AETC AIDS Education & Training Center Program Mountain West

Doxycycline post-exposure for prevention of STIs in MSM and TGW: Rationale and Results of the DoxyPEP study and Implementation Considerations

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Project ECHO®

Disclosures

Connie Celum:

Scientific Advisor to Merck and Gilead Sciences
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Disclaimer

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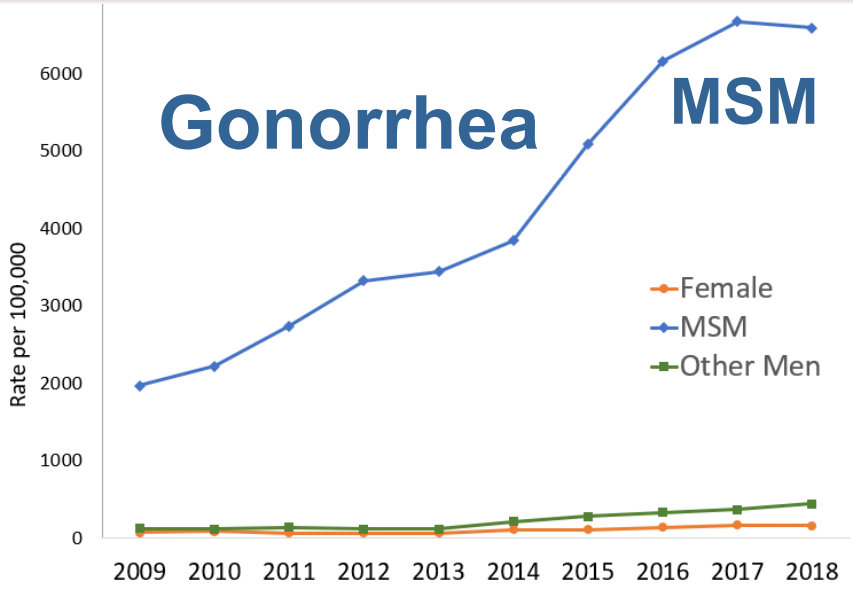
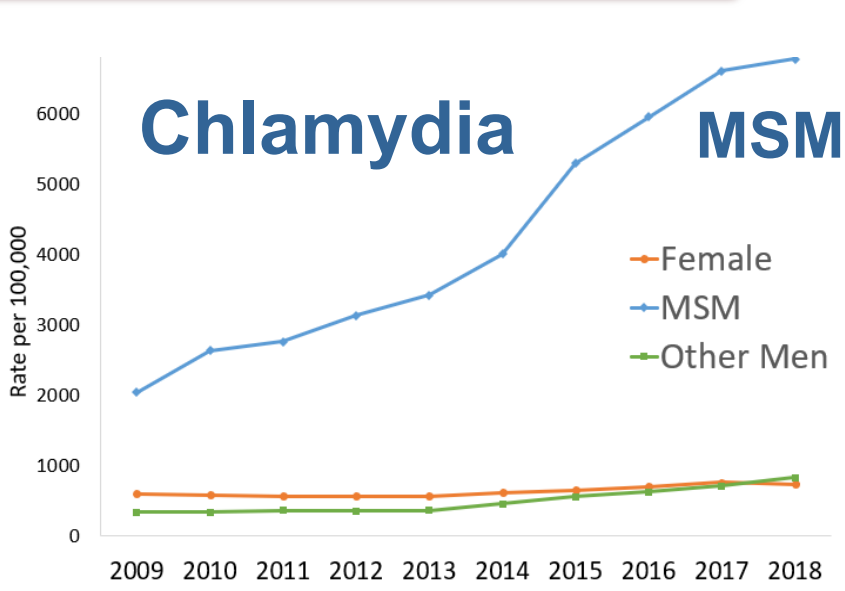
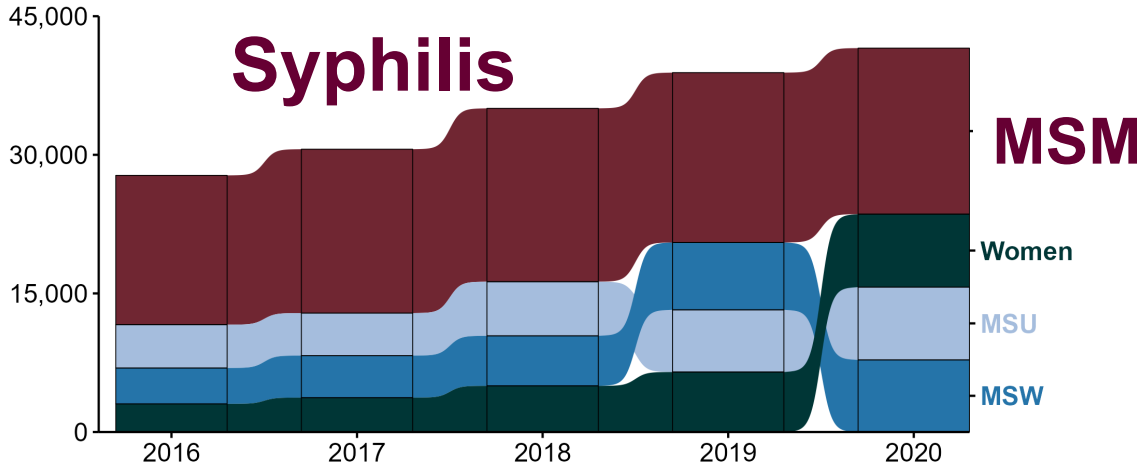
The global epidemic of STIs disproportionately impacts men who have sex with men (MSM)







