

DoxyPEP for STI Prevention

Rationale, Results & Next Steps

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Disclosures

Doxycycline provided by Mayne Pharmaceuticals

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Disclaimer

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Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.



To Learn More:

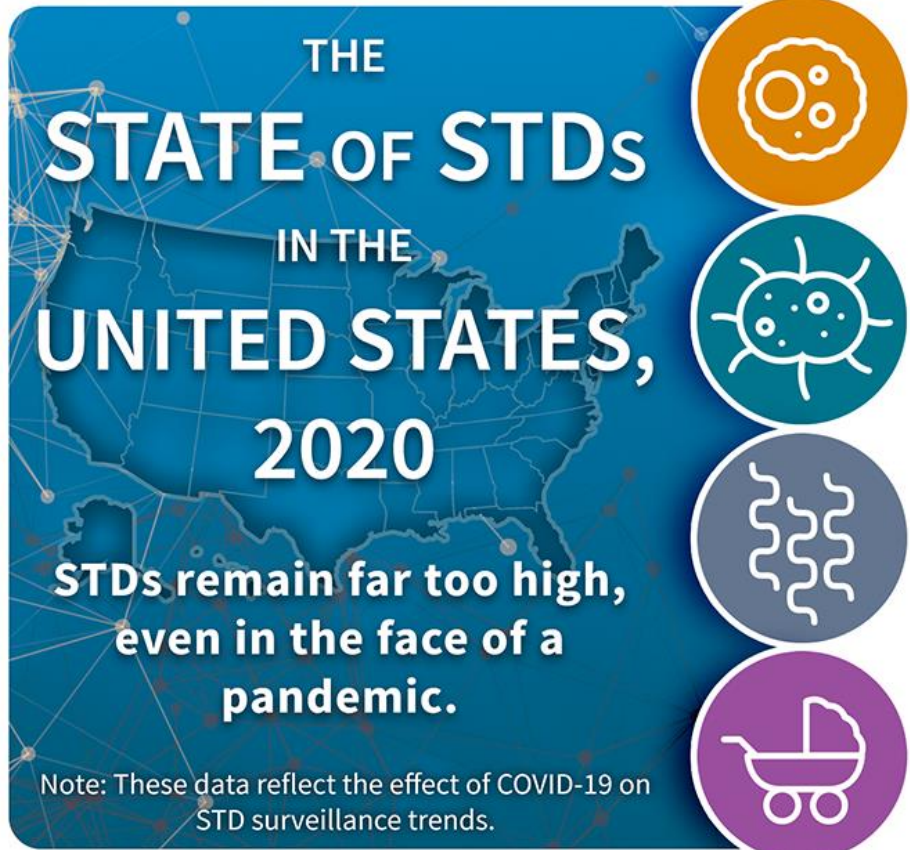
<https://www.cdc.gov/minorityhealth/racism-disparities>

US is Experiencing Steep, Sustained Increases in Sexually Transmitted Infections

THE
STATE OF STDs
IN THE
UNITED STATES,
2020

STDs remain far too high,
even in the face of a
pandemic.

Note: These data reflect the effect of COVID-19 on
STD surveillance trends.



1.6 million
CASES OF CHLAMYDIA
1.2% decrease since 2016



677,769
CASES OF GONORRHEA
45% increase since 2016

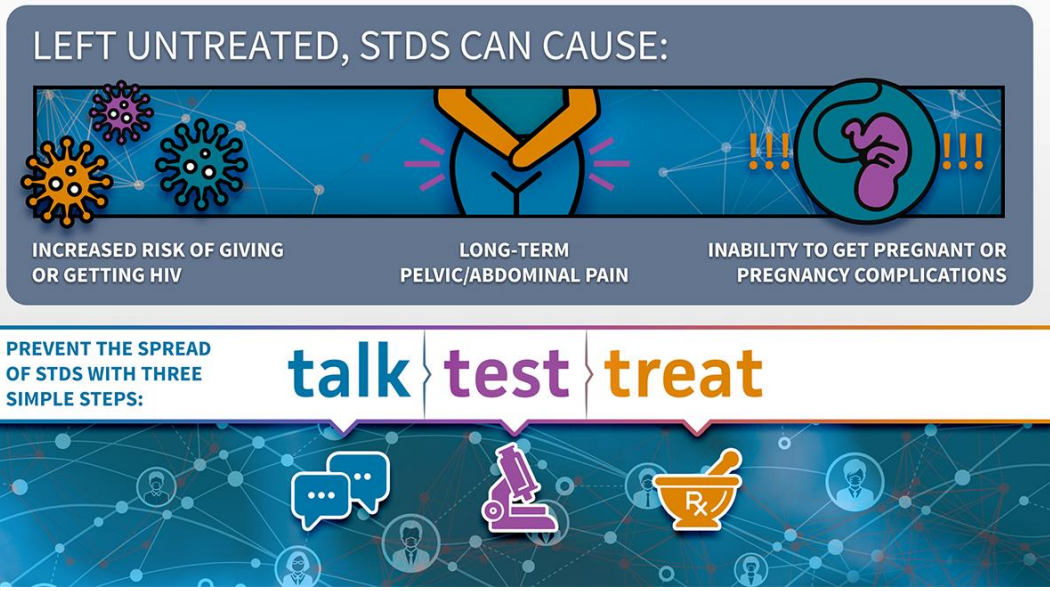


133,945
CASES OF SYPHILIS
52% increase since 2016



2,148
CASES OF SYPHILIS
AMONG NEWBORNS
235% increase since 2016

LEFT UNTREATED, STDS CAN CAUSE:



INCREASED RISK OF GIVING OR GETTING HIV

LONG-TERM PELVIC/ABDOMINAL PAIN

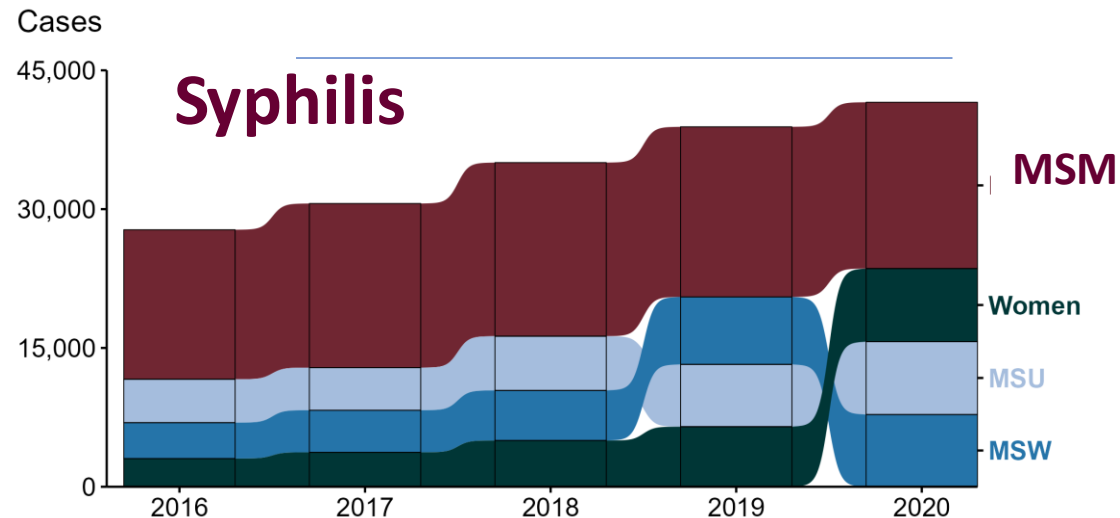
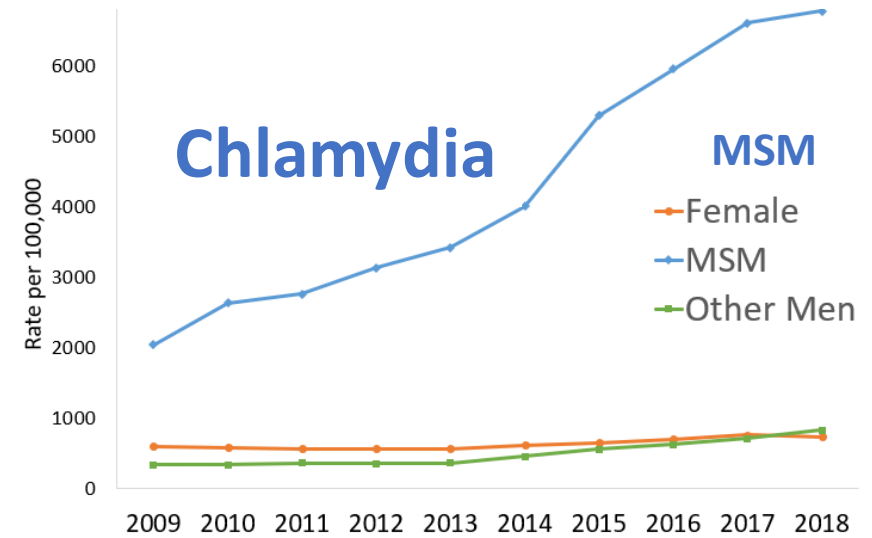
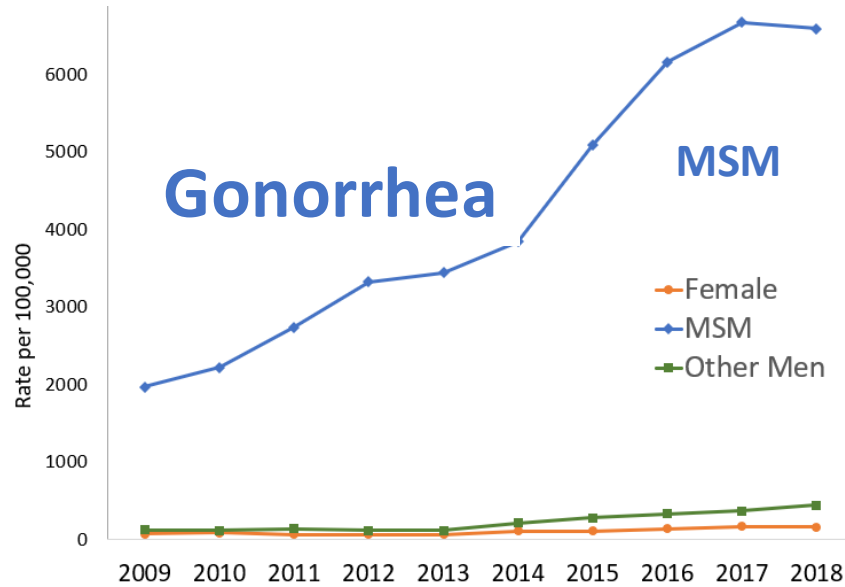
INABILITY TO GET PREGNANT OR PREGNANCY COMPLICATIONS

