# CROI 2023 Highlights

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Gus Cairns

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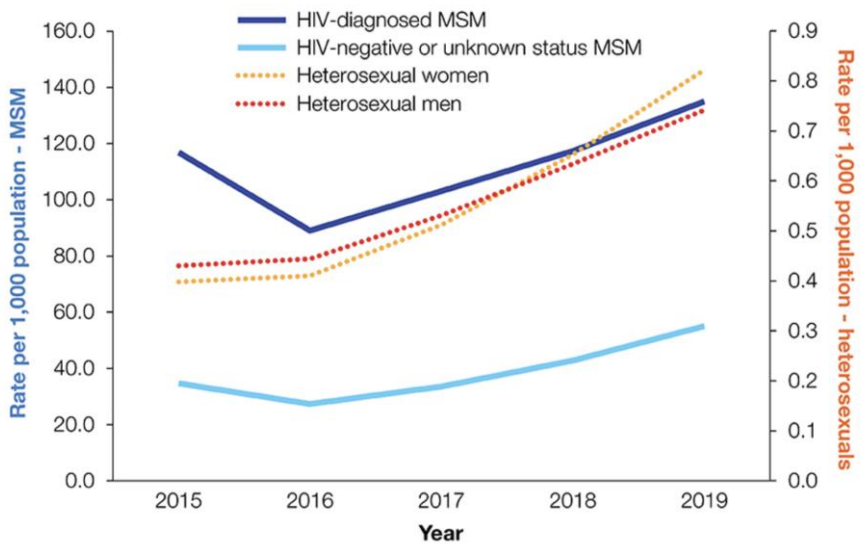
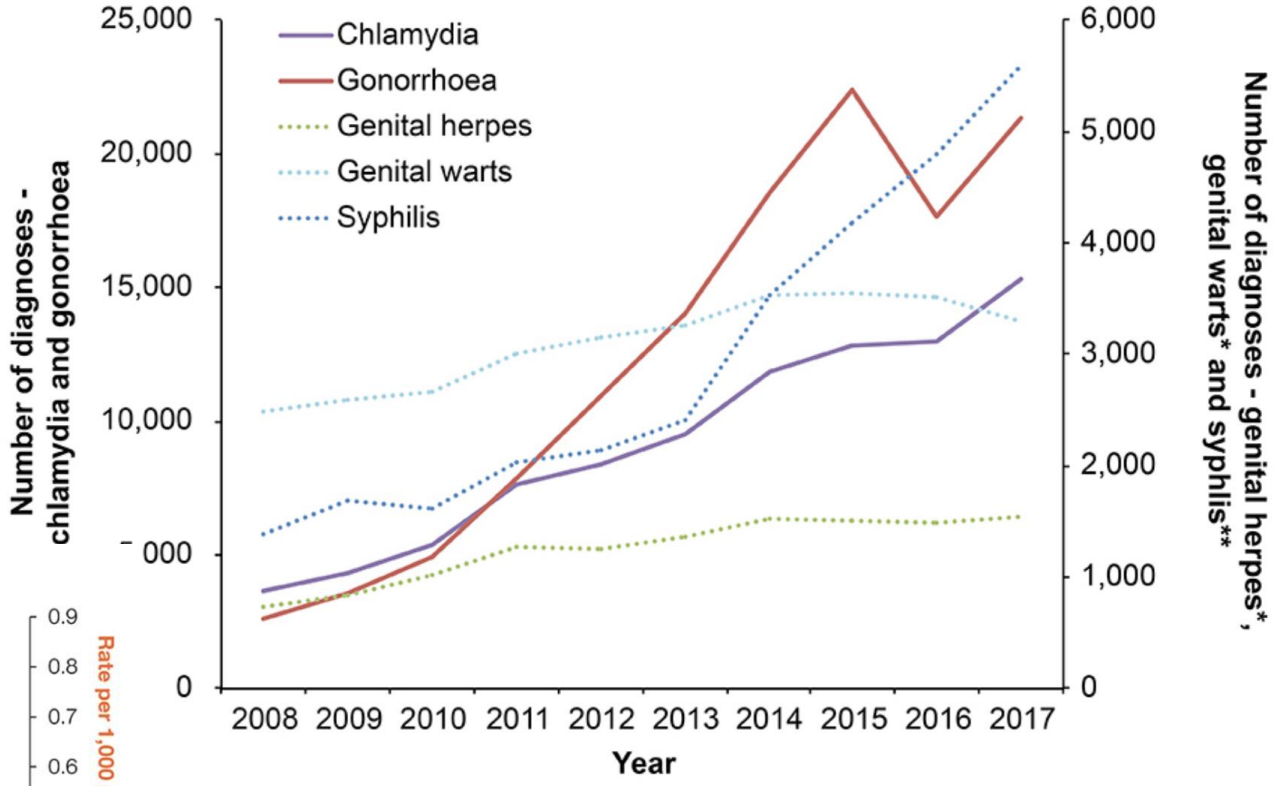
# Using antibiotics to prevent STIs – as PrEP or PEP

- We already use antivirals to prevent some STIs other than HIV, e.g. aciclovir to prevent herpes
- Incidence of the three important bacterial STIs – gonorrhoea, chlamydia, syphilis – have increased greatly since AIDS years (right)
- Especially in gay men: note in graph (below) gonorrhoea rates in gay men are >100x what they are in heterosexuals!




In graph above, gonorrhoea = red solid line, chlamydia = purple solid line, syphilis = dark blue dashed line. NB Syphilis is at 5x larger scale.

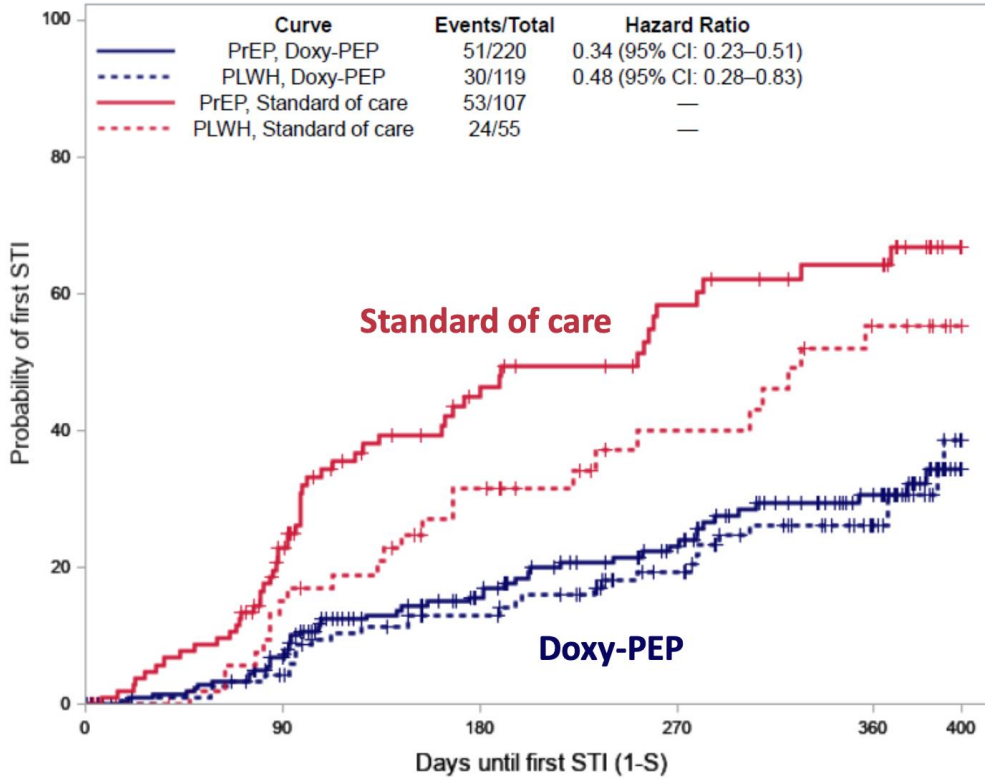
## Previous studies

See HPE briefing: Using antibiotics to prevent STIs

- 2015: Pilot study, Los Angeles: 30 **daily** doxycycline vs 30 on financial incentives to avoid STIs: overall **73% fewer STIs** in doxy-PrEP arm

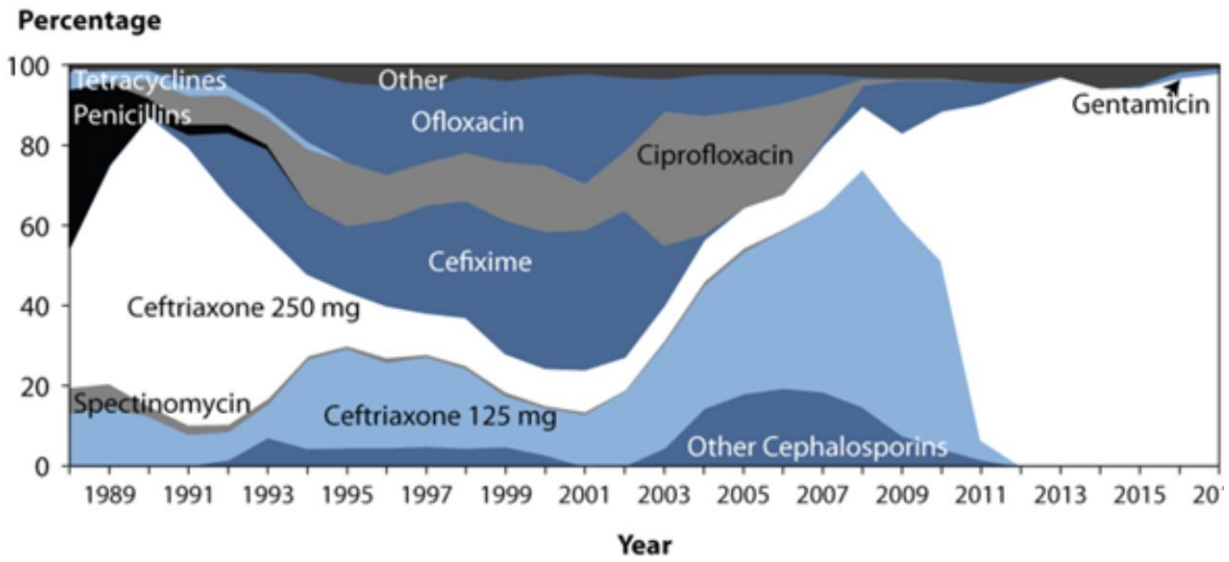
- 2017: French study in IPERGAY participants: 106 randomized to doxycycline **PEP** (200mg <72h after exposure) vs no PEP. Overall efficacy 47%: 70% efficacy vs. chlamydia, 73% vs syphilis but 16% against gonorrhoea was not significant (i.e. statistically zero).

