DoxyPEP 101

Everything you need to know about taking an antibiotic after sex to help prevent sexually transmitted infections.

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A decade after the debut of HIV pre-exposure prophylaxis (PrEP), there's a new way to have safer sex. Doxycycline post-exposure prophylaxis, or doxyPEP, is a morning-after pill that lowers the risk of chlamydia, gonorrhea and syphilis. Studies show that this can be an effective approach for people at high risk for sexually transmitted infections (STIs)—but it's not for everyone.

STI rates have been rising worldwide in recent decades. In the United States, there were more than 2.5 million cases of chlamydia, gonorrhea and syphilis in 2021, according to the Centers for Disease Control and Prevention (CDC). Gay and bisexual men, transgender women, young people and Black people are disproportionately affected. While PrEP is highly effective at preventing HIV, forgoing condoms leaves people prone to bacterial STIs. Although usually not life-threatening, STIs are more than just a nuisance: Left untreated, they can lead to serious long-term complications. Regular screening allows for prompt treatment, but it would be better to prevent STIs in the first place.

Here's how doxyPEP works: A single 200 milligram dose of doxycycline is taken ideally within 24 hours—but no later than 72 hours—after anal, vaginal or oral sex. Doxycycline can be taken on consecutive days if sex is repeated, but no more than one dose in a 24-hour period. It is safe to take doxycycline with PrEP. Because it's an antibiotic, doxycycline doesn't prevent viral STIs, such as human papillomavirus (HPV), mpox or herpes.

In October 2023, the CDC issued the first national doxyPEP guidelines. Even before that, some clinics with a large gay clientele were already rolling it out. Public health officials and advocates are hopeful that this approach might finally make a dent in high and rising STI rates.

"DoxyPEP is moving STI prevention efforts into the 21st century," says Jonathan Mermin, MD, MPH, director of the CDC's National Center for HIV, Viral Hepatitis, STD and TB Prevention. "We need game-changing innovations to turn the STI epidemic around, and this is a major step in the right direction."

What Does the Research Show?

STI prophylaxis is not new. In a small pilot study started in 2011, Jeffrey Klausner, MD, MPH, now at the University of Southern California, and colleagues found that gay and bisexual men who were randomly assigned to receive daily doxycycline prophylaxis were significantly less likely to test positive for chlamydia, gonorrhea or syphilis.

“It’s amazing to see almost 15 years later how an idea can become a reality,” Klausner told POZ. “The CDC guidelines on doxycycline prophylaxis for STIs are testament to the adage ‘Never give up,’ because one day your ideas, through rigorous research and the hard work of many people, can become a reality.”

Other researchers asked whether taking an antibiotic as a morning-after pill, rather than every day, could also be effective. As part of the IPERGAY trial, a French PrEP study, a subgroup of 232 men who have sex with men were randomized to receive a single dose of doxycycline within 24 hours after sex or no STI prophylaxis. In 2017, Jean-Michel Molina, MD, of the University of Paris Cité, and colleagues reported that doxyPEP lowered the risk of chlamydia by 70% and syphilis by 73%, but it did not significantly reduce gonorrhea risk.

Following up on these early findings, the DoxyPEP trial, conducted at public health clinics in San Francisco and Seattle, enrolled more than 500 men who have sex with men and transgender women who’d had an STI during the past year. They were randomly assigned to receive a single dose of doxycycline within 72 hours after sex or standard care, which is regular STI testing and treatment.

At the 2022 International AIDS Conference in Montreal, Annie Luetkemeyer, MD, of the University of California San Francisco, reported that doxycycline reduced STI diagnoses by 62% per quarter for HIV-positive participants and by 66% for people on PrEP. STIs were diagnosed at 11% to 12% of quarterly visits in the doxycycline group versus 31% to 32% in the standard care group. But here, too, the risk reduction was greater for chlamydia (74% in the HIV-positive group and 88% in the PrEP group) and syphilis (77% and 87%, respectively) than for gonorrhea (57% and 55%, respectively).

“Using doxycycline after condomless sex has potential as an effective strategy to substantially reduce sexually transmitted infections in targeted populations with ongoing high rates of STIs,” Luetkemeyer told POZ at the time.

At the 2023 Conference on Retroviruses and Opportunistic Infections (CROI), Molina reported comparable results from the French DoxyVAC study, in which gay and bisexual men on PrEP were randomly assigned to receive doxycycline or standard care and separately randomized to receive a gonorrhea vaccine or not. DoxyPEP reduced the risk of chlamydia, syphilis and gonorrhea by 89%, 79% and 51%, respectively.

But CROI attendees also heard some bad news. A study called dPEP Kenya found that taking

doxycycline after sex did not offer the same protection for young cisgender women. Overall STI incidence was high, with no significant differences between the doxyPEP and standard care groups, reported Jenell Stewart, DO, MPH, of the Hennepin Healthcare Research Institute in Minneapolis.

