Biomedical Prevention of HIV and STIs

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Napneung Workshop, Bangkok, June 23, Thailand

Université de Paris

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anrs MALADIES INFECTIEUSES ÉMERGENTES

Global HIV Epidemic

2021

Globally

38.4 million

People living with HIV

1.5 million

People newly infected

- 32%

New infections annually relative to 2010

- 52%

Deaths annually relative to 2010

+ 52% New diagnoses annually relative to 2010 in Eastern Europe and Central Asia

The region with the fastest growing epidemic in the world !

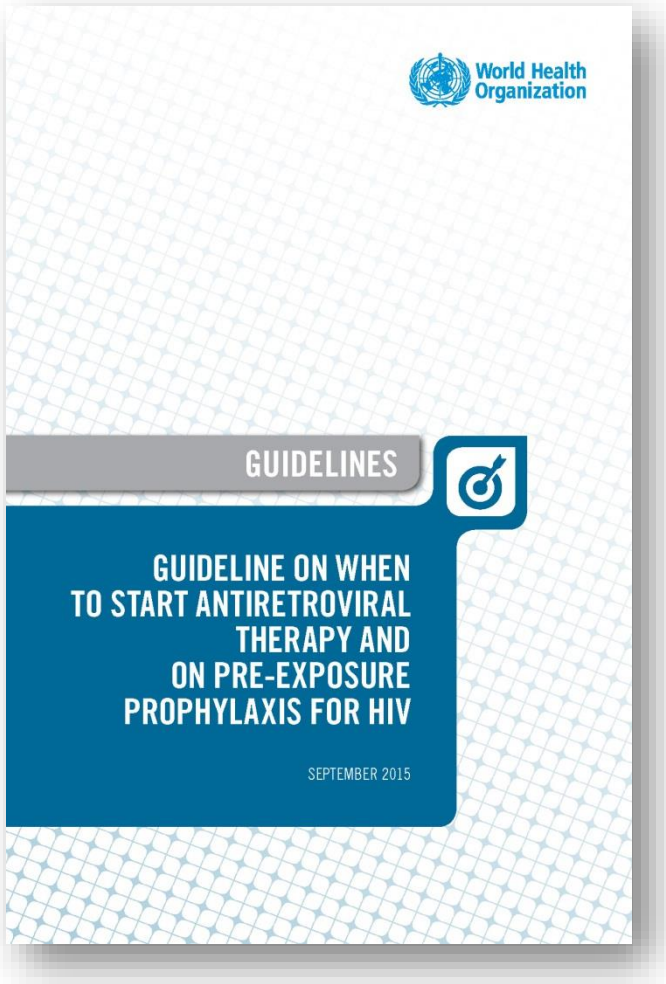
UNAIDS/WHO estimates 2022

Prevention of HIV/AIDS without a Vaccine on the Horizon

- **Abstain, Be Faithful, Condoms**: 70-90% risk reduction of HIV sexual transmission (observational studies)
- **Circumcision in males** : 60% risk reduction of HIV transmission from women to men
- **Harm reduction** in IV drug users: opoid substitution therapy, needle and syringes programs
- **Drugs (Antiretrovirals) for HIV Prevention**
  - ✓ Prevention of mother to child transmission
  - ✓ Post-Exposure Prophylaxis
  - ✓ Treatment of HIV-infected individuals: Undetectable = Untransmissible
  - ✓ Pre-Exposure Prophylaxis (PrEP)

PrEP is Changing HIV Prevention

WHO 2015 Guidelines



Oral PrEP should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches

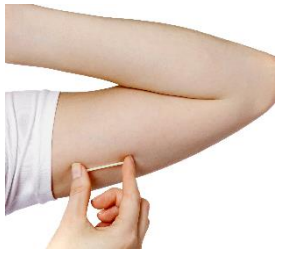
Defining "substantial risk": *Substantial risk of HIV infection is provisionally defined as HIV* ***incidence greater than 3 per 100 person–years*** *in the absence of PrEP. HIV incidence greater than 3 per 100 person–years has been identified among some groups of men who have sex with men, transgender women in many settings and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.*

http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/

http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/ (Accessed October 2015)

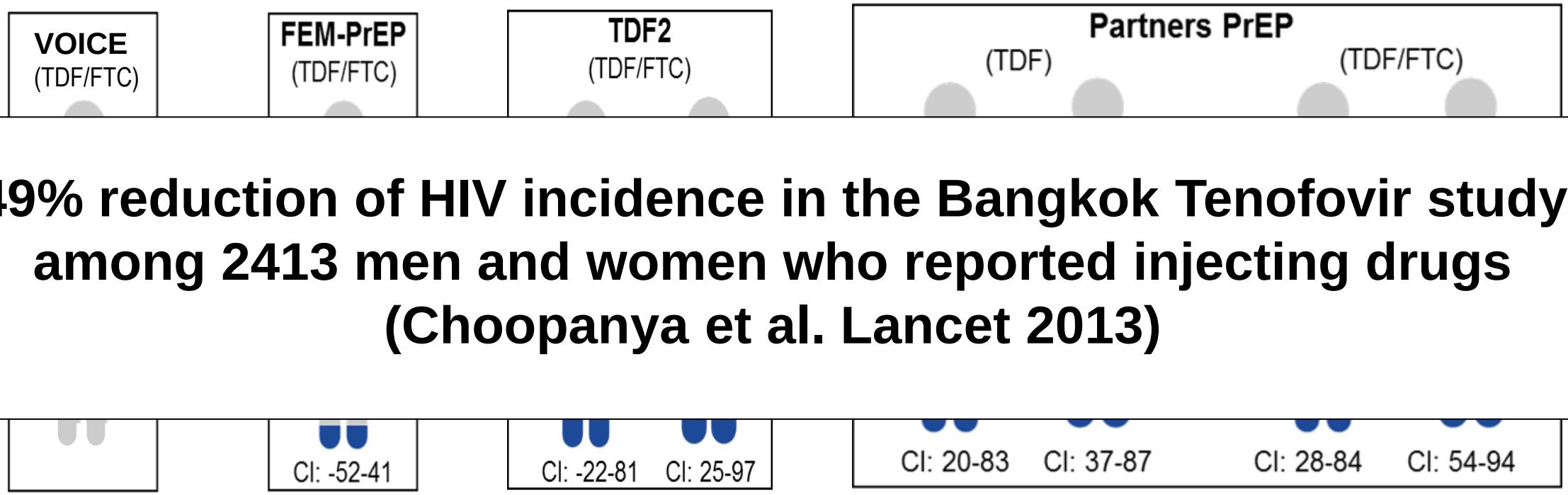
PrEP Regimens Approved

- **Oral TDF/FTC (use generics when available)**
- Oral TAF/FTC
- Dapivirine vaginal ring
- Cabotegravir LA intramuscular injections
- Investigational agents:
  - Neutralizing antibodies
  - LA oral or parenteral agents (Lenacapavir)
  - Subcutaneous implants (TAF)



Oral TDF/FTC for Heterosexual Men and Women

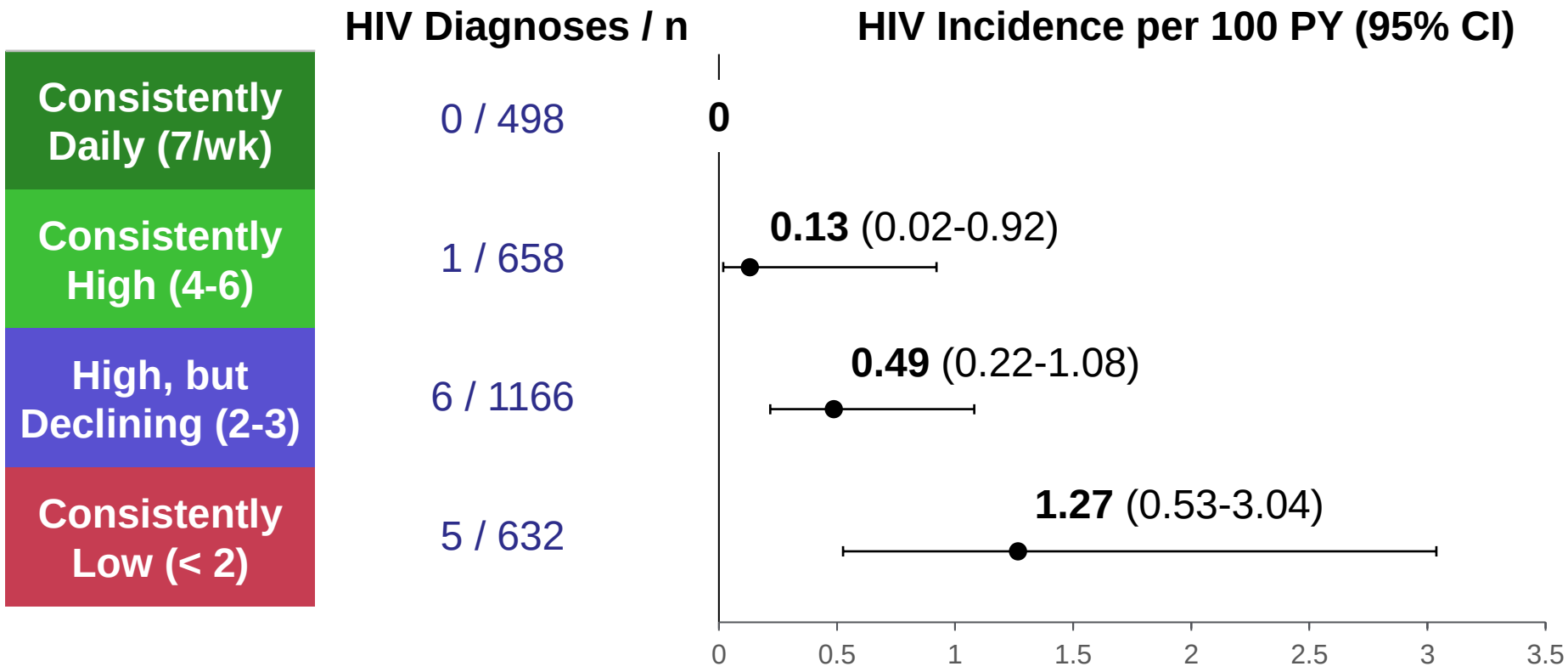
Daily Regimen: One pill of 300 mg TDF/200 mg FTC every day, started 7 days before the first exposure, and stopped 7 days after the last exposure



49% reduction of HIV incidence in the Bangkok Tenofovir study among 2413 men and women who reported injecting drugs (Choopanya et al. Lancet 2013)

Marrazzo J et al NEJM 2015; Van Damme L et al NEJM 2012; Thigpen MC et al NEJM 2012; Baeten J et al NEJM 2012; Landovitz RJ et al. AIDS 2020

HIV Incidence Rates Among Women on Oral TDF/FTC with Adherence Data (n = 2955)



- Even with low incidence overall, higher patterns of adherence were directly associated with lower risk of HIV acquisition

Calculated by Poisson regression.

Marrazzo J et al. CROI 2023

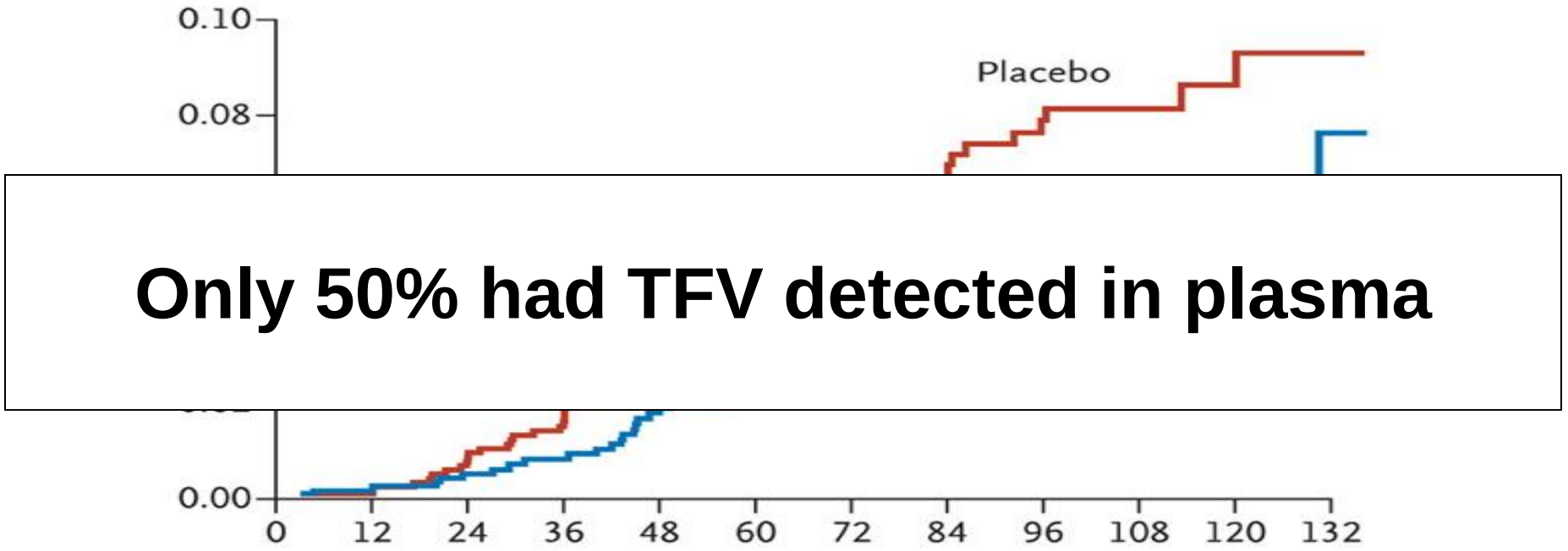
PrEP Regimens for MSM

- Oral TDF/FTC:
  - Daily: One pill of 300 mg TDF/200 mg FTC every day, started with a loading dose of 2 pills at least 2h before sex, and stopped 2 days after the last exposure
  - On demand: 2-1-1 regimen for each sexual intercourse
  - Regimen extended to all men

Oral TAF/FTC:

- Daily: One pill of 25 mg TAF/200 mg FTC every day, started 7 days before the first exposure, and stopped 7 days after the last exposure
- Recommended when creatinine clearance rate is between 30 and 60 mL/mn, prior history of osteopenia or osteoporosis, or a high risk for these complications.
- Clinical correlates of renal biomarker differences and DXA differences have not been demonstrated.

iPrEx : KM Estimates of Time to HIV Infection with Daily oral TDF/FTC



Only 50% had TFV detected in plasma

After a median follow-up of 14 months, 100 subjects became infected, 36 in the TDF/FTC arm and 64 in the placebo arm :

44% reduction in the incidence of HIV (95% CI : 15-63, p=0.005)

Grant RM et al N Engl J Med, Nov 23, 2010.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Double-Blinded Randomized Placebo-Controlled Trial

- 400 HIV negative MSM
- Condomless anal sex with ≥ 2 partners within 6 m
- eGFR > 60 mL/mn

→ **Full prevention services* TDF/FTC before and after sex**

→ **Full prevention services* Placebo before and after sex**

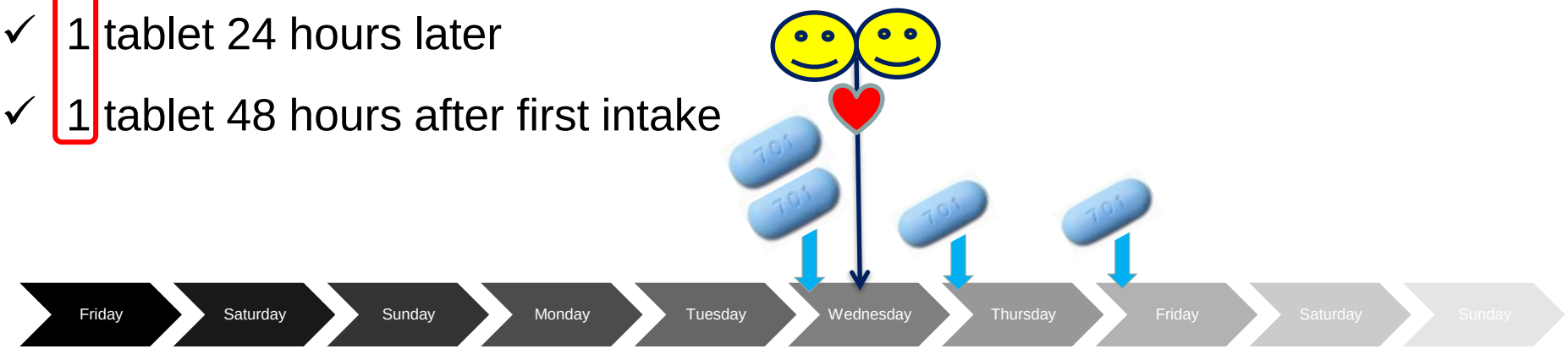
* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- Follow-up visits: month 1, 2 and every two months thereafter with 4th generation HIV ELISA assays (combined Ab/Ag detection) on serum

Molina JM et al. NEJM 2015

IPERGAY: Sex-Driven iPrEP

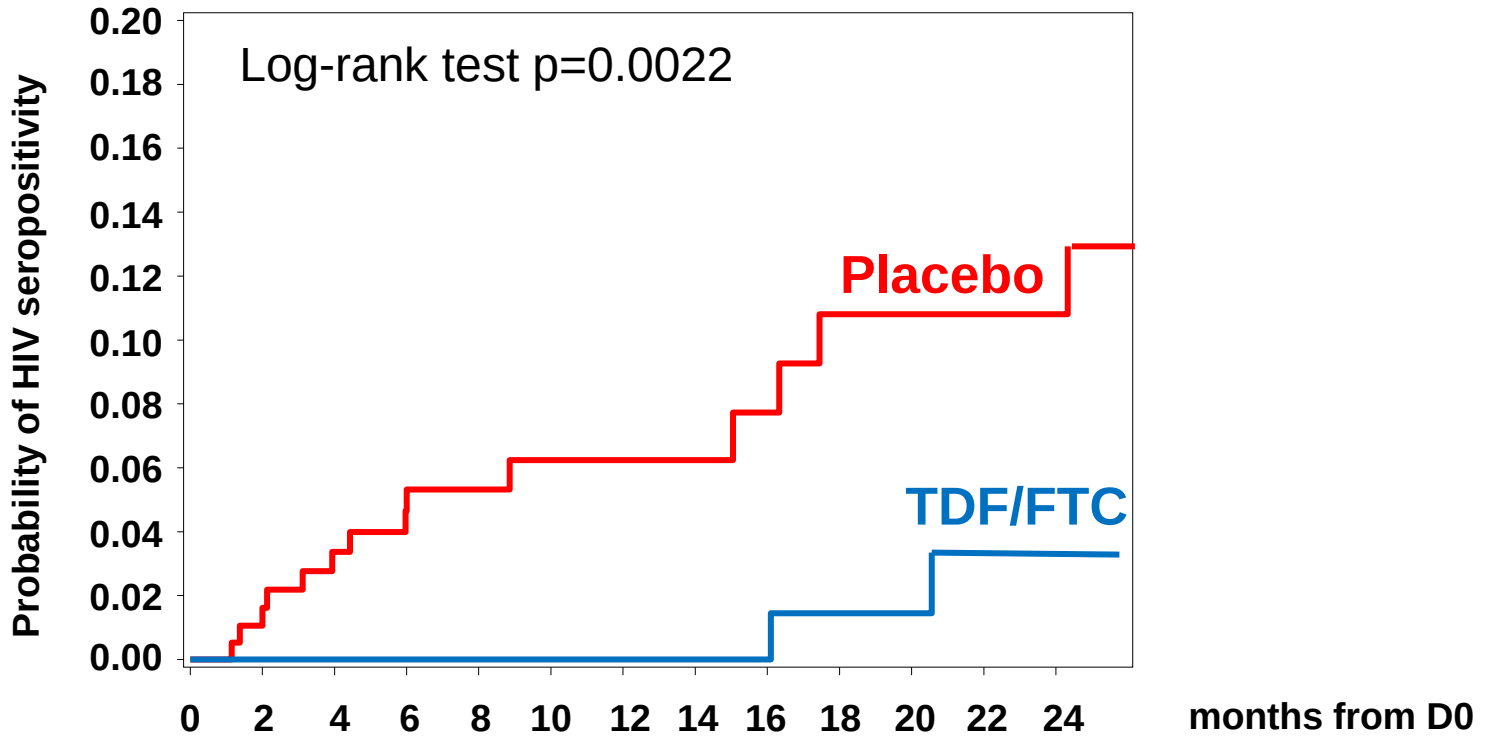
- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet 24 hours later
- ✓ 1 tablet 48 hours after first intake



