



BIG IDEAS

ENDING THE HIV EPIDEMIC —
SUPPORTING ALL PEOPLE LIVING WITH HIV AND REDUCING NEW TRANSMISSIONS

PROMOTING EQUITY IS ESSENTIAL TO EFFECTIVELY IMPLEMENT DOXYCYCLINE AS STI PEP

DOXYCYCLINE, A COMMONLY PRESCRIBED ANTIBIOTIC that has been in use for more than fifty years, recently has been shown to be useful in preventing the bacterial sexually transmitted infections (STIs) chlamydia, gonorrhea, and syphilis.¹ This offers a new tool for preventing STIs when administered as post-exposure prophylaxis (PEP); that is, after sex, as part of a comprehensive sexual health intervention that also includes risk reduction counseling,

STI screening and treatment, recommended vaccinations, and linkage to HIV pre-exposure prophylaxis (PrEP) and HIV PEP, HIV care, or other services. The Centers for Disease Control and Prevention (CDC) is considering public comments on draft guidelines for the use of doxycycline as STI PEP (hereafter doxy PEP) to guide prescribers,² but additional policies and actions are needed. The CDC draft guidelines recommend doxy PEP only for populations at elevated risk for these STIs, specifically gay, bisexual and other men who have sex with men (MSM) and transgender women with at least one bacterial STI in the last 12 months. These STIs are often asymptomatic and undetected in these populations, however, suggesting that a broader range of MSM and transgender women (and possibly other populations) could benefit from doxy PEP based on individual sexual behaviors. Because this is a new intervention that is connected to sex and focused on often stigmatized and marginalized populations, adopting strategies to counter negative public attitudes and

REDUCING STIs AMONG MSM AND TRANSGENDER WOMEN

Policy action is needed to:

EMBRACE A SEXUAL HEALTH PARADIGM

- Center MSM and transgender women as the front-line educators, ambassadors, and implementers of doxy PEP
- Develop pro-active messaging for the general public to counter anti-LGBTQ+ messages and sexual shaming
- Standardize sexual health training during medical education and conduct detailing with clinical providers and clinics

FOCUS ON EQUITY

- CDC and other federal health agencies should fund and encourage their grantees to support and deliver doxy PEP implementation activities that focus on Black and Latinx MSM and transgender women
- HRSA should develop a strategy for implementing doxy PEP that leverages the Health Centers Program and Ryan White HIV/AIDS Program.
- Non-governmental entities, including pharmaceutical manufacturers, foundations, and corporations should fund community efforts to implement doxy PEP

BRIDGE KNOWLEDGE GAPS

- CDC and NIH should convene a cross-agency working group to fund priority studies to maximize the benefits of doxy PEP

ensure that the populations that can benefit the most are aware of, have access to, and are encouraged to use doxy PEP will determine its impact.

While condoms and barrier methods of prevention are considered highly effective at preventing STI acquisition, condom use has never been universal and has been declining among MSM.³ Doxy PEP offers a new tool for preventing STIs that is more consistent with supporting many users' own sexual health goals and priorities. How this new intervention is integrated into practice is critically important and calls for new approaches to prevention. Acknowledging three concepts can offer a framework for effective implementation:

1. EMBRACE A SEXUAL HEALTH PARADIGM

The benefit of doxy PEP as an intervention is not only that it is a safe, widely available, and relatively inexpensive medication that is easy to use and distribute, but it is the first biomedical STI prevention tool that also is a necessary element of a comprehensive sexual health approach that has the potential to reduce the stigma and shame about sex that complicates STI prevention efforts.

In 2021, the National Academies of Sciences, Engineering and Medicine (NAEM) published a consensus study report funded by CDC to review the current state of STIs in the United States, *Sexually Transmitted Infections: Adopting a Sexual Health Paradigm*.⁴ The report is organized around four key areas of action: 1) adopt a holistic sexual health paradigm, 2) broaden ownership and accountability for responding to STIs, 3) bolster existing systems and programs for responding to STIs, and 4) embrace innovation and policy change to improve sexual health. These recommendations may sound intuitive, but they actually represent a sea change in how the nation has sought to prevent and treat STIs. For more than a hundred years, society and public health have focused on individual risk behaviors and behavior change as the primary strategies for countering STIs. We have moralized against sex outside of monogamous heterosexual marriage. This has largely failed for many reasons, but for MSM and transgender people, it offered no path for sexual enjoyment and pleasure. Adopting a sexual health approach is an opportunity to move away from failed strategies by integrating sex, pleasure, and STI prevention and treatment in a broader conception of what it means to be healthy.

