Clinical Education Initiative
Support@ceitraining.org

EMERGING ISSUES IN THE MANAGEMENT OF STIS: DOXYCYCLINE AND STI PREVENTION

Daniela DiMarco, MD, MPH

04/11/2023

Emerging Issues in the Management of STIs: Doxycycline and STI Prevention [video transcript]

00:08

Dr. Ervin is a professor of medicine and the Division of infectious diseases at the University of Rochester School of Medicine and Dentistry. Dr. Urban is also the Medical Director of the Monroe County sexual health clinic and as the director of the CEI Sexual Health Center of Excellence, welcome Dr. Irvin.

00:24

Hey, thanks very much. And thanks, all of you for joining us this early morning. We're going to talk today about doxycycline. Used as a preventative antibiotic to prevent STIs. And I'm going to go through the evidence that's available to date. I have no disclosures as mentioned earlier, and the objectives particularly for this session are to describe the findings from recent literature regarding doxycycline used as PrEP pre exposure prophylaxis, to prevent STIs. And used as PEP post exposure prophylaxis to prevent STIs. So the background of course, I'm sure if you're on here, you know that rates of STIs have been increasing year over year. And then now we have evidence of success with the prevention of HIV infection with the use of both PrEP and PEP Pre Exposure and post exposure prophylaxis. And that sort of led to the thinking that here we have evidence of biomedical interventions that are feasible and acceptable to the community. There's also background that doxycycline has been used as prophylaxis and other conditions including acne, malaria, Lyme disease, leptospirosis, so there was potential to consider this for the reduction of at least bacterial STIs, such as chlamydia, syphilis, maybe got a caucus, we know there's some doxycycline or tetracycline resistance and maybe Mycoplasma genitalium. And there are ongoing clinical trials, so we're really looking at the evidence kind of midstream have a number of trials. So I'm gonna go through the literature to date, but I'm not really going to review a bulk of the literature that was related to interest surveys and lead. These have been conducted since over about 10 years 2011 to 2022. And I put the references here for you can look at later. But essentially, they've all shown high interest among the community surveyed about their interest in using this, which included men who have sex with other men and transgender women in most of these publications. And that interest was high ranging somewhere between 45 and 90%. With most clustering between 60 and 80%, these surveys were done in a variety of locations shown here. And most included a high proportion of people already using HIV crowd. There have also been some surveys that looked at off label current use of doxycycline, or antibiotics to prevent STIs. These haven't been done in the US that I found, but there have been others from around the world. And these looked at in self reported use and found rates up between two and 10%. Already, but notably, some were using antibiotics other than doxycycline, such as ciprofloxacin, or amoxicillin, which really there's not any data at all. Showing effectiveness of of those drugs, therefore, also been some projections

