

Doxycycline Post Exposure Prophylaxis (Doxy PEP)

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Southeast AETC

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AETC Program National Centers and HIV Curriculum

- **National Coordinating Resource Center** – serves as the central web –based repository for AETC Program training and capacity building resources; its website includes a free virtual library with training and technical assistance materials, a program directory, and a calendar of trainings and other events. Learn more: <https://aidsetc.org/>
- **National Clinician Consultation Center** – provides free, peer-to-peer, expert advice for health professionals on HIV prevention, care, and treatment and related topics. Learn more: <https://nccc/ucsf.edu>
- **National HIV Curriculum** – provides ongoing, up –to-date HIV training and information for health professionals through a free, web –based curriculum; also provides free CME credits, CNE contact hours, CE contact hours, and maintenance of certification credits. Learn more: www.hiv.uw.edu

Learning Objectives

- Define Doxy PEP
- Discuss literature regarding efficacy and safety of Doxy PEP
- Recommend appropriate therapy and monitoring for patients receiving Doxy PEP
- Describe the potential impacts on antimicrobial resistance as it relates to Doxy PEP

Background Information

Doxy PEP

- What is Doxy PEP?
 - The use of doxycycline orally after a sexual exposure to prevent bacterial STIs
 - Used within 72 hours after condomless sex
 - Ideally within 24 hours, as soon as possible
- STI rates, including gonorrhea, chlamydia, and syphilis, are disproportionately high in MSM
- Doxy PEP is a potential tool to help reduce the incidence of bacterial STIs

Doxycycline

Tetracycline antibiotic	Broad spectrum including coverage for <i>Chlamydia trachomatis</i> (chlamydia), <i>Treponema pallidum</i> (syphilis) and <i>Neisseria gonorrhoeae</i> (gonorrhea)
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Mechanism of Action	Inhibits bacterial protein synthesis
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Dosage Form for PEP	Either doxycycline hyclate delayed release 200 mg (1 tab) OR doxycycline hyclate or monohydrate immediate release 100 mg (2 tabs/caps taken simultaneously) can be used
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Doxycycline for Treatment of STIs

According to current CDC STI guidelines:

Syphilis and chlamydia can be treated with doxycycline, however it is not recommended to treat gonorrhea with doxycycline due to the frequency of resistance

Broad spectrum activity

- Great coverage (1st line) for chlamydia
- Covers syphilis (alternative for treatment for patients with PCN allergy)

Counseling Points

Adverse effects:

- increases sun sensitivity
- take with a full glass of water and remain upright for 30 minutes after taking doxycycline to reduce the risk of pill esophagitis
- rare risk of benign intracranial hypertension
- GI upset (nausea, diarrhea and abdominal discomfort)

Contraindications: doxycycline allergy, or use of systemic retinoids or high-dose vitamin A

Doxycycline is not recommended in pregnant women



Discuss literature regarding efficacy
and safety of Doxy PEP

Populations Evaluated

- MSM and TGW- 3 studies
- Cisgender women- 1 study
- Mucosal pharmacology – 1 study

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

*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

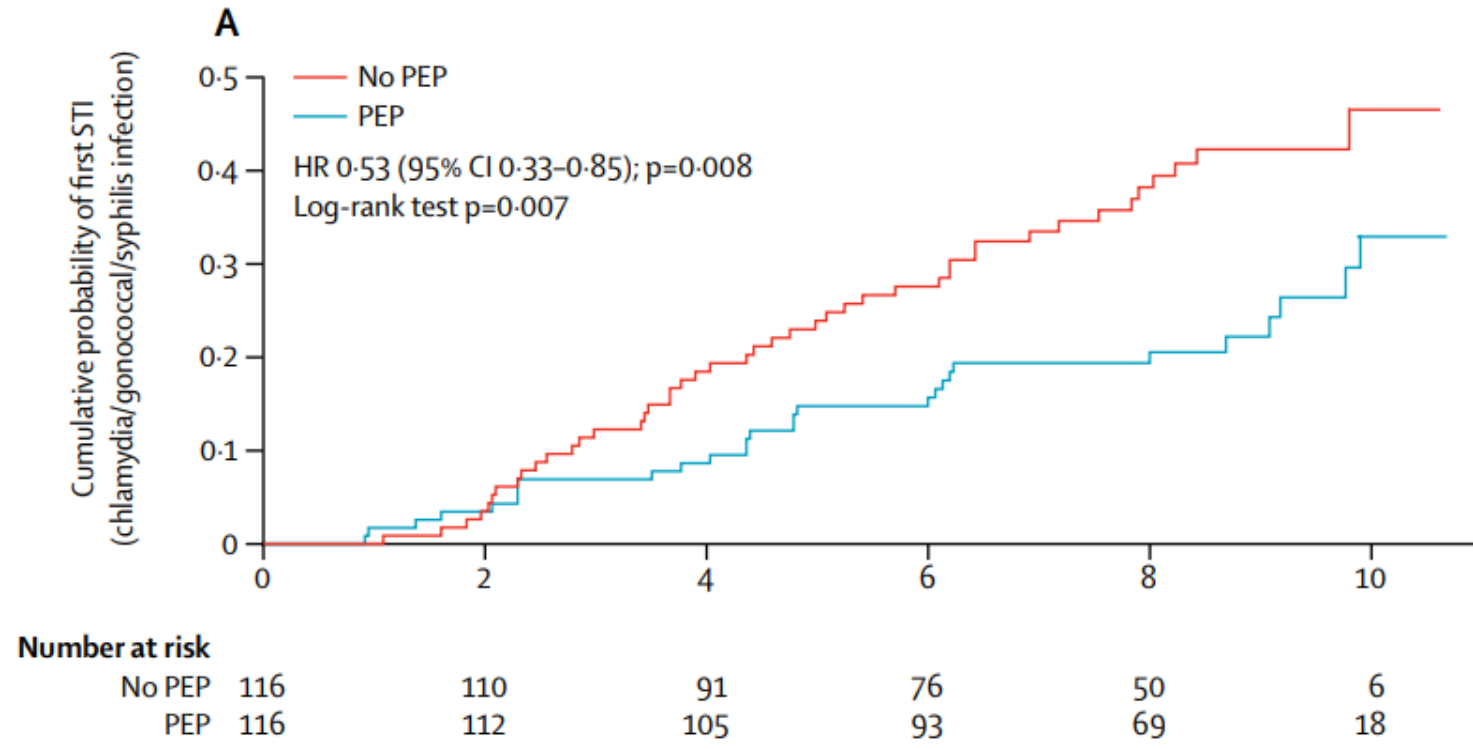
Summary

Background Increased rates of sexually transmitted infections (STIs) have been reported among men who have sex with men. We aimed to assess whether post-exposure prophylaxis (PEP) with doxycycline could reduce the incidence of STIs.

