3rd Long-Acting HIV Treatment and Prevention Conference

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SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

A warning sign or manageable risk?

Emerging resistance in LAIs

Jeremy Nel

Division of Infectious Diseases
University of Witwatersrand &
University of North Carolina

Outline

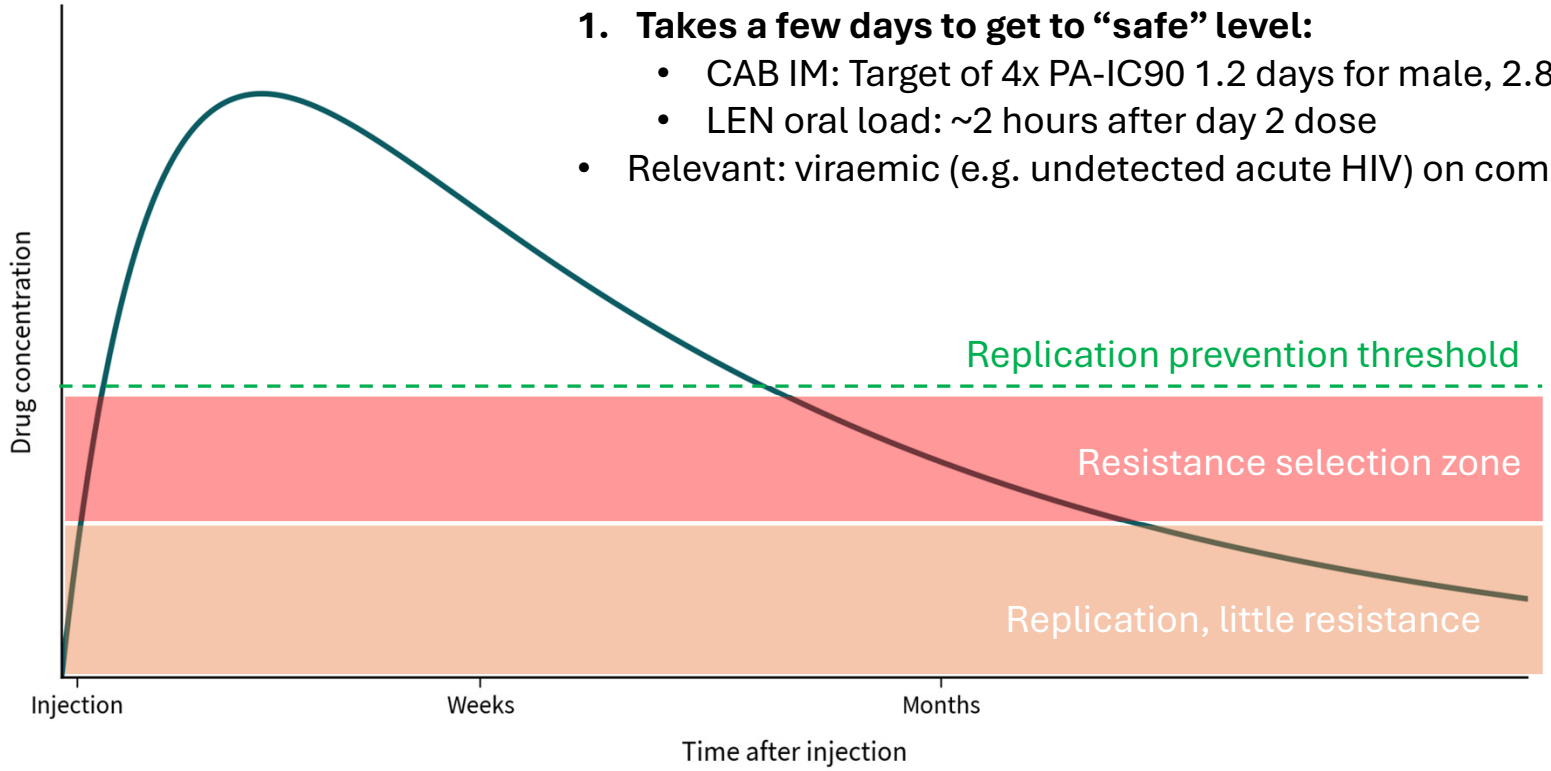
- What's the worry?
- What we have seen so far?
- What we might see in the future?
- How relevant is it?

What’s the worry?

What might we expect to see, on first principles?

