

# **Luci e ombre sulla profilassi pre-esposizione antibatterica e antivirale**

Antonio Di Biagio

# Conflicts of Interest

**Member of the writing committee of The Italian HIV Guidelines**

**Received honoraria for presentation and scientific advise from: MSD, Janssen, ViiV Healthcare and Gilead**

**Investigator in clinical trials and research grants from ViiV Healthcare and Gilead**

# Di cosa parliamo?

- **PrEP: Profilassi pre esposizione, riguarda antivirali per HIV**
- **PEP: Profilassi post esposizione, riguarda antibiotici per le STI, ma riguarda anche antivirali per HIV**

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- 
- **PrEP: chemiopprofilassi (malaria)**
  - **PEP: chemiopprofilassi (meningococco)**

# Luci e Ombre

- **Stato dell'arte**
  - **PrEP HIV**
  - **DoxyPEP**

# Luci e Ombre

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**Theoretically, if we accessed and put on antiretroviral therapy everyone who has HIV and provide PrEP for all at high risk of HIV, we we could rapidly end the epidemic.**

# **HIV Pre-Exposure Prophylaxis (PrEP)**



One pill per day



**>95% effective in  
preventing HIV  
acquisition**

• **DAILY**

PROUD, McCormack  
The Lancet 2016, 387, 53 - 60

• **ON DEMAND**

IPIRGAY, Molina  
N Engl J Med 2015;373:2237-2246



# HPTN 083 and 084: LA IM CABOTEGRAVIR Q2M vs Daily Oral FTC/TDF for PrEP

International, randomized, double-blind phase IIb/III (083) and phase III (084) trials  
LA IM CAB met criteria for **superiority** vs daily oral FTC/TDF in both trials



## HPTN 083<sup>1</sup>

- N = 4566 MSM and TGW
- 13 incident infections with LA CAB vs 39 with oral FTC/TDF
  - 4 with on-time CAB injections
  - 1 CAB infection later determined to be baseline infection
- HR for CAB vs FTC/TDF:  
**0.34 (95% CI: 0.18-0.62)**



## HPTN 084<sup>2</sup>

- N = 3224 cisgender women
- 4 incident infections with LA CAB vs 36 with oral FTC/TDF
  - 0 with on-time CAB injections
  - 1 CAB infection later determined to be baseline infection
- HR for CAB vs FTC/TDF:  
**0.12 (95% CI: 0.05-0.31)**

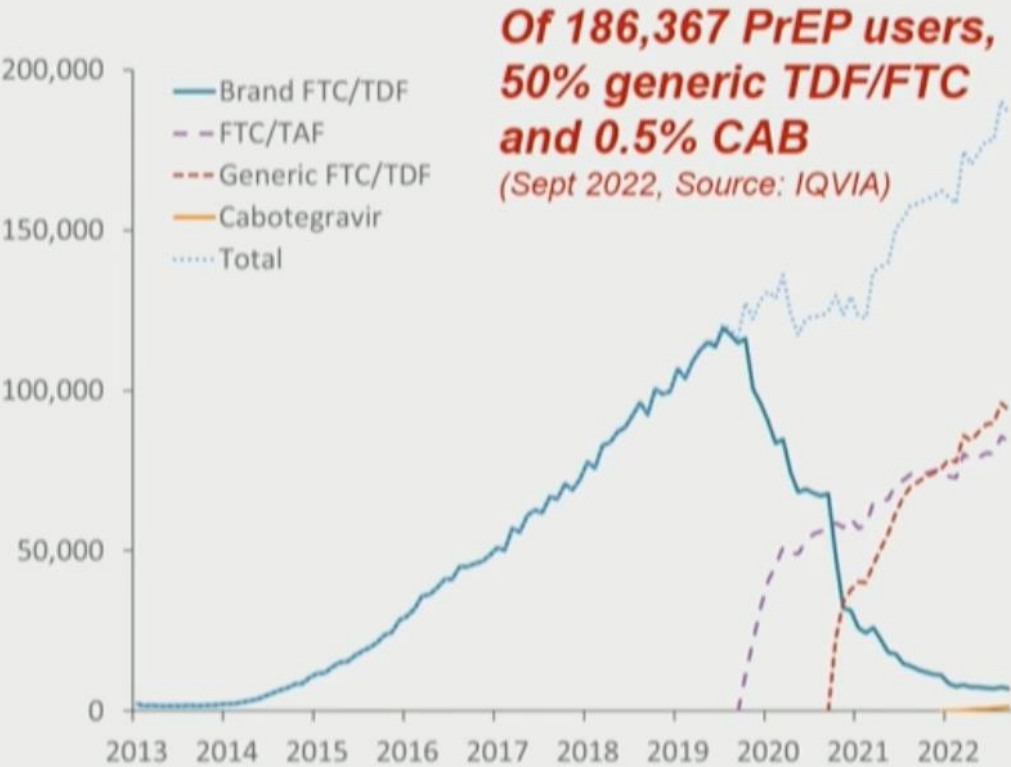
GAME CHANGING in HIV

# IAS-USA 2024 Recommendations for HIV PrEP

Type of Exposure	Daily TDF/FTC	On-Demand ("2-1-1") TDF/FTC	Daily TAF/FTC	Every other month IM CAB-LA
Insertive anal/vaginal sex	✓	✓	✓	✓
Receptive anal sex	✓	✓	✓	✓
Receptive vaginal sex	✓			✓
Receptive neovaginal sex	✓			✓
Injection drug use	✓			
Pregnant and breastfeeding people	✓			✓

# PrEP Prescribing in the United States

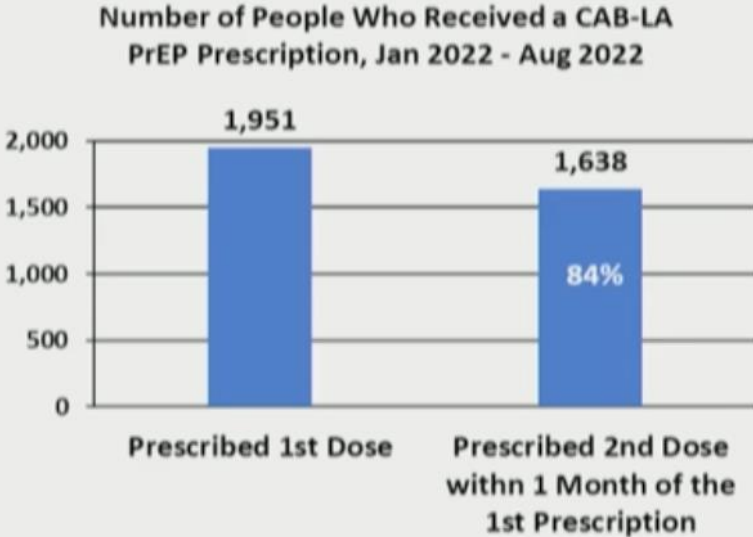
Genova 10 giugno 2025



186,367 persons were prescribed PrEP (Sept 2022):

Generic FTC/TDF:	93,808	(50.3%)
FTC/TAF:	84,141	(45.1%)
Brand FTC/TDF:	7,065	(3.8%)
<b>CAB-LA:</b>	<b>1,353</b>	<b>(0.5%)</b>

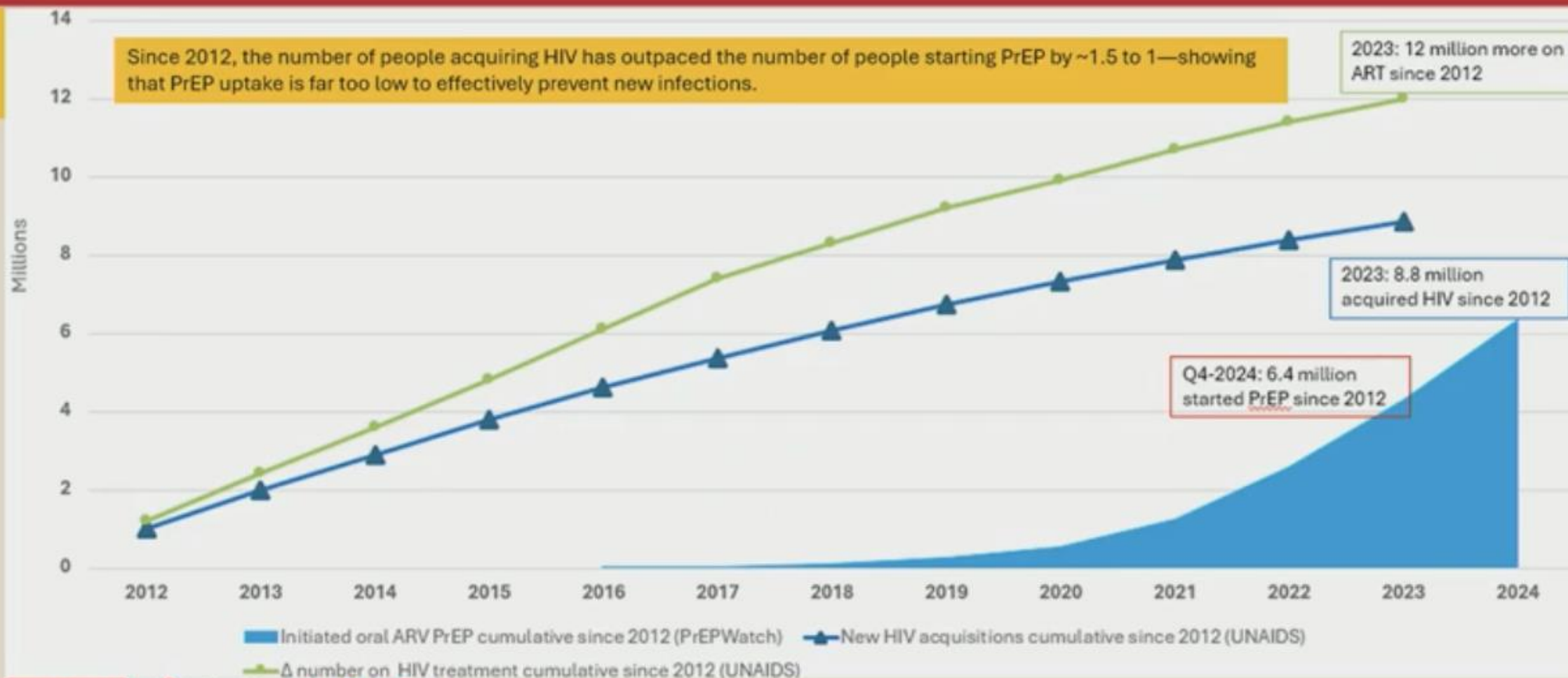
Table. Characteristics of persons prescribed long-acting cabotegravir, United States, January 2013 through September 2022				
	Oral PrEP		Injectable PrEP	
	N	%	N	%
Total	381,883		2,695	
Sex				
Male	355,087	93.0	2,359	87.5
Female	26,697	7.0	336	12.5
Unknown	99	0.0	0	0.0
Age				
13-24	46,814	12.3	369	13.7
25-34	150,864	39.5	1,111	41.2
35-44	96,243	25.2	698	25.9
45-54	47,668	12.5	297	11.0
55-64	31,427	8.2	149	5.5
65+	8,867	2.3	71	2.6



