Dear Health Officers and Medical Directors,

Please see the attached Doxy PEP protocol and associated attachments. These protocols are approved for people at LHD STI clinics, those over the age of 18 (MDHHS is looking into this further), and men and transgender women with at least 1 bacterial STI in the last year. This will also be shared with MAPPP and STI Clinic Coordinators.

Thank you.

STATE OF MICHIGAN
DEPARTMENT OF HEALTH AND HUMAN SERVICES
LANSING

GRETCHEN WHITMER
GOVERNOR

ELIZABETH HERTEL
DIRECTOR

August 8, 2023

Local Health Department Medical Directors
RE: Recommendations for Doxy PEP in Adults

Dear Medical Director:

In order to combat alarming increases in bacterial STIs, the Michigan Department of Health and Human Services would like to encourage the use of doxy-PEP in local health department STI clinics for adult men who have sex with men (MSM) and transgender women with more than 1 bacterial STI in the last 12 months.

Emerging evidence suggests doxycycline (200mg), when taken as doxy-PEP within 24 hours but no later than 72 hours after condomless sex, significantly reduces acquisition of chlamydia, gonorrhea, and syphilis in this population.

Evidence

A randomized controlled trial (RCT) using a single, oral dose of doxycycline 200mg within 72 hours after condomless oral, anal, or vaginal sex in MSM and transgender women, who were either persons living with HIV (PLWH) or taking HIV PrEP, showed significant reductions in CT, GC, and syphilis per quarter of study follow up. In persons on HIV PrEP, taking doxy-PEP reduced syphilis by 87 percent, CT by 88 percent, and GC by 55 percent while in PLWH doxy-PEP reduced syphilis by 77 percent, CT by 74 percent, and GC by 57 percent.

Safety

Taking doxycycline is safe and well tolerated, with no reported doxycycline associated Grade 2 or higher adverse events (AEs) and no documented laboratory-related severe AEs in the doxy-PEP RCT. Long-term use of doxycycline has been prescribed safely for other medical indications (e.g., acne treatment or malaria prophylaxis). Considering the safety of doxycycline as a preventative medication far outweighs the potential outcomes of untreated STI infections which include infertility, an increased risk of cancer and HIV infection.

Unknowns

Data continue to be collected and reviewed for possible antimicrobial resistance among bacterial STIs, commensal Neisseria (as a potential reservoir for tetracycline resistant plasmids), and Staphylococcus aureus. The effects of doxy-PEP on the gut microbiome are also being studied.

Prescribing doxy-PEP

Doxycycline is not FDA approved for STI PEP and there is no national organizational guidance for its use as STI prevention. However, Centers for Disease Control and Prevention (CDC) has released considerations for doxy-PEP as an STI preventative strategy. Doxy-PEP has recently been approved as a 340b drug pricing covered medication. San Francisco Department of Public Health has released their own clinical protocol with counseling messages. The National Coalition of STD Directors (NCSD) has set up a command center that includes marketing messages. The Detroit Public Health HIV/STI Clinic has also attached their clinical protocol.

References

Luetkemeyer et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934
CDPH 2020 STI Surveillance Report

We encourage you to consider incorporating a doxycycline-PEP clinical protocol in your STI clinical settings. While we know that not all STI clinics can offer HIV PrEP please ensure clients on doxycycline-PEP receive comprehensive HIV PrEP education and referrals.

Should there be any questions, please contact Dan Lowery at loweryd@michigan.gov. Thank you.

Sincerely,

Natasha Bagdasarian, MD, MPH, FIDSA
Chief Medical Executive

Attachments

NB:dg

January 4, 2022

Detroit Public Health STD Clinic

Doxycycline Post-Exposure Prophylaxis Protocol

The CDC has released considerations for doxy-PEP as an STI prevention strategy, but there is not yet detailed guidance from CDC on doxy-PEP, for which its indication is currently off-label. STIs can cause significant morbidity and reducing STI rates in Detroit is an urgent public health priority. Doxy-PEP is the first biomedical prevention tool that has been shown to be effective and well-tolerated and community awareness is growing.

The protocol proposed here has been adapted from the San Francisco Department of Health, who released recommendations on October 20, 2022 on the use of doxy-PEP to reduce STI incidence in MSM and TGW at risk of bacterial STIs.

Efficacy/Evidence

I. In persons taking HIV PrEP, doxy-PEP reduced syphilis by 87%, chlamydia by 88% and gonorrhea by 55%.
II. In PLWH, doxy-PEP reduced syphilis by 77%, chlamydia by 74% and gonorrhea by 57%.
III. Doxy-PeP does NOT prevent HIV, MPox, HPV, or HSV.

Guidelines and Recommendations

I. Who to Recommend Doxy-PeP To

a. Cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men :
    i. Have had a bacterial STI in the past year AND
    ii. Report condomless anal or oral sexual contact with ≥ 1 cis male or trans female partner in the past year

** These were the eligibility criteria used for the DoxyPEP study.

**Patients with a history of syphilis should be prioritized for doxy-PEP.

b. Consider offering to MSM and TGW who have had multiple sex partners in the past year or engages in group sex or chem-sex, even if they have not been previously diagnosed with an STI

** At this time, there is insufficient evidence to recommend doxy-PEP for STI prevention for individuals who report receptive vaginal sex

** If used in people who are able to become pregnant, pregnancy testing should be conducted as doxycycline use should be avoided in pregnancy.

II. Dosing and Prescribing

a. 200 mg of doxycycline should be taken ideally within 24 hours but no later than 72 hours after condomless oral, anal or vaginal sex.
b. Doxycycline can be taken as often as every day, depending on frequency of sexual activity, but individuals should not take more than 200 mg within a 24 hour period.
c. Either doxycycline hyclate delayed release 200 mg (1 tab) OR doxycycline hyclate or monohydrate immediate release 100 mg (2 tabs taken simultaneously) are acceptable.
d. Immediate release may be less expensive than delayed release and should be equivalently bioavailable.
e. For ICD10 diagnosis code, use Z20.2 (Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission).

III. Monitoring While Taking Doxycycline

a. Per the doxycycline package insert, LFTs, renal function and a CBC should be checked periodically in patients taking doxycycline for a prolonged period.

