

Prevention of STIs among People at Risk for HIV

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 **HPTN** Annual Meeting



STI incidence before/after PrEP in MSM

- 1378 participants of the PrEPX study in Australia with pre-enrollment testing data
- Mean follow-up of 1.1 years

	STI incidence 1 year before per 100 PY	STI incidence post entry per 100 PY	Incidence rate ratio (IRR) (95% CI)	Adjusted IRR* (95%CI)
All	69.5	98.4	1.41 (1.29–1.56)	1.12 (1.02–1.23)
PrEP-experienced (n=541)	92.4	104.1	1.13 (0.99–1.28)	1.05 (0.92–1.19)
PrEP-naive (n=837)	55.1	94.2	1.71 (1.49–1.96)	1.21 (1.06–1.39)

*Adjusted for testing frequency

How to contain the STI Epidemic?

- A, B and C: Promotion of condom use
 - Counselling and behavioural changes
- Test and Treat
 - Frequent testing for STIs MSM on PrEP and immediate treatment
- Partner notification and treatment
- Antibiotic prophylaxis
- Vaccines
 - For viral STIs (hepatitis A and B, HPV, MPox)
 - For bacterial STIs when available (gonorrhoea, chlamydia, syphilis)
 - Case-control studies suggest 4CMenB vaccine could reduce gonorrhoeae incidence

Doxycycline PEP in MSM

Randomized open-label trial

- HIV-negative MSM on PrEP
- Enrolled in the ANRS IPERGAY open-label extension study
- No contra-indication to Doxy

On Demand PEP with doxycycline
(200 mg, within 24-72h after sex)
N=116

No PEP
N=116

- * ≤ 6 pills/week to limit antibiotic exposure: **use of a median of 6.8 pills/month per patient**
- Visits at baseline and every two months with serologic assays for HIV and syphilis and PCR assays for CT and NG in urine samples, anal and throat swabs

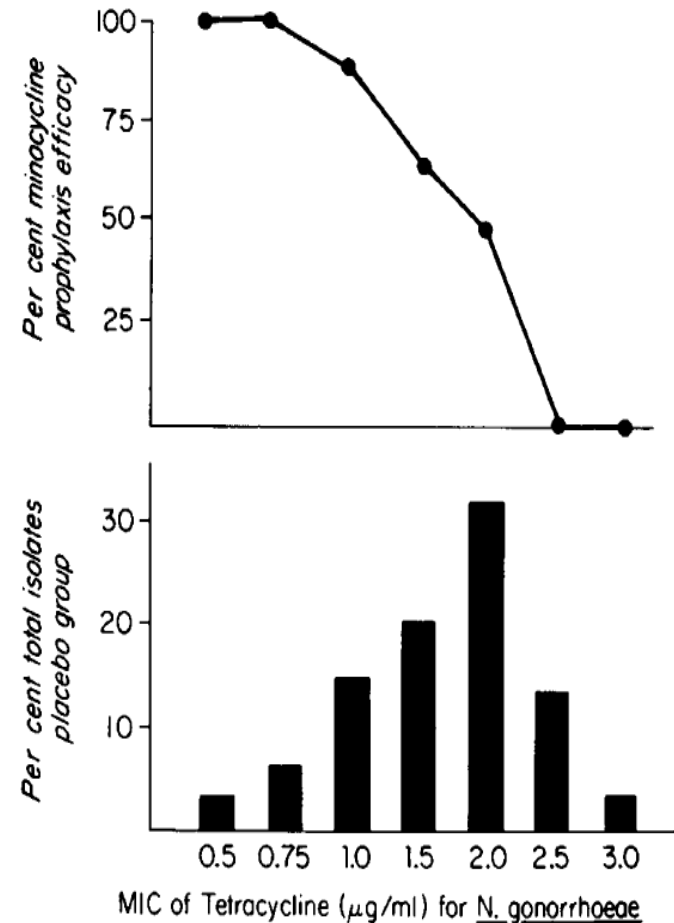
Why Testing Doxycycline PEP ?

- No known resistance to doxycycline in *C. trachomatis* and *T. pallidum*
- Doxycycline PEP successfully used for prevention of Lyme disease and Leptospirosis (Nadelman, NEJM 2001; Takafuji, NEJM 1984)
- Limited use of doxycycline in France for the treatment of bacterial infections, mostly used for acnea and malaria prophylaxis
- *N. gonorrhoeae* in France already resistant to tetracycline (65% in 2020-21, 20-30% high level with *tetM* acquisition)

A TRIAL OF MINOCYCLINE GIVEN AFTER EXPOSURE TO PREVENT GONORRHEA

WILLIAM O. HARRISON, M.D., RICHARD R. HOOPER, M.D., PAUL J. WIESNER, M.D.,
 AXEL F. CAMPBELL, M.D., WALTER W. KARNEY, M.D., GLADYS H. REYNOLDS, PH.D.,
 OSCAR G. JONES, B.S., AND KING K. HOLMES, M.D., PH.D.

- 1089 men were given oral minocycline (200 mg) or placebo after sex (median : 8 h)
- **At sea, gonorrhea in 57/565 (10%) with placebo and 24/515 (4.7%) with PEP (p<0.001)**
- Isolates from patients given PEP were more resistant to tetracyclin vs. those given placebo
- Efficacy of PEP related to NG MIC
- High failure rate with minocycline treatment: 65%
- « **Limited effectiveness as a public health measure** »



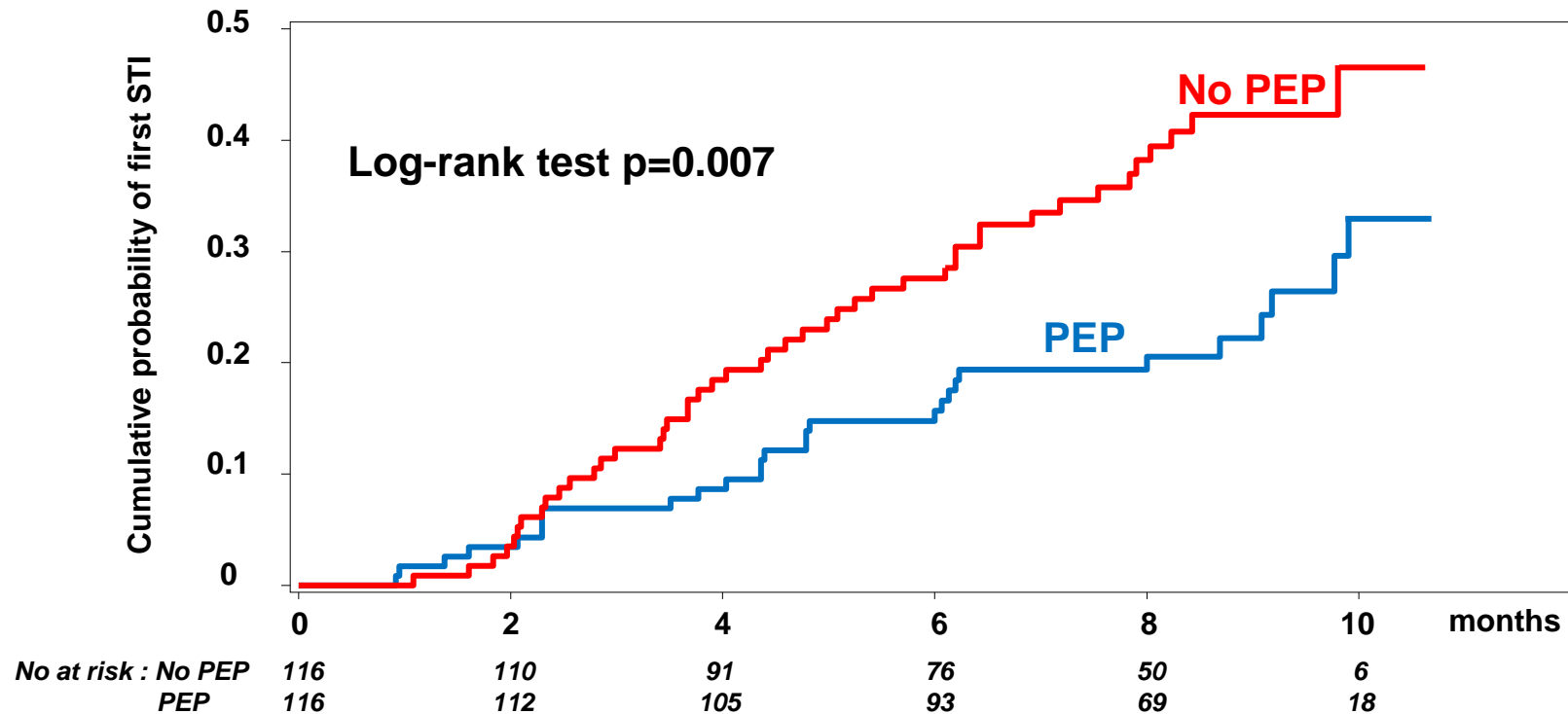


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de l'Exposition aux Risques
avec et pour les Gays

