IUSTI Europe – Webinar 21
14 Dec 2023
To DoxyPEP or not to DoxyPEP

Questions from participants

Disclaimer: This summarises responses given on the night with some additional information and references. It is not intended as a position statement of IUSTI Europe or of any of the webinar presenters and is provided solely to encourage debate and personal reflection on this particular educational event.

Epidemiology

Could the increase in infections be in part due to a big increase in screening - online STI kits and regular PrEP screening?

From the European STI Surveillance data, we cannot retrieve evidence for changes in screening/testing policies or testing rates, as these data are not collected in relation to notified cases. However, both of these factors can play a role. Expansion of PrEP for HIV programmes, which come with an enhanced opportunity for regular and more frequent STI testing, is an important driver of the increases in bacterial STI diagnoses observed in recent years among men who have sex with men with HIV-negative status. However, we cannot exclude an increase in transmission intensity through MSM sexual networks.

What lies behind the unequal distribution of congenital syphilis in EU/EEA – notably the high prevalence in just three countries? Do those three countries -- as in the US -- lack regular screening of pregnant women? Has there been a reduction in screening of pregnant women in those three countries? Are we talking about single cases or significant numbers?

Indeed, in recent years, congenital syphilis cases have been reported in higher numbers in Bulgaria, Portugal, and Hungary. Based on the existing data, the main risk factors for this concern pregnant women from key populations such as those with a migrant background and those from certain ethnic groups, who present late for antenatal care or present at the time of delivery. Failures from the part of healthcare services to test pregnant women for syphilis and provide appropriate treatment have been also documented. Although we are discussing

small numbers and congenital syphilis rates are well below the WHO targets, there are still remaining 'hot spots' or pockets of vulnerable populations. Even with a 95% antenatal screening coverage in many countries, there will be failures in preventing vertical transmission.

Has anyone looked at sexual behaviours (pansexuality etc) where previously there were clearer separations between heterosexuals and MSM? We now see parties with more than two people having sex and of differing orientation which supports transmission across different risk groups

The role of bridging populations (e.g. heterosexually-identified men who have sex with men) and mixing between MSM and heterosexuals can be considered as contributing factor. What the European surveillance data have shown over the last decade is an important gap between the high levels of syphilis notifications among MSM and the stable, low levels of case notification in heterosexual men and women. This seems to change in 2022, with an increase in the number of cases among heterosexuals. The ECDC aims to implement behaviour surveillance in the coming years.

DoxyPEP and off-target effects

Could you tell me if the impact of doxycycline as PrEP or PEP on the gut microbiota has been studied? Has this not been looked at in patients treated for acne?

This is covered in the webinar presentation from Prof. Chris Kenyon

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DoxyPEP and testing policy

What would be the benefit of DoxyPEP if you advocate for 3-monthsly STI screening anyway?

To reduce incidence of syphilis and chlamydia at the individual and population level especially in areas with high syphilis incidence

Where does DoxyPEP fit given the discussion and paradigm shift towards not screening for or treating asymptomatic chlamydia? You recommend to test every 3 months patients on doxy PEP - but the trend is that of reducing testing in asymptomatic patients... can you please further elaborate?

Prof. Molina comments: I agree that with doxy PEP there is a pretty strong rationale to test less frequently, say once a year plus in case of symptomatic STIs, but we have limited data to support this recommendation

Prof. Kenyon's view: If one's primary focus is reducing STIs then one can make a compelling case for doxyPEP. If however one focus is the health of one's clients and the general population then the case for doxyPEP is far weaker. We have empirical data that doxycycline selects for AMR and has adverse effects on the microbiome, resistome and metabolome.

Most of the STIs that are averted by doxyPEP are asymptomatic STIs and so a big divergence of opinion is now is what could be termed the "antibiotic-based" versus the "stewardship" approaches to health care for PrEPers. The AB-approach is based on the primary focus of decreasing STIs and would thus favour 3 site, 3 monthly (3x3) NG/CT screening and doxyPEP. The stewardship approach would follow the Belgian PrEP guidelines and stop routine screening for CT/NG in MSM and limit doxyPEP to study settings where we can get a clearer idea of the risks vs. benefits.

*According to Vanbaelen at al modelling paper, the introduction of doxyPEP in the setting of 3x3 NG/CT screening would lead to a halving of ceftriaxone and azithromycin consumption but a 17-fold increase in overall antibiotic consumption driven by a 26-fold increase in doxycycline use. If one stops 3x3 screening then the introduction of doxyPEP leads to a halving of ceftriaxone and azithromycin consumption but now a 55-fold in overall antibiotic consumption driven by a 92-fold increase in doxycycline use. Note that's a **55-fold** not a 55% increase in antibiotics.*

So there's clearly interaction between doxyPEP and screening. We need RCTs to see what the net benefits and risks are in both scenarios.

What is your opinion regarding the lack of evidence supporting asymptomatic screening for GC/CT as we all routinely do in PrEP services?

The 'Gonoscreen' RCT that addressed this issue is now in press at Lancet HIV but can be seen as a preprint. More studies are needed:

DoxyPEP and impact on STIs

What is known on the effect of doxycycline on VDRL titres? Is there any evidence about the impact of Doxy PEP on the RPR of someone who might already be +ve for Syphilis before starting?