4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

On demand PrEP tells you How to Start and How to Stop PrEP

Effectiveness of On Demand PrEP with TDF/FTC in MSM in France and Canada



Mean follow-up of 12 months: 16 subjects infected (**14 placebo, 2 in TDF/FTC)**

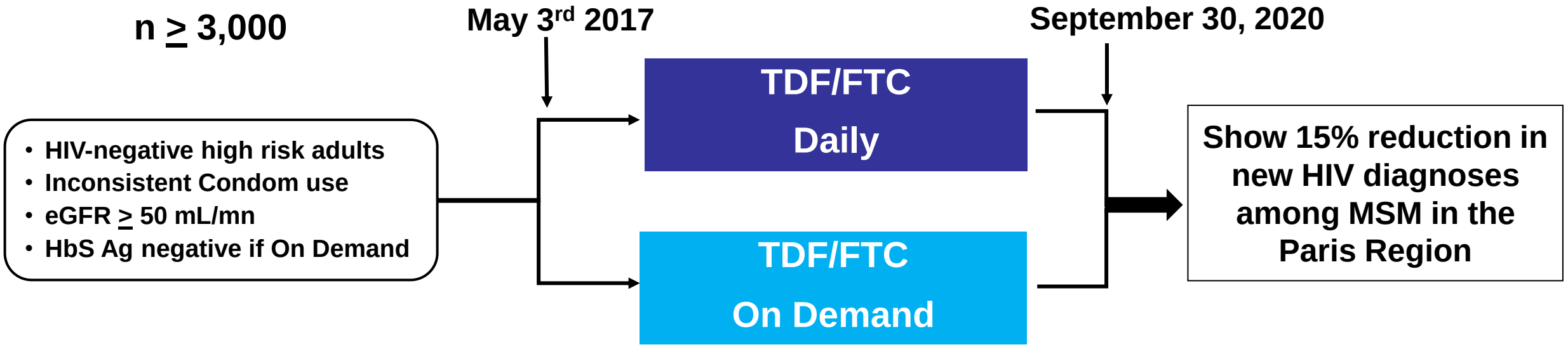
Incidence : 6.6 /100 PY (9.17 in Paris) placebo and 0.9/100 PY with TDF/FTC

Effectiveness = 86% in relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

Molina JM et al NEJM 2015

PrEP with Daily or On Demand TDF/FTC among MSM

Open-Label Prospective Cohort Study in the Paris Region



- **Participants opted for either Daily or On Demand PrEP and could switch regimen**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Molina JM et al CROI 2021

PrEP with Daily or On Demand TDF/FTC among MSM

Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases)

Mean Follow-up of 22.1 months and 5633 Person-Years

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)	IRR (95%CI)
TDF/FTC Daily	2583.25	0.12 (0.02 – 0.34)	**0.99** (0.13-7.38)
TDF/FTC On Demand	2553.68	0.12 (0.02 – 0.34)	

Molina JM et al Lancet HIV 2022

TECHNICAL BRIEF

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN: UPDATE TO WHO'S RECOMMENDATION ON ORAL PREP

JULY 2019

World Health Organization

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2020 Recommendations of the International Antiviral Society–USA Panel

Michael S. Saag, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Melanie A. Thompson, MD; Paul E. Sax, MD; Davey M. Smith, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

Supplemental content

IMPORTANCE Data on the use of antiretroviral drugs, including new drugs and formulations, for the treatment and prevention of HIV infection continue to guide optimal practices.

OBJECTIVE To evaluate new data and incorporate them into current recommendations for initiating HIV therapy, monitoring individuals starting on therapy, changing regimens, preventing HIV infection for those at risk, and special considerations for older people with HIV.

US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

DEPARTMENT OF HEALTH & HUMAN SERVICES USA

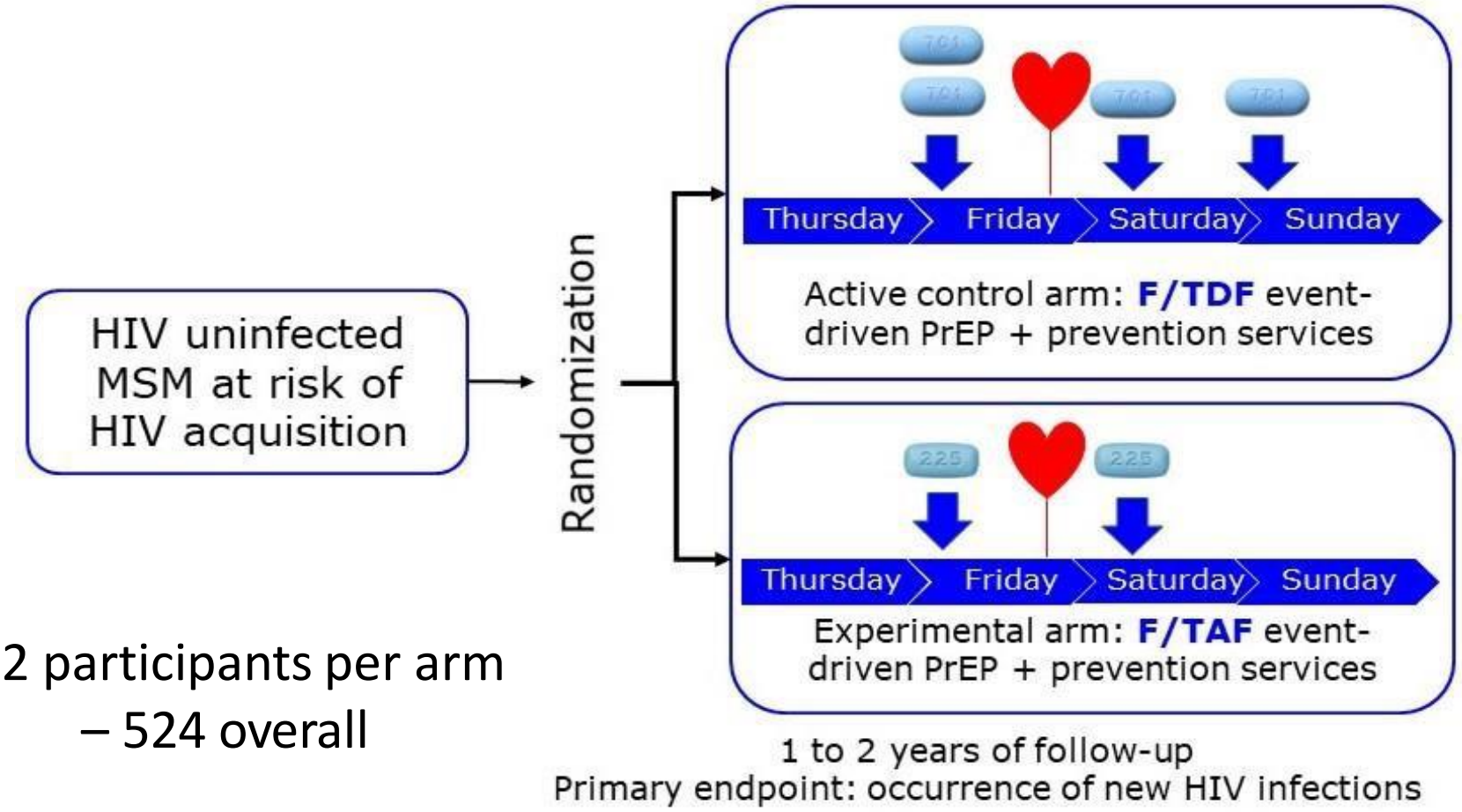
CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Interest of On Demand PrEP

- High effectiveness among MSM
- Provides an alternative to daily PrEP and expands PrEP options
- Could increase adherence and coverage of sex events among individuals not able to take daily PrEP
- Could improve safety and cost-effectiveness
- Could facilitate diagnosis of breakthrough HIV infection and reduce the risk of emergence of resistance mutations

Simplify On Demand PrEP with TAF/FTC: SimpPrEP Trial

A phase III, open-label, randomized trial in MSM with condomless anal sex twice a month or less and able to plan their sexual activity, in France and Thailand.



262 participants per arm – 524 overall

MALADIES INFECTIEUSES ÉMERGENTES

PrEP Regimens for MSM

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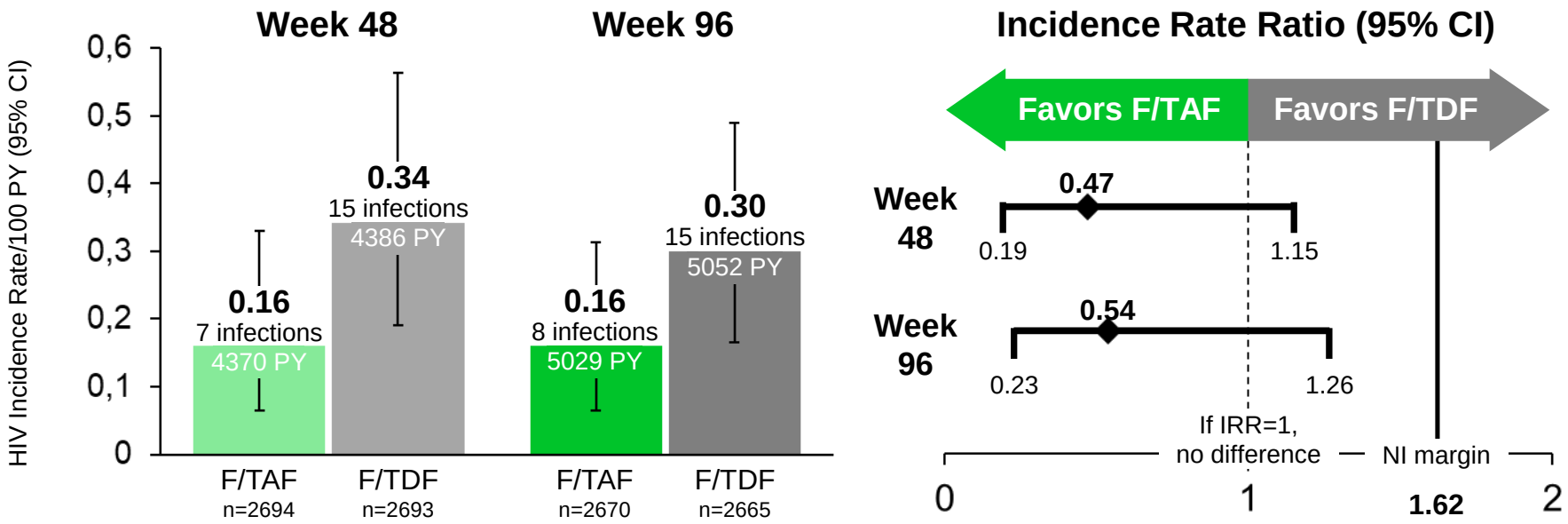
  - Daily: One pill of 300 mg TDF/200 mg FTC every day, started 7 days before the first exposure, and stopped 7 days after the last exposure
  - On demand: 2-1-1 regimen for each sexual intercourse
  - Regimen extended to all men
- Oral TAF/FTC:
  - Daily: One pill of 25 mg TAF/200 mg FTC every day
  - Recommended when creatinine clearance rate is between 30 and 60 mL/mn, prior history of osteopenia or osteoporosis, or a high risk for these complications.
  - Clinical correlates of DXA and renal biomarker differences and have not been demonstrated.

Ghandi R. et al. IAS-USA guidelines panel JAMA 2022

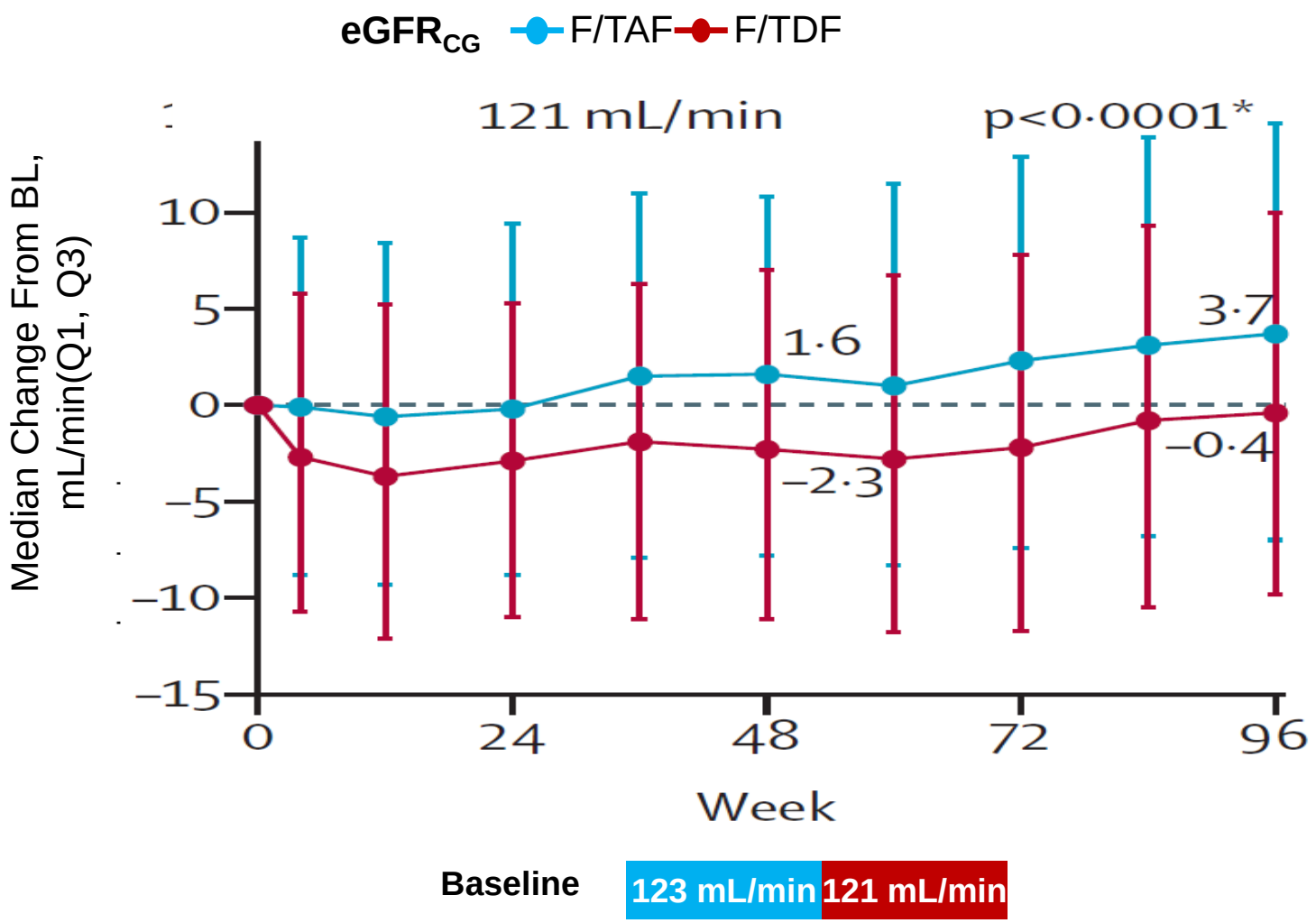
Daily F/TAF is Non-Inferior to Daily TDF/FTC for PrEP among MSM



- F/TAF is noninferior to F/TDF for HIV prevention (upper bound of the IRR 95% CI: <1.62)

Mayer K et al. Lancet 2020; Ogbuagu O et al. Lancet HIV 2021

DISCOVER: eGFR changes at Week 96



- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1 (at day 421 in a 49-yr old man with no comorbidities)

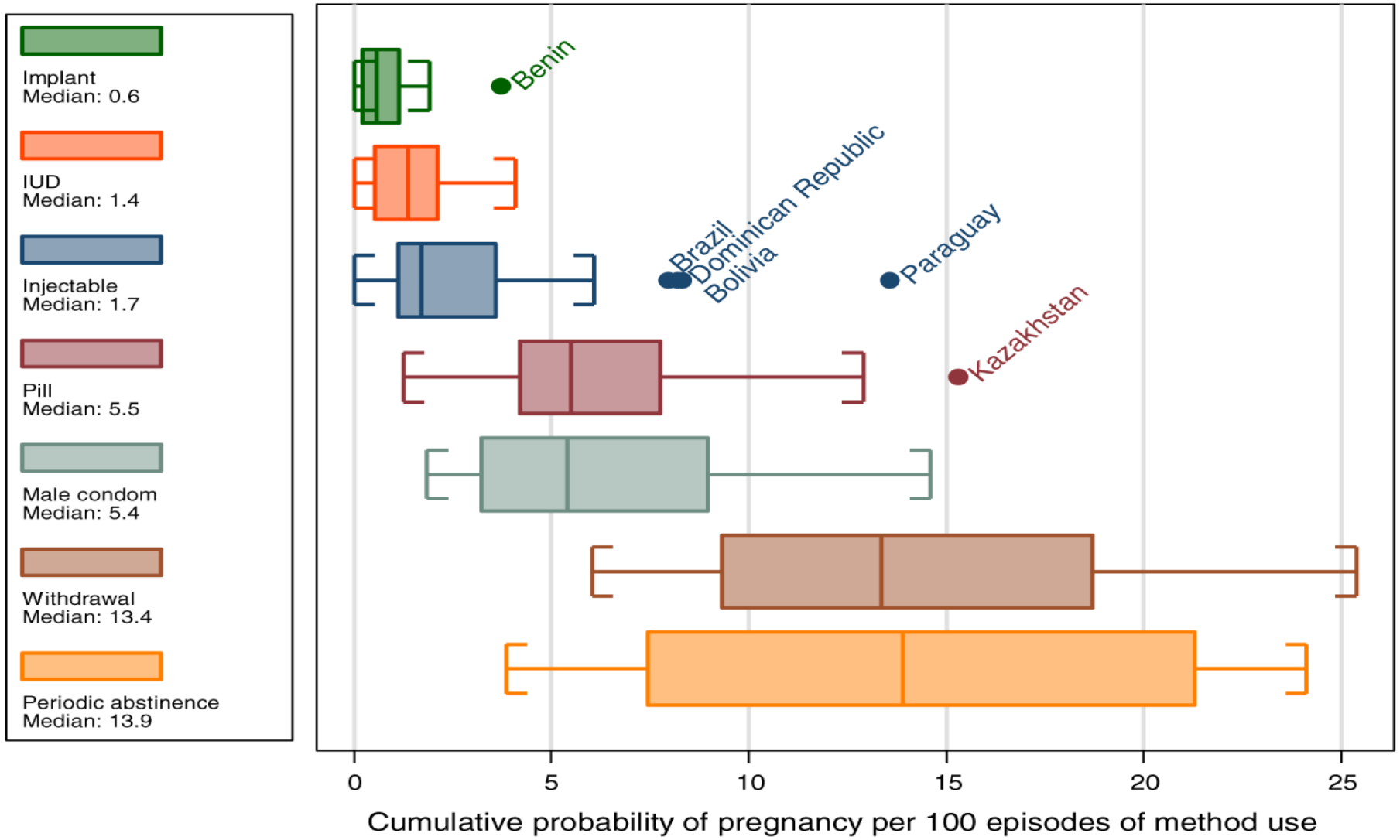
β2M, β2-microglobulin; Cr, creatinine; Q, quartile; RBP, retinol-binding protein.