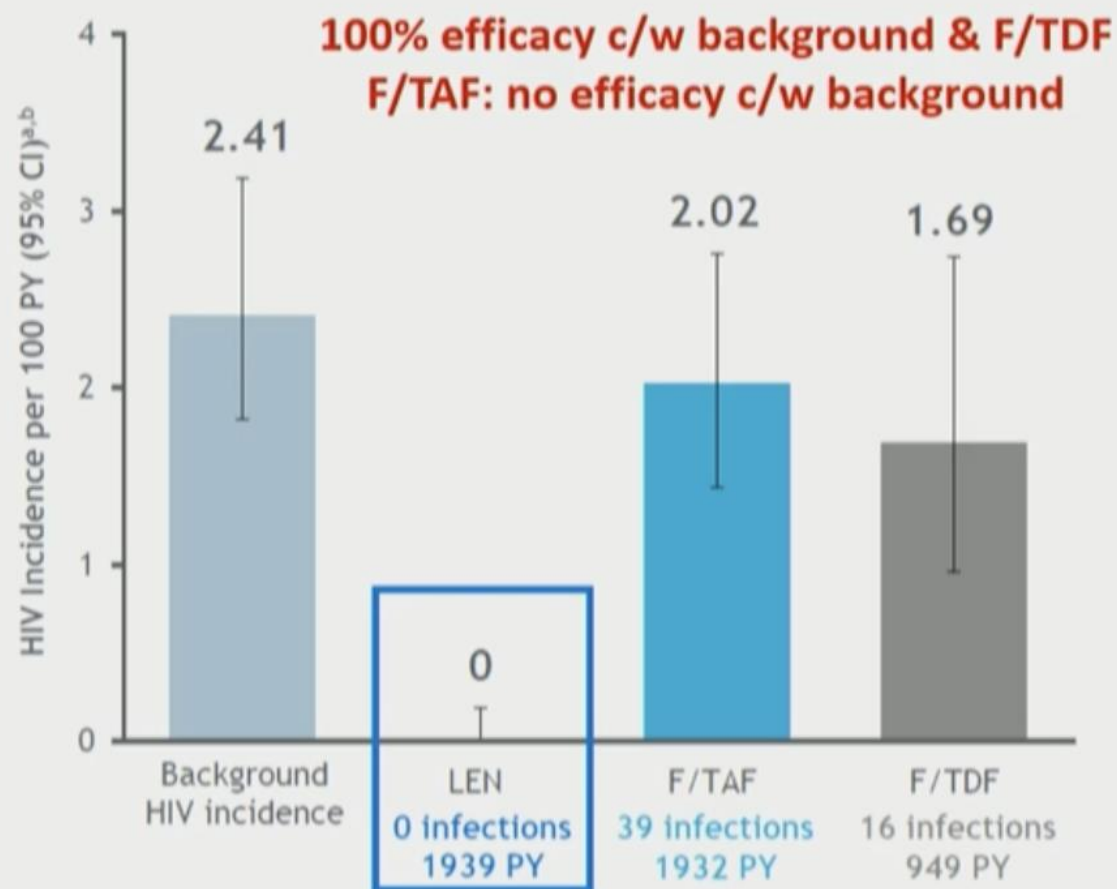


# HIV, ART & PrEP 2012-2024 – Eastern and Southern Africa

HIV : PrEP  
~1.5:1

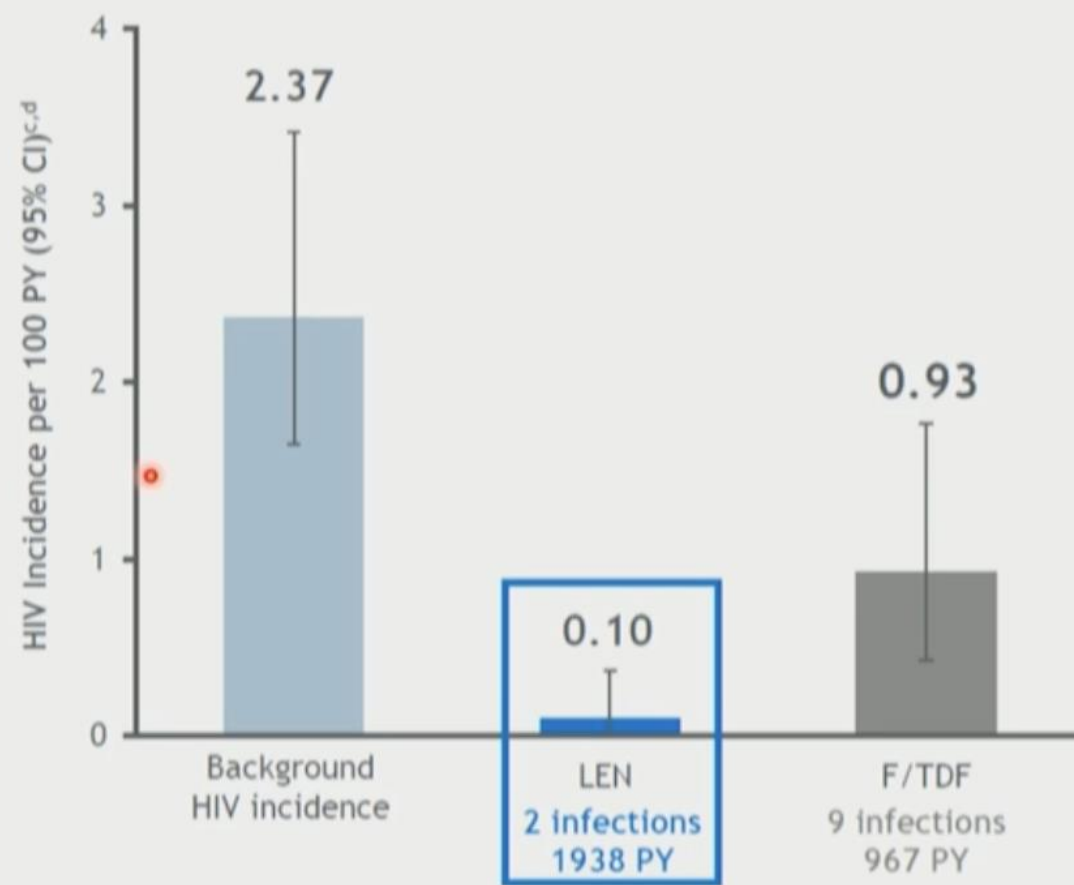


## **PURPOSE 1: Zero HIV Infections in Cisgender Women Receiving LEN**



Median follow-up duration: 44.0 weeks

## **PURPOSE 2: Two HIV Infections in Participants Receiving LEN**





Median follow-up duration: 39.4 weeks

<sup>a</sup>Overall n: background HIV incidence group, 8094; LEN, 2134; F/TAF, 2136; F/TDF, 1068. <sup>b</sup>95% CIs: background HIV incidence group, 1.82-3.19; LEN, 0-0.19; F/TAF, 1.44-2.76; F/TDF, 0.96-2.74. <sup>c</sup>Overall n: background HIV incidence group, 4634; LEN, 2179; F/TDF, 1086. <sup>d</sup>95% CIs: background HIV incidence group, 1.64-3.417; LEN, 0.012-0.373; F/TDF, 0.426-1.768. PY, person-years.

# Current status of long-acting PrEP options

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Strategy	FDA	EMA	Availability
Dapivirine ring	N/A	✓ 	In certain African countries
Cabotegravir	✓	✓	Limited
Lenacapavir	Review date June 19, 2025	Submitted Feb 3, 2025	 None

 Positive opinion by the European Medicines Agency (EMA)