PREVENT THE SPREAD OF STDS WITH THREE SIMPLE STEPS:

talk | test | treat



The global epidemic of STIs disproportionately impacts men who have sex with men (MSM)



San Francisco DPH
STI surveillance data 2018

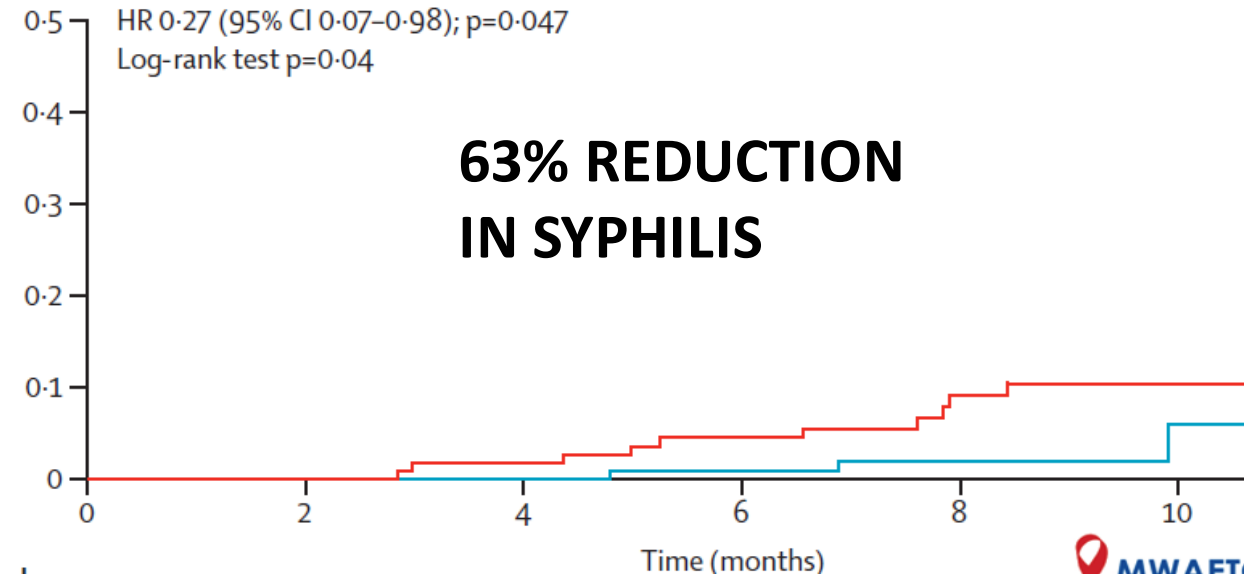
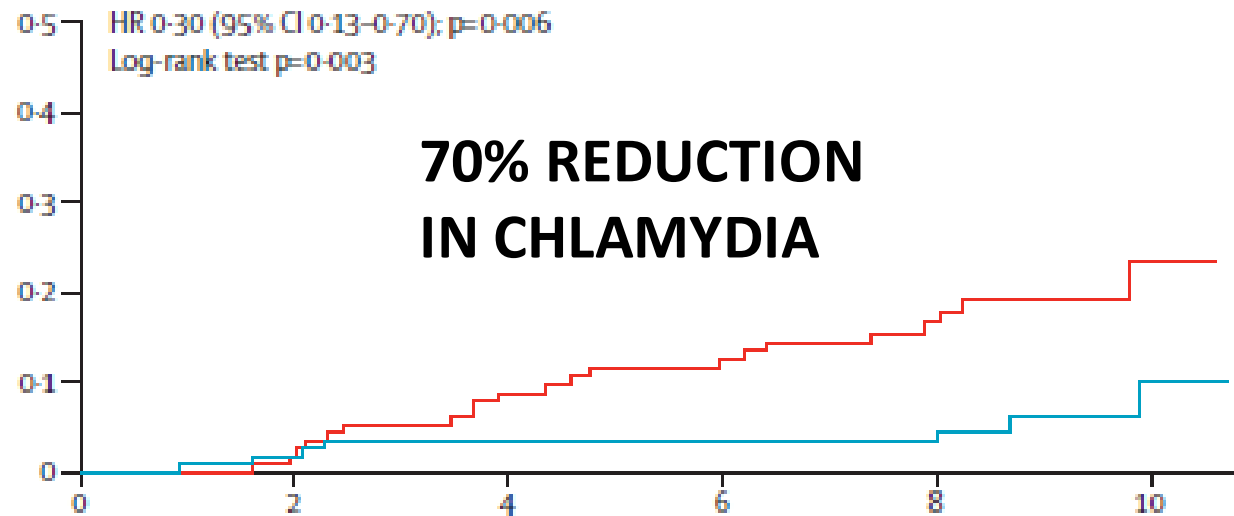
CDC 2020 STI surveillance
<https://www.cdc.gov/std/statistics/2020/default.htm>



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)



Doxy for STI prevention

- Oral antibiotic doxycycline has shown promise to reduce new sexually transmitted infections when taken after sex (post exposure prophylaxis, or “PEP”).
- Studies were done to understand if taking doxy-PEP after sex would 1) decrease the 3 most common bacterial STIs, *and* 2) the impact of intermittent doxy use on antibiotic resistance in STIs and other bacteria.
- **Why Doxycycline?**
 - Generally safe, well tolerated, and inexpensive.
 - Active against chlamydia & syphilis without evidence of resistance.
 - Some gonorrhea have resistance; unknown how much activity is needed for PEP.

Intervention: Open label doxycycline 200mg taken as PEP within 72 hours after condomless sexual contact
Maximum of 200 mg every 24 hours

Inclusion criteria:

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

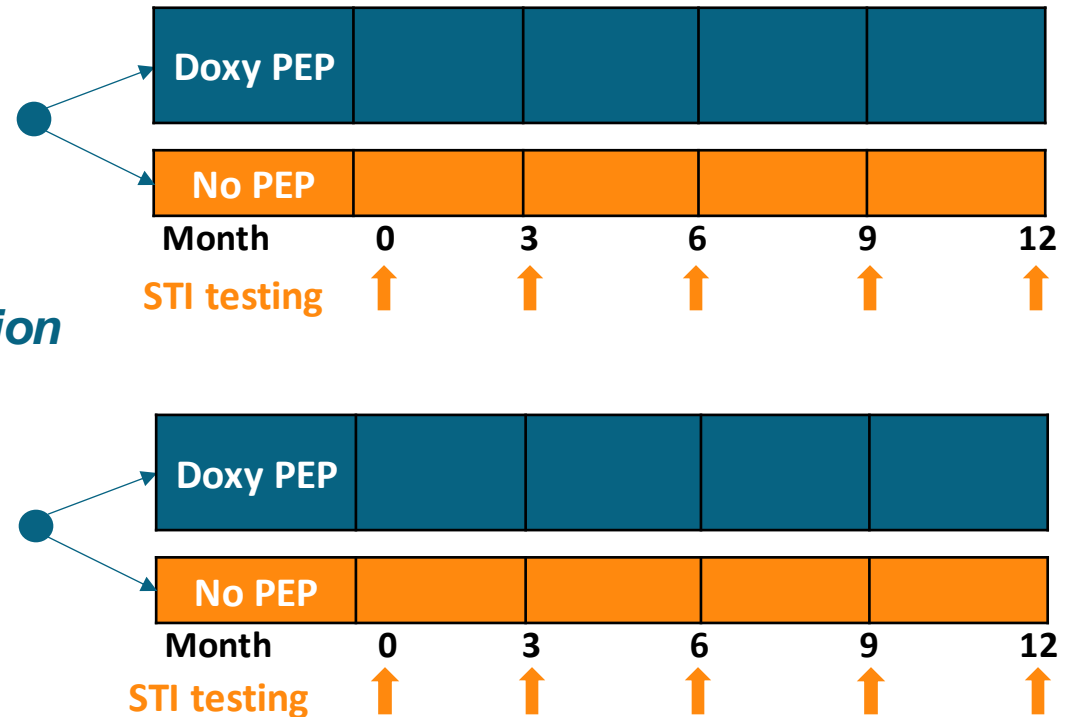
STI Testing: Quarterly 3 site GC/CT testing + RPR, GC culture before treatment