** LFTs and CBCs were monitored in the DoxyPEP study, and there were no laboratory-related severe adverse events.

b. Persons taking doxy-PEP should be screened every three months for gonorrhea and chlamydia at all anatomic sites of exposure, syphilis, and HIV (if not known to be living with HIV).
c. If a patient is diagnosed with an STI while using doxy-PEP, they should be treated according to standard CDC STI Treatment Guidelines

IV. Counseling Messages

a. Counsel about possible drug interactions:
    i. Risk of sun sensitivity
    ii. Remaining upright for 30 minutes after taking doxycycline to reduce the risk of pill esophagitis
    iii. The rare risk of benign intracranial hypertension.
b. Study data on the impact of doxy-PEP on antibiotic resistance and the gut microbiome are being collected and reviewed.
c. Impacts of long-term use of doxy-PEP for STI prevention for individual patients and for population-level rates of antimicrobial resistance are unknown, but doxycycline has been previously used safely for long-term prophylaxis of malaria and treatment for acne.

V. Recommend Comprehensive Package of Sexual Health Services

a. Counsel all HIV-negative patients on HIV PrEP options
    i. Daily oral PrEP
    ii. 2 -1-1 dosing strategy
    iii. Long-active Cabotegravir for PrEP
b. Ensure people living with HIV are in care and inform patients on U = U - that maintaining an undetectable HIV viral load eliminates the risk of transmitting HIV to sexual partners
c. Screen for other STIs every 3 months, regardless of HIV serostatus patients
    i. gonorrhea and chlamydia using urine, pharyngeal and rectal NAAT testing,
    ii. Serologic test for syphilis
d. Recommend and offer the following vaccines which protected against sexually transmitted or sexually associated infections according to current local eligibility and ACIP Guidance
    i. MPX Vaccine (Jynneos)
    ii. Meningococcal Vaccine (MenACWY)
    iii. Hepatitis A/ Hepatitis B
    iv. HPV

STI Post-Exposure Prophylaxis with Doxycycline

Doxy PeP

Shira Heisler, MD

Medical Director, Detroit Public Health STD Clinic

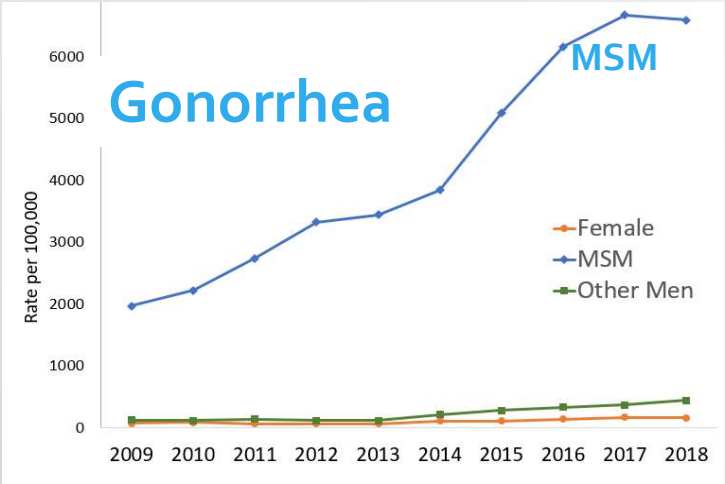
Assistant Professor, Wayne State University, Infectious Disease

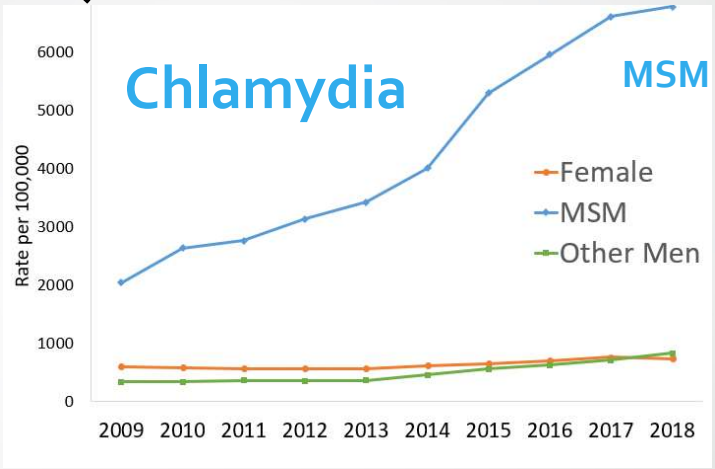
Objectives

- Review of STI epidemiology
- Review the evidence and efficacy of Doxy PeP
- Review the concerns of Doxy PeP
- Overview of implementation of Doxy PeP in clinical practice

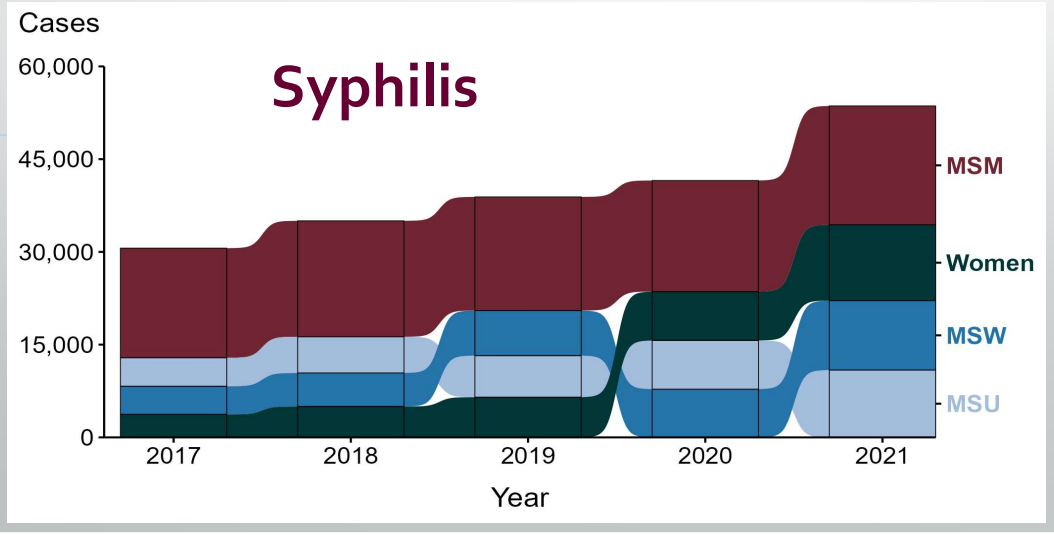
Epidemiology of STIs in the US

STIs Disproportionately Impacts Men who have Sex with Men (MSM)





San Francisco DPH
STI surveillance data 2018



CDC 2020 STI surveillance
https://www.cdc.gov/std/statistics/2020/default.htm

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Polling Question

What is the Doxy PeP Protocol?

