

Addressing Implementation Science Gaps for Doxycycline Post-Exposure Prophylaxis  
(doxy-PEP) Among Men Who Have Sex with Men Who Use Antiretrovirals for HIV Treatment or  
Prevention

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Abstract

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**Background:** The epidemic of bacterial sexually transmitted infections (STIs) among men who have sex with men (MSM) in the US is unremitting, as demonstrated by 2.5 million diagnoses of chlamydia (CT), gonorrhea (GC), and syphilis reported in 2019 and 56% increases in GC cases and 74% increases in syphilis since 2019. Doxycycline is an inexpensive, widely available, and well-tolerated antimicrobial that has activity against CT, syphilis, and GC isolates that are susceptible to tetracycline. Recent studies have found that post-exposure prophylaxis with doxycycline (doxy-PEP) reduced incident CT, GC, and syphilis in populations of MSM. Lessons learned about user and provider barriers to implementing novel prevention interventions for which there may be divergent perspectives among MSM on preexposure prophylaxis (PrEP) or

living with HIV (MLWH) and health care providers (HCPs). Biomedical HIV prevention through PrEP and treatment with antiretroviral (ARVs) are effective and almost eliminate HIV transmission when ARVs are used effectively to prevent HIV acquisition (PrEP) or transmission (undetectable equals untransmittable for people living with HIV) among MSM.

Several factors may influence introduction and implementation of doxy-PEP in routine care, including sexual pleasure, partner communication, and perceived risk; however, few behavioral science evaluations have examined this in the context of biomedical STI prevention tools such as doxy-PEP. Furthermore, HCPs play an important role in the introduction of new medical interventions, yet little is known about HCPs perspectives on doxy-PEP to date. This study aimed to understand how doxy-PEP use influences MSM's motivations and experiences with sexual decision-making, including pleasure-seeking and sexual quality of life, sampling both MSM who currently use PrEP and MSM living with HIV.

**Methods:** We conducted two qualitative analyses; for the first study (Chapters 2 and 3), we leveraged existing research infrastructure to nest a qualitative evaluation in an ongoing randomized, open-label trial of doxy-PEP (R01AI143439). We recruited both MSM HIV-negative on PrEP and living with HIV who were randomized to take a single dose of doxycycline after condomless sex (“doxy-PEP”) and consented to participate in the in-depth interviews guided by the Sexual Health Model. We examined how doxy-PEP influences sexual health and safer sex, positive sexuality, and intimacy and relationships. For the second study (Chapter 4), we recruited HCPs from major cities with high STI rates according to the Center for Disease Control (CDC) through newsletters, emails, and in-person outreach to referrals from participants and local community-based organizations to identify providers known to be advocates for sexual

health. HCPs with PrEP prescribing expertise and a large panel of MSM patients were invited to participate. The Diffusion of Innovation Theory guided the in-depth interviews. We examined knowledge of doxy-PEP, perspectives on prescribing doxy-PEP for bacterial STI prevention, and what it would take to get doxy-PEP implemented in their health setting.

**Results:** In the first analysis of IDIs among MSM on PrEP and living with HIV, we interviewed 24 MSM on PrEP, participants reported that doxy-PEP improved their quality of life and was associated with more enjoyable sex experiences and increased intimacy. Participants generally felt doxy-PEP offered 'peace of mind' by reducing stress and anxiety associated with acquiring or transmitting an STI. Men also reported that taking doxy-PEP led to more open communication about their HIV status and PrEP use, STI testing, and sharing STI/HIV results and that doxy-PEP provided an additional layer of protection. We interviewed 19 MSM living with HIV, participants taking doxy-PEP reported less worry about STI transmission, and that doxy-PEP provided sexual freedom to have the type of sex they desired and decreased anxiety related to rejection from sexual partners because of their HIV status. In the second analysis, 30 HCPs reported that while they thought doxy-PEP provided another tool in a toolkit to prevent STIs, they also had concerns about prescribing doxy-PEP for STI prevention, specifically related to antibiotic resistance, and identified the need for more data to understand the long-term safety of doxy-PEP. HCPs reported that normative guidelines about doxy-PEP would facilitate provider adoption of doxy-PEP and prescriptive practices.

**Conclusion:** There is excitement and hope for the potential benefits of doxy-PEP use among MSM and their HCPs. Sexual pleasure will be essential in messaging and introduction of doxy-

PEP use among MSM, regardless of HIV status. Formalized guidelines and messaging for HCPs are needed to introduce doxy-PEP prescription into widespread clinical practice.

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## Chapter 1: Introduction

There is a growing global epidemic of bacterial sexually transmitted infections (STIs) among MSM -- *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (GC), and *Treponema pallidum* (syphilis) [1]. In 2019, the incidence of these bacterial STIs was at an all-time high, with nearly 2.6 million diagnoses of CT, GC, and syphilis [1]. Over the past five years, GC and syphilis rates among men have risen dramatically ( 61% and 83%, respectively) and MSM account for nearly half of all bacterial STIs and over half of all new HIV infections in the United States [2]. In the past decade, there have been two advancements in sexual health to prevent HIV -- preexposure prophylaxis (PrEP) and HIV viral suppression among persons living with HIV and on antiretroviral treatment (called undetectable equals untransmittable, or U=U) [3-5]. Current oral PrEP is daily or event-driven dosing of a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), which if taken as directed, can provide high levels of protection from HIV for persons at risk of HIV acquisition, regardless of condom use [3-5]. The U=U slogan is based on the use of antiretrovirals to reduce the viral load to undetectable levels, which protects from HIV transmission with condomless sex [4, 6].

PrEP is more than a prescription for an antiretroviral medication for HIV prevention; it is a combination HIV/STI prevention strategy that includes STI screening for early diagnosis and treatment of STIs which will help control the STI epidemic among MSM [4, 7]. However, some studies have associated PrEP with increased incidence of STIs, in part due to quarterly or biannual STI testing in PrEP programs as well as lower condom uses among MSM on PrEP. An indicator of sexual behavior change among MSM was reported by a study of MSM in Seattle from 2002 to 2018, which reported that those ever using PrEP were more likely than non-PrEP users to report condomless anal sex with a serodiscordant partner (49% vs. 32%) and that those

reporting condomless anal sex had a higher risk of HIV and STIs compared to MSM who reported using condoms [8].

Health care providers (HCPs) are essential in disseminating HIV prevention information and determining PrEP uptake because of their medical training, capacity to link individuals to prevention resources, and their role in performing laboratory monitoring for PrEP users [9]. Since PrEP requires a prescription, providers may function as ‘gatekeepers’ for potential PrEP candidates [10]. They are also uniquely situated to educate patients on the risks and benefits of PrEP which can influence their motivation and uptake of PrEP, HCPs can reach many individuals who would benefit from PrEP [11] and are the preferred source of health information by MSM seeking HIV information [12]. Understanding HCPs’ attitudes and beliefs about HIV prevention and PrEP, and training providers about PrEP and care for sexual and gender minority populations are essential to improving relationships between MSM and their HCPs [13]. Therefore, HCPs and patient perspectives, communication, and trust are critical for implementation of scientific advances, such as doxy-PEP, in order to translate these novel interventions into meaningful prevention strategies for MSM and to decrease disparities.

Doxycycline is an inexpensive, well-tolerated broad-spectrum antibiotic taken by mouth to treat several bacterial infections such as acne or malaria prophylaxis [14, 15]. Studies have shown that doxycycline prophylaxis can reduce STI incidence and is under-considered as an STI prevention strategy for MSM. Understanding how new strategies to prevent STIs influence sexual decision-making and sexual quality of life among MSM can guide the development of successful doxy-PEP messaging and implementation strategies. Sexual health is "a state of physical, emotional, mental and social well-being with sexuality" [16]. It acknowledges the importance of sexual knowledge and recognizes the great value of sexual pleasure, joy,

relationships, and effective communication [17]. Data suggest that pleasure-seeking has been associated with condomless sex and a motivator for PrEP use and may also be associated with MSM prioritizing pleasure and sexual satisfaction over STI risk [18, 19].

Pleasure can be an essential factor in the decision-making about sexual partners and practices [20], especially among MSM, and should be a necessary consideration for HIV/STI prevention efforts [21]. The ANRS-IPERGAY sub-study of French MSM using on-demand PrEP found that participants perceived condoms as a material and symbolic barrier to pleasure and desire, causing anxiety and stress considering sexual intercourse. However, PrEP allowed participants to freely choose their desired sexual behavior and positions and enjoy greater intimacy [20]. Pleasure is a crucial component of sexual health [22], and interventions that incorporate strategies beyond condoms, including PrEP, post-exposure prophylaxis (PEP), U=U, and now doxy-PEP, are likely to be more realistic and practical than those exclusively focused on condoms, [21] especially for MSM [23].

Qualitative methodologies can improve understanding of the commonalities and differences in sexual pleasure experienced by MSM [23] and identify key influences informing sexual decision-making. Evidence supports that PrEP has changed how MSM engage in sex and provides practical benefits beyond HIV mitigation, such as increased sexual satisfaction and intimacy, increased STI testing, engagement with the health system, and reduced shame and anxiety surrounding sex [20, 24, 25]. These benefits highlight the psychological burden of living with high HIV risk and demonstrate the potential for PrEP use to positively affect the mental and emotional aspect of MSM sexual health [25, 26]. Yet, clear messaging to MSM on the full range of safe sex practice options, including benefits of PrEP beyond HIV prevention, may improve motivation for prevention strategies and provide opportunities for pleasure, intimacy, agency, and

sexual expression [19, 23]. To date, there are very little data from populations of MSM on pleasure and its influence on sexual decision-making despite the inequitable access to biomedical HIV prevention methods [23]. How doxy-PEP may influence pleasure-seeking with sexual partners and HIV/STI vulnerability in sexual decisions among MSM remains unclear. Improved understanding of pleasure-seeking and its influences on sexual decision-making among MSM can support the development of effective messaging for doxy-PEP programs.

## **Chapter 2: “It’s been a very liberating experience.”: Experiences with doxycycline post-exposure prophylaxis (doxy-PEP) for STI prevention and sexual pleasure among men who have sex with men (MSM taking HIV pre-exposure prophylaxis (PrEP))**

### **Abstract**

**Background:** Sexual pleasure is key to sexual health and is associated with condomless sex and PrEP use among men who have sex with men (MSM). We sought to understand how doxycycline post-exposure prophylaxis (doxy-PEP) use impacts sexual pleasure among MSM taking HIV PrEP enrolled in a 12-month open label trial of doxy-PEP in sexual health and HIV clinics in Seattle and San Francisco.

**Methods:** We conducted in-depth interviews (IDIs) with MSM who had a bacterial STI in the past year and who were randomized to the doxy-PEP arm in the DoxyPEP open label trial in San Francisco and Seattle (NCT03980223). IDI sampling was stratified by quarterly doxycycline dispensation, based on low (<30 doses) and high (>30 doses), which were indicative of sexual activity frequency and/or doxy-PEP use. IDIs were conducted after the 9- or 12-month study visits, and interview transcripts and debrief reports were grounded in the Sexual Health Model because it advocates for sex positivity and comprehensive approaches to sexual health centered on the population under study to design culturally relevant interventions.. We used thematic analysis to explore the influence of doxy-PEP use on sexual health, safer and positive sexual experiences, and intimacy and relationships.

**Results:** We interviewed 24 MSM on PrEP who were randomized to the doxy-PEP arm who had a median age of 36 years, and 8.7% were Black and 29.2% Hispanic. Participants reported that use of doxy-PEP improved their quality of life and was associated with more enjoyable sex experiences

and increased intimacy. Participants generally felt doxy-PEP offered "peace of mind" by reducing stress and anxiety associated with acquiring or transmitting an STI by providing an additional layer of protection. Participants also reported that taking doxy-PEP led to open communication about their HIV status and PrEP use, STI testing, and sharing STI/HIV results.

**Conclusion:** Among MSM with experience taking both HIV PrEP and doxy-PEP, we found that increasing sexual pleasure was a factor that motivated their PrEP and doxy-PEP use.

## Introduction

The epidemic of bacterial sexually transmitted infections (STIs) among men who have sex with men (MSM) in the United States (US) continues. In 2019, there were nearly 2.6 million diagnoses of chlamydia (CT), gonorrhea (GC), and syphilis reported in the US. Since then, GC cases have increased by 56% and syphilis by 74% [1, 2]. Use of pre-exposure prophylaxis for HIV prevention (PrEP) among MSM has also been associated with increased rates of bacterial STIs, in part due to increased frequency of STI testing as well as behavior change including decreased condom use [27].