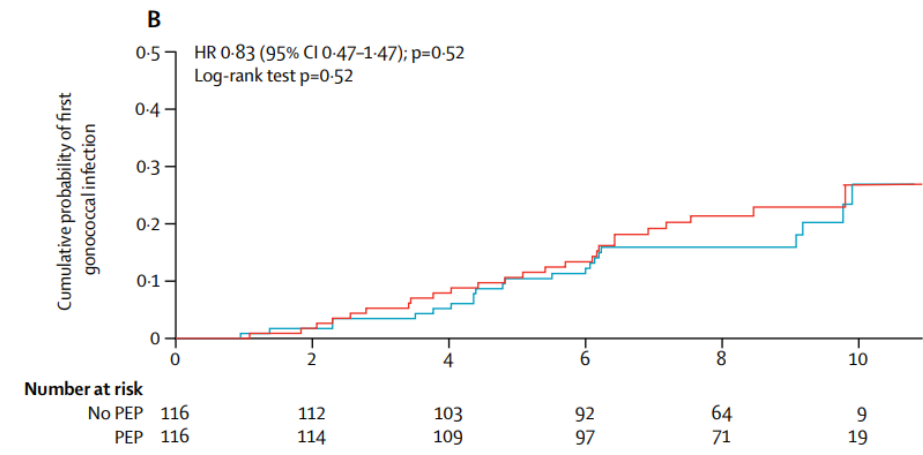
- In July, 2015, the ANRS IPERGAY protocol was amended to implement the study of doxycycline PEP for STIs among French sites only
- Participants in PEP group were instructed to take two oral 100 mg pills of doxycycline within 24 h after sex and no later than 72 h



Doxy PEP Reduced the Cumulative Probability of STIs



■ Did **not** show difference in incidence of gonorrhea



Results and Conclusions From IPERGAY Substudy

Safety Endpoints

- 8 participants discontinued due to drug related gastrointestinal adverse events
- Frequency of SAEs or of grade 3 or 4 AEs did not differ significantly between the study groups
- Median number of pills used per participant in PEP group was 6.8 per month (IQR 2.8–14.5)

Intermittent doxycycline PEP was able to reduce occurrence of initial episode of a bacterial STI in MSM at high risk for STIs

- 70% and 63% reduction in chlamydia and syphilis, respectively
- No prevention efficacy for gonorrhea observed
- However, study conducted in France where doxy R gonorrhea is common



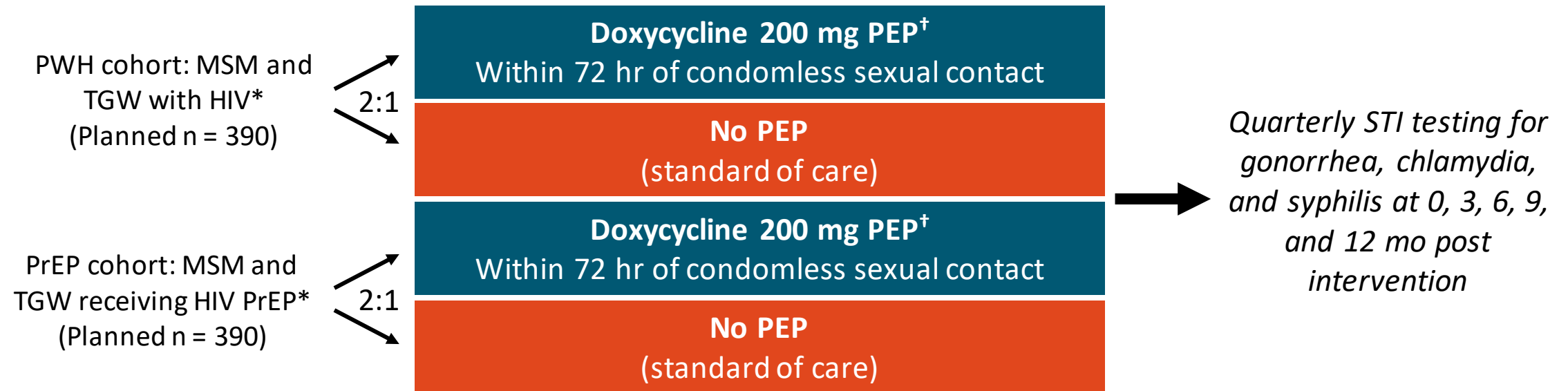
ORIGINAL ARTICLE

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

- Open-label, randomized study conducted at HIV and STI clinics in San Francisco and Seattle
- MSM and TGW taking preexposure prophylaxis (PrEP) or living with HIV infection and who had had gonorrhea, chlamydia, or syphilis in the past year
- Randomly assigned in a 2:1 ratio to take 200 mg of doxycycline w/in 72 hrs after condomless sex or receive standard care
- STI testing was performed quarterly. The **primary end point** was the incidence of at least one STI per follow-up quarter



DoxyPEP: Study Design



*All participants were assigned male sex at birth, had ≥ 1 STI in past 12 mo, and had condomless sex with ≥ 1 partner in past 12 mo.

[†]Maximum dose of 200 mg/24 hr.