Ogbuagu O et al. Lancet HIV 2021

Limitations of Oral PrEP

- Stigma associated with pill intake
- Gastro-intestinal AEs (nausea, diarrhea)
- No data yet with TAF/FTC in women and with on demand use
- Cost of TAF/FTC (300 Euros/month) vs generic TDF/FTC
- **Long-term adherence to pills: daily or on demand regimen**

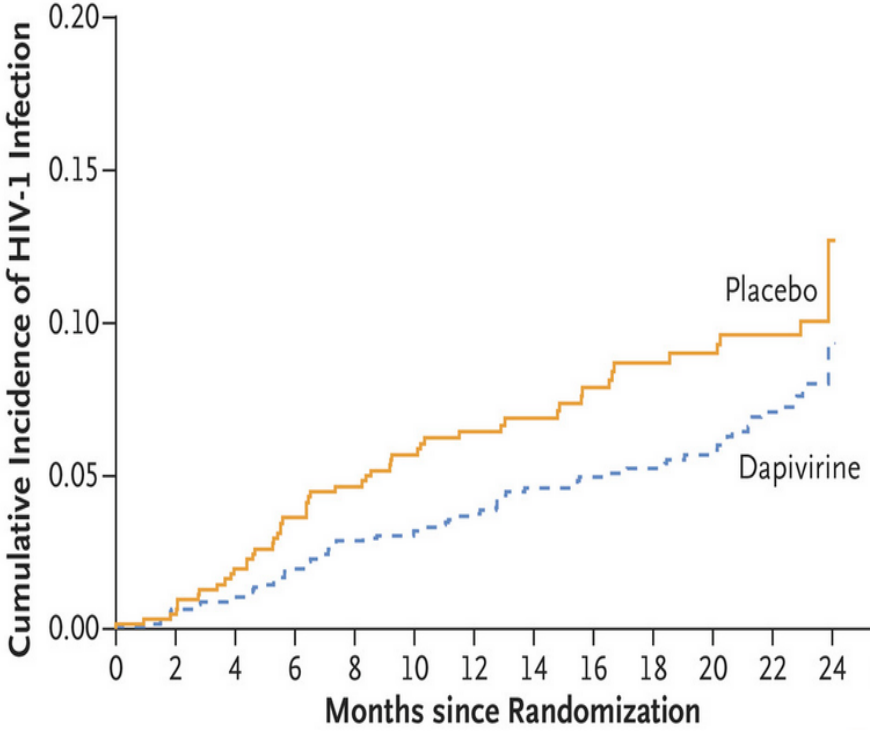
Failure Rate of Different Contraceptives Methods in 43 Countries



Polis CB et al. Contraception 2016

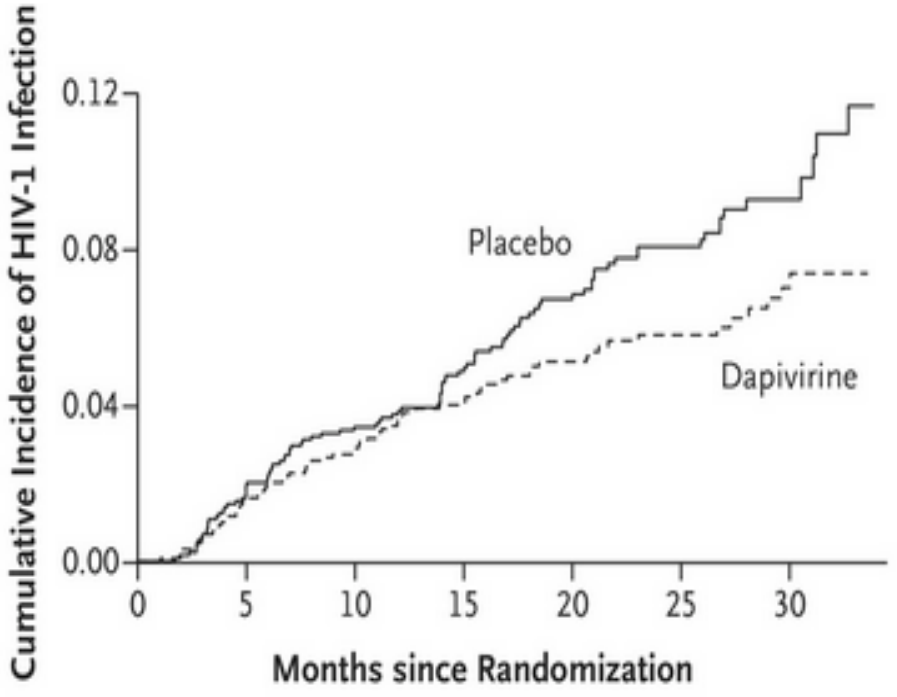
Dapivirine Vaginal Ring

. Randomized double-blinded study
. Dapivirine vaginal ring vs placebo
. Flexible, silicone matrix
. Ring with 25 mg Dapivirine
. Self-inserted every 4 weeks
. Releases drug into vaginal tissue



1959 young women, median age 25.9 years in South Africa and Uganda
31% reduction in HIV-incidence HR: 0.69 (95% CI: 0.49-0.99; p=0.04)
62% reduction in HIV-incidence in DREAM:

Nel et al. NEJM 2016; Lancet HIV 2021



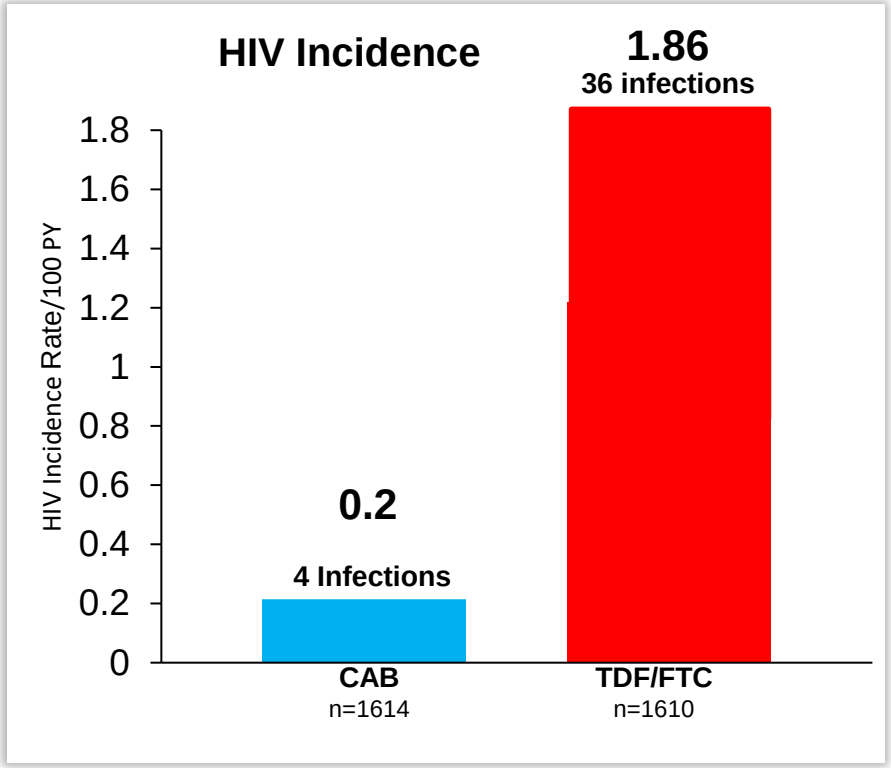
2629 women, mean age 27 years in Sub-Saharan Africa
Reduction in HIV incidence : **27%** (95% CI:1-46, p=0.046)
39% reduction (95% CI: 14-65) in HIV-incidence in HOPE:

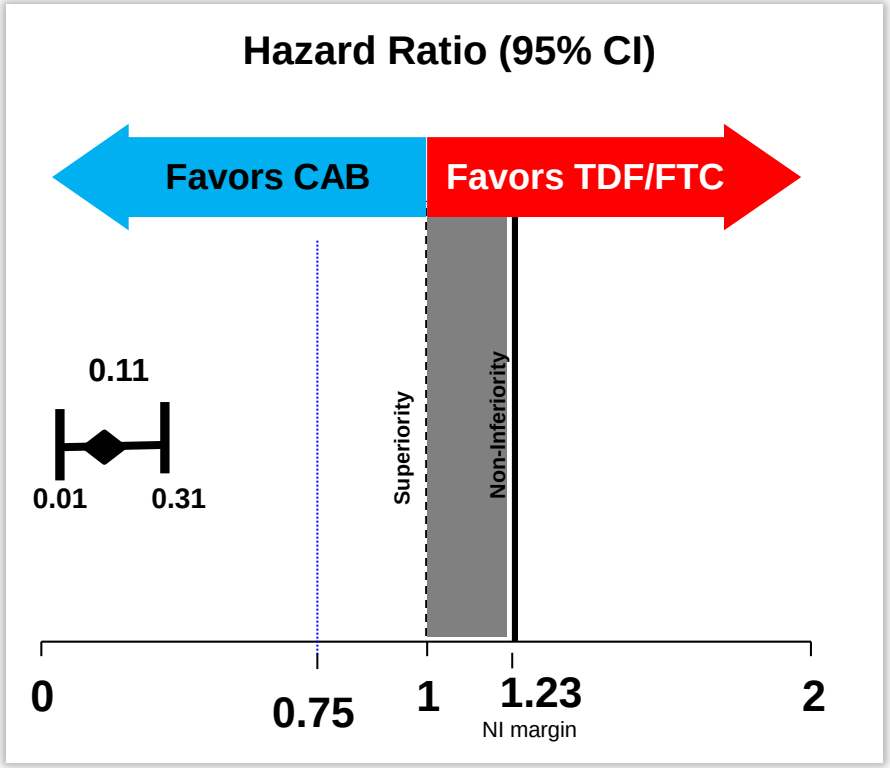
Baeten et al. NEJM 2016; Lancet HIV 2021

PrEP with LA Injectable Cabotegravir Highly Effective for Women

38 HIV infections in 3223 women, median age 26 years

Botswana, Eswatini, Kenya, Malawi, Uganda, Zimbabwe





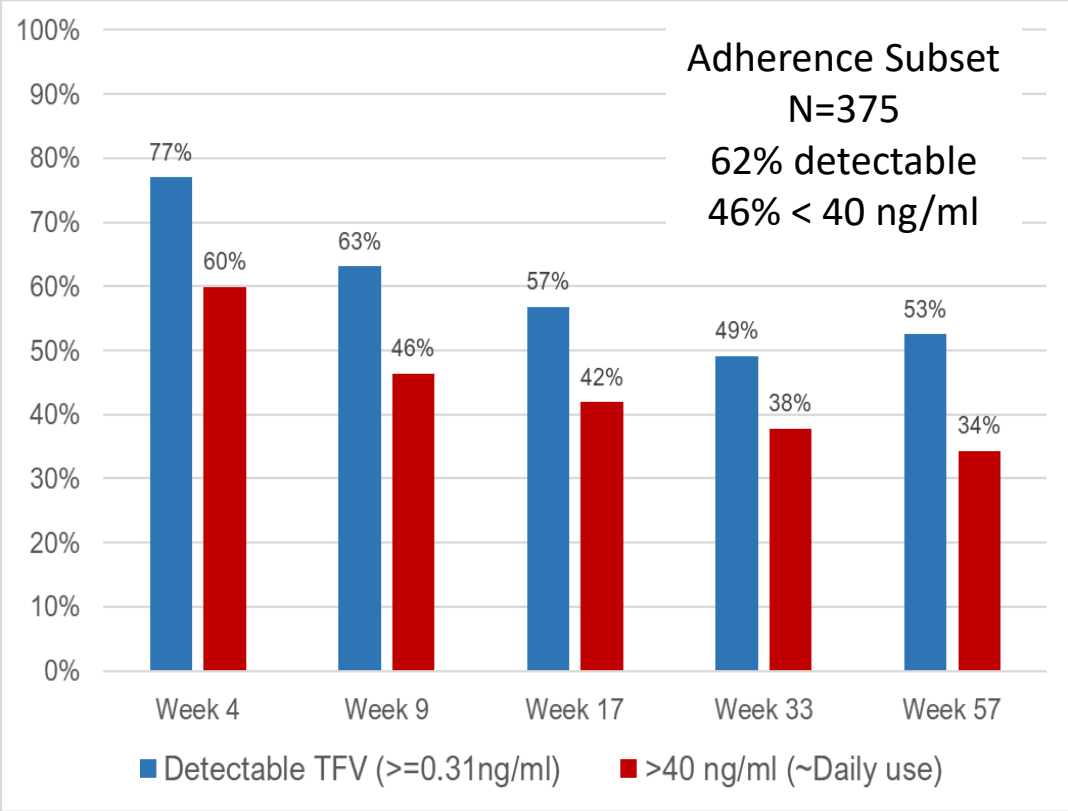
CI, confidence interval

HIV RESEARCH FOR PREVENTION
CAPE TOWN, SOUTH AFRICA · 17-21 JANUARY 2021

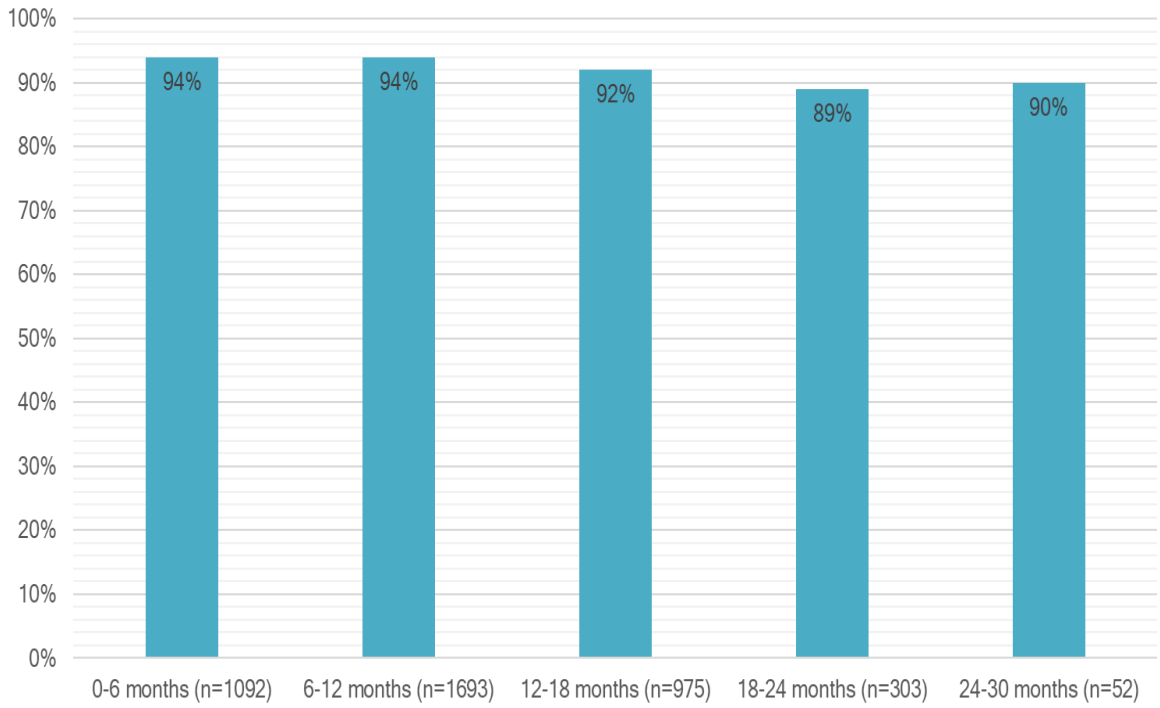
Delany-Moretllwe S. et al. Lancet 2022; Eshleman S J Infect Dis 2022

Adherence to Pill and Injections

TFV Plasma Concentrations



Cabotegravir Injections Coverage



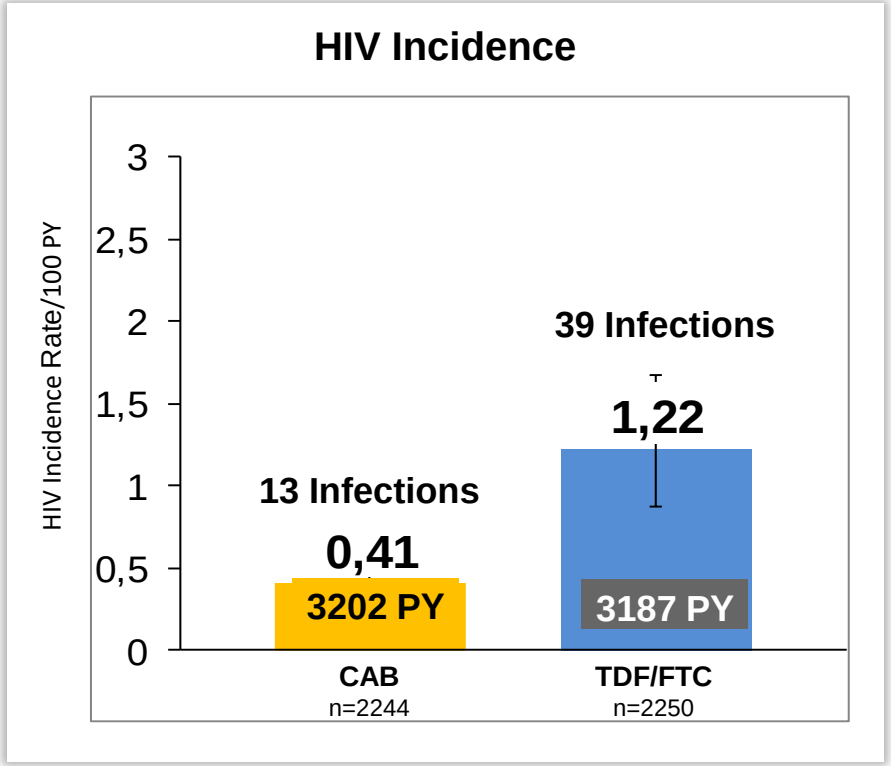
- Both products safe and well tolerated
- No discontinuation due to injection site reaction
- Similar pregnancy outcomes