San Francisco DPH
STI surveillance data 2018

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

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Rationale for studying doxycycline for STI prophylaxis

- Safe, well-tolerated, inexpensive
- Used safely & effectively for prophylaxis
  - Lyme disease (also a spirochete)
  - malaria prophylaxis
- No tetracycline resistance detected in *C. trachomatis* or *T. pallidum*
- TCN resistance is already high in GC and doxy isn't recommended for GC treatment
- Used chronically in persons with acne
- Not commonly used to treat infectious diseases
- Promising efficacy and safety from IPERGAY
- No interim data from other studies that has definitively answered the question of efficacy or safety in MSM with HIV, or HIV- MSM and women on PrEP

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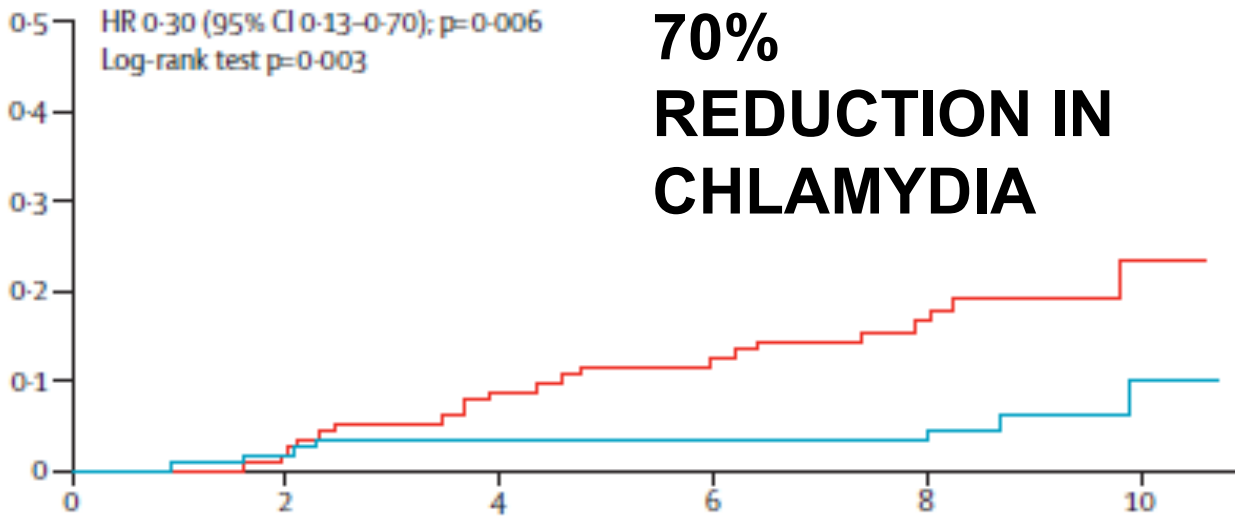
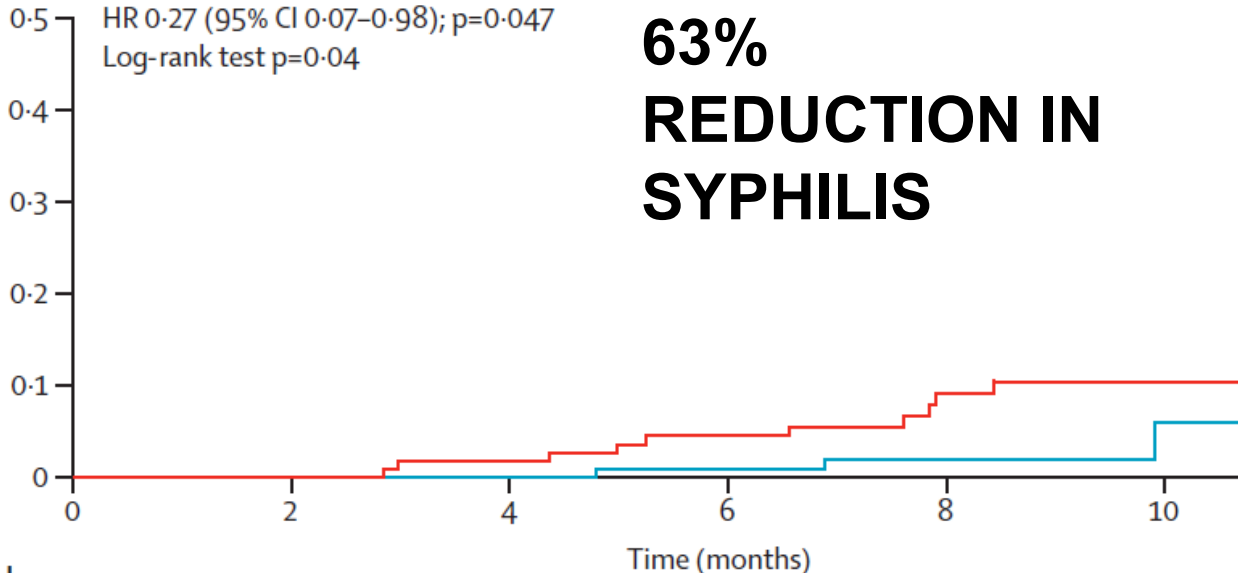
Doxycycline taken after condomless sex as post-exposure prophylaxis (PEP) is a promising intervention