Resistance in LAIs

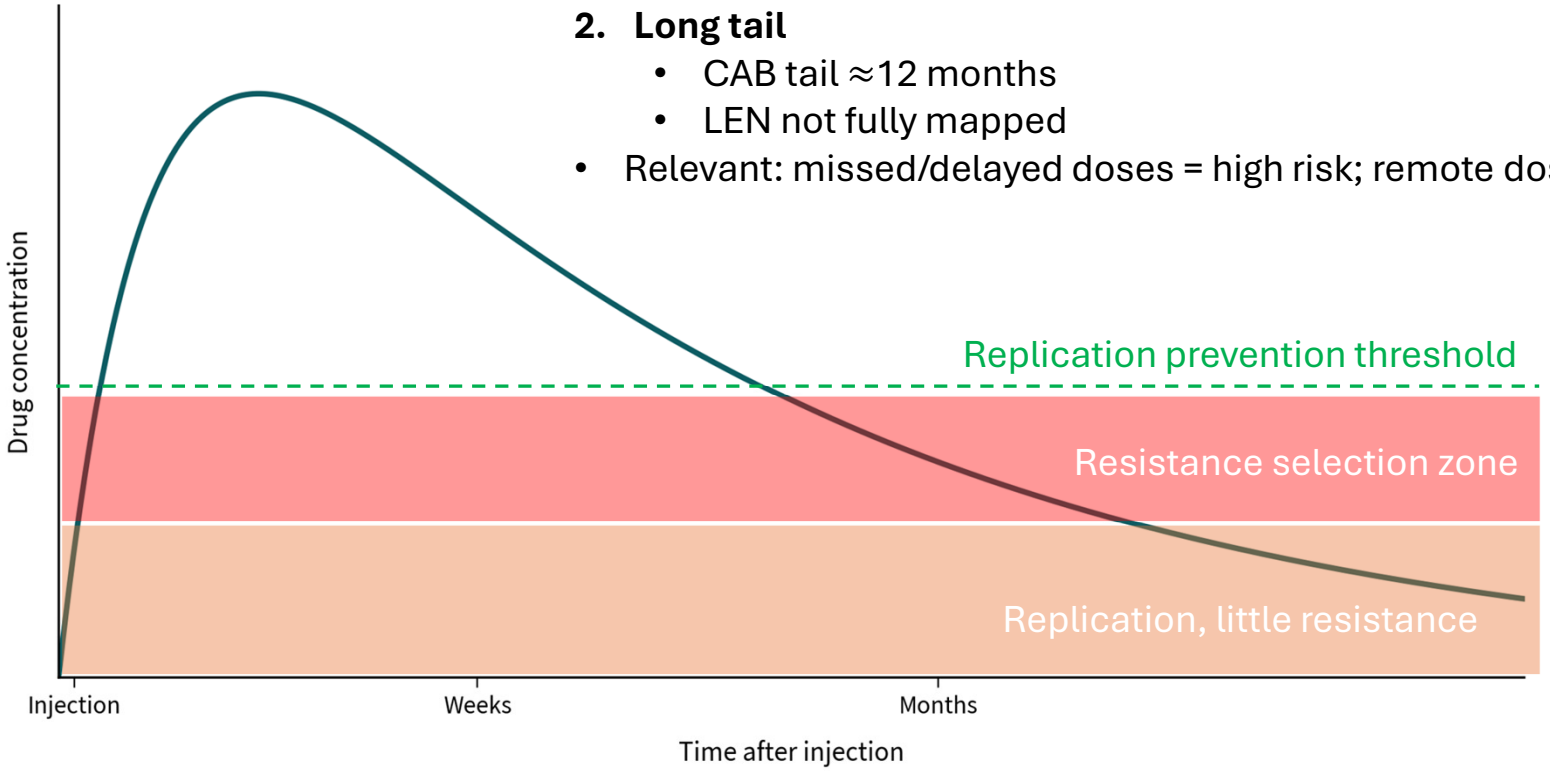
1. **Takes a few days to get to "safe" level:**
   - CAB IM: Target of 4x PA-IC90 1.2 days for male, 2.8 days for female.
   - LEN oral load: ~2 hours after day 2 dose
- Relevant: viraemic (e.g. undetected acute HIV) on commencement = risk



"flip-flop" kinetics: terminal phase of the concentration-time profile attributable to drug absorption, not drug elimination

Resistance in LAIs

2. **Long tail**
   - CAB tail ≈12 months
   - LEN not fully mapped
- Relevant: missed/delayed doses = high risk; remote doses = lower risk



Made worse by

PrEP: delayed diagnosis - LEVI syndrome (CAB)

ART: two tails aren’t locked together

What have we seen so far?

