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SEXUAL HEALTH

Interim position statement on doxycycline post-exposure prophylaxis (Doxy-PEP) for the prevention of bacterial sexually transmissible infections in Australia and Aotearoa New Zealand – the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)

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ABSTRACT

Recent studies have provided evidence for the effectiveness of using doxycycline (Doxy-PEP) to prevent bacterial sexually transmissible infections (STI), namely chlamydia, gonorrhoea, and syphilis, among gay, bisexual, and other men who have sex with men who have experienced multiple STIs. However, there remain several unanswered questions around potential adverse outcomes from Doxy-PEP, including the possibility of inducing antimicrobial resistance in STIs and other organisms, and the possibility of disrupting the microbiome of people who choose to use Doxy-PEP. This interim position statement from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine aims to outline the current evidence for Doxy-PEP, and to highlight potential adverse outcomes, to enable clinicians to conduct evidence-based conversations with patients in Australia and Aotearoa New Zealand who intend to use Doxy-PEP.

Keywords: Australia, chlamydia, doxycycline, gonorrhea, men who have sex with men, New Zealand, prevention, STIs, syphilis.

Introduction

Despite ongoing public health efforts to control the spread of bacterial sexually transmissible infections (STI), rates of chlamydia, gonorrhoea and syphilis have continued to rise in Australia in recent years, especially among gay, bisexual and other men who have sex with men (GBMSM), with the exception of a transient decline in STI diagnoses early during the coronavirus disease 2019 (COVID-19) pandemic.[1–3] The ongoing high rates of STI transmission have prompted exploration of antibiotic prophylaxis using doxycycline (Doxy-PEP) to prevent STIs in people with high risk of STIs. Biomedical STI prevention is not a new concept; for example, during World War I, soldiers were encouraged to apply mercury-containing (Calomel) ointment to their penis after sexual intercourse to prevent genital syphilis;[4] and as early as 1971, the Australian Defence Force utilised doxycycline as STI prophylaxis in Vietnam.[5] The most recent studies on Doxy-PEP, described below, were conducted in San Francisco and Seattle (USA) and by the ANRS (French National Agency for AIDS Research – L'Agence nationale de recherches sur le sida et les hépatites virales) in France and their latest data were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle on 20 February 2023. Based on the results of earlier studies, the San Francisco Health Department now recommend Doxy-PEP, using the eligibility criteria from the USA Doxy-PEP study.[6] The International Antiviral Society-USA Panel also recommend Doxy-PEP 'on a case-by-case basis'.[7] Other jurisdictions are reviewing their positions, including the UK and the USA.[8] Health

authorities in Australia and Aotearoa New Zealand (AoNZ) currently do not endorse Doxy-PEP. However, some GBMSM in Australia are already taking Doxy-PEP, as a survey at Melbourne Sexual Health Centre showed that 9.9% of 1065 PrEP-using GBMSM had used Doxy-PEP during the previous month.[9] The purpose of this statement is to enable clinicians to conduct evidence-based conversations with their patients on the effectiveness and potential risks of using Doxy-PEP.

Effectiveness of Doxy-PEP

Results from the most recent USA and French Doxy-PEP studies

The USA Doxy-PEP study was an open-label study that assessed the effectiveness of 200 mg of doxycycline taken within 72 h after condomless sex to reduce the incidence of chlamydia, gonorrhoea and syphilis. The 554 study participants consisted of GBMSM, transgender women and non-binary people, who were either living with HIV (n = 194) or were taking HIV pre-exposure prophylaxis (PrEP) (n = 360). Participants were randomised (2:1) to either receive Doxy-PEP or not receive Doxy-PEP ('standard of care'), and all participants were then tested for STIs at enrolment, every 3 months, and whenever they developed symptoms of STIs.[10]

The USA Doxy-PEP study observed a 62–66% lower frequency of bacterial STIs in the active arm compared to the 'standard of care' arm ($P < 0.001$). Among 180 participants in the 'standard of care' arm, 95 of 328 (29.0%) quarterly study visits resulted in an STI diagnosis, compared to the 374 participants in the Doxy-PEP arm, for whom 78 of 757 (10.3%) quarterly study visits resulted in an STI diagnosis. They primarily observed reductions in asymptomatic gonorrhoea (decreased from 19.8% to 8.1% of visits) and chlamydia (decreased from 11.9% to 2.5% of visits), reduction of syphilis was not statistically significant (decreased from 2.1% to 0.5% of visits), possibly due to low overall syphilis incidence. No serious adverse effects were seen during 12 months of follow-up, and only 1.5% of participants stopped due to either side effects or preference. A total of 88% of participants in the active arm found Doxy-PEP acceptable or very acceptable.[10]

