DoxyPEP?

Of corse, We must!

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BCN checkpoint HOMES · SEXUALITAT · SALUT
Fundació Lluita contra les Infeccions
Germans Trias i Pujol Hospital

Conflicts of interest

- Participation in sponsored clinical sessions by Gilead scinces, ViiV Healthcare, MSD, Janssen Cilag and Rovi.
- Has participated in advisory boards organized by Gilead sciecnes and ViiV Healthcare.
- Has received investigational grants from ViiV Healthcare, Gilead sciences, and has participated in grants granted by ViiV, Gilead, MSD and Janssen Cilag.
- Has participated as PI or sub investigator in clinical trials sponsored by GSK, ViiV Healthcare, Gilead sciences, MSD, Abbie, Moderna. Trials related with PrEP, HIV, Hepatitis and STI antibiotics.

** any of the mentioned conflicts has not affected the content of the talk.

Doxy PEP overview

- Guidelines support doxy-PEP
- Why does we need doxy-PEP.
- Why Doxycycline?
- Does it Work as prevention?
- Other benefits of Doxy-PEP
- Doxy-PEP Balance

Guidelines support doxyPEP

- CDC: Doxy PEP, when offered, should be implemented in the context of a comprehensive sexual health approach, including risk reduction counseling, STI screening and treatment, recommended vaccination and linkage to HIV PrEP, HIV care, or other services as appropriate. Persons who are prescribed doxy PEP should undergo bacterial STI testing at anatomic sites of exposure at baseline and every 3–6 months thereafter. Ongoing need for doxy PEP should be assessed every 3–6 months as well. HIV screening should be performed for HIV-negative MSM and TGW according to current recommendations.

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Guidelines support doxyPEP

EACS:

All persons under PrEP should be offered vaccinations against HAV, HBV, HPV and monkeypox virus. Doxycycline post exposure prophylaxis, 200 mg within 24 to 72h after sexual intercourse, proved to be effective in preventing bacterial STIs in MSM with the caveat of the unknown long terms effects on microbiota and STIs resistance. It can be proposed to persons with repeated STIs on a case by case basis

EACS European AIDS Clinical Society

Guidelines support doxyPEP

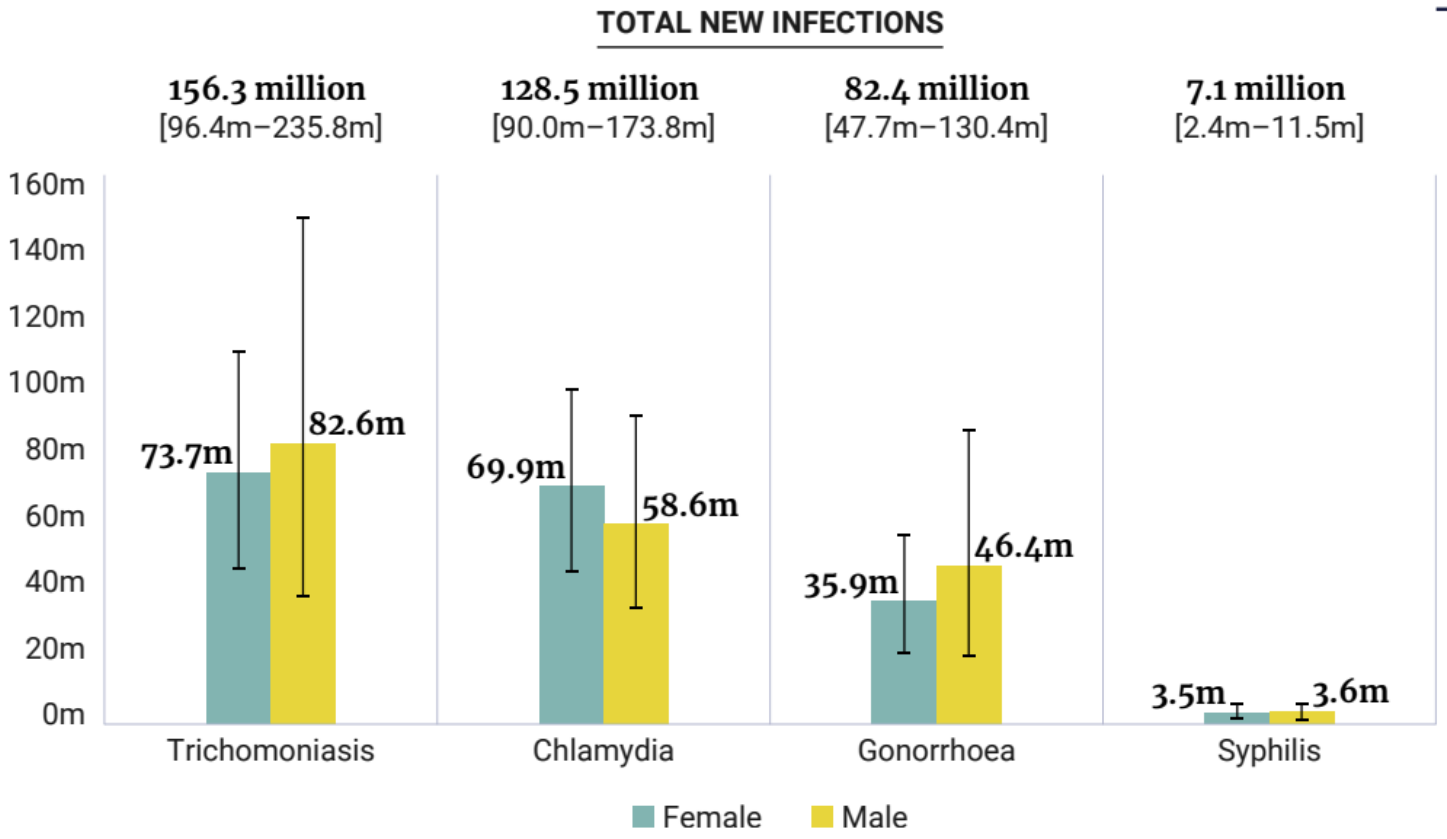
ASHM:

1. Doxy-PEP should be considered primarily for the prevention of syphilis in GBMSM who are at risk of this STI, although for some individuals the reduction in chlamydia, and the lesser reduction of gonorrhoea might be important. Some stakeholders held the view that Doxy-PEP should be considered *only* for the prevention of syphilis in GBMSM, for the reasons listed above.
2. While evidence for appropriate suitability criteria for commencing Doxy-PEP is limited, the following might be appropriate for considering doxy-PEP until further data emerges:
    1. GBMSM with a recent syphilis diagnosis (e.g., within the previous six or twelve months); or
    2. GBMSM with two or more recent other (i.e., not syphilis) bacterial STI diagnoses (e.g., within the previous six or twelve months); or
    3. GBMSM who identify an upcoming period of heightened STI risk, for example, attendance at a sex event, or holiday plans that likely involve sexual activity with multiple casual sexual partners; or
    4. GBMSM with concurrent male and cisgender female sexual partners or other sexual partners with a uterus, recognising the additional health risks posed by chlamydia, gonorrhoea and syphilis for people with a uterus.
    5. GBMSM who present for HIV PEP can also consider Doxy-PEP, although the indications for HIV PEP do not necessarily indicate a need for Doxy-PEP.

ashm

Why does we need doxy-PEP

Fig.3. New cases of four curable STIs among adults (15–49 years old) per year, by sex, global, 2020

