Doxycycline as Post-Exposure Prophylaxis for Bacterial STIs (Doxy-PEP)

Jorge A. Gallardo-Cartagena, MD, MPH

Universidad Nacional Mayor de San Marcos, Lima, Perú

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HPTN Regional Meeting

Presentation Highlights

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1. What is the main issue or question the presentation addresses?
   - **Bacterial STIs are increasing worldwide and disproportionally affecting MSM and TGW**

2. What is the key finding or ‘takeaway message’?
   - **Doxy-PEP can reduce the incidence of chlamydia, syphilis, and to a lesser extent, gonorrhea in MSM and TGW according to data from 3 randomized clinical trials**

3. How does the research advance HIV prevention efforts?
   - **We should advance the implementation of Doxy-PEP, while continuing to address concerns such as long-term effectiveness and antimicrobial resistance**

Bacterial STIs are a Public Health Threat

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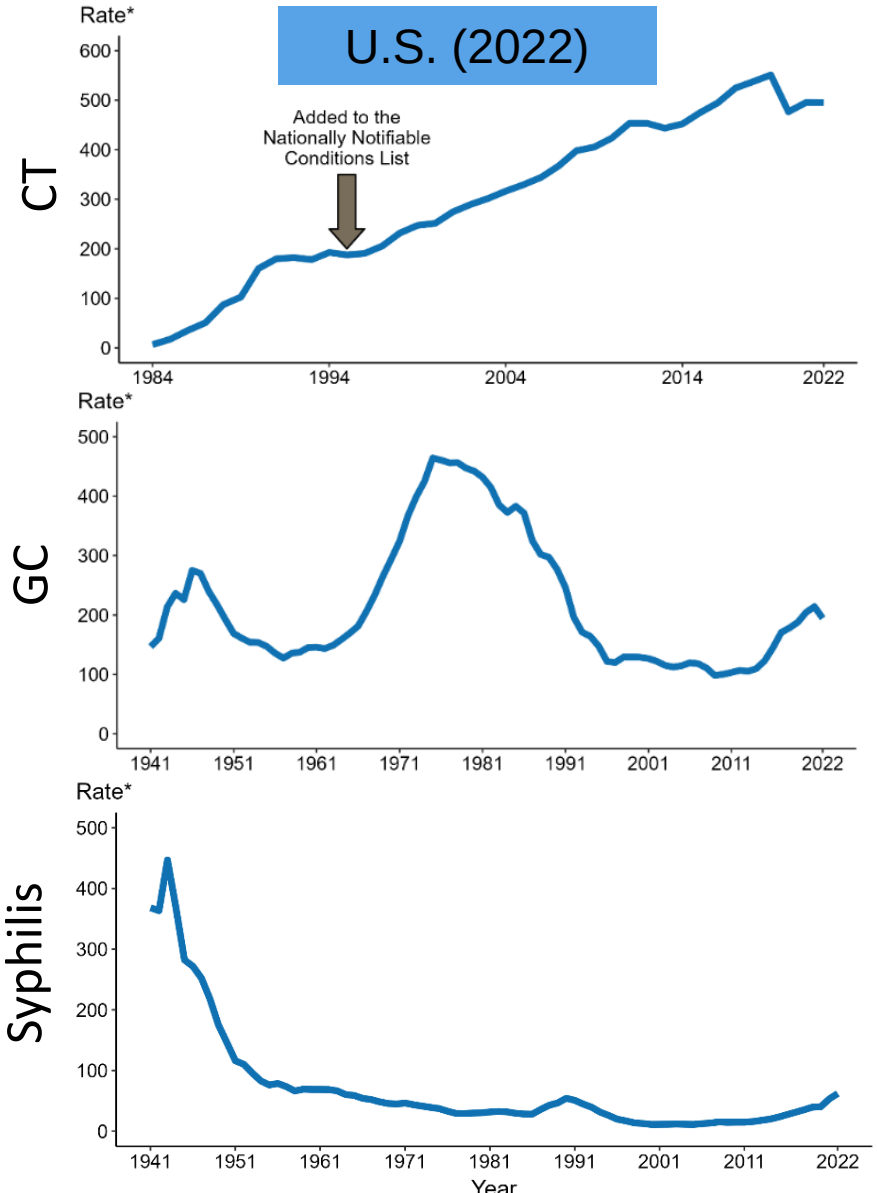
1 million of new bacterial STIs everyday

U.S. (2022)



Sustained increases in the era of effective HIV treatment and prevention

WHO. 2021
CDC STI Surveillance. 2022

Prevention Toolbox for STI Prevention

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All these strategies have shown inconsistent results

- Risk reduction counseling
- Promoting condom use
- Testing and treating STIs
- Notification of sexual partners

STI Post-Exposure Prophylaxis (PEP)

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Old studies proposed using sulfathiazole and penicillin for GC PEP

Public Health Reports

Vol. 63 • OCTOBER 29, 1948 • *No. 44*

Prevention of Gonorrhea With Penicillin Tablets

Preliminary Report

By HARRY EAGLE, *National Institutes of Health, Public Health Service*; A. V. GUDE, M. D., Lt. jg., MC, USNR; G. E. BECKMANN, M. D., Lt. jg., MC, USNR; GEORGE MAST*, M. D.; J. J. SAPERO, M. D.; Capt., MC, USN, *Research Division, Bureau of Medicine and Surgery*; and J. B. SHINDLEDECKER, HMC, USN.

THE ORAL USE OF SULFATHIAZOLE AS A PROPHYLAXIS FOR GONORRHEA

PRELIMINARY REPORT

CAPTAIN JAMES A. LOVELESS
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
COLONEL WILLIAM DENTON
MEDICAL CORPS, ARMY OF THE UNITED STATES