- **Primary endpoint:** ≥ 1 incident STI (gonorrhea, chlamydia, or syphilis) during quarterly STI test
- **5/13/2022:** Enrollment stopped early per DSMB after interim analysis showed significant effectiveness in both cohorts

Doxy PEP

N= 501

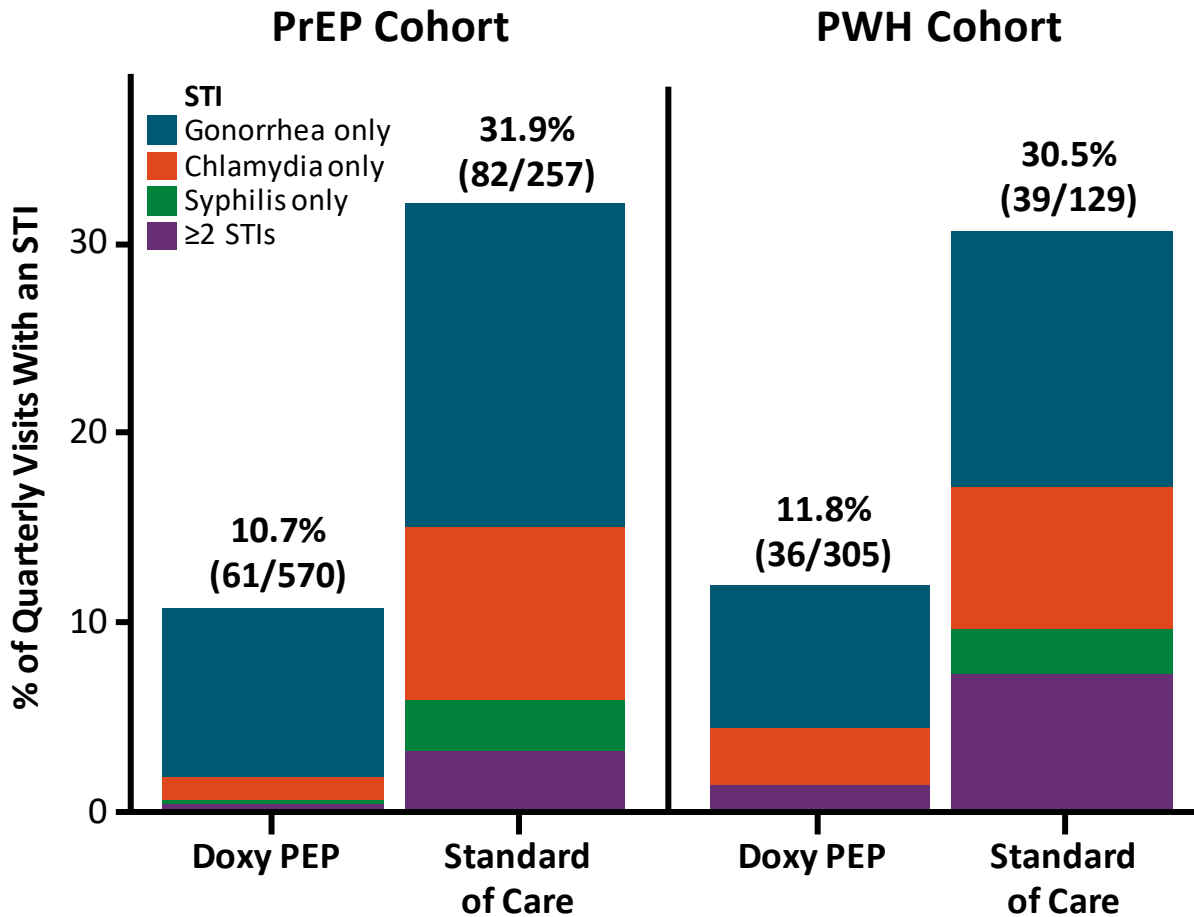
- 327 in the PrEP cohort and 174 in the PLWH cohort
- Trial stopped early (planned to enroll 390 in each cohort)

In the PrEP cohort STI was diagnosed in:

- 61 of 570 quarterly visits (10.7%) in the doxycycline group
- 82 of 257 quarterly visits (31.9%) in the standard-care group
- Absolute difference of -21.2 percentage points
- Relative risk of 0.34 (95% confidence interval [CI], 0.24 to 0.46; P<0.001)



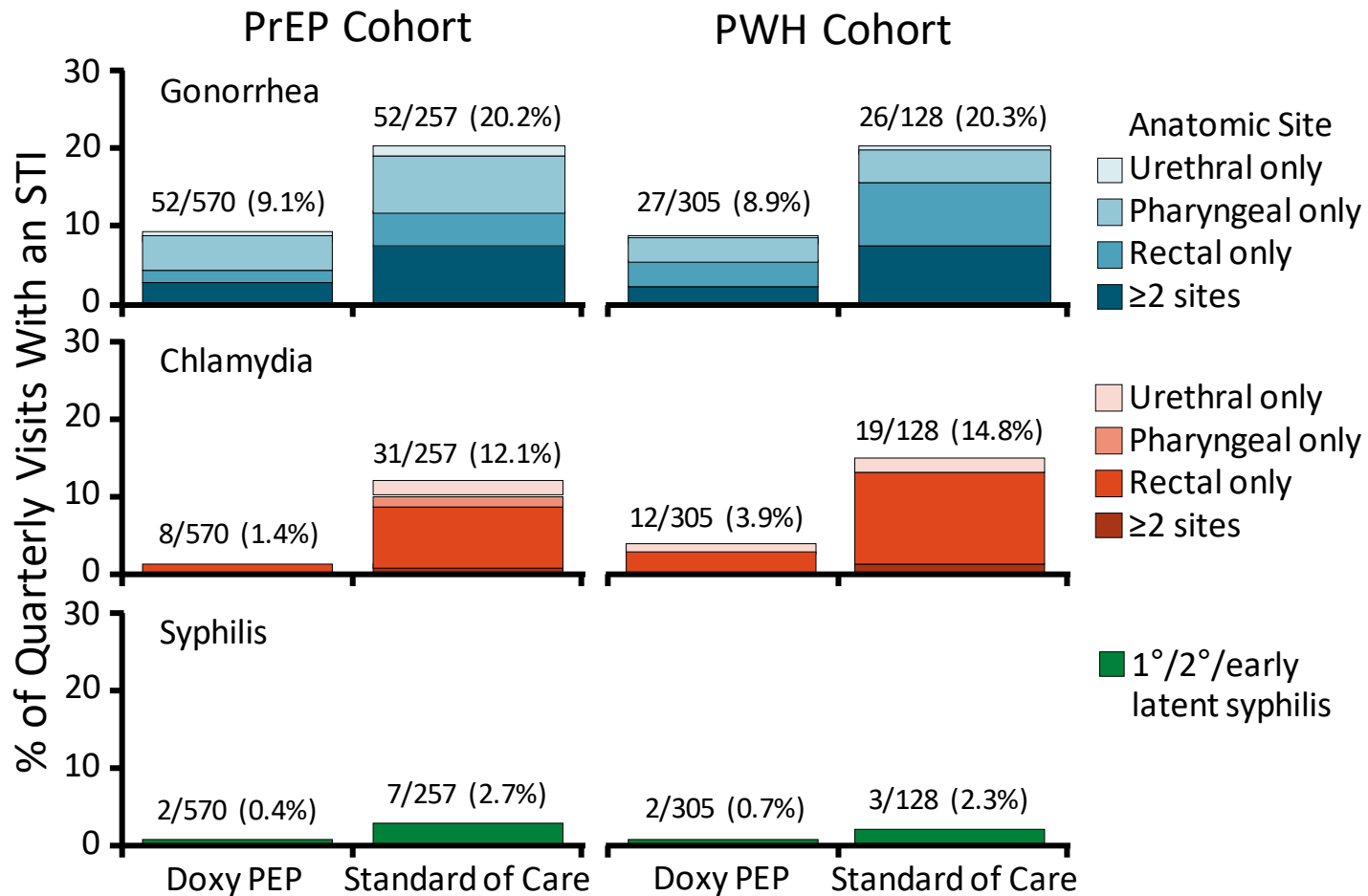
DoxyPEP: Quarterly STI Incidence (Primary Endpoint)