70% REDUCTION IN CHLAMYDIA



63% REDUCTION IN SYPHILIS

Earlier investigation has shown doxycycline PEP led to ~ 2/3rds reduction in syphilis and chlamydia (CT) in MSM taking intermittent HIV PrEP but was not effective for gonorrhea (GC).

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Molina et al Lancet 2018;18(3): 308-317

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

Maximum of 200 mg every 24 hours

Inclusion criteria:

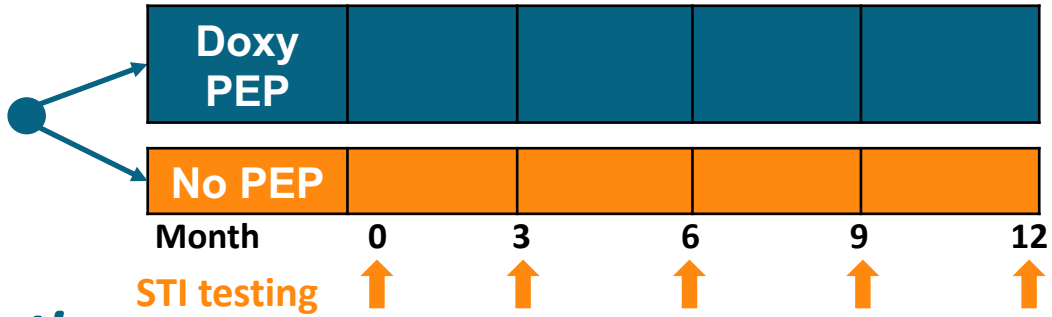
- Male sex at birth
- With HIV or on PrEP
- ≥ 1 STI in past 12 months
- Condomless sex with ≥ 1 male partner in past 12 months

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

Sites: San Francisco & Seattle HIV & STI clinics

MSM & TGW with HIV

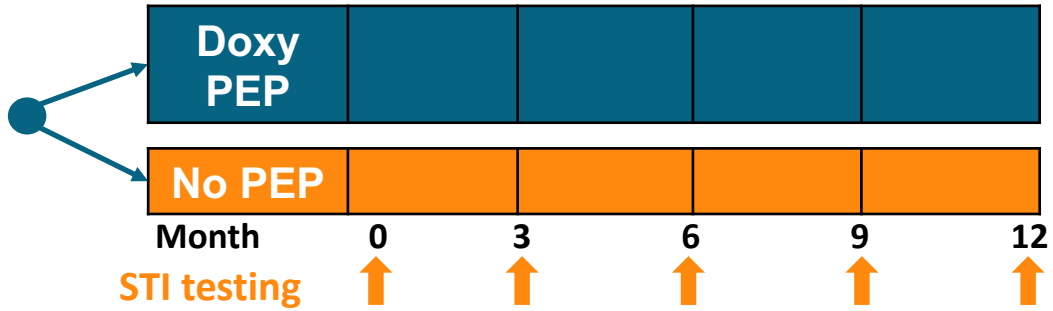
(planned n = 390)



2:1 randomization

MSM & TGW on HIV PrEP

(planned n = 390)



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Primary endpoint and stopping rules

- **1º Endpoint:** At least one incident STI (GC/CT/syphilis) during a follow-up quarter
  - All STI endpoints adjudicated by blinded endpoint committee