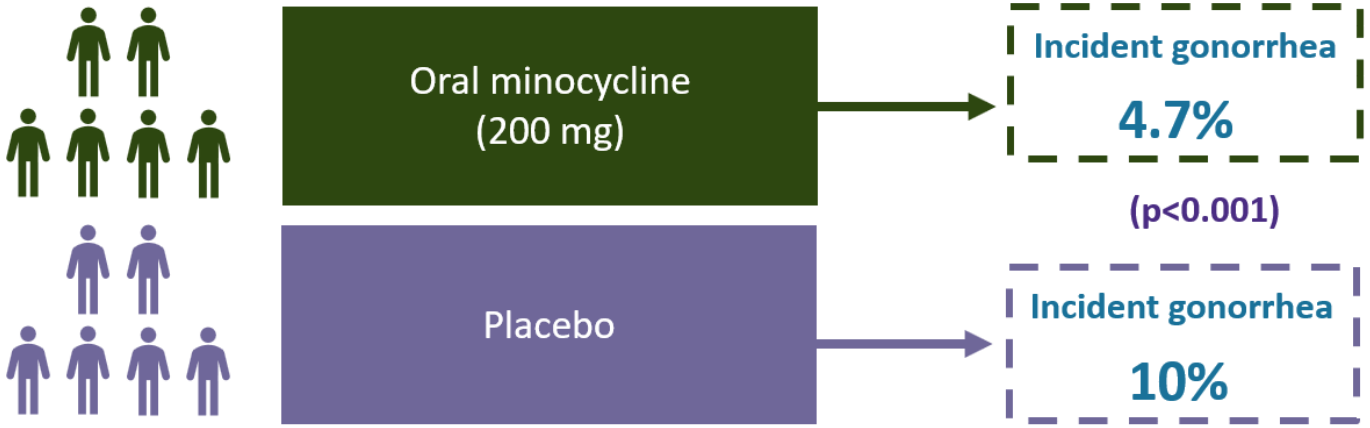
Our purpose in this study is to determine whether the prophylactic administration of sulfathiazole prevents the development of gonorrhea. The existence of an inordinately high gonorrhea rate among certain troops makes the development of an easily administered chemical prophylaxis particularly important. The fol-

1074 THE NEW ENGLAND JOURNAL OF MEDICINE May 10, 1979

A TRIAL OF MINOCYCLINE GIVEN AFTER EXPOSURE TO PREVENT GONORRHEA

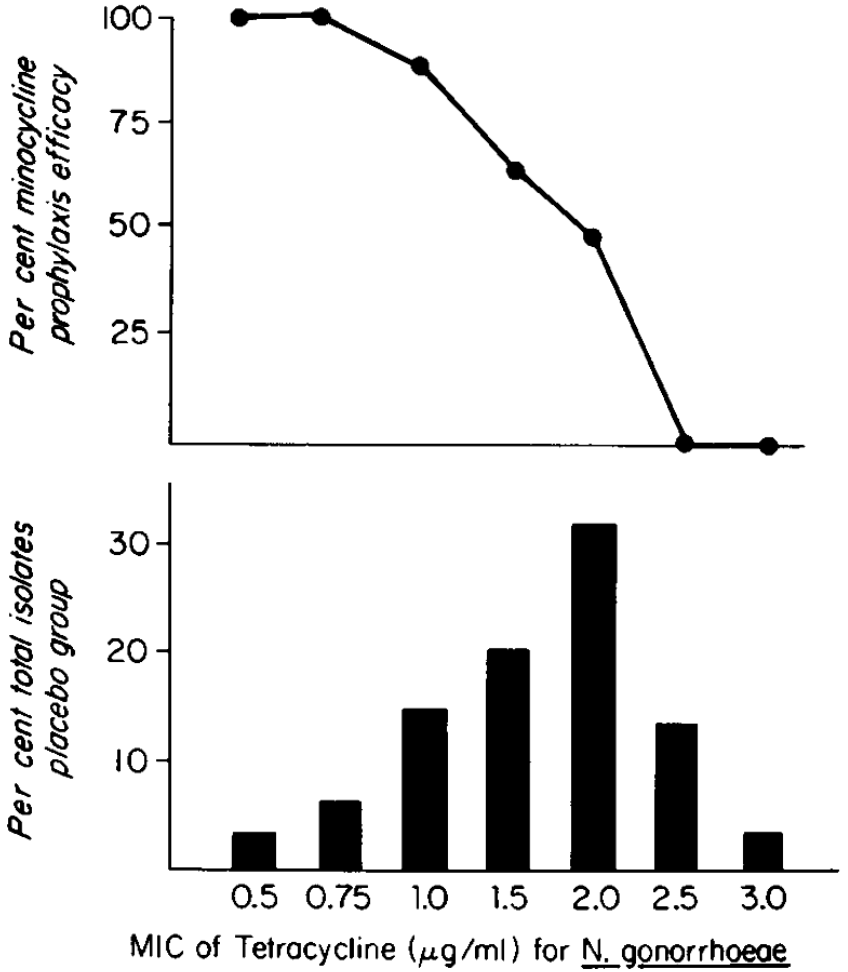
WILLIAM O. HARRISON, M.D., RICHARD R. HOOPER, M.D., PAUL J. WIESNER, M.D., AXEL F. CAMPBELL, M.D., WALTER W. KARNEY, M.D., GLADYS H. REYNOLDS, PH.D., OSCAR G. JONES, B.S., AND KING K. HOLMES, M.D., PH.D.

N = 1089 U.S. Navy men
RCT: oral minocycline (200 mg) or placebo a median of 8 hours after sex with FSW



Significant reduction in GC incidence with minocycline, but efficacy was dependent on tetracycline MIC

"Limited effectiveness as a public health measure because of the potential to select strains of gonococci with resistance to minocycline"



Harrison et al, 1979

Reasons for Revisiting STI PEP with Doxycycline

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- Better toxicity profile compared to older tetracyclines
- Relatively cheap and available as generics
- Successfully used as prophylaxis for other diseases
- Active against CT, GC, and syphilis
- Some resistance in GC (≈20% in the US, higher in other settings)

- Not used as first line treatment for GC
- We don’t know how much activity is needed for PEP

Daily Doxycycline PrEP (2015)

Study design	Open-label, randomized 1:1 **daily doxy-PrEP vs $$**
Inclusion criteria	Adult MSM/TGWSM with HIV and ≥2 prior syphilis episodes
Participants	30
Primary outcome	Any bacterial STI over 48 weeks
Results	**Decreased any STI by 73%**

STI = gonorrhea, chlamydia and syphilis
MSM = men who have sex with men
TGWSM = transgender women who have sex with men

Outcome	No. Visits With Outcome		Follow-Up Analysis (Through 48 wk)		On-Drug Analysis (Through 36 wk)	
	Doxy Arm	CM Arm	*P*	OR (95% CI)	*P*	OR (95% CI)
STI contraction						
Gonorrhea or chlamydia only	4	8	0.18	0.36 (0.08–1.56)	0.25	0.42 (0.09–1.89)
Syphilis only	2	7	0.10	0.24 (0.04–1.33)	0.16	0.27 (0.04–1.73)
Any STD (gonorrhea, chlamydia, syphilis, or any combination thereof)	6	15	0.02	0.27 (0.09–0.83)	0.07	0.30 (0.08–1.09)

*ORs or rate ratios below 1 indicate the decreased odds/rates in the doxycycline arm compared with CM arm; OR or rate ratios above 1 indicate increased odds/rates in the doxy arm compared with the CM arm.

