Doxycycline prophylaxis for bacterial sexually transmitted infections

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Summary: Sexually transmitted infections have been increasing among men who have sex with men. Doxycycline prophylaxis for syphilis and chlamydia has been effective in initial trials. Future research should focus on populations with high incidence/morbidity, dose and regimen, and antimicrobial resistance.

Abstract

Background: Bacterial sexually transmitted infections (STI) have been increasing over the past two decades in gay, bisexual, and other men who have sex with men (MSM). With the widespread use of early HIV treatment, which virtually eliminates transmission risk, and the availability of HIV pre-exposure prophylaxis there have been attitudinal changes regarding HIV infection with resultant increases in sexual contact and declines in condom use. Doxycycline is used for primary prophylaxis in a number of infectious diseases.

Methods: We conducted a state-of-the-art review to examine the current state of research, knowledge gaps, and challenges around the use of doxycycline prophylaxis to prevent syphilis and other STIs. International academic and government experts met in March 2019 to frame the initial inquiry, which was supplemented by focused literature searches.

Results: Two small short-term randomized-control trials examining doxycycline prophylaxis have found high efficacy. Five additional clinical studies are underway or in development. Studies differed in design, population, outcomes and safety measures.

Conclusions: Doxycycline prophylaxis for bacterial STIs shows promise. Better and more robust data are needed on efficacy; target population; community acceptability; behavioral risk compensation; doxycycline dose, regimen, and formulation; long-term safety; antimicrobial resistance; cost-effectiveness and risk-benefit.

Key words: doxycycline, prophylaxis, syphilis, chlamydia, men who have sex with men

1. Background

Bacterial sexually transmitted infections (STI) have been steadily increasing in gay, bisexual, and other men who have sex with men (MSM) over the past two decades.[1-4]. While that trend started prior to the introduction of human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) in 2012,[1, 3] HIV PrEP has been associated with increases in sexual contacts and decreases in condom use with an resultant acceleration in the increase of bacterial STIs like gonorrhea, syphilis and chlamydia.[5-8] However, the increasing adoption of HIV PrEP[8] has shown that biomedical interventions for STI prevention can be effective, safe, and highly acceptable.

This state-of-the-art review was conducted to examine the current state of research, knowledge gaps, and challenges around the use of doxycycline prophylaxis to prevent syphilis, caused by *Treponema pallidum* (TP), and other bacterial STIs such as *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG). International public health and clinical experts from academia, government, and community-based organizations met on March 3, 2019, in Seattle, Washington to frame the initial inquiry which was then supplemented by focused literature searches to address specific questions of interest. Findings are summarized using the Grading of Recommendations, Assessment, Development and Evaluations framework specifically focusing on the quality of evidence and benefits versus harms.[9]

2. Current evidence on doxycycline prophylaxis

Doxycycline is a moderate-spectrum second-generation tetracycline that is generally well tolerated.[10] It is rapidly and almost completely absorbed after oral administration.[10] First introduced commercially in the 1960s, doxycycline has been used by millions to manage acne and as primary prophylaxis for scrub typhus,[11] leptospirosis,[12] malaria,[13] and Lyme disease.[14] There are anecdotal reports of doxycycline used for syphilis prophylaxis among U.S. and Australian military personnel during the Vietnam War. Doxycycline is a first-line agent for treatment of chlamydia and an alternative regimen for syphilis.[10, 15]

Several studies examined doxycycline prophylaxis for STI prevention.(Table 1) In a small open-label pilot study, 30 HIV-infected MSM with prior syphilis were randomized 1:1 to daily doxycycline 100 mg as pre-exposure prophylaxis (Doxy PrEP) for 48 weeks versus a financial incentive-based behavioral intervention.[16] There was a 73% reduction ($p = .02$) in syphilis, GC, or CT in the Doxy PrEP group compared to the control group. Most intervention-arm participants maintained blood doxycycline levels >1 μg/mL. Reported sexual behaviors were similar in both groups.