Incidence of First Episode of STIs



Median follow-up of 8.7 months (IQR: 7.8-9.7): 73 subjects infected

45 in No PEP arm (incidence: 69.7 per 100 PY), **28 in PEP arm** (incidence: 37.7 per 100 PY)

Hazard Ratio: 0.53 (95% CI: 0.33-0.85, $p=0.008$)

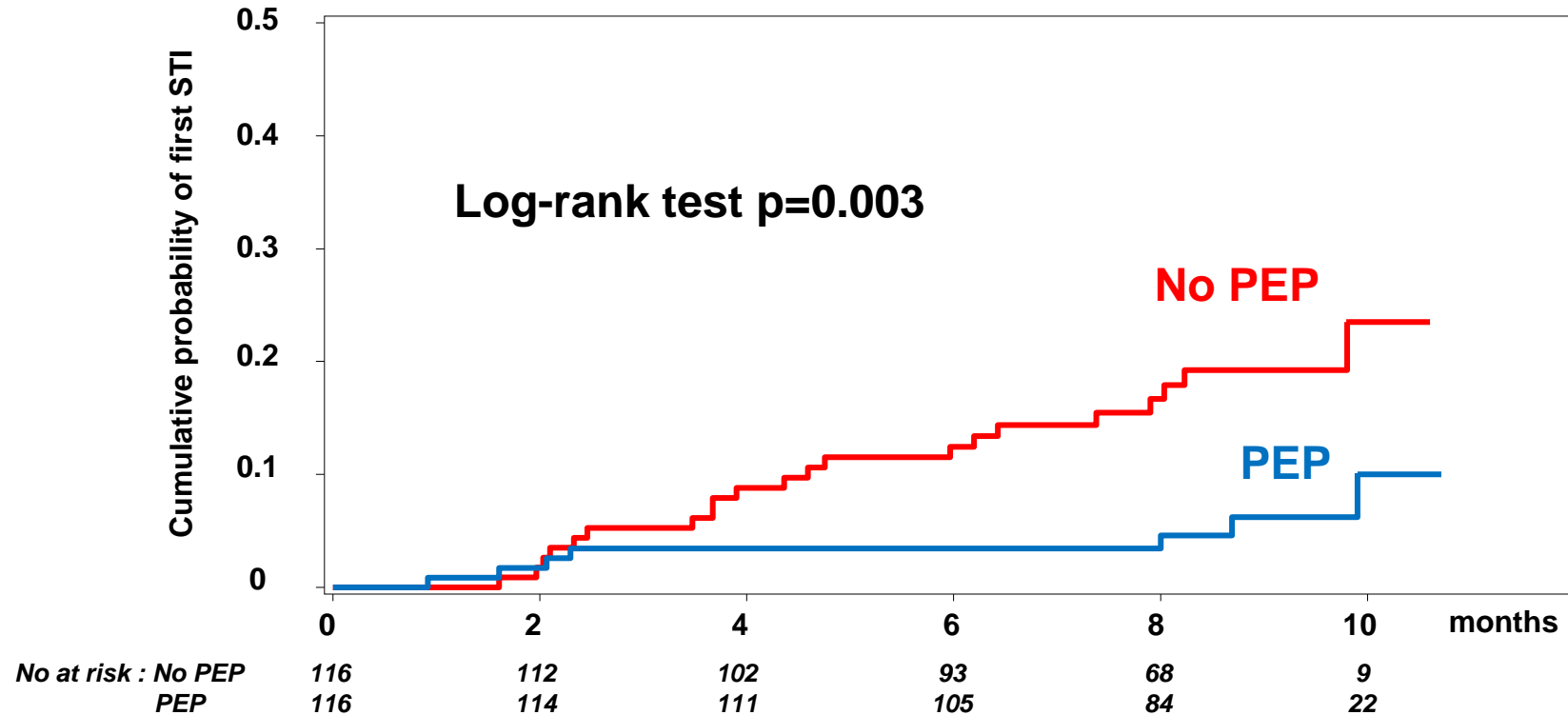


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Incidence of First Episode of Chlamydia



- Median follow-up of 8.7 months (IQR: 7.8–9.7): 28 subjects infected
- **21 in no PEP arm** (incidence: 28.6/100 PY), **7 in PEP arm** (incidence: 8.7/100 PY)
- **Hazard Ratio: 0.30 (95% CI: 0.13-0.70, $p=0.006$)**

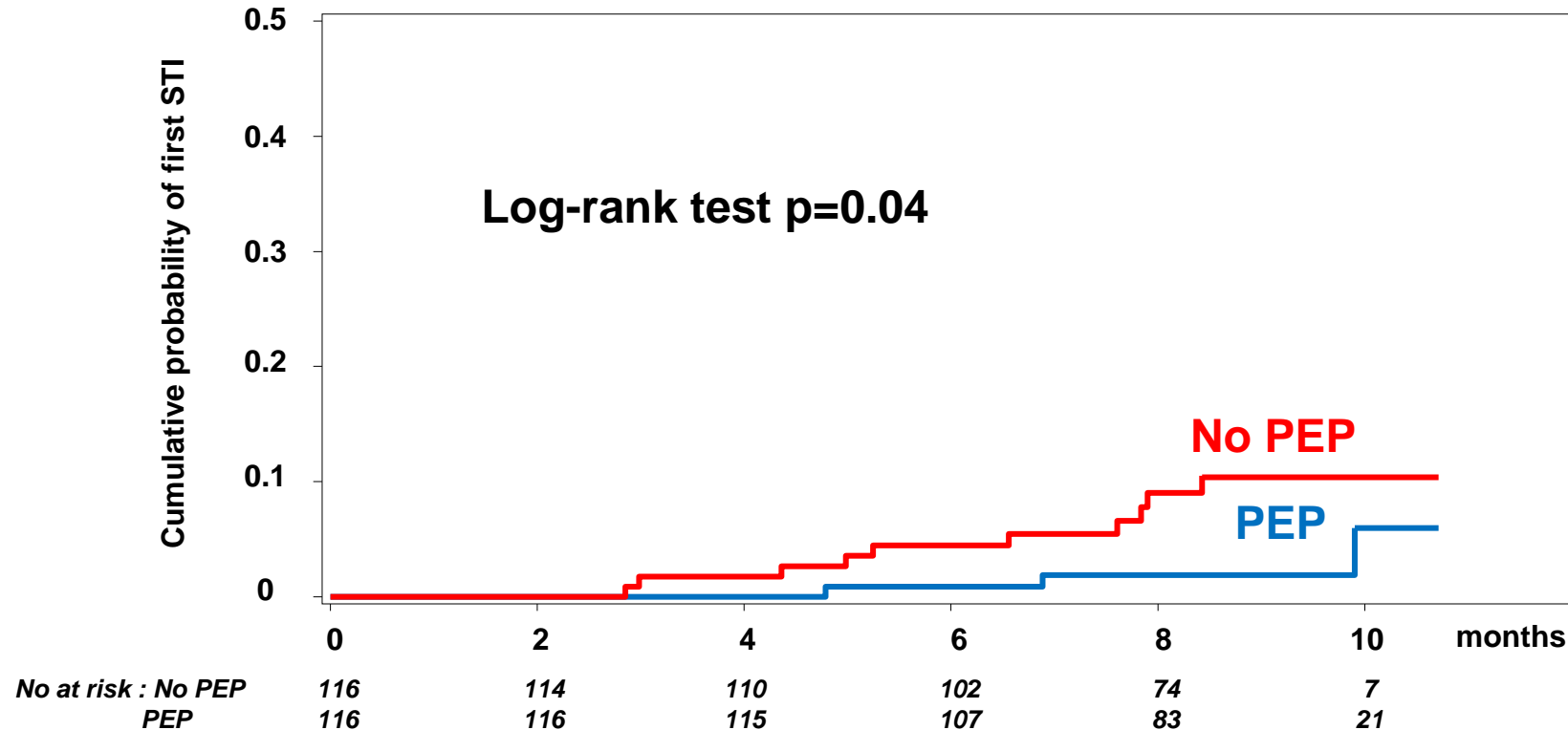


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Incidence of First Episode of Syphilis



