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Review

Doxycycline in STI Prophylaxis—A Literature Review

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Abstract: Background: Since the implementation of pre-exposure prophylaxis (PrEP) in HIV prevention, a significant increase in the prevalence of other sexually transmitted infections (STIs) has been reported, especially among men who have sex with men (MSM). Doxycycline is being examined as a potential pharmacological agent in preventing these infections. This review aims to summarize available data on the effectiveness and potential side effects of doxycycline for the prevention of bacterial STIs. Methods: We reviewed the National Library of Medicine and the National Center of Biotechnology Information in order to find clinical trials and relevant observational studies regarding doxycycline usage in STI prophylaxis. Results: Doxycycline prophylaxis reduced the risk of acquiring chlamydia, syphilis, and, in a majority of the trials, the risk of gonorrhea. The clinical trials on doxycycline STI prophylaxis were underpowered to determine if doxycycline promotes the selection of resistance in *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Additionally, no serious side effects of this preventive measure have been reported. None of the studies aimed to compare the efficacy of post- and pre-exposure prophylaxis of STDs with doxycycline. Conclusions: The preliminary results regarding STI prophylaxis with doxycycline seem to be promising. Further research is needed to determine the potential risk of doxycycline prophylactic prescription.

Keywords: PrEP; PEP; STI; HIV; doxycycline

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1. Introduction

Since the broad implementation of pre-exposure prophylaxis (PrEP) in Human Immunodeficiency Virus (HIV) prevention, a decline in the use of barrier prevention has been observed in some studies [1–3]. Although antiretroviral drugs are highly effective in the prevention of HIV acquisition, they have no efficacy in the prophylaxis or treatment of other viral and bacterial sexually transmitted infections (STIs) [4,5]. Concurrently, a significant increase in prevalence, mainly of bacterial STIs among men who have sex with men (MSM), has been reported by some authors [1–5]. Recent CDC reports also demonstrate that congenital syphilis cases have increased by over ten-fold [6].

In the absence of effective vaccines against bacterial STIs, condom use is regarded as the cornerstone of prevention. In spite of its efficacy, a percentage of the population uses condoms with casual sex partners inconsistently or not at all [7–12]. As a result, the attention of researchers has been drawn to the use of other pharmacological agents that could protect against bacterial STIs either as an alternative for those unwilling to use condoms or as an adjunct for condoms for patients with particularly high risk.

Doxycycline is being examined as a potential agent in the prevention of STIs, given its broad antimicrobial spectrum. There are two suggested regimens of prophylactic doxycycline dosing. The most common one, namely post-exposure prophylaxis (PEP), recommends taking 200 mg of doxycycline monohydrate/hyclate within 24–72 h of exposure. Pre-exposure prophylaxis (PrEP) entails the use of 100 mg daily throughout the duration of risk [13].

The use of doxycycline in STI prophylaxis is gaining more and more attention and is being thoroughly examined. A limited number of reviews summarizing current research in doxycycline as STIs, PEP, and PrEP have already been published. In 2022, a summative review by Venkatesan characterized clinical trials concerning doxycycline prophylaxis that had been published at that point. The study aimed to provide a detailed description of doxycycline efficacy and potential adverse effects when used as STI prophylaxis [14]. However, there is currently more evidence beyond that, as reports from three more clinical trials have been available since then, and the variety of studies is ongoing. Another review by Kong et al., published in 2023, pointed out important considerations regarding bacterial resistance. The study accentuated the antibiotic resistance of *C. trachomatis*, *N. gonorrhoeae*, *T. pallidum*, *M. genitalium*, and more bacteria in people undergoing STI prophylaxis with doxycycline [15]. In 2023, a subsequent study by Mayer et al. evaluating doxycycline as STI prophylaxis was published. The study was a review of clinical trials that put emphasis mostly on post-exposure prophylaxis [16].

In this review, we aimed to summarize the available data from the latest clinical trials and from relevant observational studies assessing the effectiveness and potential side effects of the use of doxycycline in both post- and pre-exposure to the prevention of bacterial STIs. In order to find available data regarding the subject, we reviewed the National Library of Medicine and the National Center of Biotechnology Information for trials published in the last 10 years. Three investigators independently searched the mentioned databases, using the following keywords in order to find and extract appropriate clinical data: pre-exposure prophylaxis, post-exposure prophylaxis, sexual transmitted infection, HIV, and doxycycline.

