Doxycycline PEP: When it works for STIs, and when it doesn't

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The incidence of bacterial sexually transmitted infections (STIs) continues its upward trajectory, particularly among men who have sex with men (MSM). This persistent rise has intensified the search for effective prevention strategies beyond traditional condom use and regular screening. Doxycycline post-exposure prophylaxis (doxy-PEP) has emerged as a significant contender, offering a new biomedical approach to an old problem.1,2

KEY TAKEAWAYS

- The Pivot: Doxy-PEP significantly reduces the incidence of chlamydia, syphilis, and gonorrhea in high-risk populations, but its efficacy against gonorrhea is notably lower and varies by region.
- The Data: In a meta-analysis of four trials, doxy-PEP reduced chlamydia by 89% (95% CI, 76-95%) and syphilis by 79% (95% CI, 64-88%).
- The Action: Clinicians should consider doxy-PEP for individuals at high risk for bacterial STIs, particularly MSM and transgender women, while carefully monitoring for antimicrobial resistance, especially for gonorrhea.

Bacterial STIs, including chlamydia, gonorrhea, and syphilis, represent a substantial public health burden. The World Health Organization estimates over 374 million new infections annually for these three pathogens alone.1 Traditional prevention methods, while effective, have not been sufficient to curb the rising rates, especially in key populations. This unmet need has driven interest in novel strategies, with doxy-PEP gaining traction as a potential game-changer.2 Doxycycline, a tetracycline antibiotic, has a long history of use in treating various bacterial infections. Its mechanism of action involves inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit, preventing the attachment of aminoacyl tRNA.1 This broad-spectrum activity makes it a candidate for prophylaxis against multiple bacterial STIs. The concept of post-exposure prophylaxis is not new; it has been successfully applied in HIV prevention with PrEP. The idea for doxy-PEP is similar: administering an antibiotic shortly after potential exposure to prevent infection from taking hold.2

The Evidence for Efficacy

Several studies that were key to understanding the benefits of doxy-PEP have investigated its efficacy. A meta-analysis of four randomised controlled trials (RCTs) and one open-label extension study, primarily involving MSM and transgender women (TGW) with a history of STIs or HIV infection, provided compelling evidence.1 These studies consistently showed a significant reduction in the incidence of chlamydia and syphilis. For chlamydia, doxy-PEP reduced the risk by 89% (95% CI, 76-95%). Syphilis incidence saw a 79% reduction (95% CI, 64-88%).1

The picture for gonorrhea, But, is more complex. The same meta-analysis reported an overall reduction in gonorrhea incidence of 57% (95% CI, 45-66%).1 This lower efficacy compared to chlamydia and syphilis is a point of concern for public health, largely attributed to pre-existing and emerging doxycycline resistance in Neisseria gonorrhoeae. Resistance patterns vary geographically, influencing the observed efficacy in different trial settings. For instance, studies conducted in regions with higher baseline tetracycline resistance in gonorrhea showed lower protective effects.2

One notable trial, DoxyPEP, enrolled 501 participants (MSM and TGW) in the US, randomising them to receive either 200 mg doxycycline within 72 hours of condomless sex or standard care.1 The trial reported a 66% reduction in overall STI incidence (chlamydia, gonorrhea, or syphilis) in the doxy-PEP group compared to the standard-care group. Specifically, chlamydia incidence decreased by 88%, syphilis by 87%, and gonorrhea by 55%.1 These numbers show the substantial benefit for chlamydia and syphilis, while highlighting the more modest, though still clinically meaningful, effect on gonorrhea. The antibiotic paradox continues to challenge public health efforts.

Patient Populations and Regimens

The majority of research on doxy-PEP has focused on specific high-risk populations: MSM and TGW. These groups often experience disproportionately high rates of bacterial STIs, making them a priority for targeted prevention strategies.1 The typical regimen involves taking 200 mg of doxycycline orally as a single dose, ideally within 24 hours but no later than 72 hours after condomless sex.2 This post-exposure timing is essential for its prophylactic effect. The intermittent nature of this dosing strategy aims to minimise continuous antibiotic exposure, thereby theoretically reducing the selective pressure for resistance development compared to daily pre-exposure prophylaxis.

But the question of whether these benefits extend to other populations, such as heterosexual men and women, remains largely unanswered by current data. Limited studies in cisgender women have not shown the same level of efficacy, particularly for chlamydia and gonorrhea.2 This disparity might be due to anatomical differences in bacterial reservoirs and pharmacokinetics, or differing patterns of sexual exposure. More research is needed to determine if doxy-PEP can be a viable strategy for broader populations, and if so, what specific regimens would be most effective. The concept of post-exposure prevention has shown promise in other areas, but generalizability is key.