- No differences by individual STI

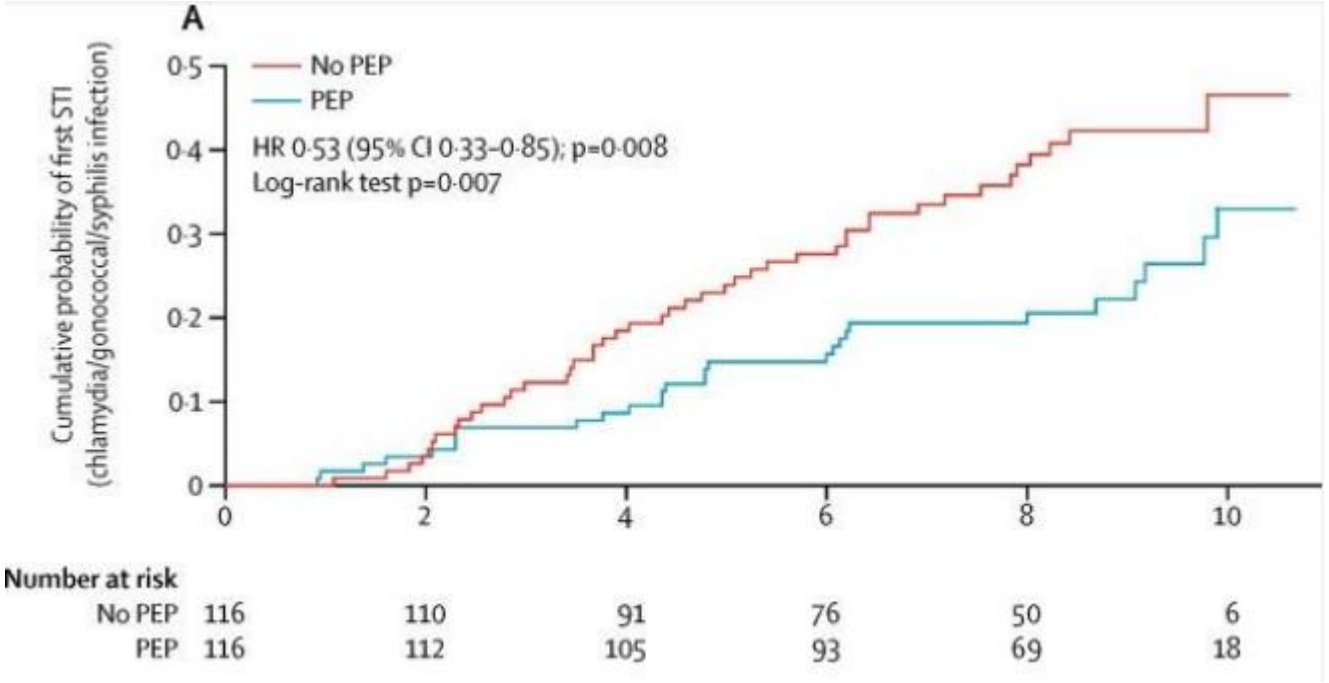
Slide adapted from Chase Cannon

Bolan, et al. Sex Transm Dis 2015

IPERGAY (2018) – France

Study design	Open-label, randomized **1:1 dPEP (limited to ≤3x/weekly) vs SOC**
Inclusion criteria	MSM on oral HIV PrEP as part of parent clinical trial
Participants	232
Primary outcome	Time to first STI
Results	**Overall ↓ 47%* Chlamydia ↓ 70%* Syphilis ↓ 73%***

Bacterial STI = gonorrhea, chlamydia and syphilis
*Statistically significant result



- Median 660 mg doxy-PEP per month (3-4 doses)
- Significant reduction in CT and syphilis; trend toward efficacy for GC
- No significant change in # sex partners or condomless sex acts between groups

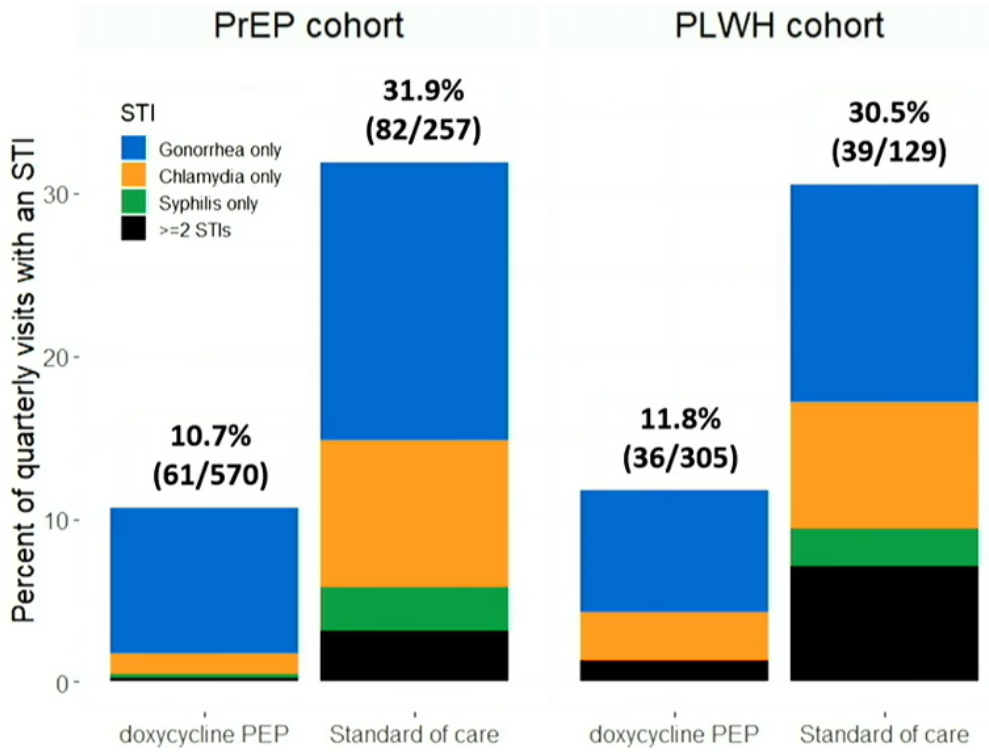
Slide adapted from Chase Cannon

Molina, et al. Lancet Infect Dis 2018

DoxyPEP (2022) – United States

Study design	Open-label, randomized **2:1** **dPEP vs SOC**
Inclusion criteria	Adult MSM/TGWSM HIV+ or PrEP; ≥1 recent STI
Participants	501
Primary outcome	STI incidence per quarter
Results	**All STIs ↓ 65%*** **Chlamydia ↓ 74-88%*** **Syphilis ↓ 77-87%*** **Gonorrhea ↓ 55-57%***

