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Doxycycline Postexposure Prophylaxis and Sexually Transmitted Infections

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Bacterial and protozoal sexually transmitted infections (STIs) cause more than 1 million treatable STIs daily worldwide.[1] Bacterial STIs can cause significant morbidity. Syphilis can cause meningitis, deafness, blindness, and congenital sequelae, including stillbirth and neonatal death. Chlamydia or gonorrheal infection can cause infertility. Although most bacterial STIs are treatable with accessible and inexpensive antibiotics, challenges to effective STI prevention remain.[2,3] Asymptomatic infections are common and may be more prevalent among individuals with low health literacy and among those who have difficulty accessing care and/or avoid medical treatment because of anticipated stigma. STI control programs have traditionally used contact tracing to identify partners of newly diagnosed individuals, but this approach is challenging when individuals meet anonymous partners and public health programs have limited resources.[4]

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Although postexposure antiretroviral medications to prevent HIV acquisition have been used for several decades, antibiotics for STI prevention have not been widely prescribed. Doxycycline is an inexpensive, broad-spectrum tetracycline that is rapidly absorbed after ingestion and is effective against multiple common bacterial STIs.[5] A pilot randomized clinical trial of 30 men living with HIV who had sex with men found that daily oral use of 100 mg of doxycycline reduced the incidence of bacterial STI over 48 weeks compared with incentive payments for remaining without STIs (STIs diagnosed at 11.3% of visits in the doxycycline group and 30.6% in the incentive group; odds ratio, 0.27 [95% CI, 0.09-0.83]), but there was no difference for any outcome at 36 weeks of follow-up when the intervention was stopped.[6] A 7-day course of doxycycline (100-mg tablets twice per day) is recommended by the Centers for Disease Control and Prevention for preventing chlamydia in people who have experienced sexual assault and for whom pregnancy has been ruled out.[2]

Recent clinical trials have evaluated a 200-mg single dose of doxycycline as postexposure prophylaxis (doxyPEP) in populations with increased rates of STIs (**Table**). In a randomized open-label clinical trial of 232 French men who have sex with men (MSM) who used antiretroviral preexposure prophylaxis (PrEP) after sexual contacts, a single 200-mg oral tablet of doxycycline within 24 hours after condomless sex significantly reduced the primary outcome of a first-incident STI compared with no doxycycline (37.7 vs 69.7 per 100 person-years). When individual infections were examined separately, significant reductions were observed for chlamydia (8.7 vs 28.6 per 100 person-years) and syphilis (3.7 vs 12.9 per 100 person-years), but not gonorrhea (28.7 vs 34.5 per 100 person-years).[7] An open-label US trial of sexually active MSM and transgender women who were living with HIV or using PrEP enrolled 501 participants. Among those using PrEP, 107 were randomized to receive only standard care and 220 were randomized to receive a 200-mg oral dose of doxycycline after condomless sex and had a significantly decreased incidence of the primary outcome of at least 1 STI, measured

Table. Randomized Clinical Trials of Doxycycline Postexposure Prophylaxis (doxyPEP) for Bacterial Sexually Transmitted Infections (STIs)

Source	Participants and setting	Intervention	Study design	Main findings
Molina et al (2018)[7]	MSM using HIV PrEP (n = 232) in France	200 mg of doxycycline within 24 h of sex and no later than 72 h after	Open-label randomized (1:1) clinical trial. Control group received standard care. Participants followed up for 10 mo (median, 8.7 mo).	Incidence of first episode of STI per 100 person-years in the doxyPEP vs control group: STIs overall (primary outcome), 37.7 vs 69.7 (HR, 0.53 [95% CI, 0.33-0.85]) Syphilis, 3.7 vs 12.9 (HR, 0.27 [95% CI, 0.07-0.98]) Chlamydia, 8.7 vs 28.6 (HR, 0.30 [95% CI, 0.13-0.70]) Gonorrhea, 28.7 vs 34.5 (HR, 0.83 [95% CI, 0.47-1.47])
Luetkemeyer et al (2023)[8]	MSM and transgender women using HIV PrEP (n = 327) or living with HIV (n = 174) in the US	200 mg of doxycycline within 72 h of condomless sex	Open-label randomized (2:1) clinical trial. Control group received standard care. Participants followed up for 12 mo (median, 8.9 mo).	Reduction in incidence of each STI in both PrEP users and people with HIV, although reductions in syphilis incidence did not reach statistical significance. Quarterly visits with test result positive for STI in doxyPEP group vs control group: People using PrEP: Overall (primary outcome), 10.7% vs 31.9% (RR, 0.34 [95% CI, 0.24-0.46]) Syphilis, 0.4% vs 2.7% (RR, 0.13 [95% CI, 0.03-0.59]) Chlamydia, 1.4% vs 12.1% (RR, 0.12 [95% CI, 0.05-0.25]) Gonorrhea, 9.1% vs 20.2% (RR, 0.45 [95% CI 0.32-0.65]) People with HIV: Overall, 11.8% vs 30.5% (RR, 0.38 [95% CI, 0.24-0.60]) Syphilis, 0.7% vs 2.3% (RR, 0.23 [95% CI, 0.04-1.29]) Chlamydia, 3.9% vs 14.8% (RR, 0.26 [95% CI, 0.12-0.57]) Gonorrhea, 8.9% vs 20.3% (RR, 0.43 [95% CI, 0.26-0.71])