# Luci e Ombre PREP

## Orale

- **Aderenza**
- **Persistenza**
- **Distribuzione**
- **Resistenza**

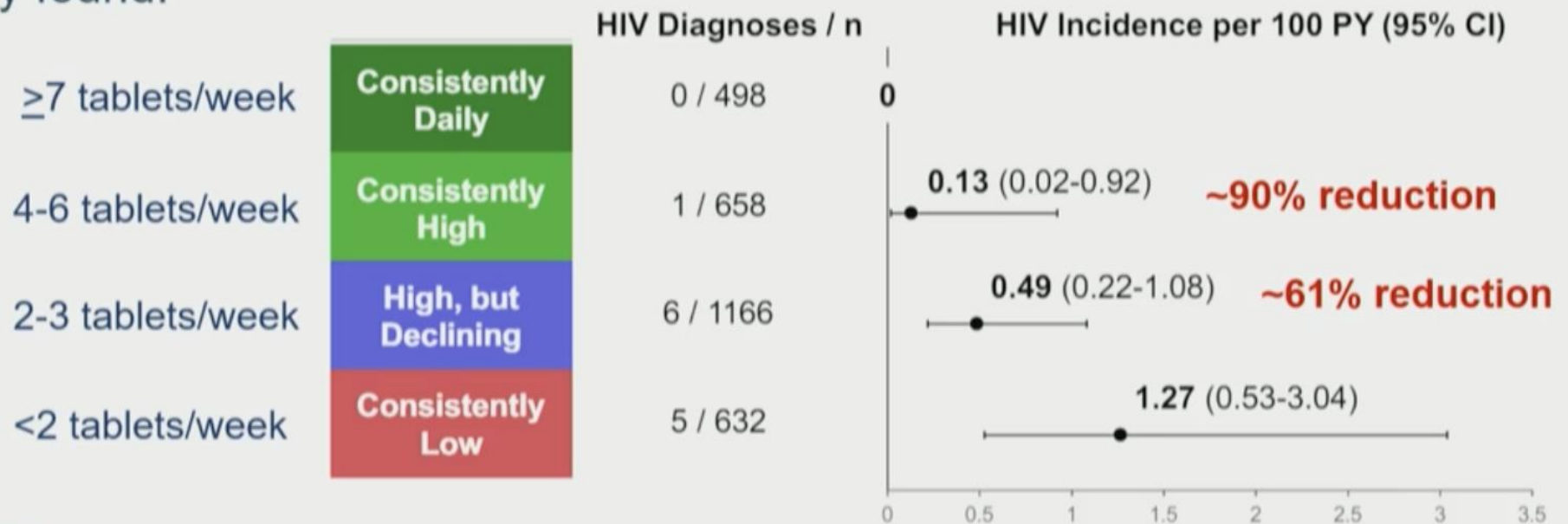
## Iniettiva

- Distribuzione
- Resistenza
- Costi



# How much adherence is needed for daily TDF/FTC?

- Modeled data from iPrEx study suggests >99% effectiveness if **cisgender men** take  **$\geq 4$  doses/week**; later data suggest even **2+ pills/week** have 99% effectiveness<sup>1</sup>
- PK data of F/TDF suggests **cisgender women** need to take **6-7 doses/week** for maximal vaginal concentrations, BUT modeled clinical data found **4-6 pills** provided 88% effectiveness<sup>1</sup>
- Data from 11 demonstration projects of daily F/TDF PrEP in >6900 **cisgender women** globally found:<sup>2</sup>



<sup>1</sup>Anderson, CID 2023

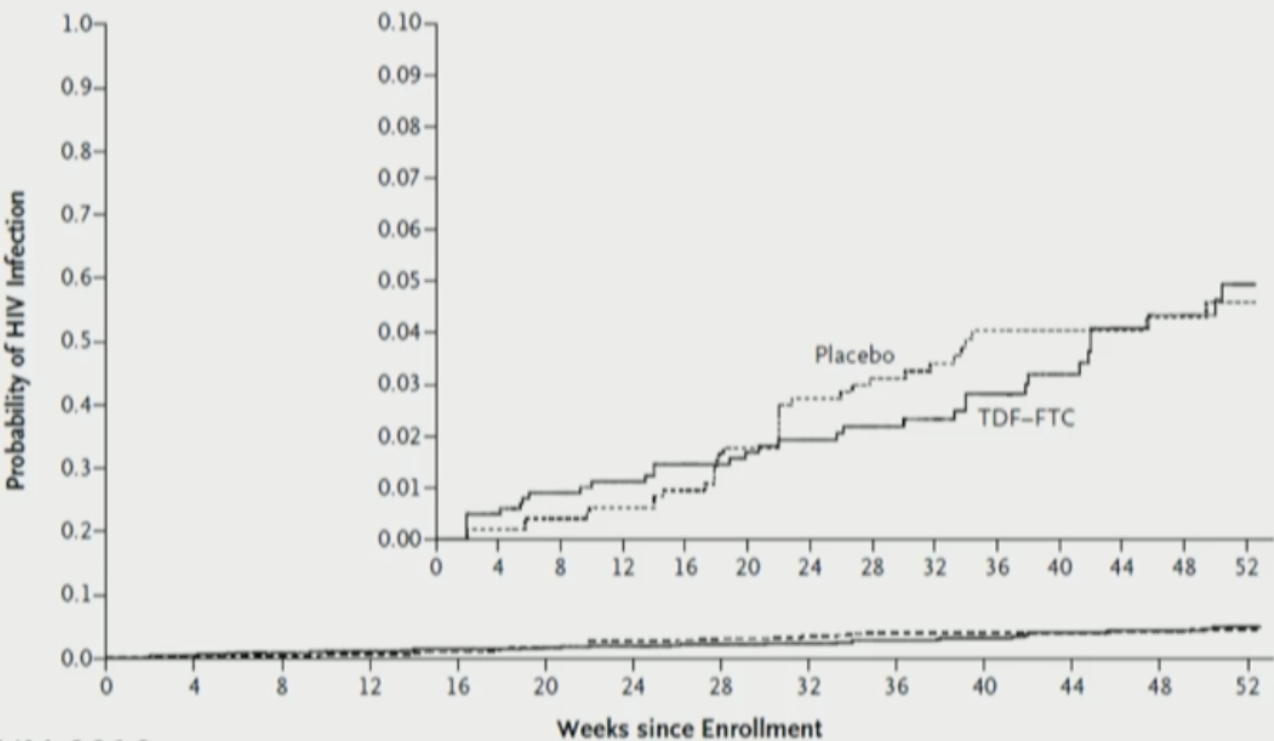
<sup>2</sup>Marrazzo, JAMA 2024



# Oral PrEP failure in studies of women linked to suboptimal pill adherence

The NEW ENGLAND JOURNAL of MEDICINE

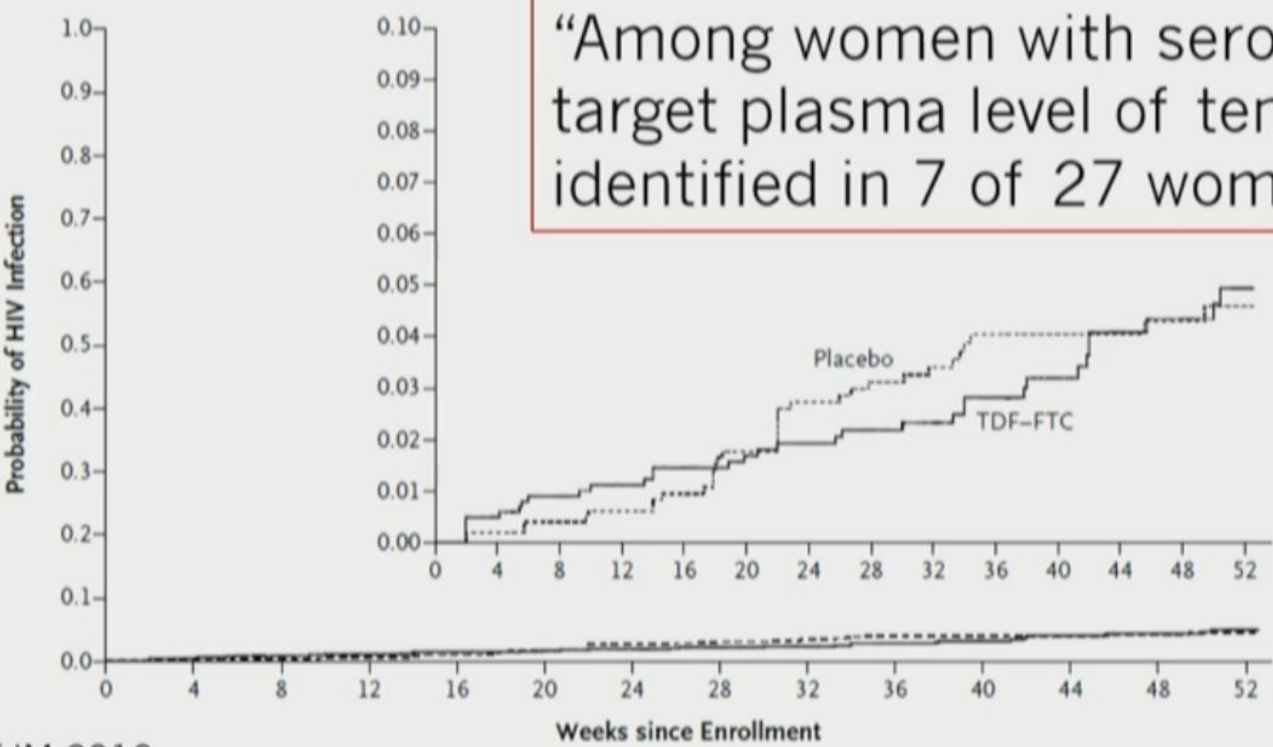
## Preexposure Prophylaxis for HIV Infection among African Women