Doxycycline is an inexpensive, widely available, and well-tolerated antimicrobial that has activity against syphilis, CT, and GC isolates that are susceptible to tetracycline [14, 28]. The IPERGAY study found that post-exposure prophylaxis with doxycycline (doxy-PEP) reduced incident CT and syphilis by 70% among HIV-negative MSM in France using event-driven HIV pre-exposure prophylaxis (PrEP) [4, 29], although no reduction in GC was observed. Our team conducted the DoxyPEP study (NCT03980223), an open label effectiveness trial of doxy-PEP among MSM in San Francisco, California, and Seattle, Washington, US, which found that doxy-PEP reduced STI incidence by two-thirds, including a more than 50% reduction in GC [30]. The more recent DOXYVAC study demonstrated an 84% reduction in the time to first CT and syphilis as well as a 50% reduction in the time to first GC infection with doxy-PEP use [31].

Understanding behavioral factors that may influence doxy-PEP use among MSM will help guide the introduction of this novel intervention into practice, as was the case with introduction of biomedical HIV prevention interventions, such as pre-exposure prophylaxis (PrEP) among persons without HIV [3, 4, 15, 32, 33]. To date, few behavioral science evaluations examine how incorporating and integrating biomedical STI prevention tools, such as doxy-PEP and HIV PrEP,

influences sexual practices among MSM [3, 4, 15, 32, 33]. Evidence suggests that improved sexual intimacy and pleasure is a major motivator for MSM to use HIV PrEP [25, 34]. In a recent cross-sectional analysis of MSM in HIV serodifferent relationships in New York City, intimacy motivations for condomless sex were associated with PrEP adoption intentions [34]. Understanding how sexual pleasure influences decision-making in the context of biomedical STI/HIV prevention could inform strategies for the introduction of doxy-PEP for MSM without HIV infection.

The Sexual Health Model is a theoretical framework [35] that advocates for sex-positivity and comprehensive approaches to sexual health [17] centered on the community's experiences to design culturally relevant interventions that improve sexuality and [36] reduce HIV/STI exposure. To guide future doxy-PEP programs, we conducted a qualitative evaluation grounded in the Sexual Health Model among MSM without HIV who used both doxy-PEP and HIV PrEP to understand how doxy-PEP use influenced their sexual pleasure and sexual quality of life.

## **Methods**

### *Study design and population*

This qualitative study was nested in a larger qualitative sub-study of the DoxyPEP trial (NCT03980223) which assessed doxy-PEP acceptability, motivations for use, and impact on sexual behavior. The trial procedures have been previously described [30]. Briefly, MSM who were living with HIV or HIV-negative and taking PrEP were randomized to take a single dose of doxycycline hyclate 299 mg within 72 hours of a condomless sexual encounter with a male partner, and not to exceed one dose every 24 hours. The study was conducted at four sites in San Francisco, and Seattle (two HIV care clinics and two sexual health clinics), which dispensed doxycycline as 200 mg dose, one dose comprised one PEP dose.

This qualitative sub-analysis includes only the HIV-negative men taking PrEP enrolled in the trial who were randomized to take doxy-PEP. From among this sub-population, we recruited a purposive sample stratified by doxycycline pills dispensed at 3-, 6-, and 9-month visits—low (<30 doses per visit), high (>30 doses per visit), or variable (a combination of low and high use which varied from visit-to visit)—and which generally corresponded with sexual activity frequency as reported by participants (e.g., >30 doses between quarterly visits indicated more frequent sexual activity). These strata were selected to represent the common patterns of doxy-PEP use identified in the parent trial. Participants were eligible for this qualitative sub-study if they were  $\geq 18$  years, able and willing to provide informed consent, reported unprotected sexual activity with  $\geq 1$  male partner (at last visit), had data available on doxy-PEP use at 9-month or 12-month visits, and were within 4 weeks of completing study follow-up. Participants with low, high, or variable levels of doxycycline pill usage were identified by research coordinators during study visits and referred to qualitative staff.

The qualitative study was informed by the Sexual Health Model to amplify participant experiences to design culturally relevant interventions to improve sexuality and reduce HIV/STI exposure [17]. The interview team included two male research scientists with behavioral science experience (R.P. and R.F) who had no prior relationship to participants. In-depth interviews (IDIs) were conducted on the same day as the study visit or scheduled for a later date, depending on the participant's preference. Study recruitment terminated once data saturation was reached (interviews no longer provided new information).

### *Data Collection*

A line of questioning informed by the Sexual Health Model was developed by qualitative study personnel (K.C., R.F., and R.P.) based on literature reviews and prior clinical and research

experience among MSM and embedded in the interview guide. Topics explored how doxy-PEP influences domains of sexual health and safer sex, positive sexuality, and intimacy and relationships [17]. Participants were asked to describe: 1) their meaning of sexual pleasure; 2) sexual experiences and pleasure while taking doxy-PEP; 3) their beliefs on disclosing HIV status within sexual partnerships, 4) experiences where they did or did not disclose doxy-PEP use; and 5) personal feelings about their doxy-PEP use.

IDIs were conducted virtually using Zoom Cloud Meeting, as the qualitative study was conducted during the COVID-19 pandemic, or in-person based on participant preference and COVID-19 precautions at the time of data collection. In-person IDIs took place in a private exam room at the study sites. Following informed consent for the IDI, the interviewer (R.F. and R.P.) recorded basic demographic information of each participant (age, race, ethnicity, enrollment clinic, and doxy-PEP use). IDIs were conducted in English, were audio-recorded, and lasted 45-60 minutes. Following each IDI, interviewers summarized their subjective impressions of the interview and briefly captured the participants' responses related to key themes in a structured debrief report [37]. All interview audio files were transcribed verbatim using Home Row, Inc. transcription services and checked for accuracy by the first author and a research scientist (R.F. and R.P.).

### *Human Subjects Considerations*

The University of California San Francisco Institutional Review Board approved all study materials. All participants provided written informed consent and received a \$50 cash reimbursement for their participation.

### *Data Analysis*

Data were analyzed using a combination of thematic network and directed content analysis methods [38, 39]. Directed content analysis, based on the Sexual Health Model, was used to capture how doxy-PEP influences sexual health care and safer sex, positive sexuality, and intimacy and relationship concepts [17]. Thematic network analysis was used to identify specific factors that influenced sexual pleasure and sexual quality of life within the context of their participation in the DoxyPEP trial and doxy-PEP use. A coding team, comprised of the first author, two research scientists (K.C. and R.F.), and a doctoral student (D.O.), read excerpts across 13 transcripts and used memos and discussions in subgroups to collectively deliberate on commonly emerging concepts. The memos and review of identified concepts were used to guide the development of the preliminary codebook. Open coding was also used to derive codes that captured key concepts from the data. The codebook was iteratively refined during team meetings where all codes were reviewed and discussed before reaching a consensus on the final codebook. Transcripts were imported into Dedoose software (version 7.0.23, Los Angeles, CA, USA: Sociocultural Research Consultants, LLC) for coding with the final version of the codebook. Codes were then categorized into broader themes, and illustrative quotes were identified that best showcased common themes of the participants' experiences.

## **Results**

Between November 2021 and December 2022, 24 HIV-negative MSM on PrEP completed the interviews, eight prior to Data Safety Monitoring Board (DSMD) unblinded the study in May 2022. The median age of participants was 36 years (IQR 27.5-42.4). Thirty percent reported a race other than White, and 29% identified as Hispanic. A majority of men completed any college or post-graduate studies (79%) and over half (63%) had an annual income of \$75,000 or less. The most frequently reported substances used in the past 3 months included ecstasy (29%), marijuana

(33%), and poppers (33%). In the last 3 months, the median number of partners in was 15.5 (IQR 10-30) and the median number of insertive anal sex acts 15 (IQR 3.5-40), and receptive anal sex acts 6.5 (IQR 1-15). 70% reported using 0-9 doses of doxy-PEP per months, 20% 10-19 doses, and 8% took 20 or more doses per month by self-reported doxy-PEP use (Table 1).

We identified three themes within the domains of positive sexuality and intimacy and relationships of the Sexual Health Model: 1) doxy-PEP with PrEP amplifies the ability to enjoy sexual pleasure; 2) doxy-PEP provides a sense of sexual liberation; and 3) doxy-PEP supported more open communication with their sexual partners.

### ***Doxy-PEP with PrEP amplifies the ability to enjoy sexual pleasure***

Doxy-PEP helped participants and their partners feel safe, allowing them to be more present in their sexual encounters. Doxy-PEP added another layer of protection, especially with ‘random sexual hookups,’ and enhanced sexual experiences by reducing anxiety related to condomless sex. Most men reported a reduction in condom use after starting PrEP. If condoms were used, it was rare, mainly at the request of a sexual partner. PrEP made them feel confident that they were protected from HIV and now, doxy-PEP provided similar confidence in reducing their risk of STIs. Participants associated doxy-PEP with improved quality of life, including more comfort with sexual experiences and confidence about not spreading an STI.

*"doxy-PEP lowered my anxiety and my stress about contracting something or passing something along." (Participant 043-9, age 38)*

*"...as far as STIs go, I feel comfortable just expressing that I'm on PrEP, and I have doxy-PEP. And it makes me feel safe. I think it makes my partners feel safe. And so,*

*it's just less of a worry around STIs. (Participant 141-6, age 26)*

*“doxy-PEP has increased my comfortability and freed up my mental capacity to be present in the moment rather than to think about all the potential consequences of that encounter related to an STIs.” (Participant 135-3, age 25)*

Men also reported feeling less worried after sex and relieved from the need to contact sexual partners about potential STI exposures. Before their use of doxy-PEP, men felt stressed about making or receiving calls about possible exposures to STIs. For some, it led to a vicious cycle of anxiety and frustration, being unsure of acquiring or transmitting an STI, getting tested, and learning that the results were negative. Doxy-PEP removed those worries and provided a substantial psychological benefit.

*“Whenever I would get an STI, it was always a very frustrating experience because you must tell your partners and go through all that. You must get tested, and sometimes you are never positive for anything. So, it's also an expense associated with that every time you get tested but doxy-PEP kind of took that away and the feeling of not wanting to be sexually active because I'm afraid of getting an STI” (Participant 156-9, age 44)*

Some men who used doxy-PEP reported no change in their sexual practices; however, they did describe some level of safety or addition to their prior safer sex strategies.

*"I wouldn't say there was a measurable difference [in condom use] either way. It's something that I was going to do the same things in the same way, either way. It just felt like I had more tools in the toolbox to keep myself and my respective partners safe the same way." (Participant 119-8, age 38)*

*"I don't think there is any way for doxy-PEP to not at least subconsciously make you feel a little safer and a little more inclined to be a little more adventurous. But I haven't consciously noted any change, no." (Participant 149-7, age 33)*

### ***Doxy-PEP provides a sense of sexual liberation***

For some, doxy-PEP was sexually liberating, allowing men to explore sexual desires they previously avoided due to their fear of increased STI exposure. Because of their perceived protection from STI acquisition due to doxy-PEP, men felt more comfortable with casual sexual hookups, seeking sex at sex parties, bathhouses, and 'dark rooms' (e.g., a dark place in gay bar or nightclub for anonymous sex)', and freer to engage in condomless sex.

*"After doxy-PEP, I've become more open to having condomless sex where I was bottoming, I guess with strangers, for lack of better words, or people I was not dating or in a committed relationship with." (Participant 147-9, age 25)*

*"I feel more comfortable when I'm at a sex party, or dark room, or sauna and would feel freer to have more sex knowing that I could take doxy-PEP afterwards." (Participant 108-5, age 40)*

A few men were curious if doxy-PEP would be effective, and to test it, they increased their sexual activity as an experiment. For some, it involved a temporary change in their sexual behavior. Some men found doxy-PEP empowering; PrEP protected them from HIV, and doxy-PEP provided an extra layer of protection, allowing them to minimize their exposure to STIs and be more sexually adventurous.