1. Taking doxycycline 100 mg daily to prevent chlamydia, gonorrhea, and syphilis
2. Taking doxycycline 200 mg daily to precent chlamydia, gonorrhea, and syphilis
3. Taking doxycycline 100 mg within 72 hours post condomless sex to precent chlamydia, gonorrhea, and syphilis
4. Taking doxycycline 100 mg within 72 hours post condomless sex to precent chlamydia, gonorrhea, and syphilis

Polling Question

What is the Doxy PeP Protocol?

1. Taking doxycycline 100 mg daily to prevent chlamydia, gonorrhea, and syphilis
2. Taking doxycycline 200 mg daily to precent chlamydia, gonorrhea, and syphilis
3. Taking doxycycline 100 mg within 72 hours post condomless sex to precent chlamydia, gonorrhea, and syphilis
4. **Taking doxycycline 100 mg within 72 hours post condomless sex to precent chlamydia, gonorrhea, and syphilis**

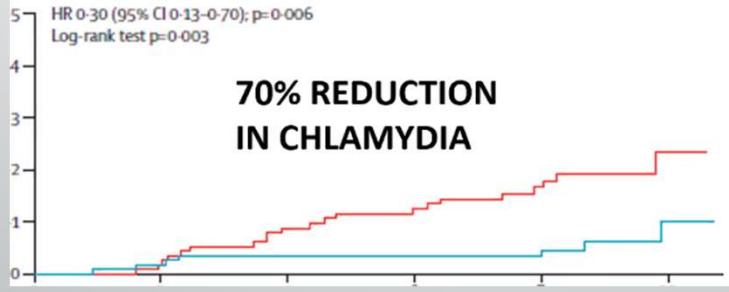
Doxy PeP Trials

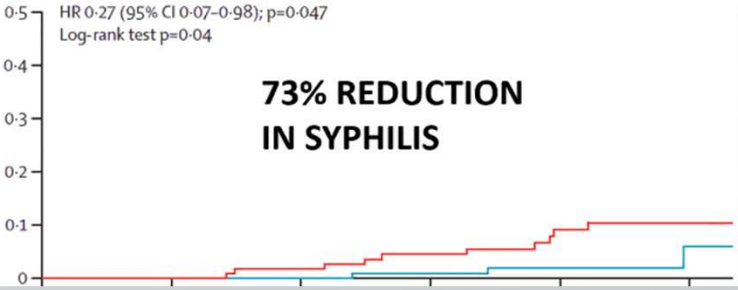
IPERGAY Doxy-Pep Substudy

IPERGAY doxy-PEP Substudy

IPERGAY substudy of doxy-PEP in 232 MSM on HIV PrEP as part of larger PrEP trial

- Open-label doxycycline PEP 200 mg with 24 hrs (and no more than 72 hrs) vs. no PEP, 1:1 randomization
- Doxy-PEP up to 3x weekly
- Median of 660 mg doxy taken per month
- Significant reduction in chlamydia & syphilis and but not effective for gonorrhea (GC)



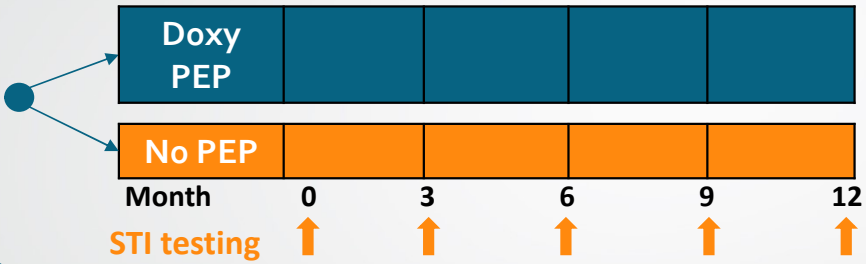


DOXYPeP Trial

Intervention: Open label doxycycline 200mg taken as PEP within 72 hours after condomless sexual contact

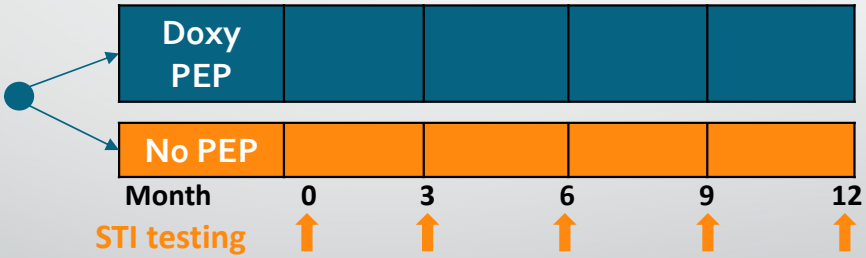
Maximum of 200 mg every 24 hours

MSM & TGW living with HIV
(planned n = 390)



2:1 randomization

MSM & TGW on HIV PrEP
(planned n = 390)



Inclusion criteria:

- Male sex at birth
- Living with HIV or on PrEP
- ≥ 1 STI in past 12 months
- Condomless sex with ≥ 1 male partner in past 12 months