HPTN 084 (women)

- 4 VF cases originally (1 baseline + 3 incident)
- Another 2 cases in unblinded year after that
- Zero on-time breakthroughs; 3334 person years
- **Overall incidence = 0.18 / 100 PY**
- **Major InSTI resistance in 0/6 incident cases.**

AIDS 2022, Montreal, abstract #OALBX0108

HPTN 083 (MSM & trans women)

Combined blinded + first unblinded year

CAB arm	
Participants contributing follow-up	**2,244**
Person-years	**4,660**
Incident infections (efficacy analysis)	**0.54 / 100 PY**
All CAB-arm infections characterized (includes baseline infections)	**34**
Major INSTI RAMs	**10 (29%)**

Antimicrob Agents Chemother. 2023 Apr 18;67(4):e0005323
Lancet HIV. 2023 Dec;10(12):e767-e778

HPTN 083

Group	n	Major INSTI RAMs
A — occult/baseline	4	1
C — oral lead-in	3	2
D — on-time injections	6	6
DX — ≥1 injection ≥10 weeks late	3	0
BR — CAB restarted after a gap	2	1
B — first positive ≥6 months after last injection	16	0
Total	**34**	**10**

Lancet HIV. 2023 Dec;10(12):e767-e778

LEN as PrEP

Trial	Population	LEN incident HIV
PURPOSE 1	Cis women, SA/Uganda	0 / 2,134
PURPOSE 2	MSM / TG / GNB	2 / 2,179

Both PURPOSE 2 incident cases had N74D despite on-time injections and good LEN levels

Another 4 in each trial had unrecognised HIV at baseline → 4/8 developed N74D

J Infect Dis. 2026 Jan 17;233(1):e203-e211

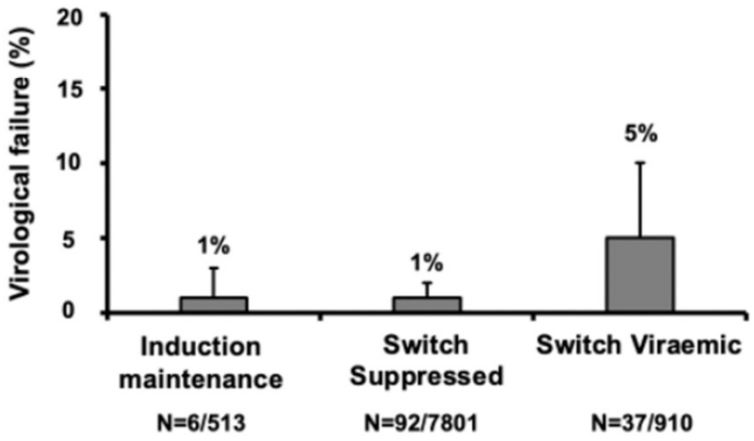
What we know: CAB/RPV as ART

Clin Infect Dis. 2025 Sep 16;81(2):274-285

- 2025 meta-analysis (Navarro et al.): observational and interventional studies.
- VF and treatment-emergent INSTI resistance at ~48 weeks (range 24–52).

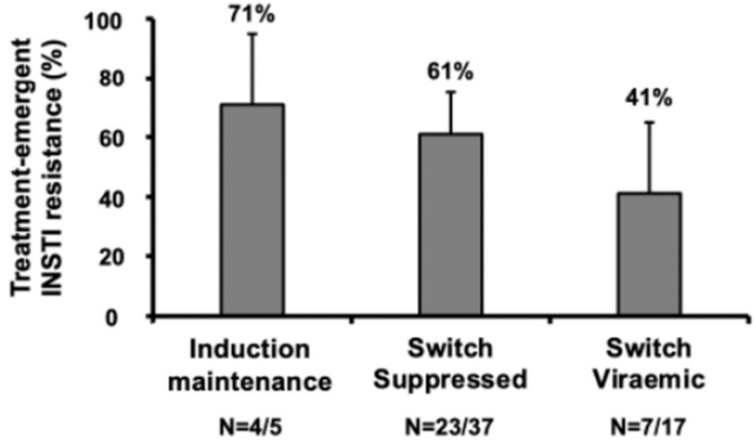
Outcome 1:
Protocol-defined Virological Failure

33 studies | **9224 participants**



Outcome 2:
INSTI-resistance at failure (in successful genotypes)

19 studies | **5662 participants**



64% of INSTI drug resistance mutations identified conferred high-to-moderate levels of DTG cross-resistance

