AWACC

ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS

Long-acting (LA) PrEP: The Past, Present and Future

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Africa Health Research Institute
Harvard Medical School

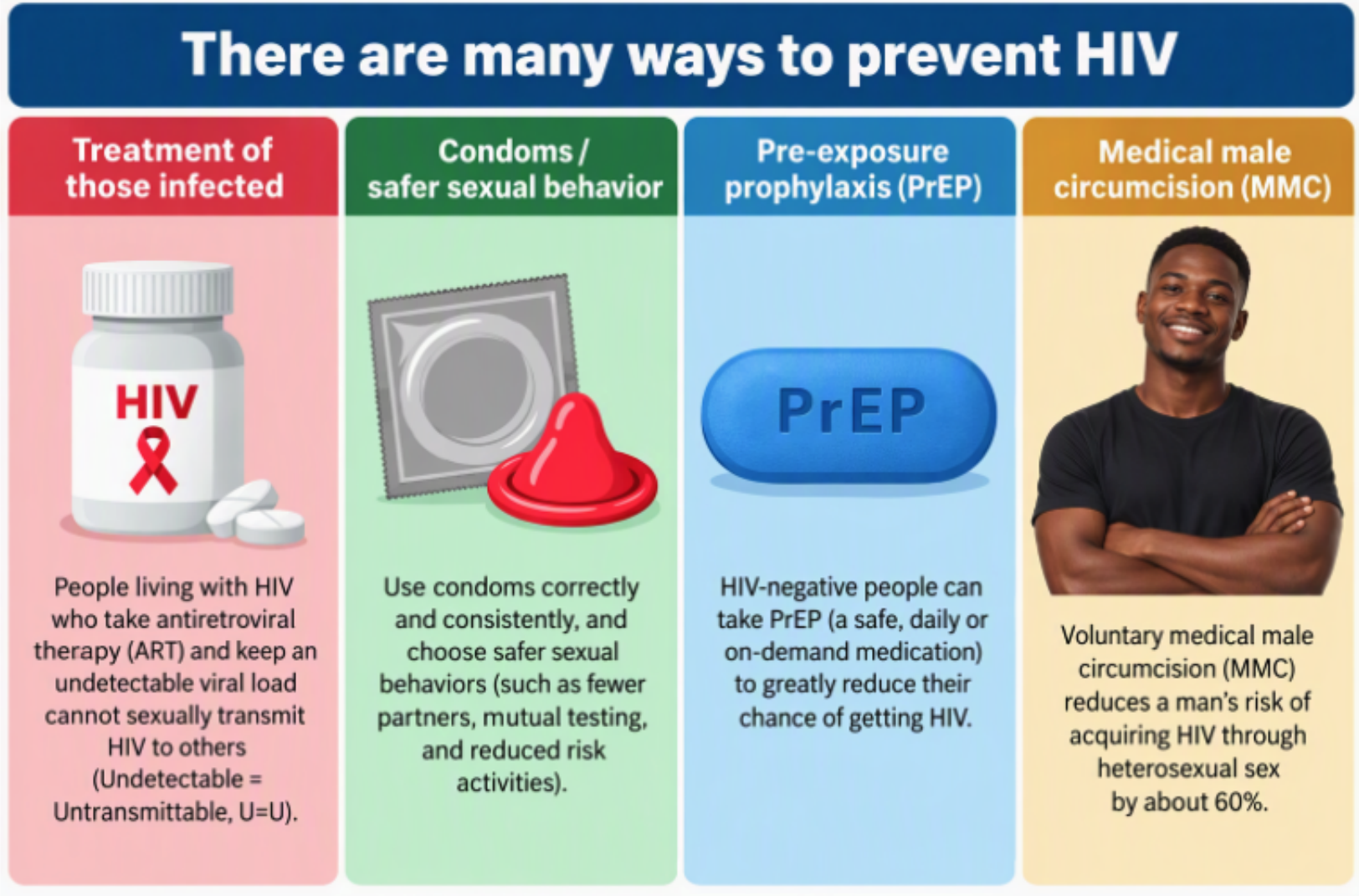
Talk summary

- ***Why*** do we need (long-acting) PrEP?
- ***How*** does long-acting PrEP work?
- ***What*** LA PrEP options are available in South Africa and hopefully coming soon?
- ***How*** and in whom should we be prescribing LA PrEP?
- ***Can*** we foresee a future of LA PrEP for all who need it?

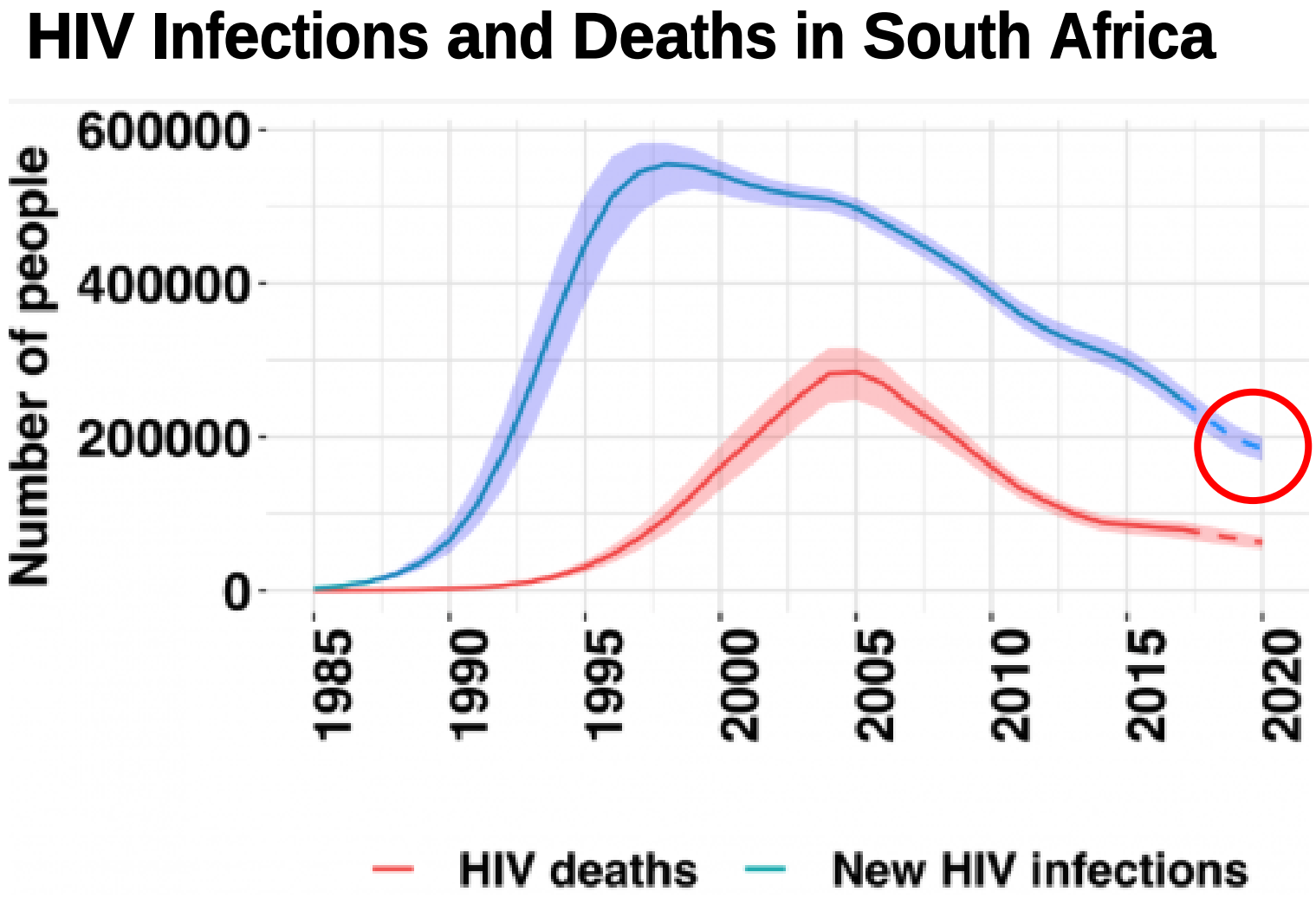
Show of hands: Do we need LA PrEP in SA?



Do we really need LA PrEP in South Africa?

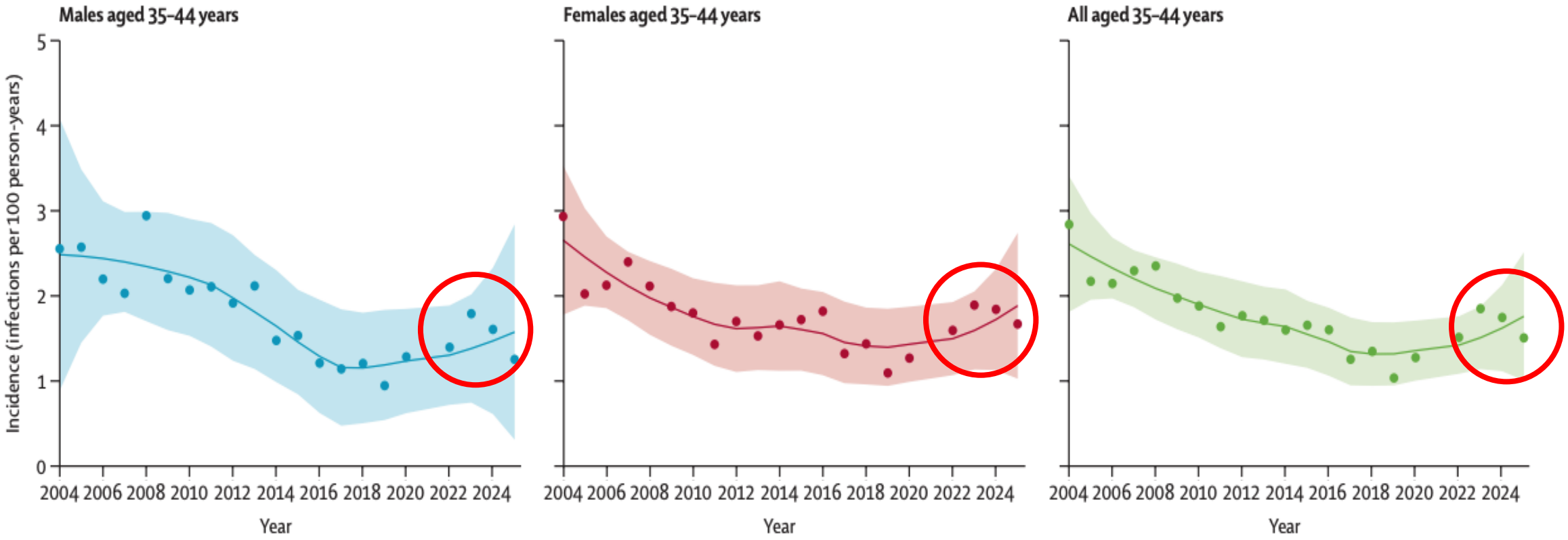


Why do we need PrEP?



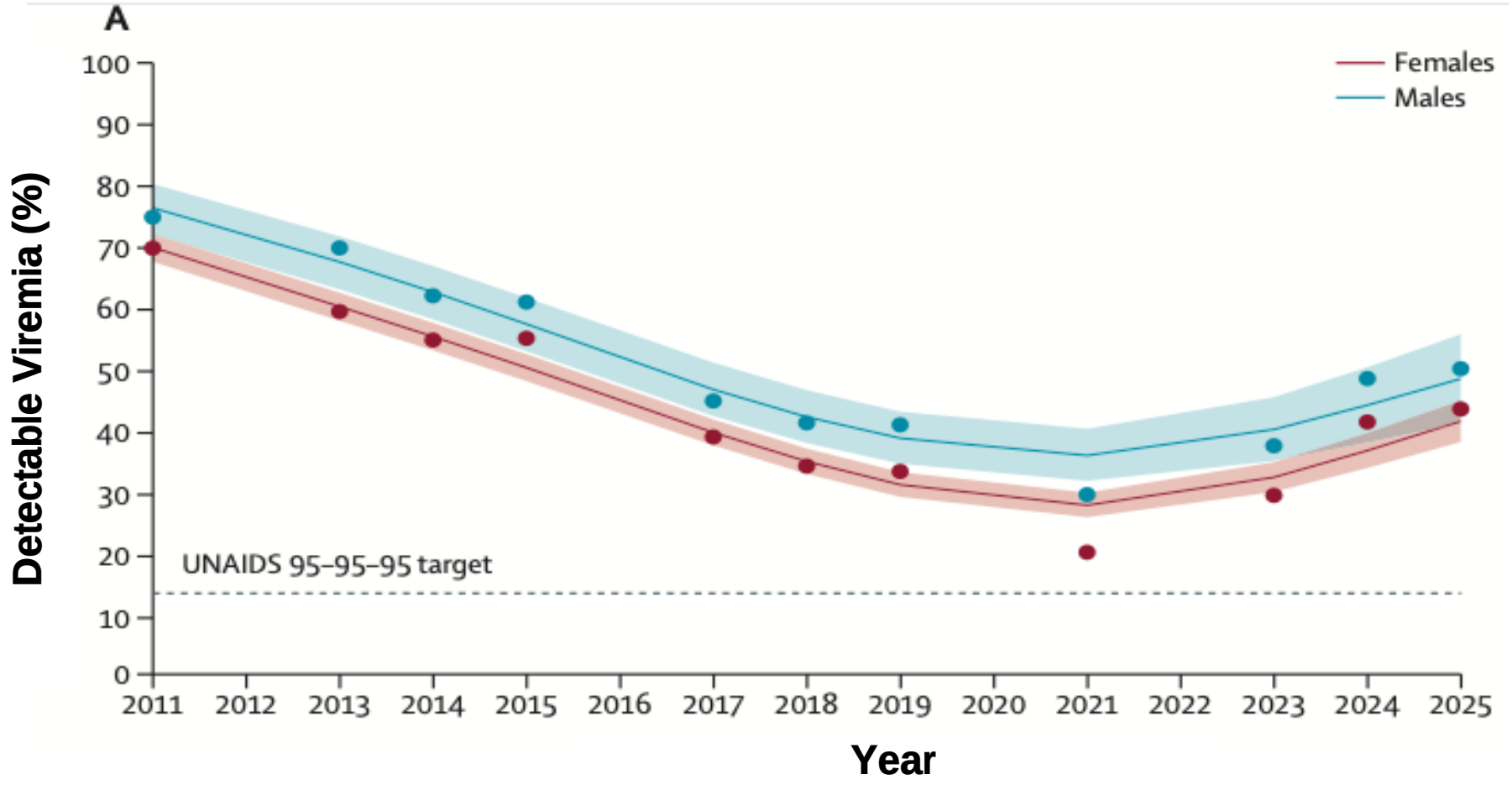
https://www.spotlightnsp.co.za/2019/07/18/hiv-in-sa-seven-graphs-that-tell-the-story/

Why do we need PrEP?