The Resistance Question

The most significant concern surrounding widespread doxy-PEP use is the potential for increased antimicrobial resistance. Doxycycline is a broad-spectrum antibiotic, and its use, even intermittently, could exert selective pressure on various bacterial species, not just STI pathogens.1 The primary worry centers on Neisseria gonorrhoeae, which already exhibits significant resistance to multiple antibiotic classes. Studies have documented increased tetracycline resistance in gonorrhea isolates from individuals using doxy-PEP.2

One study reported a 7.7% increase in tetracycline resistance in N. gonorrhoeae isolates among doxy-PEP users compared to non-users.1 While this is a concern, the clinical implications are still being assessed. It is important to distinguish between tetracycline resistance and resistance to other first-line gonorrhea treatments, such as ceftriaxone. So far, there is no clear evidence that doxy-PEP use directly drives resistance to these other important antibiotics. Still, the potential for cross-resistance or co-selection of resistance genes is a serious consideration for public health. The role of AI in infection prevention might offer new tools to track these trends.

Beyond gonorrhea, there are concerns about the impact on commensal bacteria, particularly in the gut and

nasopharynx. Alterations to the microbiome could lead to the emergence of resistant strains of other pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant enterococci (VRE).2 Long-term surveillance studies are essential to monitor these broader ecological effects. The intermittent dosing schedule of doxy-PEP is intended to mitigate this risk compared to daily dosing, but the extent of this mitigation is not fully understood. Clinicians must weigh the immediate benefits of STI prevention against the long-term, population-level risks of resistance. For a deeper dive into managing infectious diseases, the Oxford Handbook of Infectious Diseases and Microbiology (3rd ed) offers practical guidance.

Adverse Events and Adherence

Doxycycline is generally well-tolerated, but common adverse events include gastrointestinal upset (nausea, vomiting, diarrhea), photosensitivity, and esophageal irritation.1 Photosensitivity, in particular, can be a nuisance, requiring patients to take precautions against sun exposure. Adherence to doxy-PEP regimens has been generally good in clinical trials, likely due to the highly motivated populations studied. However, real-world adherence might vary, impacting overall effectiveness.2

The open-label design of many doxy-PEP trials is an obvious caveat. While blinding is challenging for a post-exposure regimen, the lack of it could introduce bias, particularly in self-reported sexual behaviors and STI symptoms. The trials were also not powered to detect differences in rare adverse events or long-term resistance trends in less common pathogens. That gap matters for broader implementation. The focus on MSM and TGW means that data on efficacy and safety in cisgender women, heterosexual men, and adolescents are sparse, limiting generalizability.1

Current Guidance and Future Directions

Several public health bodies, including the US Centers for Disease Control and Prevention (CDC), have issued guidance on doxy-PEP. The CDC recommends doxy-PEP for MSM and TGW who have had a bacterial STI in the past 12 months and are at high risk for future STIs.1 This recommendation reflects the strong evidence base in these specific populations. However, implementation requires careful patient selection, counseling on potential side effects, and ongoing monitoring for STIs and antimicrobial resistance. Regular STI screening, including extragenital sites, remains vital for public health for individuals using doxy-PEP.2

Future research needs to address several key questions. Studies are needed in cisgender women and heterosexual men to determine efficacy and safety in these populations. Long-term surveillance of antimicrobial resistance patterns, not just for gonorrhea but for other commensal and pathogenic bacteria, is paramount. Understanding the impact on the microbiome and the potential for co-selection of resistance genes requires dedicated investigation. Optimising dosing regimens, perhaps exploring alternative antibiotics or combinations, could also help mitigate resistance concerns while maintaining efficacy. The ultimate goal is to integrate doxy-PEP into a comprehensive STI prevention strategy that includes vaccination, condom use, regular screening, and prompt treatment of infections.2

> **CLINICAL IMPLICATIONS**
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> Doxy-PEP offers a tangible, evidence-based tool for clinicians managing bacterial STIs in high-risk populations. The data for chlamydia and syphilis are compelling, providing a clear benefit that should be discussed with eligible patients. It is a pragmatic addition to our prevention arsenal, particularly for those who

> struggle with consistent condom use or have a history of recurrent infections.
> But the enthusiasm must be tempered with a healthy dose of caution, especially regarding gonorrhea. The variable efficacy and the undeniable risk of fostering antimicrobial resistance in N. gonorrhoeae cannot be ignored. Clinicians must educate patients on these nuances, emphasising that doxy-PEP is not a silver bullet and does not replace regular STI screening. We are already battling a rising tide of untreatable gonorrhea; adding another selective pressure without robust surveillance would be irresponsible.
> The lack of strong data in cisgender women and heterosexual men means we cannot broadly extrapolate these benefits. Applying doxy-PEP outside the studied populations risks both inefficacy and accelerating resistance without clear clinical gain. For now, its role is defined by the evidence: a targeted intervention for specific high-risk groups, not a universal panacea. The industry must invest in trials that address these demographic gaps, rather than assuming a one-size-fits-all approach.

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