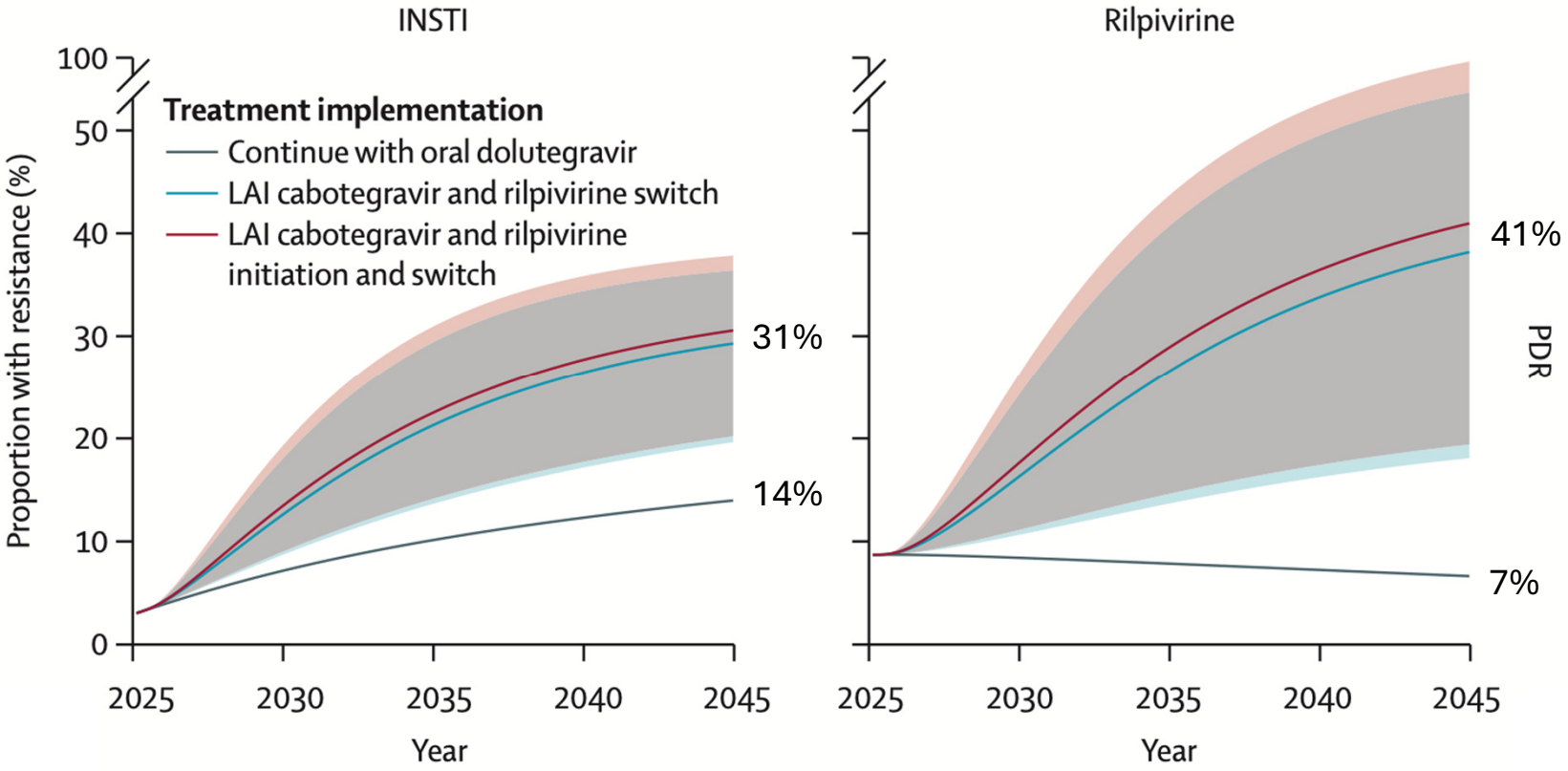
What might we see in the future?

SA modelling

- **Modelled effect of introducing LAI CAB/RPV in SA from 2025-2045.**
- **2 CAB/RPV strategies vs DTG-based oral therapy:**
  - CAB/RPV switch for those with viral suppression
  - CAB/RPV as initiation and switch
- **CAB/RPV coverage capped at 10, 30%, and 50%.**

