

DoxyPEP STI Prevention Works Well for Gay Men—But Maybe Not for Women

Doxycycline after sex reduces the risk of gonorrhea, chlamydia and syphilis for gay men, and it does not appear to drive resistance.

March 8, 2023 By [Liz Highleyman](#)

UPDATE: Results from the [DoxyPEP study](#) were published in the April 6, 2023, issue of The New England Journal of Medicine. Results from the [dPEP Kenya trial](#) were published in the December 21, 2023, issue.

Doxycycline post-exposure prophylaxis (doxyPEP) after sex is highly effective for preventing bacterial sexually transmitted infections (STIs) among gay men and transgender women—and adding a vaccine reduces the risk for gonorrhea—but this approach did not work well for cisgender women in Africa, according to research presented at the [30th Conference on Retroviruses and Opportunistic Infections \(CROI\)](#).

DoxyPEP Plus Vaccine

[As reported at last summer's international AIDS Conference](#), the DoxyPEP trial enrolled gay men and transgender women in San Francisco and Seattle who were either living with HIV or taking [pre-exposure prophylaxis \(PrEP\)](#). The study found that HIV-positive people who took a 200 milligram dose of the antibiotic doxycycline within 72 hours after condomless sex saw a 74% reduction in the risk for chlamydia, a 57% decrease for gonorrhea and a 77% reduction for syphilis per quarter. Among HIV-negative participants on PrEP, the corresponding reductions were 88%, 55% and 87%, respectively.

At CROI, Jean-Michel Molina, MD, of the University of Paris Cité, presented findings from another study that evaluated doxycycline PEP plus a vaccine to prevent gonorrhea. The meningococcal B vaccine (Bexsero, also known as 4CMenB) is approved for the prevention of *Neisseria meningitidis*, which causes bacterial meningitis. But it also prevents infection with the related bacteria *Neisseria gonorrhoeae*, which causes gonorrhea.

The DoxyVAC study included 502 men who have sex with men in the ANRS Prevenir trial who were taking tenofovir disoproxil fumarate/emtricitabine (Truvada or generic equivalents) for HIV prevention and had an STI within the past year. Most were white men born in France, and the median age was 39 years. They were randomly assigned to receive doxycycline PEP or the

standard of care (STI testing and treatment after diagnosis) and separately randomized to receive two shots of the vaccine spaced two months apart or no vaccine. Roughly half received doxycycline alone, half got doxycycline plus the vaccine, a quarter received the vaccine alone and a quarter got neither. They were tested for chlamydia, gonorrhea and syphilis every three months.

The study was stopped early in September 2022 after a preliminary analysis showed that the intervention was effective. Adherence was high, with the men reporting that they took doxycycline after sex about 80% of the time. Over a median nine months of follow-up, the risk for chlamydia declined by 89%, while syphilis declined by 79%. The risk for gonorrhea fell by 51% in the doxyPEP group, with greater protection against anal or urethral infection compared with throat infections. The likelihood of gonorrhea decreased by the same amount in the vaccine group. DoxyPEP and the vaccine were safe and well tolerated, and no serious adverse events were reported.

The effects of the two interventions on gonorrhea were independent, and people who received both benefited from both, Molina told reporters at a CROI media briefing. “Even a vaccine with moderate effectiveness could have a big impact,” he said. “It could reduce the overall burden of gonorrhea, which is becoming more and more resistant.” He said it is not yet known how long vaccine protection will last or whether boosters will be needed, but literature suggests it’s good for at least a year.

[A Phase II trial](#) of the meningococcal vaccine for gonorrhea prevention is currently underway at the University of Alabama at Birmingham, Emory University in Atlanta and Louisiana State University in Baton Rouge.

DoxyPEP for Women

In contrast to the good outcomes for gay men and transgender women in the DoxyPEP and DoxyVAC studies, doxycycline PEP did not reduce the risk for STIs among African cisgender women in the dPEP Kenya trial.

“The results from the study are deeply disappointing, and we are committed to understanding why doxycycline PEP did not work in this population and also determining the next steps for how to identify prevention tools that will work for and can be used by women,” principal investigator Elizabeth Bukusi, MD, PhD, MPH, of the Kenya Medical Research Institute, said in a [press release](#).