- Median follow-up of 8.7 months (IQR: 7.8-9.7): 13 subjects infected
- **10 in no PEP arm** (incidence: 12.9 / 100 PY), **3 in PEP arm** (incidence: 3.7/100 PY)
- **Hazard Ratio: 0.27 (95% CI: 0.07–0.98, p<0.05)**

Sites of *N. gonorrhoeae* Infection

	PEP Doxy	No PEP	P value
SITE PCR +			
Anus	11	19	
Throat	15	12	
Urine	1	7	
Total sites	27	38	
Total infections	27	30	
Infections per 100 py	32.6	37.3	0.63



Co-Chairs Choice

Doxycycline post-exposure prophylaxis for prevention of STIs among MSM and TGW who are living with HIV or on PrEP

Annie Luetkemeyer, Julie Dombrowski, Stephanie Cohen, Deborah Donnell, Cole Grabow, Clare Brown, Cheryl Malinski, Rodney Perkins, Melody Nasser, Carolina Lopez, Susan Buchbinder, Hyman Scott, Edwin Charlebois, Diane Havlir, Olusegun Soge, Connie Celum on behalf of the **DoxyPEP Study Team**



 **AIDS 2022**

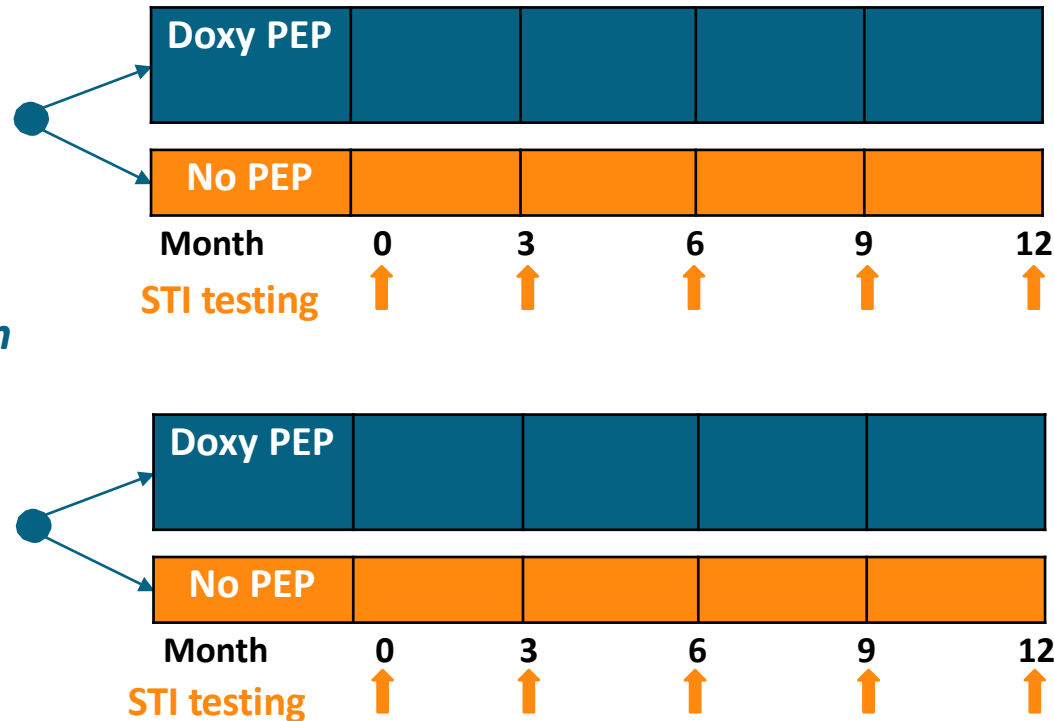
DOXYPEP

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

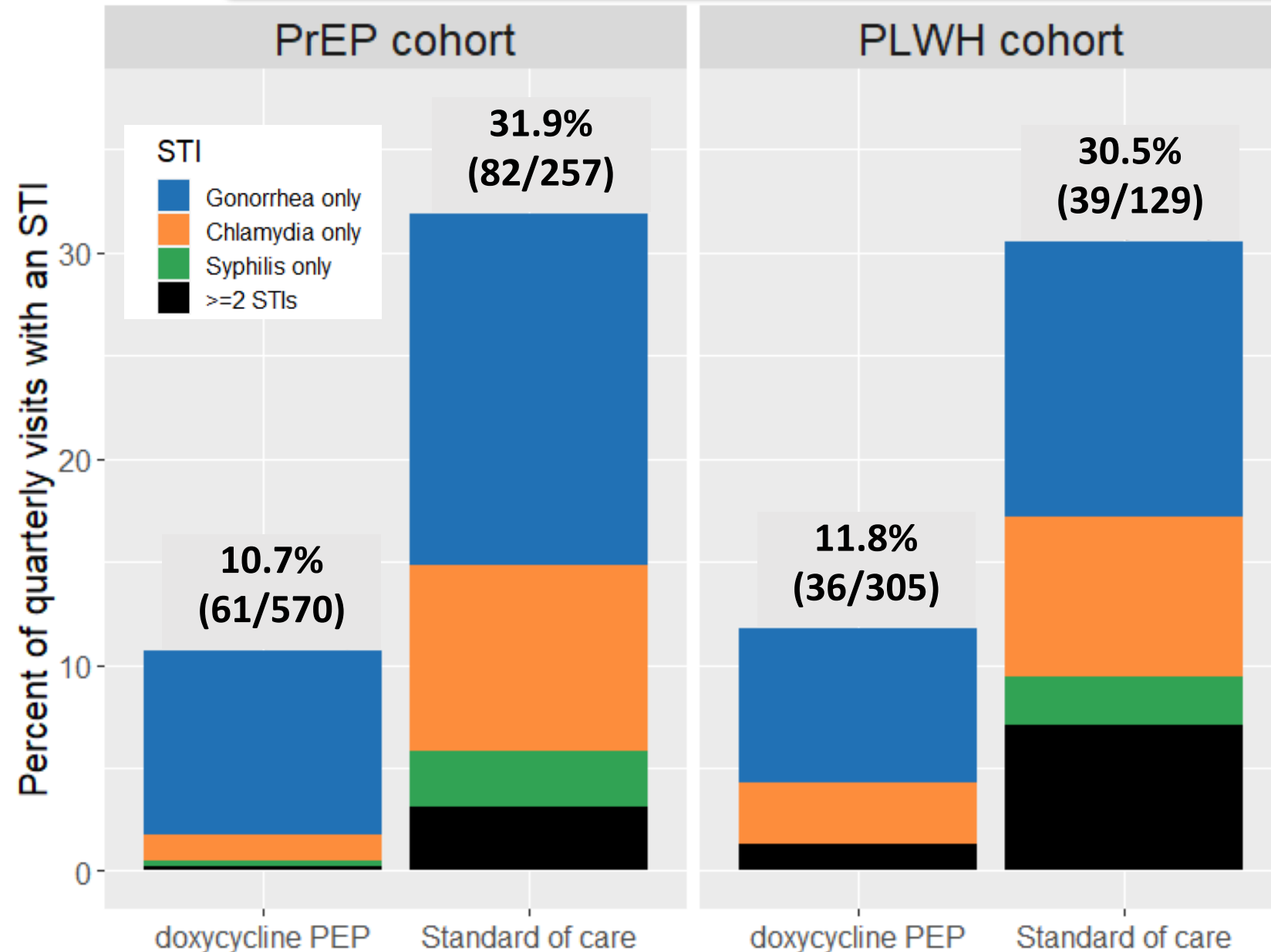
Detect a 50% reduction of STIs/quarter with doxyPEP

