a 12% increase (adjusted incidence rate ratio, 1.12 [95% CI, 1.02-1.23]). This finding led the authors to conclude that increased detection of asymptomatic infections may have accounted for much of the observed increase in STI incidence among PrEPX participants, but not all. Most STIs diagnosed during follow-up occurred among a small subgroup of participants who experienced high rates of reinfection, ie, 736 individuals (25% of the entire study population) accounted for 2237 (76% of all STIs during follow-up) STIs; such individuals represent a clear focus for STI prevention efforts.[8]

The results of the study by Traeger et al[7] should not be interpreted in isolation. Initial open-label studies did not report an increase in STIs among PrEP users, although more recent data from demonstration projects and observational cohorts have been mixed.[9,10] Condom use among MSM, both those living with HIV and without HIV, began to decline even prior to the availability of PrEP, likely related to knowledge of the high efficacy of treatment as prevention and the fact that HIV infection, in the era of effective antiretroviral therapy, is no longer a "death sentence."[10] Indeed, increases in STI incidence began prior to PrEP rollout.[10]

Even though many individuals do not change their condom use behavior after starting PrEP, there is evidence that the concerns of some clinicians about behavioral change may lead them not to offer PrEP to MSM, particularly black MSM,[11] or reserve PrEP for heterosexual serodifferent couples attempting to conceive.[11,12] It is likely that some individuals with knowledge of the high efficacy of PrEP in preventing HIV infection will change their behavior and that higher-risk behavior is contributing to the current STI epidemic.[10] However, concerns about behavioral change after starting PrEP should not decrease the willingness of clinicians to offer PrEP. These concerns may contribute to lack of progress in reducing HIV infections among MSM in the United States, despite it being the first country to approve PrEP.[13] To continue to achieve the population-level influence on HIV incidence through PrEP that appears imminently achievable,[4] PrEP will need to be available for and used by the populations that can benefit the most, including those having condomless sex.

Although knowledge of the efficacy of PrEP and subsequent changes in sexual behavior may increase STI incidence in the years following approval of a new HIV prevention strategy, increased testing for STIs in the context of PrEP could eventually help control the STI epidemic. Timely diagnosis and treatment of STIs reduces the duration of infection and transmissibility. Partner notification and testing can further prevent forward transmission of STIs among sexual networks. A modeling study suggested that even if there was an increased rate of condomless sex among MSM using PrEP, the benefits of increased detection and early treatment of STIs could still eventually decrease the overall STI burden.[14]

While STI screening has been historically underutilized, potentially due to both out-of-pocket cost and lack of coverage under some health plans for rectal and pharyngeal nucleic acid amplification testing,[15,16] the anticipated addition of PrEP to the evidence-based preventive strategies recommended by the US Preventive Services Task Force[17] could help pave the way for improved insurance coverage of STI screening in the United States. Although condom use remains an important tool to prevent STIs in the general population, increases in STI incidence in the study by Traeger et al[7] did not differ when comparing those using condoms and those who did not. This finding could be secondary to the overall low levels of consistent condom use across the cohort, the frequency of sexual practices (such as oro-penile and oro-anal sex) for which condom use is not consistent, or the finding that condoms may be somewhat less effective among MSM even with consistent use.[18] Therefore, the use of complementary prevention strategies must be continued. STI home testing, which can be combined with home PrEP delivery, can reach populations that do not have STI testing available or experience stigma in accessing sexual health services.[19] Panel management, a population-based approach to preventive health care using registries and dedicated medical home team members (including nurses and patient navigators), can be used to track STI testing and ensure completion among PrEP users.[16]

Several novel STI prevention tools are on the horizon. For instance, in a preliminary randomized study involving 232 participants, doxycycline postexposure prophylaxis has shown promise in preventing chlamydia and syphilis infection in those (n = 116) who received a single dose of doxycycline, 200 mg, 24 hours after sex.[20] Doxycycline had limited effect on gonorrhea incidence, likely due to preexisting drug resistance in *Neisseria gonorrhoeae*. Given the tendency for the majority of STIs to be concentrated within specific sexual networks,[8] the benefits of doxycycline postexposure prophylaxis in breaking forward transmission may outweigh its risks, particularly among individuals who have previously experienced STIs. A large randomized clinical trial is currently being developed to test the ability of doxycycline postexposure prophylaxis to reduce population-level STI incidence among MSM in Seattle and San Francisco, as well as examine its potential effect on antibiotic resistance. Furthermore, novel antibiotics for gonorrhea are being developed.[21] In addition, a recent case-control study demonstrated a decreased odds of gonorrhea infection following receipt of the Neisseria meningitis group B vaccine,[22] although additional research examining this association is needed.

Offering PrEP to patients and preventing STIs should not be viewed as a trade-off. The HIV and STI epidemics comprise a syndemic that is now addressable. The tools are now available to end the HIV epidemic, including treatment as prevention and PrEP. Increased PrEP prescribing should lead to more frequent STI screening, which should eventually lead to a reduction in overall STI prevalence. The onus is now on health care systems and clinicians to promote and implement the comprehensive sexual health services that are needed to achieve the elimination of HIV transmissions and the end of the current STI epidemic.

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