2. Doxycycline Prophylaxis Efficacy

2.1. Current Evidence on Doxycycline Prophylaxis Efficacy

The subject of doxycycline as a prophylaxis of sexually transmitted infections has not yet been exhaustively examined. Until now, only four clinical trials on the efficacy of doxycycline in preventing STIs have been published. The first clinical trial was a randomized, controlled pilot study which was conducted by Bolan et al. in 2015 in the United States. The trial aimed to analyze the efficacy of daily doxycycline intake in preventing gonorrhea, chlamydia, and syphilis among people living with HIV (PLWH). Thirty MSM with a past medical history of syphilis were included in the study and randomized into two groups—one received doxycycline prophylaxis, and the other was offered contingency management and was paid for remaining free of STIs. Both groups were observed for 48 weeks. At weeks 12, 24, 36, and 48, rectal and pharyngeal swabs and urine samples were taken for *Neisseria gonorrhoeae* nucleic acid amplification tests. Simultaneously, rectal swabs and urine samples were collected for *Chlamydia trachomatis* nucleic acid amplification tests, and a blood draw for rapid plasma regain for syphilis. There were no significant differences in sexual risk behaviors between individuals in those groups. The study showed that men receiving doxycycline had a 73% reduction in the incidence of syphilis, gonorrhea, chlamydia, or a combination of STIs compared to the group of people receiving contingency management [17].

Another study was performed in France in 2018 by Molina et al. It was an open-label randomized sub-study of the ANRS IPERGAY trial, which aimed to evaluate the efficacy of intermittent or "on demand" HIV PrEP. The sub-study's purpose was to analyze the efficacy of single-dose oral 200 mg doxycycline PEP, taken no later than 24 h after condomless sex, in preventing gonorrhea, chlamydia, and syphilis among 232 MSM and transgender women. The control group received no intervention after sexual intercourse. The participants were followed up for a median of 8.7 months. Every 2 months, *T. pallidum* hemagglutination assay or enzyme immunoassays and venereal disease research laboratory or rapid plasma reagin tests for syphilis were performed. Specific PCR assays on anal and throat swabs and first-void urine samples were carried out for testing for gonorrhea and chlamydia. In some samples, cultures for gonorrhea and chlamydia were also performed. In the group of individuals taking doxycycline, there was a 47% relative reduction in the risk of acquiring

any STIs. Moreover, the occurrence of the first episode of chlamydia and syphilis was lower in the group taking PEP (hazard ratio, respectively: 0.30, 0.27). No significant difference was observed in the prevalence of the first event of gonorrhea. All included individuals received HIV PrEP, and there were no incidences of acquiring HIV infection [18].

The next clinical trial was held in France in 2021, and it was also a sub-study of the ANRS IPERGAY Pre-exposure Prophylaxis Trial. It enrolled 210 MSM taking doxycycline PEP and HIV PrEP. The study analyzed the prevalence of *Mycoplasma genitalium* in the group of individuals receiving and not receiving doxycycline post-exposure prophylaxis. The included individuals were tested at baseline before randomization and after 6 months. *Mycoplasma genitalium* was detected using real-time PCR assays in urine samples and oropharyngeal and anal swabs. The prevalence of Mycoplasma genitalium did not differ significantly between the arms: the baseline prevalence of *M. genitalium* was 10.5%, and the prevalence of that bacterium at 6 months was 10.2% in the group receiving doxycycline PEP and 9.6% in the group of individuals not receiving PEP, which was not a statistically significant difference [19].

In 2023, another clinical trial on doxycycline prophylaxis was conducted. It was an open-label randomized study conducted by Luetkemeyer et al. in the United States. It involved MSM and transgender women who were either living with HIV or taking HIV PrEP and who had contracted gonorrhea, chlamydia, or syphilis diagnosed in the past year. The study included 501 participants. Both PLWH and individuals receiving HIV PrEP were further divided into the group receiving doxycycline within 72 h after exposure and the groups receiving standard of care without doxycycline. All patients underwent quarterly testing for gonorrhea and chlamydia using nucleic acid amplification testing of samples obtained from the pharynx, rectum, and urine. Blood serologic tests were performed for syphilis, according to the Centers for Disease Control and Prevention guidelines; however, it was not specified explicitly which tests were performed. Doxycycline proved to be effective in preventing STIs in both cohorts of MSM and transgender women. The combined incidence of gonorrhea, chlamydia, and syphilis was two thirds lower with doxycycline post-exposure prophylaxis than with standard of care [20].