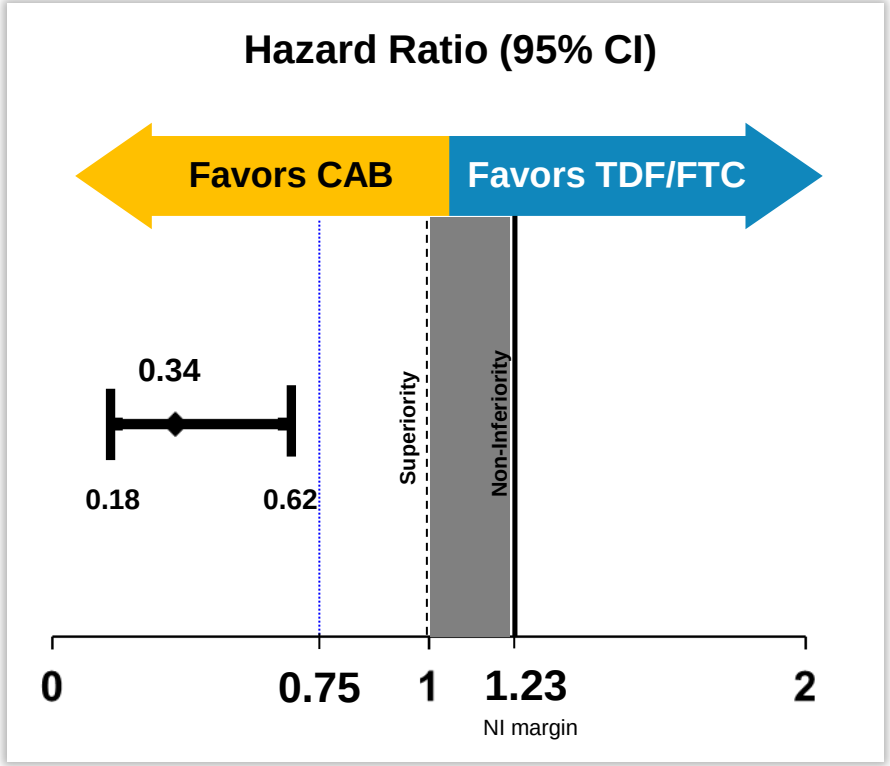
Delany-Moretllwe S. et al. Lancet 2022

PrEP with LA Injectable Cabotegravir Highly Effective for MSM and TGW

52 HIV infections in 6389 PY of follow-up

1.4 (IQR 0.8-1.9) years median per-participant follow-up





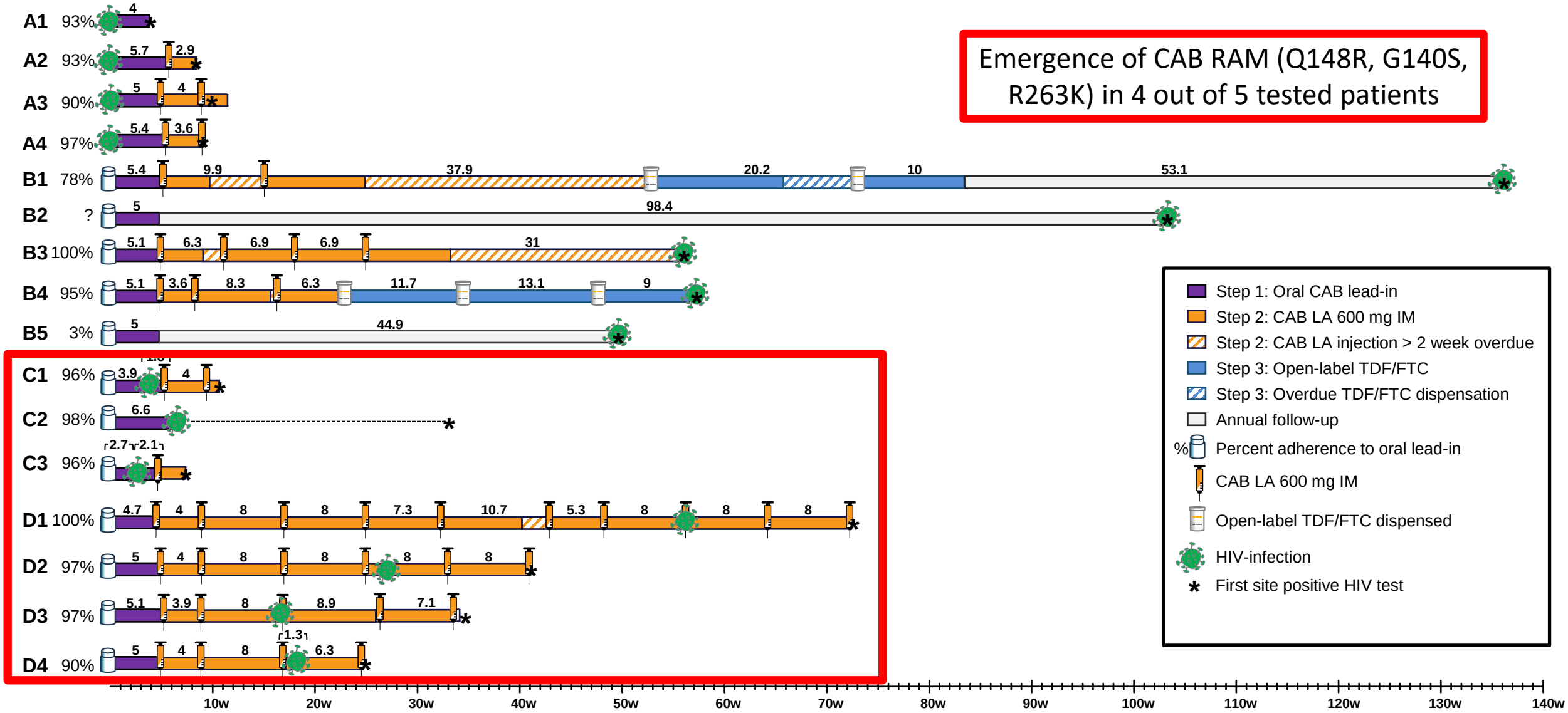
CI, confidence interval

Landovitz RJ et al. NEJM 2021

virtual CROI2021
Conference on Retroviruses and Opportunistic Infections
March 6-10, 2021

Prevalent and Incident HIV Infections with Cabotegravir

Emergence of CAB RAM (Q148R, G140S, R263K) in 4 out of 5 tested patients

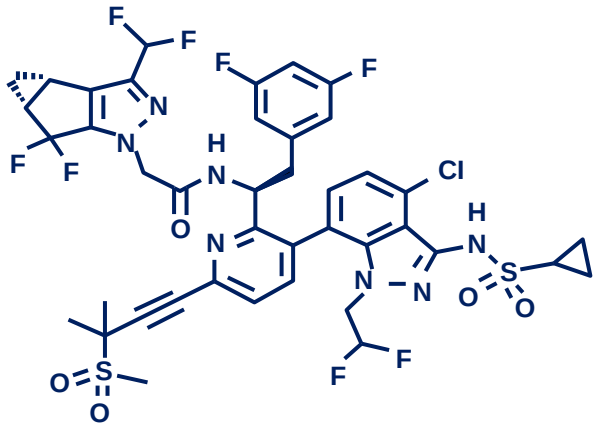


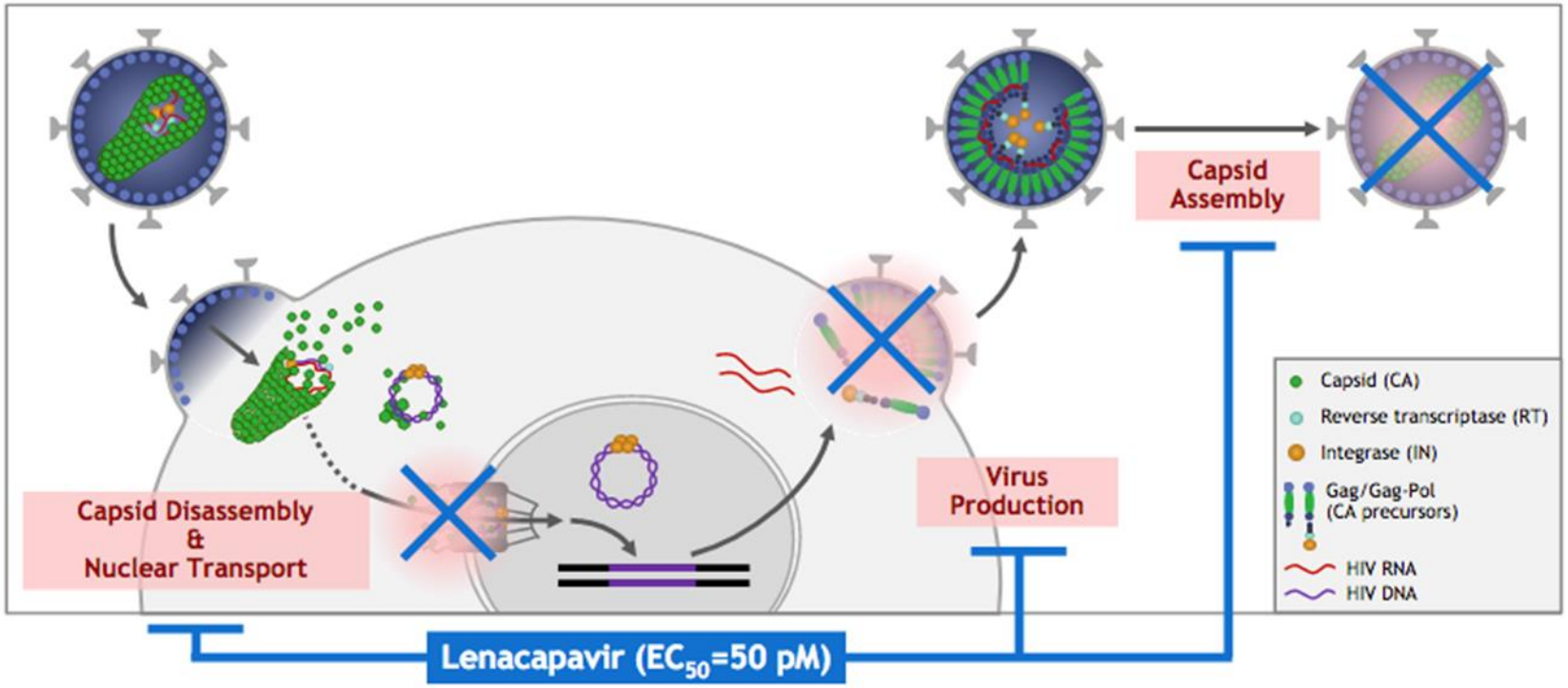
Limitations of Cabotegravir LA for the Prevention of HIV

- Burden of two-monthly injections
- Not self-administered
- Lead-in phase and tail coverage
- Unknown time to protection and forgiveness
- Injection site reactions
- Emergence of INSTI-R with potential cross-resistance to DTG
- Dissemination of INSTI- Resistance
- Cost of drug (450 Euros/month) and implementation
- **Breakthrough infections despite correct use with delayed diagnosis**

Lenacapavir: First in Class Long-Acting HIV Capsid Inhibitor for Treatment and Prevention

Lenacapavir (GS-6207)





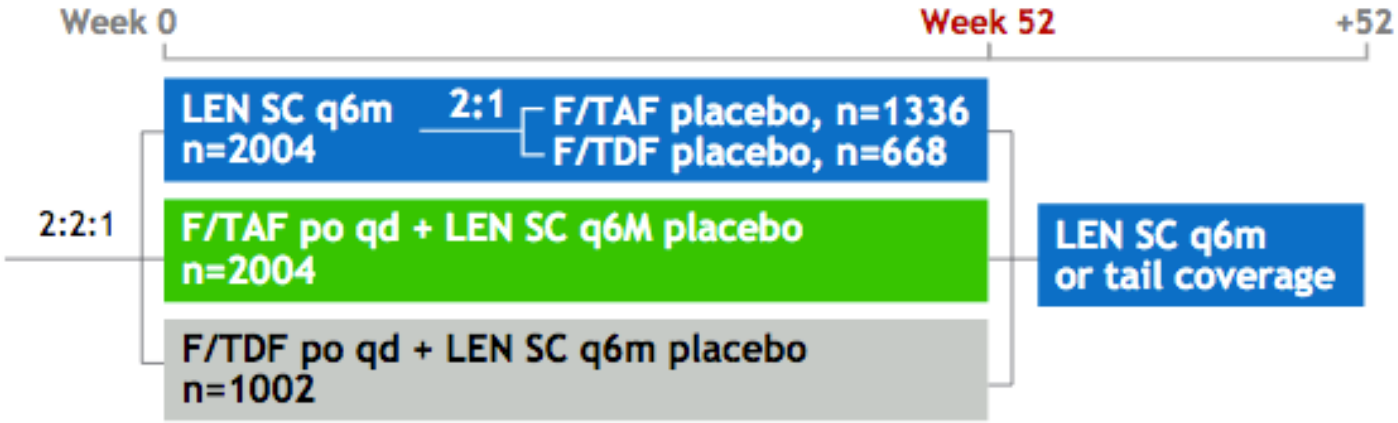
- Small molecule which disrupts the functions of HIV capsid protein
- High potency: Antiviral activity at very low doses (pM) and no cross-resistance with approved drugs
- Low in vivo systemic clearance
- Slow release kinetics from the subcutaneous injection site

Link JO et al. Nature 2020; 584: 614-8

Lenacapavir Prevention Trials

Two Primary Endpoints:
1. LEN vs bHIV
2. F/TAF vs bHIV

Women's HIV Prevention Study
Cisgender women and adolescent girls ≥35 kg at risk for HIV
N = ~5000



- Sites in South Africa, Kenya, and Uganda with bHIV ≥3.5/100 PY
- External controls:

Non-PrEP background HIV (bHIV)	Active
▪ Recency assay ▪ bHIV historical HIV incidence	▪ D4P F/TAF ▪ D4P F/TDF

Other trials conducted in MSM and TGW vs daily TDF/FTC in 3,000 in USA and South Africa, and among IVDU in the USA

PrEP Initiations by Country, 2022

THE GLOBAL PREP TRACKER

Cumulative Number of PrEP Initiations

METHODS AND SOURCES

METRIC

- INITIATIONS
- IMPLEMENTATION PROJECTS
- SERVICE DELIVERY SETTINGS
- REGULATORY APPROVALS

VIEW

- BY GEOGRAPHY
- ACROSS TIME

PRODUCTS

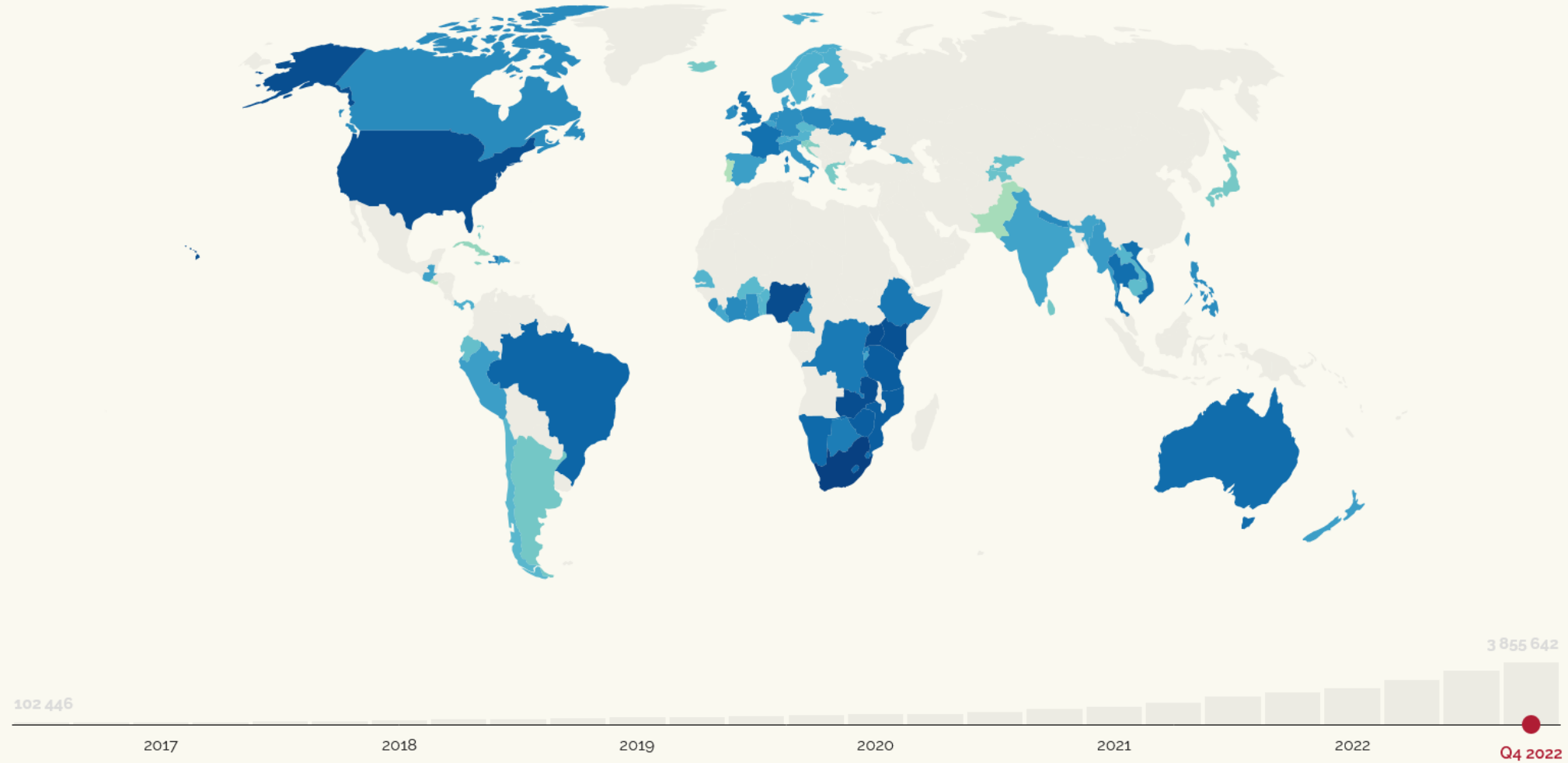
- ALL PRODUCTS
- ORAL PREP TDF/XTC (TDF PRODUCTS AND GENERIC)
- ORAL PREP F/TAF (DESCOVY)
- PREP RING
- INJECTABLE PREP