- **Power:** 80% power to detect a decrease in quarterly STI prevalence from 10% to 5%, powered separately for PrEP & PWH cohorts

- **Stopping rules:** only if both cohorts cross stopping boundary for proven effectiveness based on one-sided alpha of 0.025 for each cohort

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5/13/2022 Scheduled interim analysis: DSMB recommended stopping enrollment due to significant effectiveness in both cohorts

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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 1º, 2º, early Latent

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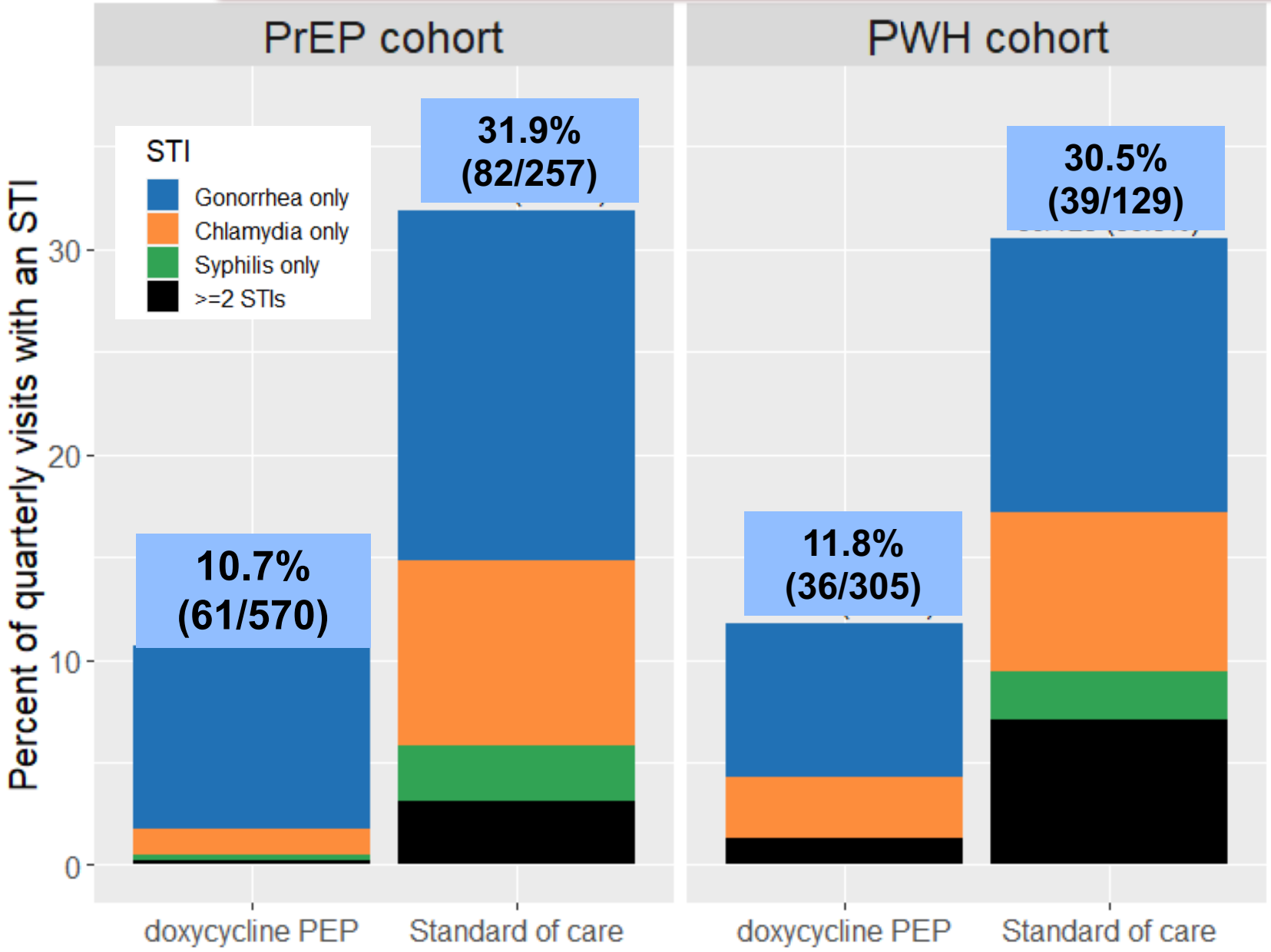
Primary Endpoint: STI incidence per quarter