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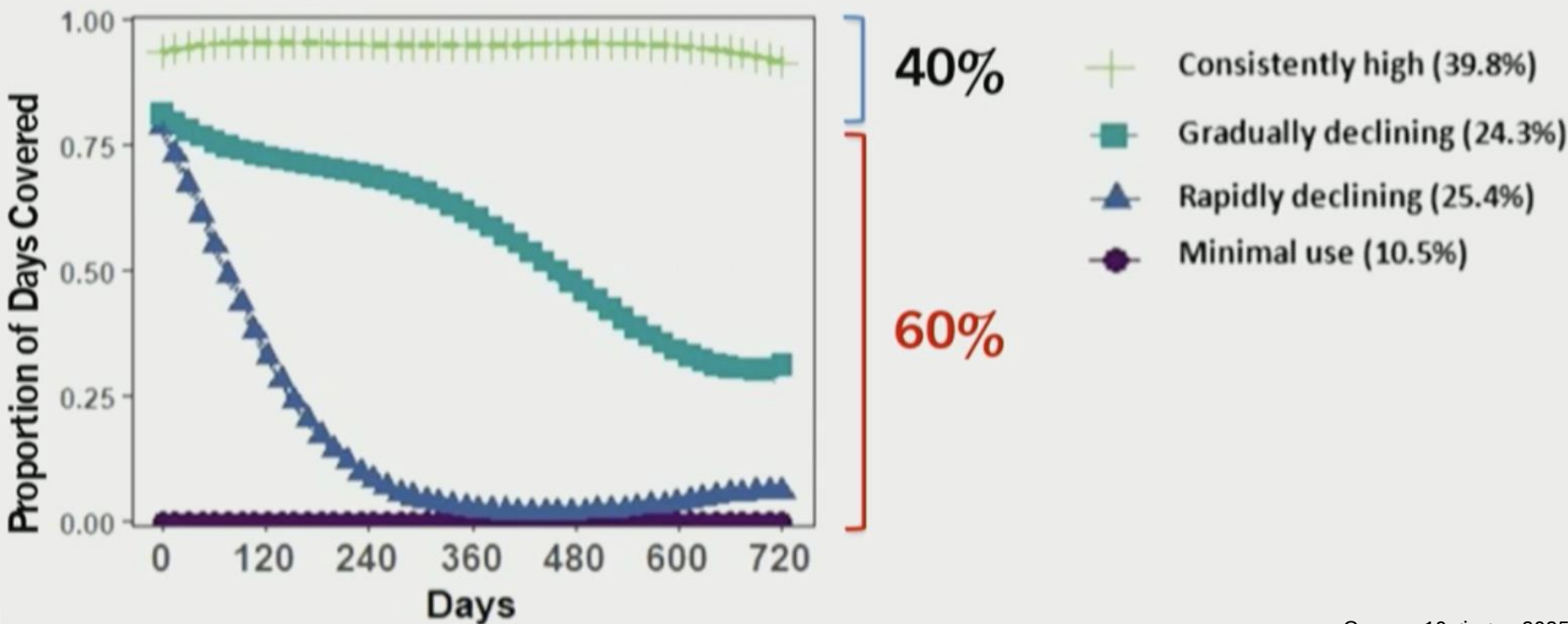


# Decreasing adherence to oral PrEP over time in the real-world

Open Forum  
Infectious  
Diseases



Trajectories of Adherence to Oral Pre-exposure  
Prophylaxis and Risks of HIV and Sexually Transmitted  
Infections



# Luci e Ombre PREP

## Orale

- **Aderenza**
- **Persistenza**
- **Distribuzione**
- **Resistenza**

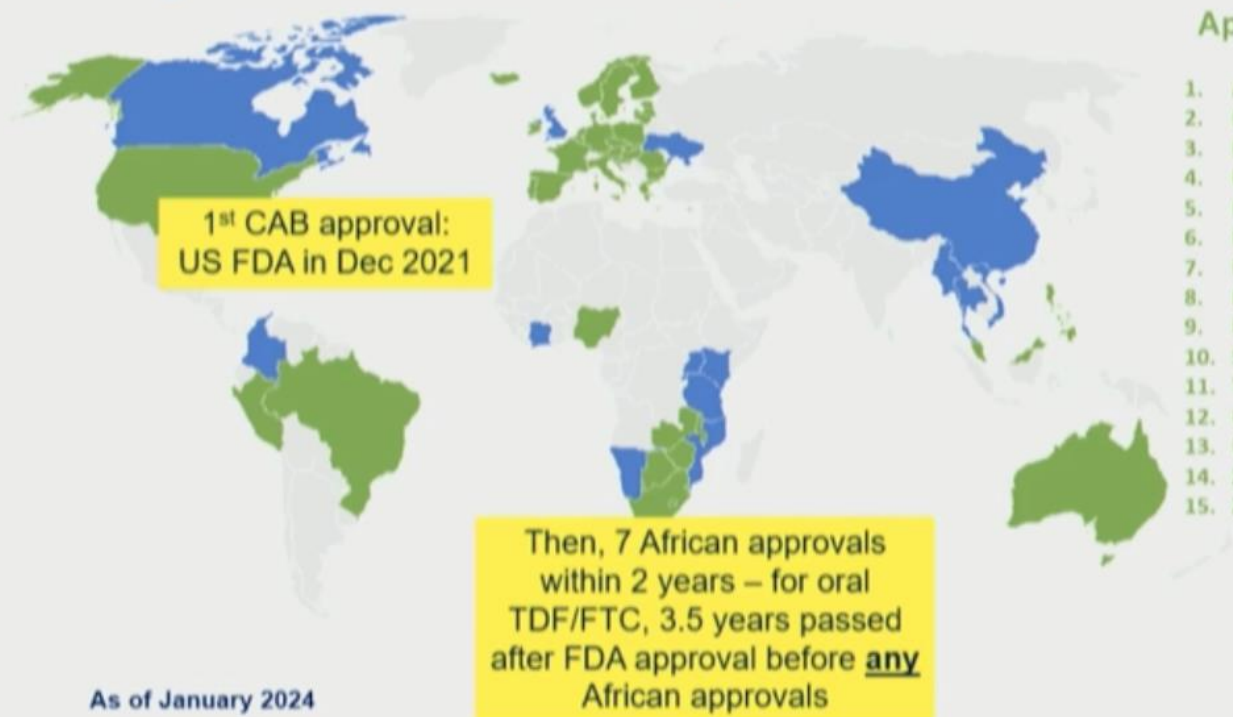
## Iniettiva

- **Distribuzione**
- **Resistenza**
- **Costi**

# CAB Availability

- ~**11,000 total** U.S. prescriptions
  - ~\$22,200/year
- PEPFAR supply, Feb 2024
  - ~\$170 - \$240/year
- Generic licensing, July 2022
- CAB regulation faster than oral PrEP
  - LMIC project product 3 years faster

15 regulatory approvals; 13 pending





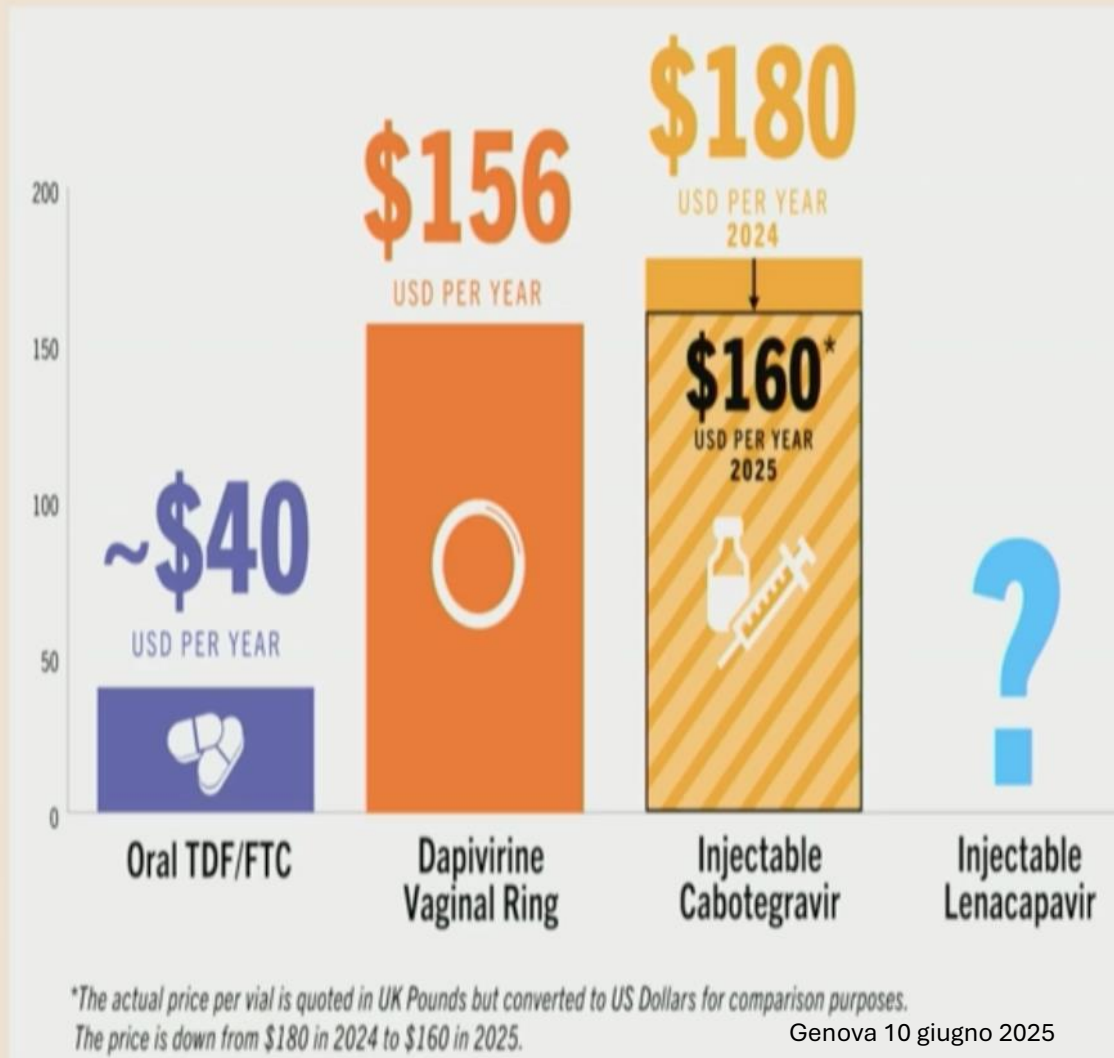
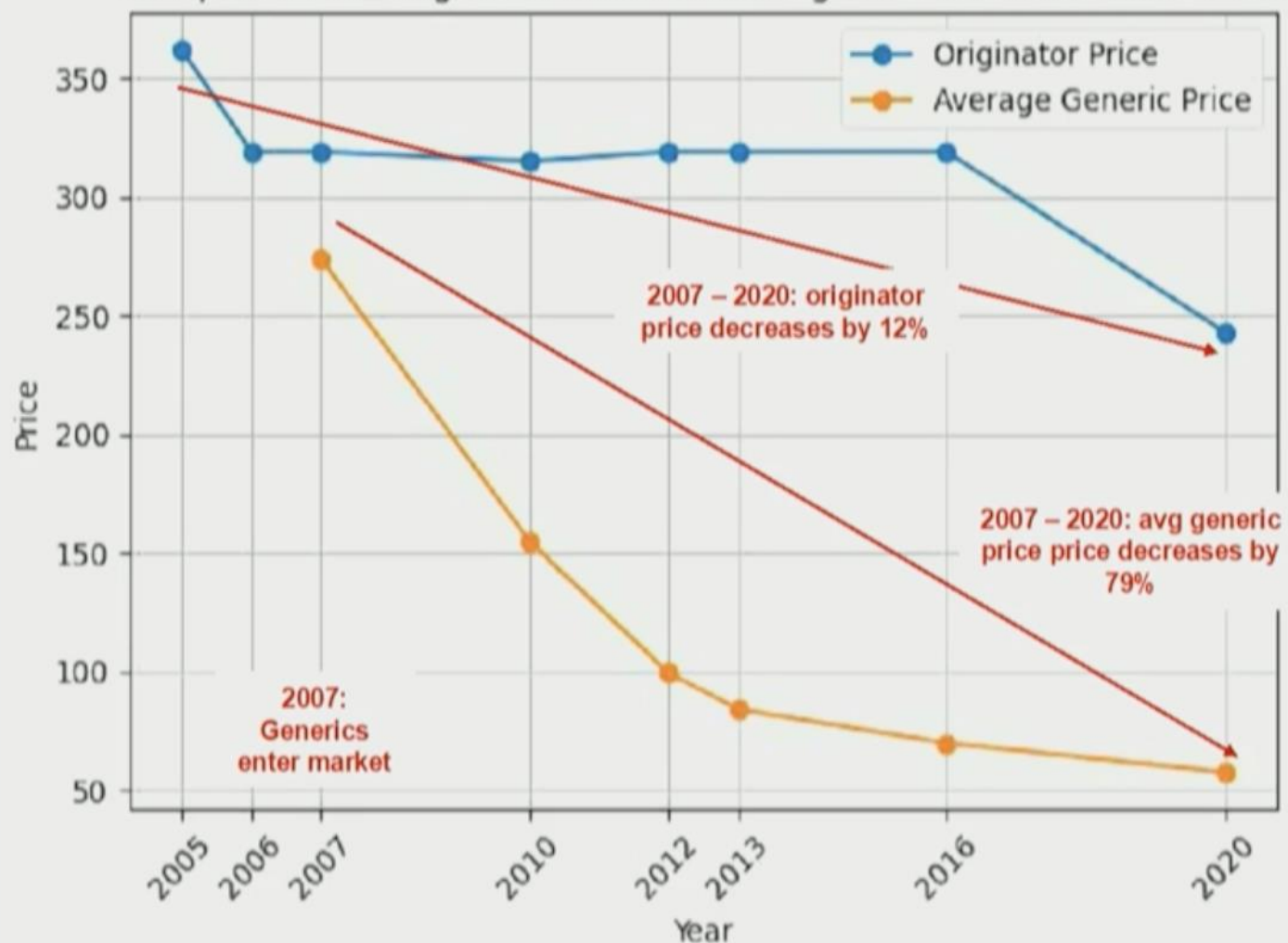