- 2022: DoxyPEP study: Seattle/San Francisco: 501 gay and bi men (174 HIV+) randomised to doxy PEP vs no PEP. 66% overall efficacy (62% in HIV+) – **see pic**
  - 88% efficacy vs chlamydia (74% HIV+)
  - 87% efficacy vs syphilis (77% HIV+)
  - 55% efficacy vs gonorrhoea (57% HIV+)

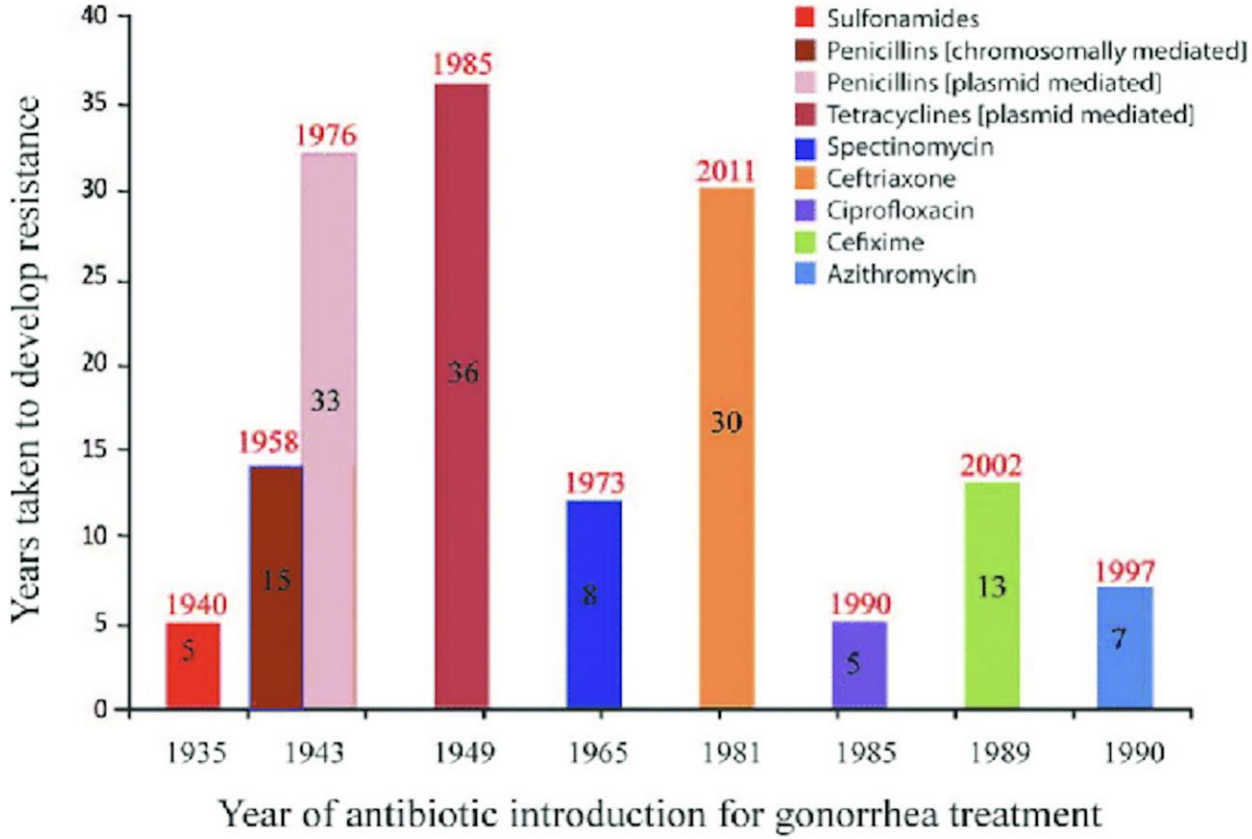


# The gonorrhoea resistance problem

- Chart (left) shows year antibiotic type first used vs gonorrhoea
- Height of bar is years it lasted before gonorrhoea became resistant
- Red figure is year this happened
- Current therapy is doubled-dose ceftriaxone (see below)
- Tetracyclines inc doxy last used mid-90s




Distribution of antimicrobial drugs used to treat gonorrhea among participants of GISP, 1988-2017.




- Chlamydia, syphilis tend to find it too costly to develop resistance:

# DoxyVAC study at CROI 2023

## If antibiotics don't (reliably) work against gonorrhoea, will a vaccine?

Gonorrhoea bacterium is from same family as meningitis  B, and vaccine already known to have some efficacy vs. gonorrhoea

Difference between previous French and US studies is that  56% - 67% of gonorrhoea had doxy resistance in France, only 20%-40% in US

Thought unlikely doxy-PEP would have efficacy

Study deigned as 2 separate studies in one: doxy vs no doxy against STIs, and vaccine vs no vaccine against gonorrhoea

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Jean-Michel Molina abstract 119

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HIV & AIDS – sharing knowledge, changing lives

News About HIV Abo

Sexually transmitted infections prevention

### Vaccine halves gonorrhoea rate in French study

Study also demonstrates effectiveness of doxyPEP

Gus Cairns | 20 February 2023 |


Professor Jean-Michel Molina at CROI 2023. Photo by Roger Pebody.

A vaccine against gonorrhoea halved the rate of repeated infections in gay and bisexual men,

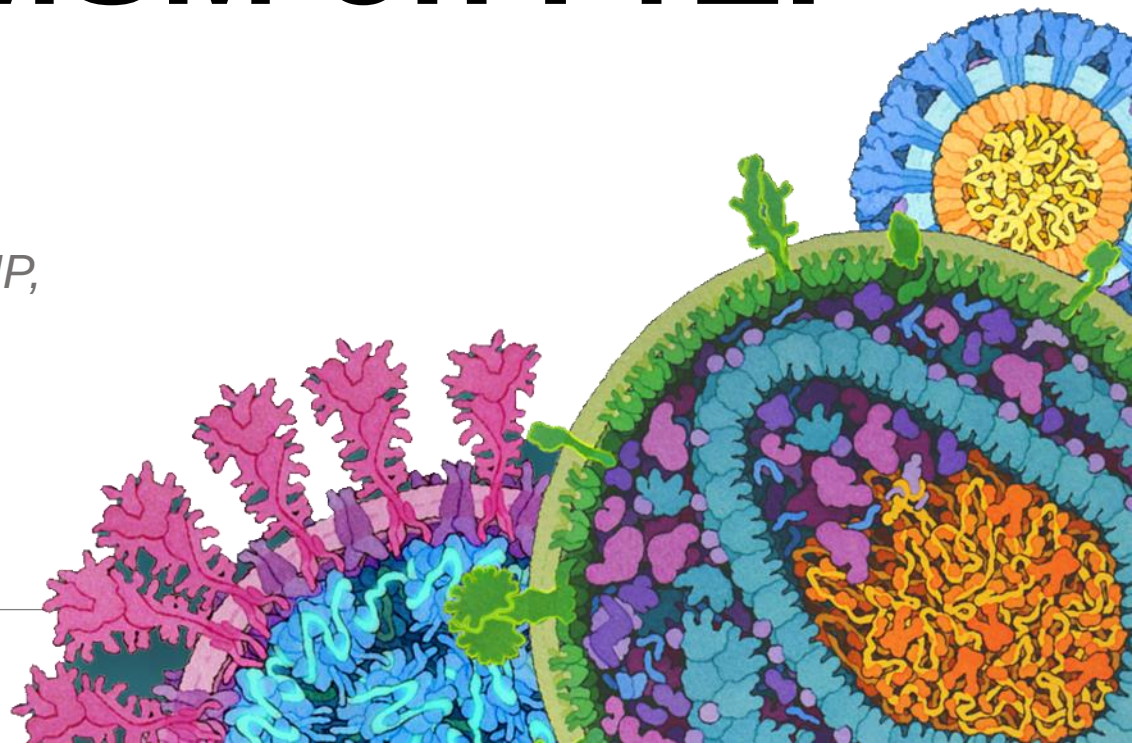
30th CROI 2023

# ANRS 174 DOXYVAC
# An Open-Label Randomized trial to Prevent STIs in MSM on PrEP

**Jean-Michel Molina**

*University of Paris Cité, St-Louis/Lariboisière Hospitals, APHP, Paris, France*

*Disclosure:* *Laboratory support from Roche*



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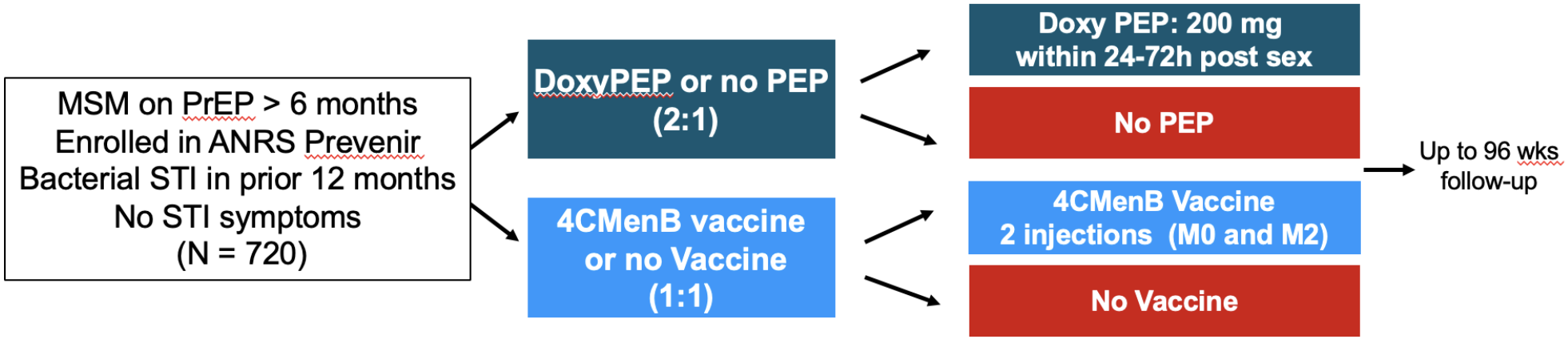
# Study Design

