

Doxycycline for Sexually Transmitted Infection Prevention: Evolving Evidence and Implementation Perspectives

Connie Celum, MD* and Anne F. Luetkemeyer, MD†

The Centers for Disease Control and Prevention recently reported a distressing rise in sexually transmitted infection (STI) incidence rates, which have increased for the sixth consecutive year with 2.5 million Americans having a diagnosis of gonorrhea, chlamydia, or syphilis, based on the 2019 data. The increase in STIs are not only concentrated among men who have sex with men (MSM) but are also evident in other populations, with increased rates of early syphilis in heterosexual women and congenital syphilis.

These worrisome trends indicate that our current approaches for STI control are not enough, and that we need to evaluate and identify new effective approaches, including antibiotic prophylaxis for STI prevention.¹ A study of doxycycline postexposure prophylaxis (PEP) among human immunodeficiency virus (HIV)-negative MSM taking event-driven HIV preexposure prophylaxis (PrEP) in the Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study in France found a 48% reduction in incident chlamydia, gonorrhea, and syphilis among MSM.² Notably, the majority of IPERGAY participants were White, well-educated, and were already taking event-driven HIV PrEP, so adherence to doxycycline PEP after condomless sex may have been higher than in other populations not accustomed to timing their pill taking for HIV or STI prevention after sex.

Persons with STIs, health care providers, regulatory agencies, and normative bodies await the results of ongoing studies, which are evaluating the effectiveness of doxycycline prophylaxis, safety, and impact on bacterial resistance.³ These studies are being conducted in the United States, Canada, Kenya, France, and Australia and should provide a more complete picture of the relative benefits and risks of doxycycline prophylaxis for bacterial STI prevention in different populations. Critical questions, which require additional data, include the relative effectiveness of doxycycline PEP after condomless sex versus doxycycline taken daily for STI PrEP, acceptability, and utility among different groups at risk for STIs, including cisgender and transgender women, persons living with HIV and more heterogeneous populations of MSM, as well as any impact on antimicrobial resistance. Additional data are also needed on the efficacy of doxycycline prophylaxis against gonorrhea, given the growing challenge of antimicrobial resistance in gonorrhea; efficacy may differ based on the prevalence of tetracycline resistance in gonorrhea, which is 20% to 30% in the United States compared with more than 50% in France, where the IPERGAY study was conducted. In addition, the effect of doxycycline prophylaxis on selecting tetracycline resistance in STIs, in potential pathogens, such as methicillin-resistant *Staphylococcus aureus*, and in the gut microflora, needs to be understood.

While awaiting the results of these studies, Park and colleagues⁴ conducted an online survey of attitudes of MSM, including 33% taking HIV PrEP and 16% living with HIV, and of health care providers in southern California regarding doxycycline prophylaxis for STI prevention, which is published in this issue of STI. In 212 MSM surveyed, approximately two thirds would take doxycycline prophylaxis for STIs if their provider recommended it, with higher acceptability among MSM who had recently received a STI diagnosis and those were currently taking PrEP. This early indication of high acceptability is encouraging as doxycycline STI prophylaxis will be an intervention targeted to persons most at risk of STIs and not for the general population. Similarly high acceptability has been found in other studies, including from a survey of a diverse population using an MSM social networking app in 6 US cities, in which 84% of 1301 respondents expressed interest in trying doxycycline to prevent STIs.⁵ A majority of MSM in STD clinics in Toronto and Vancouver, Canada reported willingness to use doxycycline

From the *Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA; and †Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General, University of California San Francisco, San Francisco, CA

Conflict of Interest and Sources of Funding: None declared.

Correspondence: Connie Celum, MD, University of Washington, International Clinical Research Center, Harborview Medical Center, Box 359927, 325, Ninth Avenue, Seattle, WA 98104. E-mail: ccelum@uw.edu.

Received for publication June 4, 2021, and accepted June 8, 2021.

DOI: 10.1097/OLQ.0000000000001501

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Sexually Transmitted Diseases Association. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

for syphilis prevention among MSM in a 2018 survey with higher willingness among men who perceived themselves at being at risk of syphilis and previous or current HIV PrEP use.⁶

The sample of 76 providers indicated that 44% would be willing to prescribe doxycycline for STI prevention, increasing to 90% if recommended by the CDC. Both community members and providers indicated that their greatest concern was the risk of drug resistance. This finding is similar to the early days of evaluation of emtricitabine/tenofovir as PrEP to prevent HIV acquisition in which drug resistance was one of the most commonly cited concerns, but selection of resistance to emtricitabine and tenofovir with PrEP use subsequently has been shown to be rare. If doxycycline prophylaxis for STI prevention is found to be effective, extended follow-up among users may be needed to detect uncommon or longer-term effects on the microbiome or resistome.

While the studies of doxycycline PEP and PrEP are ongoing, surveys from England⁷ and the Netherlands⁸ indicate that a minority of MSM on PrEP or attending sexual health services has taken doxycycline or other antibiotics as PEP and that doxycycline PEP has been included in HIV PrEP services in some US settings.⁹ Providers should be aware that some patients may already be taking doxycycline for STI prevention in advance of guidelines, obtained either from providers or outside regular medical care. The goal of the ongoing studies is to provide sufficient data to inform guidelines and if doxycycline prophylaxis is shown to be safe and effective for STI prevention to determine how best to deliver this to the subset of persons at greatest risk for bacterial STIs. As providers and public health officials interested in addressing the ongoing STI epidemic, we should be ready to respond to data as they emerge about much needed, innovative STI prevention strategies.

REFERENCES

1. Eisinger RW, Erbedding E, Fauci AS. Refocusing research on sexually transmitted infections. *J Infect Dis* 2020; 222:1432–1434.
2. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis* 2018; 18:308–317.
3. Grant JS, Stafylis C, Celum C, et al. Doxycycline prophylaxis for bacterial sexually transmitted infections. *Clin Infect Dis* 2020; 70:1247–1253.
4. Park JJ, Stafylis C, Pearce DD, et al. Interest, concerns, and attitudes among men who have sex with men and health care providers toward prophylactic use of doxycycline against *Chlamydia trachomatis* infections and syphilis. *Sex Transm Dis* 2021; 48:615–619.
5. Spinelli MA, Scott HM, Vittinghoff E, et al. High interest in doxycycline for sexually transmitted infection postexposure prophylaxis in a multicity survey of men who have sex with men using a social networking application. *Sex Transm Dis* 2019; 46:e32–e34.
6. Fusca L, Hull M, Ross P, et al. High interest in syphilis pre-exposure and post-exposure prophylaxis among gay, bisexual and other men who have sex with men in Vancouver and Toronto. *Sex Transm Dis* 2020; 47:224–231.
7. Carveth-Johnson T, Stingone C, Nwokolo N, et al. Doxycycline use in MSM taking PrEP. *Lancet HIV* 2018; 5:e482.
8. Evers YJ, van Liere GAFS, Dukers-Muijters NHTM, et al. Use of doxycycline and other antibiotics to prevent STIs among men who have sex with men visiting sexual health clinics in the Netherlands. *Sex Transm Infect* 2020; 96:550–551.
9. Joseph S. Initiation of doxycycline pre-exposure prophylaxis in patients attending an HIV PrEP clinic—Philadelphia, 2019. STD Prevention Conference. Virtual. Available at: https://s6.goeshow.com/ncsd/prevention/2020/week_2_schedule.cfm?session_key=A70A6700-A0F0-B8AC-8A0D-58558450E557&session_date=Monday,%20Sep%2021,%202020. Accessed September 14–24, 2020.