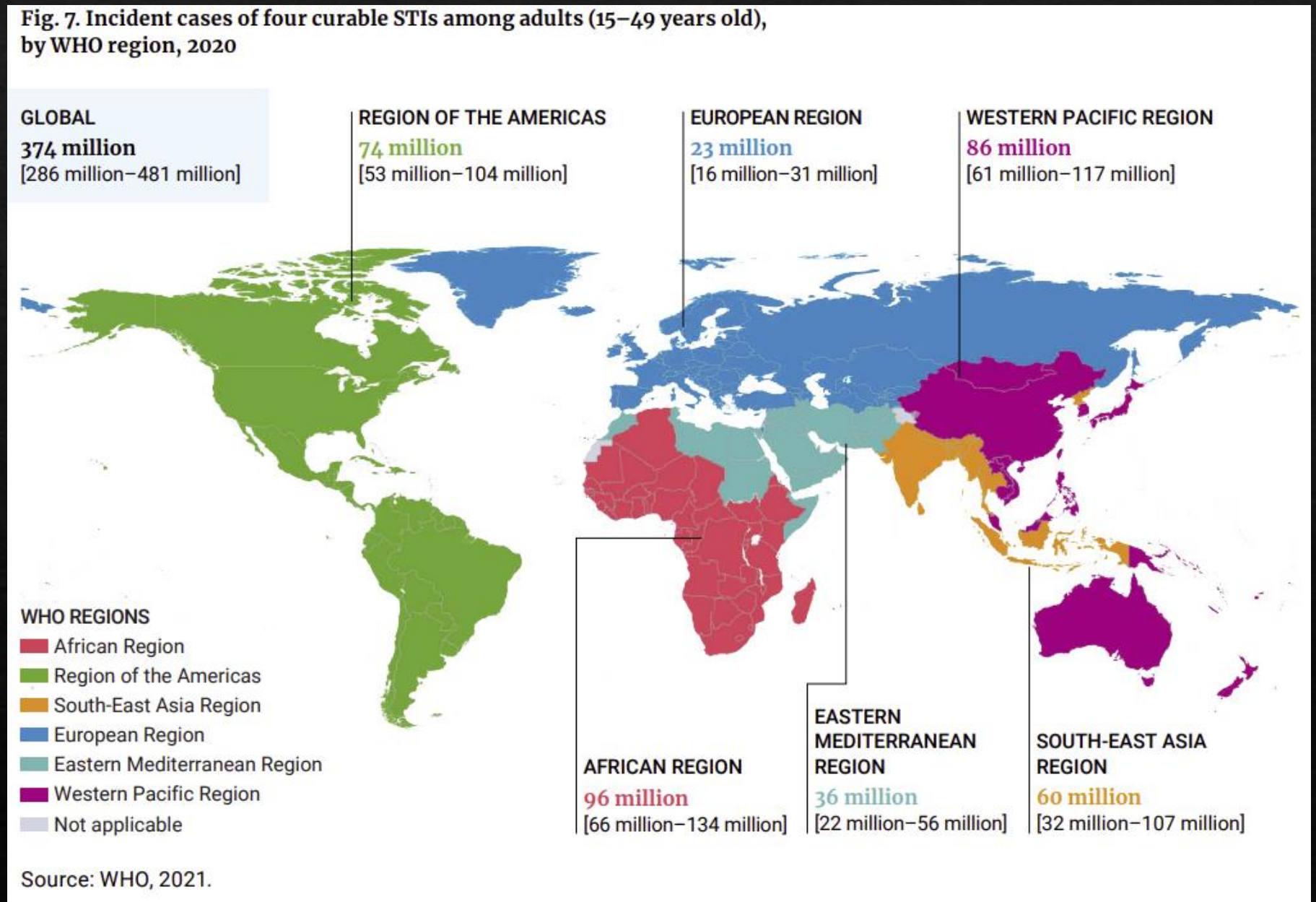


Source: WHO, 2021.

1m

new STI infections each day

Why does we need doxy-PEP



Why Doxycycline?

- Safe.

Safe

- 2n Generation Tetracycline approved by FDA in 1967; broadly active against bacteria and parasites
- Wide experience in treating and preventing acne, chronic periodontitis, cholera, malaria, Lyme, leptospirosis, Staphylococcus infections, etc.
- In STI: Syphilis, chlamydia (LGV), Mycoplasma genitalium, Ureaplasma urealyticum, donovanosis…

Why Doxycycline?

- Safe.
- Well tolerated

Safe and well tolerated

- Systematic review from 1987-2022

- 67 studies with 10,106 people using doxycycline doses 20-200mg/day from 8w to>3y.

- Moderte AE 0-88% and SAE (0-14%)
  - GI 0-50%
  - Derm (0-38%)
  - Metabol: No results. Weight gain paper retracted for ethical misconduct.
  - Microbiom effect: Limited data.

TABLE 2. Relative Risk of Adverse Events Between Doxycycline and Placebo Arms of Randomized Controlled Trials

Outcome	κ	Relative Risk (95% CI)	I^2%	P
Included RCT studies				
Any AE	9	1.03 (0.89–1.21)	59.6	0.66
Severe AE	12	0.83 (0.59–1.16)	2.20	0.28
Neurological AE	11	0.88 (0.73–1.05)	0.90	0.15
Gastrointestinal AE	12	1.68 (1.19–2.38)	72.2	<0.01
Dermatological AE	9	3.55 (1.39–9.01)	45.9	0.01
Dropped due to AE	18	1.62 (1.12–2.34)	7.50	0.01
100- to 200-mg dosages				
Any AE	3	1.35 (0.69–2.64)	74.7	0.38
Severe AE	6	0.94 (0.65–1.34)	0.00	0.73
Neurological AE	5	0.99 (0.97–1.02)	0.17	0.68
Gastrointestinal AE	6	1.78 (1.16–2.74)	81.9	0.01
Dermatological AE	4	5.52 (1.75–17.42)	68.3	<0.01
Dropped due to AE	10	1.82 (1.06–3.11)	20.9	0.03

I^2 variation across studies because of heterogeneity rather than chance.

AE indicates adverse event; κ, number of studies; RCT, randomized controlled trial.

Chan et al. Sex transm Dis 20232023

Safe and well tolerated

Table 2.

Number and Frequency of Reported Laboratory Abnormalities, Adverse Events, and Other Outcomes From Clinical Doxy-PEP Trials

Randomized clinical trial	Laboratory abnormalities	Adverse events	Discontinuations	Other outcomes
IPERGAY	Grade 4 transaminitis due to acute hepatitis C infection (n = 3)	Drug-related gastrointestinal adverse events (n = 29); more common in PEP group (*P* = .03)	29 (26%) for all reasons; 8 (7%) due to drug-related adverse events	No difference between groups in serious adverse events
DoxyPEP	Grade 2 transaminitis (n = 1)	Grade 3 diarrhea or headache (n = 5)	2%	No weight gain compared to standard of care
DOXYVAC	None as of July 2023	Gastrointestinal adverse events (n = 2)	3 (0.9%) due to gastrointestinal adverse events or fear of adverse events	Further data pending final review
dPEP (Kenya)	Not collected	7% (gastrointestinal side effects)	5%	Social harms related to PEP use among 3 participants

Abbreviations: DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-Infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya); IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; PEP, postexposure prophylaxis.