POLICY ACTION: Center MSM and transgender women as the front-line educators, ambassadors, and implementers of doxy PEP

MSM and transgender women must be allowed to define for themselves what it means to be sexually healthy, and this may be very different than how

THE U.S. HAS AN STI CRISIS

The United States is facing a serious crisis of STIs.

1 in 5 adults: The CDC estimates that at any given time, one in five U.S. adults has an STI.(1)

Rapidly rising rates: Since 2000, the number of syphilis cases has increased more than five-and-a-half times (up 555%), chlamydia cases have nearly doubled (up 197%) and gonorrhea cases increased by half (up 51%).(2)

MSM and transgender people heavily impacted: STI cases are not evenly spread across the population with gay, bisexual, and other men who have sex with men (MSM) and transgender people being disproportionately impacted. For example, MSM make up 2-3% of the U.S. population yet accounted for 34% of primary and secondary syphilis cases in 2022.(3) Indeed, MSM make up more than two-thirds of new HIV cases, and 10.2% of HIV cases among MSM are attributed to co-infection with chlamydia and/or gonorrhea.(4)

Significant Economic Impact: CDC estimates that STIs cost more than \$16 billion per year in direct medical costs.(5)

Sources: (1) Sexually Transmitted Infections Prevalence, Incidence, and Cost Estimates in the United States, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/std/statistics/prevalence-2020-at-a-glance.htm>, (last visited Jan. 25, 2024), (2) CDC's 2022 STI Surveillance Report underscores that STIs must be a public health priority, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/std/statistics/2022/default.htm> (last visited Feb. 15, 2024), (3) Id. (4) Jones J, et al. *Proportion of Incident Human Immunodeficiency Virus Cases Among Men Who Have Sex With Men Attributable to Gonorrhea and Chlamydia: A Modeling Analysis*. 46 SEX TRANSM. DIS 357,363 (2019), (5) *Reversing the Rise of STI's: Integrating services to address the syndemic of STIs, HIV, substance use, and viral hepatitis*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://stacks.cdc.gov/view/cdc/128691> (last visited Jan. 25, 2024).

cisgender heterosexuals define sexual health for themselves. While MSM and transgender communities overlap, they also have distinct identities and needs. Programs to implement doxy PEP should be established to reinforce community values and norms and should be developed to allow community members to educate and deliver services in ways that are accessible and acceptable to these communities.

- **CDC** should enhance funding for LGBTQ+ organizations through its STD prevention and HIV programs and other parts of the National Centers for HIV, Viral Hepatitis, STD and TB Prevention (NCHHSTP), to articulate and promote a vision for sexual health that proactively promotes the benefits of doxy PEP and provides resources for individuals to access it.

- The **Health Resources and Services Administration (HRSA)** through its Health Centers and the **Ryan White HIV/AIDS Programs**, along with the **Substance Abuse and Mental Health Services Administration (SAMHSA)** and the **Indian Health Service**, should enhance their efforts not only to educate patients and providers about doxy PEP, but should ensure access to this low-cost intervention for their clients.
- **State and local health departments** should not only hire members of these communities as staff, but also should fund individuals and organizations with the deepest roots into communities that are often overlooked to conduct doxy PEP education and linkage to clinical care.

POLICY ACTION: Develop pro-active messaging for the general public to counter anti-LGBTQ+ messages and sexual shaming

While there is much greater acceptance of LGBTQ+ people in this country compared to a decade ago, we are still living through a period of prejudice and backlash where LGBTQ+ people are facing stigma, discrimination, and the threat of violence. In addition, debates about bodily autonomy have been renewed in the last few years because of controversial decisions regarding gender affirming care and sexual and reproductive health. We must anticipate that opponents of LGBTQ equality will seek to use doxy PEP as a new tool to shame and stigmatize LGBTQ+ people.