An open-label extension of the French national HIV research agency (ANRS) IPERGAY HIV prevention study continued participant access to HIV PrEP and examined doxycycline post-exposure prophylaxis (Doxy PEP) in HIV-uninfected MSM and

transgender women.[17] Participants (n=232) were randomly assigned 1:1 to the intervention, doxycycline 200 mg within 24-72 hours of condomless sexual encounters up to three times per week, or to no prophylaxis. Those taking Doxy PEP had lower STI incidence (hazard ratio = 0.57, p = .014). CT and syphilis diagnoses were significantly lower in the intervention arm with a relative reduction of 70-73% in the intention-to-treat analysis. NG diagnoses did not differ except for fewer urethral cases in those using Doxy PEP. Four of nine NG-positive cultures, all from the control arm, had high-level tetracycline resistance consistent with the French background rate.[10] Eighty-two percent (n=31) of participants with NG detected by nucleic acid amplification testing had genotypic markers of tetracycline resistance; there was no difference between study arms (p = .4). All CT culture isolates (n=5) were doxycycline-susceptible. Adherence was high in the Doxy PEP arm; 63% had doxycycline detected in at least one plasma specimen. Twenty-nine (21.5%) Doxy PEP patients discontinued doxycycline, eight for gastrointestinal side effects. Sexual behaviors did not generally differ between the two groups.

While not direct clinical evidence, a modeling study examining the impact of Doxy PrEP on syphilis among Australian MSM estimated that if 50% of MSM used Doxy PrEP and it was 70% effective, syphilis would decrease by 50% after 12 months and 85% after 10 years.[18] The authors predicted a similar effect if only 50% of men with > 20 partners in six months were taking doxycycline.

3. Studies underway or in development

The meeting participants discussed five studies underway or in development on Doxy PEP/PrEP.(Table 2) A pilot study of Dual Daily HIV and Syphilis PrEP (The DuDHS Study) in Canada is examining concurrent daily HIV PrEP and Doxy PrEP in HIV-uninfected MSM. The study will randomize 50 participants 1:1 to immediate Doxy PrEP versus delayed initiation after 6 months; all participants will receive one year of HIV PrEP. The primary objective is to examine the acceptability, adherence, and tolerability of daily HIV PrEP and Doxy PrEP. The study will also evaluate STI incidence, sexual behavior, tetracycline-class bacterial resistance through culture of the oropharynx and nares, and an evaluation of the rectal microbiome. As of March 2019, investigators have not detected any STIs in the patients on Doxy PrEP in contrast to three rectal CT cases in the delayed arm. No serious adverse events have occurred, although participants in the treatment arm have reported more nausea. The Daily Doxycycline in HIV+ for Syphilis PrEP (The DaDHS Study) is examining Doxy PrEP in HIV-infected MSM; 52 participants with a prior history of syphilis will be randomized 1:1 to daily doxycycline 100 mg or placebo.

The Syphilaxis study in Australia will be a single-arm study of Doxy PrEP in 350 MSM and transgender persons reporting recent sex with men. Both HIV-infected and HIV-uninfected HIV PrEP users with a history of regular STI testing are eligible. The study will use medical records to measure before-after frequencies of STI diagnoses and an

existing STI surveillance database to compare frequencies between study participants and unenrolled MSM. Participants will record doxycycline use daily and complete quarterly questionnaires. The primary goals are to measure acceptability of daily doxycycline and effectiveness in preventing syphilis, NG, and CT.

In France, a sub-study within the large ANRS Prevenir PrEP cohort (n=3,000) [19] will use a randomized open-label factorial design to examine the efficacy of meningococcal type B vaccine in preventing NG infection and the use of Doxy PEP 200 mg to prevent chlamydia and syphilis in participants with a prior STI diagnosis in the past 18 months. Seven hundred participants will be randomized 2:1 to Doxy PEP or no PEP, and 1:1 to meningoccal type B vaccine or no vaccine.