Abbreviations: HR, hazard ratio; MSM, men who have sex with men; RR, relative risk.

quarterly (10.7% vs 31.9%).[8] Decreases also occurred for the outcomes of syphilis (0.4% vs 2.7%), chlamydia (1.4% vs 12.1%), and gonorrhea (9.1% vs 20.2%). Among 174 people with HIV randomized to receive doxycycline (n = 119) or standard care (n = 55), 200 mg of doxyPEP significantly reduced the primary outcome of at least 1 STI compared with standard care (11.8% vs 30.5%).[8] Significant reductions were observed for chlamydia (3.9% vs 14.8%) and gonorrhea (8.9% vs 20.3%), but not syphilis (0.7% vs 2.3%). In this clinical trial of doxyPEP, self-reported adherence exceeded 85%, with 71.3% of participants reporting never missing a dose.[8]

Doxycycline is generally safe and well tolerated.[9] In the US trial, the most common symptoms attributable to doxyPEP were diarrhea (reported at 2.8% of quarterly visits), sunburn (2.3%), nausea (1.5%), and skin exanthem (0.5%). Less common adverse effects were vomiting, abdominal pain, headache, visual changes, and difficulty swallowing (all ≤0.3%).[7] Five severe adverse events (diarrhea [n = 3] and migraine [n = 2]) were possibly or probably related to doxycycline. People using doxyPEP should be advised to avoid sun exposure. If this cannot be avoided, patients should be advised to wear sunscreen, a hat, sunglasses, and sun-protective clothing. Doxycycline is associated with teratogenicity and should be avoided in people who are pregnant or trying to become pregnant.[5]

Chronic episodic antibiotic use raises concerns about selection for multidrug-resistant gonococci, methicillin-resistant *Staphylococcus aureus,* and *Mycoplasma genitalium* and possible deleterious effects on the host microbiome (eg, *Clostridioides difficile* infection).[10] Although these problems did not occur in the current trials, this requires further study, along with clarifying the effect of doxyPEP on the natural history and serological expression of syphilis and the effect of chronic doxycycline use on body weight and other metabolic parameters related to changes in the gut microbiome.

In the US clinical trial of doxyPEP,[8] individuals receiving doxycycline were more likely to become infected with tetracycline-resistant *S aureus* (5% in the doxycycline group vs 4% in the control group) and had higher rates of tetracycline-resistant gonococcal isolates (38% in the doxycycline group vs 12% in the control group), but the absolute number of gonococcal infections was significantly lower in the doxycycline group than the control. Clinical trials of gonococcal vaccines are underway. If the vaccines are effective, they could reduce the spread of multidrug-resistant organisms. Antimicrobial drug resistance surveillance by public health authorities is necessary to determine whether doxyPEP use increases the risk for more resistant microbes.

Several local and state health departments have recently recommended offering doxyPEP to MSM or transgender women with at least 1 bacterial STI in the past 12 months. The Centers for Disease Control and Prevention currently suggests that clinicians engage in shared decision-making with patients who may benefit from doxyPEP. Formal guidelines are being developed. Uncertainties remain about the efficacy of doxyPEP in some populations, particularly cisgender women. Although indiscriminate use of antibiotics should be avoided, offering doxyPEP to MSM and transgender women at increased risk for bacterial STIs should be considered because of the growing bacterial STI epidemic and the efficacy of doxyPEP.

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REFERENCES

1. World Health Organization (WHO). Sexually transmitted infections (STIs). Accessed February 23, 2023. https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)

2. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Disease Surveillance 2020. Accessed February 9, 2023. https://www.cdc.gov/std/statistics/2020/default.htm

3. Unemo M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: challenges ahead. *Lancet Infect Dis*. 2017;17(8):e235-e279. doi:10.1016/S1473-3099(17)30310-9

4. Leichliter JS, Heyer K, Peterman TA, et al. US Public Sexually Transmitted Disease Clinical Services in an Era of Declining Public Health Funding: 2013-14. *Sex Transm Dis*. 2017;44(8):505-509. doi:10.1097/OLQ.0000000000000629

5. Peyriere H, Makinson A, Marchandin H, Reynes J. Doxycycline in the management of sexually transmitted infections. *J Antimicrob Chemother*. 2018;73(3):553-563.

6. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. 2015;42(2):98-103. doi:10.1097/OLQ.0000000000000216

7. Molina J-M, Charreau I, Chidiac C, et al; ANRS IPERGAY Study Group. 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(3):308-317. doi:10.1016/S1473-3099(17)30725-9

8. Luetkemeyer AF, Donnell D, Dombrowski JC, et al; DoxyPEP Study Team. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med*. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

9. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther*. 2005;27(9):1329-1342. doi:10.1016/j.clinthera.2005.09.005

10. Vanbaelen T, Manoharan-Basil SS, Kenyon C. Doxycycline post exposure prophylaxis could induce cross-resistance to other classes of antimicrobials in neisseria gonorrhoeae: an in-silico analysis. *Sex Transm Dis*. 2023;50(8):490-493. doi:10.1097/OLQ.0000000000001810