The reason for these disappointing results is unclear. Although drug concentrations appeared high enough to inhibit bacterial STIs, many of the women reported suboptimal adherence, and less than a third had detectable doxycycline levels at all study visits. This suggests that doxyPEP might still work for women who use it consistently.

DoxyPEP Concerns

In all these studies, doxyPEP was generally safe and well tolerated. But doxycycline can cause side effects—mainly gastrointestinal symptoms, such as nausea, diarrhea and heartburn. Taking the pills with food and at least a half hour before lying down helps reduce these effects. The antibiotic can also cause photosensitivity, so people who use it are advised to avoid direct sunlight and wear sunscreen. Pregnant people should not use doxycycline because it can harm the fetus.

Another doxyPEP concern is that frequent antibiotic use could disrupt the microbiome, the ecosystem of healthy bacteria that normally live in the gut and elsewhere in the body. The new CDC guidance states that this risk will have to be closely monitored going forward.

Perhaps the biggest worry is that widespread use of antibiotics can lead to drug resistance. While analysis is still ongoing, early findings from the DoxyPEP trial are reassuring. “We didn’t see a marked increase in antimicrobial resistance associated with doxyPEP use,” Luetkemeyer told reporters at CROI. “We need larger and longer studies of what happens to common bugs,” but this must be weighed against the benefits of a substantial reduction in STIs.

Another problem is that doxyPEP will likely be less effective in areas where gonorrhea is highly resistant to tetracycline antibiotics. Even if doxyPEP doesn’t drive emergent resistance itself, people using doxycycline could be more likely to acquire resistant strains. In fact, higher local prevalence of resistant gonorrhea may help explain why doxyPEP didn’t work as well in France as it did in the U.S. trial and did not adequately protect women in Kenya.

On the other hand, doxycycline is widely used to treat acne and to prevent malaria and Lyme disease, and this doesn’t seem to have driven resistance. Molina said he does not expect that a small amount of additional use by gay and bisexual men would change that. What’s more, this pales in comparison with overuse of antibiotics in hospitals and the meat industry, Jorge Roman, NP, senior director of clinical services at the San Francisco AIDS Foundation, suggests.

“I think a lot of the focus on antibiotic resistance is really based on stigma,” he says. “People are uncomfortable talking about the sex lives of people who are already stigmatized.” He noted that fears about drug resistance and condomless sex were also used to discourage PrEP—fears that proved to be unfounded.

Ultimately, doxyPEP could potentially reduce the use of antibiotics if it lowers STI prevalence. Luetkemeyer noted that participants taking doxyPEP in her study used about half as much ceftriaxone (a medication commonly used to treat gonorrhea), while those in the control group acquired STIs so often that they spent a substantial amount of time on antibiotic treatment anyway.

DoxyPEP Implementation

Long before the recent clinical trials, some gay and bisexual men were already using doxycycline or other prophylactic antibiotics on their own, obtaining the meds from sympathetic doctors or through informal channels and sharing experiences and advice on social media. In fact, surveys conducted in Australia and the United Kingdom suggested that some 10% of gay men on PrEP had used antibiotics for STI prevention. But without definitive evidence and official guidelines, it was "doxy anarchy," in the words of Oliver Bacon, MD, MPH, of San Francisco City Clinic.

As more study results came in, health departments and clinics in cities with large gay populations decided it was time to start rolling out doxyPEP. The San Francisco Department of Public Health issued the first guidance in October 2022.

The San Francisco AIDS Foundation's Magnet clinic "jumped on board right away, came up with our own protocols and communicated it out to the community," according to Roman. To date, almost 2,400 clients have started doxyPEP; 40% of them are in Magnet's HIV PrEP program as well. "I really think of it as a game changer, very similar to how we saw PrEP in 2012," Roman told POZ.

It's still too early to determine effectiveness, but things look promising so far. "We've preliminarily been able to demonstrate really sharp declines in positivity rates for syphilis and chlamydia, but also for gonorrhea," Roman says. "At least early on, we're able to show that [doxyPEP] really is making an impact. We're hoping as more people are on it longer, we'll be able to show a decrease in STI rates in San Francisco."

Howard Brown Health in Chicago, the Fenway Institute in Boston, the Los Angeles LGBT Center and health departments in Seattle and New York state also adopted doxyPEP early on. Notably missing is the South—the region with the highest HIV and STI rates.

Howard Brown Health created a doxyPEP protocol about two years ago, but implementation was initially slow due to competing demands, including COVID-19 and mpox, according to Anu Hazra, MD, of Howard Brown and the University of Chicago. The new data have revitalized the effort. "It's sort of in the conversation right now, and people are sometimes coming to us asking for it," he told POZ.