In 2023, a study assessing the efficacy of doxycycline PEP among women was conducted in Kenya by Oware et al. (dPEP-KE trial). The study included 449 women who were receiving HIV PrEP. All the women were randomized in a ratio of 1:1. Individuals in the first group were taking 200 mg of doxycycline up to 72 h after exposure and participants in the second group were undergoing regular STI testing and standard treatment. Biological sample collection (including serum, endocervical, and vaginal swabs) and testing were performed by trained study clinicians and laboratory technologists on site. Testing for chlamydia and gonorrhea was performed using nucleic acid amplification tests of endocervical and vaginal swabs. A rapid plasma regain test followed by *Treponema pallidum* hemagglutinin assay was used for syphilis screening. All patients underwent testing quarterly for 12 months. The prevalence of bacterial STIs was 18%. Doxycycline did not significantly reduce the risk of acquiring STI. In the group of patients receiving doxycycline, there were 50 new cases of STIs, and among the women receiving standard of care, there were 59 cases [21].

A summary of the conducted trials is presented in Table 1.

2.2. Ongoing Studies

In 2021, during the Conference on Retroviruses and Opportunistic Infections (CROI), the results of an open-label pilot study on Dual Daily HIV and Syphilis PrEP (the DuDHS study) were presented. The study included 52 MSM, all of whom were receiving HIV PrEP. The participants were randomized into two groups: the first group took doxycycline daily, and another one received deferred treatment. The prevalence of chlamydia, gonorrhea, and syphilis was analyzed in both groups. Daily doxycycline intake reduced the probability of any STI. Reduced rates of chlamydia in the group of individuals receiving daily doxycycline were observed. There was no statistically significant difference in the occurrence

of gonorrhea, and the efficacy of doxycycline in preventing syphilis could not have been analyzed since there were no cases of syphilis in both groups of participants [22].

Table 1. Summary of conducted trials.

Study Author, Year	Study Design	Participants (n); Randomization	Intervention *	Median Follow-Up	Results		
				(Weeks)	Efficacy **	Resistance	Adverse Events *
Bolan et al., 2015 [9]	Prospective, open-label, randomized	n = 30; (1:1)	100 mg once daily (PrEP) during follow-up	48	11% vs. 31% for any STI ($p < 0.05$)	no data	7%
Molina et al., 2018 [10]	Prospective, open-label, randomized	n = 232; (1:1)	200 mg of doxycycline up to 72 h after exposure (PEP)	36	22% vs. 45% for any STI ($p < 0.05$)	25% resistant isolates from PEP group and 75% from control group (*N. gonorrhoeae*) No resistance in *C. trachomatis*	4%
Berçot et al., 2021 [11]	Prospective, open-label, randomized	n = 210; (1:1)	200 mg of doxycycline up to 24 h after exposure (PEP)	24	6.5% vs. 4% for M. genitalium ($p > 0.05$)	12.5% in PEP group (*M. genitalium*)	no data
Luetkemeyer et al., 2023 [12]	Prospective, open-label, randomized	n = 501; (2:1)	200 mg of doxycycline up to 72 h after exposure (PEP)	52	10.7% vs. 31.% in HIV PrEP group 11.8% vs. 30.5% in PLWH for any STI ($p < 0.05$)	38% in PEP group vs. 12.5% in control group (*N. gonorrhoeae*)	1.5%
Oware et al., 2023 [13]	Prospective, open-label, randomized	n = 449; (1:1)	200 mg of doxycycline up to 72 h after exposure (PEP)	52	22% vs. 26% in WLWH for any STI ($p > 0.05$)	no data	no data

* doxycycline group; ** doxycycline vs. control group.

An open-label study on doxycycline PEP is also being conducted by Molina et al., which includes individuals who are MSM already enrolled in the ANRS Prevenir PrEP trial with a history of recent STIs [13]. Participants will be randomized 2:1 into two groups, which will either be receiving 200 mg of doxycycline after exposure or will undergo standard of care. The incidence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Treponema pallidum* will be analyzed by culture and molecular-based resistance testing [13].

Another study that will be conducted in the United States, namely DOXY-PEP, aims to evaluate the ability of various oral doses of doxycycline to penetrate mucosal tissues in men and women. The further aim is to develop a single-dose event-driven combination of doxycycline with antiretroviral drugs for the prevention of both HIV and sexually transmitted infections. It is a randomized open-label trial that aims to assess the concentrations of doxycycline in rectal, vaginal, and penile secretions after a single doxycycline dose and after five doxycycline doses on days 0, 1, 3, 7, and 10 [23].