dPEP = doxycycline post-exposure prophylaxis
SOC = standard of care | MSM = men who have sex with men
STI = gonorrhea, chlamydia and syphilis
*Statistically significant result



DOXYPEP

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

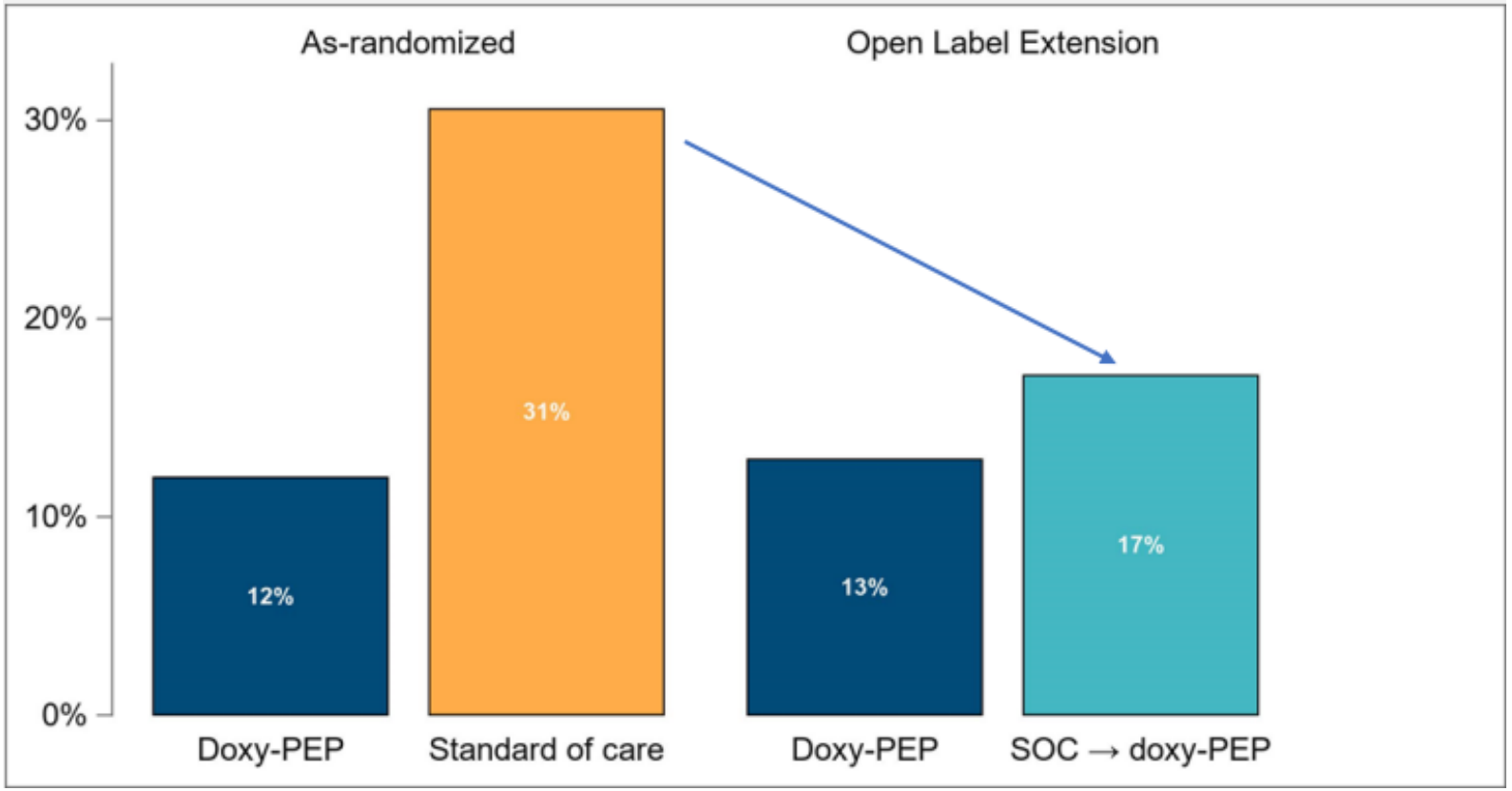
- Median 4 doses per month (IQR 1-10)
- No significant change in sexual behavior during follow-up
- Study stopped early due to significant results

Slide adapted from Chase Cannon

Luetkemeyer, et al. NEJM 2023

DoxyPEP Open Label Extension (OLE)

Incidence of >1 STIs per quarter



- Sustained reduction in STIs during DoxyPEP OLE
- Despite modest increases in # of sex partners and condomless sex, doxy-PEP was still effective