The evidence so far in DoxyPEP trials does not suggest much impact. Someone incubating syphilis who then takes DoxyPEP once infection is established without realising may have a blunted RPR response. Up to 60% of syphilis infections occur in people with previous infections and these are frequently

asymptomatic. We currently assume that harm only comes once there is a significant rise in RPR which suggests syphilis disease activity. DoxyPEP RCTs used a 2-titre (4-fold) rise in RPR titre as diagnostic. Longer term studies are required.

May I ask if there is any breakdown of symptomatic vs asymptomatic CT/GC effect?

We looked at that issue and there is a benefit of doxyPEP also in those with symptomatic infections, although the number of events is lower, so the evidence is less clear

Is the less than 100% efficacy believed to be due to non compliance

Most likely, this was an intent-to-treat trial

DoxyPEP – how to use

Why do you advocate to only use Doxy once or twice per week? how did you check? Did some people go over the top — who were they?

It was a recommendation to avoid too much selective pressure by antibiotics . We need modelling studies to look at this issue in more detail.

Can people buy Doxy on the internet? Is it known if they do so and use it as PEP or PrEP?

Yes this varies by country/local restrictions but is being reported - one reason for tonight's webinar; the other concern is people buying alternative antibiotics like macrolides instead of doxycycline hoping this will work.

DoxyPEP – managing clinical presentations

Could the use of doxyPEP make LGV infections less symptomatic and thus delay diagnosis?

We did not have evidence for that in our trial. There was such a strong reduction of chlamydia infection with doxy that it is difficult to answer.

In terms of partner notification, how should we manage contacts of syphilis, who took doxyPEP? Would you give epidemiological treatment to someone who shows up two weeks after a contact with syphilis, but he took doxyPEP? The issue is that at that time it might be too early to rule out syphilis...

This has to be an individual choice. If relying on DoxyPEP, syphilis cannot be excluded until the end of the serological window period, and there is a small risk if DoxyPEP fails of developing symptomatic syphilis. We know that post-

exposure treatment with benzathine penicillin has very high efficacy and some patients may prefer this.

DoxyPEP and setting

The only study done with cisgender women participants – the dPEP Kenya trial – found that doxyPEP was not effective at preventing bacterial STIs. Which do you think were the reasons making it different from your studies in France and the SanFrancisco study in MSM?

We know that PrEP adherence is lower in LMIC in particular in women who do not always considered themselves to be at risk. I suspect this would be the same for DoxyPEP, explaining the low adherence in young women in particular.

MSM enrolled in DoxyPEP trials were used to being tested for STIs, were mindful of STIs and the interest for reducing their incidence

Do you see different challenges in using DoxyPEP in LMIC?

Adherence may be an issue, as reported by Stewart et al in the Chicago meeting. We need demonstration projects in LMIC countries

How do we draw a line between the many people who extrapolate the demonstrated relative-risk-reduction to much-lower-incidence populations, and what would this mean regarding the AMR concerns that Chris has brought forward?

We really need trial data and modelling studies to guide this decision making. People enrolled in doxyPEP studies were at high risk with a high number of partners

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DoxyPEP – communication and patient engagement

I appreciate your cautious approach and the need for monitoring — but there is a large pressure for some groups (both clinicians and certainly clients) — what would you tell these people?

We should tell them what we know, (effectiveness, safety) and what we do not yet know (impact of the microbiome, selection of drug resistance…). Be non judgmental and monitor people who want to use doxyPEP

Is anyone aware of any qualitative research on motivations/decision making/concerns within the populations of interest? I'd imagine there is diversity in how people would use DoxyPEP ie. some after every sexual encounter, others maybe just when they consider their sex as 'higher risk'

These studies are planned

DoxyPEP – contribution to antimicrobial resistance

In comparison to antibiotic consumption by food industry, its levels in soil and water due to uncontrolled wastes - how much to we expect strategies as DoxyPEP to be adding to the AMR?

All sources of antibiotic exposure are important. We need to practise stewardship everywhere if we want to retard the current trend we are on towards more AMR – related deaths than cancer by 2050. It's analogous to climate change: everyone needs to do their bit. So the food industry is clearly important but we need to play our part and ensure that our clients get the antibiotics they need but not an excess.

DoxyPEP- future research questions

What is the study/ studies do we need to do to answer the questions you highlight? Over what timeframe to conduct these studies?

There was not time to go into this on the night. Those viewing the webinar may wish to review clinical trials.gov at this link to see active trials in this area

I think Professor Kenyon's argument on MIC re-analysis of Professor's Molina's data is quite compelling — could the investigators of the trials perhaps present a reanalysis of their own findings?

Prof Kenyon comments: As part of a systematic review on the topic, we asked the authors of the doxyPEP and IPERGAY trials to provide us with their individual colony MICs for NG so that we could reanalyse their data according to effect of doxyPEP on MIC distributions rather than proportion resistant. Only the authors of IPERGAY provided this data and the number of isolates provided (around 10) was too small to warrant analysis

Prof Molina comments: We agree and already provided our MIC data to Dr. Kenyon. Still the effect is not so clear as isolates in France are already mostly resistant, and there is little room to show a shift in MICs