or modeling kinds of studies. And one modeling study that's cited quite often assumes a 70% effectiveness of antibiotic prophylaxis. And they show that if this were used by 50% of the community of men who have sex with men, you would reduce syphilis cases by 50%, after a year, or 85%, after 10 years using the assumptions that they did in their model. Also, there was a presentation at CROI this year, just in February, that looked at not not really modeling but but use their history of STIs at Fenway center, and then applied various mathematical projections of how many would have been prevented if they had used Doxie PEP as as presented at that I'll tell you about later with about a 70% effectiveness, what would be the most efficient way to use this intervention. So that's a publication that will likely come out in the next year or so. But really, what we're going to talk about today are efficacy trials and there are three trials now I have to change this talk sort of suddenly, because the third one was published on Friday. So there are three published efficacy trials one a day oxy PEP study, a pilot study and other Doxy PEP study. And now the third just on Friday, a second Doxie PrEP, randomized clinical trial. There are also another four presentations that are available that are not formally published, but were presented at meetings and were peer reviewed to get into those meetings. And so we'll talk about those as well. So the first I'm going to mention is doxycycline prophylaxis to as PrEP. This was a small pilot study, you can see back here in 2015, it was published and it involved 37 subjects who were living with HIV, and were adults over the age of 18. They were men who have sex with men or transgender women. And to be enrolled in this, they had to have two or more episodes of syphilis that was already treated since their HIV diagnosis. This intervention was doxycycline 100 milligrams once daily for 36 weeks. And the control arm was a standard of care of STI testing and treatment, but also with sort of a financial reward if you were STI free at your follow up visits. And this model actually hasn't been replicated in any of the subsequent studies. They ended up screening 37, they had to some screened out for a variety of reasons. And they ended up with 15 subjects in each arm, that doxycycline arm and the financial incentive arm, there is about a 20 to 27% loss to follow up. So even though this is quite a small study, they lost several two follow up. And they ended up having 353 visits to evaluate in the ducts, the arm and 49 visits to evaluate in the control arm. Here you can see from the paper the results. So they had a trend toward less infection in the doxycycline arm with four cases of gonorrhea, chlamydia versus eight, two cases of syphilis versus seven, and that they achieved statistical significance in follow up at 48 weeks after the study was over, so it was sort of a promising study, there was a trend toward STI protections were 36 weeks and then statistical significance at 48 weeks, they did note that there was some doxycycline use and the control arm, so they didn't exactly know why that was and that could have interfered with the study. But they felt that this was promising to lead to future studies to evaluate doxycycline as pre exposure prophylaxis to prevent syphilis, and Chlamydia but not necessarily gonorrhea. There were concerns about resistance. There is a second pilot study. This was not formally published, but was presented in 2021. At the coin meeting, it comes out of Canada. And this was also a randomized clinical trial one to one for 48 weeks. Again, it was individuals in this trial, these

were individuals not living with HIV, but on HIV PrEP with TDF FTC. And there, they weren't randomized to 100 milligrams daily of doxycycline for two years for 48 weeks, versus 100. Man milligrams daily of doxycycline, but not starting until week 24. So the comparison was in that first 24 weeks. They did sort of standard follow up in most of these studies where they looked at quarterly STI and HIV testing, they assess tolerability assess acceptability. They also looked for evidence of Tetra cyclin resistance and other bacteria including Staph aureus. And they did a rectal microbiome evaluation which hasn't been

09:01

recorded yet. So they found that of the 52, there were 51, who were men who have sex with men, one transgender woman, the average age was similar to the prior study. So in the mid 30s, they had us very high adherence 89% and the immediate arm and 72% in the deferred arm, and notably no one on doxycycline develop syphilis work for medica. So that was highly statistically significant. There were no cases after 24 weeks when everyone was on drug. And you could see there were 10 cases in the deferred arm in the first 24 weeks versus zero in the immediate arm. Syphilis was not statistically significant because there were so few cases one case in a different arm versus zero in the immediate arm. In contrast, gonorrhea there were eight cases in the deferred arm versus four in the immediate arm. And one case also happened after the 24 weeks from now. And the individual was on therapy. They did note that in the obedient arm one out of two at 24 weeks, and three out of six at 48 weeks, had Staph aureus that was resistant. So 50% resistance to tetracycline, and then with the deferred arm also 50% resistance, so relatively low colonization with staff, but a high rate of tetracycline resistance. So they concluded, similarly to the first study that Doxy PrEP did reduce the incidence of chlamydia, they were unable to comment on syphilis because there were not very many cases, adherence was good. They were a little concerned about the high rate of resistance of tetracycline, although it was the same in both arms. And they propose a larger study, which they have now announced is enrolling. It's called the disco trial. And it's Doxie PrEP, versus Doxie, PEP versus standard of care, which is a test and treat quarterly. So we'll await the results of that trial. Then comes the next published study, which is a Molina's trial, which was a sub study of an HIV PEP title conducted in France known as super gay. This was also adults, who were men who had sex with other men who were on PrEP TDF FTC. In this trial, it was a one to one randomization, and it was the same. This is the first stocksy PEP we're talking about. So the intervention is doxycycline 200 milligrams as post exposure prophylaxis to be taken within 24 hours and up to 72 hours. After unprotected oral or anal sex, you were advised not to take more than one dose in a 24 hour period. And in this trial, they were concerned about leading to antibiotic resistance of other bacteria. So they were instructed to take no more than three doses per week. The control arm was standard of care, so no prophylaxis and test and treat in a quarterly manner. They did follow up. Similar to what I've mentioned. So socio demographics, sexual and drug use behaviors, adherence, they do do pill counts and self report abuse of Doxy.