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

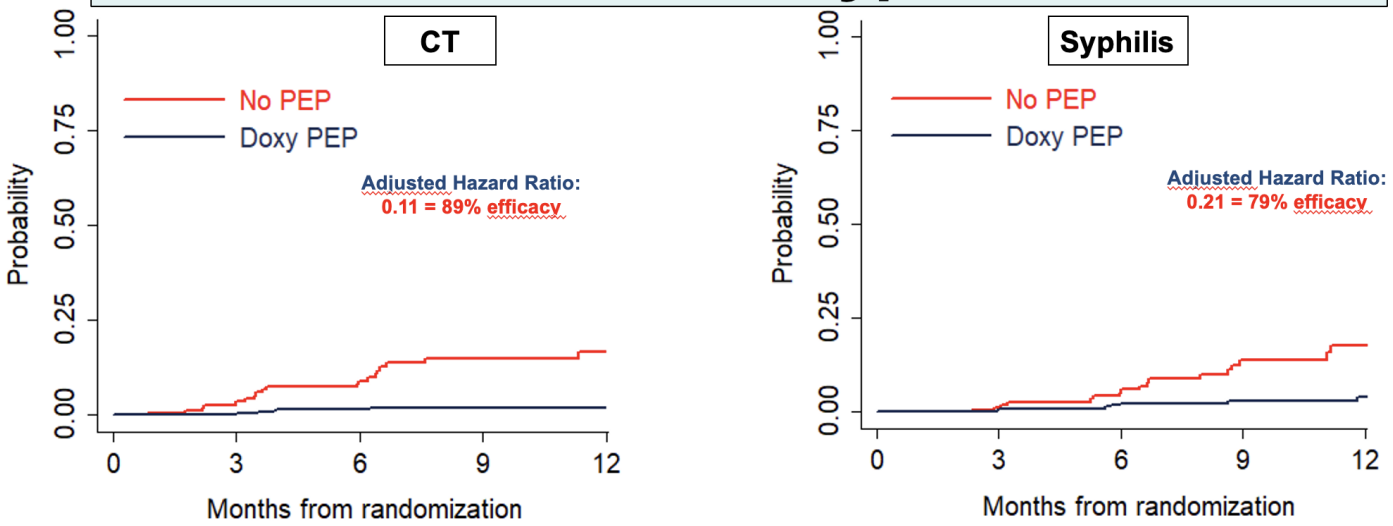



- Primary efficacy end-points: impact of DoxyPEP on time to a first episode of syphilis or chlamydia and impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoae* infection.
- Sample size: based on vaccine effectiveness assuming no impact of Doxy PEP on GC: 720 subjects needed for an HR: 0.70 (Estimated probability of a first GC episode over 18 months: 52%, 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



(Note: twice as many on PeP as no PEP. So 480 on doxy-PEP vs 240 on no PEP: 360 on vaccine vs 360 on no vaccine)

# Doxycycline PEP
# Time to First CT and Syphilis Infection

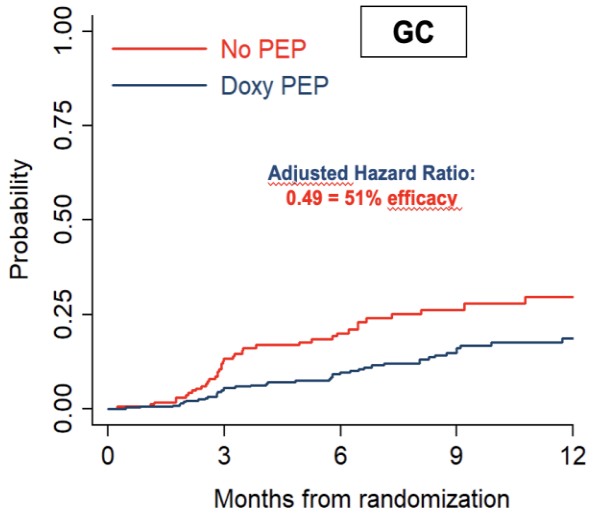






Doxy-PEP worked against chlamydia and syphilis with efficacy similar to other trials…

# Doxycycline PEP
# Time to First GC infection

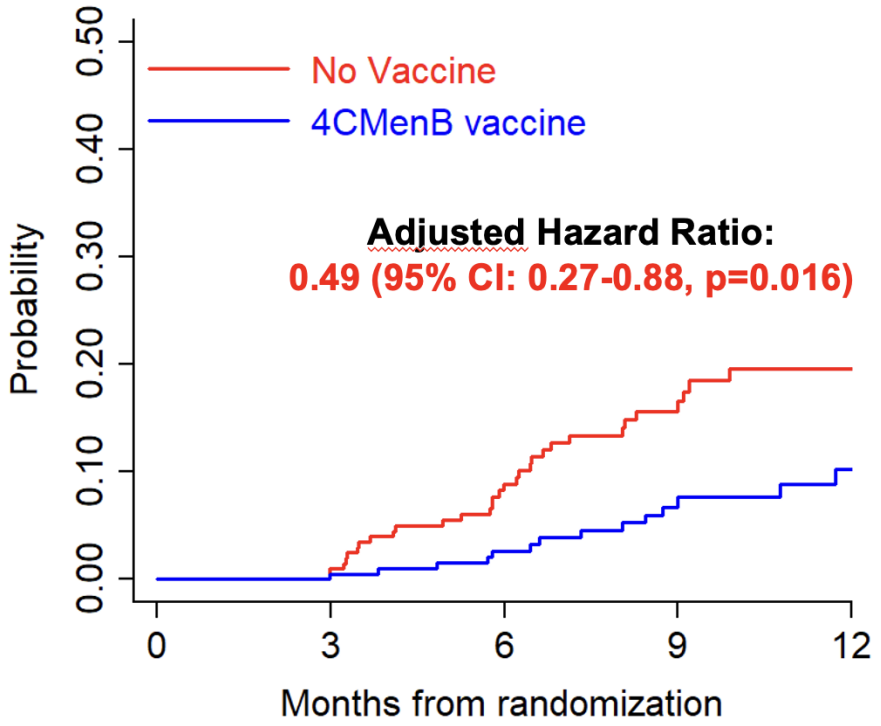



- Unexpectedly, doxy-PEP worked against gonorrhoea too (51% efficacy)

# 4CMenB Vaccine
# Time to First GC infection

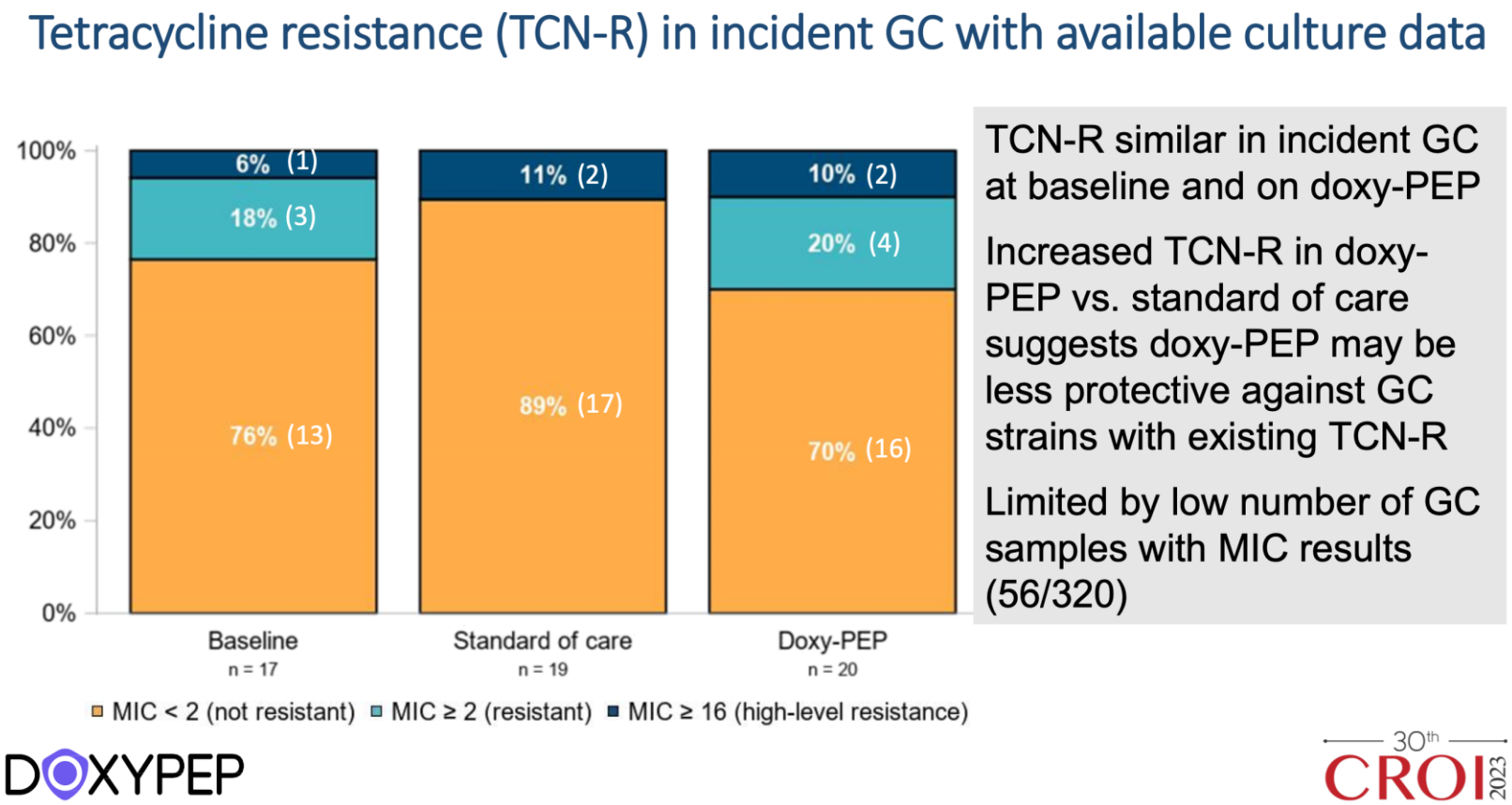
**No interaction between Doxy PEP and 4CMenB vaccine (p=0.41)**

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




Vaccine worked with similar efficacy to doxyPEP, but quite independently i.e. responding to one didn't make you more likely to respond to the other one too
Suggestion of site-specificity: doxyPEP worked better against anal and urethral infections, vaccine better against ones in throat
Because of trial design, we can't say that both together would have 75% efficacy vs. gonorrhoea

# How much influence does doxy-PEP have on gonorrhoea resistance? (revisit of DoxyPEP study)

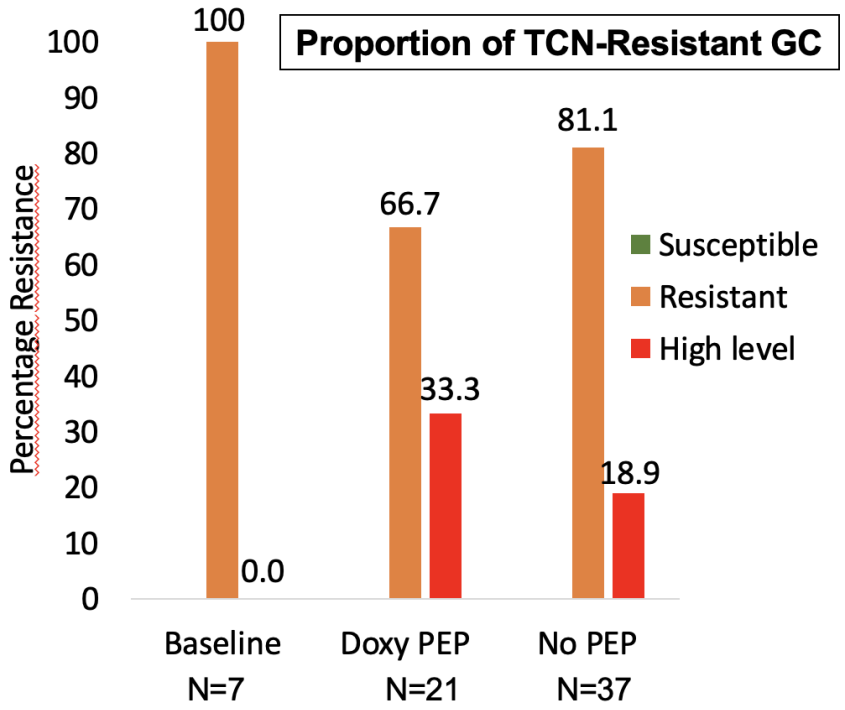



**Intermediate-level resistant-gonorrhoea may still respond to PEP: high-level won't: suggestion of increase in PEP, but not significant**