Howard Brown's doxyPEP program focuses on "frequent flyers" who come through the clinics with STIs every few months as well as HIV patients who have had more than one STI during the past year. To date, about 300 people have started doxyPEP. Again, it's too soon to tell how well it's

working, “but I will tell you anecdotally that I see some of my frequent flyer patients on doxyPEP much less frequently, if at all, for symptomatic bacterial STIs,” Hazra says.

According to the CDC’s new national doxyPEP guidelines, a single dose of doxycycline taken within 72 hours after anal, vaginal or oral sex “should be considered” for gay, bisexual and other men who have sex with men and for transgender women who have had gonorrhea, chlamydia or syphilis at least once during the past year. In addition, doxyPEP “could be considered” for gay and bi men and trans women who have not been diagnosed with an STI if they will be participating in sexual activities known to increase the likelihood of STI exposure. However, due to a lack of supporting evidence, “no recommendation can be given at this time” for cisgender women, cisgender heterosexual men, transgender men or other queer or nonbinary people.

These guidelines recommend doxyPEP for the group with the strongest evidence of benefit but “leave the door open for other populations,” Luetkemeyer says. “Clinicians can use the guidance to have a case-by-case discussion with people who aren’t included in the recommendation to decide if doxyPEP makes sense while we are learning more.”

Local and practice-specific guidelines generally align with the CDC’s, but some are a bit broader. San Francisco’s guidance includes transgender men along with cisgender gay and bi men and trans women, and it applies to those who have multiple male sex partners even if they have not recently had an STI. The California Department of Public Health goes further, saying providers can offer doxyPEP to all nonpregnant people at increased risk for STIs and to those requesting doxyPEP, even if they have not previously been diagnosed with an STI or have not disclosed their risk status.

Seattle says providers can consider prescribing doxyPEP on an episodic basis when patients anticipate periods of higher risk. New York state includes men who have condomless sex with multiple female partners—an important consideration since STI complications can be especially severe for women and their babies.

Experts hope the CDC guidelines will encourage use of doxyPEP beyond the pioneering cities and will make more providers feel comfortable discussing and prescribing it.

“Guidelines are an important first step to address equitable access for those who are most impacted by recurrent STIs and who may be at risk for lack of access, given existing health disparities,” says Luetkemeyer.

Equitable Access

DoxyPEP early adopters have positive things to say about it. The DoxyPEP trial investigators interviewed a subset of 44 participants about their experiences. In general, they found doxyPEP acceptable and easy to adhere to, and they said side effects were manageable. They reported little change in their sexual practices.

Users said doxyPEP benefited their quality of life and mental health, reduced their anxiety, gave them peace of mind and helped them feel more in control. Notably, though, many thought doxyPEP was not necessary for oral sex. While oral sex carries little risk for HIV, it can transmit chlamydia, gonorrhea and syphilis.

But equitable access to doxyPEP is a big concern. Health officials and advocates worry that it won't reach the people who need it most, mirroring what is happening with PrEP. Twelve years after its approval, Black and Latino men who have sex with men and cisgender women of all races and ethnicities are still much less likely to use PrEP than white gay men.

"That's always the concern with interventions such as this. It always comes down to who has the most access, who has the most information, who can take time out of their busy lives to even step into a clinic," Roman says. "Equity has always been on our mind since the very beginning."

People who could potentially benefit from this new prevention tool may not have access to sex-positive providers who know about doxyPEP and will offer it without stigma. Others have little connection with the health care system, don't trust medical providers or have competing priorities. Fortunately, unlike PrEP in its early years, generic doxycycline is inexpensive—as little as $1 per pill—so cost should not be a major barrier.

"As with any newfangled intervention, whether it be PrEP or long-acting injections for HIV treatment or prevention, these inequities fall along racial and socioeconomic fault lines," Hazra says.

The largely white clients at Howard Brown's North Side Chicago clinics have been accessing doxyPEP first, he says, and "we are trying really intentionally to make sure that our South Side clinics that largely serve Black and brown men who have sex with men and trans women will have the capability to implement this among their patients too."

"I feel like, in a lot of ways, we're making the same mistakes we made with HIV PrEP a decade ago in terms of who is getting doxyPEP versus who truly needs it," Hazra continues. What's more, "Women and trans men and nonbinary folks assigned female at birth continue to find themselves in a really frustrating place where they don't have access to this intervention because there aren't more studies looking at them."

If it's properly implemented, though, doxyPEP could help turn the tide on the burgeoning STI epidemic.

"When I discovered PrEP at age 40, it ended the connection between condomless intimacy and a life-threatening illness. However, PrEP did not eradicate the fear of other STIs," Damon Jacobs, a licensed marriage and family therapist and longtime prevention advocate, told POZ.

"Once I started utilizing doxyPEP in 2017, that last bond between sex and fear was severed," he says. "It is important to me that people of all HIV statuses understand this unprecedented opportunity before us—not only to collectively participate in reducing STI transmission in our

sexual networks but also to individually experience the abundant joy that comes from being proactive, responsible and empowered about one’s pleasure and protection from STIs.”

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