The next ongoing study, Syphilaxis, is a non-randomized observational cohort trial aiming to evaluate the efficacy of daily doxycycline PrEP in preventing gonorrhea, syphilis, and chlamydia among MSM. All participants will be taking an oral dose of 100 mg doxycycline daily for three months and will be followed up for 12 months. STI testing will be performed every three months [24].

The DPMSM trial is a pilot study that aims to enroll MSM living with HIV who have had syphilis twice or more since their HIV diagnosis. Participants will be randomized. The first cohort will receive daily oral doxycycline, and the second group will be offered a financial incentive to remain STI-free. Subjects will be observed for 48 weeks. One of the aims of the trial is to compare the effectiveness of doxycycline with a monetary incentive in preventing STIs [25].

Another study aiming to evaluate the efficacy of doxycycline PrEP among MSM living with HIV is the DaDHS trial. DaDHS aims to be the first large-scale study. Subjects will be randomized into receiving daily 100 mg doxycycline or a placebo. One of the aims is to evaluate syphilis and other STI incidences over the study period, which aims to last for 15 months [26].

The next study will be conducted among MSM living with HIV or HIV PrEP users. The trial aims to assess the efficacy of doxycycline post-exposure prophylaxis in preventing gonorrhea, chlamydia, and syphilis. Subjects will be randomized into two arms: one receiving 200 mg doxycycline dose no later than 72 h after condomless sexual intercourse and the second receiving standard of care control. The study will compare the incidence of gonorrhea, chlamydia, and syphilis in a one-year observation period [27].

The last ongoing study, namely DISCO, aims to be the first open-label randomized controlled trial of doxycycline-based STI PrEP (daily 100 mg doxycycline) versus STI PEP (200 mg doxycycline after exposure event) for the prevention of syphilis, chlamydia, and gonorrhea. The trial will be held among MSM regardless of HIV status, and the observation period will last 60 weeks [28].

Table 2 summarizes the ongoing clinical trials.

2.3. Summary of the Evidence

The research on doxycycline pre- or post-exposure prophylaxis demonstrates that doxycycline seems promising in reducing the prevalence of STIs. Doxycycline prophylaxis reduced the risk of acquiring chlamydia, syphilis, and gonorrhea in a majority of the trials. However, the results may be biased due to the differences in diagnostic tests performed, samples obtained, and the frequency of testing in the analyzed studies. The testing used for the diagnosis of chlamydia and gonorrhea was either nucleic acid amplification testing or PCR assay and, in some cases, culture. The samples for chlamydia and gonorrhea testing were obtained either from throat and urine or pharynx and urine or pharynx, rectum and urine. The testing for syphilis included either a nontreponemal test or both a treponemal and nontreponemal test. Some patients were tested bimonthly, whereas in other studies, testing was repeated quarterly. All these differences can bias the accuracy of the obtained results. Doxycycline did not seem effective in preventing *Mycoplasma genitalium* infection; however, this was based only on one trial. Unfortunately, none of the presented studies aimed to compare the efficacy of post- and pre-exposure prophylaxis. Hopefully, the variety of ongoing trials will bring a broader perspective on the real-life effectiveness of doxycycline in preventing STIs.

Table 2. Summary of ongoing clinical trials regarding doxycycline STI prophylaxis.

Study Name	Participants	Study Arms	Randomization	Intervention	Study Period	Outcome
DuDHS Study	52 MSM receiving HIV PrEP	Immediate: daily doxycycline Deferred: deferred doxycycline	1:1	100 mg of doxycycline	24 weeks	Incidence of gonorrhea, chlamydia or syphilis
ANRS Prevenir PrEP	232 MSM and transgender women	Experimental: Doxycycline prophylaxis Control: no prophylaxis	1:1	200 mg of doxycycline up to 72 h after exposure	Median follow-up 8.7 months	Incidence of gonorrhea, chlamydia or syphilis