Effective bacterial STI prevention for women is urgently needed as infections can lead to severe complications including pelvic inflammatory disease, chronic pain, infertility, pregnancy complications and increased susceptibility to HIV, presenter Jenell Stewart, DO, MPH, of the Hennepin Healthcare Research Institute in Minneapolis, noted as background.

The dPEP Kenya trial was conducted in Kisumu an area with high STI rates and a high prevalence of antibiotic-resistant gonorrhea. The trial, which ran from 2020 through 2022, enrolled 449 nonpregnant cisgender women ages 18 to 30 who were taking HIV PrEP. About 60% were using hormonal contraception, and 37% reported transactional sex. At baseline, 18% had a bacterial STI,

mostly chlamydia.

The women were randomly assigned to take a 200 mg dose of doxycycline after sex or received standard care. Each week, they received text messages asking about the frequency of sex and doxycycline use, and they were tested for STIs every three months. Eighty women became pregnant during the study, and doxycycline use was suspended during pregnancy.

Almost all follow-up visits were completed, and the weekly survey response rate was 81%. But doxycycline did not significantly reduce the risk for STIs. “Overall STI incidence was high with no significant differences between groups,” Stewart reported.

There were 35 new cases of chlamydia in the doxyPEP group and 50 cases in the standard care group. For gonorrhea, there were 19 and 12 cases in the two groups, respectively. Neither of these differences met the threshold for statistical significance. There was only one case of syphilis.

Doxycycline was generally safe and well tolerated, and no severe adverse reactions were reported. There were no new cases of HIV in either group. Four women reported “social harms” related to doxyPEP use, including verbal or physical violence.

Possible explanations for the “stark contrast” between these findings and those from the studies of gay men and trans women include anatomical differences, suboptimal adherence and variations in antibiotic resistance, according to Stewart. She noted that cervical tissue may differ from urethral, rectal and throat tissues, but another study presented at CROI suggests this is not an adequate explanation.

Richard Haaland, PhD, of the Centers for Disease Control and Prevention (CDC), performed a pharmacokinetic analysis, measuring doxycycline concentrations in men and women at sites of STI exposure. Participants provided blood samples and mucosal swabs up to seven days after receiving doxycycline. In addition, rectal, vaginal and cervical tissue biopsies and urethral swabs were collected 24 hours after dosing.

Doxycycline concentrations peaked sooner in vaginal secretions compared with rectal secretions, and concentrations were higher in rectal tissue compared with vaginal tissue, but there were no differences in blood drug levels between men and women. Drug concentrations in rectal, vaginal and cervical tissue remained well above the minimum level needed to inhibit chlamydia and syphilis for three to four days, but for just two days for gonorrhea. Haaland said the lack of protection in the dPEP Kenya trial was “a really bleak finding,” and he was surprised because his analysis did not suggest this would be the case based on biological differences.

Suboptimal adherence may be a more likely explanation. Although the trial was designed to maximize adherence, participants said their adherence was “imperfect.” So doxycycline might have protected women from STIs if they used it more regularly. The poor showing of doxy PEP in this study resembles outcomes in some trials of oral PrEP for HIV prevention, which saw lower effectiveness for cisgender women in Africa compared with gay men and trans women, largely due to less consistent use. Stewart said that stigma around HIV and STIs is a major issue for women

that needs to be addressed in order to make progress in this area.

Drug Resistance

With regard to resistance, while there have not yet been any reported cases of antibiotic-resistant chlamydia, drug-resistant gonorrhea is a growing problem worldwide. In fact, in the dPEP Kenya study, 100% of gonorrhea present at baseline was already resistant to doxycycline.

Discussing the research at the media briefing, Annie Luetkemeyer, MD, of the University of California at San Francisco, noted that doxycycline PEP was effective in the DoxyVAC study even though antibiotic-resistant gonorrhea is common in France, at around 60%, compared with 20% baseline resistance to tetracyclines (the drug class that includes doxycycline) among DoxyPEP participants in San Francisco and Seattle. Molina explained that gonorrhea can have either high-level or low-level resistance, and only a few people in his study had high-level resistance. He suggested that the poor performance of doxyPEP in Stewart's study might be due to more high-level resistance in Africa.