Note: Data obtained and compiled from Molina,[18] Luetkemeyer et al,[16] Molina,[19] and Stewart[20] (Jean-Michel Molina, MD, PhD, email, August 26, 2023; Jenell Stewart, DO, MPH, email, August 8, 2023).

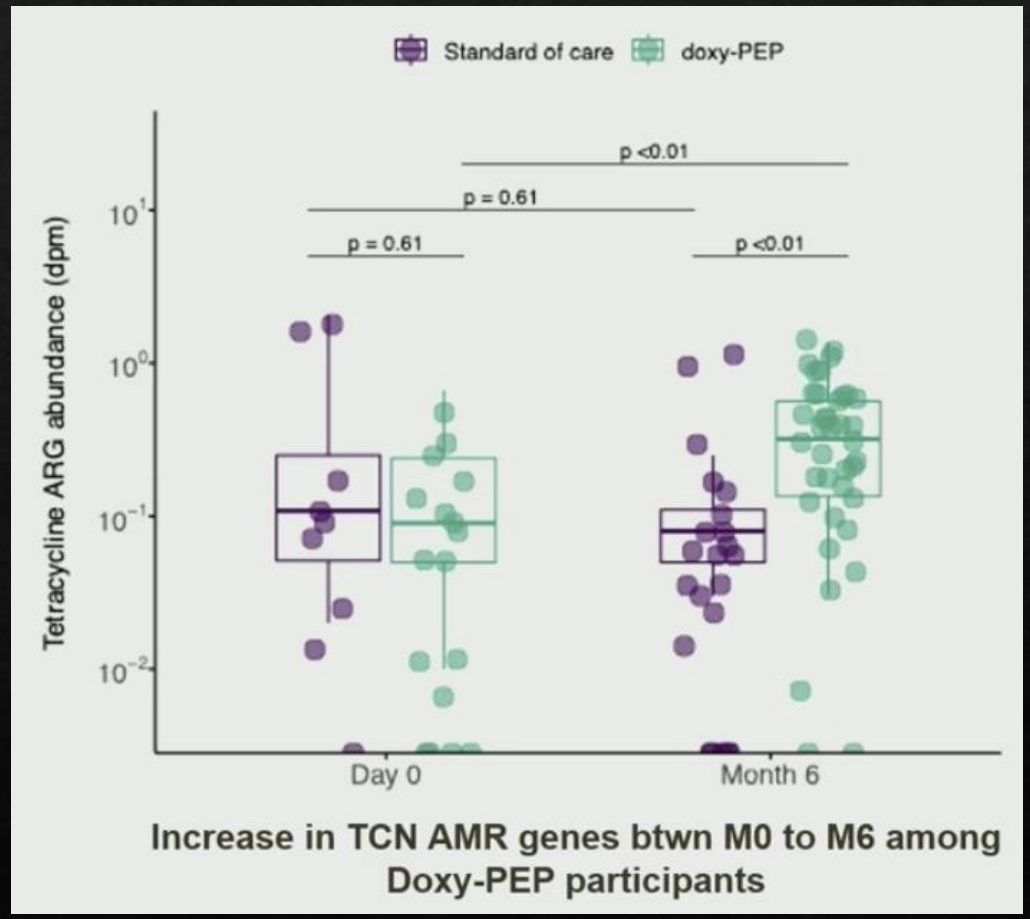
Cannon CA, Celum CL. Doxycycline postexposure prophylaxis for prevention of sexually transmitted infections. Top Antivir Med. 2023 Dec 5;31(5):566-575.

Limited impact in Gut microbiome diversity

AMR genes expression 46 dPEP Vs 24 SOC patients

No differences in gut microbiome diversity or abundance between M0 and M6 or between both arms.

Actively expressed TCN-R genes increased by median of 2 in dPEP group (p<0,01) without change to non-TCN classes.



Increase in TCN AMR genes btwn M0 to M6 among Doxy-PEP participants

Chu et al. CROI 2024 (abstract 3404)

Why Doxycycline?

- Safe.
- Well tolerated
- Inexpensive
- It Works in the main STIs
- Neisseria gonorrea (NG) (in USA 20% resist aprox)

Does it Work as prevention?

Open-Label 1:1 daily Doxy-PrEP /$$

Population: MSM/TGWSM with HIV and ≥ 2 prior syphilis episodes

N=30

Primary outcome: Any STI over 48 Weeks

Results: 73% resuction of any STI

Results of Generalized Linear Mixed Models for Sexually Transmitted Diseases (n=30).[‡]

	Number of Visits with Outcome		Follow-Up Analysis (thru 48 Weeks)		On-Drug Analysis (thru 36 Weeks)	
Outcome	**Doxy Arm**	**CM Arm**	**p-value**	**OR (95% CI)**	**p-value**	**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)

[†]Odds ratios (OR) or Rate ratios (RR) below 1 indicate the decreased odds/rates in the Doxycycline arm compared to Contingency Management (CM) arm; OR or RR above 1 indicate increased odds/rates in the Doxy arm compared to the CM arm

Bolan, et al. Sex Transm Dis 2015

Does it Work as prevention?