Stopping boundaries for effectiveness: $\alpha < 0.025$ for both cohorts

DSMB recommended early discontinuation in May 2022 at first interim analysis

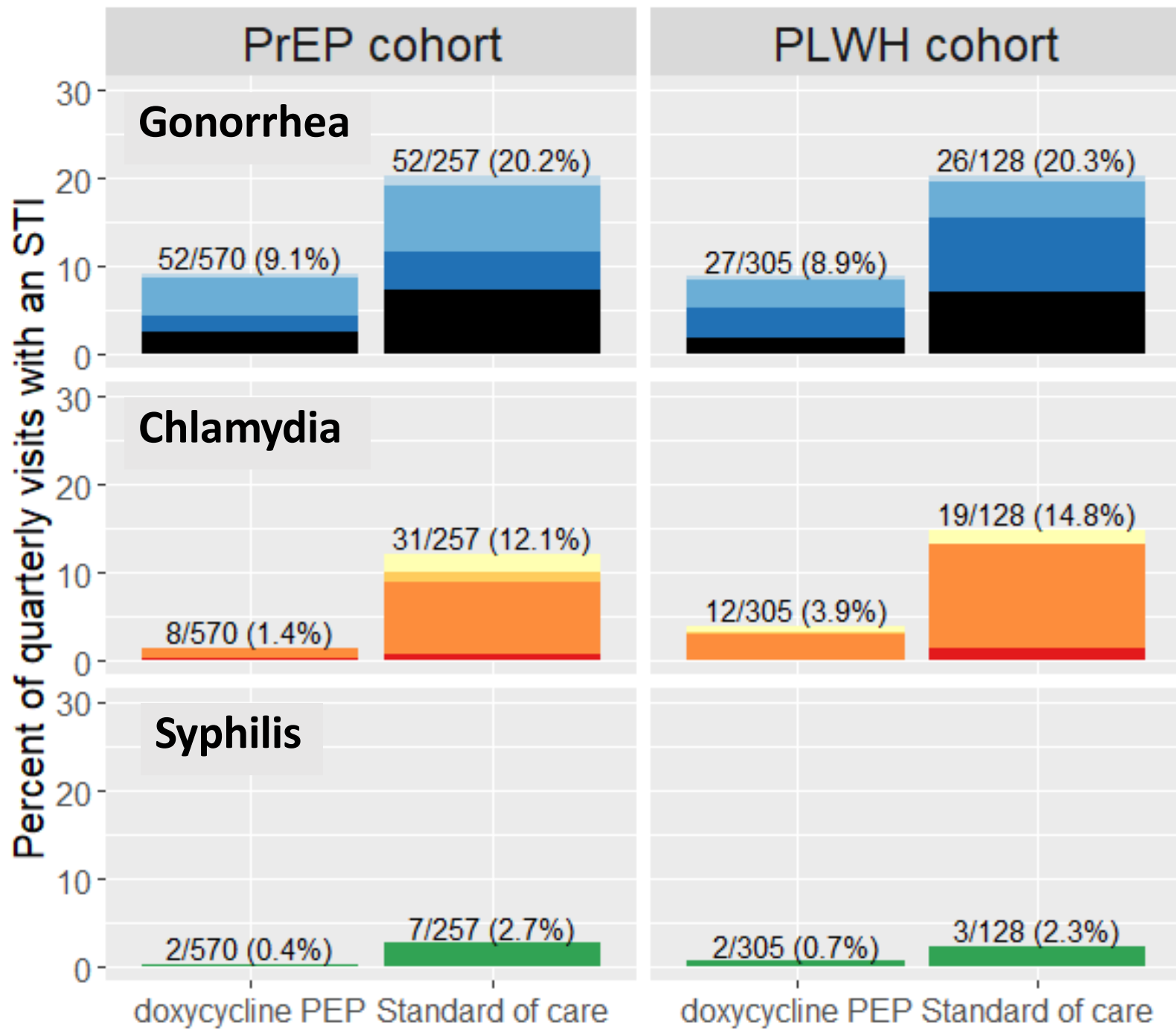


Primary Endpoint: STI incidence per quarter (501 pts enrolled)

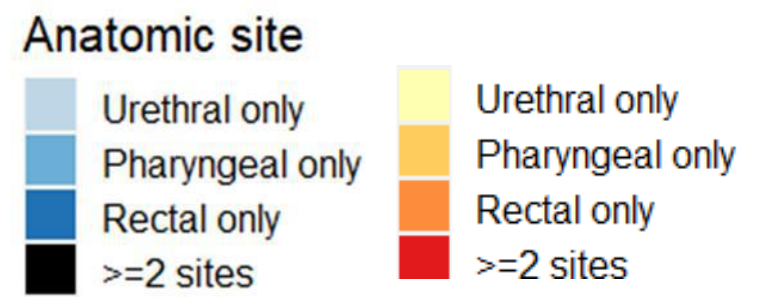


Reduction in STI incidence/quarter	
risk reduction (95% CI)	
PrEP	0.34 (0.24 - 0.46)
Living with HIV	0.38 (0.24 - 0.60)
Total	0.35 (0.27 - 0.46)

all p < 0.0001



Individual STI incidence by study arm & cohort



Reduction in each STI per quarter

risk reduction (95% CI)

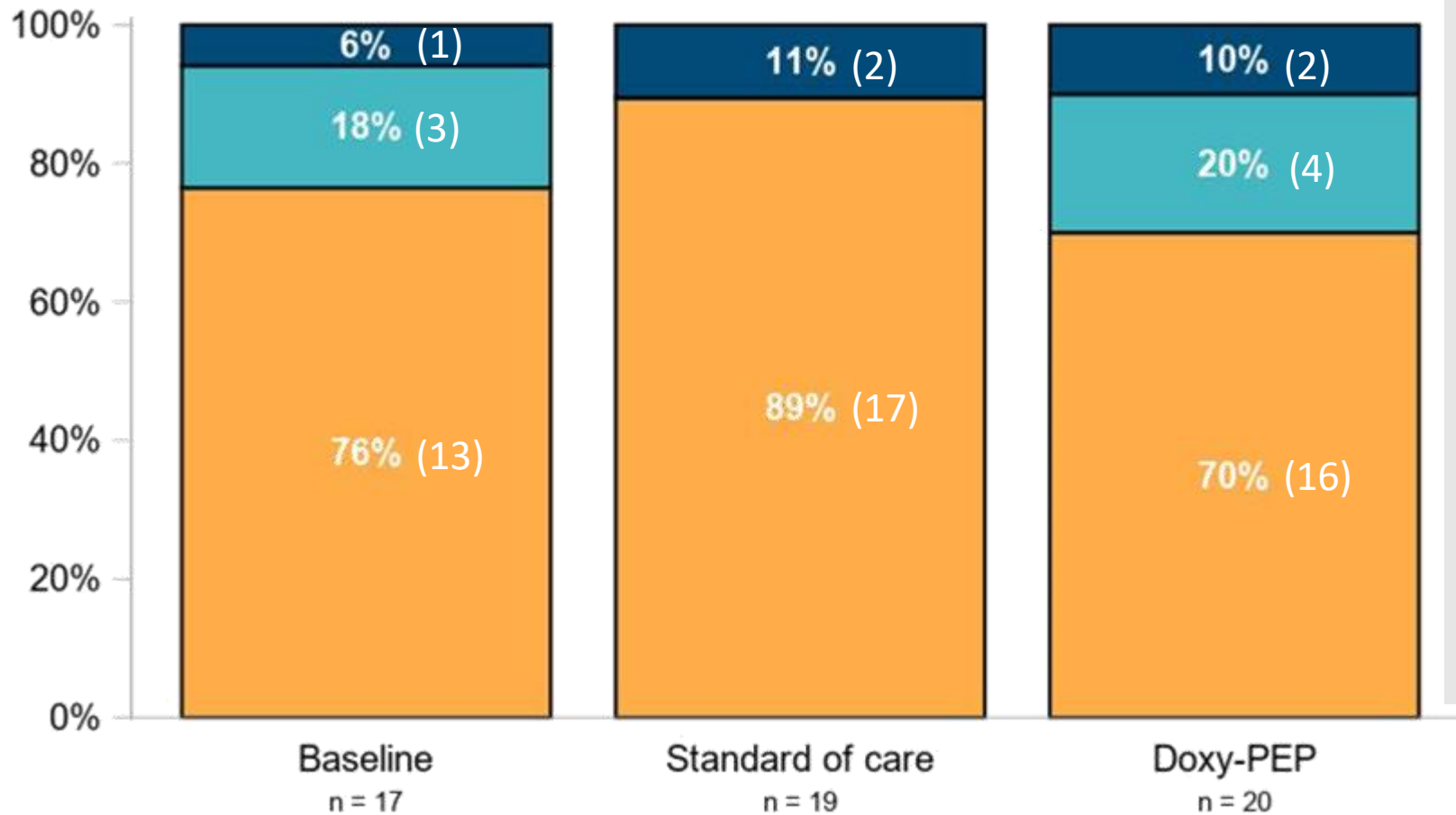
	PrEP	PLWH
GC	0.45 (0.32 - 0.65) <i>p</i> <0.0001	0.43 (0.26 - 0.71) <i>p</i> =0.001
CT	0.12 (0.05 - 0.25) <i>p</i> <0.0001	0.26 (0.12 - 0.57) <i>p</i> =0.0007
Syphilis	0.13 (0.03 - 0.59) <i>p</i> =0.0084	0.23 (0.04 - 1.29) <i>p</i> =0.095