# How much influence does doxy-PEP have on gonorrhoea resistance? (DoxyVAC study)

## Tetracycline (TCN) Resistance for GC and CT

- **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
- **CT:**
  - 4/23 strains tested for TCN-R in culture: no resistance (but none from PEP arm)
  - 53/65 PCR+ swabs with16S rRNA sequenced: no TCN-R mutation (only 3 from PEP arm)




**No high-level resistance at baseline: 1/3 of resistance is high-level after PEP: but so is nearly 20% NOT on PEP – community-acquired?**

# Which gay and bisexual men should doxyPEP be offered to?

- Analysis based on people attending Fenway Health, the largest PrEP provider in New England - specialises in LGBTQ+ healthcare
- Efficacy of doxyPEP as in previous US study

## Methods *Potential doxy-PEP prescribing strategies*

- Explored 10 potential doxy-PEP prescribing strategies

**Prescribe doxy-PEP to patient groups**

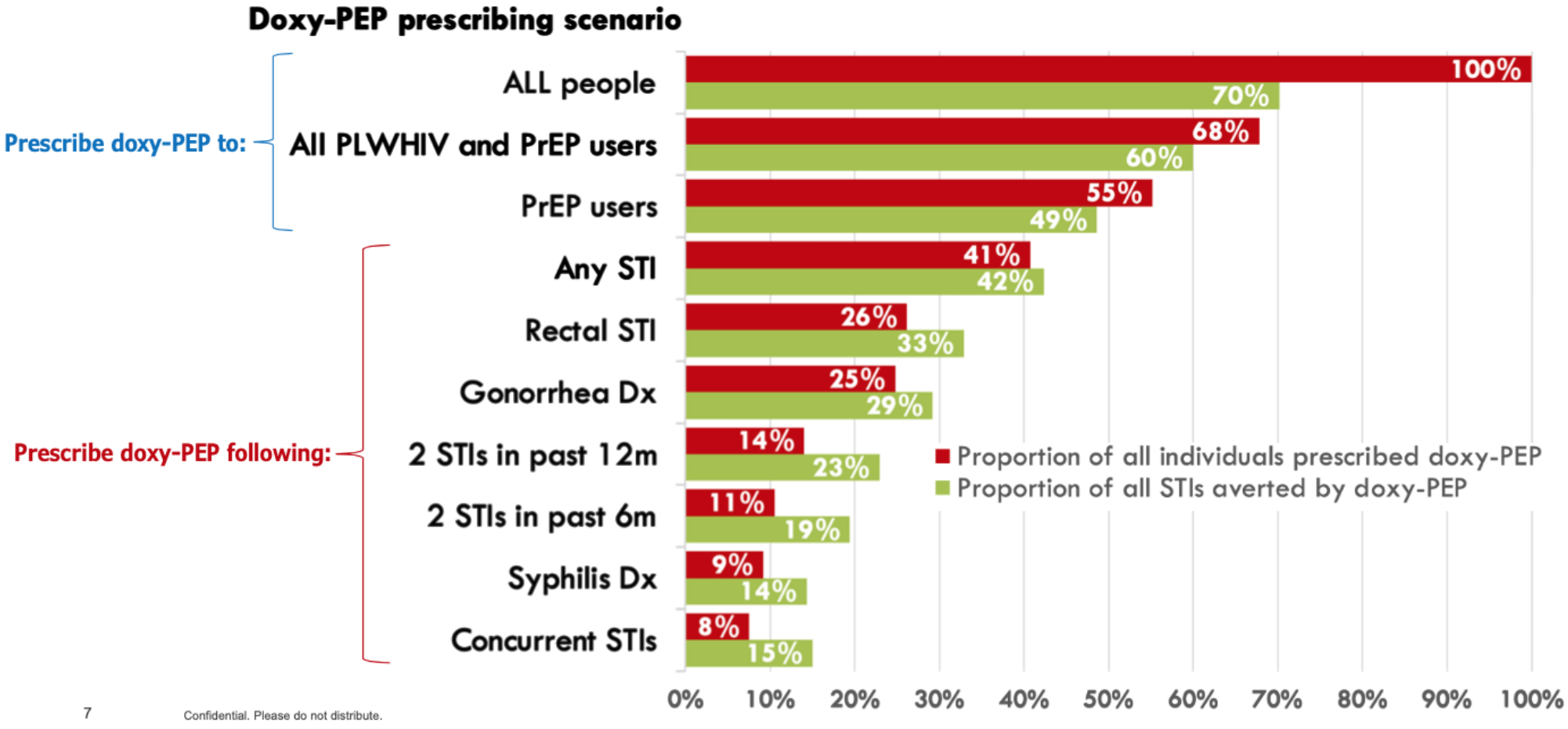
1. All patients accessing care
2. People with HIV & PrEP users
3. PrEP users only

**Prescribe doxy-PEP for 12m after STI* diagnosis**

4. Any STI diagnosis
5. Rectal STI diagnosis
6. STI at current visit + STI in past 12 months
7. STI at current visit + STI in past 6 months
8. Concurrent (2+) STIs at same visit
9. Syphilis diagnosis
10. Gonorrhea diagnosis

*STI = chlamydia, gonorrhea, syphilis

# Results *Doxy-PEP use vs STIs averted*



# Guidelines for doxyPEP

POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH


**Recommendations**

1. **Recommend doxy-PEP** to cis men and trans women who: 1) have had a bacterial STI in the past year and 2) report condomless anal or oral sexual contact with ≥ 1 cis male or trans female partner in the past year. These were the eligibility criteria used for the DoxyPEP study. Patients with a history of syphilis should be prioritized for doxy-PEP.

2. **Offer doxy-PEP using shared decision making** to cis men, trans men and trans women who report having multiple cis male or trans female sex partners in the prior year, even if they have not previously been diagnosed with an STI.

3. An ongoing randomized controlled trial in Kenya is assessing the safety and efficacy of doxy-PEP in cis women. **At this time, there is insufficient evidence to recommend doxy-PEP for STI prevention for individuals who report receptive vaginal sex.** If used in people who are able to become pregnant, pregnancy testing should be conducted as doxycycline use should be avoided during pregnancy.

4. **When initiating doxy-PEP, discuss the following key points with patients:**

# Guidelines for doxyPEP

BASHH position statement on doxycycline as prophylaxis for sexually transmitted infections (2021 update)

*Updated on:* ***09 November 2021***

**Key points:**

- Doxycycline taken as Pre- or Post-Exposure Prophylaxis for syphilis or chlamydia is not endorsed by BASHH or the UK Health Security Agency (UKHSA).
- The use of other antibiotics as prophylaxis for syphilis and chlamydia or to prevent other sexually transmitted infections (STIs) is unlikely to be effective and should be discouraged.
- Recognising that many patients are taking doxycycline as prophylaxis for STIs, BASHH and the UKHSA recommend that clinicians inform patients about potential risks and limited benefit. Clinical monitoring for adverse effects and advice should be offered to patients who are using doxycycline as prophylaxis for STIs.
- Several clinical studies are currently underway to measure the impact of prophylactic doxycycline on antimicrobial resistance (AMR) at an individual and population level.

# doxyPEP for women

## Background

**Cisgender women bear the highest burden** of morbidity and mortality from bacterial STIs (*Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Treponema pallidum)*[1,2].

Cisgender men and transgender women taking HIV PrEP with high rates of STIs **doxycycline PEP significantly reduced incident STIs**[3,4,5,6].

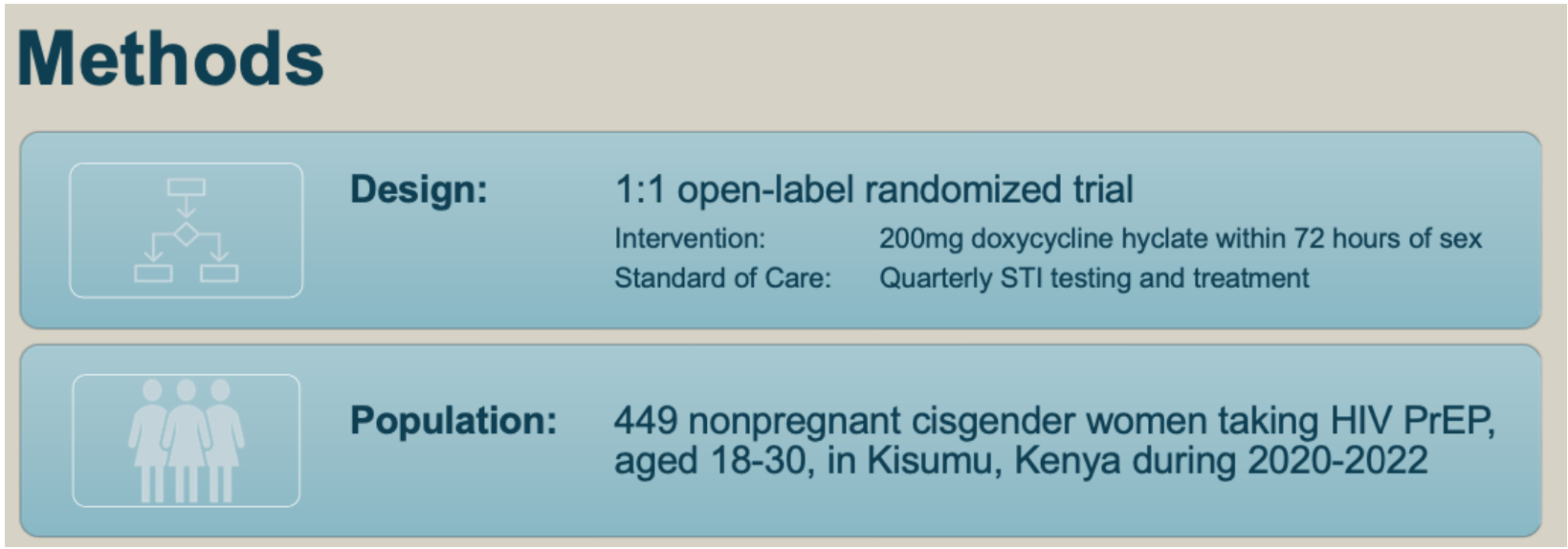
**Cisgender women taking HIV PrEP also have high incidence** of bacterial STIs: *C. trachomatis* (27-53% per year) and *N. gonorrhoeae* (11-20% per year)[7].