A U.S. study examining Doxy PEP effectiveness and safety/tolerability will enroll 780 MSM and male-to-female transgender individuals (390 HIV-infected and 390 HIV-uninfected using HIV PrEP) who had ≥1 bacterial STI(s) and ≥1 episode(s) of condomless sexual contact with ≥1 male partner(s) in the previous year. The trial will be open-label with 2:1 randomization to Doxy PEP 200 mg post-condomless sexual contact, up to daily use, versus standard of care with 12 months follow-up. All positive NG cultures will undergo tetracycline susceptibility testing. Specimens from patients diagnosed with syphilis or CT will undergo molecular tetracycline resistance evaluation using a novel CRISPR/Cas9 targeted sequencing technique.[20] That will provide a broad reaching, rapid throughput methodology for assessing tetracycline and other antimicrobial resistance genes. Participants will have nasopharyngeal swabs cultured to

assess for tetracycline susceptibility in *Staphylococcus aureus* and *Neisseria spp*., and rectal swabs and stool samples for metagenomic tests to determine predominant species, species diversity, and changes in the presence of tetracycline resistance genes over time.

4. Knowledge gaps and challenges

While the studies described above help address some of the knowledge gaps around Doxy PEP/PrEP, there remain multiple areas for further research particularly around efficacy, and potential benefits and harms.

4.1. Quality of the evidence

4.1.1. Efficacy

Studies on Doxy PEP/PrEP use two doxycycline dose/regimen options: 100mg daily [16] or 200 mg single dose post-condomless sex event.[17] Investigators selected those regimens from experience with doxycycline prophylaxis in other infectious diseases[12, 14] and the minimum inhibitory concentration (MIC) of TP.[21] The efficacy of doxycycline for pre- or post-exposure prophylaxis has yet to be definitively determined. While the two randomized controlled trials (RCT) conducted to date had similar levels of efficacy (approximately 70%), the estimated effect sizes were imprecise because of modest sample sizes.[16, 17, 22] Additionally, it is unknown which specific sex acts were protected. Studies underway will lead to more precise measures of overall efficacy and efficacy for specific sexual behaviors. Those measures are important to inform

clinical decision-making, cost-effectiveness analyses, community education, and patient counseling.

4.1.2. Population of focus

Public health experts have long promoted controlling STIs in a core population of individuals with a high number of sexual contacts as an approach to reduce STIs in the general population.[23, 24] Modeling based on Australian parameters[18] suggests that focusing on MSM with higher numbers of sex partners (>20 partners in 6 months) would be almost as effective as broader Doxy PrEP use. Current and planned studies have generally focused on MSM at higher risk for STIs and/or HIV infection, but criteria vary and sample sizes may not be sufficient to stratify results for sub-populations with more elevated risk. Additional modeling studies or pooled analyses may be useful to identify the characteristics of populations most suitable for maximizing the impact of doxycycline prophylaxis.

4.2. Benefits and harms

4.2.1. Safety

Adults generally tolerate doxycycline well.[10] Studies demonstrate the most commonly-reported side effects are related to gastrointestinal (<1%-55% of patients) and skin (<1%-42% of patients), including photosensitivity (6-42%), toxicity over 7 days-6 months of use.[10] The most severe gastrointestinal effects are esophageal erosion and ulceration; these are most commonly associated with uncoated doxycycline hyclate.[25] Infrequent more serious side effects in adults including allergic reactions, exacerbation

of systemic lupus erythematosus, anemia, hemolytic anemia, thrombocytopenia, eosinophilia, neutropenia, intracranial hypertension, and tooth staining are rare.[25] Most serious adverse effects resolve with discontinuation of doxycycline.[25] Despite the known side effects, in clinical trials discontinuation due to side effects has been uncommon.[13, 16, 17, 26]

Clinicians routinely prescribe low doses (40-100 mg daily) of doxycycline for weeks to months for acne and rosacea[25] and months to years for malaria prophylaxis.[13] Multiple studies on side effects among patients using doxycycline for malaria prophylaxis have been contradictory or insufficient to draw clear conclusions.[13] Researchers have studied prolonged doxycycline use (3-18 months) for the management of abdominal aortic aneurysm. No serious adverse reactions were seen in those studies and <10% of patients withdrew because of medication side effects.[26-29]