STI Testing: Quarterly 3 site GC/CT testing + RPR, GC culture before treatment

Sites: San Francisco & Seattle HIV & STI clinics

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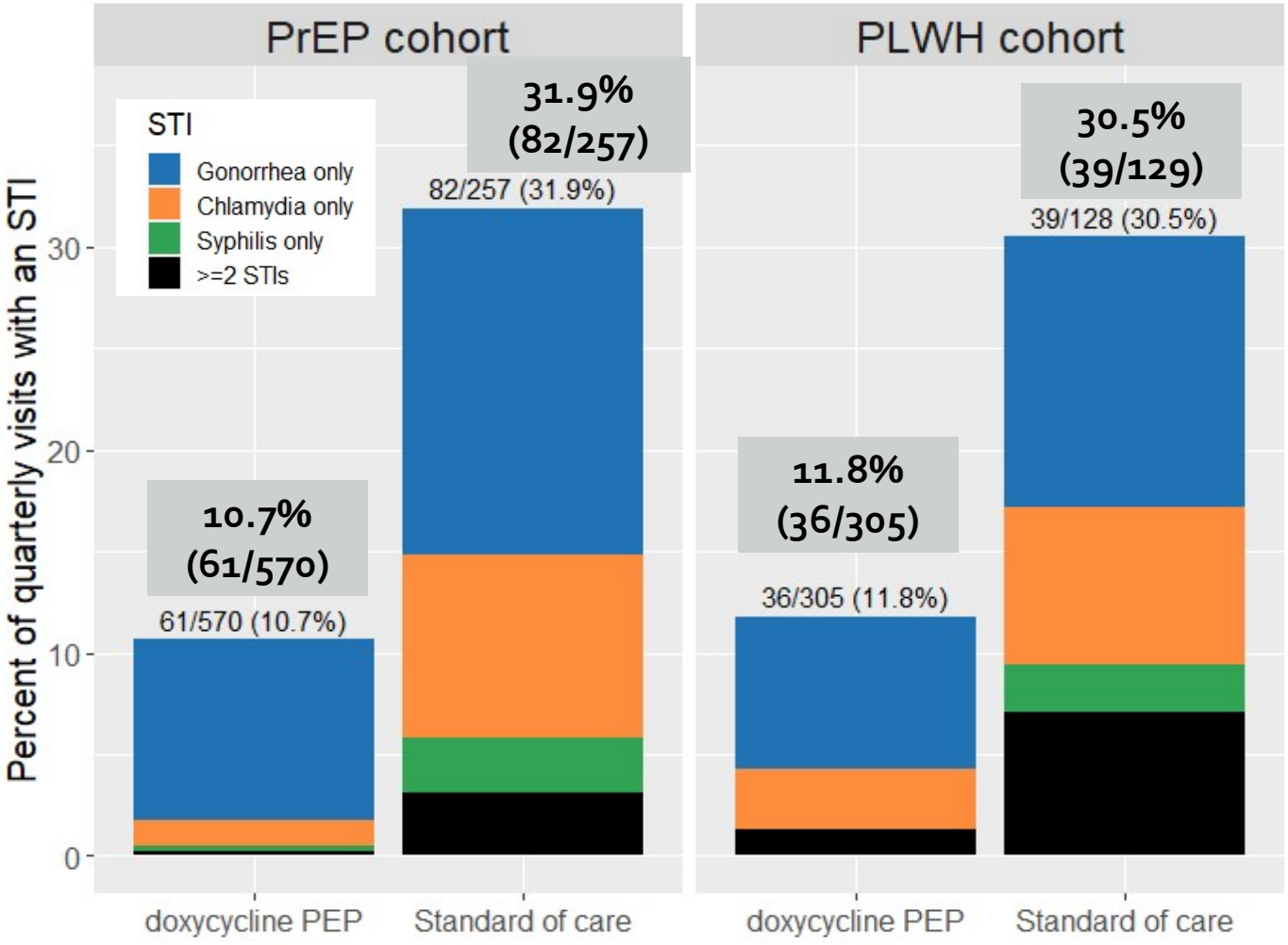
DOXYPEP

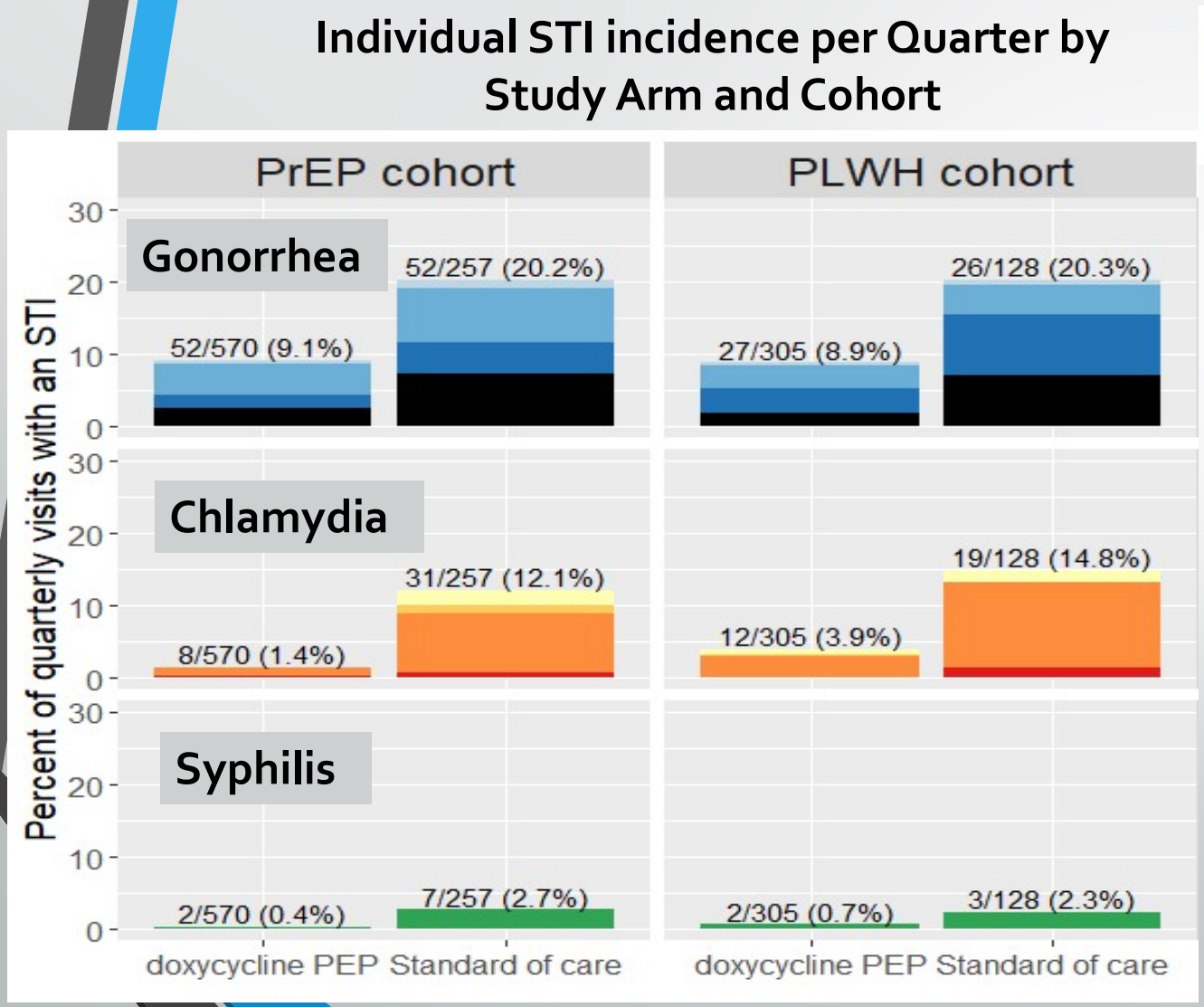
DOXYPeP Results: STI incidence per Quarter