*“At first, I was like, wahoo! Let’s go have some fun! So, for the first couple of months, I ramped it up a bit more. But then I think leveled out to be more normal.” (Participant 107-8, age 34)*

*“Doxy-PEP gave me that reassurance that I could push my boundaries and that I could try things that I was hesitant to try before. It’s been a very liberating experience, and I’m glad that I had the opportunity.” (Participant 013-5, age 55)*

### ***Doxy-PEP supported open communication with sexual partners***

Taking doxy-PEP sparked conversations. Most participants added taking doxy-PEP to their pre-sex communication with their partners—specifically the time before sex when participants reported sharing the date and results of their last STI testing or disclosing their HIV status or PrEP use. Disclosing doxy-PEP use allowed participants to share something extra they were doing to protect themselves from STIs with their sexual partners, putting partners more at ease in the sexual encounter. Doxy-PEP use created a space for open communication with sexual partners and supported decision-making around safe sex, intimacy, and relationships. Some added doxy-PEP to

their hookup site profile. Doxy-PEP was acceptable to their sexual partners, who appreciated the potential extra protection doxy-PEP provided, and most were curious to learn more.

*“There’s always that exchange before a hookup like, when was the last time you were tested, yadda, yadda. So, it’s kind of just became an additional, like, bullet point in that spiel. I was like, yes, I’m on PrEP, I recently tested negative, and I’m on doxy-PEP.” (Participant 147-9, age 25)*

*“In my experience, it feels common to not even ask. Just to say, “Oh by the way, I’m on PrEP, doxy-PEP, and I was tested this month. And most of my sexual partners bring that up very casually. Yeah, I do. I think it’s very important.” (Participant 141-6, age 26)*

*“I’m on doxy-PEP, an antibiotic you take within 72 hours to prevent chlamydia, gonorrhea, and syphilis infections. I leave it at that, and if they have any questions, I’ll answer them. However, it puts my mind at ease, and I think it does the same for my sexual partners.” (Participant 145-0, age 35)*

*“If I am on doxy-PEP, I am protecting myself, I’m protecting my partners, and I inform all my partners that I was on this trial, and they really appreciated learning more about it and understanding, what it was and asked for more information. (Participant 156-9, age 44)*

## **Discussion**

In this qualitative analysis of MSM on HIV PrEP with experience using doxy-PEP, in the open label trial, we found that doxy-PEP use amplified their ability to enjoy sexual pleasure, provided a sense of sexual liberation and supported open communication. Sexual pleasure is an alternative to risk-reduction approaches for engagement with biomedical prevention, such as HIV PrEP [24]. However, sexual pleasure and its contribution to prevention messaging are not clearly understood. Few studies have used sexual pleasure to better understand MSM PrEP experiences and engagement in sexual decision-making [20]. Our data add to the few studies on user experiences of doxy-PEP among MSM who were also taking HIV PrEP and adds to the limited evidence on how biomedical HIV/STI interventions influence sexual pleasure among MSM.

Reduced stress and anxiety from doxy-PEP use were reported as an important psychological benefit, including more comfort with sexual experiences and confidence about not spreading an STI in the current study. Whitfield et al. found similar findings in a longitudinal study of 137 gay and bisexual men living in the US who experienced less sexual anxiety while on HIV PrEP compared to periods not on PrEP [40]. Similar to other studies, HIV PrEP adoption was associated with psychological benefits and positive impacts on relationships that also may have influenced sexual decision-making [40, 41]. Sexual ‘liberation’ was another benefit that allowed men to push their sexual boundaries and be more adventurous in achieving the type of sex they desired. Several studies have found HIV PrEP to be sexually liberating, allowing men to broaden their pool of sexual partners, being open to individuals living with HIV as sexual partners [24, 25], increased willingness to being the receptive partner in anal sex [20, 24, 42] and feeling more at ease at sex venues and parties [24, 43]. As doxy-PEP is implemented, messaging and campaigns around the benefits of doxy-PEP for increasing comfort with sexual experiences should be considered.

Open communication with sexual partners, including about PrEP and doxy-PEP use, strengthened men's decision-making around safe sex, intimacy, and relationships. Doxy-PEP use disclosure was perceived as an additional layer of protection against STI transmission and led men to feel more empowered. Subsequently, this catalyzed open and honest communication that increased their sexual partner(s)' comfort and strengthened their sexual relationships. Other studies have shown PrEP to be a catalyst for open communication about knowledge of STI/HIV, prevention practices, and preferred type and frequency of sex [44-46]. HIV PrEP has reshaped sexual relationships and communication patterns among MSM, and it is essential to approach doxy-PEP similar to what has been reported by MSM about HIV PrEP in order to strengthen communication for better sexual quality of life [45].

More research is needed to understand the role of sexual pleasure in the decision-making process of prevention strategies among MSM [20]. Pleasure and intimacy are a part of sexual health and well-being and, therefore, should be considered in the health promotion and education for HIV and STI prevention [20]. Findings from this qualitative study situate doxy-PEP users' narratives of their sexual practice and decision-making within the biographical, social, and historical experiences in which they were produced [42], offering insight into sexual health goals and benefits of doxy-PEP use beyond STI mitigation. Health providers are the preferred source for health information among MSM when seeking PrEP or sexual health services [25, 41, 47]. To support the sexual health goals of MSM, HCPs must adopt open-minded approaches that center the lived experiences of MSM and contribute to open communication [25, 41, 47]. Our findings offer support for pleasure-based messaging and positively depicting sex among MSM, which may result in greater adoption of doxy-PEP [24, 48-50].

### *Limitations*

Our study has limitations, including that the generalizability of our findings are limited to MSM PrEP users enrolled in an open label trial and may not reflect all PrEP users with recent STIs. Despite our attempt to recruit a diverse sample based on race and ethnicity, most of the participants in the qualitative sub study were white, males, which is reflective of the parent study population. As Black, Latinx, and multiracial MSM may have unique experiences with sexual health and pleasure, studies further exploring these subgroups are recommended [25]. In addition, because participants were asked to discuss and share potentially stigmatizing practices, their reporting could be subject to social desirability bias. To minimize this bias, interviewers openly discussed the research's purpose with participants, ensured their confidentiality, and strived to phrase questions in a non-judgmental approach [25].

### *Conclusion*

In summary, the use of doxy-PEP was reported by MSM taking PrEP to be associated with improved quality of life, including more open communication, reduced stress and anxiety, a more enjoyable sexual experience, and a sense of sexual liberation. Our findings may contribute to the message and discourse about pleasure-based messaging, which could support the implementation of doxy-PEP and uptake by MSM.

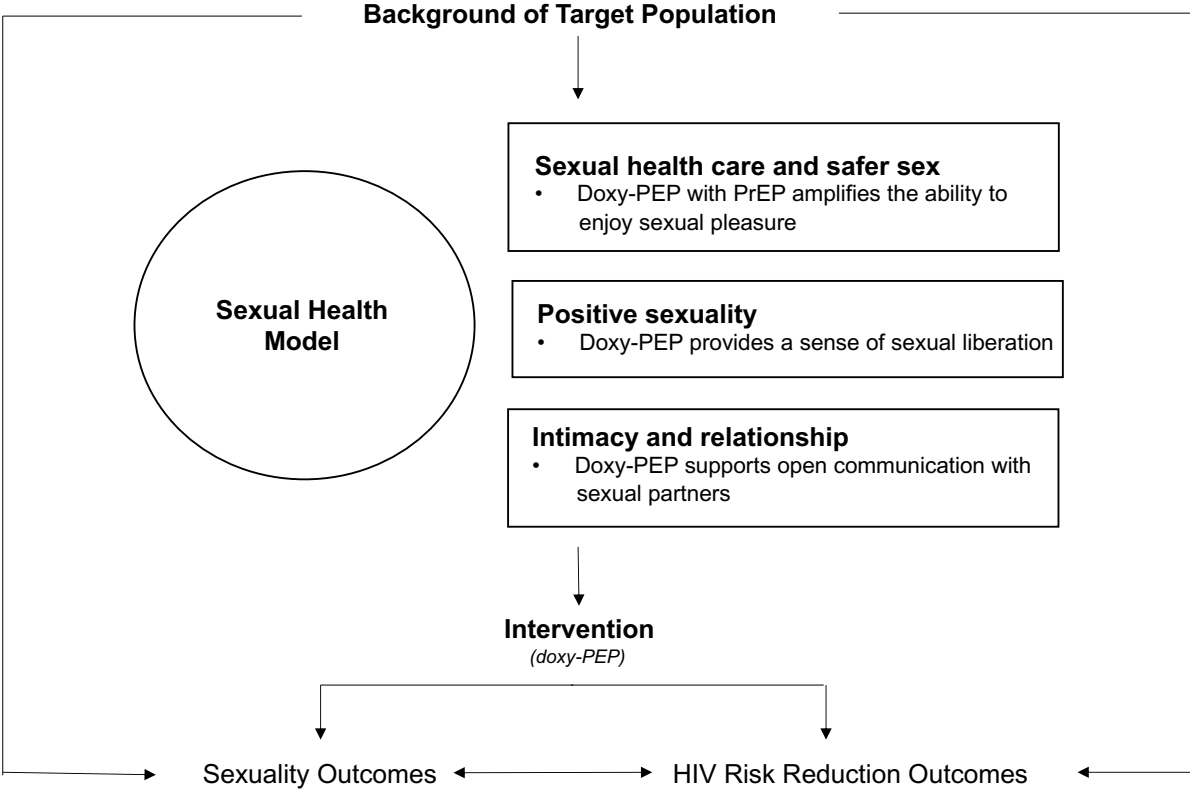
**Table 1. Demographic characteristics of interview participants (n=24)**

<b>Characteristics</b>		<b>N (%) or median (IQR)</b>
Home city	San Francisco	5 (20.8%)
	Seattle	19 (79.2%)
Age		36 (27.5 - 42.5)
Gender Identity	Man	24 (100.0%)
Race	Asian/Pacific Islander	1 (4.3%)
	Black	2 (8.7%)
	Multiracial	4 (17.4%)
	White	16 (69.6%)
Ethnicity	Latinx	7 (29.2%)
	Not Latinx	17(70.8%)
Gender of sex partners	Men only	22 (91.7%)
	Multiple genders	2 (8.3%)
Education	High school graduate or GED	5 (20.8%)
	Any college or post-graduate studies	19 (79.2%)
Annual income	Less than \$20,000	4 (16.7%)
	\$20,001 - \$50,000	5 (20.8%)
	\$50,001 - \$75,000	6 (25.0%)
	More than \$75,000	9 (37.5%)
Insurance status	Private	18 (75.0%)
	Public	2 (8.3%)
	None	4 (16.7%)
Substance use in prior 3 months		9 (37.5%)
	Stimulants (meth, cocaine, crack)	6 (25.0%)
	Heroin/opioids	1 (4.2%)
	Ecstasy, GHB, ketamine	7 (29.2%)
	Amyl nitrates (poppers)	8 (33.3%)
	Marijuana	8 (33.3%)
Anal sex in the past 3 months	Insertive sex acts	15 (3.5-40)
	Receptive sex acts	6.5 (1-15)

Number of partners in past 3 months		15.5 (10-30)
Self-reported doxy-PEP use in past month	0-9 doses/month	17 (70.8%)
	10-19 doses/month	5 (20.8%)
	20-29 doses/month	2 (8.3%)
	30+ doses/month	0

doxy-PEP=doxycycline post-exposure prophylaxis

**Figure 1. Modified Sexual Health Model used as theoretical framework for understanding sexual pleasure and doxy-PEP use among MSM on PrEP**



**Chapter 3: “I don’t have to worry about getting STIs every time I have sex.”: the influences of doxycycline post-exposure prophylaxis (doxy-PEP) on sexual pleasure among men who have sex with men who are living with HIV**

**Abstract**

**Background:** Pleasure can be an essential factor in decision-making by men who have sex with men (MSM) about sexual partners and practices. Doxycycline postexposure prophylaxis (doxy-PEP) is an innovative and effective strategy to reduce STI acquisition among MSM. Using the Sexual Health Model, we sought to understand the influences of doxy-PEP use among MSM living with HIV.

**Methods:** From November 2021 through December 2022, we conducted individual interviews with MSM living with HIV who had a bacterial STI in the past year and who were randomized to doxy-PEP in the DoxyPEP open label trial in San Francisco and Seattle (NCT03980223). We purposively sampled participants to capture a range of low doxy-PEP use (<30 pills per quarter), high use (>30 pills per quarter), or variable (a combination of high/low across visits). Interviews explored how doxy-PEP influenced sexual health, safer sex, positive sexuality, and intimacy and relationships. Interview transcripts and debrief reports were thematically analyzed.