Okango et al, Lancet HIV, 2026

Why do we need PrEP?



Okango et al, Lancet HIV, 2026

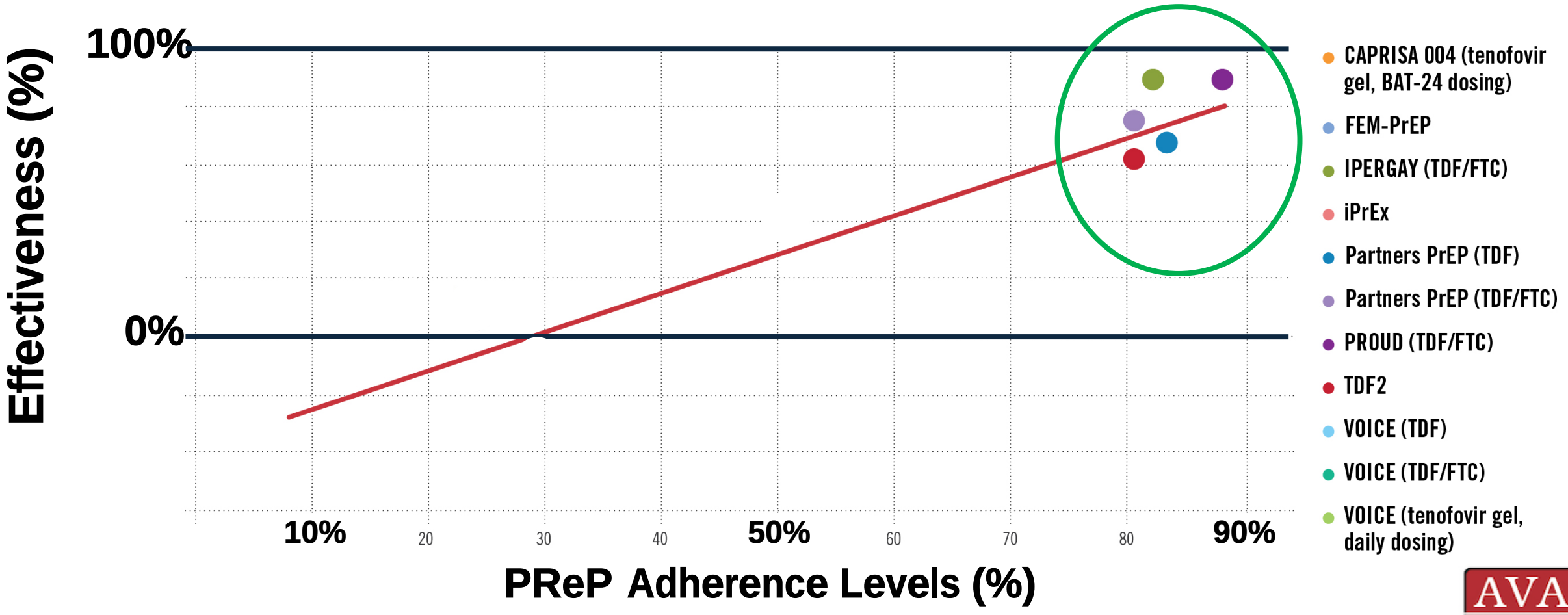
Why do we need PrEP?

- Because current HIV prevention methods are not sufficient

- **But do we need long-acting PrEP?**

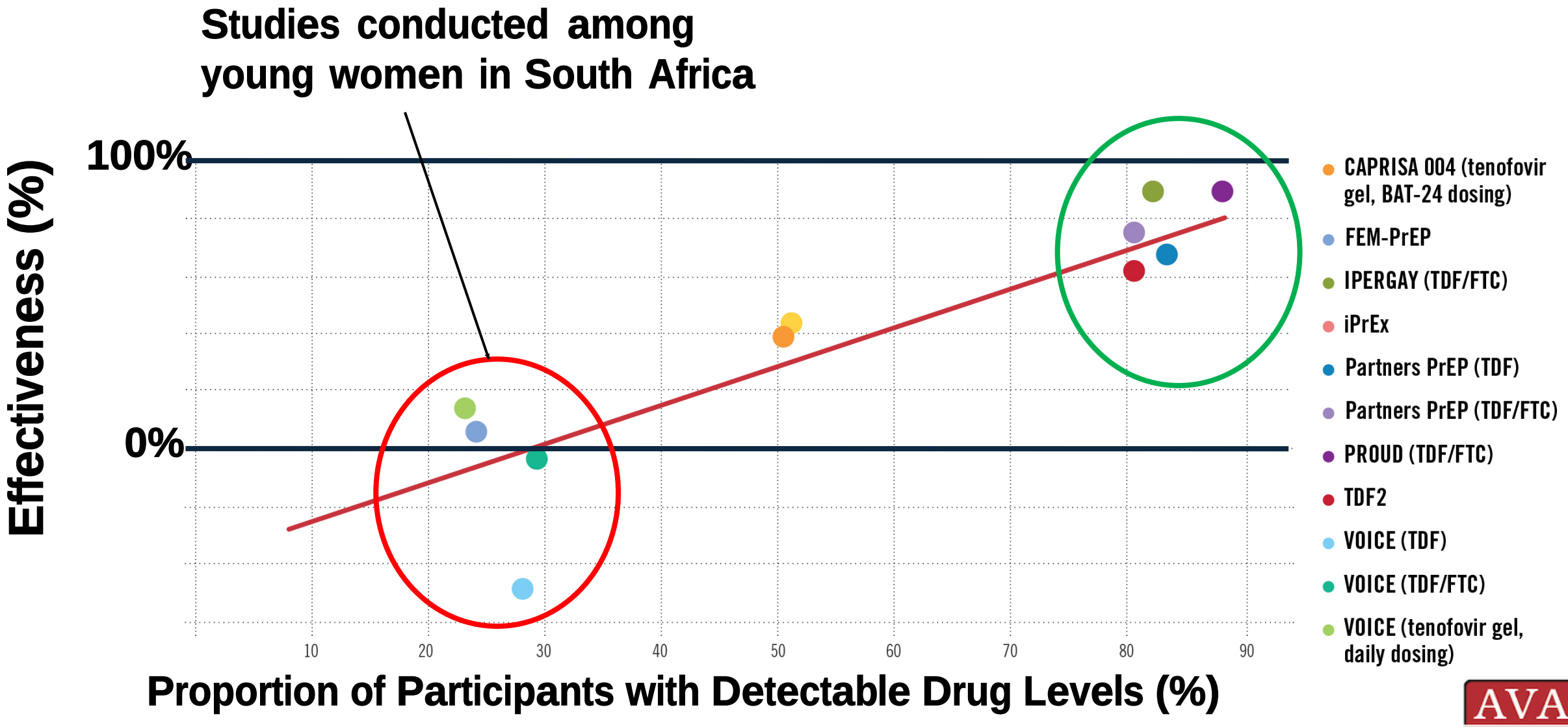
Jin & Ahmed et al., Lancet Glob Health, 2025

Why do we need **long-acting** PrEP?



AVAC
Global Advocacy for HIV Prevention

Why do we need **long-acting** PrEP?



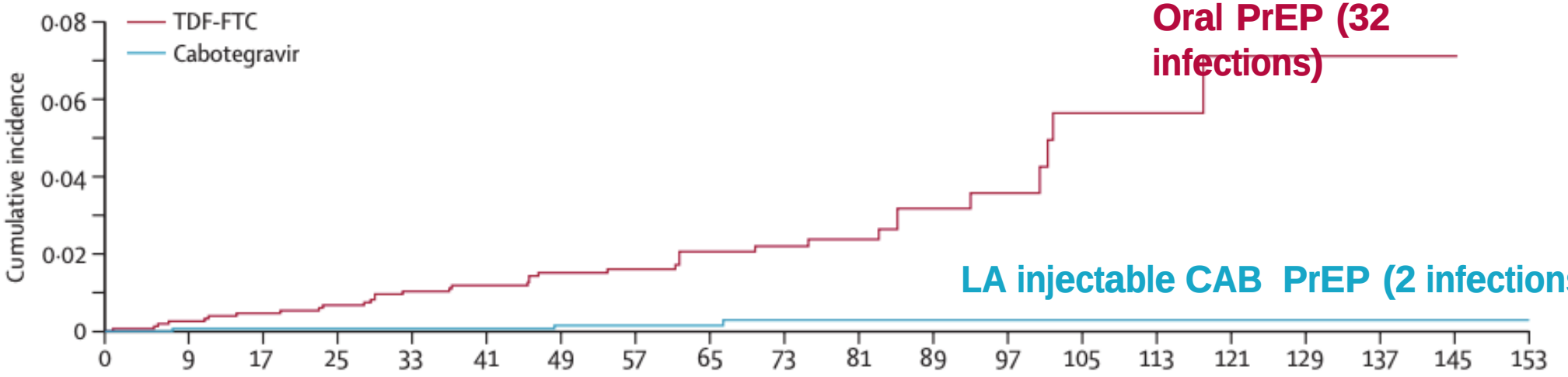
AVAC
Global Advocacy for HIV Prevention

Why do we need long-acting PrEP?

You know it's scary to hear that you will take tablets meant for HIV-positive people if you know very well that you don't have it. So that won't just be easy on you, even when you tell someone else that you are taking these kind of tablets they won't understand and they will think that you are lying and you have the disease…

Van der Straten et al, *PLoS One*,

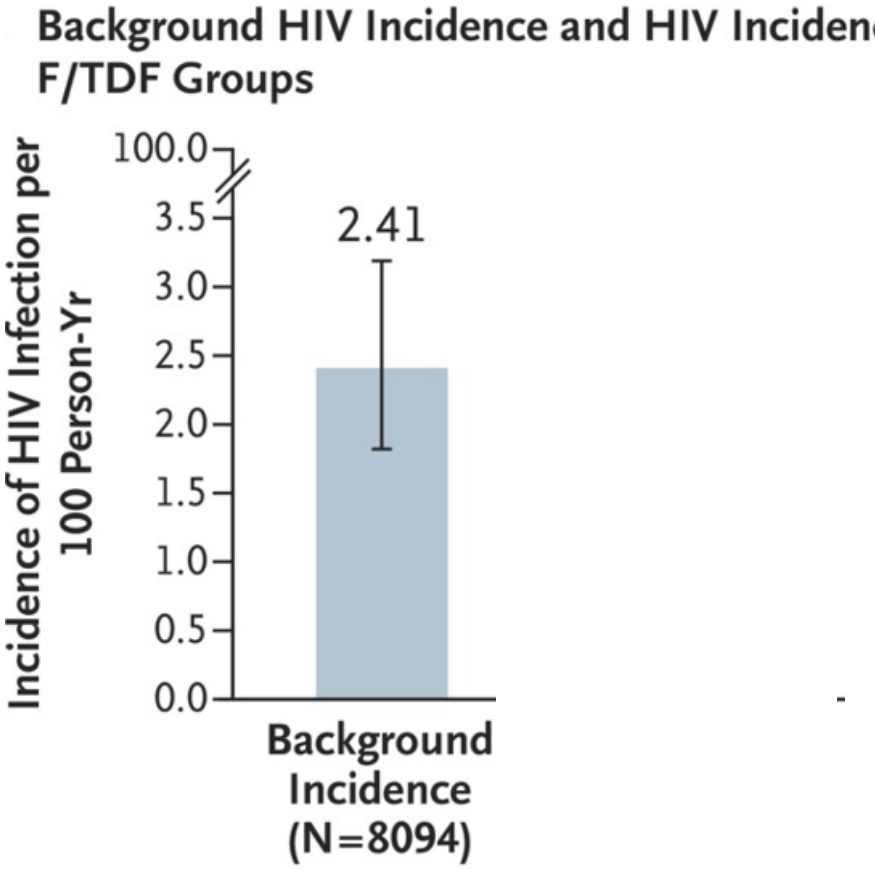
Why do we need long-acting PrEP?



Number at risk																				
TDF-FTC	1610	1490	1429	1410	1353	1260	1160	984	800	656	485	306	201	115	70	63	52	22	3	0
Cabotegravir	1614	1488	1441	1429	1371	1279	1181	988	801	647	482	304	204	116	67	58	50	23	3	2
Cumulative number of events																				
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4

Delany-Moretlwe et al., Lancet, 2022

Why do we need long-acting PrEP?