Table 2. *Cont.*

Study Name	Participants	Study Arms	Randomization	Intervention	Study Period	Outcome
DOXY-PEP	Men and women	1 arm: 100 mg doxycycline 2 arm: 200 mg doxycycline	Not provided	100 mg or 200 mg of doxycycline received on days 0, 3, 7, and 10	15 days	Doxycycline concentrations in rectal and vaginal tissues
Syphilaxis	Men and transgender women	All participants will receive doxycycline prophylaxis	Non-randomized	100 mg of doxycycline daily	12 months	Incidence of gonorrhea, chlamydia or syphilis
DPMSM	MSM or transgender women living with HIV	Experimental: doxycycline prophylaxis Control: Financial incentive	Not provided	Experimental: 100 mg of doxycycline daily Behavioral: incentive	48 weeks	Incidence of gonorrhea, chlamydia or syphilis
DaDHS	Adult MSM living with HIV	Experimental: doxycycline prophylaxis Control: Placebo	Not provided	100 mg of doxycycline daily	15 months	Incidence of syphilis
Evaluation of Doxycycline Post-exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-infected Men Who Have Sex With Men	Men living with HIV or receiving HIV PrEP	Experimental: doxycycline prophylaxis Control: standard of care STI testing	Not provided	200 mg of doxycycline after exposure	12 months	Incidence of gonorrhea, chlamydia or syphilis
DISCO	Adult men	1 arm: daily doxycycline prophylaxis 2 arm: post-exposure doxycycline prophylaxis	1:01	1 arm: 100 mg doxycycline daily 2 arm: 200 mg doxycycline after exposure	60 weeks	Incidence of gonorrhea, chlamydia or syphilis

3. Potential Side Effects of Prophylaxis with Doxycycline

3.1. Antibiotic Resistance of Bacteria

In addition to STI treatment, doxycycline has other applications that could potentially be negatively influenced by exposure of pathogens to subtherapeutic doses of doxycycline. A number of clinical trials have shown the potential of doxycycline for the treatment of non-severe community-acquired pneumonia, with cure rates as high, if not higher, than with the use of macrolides and fluoroquinolones [29], and doxycycline is still a viable option in the treatment of acne vulgaris [30]. There is evidence suggesting that doxycycline can have antifungal activity when used in conjunction with classical antifungals [31–33]. Given the growing epidemiological importance of fungal infections with multi-resistant strains, doxycycline may potentially be a useful agent in such cases in the future [34]. This has brought about anxieties regarding the potential for antibiotic resistance both in bacteria responsible for STIs and in other groups of resistance acquisition-prone bacteria, such as medically relevant Gram-positive cocci and Gram-negative rods [35]. Unfortunately, *N. gonorrhoeae* and *C. trachomatis* are notoriously fastidious microorganisms, which makes the determination of antibiotic resistance very difficult.

3.1.1. Antibiotic Resistance of the STI-Causing Bacteria

This subject was partially explored in the mentioned clinical and open-label trials. In Molina et al.'s clinical trial, 28 cases of gonorrhea, that is, 49% of all cases of gonorrhea, underwent an attempt at culture, of which only nine isolates were successfully cultured from two patients in the group receiving doxycycline and six patients in the control group. All fully resistant isolates were found in the control group, with isolates showing intermediate resistance in both groups. For patients with a positive PCR result for *C. trachomatis*, an attempt at culture was conducted in samples from 22 anal and two oral swabs, with successful culture in five samples from two patients from both the group receiving doxycycline and the control group. No tetracycline resistance was found [18].

In the open-label study from 2023 published by Luetkemeyer et al., isolates of *N. gonorrhoeae* were evaluated for tetracycline resistance as a surrogate for doxycycline resistance. Only 17.2% of PCRs positive for *N. gonorrhoeae* DNA yielded a positive culture with antibiotic resistance testing, with the authors attributing this low percentage to the inability to collect samples for culture before treatment in roughly half of the patients, as well as a lack of culture growth in samples from a large percentage of PCR-positive patients. At the start of Luetkemeyer et al.'s trial, that is, before randomization, 15 cases of gonorrhea were found, four of which (27% of cases) showed tetracycline resistance. During the course of the study, 13 cultures were positive for *N. gonorrhoeae* in the group receiving doxycycline and 16 in the control group, with tetracycline resistance found in five and two cases (38% and 12% of cases), respectively [20].

In Bolan et al.'s clinical trial, no resistance data were reported, as no cultures were performed as a follow-up to PCRs [17].