**Results:** We interviewed 19 MSM living with HIV with a median age of 41 years (IQR 35-54), who had been living with HIV for a median of 12.5 years (IQR 8.5-19). Half (53%) identified as white, 29% as Black, and 26% as Hispanic. We identified three themes from within the domains of the Sexual Health Model: 1) men worried less about STI transmission after they started taking doxy-PEP; 2) doxy-PEP provided sexual freedom to have the types of sex that they desired; and

3) doxy-PEP decreased anxiety about possible rejection from sexual partners because of living with HIV.

**Conclusion:** In this qualitative study, MSM living with HIV reported that use of doxy-PEP improved quality-of-life and sexual pleasure by reducing worry about STI acquisition, providing more sexual freedom, and decreasing anxiety about HIV stigma and possible rejection from sexual partners.

## Introduction

Over the past decade, antiretrovirals for treatment that achieve viral suppression and secondarily also prevent HIV transmission have influenced the sexual health of men who have sex with (MSM) who are living with HIV [3, 4, 32]. Antiretroviral treatment that rapidly and durably suppresses viral load is effective in preventing HIV transmission among those that have sustained undetectable levels, catalyzing the “undetectable equals untransmittable” (U=U) campaign [3, 4, 51, 52] In addition, oral tenofovir-based pre-exposure prophylaxis (PrEP), either daily or event-driven dosing, is highly effective as primary prevention of HIV acquisition [3, 4, 53]. PrEP has also been associated with improved communication about HIV status and reduced HIV-related stigma for persons living with HIV [45, 54].

Since the introduction of these new antiretroviral-based HIV prevention strategies, rates of bacterial sexually transmitted infections (STIs) have increased among MSM, including chlamydia (CT), gonorrhea (GC), and syphilis [3, 4, 15, 32]. Some studies suggest that the confidence in ART to prevent HIV transmission and PrEP to prevent HIV acquisition has decreased condom use and increased numbers of sexual partners among MSM and contributed to increasing STI rates [4, 32, 53, 55].

Doxycycline is a moderate-spectrum antibiotic used for common infections, including CT, syphilis, and although doxycycline is not used for GC treatment, it can also prevent tetracycline-susceptible strains of GC [14, 15, 56]. Three studies have shown high efficacy of doxycycline post-exposure prophylaxis (doxy-PEP) for STI prevention among MSM. The IPERGAY study of doxy-PEP among MSM taking event-driven HIV PrEP found a 70% reduction in incident CT and syphilis in the doxy-PEP arm [30]. The DoxyPEP Study among MSM in San Francisco and Seattle found a 62% reduction in CT, GC, and syphilis among men living with HIV and 66% among MSM

on PrEP who were randomized to the doxy-PEP arm [30]. The recent DOXYVAC study demonstrated an 84% reduction in the time to first CT and syphilis as well as a 50% reduction in the time to first GC infection in the doxy-PEP arm [57]. With the transition from efficacy trials to guidelines and implementation of doxy-PEP, understanding factors that influence doxy-PEP use among MSM living with HIV could inform guidance for implementation in order to optimize uptake and impact in reducing STI transmission [15, 29].

Most studies that examine the impact of biomedical HIV and STI prevention options among MSM living with HIV exclusively focus on disease mitigation rather than sexual well-being, agency, or sexual pleasure [8, 53, 58]. To date, few behavioral science studies have assessed how biomedical HIV and STI prevention tools, including doxy-PEP, influence sexual practices among MSM living with HIV. Evidence suggests that increased sexual intimacy and pleasure are benefits of viral suppression among MSM living with HIV [51]. Openly promoting sexual pleasure with biomedical HIV and STI prevention tools may contribute to decreased HIV-related stigma for MSM living with HIV and may guide the implementation of doxy-PEP [24].

The Sexual Health Model is a theoretical framework [35] for improving overall sexual well-being and a comprehensive approach to sexual health [17]. The model explores the experiences of the background community to design culturally relevant interventions that improve sexuality and [36] reduce HIV/STI exposure. To guide future doxy-PEP programs for MSM living with HIV, we conducted a qualitative evaluation among MSM living with HIV who have experience with doxy-PEP to understand how doxy-PEP use influences sexual pleasure and sexual quality of life among MSM living with HIV (Figure 1.).

## **Methods**

### *Study design and population*

From November 2021 to December 2022, we conducted individual interviews with MSM living with HIV enrolled in the DoxyPEP study (NCT03980223). The DoxyPEP study is an open-label randomized clinical trial of doxy-PEP to prevent CT, GC, and syphilis among MSM. Recruitment and procedures of the parent study have been previously described [30]. Briefly, men from San Francisco or Seattle, who use antiretrovirals for HIV treatment or PrEP, were randomized to take a single dose of doxycycline hyclate within 24-72 hours of a condomless sexual encounter with a male partner, not to exceed one dose every 24 hours. All participants recruited for the qualitative study were recruited from those randomized to the doxy-PEP arm, >18 years, able and willing to provide informed consent, reported unprotected sexual activity with  $\geq 1$  male partner (at last visit), had data available on doxy-PEP use at 9-month and 12-month visits, and were within 4 weeks of their 12-month study exit visit. For this qualitative study, we conducted in-depth interviews with a subset of trial participants and analyzed data among MSM living with HIV for the current analysis

### *Recruitment*

Participants were sampled based on low, high, or variable levels of doxycycline pill use based on number of pills dispensed and reported used at the three-, six-, and nine-month visits—low (<30 pills per visit), high (>30 pills per visit), or variable use (a combination of low and high use from visit-to-visit). Research coordinators assessed participants' eligibility and interest during study visits and referred to qualitative staff if interested in participating in an IDI. These strata were selected to represent the common patterns of doxy-PEP use identified in the parent trial.

### *Data Collection*

Semi-structured interview guides containing open-ended questions were developed collaboratively between study team members (K.C., R.F., and R.P.) based on literature reviews and prior clinical and research experiences among MSM and informed by the sexual health care and safer sex, positive sexuality and intimacy and relationships of the Sexual Health Model [17]. Interview guides specifically explored how doxy-PEP influenced domains of sexual health and safer sex, positive sexuality and intimacy, and relationships. To capture perspectives on these domains, participants were asked to describe: 1) the meaning of sexual pleasure; 2) sexual experiences and pleasure while taking doxy-PEP; 3) their beliefs about disclosing HIV status with sexual partners; 4) experiences where they did or did not disclose doxy-PEP use; and 5) personal feelings about their doxy-PEP use.

Interviews were conducted by two male research scientists with behavioral science experience (R.P. and R.F.) who had no prior relationship with participants. Interviewer characteristics (i.e., age, race, ethnicity, enrollment clinic, and doxy-PEP use) reflected the study population's characteristics.

In-depth interviews (IDIs) were conducted on the same day as the study visit or scheduled for a later date, depending on participant preference, IDIs were conducted virtually using Zoom Cloud Meeting or in person based on participant preference and COVID-19 precautions at the time of data collection. In-person IDIs took place in a private exam room at parent study sites. IDIs were audio-recorded and lasted 45-60 minutes. Following each IDI, interviewers summarized their subjective impressions of the interview and briefly captured the participants' accounts related to key themes in a structured debrief report [37]. Using an iterative process to review and compare new interviews with previously conducted interviews, study recruitment terminated after reaching

data saturation (interviews no longer provided new information). All interview audio files were transcribed verbatim using Home Row, Inc. transcription services and checked for accuracy.

### *Human Subject Considerations*

The Institutional Review Board of the University of California San Francisco approved all study materials. All participants provided informed consent and received a \$50 cash incentive for their participation.

### *Data Analysis*

Dedoose software (version 7.0.23, Los Angeles, CA, USA: Sociocultural Research Consultants, LLC) was used to manage and analyze qualitative data. Interview transcripts were iteratively coded, sorted, and analyzed using a combination of thematic network and directed content analysis methods [38, 39]. Directed content analysis, based on the Sexual Health Model, was used to capture how doxy-PEP influenced sexual health care and safer sex, positive sexuality, and intimacy and relationship concepts [17]. Thematic network analysis was then used to map how doxy-PEP use influenced participant's experiences and beliefs about sexual pleasure and sexual quality of life. The analysis team, comprised of two investigators with qualitative expertise (K.C. and R.F.) and a doctoral student (D.O.), read excerpts across 10 transcripts and used open coding and memoing to derive codes that captured concepts and in subgroups to deliberate on commonly emerging key concepts. Memos were used to guide the development of the preliminary codebook. The codebook was iteratively refined during team meetings and codes selected were based on their frequency across the dataset. Codes were then categorized into broader themes, and illustrative quotes were removed that best showcased common themes of the participant experiences.

## Results

Nineteen MSM living with HIV participated in the qualitative study. Median age was 41 years (interquartile range, IQR 35-54 years). Men reported a median of 12.5 years (IQR 8.5-19 years) living with HIV. Participants identified as white (53%), Black (29%), and Hispanic (26%). Most men reported completing some college (84%), and 53% reported an annual income of less than \$50,000. Over half of the participants reported substance use in the past three months (53%), most reported recreational substances used in the past three months were marijuana (47%), amyl nitrates (“poppers”, 26%), and ecstasy (26%). Since the prior quarterly visit, participants reported a median of 12 sex partners (IQR 4-18), and a median of 10 insertive anal sex acts (IQR 4-18), and 10 receptive anal sex acts (4-28). Approximately two-thirds (63%) reported taking 0-9 doses of doxy-PEP in the prior 3 months (Table 1).

We identified three themes related to how doxy-PEP influenced sexual pleasure and quality of life among MSM living with HIV within the domains of the Sexual Health Model, which are described in greater detail below: 1) less worry about STI transmission (*sexual health care and safer sex domain*); 2) greater sexual freedom to have the type of sex they desired (*positive sexuality domain*); and 3) decreased anxiety related to possible rejection from a sexual partner because of their HIV status (*intimacy and relationships domain*).

### ***Men taking doxy-PEP worried less about STI transmission***

Most men reported that dox-PEP was associated with much less worry about getting an STI. Some men described doxy-PEP as an additional layer of protection and encouraged their sexual partners to consider using it. Men who perceived themselves as very sexually active would get tested more often, which in a minority involved monthly testing to ensure that they did not have an STI. Doxy-PEP offered a break from the need to get tested for STIs so often, and men felt

assured because they had not acquired an STI during their time in the study despite the amount of sex they were having. Before the known efficacy of PrEP and U=U in preventing HIV acquisition and transmission, most men described prevention practices that included serosorting (exclusively having sex with other men living with HIV), condoms, or abstinence, which they described as less pleasurable and more stigmatizing. Doxy-PEP was seen as ‘increasing security’ beyond what PrEP and U=U provide.

*“My partner and I use to always worry about STIs since we have an open relationship. We must tell the other if we play with someone else because there was a chance of getting an STI, right? Every time we had sex with somebody else, we had to get tested first to have sex with each other again, right? DoxyPEP helped me to not feel worried about getting an STI anymore and feel freer about it.” (Participant 048-2, age 35)*

*“I think it heightened my sense of pleasure because I don’t have that fear in the back of my thoughts and my mind of, am I going to contract an STI? Or does this person even have an STI? That becomes no longer a concern for me, because I’m protecting myself.” (Participant 065-5, age 48)*

*“My sex life is very active in general and before the study I was at the point of testing monthly because of the amount of sex I was having. Taking doxy-PEP has like taken away a worry and I feel very secure that while in the study I had no STIs at all.” (Participant 031-7, age 46)*

For some men, doxy-PEP had no impact on their experience of sexual pleasure. However, a few men reported that doxy-PEP offered them mental assurance of protecting themselves and others from STIs. When asked if their relationship with, approach to, or perspectives about sex changed due to doxy-PEP use, most men reported that doxy-PEP use did not directly change their sexual practices. However, they perceived that doxy-PEP minimized or eliminated the chance of getting an STI, even before the study was unblinded due to high efficacy. PrEP and U=U were both seen as a benefit to protect their community from HIV, and that doxy-PEP may offer similar protection against STI acquisition and transmission. Most men felt it was important to protect themselves and advocated for prevention practices that kept men safe.