Reduction in STI incidence/quarter	
	risk reduction (95% CI)
PrEP	**0.34 (0.24 - 0.46)**
Living with HIV	**0.38 (0.24 - 0.60)**
Total	**0.35 (0.27 - 0.46)**

all p< 0.0001

DOXYPeP Results: Individual STI incidence per Quarter by Study Arm and Cohort

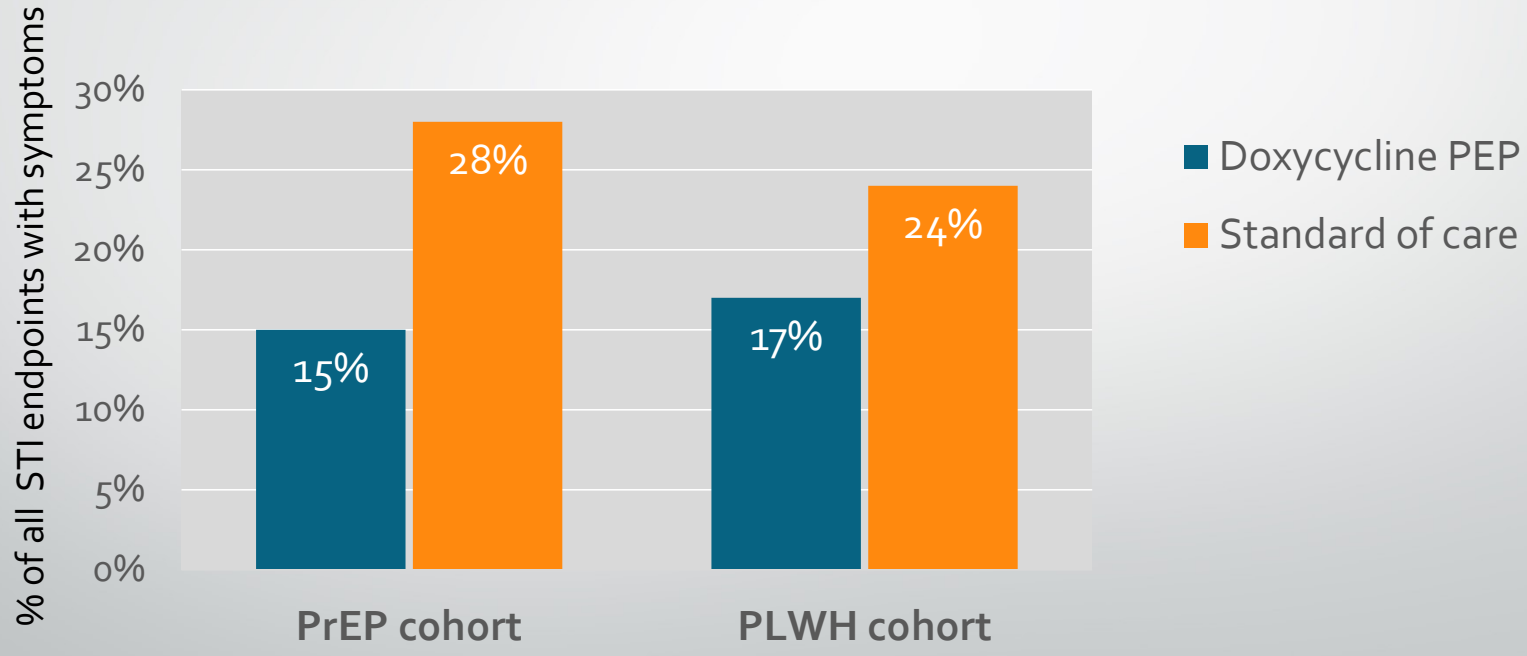


Reduction in each STI per quarter

risk reduction (95% CI)

	PrEP	PLWH
GC	0.45 (0.32 - 0.65) *p<0.0001*	0.43 (0.26 - 0.71) *p=0.001*
CT	0.12 (0.05 - 0.25) *p<0.0001*	0.26 (0.12 - 0.57) *p=0.0007*
Syphilis	0.13 (0.03 - 0.59) *p=0.0084*	0.23 (0.04 - 1.29) *p=0.095*

STI Endpoints with Symptoms Reported at Diagnosis



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DOXYPEP

DOXYPeP Results Summary

Table: Quarterly STI incidence by HIV status and by randomization to doxyPEP & control arms

	HIV uninfected MSM/TGW on PrEP		MSM/TGW living with HIV		Total	
	Doxy arm N=240	Control arm N=120	Doxy arm N=134	Control arm N=60	Doxy Arm N=374	Control arm N=180
Follow up quarters	491	220	266	108	757	328
Participants with an incident STI (GC, CT or syphilis)	41	42	24	18	65	60
Primary STI endpoints	47 (9.6%)	65 (29.5%)	31 (11.7%)	30 (27.8%)	78 (10.3%)	95 (29.0%)
Gonorrhea	40 (8.1%)	45 (20.5%)	21 (7.9%)	20 (18.5%)	61 (8.1%)	65 (19.8%)
Chlamydia	7 (1.4%)	23 (10.5%)	12 (4.5%)	16 (14.8%)	19 (2.5%)	39 (11.9%)
Syphillis	1 (0.2%)	5 (2.3%)	3 (1.1%)	2 (1.9%)	4 (0.5%)	7 (2.1%)