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

all p < 0.0001

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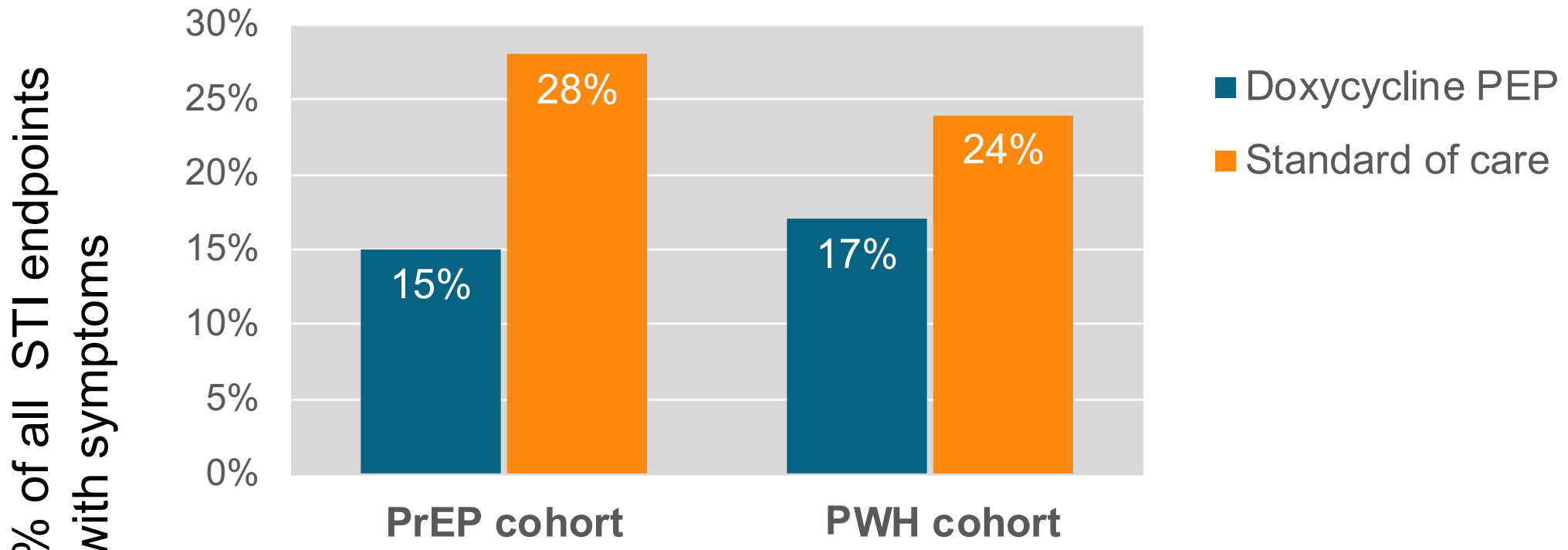
STI endpoints with symptoms reported at diagnosis



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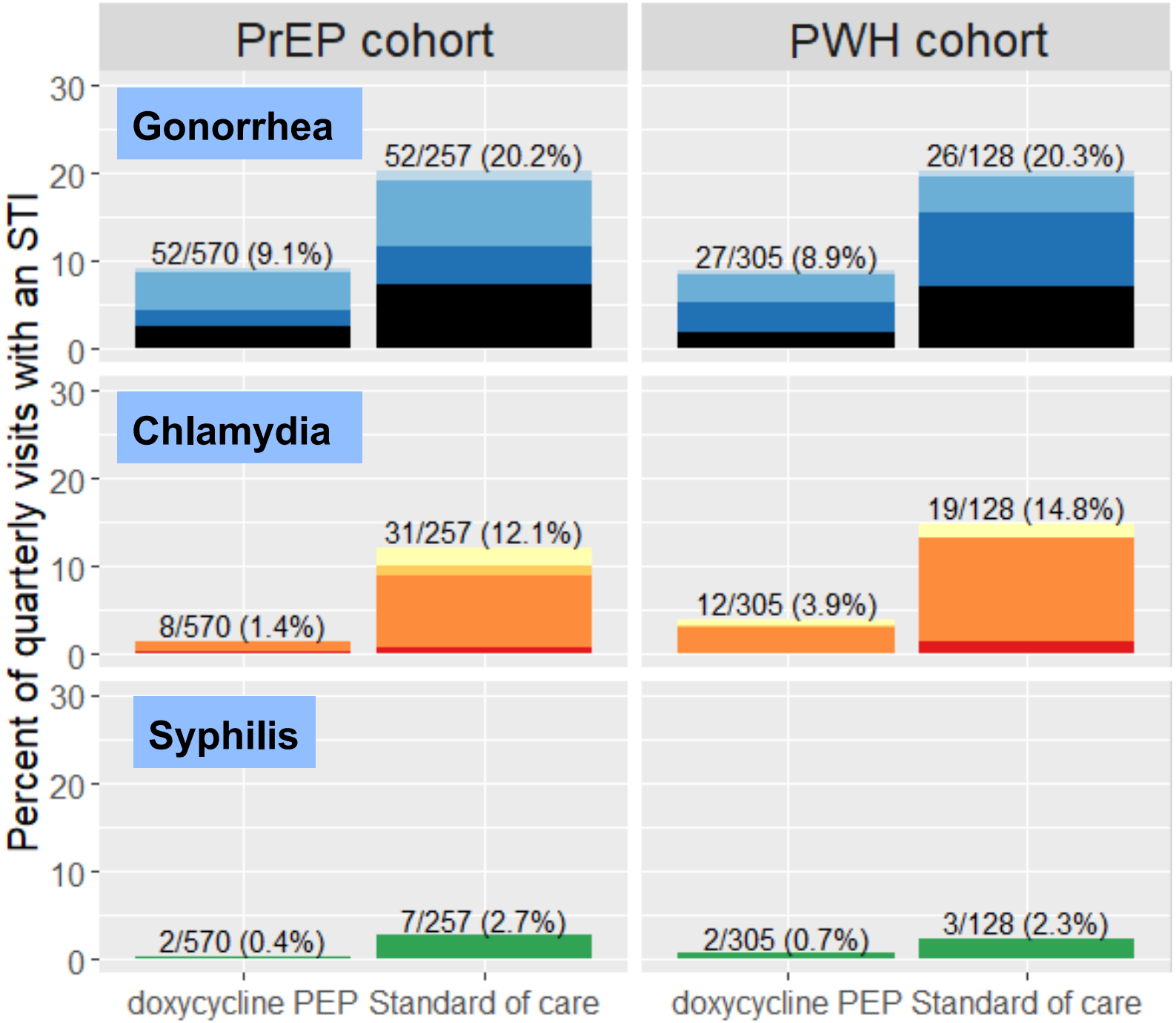
Individual STI incidence by study arm & cohort