Number of Initiations

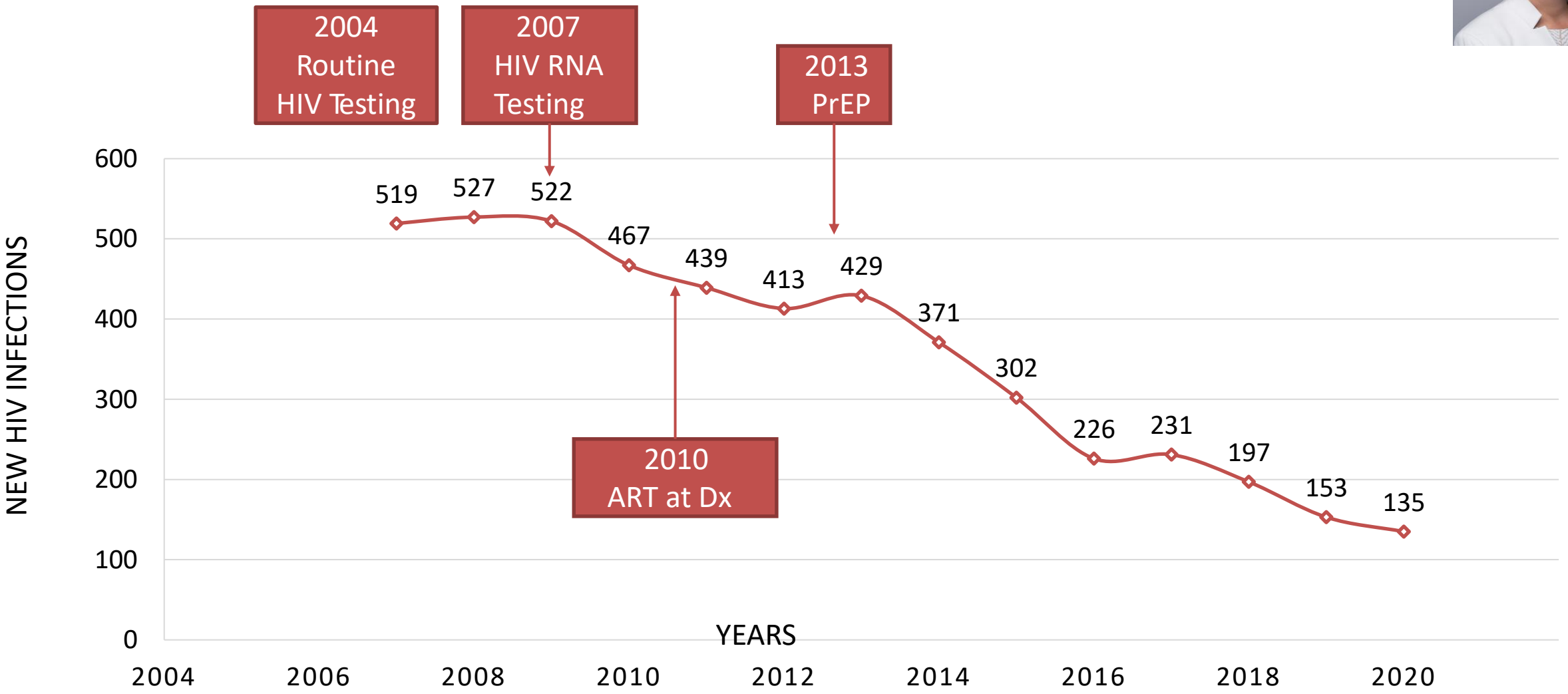
1 — 890 — 26 560 — 792 434

Q4 2022

3 855 642 initiations

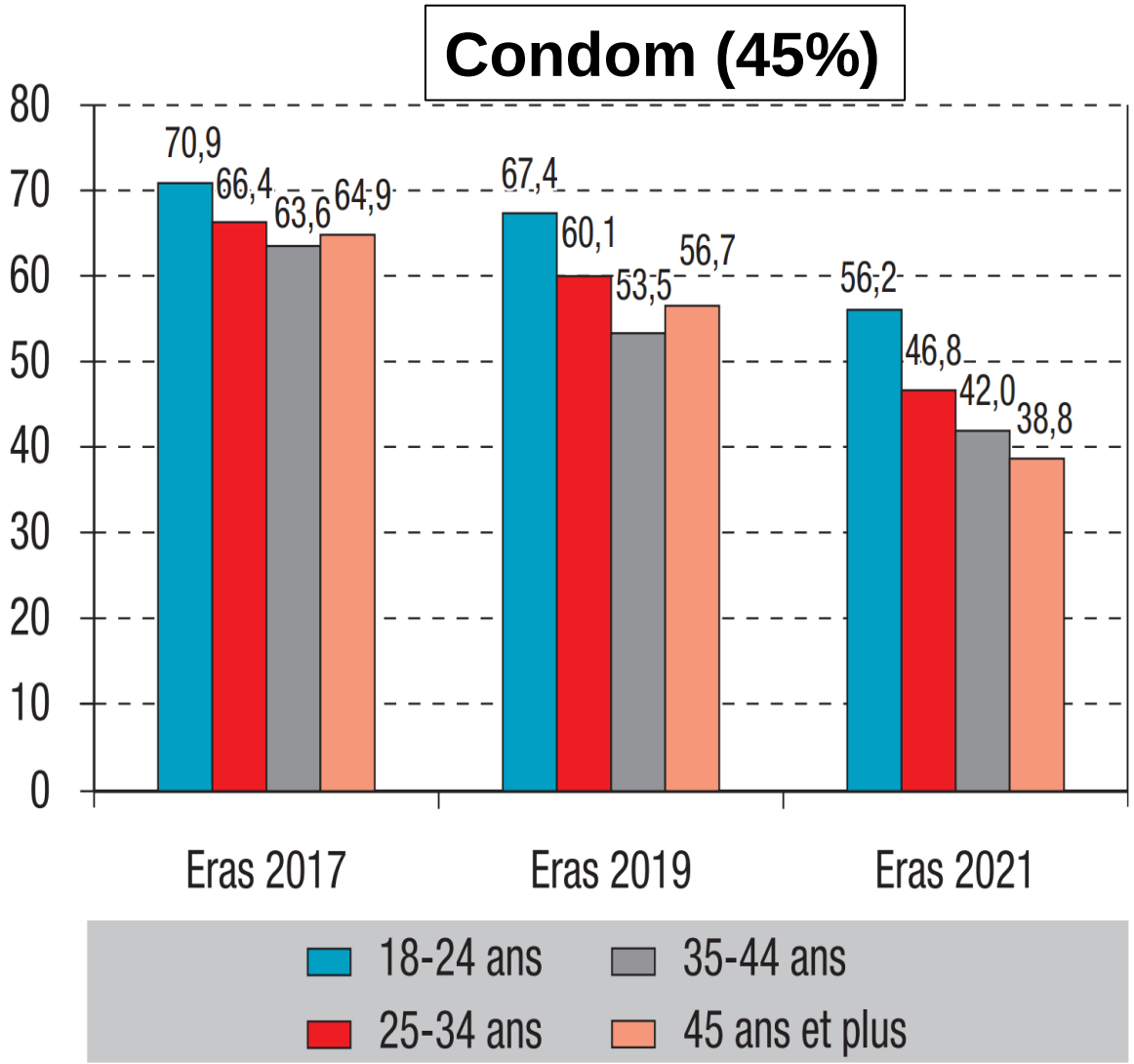


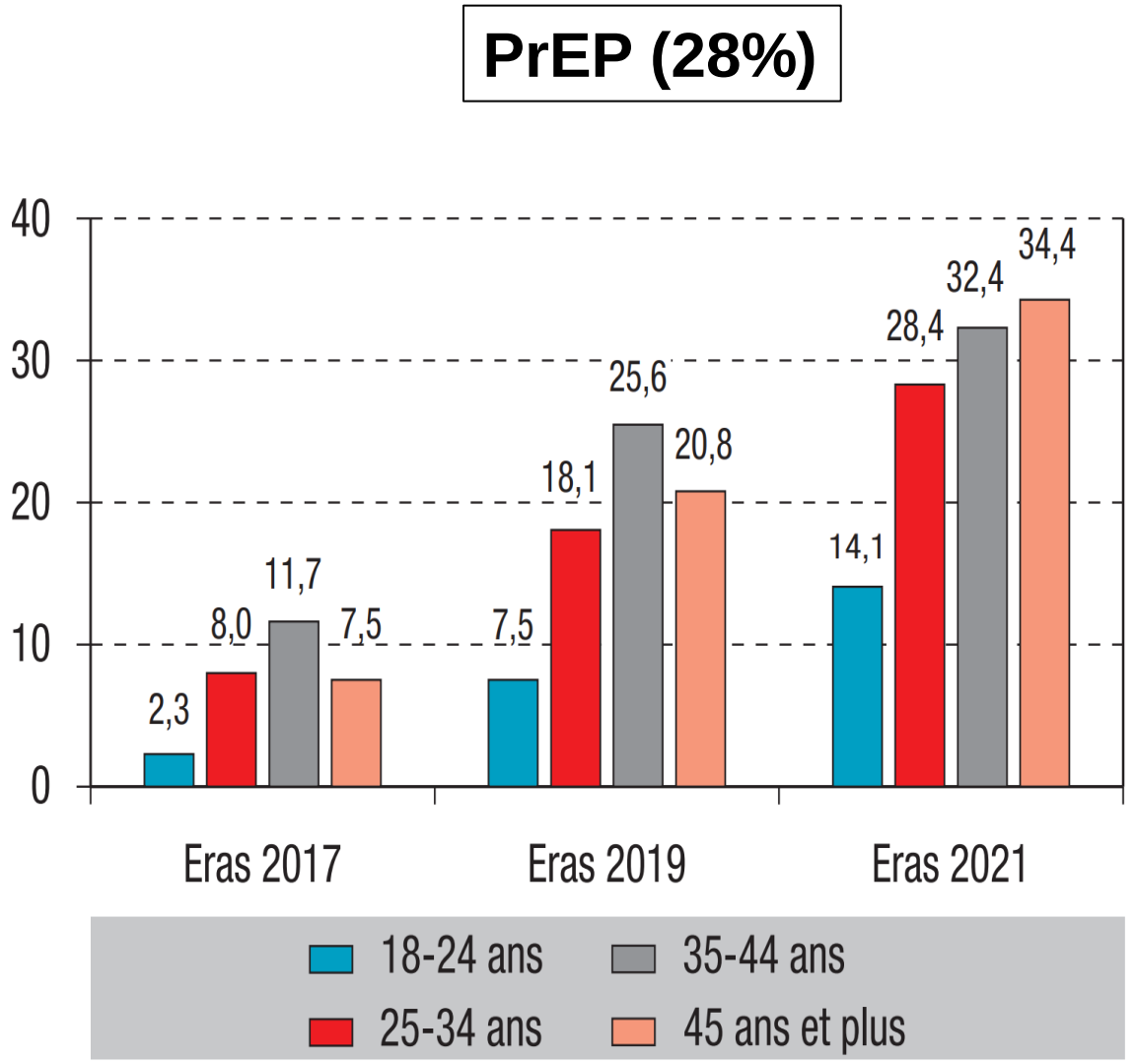
HIV Epidemic Trends in San Francisco



Adapted from SF DPH, HIV Epidemiology Annual Report 2020

Condom and PrEP Use by MSM at Last Anal Sexual Intercourse with a Casual Partner in France



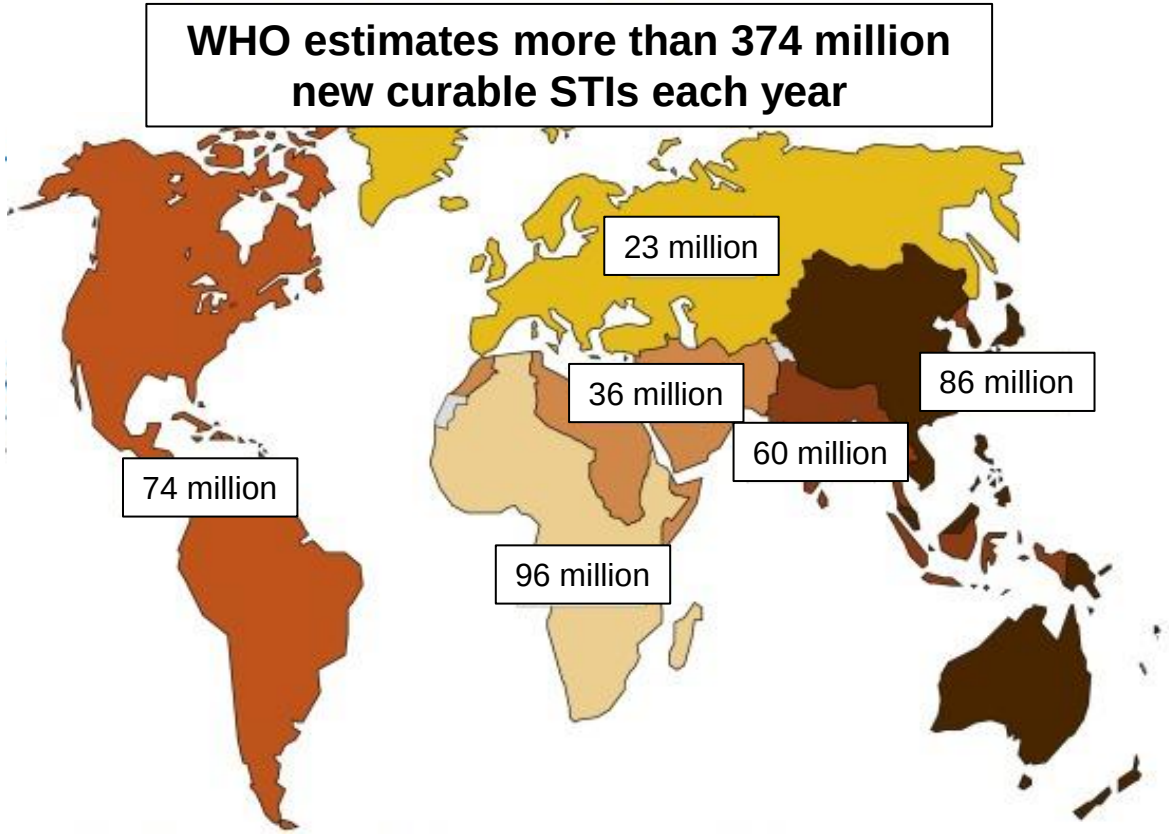


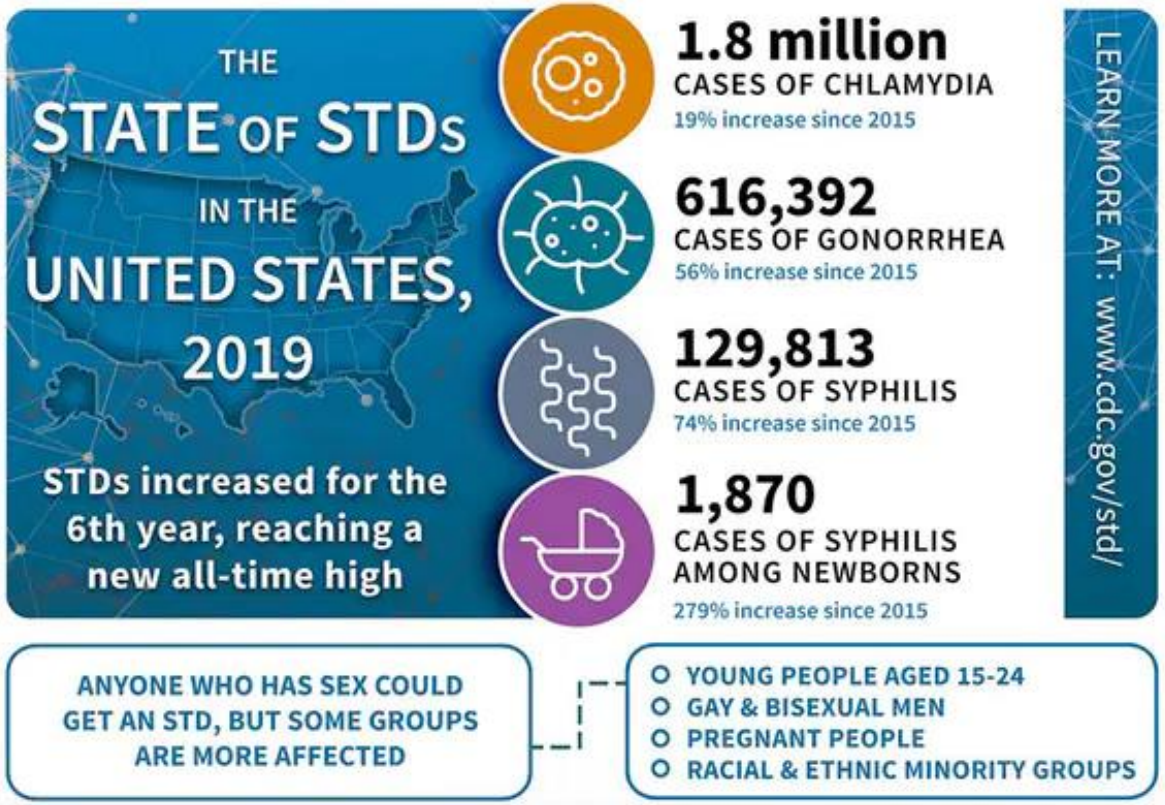
Velter A et al BEH November 2022

Summary

- High incidence of HIV-infection in key populations
- PrEP highly effective when taken as recommended
- **PrEP is underutilized and people at risk should have access**
- PrEP options are expanding and should be available everywhere
- PrEP is an opportunity to provide global sexual health care

Dramatic Increases in Bacterial STI Incidence in an Era of Effective HIV Treatment and Prevention





- **Gonorrhea:** threat of increasing incidence of antimicrobial resistance
- **Syphilis:** spread into heterosexual networks with congenital syphilis
- **Reappearance of classics:** LGV proctitis in MSM

WHO global progress report on HIV, viral hepatitis and sexually transmitted infections 2021; https://www.cdc.gov/std; Pathela *Sex Transm Dis* 2019; WHO; Oliver *Clin Infect Dis* 2018; Braun DL *CID* 2018, Marrazzo JM. CROI 2019 Seattle USA