- **CDC and state and local health departments** should develop messaging and public communications that introduces doxy PEP to broader audiences within a sexual health framework. Messaging should convey that we all want to live healthy lives, and that STI rates are rising, imposing significant financial burdens on individuals and health care programs, with devastating impacts on neonates and reduced future fertility of sexually active adults. Doxy PEP is a new evidence-based intervention that is currently recommended only for MSM and transgender women, but which could reduce the burden of STIs for other populations and provide evidence that STI PEP offers a pathway for population-level reductions in STIs.
- **HIV and LGBTQ+ organizations** should apply lessons related to the introduction and rollout of HIV PrEP in communities. Regrettably, there was

significant sex shaming from both providers and community members tied to HIV PrEP along with unaddressed access issues, and messages of caution that inaccurately suggested that PrEP was only for some people. In implementing doxy PEP, we need educational campaigns, community forums, and other activities that are less judgmental, and more affirmatively positive in promoting sexual health and pleasure and that introduce doxy PEP as an important tool to reduce the risk of acquiring bacterial STIs.

- **Philanthropic organizations and social marketing agencies** should develop messaging, visuals, and social media resources to create acceptance of and excitement for doxy PEP as a way to prevent STIs. CDC has experience with its prior Business and Labor Respond to AIDS initiative, KFF operates its Greater Than HIV social marketing campaigns, and the Ad Council promotes socially conscious public service announcements. These and other agencies have resources that may be able to create knowledge and acceptance of doxy PEP as a critical public health intervention.

POLICY ACTION: Standardize sexual health training during medical education and conduct detailing with clinical providers and clinics

Primary care and specialist physicians, physician assistants (PAs), Advanced Practice Registered Nurses (APRNs) and other providers receive non-standardized and often inadequate sexual health education during their medical education and many were trained with the same societal beliefs that valued shaming as a tool to curb sexual activity. We currently have a clinical workforce with inadequate capacity to deliver quality sexual health services, especially to sexual and gender minorities whose share of the population is growing with successive generations.⁵ Further, a study of STI- and non-STI provider attitudes about doxycycline for STI prevention found the majority of providers in both groups are concerned about resistance, which may limit its use in practice.⁶

- **CDC** should review and implement the Sexually Transmitted Infections: Adopting a *Sexual Health Paradigm*, recommendation 11-1 that provides comprehensive policy actions to improve sexual health education and training. This could include working with accreditation bodies such as the **American Council for Graduate Medical Education** and the **National League for Nursing** to train a new generation of clinical providers in the core precepts of sexual health so they can have the skills to provide the affirming and non-stigmatizing health care (inclusive of sexual health) that gender and sexual minorities need and deserve.
- **Health Departments, the National Network of STD Clinical Prevention Training Centers (NNPTC), Title X Family Planning Programs, AIDS Education and**

1 IN 10 HIV DIAGNOSES IN MSM ARE ATTRIBUTED TO CO-INFECTION WITH CHLAMYDIA AND/OR GONORRHEA

IS DOXYCYCLINE SAFE AND EFFECTIVE?

In developing its draft guidelines, CDC examined several important questions that are raised by the use of doxycycline as PEP(1). These include:

Is it safe? Doxycycline first received FDA approval in 1967. It is used for a range of conditions including as prophylaxis or treatment for malaria and Lyme disease, as well as to treat acne and rosacea. It is well-absorbed and tolerated with a half-life of roughly twelve hours. Adverse events associated with doxycycline are typically not severe and include photosensitivity and

gastrointestinal symptoms that went away when it was discontinued.(2) Further studies are needed to assess the safety of doxycycline for long-term use at the dosages in the current doxy PEP regimen.

Is it effective for MSM and transgender women (TGW)? A 2015 study of MSM with HIV showed promise of doxycycline as STI PrEP,(3) but additional follow-up studies have not been conducted to support recommending it as PrEP at this time. CDC reviewed three recent studies, however, of doxycycline as PEP for MSM and TGW:

IPERGAY (OPEN-LABEL EXTENSION)(4)

Randomized MSM/TGW HIV PrEP users (TDF/FTC)

200mg doxycycline 24-72 hours after condomless anal or oral sex up to 3x per week vs. no medication

- Chlamydia: HR: 0.30 (CI: 0.13-0.70)
- Syphilis: HR: 0.27 (CI: 0.07-0.98)
- Gonorrhea: HR: 0.83 (CI: 0.47-1.47)

Results show a 70% reduction in chlamydia and syphilis and a non-statistically significant reduction in gonorrhea cases

SAN FRANCISCO/SEATTLE DOXYPEP(5)

Randomized MSM/TGW HIV PrEP users + People with HIV with history of condomless sex and STI in past 12 months

200mg doxycycline 24-72 hours after sex up to once every 24 hours vs. no medication