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 per month, with 87% covered by doxycycline per self-report
- **Doxycycline use:** Median of 4 doses (800 mg) per month (IQR: 1-10)

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

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

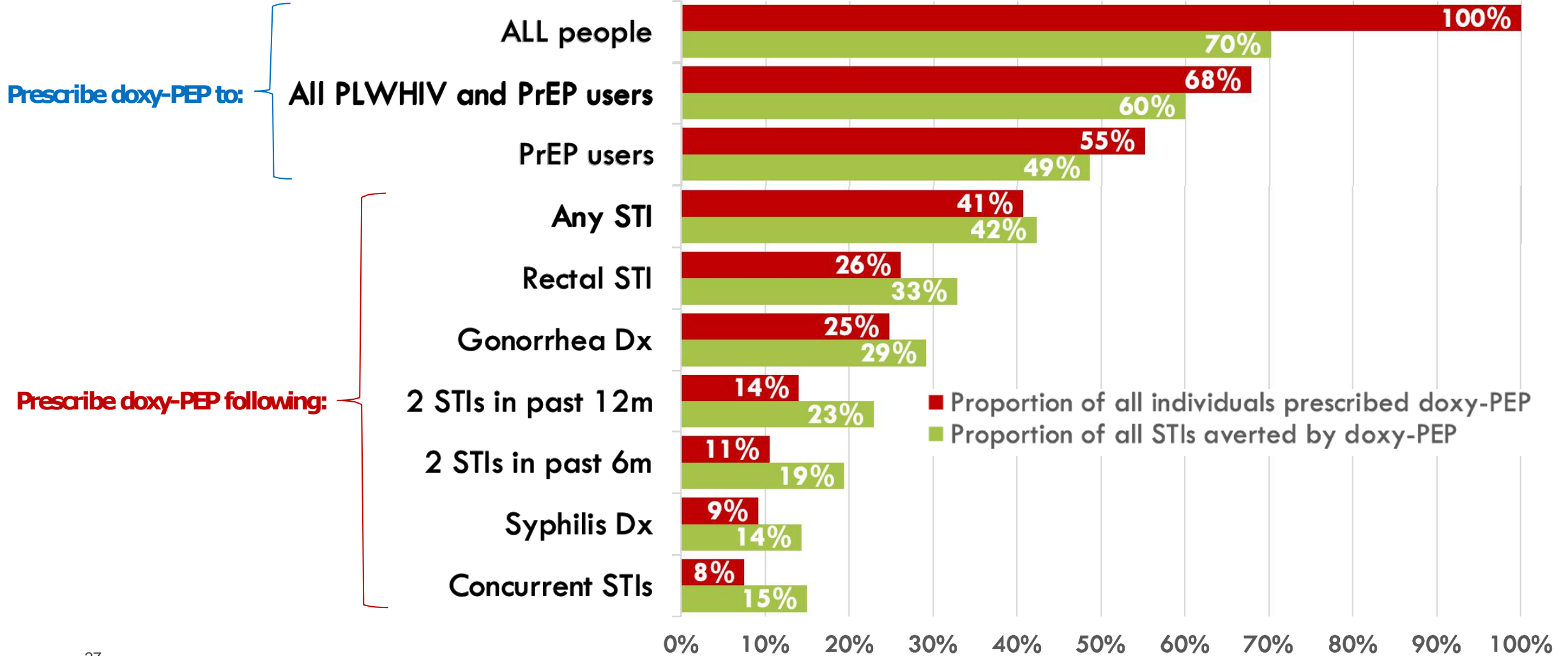


- TCN-R similar in incident GC at baseline and on doxy-PEP
- Increased TCN-R in doxy-PEP vs. standard of care suggests doxy-PEP may be less protective against GC strains with existing TCN-R
- Limited by low number of GC samples with MIC results (56/320)

■ MIC < 2 (not resistant) ■ MIC ≥ 2 (resistant) ■ MIC ≥ 16 (high-level resistance)

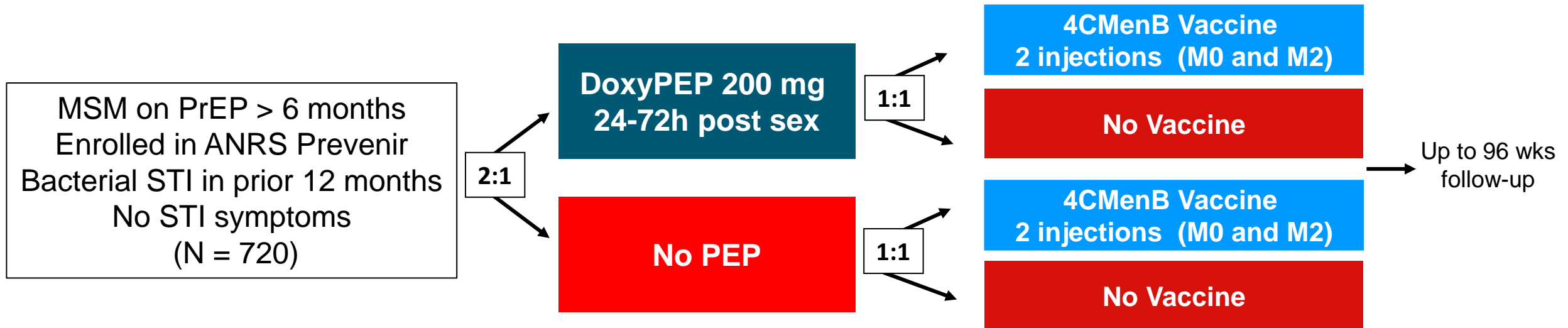
Doxy-PEP use vs STIs averted in a US Sexual Health Clinic

Doxy-PEP prescribing scenario



ANRS DOXYVAC Study Design

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



- 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 on GC: 720 subjects needed for an HR: 0.70 (Estimated probability of a first GC episode over 18 months: 52%, power 85%, 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



ANRS 174 DOXYVAC

Premature Study Discontinuation

- August 2022 DOXYPEP results: 65% reduction in STIs incidence (CT and syphilis ~ 80%; GC ~ 55%)
- September 2, 2022: DOXYVAC DSMB requested unblinded analysis on participants enrolled from 01/19/2021 to 07/15/2022
- Significant effectiveness of both interventions and DSMB recommended to:
 - stop enrollment of new participants
 - offer Doxy PEP and 4CMenB vaccine to all
- Recommendations endorsed by the scientific committee and ANRS