Anatomic site

- Urethral only
- Pharyngeal only
- Rectal only
- >=2 sites

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- Pharyngeal only
- Rectal only
- >=2 sites

- 1º/2º/early latent syphilis

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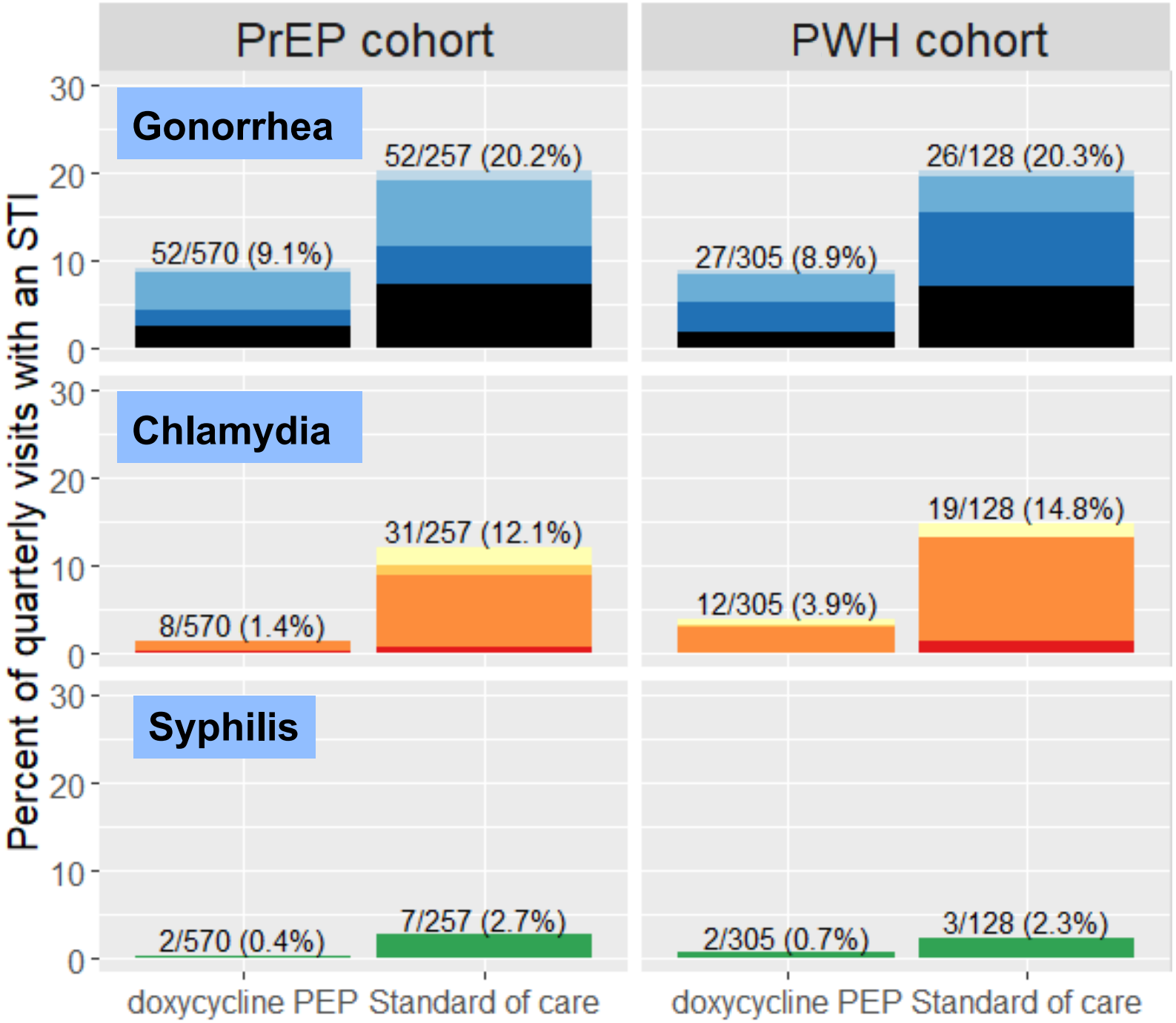
Individual STI incidence by study arm & cohort