DOXYPeP: Staph Colonization and Doxycycline Resistance

	Doxy-PEP treatment group	
	S. aureus colonization	Doxycycline resistance
Baseline (N = 428)	44%	5%
Month 6 (n = 360)	29%	13%
Month 12 (n = 222)	31%	13%

- **4% absolute reduction in *S. aureus* colonization**
- **8% increase in doxycycline resistance in MSM and TGW[2]**

Doxy PEP:
Safety, Acceptability, Adherence

- **AEs attributed to doxycycline PEP:**
  - No grade 3+ adverse events, grade 2+ lab abnormalities, or SAEs
- **Tolerability and acceptability:**
  - 1.5% discontinued due to intolerance or participant preference
  - 88% reported doxycycline PEP was acceptable/very acceptable
- **Adherence:** Median 7.3 (IQR 1–10) sex acts (anal/vaginal/frontal) per month, with 87% covered by doxycycline per self-report

< 10 doses/month:	54%
10–20 doses/month:	30%
≥ 20 doses/month:	16%

Based on mean difference between pills dispensed and returned for pill count

AIDS 2022

DOXYPEP

DOXYPeP Conclusions

- **Doxycycline PEP within 72 hours of condomless sex substantially reduced the incidence of bacterial STIs**
- Quarterly STI reduction of **62% in PLWH** and **66% in those taking PrEP**
- **Substantial reduction in the incidence of *each* bacterial STI per quarter**, including gonorrhea
- Well tolerated and high self-reported adherence
- Doxycycline PEP has potential as an effective prevention strategy in populations with high STI incidence; 30% per quarter in this study

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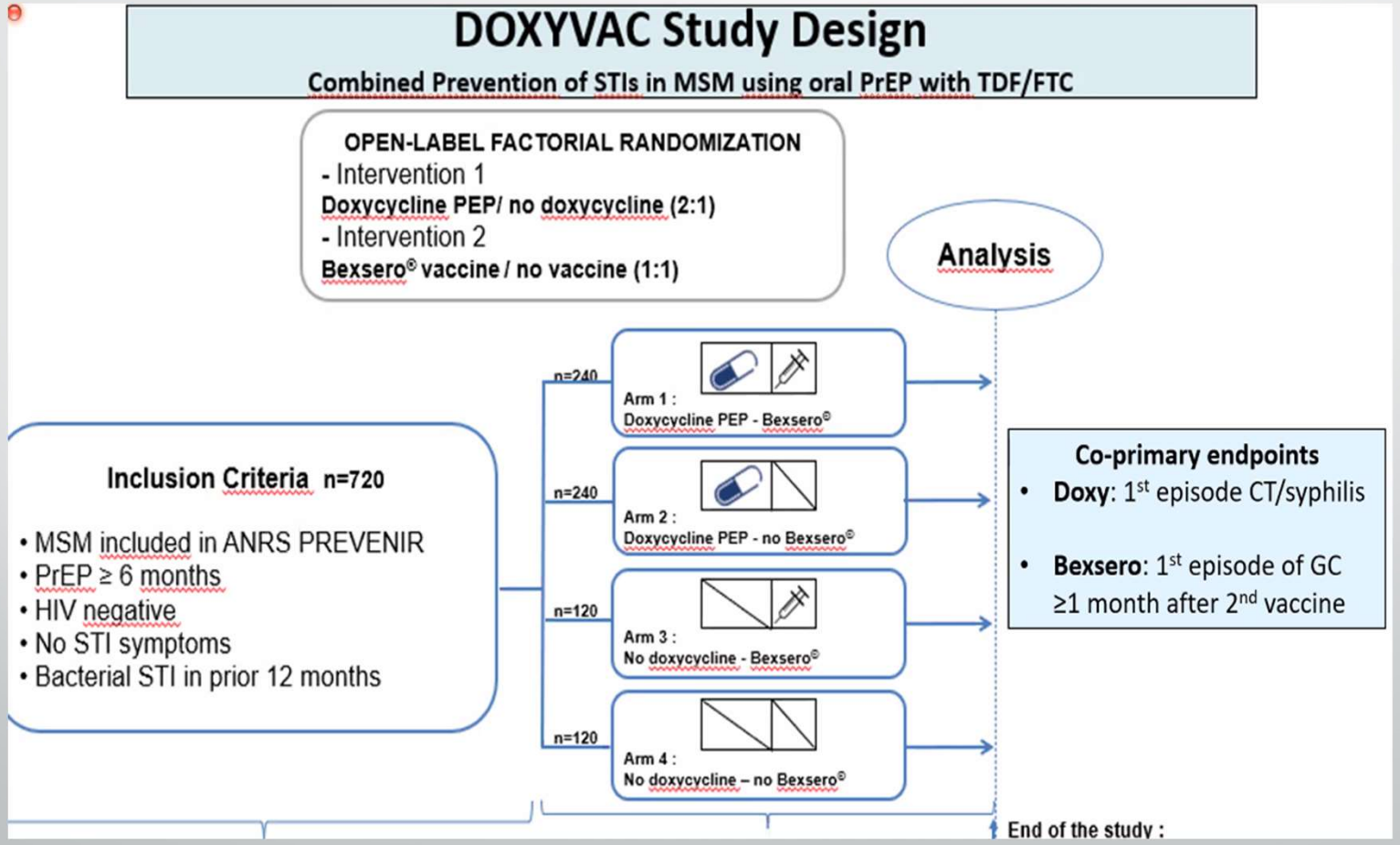
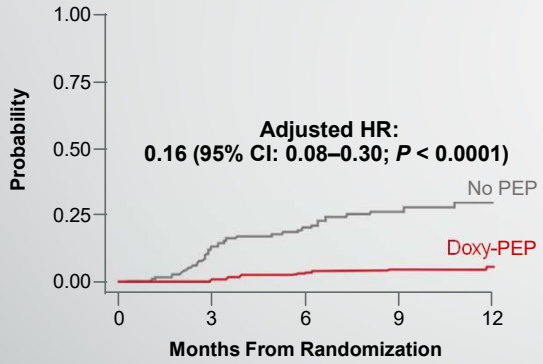
DOXYPEP