Becker et al., NEJM, 2024

Yeah, taking pills is very hard hey, especially if you are someone like me who is never home, no, it's quite difficult. MMM. You have to pack your bags and be somewhere, maybe with your friends, [be]cause a few of my friends know about it, but others they don't, I don't feel like they should know.

As I mentioned before, it's just a matter of getting my jab and going home. I do not have to carry anything else with me. This makes the injection different from pills which might get lost on the way, or which I might forget to take. I might travel to some place and forget to carry the pills with me. With the injection, I have no such pressures. After getting injected, it's done.

Chen-Charles et al, AIDS & Behav, 2025
Tolley et al, PLoS One, 2024

Why do we need long-acting PrEP?

- Because current HIV prevention methods are not sufficient
- Because LA PrEP works very, very well.
  - And, at least among many young women in Southern Africa, daily oral PrEP is not a preferred modality
- At prices ~R,1000/year, it is projected to save the health system money

Jin & Ahmed et al., Lancet Glob Health, 2025

Show of hands: Do we need LA PrEP in SA?

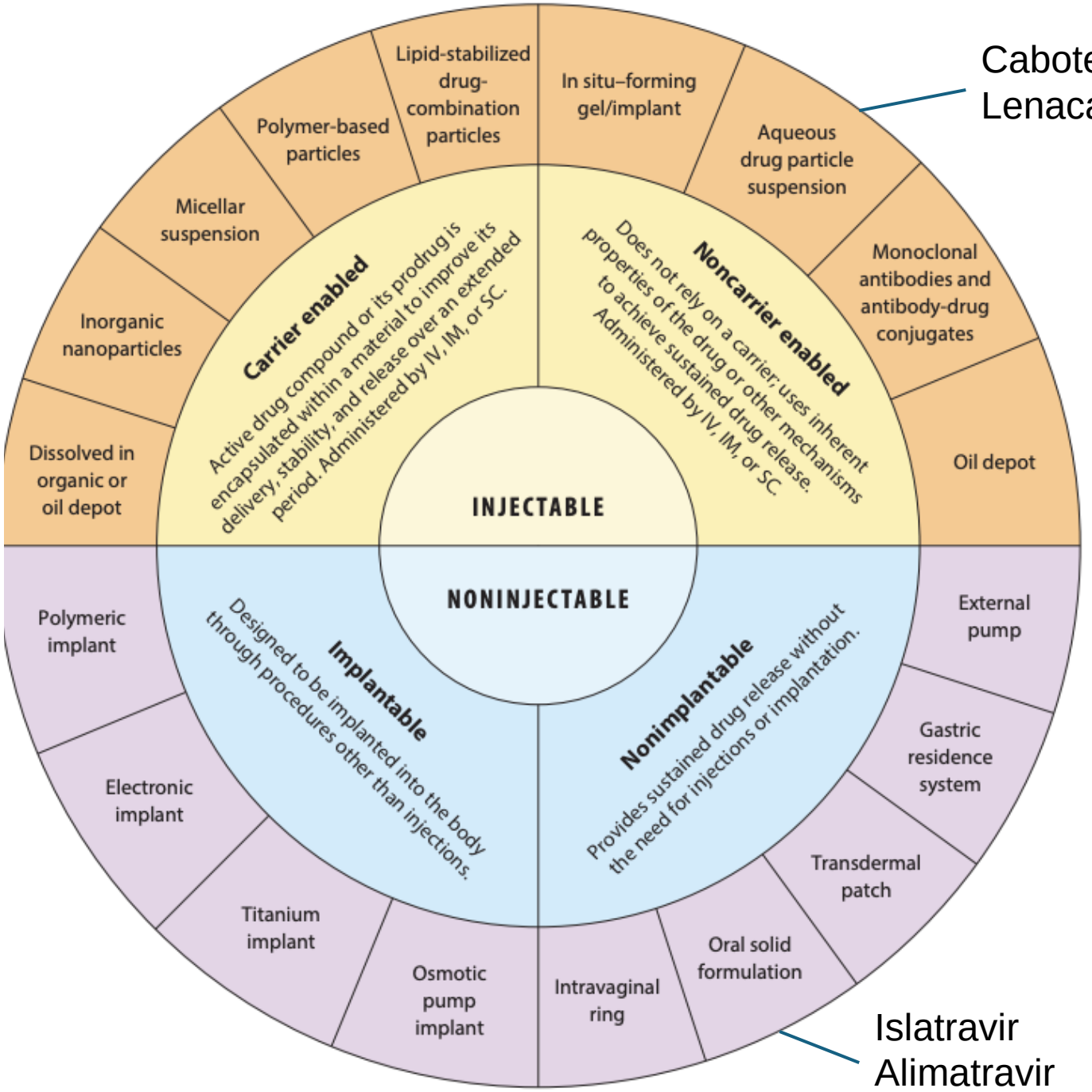


How the heck do LA injectables work?



How do long-acting injectables work?

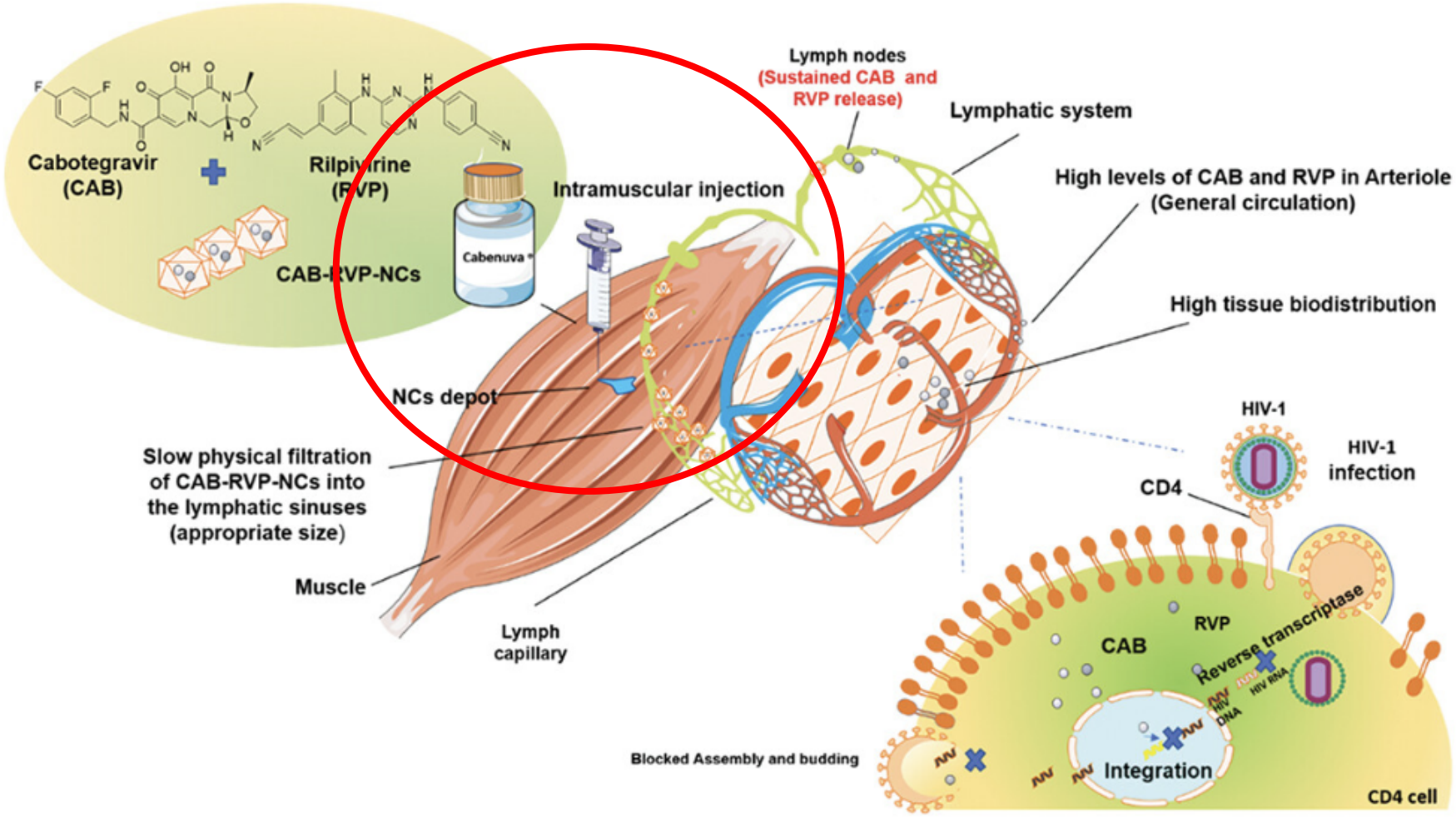
Ojaguju et al, Ann Rev Pharm & Tox, 2026



Cabotegravir
Lenacapavir

Islatravir
Alimatravir

How do long-acting injectables work?