*“I don’t think doxy-PEP really changed any of my actual behaviors. But my feeling about it changed. Because I felt, thank God. I don’t have to worry about getting STIs every time I have sex with somebody.” (Participant 027-7, age 66)*

*“If he’s a regular that I have sex with, and I know he likes to play a lot, I will say, “Hey, have you heard about doxy-PEP? It works so well. You should try it. You should enroll in the study if you want to try it.” (Participant 048-2, age 35)*

### ***Doxy-PEP provided sexual freedom to have the type of sex they desired***

Some men expressed a sense of greater sexual freedom because of having an undetectable viral load and that doxy-PEP liberated them from worries about STI transmission, which allowed them to have the type of sex they desired, with whom and where they wanted. To some men, sexual freedom also meant they felt comfortable not using condoms; others were already regularly

engaging in condomless sex prior to doxy-PEP use. Doxy-PEP provided peace of mind for not acquiring or transmitting an STI, allowing for more intimacy with their sexual partners. Some men found themselves having more condomless sex during the study. For others freedom included feeling more at ease in group settings (e.g., saunas, bathhouses, or sex parties), having more frequent sex or with multiple partners, and seeking anonymous sexual hookups.

*“Since I started taking doxy-PEP, I have definitely had more unprotected sex than ever.”*  
*(Participant 058-0, age 37)*

*“Doxy-PEP is helping me to explore what I like and just to make sure of what I like to do and how I’m going to do that safely.”* (Participant 048-2, age 35)

Few men described themselves as highly sexually active and did not recognize a difference in their sexual freedom related to doxy-PEP use. However, when asked about their last STI, most men could not recall getting an STI since they enrolled in the study. Other men reported no change in sexual behavior related to doxy-PEP because they reduced or refrained from sex due to COVID-19 restrictions. Some limited their number of sexual partners to a select group who followed COVID-19 guidelines and were vaccinated once COVID-19 vaccines became available. These men were perceived to be safe because they were observing COVID-19 guidelines and reduced their exposure to STIs by limiting their sexual activity to only men in the group. There were a few men who started a monogamous relationship during the trial who also reported no change in their doxy-PEP use.

***Doxy-PEP decreased anxiety related to rejection from a sexual partner because of one's HIV status***

Having HIV prevention options improved status disclosure about HIV, and most men felt having STI prevention options like doxy-PEP would open the doors for more conversations. Men were asked if U=U or PrEP changed how they interacted with sexual partners; most men reported that PrEP shifted the conversation about being HIV-positive, no longer feeling the need for deep conversations about living with HIV, which for some was described as stigmatizing or being shamed. However, with PrEP, the discussion was narrowed down to one question, "*Are you on PrEP?*" as stated by one man who felt most of his HIV-negative partners were open to having a sexual encounter with someone living with HIV. U=U was perceived as a good thing, though most men felt a lot of people did not understand or 'get it'. One man reported that U=U enabled him to openly discuss living with HIV, as confidence in U=U made him feel braver to talk about it.

*"Since PrEP has come out, it's been so much easier to discuss status; I feel like it's been more accepting, much more accepting. If doxy-PEP was more accessible to the community, I believe people would also be more open about their STI status."*

*(Participant 050-2, age 34)*

*"I felt like I had something to stand on when I heard U=U; it just made me feel a little more normal, brave to talk about living with HIV." (Participant 058-0, age 37)*

For some men adding doxy-PEP to most hookup site profiles alongside "PrEP" or "undetectable" sparked communication among sexual partners that were curious and wanted to learn more about doxy-PEP.

*"It's even on my profile that I am on doxy-PEP. After exchanging your status, negative and on PrEP, and I am undetectable, I would say that I'm on doxy-PEP, people usually ask me what it is. And I'd be like, it's a pill that I take, one to three days after an unsafe sexual encounter, and it prevents, you know, other STIs other than HIV, like gonorrhea, chlamydia, and that kind of stuff. If they have more questions, I tell them to Google it or pass them the study coordinator's number." (Participant 031-7, age 46)*

*"When I am online, some usually will ask, "Are you clean," which I don't like that comment, but I tell them it's in my profile that I am undetectable, and then I add that I am on doxy-PEP too." (Participant 035-1, age 60)*

Most men were open and honest about living with HIV and felt people were more aware and open to having a sexual encounter with someone with HIV. Men found themselves educating their partners on doxy-PEP; some compared doxy-PEP to going to a clinic for testing and getting treated. They saw it as no different than what men currently do for STI exposure or if they had symptoms. However, a few men felt that their sexual partners perceived them to be promiscuous because of their doxy-PEP use. One man described doxy-PEP as a form of "PrEP" because he felt it was the same and did not want to explain to his sexual partners that he was in a clinical trial.

## **Discussion**

In this study of MSM living with HIV who had experience using doxy-PEP during the open label trial of doxy-PEP effectiveness, men reported less worry about STI transmission, more sexual

freedom, and decreased anxiety about HIV stigma-related to potential rejection from sexual partners. Men described the benefits of doxy-PEP included enhanced sexual pleasure and quality of life that motivated them to continue their doxy-PEP use. In the context of PrEP and the prevention benefits of ART men reported that conversations about HIV were less stigmatizing and subsequently doxy-PEP increased their sexual pleasure. Considering the benefits of biomedical prevention on intimacy and sexual pleasure is an alternative to risk-focused public health messaging and may increase receptivity to campaigns such as U=U [24, 51].

The Sexual Health Model is a useful framework for HIV/STI prevention messaging in a sex-positive way. MSM living with HIV are often overlooked or excluded from messaging around sexual pleasure in place of disease mitigation and more risk-based messages. Few studies have sought to understand how sexual pleasure influences the experiences and engagement in sexual decision-making of MSM living with HIV [20, 54]. Our data add to the limited research about users' perspectives about biomedical HIV/STI interventions, including doxy-PEP, among MSM living with HIV, particularly with regards to sexual pleasure.

More research is needed to understand the fluctuating sexual decision-making landscape [45] formed by growing awareness, knowledge and use of new HIV and STI prevention strategies among MSM, including those living with HIV who historically experience high stigma. A sex-positive approach offers a unique approach to understanding the psychological and physical well-being of MSM living with HIV [51] and should be considered in health promotion and education about HIV and STI prevention [20]. Findings from this study center doxy-PEP users' sexual experiences and decision-making to highlight the benefits of doxy-PEP use for MSM living with HIV in achieving their goals of sexual health, sexual safety, and intimacy. In addition, these findings support sex-positive messaging as an alternative to risk and disease mitigation messaging

which MSM often find stigmatizing [48, 59], and highlight the benefits of HIV and STI biomedical interventions that could enrich MSM living with HIV experiences by minimizing stigma [24, 48-51].

Men taking doxy-PEP reported less worry about STI transmission and decreased anxiety related to rejection from a sexual partner because of living with HIV were related to perceived knowledge of sexual partners about U=U and PrEP that appeared to be growing and shifting conversations about HIV and HIV status disclosure. Doxy-PEP was seen as increased security beyond PrEP and U=U because men were able to prevent STIs, discussing STIs and prevention practices facilitated STI disclosure, sexual partner interest in doxy-PEP as a prevention method. This study contributes to the growing evidence that increased community knowledge of HIV/STI biomedical prevention reduces social stigma related to HIV and STIs [45, 51, 54]. Tester et al. found similar findings in a qualitative analysis using the Sexual Scripts Theory among 22 men living with HIV and HIV-negative men with experience using PrEP in Seattle [45]. The authors identified new prevention approaches based on shifting perceptions of and experiences with HIV that foster sexual communication, opportunities for satisfaction, and appropriateness of sex partners [45]. In other studies, knowledge and acceptance of U=U increased personal health, sexual safety, and intimacy [51, 60] and reduced social stigma [45, 51, 60]. PrEP knowledge and adoption among HIV-negative MSM may reduce sex-related HIV stigma [51, 54]. Highlighting the benefits of biomedical interventions, including doxy-PEP to reduce STI acquisition and transmission among MSM, may support increased intimacy, pleasure, and reduced social stigma among MSM living with HIV and should be presented in addition disease mitigation messaging [21].

In our study, freedom to have the type of sex desired was a benefit of having an undetectable HIV status among MSM living with HIV. Doxy-PEP use reduced MSM's concerns

about STI transmission. Sexual freedom also meant some MSM reported that they were more comfortable in not using condoms. For others, doxy-PEP provided peace of mind for not acquiring an STI, allowing for more intimacy with their sexual partners. Studies have shown that the desire for more pleasure [61, 62] and intimacy [34, 50, 61, 62] are associated with condomless sex among MSM; doxy-PEP increases the safety and sexual pleasure of condomless sex for MSM living with HIV.

### **Limitations**

There are limitations of our study, including that the generalizability of these findings is limited to MSM living with HIV who were randomized to doxy-PEP use through participation in an open label doxy-PEP effectiveness trial in San Francisco and Seattle. Variability in access to doxy-PEP may make our study population not representative of MSM living with HIV across the US. Our objective was to recruit a diverse sample by race and ethnicity; however, most of our sample identified as white men, consistent with the main study population. As Black and Hispanic MSM may possess distinct experiences with sexual health and pleasure, we could not detect a difference in our findings which may be related to the low number of Black and Hispanic MSM enrolled in the main study population. Our study asked men to respond to questions about highly sensitive and potentially stigmatizing practices, which may have limited participants' willingness to fully share their decisions and experiences.

### **Conclusion**

Use of doxy-PEP improved the quality of life and experience of sexual pleasure among MSM living with HIV through less concerns about STI transmission, more sexual freedom, and

decreased anxiety about HIV stigma and potential rejection from sexual partners. Our findings have the potential to contribute to sex-positive messaging and reduced stigma, supporting the implementation of doxy-PEP and uptake by MSM living with HIV.

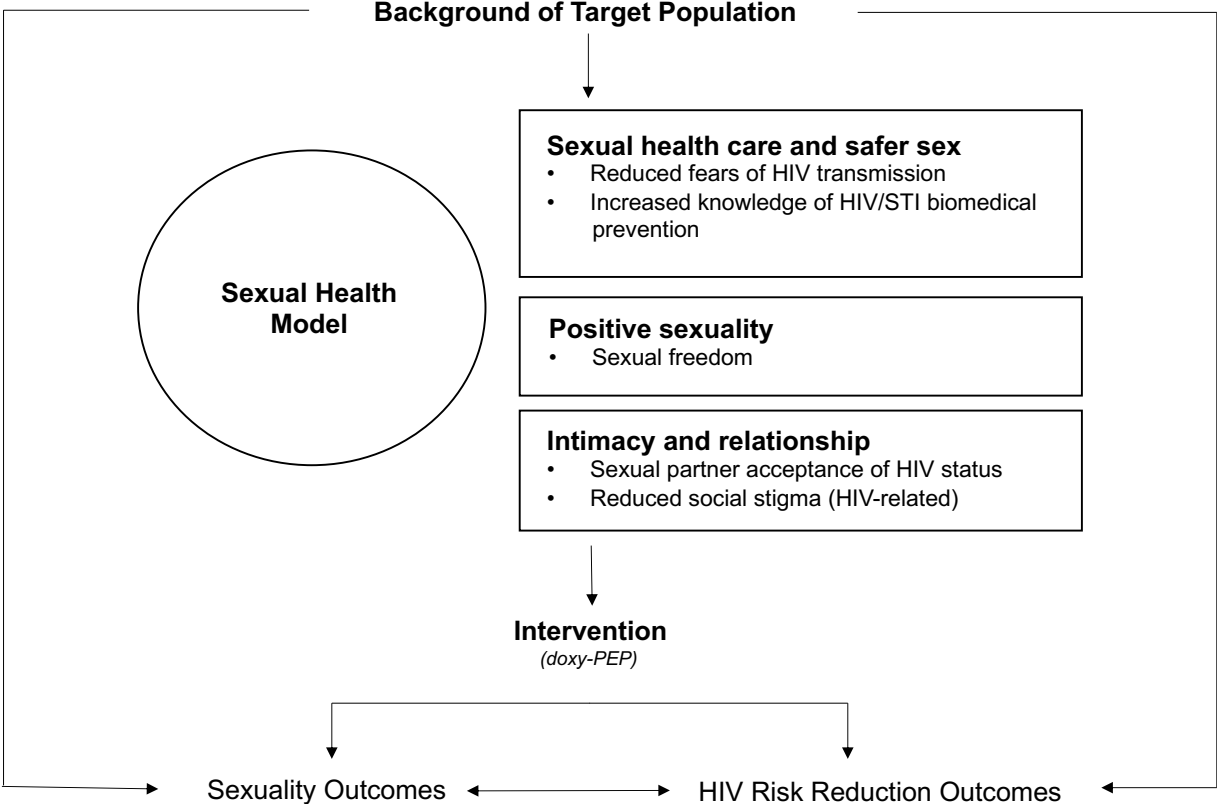
**Table 1. Demographic characteristics of interview participants (n=19)**