4.2.2. Formulation, tolerability, and regimen

Doxycycline monohydrate and doxycycline hyclate are the most commonly used formulations of doxycycline. Due to the pH at which they are soluble, esophageal side effects may be less frequent with doxycycline monohydrate or enteric-coated doxycycline hyclate compared to un-coated doxycycline hyclate.[30] Since the formulation of doxycycline used may impact side effects and patient adherence, this should be tracked closely in future RCTs.

Patient preference is another major consideration. A small qualitative study in Australia (n=13) found that participants have a strong preference for daily dosing. Patients preferences may vary by HIV infection status, and use of HIV PrEP and how individuals use HIV PrEP (e.g., daily or intermittent).

4.2.3. Antimicrobial resistance

Concern around antimicrobial resistance has been raised by some clinicians and public health organizations, along with a call for more research in this area.[31] In the U.S., 23.1% of NG isolates tested in 2017 were resistant to tetracycline[1]; NG resistance to tetracycline is higher in some parts of Europe (France: 45%; England: 49%).[10, 32] Additionally, gonococcal antimicrobial resistance is frequently higher among MSM,[1, 32] the population most likely to use Doxy PEP/PrEP. However. given the existing high rates of tetracycline resistance in NG and the fact that doxycycline is not recommended for treatment, another perspective may be that the additional contribution of prophylactic use to NG resistance in this context is negligible.

There are no established standards for identifying or measuring doxycycline resistance in NG, CT, or TP via culture or molecular techniques, although investigators have developed methods for research purposes and most clinicians apply tetracycline susceptibility data for NG to doxycycline.[33-35]

Treatment failure in CT has been reported in 5-23% of persons,[36] although these studies did not test for resistance and the causes of treatment failure are unclear.

Treatment failure in patients with CT has been associated with a range of in vitro doxycycline MICs of >0.125 μg/mL to >4.0 μg/mL,[33, 37] however there is not a strict correlation between treatment failure and tested MIC[33] so the clinical relevance of these findings are unclear. Several small population-level studies in communities with high background doxycycline use or subsequent to mass-treatment programs for trachoma did not find evidence of doxycycline resistance in CT.[36]

Two studies have evaluated tetracycline resistance in TP. In China, molecular typing of serum from 438 case-patients [34] with syphilis found no evidence of a mutation in the 16S rRNA gene that is associated with tetracycline resistance in other bacterial species. A similar study of 53 case-patients in Italy [38] also did not identify any doxycycline resistance mutations. Complete genome sequencing of TP [39] has not found genetic elements associated with gene transfer mechanisms. That suggests that TP is less likely than other bacteria to develop plasmid-mediated antimicrobial resistance. However, macrolide resistance in TP has been documented to occur due to a single point mutation[40] suggesting the potential for tetracycline resistance.[41]

Antimicrobial resistance in *Mycoplasma genitalium* (MG), a frequent cause of non-gonococcal urethritis in men, is also a growing concern.[42, 43] Even though tetracyclines have low efficacy against MG[15], doxycycline is a recommended alternative regimen[15] because of emerging resistance to first-line treatments. In a sub-study of the ANRS IPERGAY doxycycline extension, 11% of the 210 participants tested positive for MG at baseline and eleven participants acquired MG during the study.[43]

Azithromycin and fluoroquinolone resistance was identified in 70% and 15% respectively of tested specimens.[43] Broad doxycycline use in populations with high prevalence rates of MG could decrease treatment options for that bacteria. MG prevalence and antibiotic susceptibilities should be examined in future studies.