Risk Reduction in STI Incidence per Quarter (95% CI)	Doxy PEP vs Standard of Care*
PrEP	0.34 (0.24-0.46)
PWH	0.38 (0.24-0.60)
Total	0.35 (0.27-0.46)

*All $P < .0001$

DoxyPEP: STI Incidence By Anatomic Distribution and Study Arm and Cohort



Reduction in STI Incidence Per Quarter	Risk Reduction (95% CI) P Value	
	PrEP Cohort	PWH Cohort
Gonorrhea	0.45 (0.32-0.65) <.0001	0.43 (0.26-0.71) .001
Chlamydia	0.12 (0.05-0.25) <.0001	0.26 (0.12-0.57) .0007
Syphilis	0.13 (0.03-0.59) .0084	0.23 (0.04-1.29) .095

DoxyPEP: Safety and Adherence

No grade ≥ 3 AEs, grade ≥ 2 laboratory abnormalities, or SAEs observed

Doxycycline PEP was well tolerated

- Discontinuation due to intolerance or patient choice infrequent (2 %)
- 89% of participants described doxycycline PEP as acceptable/ very acceptable

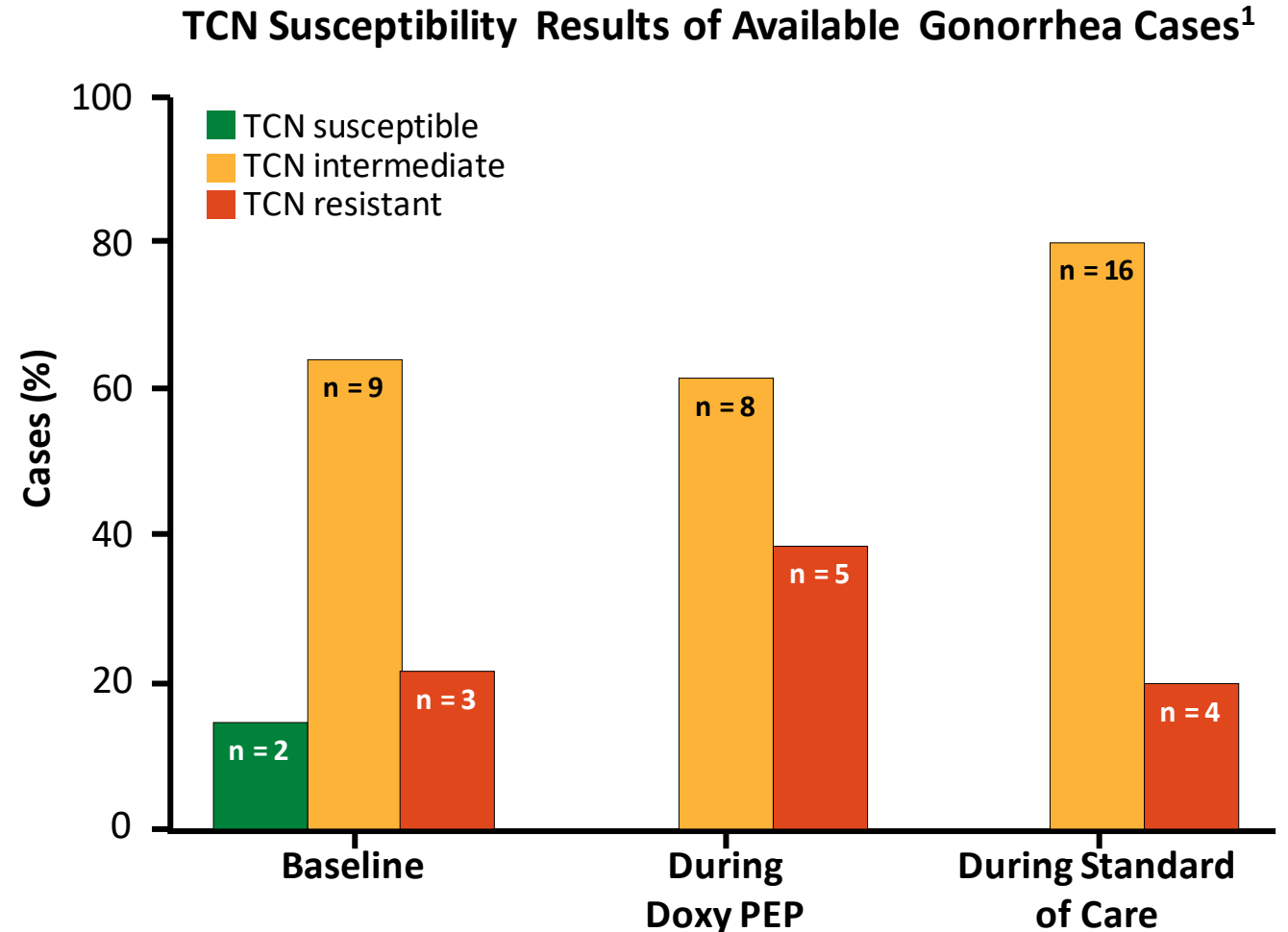
Median 4 (IQR: 1-10) doses/mo reported, 86% acts covered by doxycycline PEP by self-report

- 54% took < 10 doses/mo, 30% took 10-20 doses/mo, 16% took ≥ 20 doses/mo (per mean difference between dispensed pills and pills returned for count)



