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Editorial

Doxycycline Post-Exposure Prophylaxis for Sexually Transmitted Infections: One Shot for How Many Infections?

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Over the past decade, the landscape of sexually transmitted infections (STIs) has evolved considerably. Epidemiological data indicate a steady increase in bacterial STIs [1], such as chlamydia, gonorrhea, and syphilis, across various populations worldwide. Contributing factors include changes in sexual behaviors, increased global mobility, and the persistent challenge of emerging antibiotic resistance [2]. In this complex scenario, conventional yet essential strategies to curb STIs, such as consistent and correct use of barrier methods, regular STI screening and testing, contact tracing with partner notification, strategies to inform sexual partners about potential exposures, and programs promoting safe sexual behaviors, have fallen short, mainly due to ineffective implementation. This gap has spurred the exploration of innovative interventions, such as doxycycline post-exposure prophylaxis (Doxy PEP), to enhance STI prevention strategies.

Doxycycline, a well-established tetracycline antibiotic, works by inhibiting bacterial protein synthesis. Its broad-spectrum activity makes it an appealing candidate for prophylactic use immediately after high-risk sexual exposure. Preliminary studies in high-risk cohorts—particularly men who have sex with men (MSM) and individuals with recurrent STIs—have shown that timely administration of doxycycline can significantly reduce the incidence of selected bacterial STIs (i.e., chlamydia, syphilis, and gonorrhea), including in people living with HIV (PLWH) [1,2].

The potential impact of Doxy PEP extends beyond its immediate antimicrobial effects. Its integration into STI prevention strategies is emblematic of a broader, new, and more adaptive approach to public health. While traditional preventive measures are largely behavioral or vaccine-based, Doxy PEP represents an active pharmacological intervention aimed at blocking infection establishment before it can take root.

Preliminary recommendations for the use of Doxy PEP emerged following real-life pioneering studies that highlighted a significant reduction in STI incidence, particularly among MSM. These promising results encouraged expert groups and STI clinical reference centers to evaluate, within controlled and experimental settings, the integration of Doxy PEP as a complementary measure to traditional preventive strategies [3]. However, a cautious approach has been adopted at the European level. Several European health authorities indicate that the use of Doxy PEP should be confined within experimental contexts or reserved for specific population groups, pending further evidence to solidify the balance between benefits and risks. European official guidelines, in general, have not yet broadly endorsed this strategy, emphasizing the need to closely monitor the emerging patterns of antibiotic resistances.

The CDC STD Treatment Guidelines still do not include Doxy PEP as a standard practice for STI prevention. This supports the claim that, as of now, Doxy PEP is not an officially endorsed intervention by the CDC [4]. Some pilot protocols have been launched

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in different U.S. metropolitan areas (e.g., San Francisco and Seattle). The San Francisco Department of Public Health (SFDPH) adopted pilot protocols of innovative STI prevention strategies potentially including also Doxy PEP. Although the SFDPH does not have a dedicated, peer-reviewed publication on Doxy PEP protocols, updates and program outlines can be found on their official website and related press releases (https://www.sfdph.org; accessed on 22 March 2025) as well as local public health bulletins [5]. Similarly, in Seattle, pilot studies and protocols are being implemented under the auspices of the local public health department [6].

All the protocols generally propose administering 200 mg of doxycycline in one shot within 24 h of a risky exposure, with subsequent follow-up to monitor efficacy and the potential development of antibiotic resistance. The dosing regimen is drawn from peer-reviewed studies that explored these interventions [1,2,4,7].

Recent data presented at the 2025 Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco have provided valuable insights into the effectiveness of Doxy PEP in reducing bacterial STIs, specifically chlamydia, syphilis, and gonorrhea, while also highlighting disparities in adherence and in access to Doxy PEP among different demographic groups [8–11], including cisgender women [12]. In particular, younger MSM, especially those from minority backgrounds or lower socioeconomic status, exhibited lower adherence rates compared to other subgroups [13]. Geographic variations and limited healthcare resources in certain communities have hindered the widespread implementation of this intervention, potentially reducing its overall public health impact [14].

To date, Italian health authorities have not issued official recommendations regarding the use of Doxy PEP for STI prevention. However, several reference centers and expert groups are launching pilot projects and observational studies to evaluate the efficacy and safety of this approach, paying particular attention to the risk of antibiotic resistance and adverse effect monitoring. Preliminary results of the Italian studies showed a reduction in all expected bacterial STIs among Doxy PEP users, with the greatest reduction for chlamydia and syphilis. These findings highlight not only the potential of Doxy PEP as an effective preventive tool against bacterial STIs but also the critical need to address structural challenges related to adherence and access to maximize its benefit [14].

In Italy, STI health professionals generally follow the IUSTI position statement and provide counseling on the benefits and harms of Doxy PEP use. This is particularly relevant for subpopulations considered at higher risk of STIs, such as Gay/Bisexual MSM who have contracted at least one bacterial STI in the last 12 months.

Some considerations regarding the use of Doxy PEP arise from observations in Europe (International Union Against Sexually Transmitted Infections, IUSTI). In the absence of long-term scientific evidence, the prescription of Doxy PEP should be considered in selected cases and carefully discussed with the patient, who must be informed about the risks and benefits of a preventive pharmacological treatment that is still under investigation [15].

Aside from the partial ineffectiveness of Doxy PEP against gonorrhea (due to the presence of tetracycline-resistant strains), we should take into account many other patient-related factors: adherence and individual pharmacokinetics (hepatic metabolism, intestinal absorption, renal elimination). Moreover, some recreational drugs as used in chemsex, such as methamphetamines or GHB, could alter gastrointestinal motility or hepatic metabolism, affecting the absorption and bioavailability of doxycycline.

An increase in risky sexual behaviors could lead to higher bacterial loads or multiple infections, meaning that prolonged exposure to antibiotics could lead to the selection of resistant bacterial strains with a reduction in microbial diversity, favoring colonization by more dangerous bacteria and dysbiosis [16,17]. Moreover, the inhibitory concentrations of doxycycline (like those of other antibiotics useful in the treatment of STIs) vary for

different bacteria causing STIs and may be insufficient for some infections (e.g., gonorrhea), potentially leading to resistance. Finally, the use of an antibiotic for prophylactic rather than therapeutic purposes requires lower drug dosages and a shorter treatment duration. Particularly in the case of syphilis, Doxy PEP can alter the natural progression of the infection, making it harder to be recognized both clinically and through serological testing, with delayed seroconversion [18] or a persistent 'serofast' status. Such an altered serological profile could mask an active infection and complicate treatment decisions [19]. These observations make it more challenging for Doxy PEP to effectively prevent all infections [20].

In conclusion, Doxy PEP represents an interesting and promising option for preventing sexually transmitted infections, particularly chlamydia and syphilis. Its effectiveness in reducing the risk of these infections, especially in high-risk populations, has been demonstrated in preliminary studies. However, there are valid concerns about the real usefulness of the Doxy PEP strategy for the prevention of STIs, given that we already have limited therapeutic alternatives that we risk losing in the near future.

Conflicts of Interest: The authors declare no conflict of interest.

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