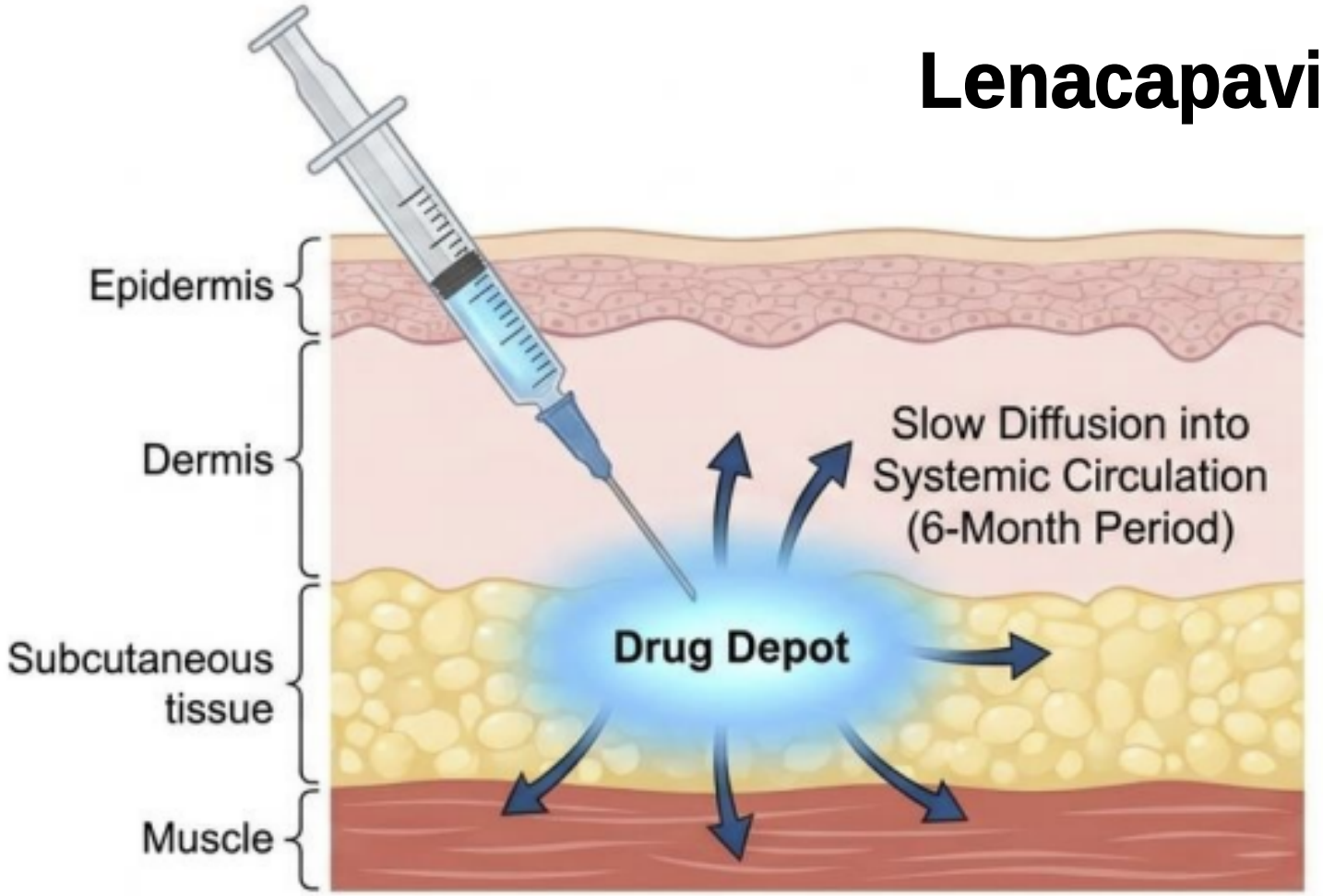


Magar et al, *Expert Op Drug Deliv*, 2025

Nayan et al, Adv Drug Del Rev, 2022

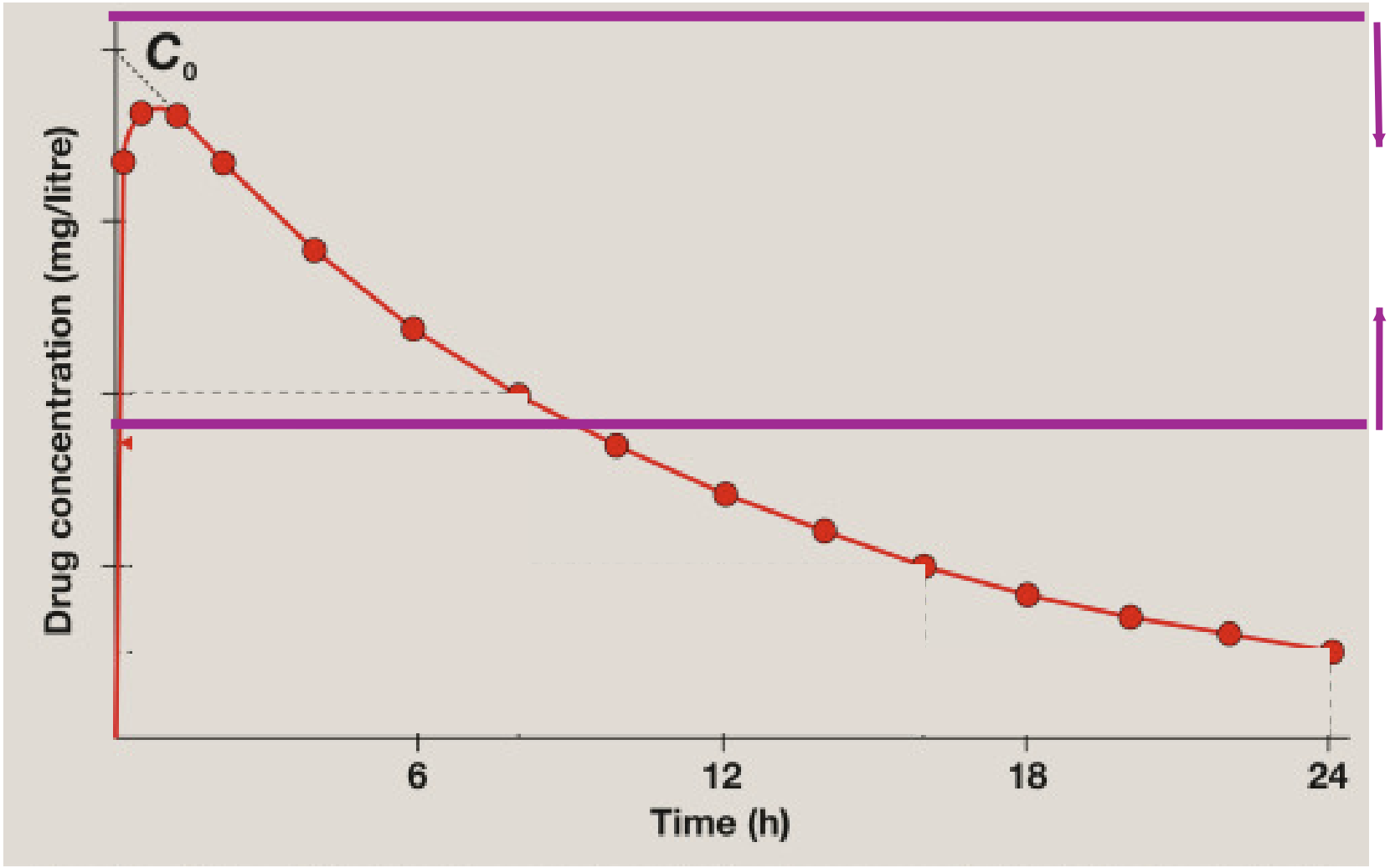
How do long-acting injectables work?

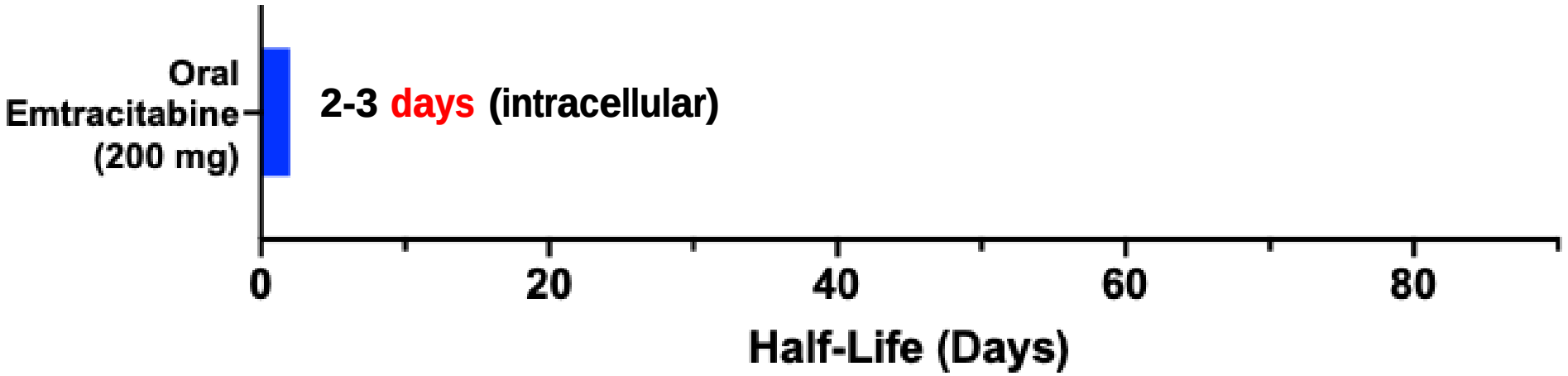
Lenacapavir



Magar et al, *Expert Op Drug Deliv*, 2025

Long-acting pharmacology in 5 minutes!




Oral
Emtracitabine
(200 mg)
2-3 days (intracellular)
0
20
40
60
80
Half-Life (Days)

How does long-acting PrEP work?

- Pharmacologically
  - By remaining active for long periods

- Logistically
  - By preventing the need for ~daily adherence
  - By removing the stigma of taking HIV medicines
  - By enhancing convenience

Jin & Ahmed et al., Lancet Glob Health, 2025

What LA PrEP options are there?

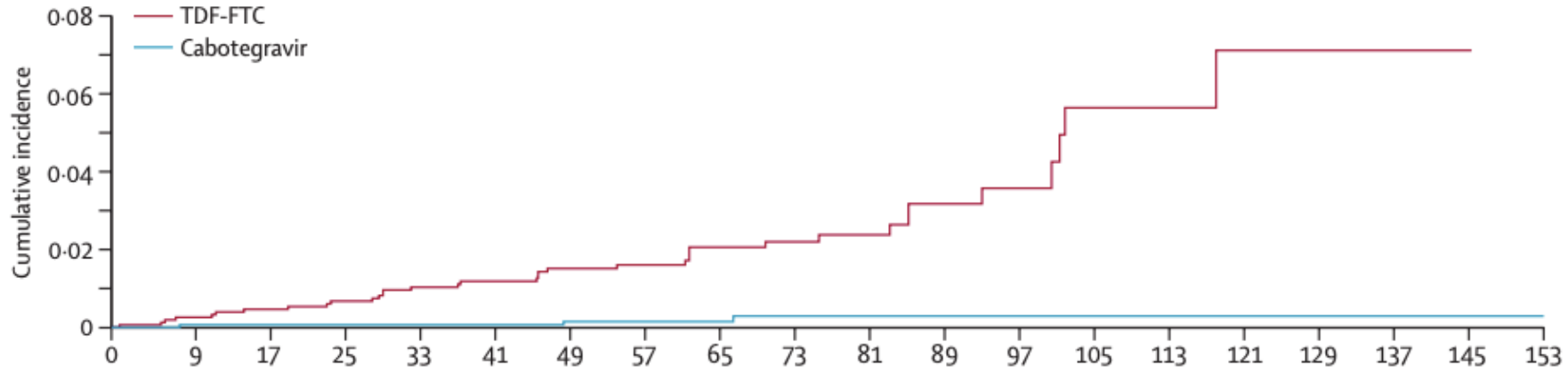
- **The graveyard of PrEP promise in SA**
  - ~~IM rilpivirine~~
  - IM cabotegravir?
  - ~~Oral islatravir~~
- **What is (mostly) available in SA and how do we use it**
  - Oral TDF/FTC
  - SC lenacapavir
- **What is (hopefully) coming down the pike**
  - (Even longer acting) SC lenacapavir
  - Oral alimatravir
  - …and more

Two-monthly IM rilpivirine

- Used as part of a long-acting treatment regimen in the United States
- Never truly advanced down the PrEP pipeline very far
  - Storage challenges
  - Resistance challenges (NNRTI cross-resistance)
  - Production and licensing challenges

Two-monthly IM cabotegravir

- HPTN 084 shows strong efficacy in reducing HIV infection compared to oral TDF/FTC among young women in South Af



Number at risk																				
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Delany-Moretlwe et al., Lancet, 2022

2022

SIGNIFICANT MILESTONE FOR HIV PREVENTION IN SUB-SAHARAN AFRICA AS SOUTH AFRICA GRANTS REGULATORY APPROVAL FOR APRETUDE

We are extremely pleased to share the news that, the South African Health Products Regulatory Authority (SAHPRA) has granted regulatory approval of *Apretude* (cabotegravir long-acting injectable), the first and only long-acting option for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

Approval of cabotegravir long-acting for PrEP in South Africa was supported by data from two international phase IIb/III multicentre, randomised, double-blind, active controlled studies, HPTN 083 and HPTN 084, which evaluated the safety and efficacy of cabotegravir long-acting for PrEP in HIV-negative men who have sex with men, transgender women, and cisgender women who were at increased risk of HIV. South Africa was the only country to take part in both studies. Regulatory submissions are currently underway in the other countries that took part in the HPTN083 and 084 studies.

South Africa bears the greatest burden of HIV worldwide and this is felt most significantly by women and young girls, where challenges with adherence, and stigma have hindered the potential impact of current PrEP are actively working with global partners to make *Apretude* an available prevention option for those who could benefit from PrEP. Following approval in South Africa, we look forward to seeing continued progress to help enable access.



Media contacts

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Senter

OR call +44 7796 707446

For US-specific media enquiries, email:
Rachel Jaikaran

OR call +1 9193578932

Two-monthly IM cabotegravir

OPINION FIRST OPINION

Tested in Africa, used in America

How can we end the practice of HIV wonder drug experimentation in Africa?

Get Alerts Save Share



A lab technician working with vials of lenacapavir, the new HIV prevention injectable drug, at the Desmond Tutu Health Foundation's Masiphumelele Research Site, in Cape Town, South Africa. Nardus Engelbrecht/AP

By Mark Siedner and Rochelle Walensky Sept. 18, 2024

Two-monthly IM cabotegravir

ViiV HEALTHCARE EXTENDS VOLUNTARY LICENSING AGREEMENT WITH MEDICINES PATENT POOL TO ENABLE ACCESS TO INNOVATIVE LONG-ACTING INJECTABLE HIV TREATMENT

- ***Agreement allows manufacturers to develop, manufacture and supply generic long-acting injectable cabotegravir (CAB LA) for treatment in 133 countries***
- ***Builds on the voluntary licence for CAB LA for HIV pre-exposure prophylaxis (PrEP), enabling increased access to innovative long-acting injectables for HIV treatment***

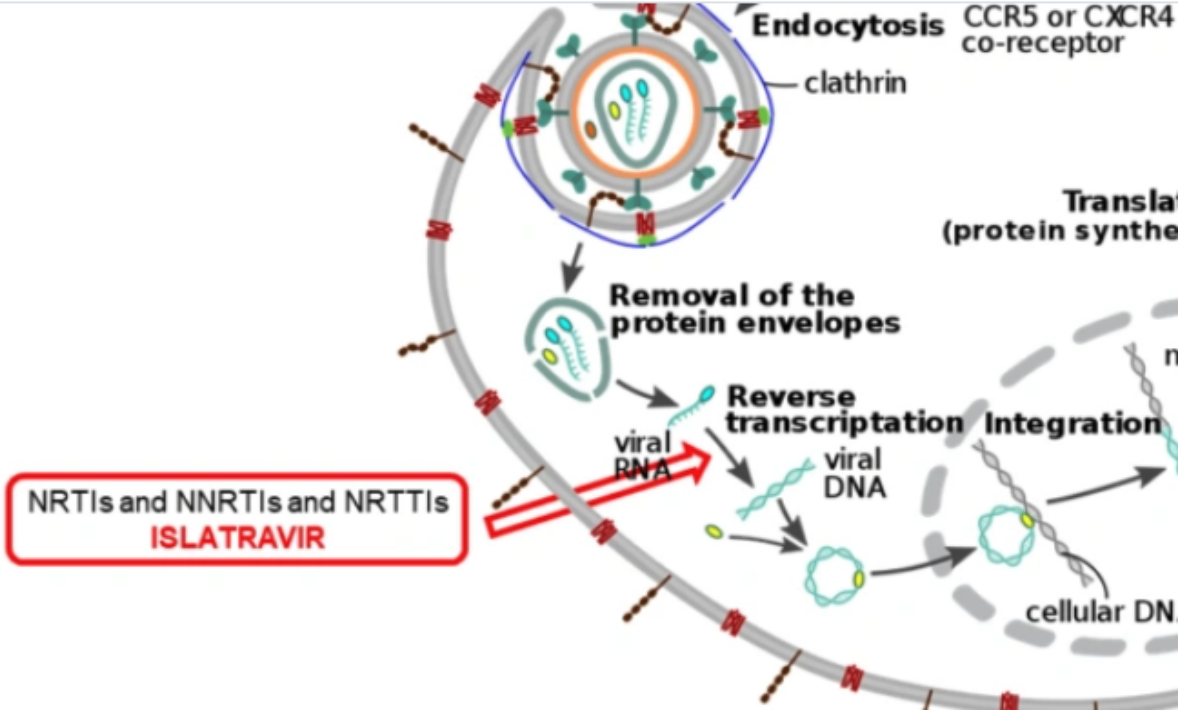
London, 14 July 2025 – ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer and Shionogi as shareholders, today announced an update to their voluntary licensing agreement with the Medicines Patent Pool (MPP) for cabotegravir to include patents relating to its use in a long-acting HIV