Reduction in each STI per quarter

risk reduction (95% CI)

	PrEP	PWH
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*

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Doxy PEP was safe & acceptable, with high 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

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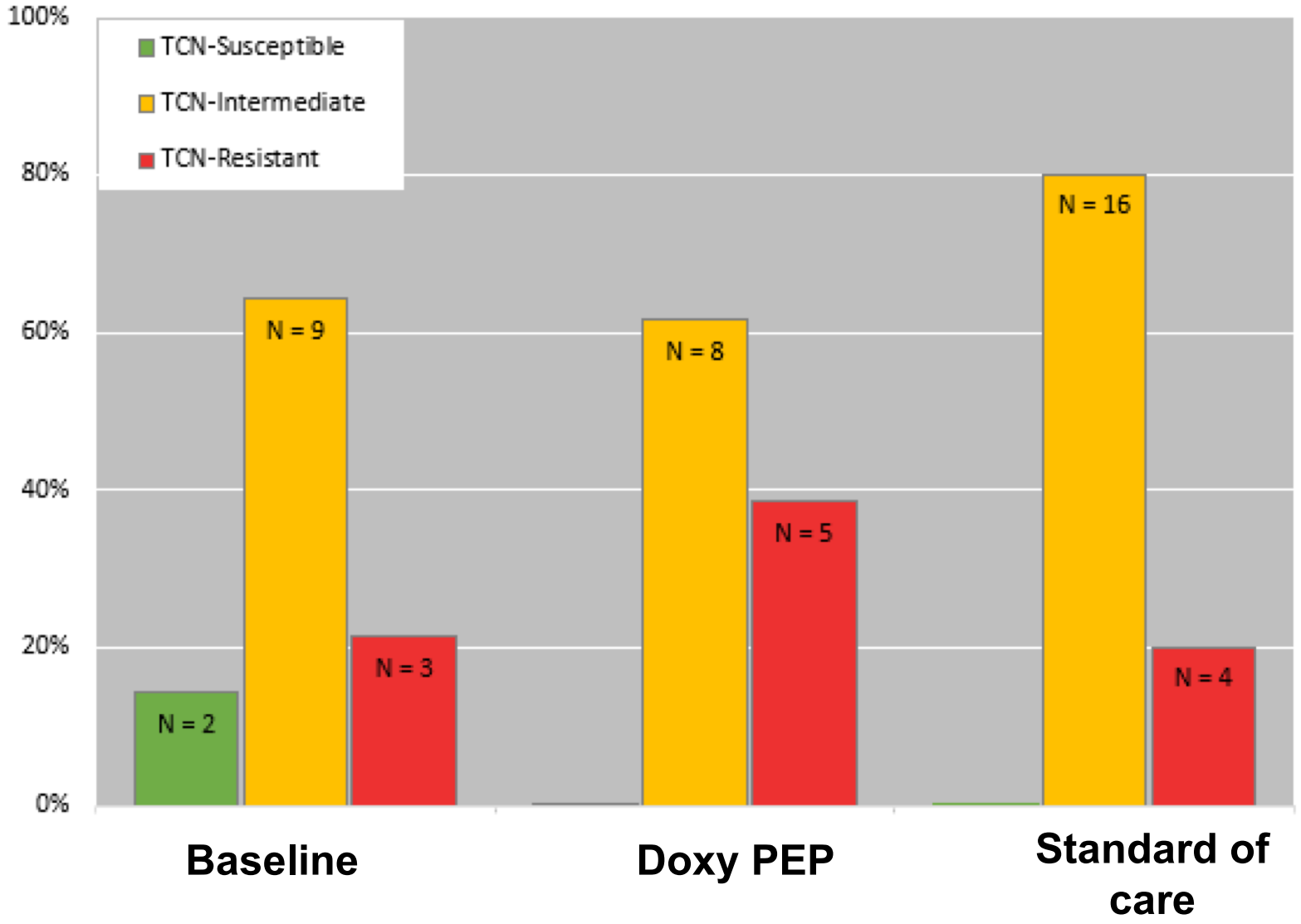
Gonococcal Tetracycline (TCN) culture-based susceptibility