<b>Characteristics</b>		<b>N (%) or median (IQR)</b>
Home city	San Francisco	7 (36.8.8%)
	Seattle	12 (63.2%)
Age		41 (35 - 54)
Race	Asian/Pacific Islander	2 (11.8%)
	Black	5 (29.4%)
	Multiracial	1 (5.9%)
	White	9 (52.9%)
Ethnicity	Latinx	5 (26.3%)
	Not Latinx	14 (73.7%)
Gender of sex partners	Men only	18 (94.7%)
	Multiple genders	1 (5.3%)
Years since HIV diagnosis		12.5 (8.5 - 19)
Educational attainment	High school graduate or GED	3 (15.8%)
	Any college or post-graduate studies	16 (84.2%)
Annual income	Less than \$20,000	6 (31.6%)
	\$20,001 - \$50,000	4 (21.1%)
	\$50,001 - \$75,000	4 (21.1%)
	More than \$75,000	5 (26.3%)
Insurance status	Private	9 (47.4%)
	Public	10 (52.6%)
Substance use (3-month history)		10 (52.6%)
	Stimulants (meth, cocaine, crack)	6 (31.6%)
	Heroin/opioids	1 (5.3%)
	Ecstasy, GHB, ketamine	5 (26.3%)
	Amyl nitrates (poppers)	5 (26.3%)
	Marijuana	9 (47.4%)
Anal sex in the past 3 months	Insertive sex acts	10 (4-18)
	Receptive sex acts	10 (4-28)

Number of partners in past 3 months		12 (4-26)
Recent doxy-PEP usage	0-9 pills/month	12 (63.2%)
	10-19 doses/month	4 (21.1%)
	20-29 doses/month	1 (8.3%)
	30+ doses/month	2 (10.5%)

doxy-PEP=doxycycline post-exposure prophylaxis

**Figure 1. Modified Sexual Health Model used as theoretical framework for understanding sexual pleasure and doxy-PEP use among MSM living with HIV**



**Chapter 4: “Another tool for the sexual health toolkit.”: health provider knowledge, attitudes, and beliefs about doxycycline post-exposure prophylaxis (doxy-PEP) to prevent bacterial sexually transmitted infections among men who have sex with men**

**Abstract**

**Background:** Emerging evidence supports that doxycycline post-exposure prophylaxis (doxy-PEP) reduces incident chlamydia (CT), gonorrhea (GC), and syphilis infections among men who have sex with men (MSM). Health providers (HCPs) are important stakeholders and potential gatekeepers for the introduction of new medical interventions. Given the high efficacy of doxy-PEP, this study used the Diffusion of Innovation Theory to explore HCP’s knowledge, attitudes, and beliefs about introducing doxy-PEP for STI prevention strategy among MSM.

**Method:** From August 2022 to January 2023, qualitative interviews were conducted with HCPs in 13 cities in regions of the U.S. with high sexually transmitted infection (STI) rates. Infectious disease and primary care physicians, nurse practitioners, physician assistants, and pharmacists with a large panel of MSM patients and PrEP prescribing expertise were invited to participate in the study. All interviews were conducted virtually via Zoom. Transcripts and debrief reports were analyzed to explore knowledge, attitudes, and beliefs about doxy-PEP for STI prevention.

**Results:** We conducted 30 IDIs, of whom 14 (47%) practiced in the Northeast region, 10 (33%) in the West, and 6 (20%) in the South with 43% having panels of >100 MSM patients. Over half (53%) identified as male, 47% were between 31-40 years, and 47% reported their sexual orientation as gay or queer. Fifty-seven percent of HCPs identified as white/Caucasian, 30% as Black, and 13% as Asian. We identified four themes for introducing doxy-PEP into practice within the knowledge and persuasion stages of the Diffusion of Innovation Theory: 1) doxy-PEP provides another tool to prevent STIs; 2) Concerns about antimicrobial resistance with doxy-PEP

limit enthusiasm; 3) Additional data about the long-term safety of doxy-PEP would improve confidence in provider use of doxy-PEP; and 4) Development of official guidelines are needed to facilitate prescription of doxy-PEP.

**Conclusion:** HCPs were aware of doxy-PEP to reduce the risk of STIs among MSM with generally favorable attitudes, though some had concerns related to antibiotic resistance and long-term safety. Development of doxy-PEP guidelines and recommendations are needed to facilitate introduction of doxy-PEP into clinical practice.

## Introduction

Doxycycline is an inexpensive, well-tolerated broad-spectrum antibiotic taken by mouth and used to treat several bacterial infections such as acne or malaria prophylaxis [14, 15]. Doxycycline postexposure prophylaxis (doxy-PEP) involves taking one 200 mg pill of doxycycline 24-72 hours after having sex without a condom [4, 30] . Studies have shown that doxy-PEP can reduce incidence of sexually transmitted infections (STIs) among cisgender men that have sex with men (MSM) and transgender women. The first study was nested within the IPERGAY trial of 232 negative MSM using event-driven HIV PrEP in France, in which doxy-PEP reduced the incidence of CT and syphilis by 70% but did not reduce GC [29]. Similarly, the DoxyPEP trial among MSM and transgender women in the US who were living with HIV or taking PrEP demonstrated that doxy-PEP reduced the incidence of gonorrhea (GC), chlamydia (CT), and syphilis per quarter by two thirds.[63] Although the researchers found a more modest reduction in GC, doxycycline is not used for the treatment of GC [63]. More recently, the DOXYVAC study demonstrated an 84% reduction in the time to first CT and syphilis as well as a 50% reduction in the time to first GC infection with doxy-PEP use [57]. To introduce doxy-PEP into clinical practice will depend on whether health providers (HCPs) are willing to prescribe it as an STI prevention strategy for MSM.

HCPs play an essential role in disseminating information on HIV and STI interventions and influence uptake because of their ability to link individuals to resources and perform associated medical monitoring [9]. Since doxy-PEP is a prescription-based medication, HCPs may function as gatekeepers or conduits for potential doxy-PEP candidates [10]. HCPs are also uniquely situated to identify MSM in their patient panel with recent STIs and to educate them about the risks and

benefits of doxy-PEP [11]. HCPs are the preferred source of health information by MSM seeking HIV and STI information and this platform could be leveraged when introducing doxy-PEP as an STI prevention intervention in this priority population [12].

The Diffusion of Innovation Theory describes factors that influence the adoption of novel technologies by a population of end-users, including medical interventions by clinicians or patients [64, 65]. According to the Diffusion of Innovation Theory model, diffusion is “the process in which an innovation is communicated through certain channels over time among members of a social system” [65]. The theory is characterized as a five-stage process -- knowledge, persuasion, decision, implementation, and confirmation -- that correlates with becoming aware of and sustaining an innovation over time [65, 66]. The persuasion and decision stages are the most important in determining the adoption or diffusion of the innovation [65-67]. The Diffusion of Innovation is well-suited to guide assessment of HCPs’ knowledge, attitudes, and beliefs on doxy-PEP as a prevention strategy to reduce STIs among MSM and identify concerns that will require additional efforts to support the introduction of doxy-PEP in clinical settings [67].

Understanding provider opinions of doxy-PEP during the diffusion process will help identify motivating and hindering factors toward adoption that may be tailored in knowledge dissemination and implementation guidelines [65, 66]. The primary aim of this study was to understand HCPs’ knowledge, attitudes, and beliefs about introducing doxy-PEP as an STI prevention strategy for MSM.

## **Methods**

### *Study Design and Population*

This qualitative evaluation among HCPs utilized the Diffusion of Innovation Theory as a theoretical framework [65]. We conducted in-depth interviews (IDI) among HCPs providing HIV and STI care to MSM from diverse regions of the U.S. which had the highest sexually transmitted infection (STI) rates, including Atlanta, Baltimore, Birmingham, Boston, Chicago, Dallas, Detroit, District of Columbia, Houston, New Orleans, New York, Provincetown, and Seattle [68]. Between August 2022 and January 2023, we recruited a purposive sample of HCPs that included infectious disease physicians, primary care physicians, nurse practitioners, physician assistants, and pharmacists. Potential participants were invited to participate in the study through email or in-person outreach by the first author (R.P.), email outreach by colleagues, and email referral from other HCPs. HCPs interested in joining the study completed a screening survey which included whether their patient panel includes MSM and if they had experience providing MSM with STI and HIV services, including PrEP. The recruitment approach was intended to select a sample with a range of clinical settings, specialties, ages, races/ethnicities, genders, sexual orientations, and self-identification as an early, middle, or late adopter of recent HIV/STI interventions (e.g., PrEP). Individuals were eligible to participate if they maintained a clinical practice within one of the selected cities, spoke English, and had PrEP prescribing experience and a large panel of patients who identify as MSM. Participants provided informed consent and completed short demographic surveys prior to interviews.

### *Data Collection*

A semi-structured interview guide, informed by the Diffusion of Innovation Theory, was developed by the first author (R.P.) based on literature reviews and prior clinical and research experience with doxy-PEP and HCPs. The interview guide was reviewed and edited by R.F., K.C.,

A.L., and C.C. The interview guide topics explored HCPs' knowledge, attitudes, and beliefs about doxy-PEP for STI prevention specifically related to the *knowledge* and *persuasion* domains of the Diffusion of Innovation Theory, including: 1) what they had heard about using doxycycline to reduce the risk of STIs (*knowledge*); 2) their thoughts about prescribing doxycycline to prevent bacterial STIs (*knowledge*); 3) key influences on their willingness to prescribe doxy-PEP (*persuasion*); 4) scenarios where they would be hesitant to or not want to prescribe doxy-PEP (*persuasion*); and 5) what it would take to doxy-PEP implement in their clinical setting (*persuasion*). Interviews were conducted virtually using Zoom Cloud Meeting by the first author (R.P.), a trained nurse-scientist experienced with behavioral science and doxy-PEP research who had no prior relationship with participants.

IDIs were conducted in English, were audio-recorded, and lasted 45-60 minutes. Following each IDI, the interviewer summarized subjective impressions of the interview and briefly captured the participants' accounts related to key themes in a structured debrief report [37]. All interview audio files were transcribed verbatim using Home Row, Inc. transcription services and checked for accuracy by the first author and a research assistant (R.P. and A.D.). Interview content was reviewed in real time, and recruitment of additional participants halted once data saturation was reached (interviews no longer provided new information).

### *Human Subjections Considerations*

The University of Washington Institutional Review Board reviewed and approved all study materials. All participants provided written electronic informed consent and received a \$50 electronic gift card for their participation.

## *Data Analysis*

Data were analyzed using a combination of framework and directed content analysis methods [38, 69]. Based on the Diffusion of Innovation Theory, directed content analysis was used to identify HP's knowledge of doxy-PEP, attitudes on prescribing doxy-PEP, and beliefs about what would influence or deter them from prescribing doxy-PEP in their clinical setting. In addition, open coding was also used to derive codes that captured key concepts from the data outside the theory. A coding team with qualitative research experience comprised of the first author, three registered nurses (J.M, A.G., and S.G.), and two research assistants (A.D. and Z.P.), read excerpts across 15 transcripts and used memoing to reflect upon the data. Memos were discussed in subgroups and as a team to collectively deliberate on commonly emerging concepts from the Diffusion of Innovation Theory and guide development of a preliminary codebook. Team meetings were used to review and discuss potential codes and code definitions, refine and delete codes, and identify exemplar quotes associated with each code before reaching consensus on the final codebook. Transcripts were imported into Dedoose software (version 7.0.23, Los Angeles, CA, USA: Sociocultural Research Consultants, LLC) for coding using the final version of the codebook. Three members (R.P, J.M., and A.G.) of the coding team reviewed and coded each transcript. Discrepancies were reviewed by the team and discussed until consensus was reached. Coded data were organized into matrices to identify specific meanings and experiences that shape the discourses that may explain knowledge, attitudes, and beliefs of doxy-PEP among HCPs.