**We conducted the first trial of doxycycline PEP among cisgender women.**

**STI sequalae**

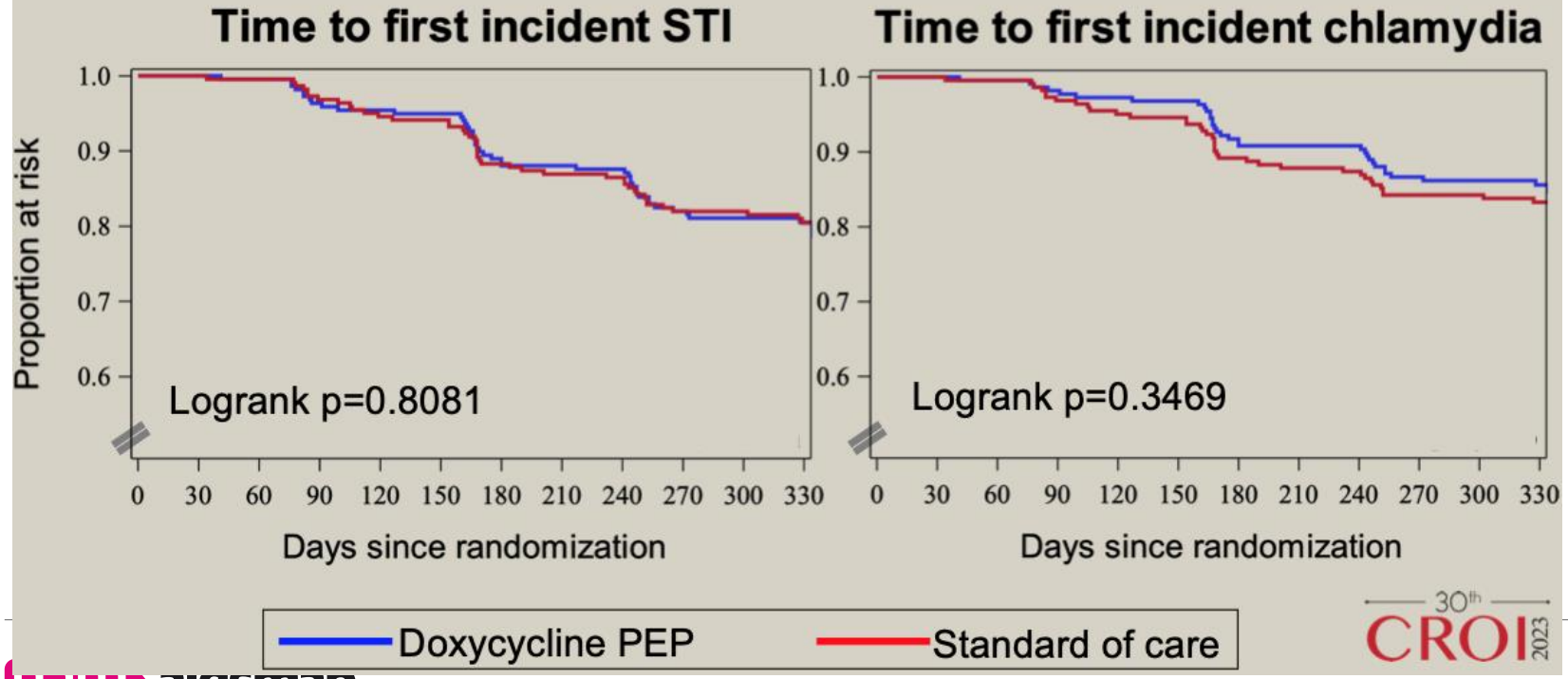
- PID
- chronic pain
- infertility
- pregnancy complications
- HIV acquisition

# doxyPEP for women



# doxyPEP for women

| 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 |



# doxyPEP for women

# Q&A

## Mpox in people with low CD4 counts

- In last year's mpox (monkeypox) outbreak, 38-50% of cases were in people living with HIV.
- Mostly people on ART, HIV viral load <50 and CD4 counts >500
- Mostly similar presentations and outcomes to people without HIV
- Some evidence from Nigeria 2018 on more severe and prolonged disease in people with low CD4 counts.

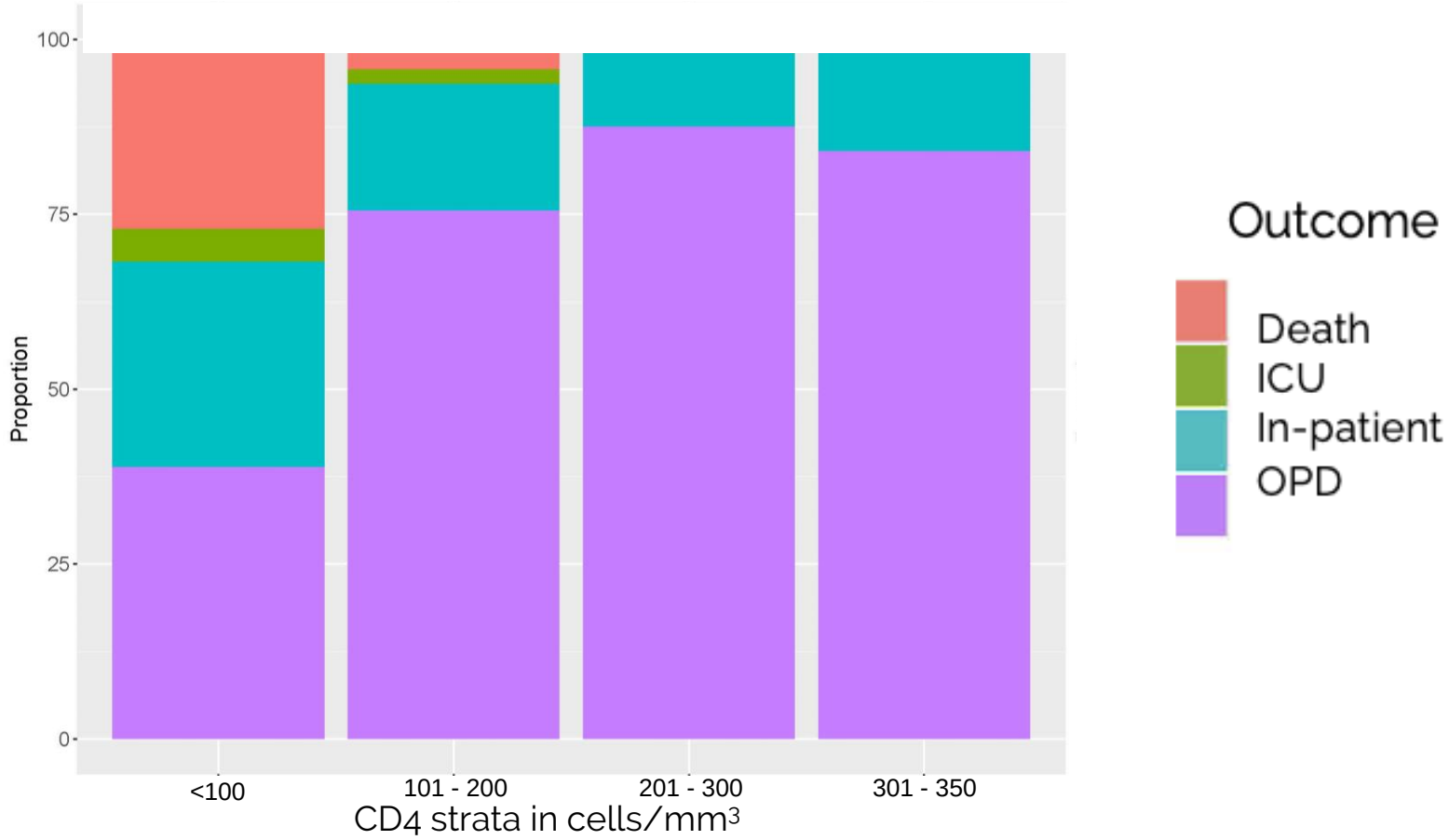
- Data from 44 clinical centres in 19 countries
- Western Europe (10), Latin America (6), US, Canada, Nigeria
- Case reports on people with mpox and HIV, with a CD4 cell count <350 (or CDC stage C)

## Mpox in people with low CD4 counts

- 382 participants
- Median age 35, 96% cis men
- HIV care
  - 60% previously diagnosed + on ART
  - 32% previously diagnosed + off ART / not taking pills regularly
  - 9% new HIV diagnosis
- CD4 counts
  - 22% <100
  - 25% 101 – 200
  - 34% 201 – 300
  - 20% 301 – 350
- Only 8% vaccinated against smallpox / mpox

# Outcome stratified by CD4 count and VL

## A. Outcome stratified by CD4 count

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# Conclusions

- **All 27 deaths occured in CD4 count <200 cells/mm$^3$**
- **Mortality rate : 15% in CD4 <200; 27% CD4 <100**
- **Severe necrotising, disseminated form of mpox described**:
  - Massive necrotising skin, genital and non-genital cutaneous and mucosal lesions
  - Lung involvement with multifocal opacities (perivascular nodules 5-20mm)
  - Severe cutaneous and bloodstream secondary bacterial infections.
- **Severity of complications and deaths correlate to CD4 and VL strata**
- **Mpox IRIS** - clinical deterioration after initiation of ARV - 57% mortality rate

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# Implications

- **Mpox is an opportunistic pathogen**
- **Severe necrotising form of mpox is an AIDS-defining condition**
- **International disease classifications (CDC** and **WHO) should reflect this**
- **Clinical recommendations in CD4< 200:**
  - Vigilance –likelihood of sepsis
  - Consider timing of ART
  - Prioritise for mpox antivirals and preventive vaccines (research needed)
- **Prioritise access to mpox antivirals & vaccines in countries without access**

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## Rapid adherence test using urine

- Indicates use of tenofovir in past 5 days
- The hope: provide real-time data on adherence, inform counselling, drive adherence interventions, improve viral suppression.
- Positive predictive value (for viral suppression) – 91%
- Negative predictive value (for viral suppression) – 63%
- Test likely to be commercialised next year

## Cabotegravir / rilpivirine injections

- Studies were done in people who were virally suppressed on pills, switching to injections.
- So drug regulators and guidelines support injections for that group.
- “For those of us treating HIV on a daily basis, we know that some patients have challenges taking pills, including substance use, housing and food insecurity and stigma.” – Dr Monica Gandhi
- Special programme in San Francisco – ‘off label’ prescribing
- Extra support: case managers, phone or text appointment reminders, follow-up for those who miss injection appointments, financial incentives, community nursing.
- 76/76 who were previously virally suppressed remained so
- 55/57 of those who had detectable virus achieved viral suppression