Sites: San Francisco & Seattle HIV & STI clinics

MSM & TGW with HIV
(planned n = 390)

2:1 randomization

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



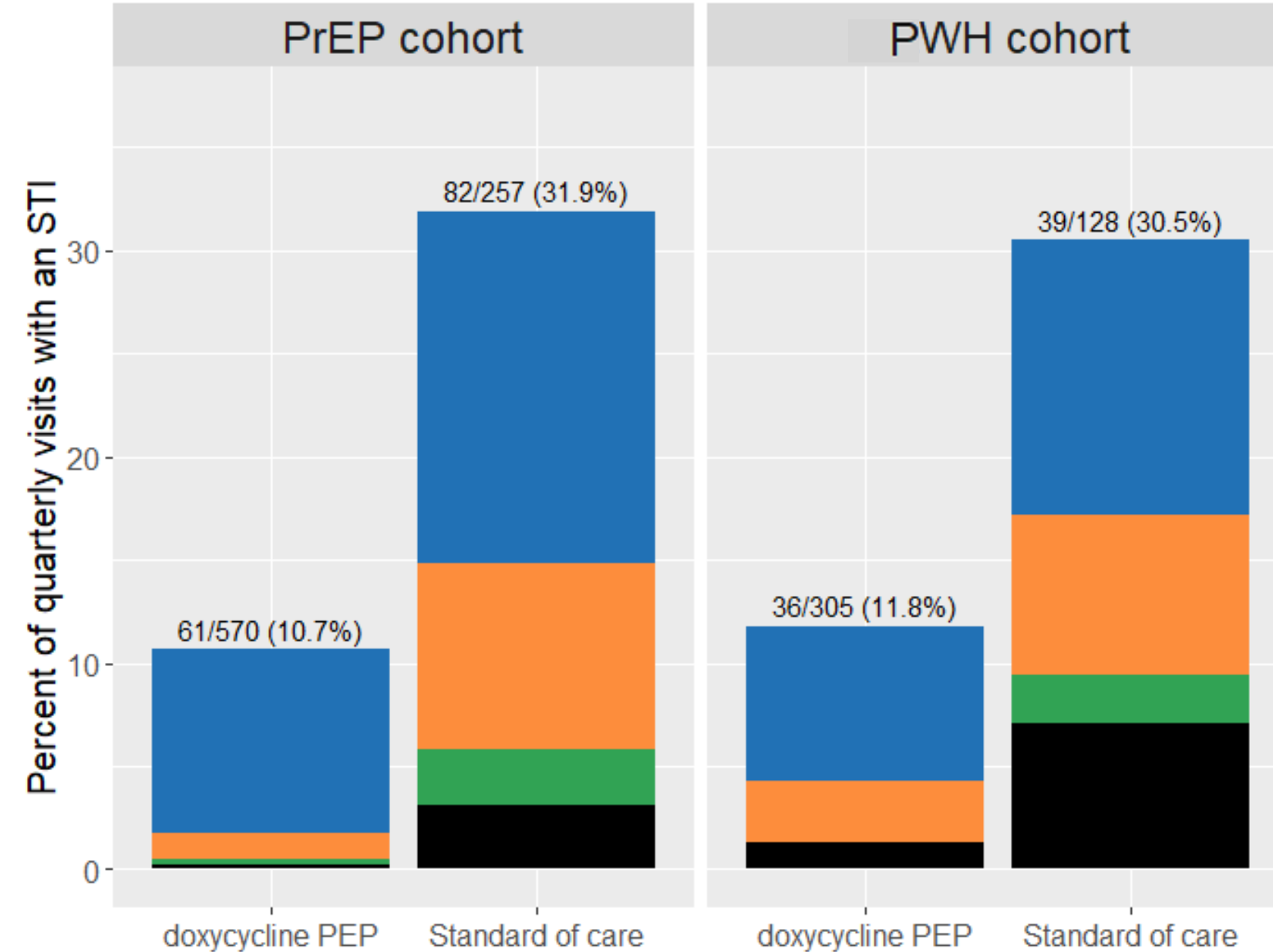
Baseline characteristics

n(%) or median (IQR)

| | PrEP | With HIV | Total |
|--|--------------|-----------------|--------------|
| Participants* (ITT population) | 327 | 174 | 501 |
| Age | 36 (31 - 42) | 43 (36 - 54) | 38 (32 - 47) |
| Race | | | |
| White | 210 (67%) | 111 (66%) | 321 (67%) |
| Black | 14 (5%) | 22 (13%) | 36 (8%) |
| Asian/Pacific Islander | 45 (14%) | 8 (5%) | 53 (11%) |
| Multiple races/other | 44 (14%) | 28 (17%) | 72 (15%) |
| Ethnicity: Hispanic/Latino | 96 (29%) | 55 (32%) | 151 (30%) |
| Gender identity | | | |
| Man | 319 (98%) | 163 (94%) | 482 (96%) |
| Trans woman/gender diverse | 8(2%) | 11 (6%) | 19 (4%) |
| Gender of sexual partners: Male only | 281 (86%) | 153 (88%) | 434 (87%) |
| STI in past 12 months** | | | |
| Gonorrhea | 233 (71%) | 110 (63%) | 343 (69%) |
| Chlamydia | 207 (63%) | 85 (49%) | 292 (58%) |
| Syphilis† | 48 (15%) | 52 (30%) | 100 (20%) |
| Sexual partners in past 3 months | 9 (4 - 17) | 8.5 (3 - 20) | 9 (4 - 17) |
| Substance use in past 3 months | 178 (55%) | 115 (68%) | 293 (59%) |
| Stimulants (methamphetamine, cocaine, crack) | 73 (23%) | 73 (43%) | 146 (30%) |
| Ecstasy, GHB, ketamine | 97 (30%) | 60 (35%) | 157 (32%) |
| Amyl Nitrates (poppers) | 140 (43%) | 84 (49%) | 224 (45%) |

* As of 5/13/22 with at least one follow-up visit **Total may exceed 100% as more than 1 STI possible, †Syphilis: Limited to 1°, 2°, early Latent

Primary Endpoint: STI incidence per quarter

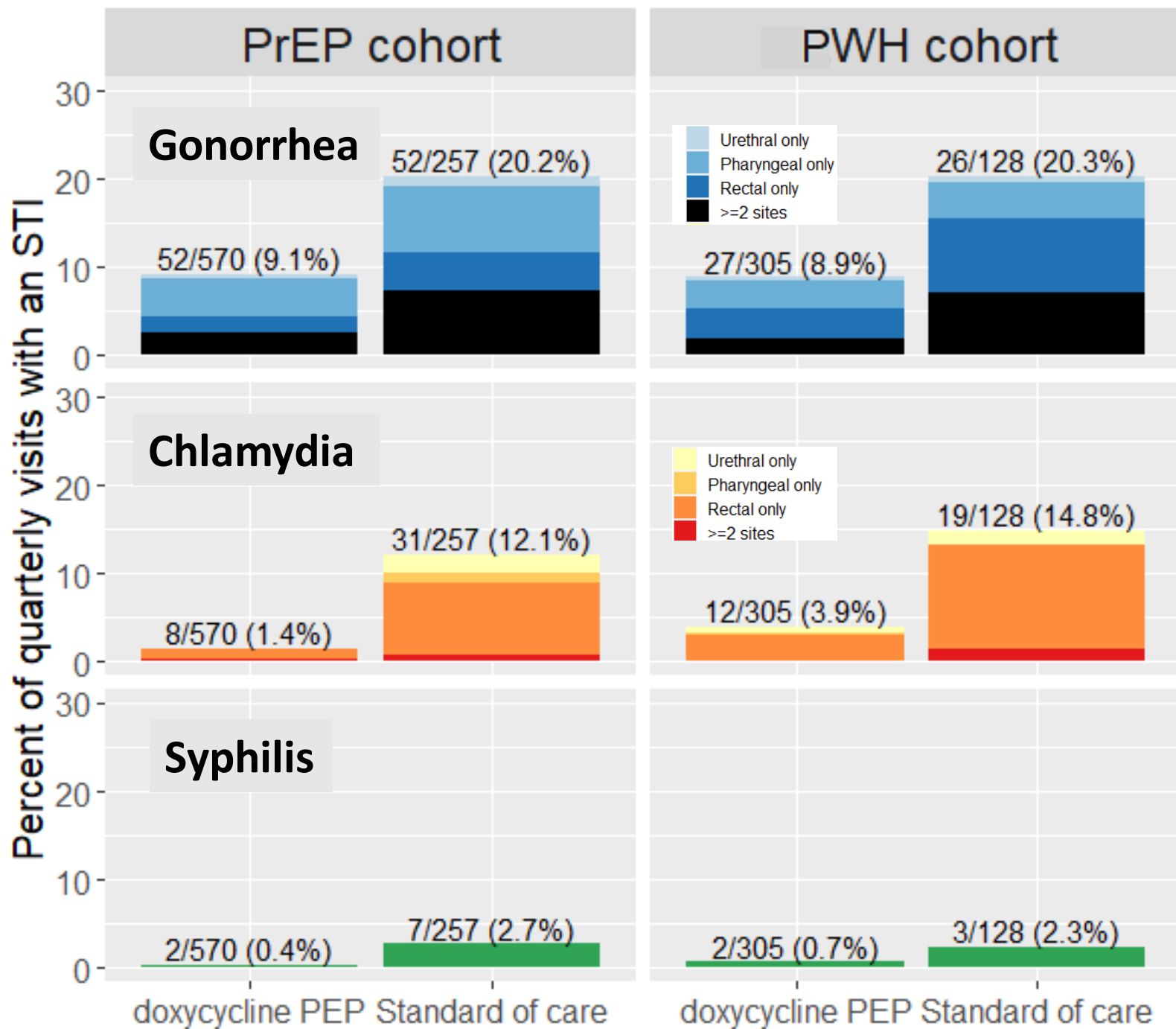


| Risk reduction in STI incidence/quarter (95% CI) | |
|--|----------------------------------|
| PrEP | 66% (54% - 76%) |
| with HIV | 62% (40% - 76%) |
| Total | 65% (54% - 73%) |