And they also did doxycycline drug levels. This was also an an HIV PrEP trial. This was a subsequent study within that, so they were receiving a counseling about risk reduction. And their outcomes were the first STI after enrolling, and then a secondary outcome of all STIs. After enrolling, they end up with approximately 300, who are screened, they had 67 excluded of which there was a high refusal rate, and we're not interested 54 And they ended up with 116 in each arm. So I'm just going to point out quickly this was also fairly old age for STI. So median age of 38. This was a largely a white population. And this is conducted in France. A high rates of use of recreational drug about 40% in both aren't number of sex partners in the last 10 months in the last two months was 10 in both arms, and you can see the range there. And baseline STIs at screening was a fairly high 90% in the PEP arm and 14% in the no pet barn. And over here you can see they had a statistical significance. Looking at this Kaplan Meier curve, so no prophylaxis is in the red. And over as month progress, the proportion of individuals who acquire an STI goes up. And you can see in the PEP arm. So the blue are the people taking Doxie out, you can see the big gap there. So that was statistically significant. So they had 28 STIs in the PEP arm versus 45 STIs in the no PEP arm in the first nine months. So that was approximately a 45% reduction in STIs. However, if you break out the STIs, this looks at the curves the graph of GC, there was no difference. So there was no protection of post exposure prophylaxis for the prevention of GC in this trial, whereas there was protection with chlamydia. And with syphilis shown here, and those ended up for chlamydia and syphilis being about a 70% risk reduction when they looked at the median number of pills, so this is number of pills, it's approximately seven per month. So that's approximately 3.5 doses per month. The PEP arm about 84% of visits had some DOCSIS Cyclingnews detected by drug levels. They did note that PEP usage decreased over time, so people stopped using it over the nine months. And of those who were taking it 83% said they took it in the first 24 hours not waiting for the 72 hours, they had a fairly high dropout rate of stopped using PEP, over time with 25%, and eight were due to gi side effects. The sexual behaviors did not change significantly over time, or between the groups except for decreased condom use in both groups over time. So they concluded that there was a reduction in bacterial STIs of 47% in the pet arm. This was if you exclude and GC up into the 70% range for reduction in relative risks for chlamydia and syphilis. With Doxie. PEP, they did have this caveat that there was a high uptake early on, and then less usage over time. And they also like, oh, that first PEP file I mentioned, had some unexpected death doxycycline usage in the control arm. So whether people were using it off label, or for some other condition was unclear. And they worry about the resistance in gonorrhea or potentially in other organisms. So then, the next chronologically to come is a report out of Philadelphia. And this is has not formally been published, it was presented at the US STD conference in 2020. And this group assessed, really the feasibility and acceptability of Doxie PEP after the Molina trial in their HIV PrEP clinic. And you don't have to read all of this. But essentially, they gave their patients on PrEP Doxie that they could use as PEP and instructed them to use it and the way it was done in the Molina trial. And then they saw roughly in just one quarter, how many used it and it turned