The French ANRS Doxyvac trial was a randomised open-label trial of GBMSM who had been diagnosed with at least one STI in the past 12 months. They received either Doxy-PEP (200 mg within 72 h after condomless sex) or no PEP (randomised 2:1); and either two doses of meningococcal B vaccine (Bexsero) or no vaccine (randomised 1:1). Participants were tested for STIs at baseline, every 3 months during follow-up, and whenever they had symptoms of STIs. Of the 546 GBMSM enrolled, 502 were included in an intention-to-treat analysis, which found significant reductions in all STIs in the Doxy-PEP arm over 9 months of follow-up: incidence of a first episode of chlamydia or syphilis was 5.6 per 100 person-years (PY) in the Doxy-PEP arm and 35.4/100PY in the no PEP arm (adjusted hazard ratio (aHR) 0.16, 95% confidence interval (CI) 0.08 to 0.30); incidence of first episode of gonorrhoea was 20.5/100PY in the DoxyPEP arm and 41.3/100PY in the no PEP arm (aHR 0.49, 95%CI 0.32 to 0.76). No drug-related serious adverse events were reported. Also, the meningococcal B vaccine proved effective against gonorrhoea (aHR 0.49, 95%CI 0.27 to 0.88). There was no interaction for the primary endpoints between these two prevention strategies.[11]

Results from earlier studies on doxycycline to prevent STIs

The first study to investigate doxycycline STI prophylaxis was published in 2015 by Bolan *et al.*, in which 30 participants in the USA were randomised 1:1 to either 'doxycycline 100 mg daily' versus 'contingency management'. During 48 weeks of follow-up, they found an overall lower frequency of STIs in the doxycycline arm (odds ratio 0.27, $P = 0.02$), but the study was not powered to assess effectiveness against individual STIs.[12]

Subsequently, Molina *et al.* in France conducted a 1:1 randomised open-label study with 232 GBMSM, enrolled in the ANRS Ipergay study, with a protocol instructing participants to take 200 mg doxycycline within 24 h after sex.[13] During 10 months of follow-up, they found reductions in first-episode STIs of 73% in syphilis (HR 0.27; 95%CI 0.07 to 0.98; $P = 0.047$) and 70% in chlamydia (HR 0.30; 95%CI 0.13 to 0.70; $P = 0.006$), but no reductions in gonorrhoea.

Other relevant information

Effectiveness against gonorrhoea will likely depend on background tetracycline resistance in gonococci, which currently sits at approximately 41% in Australia nationally, and at 51% in the state of Victoria, which is the highest level in the country, and at 35% in AoNZ.[14,15] It is postulated that the lack of effectiveness against gonorrhoea in the French ANRS Ipergay substudy, and the relatively lower effectiveness in the French Doxyvac study may have been due to relatively high background rates of tetracycline resistance in gonorrhoea isolates in France.[13]

Other antibiotics are unlikely to be suitable as Doxy-PEP, particularly against syphilis, which is the bacterial STI with the most serious common clinical manifestations.

Potential risks of Doxy-PEP

Antimicrobial resistance (AMR) in STIs

Use of Doxy-PEP might increase the likelihood of infection with tetracycline-resistant strains of gonorrhoea. Indeed, the USA Doxy-PEP study found that 20% of gonorrhoea cases had tetracycline resistance when diagnosed at study baseline, which doubled to 40% of gonorrhoea cases diagnosed during

follow-up.[10] These data were updated at CROI 2023, with the same study now reporting that among participants on Doxy-PEP 38.5% of gonorrhoea cases (i.e. 5 of 13) were tetracycline resistant, versus 12.5% of gonorrhoea cases (i.e. 2 of 16) in participants not on Doxy-PEP.[16] It is unclear whether this represents selective infection with resistant strains, or induction of resistance mutations. However, given that tetracyclines are not used to treat gonorrhoea in Australia or AoNZ, and given the already high rates of tetracycline resistance, as mentioned above, there is no known negative clinical implication for tetracycline resistance in gonorrhoea, unless it confers cross-resistance to the antibiotic classes used to treat gonorrhoea. Importantly, considerations of offering Doxy-PEP outside of clinical trial settings should include considerations of simultaneously offering meningococcal B vaccines to the target population, to reduce the amount of gonorrhoea potentially exposed to doxycycline. The latter intervention is the subject of ongoing studies, including the 'GoGoVax' trial coordinated by The Kirby Institute and Griffith University in Australia.