- Conducted through CDC SURRG & ARLN programs
- ~ 30% of GC endpoints have resistance data available
- Tetracycline susceptibility by ARLN agar dilution method[1]
- Baseline: ≈ 20% with TCN resistance, consistent with US GISP GC TCN resistance data[2]
- Population level GC TCN resistance: US (20%) < France (56%) during IPERGAY[3]



[1] https://www.cdc.gov/std/gonorrhea/arg/carb.htm
https://www.cdc.gov/std/gonorrhea/lab/agar.htm
[2] CDC STD Surveillance Report 2020, [3] LaRuche et al Eurosurveillance 2014;19(34)

Doxycycline PEP within 72 hours of condomless sex substantially reduced the incidence of bacterial STIs

- Quarterly STI reduction of **62% in PWH** 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
- Larger studies and ongoing surveillance needed in doxycycline PEP users to assess impact on TCN resistance development in GC
- Evaluation of impact on sexual behavior & antibiotic resistance are underway (including *S. aureus*, commensal *Neisseria,* gut microbiome)

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Ongoing DoxyPEP studies

- DoxyVacc: DoxyPEP +/- Bexsero meningococcal vaccine for GC prevention in factorial design among 720 MSM in France (Molina)
- dPEP: DoxyPEP among 422 AGYW in Kenya who are on HIV PrEP (Stewart, Baeten, & Bukusi)
- DISCO: DoxyPEP vs DoxyPrEP in MSM in Canada (Grennan)
- Syphilaxis: DoxyPEP or PrEP in MSM in Australia (Haire & Kaldor))
- PEACH: Observational study of flexible approaches to HIV PrEP and option for DoxyPEP among MSM in Atlanta (Sullivan & Kelley)

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Next steps

- Interim guidance from CDC anticipated in parallel with publication of primary results
- CDC consultation with stakeholders planned for fall 2022
- Review by WHO for STI guidelines

Disclosures

Julie Dombrowski:

I have participated in research with study materials donated by Mayne Pharmaceuticals and Hologic

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Current Status of Implementation

- No federal guidance yet (in progress)
- In Seattle: no clinic- or county-wide recommendations yet
- Some individual clinicians opt to prescribe for individual patients
- This presentation reflects ongoing discussions & includes my personal opinions

Key Implementation Questions

- Who should be offered doxycycline PEP?
  - Who should be prioritized for doxycycline PEP?
- What are the key counseling messages?
- What monitoring & follow-up is needed?

- Medication cost is not a substantial issue
  - 340b pricing: $0.02-$0.06 cents per tab (typical use = $0.84/month)
  - Direct purchase online pharmacy: $0.28 cents per tab (typical use = $3.92/month)

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First: Should we be doing this at all?

Concern	Consideration
Antimicrobial resistance	• May not be answerable in the near-term. We cannot prove the absence of an effect. • Most study participants took <10 doses per month • Rationale for different standard in STI prevention vs. acne treatment?
Adherence	• Study participants did not have perfect adherence
Side effects	• Address in shared decision-making with patients
Do the benefits justify the risks?	• This intervention can be targeted to maximize benefit and does not need to be implemented exactly as in the trial

My opinion: yes

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Key Questions (My opinion in blue)

- Who should be offered doxycycline PEP?
  - Who should be prioritized for doxycycline PEP?
  - People with multiple STIs in the past year; people at highest risk of syphilis
  - For patients who do not have HIV: only in combination with HIV PrEP
- What are the key counseling messages?
  - What we know (effectiveness) & don't know (impact on antimicrobial resistance)
  - Centered on principle of shared decision-making
- What monitoring & follow-up is needed?
  - Standard-of-care STI/HIV testing and follow-up as for PrEP or HIV care

DOXYPEP Acknowledgments

With profound thanks to our study participants for their time & commitment

UCSF

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

CHAN ZUCKERBERG BIOHUB

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SAN FRANCISCO City Clinic A landmark in prevention

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