# PrEP Prices in LMICs

Oral TDF/FTC from Gilead and then the average over time from 15 generics

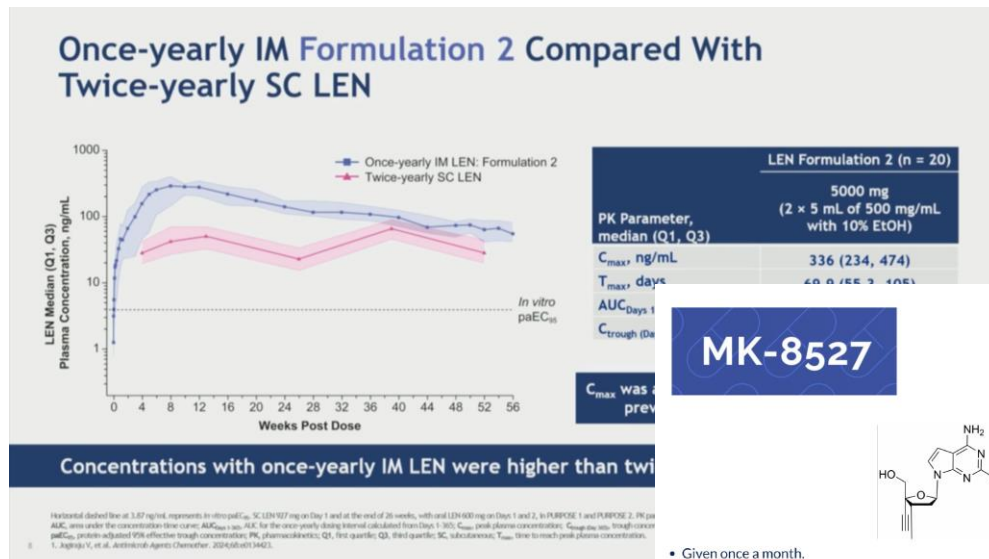
Low prices = Increasing Access

Comparison of Originator Price vs Average Generic Price Over Years

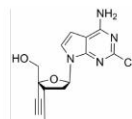


# Il futuro sarà long acting

## • Sostenibilità il vero ostacolo



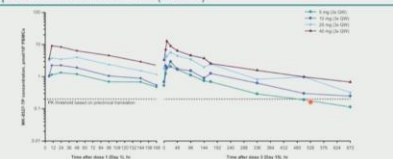
**MK-8527**



- Given once a month.
- An oral pill.
- Developed by Merck.
- An ARV from a class of drugs first tested by another drug known as islatravir.
- Drugs are classed by how they work in the body. Islatravir studies for prevention were discontinued when a fall in white blood cell counts (sometimes referred to as lymphocyte levels) was detected after the drug was administered. MK-8527 has a different chemical structure than islatravir, and studies so far show no safety risk.
- Currently under investigation for use as prevention in a small Phase II clinical trial.

MK-8527 is a novel oral NRTTI dosed monthly for PrEP

Mean MK-8527-TP concentrations after ascending multiple doses of MK-8527 (trial B)



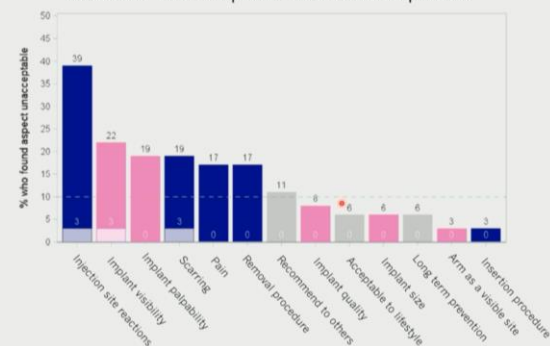
Gillespie, CROI 2024 (abstract 129); <https://clinicaltrials.gov/study/NCT06045507>; Kapoor, CROI 2025 (abstract 1232)

Abbreviated Title		Oral MK8527 QM as PrEP in Cisgender Men, TGM, TSM, and GNB People Who Have Sex With Partners Assigned Male Sex at Birth
Trial Phase		3
Clinical Indication		Prevention of HIV-1 infection
Trial Type		Interventional
Type of Control		Emtricitabine/ Tenofovir Disoproxil Fumarate (FTC/TDF)
Route		Oral
Administration		Double-blind
Treatment Groups		Randomized 1:1 to MK-8527 (monthly) or FTC/TDF (daily)
No. Trial Participants		4380

Annual tenofovir implant associated with substantial insertion site side-effects




Reasons that implant was unacceptable



# Modeling Interventions Required to Achieve EHE Goals in gbMSM



gbMSM<sup>a</sup>  
included:  
  
N=4,503,080

Status quo

Combined testing/care; status quo<sup>b</sup> PrEP, low improvement

Combined testing/care; status quo<sup>b</sup> PrEP, high improvement


Combined testing/care; PrEP (gbMSM – higher risk of HIV acquisition), low improvement

Combined testing/care; PrEP (gbMSM – higher risk of HIV acquisition), high improvement

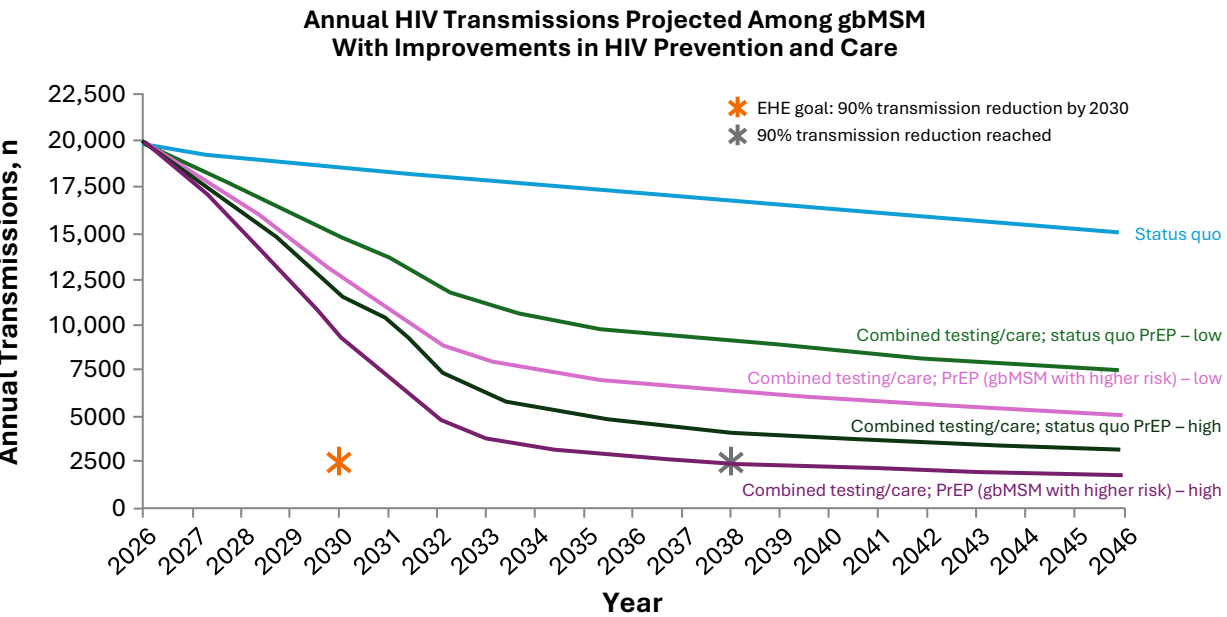
Select Model Input Parameters				
Parameter		Value		
Total population, n		4,503,080		
HIV prevalence, n (%)		601,930 (13.4)		
gbMSM with higher risk of HIV acquisition, n (%)				
Among gbMSM without HIV		543,634 (13.5)		
Among gbMSM with HIV		421,382 (69.8)		
Average monthly risk of HIV acquisition, %				
Among gbMSM with higher risk of HIV acquisition		0.38		
Among gbMSM with lower risk of HIV acquisition		0.08		
Relative risk among gbMSM with risk of HIV acquisition		4.7		
Prevention and care continuum strategies		Status quo	Interventions	
			Low improvement	High improvement
HIV testing frequency (monthly intervals)		82	12	6
Probability of linkage to HIV care, %		77	90	98
Engagement in HIV care at 24 months, %		75	90	98
VS, %		81	93	98
PrEP coverage, higher chance/lower risk of acquisition, %		40/7	75/15	90/20
PrEP effectiveness, %		76	90	96