## **Results**

A total of 30 HCPs completed interviews, with 14 (47%) practicing in the Northeast, 10 (33%) in the West, and 6 (20%) in the South of the US (Table 1). Overall, 43% of HCPs reported

panels of >100 patients who identified as MSM. The most common provider level were physicians (43%) and provider specialties were primary care (43%) and infectious diseases (37%), and the most common practice setting was community health clinics that were not affiliated with universities (47%). Almost half (47%) were between 31-40 years old, 53% identified as male, and 47% reported their sexual orientation as gay or queer. Over half (57%) of participants identified as white/Caucasian, 30% as Black, 13% as Asian; 97% identified as non-Hispanic.

We identified four themes related to the implications for introducing doxy-PEP into clinical practice within the *knowledge* and *persuasion* stages of the Diffusion of Innovation Theory: 1) doxy-PEP provides another tool to prevent STIs; 2) apprehension and concerns about prescribing doxy-PEP as a strategy for STI prevention, including antibiotic resistance; 3) the need for more data to understand the long-term safety of doxy-PEP; and 4) development of official doxy-PEP guidelines to facilitate and motivate prescriptive practices, and inform implementation.

### ***Doxy-PEP provides another tool to prevent STIs***

At the time of the interview, most HCPs had heard of doxy-PEP as an approach to reduce the risk of STIs, primarily from sources such as scientific conferences/webinars, patient inquiries, and recent publications. HCPs unfamiliar with doxy-PEP were open to learning, especially if it would benefit their patients. Most HCPs reported that they thought of doxy-PEP as a new and exciting STI prevention strategy that would make a significant contribution to the STI prevention toolkit. HCPs described preferences for preventing rather than having to later treat STIs, especially when the patient may not realize they have an STI and subsequently unknowingly pass it to others.

*"I think it is another tool in the toolkit for sexual health and for people looking for options to have sex the way they want to and not have to deal with STIs as often."*

*(Participant 014, Physician)*

Despite knowledge of the lower reduction in GC associated with doxy-PEP found in the recent DoxyPEP and DoxyVacc trials [29, 30], some HCPs still supported doxy-PEP use to reduce transmission of CT and syphilis. HCPs felt that doxy-PEP could be an effective strategy for asymptomatic STIs, especially among individuals from groups that are disproportionately affected by STIs, including MSM on PrEP and those living with HIV. Some HCPs reported that they thought doxy-PEP would offer patients more agency to protect themselves, empower them to make more informed decisions about their prevention practices, and overall improve their sexual health.

*"This could prevent STIs from spreading to others, especially with asymptomatic patients, who don't end up finding an STI until their yearly visit, and by then, they have spread the infection to other people. I think doxy-PEP is a good public health strategy to adopt widely." (Participant 025, Physician)*

*"I think the more pill and pocket [biomedical prevention options to choose from] strategies we have, the more empowerment you can give patients, the better sexual health you'll have. So, I am excited about doxy-PEP as a prevention strategy for STIs." (Participant 001, Physician)*

A few HCPs reported already prescribing doxy-PEP for some of their MSM patients, despite lack of normative clinical guidance. Some HCPs believed that doxy-PEP ‘worked’, and the patients for whom they prescribed doxy-PEP reported feeling happy and secure in their sex life. One HCP reported doxycycline use in the military for malaria prophylaxis as an example for how well the medication is tolerated and noted that the worst adverse reactions from doxycycline are preventable (e.g., using sunscreen to reduce the risk of photosensitivity). HCPs described weighing the pros of doxy-PEP (e.g., high tolerability, high efficacy in studies among MSM, low cost) against the cons (e.g., not approved by the FDA for STI prevention, the potential to increase antibiotic resistance) to inform their prescriptive practices while awaiting guidelines. Some HCPs indicated that they thought the pros outweigh the cons, even at this time when the data are new.

*“I may be a little biased because I have been prescribing it [doxy-PEP]. As a young provider, I think it is a part of our job to promote interventions that work. Doxycycline has been around for a long time, it's cheap, and you don't have to worry about getting it insured, and the side effect profile is so marginal, especially if you're taking it as PEP.” (Participant 010, Physician)*

*“I like the idea of it, and I have a few patients that I have prescribed it for: however, I don't have the full support of our medical director because it is not FDA approved, and until there is more evidence, the belief of the clinic is not to provide it. However, I believe patients who want it feel much better on doxy-PEP.” (Participant 008, Physician Assistant)*

HCPs who reported feeling hesitant or skeptical of doxy-PEP had limited knowledge of the literature on the efficacy of doxy-PEP for STI prevention or had not heard of the strategy at all prior to participating in the qualitative study. However, most were curious about doxy-PEP and wanted more information.

*"This [interview] was my first time hearing about doxy-PEP and the first time I started to pay attention and just do a little research into doxy-PEP." (Participant 018, Physician)*

*"I have been hearing about it, and I knew providers were prescribing it for their patients who requested it, but I was not familiar with prescribing it." (Participant 009, Nurse Practitioner)*

*"I am open to learning about it. I haven't seen any of the data or explored if there is a real concern whether it can cause antimicrobial resistance." (Participant 005, Nurse Practitioner)*

### ***Concerns about antimicrobial resistance with doxy-PEP limit enthusiasm***

Although HCPs felt that patients seeking to use doxy-PEP as a prevention strategy would be more likely to be engaged in their sexual health care and would take doxy-PEP as prescribed, some HCPs still had concerns about the development of antimicrobial resistance. Most HCPs felt quarterly follow-ups with STI testing from all three sites (throat, rectal, and urine) would support doxy-PEP management and limit resistance opportunities by identifying new STIs early. One HP felt getting patients to take doxy-PEP consistently would be challenging, and a few reported

concerns with side effects of doxycycline as a barrier to doxy-PEP adherence. However, HCPs noted that side effects mainly included gastrointestinal disturbances and photosensitivity, which could be easily treated.

One HCP was most concerned with the lack of Black MSM in the study populations that demonstrated efficacy of doxy-PEP against STIs. Despite the reduction in STI incident cases, they felt a need to understand if doxy-PEP will work among Black MSM communities with high rates of STIs. They would like to see more inclusive data to feel more comfortable as an HCP and advocate for his patients.

*“I don’t think we have done a good job trying to reach communities that could use this intervention most. Yes, there was 62% less incident infections, but my concern is there were only eight percent were black MSM in the study....” (Participant 022, Nurse Practitioner)*

HCPs were most concerned about the development of antibiotic resistance if the patient acquired CT or syphilis, as a single dose of doxy-PEP would be insufficient for treatment. HCP’s concerns around antibiotic resistance were mainly associated with fear of losing doxycycline as an antibiotic for other purposes. For example, HCPs raised that doxycycline can be the first or second line of therapy against commonly occurring bacteria (e.g., *Mycoplasma genitalium* and *Treponema pallidum*) for patients with a penicillin allergy. Broad doxycycline use in the population could lead to decreased treatment options generally, which caused concern among HCPs about doxy-PEP as a strategy for STI prevention. One HCP gave the treatment for chlamydia with azithromycin as an example but developed antibiotic resistance and no longer effective which led to a change in

guidelines to use doxycycline as first line treatment for CT and did not want to lose doxycycline as a treatment option.

*"We are kind of treating CT, but not really [with doxy-PEP], and then the bacteria that resides can now develop mutations to become resistant to doxycycline; then we don't have any treatment option for them; that is what concerns me."  
(Participant 030, Pharmacist)*

*"We may be creating problems for the future with antibiotic resistance, for example, mycoplasma genitalium, I see a lot them [cases] in practice, we used to prescribe doxycycline, but now it's like 30% effective. We are creating all these [prevention] options, but we must realize what this might do to other STIs within antibiotic and doxycycline resistance in general." (Participant 022, Nurse Practitioner*

Some HCPs expressed that antibiotic stewardship is currently emphasized within the medical community, making it more difficult to promote using doxycycline for STI prevention. One HCP reflected on the last update of the CDC guidelines for STIs highlighting the higher dose of ceftriaxone to treat gonorrhea and worried that with broad use of doxycycline, we may see similar changes due to increasing resistance .

*"Any kind of conversation around antibiotics is so steeped in stewardship and fear of resistance that I think that would be like the first thing that many of us think about*

*when we hear about long-term antibiotics or prevention with antibiotics."*  
(Participant 004, Physician)

*"I think I am starting to get on the doxy-PEP train where I'm like, this looks good. I've seen these trials, and it seems like this might actually be something I need to start recommending, but initially, I was a little skeptical because of antibiotic overuse."* (Participant 013, Physician)

Although HCPs acknowledged valid fears of antibiotic resistance, they felt that current antibiotic prescriptive practices for other conditions were equally as 'risky' for developing resistance, and the possibility of developing resistance to doxy-PEP is likely small.

*"I worry about antibiotic resistance, but I think we use doxycycline for other things, and antibiotic resistance hasn't emerged, so why worry when queer men take it to prevent infections. It sucks to get chlamydia and gonorrhea."* (Participant 009, Nurse Practitioner)

*"I feel like I'm at the 'recommendation with reservation' stage. If more studies can tell us where there is some harm to be done, I want to know, listen, and hear. But for those who feel we may cause resistance, I will remind them we treat acne with daily doxycycline, so we should be doing it if it's safe for acne."* (Participant 028, Nurse Practitioner)

*"One could be concerned about antimicrobial resistance and topics of that nature, however, if we're preventing symptomatic infections relative to presumed empiric treatments, I think doxycycline is certainly less of a problem than, for example, empirically treating with Azithromycin or Ceftriaxone for each episodic occurrence of a presumed urethritis." (Participant 018, Physician)*

***Additional data about the long-term safety of doxy-PEP would improve confidence in provider use of doxy-PEP***

Most HCPs reported that more data and information on the safety of doxy-PEP, specifically implications for antibiotic resistance, would influence their willingness to prescribe it. HCPs wanted reassurance and national data to understand the value of doxy-PEP and costs of doxy-PEP. Some HCPs believed the evidence of antibiotic resistance would not be elucidated until doxy-PEP is used on a larger scale. However, most HCPs felt doxycycline is highly regarded as a safe medication without a profile consistent with fears of antimicrobial resistance. Based on the information that is available clinically and its effectiveness, they would not have an issue with its use.

*"I would love more evidence on the resistance question. However, I know we won't have that answer until we use doxy-PEP on a larger scale. But to make me a little more comfortable, I feel like we could develop a good criterion (who should have access) for doxy-PEP and identify who would be the best candidate for its use." (Participant 011, Nurse Practitioner)*

*"I think we need to be judicious; people should be screened; be sure they are taking it as prescribed and understand that doxy-PEP may not be for all individuals susceptible to STIs. We need more studies: we don't know if doxy-PEP could lead to resistance. We assume a lot, but we don't know." (Participant 019, Physician)*

*"The CDC would like to see more evidence to understand the appropriate regimen and safety efficacy with dosing. But as an off-label, doxycycline is highly regarded as a safe medication, and for the information that's available clinically and its effectiveness, I wouldn't have issues with its use." (Participant 018, Physician)*

HCPs expressed wanting to have additional data on the long-term safety implications of doxy-PEP. The most reported concerns were implications for the microbiome, drug-drug interactions, and unknown risks associated with long-term doxycycline use. One HCP used clostridium difficile (C. diff) as an example of a risk to the microbiome but shared findings from a study that doxycycline was protective against developing C. diff, highlighting that there is still a lot to learn about the implications of long-term doxycycline use on the microbiome.

*"Whenever we talk about the microbiome, the big infection risk that we talk about is C. diff. And I think a study showed that doxycycline was protective against developing C. diff. So, presumably, there is probably not too much global microbiome disruption, although we learn more and more about the microbiome. So, I'm sure I'll regret saying these words in a couple of years." (Participant 29, Pharmacist)*

Another HCP was hesitant to prescribe doxy-PEP because of potential drug-drug interactions, especially with drugs prescribed by specialty HCPs.