Cancer	• HPV causes over 500,000 cases of cervical cancer annually
Adverse effects of pregnancy	• MTCT of syphilis leads to >200,000 fetal/neonatal deaths per year
Infertility	• Gonorrhoea and chlamydial are important causes of infertility
Increase HIV risk	• Several STIs, in particular HSV-2, increase HIV acquisition and transmission risk

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
- Vaccines for viral STIs (hepatitis A and B, HPV, MPox)
- Antibiotic prophylaxis

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

PCR, Polymerase chain reaction; CT, chlamydia trachomatis; NG, Neisseria gonorrhoeae

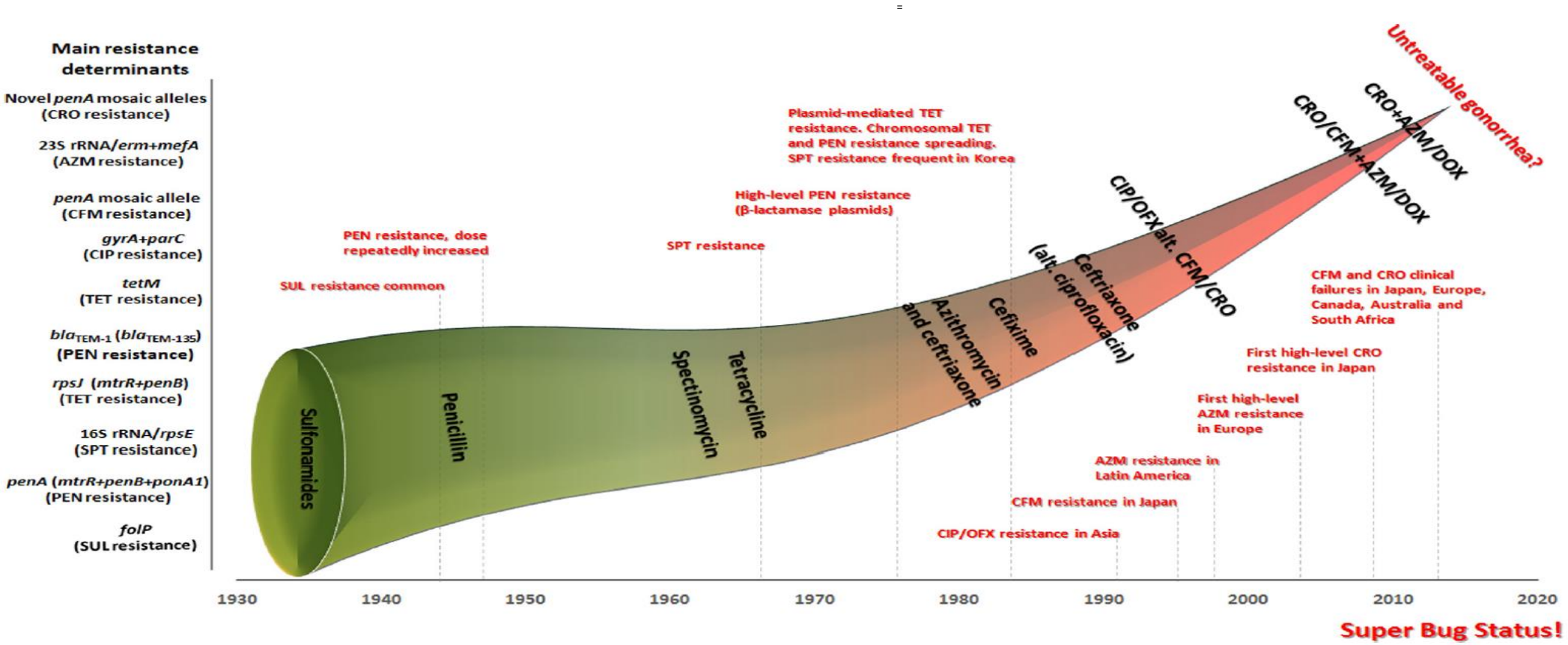
Molina JM et al. Lancet Inf Dis. 2018;18:308-317

Why Testing Doxycycline for 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)

Neisseria gonorrheae

- NG has an extraordinary capacity to alter its genetic material
- It is naturally competent for transformation and can also change its genome through all types of mutations

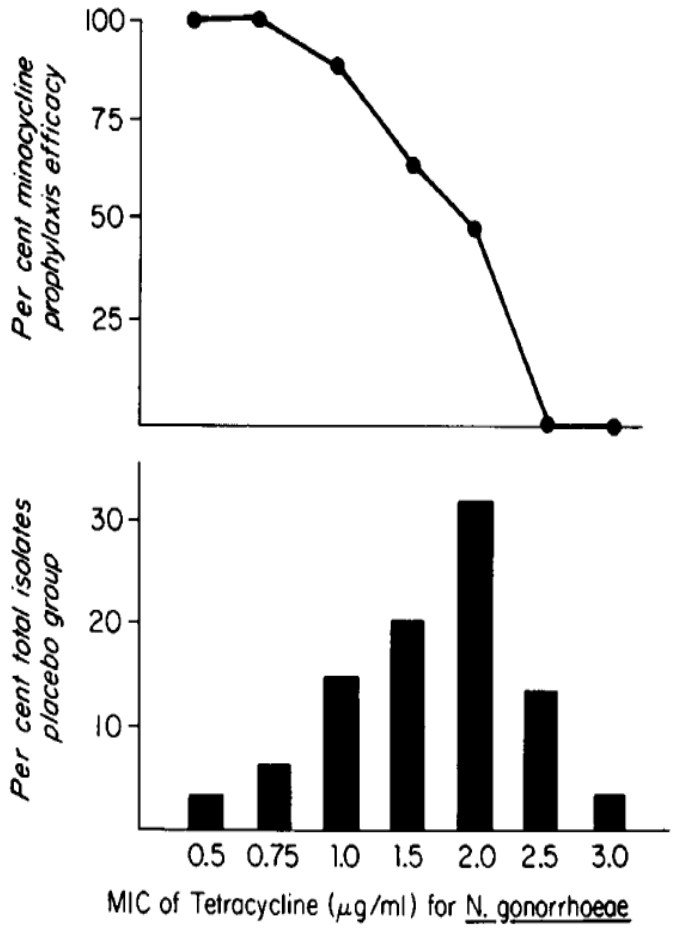


Unemo and Shafer Clin Microbiol Rev 2014, 27:587

A TRIAL OF MINOCYCLINE GIVEN AFTER EXPOSURE TO PREVENT GONORRHEA

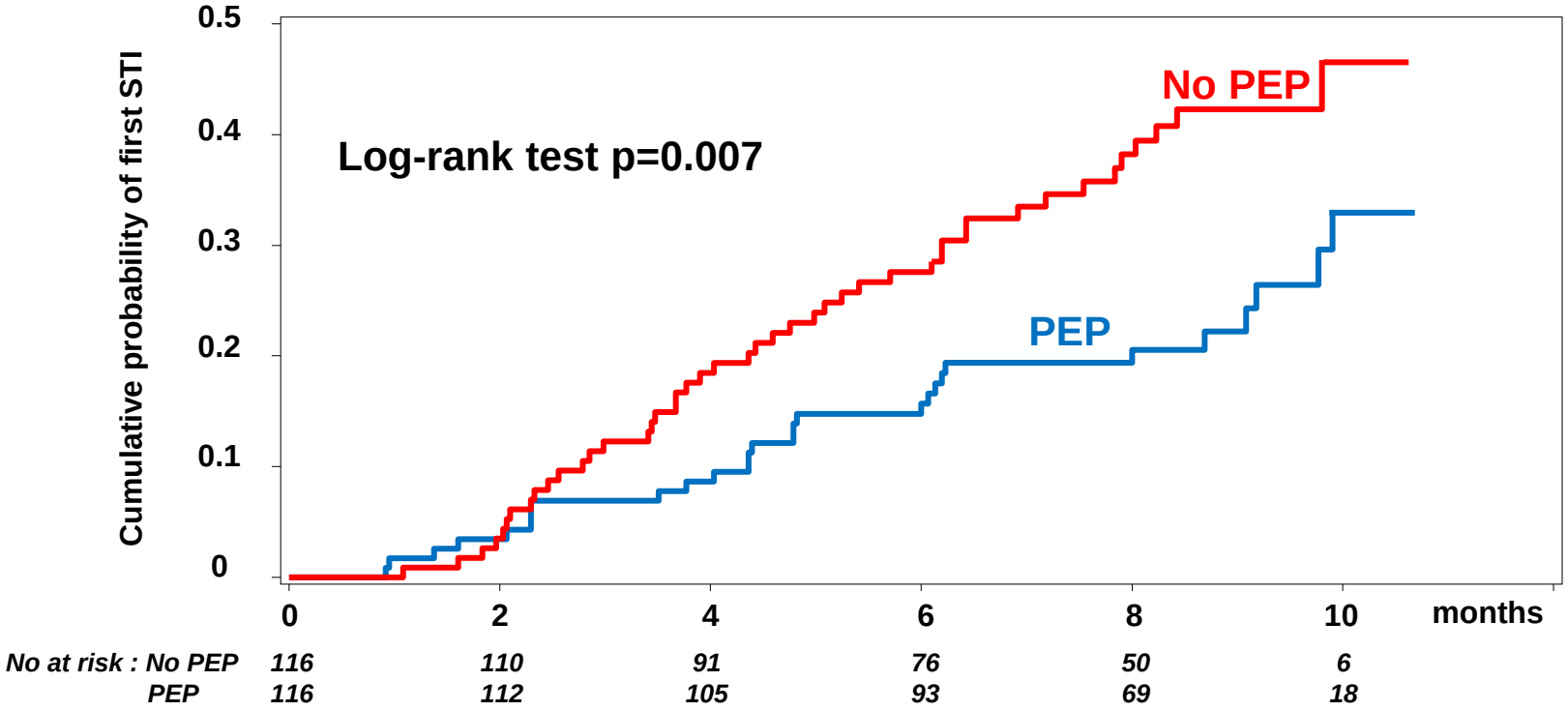
WILLIAM O. HARRISON, M.D., RICHARD R. HOOPER, M.D., PAUL J. WIESNER, M.D., AXEL F. CAMPBELL, M.D., WALTER W. KARNEY, M.D., GLADYS H. REYNOLDS, PH.D., OSCAR G. JONES, B.S., AND KING K. HOLMES, M.D., PH.D.

- 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** »



ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Incidence of First Episode of STIs



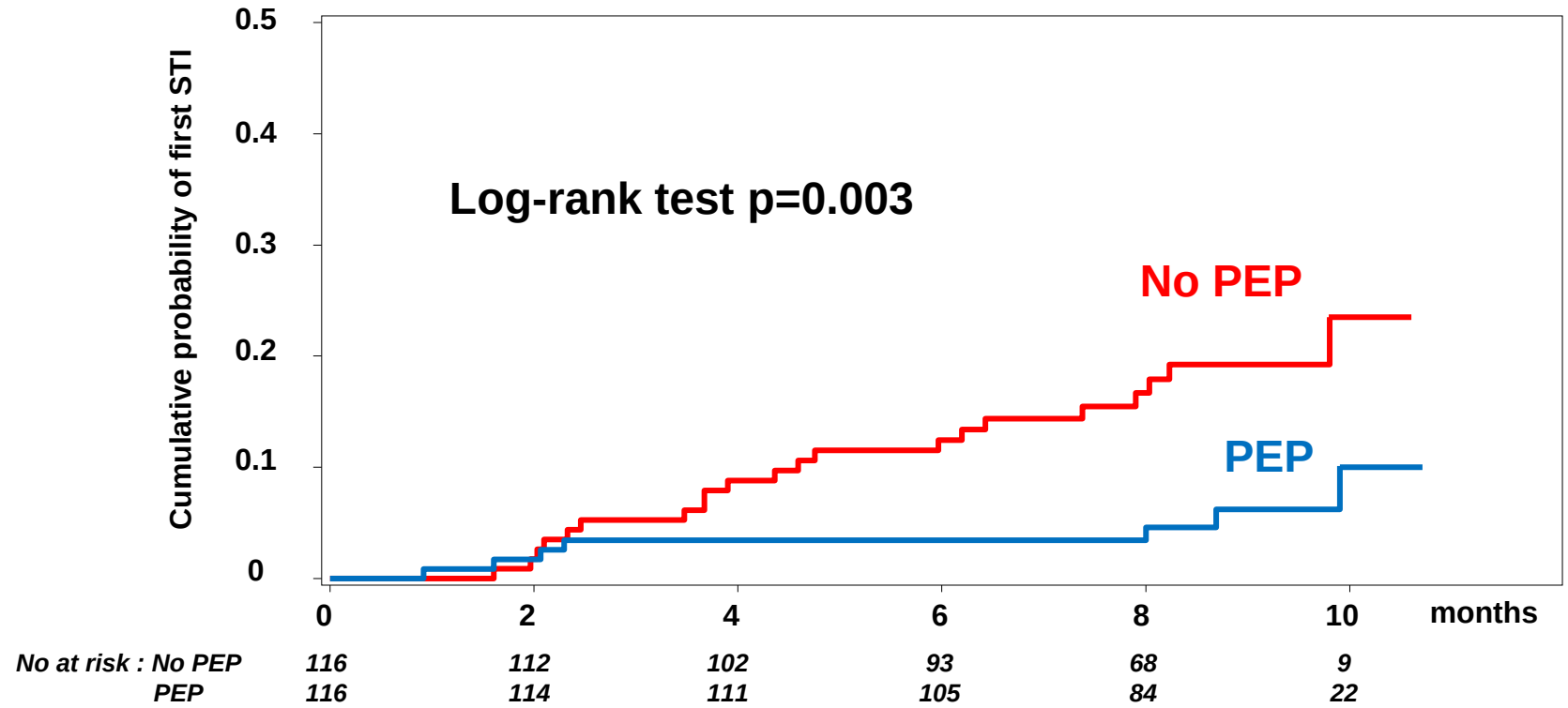
Median follow-up of 8.7 months (IQR: 7.8-9.7): 73 subjects infected

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)

Molina JM et al. Lancet Inf Dis. 2018;18:308-317

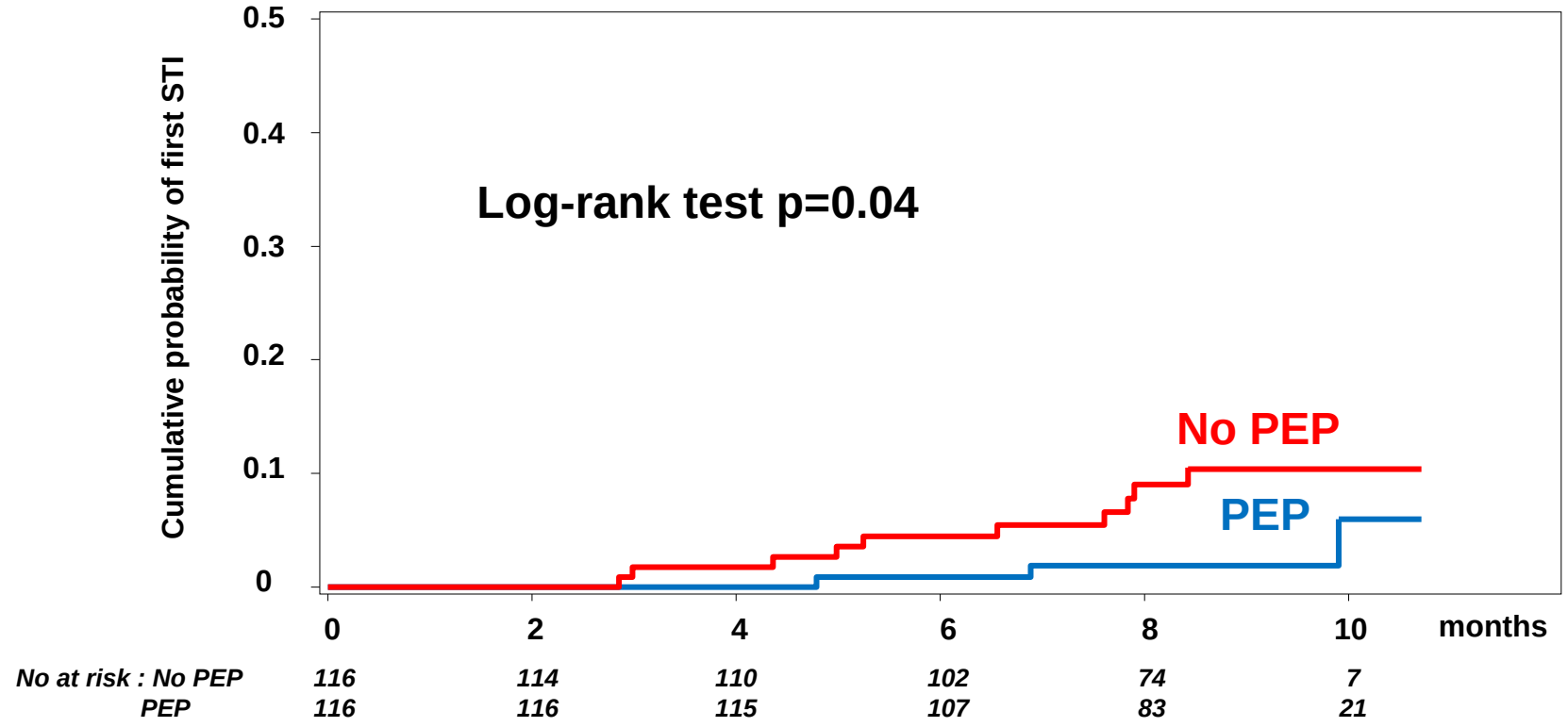
Incidence of First Episode of Chlamydia



- 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)**

Molina JM et al. Lancet Inf Dis. 2018;18:308-317

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)**

Molina JM et al. Lancet Inf Dis. 2018;18:308-317

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Sites of *N. gonorrheae* 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