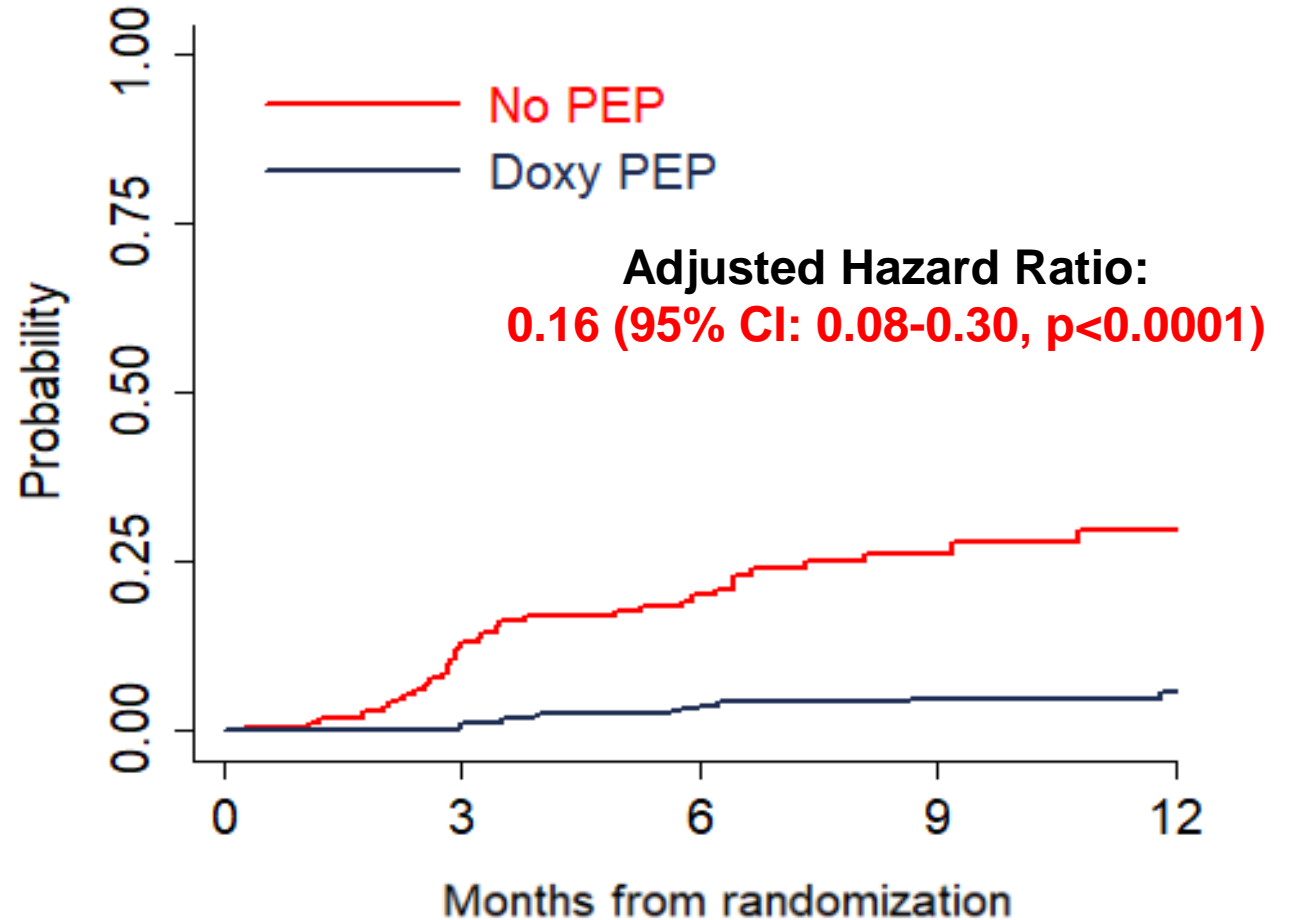
Doxycycline PEP

Time to First CT or Syphilis Infection

No interaction between Doxy PEP and 4CMenB vaccine (p=0.99)

Median follow-up: **9 months**
(IQR: 6 to 12)

49 subjects infected
36 in No PEP arm
(incidence: 35.4/100 PY),
13 in Doxy PEP arm
(incidence: 5.6/100 PY)



Number at risk

No PEP	170	137	99	47	22
Doxy PEP	332	271	220	144	83

Doxycycline PEP

Time to First GC infection

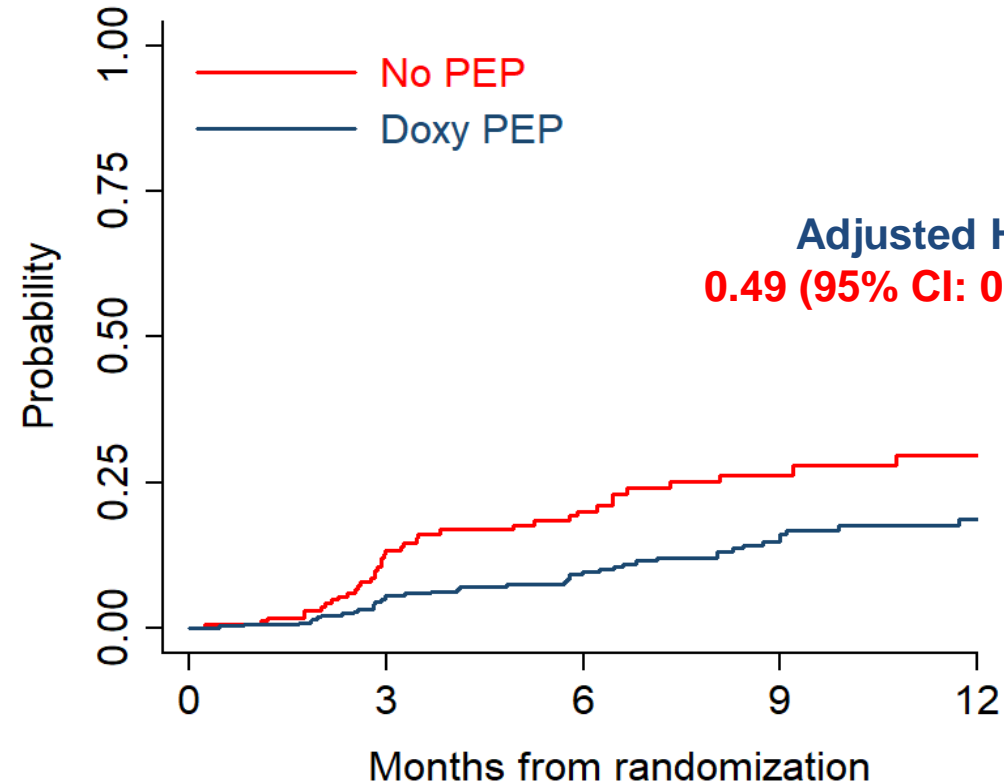
84 subjects infected

40 in No PEP arm

(incidence: 41.3/100 PY),

44 in Doxy PEP arm

(incidence: 20.5/100 PY)