out only 40% actually took the Doxy PEP so this is the only sort of real world trial. And we don't have really any other information about that this population and people gradually used it with more frequency as time went on. But just one snapshot presented at the STD conference. And then we come to sort of the big news. So on Friday, we had the publication in the New England Journal of a report that was first presented in July of this year at the International AIDS Society meeting and has generated a lot of headache have actually published editorials, and sort of popular press articles. So this is a study conducted in the US in San Francisco and Seattle, it was called the Doxy PEP trial, and it was post exposure doxycycline to prevent bacterial STIs. It was set up similarly to the Molina trial I just talked about, and except that it was randomized two to one to favorite Doxy PEP, so there are twice as many randomized to the intervention of doxycycline versus the standard of care of testing treat at QUT to three months. This trial also included two cohorts of individuals who were on Doxie PEP, and they were those cohorts were evaluated separately. So you were either on HIV PrEP, or you were living with HIV and on antiretroviral therapy. In both of those cohorts, you had to have a male sex at birth, and be having condomless sex with a male partner in the last year. Although you could be a man man having sex with other men or transgender woman with male partners, and you had to have greater than or equal to one STI in the prior year. That included gonorrhea, chlamydia, or syphilis. The intervention was the same as in the Molina trial of 200 milligrams of doxycycline. within 72 hours of sex, and no more than one dose in 24 hours. The individuals were given a three month supply at entry and then refilled as needed at the quarterly visits based on their use in the prior quarter. They did assess STIs quarterly, and if individuals develop symptoms, similar to all of the others, they assess adherence sexual behaviors and side effects. And they also looked at resistance patterns in GC that was isolated in commensal Neisseria species in the art of pharynx. And in Staph aureus, in the oral, oral pharynx and nasal pharynx. primary outcome was incident STIs up per quarter. And when this was about I waited by the data safety monitoring board at 50% of the follow up time, they found effectiveness of the intervention. And they call for the trial to call at that point. And everyone, even the control arm got Doxy PEP, and then they continue to evaluate going forward.

20:19

So they ended up with 501, or evaluated in the attempt to treat after this halt of the trial midstream. And because of the two to one randomization, there were more on on I'm sorry, that should say PEP Doxie, PEP 327 on PEP, and 174. I'm sorry, I confused that there were 327 in the PrEP group, and 174, who were living with HIV, these are the two cohorts. The age range was the same with a median again sort of old for STIs, of median of 38. With the range here 67% were white 30% reported Latin X or Hispanic 11% Asian or Pacific Islander and 7% Black 96% were cisgender males 4% were transgender women or gender diverse. They reported median of nine sex partners in the prior three months, with a high rate of STIs in the prior year, most of which were gonorrhea 58% 20% For Mania 43%, early syphilis and STIs and enrollment