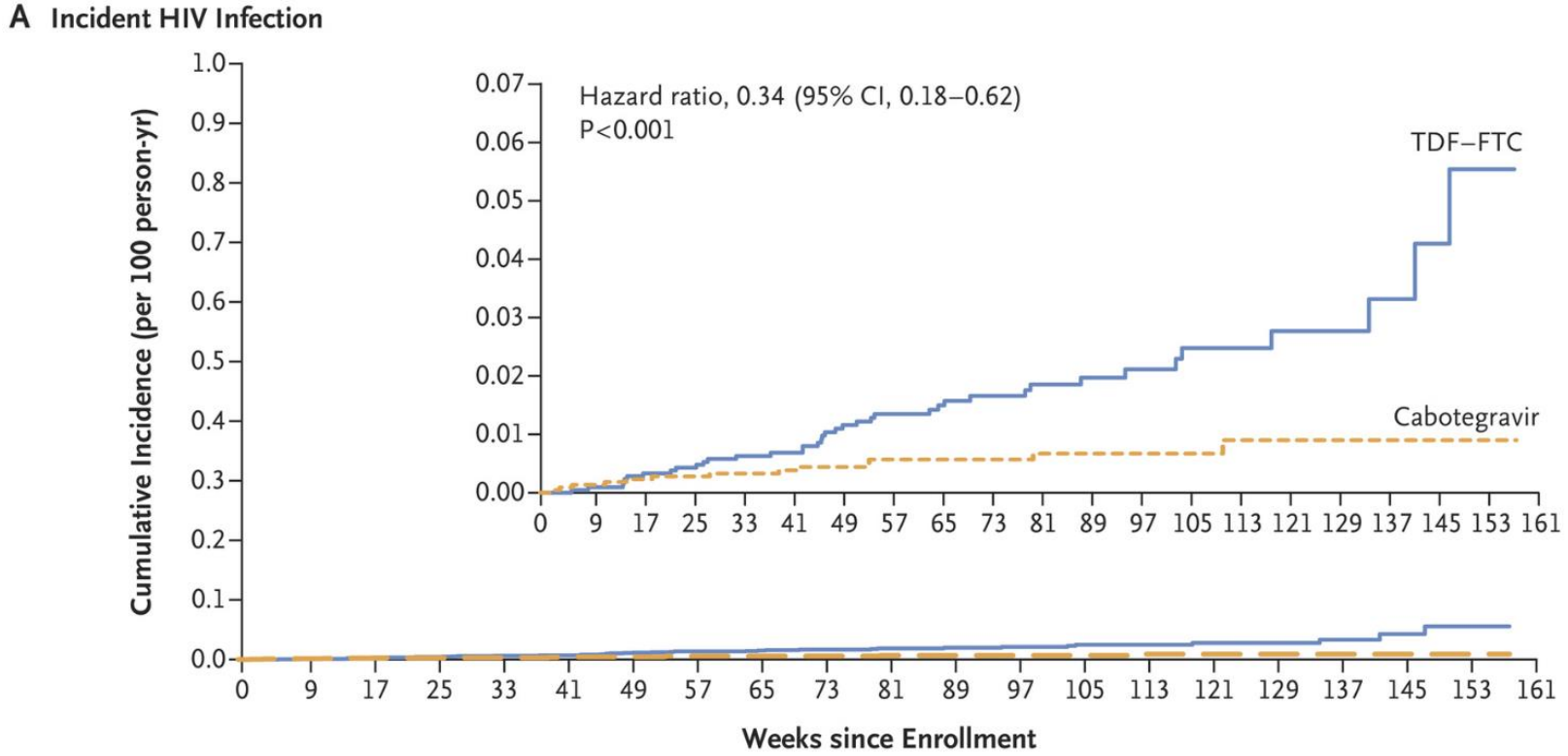
## Cabotegravir / rilpivirine injections

- Large volume of drug, needs to be injected deep into a muscle
- Developed for buttocks, delivery by nurse
- Many trans women and others have had implants in buttocks, making this unsuitable

- 118 people with HIV who had already had buttocks injections for >3 years
- Tried thigh injections for 4 months
- No clinically relevant differences in drug levels between thigh and buttocks
- Injection site reactions common (40% after monthly, 60% after every other month)
- Nearly one third of participants preferred thigh injections, about 60% preferred buttocks injections, about 10% had no preference.

# Injectable PrEP for gay and bisexual men and trans women (HPTN 083): update

- Update at last year's CROI
- Now 84 HIV infections in 2282 people on TDF/FTC
  28 on cabotegravir
- So cabotegravir injections prevent 66% more HIV infections than oral PrEP does
- By halfway through study, adequate adherence in TDF/FTC arm was 66%
- This suggests efficacy of cabotegravir injections vs. no PrEP would be c. 90%




| No. at Risk | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TDF–FTC | 2281 | 2132 | 2081 | 2019 | 1913 | 1765 | 1624 | 1494 | 1295 | 1132 | 965 | 817 | 644 | 517 | 401 | 311 | 231 | 150 | 85 | 33 | 0 |
| Cabotegravir | 2280 | 2138 | 2091 | 2031 | 1920 | 1776 | 1633 | 1489 | 1315 | 1124 | 957 | 798 | 644 | 503 | 401 | 318 | 243 | 173 | 111 | 42 | 0 |

| Cumulative No. of Events | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TDF–FTC | 0 | 2 | 7 | 9 | 13 | 14 | 22 | 25 | 27 | 29 | 31 | 32 | 33 | 35 | 35 | 36 | 36 | 37 | 38 | 39 | 0 |
| Cabotegravir | 0 | 3 | 5 | 6 | 7 | 8 | 9 | 11 | 11 | 11 | 12 | 12 | 12 | 12 | 13 | 13 | 13 | 13 | 13 | 13 | 0 |

## There were some infections on the injections

Most due to drop-outs and delayed injections, but 6 despite on-time injections

## 'Breakthrough infections' can be hard to detect

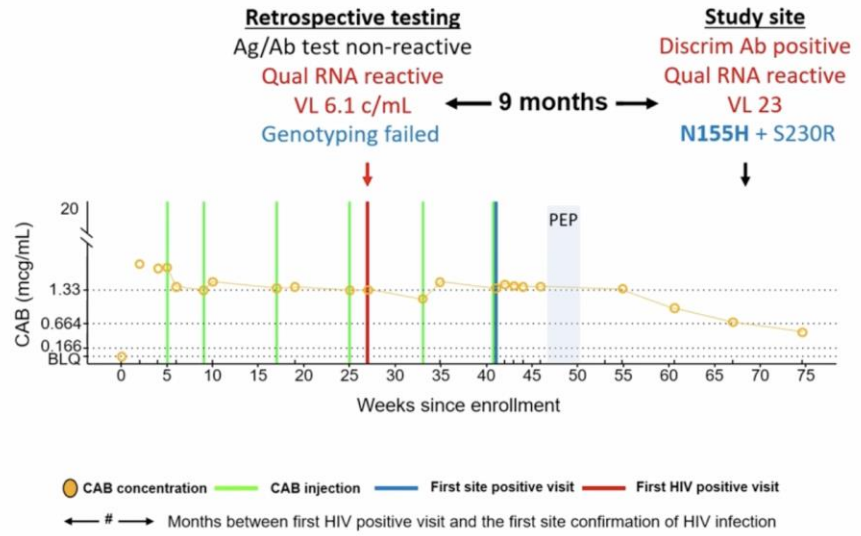
Now has a name – LEVI syndrome = Long-Acting Early Viral Inhibition

### HPTN 083 – CAB arm HIV infections

6 infections occurred despite on-time injections among 2,282 participants randomized to CAB-LA

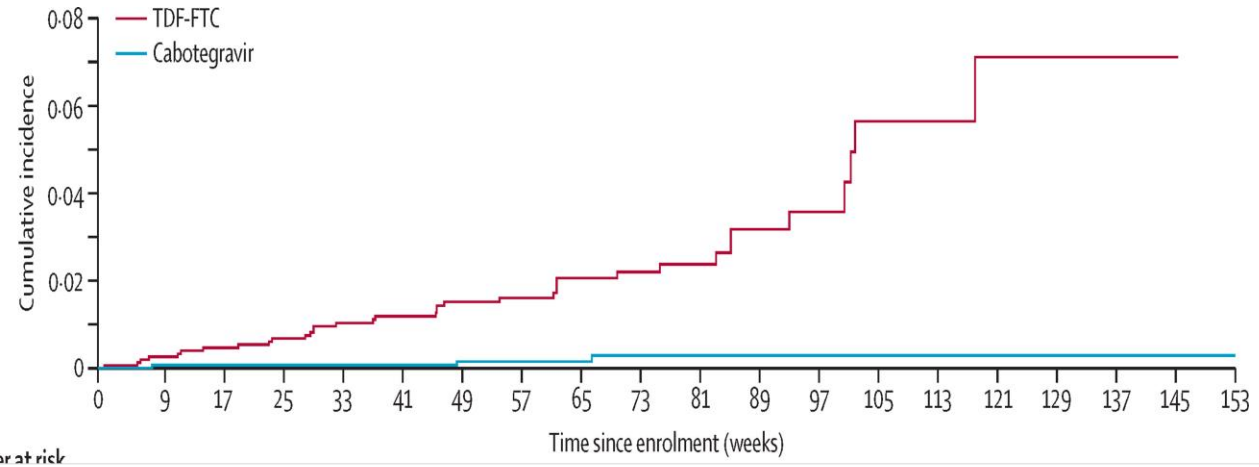
| Type of case | # Cases |
|---|---|
| **Infected despite on-time injections** | **6** |
| 28 other infections | |
| No recent CAB exposure (within 6 months) | 16 |
| HIV+ at enrollment | 4 |
| Infected while receiving oral CAB | 3 |
| Infected after ≥ 1 delayed injection | 3 |
| Infected near the time of CAB re-initiation | 2 |