all p < 0.0001

DOXYPEP





Individual quarterly STI incidence by study arm & cohort

Risk reduction in each STI per quarter (95% CI)

| | PrEP | PWH |
|-----------------|---|--|
| GC | 55% (35%-68%) <i>p</i> <0.0001 | 57% (29%-74%) <i>p</i> =0.001 |
| CT | 88% (75%-95%) <i>p</i> <0.0001 | 74% (43%-88%) <i>p</i> =0.0007 |
| Syphilis | 87% (41%-97%) <i>p</i> =0.0084 | 77% (-71%, 96%) <i>p</i> =0.095 |

Sexual behavior, Adherence & Antibiotic Use

- **Sexual behavior at enrollment:** Median of 9 sexual partners (IQR 4,17) with 5 sexual acts per month (IQR 1.7, 10.7) and 90.1% of sex as condomless.
- **No significant change in sexual behavior during follow-up in doxy-PEP arm**
- **Adherence to doxy-PEP:**
 - 86% reported doxy-PEP always/often after anal/vaginal sex
 - Median doxyPEP doses: **4.0 per month** (IQR 1.0- 10.0)
 - 25% with ≥ 10 doses/month, based on quarterly interview
- **Ceftriaxone use: 50% less in doxy-PEP arm**
 - Doxy-PEP: 48.4 person-years vs SOC: 103.6 person years

Impact on symptomatic STIs & by anatomic site

| | Doxy-PEP n/1,201 quarters | Standard of care n/533 quarters | RR (95% CI) | p |
|------------------------------|------------------------------|------------------------------------|------------------|--------|
| Gonorrhea | 79 (6.6%) | 78 (14.6%) | 0.45 (0.33–0.60) | <.0001 |
| Symptomatic rectal GC | 6 (0.5%) | 8 (1.5%) | 0.33 (0.11–0.99) | 0.0478 |
| Symptomatic urethral GC | 3 (0.2%) | 15 (2.8%) | 0.09 (0.03–0.31) | 0.0002 |
| Chlamydia | 20 (1.7%) | 50 (9.4%) | 0.18 (0.10–0.31) | <.0001 |
| Symptomatic rectal CT | 0 (0.0%) | 6 (1.1%) | – | – |
| Symptomatic urethral CT | 0 (0.0%) | 6 (1.1%) | – | – |
| Site specific GC + CT | | | | |
| Pharyngeal (GC or CT) | 55 (4.6%) | 52 (9.8%) | 0.47 (0.33–0.67) | <.0001 |
| Rectal (GC or CT) | 54 (4.5%) | 77 (14.4%) | 0.31 (0.21–0.46) | <.0001 |
| Urethral (GC or CT) | 11 (0.9%) | 23 (4.3%) | 0.21 (0.09–0.49) | 0.0003 |
| Syphilis | 4 (0.3%) | 10 (1.9%) | 0.18 (0.06–0.56) | 0.0031 |

- Doxy-PEP ↓ the incidence of STIs associated with greater morbidity: syphilis and symptomatic rectal & urethral GC/CT
- More than 80% of rectal GC & CT infections were asymptomatic in both arms—doxy-PEP also significantly reduced incidence of asymptomatic infections.

Doxy-PEP AMR Data

GC: Resistance testing through CDC SURRG & ARLN

Chlamydia: culture w/ phenotypic susceptibility

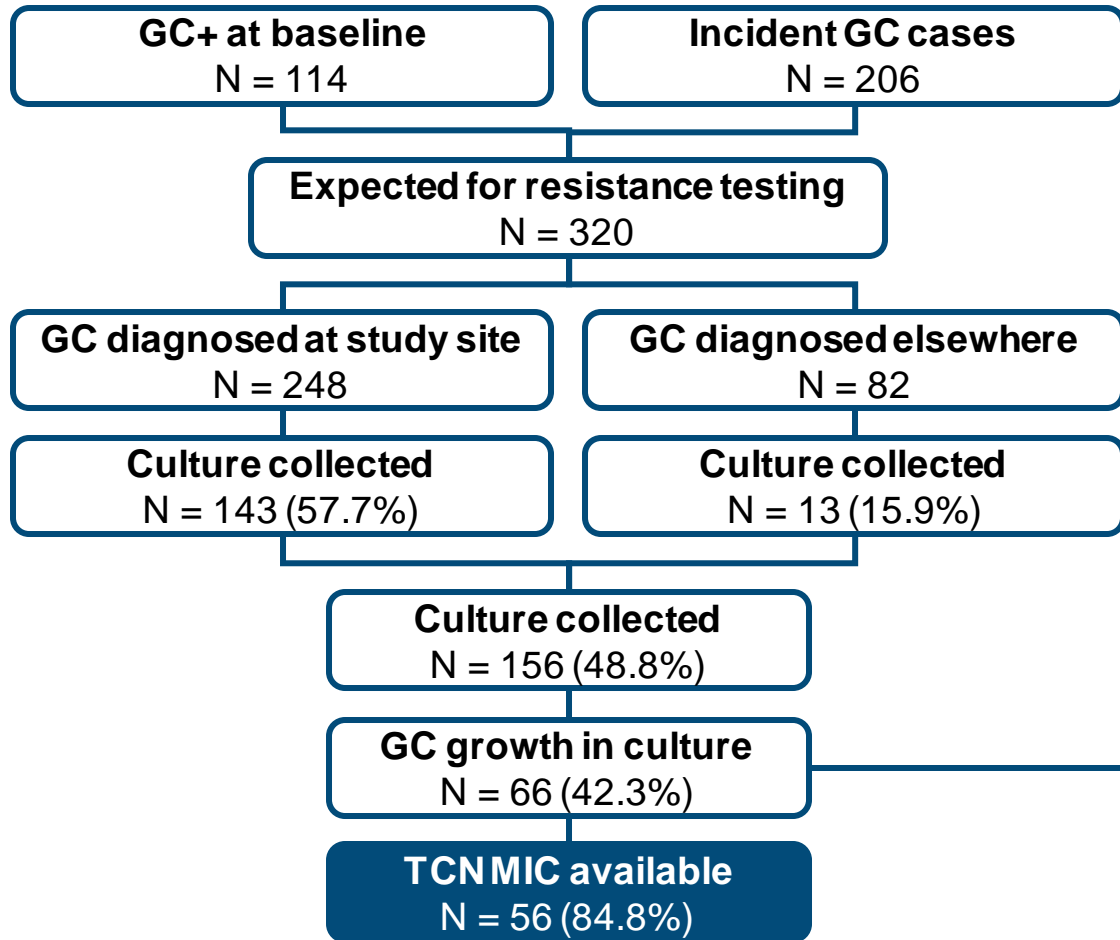
Syphilis- molecular testing (exploratory)