It is important to note that doxyPEP trials were conducted in the United States and France, where baseline tetracycline resistance of *N. gonorrhoeae* was relatively low at the time of the trials conducted by Bolan et al. (25.3% in 2014 in the US [36]) and Molina et al. (56% in France in 2014 [37]), which was reflected in the prevalence of resistant strains found by Luetkemeyer et al. at the beginning of their trial (27% [20]). High rates of tetracycline resistance have recently been reported in many localizations, including China (88–100% of *N. gonorrhoeae* strains [38]), many parts of Sub-Saharan Africa (some areas exhibiting a prevalence of resistance of 75–100% [39]), and even in France in 2022 (91.4% [40]). When considering doxycycline as a prevention method of gonorrhea for a particular population, this should be taken into account.

The results of Reichert's and Grad's modeling study (at the time of writing, it was published as a preprint pending peer review [41]) suggest that the use of doxyPEP could increase the proportion of doxycycline-resistant *N. gonorrhoeae* to 87% in a span 1.8–14.1 years, depending on the proportion of MSM taking doxyPEP (1.8 years with 75% doxyPEP uptake, 14.1 years with 10% doxyPEP uptake). According to the authors, this would be driven not by de novo resistance promoted by doxyPEP but by the spread of resistant strains already present in the population. Whether this has a lasting effect on the incidence and prevalence of gonorrhea in the model was dependent on the relative loss of fitness of the strain due to the mutations associated with doxycycline resistance. Assuming in Reichert's and Grad's model that the loss of fitness was 2% then doxyPEP with an uptake between 10 and 75% has the potential to prevent, respectively, 19.5–49.7% of new *N. gonorrhea* infections in the first 5 years. Unfortunately, the model predicts that at the 20-year mark, the cumulative reduction of new cases will be only 13.5–14.6%, driven by the accumulating dominance of the doxycycline-resistant strains. This suggests that, at least for the epidemiology of *N. gonorrhoeae*, doxyPEP is not a long-term solution. On the other hand, if one assumes the fitness cost to be higher than with enough uptake, doxyPEP could potentially have a more prolonged effect on decreasing the incidence of *N. gonorrhoeae* infection (e.g., a fitness loss of 20% paired with an uptake of 25% would lead, in the first 20 years of use, to a dramatic decrease in new N. gonorrhoeae infections by 91.2%). This estimate of loss of fitness, however, seems to be an unlikely scenario, given the high prevalence of doxycycline resistance already reported in the literature.

Reichert's and Grad's model also predicts that although doxyPEP use could lead to a decrease in ceftriaxone utilization for gonorrhea treatment (due smaller incidence of gonorrhea), there would be no effect on slowing the increase in ceftriaxone resistance rates.

Mycoplasma genitalium is another cause of clinically relevant STIs. This species of bacterium is characterized by its extraordinary ability to develop antibiotic resistance to multiple agents [19,42]. Although *Mycoplasma genitalium* has been linked to urethritis, cervicitis, pelvic inflammatory disease, infertility, an increased risk of HIV acquisition, proctitis, and others, the high percentage of asymptomatic infections results in a lack of indication for screening for *Mycoplasma genitalium* in populations such as pre-exposure prophylaxis users or HIV-positive MSM [43]. Empiric treatment has focused on monotherapy or combination therapy with azithromycin, doxycycline, and fluoroquinolones such as gemifloxacin or moxifloxacin, but in clinical practice, resistance to macrolides and tetracyclines is both very prevalent and costly to detect [43,44]. It is important to note, however, that doxycycline monotherapy has been associated with a high rate of treatment failures in patients reporting no post-exposure prophylaxis with doxycycline use [45,46]. In Bercot et al.'s study, after six months of doxycycline post-exposure prophylaxis, the number of isolates harboring mutations associated with resistance to azithromycin and fluoroquinolones and mutations suspected to be associated with tetracycline resistance were compared between doxycycline users and controls. Six months into the study, the number of infections in the study was 19, and some specimens that were positive for *Mycoplasma genitalium* with the PCR could not be amplified further in order to test for resistance-associated mutations. In total, in the group receiving doxycycline, the number of specimens positive for resistance-associated mutations was 5/8 for azithromycin (vs. 6/7 among controls), 2/6 for fluoroquinolones (vs. 0/9 among controls), and 1/2 for tetracyclines (vs. 0/3 for controls) [19].