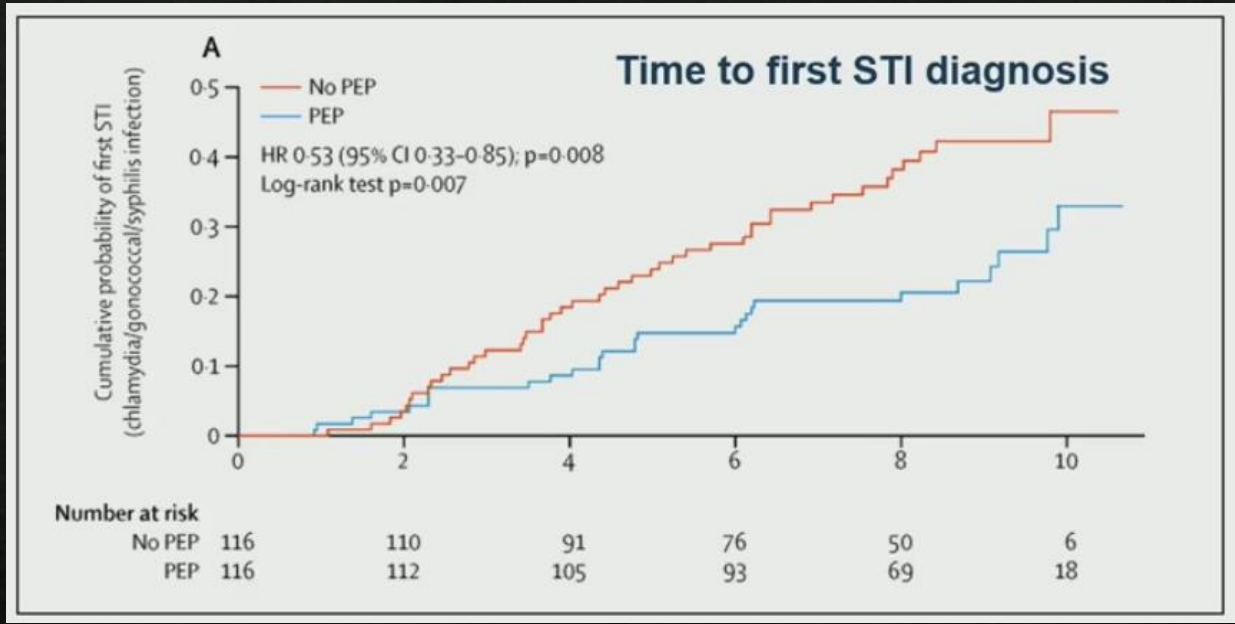
Open-Label 1:1 Doxy-PEP max3xW /SoC

Population: high risk MSM on HIVPrEP

N=232

Primary outcome: time to first STI

Results: 47% global STI, 70% CT, 73% Syph



Median use 3,3times/month.
No significant changes on sexual behaviors.

Molina, et al. Lancet infect Dis 2018

Does it Work as prevention?