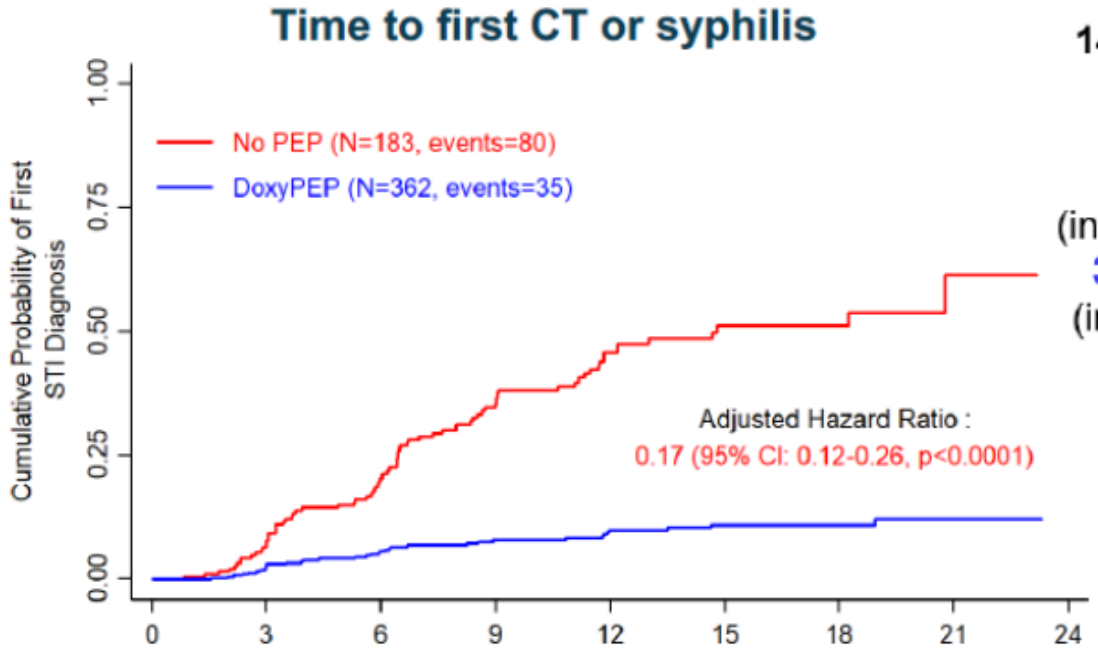
Slide adapted from Chase Cannon

Luetkemeyer, et al. CROI 2024

DOXYVAC (2023) – France

Study design	Factorial: **2:1 dPEP vs none** + Men B vax vs none
Inclusion criteria	Adult MSM with ≥1 recent STI, at least 6 mo on oral HIV PrEP
Participants	502; early stop for effectiveness
Primary outcome	Time to first syphilis or CT
Results	**CT or syph ↓ 83%* GC: ↓ 33%***

dPEP = doxycycline post-exposure prophylaxis
MSM = men who have sex with men
STI = gonorrhea, chlamydia and syphilis
*Statistically significant result



Median follow-up:
14 months (IQR: 9-18)

115 subjects infected
80 in No PEP arm
(incidence: 53.2/100 PY),
35 in Doxy PEP arm
(incidence: 8.8/100 PY)

- Median 3.5 doses per month (IQR 2-5.5)
- Significant STI risk reduction for CT, syphilis & Mgen (aHR: 0.55, 95% CI: 0.34-0.89)
- Smaller decrease for GC (aHR: 0.67; 95% CI: 0.52-0.87)
- No significant change in sexual behavior during follow-up

Slide adapted from Chase Cannon

Molina, et al. Lancet ID. 2024

dPEP (2023) – Kenya

Study design	Open-label, randomized 1:1 **dPEP vs SOC**
Inclusion criteria	Adult women on oral HIV PrEP
Participants	443
Primary outcome	STI incidence over 12 months
Results	High incidence (27%) but **no difference between groups**

dPEP = doxycycline post-exposure prophylaxis
STI = gonorrhea, chlamydia and syphilis
*Statistically significant result

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

- Median 4 doses of doxy-PEP per month (IQR 0-8)
- High self-reported adherence (≥80%)
- Low hair drug levels in women in doxycycline group suggest low adherence to doxy-PEP

100% (n=6) tetracycline-resistant (*tet*M) *Neisseria gonorrhoeae* at baseline and 100% at follow-up (n=22).

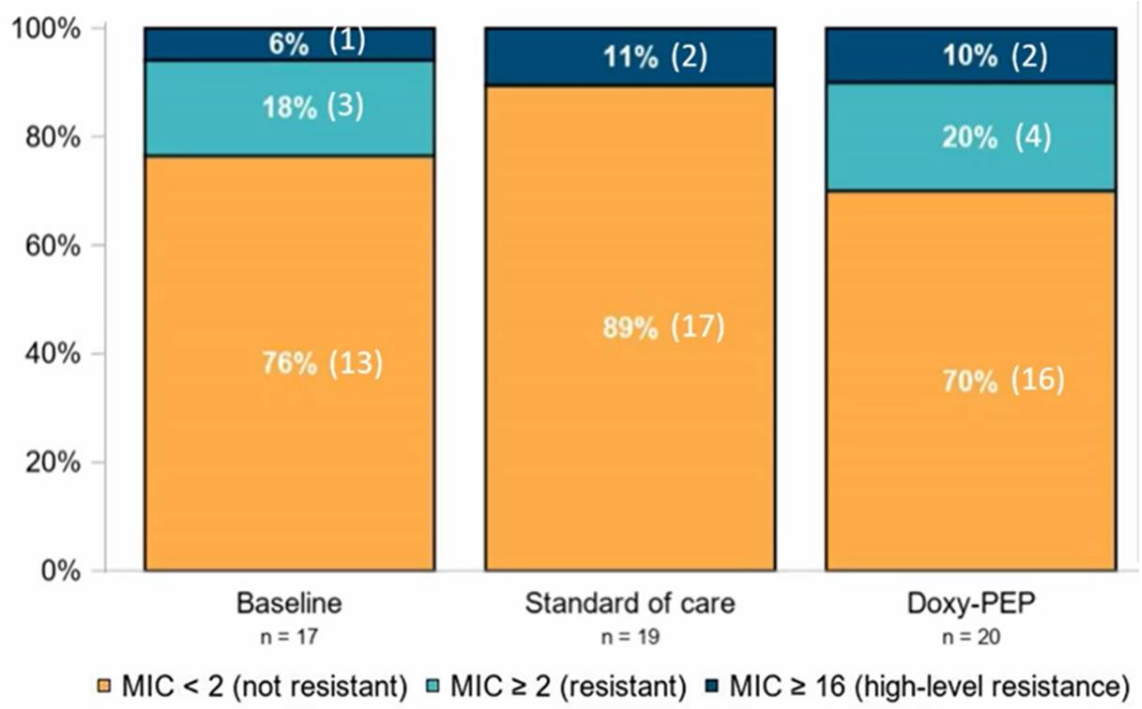
0% (n=66) detection of *tet*C in *Chlamydia trachomatis*.

