

Title: Position Statement on Doxycycline as Prophylaxis for Sexually Transmitted Infections 2021 Update

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Key points:

- Doxycycline taken as Pre- or Post-Exposure Prophylaxis for syphilis or chlamydia is not endorsed by BASHH or the UK Health Security Agency (UKHSA).
- The use of other antibiotics as prophylaxis for syphilis and chlamydia or to prevent other sexually transmitted infections (STIs) is unlikely to be effective and should be discouraged.
- Recognising that many patients are taking doxycycline as prophylaxis for STIs, BASHH and the UKHSA recommend that clinicians inform patients about potential risks and limited benefit. Clinical monitoring for adverse effects and advice should be offered to patients who are using doxycycline as prophylaxis for STIs.
- Several clinical studies are currently underway to measure the impact of prophylactic doxycycline on antimicrobial resistance (AMR) at an individual and population level.

1. Background

In 2017, the British Association for Sexual Health and HIV (BASHH) and Public Health England (PHE) published a position statement on the use of Doxycycline as Prophylaxis for STIs which advised 'extreme caution in the use of doxycycline [PEP]...[and] that the use of doxycycline PEP should be restricted to the research setting.'⁽¹⁾

Since that time, although little new evidence has emerged, cross-sectional surveys suggest that many individuals at higher risk of acquiring STIs are already using antibiotics for STI prophylaxis, accessed through several routes.

To support a person-centred approach to care, this document aims to provide an updated summary of the evidence and practical recommendations for clinicians working in sexual health services.

2. What is STI PEP and PrEP?

Antibiotic STI prophylaxis is the use of antibiotics after (post-exposure prophylaxis (PEP)) or before and after (pre-exposure prophylaxis (PrEP)) to reduce the risk of acquiring certain STIs. Only the use of doxycycline to prevent syphilis and chlamydia in men who have sex with men (MSM) and transgender women has been researched (2). Other antibiotics and prophylaxis against other STIs have not been researched, but expert opinion is that they are unlikely to be effective.

Only one published study exploring doxycycline STI prophylaxis was powered to show efficacy. This sub-study of the Ipergay HIV pre-exposure prophylaxis (HIV-PrEP) trial was an open label, randomised controlled trial to determine the efficacy of doxycycline hyclate STI PEP taken as a single 200mg dose within the first 24 hours, and no later than 72 hours, after condomless sex among 232 MSM and transgender women using HIV-PrEP (3).

A significant decrease was observed in the occurrence of the first episode of chlamydia (HR = 0.30, 95% CI 0.13-0.70, $p=0.006$) i.e. a 70% reduction, and for a first episode of syphilis (HR = 0.27, 95% CI 0.07-0.98, $p=0.047$), i.e. a 73% reduction. No significant difference in the incidence of gonorrhoea was observed (HR = 0.83, 95% CI 0.47-1.47, $p=0.52$).

An earlier open-label pilot randomised controlled trial (RCT) of 100mg doxycycline hyclate daily involving 30 MSM living with HIV was not powered to show a reduction, but did observe a reduction in STIs that were not statistically significant (4).

3. How many people are using STI prophylaxis?

The 2019 HIV-PrEP User (cross-sectional, online) Survey found that 9% (167/1,856) of respondents using HIV-PrEP reported taking antibiotic STI prophylaxis and that it was associated with higher risk behaviours compared to those who did not use it (≥ 5 condomless sex partners in the past 6 months (aOR=1.80; 95% CI 1.22 to 2.64), chemsex in the past 12 months (aOR=1.88; 95% CI 1.20 to 2.93) and an STI diagnosis in the past 12 months (aOR=1.54; 95% CI 1.08 to 2.18)(5). Similarly use was reported by 8% (6/106) of HIV PrEP users attending the 56 Dean Street sexual health service, 9.9% (105/1065) attending the Melbourne Sexual Health Centre and 2.2% (7/321) MSM attending Dutch sexual health services (6-8).

Early analyses of cross sectional, community-based survey data collected during the COVID-19 pandemic in the UK suggests that up to 40% of MSM who report having ever used antibiotics as STI prophylaxis used something other than doxycycline [Kohli/HPRU, unpublished].

4. Antimicrobial resistance

The main concern about using doxycycline prophylaxis is in relation to antimicrobial resistance (AMR) in sexually and non-sexually transmitted infections. Every effort should be taken to ensure the optimal use of antibiotics.

Tetracycline resistance in *Treponema pallidum* (*subsp. pallidum*), the bacterium that causes syphilis, has not been demonstrated. There is no definitive evidence for stable tetracycline resistance in *Chlamydia trachomatis*. Small studies have reported detection of AMR determinants but correlation between *in vitro* doxycycline minimum inhibitory concentrations (MICs) and treatment failure is poor (9). However, stable and transmitted resistance has been seen in non-human chlamydia species such as *Chlamydia suis* (in pigs) due to antibiotic use in farming (10).

Selection pressure on other STIs may not be clinically significant; high rates of tetracycline (doxycycline) resistance in *Neisseria gonorrhoeae* already preclude treatment of gonorrhoea with doxycycline. Doxycycline has poor efficacy against *Mycoplasma genitalium*, although the reason for this is not clear as no molecular basis for tetracycline resistance has been identified in *Mycoplasma genitalium*.

The most difficult, but potentially most significant, risk to quantify is selection of resistance amongst potentially pathogenic bacterial flora such as *Staphylococcus aureus* and respiratory tract pathogens;

doxycycline is a first-line antibiotic for both community and hospitalised patients with skin and soft tissue infections and respiratory tract infections. In an era of increasing AMR, stewardship remains critical to preserve antibiotics.

5. Safety and tolerability

Mild to moderate side effects of doxycycline are common, particularly in combination with HIV-PrEP and are predominantly gastroenterological and dermatological (3, 4). Doxycycline is largely safe when prescribed or supervised by clinicians highly experienced in identifying known safety concerns. Widespread use without clinical monitoring and advice, may lead to unsafe exposures (e.g. in cisgender women or transmen who are or might become pregnant) or failure to recognise rare toxicities.

Box 1: Recommendations for clinicians

- Make asking about the recent use of antibiotics, for any reason, routine. This includes specifically asking about the use of antibiotics to prevent STIs (i.e. as prophylaxis).
- If someone reports using antibiotics for STI prophylaxis:
 - Enquire about and document:
 - which antibiotic(s) they are using
 - how they are taking them (regimen); e.g., as PrEP, PEP or in another way
- Additional tests are not required – the person should be managed in accordance with national and local guidelines for their presenting complaint and subsequent follow up.
- Offer information about the use of antibiotics for STI prophylaxis:
 - The use of antibiotics as STI prophylaxis is not recommended by any national professional organisation because of concerns of antimicrobial resistance in STI and non-STI organisms. Use of antibiotics in this way is off-label and not supported by any guidelines.
 - Studies have only explored the use of doxycycline as prophylaxis for STIs. There are no studies to suggest any other antibiotics might work.
 - The current evidence base is small and only supports the use of doxycycline as post-exposure prophylaxis (PEP) to reduce the risk of infection with chlamydia and syphilis. It would not prevent gonorrhoea or mycoplasma and will not prevent viral STIs.
 - Doxycycline PEP, as used in the Ipergay sub-study, involves taking 200mg as a single oral dose within 24hours of condomless sex, used a maximum of three times per week (600mg total weekly dose).
 - Doxycycline is well tolerated by most people but is not safe in pregnancy. Individuals using doxycycline and for whom pregnancy is a possibility should be advised about options for contraception.
 - Discuss side effects of doxycycline as per the summary of product characteristics (SPC).

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