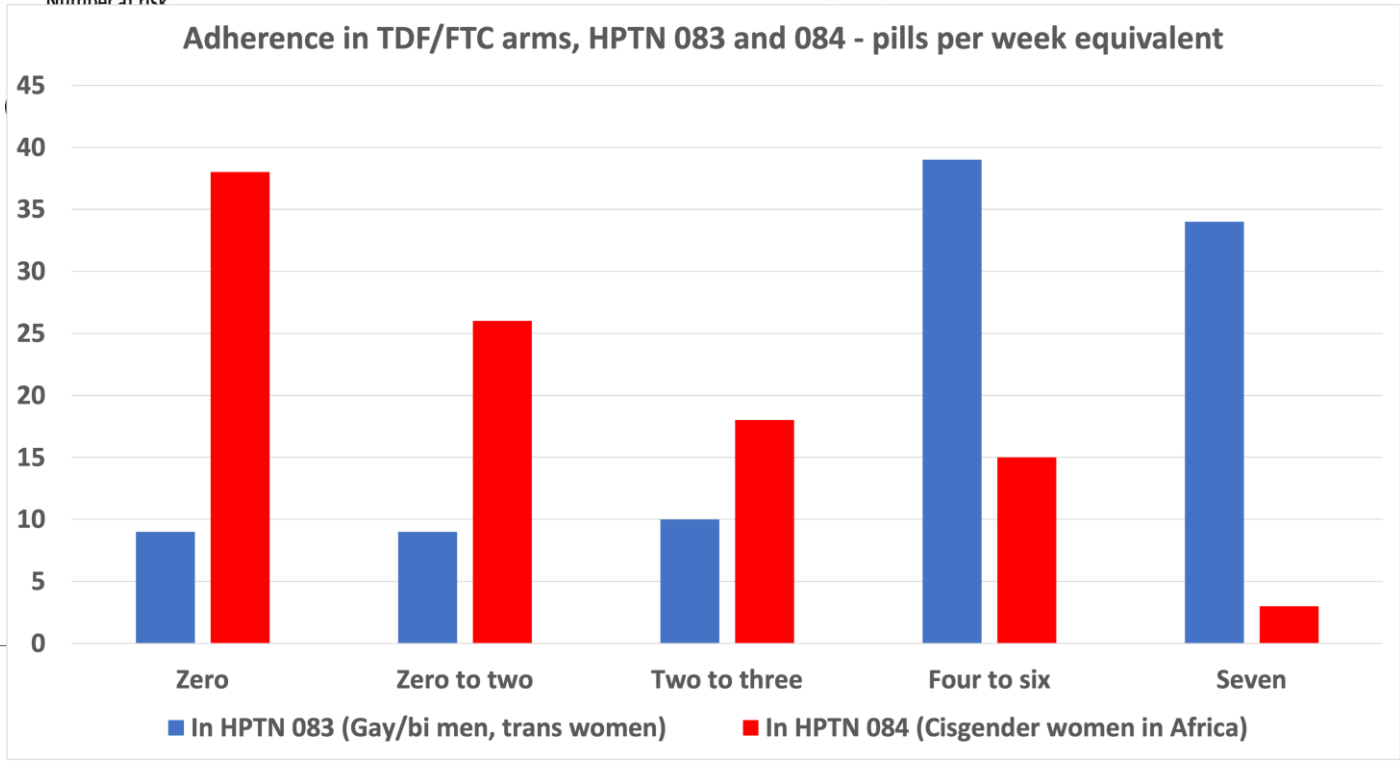
### Case Study: Confirmation of Infection



## Injectable PrEP for cisgender women in sub-Saharan Africa (HPTN 084): update

- Cabotegravir injections prevented 91% more HIV infections than oral PrEP did in HPTN 084
- Only one infection seen in a participant remaining on CAB – after she missed one injection completely (i.e. four-month gap between injections). Still no breakthrough infections.
- One 'breakthrough' infection in a participant on TDF/FTC with almost perfect adherence (= 6-7 doses a week )
- Adherence in TDF/FTC arm generally low – see pic



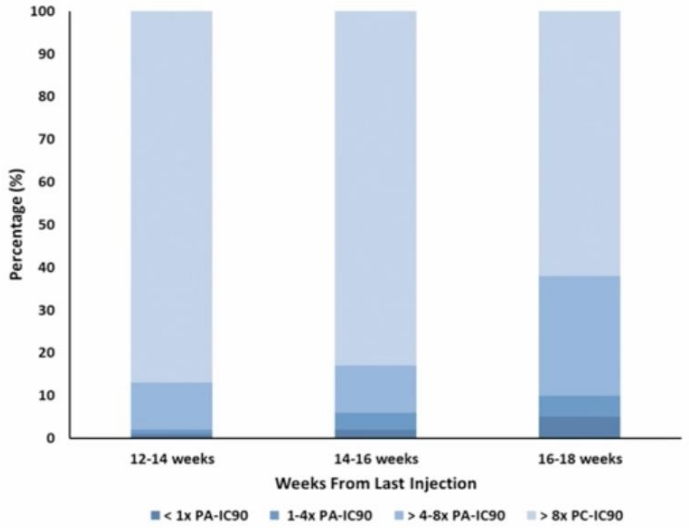



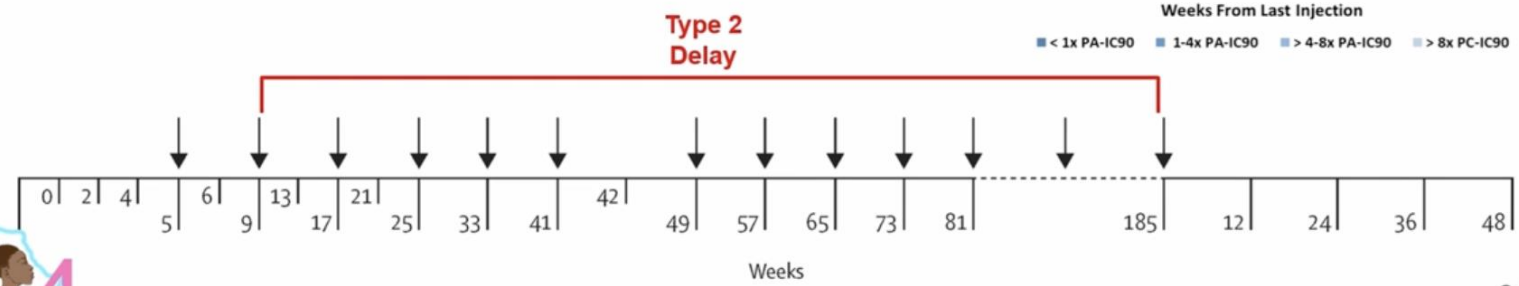
## Some good news for women: quarterly CAB injections should be enough to protect

- Analysis of delayed injections in 194 participants in HPTN 084
- If women missed an injection by 4-6 weeks (i.e. gap of >3 months between injections), 97% still had >8 times the $IC_{90}$ of cabotegravir in their blood
- ($IC_{90}$ = amount needed to prevent 90% of viral replication)
- If they missed injection by 8-10 weeks, i.e. gap of >4 months or one completely missed injection, 62% still had >8x the $IC_{90}$ and 90% > 4x the $IC_{90}$
- Only one woman had less than the $IC_{90}$ up to 4 months after last injection

### Injection Delays *After* the 2nd Injection (Type 2 Delays)

| [CAB] Trough | 12-14 weeks Between Injections | 14-16 weeks Between Injections | 16-18 weeks Between Injections |
|---|---|---|---|
| | N=109 | N=57 | N=39 |
| >8x PA-$IC_{90}$ | 95 (87%) | 48 (84%) | 24 (62%) |
| >4-8x PA-$IC_{90}$ | 12(11%) | 6 (11%) | 11 (28%) |
| 1-4x PA-$IC_{90}$ | 1 (1%) | 2 (4%) | 2 (5%) |
| <1x PA-$IC_{90}$ | 1 (1%) | 1 (2%) | 2 (5%) |




HPTN 084 LIFE

30th CROI 2023

## Provision of long-acting PrEP

- Approved by US FDA in December 2021
- Recommended for HIV prevention by the World Health Organization (WHO) in July 2022
- In Europe, marketing application only accepted by EMA in October 2022 (NB not yet applied to UK MHRA)
- US, Australia, Zimbabwe, South Africa, and Malawi have now licensed injectable cabotegravir as PrEP
- MSF also planning demonstration projects in Mozambique, Eswatini
- ViiV signed licensing agreement with 3 generic companies to produce CAB-LA for lower-income countries on 28 July 2023 – announced these would be Cipla, Aurobindo, Viatris on 30.03.2023
- Manufacturing is complex; according to MSF, may take “years” for generic companies to develop capacity
- Issue is price: cost-effectiveness studies find even in US injectable PrEP can’t cost more than $3000 dollars more than generic TDF/FTC to be cost-effective and in South Africa it can’t cost more than about $90-$115 a year

## Looking into the future: lenacapavir and bNabs

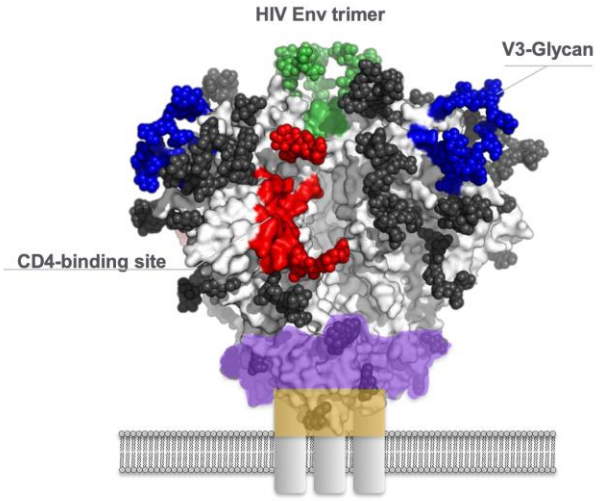
Treatment study: but lenacapavir also being studied for PrEP: PROMISE 1 and 2 studies, currently ongoing

Lenacapavir given as one subcutaneous injection every six months

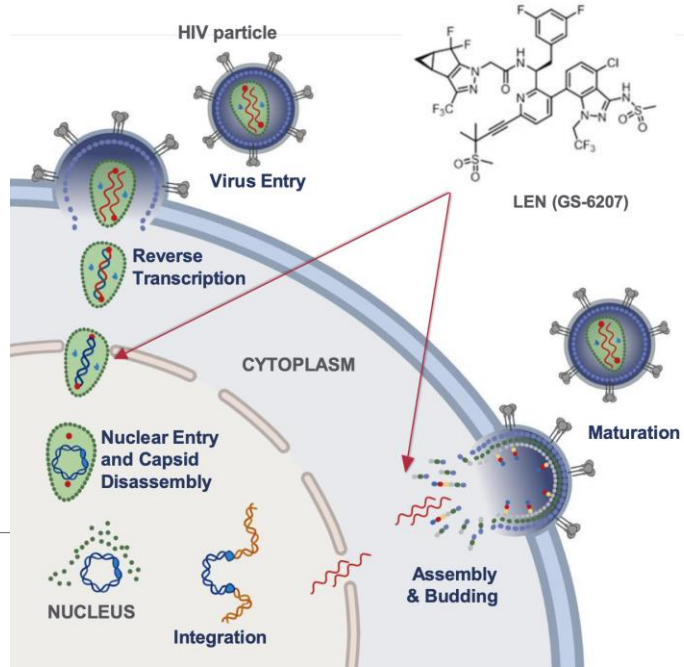
bNAbs (TAB and ZAB) as six-monthly infusions

## Background

- Teropavimab (TAB; GS-5423; 3BNC117-LS) and zinlirvimab (ZAB; GS-2872; 10-1074-LS) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively.
- Both antibodies were modified to extend their half-lives for long-acting therapy that may allow for dosing every 6 months.
- An estimated > 50% of clade B viruses are highly susceptible to both bNAbs and > 90% are highly susceptible to either bNAb with a 90% inhibitory concentration ($IC_{90}$) < 2 µg/mL.[1]




- **We hypothesize that combining TAB and ZAB with a long-acting antiviral agent could provide a complete long-acting therapeutic regimen for HIV treatment.**




- Lenacapavir (LEN) is a first-in-class, small molecule capsid inhibitor with:
  - Multimodal mechanism, a long half-life and low potential for drug-drug interactions
  - Subcutaneous administration every 6 months
- LEN plus an optimized background regimen has demonstrated clinical efficacy in highly treatment experienced patients with multidrug resistant HIV-1 infection failing antiretroviral regimen.