- Chlamydia: PrEP RR: 0.12 (CI: 0.05-0.25)
— HIV RR: 0.26 (CI: 0.12-0.57)
- EARLY Syphilis: PrEP RR: 0.13 (CI: 0.03-0.59)
— HIV RR: 0.23 (CI: 0.04-1.29)
- Gonorrhea: PrEP RR: 0.45 (CI: 0.34-0.65)
— HIV RR: 0.43 (CI: 0.26-0.71)

Results show more than a 70% reduction in chlamydia, more than a 75% reduction in early syphilis, and more than a 55% reduction in gonorrhea. Study stopped early due to effectiveness

FRENCH ANRS DOXYVAC(6)

Randomized MSM HIV PrEP users with at least one STI in past 12 months

200mg doxycycline 24-72 hours after sex vs. no medication and then randomized to receiving or not 4CMenB vaccine approved for individuals 10-25 for *Neisseria meningitidis* serogroup B with potential effectiveness against gonorrhea

- Chlamydia: aHR: 0.11 (CI: 0.04-0.30)
- Syphilis: aHR: 0.21 (CI: 0.09-0.47)
- Gonorrhea: aHR: 0.49 (CI: 0.32-0.76)

Results showed nearly a 90% reduction in chlamydia, nearly an 80% reduction in syphilis, and a 50% reduction in gonorrhea. Study stopped early due to effectiveness

Sources: (1) *Guidelines for the use of doxycycline post-exposure prophylaxis for bacterial sexually transmitted infection prevention*, Ctrs. For Disease Control, <https://www.cdc.gov/std/treatment/guidelines-for-doxycycline.htm>, (last visited Feb. 1, 2024), (2) Doxycycline use and adverse events, Ctrs. For Disease Control, <https://www.cdc.gov/std/treatment/doxy-adverse-events-toe.htm>, (last visited Feb. 1, 2024), (3) Bolan RK et al. *Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study*. 42 SEX TRANSM DIS. 98,103 (2015) (4) Molina JM et al. *Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial*. 18 LANCET INFECT DIS. 308,317 (2018), (5) Luetkemeyer AF et al. *Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections*. 388 N ENGL. J. MED. 1296,1306 (2023), and, (6) Molina JM et al. *ANRS 174 DOXYVAC: An Open-Label Randomized Trial to Prevent STIs in MSM on PrEP*. CROI [Internet]. 2023 Feb 19;Seattle, Washington.

WHAT HAS BEEN OBSERVED REGARDING DOXY PEP AND DRUG RESISTANCE?

Antimicrobial resistance is a serious issue that threatens the safety and effectiveness of a broad range of antibiotics and other therapeutics. Arising naturally, but spurred on by over-use in agriculture and medicine, concern over resistance is leading to greater efforts to provide proper stewardship of effective therapeutics. This causes legitimate questions to be raised over whether the benefits of use of doxycycline outweigh the potential risks of resistance.

CDC's draft guidance provides the available evidence related to resistance from the three previously cited studies of doxy PEP in MSM and transgender women. These data, however, do not provide a context for understanding this information. An article describing the San Francisco/Seattle DoxyPEP study, however, provides a useful way to interpret these initial observations on resistance. Annie Leutkemeyer, MD a co-principal investigator of the study stated that, "this isn't a choice between antibiotics and no antibiotics in men and transgender women with a history of recurrent STIs. The alternative here for many is repeated STIs that lead to recurrent antibiotics. Doxy PEP may mitigate the amount of antibiotics used, including broader spectrum antibiotics like ceftriaxone, the use of which was reduced by 50% by those taking doxy PEP." The study examined resistance in 1) gonorrhea, 2) *Staphylococcus aureus* that lives

on the skin and, 3) non-disease-causing *Neisseria* species that live in the throat. Researchers found:

- More tetracycline resistant gonorrhea (30% vs 11%) in those taking doxy PEP than those not taking it, which suggests that doxy PEP may be less protective against strains of gonorrhea that already have tetracycline resistance. More studies are needed to determine if doxy PEP use increases tetracycline resistance in gonorrhea.
- Doxy PEP reduced colonization by *Staphylococcus aureus* from 44% to 31%, but the cultures resistant to doxycycline went up from 5% to 13%, a small but statistically significant increase. There was no increase in methicillin-resistant *Staphylococcus aureus* (MRSA) overall or with doxycycline-resistant MRSA.
- *Neisseria* species live in the throat without causing disease and can be a reservoir for resistance genes. *Neisseria* species did not appear to be affected by doxy PEP use.