3.1.2. Future Directions of Preventive Measures

Of note, one potential approach to limiting the impact of doxycycline prophylaxis-induced tetracycline resistance in *N. gonorrhoeae* is to simultaneously vaccinate doxycycline prophylaxis users with the 4CMenB anti-meningococcal vaccine in order to limit the number of total cases of gonorrhea. The usefulness of this anti-meningococcal vaccine in preventing *N. gonorrhoeae* infection was suggested by the results of observational studies [47,48], and the efficacy of the 4CMenB vaccine, in particular, is currently being studied in three separate clinical trials in the population of men, transgender women, and non-binary people who have sex with men [49–51].

3.1.3. Antibiotic Resistance of the Other Bacteria

There is, unfortunately, scant data on the impact of doxycycline use on the acquisition of drug-resistant bacteria in other contexts. This subject was partially explored in Luetkemeyer et al.'s open-label trial where nasal Staphylococcus aureus isolates were evaluated for doxycycline resistance. Study participants were tested for Staphylococcus aureus carriage in the anterior nares and oropharynx at baseline and at 12 months. At the start of the study, 45% of the participants were positive for S. aureus carriage, and 12% of the isolated strains harbored resistance to doxycycline. At 12 months, 28% of doxycycline users were positive for carriage, of which 16% were positive for doxycycline-resistant strains. In the control group, the carriage percentage was higher (47% of participants), but the percentage of resistant isolates was lower (8% of isolated strains). Interestingly, the proportion of participants positive for carriage of doxycycline-resistant S. aureus was similar in both groups (5% in the doxycycline-receiving group; 4% in controls) [20].

The possibility of doxycycline promoting cross-resistance in other bacteria was also examined in studies of doxycycline as a potential agent in the prophylaxis of traveler's diarrhea, during which doxycycline was administered for a longer period of time than in doxycycline STI prophylaxis. Among others, in Kantele et al.'s prospective study, travelers who used doxycycline as malaria chemoprophylaxis were not more likely to acquire stool carriage of ESBL-producing Enterobacteriaceae, although ESBL-producing

Enterobacteriaceae isolated from doxycycline users were more likely to be resistant to doxycycline. Other studies had similar findings; see Kantele et al. for further details [52].

There is an absolute lack of studies on the effect of doxyPEP and doxyPrEP on the human microbiome, as current data on doxycycline may not be translatable to the context of STI prevention. Admittedly, there have been reports on the effect of doxycycline on the human microbiome [53–56], but these were conducted mainly for dosing used in (and in patients with) acne and rosacea [57,58] or treatment of malaria prophylaxis [59,60]. What is more, these studies were performed on the general population, and it is known that sexual behavior (including sex between men) may influence the microbiome in ways that have neither been fully documented nor understood [61,62]. On the other hand, these studies, although vital for our understanding of human physiology and pathology, may not be easy to translate into clinical recommendations, especially in the population of MSM [61].

3.2. Other than Antibiotic Resistance Side Effects of Doxycycline

Besides the induction of antibiotic resistance in bacteria, doxycycline, like every xenobiotic, may have other side effects. The most common adverse events include symptoms from the gastrointestinal tract such as diarrhea (also antibiotic-associated diarrhea), nausea or vomiting, as well oral or vaginal fungal infections, photosensitivity, rash, lesions on nails, taste disturbances, dizziness, and tinnitus. Serious side effects caused by doxycycline intake are rare but may need urgent medical attention. They include increased intracranial pressure, thrombocytopenia and bleeding, drug-induced liver injury, esophagitis, and severe allergic reactions. Usually, adverse events are recorded, and the toxicity is graded according to the ANRS scale of the severity of adverse events in adults [63]. Moreover, besides adverse effects, doxycycline may have pharmacokinetic interactions with other agents such as antacids, penicillin, anticoagulants, sulfonylurea derivatives, hormone replacement therapy, alcohol, and many others. On the other hand, it is very important, especially for patients who take other drugs such as combined antiretroviral therapy or hormonal contraception, to provide STI prophylaxis with doxycycline [64].

In Molina et al.'s clinical study, safety analyses included all randomized participants, and adverse events were recorded at each visit, regardless of their relation to study drugs. Toxicity was graded according to the ANRS scale of the severity of adverse events in adults. The frequency of serious events or of grade 3 or 4 adverse events did not differ significantly between doxycycline and the control group, and no participant died during the study. Seven percent of patients receiving doxycycline discontinued prophylaxis because of multiple drug-related adverse events, mostly from the gastrointestinal tract: abdominal pain, nausea, diarrhea, bloating, and gastric reflux, as well because of fatigue and dizziness. The difference between the two groups was statistically significant. It is worth mentioning that all patients with grade 4 alanine aminotransferase elevation had acute Hepatitis C Virus (HCV) infection [18].