similar to the trial trial about 20%, gonorrhea 12%, Chlamydia 4%, syphilis, and high rates of substance use as well. I just showed this to show how hard it was to evaluate this because it sort of stopped midstream. So people were at various points of follow up. And you can look at that complicated graph when you when you read the paper. But it does lead to sort of a different assessments because of this stopping extreme. So in the PrEP cohort, the individuals on PrEP the Doxy PEP arm had 61 of 570 quarterly visits with an STI, which was approximately 11% versus the standard of care arm test and treat had 82 STIs, which was approximately 32%. And that was statistically significant, quite similar results in the HIV living with HIV cohort 11.8% in the Doxy, PEP versus, again 30.5%. In the standard of care, the number needed to treat in order to prevent a quarter without an STI was approximately five in both cohorts, so relatively low number needed to treat to get the outcome that they were hoping for. And here's a similar curve to what I showed you with the prior study. So in red is the standard of care group, the PrEP cohort had more STIs than the persons living with HIV cohort. Both of you these you can see as you go across in time, are higher than the doxycycline group, where STIs were reduced. In the paper, they also show this this table, which I thought was really helpful to see how this played out. And so so these bars the.in, the middle is the relative risk. And the bar, the bars shown are the confidence interval to the left of this line is is less than one so statistically significant for the effect of doxycycline at preventing the STI and to the right of the line would be not statistically significant. And you can see for gonorrhea at any site, these are all to the left of the line. Similarly for chlamydia, with the exception of a confidence interval crossing for pharyngeal infection, all to the left of the line. And for any early syphilis also all to the left of the line. They also looked because it was an older cohort at age and both young less than 30. And over 30, there was a effect. And they also looked at those who only had one STI versus more than one STI, and similar effect of a reduction in relative risk. There were no significant adverse effects. 88% reported doxycycline was acceptable. They had a median of 7.36x per month, and 86% of the sex acts were covered for self report. So much, much higher usage than in prior trial by Molina there was a median of four doses per month but a call Letter of individuals reported more than 10 doses per month. They also had looked at resistance. And in Staph aureus, Neisseria and GC, there was about the same rate of colonization of staph aureus around 45%. And in the doc CRM at 12 months, they found a reduction in that, and a slight increase in Doxy cyclin resistance but not statistically significant. Most Neisseria were already resistant commensal nice areas were already resistant to doxycycline. And in GC, they were only able to evaluate 15 culture positive they couldn't recover by culture for the others. But they did find a slightly higher evidence of tetracycline resistance at 12 months in the Doxy arm versus the standard of care arm. So they had a significant reduction in both the persons living with HIV and in PrEP, in all three STI so different than the prior study that was well tolerated and high self reported adherence. There were carriage of staph aureus was lower and the doxycycline arm, although the Doxy resistance at our awareness was slightly higher, after 12 months of

doxycycline. And there was a higher proportion of tetracycline resistant GC at 12 months in the Doxy PEP on. So

26:29

they call for larger studies and ongoing surveillance, particularly to assess resistance. I see I'm getting short on time, so I'm going to speed up a little bit. I'm also presented at CROI. This year was a Doxy. Back. This is a multicenter randomized open label trial two by two, and they ended up with MSM who are audit PrEP for more than six months. They've had an STI in the last year and no symptoms at enrollment. They are randomized to to one Doxie PEP Renaud Doxie PEP similar to the last trial we just talked about, and in addition are randomized one to one to receive mini meningitis B vaccine or no vaccine. They ended up with four groups having both Doxie PrEP and an NG vaccine Doxie PEP no Minhaj vaccine, no Doxie PEP Budman ng vaccine, and neither. And they follow for 96 weeks but after the form of trial showed effectiveness, and their data safety monitoring board, stopped the trial. This trial also took a look at the data and ended up stopping enrollment and offered the interventions to everyone. They presented their results at Croix as I said, and the first result was looking at GC what was the effect of an inch B vaccine. And they found a reduction in gonorrhea cases 32 In the no vaccine arm versus 17 in the vaccine arm. So it was there was a reduction in the first GCC case, but no reduction in cumulative incidence at the time they they evaluated it, they're still looking at this. For Doxie PEP they found similar to the prior trial, highly statistically significant reductions in gonorrhea, chlamydia and syphilis. And still statistically significant, but not with quite a strong P value for reduction in Mycoplasma genitalium. They also looked at resistance all of their GC were resistant to tetracycline at baseline and follow up the rates are much higher. In France, there was no resistance seen and Chlamydia, there was no difference in Mersa detection. And there was no change in extended spectrum beta lactamase Ecoli detected in phenol swabs, they also had very high rates of adherence, still only 3.5 doses per month, and a low rate of discontinuation. And then finally, one last trial also presented at a CROI. This year in February. This looked at Doxie PEP in women cisgender women in Africa. These were women ages 18 to 30, who were also on PrEP and not pregnant. They were randomized one to one to Doxie PEP same dosing, and there was no difference. They there was no difference in chlamydia, gonorrhea, all STIs and no difference if you've sorted by age, oral contraceptive use for sex work. So that really contrasted with the prior two trials I just mentioned. In light of these findings, there have been some reactions from various public health organizations. So both the CDC and the British organization are cautious, await further study and if you use this stick to the study protocol, San Francisco Department of Health came out in October with a recommendation to use Doxie PEP were the same group that was included in the trials sis men and trans women with bacterial STI in the past year, and who have condomless sex with sis male or trans female partner, they don't specify that you have to be on PrEP. They also say shared decision making in those who have not had a prior STI but who have many partners in