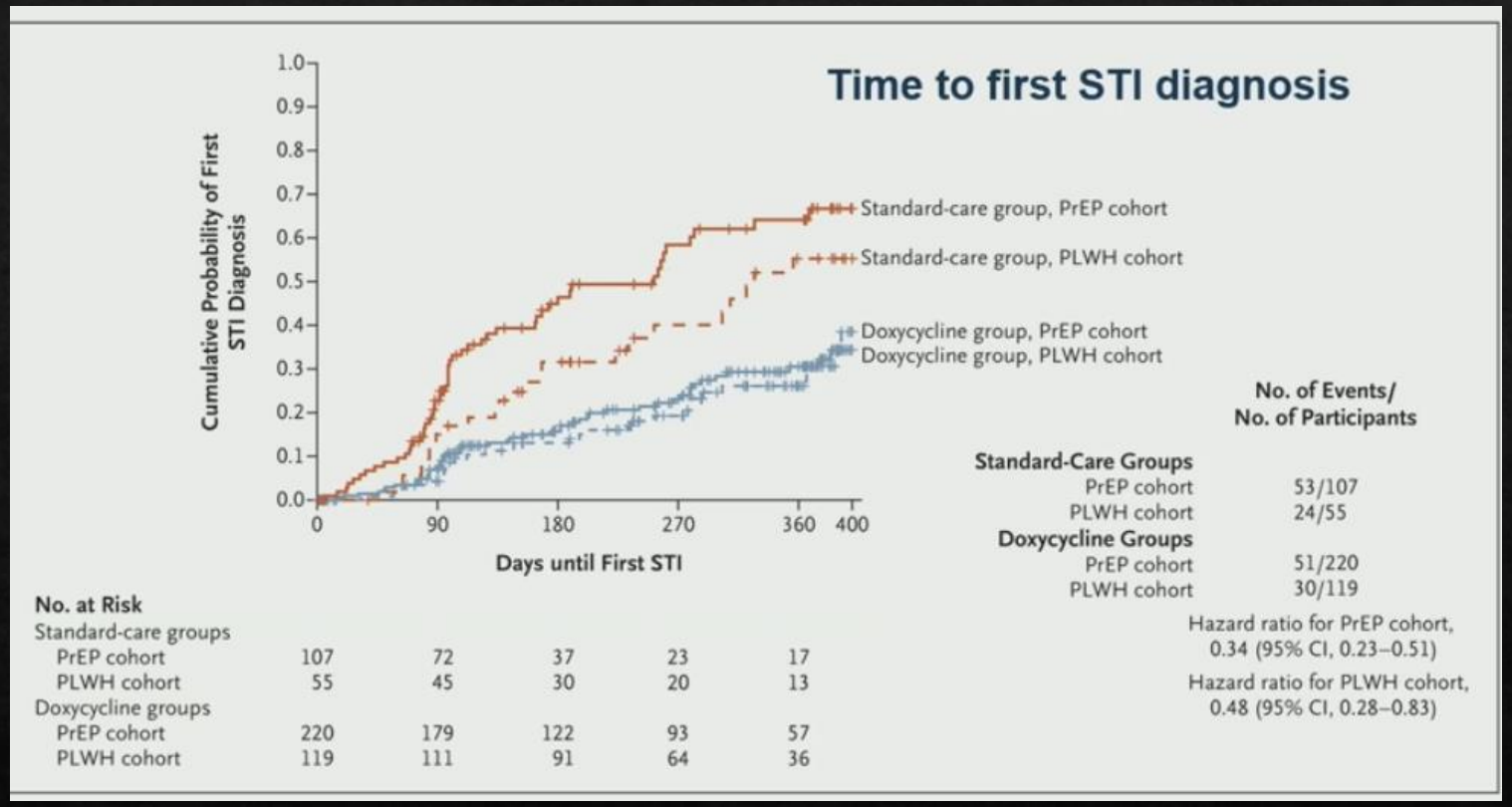
Open-Label 2:1 Doxy-PrEP /SoC

Population: high risk MSM on HIV+ or HIVPrEP; ≥1 recent STI

N=501

Primary outcome: STI incidence/quarter

Results: 65% global STI, 74-88% CT, 77-87% Syph, 55-77% GC



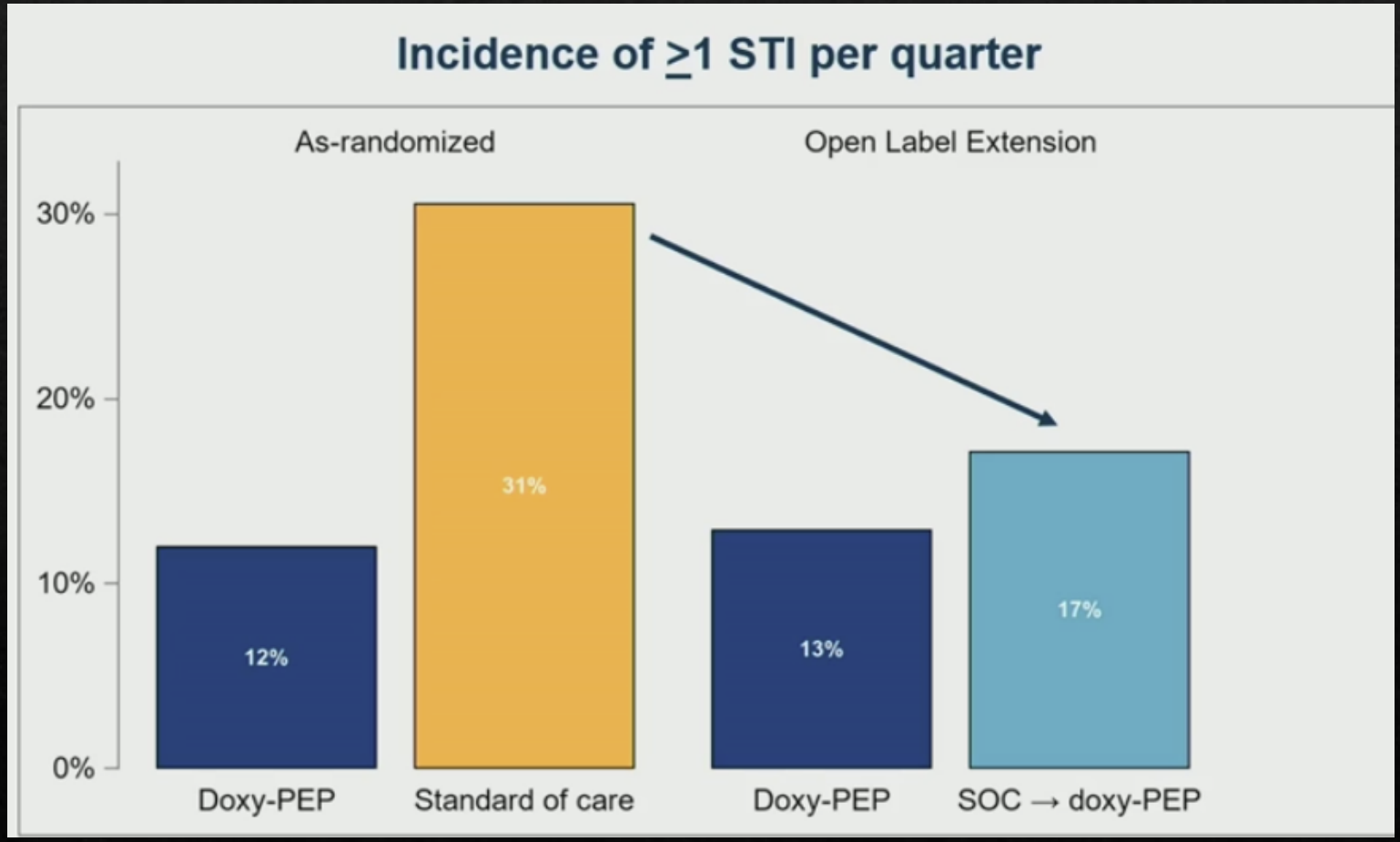
Median use 4 times/month.
Significant reduction in PrEP and PWLH cochorts
No significant changes on sexual behaviors.