While pre-existing resistance may hamper the effectiveness of doxycycline PEP, a major concern with this approach is that overuse of antibiotics can drive the development of resistance.

Luetkemeyer presented findings from a follow-up analysis of emergent drug resistance in the DoxyPEP trial. The researchers looked at three types of bacteria: *Neisseria gonorrhoeae*, commensal *Neisseria* (related bacteria that normally live in the throat and don't cause disease but could transfer resistance elements to *Neisseria gonorrhoeae*) and *Staphylococcus aureus* (bacteria that commonly live in the nose and throat), including methicillin-resistant *Staph aureus* (MRSA). At baseline and one year later, nasal and throat swabs were collected to test for doxycycline and tetracycline resistance; however, less than half of the samples could be grown in the lab and tested for resistance.

Staph aureus colonization decreased by 14% among people in the doxyPEP group, from 44% to 30%, but it did not change in the standard care group. However, resistant *Staph aureus* rose in the doxyPEP group, from 5% to 13%, while declining in the standard care group. MRSA declined from 6% to 4% in the doxyPEP group and remained stable in the standard care group, but the number of samples was too small for a meaningful comparison.

Nearly two thirds (62%) of tested participants had doxycycline-resistant commensal *Neisseria* at baseline. After a year, this rose slightly in the doxyPEP group while falling to 42% in the standard care group. Looking at the samples from people newly diagnosed with gonorrhea, three had low-level tetracycline resistance and one had high-level resistance at baseline. After a year, six samples from the doxyPEP group showed resistance (four low-level and two high-level) as did two samples from the standard care group (both high-level).

These findings are "reassuring," according to Luetkemeyer. "We didn't see a marked increase in antimicrobial resistance associated with doxyPEP use." Doxycycline PEP reduced *Staph aureus* colonization without a significant increase in doxycycline resistance. MRSA colonization was low

with no significant change over time. There was a trend toward more tetracycline-resistant gonorrhea, which suggests doxyPEP may be less protective against circulating resistant gonorrhea strains, but the study was unable to assess whether it's actually a driver of resistance, Luetkemeyer said. Overall, these “modest changes” are “unlikely to have clinical significance,” the researchers concluded.

“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, Luetkemeyer told reporters. She added that doxy PEP is not for everyone, and implementation should start with people who have a demonstrated high risk for STIs. When she presented the main study findings last summer, she noted that people in the standard care group acquired STIs so often that they spent a lot of time on antibiotic treatment anyway. Using doxycycline as PEP reduces suffering and decreases the amount of time people can transmit STIs. By lowering STI incidence, doxyPEP might actually reduce the use of antibiotics for treatment. Indeed, trial participants in the doxyPEP group used about half as much ceftriaxone, the drug currently used to treat gonorrhea.

In the DoxyVAC study, there was some evidence of an increase in tetracycline-resistant gonorrhea, but high-level resistance was uncommon. Speaking at the CROI briefing, Molina noted that doxycycline and related drugs have been used for years unhampered by resistance, and he didn't expect that a small amount of additional use by gay men would change that.

Asked whether the CDC should recommend doxyPEP, Luetkemeyer said, “I think there's enough data out there, and people are looking for guidance. I think it's time to weigh in now as we continue to learn more.”

“As these promising findings are shared, it is exciting to see important pieces of a much larger puzzle falling into place, but there are still many gaps left to fill,” Leandro Mena, MD, MPH, director of CDC's Division of STD Prevention, [said in a statement](#). “These and other data will be vital to our ongoing efforts to ensure CDC's STI treatment and prevention guidance and the Advisory Committee on Immunization Practices vaccine recommendations are aligned with the latest science. In the meantime, [CDC has posted considerations](#) for the use of doxycycline as STI PEP for providers and individuals considering this strategy as the agency finalizes the development of CDC's more detailed interim clinical guidance on the use of doxycycline as post-exposure prophylaxis.”

[In this HIV.gov video](#), Carl Dieffenbach, PhD, director of the Division of AIDS at the National Institute of Allergy and Infectious Diseases, discusses findings from these three STI prevention studies.

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