this same cohort. And they specifically say there's insufficient evidence to recognize, recommend this and vaginal sex. And just a couple of weeks ago, the Australia Association Australia, Asian society for HIV, Hepatitis and sexual health have a less robust recommendation, they say could be useful for people who have multiple STIs. But they call attention to significant unknowns related to unintended consequences of using this in a large scale manner, with possible interruptions in the microbiome and increasing antibiotic resistance, or even community harm through increased population level antibiotic resistance. So they say you really have to weigh the potential benefit with the concern for potential harm. And they support sort of more evidence based interventions to look at long term consequences of using this in a on a large scale. So in conclusion, it does seem that Doxy PEP is effective in the population of men who have sex with men and transgender women to prevent certainly chlamydia and syphilis and likely gonorrhea, at least for now. Thus far, all reports have been in individuals on HIV PrEP, or AR t. So people who are already routinely taking Metaphysik medication, most of them white, and over 35. So not the highest age groups who have gonorrhea and chlamydia. There are some discontinuation differences from the early study versus the current studies of 26% versus 1.5%. And importantly, GC resistance rates to tetracycline vary geographically, it's quite high in France over 60%, whereas in the US around 20%. So with this selected for tetracycline resistance, we could see the effectiveness, Wayne Doxie. PrEP may be effective, the numbers are still quite quite small. So I think too soon to say with only about 60 people studied, public health organizations appear to be divided about if how and when to recommend this as Doxie PrEP, but non are currently recommending Doxie route. I think there's a lot of remaining questions. Why are there breakthrough infections? Is it efficacy or adherence? Why didn't it work and sis women is it at Aaron's or something about biology? We still need to know more about long term use and the microbiome. We need to know about the impact of intermittent use. On other STIs does it impact syphilis titers? For instance? What happens if people don't actually come in for two, three months screening because there was no 100% preventable percent protection? And we need to know sort of more about implementing this in practical matters? And I think you have to think about what are the goals? Is it individual decrease in infection? Is it community transmission? Is it a decrease in complications, which actually are more likely to happen in sis women? And these are all the studies that are still ongoing, that that will still have more data to come? At most of which I talked a bit about today. So sorry, I think I went over a minute or two. This is a pretty hot topic. And we will talk more about this in more detail at our STI conference in June. So I'll stop there and see if there's any questions.

33:59

So some questions are coming in. Are you going to start using daxi PEP in your center? No pressure?

34:08
I think we probably are. I feel like now that we have a published study for individuals who ask which we've already had a couple. We haven't actually formally discussed this. But I think with the public study, I think it's a little hard to say absolutely. No, I don't I don't know that. I do think there are concerns about widespread is about resistance in the microbiome. And we use doxycycline a lot for people with resistant staph aureus, and I would look at you to lose that. So from a population level, like they're like the questions haven't formally been answered.

35:00
Next question, is this information out in the community?

35:03
I think so I think that like if you if you just google doc see PEP, get a lot of popular press kinds of articles. I think there's, there's almost actually more editorials than there are published papers. Not all of us there are definitely more published editorials than published papers.

35:25
And one more question is Doxie PEP PrEP as effective in HIV versus non HIV patients.

35:35
We only have data, enough data to answer that question, I think for Doxie PEP. And in the one published trial, just on Friday, it did look equally effective in those living with HIV, as those on prem. We have no data at all for people who are not on either of those things. So all of the data are in individuals who are taking medication related to HIV prevention, or treatment. So we don't really have any data on the general population not already taking medication.

36:16
All right. I think that wraps up the question

[End Transcript]