Limiting antimicrobial exposure is an important objective to prevent antibiotic resistance and must be carefully balanced with the potential benefits of doxy PEP. The high prevalence of STIs among MSM and transgender women influences the calculation of net benefit for these populations. The balance may be different for other populations with lower STI prevalence.

Sources: "Doxycycline for STI Prevention: Highly Effective, Minimal Drug Resistance," Laura Kurtzman, University of California San Francisco, February 22, 2023, available at <https://www.ucsf.edu/news/2023/02/424861/doxycycline-sti-prevention-highly-effective-minimal-drug-resistance>.

Training Centers (AETCs), and the Health Centers Program should fund detailing efforts (face-to-face education of providers about a product or intervention to support its use in clinical practice). This should include education in the concepts of sexual health, and a forthright discussion of antimicrobial stewardship that gives current evidence in support of the use of doxy PEP for MSM and transgender women.

2. FOCUS ON EQUITY

If the goal of an intervention is to produce the largest possible public health benefit, then it is imperative that implementation efforts are focused on equity. Time and again, when we have implemented interventions and assumed that all people could benefit, racial and ethnic minorities, lower-income people, and sexual and gender minorities have been left behind. When COVID-19 testing was first rolled out, in place after place, testing sites were

either located in more affluent and largely white communities, or when they were located in lower-income communities, they were still inaccessible, such as by setting up drive-through testing sites accessible only to people with cars.⁷ The states with the highest rates of STIs are often those with the greatest access barriers and where a far larger share of the population are people of color than the nation as a whole.⁸

Implementation of HIV PrEP offers perhaps the most salient example of what happens when equity is not a central implementation focus from the outset. HIV PrEP was approved by the Food and Drug Administration (FDA) in 2012. CDC recently published estimates of PrEP use in 2022 that show that while 94% of white people with an indication for PrEP were using it, only 24% of Latinx and 13% of Black people with an indication for PrEP were using it.⁹ AIDSVU analyzed these data and found that as PrEP use has increased, equity has decreased. Regionally, Black people made up 52% of new HIV diagnoses in the

South, but only 21% of PrEP users; in the Midwest, Black people made up 48% of new HIV diagnoses, but only 12% of PrEP users. Additionally, they found that in 2022, there were only 5 Black PrEP users for every Black HIV diagnosis and only 9 Latinx PrEP users for every Latinx HIV diagnosis, compared to 36 white PrEP users for every white HIV diagnosis.¹⁰ The success of doxy PEP may hinge on pro-actively countering these inequities from the beginning. To monitor doxy PEP coverage (i.e., the proportion of the population using the intervention), emerging disparities, and population-level impact, CDC and their health department partners will need estimates of the population that can benefit from the intervention by race/ethnicity, and other relevant demographic information, applying lessons from HIV PrEP monitoring activities.

POLICY ACTION: CDC and other federal health agencies should fund and encourage their grantees to support and deliver doxy PEP implementation activities that focus on Black and Latinx MSM and transgender women.

CDC and other federal agencies and their health department partners have a critical role in creating the infrastructure to educate about doxy PEP, provide guidance to integrate doxy PEP services with HIV and STI screening and treatment, and support a network of publicly funded clinics. Eighty percent of STIs

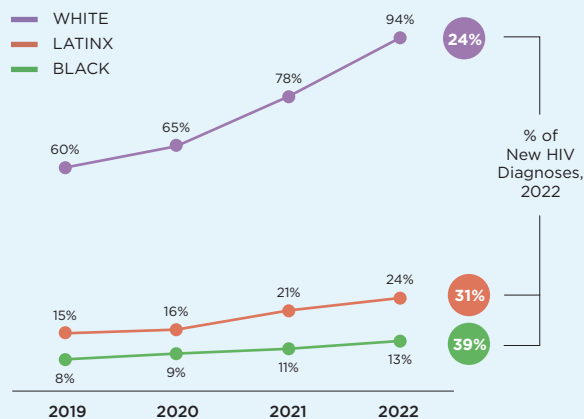
are reported, however, from non-STD clinics.¹¹ While support for safety net clinics remains critical, the most effective outreach and messaging likely will come from non-governmental partners. Therefore, CDC and state and local health departments need to prioritize funding for community-based organizations led and trusted by Black and Latinx MSM and transgender people. Additionally, public health has long recognized the value of community leaders in engaging diverse communities, whether it is through barbershops, faith institutions, or social clubs.¹² For MSM and transgender communities, key partners may include event promoters, social media influencers, bartenders, and others. To support such individuals to promote sexual health and the use of doxy PEP, new avenues for training and engagement are needed. This may include funding educational retreats, offering webinars and trainings, creating new LGBTQ Lay Health Educator certifications, or other means of creating a community of sexual health ambassadors and connecting them to researchers and clinical providers so that their work is based on the latest clinical information.