Finally, Doxy PEP/PrEP could contribute to development of doxycycline resistance in commensal organisms, including those with the potential to transmit resistance. Studies of military deployed overseas taking doxycycline for malaria prophylaxis have found conflicting data on the impact of doxycycline prophylaxis on antimicrobial resistance in oropharyngeal and intestinal commensal organisms.[44-46] Further study is needed. While it is possible to evaluate the impact of doxycycline on oral and rectal flora by examining the microbiome and resistome in these areas, there are no standard guidelines for interpreting findings.

4.2.4. Community acceptability and perceptions

Multiple surveys have demonstrated that doxycycline prophylaxis is acceptable to MSM. In an online survey of 2,095 Australian MSM, 53% indicated they would be likely to take doxycycline to prevent syphilis and 76% indicated they would take doxycycline to reduce syphilis in the community.[18] Among 1,301 users of a U.S. social-networking app for MSM, 84% were interested in trying Doxy PEP.[47] Interest was higher among African American and Latino/a respondents.[47] At a joint Australia-New Zealand HIV/STI scientific meeting of clinical and public health experts in 2015, 52% of 63

providers felt that the benefits of doxycycline prophylaxis outweighed the risks, although 88% had concerns about antimicrobial resistance.

Some MSM in North America and Europe may already be using doxycycline for STI prophylaxis. In a survey of MSM taking HIV PrEP in the U.K.[48] six of 106 respondents reported taking doxycycline to prevent STIs in the previous 6 months. In the ANRS IPERGAY Doxy PEP study [17] 3-13% of participants in the placebo group had detectable doxycycline blood levels at each study visit. Doxycycline is also frequently available through online companies selling HIV PrEP.[31]

Researchers and study participants have expressed concern about the potential for confusion between Doxy PEP/PrEP and HIV PrEP. Both medications can be used daily or intermittently. HIV-infected individuals may believe themselves ineligible for Doxy PEP/PrEP. HIV-uninfected individuals may not understand that HIV PrEP does not protect them against STIs and Doxy PEP/PrEP does not protect them from HIV. Effective educational campaigns, designed using evidence from ongoing and future studies, will be critical to address those concerns.

4.2.5. Risk compensation

Investigators have documented decreased condom use among MSM using HIV PrEP.[8] While reports from completed Doxy PEP/PrEP trials have not identified similar changes in risk behavior,[16, 17] findings from the ongoing Canadian DuDHS study suggest some risk compensation might occur. Notably, risk compensation among

people taking HIV PrEP was not identified in the initial placebo-controlled trials, but only became evident in later uncontrolled trials.[8]

4.2.6. Risk/benefit and cost-effectiveness

While the benefits of HIV PREP as a way to prevent a life threatening infection are clear, the risk-balance of STI prevention may be more uncertain. As Golden and Handsfield suggest,[22] a key issue to consider is which benefits of Doxy PEP/PrEP are most important to prioritize. While STI treatment has significant personal and financial costs, and STIs can cause serious sequelae in men (e.g., blindness and hearing loss due to syphilis), much of the direct STI morbidity is in women (infertility and adverse pregnancy outcomes). Primarily using Doxy PEP/PrEP in MSM, a population at high risk for bacterial STIs, might have relatively limited impact on reproductive health outcomes at the population level. The question of which benefits to focus on will also directly impact the cost-effectiveness of Doxy PEP/PrEP as the number of people who would need to receive treatment to avert a negative outcome will vary substantially depending on the outcome selected.[22]

5. Conclusions

Based on our review of the current evidence and studies underway, doxycycline prophylaxis for bacterial STIs shows promise. However, there are several research priorities that need to be addressed before it be adopted broadly.(Figure) In addition to increasing the evidence base on the efficacy of Doxy PEP/PrEP, researchers should carefully consider which populations to focus on, doxycycline formulation and regimen,

and ensuring that findings can be translated to real-world implementation. Pooled analyses across studies may be helpful in examining issues such as identifying sub-populations most likely to benefit from Doxy PEP/PrEP. There is also a clear and immediate need to develop consistent laboratory methods for evaluating doxycycline resistance in NG, CT, TP, and MG, as well as other common pathogens like *Staphylococcus aureus* and *Streptococcus pneumonia.* and broader guidance on how to interpret and use microbiome and resistome data. Finally, cost-effectiveness and modeling studies that consider different scenarios around the most suitable population to focus on and individual versus population-level impacts of Doxy PEP/PrEP are needed to guide conclusions around the appropriateness of Doxy PEP/PrEP to prevent bacterial STIs.