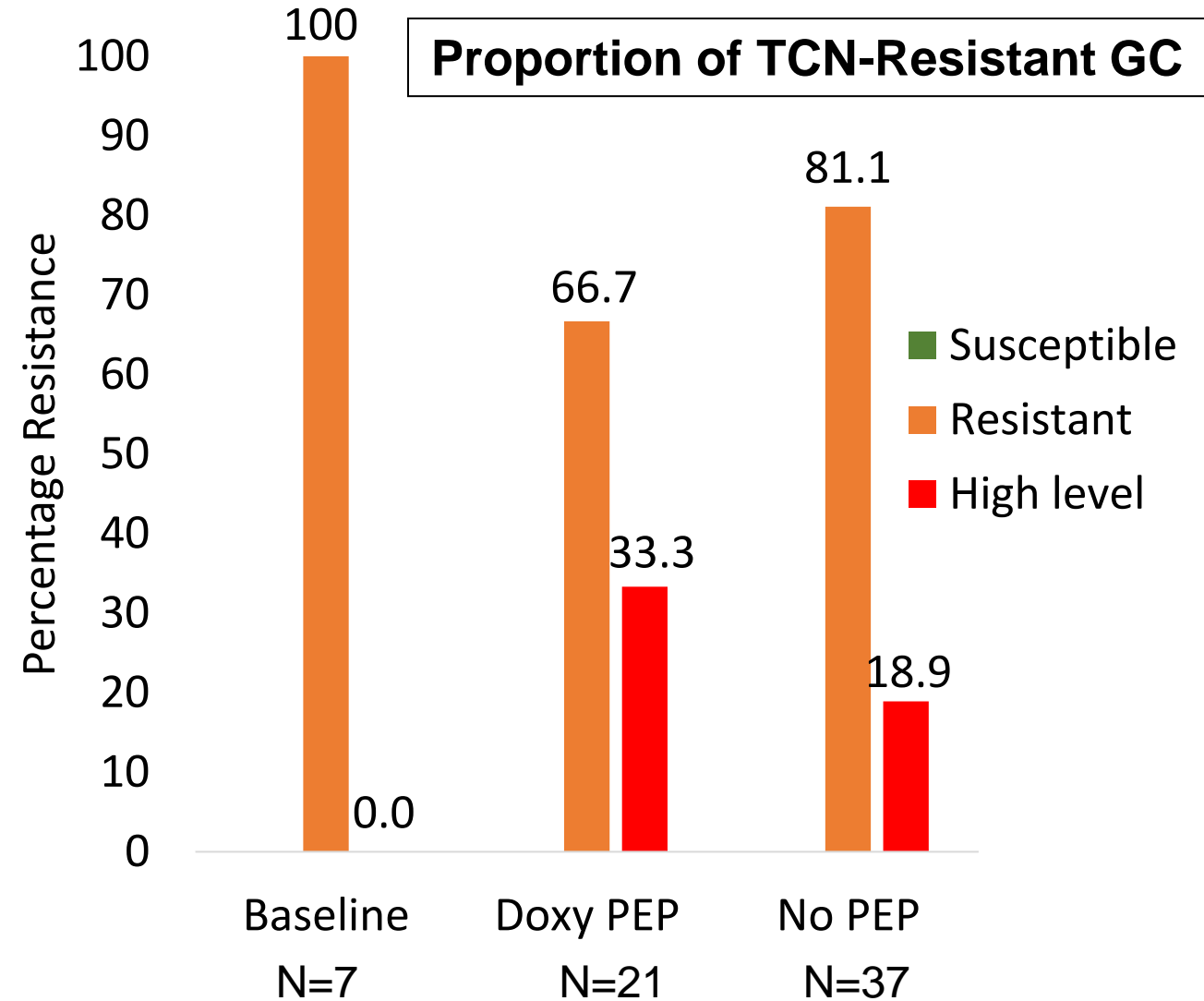


Number at risk

No PEP	170	125	90	47	20
Doxy PEP	332	259	201	128	66

Tetracycline (TCN) Resistance for 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



Doxycycline PEP for Prevention of STIs among Kenyan Women on HIV PrEP

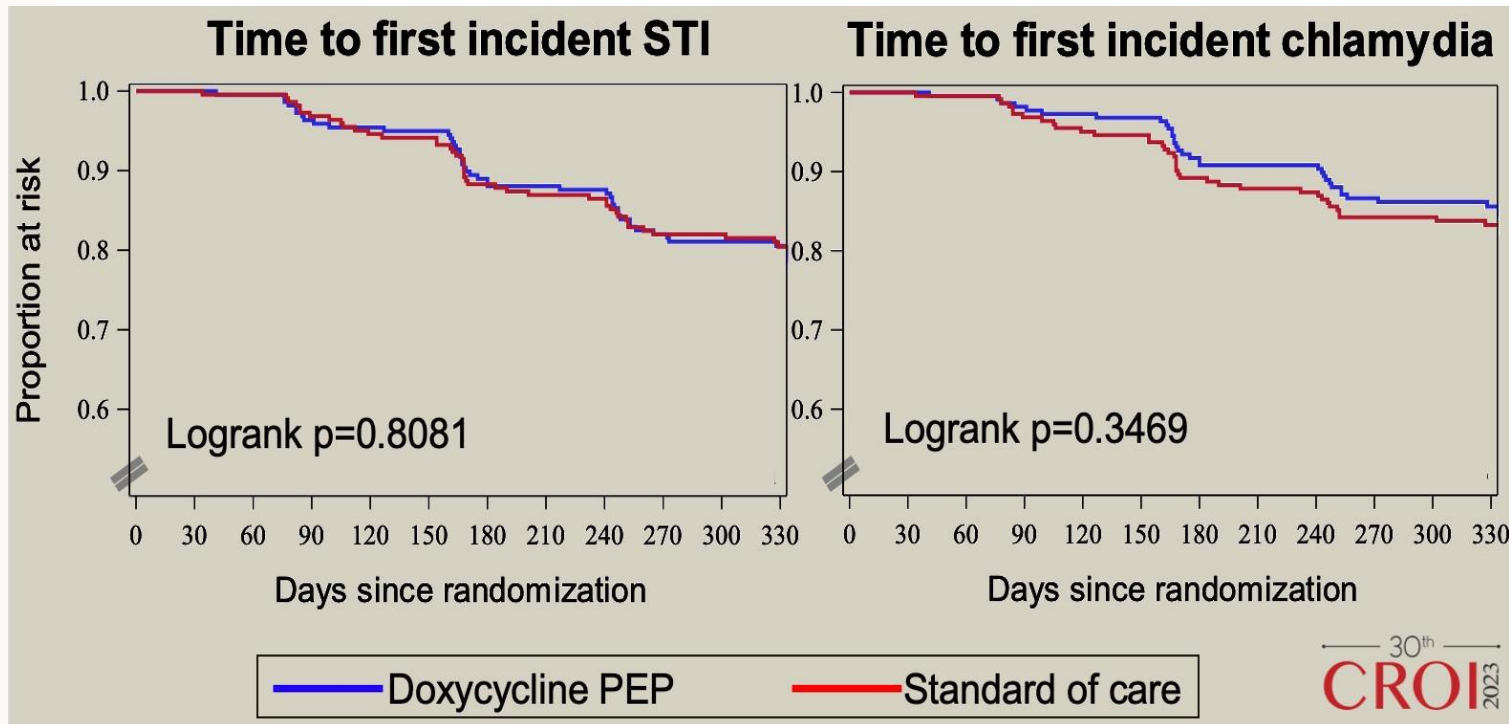


- 1:1 open-label randomized trial of dPEP (200mg doxycycline) taken within 72 hours after sex
- N=449 women taking PrEP, aged 18-30 (median age: 24 years)
- Quarterly follow-up for 12 months in Kisumu, Kenya



DPEP KENYA TRIAL RESULTS

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
	Gonorrhea	31	19	12	1.64	0.78-3.47	0.19

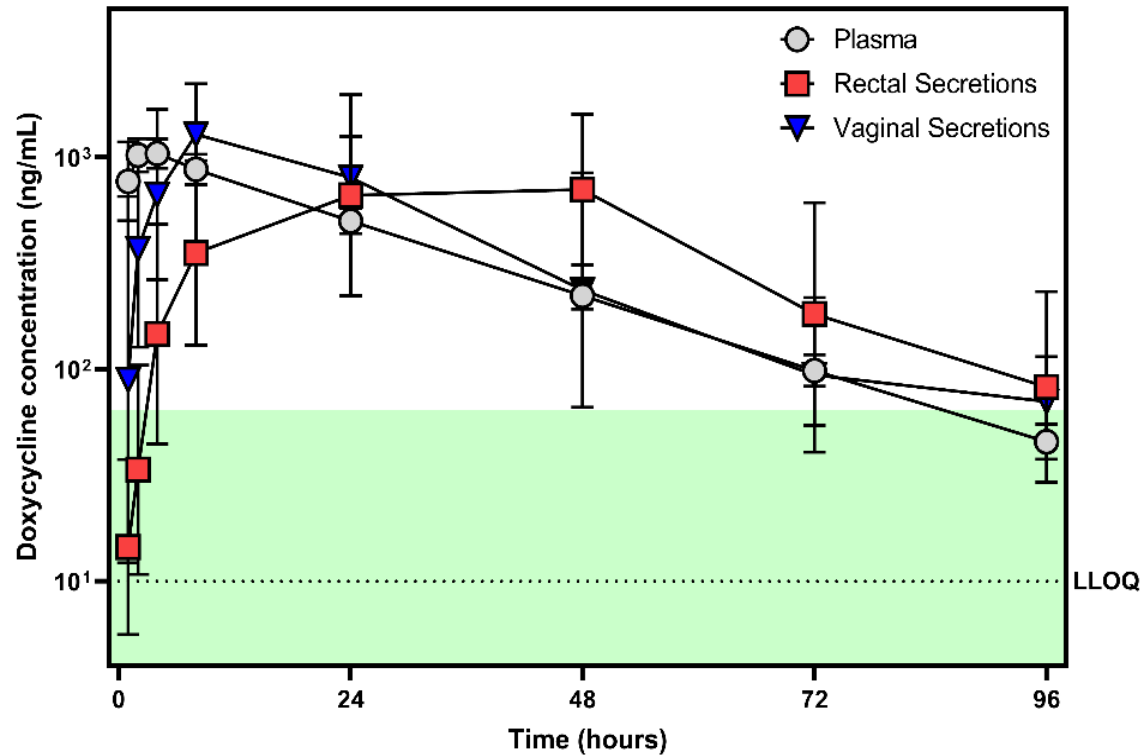


No HIV infection, 1 syphilis
Genomic test for tetracycline R
 (tetM et tetC)