DoxyPEP: Tetracycline Resistance

- Tetracycline (TCN) susceptibility data available for ~30% of gonorrhea cases¹
 - ARLN agar dilution method used for susceptibility determination
 - ~20% TCN resistance observed at baseline
- Resistance rates consistent with US GISP gonorrhea data (20%)
 - 56% TCN resistance reported in IPERGAY study²



Conclusions from DoxyPEP

- Doxycycline PEP taken within 72 hr of condomless sex reduced STI incidence in MSM and TGW
 - Reduced by 62% in PWH cohort and 66% in PrEP cohort per quarter
 - Incidence of gonorrhea, chlamydia, and syphilis each reduced substantially
- Doxycycline PEP was well tolerated and associated with high adherence (by self-report) and few discontinuations
- Investigators concluded that doxycycline PEP may provide effective prevention against STIs in populations where STI incidence is high
 - Ongoing surveillance needed to monitor for TCN resistance in gonorrhea and for other organisms, such as *Staphylococcus aureus*, commensal *Neisseria*, and gut microbiome

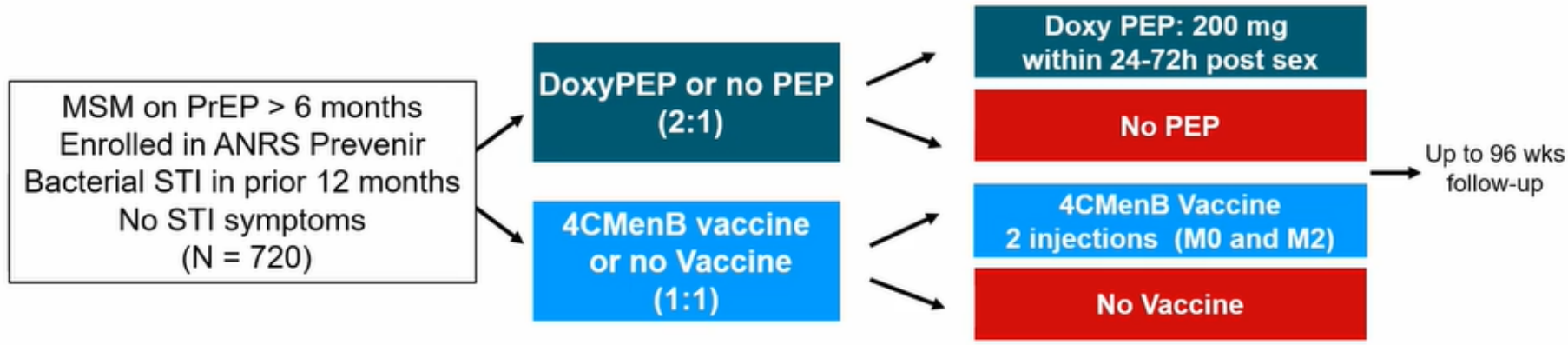


DoxyVac

Study Design

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)

- DoxyVac results were presented at CROI 2023
- Patients: MSM on PrEP
- Study conducted in France



- Primary efficacy end-points: impact of DoxyPEP on time to a first episode of syphilis or chlamydia and impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoeae* infection.
- Sample size: based on vaccine effectiveness assuming no impact of Doxy PEP on GC: 720 subjects needed for an HR: 0.70 (Estimated probability of a first GC episode over 18 months: 52%, 18% lost to FU).
- Quaterly visits with PCR tests (Roche dual target Cobas^o) for GC/CT/MG (3 sites) and serology for TP
- Doxycycline monohydrate purchased from Arrow and 4CMenB vaccine purchased from GSK



Molina et al. ANRS 174 DoxyVac: An Open-label Randomized Trial to Prevent STIs in MSM on PrEP. Abstract 119. CROI2023

Results and Conclusions From DoxyVac

Syphilis or Chlamydia

- 36 in no PEP
- 13 in Doxy PEP
- Adjusted HR 0.16 [95%CI 0.08-0.3, $p < 0.0001$]

Syphilis

- 18 in no PEP
- 8 in Doxy PEP

Chlamydia

- 21 in no PEP
- 5 in Doxy PEP

Doxy PEP is well tolerated and reduced incidence of syphilis and chlamydia in MSM patients taking PrEP

65% reduction in STI (~80% for CT and Syphilis; ~55% GC)

Molina et al. ANRS 174 DoxyVac: An Open-label Randomized Trial to Prevent STIs in MSM on PrEP. Abstract 119. CROI2023

Doxycycline PEP for STI prevention among cisgender women

- Open-label randomized trial of doxycycline PEP (doxycycline hyclate 200mg taken within 72 hrs of sex)
- Compared with standard of care (e.g., quarterly screening and treating STIs)
- Women aged 18-30 years in Kisumu, Kenya.

Stewart et al. Doxycycline Postexposure Prophylaxis for Prevention of STIs
Among Cisgender women. Abstract 121. CROI 2023.

September 27, 2023



Results: Doxycycline PEP for STI prevention among cisgender women

Analysis	Endpoint	Total	PEP (n=224)	SOC (n=225)	RR	95% CI	P- Value
Intention to Treat	All STIs	109	50	59	0.88	0.6-1.29	0.51
	Chlamydia	85	35	50	0.73	0.47-1.13	0.16
	Gonorrhea	31	19	12	1.64	0.78-3.47	0.19

Stewart et al. Doxycycline Postexposure Prophylaxis for Prevention of STIs
Among Cisgender women. Abstract 121. CROI 2023.

September 27, 2023

Doxycycline PEP for STI prevention among cisgender women

- Authors presented data at CROI 2023 and offered several possible explanations

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

Resistance: to date,
no known cases of
resistant chlamydia,
however high rates
of tetracycline
resistant *N
gonorrhoeae*

Adherence: **self
reported** adherence
was high but
imperfect*

Stewart et al. Doxycycline Postexposure Prophylaxis for Prevention of STIs
Among Cisgender women. Abstract 121. CROI 2023.