Outcomes

Number of annual transmissions and percent reduction in HIV transmissions<sup>c</sup>



HIV transmissions were predicted from 2022 to 2045



Modeling suggests that major improvements in testing, care and prevention are needed to reduce HIV transmissions by 90% among gbMSM in the US by 2038 and achieve EHE goals

<sup>a</sup>With and without HIV. <sup>b</sup>Defined as current levels of testing, care and PrEP use. <sup>c</sup>Modeled on the status quo<sup>b</sup> or potential improvements based on the implementation of 8 single interventions and 2 combination interventions. EHE, Ending the HIV Epidemic; gbMSM, gay, bisexual and other men who have sex with men; VS, virologic suppression  
Scott JA, et al. CROI 2025, Poster 1295

Genova 10 giugno 2025



# Luci e Ombre

- **Stato dell'arte**
  - PrEP HIV
  - **DoxyPEP**

ORIGINAL ARTICLE

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

Anne F. Luetkemeyer, M.D., Deborah Donnell, Ph.D., Julia C. Dombrowski, M.D., M.P.H., Stephanie Cohen, M.D., Cole Grabow, M.P.H., Clare E. Brown, Ph.D., Cheryl Maer, M.D., M.P.H., Rodney Perkins, R.N., M.P.H., Melody Nasser, B.A., Caroli... Eric Vittinghoff, Ph.D., Susan P. Buchbinder, M.D., Hyman Sc... Edwin D. Charlebois, Ph.D., M.P.H., Diane V. Havlir, M.D., Oluse... and Connie Celum, M.D., M.P.H., for the DoxyPEP Study Group

ABSTRACT

BACKGROUND

Interventions to reduce sexually transmitted infections (STIs) among people who have sex with men (MSM) are needed.

The effectiveness data provide evidence for doxy-PEP as an effective STI prevention intervention for MSM with recent STIs and ongoing condomless sex, regardless of HIV serostatus. The

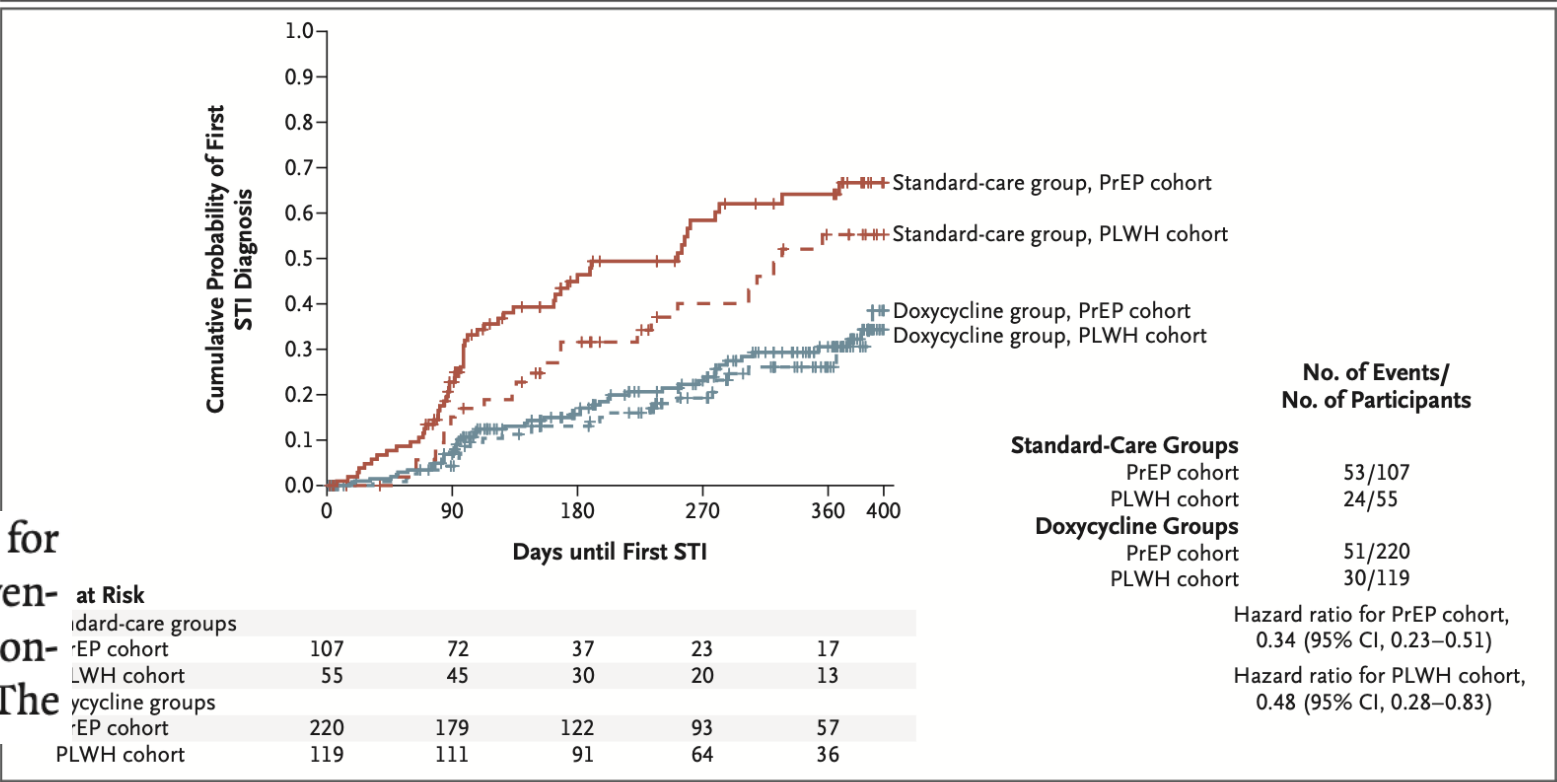


Figure 3. Kaplan–Meier Estimate of Time to First STI Diagnosis.

The cumulative probability of any incident bacterial STI (chlamydia, gonorrhea, or syphilis) is shown according to study group (doxycycline and standard care) and participant cohort (PrEP and PLWH).

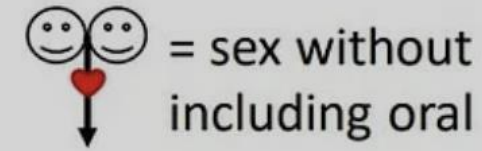


# Doxycycline as Post-Exposure Prophylaxis (doxy-PEP)

- Why doxycycline?
  - Safe, well-tolerated, inexpensive
  - Active against chlamydia (CT) and syphilis
  - Some resistance to gonorrhea, but
    - Not used as 1<sup>st</sup> line treatment of gonorrhea
    - Unknown how much activity is needed for PEP
- Dose: 200 mg within 72 hours after sex
- Four recent RCTs
  - 3 in MSM/transgender women showed substantial decline in CT (70-86%), syphilis (73-79%), variable efficacy against gonorrhea (33-55%)
  - 1 in cis-gender women showed no efficacy, but adherence poor



## Doxy PEP – How to Take

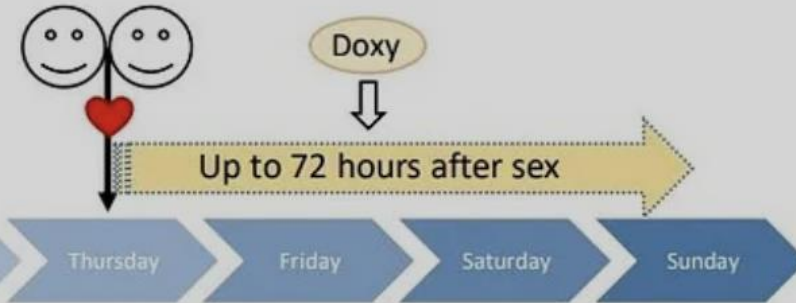


**Two 100 mg pills of doxycycline ideally within 24 hours but no later than 72 hours after condomless oral, anal or vaginal sex**