Slide adapted from Chase Cannon

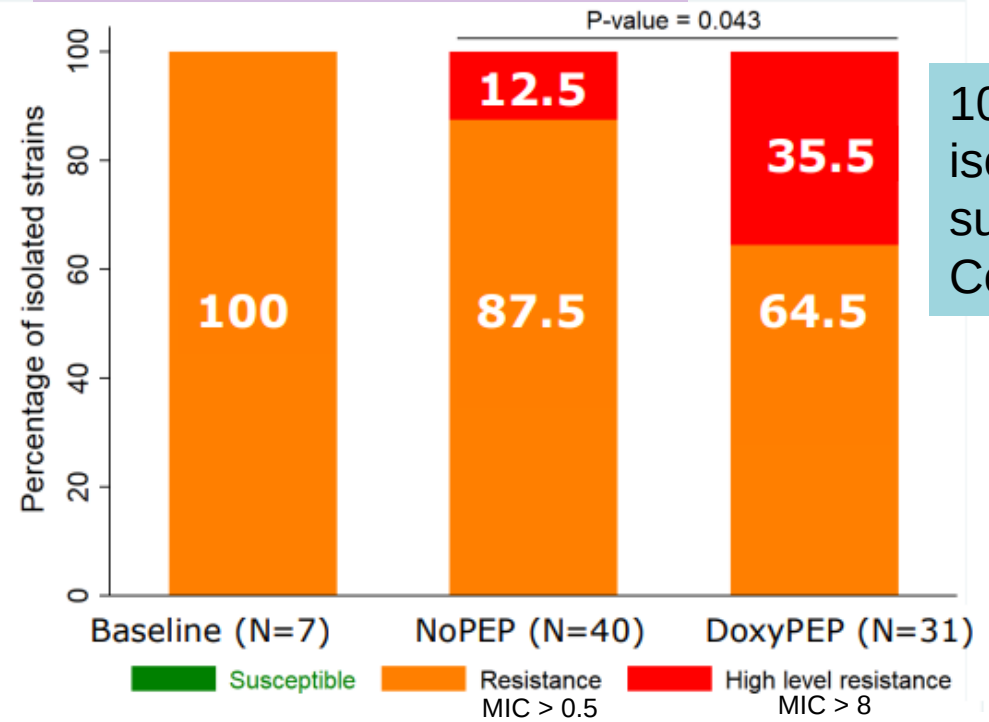
Stewart, et al. NEJM 2023

Doxy-PEP: Antimicrobial Resistance

DoxyPEP: **56** GC cultures



DOXYVAC: **78** GC cultures



100% of isolates fully susceptible to Ceftriaxone

DOXYVAC: **231** GC-NAAT-positive samples

tetM: 59.1% in Doxy-PEP vs 23.7% in No-PEP (p<0.001)

Increased tetracycline resistance in Doxy-PEP vs SOC suggest Doxy-PEP is less protective against GC strains with **pre-existing tetracycline resistance**

Luetkemeyer, et al. NEJM 2023
Molina, et al. Lancet ID. 2024
Bercot B, et al. AIDS 2024

Doxy-PEP and the Gut Microbiome

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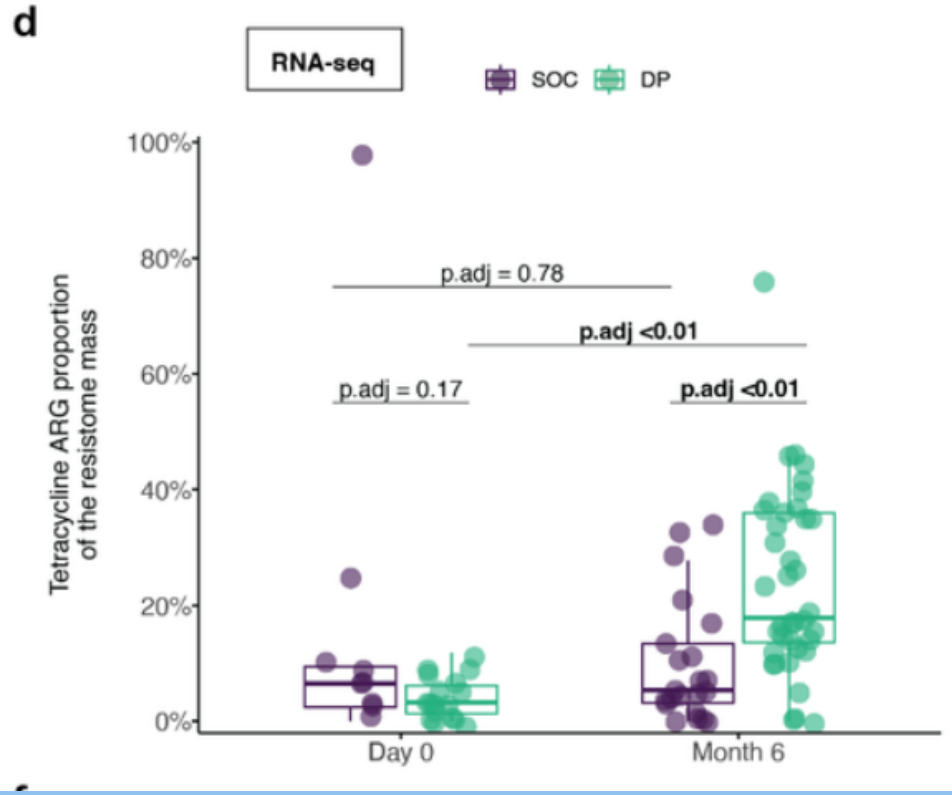
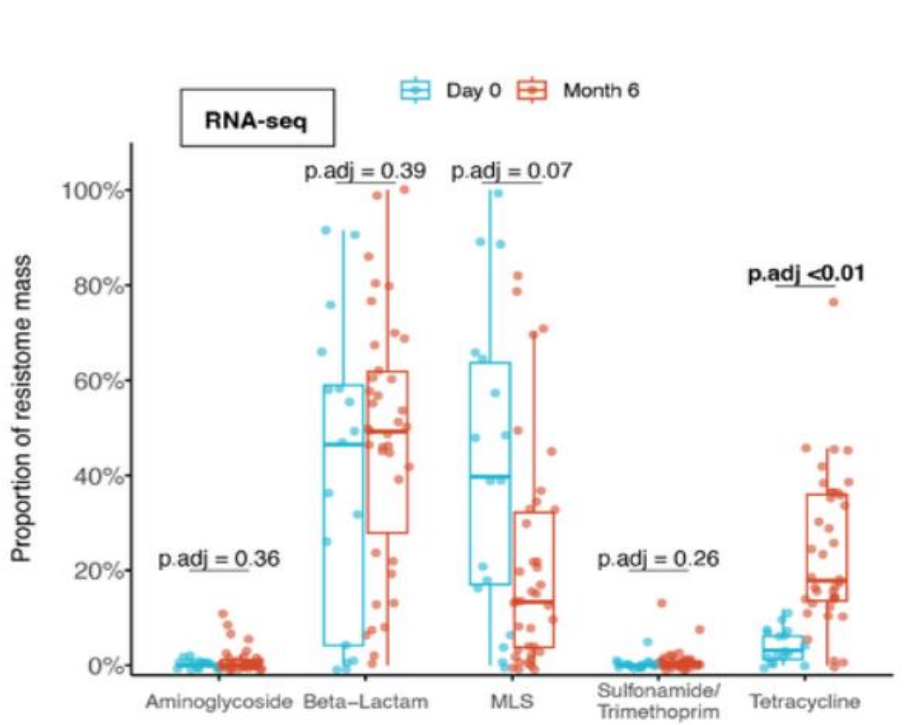
DOXYPEP

