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**Review Article**

# Role of doxycycline post exposure prophylaxis in the prevention of sexually transmitted infections: a narrative review

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## ABSTRACT

Sexually transmitted infections (STIs) spread through sexual intercourse. They are caused by pathogens like *Neisseria gonorrhoeae*, *Treponema pallidum, Chlamydia trachomatis*, and *Mycoplasma genitalium*, and can be transmitted through direct contact or contact with genital secretions. Doxycycline is a second-generation tetracycline antibiotic with a broad antimicrobial spectrum, acting on intracellular and extracellular organisms. This review aims to explore the efficacy of doxycycline post-exposure prophylaxis (PEP) in the prevention and treatment of STIs. Some of the areas of uncertainty with the use of doxycycline PEP for STIs include the concern for developing antimicrobial resistance (AMR), the effect on the normal microbiome of the body, public acceptability, drug formulation and dosage and compliance issues. Recent clinical and observational studies have looked at using doxycycline PEP to reduce the transmission of STIs. This review aims to explore these studies to provide a comprehensive account of the current state of doxycycline PEP and its future prospects. We also look at the limitations and areas of improvement in using doxycycline PEP, opening avenues for future research. High-quality studies have shown that using doxycycline PEP can effectively reduce the transmission of STIs in a number of clinical trials as well as systematic reviews., making it a potential standard treatment for high-risk groups such as immunocompromised patients, individuals living with HIV, sex workers, and men who have sex with men (MSM).

**Keywords:** Doxycyline, PEP, STIs, Preventive medicine

## INTRODUCTION

Doxycycline is a second-generation tetracycline antibiotic. It is a bacteriostatic antibiotic that acts on ribosomal protein synthesis. It is highly lipid soluble, which means it has a high tissue and fluid penetration. Its antibacterial spectrum is broad, it acts on both intracellular and extracellular pathogens. Doxycycline is effective against the bacteria causing STIs such as *Treponema pallidum, Neisseria gonorrhoeae, and Mycoplasma genitalium*.[1] Apart from its use in STIs, Doxycycline is also used commonly in the treatment of acne vulgaris, Rickettsia fever, COPD exacerbation in patients with penicillin allergy, and as prophylaxis for malaria.

The rates of STIs have been gradually increasing worldwide.[2-4] The introduction of HIV pre-exposure prophylaxis in 2012 has been associated with an increase in STI rates, due to an increase in sexual contacts and a decrease in condom use.[5,6] However, the success of HIV pre-exposure prophylaxis shows that biomedical interventions for STI prevention can be safe, effective, and highly acceptable.[7]

## AREAS OF UNCERTAINTY

Some of the areas of uncertainty with the use of doxycycline as PEP are as follows: formulation, dosage, safety and efficacy, population of interest and AMR.

### *Formulation, dosage, safety, and efficacy*

The two most used formulations of doxycycline in practice are doxycycline monohydrate and doxycycline hyclate, these two forms are soluble at different pH, with esophageal side effects being less common with doxycycline monohydrate and enteric-coated doxycycline hyclate as compared to uncoated doxycycline hyclate.[8] Since the formulation of doxycycline may affect side effects and patient adherence, these should be studied in future RCTs.

Similarly, the clinical trials conducted on doxycycline pre and PEP for STI used either a 100 mg daily dosing regimen or a 200 mg single dose post-condomless sexual event.[5,9] These dosages were selected based on clinician experience with the use of doxycycline prophylaxis for other infectious diseases and the minimum inhibitory concentration (MIC) of *Treponema pallidum*. While both studies resulted in similar efficacies (~70%) further studies are needed considering different dosing regimens to maximize efficacy and patient safety.

### *Population of interest*

Controlling STIs in high-risk core populations has long been promoted as an approach to reduce STIs in the general population.[10,11] Current and planned studies have generally focused on MSM with a high risk of history of STIs, taking HIV pre-exposure prophylaxis, and have a history of HIV, but criteria vary and sample sizes may not be sufficient to stratify results for subpopulations with more elevated risk. Additional studies or pooled analyses may be useful to identify the characteristics of populations most suitable for maximizing the impact of doxycycline prophylaxis.