DOXYVAC Study



DOXYVAC Study Results

DOXYVAC Study:
Time to First Chlamydia or Syphilis Infection†,1



Chlamydia or syphilis infections:

- **No PEP: n = 36**
  Incidence rate:
  35.4/100 PY
- **Doxy-PEP: n = 13**
  Incidence rate:
  5.6/100 PY

	Doxy-PEP	No PEP	aHR
1st episode CT/Syphilis	5.6/100 PY	35.4/100 PY	0.16 95%CI: 0.08-0.30
1st episode GC	20.5/100 PY	41.3/100PY	0.49 95%CI: 0.32-0.76

	Meningococcal B vaccine	No Vaccine	aHR
1st episode GC	9.8/100 PY	19.7/100PY	0.49 95%CI: 0.27-0.88

Doxy-PEP significantly ↓incidence of CT & syphilis, as well as GC
Meningococcal B vaccine also ↓incidence of GC

Open-label, randomized trial of doxy-PEP in women (Kenya)

Prevention of STIs in a Doxy-PEP Study in Cisgender Women

N = 449[1]

Non-pregnant, cisgender women aged 18–30 years, taking HIV PrEP

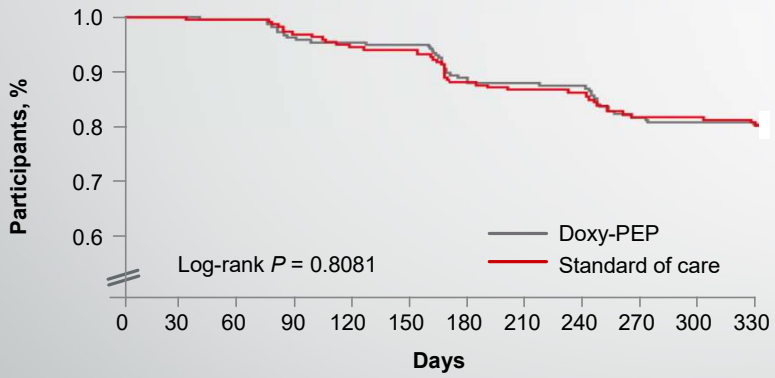
- 200 mg doxy-PEP ≤ 72 hours after sex
- Standard of care

Outcomes

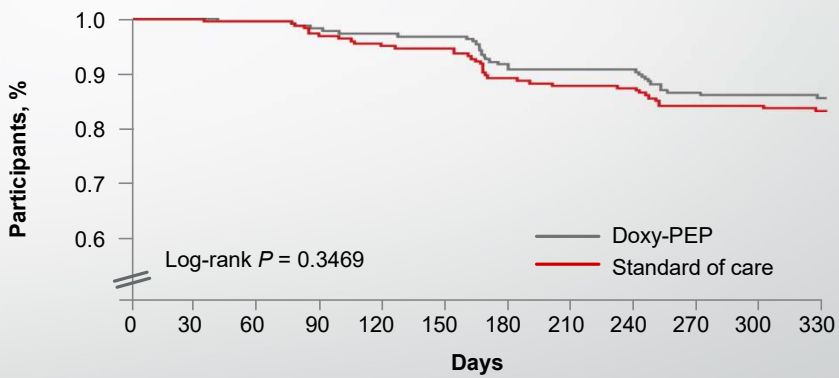
Time to first incident *C. trachomatis, N. gonorrhoeae* or *T. pallidum* infection[1]

2020–2022[1]

Time to First Incident STI[1]



Time to First Incident Chlamydia Infection[1]



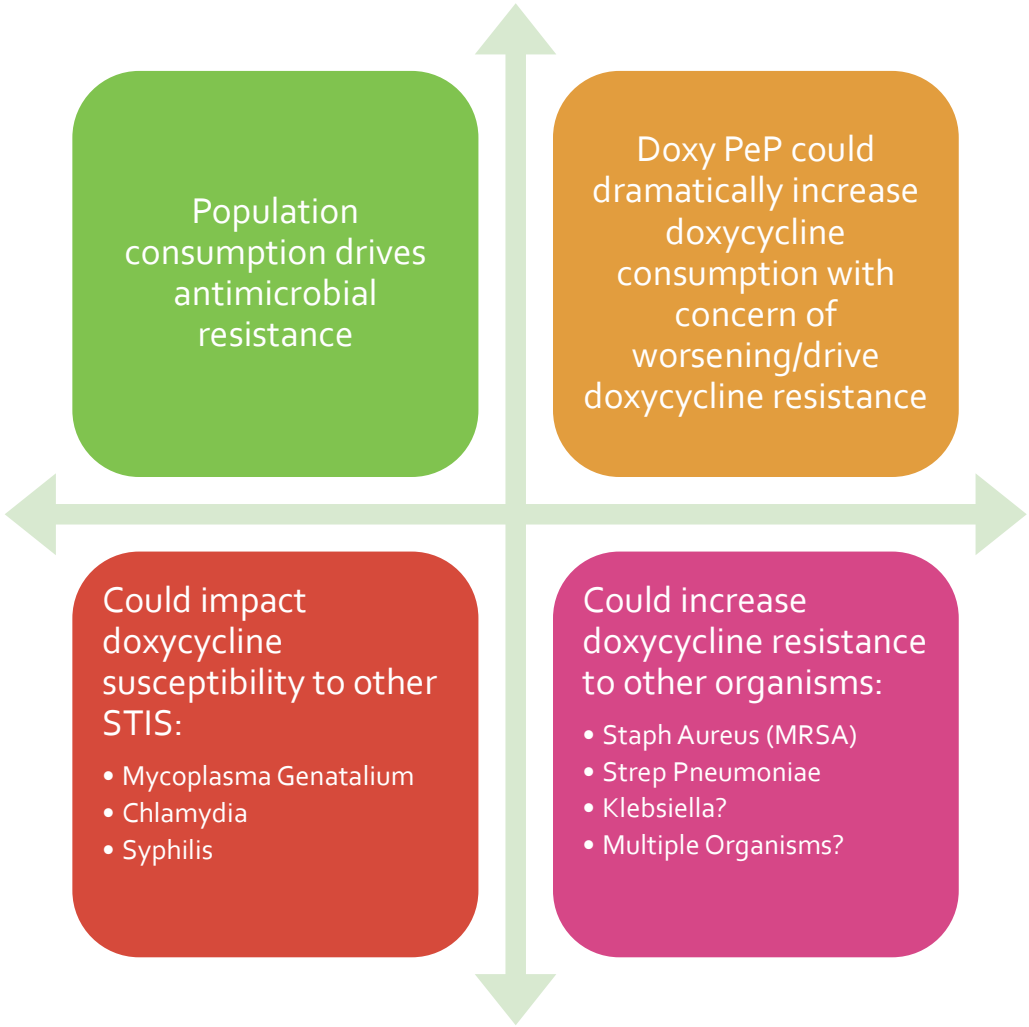
In a study of 11 cisgender men and 9 cisgender women receiving a single dose of 200 mg doxycycline, doxycycline was efficiently distributed to mucosal sites of STI exposure (vaginal, cervical and rectal tissue) and persists at concentrations exceeding reported MIC values[2]