Mucosal Pharmacology of Doxycycline for Bacterial STI Prevention in Men and Women

A single 200 mg doxycycline extended-release dose was given

Drug concentrations in rectal, vaginal, and plasma concentrations

- For chlamydia: at all sites remain above 4XMIC for > 2 days
- For syphilis: at all sites remain above 4XMIC for up to 2 days
- For gonorrhea: rectal sites had **lower** concentrations, all three sites only remains above 4XMIC for 12 hours
 - For male urethral secretions in 9 out of 11 men there was a doxycycline concentration > 4X MIC 24 hours after the dose

Tissue and Urethral Doxycycline Concentrations

	C ₂₄ (ng/g or ng/mL) [95% CI]	Fold above MIC		
		<i>C trachomatis</i>	<i>T pallidum</i>	<i>N gonorrhoeae</i>
Rectal Tissue	616 [495 – 766]	9x	6x	2x
Vaginal Tissue	301 [130 – 698]	4x	3x	1x
Cervical Tissue	430 [220 – 840]	6x	4x	1x
Urethral Secretions	1166 [598 – 2394]	18x	11x	4x

- Tissue concentrations 24 hours after dose reach up to 9x MIC values
- Doxycycline detected on 9/11 male urethral swabs
 - Concentrations exceed 4x MIC values

Minimum Inhibitory Concentrations (MIC): Zheng *Sex Transm Dis* 2015; Edmondson *Antimicrob Agents Chemother* 2020; CDC Antimicrob Resist Susc Test

Education & Center Program

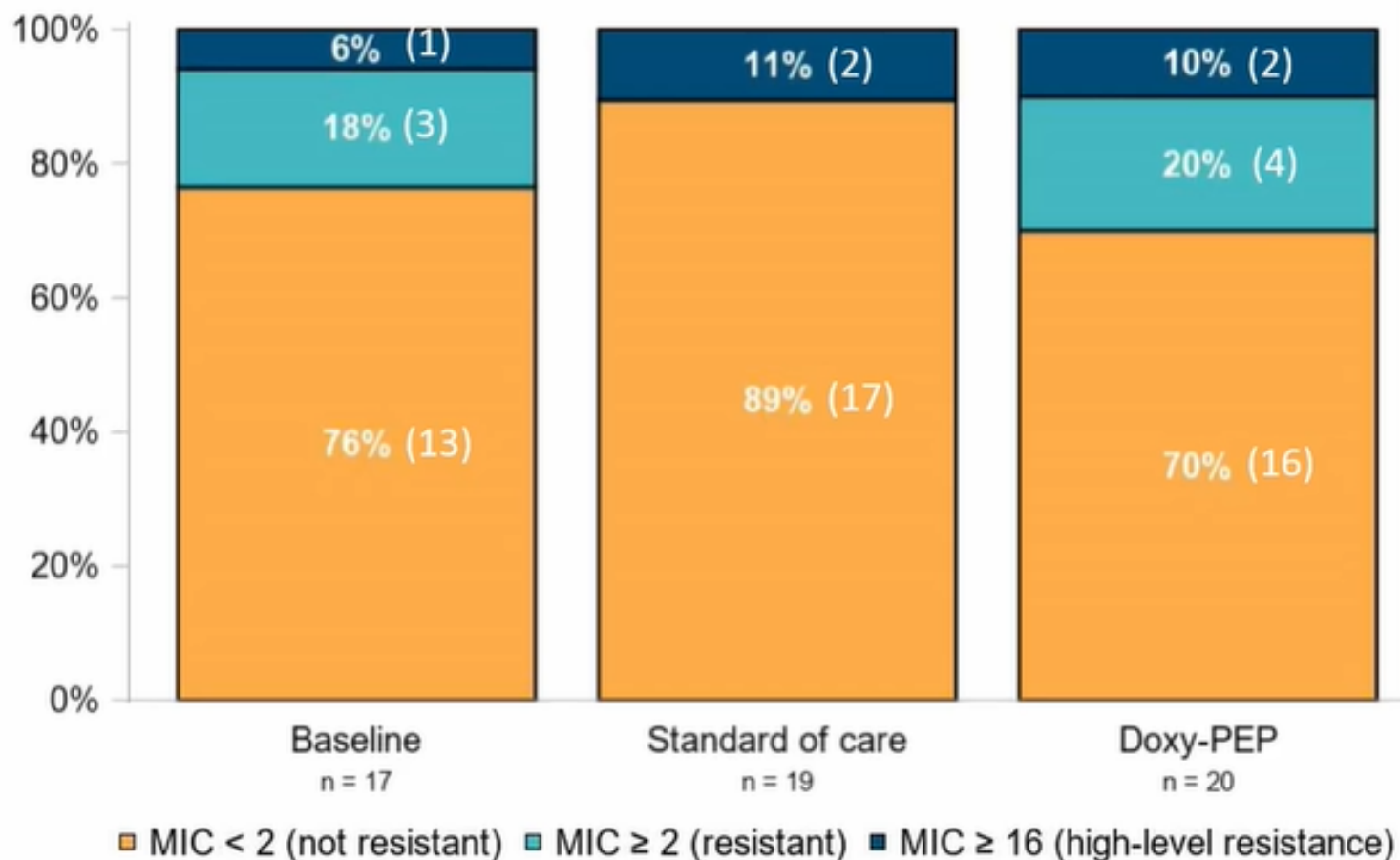


Describe the impacts on antimicrobial resistance as it relates to Doxy PEP

DoxyPEP and Antimicrobial Resistance in N. Gonorrhoeae, Commensal Neisseria and S. Aureus