M. gen: Asymptomatic prevalence & symptomatic incidence, urine/rectal, & TCN-R

***S. aureus* & commensal *Neisseria*:**
tetracycline class resistance

Gut microbiome: change in flora, diversity & tetracycline resistance genes

N. gonorrhoeae resistance data limited by rates of sample collection (~50%) before treatment and culture growth (~40%)

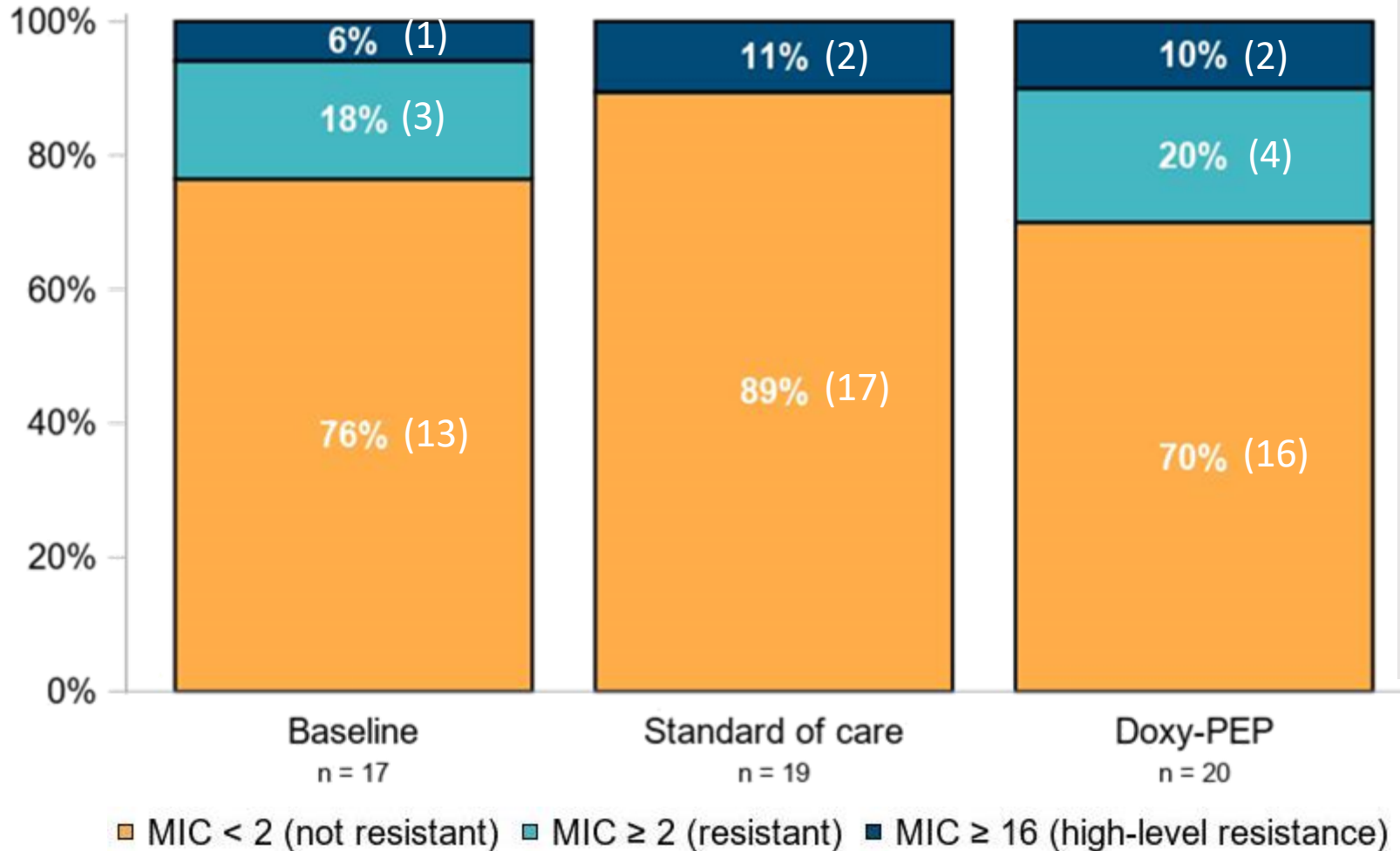


| Site of infection | Sample collected | GC growth | % |
|-------------------|------------------|-----------|-----|
| Pharyngeal | 110 | 26 | 24% |
| Rectal | 83 | 38 | 46% |
| Urethral | 20 | 16 | 80% |

Participants were evaluated for STI endpoints every 3 months at study visits and were asked to report STI testing conducted outside of study clinic visits.



Tetracycline resistance (TCN-R) in incident GC with culture data

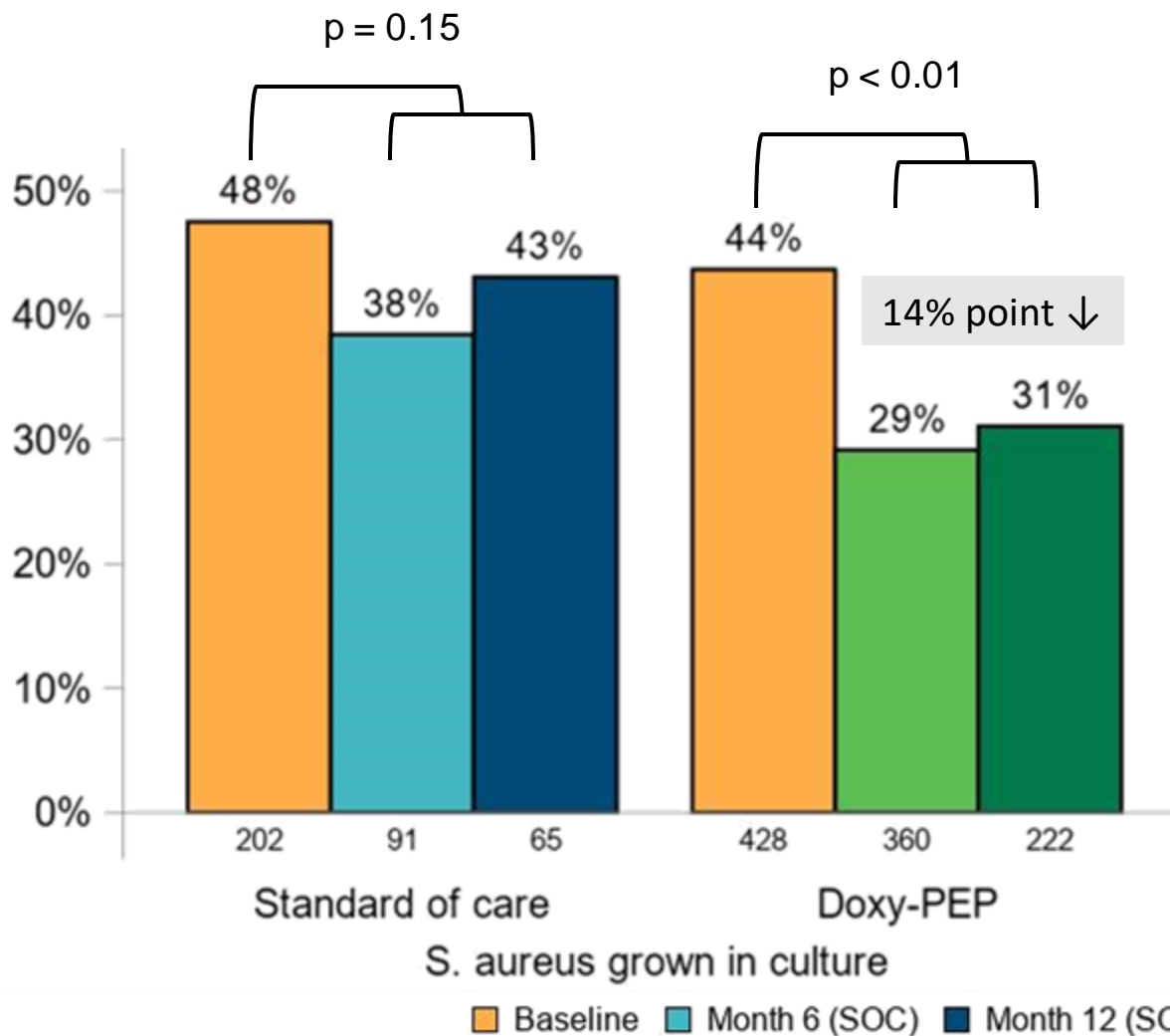


- TCN-R similar in incident GC at baseline and on doxy-PEP
- Increased TCN-R in doxy-PEP vs. standard of care suggests doxy-PEP may be less protective against GC strains with existing TCN-R
- Limited by low number of GC samples with MIC results (56/320)

DOXYPEP



S. Aureus colonization: 14% absolute decrease in doxy-PEP arm



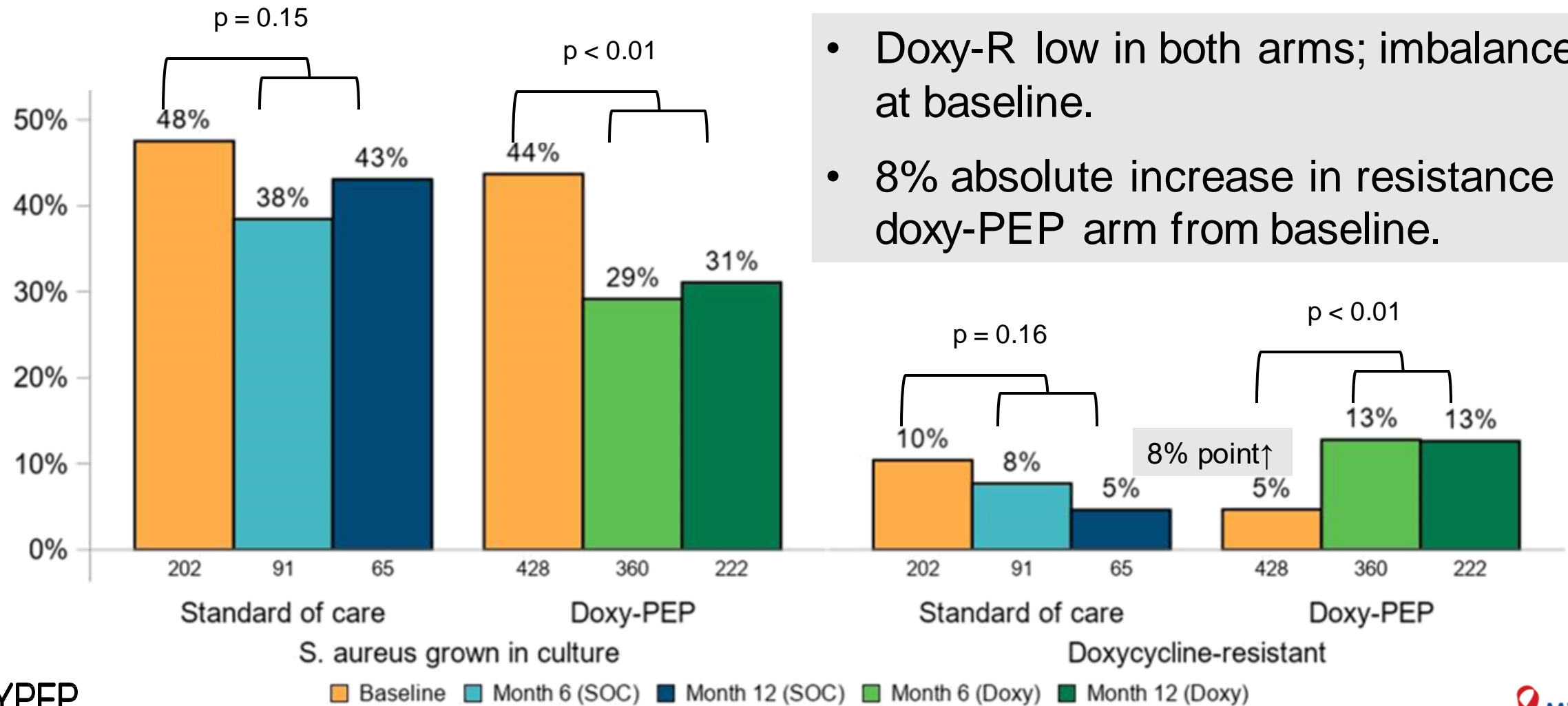
- *S. aureus* colonization is associated with subsequent clinical *Staph* infections, such as surgical infections and bacteremia.²
- DoxyPEP use associated with 14% absolute decrease in *S. aureus* colonization.

