STIs and doxyPEP at EACS: community effectiveness, gonorrhoea resistance and 'blunted' syphilis

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A significant number of presentations at last week's 20th European AIDS Conference (EACS 2025) in Paris were concerned with the bacterial sexually transmitted infections (STIs) syphilis, gonorrhoea and chlamydia rather than HIV. This is largely because using the antibiotic doxycycline to forestall infection after possible exposures – doxyPEP – has become more common in western Europe.

This is despite doxyPEP being subject to differing opinions among experts. Whereas the UK's STI professional society BASHH issued guidelines for doxyPEP use on 9th June this year, a year after the US CDC issued its own, the European equivalent, ECDC, has yet to release its guidelines, though a draft document is currently out for consultation. Reservations concerning doxyPEP centre on its limited efficacy against gonorrhoea and whether it will lead to an increase in antimicrobial drug resistance.

This has left European doxyPEP advice and guidance largely in the hands of community and patient advocacy organisations like The Love Tank and EATG. Possibly because of this and because of widespread informal use by the LGBT+ community, clinics are now offering doxyPEP, even in countries where official guidelines still do not recommend it.

One such is Switzerland, where despite doxyPEP not being recommended by the Swiss health authority, several studies have been conducted and the Zurich City Hospital started offering doxyPEP to attendees at its HIV clinic in late 2023.

They also offered the meningitis B vaccine 4CMenB (*Bexsero*), which offers some protection against gonorrhoea and which the English NHS has already licensed.

The Swiss doxyPEP and gonorrhoea vaccine study

A non-randomised, observational study looked at the effect of offering both doxycycline and the 4CMenB vaccine to the HIV-positive gay men and trans women attending the Zurich City Hospital's clinic.

Dr David Wimmersberger told the conference that the study compared the incidence of the three STIs in clinic attendees in the 19 months after these interventions were made available (from November 2023 to June 2025) with incidence in the same people during the three years leading up to its introduction (starting November 2020).

The criteria for offering doxyPEP were considerably wider than in randomised controlled studies. DoxyPEP and 4CMenB were offered to people with HIV who had had condomless sex with a casual partner and/or one or more bacterial STIs in the last three years.

There were a total of 266 people in the study of whom 152 (57%) were prescribed doxyPEP alone and 114 (43%) had both doxyPEP and the 4CMenB vaccine. The two groups were similar in age and in the median number of STI diagnoses in the three years prior to doxyPEP (just

one). But the group receiving 4CMenB were slightly more likely to be White and, not surprisingly, had higher gonorrhoea incidence (22.4% annual incidence vs 15.8%).

Uptake of doxyPEP was rapid, with all participants receiving it by April 2024. Incidence of the three STIs taken together halved after doxyPEP was introduced (49% efficacy). Chlamydia diagnoses fell by 71% and syphilis by 68%, broadly in line with other studies. But gonorrhoea cases overall only fell by 11%, and this was not statistically significant.

Considered longitudinally from the start of the study period, syphilis incidence peaked at 15% a year in 2022 but has since declined to 6%; chlamydia incidence peaked at 20% in 2023 but is now down to 7%. However, gonorrhoea incidence, at 21% a year, has not declined since 2021.

Among those who received the vaccine as well as doxyPEP, annual gonorrhoea incidence fell by 29% in 4CMenB vaccine recipients (from 22.4% a year to 15.8%) whereas it actually rose by 11% in non-recipients (from 14.8% to 16.4%). Although these changes in incidence were not statistically significant, they compare to an average efficacy of 32.4% in nine previous studies of the vaccine.

Other gonorrhoea vaccine studies

In an EACS 2025 symposium, Professor Jean-Michel Molina said that gonorrhoea remained a global health problem, especially due to its capacity to develop drug resistance.

Although a modelling study had found that a vaccine with an efficacy as low as 25% could reduce the overall community prevalence of gonorrhoea by 30% within two years, its prevalence would quickly rebound after that and return to baseline prevalence within 10 years. A 90% effective vaccine would be needed to achieve a permanent reduction in gonorrhoea prevalence.

Molina noted that the only study of a vaccine specifically tailored to the gonorrhoea bacterium rather than to meningitis B has been halted at the end of last year due to disappointing results. Molina was the principal investigator of the only randomised trial of the 4CMenB vaccine so far, the DOXYVAC study, which did not show a statistically significant difference in gonorrhoea incidence. But the results of three randomised studies of 4CMenB are awaited: GoGoVax in gay and bisexual men in Australia, MAGI in men and women in Thailand, and Biyela in young women in South Africa. Results from the first two are expected next year and the third in 2027.