Media contacts

For our corporate press office, email: Kate Senter

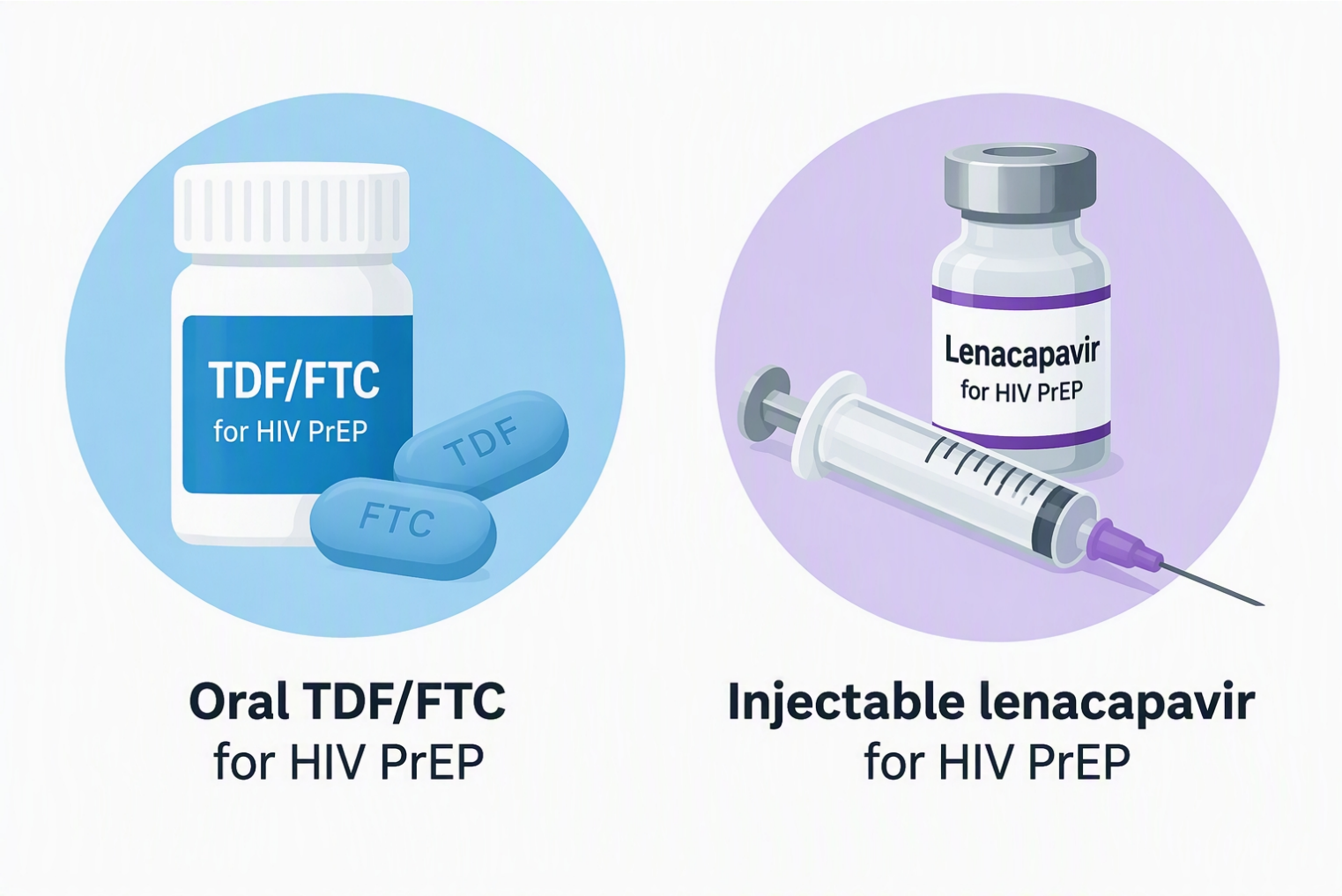
~~Monthly oral (and implantable) Islatravir~~

- Translocation inhibitor
- Extremely promising PK profile
  - Evidence of active levels in lymphocytes 4-8 weeks after final dosing in early-stage trials
- Phase III RCTs stopped due to finding of reduced lymphocyte counts in people taking islatravir
- Drug was abandoned as a PrEP agent (currently in use as weekly and daily agent for ART)



Plank et al, J Infect Dis, 2025

Where does that leave us



Show of hands: Have you prescribed oral PrEP?



A quick refresher on using PrEP



In whom should I use PrEP?

- **People at risk for HIV**
  - Adolescents and young adults
  - People with more than one partner or a history of STIs
  - HIV-negative members of sero-discordant partnerships
  - People who use drugs
  - Sex workers
  - Migrants
  - Men who have sex with men
  - Pregnant and breastfeeding women

https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

In whom should I use PrEP?

- **In whom should you <u>NOT</u> consider the use of PrEP?**

Any person requesting PrEP, even if the healthcare worker does not perceive her/him to be at substantial risk, should be considered for PrEP.

https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

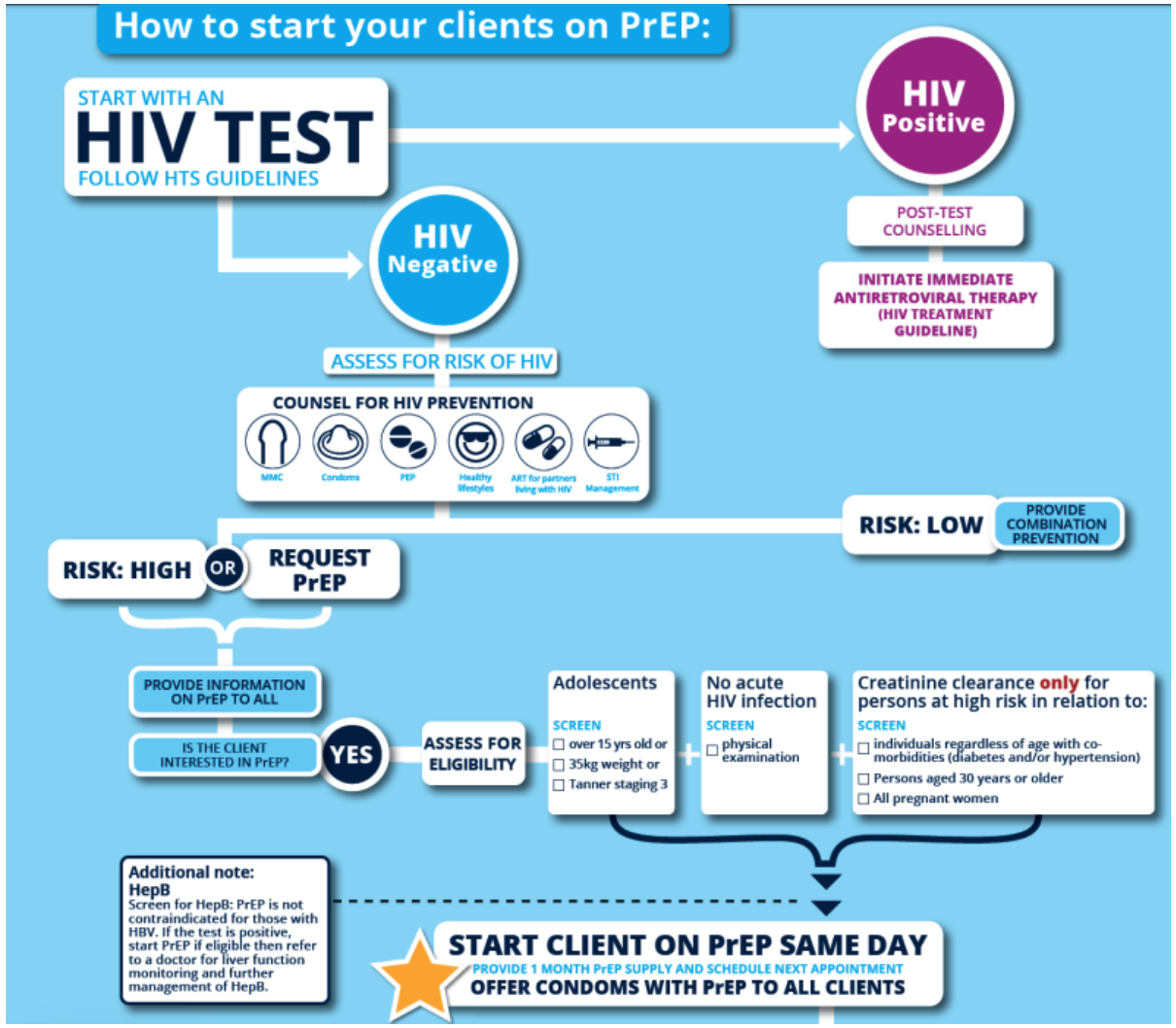
Who is *medically* eligible for PrEP?

- **Adolescents >35kg**
- **HIV uninfected (PrEP is not treatment)**
  - Rapid antigen test negative
  - No signs/symptoms of acute HIV infection (fatigue, fever, LAD, rash, sore throat)
- **No contraindications to the selected therapy (e.g., TDF/FTC, LEN)**

https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

Baseline evaluations before starting (oral) PrEP

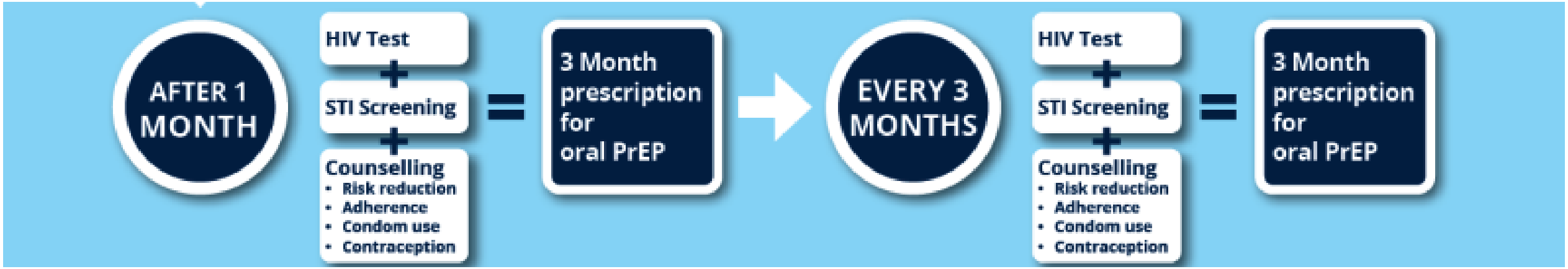
- HIV testing
- STI screening
- HBV sAg testing
  - Not a contraindication, refer to a physician
- Counseling on PrEP options
- Renal function (if >30 years old, pregnant, and/or known renal disease risk such as HTN or DM)
- **Start PrEP same day!**



https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

Maintenance of (oral) PrEP

- Return after **1 month**
- Then prescribe **3-monthly** with HIV and STI testing at each visit (and annual creatinine if high risk)



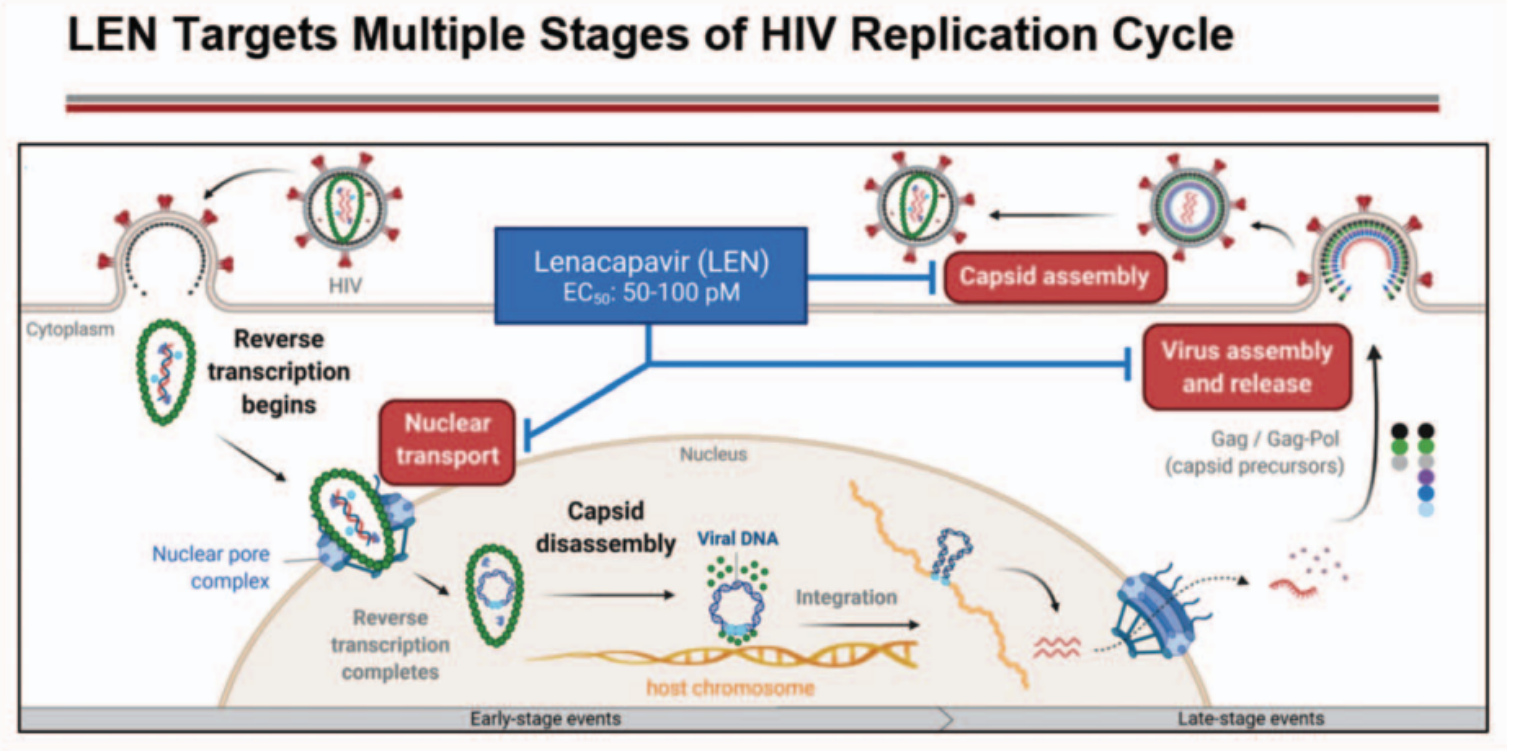
https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

Show of hands: Have you prescribed LEN?