² Oestergard *AIM* 2016; Jacobsson *Scand JID* 2008; Septimus *CID* 2016; Bode *NEJM* 2010

DOXYPEP

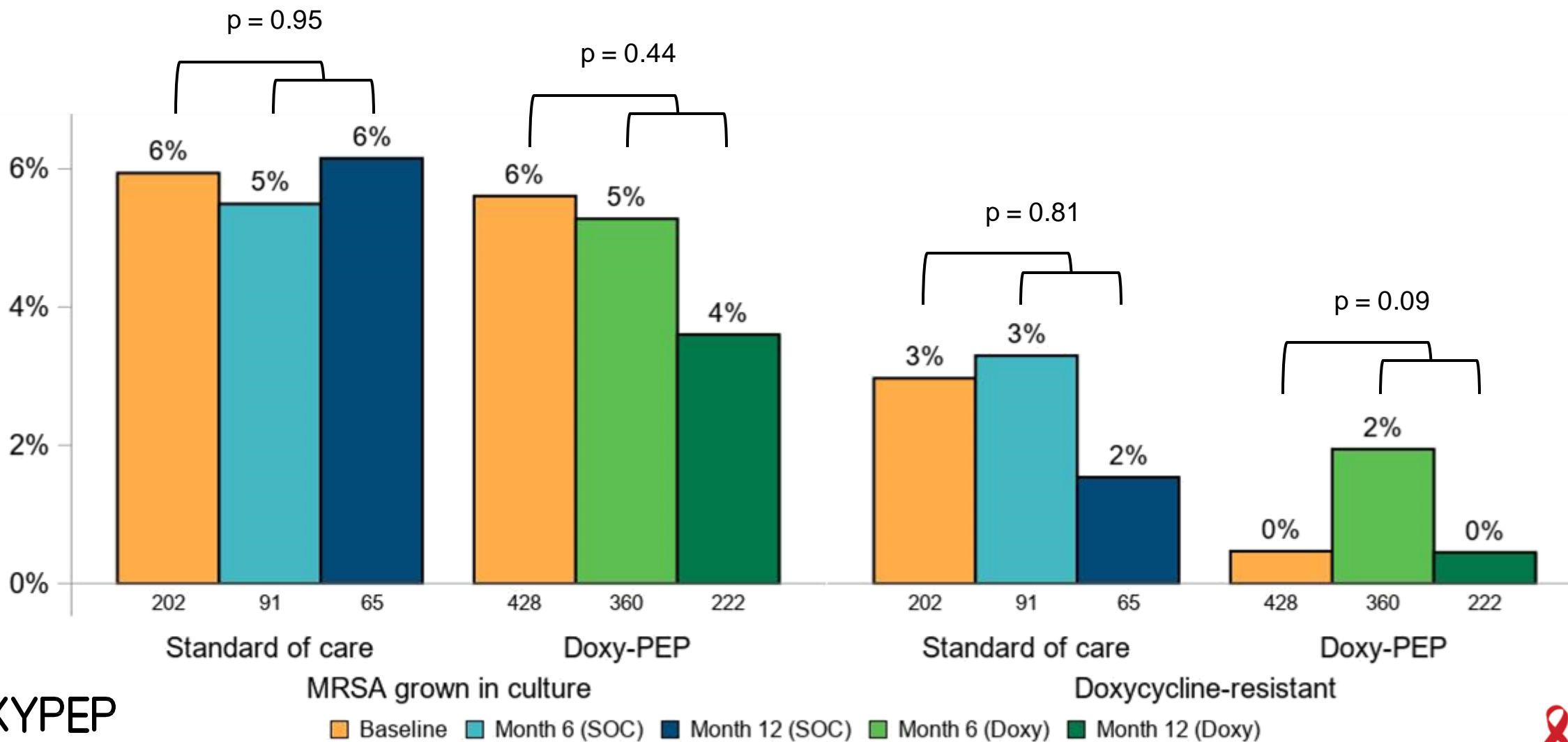


S. aureus: 8% absolute increase in doxycycline resistance (doxy-R) in doxy-PEP arm



- Doxy-R low in both arms; imbalance at baseline.
- 8% absolute increase in resistance in doxy-PEP arm from baseline.

MRSA: Low rate of doxycycline resistance & no change with doxy-PEP



Qualitative study: key findings

44 participants from doxy-PEP arm interviewed

- Structured 1:1 interviews, oversampled racial and ethnic minorities
 - 17% Black, 30% Hispanic; 45% With HIV

Overarching themes about doxy-PEP

- Lived experience of DOXY-PEP generally expressed as giving more sexual pleasure and “peace of mind.”
- Did not believe it changed their sexual behavior (just their mindset about it).
- Viewed as being proactive, responsible about one’s health & health of community.
“It just means that I’m taking care of myself, I’m staying healthy, that I care, that I don’t want to be transmitting STDs.”
- Aware of risk of AMR, but not a barrier to use.

Documented benefits

- Doxy PEP reduced STIs by >60% in MSM & TGW with recent STIs, regardless of HIV status
 - High STI incidence (30% per quarter) in SOC arm
- Prevented *each* bacterial STI, including GC
- Need to treat 5 people to prevent a quarter with an STI
- Safe & well tolerated
- High adherence and acceptability
- Reduced exposure to ceftriaxone by 50%

Potential risks

- Impact on bystander bacteria like Staph aureus and on gut microbiome
- Impact on doxy susceptibility for chlamydia, gonorrhea, syphilis and *Mycoplasma genitalium*
- Possible increase in higher risk sexual behavior (not observed)

DOXYVAC Study Design

Combined Prevention of STIs in MSM using oral PrEP with TDF/FTC

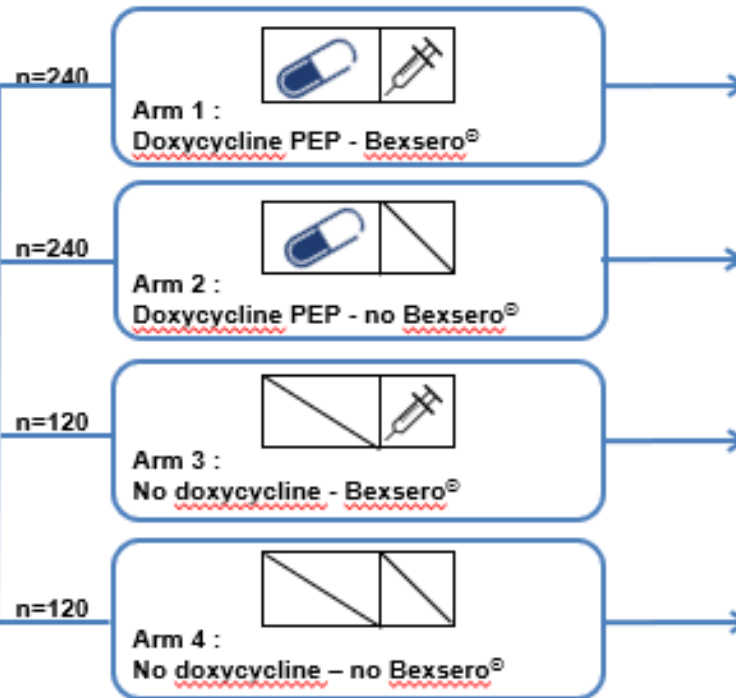
OPEN-LABEL FACTORIAL RANDOMIZATION

- Intervention 1
Doxycycline PEP / no doxycycline (2:1)
- Intervention 2
Bexsero[®] vaccine / no vaccine (1:1)

Analysis

Inclusion Criteria n=720

- MSM included in ANRS PREVENIR
- PrEP ≥ 6 months
- HIV negative
- No STI symptoms
- Bacterial STI in prior 12 months