Molina commented on this vaccine: “The data is inconclusive. A small benefit cannot be ruled out, but clinical relevance seems very limited.”

DoxyPEP and gonorrhoea drug resistance

Professor Molina also presented results from the open-label extension of the DOXYVAC study, focusing this time on doxyPEP (the study investigated both the 4CMenB vaccine and doxyPEP). He compared the results of the randomised, placebo-controlled phase of the study from January 2021 to September 2022, to the open-label phase of the study from September 2022 to September 2023. The randomised phase was stopped earlier than intended because the benefit of doxyPEP for chlamydia and syphilis was clearcut and all participants were offered doxyPEP.

In the randomised arm, doxycycline had 86% efficacy against chlamydia, and 79% against syphilis but only 33% against gonorrhoea. In the open-label phase, efficacy in the 149 people who switched from placebo to doxyPEP was 75% against chlamydia and 76% against syphilis.

A piece of good news was that efficacy against gonorrhoea was 55% in the open-label phase, with annual incidence reducing from 68% to 31% – though, as this is non-randomised data, changes in behaviour could have played a part in this result too.

Less encouraging was the increase in drug resistance in the gonorrhoea bacterium *Neisseria gonorrhoeae*, not only to the tetracycline class of which doxycycline is part, but to cefixime, a drug in the cephalosporin class, which is now the drug family mainly used to treat gonorrhoea. High-level phenotypic resistance to tetracyclines, meaning drug failure in the test-tube against samples of *N. gonorrhoeae*, was 10.6% in samples not exposed to doxycycline and 37.5% in exposed samples. Genotypic resistance, meaning the detection of a protein that confers resistance called tetM, was 27.9% in non-exposed samples and 54.5% in exposed samples.

High-level resistance to cefixime was thankfully not detected in the samples, but 8.5% of non-exposed samples and 35.4% of exposed samples had 'reduced susceptibility' to this drug. Another drug from the cephalosporin family, ceftriaxone, is now the first-line drug used for gonorrhoea as its longer half-life makes it less susceptible to resistance, and so far cases of ceftriaxone-resistant gonorrhoea are rare.

Silent syphilis infections on doxyPEP

Finally, another study presented at EACS 2025 discussed 'breakthrough' syphilis infections – cases where people acquired syphilis despite taking doxyPEP.

Dr Cristina Gómez-Ayerbe from Malaga University Hospital in Spain described a diagnostic challenge similar to one seen with HIV infections in PrEP users. Like HIV, syphilis is diagnosed by detecting antibodies to the pathogen. However, this can be difficult or delayed when doxyPEP partially suppresses syphilis – especially with sub-optimal use – because it results in unusually low levels of antibodies.

Syphilis testing is additionally complicated because previous infections don't provide immunity, so people can be re-infected after being treated and cured. Normally, low levels of antibodies to syphilis remain after a resolved infection and can be distinguished from the high levels seen in new infections. But in breakthrough infections in people taking doxyPEP, this distinction becomes blurred. Being unable to distinguish between old and new infections has implications for clinical decision-making and prevention of onward transmission too.

She presented data from nine gay and bisexual men with breakthrough infections from a randomised trial at her clinic, whose main results were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) this year. In that study doxyPEP efficacy against syphilis was 85%; in practice this meant that there were 61 syphilis cases before the initiation of doxyPEP and nine cases afterwards.

Eight of the men were HIV-negative PrEP users, and one was living with HIV. Their ages ranged from 27 to 49. Three had pre-existing low levels of syphilis antibodies, indicating previous infections; two of them were among the youngest in the study. Adherence to doxyPEP was good or adequate in all but one person, whose adherence was poor.

Antibody levels in syphilis are indicated by titres, which are the degree to which an antibody culture has to be diluted with normal saline to be ineffective.

A 1:1 or 50/50 dilution indicates a very weak antibody response, almost certainly not associated with an active infection, where titres of 1:16 to 1:64 are more usually seen. Higher

numbers indicated more antibodies, and in this study a 1:32 titre was only seen in the person with poor doxyPEP adherence.

The others had titres of 1:2 to 1:8, which usually indicate a treated or latent infection. One person had a primary (very recent) infection and had a very low antibody level of 1:2 because of that; but the other seven had levels between 1:4 and 1:8, which would normally indicate an infection that had been treated but where antibody levels declined more slowly than average. In these cases it appears that the antibody response was 'blunted' by exposure to doxyPEP.

All nine people were successfully treated, but Dr Gómez-Ayerbe warned that clinicians needed to be aware that the use of doxyPEP could lead to a rise in 'silent' or serologically atypical infections.

References

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