Doxycycline resistance has so far not been described for syphilis or chlamydia, and this is generally not considered likely to occur.[17] However, we do not know whether doxycycline resistance in *Chlamydia trachomatis* (for which it is the first line and most effective treatment) and *Treponema pallidum* (for which it is the treatment of choice in case of penicillin allergy) could emerge with long term and broader use of Doxy-PEP, as was reported a few years ago with azithromycin-resistant *T. pallidum*.[18] Perhaps the STI with the greatest potential for being impacted by Doxy-PEP is *Mycoplasma genitalium* (Mgen), as this organism has a history of rapidly acquiring resistance mutations.[19] Mgen is common among asymptomatic GBMSM in Australia, with estimates ranging from 9.5% of asymptomatic GBMSM attending Melbourne Sexual Health Centre, to 11.8% of asymptomatic GBMSM on HIV PrEP attending Sydney Sexual Health Centre.[20,21] Doxycycline alone is not usually curative for Mgen infections, but doxycycline is currently used to pre-treat Mgen infections to decrease Mgen bacterial load, and is then followed by a curative antibiotic such as azithromycin, moxifloxacin or pristinamycin.[22,23] It is unclear whether the effectiveness of this treatment protocol could be diminished if GBMSM with asymptomatic Mgen are regularly exposed to Doxy-PEP.

AMR in other (non-target) organisms

AMR is now a leading cause of death around the world,[24] and we must consider that widespread implementation of Doxy-PEP could generate AMR in non-target pathogens and commensals. This was highlighted in a recent systematic review, which found that oral tetracyclines for 2–18 weeks may increase AMR in subgingival, gastrointestinal and upper respiratory tract flora.[25] The USA Doxy-PEP study assessed AMR in nasal/oropharyngeal *Staphylococcus aureus* and pharyngeal non-gonococcal *Neisseria* species among 501 participants, and at month 12 found that participants on Doxy-PEP had lower carriage of *S.aureus*, compared with participants not on Doxy-PEP (29.2% vs 45.2%, $P = 0.036$), but a greater proportion of *S. aureus* culture samples were doxycycline resistant in the Doxy-PEP arm (11.7% vs 4.8%, $P = 0.19$). They found no increase in methicillin-resistant *S. aureus* (MRSA) overall, nor in doxycycline-resistant MRSA. After 12 months, there was no difference in carriage of non-gonococcal *Neisseria* species between the treatment arms, but participants in the Doxy-PEP arm were more likely to carry doxycycline-resistant *Neisseria* species (69.7% vs 44.6%, $P = 0.017$).[16] The Australian Strategic and Technical Advisory Group on Antimicrobial Resistance currently rate doxycycline use as being of 'low importance' for the mitigation of AMR, on the basis of there being a reasonable number of alternative antimicrobial classes available to treat or prevent most human infections even if antibacterial resistance were to develop.[26] Correspondingly, the long-standing practice of using doxycycline for primary prophylaxis for malaria, leptospirosis, Lyme disease, and scrub typhus means that many people have taken long courses of doxycycline for many weeks to months.[27] In addition, millions of people have used long courses (lasting from weeks to months) of doxycycline and other tetracyclines to treat acne.[28] Furthermore, in non-human animals, including pets and livestock animals, large quantities of tetracyclines are used as growth promoters and to treat and prevent various infections.[29] While recent data are lacking, the Australian Pesticides and Veterinary Medicines Authority reports that between 2005 and 2010, tetracyclines were the most commonly used antibiotics in animal husbandry in Australia, at 44–66 tonnes of active constituent per year.[30] Concerns around AMR resulting from Doxy-PEP must be placed in this context of widespread tetracycline use in humans and non-human animals. It is also important to consider that, the GBMSM population is currently prescribed very high quantities of antibiotics to treat STIs. For example, on a yearly basis GBMSM in a HIV PrEP cohort in Antwerp (Belgium) were found to consume up to 52 times the average amount of macrolides consumed by residents of 30 European countries.[31] If Doxy-PEP is targeted to be delivered to those people at highest risk of STIs, and if Doxy-PEP achieves reductions in population-level transmission of STIs, then this could reduce population-level consumption of antibiotics used to treat STIs (e.g. doxycycline, penicillin, ceftriaxone and azithromycin), which might offset some of the increase in the use of doxycycline for Doxy-PEP.