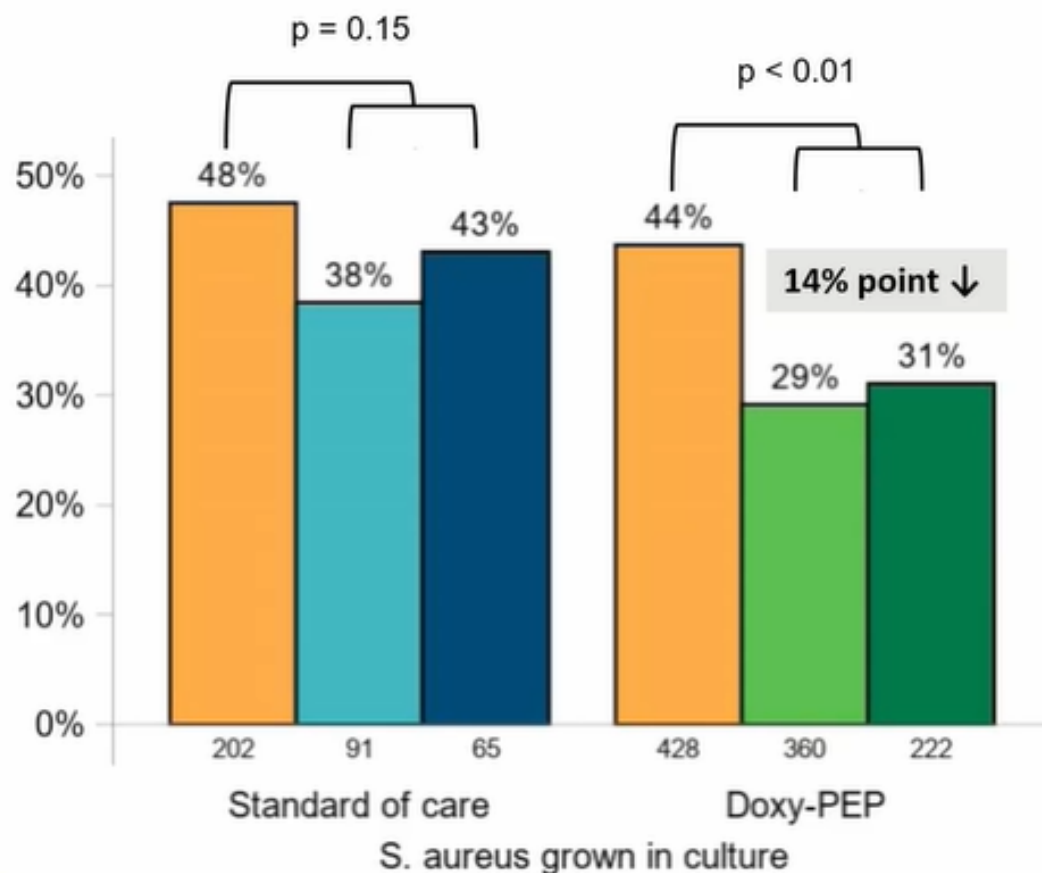
- Objectives: examine impact of intermittent doxycycline use in N. Gonorrhoeae, Commensal Neisseria and S. Aureus
- Participants from DoxyPEP trial were tested for STIs
 - Resistances samples for N. Gonorrhoeae, Commensal Neisseria and S. Aureus were collected from both arms

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)

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.¹
 - DoxyPEP use associated with 14% absolute decrease in *S. aureus* colonization.
1. Oestergard *AIM* 2016; Jacobsson *Scand JID* 2008; Septimus *CID* 2016; Bode *NEJM* 2010

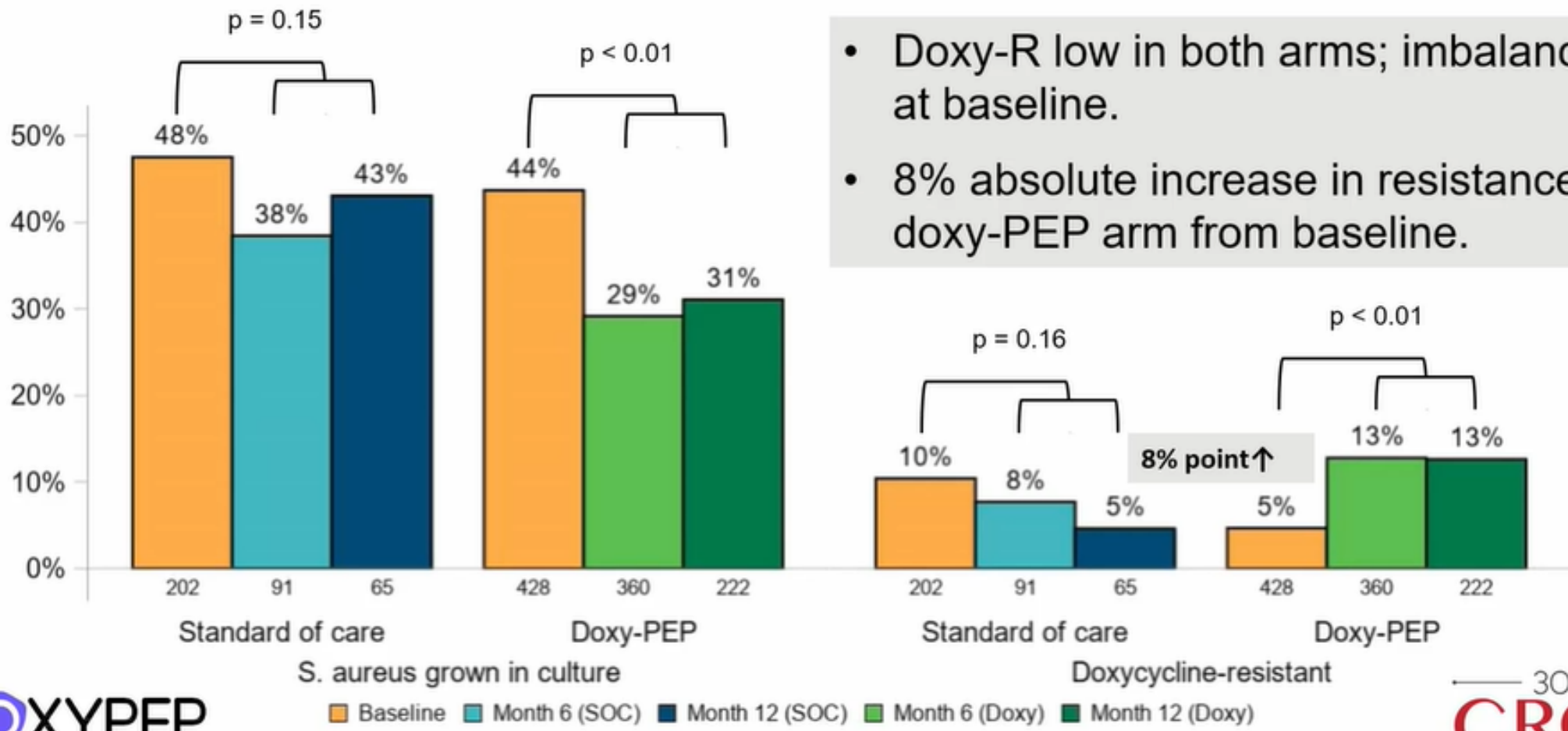


S. aureus grown in culture

■ Baseline
 ■ Month 6 (SOC)
 ■ Month 12 (SOC)
 ■ Month 6 (Doxy)
 ■ Month 12 (Doxy)



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.