46 Doxy-PEP ppts
24 SOC ppts

No changes in **total resistome mass** or **α- or β- diversity** or **taxonomic composition** of the gut microbiome



2-fold increase in expression of **TCN antimicrobial resistance genes (ARG)** in doxy-PEP arm



No increases in **non-TCN antimicrobial resistance genes (ARG)** expression over time

Chu, et al. CROI 2024

Doxy-PEP: Evidence Summary

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Proven efficacy for bacterial STI reduction among MSM/TGW
NNT = 5

Safe, cheap, well tolerated, highly acceptable

Syphilis & CT (~75%)
GC (~55%)

Reduces Ceftriaxone use by 50% (positive trade-off?)

Less protective against GC strains with high-level TCN-resistance

Doxy-PEP: Population Level Impact

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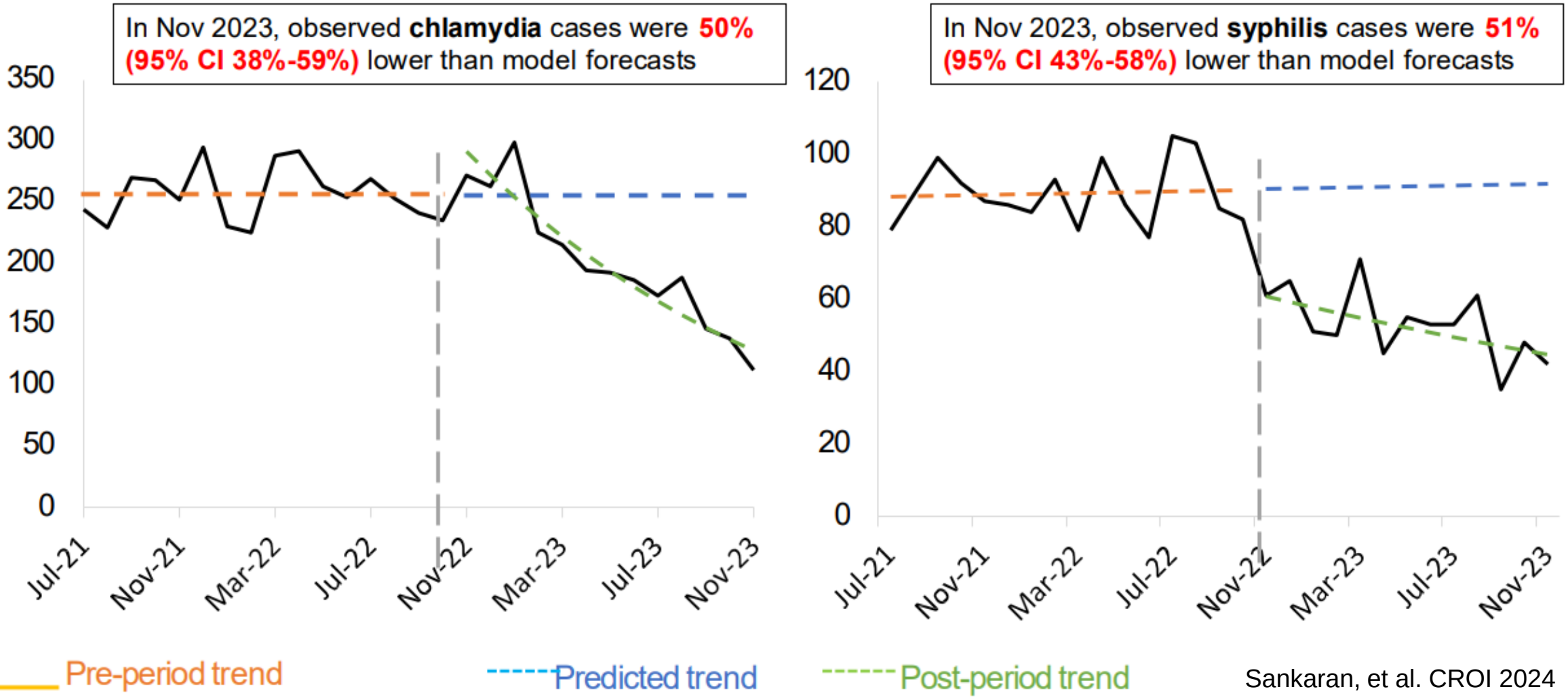
Decline in citywide CT and early syphilis cases in MSM in SF after release of doxy-PEP guidelines



Sankaran, et al. CROI 2024

2024 CDC Doxy-PEP Guidelines

Doxycycline 200 mg taken once orally within 72 hours of oral, vaginal or anal sex

- Gay, bisexual, and other men who have sex with men
- Transgender women

+ History of at least one bacterial STI in the past 12 months

2024 CDC Doxy-PEP Guidelines

No recommendation can be given at this time on the use of doxycycline as PEP for:

- Cisgender women
- Cisgender heterosexual men
- Transgender men
- Other queer and nonbinary individuals

If this intervention is offered, it should be implemented with consideration for ancillary services.