POLICY ACTION: HRSA should develop a strategy for implementing doxy PEP that leverages the Health Centers Program and Ryan White HIV/AIDS Program.

HRSA is the prime federal agency to provide leadership in extending doxy PEP access both through its Health Center Program and the Ryan White HIV/AIDS Program. They also have experience working with the Centers for Medicare and Medicaid Services (CMS) to provide leadership and technical assistance to Medicaid and Medicare programs. Indeed, the Ryan White HIV/AIDS Program has a proven track record at improving equity in HIV outcomes that should be applied to doxy PEP implementation. CDC reports that in 2021, only 66% of all people with HIV were virally suppressed.¹³ Within the Ryan White HIV/AIDS Program, however, in 2022, 89.6% of all clients were virally suppressed, including 87.1% of Black clients and 91.3% of Latinx clients.¹⁴

U.S. PREP USE, BY RACE AND ETHNICITY

PERCENTAGE OF POPULATION WITH AN INDICATION FOR PREP USING IT AND SHARE OF NEW HIV DIAGNOSES



SOURCE: Sources: Centers for Disease Control, *Overall Trends in PrEP Prescriptions Among People Who Could Benefit, 2019-2022*, CDC Division of HIV Prevention: Dear Colleagues (October 17, 2023), <https://www.cdc.gov/hiv/policies/dear-colleague/dcl/20231017.html>. and *NCHHSTP AtlasPlus*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/nchhstp/atlas/index.htm> (last visited Feb. 1, 2024).

POLICY ACTION: Non-governmental entities, including pharmaceutical manufacturers, foundations, and corporations should fund community efforts to implement doxy PEP.

Doxycycline is a generic medication and there are no company-sponsored access programs. Non-governmental resources are needed to: 1) support sexual health messaging and communications by MSM and transgender communities that are not constrained by governmental clearance processes, 2) purchase medication and pay for related services for the uninsured, in limited circumstances; and, 3) integrate doxy PEP messaging as part of a sexual

CRITICAL QUESTIONS REQUIRE A COMPREHENSIVE RESEARCH AGENDA

As doxy PEP is a new intervention that offers great promise, it will be important to develop a prioritized research agenda that tackles critical questions, including:

1. IS DOXYCYCLINE VIABLE AS STI PrEP?

Doxycycline has been shown to be effective as PEP, but questions about its effectiveness suggest that the timing of dosing is important. This further raises questions as to whether it is best delivered as PrEP or PEP. As stated previously, a 2015 study found that doxycycline was effective as PrEP among MSM with HIV. Further studies must be conducted to evaluate this for different populations, and to compare the relative effectiveness of daily doxy PrEP, event-driven doxy PrEP, and doxy PEP.

2. WHAT ARE KEY ELEMENTS OF A DOXYCYCLINE RESISTANCE MONITORING PLAN?

In recommending doxy PEP, CDC is indicating that their judgment is that the limited resistance observed is outweighed by the clinical benefits for MSM and transgender women. It will be essential, however, to create a monitoring plan, consider new resistance reporting requirements, and educate providers, doxy PEP users and potential users, and policymakers about how to understand and interpret available data on resistance.

3. IS LONG-TERM USE OF DOXYCYCLINE SAFE AND WHAT IS THE IMPACT ON THE MICROBIOME?

To date, doxy PEP studies have evaluated safety for only up to 12 months. Longer-term studies for other uses of doxycycline have looked at lower doses. Further, there are no data on the intermittent use of doxycycline. Additional safety assessments are needed as this new use of doxycycline is put into practice. A related issue is the impact of doxycycline on the microbiome. The use of antibiotics has been described as akin to clear-cutting a forest wherein they indiscriminately wipeout the flora of the gut microbiome, which is believed to be essential for maintaining health. Studies are needed to assess the impact of extended use of doxycycline on the microbiome, and how this affects overall health. Further, research must elucidate proactive steps that can be taken to protect or reconstitute the microbiome during or after using doxycycline.