Co-primary endpoints

- **Doxy:** 1st episode CT/syphilis
- **Bexsero:** 1st episode of GC ≥1 month after 2nd vaccine

Bexsero = Meningococcal Group B Vaccine

Period of enrolment : 24 months

12 to 24 months follow-up by participant :

End of the study :
12 months after the last inclusion

DOXYVAC Study Design

Combined Prevention of STIs in MSM using oral PrEP with TDF/FTC

- Single interim analysis 9/2022-> DSMB recommended stopping trial for efficacy
- Data from 1/19/2021- 7/15/2022
- 546 MSM randomized, 502 analyzed
- Median follow-up 9 months
- Median age 39
- Median 10 sexual partners in past 3 months
- No interaction between the 2 interventions for the 1^o endpoints

DOXYVAC Study Design

Combined Prevention of STIs in MSM using oral PrEP with TDF/FTC

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

- Doxy-PEP significantly ↓incidence of CT & syphilis, as well as GC

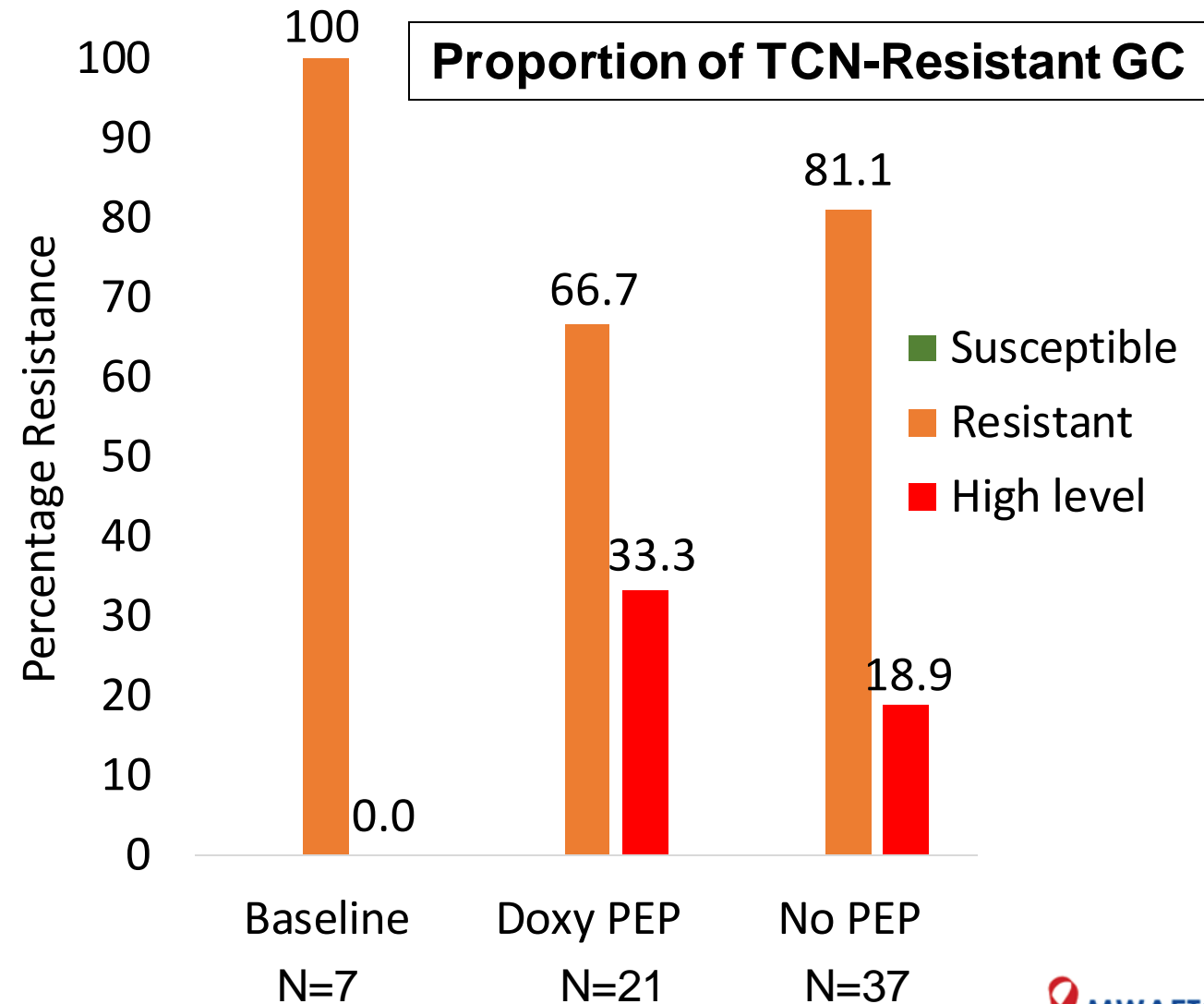
DoxyVac: TCN Resistance for GC and CT

GC:

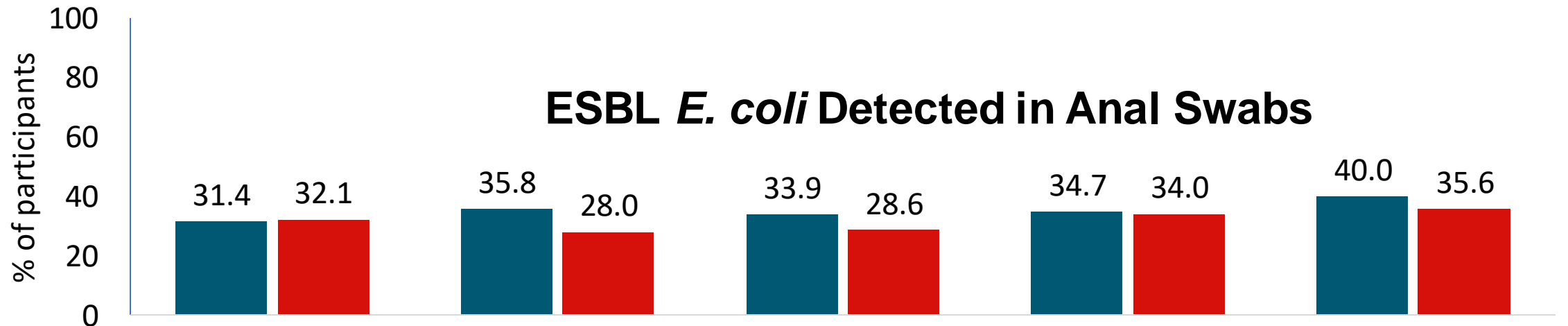
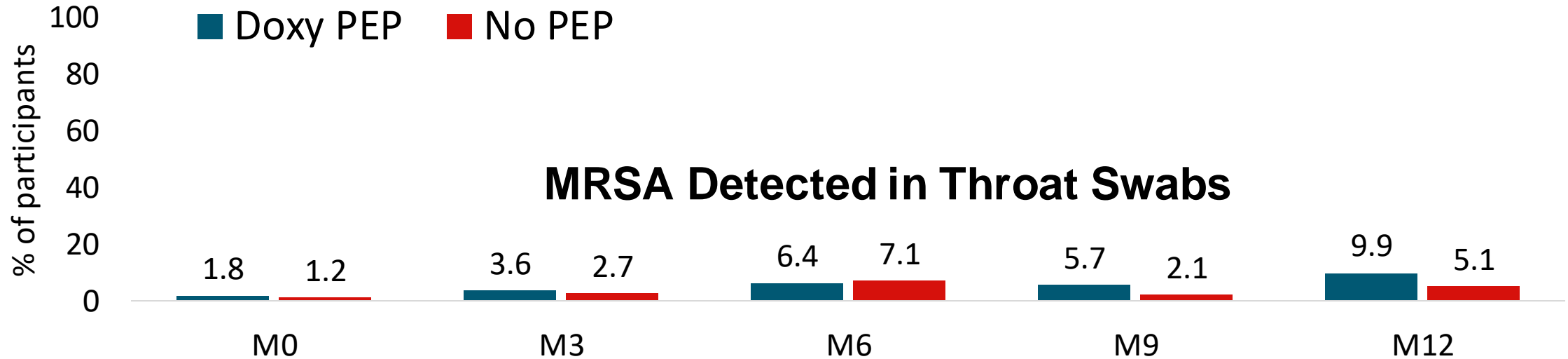
- 65 cultures available for resistance testing (15% of PCR positive samples)
- Tetracycline MICs determined by Etest
- Resistance using EUCAST 2023 breakpoints
 - Resistance: MIC > 0.5 mg/L
 - High level resistance: MIC > 8 mg/L

CT:

- 4/23 strains tested for TCN-R in culture: no resistance (but none from PEP arm)
- 53/65 PCR+ swabs with 16S rRNA sequenced: no TCN-R mutation (only 3 from PEP arm)