Doxy-PEP: Next Steps in Research

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From Evidence to Implementation: Doxy Impact Study

2024-2029

- **Will doxy-PEP reach & be used effectively by those who most need it?**
- **What is the impact of doxy-PEP on AMR with longer term use?**
- Observational, multi-city cohort study to evaluate doxy-PEP patterns of use, effectiveness and impact on AMR in MSM & transwomen

Aim 1: Doxy-PEP cohort effectiveness

SubAim1:	SubAim 2:	SubAim 3:
STI incidence & patterns of doxy-PEP use	Qualitative analysis of drivers of persistence & sub-optimal use	Doxy-PEP to need ratios to assess gaps in access & uptake

Aim 2: Antimicrobial resistance

GC: Antibiotic resistance
S.Aureus & Strep pneumo: colonization & TCN-class resistance

ATLANTA DETROIT MIAMI SAN FRANCISCO SEATTLE

MPIs
Luetkemeyer
Celum
Co-investigators
Oliver Bacon
Susan Buchbinder
Chase Cannon
Chip Chambers
Stephanie Cohen
Susan Doblecki-Lewis
Julie Dombrowski
Deborah Donnell
Shira Heisler
Colleen Kelley
Meredith Lora
Gretchen Newman
Hyman Scott
Olusegun Soge
Patrick Sullivan

NIH R01: AI181732

Coming soon:

HPTN 113

HPTN 113 DUO
PREP DOXYPEP
Find your rhythm, find your voice, find your prevention options.

Doxy-PEP in the context of PrEP choice:
Uptake, acceptability and patterns of use

Next presentation by Susan Buchbinder

Slide courtesy from Connie Celum

Is Doxy-PEP Being Used in Peru?

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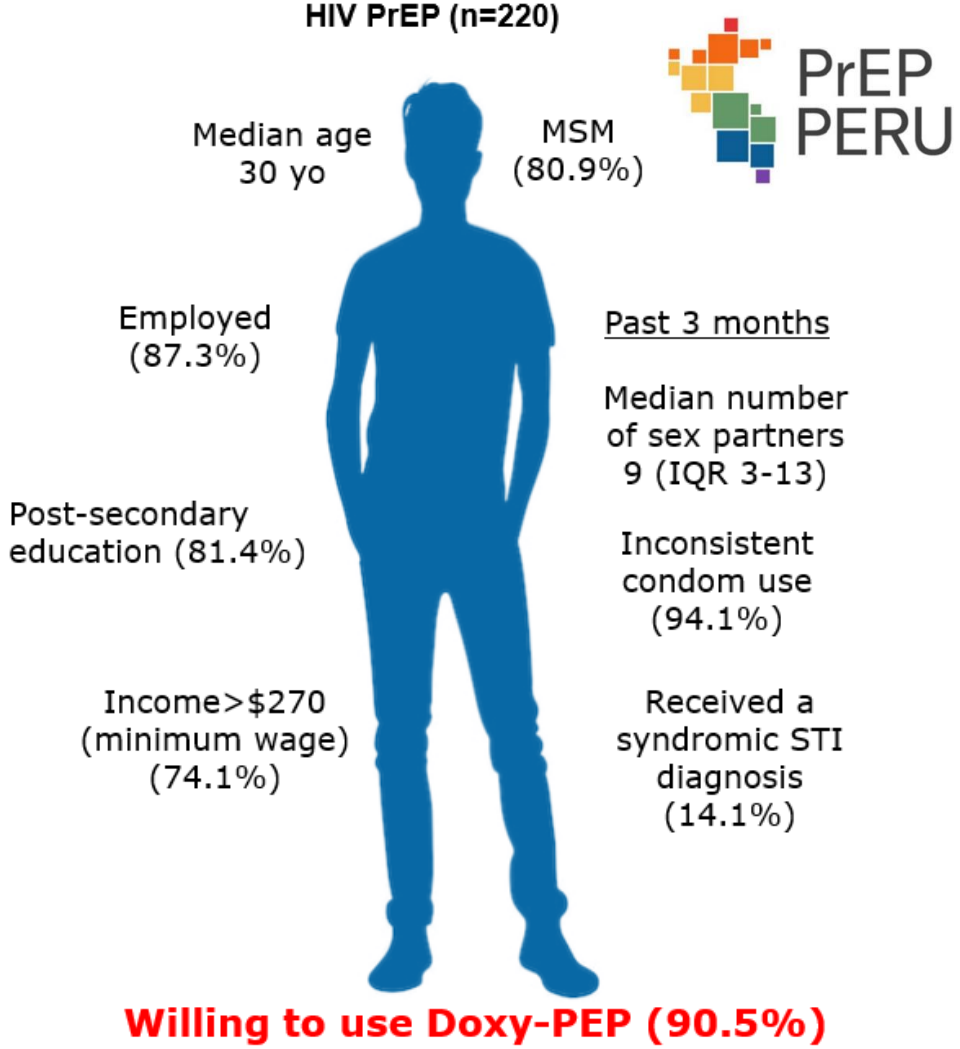
Figure 1. Socio-demographics characteristics of MSM initiatinc HIV PrEP (n=220)



Gallardo-Cartagena J, et al. HIVR4P 2024 ***(Confidential)***

IMPULSO: Ongoing online survey among Peruvian MSM

Current N = 365

Sociodemographics:
- Median age: 28 yo
- Cisgender male: 82.2%
- Transgender women: 0.7%
- Gender non-binary: 12.2%
- Living in Lima: 63.2%
- Post-secondary education: 61.9%

- PLWH: 11.8%
- Current PrEP users: 10.1%
- Never attended MoH sexual health clinics: 30.2%

STI dx in past 12 months:
- Syphilis: 8.2%
- CT/GC: 6%
- Urethral discharge: 7.2%

Ever heard of Doxy-PEP: 16.7%

Ever used Doxy-PEP: 5.2%

Unpublished data

Peru's context:
- No official guidelines on Doxy-PEP use yet
- Despite existing regulations, antibiotics can still be acquired over-the-counter
- Data calls out the need for a rapid response and guided implementation of Doxy-PEP

Conclusions

Doxy-PEP has proven efficacy in reducing incidence of CT & syphilis, and to a lesser extent, GC in MSM and TGW

- Mounting evidence for the real-world effectiveness of Doxy-PEP in places where it has been already implemented

Efficacy for other populations (cisgender women, heterosexual men) yet to be determined

Need for further research and surveillance data from settings where Doxy-PEP is used to address concerns about antimicrobial resistance and microbiome effects

Real-world implementation of Doxy-PEP: Considerations to avoid increasing existing disparities between and within countries and regions.

Thank you

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