Lenacapavir for HIV Prevention

- First-in-class capsid inhibitor
- Highly potent, acts at multiples stages of HIV life cycle
- No pre-existing drug resistance
- Extremely long half-life
  - Oral (10-12 days)
  - SC (8-12 weeks)



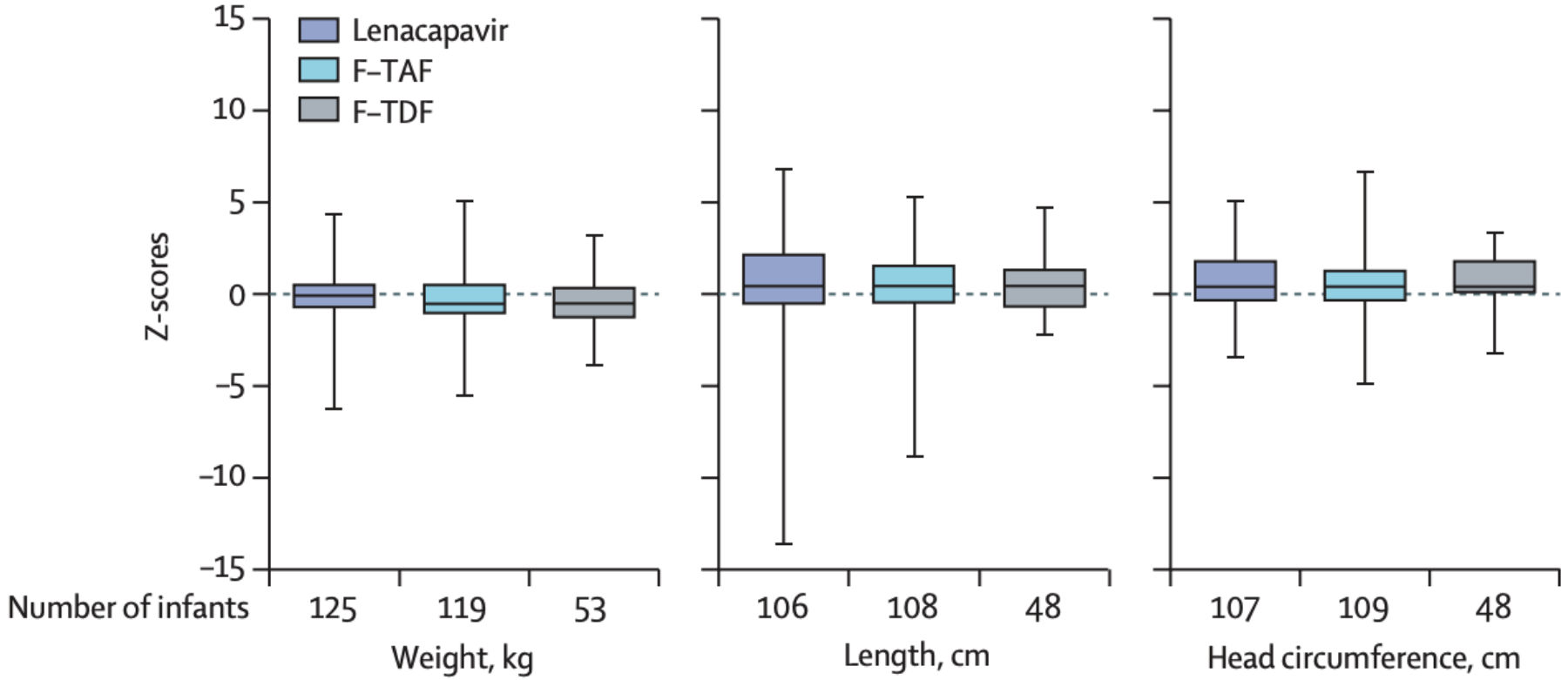
Di Perri et al, Inf Med, 2023
Dvory-Sobol et al, Curr Opin HIV/AIDS, 2021

What's **the same** about LEN for PrEP?

- **Eligibility: (mostly) the same!**
  - At risk or believes to be at risk for HIV
  - Confirmed HIV-negative adolescents (>35kg) or older
- **Screening and preparation: (mostly) the same!**
  - Rapid HIV testing (and confirmation of new acute HIV symptoms)
  - STI screening
  - HBV testing
  - Pregnancy testing
  - Counsel about all prevention options
- **Two points to keep in mind**
  - Few data on LEN use in people over 50
  - Creatinine monitoring is *not* required for LEN

What's **the same** about LEN for PrEP?

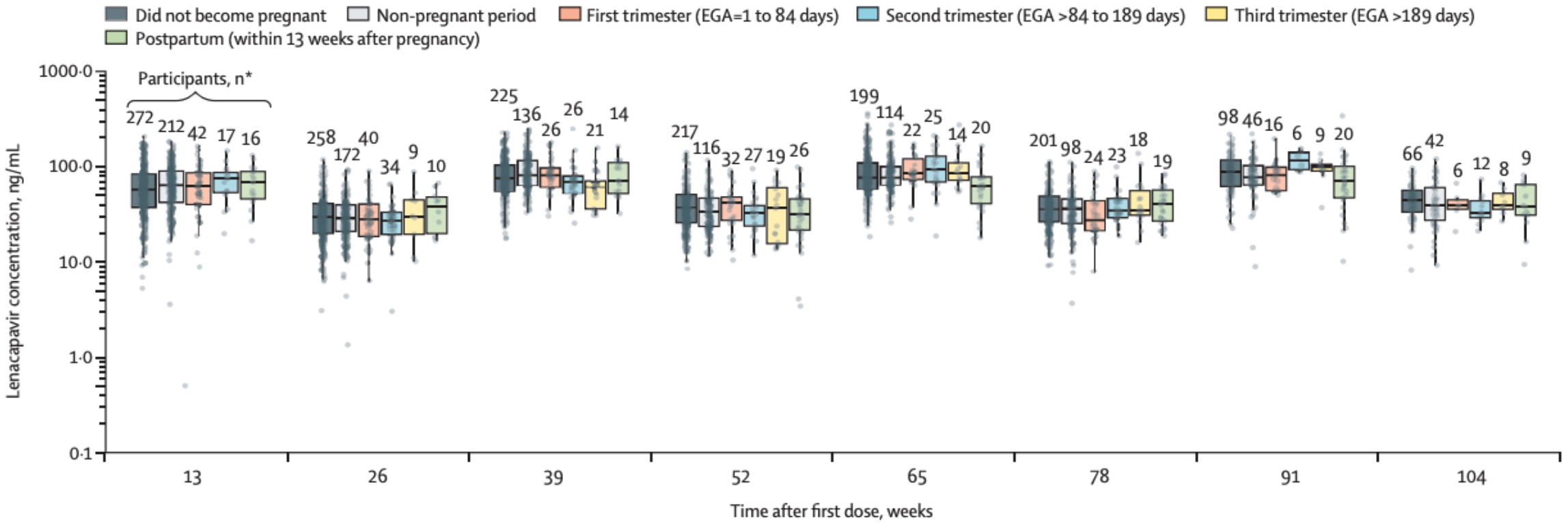
- **Efficacy and safety in pregnancy!**
  - PURPOSE-1 (SA PrEP Study) pregnancies: 184 (LEN), 208 (F-TAF), 95 (F-TDF)



Bekker et al, Lancet HIV, 2026

What's **the same** about LEN for PrEP?

- **Efficacy and safety in pregnancy!**
  - PURPOSE-1 (SA PrEP Study) pregnancies: 184 (LEN), 208 (F-TAF), 95 (F-TDF)



Bekker et al, Lancet HIV, 2026

What's **the same** about LEN for PrEP?

- **Efficacy and safety in pregnancy!**
  - PURPOSE-1 (SA PrEP Study)
  - HIV infections in newborns
    - LEN: 0/184
    - F-TAF: 4/208
    - F-TDF: 1/95

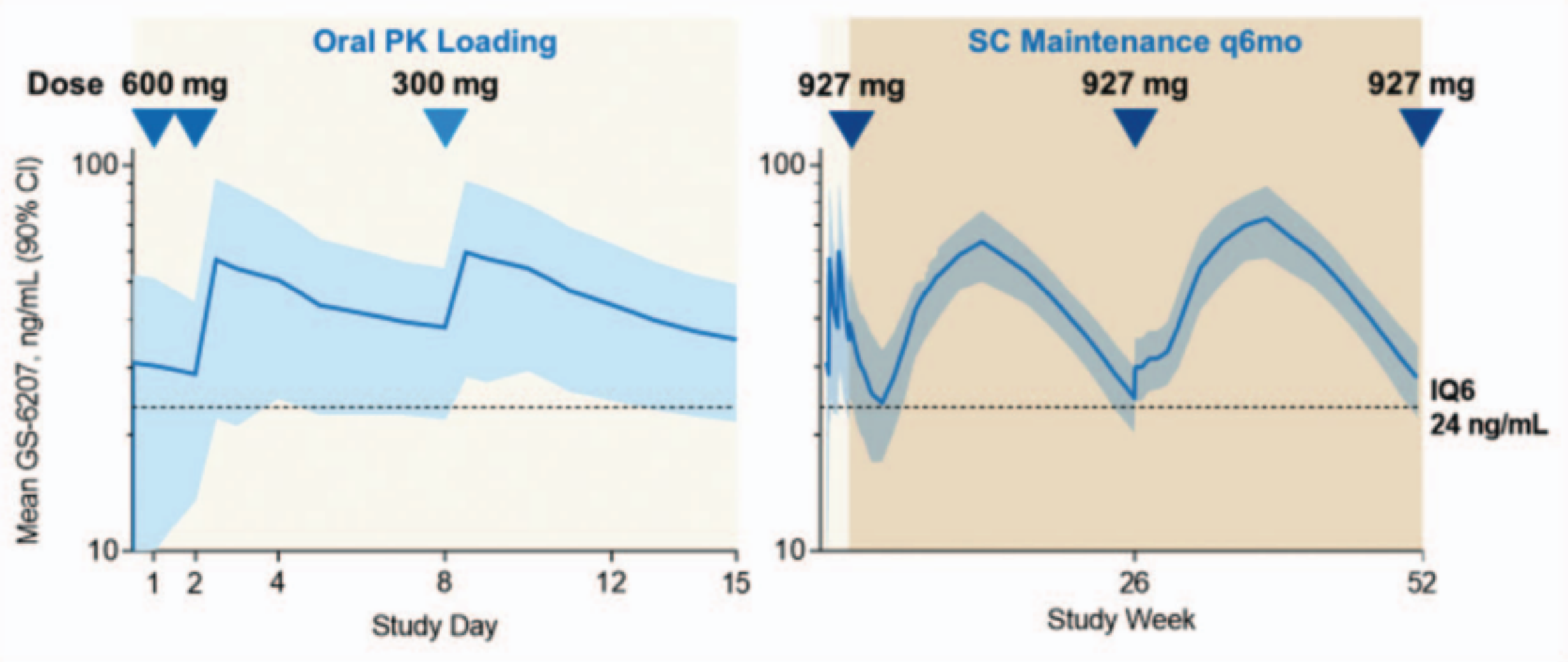
Bekker et al, Lancet HIV, 2026

What's **different** about LEN for PrEP?

- **Dosing and frequency of LEN**



*If next dose received within two weeks of the 6-month window (<28 weeks), no oral dosing need for subsequent



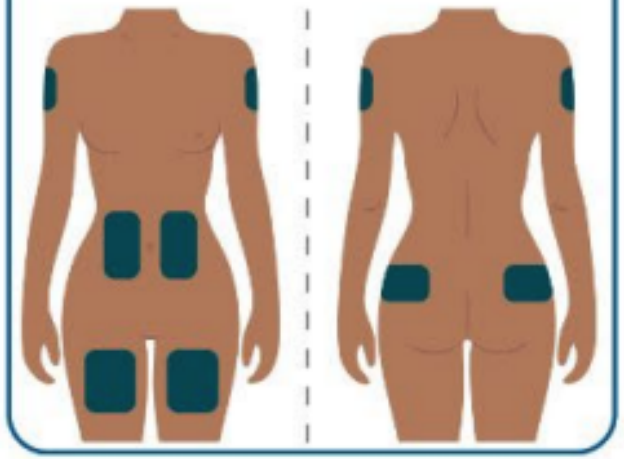
Dvory-Sobol et al, Curr Opin HIV/AIDS, 2021

You will need:

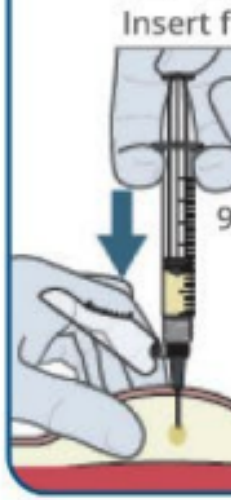
- Lenacapavir vials X 2
- 2.5ml syringes X 2
- 18 gauge withdrawal needles X 2
- 22 gauge (12.7 mm) injection needles X 2
- Alcohol wipes
- Gauze pads/ cotton balls
- Sharps container

Note: Any dose not administered within 2

6 **Possible injection site options - at least 5cms from navel (two injections should be at least 10cms apart), or buttocks**



7 **Inject 1.5ml of lenacapavir subcu**



8 **Administer 2nd injection**

Oral PrEP → LEN

Stop oral PrEP and initiate LEN as soon as possible or any time after. Advise client to use other prevention tools (condoms) for the first two days from initiation.