Doxy-PEP did NOT significantly reduce the incidence of STIs in cisgender women taking PrEP.[1]
Further studies are needed to fine-tune STI prevention using antimicrobials in cisgender women

1. Stewart J, et al. CROI 2023, Oral 121; 2. Haaland R, et al. CROI 2023, Oral 118

Concerns and Potential Risks of Doxy PeP

Increasing Doxycycline Resistance



Long Term Effects on the Microbiome

- Studies have shown that antibiotics can disrupt the gut microbiome
- Studies have also shown that disruption to the gut microbiome can be linked to chronic diseases such as type 2 DM, obesity, and advanced chronic livers disease, colorectal cancer, and others

- **Studies are ongoing to determine if long term doxycycline used in doxy PEP will negatively affect the gut microbiome and increase risk for other diseases**

Implementation of Doxy PeP in the Clinical Setting

Polling Question

Who should be offered Doxy PeP?

1. Anybody who is sexually active
2. Cisgender women, cisgender heterosexual men, cisgender men who have sex with men, transgender women who have sex with men who have had history of syphilis.
3. Cisgender men who have sex with men, transgender women who have sex with men who have had history of syphilis
4. Only cisgender women who have a history of syphilis

Polling Question

Who should be offered Doxy PeP?

1. Anybody who is sexually active
2. Cisgender women, cisgender heterosexual men, cisgender men who have sex with men, transgender women who have sex with men who have had history of syphilis.
3. **Cisgender men who have sex with men, transgender women who have sex with men who have had history of syphilis**
4. Only cisgender women who have a history of syphilis

Doxy PeP Protocol

Who Should be offered PrEP?

- Offer to MSM and TGW who have had > 1 bacterial STI in the past year
- Consider for others at risk (chem sex, group sex, sex work)

What dose and when should doxy PeP be taken?

- **1 dose of 200 mg of doxycycline ideally within 24 hours but no later than 72 hours** after condomless oral, vaginal, or anal sex
  - (100 mg immediate release tabs may be less expensive)
- Doxycycline can be taken as often as every day, depending on frequency of sexual activity, but individuals should NOT take more than 200 mg within a 24 hour period.
- 30 doses (60 tablets if using 100 mg tabs) are usually prescribed with 2 refills

Frequency of STI Screening while on Doxy Pep?

- Every 3 months

Doxy Pep Protocol

For patients on doxy PeP, how to treat for patients with symptoms or if they test positive for an STI?

- Treat all STIs as per CDC treatment guidelines and discontinue doxy PeP while being treated for STI and can resume doxy PEP once STI treatment is completed

For patients on doxy PeP, emperic treatment for STI if partner tested positive?

- For contact to Chlamydia or Gonorrhea?
  - Defer empiric treatment, and treat only if test is positive
- For contact to Syphilis?
  - Continue empiric treatment, because testing for syphilis is not reliable in early syphilis infection and doxy PeP may alter serologic response

For persons without HIV, should Doxy PeP only be provided with HIV PrEP?

- Clinicians should ensure that MSM and transgender persons are offered doxy PeP co-prescription with HIV PrEP
- However, doxy PeP should not be withheld if patient declines HIV PrEP

San Francisco Health Department: Doxy PeP Recommendations

POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

Health Update

Doxycycline Post-Exposure Prophylaxis Reduces Incidence of Sexually Transmitted Infections

October 20, 2022

Thank You!

Detroit Public Health STD Clinic

Doxycycline Post-Exposure Prophylaxis Protocol ("Doxy PeP")

Instructions:

- Take **200 mg of doxycycline (two tablets) within 24 hours**, but no later than 72 hours, after a **condomless** oral, anal or vaginal sex that you feel is **high risk**.
- Doxycycline can be taken as often as every day, depending on frequency of sexual activity, but you **should not take more than 200 mg within a 24 hour period**.
- While on Doxy PeP, you will require **STI testing every 3 months**.

Efficacy/Evidence:

- In persons taking HIV PrEP, doxy-PEP reduced syphilis by 87%, chlamydia by 88% and gonorrhea by 55%.
- In persons living with HIV, doxy-PEP reduced syphilis by 77%, chlamydia by 74% and gonorrhea by 57%.
- Doxy-PeP does NOT prevent HIV, MPox, HPV, or HSV.

Please note: *If you are diagnosed with an STI while using doxy-PEP, you will be treated according to standard CDC STI Treatment Guidelines.*

Potential side effects:

- Sun sensitivity - Wear sunscreen when outdoors
- Esophagitis - Take medication with a full glass of water and remain upright for 30 minutes after taking medication
- Impact on antibiotic resistance is still being studied

_____

Doxy PeP Medication Log

Date of condomless sex encounter	Date 200 mg doxycycline Taken	Any side effects?