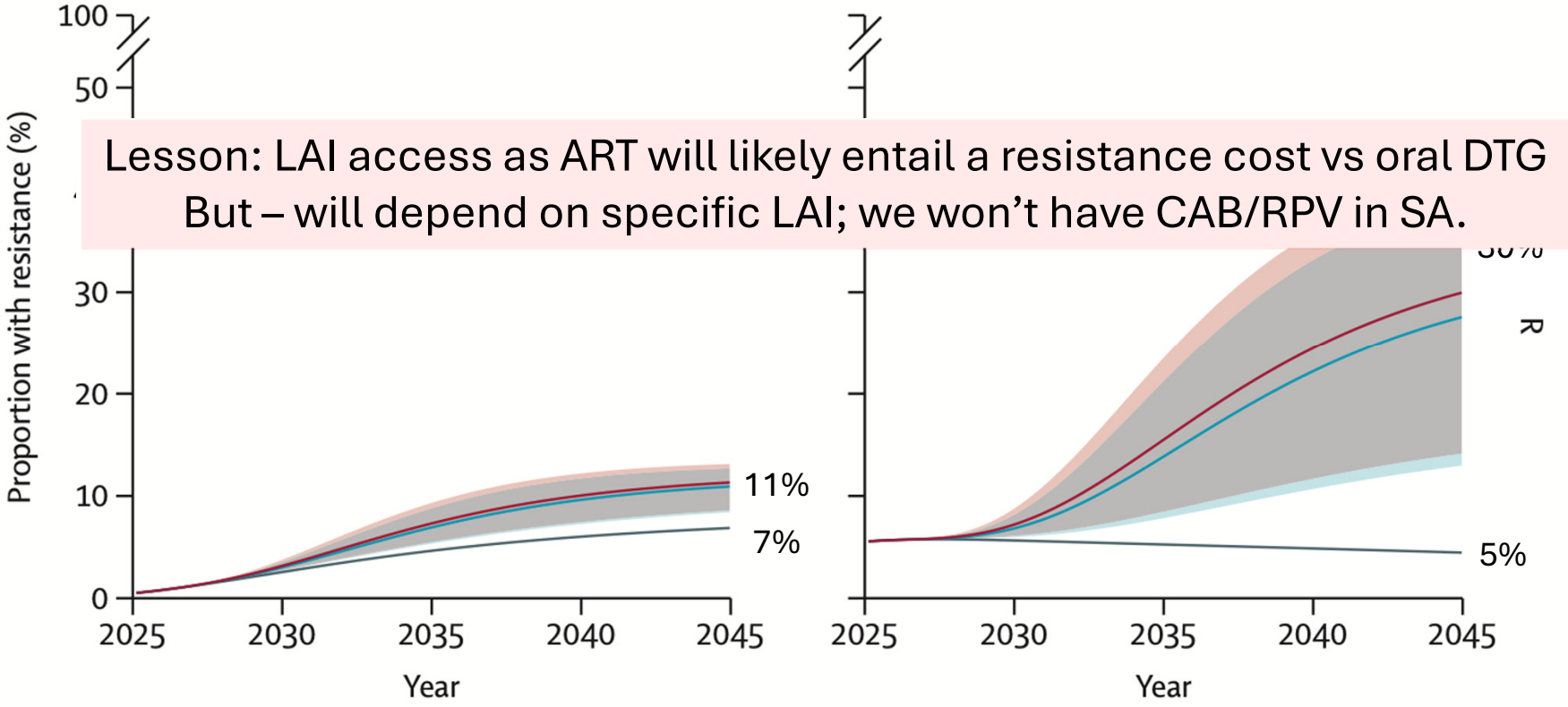
Lancet Glob Health 2025; 13: e2133–43

SA modelling – pre-treatment drug resistance



Lancet Glob Health 2025; 13: e2133–43

SA modelling – transmitted drug resistance



Lesson: LAI access as ART will likely entail a resistance cost vs oral DTG
But – will depend on specific LAI; we won't have CAB/RPV in SA.

Lancet Glob Health 2025; 13: e2133–43

Why worry?

How relevant is this?

If you get resistance

CAB	cross-resistance[1] to DTG in 1/3 (PrEP) to 2/3 (ART)	**No DTG-based therapy (TLD, etc.)** **No dual therapy** **Need PI**
RPV	cross-resistance[2] to DOR in ~60%	**No oral RPV options** **DOR could be important for future regimens** (DOR/ISL, DOR/DTG, etc.)
LEN	no cross-resistance	**No ISL/LEN option** **Future capsid inhibitor options?**

1. Clin Infect Dis. 2025 Sep 16;81(2):274-285. 2. Clin Infect Dis. 2026 Jul 8;82(6):1023-1031

Conclusions

LAIs are such good drugs; **incident drug resistance is very low because incident HIV (PrEP) and virological failure rates (ART) are low.**

- Unrecognised infection at 1st injection = main thing we should prevent

Unlikely to change rapidly in SA because of very limited LAI access (apart from LEN).

If resistance does develop, it has important implications for future regimens, though these are **mostly manageable**.

- A person who seroconverts on LEN can get TLD (different from many CAB PrEP failures).