Note:

Acknowledgements: We thank Robert Bolan and Matt Golden for their expertise and assistance in developing this manuscript. We also thank the attendees of the Doxycycline for Prevention of Syphilis in High-Risk Populations pre-conference leadership meeting for CROI 2019 who contributed to a useful and insightful discussion: Cherie Blair, Robert Bolan, David Burns, Phillip Chan, Vincent Cornelisse, Carlos Del Rio, Julie Dombrowski, Deborah Donnell, Richard Gilson, Matt Golden, Rebecca Guy, Elske Hoornenborg, Tarek Mikati, Sheldon Morris, Vincent Ofori, Darrell Tan.

Financial support: This work was supported by Team Klausner Saving Lives, UCLA Center for AIDS Research UCLA CFAR grant number 5P30 AI028697.

Potential conflicts of interest: The authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Luetkemeyer has received grants from ViiV Healthcare Limited. Dr. Molina has received personal fees from Gilead Science Inc., Merck & Co., ViiV Healthcare Limited, Bristol-Myers Squibb, and Teva Pharmaceutical Industries, and grants from Gilead Sciences Inc. The remaining authors have nothing to disclose.

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Table 1. Key characteristics of completed studies on doxycycline prophylaxis for sexually transmitted infections (STI)

Study, first author [Ref]	Design	Sample size	Intervention	Study population and inclusion criteria	Duration	Findings
Bolan[16]	Open-label RCT[c] Patients randomized 1:1 to intervention and standard of care	30	Daily doxycycline hyclate, 100 mg tablet	MSM living with HIV infection Two or more treated syphilis diagnoses since HIV diagnosis	48 weeks	Diagnosis of any bacterial STI at any site: odds ratio 0.27 (0.09-0.83), p=.02 No significant differences in sex behaviors at baseline or follow-up. One patient discontinued doxycycline due to GERD[d]
ANRS IPERGAY Doxy PEP study, Molina[17]	Open label RCT Patients randomized 1:1 to intervention and no prophylaxis	232	Doxycycline hyclate, 200 mg tablet, single dose within 24-72 hours post-condomless sexual encounter; maximum three/week	HIV-uninfected MSM and transgender women on HIV PrEP[e] having condomless sex with men	Median follow-up 8.7 months	Diagnosis of any bacterial STI at any site hazard ratio = 0.57 (0.13-0.62), p=.014 No substantive difference in sexual behaviors at baseline or during study 32 patients discontinued doxycycline, 8 for gastrointestinal side effects. Remainder discontinued for multiple reasons with no discernable pattern
Wilson[18]	Model of sexual behavior	NA[a]	Daily doxycycline, 100 mg	MSM[b]	NA	Assuming 50% adoption and 70% efficacy, ~50% reduction in syphilis after 12 months and 85% reduction after 10 years Similar effect seen if only MSM with >10 partners in 6 months receiving intervention
Wilson[18]	Survey and	2,095	NA	MSM	NA	52.7% (95% confidence

	focus groups using respondent-driven and convenience sampling		interval: 50.6%-54.8%) very/slightly likely to use doxycycline to prevent syphilis in themselves 75.8% (74.0%-77.6%) very/slightly likely to use doxycycline to help control syphilis in MSM community Survey findings supported by focus groups

[a] NA: not applicable.
[b] MSM: gay, bisexual, and other men who have sex with men.
[c] RCT: randomized controlled trial.
[d] GERD: gastroesophageal reflux disease.
[e] HIV PrEP: pre-exposure prophylaxis for HIV.