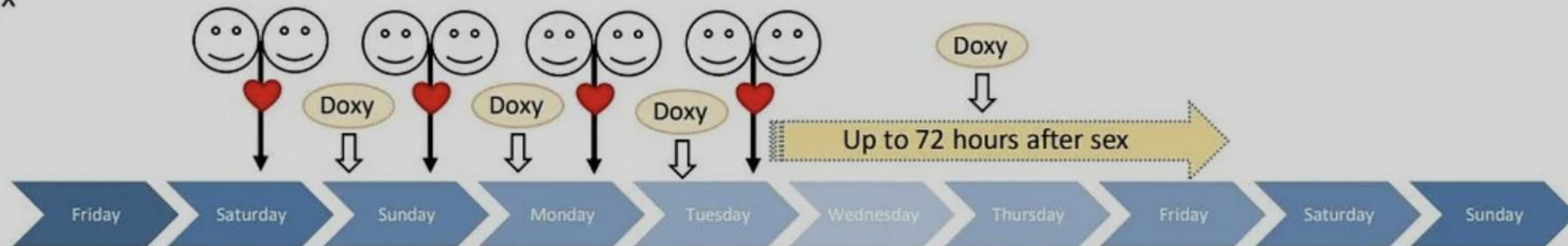
Example: Sex on Sat; take dose of doxy by Tues



Example: Sex on Thursday; take dose of doxy by Sunday



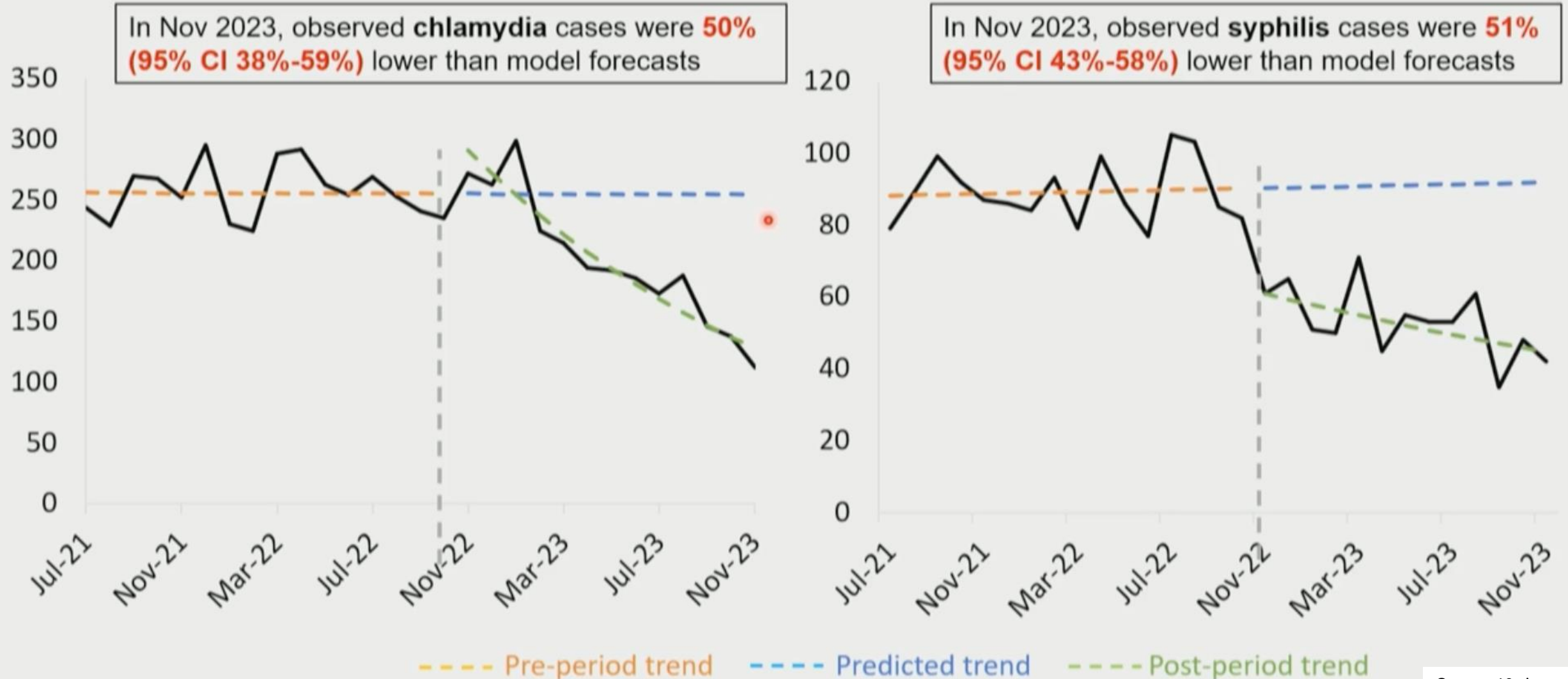
Example 2: Daily (or more) sex Sat-Tues; take daily dose of doxy and last dose within 24 hours *but not later than 72 hours* after last sex



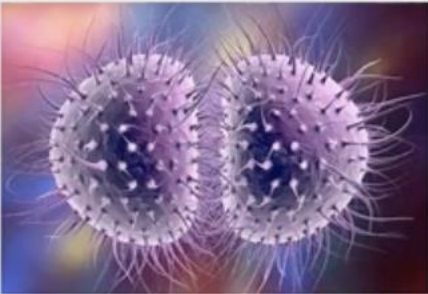
**No more than 200 mg every 24 hours**



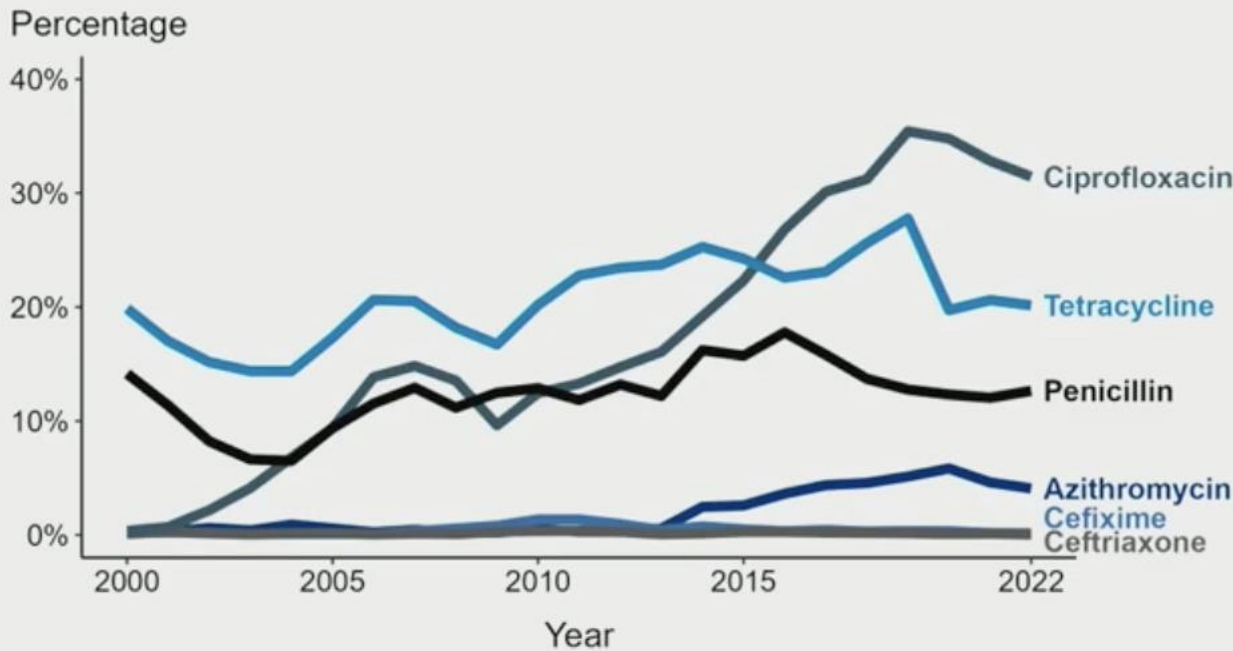
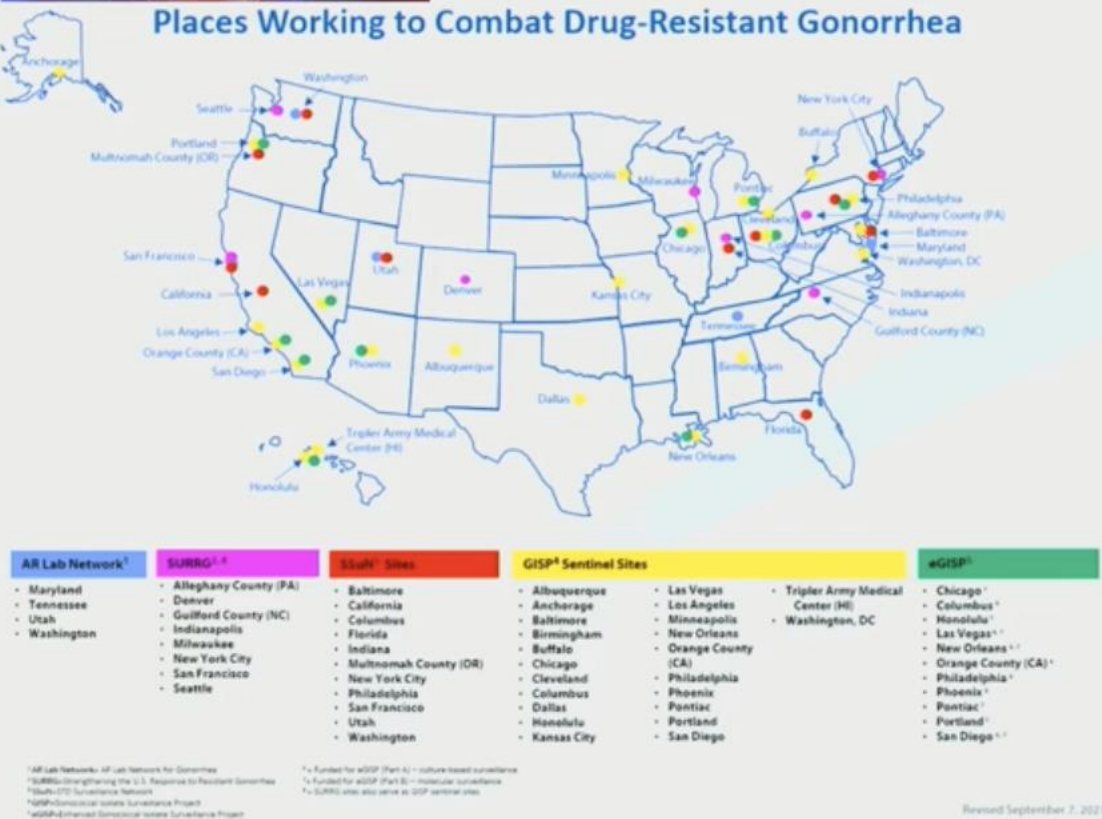
# Decline in citywide chlamydia and early syphilis cases in MSM and TGW in SF after release of doxy-PEP guidelines