4. WHAT ARE OPTIMAL WAYS TO USE DOXYCYCLINE TO BOTH ACHIEVE PUBLIC HEALTH IMPACT AND REDUCE THE RISK OF RESISTANCE?

CDC's draft guidance is based on available evidence yet is limited by gaps in knowledge. The guidance states that it is safe to take 200mg of doxycycline daily and it should be taken within 72 hours of a sexual encounter. Given concerns over the microbiome and side-effects from long term use, many users will make decisions about how to use doxycycline in the absence of additional data. Some MSM and transgender women may be more sexually active than others. Even if it is safe, should they take doxycycline daily, day after day? Are there alternative dosing strategies that may reduce exposure to doxycycline without impacting its effectiveness? It will be important for NIH, CDC and health departments to conduct consultations with community members to inform a research agenda and also to create avenues for doxy PEP educators and ambassadors to answer questions in an evidence-informed way even when evidence-based answers for user questions may not be available.

5. IS DOXY PEP APPROPRIATE FOR OTHER POPULATIONS?

CDC draft guidance says that no recommendation is given for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary individuals because of insufficient evidence to assess the balance of benefits and harms of doxy PEP in these populations. Notably, it does not say that doxy PEP should not be offered to these other populations. A randomized trial from 2020 to 2022 of cisgender women in Kenya found no reduction in bacterial STIs, but analysis of hair samples detected doxycycline in only 44% of participants suggesting that lack of use of this intervention may have led to this result (Stewart J et al. Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. *New England Journal of Medicine*. 2023). Additional studies among these populations are needed and consideration must be given to how to use population prevalence of STIs and the number needed to treat to guide recommendations for use of doxy PEP for other populations.

health package of actions when pharmaceutical manufacturers are promoting their products.

3. BRIDGE KNOWLEDGE GAPS

Available evidence suggests that doxy PEP is safe and effective, yet we have much to learn about how to maximize its public health impact. Various parts of HHS can contribute to understanding how to best use doxy PEP and they must come together and delineate responsibilities for working collaboratively.

POLICY ACTION: CDC and NIH should convene a cross-agency working group to fund priority studies to maximize the benefits of doxy PEP.

To ensure that doxy PEP is implemented in ways that prioritize the populations of MSM and transgender women with the greatest needs, there is a need for a cross-agency research strategy that sets clear priorities and delineates lead agency responsibilities. CDC's Division of STD Prevention (DSTDP) and the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) both have critical expertise and lead responsibility for answering many of these research questions. Either these agencies working together, or some other component of the Department of Health and Human Services (HHS), should establish a broadly-represented cross-agency working group to establish a doxy PEP research plan. This working group should consult broadly with various stakeholders including clinicians, researchers public health professionals, and community-based services providers with a special emphasis on engaging affected communities in meaningful ways.

THE TIME IS NOW

MSM and transgender women in the U.S. face high and often rising rates of chlamydia, gonorrhea, and syphilis. Doxycycline as PEP offers an important new tool to prevent these infections. Policymakers must prioritize the Black and Latinx communities that rarely receive sufficient culturally and linguistically congruent health services by partnering with individuals and organizations to deliver affirming messaging and sexual health services. While acknowledging uncertainty and carefully monitoring for the emergence of drug resistance,

policymakers and health care providers must not allow unsubstantiated fears to negate the potential benefits of doxy PEP for MSM and transgender women.

ENDNOTES

- 1 *Doxycycline*, WIKIPEDIA, <https://en.wikipedia.org/wiki/Doxycycline> (last visited Jan. 25, 2024).
- 2 *Guidelines for the use of Doxycycline Post-Exposure Prophylaxis for Bacterial STI Prevention*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/std/treatment/guidelines-for-doxycycline.htm> (last visited Jan. 25, 2024).
- 3 Gabriela Paz-Bailey, et al., *Trends in condom use among MSM in the United States: the role of antiretroviral therapy and seroadaptive strategies*, 30 AIDS 1985, 1990 (2016).
- 4 Sten H. Vermund, Amy B. Geller, & Jeffrey S. Crowley, SEXUALLY TRANSMITTED INFECTIONS: ADOPTING A SEXUAL HEALTH PARADIGM, (National Academies of Sciences, Engineering, and Medicine, 2021).
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