Luetkemeyer et al. NEJM 2023

Does it Work as prevention?

Doxy-PEP offered as SOC in OLE phase.

Modest increase on # of sexual partners



Luetkemeyer et al. CROI 2024

Does it Work as prevention?

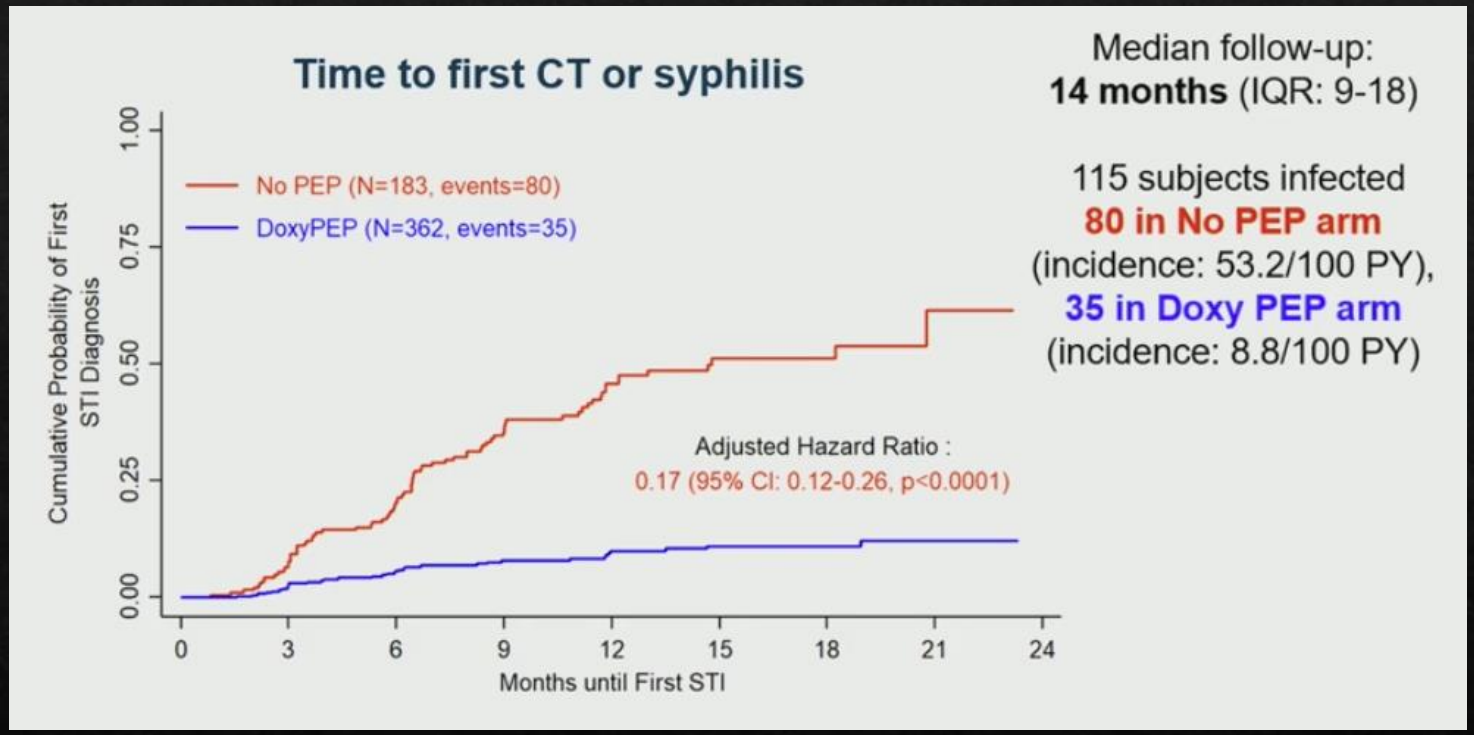
Open-Label 2:1 Doxy-PEP /SoC + MenB/None

Population: Adul MSM on HIVPrEP>6months ; ≥1 recent STI

N=502

Primary outcome: time to first Syphilis or CT

Results: 83% global STI, 33% GC



Median use 3,5 (2-5,5) times/month.
No significant changes on sexual behaviors.