■ Baseline
 ■ Month 6 (SOC)
 ■ Month 12 (SOC)
 ■ Month 6 (Doxy)
 ■ Month 12 (Doxy)



Resistance Results Summary

- *N. gonorrhoea*
 - In setting of a 50% reduction in GC infections, tetracycline resistance was present in 4 baseline GC isolates, 6 incident isolates in Doxy PEP and 2 incident GC isolates in the SOC group
 - Possibly doxycycline is less protective against resistant strains
- *S. aureus*
 - Doxy PEP associated with a 14% absolute reduction in colonization and an 8% absolute increase in doxycycline resistance compared to baseline
- Non-pathogenic *Neisseria* species
 - Nearly 2/3rd of isolates had pre-existing doxycycline resistance
- Limitations: patients in SOC arm also got doxycycline for incident STIs

Bacterial Resistance After Taking Doxy PEP

- Long term data is not available
- Studies ongoing looking at the long term impact on microbiome of using intermittent doxycycline
- Important to remember that people in both Doxy PEP and standard of care arms in all Doxy PEP studies also received doxycycline (or other antibiotics) for treatment of incident STIs
 - This means that it is not that SOC never is exposed to antibiotics and the Doxy PEP arm is exposed

Clinical Management and Monitoring

Doxy PEP Clinical Management

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

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).

If a patient is diagnosed with an STI while using doxy-PEP, they should be treated according to standard CDC STI treatment guidelines.

Doxy PEP monitoring



In addition to screening regularly for STIs:

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

Doxycycline as STI PEP: Considerations for Individuals and Healthcare Providers of Gay or Bisexual Men or Transgender Women

As CDC and others work quickly to [evaluate data](#) to inform clinical guidance on the safe and effective use of post-exposure prophylaxis with doxycycline (also called doxy as PEP) to prevent gonorrhea, chlamydia, and syphilis, we acknowledge there are individuals and clinicians who are already engaged in the off-label use of doxycycline as bacterial STI post-exposure prophylaxis or considering it. As such, we are providing the following considerations to inform those decisions:

- [Current efficacy data](#)  only applies to gay and bisexual men and transgender women. Studies among heterosexual cis-gender women are ongoing.
- Doxycycline 200 mg administered within 24-72 hours of condomless sex was the regimen evaluated in this study. Other antibiotics should not be considered for PEP.
- In addition to informing patients about the potential STI prevention benefits of doxy as PEP, providers should also counsel patients about potential adverse side effects of doxycycline including phototoxicity, gastrointestinal symptoms, and more rarely esophageal ulceration.
- Providers should continue to screen, test, and treat for bacterial STIs in accordance with [CDC's STI Treatment Guidelines](#) and [CDC's PrEP for the Prevention of HIV guidelines](#) , even among people who may be using doxycycline as PEP or PrEP.

What does
the CDC
say?

Recent Updated Statement Included in OI Guidelines

Pre-Exposure Prophylaxis and Post-Exposure Prophylaxis for Prevention

Doxycycline pre-exposure prophylaxis (PrEP) has been examined for prevention of bacterial STIs. In a pilot study, 30 MSM with HIV with previous syphilis were randomly assigned to doxycycline 100 mg daily for 48 weeks versus a financial incentive-based behavioral intervention; doxycycline was associated with a lower incidence of syphilis, but this did not reach statistical significance due to small sample size.⁸³

Post-exposure prophylaxis (doxycycline 200 mg after unprotected anal sex) has been studied among MSM and transgender women, with a reduction in incident syphilis by 73%.⁸⁴ Several recent randomized open-label clinical trials have found that doxycycline 200 mg after condomless sex among MSM or transgender women with HIV or on HIV PrEP significantly reduced chlamydia, gonorrhea, and syphilis acquisition; a randomized trial of cisgender women on HIV PrEP administered doxycycline 200 mg within 72 hours after sex did not reduce chlamydia, gonorrhea, or syphilis acquisition.⁸⁵ There is ongoing evaluation regarding the potential impact of STI postexposure prophylaxis on antimicrobial resistance and the microbiome. Other studies are underway or in development regarding doxycycline prophylaxis for bacterial STIs.^{86,87}

Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.⁸⁸ Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in people with HIV and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum*.⁸⁹⁻⁹³

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.
<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new>. Accessed September 26, 2023.

Key Take Away Points

- STIs have been increasing in the US and additional prevention strategies are needed
- Doxy PEP has demonstrated efficacy in MSM and transgender women for reduction of bacterial STI rates
- Doxy PEP has demonstrated safety in MSM and transgender women
- Doxy PEP has uncertain efficacy in cisgender women for reduction of bacterial STIs, more research is needed
- Overall long-term impacts on microbiome and future infections need to be monitored, more research is needed



Resources

- <https://www.ncsddc.org/resource/doxy-as-sti-pep-command-center/>

The screenshot shows the website for the National Coalition of STD Directors. At the top left is the logo and name. To the right are search and contact options, and two highlighted menu items: 'STI INFORMATION & RESOURCES' and 'LEARNING CENTER'. Below this is a dark blue navigation bar with links for 'ABOUT', 'OUR WORK', 'MY NCSDD LOGIN', 'GET INVOLVED', 'RESOURCES', 'EVENTS', and 'NEWS & ANNOUNCEMENTS'. Social media icons for YouTube, Facebook, and Twitter are also present. A breadcrumb trail reads 'Home > Resources > Doxy as STI PEP Command Center'. The main content area features a green 'STD RESOURCE' tag, a large orange box with the title 'DOXY AS STI PEP COMMAND CENTER', and a descriptive paragraph: 'Your hub for tools, templates, model policies, and an implementation toolkit to begin offering doxycycline as STI PEP to patients in your community.' To the right is a purple graphic with the title 'DOXY AS STI PEP COMMAND CENTER' in white text.



References

- Stewart et al. Doxycycline Postexposure Prophylaxis for Prevention of STIs Among Cisgender women. Abstract 121. CROI 2023
- AF Luetkemeyer et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. *N Engl J Med* 2023;388:1296-306. DOI: 10.1056/NEJMoa2211934
- Anne F. Luetkemeyer. DoxyPEP and Antimicrobial Resistance in *N. Gonorrhoeae*, Commensal *Neisseria* and *S. Aureus*. Abstract 120, CROI 2023.
- Richard Haaland. Mucosal Pharmacology of Doxycycline for Bacterial STI Prevention in Men and Women ABSTRACT 118 CROI 2023
- Molina 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. *Lancet Infect Dis* 2018; 18: 308–17.