Doxycycline Postexposure Prophylaxis for STIs in Women — Uncertain Benefit, Urgent Need

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The global incidence of reportable sexually transmitted infections (STIs), including gonorrhea, chlamydia, and syphilis, remains high and in some populations has relentlessly increased. In the United States in 2021, the incidence of early syphilis among men who have sex with men surpassed any previous record.[1] The human and economic consequences of untreated STIs can be severe. Moreover, concurrent acquisition of human immunodeficiency virus (HIV) infection and another STI continues to occur, especially with a lack of HIV preexposure prophylaxis (PrEP), and the presence of STI increases the risk of HIV acquisition in this context.

What is fueling this increase, and what can be done to address it? The use of HIV PrEP is generally associated with a decline in condom use; for many men who have sex with men, having sex without protective physical barriers enhances sexual pleasure. Although HIV PrEP dramatically reduced the incidence of HIV infection among participants in clinical trials, the incidence of syphilis, gonorrhea, and chlamydia, as detected through regular screening, remained high. For example, in the IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) trial of on-demand HIV PrEP, 20% of the participants acquired chlamydia, 22% acquired gonorrhea, and 10% acquired syphilis during follow-up.[2]

Doxycycline is active against *Chlamydia trachomatis* and *Treponema pallidum*, and some strains of *Neisseria gonorrhoeae* remain susceptible. Thus, randomized, controlled trials of oral doxycycline as postexposure prophylaxis (PEP) in men who have sex with men and in transgender women were designed and implemented soon after the trials of HIV PrEP — to a large extent, with the acknowledgment that highly effective biomedical HIV prevention effectively reduced incentives to change sexual behavior and that alternative approaches were needed.

The Centers for Disease Control and Prevention recently issued draft guidance for the use of doxycycline PEP to prevent the acquisition of chlamydia, gonorrhea, and syphilis in men who have sex with men and in transgender women.[3] On the basis of positive findings from trials, including the open-label extension of the IPERGAY trial (hereafter, IPERGAY substudy),[4] among these groups, several jurisdictions have already issued local guidance endorsing this approach. With no vaccines for these infections on the near horizon, doxycycline PEP has potential to slow the upward trajectory of STI incidence among these groups. Concerns have been well articulated, including the possibility that selection for tetracycline resistance in *N. gonorrhoeae* may influence the prevalence of multidrug-resistant strains and that widespread uptake may deplete available stores of doxycycline.[5-7]

Against this backdrop, Stewart and colleagues report in this issue of the *Journal* the results of a randomized, controlled trial of doxycycline PEP in cisgender Kenyan women.[8] The investigators essentially recapitulated the design of the IPERGAY substudy, enrolling women who were at risk for bacterial STI. The intervention did not reduce the incidence of STI. The authors hypothesized that these results may be explained by the low uptake of doxycycline (as substantiated by measurement of the drug product in hair samples), the high background prevalence of the *tet*(M) resistance plasmid in Kenya, and the low incidence of syphilis.

Although the findings are disappointing, the trial provides a needed opportunity to reconsider how to strategically inform the design and conduct of biomedical intervention trials involving women of reproductive age. In 2012, the Food and Drug Administration approved Truvada (emtricitabine–tenofovir disoproxil fumarate) as HIV PrEP for adults at increased risk for HIV infection. Shortly after, the DISCOVER trial involving cisgender men who have sex with men and transgender women who have sex with men showed that Descovy (emtricitabine–tenofovir alafenamide), a drug with a more favorable safety profile, was noninferior to emtricitabine–tenofovir disoproxil fumarate.[9] To this day, daily oral PrEP with emtricitabine–tenofovir alafenamide is not recommended for cisgender women because no

trial data are available. The dapivirine vaginal ring is effective and acceptable for HIV PrEP,[10] but it is not available in the United States. This situation has informed a perception that studies of STI and HIV interventions in women too often follow a "one size should fit all" approach, yet the biology of transmission and infection have some important differences.

One way forward is to recognize that any biomedical intervention needs to be studied not only to address a high incidence of a specific pathogen but also to address such incidence in the context of the biologic and behavioral characteristics that underlie individual susceptibility. For example, the pharmacodynamics of systemic drug delivery differ in rectal and cervicovaginal tissue and directly affect the adherence–concentration–efficacy relationships at these sites, and the cervicovaginal environment may be more vulnerable to disruptive effects of drug toxicity. Little is known about tissue levels of doxycycline that are required in the cervicovaginal environment to protect against *C. trachomatis*, let alone *T. pallidum*. Moreover, the frequency of reported sex in the trial by Stewart et al. was lower than that observed in the IPERGAY substudy, as reflected in the reports of less frequent use of doxycycline. Do women who are especially vulnerable to bacterial STI want to use doxycycline PEP, and if so, when, at what frequency, and with what type of sex partner? The calculus of invoking STI or HIV prevention with a given sex act may be informed by a person's sexual network, perception of partner risk, and ability to define the timing and terms of how sex occurs.

Where does this leave us as we consider the next steps for chemoprevention against STI — specifically, doxycycline PEP — in cisgender women? Do these latest trial results leave us in yet another situation in which a promising and effective intervention in men who have sex with men "just doesn't work" in women? In the United States, the incidence of congenital syphilis has reached an all-time high,[11] and increased uptake of oral PrEP has not reached enough women, leaving the incidence of HIV among them unchanged. For chemoprophylaxis against STI, we need to do better in working out the science of drug delivery, the motivation and context for product use, and the background antibiotic susceptibility to inform the design of interventional trials. With women bearing the brunt of the long-term consequences of untreated STI, we owe them no less.

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