Molina et al. CROI 2023 and 2024

Does it Work as prevention?

Open-Label 1:1 Doxy-PEP /SoC

Population: Adult Women on HIVPrEP

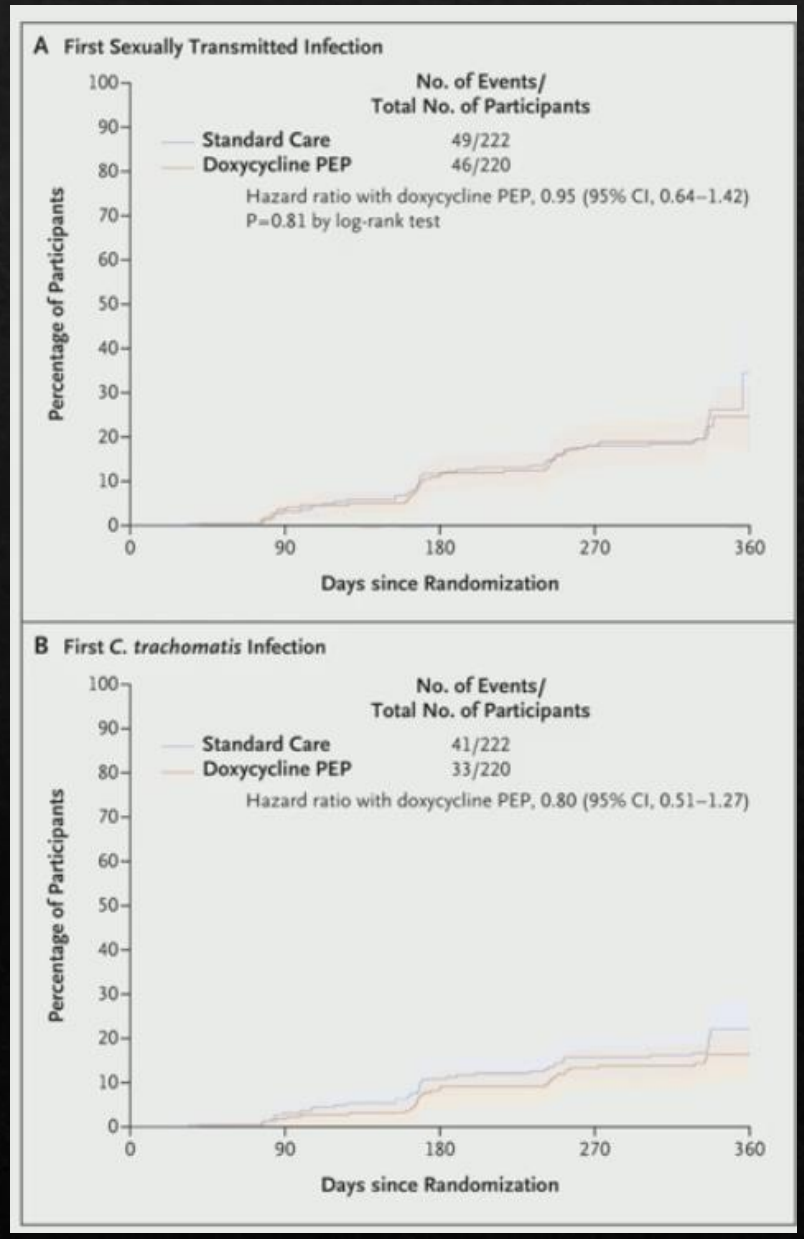
N=449

Primary outcome: STI incidence over 12 months

Results: high incidence but no differences between groups

Median use 4 (0-8) times/month.
Hair drug levels suggested low adherence.
No molecular resistance found in CT, 100% tetM in GC

Stewart et al. NEJM 2023



Other benefits of Doxy-PEP

- S. Aureus 14% absolute reduction in colonization and 8% resistance increase compared to baseline
- MRSA prevalence 6% lower and without MRSA doxy-R increase after doxy-PEP use.
- Limited data about GC TCN-R resistance increase.

Doxy PEP Balance

- Proven efficacy for bacterial STI reduction. NNT=5
  - Syphilis and CT rates (75%)
  - Lower for GC (55%), assuming isolate susceptibility.
- Ceftriaxone reduction in about 50%
- PEP Vs PrEP: fewer total days of doxycycline exposure.

Are we able to avoid Doxy-PEP use?