ANRS 174 Doxyvac Microbiome Analysis

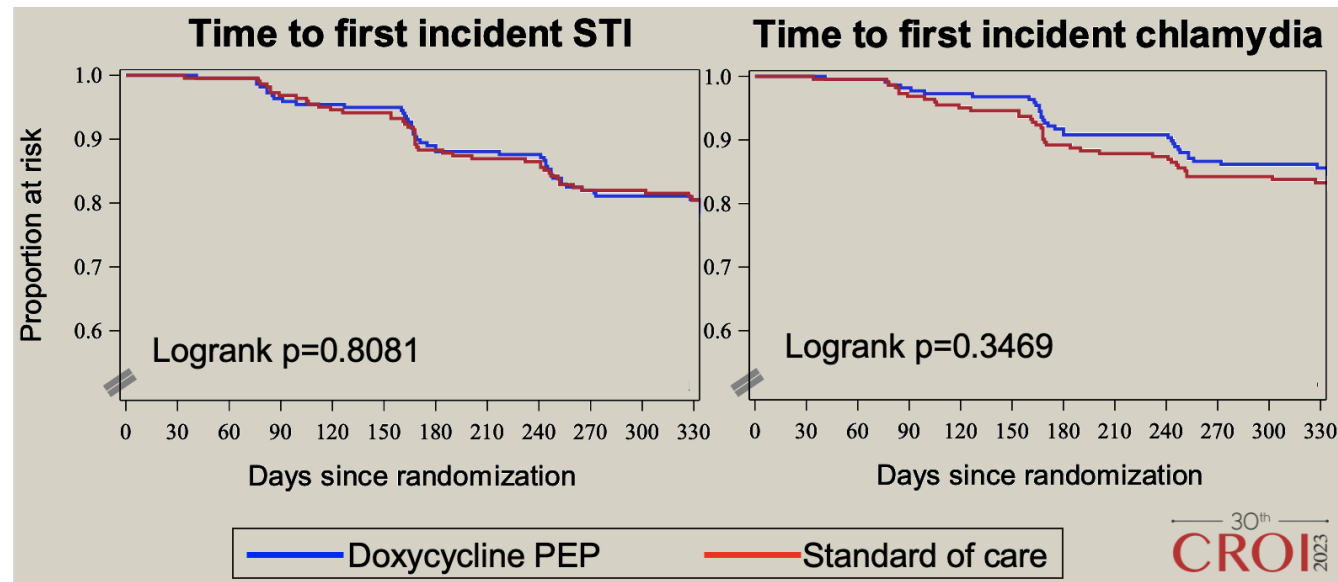


| | M0 | M3 | M6 | M9 | M12 |
|-----------------|-----|-----|-----|-----|-----|
| Doxy PEP | 331 | 304 | 251 | 193 | 121 |
| No PEP | 168 | 150 | 126 | 94 | 59 |



Doxy-PEP in cisgender women: dPEP KENYA Trial

| Analysis | Endpoint | Total | PEP (N=224) | SOC (N=225) | RR | 95% CI | P-value |
|--------------------------|------------|-------|-------------|-------------|------|-----------|---------|
| Intention to Treat | All STIs | 109 | 50 | 59 | 0.88 | 0.60-1.29 | 0.51 |
| | Chlamydia | 85 | 35 | 50 | 0.73 | 0.47-1.13 | 0.16 |
| | Gonorrhoea | 31 | 19 | 12 | 1.64 | 0.78-3.47 | 0.19 |
| Censoring Pregnancy Time | All STIs | 105 | 48 | 57 | 0.91 | 0.62-1.35 | 0.65 |
| | Chlamydia | 82 | 33 | 49 | 0.73 | 0.46-1.15 | 0.18 |



Kenya dPEP trial in cis-gender women: Interpretation

Several possible explanations for the null results to consider:

Anatomy: endocervical tissue may differ from urethral, rectal, and pharyngeal tissues.

Exposures: type and frequency of STI exposures may differ in high prevalence setting and fewer average number of partners

Resistance: to date, no known cases of resistant *C. trachomatis* globally; however, high rates of resistant *N. gonorrhoeae*.

Adherence: our trial was designed to maximize adherence and self-reported adherence was high but imperfect.

- recruitment
- open-label design
- adherence support

Summary of doxy-PEP for STI prevention: What we don't know

| Question | Educated (?) guess | Time horizon for answer to question | Notes |
|--|---|-------------------------------------|--|
| Will GC become R to doxy? | Yes, very likely | Years | TetR and TetHLR has increased in U.S. from 1987-2022 and higher in MSM |
| Will doxy induce resistance in commensals/concurrent pathogens? | <i>S. aureus</i> – definite maybe | Years | Need to set up systems to monitor; collaborate with other areas of CDC to monitor non-STI bugs |
| | <i>S. pneumo</i> – definite maybe | | |
| | <i>C. trachomatis</i> – probably not | | |
| | Syphilis – Theoretically but not likely | | |
| | <i>M. gent</i> – possible? | | |
| Will doxy use alter microbiome? | Yes, very likely | Years | MSM have altered microbiome at baseline (lubricant use, anal sex, heavy antimicrobial exposure?) |
| Will alterations in microbiome lead to adverse health outcomes (including in offspring)? | Possibly | Decade or so | |



Summary of doxy-PEP for STI prevention: What we don't know

| Question | Educated (?) guess | Time horizon for answer to question | Notes |
|--|--------------------|---|--|
| Will DoxyPEP induce resistance to last resort tetracyclines (tigecycline, eravacycline, sarecycline, and omadacycline) | Not clear | ?several years | |
| Can DoxyPEP reduce STIs on a population level? | Possibly | ?several years | MSM? General population? |
| Can DoxyPEP be an antibiotic-sparing approach? | Possibly | Near future - modeling | DoxyPEP investigators cite 50% reduction in cephalosporin use |
| Will DoxyPEP be implemented in an equitable fashion? | Probably not | Nearer term - <1 year post-implementation | Need to address proactively with implementation and set up measures to monitor |



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Doxy-PEP: Implementation Update

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CURRENT STATE OF IMPLEMENTATION

- Guidelines from San Francisco, Santa Clara, Alameda, CA State
- Pending guidelines from Seattle & King County
- No CDC guidelines yet
- People already using DoxyPEP
 - Annual PRIDE survey, MSM, 2022 (N=268): 11% (N=25) reported using Doxy-PEP or PrEP

Focus here on **who** should be offered doxy-PEP

San Francisco



POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH



Health Update

**Doxycycline Post-Exposure Prophylaxis
Reduces Incidence of Sexually Transmitted
Infections**

October 20, 2022

- 1. Recommend doxy-PEP** to cis men and trans women who: 1) have had a bacterial STI in the past year and 2) report condomless anal or sexual contact with ≥ 1 cis male or trans female partner in the past year
- 2. Offer doxy-PEP using shared decision-making** to cis men, trans men, trans women who report having multiple cis male or trans female sex partners in the prior year, even if they have not been diagnosed with an STI
- 3. Insufficient evidence to recommend doxy-PEP for individuals who report receptive vaginal sex**

Alameda



ALAMEDA COUNTY HEALTH CARE SERVICES AGENCY
PUBLIC HEALTH DEPARTMENT

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1100 San Leandro Blvd.
San Leandro, CA 94577

Colleen Chawla, Director
Kimi Watkins-Tartt, Director

Nicholas J. Moss, MD, MPH
County Health Officer
(510) 267-8000

February 3, 2023

1. Healthcare providers **should counsel** MSM and trans women about doxy-PEP as part of comprehensive sexual health counseling
2. MSM and trans women who are interested in doxy-PEP and who have had a recent STI, are taking PrEP, have >1 condomless sex partner in the last year or who are PWH **should be offered** doxy-PEP

(emphasis added)



March 20, 2023

1. **Recommend doxy-PEP** for cis men and trans women who are sexually active with cis male or trans female partners, have had condomless sex with >1 partner and have had a bacterial STI in the past year
2. **Offer doxy-PEP after shared decision-making for**
 1. Cis men and trans women who have had condomless sex with >1 partner in past year
 2. Trans MSM who have had more than one cis male or trans female partner in past year
3. **Can consider doxy-PEP on a case-by-case basis after shared decision making for** cis men who have had a bacterial STI
4. ...(data insufficient to recommend for cisgender women)

April 28, 2023

- 1. Recommend doxy-PEP** to MSM or trans women who have had ≥ 1 bacterial STI in past 12 months
- 2. Offer doxy-PEP using shared decision** making to **all non-pregnant individuals** at increased risk for bacterial STIs and to those requesting doxy-PEP, even if these individuals have not been previously diagnosed with an STI or have not disclosed their risk status

DRAFT Seattle & King County Guidelines – Part 1

- 1) Medical providers should **inform** cis-MSM and trans women who have sex with men with a history of bacterial STI in the prior year about the doxyPEP, its efficacy, the potential benefits and risks of the intervention, and the alternative options available to prevent, diagnose, and treat STIs.
- 2) The decision to prescribe doxy-PEP should result from a **shared decision-making process** between the medical provider and the patient. Providers should give particular consideration to prescribing doxyPEP to patients with a history of syphilis or a history of multiple STIs in the prior year and may consider prescribing doxy-PEP on an episodic basis when patients anticipate periods when their risk of STI may be higher (e.g., group sex events).

DRAFT Seattle & King County Guidelines – Part 2

- 1) Not recommended for cisgender women. A recent study found no effect of doxy-PEP in cisgender women in Kenya.
- 2) Unknown benefits and risks for transgender men (and other gender diverse patients assigned female sex at birth) who have anal sex with men.

Summary

- No national (CDC) guidelines yet
- Heterogeneity in
 - strength of recommendation for MSM and trans women (“recommend” “offer” “inform”)
 - recommendations for cis women (mostly not recommended)
 - recommendation for trans MSM
- Emphasis on shared decision-making

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