### *AMR*

A major concern regarding the use of doxycycline as PEP against STIs is the development of AMR, cross-resistance, change in normal human flora, and development of by-stander resistance in other respiratory and gastrointestinal bacteria.[12,13] Studies with large sample sizes and longer follow-up times are required to better understand the impact of doxycycline PEP on STIs, other pathogens, and the microbiome. This could be done by close monitoring and AMR surveillance of individuals using doxycycline PEP in health programs.

## THERAPEUTIC ADVANCES

Doxycycline PEP has promising outcomes in the prevention of STIs namely chlamydia, syphilis, and possibly gonorrhea in a number of clinical studies. These outcomes are more evident among gay, bisexual, and other MSM who have experienced multiple STIs.[14] This nascent prevention strategy that involves taking 200 mg doxycycline within 24 hours after condomless oral, anal, or vaginal sex helps to reduce the risk of acquiring bacterial STIs.[15]

A study reported in The Lancet, a study revealed that doxycycline PEP has significantly reduced the risk of acquiring chlamydia or syphilis by 70% and 73%, respectively. However, there was no effect on gonorrhea rates. Participants took the drug within 24 hours and no later than 72 hours after having condomless sex.[16] In the DOXYYAC trial by the same investigators, a similar trend of reduction in STIs was observed. With an 84% lower incidence of *C. trachomatis* and syphilis and a 51% lower incidence of *N. gonorrhoeae*.[17]

In the USA, a recent trial by Luetkemeyer et al assigned 501 men or transgender women who have sex with men (MSM or TGW) at high risk of acquiring HIV to take doxycycline after condomless sex with at least one male in the past 2 months and taking HIV PrEP. This resulted in a 66% drop in STI cases, with gonorrhea cases specifically falling by 55%.[15]

Based on the findings of these and related studies, the San Francisco public health unit has advised using Doxy-PEP as an STIs prevention strategy. This recommendation is for cisgender and trans-women who have had a bacterial STI in the past year, involved in condomless anal or oral sex, or have a history of syphilis.[18]

A survey conducted in parts of Germany's MSM community found that a relevant proportion of community members are already familiar with the use of doxycycline for STI prophylaxis. The second most common way to obtain doxycycline, accounting for 40% of all the cases was without a prescription such as receiving doxycycline from a friend or contacts without the involvement of healthcare professionals, or by ordering it online.[19]

Projections indicate a rise in antibiotic use with the adoption of doxycycline PEP in the US.[20]

This data provides encouraging evidence that doxycycline PEP has the potential to not only lower the population burden of STIs and their associated morbidity but also their future transmission.

The post-exposure use of doxycycline extends beyond the STIs to prevent other bacterial infections. A study found that a single dose of doxycycline PEP was 78% effective for preventing 3 clinically relevant spirochetal infections including Lyme disease, syphilis, and tick-borne relapsing fever. [21]

## DISCUSSION

STIs are spreading rapidly in the United States disproportionately affecting gay, bisexual, and other MSM and TGW. Three large randomized controlled trials have reported that the incidence of chlamydia, and syphilis can be lowered by >70% gonococcal infections by approximately 50% after taking 200 mg of doxycycline within 72 hours after sex.[22]

From public health perspective, it may be challenging to convince a large percentage of the at-risk population to take doxycycline regularly. This difficulty is mainly due to concerns about antibiotic resistance and potential side effects. Findings highlight the importance of prioritizing routine STIs screening and treatment, as well as promoting condom use as the primary method for preventing infection transmission. Using doxycycline PEP as a secondary measure, in conjunction with other prevention strategies, may be a more practical public health approach, towards STIs chemoprophylaxis.

Despite being highly prevalent globally, STIs continue to be an area of research that is often overlooked. There is a need for future research to fill the gaps in available data. More comprehensive and reliable data is required regarding efficacy, target population, community acceptability, doxycycline dose, regimen, formulation, long-term safety, AMR, cost-effectiveness, and risk-benefit.

## CONCLUSION

High-quality data from a number of clinical trials and observational studies supports the use of doxycycline PEP in the prevention of STIs. PEP is especially important in high-risk populations, such as HIV-positive patients and MSM. In these populations, the use of doxycycline PEP has shown reduced incidents of STIs as well as transmission. Although concerns regarding AMR, public acceptability, and adverse effects of long-term use are there, further research and follow-up studies are required to answer these questions.

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