Table 2. Key characteristics of studies in progress or development on doxycycline prophylaxis for sexually transmitted infections (STI), March 2019

Study, PI	Design	Sample size	Intervention	Study population, inclusion criteria	Duration (months)	Endpoints
DuDHS, Grennan	Immediate/deferred initiation single-blind RCT[a] Patients randomized 1:1 to intervention and deferred intervention	50	Daily doxycycline hyclate, 100 mg	MSM[b] on HIV PrEP[c] Condomless sex in last 6 months, and syphilis diagnosed and treated within last 3 years	6/12	Acceptability, adherence, and tolerability Resistance in oral flora Change in sexual activity STI diagnosis
DaDHS, Grennan	Single-blind RCT Patients randomized1:1 to intervention and placebo	52	Daily doxycycline hyclate, 100 mg	MSM living with HIV infection Condomless sex in last 6m, and syphilis diagnosed and treated within last 3 years	12	Adherence and tolerability Resistance in oral flora Change in sexual activity Bacterial STI diagnosis
Syphilaxis Mark X, Kaldor	Non-randomized single-arm trial Before-after comparisons using medical records STI surveillance data comparing study patients to unenrolled MSM with matching risk profiles	350	Daily doxycycline monohydrate tablet, 100 mg	HIV-infected and HIV-uninfected MSM and transgender persons reporting recent sex with men Diagnosed syphilis in prior 12 months, or any STI in last 12 months and syphilis in last 24 months At least two episodes of STI screening in	12	Use and acceptability NG, CT, and syphilis diagnosis Rectal and oropharynx microbiome sub-study on antimicrobial resistance (n=100)

				prior 12 months		
Molina	RCT open-label Patients randomized 2:1 to intervention Doxy PEP or no PEP combined with RCT on impact of meningococcal type B vaccination on NG incidence (randomization 1:1)	700	Doxycycline monohydrate, 200 mg, single dose post-condomless sexual encounter	MSM already enrolled in the ANRS Prevenir PrEP trial with a history of recent STI	18	CT and syphilis incidence, NG incidence, Culture and molecular-based resistance testing Rectal and oral microbiome sub-study on antimicrobial resistance
Luetkemeyer, Celum	Open-label RCT Patients randomized to 2:1 to intervention and no prophylaxis	780	Doxycycline formulation to be determined, 200 mg, single dose within 24-72 hours post-condomless sexual encounter, up to daily use	MSM living with HIV infection and MSM on HIV PrEP One or more bacterial STI and condomless sex with one or more male partners in past year	12	NG, CT, and syphilis diagnosis Culture and molecular-based resistance testing Commensal flora and gut microbiome resistance testing

[a] RCT: randomized controlled trial.
[b] MSM: gay, bisexual, and other men who have sex with men.
[c] HIV PrEP: pre-exposure prophylaxis for HIV.

Figure. Recommendations for research activities

Figure 1

Figure. Recommendations for research activities

- **Clinical efficacy**: Quantifying clinical efficacy in a variety of populations is needed.
- **Dosing strategies**: Daily and post-exposure/event-driven dosing is being studied. Other options, such as weekly dosing, should be investigated.
- **Core group focused intervention**: Modeling and analyses of pooled study data are needed to identify the populations most suitable for maximizing the impact of doxycycline prophylaxis.
- **Formulation**: Clear information on the frequency of side effects for different doxycycline formulations is needed. Direct comparisons using randomized clinical trials may be appropriate. Further long-term studies on side effects are also needed.
- **Educational efforts**: Prior to broad implementation, effective educational campaigns are needed to ensure that high-risk populations clearly understand the difference between HIV PrEP and Doxy PEP/PrEP
- **Risk compensation**: Ongoing monitoring for risk compensation in all trials is critical.
- **Resistance monitoring:** All studies should robustly investigate development of resistance in bacterial STIs as well as commensal organisms. Standardized laboratory methods for defining and monitoring doxycycline resistance in STIs are needed.
- **Cost-effectiveness:** Cost-effectiveness analyses are needed to better understand the utility of Doxy PEP/PrEP.