**We investigated whether LEN in combination with TAB and ZAB can maintain HIV suppression for 6 months.**

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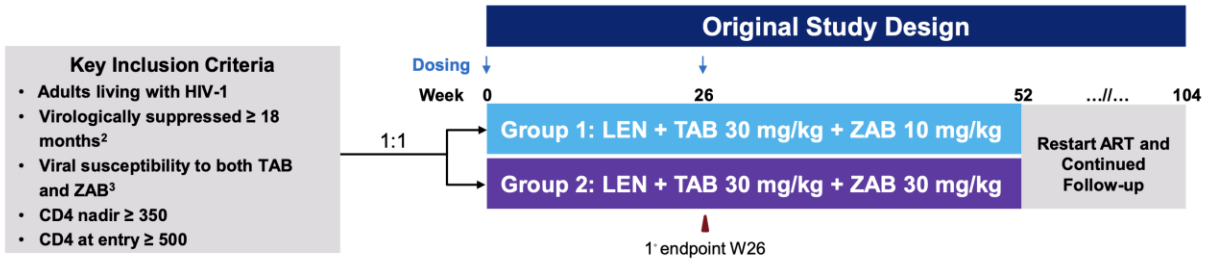
# Study had to be shortened because of LEN formulation problems (resolved)

## Study Design

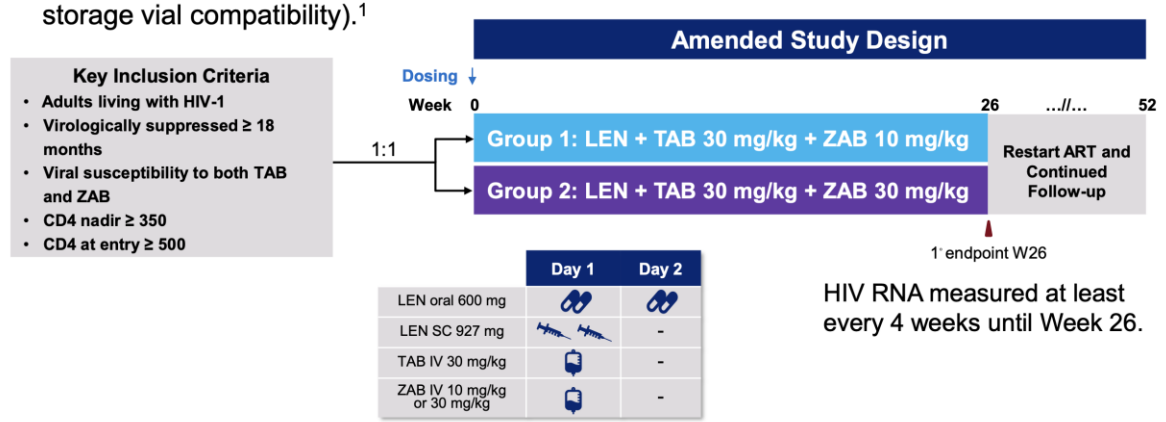
- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses.[1] (NCT04811040)




HIV RNA measured at least every 4 weeks until Week 52.

## Study Design

- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]




HIV RNA measured at least every 4 weeks until Week 26.

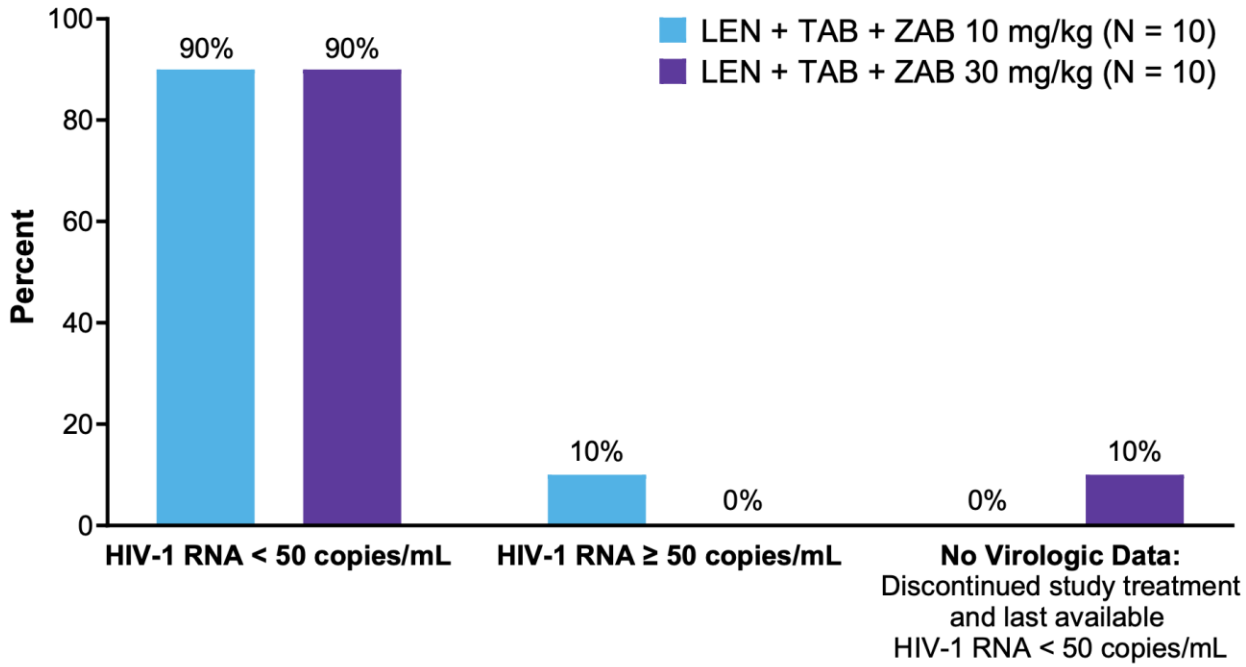
# Participants: moderately treatment-experienced

## Enrolled Participant Demographics and Baseline Characteristics

| | | LEN + TAB + ZAB 10 mg/kg (N = 11) | LEN + TAB + ZAB 30 mg/kg (N = 10) | Total (N = 21) |
|---|---|---|---|---|
| Age, median (range) | | 46 (31 to 61) | 37 (25 to 59) | 44 (25 to 61) |
| Sex at birth, n | Male | 11 | 7 | 18 |
| | Female | 0 | 3 | 3 |
| Race, n | Asian | 2 | 1 | 3 |
| | Black | 1 | 2 | 3 |
| | White | 7 | 5 | 12 |
| | Other | 1 | 2 | 3 |
| Hispanic or Latino ethnicity, n | | 4 | 3 | 7 |
| Weight (kg), median (range) | | 90.2 (58.9 to 150.0) | 92.9 (60.2 to 143.0) | 90.2 (58.9 to 150.0) |
| Body mass index (kg/m$^2$), median (range) | | 30.2 (21.6 to 42.9) | 30.2 (21.6 to 54.1) | 30.2 (21.6 to 54.1) |
| CD4 cell count (per mL), median (range) | | 778 (547 to 1391) | 1024 (667 to 1644) | 909 (547 to 1644) |
| Duration of baseline ART (years), median (range) | | 3.6 (2.4 to 4.8) | 2.6 (2.0 to 5.5) | 2.6 (2.0 to 5.5) |
| Time since HIV diagnosis (years), median (range) | | 12.4 (6.4 to 26.3) | 5.3 (2.6 to 22.4) | 8.2 (2.6 to 26.3) |

# Results: one/20 failure, one withdrew

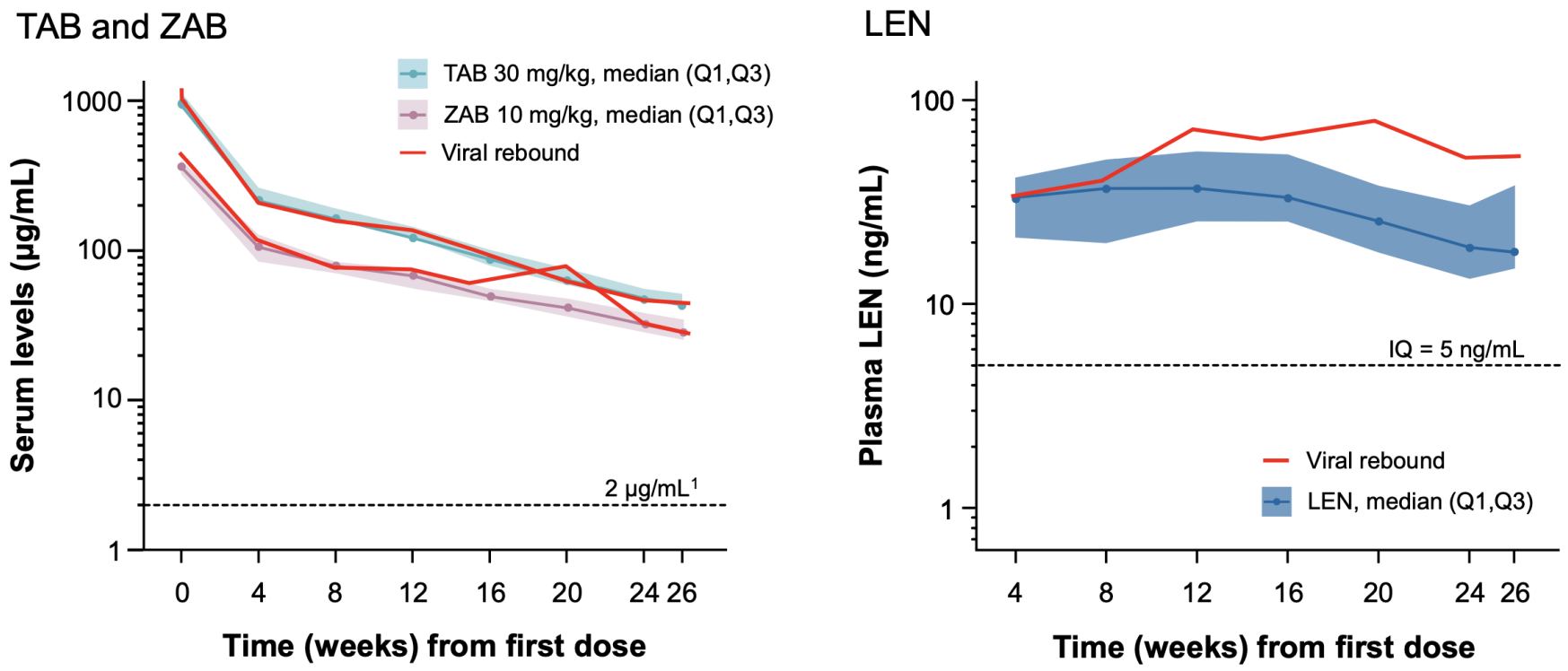
## Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm




- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

**Virological failure case is a puzzle: drug levels were OK (note levels of all 3 drugs in all participants well above effective concentrations after six months)**

## Pharmacokinetics in Participant with Viral Rebound




- TAB, ZAB, and LEN PK for virologic rebound participant was consistent with others in their dosing group.

# Q&A

# Thank you

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