- 100 % (28/28) for Ng
- 0 % (0/66) for Ct

DoxyPEP self-reported adherence 78%

Doxycycline Concentrations following 200 mg SD



Minimum Inhibitory Concentrations (MIC): *C trachomatis* MIC₉₀ = 64 ng/mL
Zheng *Sex Transm Dis* 2015

Mucosal doxycycline concentrations greater than in plasma

- Reach >10x *C trachomatis* MIC
- Remain >4x *C trachomatis* MIC up to 2 days after dosing

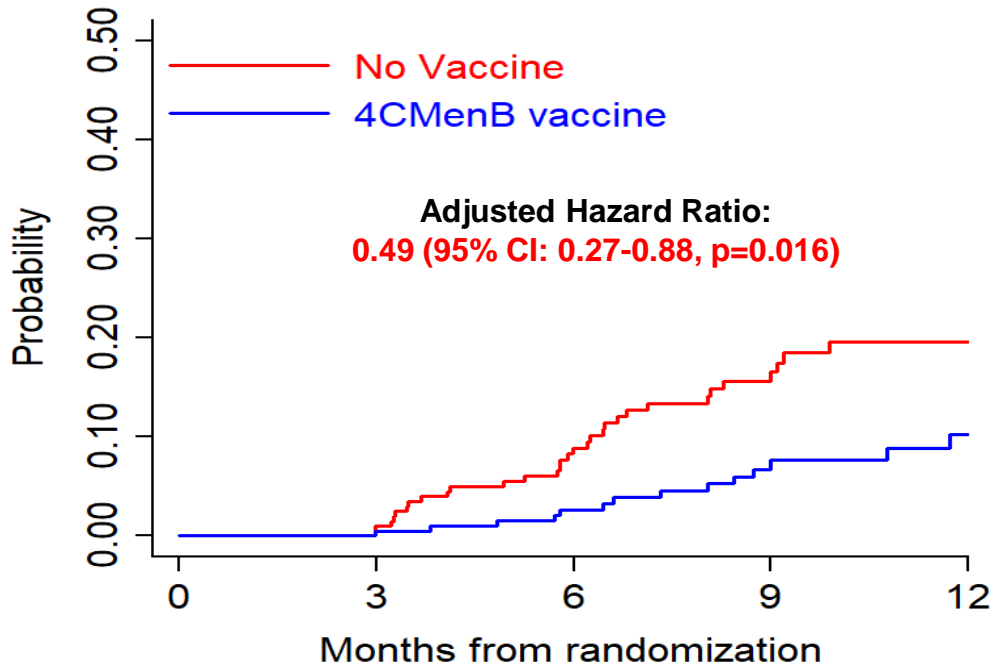
Time above <i>C. trachomatis</i> MIC			
	C _{max}	MIC	4x MIC
Plasma	16x	87 hr	44 hr
Rectal Secretions	11x	97 hr	62 hr
Vaginal Secretions	20x	101 hr	45 hr

	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

DOXYVAC: 4CMenB Vaccine to Prevent Gonorrhoeae

Time to First GC Infection

49 subjects infected
32 in No Vaccine arm (incidence: 19.7/100 PY),
17 in 4CMenB vaccine arm (incidence: 9.8/100 PY)



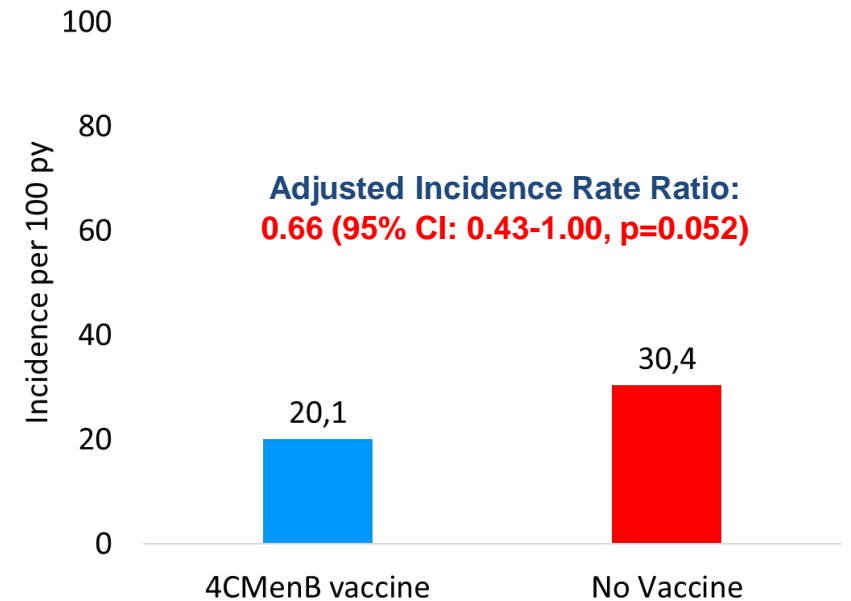
Number at risk

	0	3	6	9	12
No Vaccine	245	208	150	91	49
4CMenB vaccine	257	208	170	102	49

GC infections were considered from M3 visit (1 month after 2nd vaccine dose)

Cumulative GC Infections

90 GC infections
54 in No Vaccine arm,
36 in 4CMenB vaccine arm





PRESS RELEASE

ANRS DOXYVAC: final analysis may modify interim results of this trial assessing the effectiveness of meningococcal B vaccination in preventing gonococcal infections

ANRS | Emerging Infectious Diseases will commission an independent audit

Paris, May 15, 2023

The Primary Outcome was Positive Was that Good Enough ?

- **Does a P value < 0.05 provide strong enough evidence ?** A P value of 0.05 carries a 5% risk of a false positive result.
 - To provide proof beyond reasonable doubt, $P < 0.001$ is wised: **P-value was 0.016**
- **What is the magnitude of the treatment benefit:** 51% incidence reduction clinically relevant
 - but **95% Confidence interval: 0.27- 0.88, only 12% reduction ensured**
- **Is the primary outcome clinically important?** Mostly **asymptomatic infections**
- **Are secondary outcomes supportive?** Cumulative GC infection rates not significant (**20.1 vs 30.4/100 PY, $p=0.052$**)
- **Was the trial stopped too early?:** Interim analysis with all available data: no significant difference
 - Quality and completeness of any interim database are inevitably imperfect
 - Investigators were too happy about the results...
- **Will the trial be underpowered?** When a trial is too small to detect modest treatment effects, findings might be **inconclusive**
- **Results of a single trial should be confirmed by a second trial.**
 - Results will hopefully guide ongoing trials
- **Physicians have the final responsibility** for accurately interpreting clinical trial results

Key Takeaway

- **Doxycycline PEP reduces STI incidence among MSM**
 - 3 studies have shown consistent reductions of chlamydia, syphilis and gonorrhoea
 - Doxycycline PEP is well tolerated with high self-reported adherence
 - Evaluation of full impact on antibiotic resistance is underway (STIs, microbiome)
 - Identify people who will benefit the most from this intervention
- **Evidence of 4CMenB Vaccine efficacy to prevent gonorrhoeae still pending**
- **STI research should continue**
 - Scientific priority to meet 2030 WHO/UNAIDS targets: reduce incidence of HIV and STIs by 90%

Acknowledgments



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Back-up Slides

Discrepancy between Interim and Final Results

- Last participant enrolled on September 19, 2023
- Participants asked to perform a last visit to be offered both interventions (scheduled until Feb 28, 2023)
- Monitoring completed April 20, 2023 and final results presented to the trial steering committee (follow-up increased from 9 to 14 months)
- Discrepancy between interim and final analysis for **vaccination effectiveness**
- Number of GC events increased from 49 to > 200....
- All cases individually reviewed to understand the discrepancy
- **Interim analysis was flawed because a whole file with GC events was omitted from the interim analysis**