Molina et al Lancet ID 2018

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

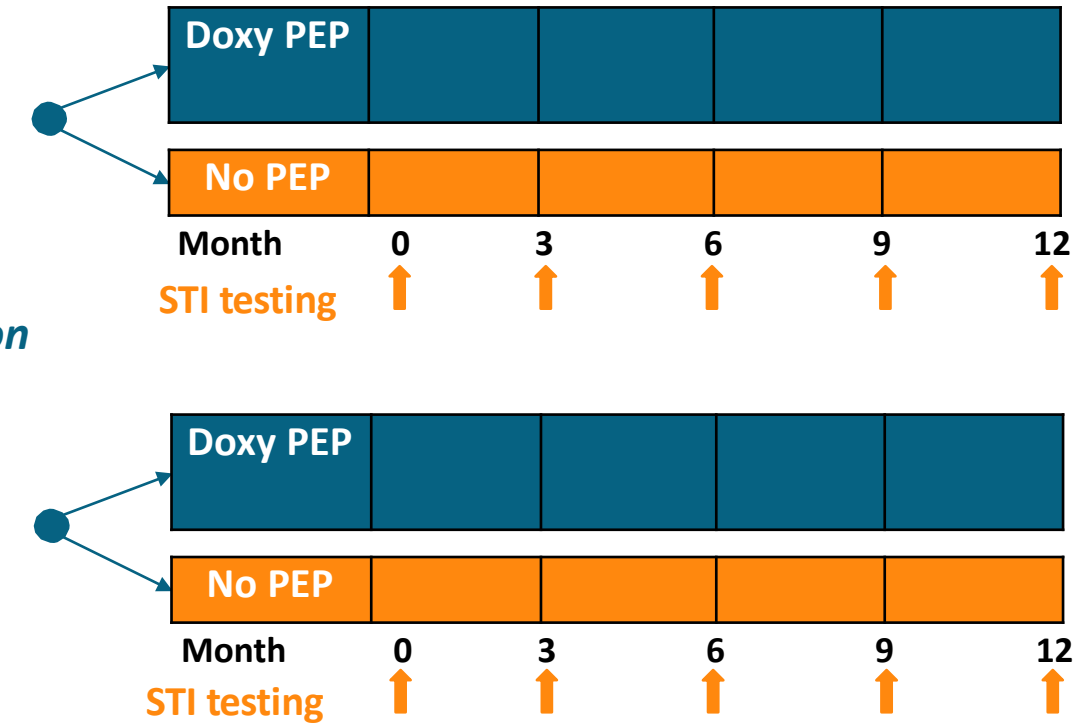
Intervention: Open label doxycycline 200mg taken as PEP within 72 hours after condomless sexual contact

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

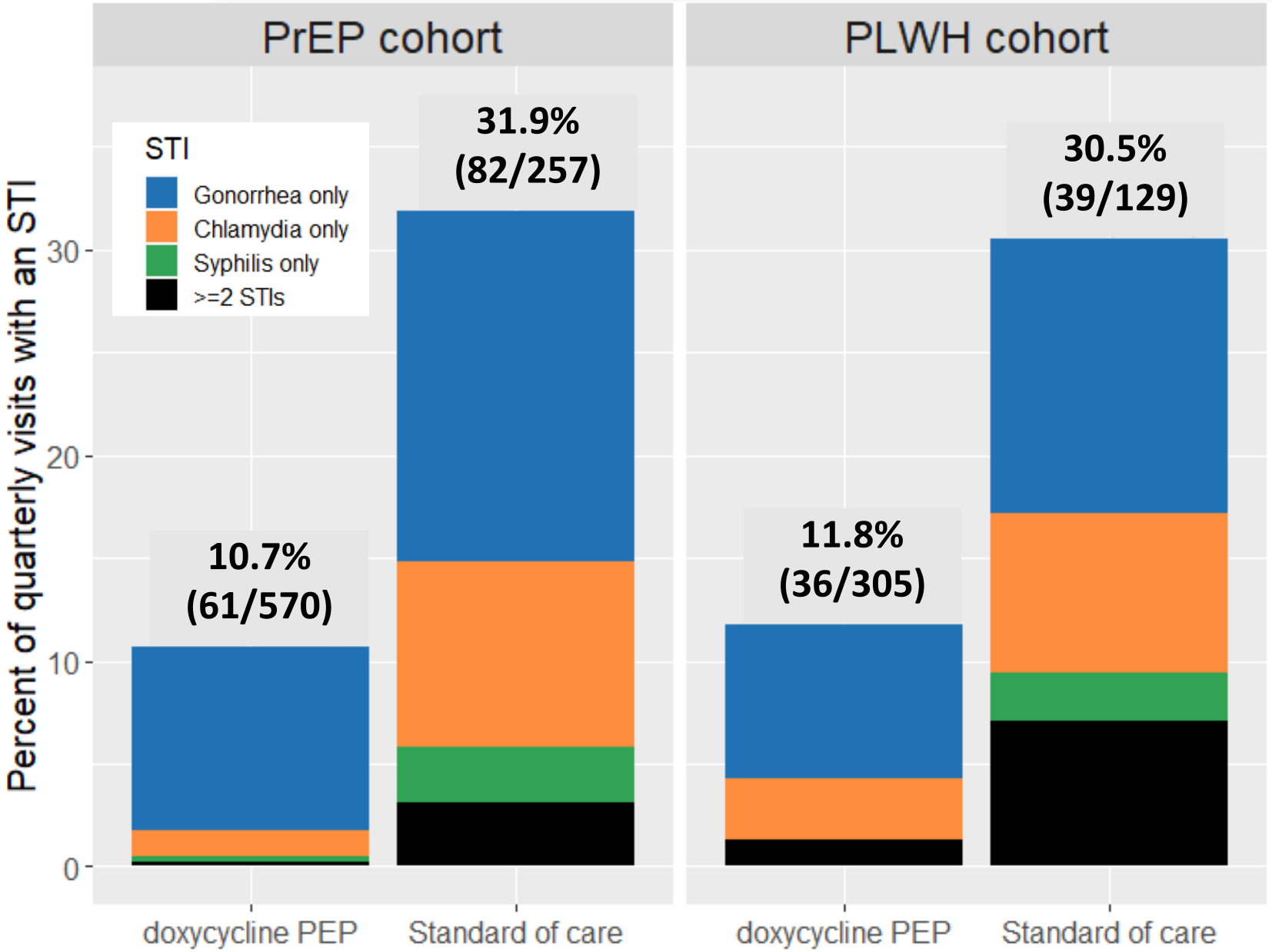
Detect a 50% reduction of STIs/quarter with doxyPEP

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

DSMB recommended early discontinuation in May 2022 at first interim analysis

AIDS 2022

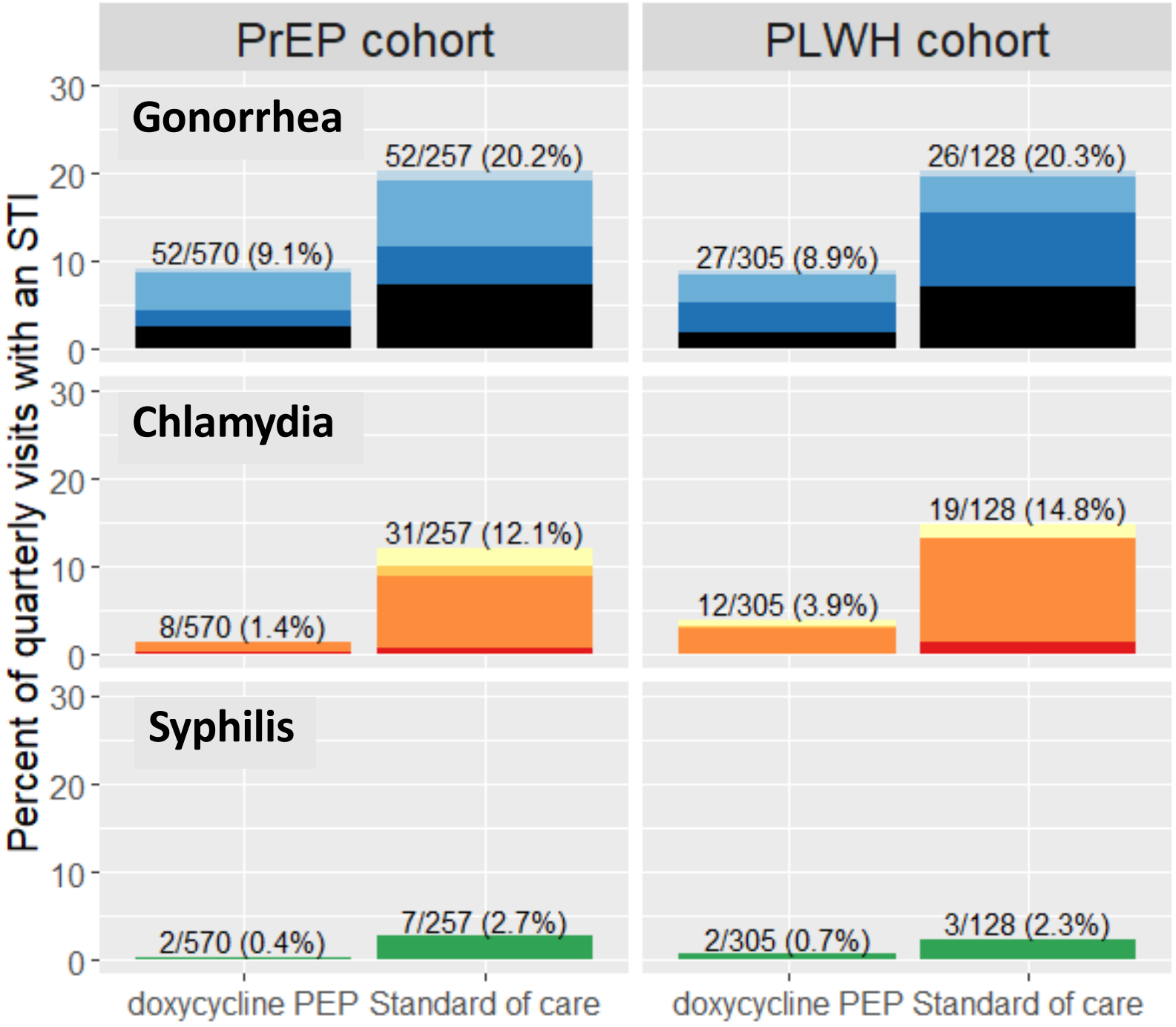
Primary Endpoint: STI incidence per quarter (501 pts enrolled)



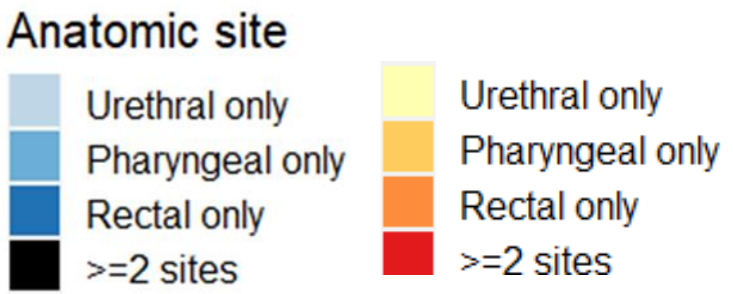
Reduction in STI incidence/quarter	
	risk reduction (95% CI)
PrEP	**0.34 (0.24 - 0.46)**
Living with HIV	**0.38 (0.24 - 0.60)**
Total	**0.35 (0.27 - 0.46)**

all p< 0.0001

Luetkemeyer et al NEJM 2023



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) *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*

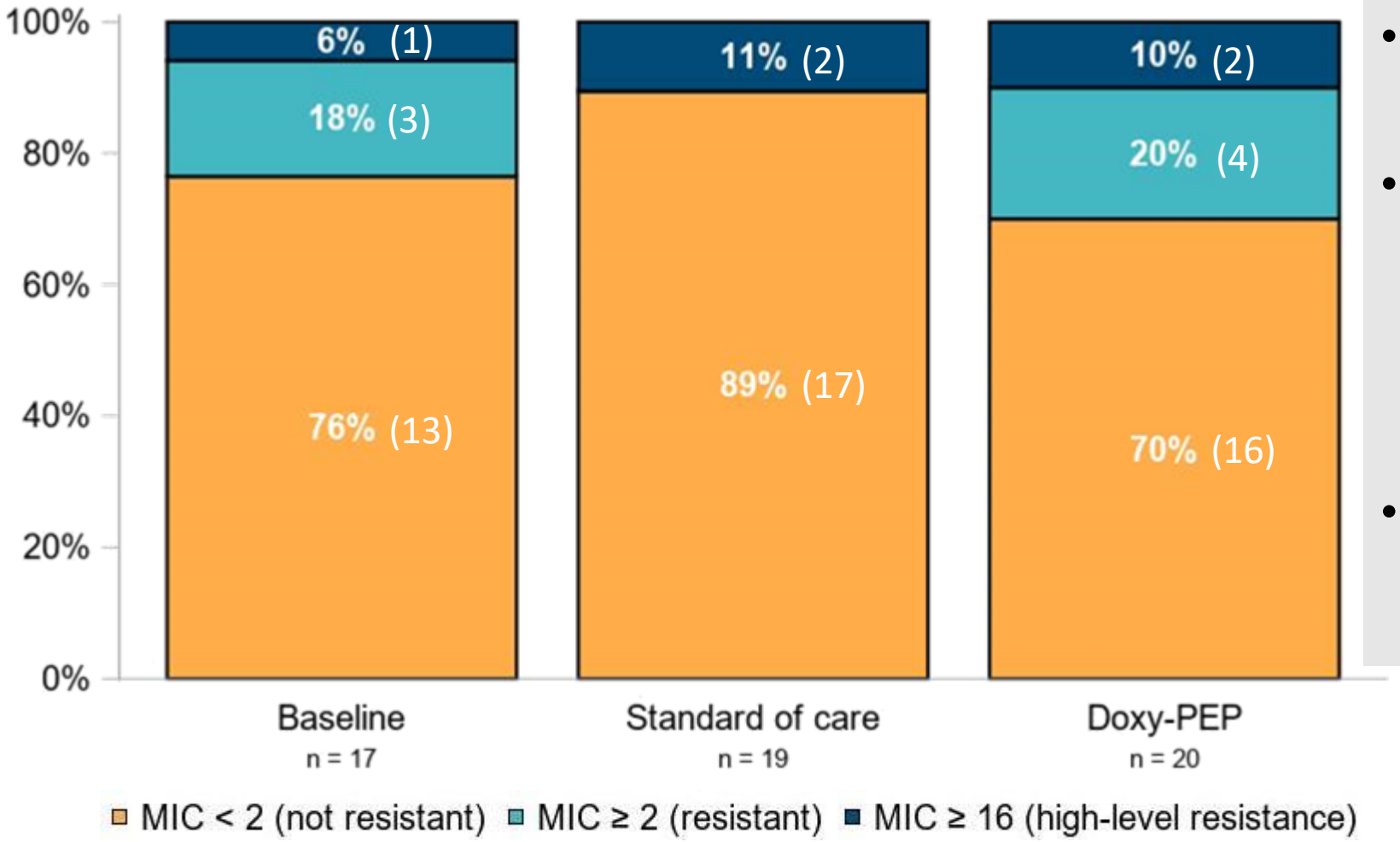
Luetkemeyer et al NEJM 2023

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

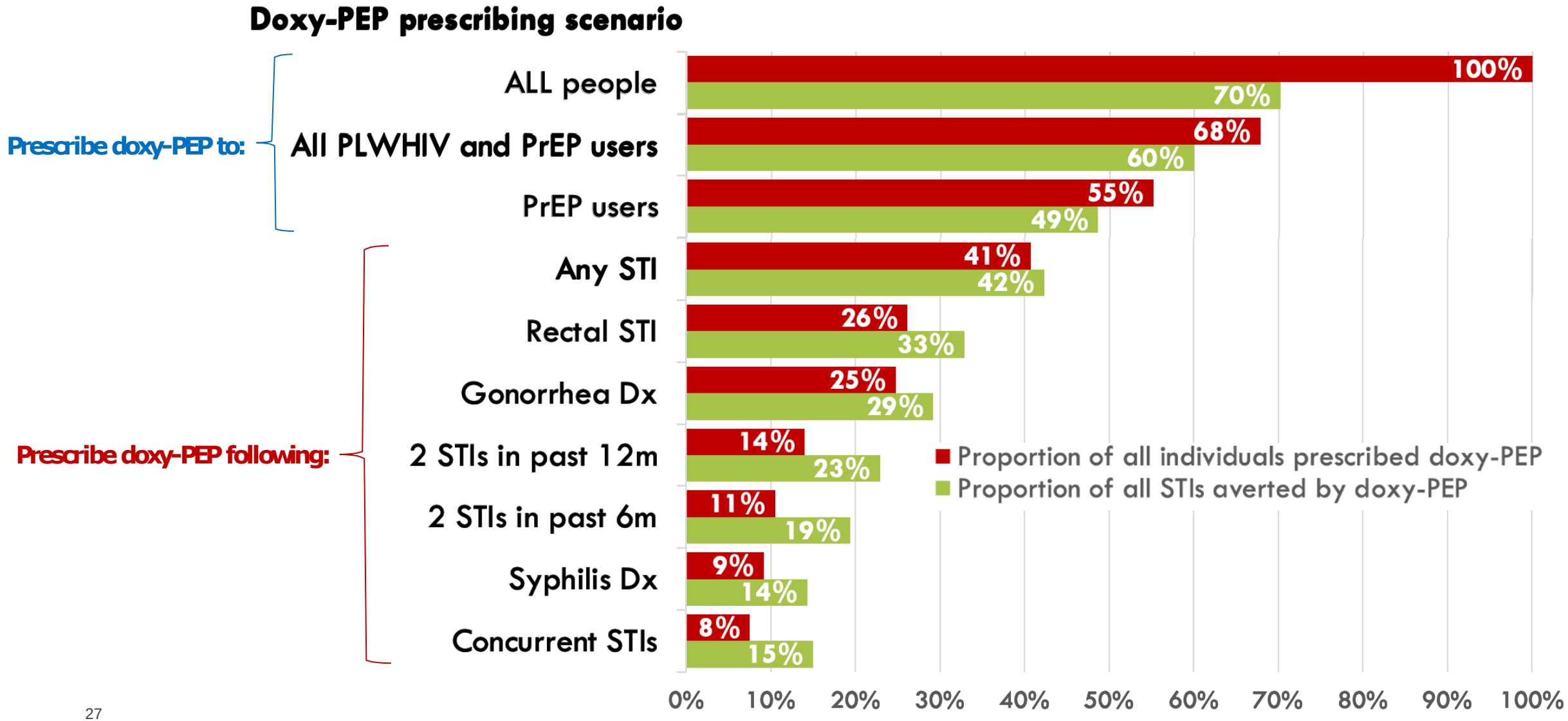


- TCN-R similar in incident GC at baseline and on doxy-PEP
- Increased TCN-R in doxy-PEP vs. standard of care suggests doxy-PEP may be less protective against GC strains with existing TCN-R
- Limited by low number of GC samples with MIC results (56/320)