# Gonococcus: tetracycline resistance

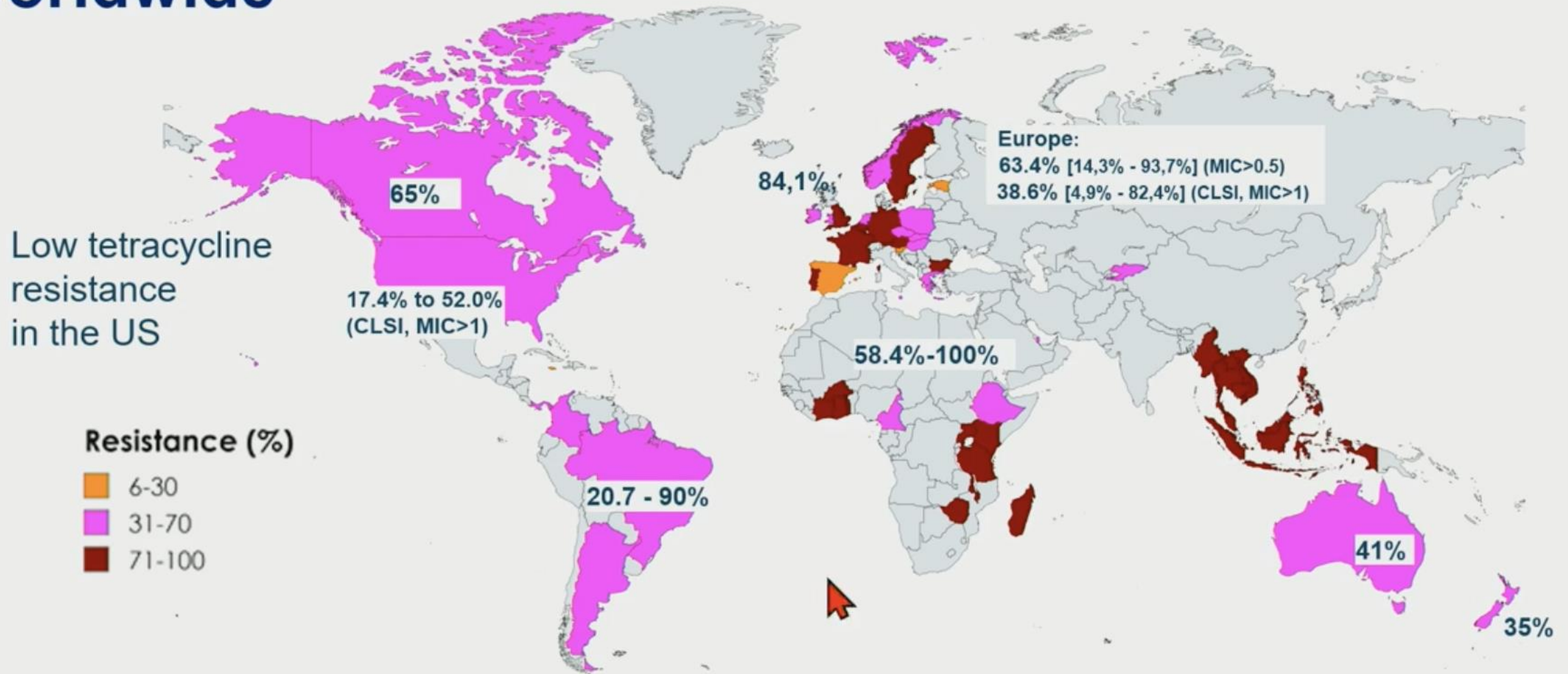


- WHO and CDC priority watch list for FQ- and 3GC-resistant gonorrhea (2017)
- Recent reports highlight the risk of gonorrhea becoming untreatable in the future.





# A large reservoir of tetracycline-resistant GC isolates worldwide



Unemo, Lancet Reg Health Eur, 2024. <https://www-cdc-gov.proxy.insermbiblio.inist.fr/std/GISP/>; Mortimer, Clin Infect Dis, 2023; Congo-Ouedraogo M, J Eur Acad Dermatol, 2022; Naiki Attram, PLoS One. 2019; Alain Yéo A, 2019 Sex Transm Dis; Crucitti T, Int J STD AIDS 2020; Nireshni Mitchev, AAC 2021; Machado H de M, JAC Antimicrob Resist. 2022; Thakur, Sexual Trans Dis, 2017; Golparian D, J Antimicrob Chemother. 2022; Cornelisse VJ, Sex Health. 2023, Sawatzky, RMTTC, 2023; Rivillas-García JC, Rev Panam Salud Publica, 2020; Kahsay AG, Infection and Drug Resistance 2023; Cameron-McDermott SM, J Antimicrob Chemother 2022; Matoga M, Sexually Transmitted Diseases, 2022; Núñez-Samudio V, Microorganisms, 2023; Aboud S, Trop. Med. Infect. Dis. 2022; Hamill MM, BMC Infectious Diseases 2022.

2025



*Clinical Infectious Diseases*

## MAJOR ARTICLE

# **Potential Impact of Doxycycline Post-Exposure Prophylaxis on Tetracycline Resistance in *Neisseria gonorrhoeae* and Colonization with Tetracycline-Resistant *Staphylococcus aureus* and Group A *Streptococcus***



# Quali sono le conclusioni del lavoro?

- La resistenza a tetracicline in *N.gonorrhoeae* è rapidamente aumentata dal 2021 al 2024 (attualmente High Level)!
- L'uso di DoxiPeP è associato a colonizzazione da *S.pyogenes* e *S.aureus* resistente a *S.aureus* (quindi impatto off-target)

Figure 1: Prevalence of tetracycline resistance among MSM with NG, PHSKC Sexual Health Clinic, 2017-2024.

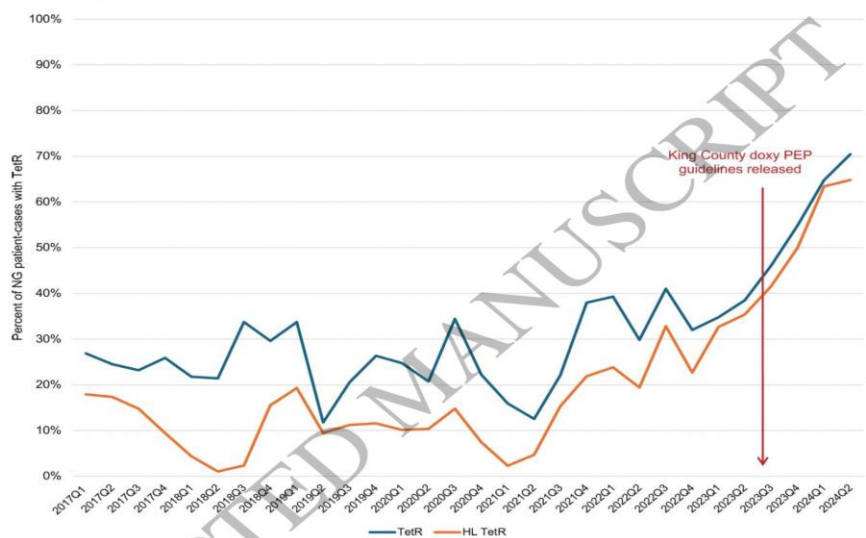
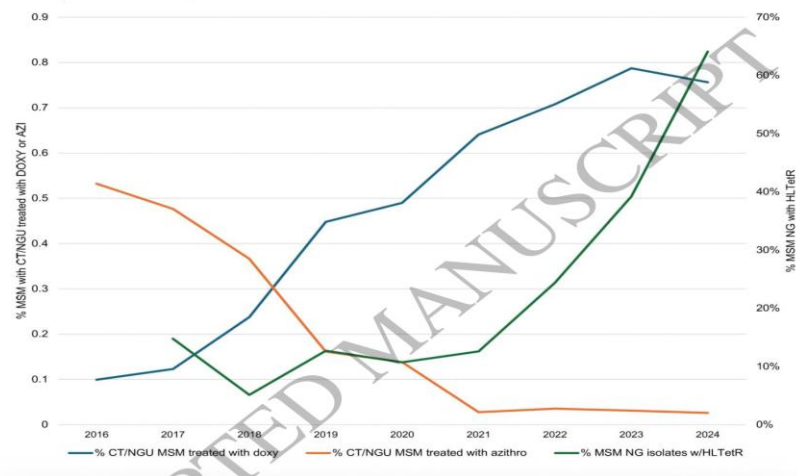


Figure 3: Proportion of PHSKC SHC MSM diagnosed with CT or NGU who were treated with doxycycline or azithromycin within 7 days, and proportion of MSM NG isolates with high level tetracycline resistance, 2016-2024



# Doxy PEP

- High effectiveness, safety, tolerability, and acceptability of doxy-PEP support the **US CDC recommendations** to counsel MSM and TGW with a recent history of bacterial STIs about doxy-PEP as an STI prevention
- Evaluation of AMR in *N gonorrhoeae* and common colonising bacteria, such as *S aureus* and *Streptococcus pneumoniae*, is warranted as part of public health surveillance and research with long-term doxy-PEP use

# Conclusioni

- **PrEP antivirale: luci maggiori delle ombre**
  - OS: aderenza, persistenza, distribuzione, resistenze
  - IM: Sostenibilità (costi diretti ed indiretti)
- **PEP: antibiotici: non ancora chiaro il vantaggio**
  - Doxy PEP: Orale, autosomministrazione, Tollerabilità, antibioticoresistenza per la comunità