LEN → Oral PrEP

The last injections provides protection for six months, so it would only be necessary to initiate oral PrEP after the six months have passed.

PEP → LEN

Complete 28-day course of PEP, as per guidelines. Initiate LEN after an HIV-negative test result.

https://www.prepwatch.org/wp-content/uploads/2025/12/South-Africa-Lenacapavir-Guidelines-Dec-2025-Signed.pdf

What's **different** about LEN for PrEP?

- **Drug interactions (CYP3A4 metabolism)**
- **Rifampin**
  - Induces CYP3A4
  - Co-administration reduces LEN levels
  - Must start lenacapavir *prior* to starting rifampin
    - If already on rifampin, guidelines suggest use of an alternate agent until rifampin course is over

https://www.prepwatch.org/wp-content/uploads/2025/12/South-Africa-Lenacapavir-Guidelines-Dec-2025-Signed.pdf

Show of hands: Have you prescribed rifampin in someone taking LEN?



What's **different** about LEN for PrEP?

Rifampin co-administration



https://www.prepwatch.org/wp-content/uploads/2025/12/South-Africa-Lenacapavir-Guidelines-Dec-2025-Signed.pdf

What's **different** about LEN for PrEP?

- **Do not use if taking other CYP3A4 inducers:**
  - Carbamazepine (for epilepsy)
  - Phenytoin (for epilepsy)
  - Phenobarbital (for seizures)
  - St. John's Wort (herbal supplement)

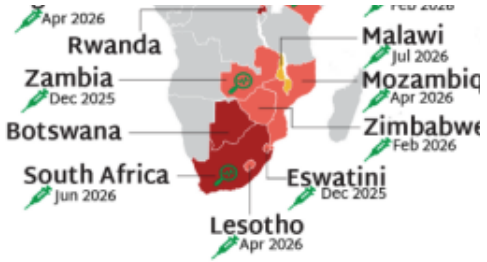
- **Select appropriate statin if indicated**
  - Atorvastatin, pravastatin, pivastatin do not interact with LEN
  - Simvastatin and lovastatin: start with low dose and titrate

Is it here for good (stay tuned)?

LEN FACILITIES BY PROVINCE

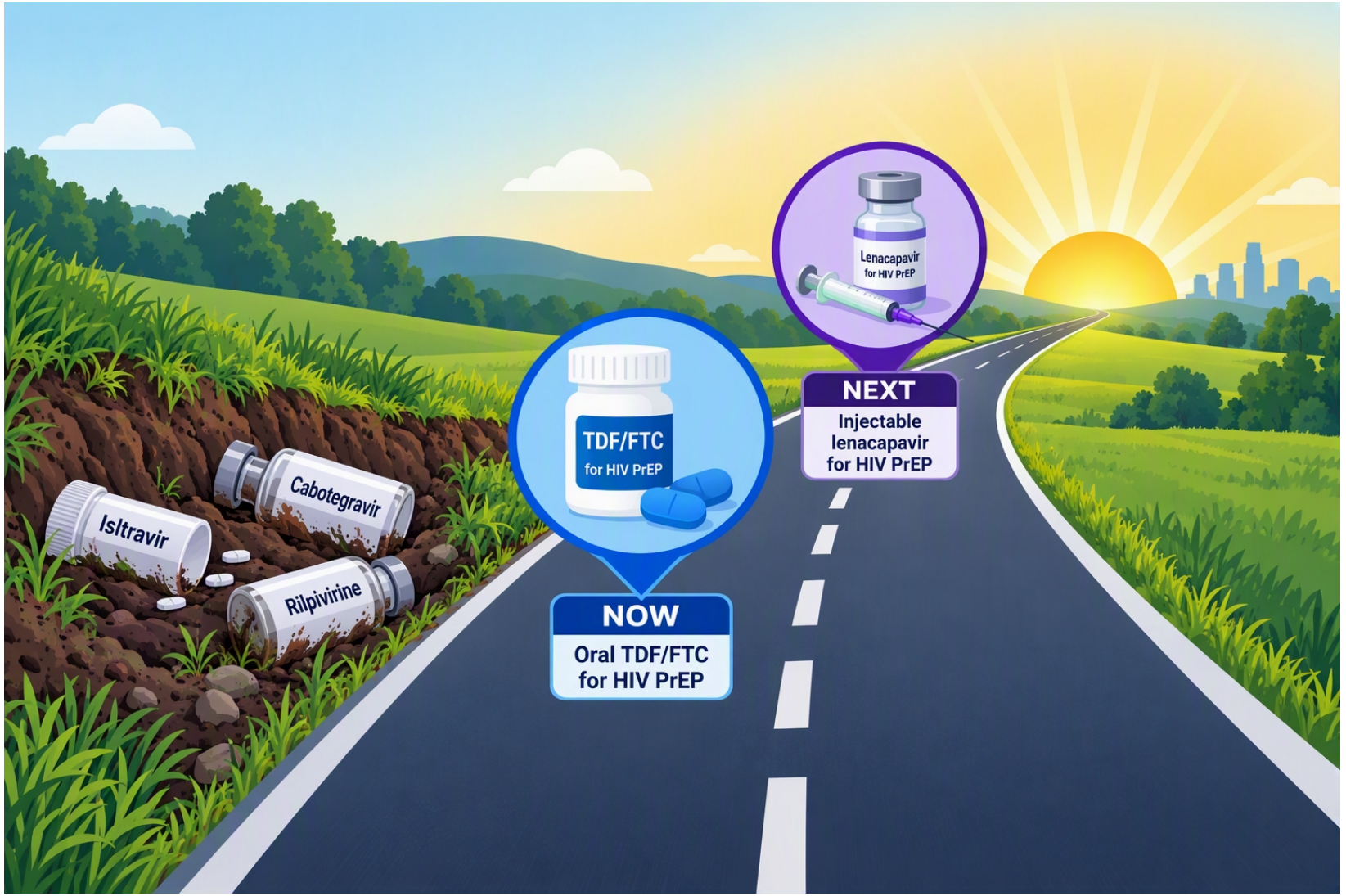
KWAZULU-NATAL.....2
EASTERN CAPE.....9
MPUMALANGA..... 12
GAUTENG.....15
NORTH WEST.....25
WESTERN CAPE.....28



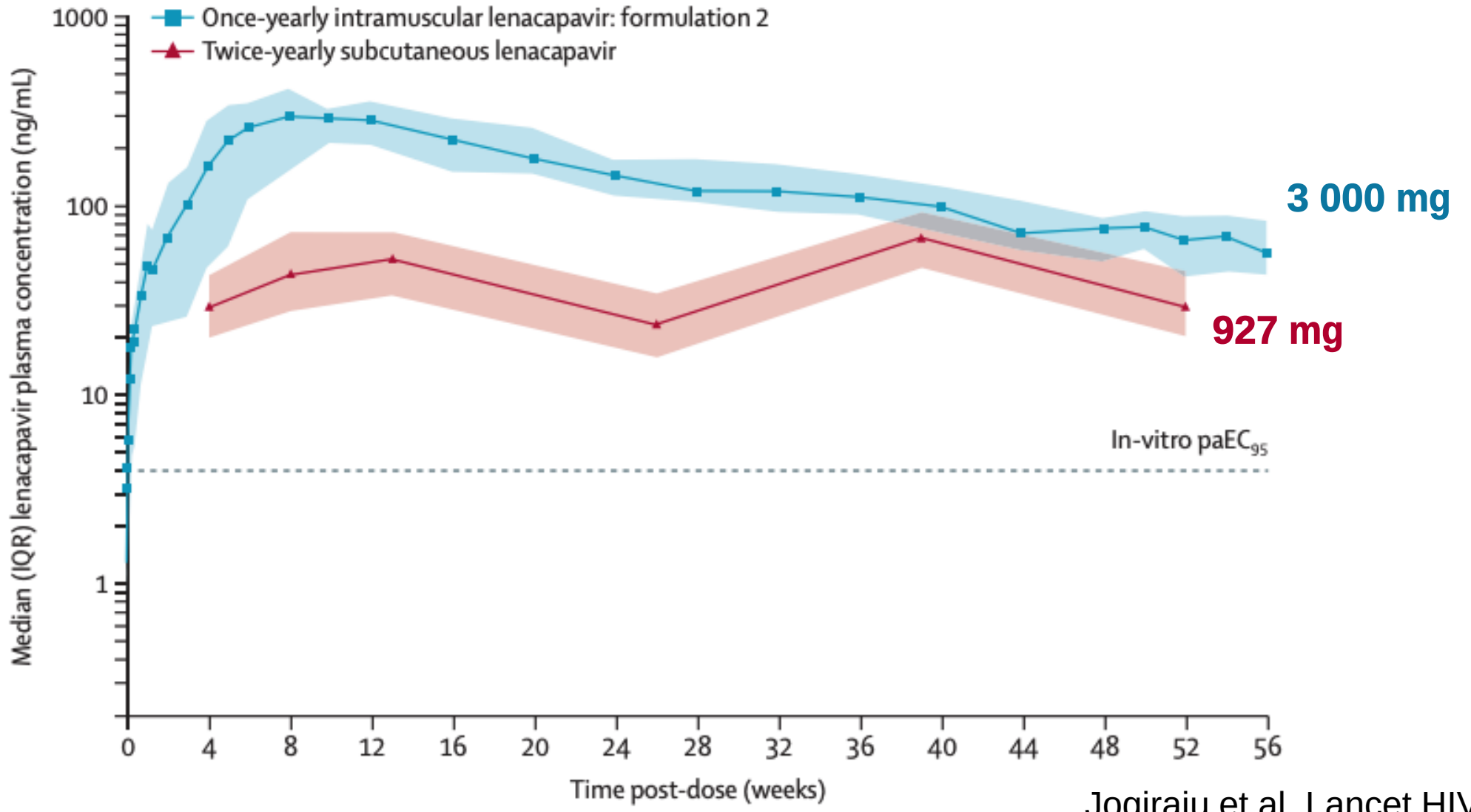


District	Facility Name	Address	Phone Number
KWAZULU-NATAL			
eThekwini Metropolitan Municipality	Goodwins Clinic	E942 Sidiya	0315032230
eThekwini Metropolitan Municipality	Ekuphileni (Umlazi L) Clinic	Cnr Kick Road	0319081212
eThekwini Metropolitan Municipality	KwaMakhutha Clinic	1364 Nana Gumede Road	0319051358
eThekwini Metropolitan Municipality	Mpumalanga Clinic	Meyiwa Main Road	0317720078
eThekwini Metropolitan Municipality	Prince Mshiyeni Gateway Clinic	V Section, Mangosuthu Highway	0319078111
eThekwini Metropolitan Municipality	Umlazi D Clinic	Cnr Asijiki and Siyavota	0319074777
eThekwini Metropolitan Municipality	Verulam Clinic	8 Wick Street, Verulam	0323221722
King Cetshwayo District Municipality	Richards Bay Clinic		0359075303
King Cetshwayo District Municipality	Eshowe Gateway Clinic	Kangela Street	0354734500
Ugu District Municipality	KwaMbunde Clinic	Ward 22, Madakane	0396877290
uMgungundlovu District Municipality	Azalea Clinic	Azalea Sport Complex	0333230006

What is coming down the pike?