DOXYPEP

30th CROI 2023

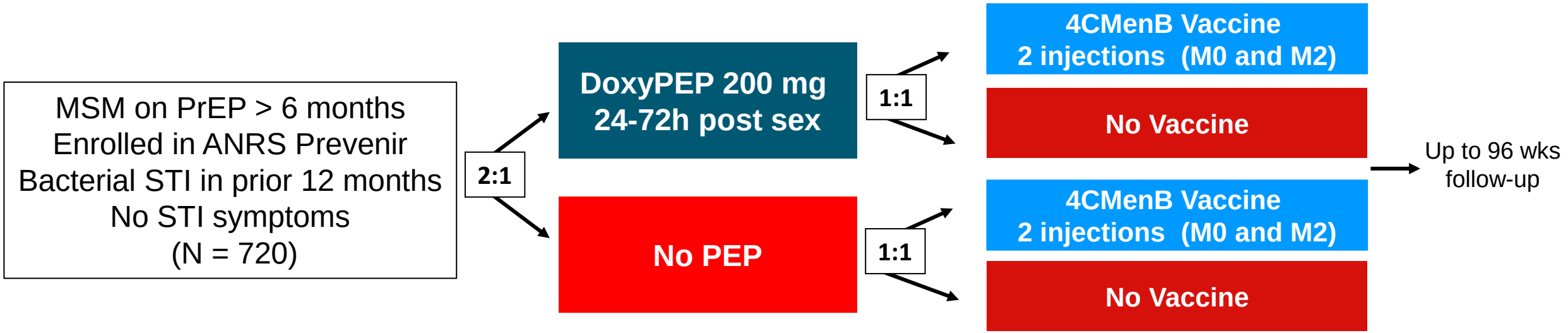
Doxy-PEP use vs STIs averted in a US Sexual Health Clinic



Traeger M, CROI 2023, Abs. 122

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°) for GC/CT/MG (3 sites) and serology for TP
- Doxycycline monohydrate purchased from Arrow and 4CMenB vaccine purchased from GSK

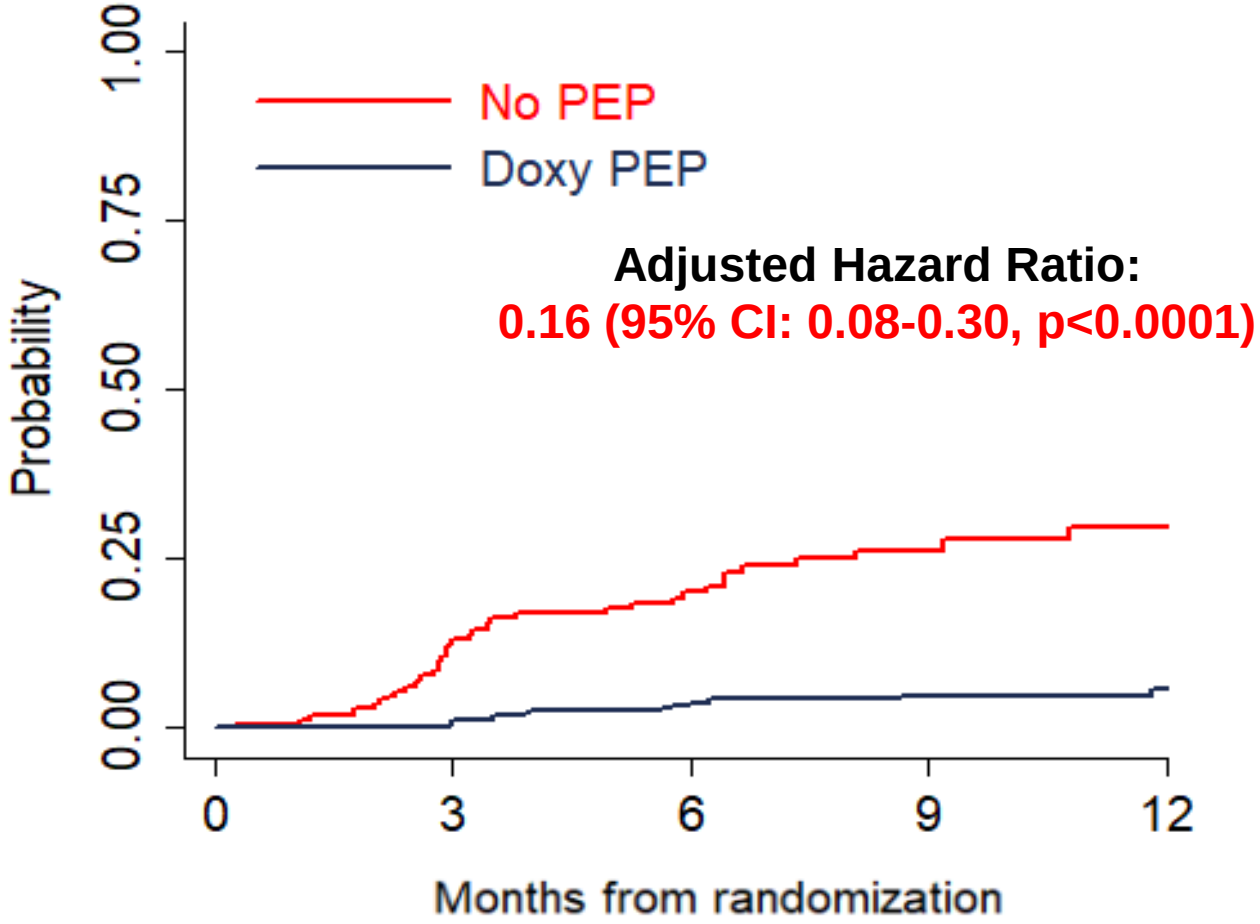
Molina JM, CROI 2023

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) in 501 participants

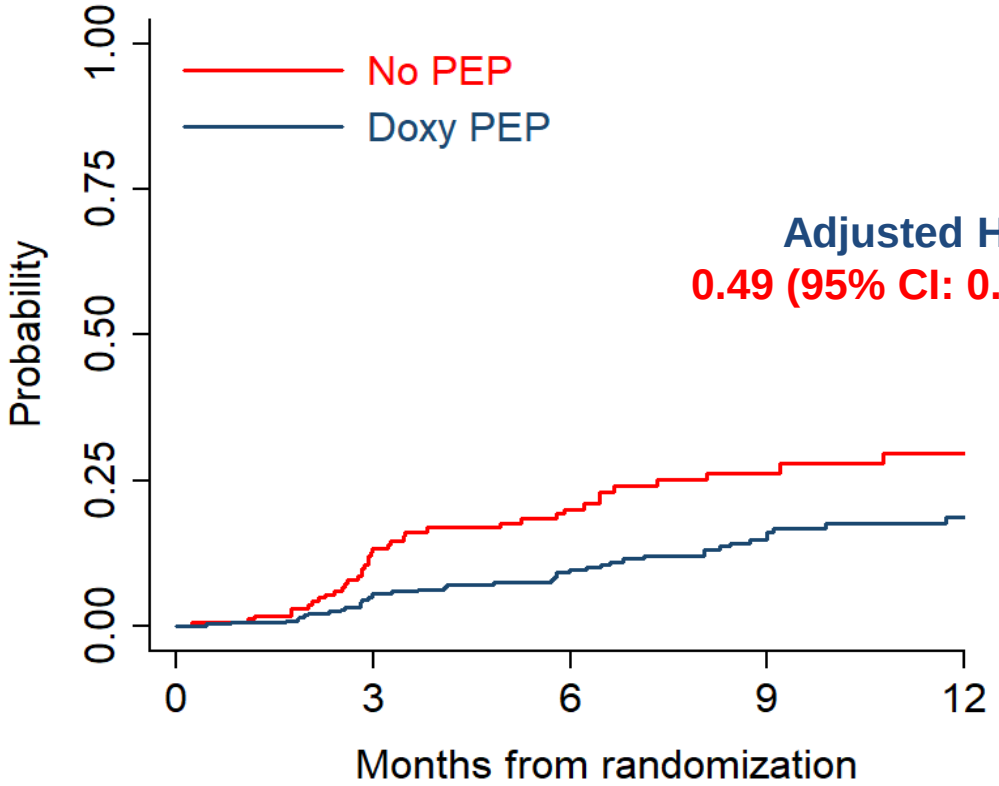
49 subjects infected
36 in No PEP arm
(incidence: 35.4/100 PY),
13 in Doxy PEP arm
(incidence: 5.6/100 PY)



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)



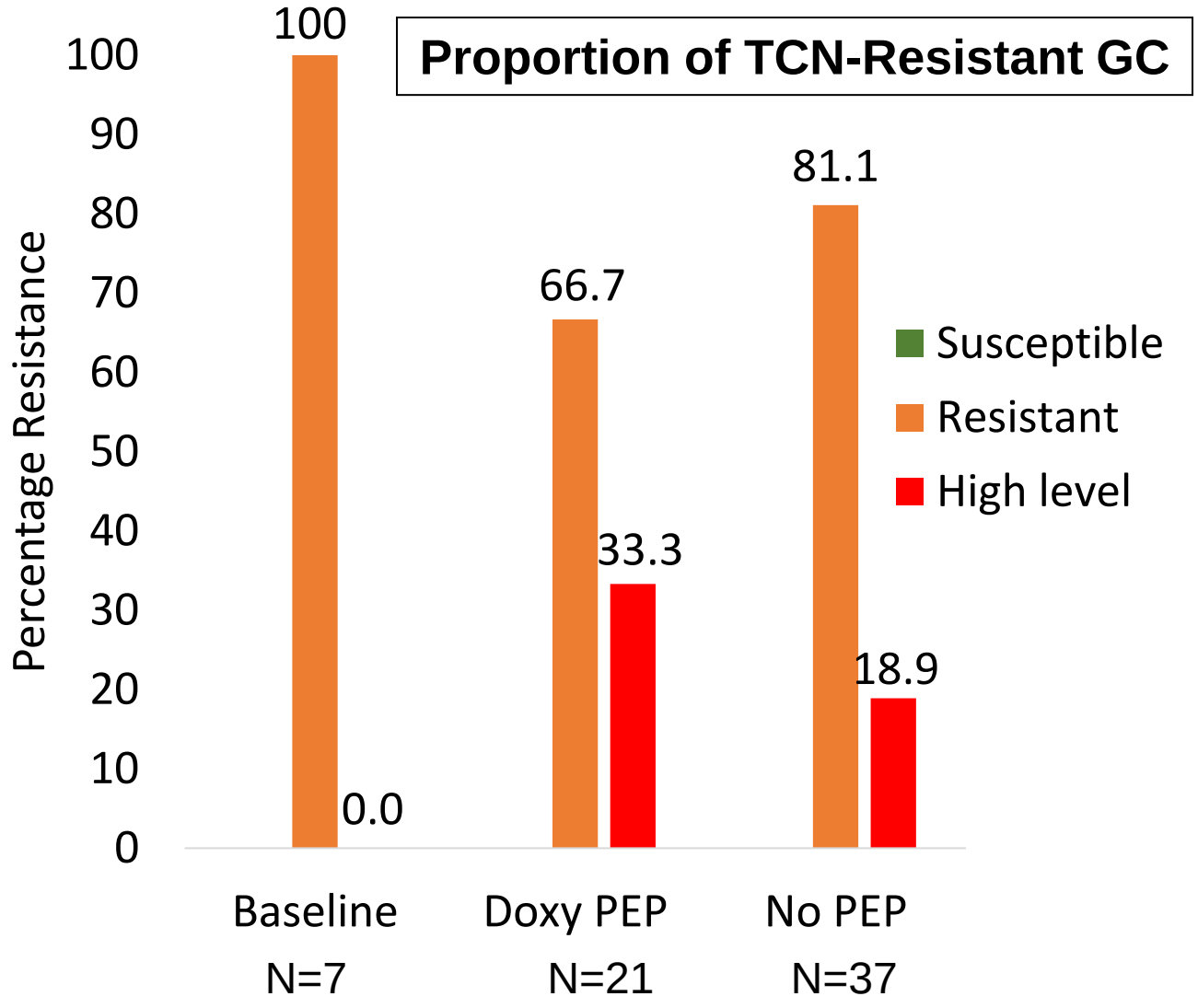
Adjusted Hazard Ratio:
0.49 (95% CI: 0.32-0.76, p=0.001)

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

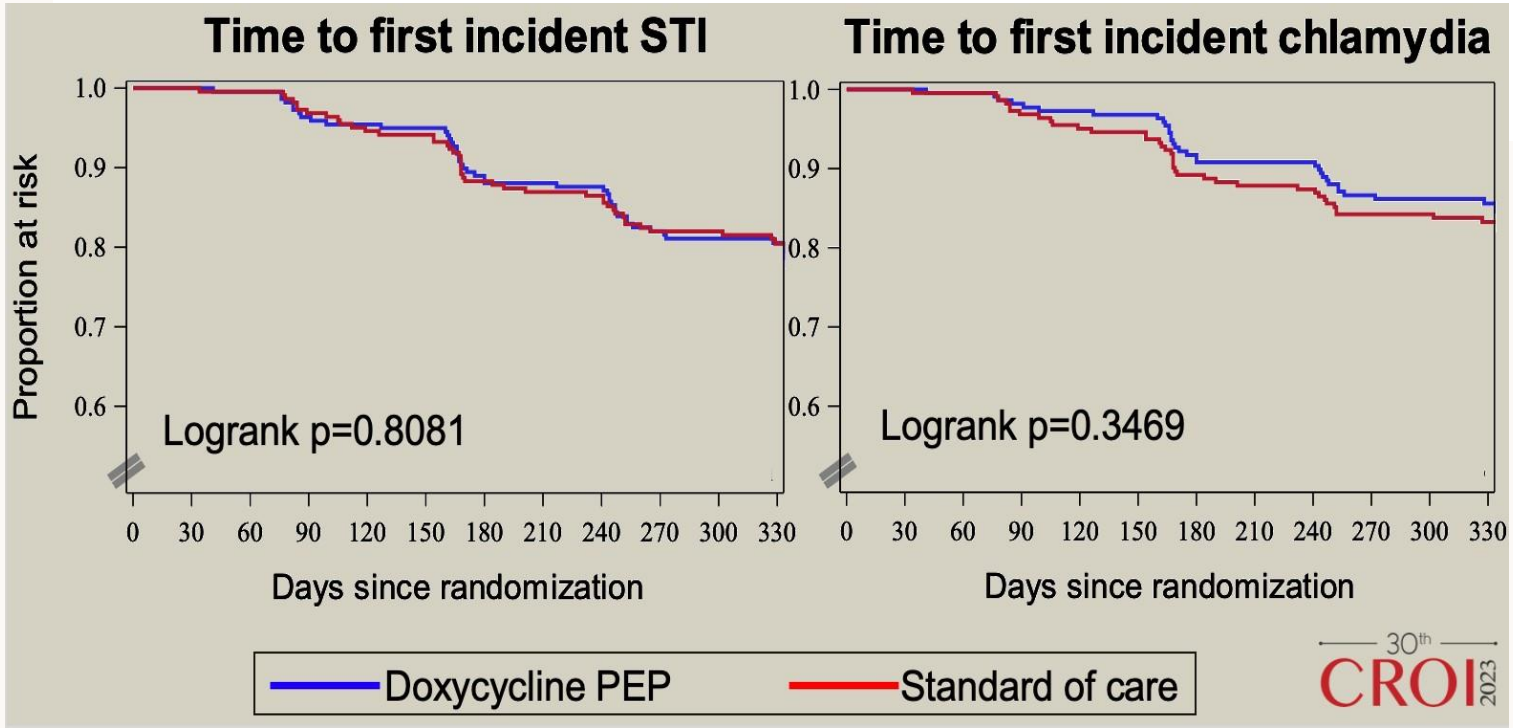
- 1:1 open-label randomized trial of dPEP (200mg doxycycline) taken within 72 hours after sex
- N=449 women taking PrEP, aged 18-30 (median age: 24 years)
- Quarterly follow-up for 12 months in Kisumu, Kenya

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER

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

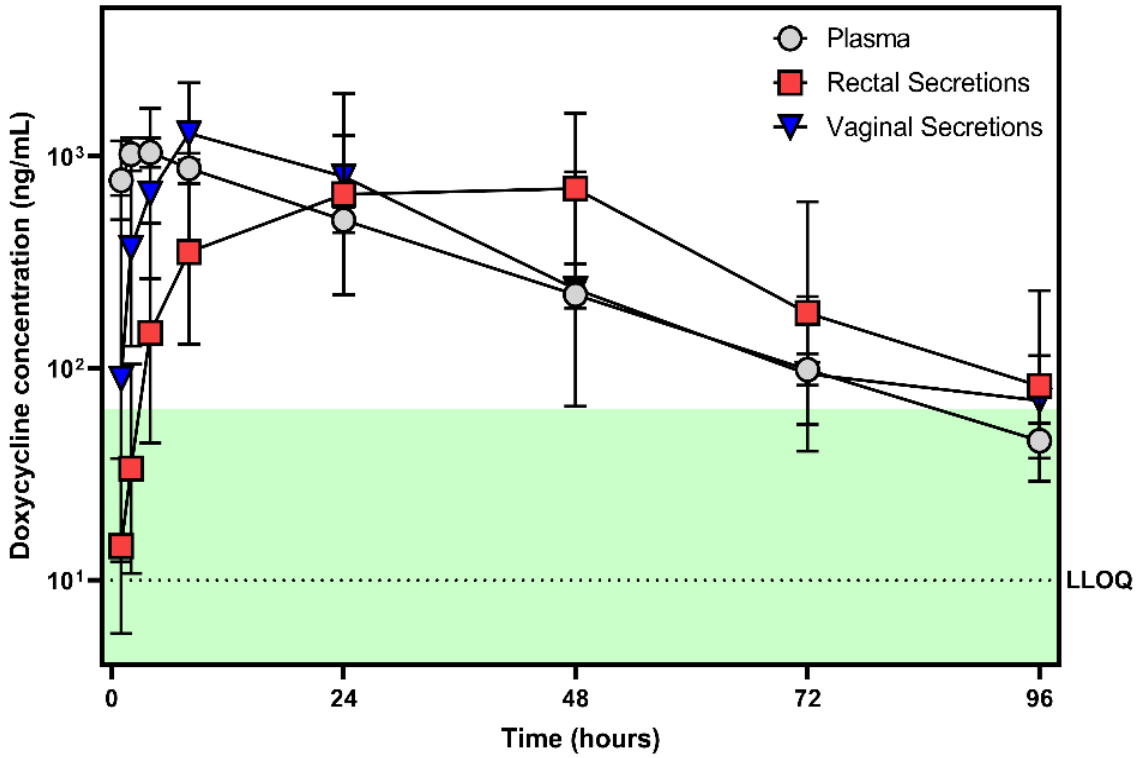
(tetM et tetC)

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

DoxyPEP self-reported adherence 78%

Stewart J, CROI 2023, Abs. 121

Doxycycline Concentrations following 200 mg SD



	Time above *C. trachomatis* 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		
		C trachomatis	*T pallidum*	*N gonorrhoeae*
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

Minimum Inhibitory Concentrations (MIC): *C trachomatis* MIC_{90} = 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

Haaland R et al. CROI 2023

Summary

- **Doxycycline PEP:**
  - 3 large studies have shown significant reductions of STIs among MSM
  - Doxycycline PEP is well tolerated with high self-reported adherence
  - Evaluation of full impact on antibiotic resistance is underway (STIs, microbiome)
- **Time for DoxyPEP implementation**:
  - Identify the population who will benefit the most
  - Monitoring of AMR and impact on the microbiome
- **There is no magic bullet:** Interest for combined approaches
- **STI research:** a scientific priority to meet 2030 WHO/UNAIDS targets to reduce incidence of HIV and STIs by 90%

Acknowledgments

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