In Bolan et al.'s study, there was only one participant from the group receiving doxycycline who reported gastrointestinal reflux symptoms. No rashes, photosensitivity, or other adverse events were reported [17].

During Luetkemeyer's et al. open-label study five grade 3 adverse events and no serious adverse events were attributed to doxycycline [20].

3.3. Summary of the Evidence

Given the small total number of isolates in the presented studies, the selection of tetracycline resistance in *N. gonorrhoeae* in doxycycline prophylaxis could not be proven. Luckily, the risk of acquisition of resistance to doxycycline in *C. trachomatis* and in *Treponema pallidum* (but not *N. gonorrhoeae*) is currently considered to be low, although the possibility exists, given the emergence of azithromycin-resistant *T. pallidum* [65], and genetic potential of *T. pallidum* for resistance against doxycycline [66], as well as reports of doxycycline-resistant *C. trachomatis* [67]. Additionally, *Mycoplasma genitalium*, as an emerging new clinically relevant STI cause with an extraordinary ability to develop antibiotic resistance

to multiple agents, should be carefully observed as a potential resistant to doxycycline infectious factor.

The results demonstrate that doxycycline prophylaxis seems to be safe and well tolerated. In the area of adverse events during doxycycline prophylaxis, in most studies, no serious adverse events were attributed to doxycycline itself, and the most commonly reported side effects were mild symptoms from the gastrointestinal tract. Moreover, in the mentioned studies, most participants were also on HIV PrEP co-administration, and cases of acute HCV infection have been reported. For that reason, the role of doxycycline in causing adverse events might be exaggerated.

4. STIs Incidence in Different Populations and Tailored Therapy

Pre-exposure prophylaxis (PrEP) for HIV might induce risk compensation, defined as increased sexual risk behavior leading to increased incidence of bacterial STIs, occurring even in 90% of PrEP users during one year of PrEP use [68]. The incidence of STIs differs among PrEP users as a result of differences in sexual behavior, but STI positivity can be found in all risk behavior groups, ranging from 14.0% in the low-risk behavior class to 35.5% in the high-risk group [69].

Compared to event-driven PrEP HIV users, the incidence rates of chlamydia and gonorrhea were higher for participants with daily PrEP use. Daily PrEP users were more often employed and younger compared to participants with event-driven PrEP HIV use [70]. Also, STI incidence was concentrated in subpopulations of PrEP users who engaged in more chemsex and condomless anal sex as well as in patients of Western origin [69,71].

On this basis, tailoring doxyPEP care according to different HIV PrEP use patterns could be an important strategy to improve efficient doxyPEP, and screening frequency for STIs could be reduced for subpopulations with low risk for incident STIs. On the other hand, reducing the STI screening frequency from quarterly to biannually among HIV PrEP users will likely result in delayed diagnoses, potentially driving onward transmission, as almost 80% have been found to be asymptomatic. Determinants for asymptomatic STIs were also identified: older participants had a lower risk of asymptomatic STI, while casual anal sex with known and unknown casual partners and chemsex increased the risk [72].

Tailoring PrEP care with doxycycline according to different PrEP use patterns could be an important strategy to improve the efficacy of STI prophylaxis.

5. Conclusions

In the background of increasing bacterial STI incidence, new means to reduce sexually transmitted infections are urgently needed. Doxycycline pre- or post-exposure prophylaxis is one of the possible interventions that may help to achieve this objective. The results of the studies on that topic that have already been published are limited; however, based on the foregoing studies, doxycycline seems promising in reducing the prevalence of STIs. In all papers published to date, doxycycline prophylaxis reduced the risk of acquiring chlamydia and syphilis. In a majority of the trials, the risk of gonorrhea was also lowered.

However, the diagnostic tests performed, the samples obtained, and the frequency of testing varied among the analyzed studies, which made them difficult to compare. Moreover, doxycycline prophylaxis in bacterial STIs seems to be safe and well tolerated: no serious adverse events were reported due to doxycycline, and the selection of tetracycline resistance in *N. gonorrhoeae*, *C. trachomatis*, and *T. pallidum* has not been proven, but data on this topic are scarce. Further research is needed to determine the potential risks of doxycycline preventive prescription. Unfortunately, none of the presented studies aimed to compare the efficacy of post- and pre-exposure prophylaxis.

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