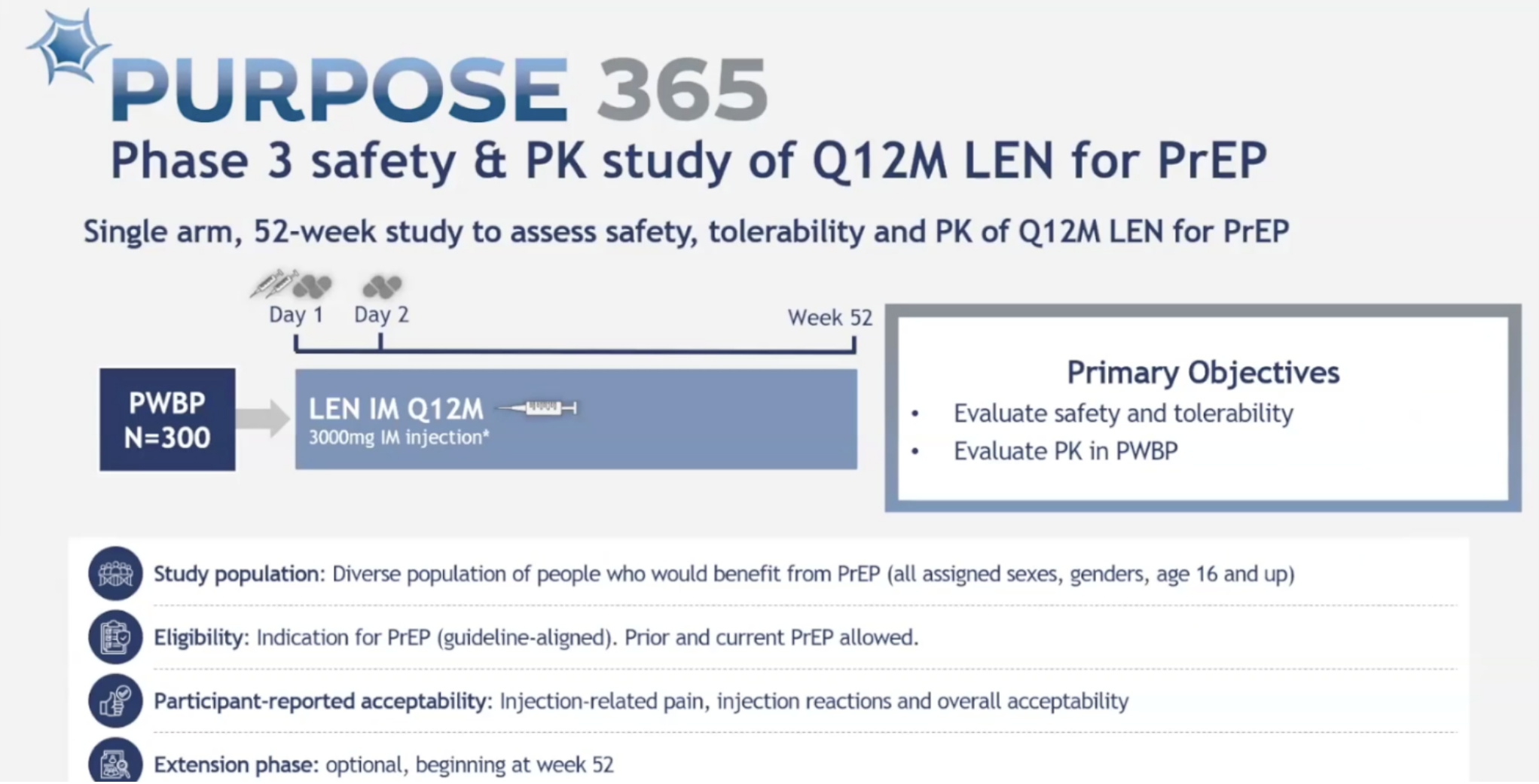


12-monthly lenacapavir



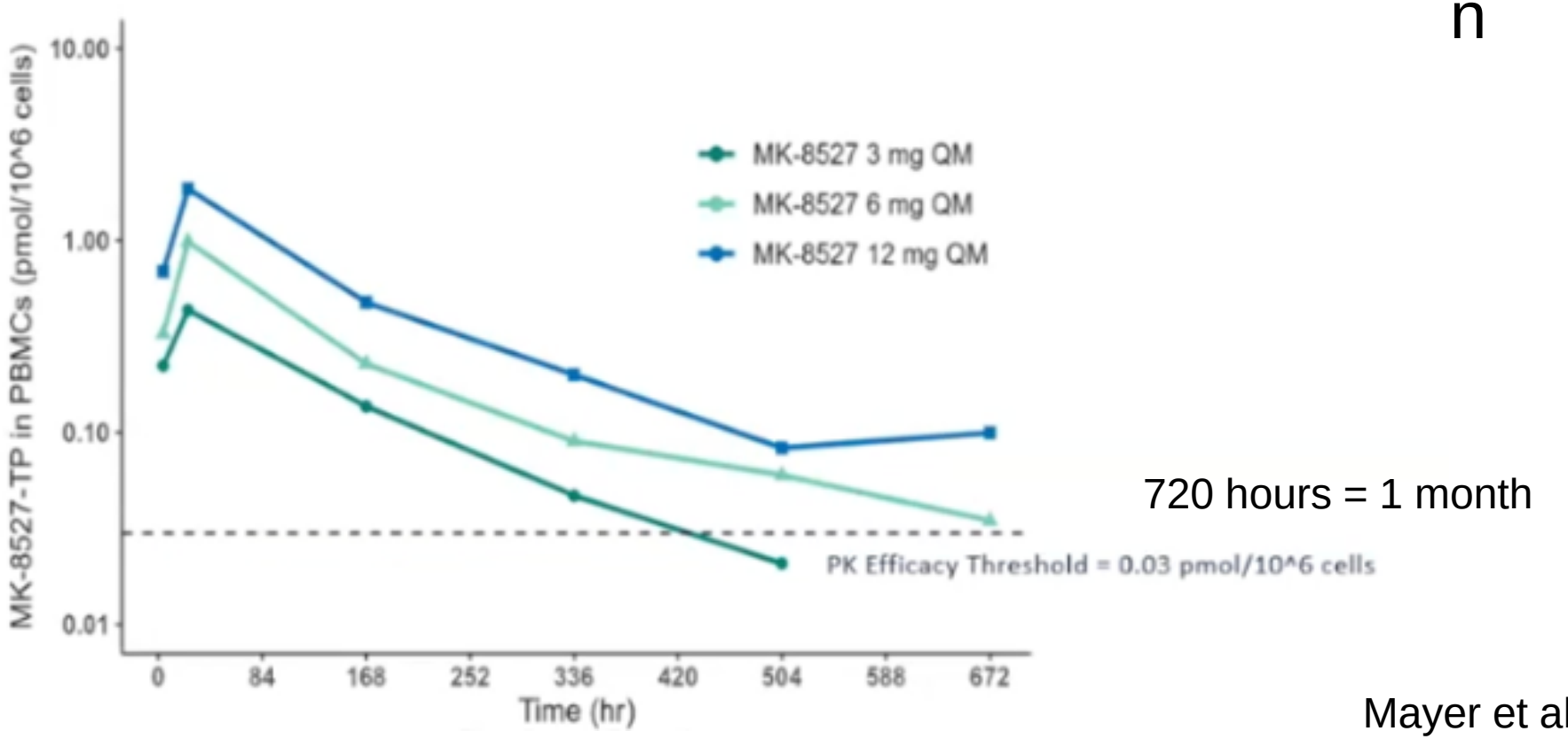
Jogiraju et al, Lancet HIV, 2025

12-monthly lenacapavir



Once monthly oral alimatravir

- Next-generation translocation inhibitor (same family as islatravir)
- Promisi[illegible] trials)



720 hours = 1 month

Mayer et al, IAS, 2025

Once monthly oral alimatravir



EXPrESSIVE

EXPrESSIVE-10	EXPrESSIVE-11
Adolescent girls and young women at greater likelihood of HIV-1 exposure	People at greater likelihood of HIV-1 exposure
N ~4,580	N ~4,390
Enrolling in Kenya, South Africa and Uganda	Enrolling Across 16 countries
Includes data generation in adolescents (from age 16) and pregnancy and lactation	Includes data generation in adolescents (from age 16)

Evaluating efficacy, safety and tolerability of monthly oral MK-8527 compared to daily FTC/TDF

Once monthly oral alimatravir

MSD

MSD Announces Initial Access Plans for Alimatravir, an Investigational Once-Monthly Oral HIV Pre-Exposure Prophylaxis in Phase 3 Development

July 24, 2026 7:58 am EDT

HIV long-acting therapeutics landscape

Formulations, regimens and compounds in the HIV long-acting space (selected). A selection of investigational and approved assets for treatment and/or prevention are shown, with live counts for the current selection.

Agent	Indication	Phase I 2	Phase I/II 1	Phase II 7
C 10E8.4/iMab	Both	●		
C CAP256V2LS (mAb)	Both			●
C fremocapavir (VH-499)	Both			●
C PGDM1400 (mAb)	Both		●	
C PGDM1400LS (mAb)	Both			●
C PGT121.414.LS (mAb)	Both			●
C VH-280 (VH-4004280) Discontinued	Both			●
C VH-310 (VH-4367310; cabotegravir stearate; XVIR-110)	Both	●		
C VRC01 (mAb)	Both			●
C VRC07-523LS (mAb) (TMB-380)	Both			●

https://lapal.ch/hiv-dashboard

Can we foresee a future of HIV PrEP for all who need it?



Can we foresee a future of HIV PrEP for all who need it?

- **We know how and where people want PrEP access**
  - Convenience
  - Low-cost or free access (including transportation and time away from work, school, family support)
  - Stigma-reducing options (eg LA formulatins)
  - Socially acceptable options (barber shops, pharmacies)

Deitrich et al, BMC Health Serv Res, 2021
Martin et al, AIDS & Behavior, 2025
Bassett et al, JAIDS, 2026

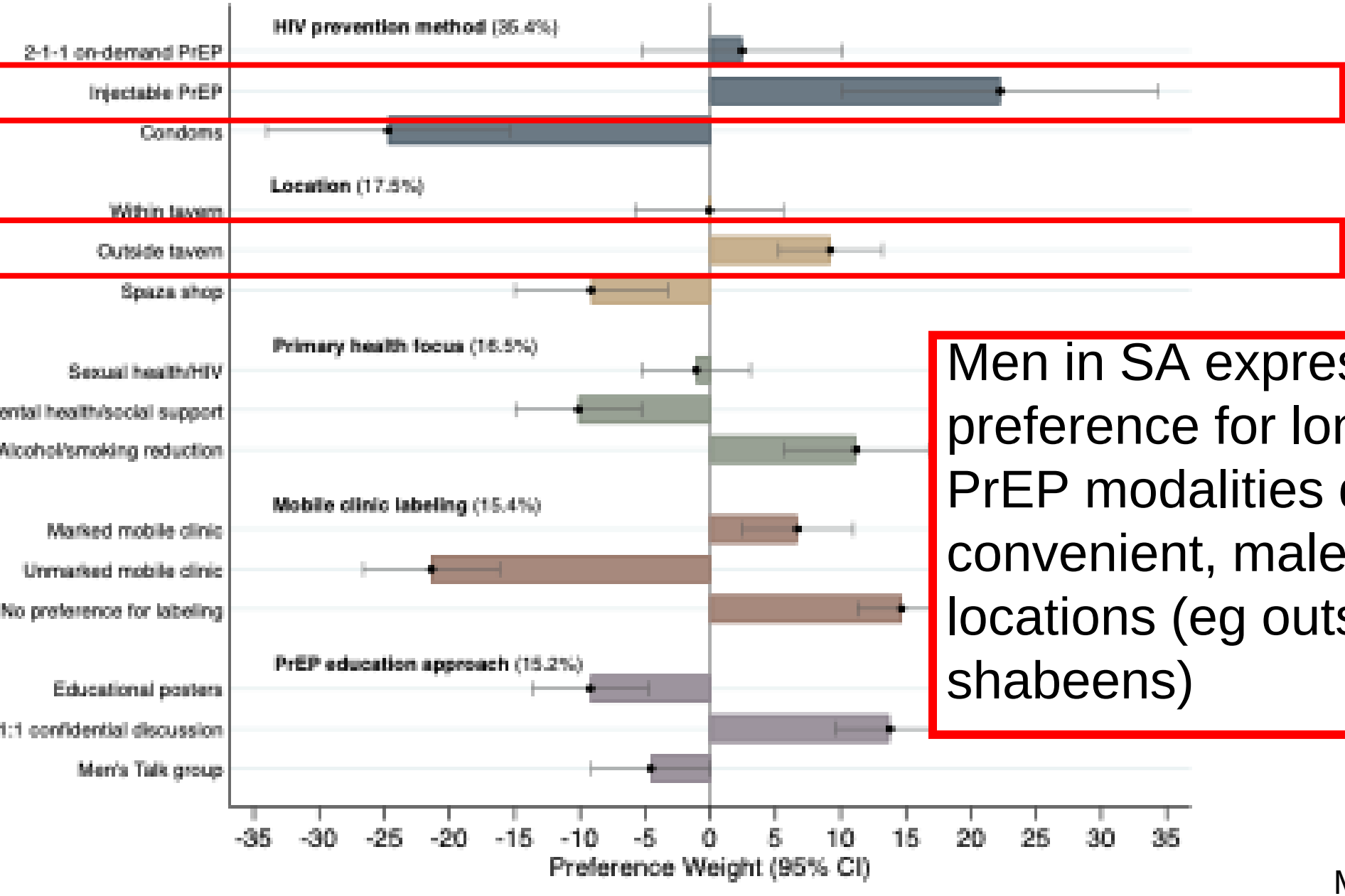
GLOBAL HEALTH: SCIENCE AND PRACTICE
Dedicated to what works in global health programs
OPEN ACCESS

PROGRAM CASE STUDY

Reaching Men and Women Through a Decentralized Mobile Service Delivery Model for HIV Prevention and Pre-Exposure Prophylaxis Services in South Africa

Pelisa Nongena,[a,*] Catherine E. Martin,[a,*] Lorrein S. Muhwava,[a] Fatima A. Cholo,[a] Glory Chidumwa,[a] Maserame V. Mojapele,[a] Vusile Butler,[a] Saiqa Mullick[a]

Nongena et al, Glob Health Sci & Pract, 2026



Men in SA express a preference for longer-acting PrEP modalities delivered in convenient, male-friendly locations (eg outside shabeens)

Montgomery et al, JAIDS, 2021
Castle et al, Under review

Can we foresee a future of HIV PrEP for all who need it?

- **How and where are we providing PrEP in practice?**

Insanity is doing the same thing over and over again and expecting different results

Thank you for your attention!

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