*"I had a patient ask for doxy-PEP, but he was also taking tretinoin for acne; at least it had been prescribed for him by his dermatologist, and you're not supposed to take tretinoin with doxycycline. Although he wanted to be on doxy-PEP, I was hesitant to do it even though he had several STIs in the past year."*

*(Participant 014, Physician)*

A few HCPs thought they did not have a patient population with clear indicators for doxy-PEP prescription. Other HCPs wanted to see larger studies within the US conducted in underserved communities with access barriers (transportation, health insurance, lack of providers, free STI testing and treatment and patient-centered HCPs). Insights about doxy-PEP use among patients with limited access to healthcare and transportation would influence their willingness to prescribe doxy-PEP.

### ***Development of official guidelines are needed to facilitate prescription of doxy-PEP***

Some HCPs felt doxy-PEP guidelines from normative bodies, such as the Center for Disease Control (CDC) or the Infectious Disease Society of America (IDSA), were needed to influence prescribing. Guidelines would support the development of protocols for doxy-PEP, including identifying patients who would benefit from doxy-PEP, dosing instructions, and management. Pharmacists reported that protocols are essential to their training and mandatory for practice.

*"You know, pharmacists operate off of a protocol; for our training we have to do everything in alliance with a protocol. Therefore, a doxy-PEP protocol would support pharmacists in determining who would be a good candidate for doxy-PEP and who would not." (Participant 017, Pharmacist)*

HCPs also described how protocols would allow optimization of delivery processes within the clinic. One HCP reported that having a doxy-PEP protocol would enable their clinic to develop a nurse-led protocol for doxy-PEP, with streamlined STI testing and treatment procedures.

*"Clinics like ours [public health clinic] cannot offer doxy-PEP until the CDC develops guidelines. Once they do, it will enable us to create protocols that will allow nurses to provide doxy-PEP with other STI prevention and treatment protocols." (Participant 012, Physician)*

Other HCPs reported that guidelines would facilitate increased knowledge of doxy-PEP prevention practices and improve support among colleagues. Most wanted to hear from STI experts, infectious disease HCPs, and key opinion leaders to obtain their approval of doxy-PEP and guide development of patient-centered educational materials.

*"Often, people rely on their experiences, and I don't necessarily have that as a reasonably new practitioner. So, maybe seeing and hearing about other HCP's experiences with doxy-PEP would make me feel more comfortable within my clinical setting or other clinics. (Participant 030, Pharmacist)*

One HCP reported that guidelines would elevate doxy-PEP to become standard of care, and in the event of an adverse event, guidelines would support the decision-making for prescribing doxy-PEP.

*"If my patients think they would benefit from doxy-PEP and didn't have any indications of harm, I wouldn't have a problem prescribing. However, you always want to say that you followed some guidelines which indicate the standard of care. So, the guideline would be helpful." (Participant 027, Nurse Practitioner)*

## **Discussion**

In this study of HCPs providing STI and HIV care to MSM in various clinical settings, most were aware of doxy-PEP as a strategy to prevent STIs. HCPs were generally excited about the potential of doxy-PEP for STI prevention as an additional tool. Despite general awareness and excitement, HCPs described gaps in knowledge, lack of guidelines, and concerns about development of antimicrobial resistance as barriers to prescribing doxy-PEP. HCPs who were not familiar with doxy-PEP were interested in learning more, especially if it would help reduce STIs among MSM patients with high STI incidence. Our findings add to the limited data about the knowledge, attitudes, and beliefs of HCPs regarding doxy-PEP as an STI prevention strategy for MSM, and can inform how doxy-PEP is introduced into clinical practice.

Concerns related to antimicrobial resistance were commonly raised regarding use of an antibiotic for prevention. These concerns mirror those initially present with the introduction of PrEP. When emtricitabine and tenofovir PrEP were first introduced for HIV prevention, HCPs were concerned about selecting HIV strains with resistance to emtricitabine or tenofovir, and the potential risk of resistance to these commonly used antiretrovirals for treatment [70]. Other

concerns were related to the higher risk of selecting antiretroviral resistance if someone seroconverted while taking PrEP [71]. However, the benefits of decreased HIV incidence with wider PrEP use outweighed risks of developing drug resistance [72, 73]. Motivated by early adopters, PrEP prescriptions increased over time [64] despite resistance concerns, and most HCPs eventually adopted PrEP based on high efficacy and safety data. The PrEP adoption trajectory, where some individuals can be persuaded to try the innovation while data accumulate, aligned with Diffusion of Innovation Theory concepts [64, 66]. Similar to PrEP, current data on doxy-PEP has motivated some HCPs to become early adopters of doxy-PEP prescription. However, there may need to be new/different interventions to encourage other HCP groups to follow early adopters.

Despite antibiotic resistance concerns, some HCPs in our study prescribed doxycycline off-label to MSM for PEP use. Off-label use of antibiotics is widespread in healthcare settings for various conditions [74-76]. Off-label antibiotic use is commonly seen in pediatric settings because antibiotics are marketed and prescribed without clear labeling for use in pediatrics [74]. Common off-labeled use of antibiotics are cephalosporins, macrolides, and tetracycline to treat STIs [74]. More research is needed to better understand antimicrobial resistance with doxy-PEP use. Although the CDC has a national surveillance program for antimicrobial resistance, including tetracycline, in GC, there are no established methods to assess doxycycline resistance in CT or syphilis with very few laboratories able to cultivate CT and syphilis [15]. To better understand the implications for antimicrobial resistance, doxy-PEP will have to be used more widely and over a longer period among populations with the highest risk of repeat STIs and which may benefit most.

The current study among HCPs provides insight into doxy-PEP knowledge and facilitators to motivate prescriptive practices for doxy-PEP. Guidelines and hearing from the experts would increase HCPs' knowledge of doxy-PEP and provide guidance on selective use among MSM with

recent STIs as priority populations for initial implementation. HCPs perceived that CDC and IDSA guidelines to support doxy-PEP use would garner acceptance among colleagues and medical directors for clinic-wide implementation of doxy-PEP. HCPs believed that official guidelines would help providers and clinics develop protocols for the provision of doxy-PEP and inform client-centered educational materials to engage patients who may benefit most from doxy-PEP. Our findings offer insight into the potential barriers and facilitators of implementing doxy-PEP as an STI prevention strategy.

### *Limitations*

Our study has limitations. The HCPs in the sample were mainly providers with PrEP prescribing experience who were recruited through professional networks. Given their experiences in prescribing PrEP, they may also become early adopters of doxy-PEP or hold a positive outlook that would be more willing to prescribe than HCPs who are less familiar with doxy-PEP or more conservative with STI/HIV prescribing practices. Given that we conducted qualitative interviews, we only have insight into our HCPs' accounts and reflections about their knowledge, attitudes, and beliefs about doxy-PEP. We do not have any data that could verify actual prescription of doxy-PEP by HCPs in our study. Despite our attempt to recruit a diverse sample of HCPs based on race, ethnicity, and sexual orientation, we were unable to interview any Black, heterosexual male HCPs, and only one HCP who identified as Hispanic. Black and Hispanic HCPs may hold different attitudes or beliefs about doxy-PEP, especially in the Southern region; studies further exploring these population subgroups are recommended to complement our findings.

### *Conclusion*

In summary, HCPs are familiar with doxy-PEP as a prevention strategy to reduce STIs among MSM and another tool for the prevention toolkit. HCPs unfamiliar with doxy-PEP were open to learning, especially if it would benefit their patient population. Despite concerns about antibiotic resistance, HCPs thought that more data on the long-term safety and implications as well as official guidelines from the CDC would facilitate adoption of doxy-PEP as a prevention strategy to reduce incident STIs among MSM.

**Table 1. Demographic Characteristics of Health Providers (n=30)**

<b>Total</b>		<b>30 (%)</b>
<b>Age</b>	Under 30	2 (7%)
	31-40	14 (47%)
	41-50	10 (33%)
	51 and over	4 (13%)
<b>Gender</b>	Female	13 (43%)
	Male	16 (53%)
	Gender-queer	1 (3%)
<b>Sexual Orientation</b>	Gay	11 (37%)
	Heterosexual	15 (50%)
	Queer	3 (10%)
	Declined to answer	1 (3%)
<b>Race</b>	Asian	4 (13%)
	Black or African American	9 (30%)
	White or Caucasian	17 (57%)
<b>Ethnicity</b>	Hispanic	1 (3%)
	Not Hispanic	29 (97%)
<b>Provider Level</b>	Nurse Practitioner	12 (40%)
	Pharmacist	3 (10%)
	Physician	13 (43%)
	Physician's Assistant	2 (7%)
<b>Provider Specialty</b>	Infectious Disease	12 (40%)
	Pharmacy	1 (3%)
	Primary Care	13 (43%)
	Sexual Health	4 (13%)
<b>Practice Setting</b>	CHC non-university affiliated	14 (47%)
	CHC university affiliated	8 (27%)
	HMO Clinic	1 (3%)
	Private Practice	3 (10%)
	Public Health Clinic	4 (13%)
<b>Geographical Region</b>	Northeast	14 (47%)
	South	6 (20%)
	West	10 (33%)
<b>Panel of Patients</b>	Less than 50	8 (27%)

	50-100	9 (30%)
	> 100	13 (43%)

\*CHC = Community Health Clinic

\*HMO = Health Maintenance Organization

## **Chapter 5: Conclusion**

This dissertation sought to better understand user experiences with doxy-PEP to reduce the transmission of STIs among MSM living with HIV and HIV-negative MSM on PrEP. Our efforts in this study are essential in advancing the translation of doxy-PEP to MSM and preventing STI infections among this population. Understanding the influence of doxy-PEP on how MSM balance vulnerability and pleasure-seeking in sexual decision-making is necessary to expedite the adaptation of doxy-PEP for use in this population. Understanding MSM's desire for sexual pleasure is particularly important for doxy-PEP implementation because it provides more insight into users' motivations and explains decision-making processes related to sexual and prevention practice, including meaning-making, and integrates positive aspects of sexuality within the disease-prevention lens commonly applied to the sexual practices of MSM [20, 21].

The three papers in this dissertation fill the gap in understanding the experiences of doxy-PEP users that may offer guidance about doxy-PEP messaging and delivery for a targeted and readily accessible population of MSM. The first study highlighted themes among HIV-negative MSM using PrEP that doxy-PEP amplified the ability to have greater sexual pleasure, provided a sense of sexual liberation, and supported open communication. Sexual pleasure is an alternative to risk-focused approaches for engagement with biomedical prevention, such as PrEP.

The second study helps better understand the experiences of MSM living with HIV taking doxy-PEP, who reported less worry about STI transmission, more sexual freedom, and decreased anxiety about HIV stigma related to rejection from sexual partners. The benefits of doxy-PEP were associated with enhanced sexual pleasure and quality of life that motivated doxy-PEP use. Additionally, biomedical HIV prevention shifted the conversation about HIV, which is now less stigmatizing and subsequently increased sexual pleasure for MSM living with HIV in

the study. Considering the benefits of biomedical prevention on intimacy and sexual pleasure is an alternative to risk-focused approaches and may increase receptivity to campaigns such as U=U.

In the final last study, HCPs were generally aware about doxy-PEP as a strategy to prevent STIs, although gaps in understanding and concerns around prescribing doxy-PEP were raised. The HCP participants in the qualitative study were generally excited about the potential of doxy-PEP to reduce the incidence of STIs among MSM. HCPs who were unfamiliar with doxy-PEP were interested in learning more, especially if it would help reduce STIs among MSM patients who had a high rate of recurrent STIs. HCPs reported various concerns regarding prescribing doxy-PEP, the most common being antibiotic resistance. To facilitate the prescriptive practice of doxy-PEP and the potential risk for drug interactions, HCPs also reported the need for official guidelines to support prescribing doxy-PEP -presenting clear, actionable steps for introducing doxy-PEP once guidelines were available. These findings provide insight into HCPs' knowledge, attitudes, and beliefs of doxy-PEP as an STI prevention strategy for MSM and can inform efforts to introduce doxy-PEP into clinical practice.

This dissertation sought to understand how doxy-PEP use influences pleasure-seeking and sexual quality of life among HIV-negative MSM on PrEP and MSM living with HIV post their HIV diagnosis and implementation of PrEP/U=U. The purpose of doxy-PEP is to provide public health benefits through reducing the incidence of STIs but also will depend on individuals experiencing personal benefits to MSM through improved quality of life in order to motivate their ongoing doxy-PEP use. Given that doxycycline requires a prescription, the perspectives of HCPs are important and we conducted an assessment of their beliefs about doxy-PEP use for STI

prevention among MSM in order to identify facilitators and barriers to doxy-PEP implementation.

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