Current Doxy-PEP studies are investigating effects on AMR, and mathematical modelling studies can help to identify optimal eligibility criteria for Doxy-PEP, to quantify the projected scale of uptake of Doxy-PEP, and to assess potential effects on consumption of other antibiotics.

Effects on the human microbiome

Doxycycline use has been associated with a loss of diversity in the human gut microbiome,[32] and disturbances of the gut

microbiome have been linked to a broad range of chronic diseases, ranging from diabetes, to autoimmune diseases and mental health disorders.[33] As one concrete example, tetracyclines such as doxycycline are used to promote weight gain in livestock, and this effect is thought to be mediated by effects on animals' gut microbiome.[34] The USA Doxy-PEP study, the ANRS Ipergay study, and the Syphylaxis study in Australia are investigating effects of Doxy-PEP on the composition of participants' microbiome.

ASHM interim position statement

Results from the USA Doxy-PEP study and the French Doxyvac study are encouraging and consistent with those of the ANRS Ipergay Doxy-PEP substudy, and indicate that Doxy-PEP could be useful for people who have experienced multiple bacterial STIs. However, there remain some significant unknowns regarding unintended outcomes from Doxy-PEP, and it is unclear how these unknowns may impact the safety of Doxy-PEP if implemented in larger numbers of people outside of a clinical trial setting. Such unintended outcomes may include harms to individuals taking Doxy-PEP, such as disruptions to their microbiome and increased AMR, and harms to the community through increased population-level AMR. Clinicians working with patients taking or considering taking doxycycline will need to balance increasing evidence of benefit with concerns about potential harm, as outlined above.

ASHM supports the implementation of evidence-based interventions that improve the lives of people who are affected by STIs, and to further explore the issues raised in this interim statement. In 2023 ASHM will convene a forum of community representatives, clinicians, and experts in infectious diseases, public health, epidemiology, and antimicrobial resistance, to thoroughly review relevant data, exchange expertise, and aim to develop clear guidance for the community and clinicians on the utility and potential risks of Doxy-PEP, and to identify relevant research priorities.

Process for development and endorsement of these recommendations

1. V. Cornelisse conducted a rapid scoping review, to identify recent Doxy-PEP studies in published literature and conference proceedings, and to identify recent authoritative literature on associated issues such as antimicrobial resistance.
2. Initial statement drafted by V. Cornelisse and N. Medland, after review of relevant evidence.
3. Draft statement reviewed by ASHM's standing National Advisory Group on Sexually Transmitted Infections, which consists of leading sexual health clinicians in Australia and Aotearoa/NZ. Advisory Group members who provided feedback are included as authors. Comments from the Advisory Group were collated by ASHM support staff.
4. Draft statement edited by V. Cornelisse to incorporate comments from the Advisory Group.
5. Final statement returned to the ASHM National Advisory Group on Sexually Transmitted Infections for endorsement.
6. Statement submitted to *Sexual Health* for peer review.
7. Peer reviewer comments addressed by V. Cornelisse, with input from additional authors (see author list), and reviewed and approved by the ASHM National Advisory Group on Sexually Transmitted Infections.
8. Revised statement returned to *Sexual Health* for publication.

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Data availability. All the relevant data referred to in this manuscript is publicly available in the references provided.

Conflicts of interest. VJC, BD and NM are co-investigators on the Syphilaxis study (ClinicalTrials.gov Identifier: NCT03709459) at The Kirby Institute, which has not received industry funding, and have no other conflicts of interest to declare. J-MM reports Advisory boards for Gilead, ViiV and Merck and research grant from Gilead. JJO is an Editor of *Sexual Health*, but was blinded from the peer review process for this paper. All other authors report no conflicts of interest.

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