Long-acting ART- Real World Evidence

Mina John

Royal Perth Hospital & PathWest, Medical Genomics, Murdoch University Perth, Western Australia.

Disclosures: ViiV, Gilead

Why is real world evidence important?

Advantages

- Evidence beyond drug registrational requirements
- Generalizability of RCT findings
  - Underrepresented populations
    - Women, pregnant, young/old, CALD
    - Social-determined vulnerability
  - Different 'routine' health settings/teams
  - Greater medical complexity
  - Extended indications
- Pharmacovigilance
- Durability of efficacy/effectiveness
- Optimize health resource allocation

Challenges

- Rigor/standardization observed in RCTs
- Greater LTFU, incomplete data,
- Biases/confounding factors in analysis
- Less funding/infrastructure support

Effectiveness; LA Cabotegravir + rilpivirine

n>16,000 including RCT and RWD, ~5 year f/u

OPERA[1]

N=3,304*
24 Months
Median follow-up not reported

95%
(n=1,229)‡

virologic suppression

2%
(n=25/1293)Δ
VF

CARLOS[2]

N=351*
Month 24

97.7%
(n=343)‡

virologic suppression

1.9%
(n=7/351)Δ
VF

BEYOND[3]

N=308*†
Month 24

97%
(n=155/160)‡§

virologic suppression

1.4%
(n=3/204)Δ
Among those treated inconsistent with label: 0/62
VF

COMBINE-2 C2C[4]

N=956*
Median follow-up
10.2 months

99%
(n=925/937)‡

virologic suppression

0.5%
(n=5/956)Δ
VF

SPLASH[5]

N=370*
48 weeks

99%
(n=167/169)¶

virologic suppression

1%**
VF

JABS[6]

N=54*
48 weeks

98%
(n=53)#

virologic suppression

0%††
VF

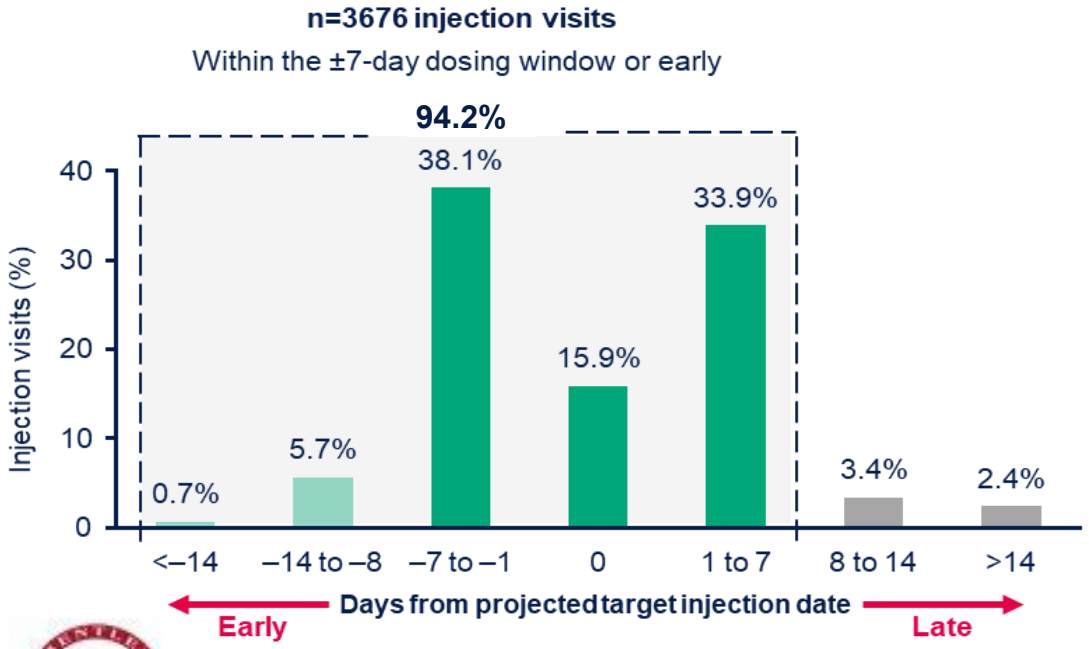
Includes discrete cohorts with >50 PLHIV and report effectiveness data (both virologic suppression and failure). Potential overlap between cohorts cannot be ruled out
*Participants with available effectiveness data; †Only includes participants who were treated consistent with label and had data available at Month 24; ‡VL<50 c/mL; §Of 210 participants who initiated CABENUVA and were consistent with the indication, ¶VL <30 c/mL; #VL<40 c/mL; ΔConfirmed HIV-1 RNA ≥200 c/mL or single HIV-1 RNA ≥200 c/mL followed by treatment discontinuation; **VL ≥30 c/mL; ††VL >200 c/mL

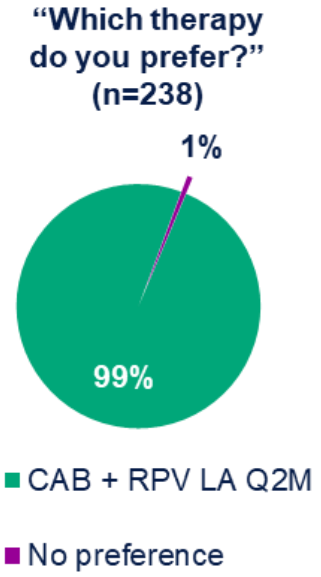
1. Hsu RK, et al. IAS 2025 **2.** Wyen et al. IAS 2025; Kigali, Rwanda. Poster TUPEB035.; **3.** Blick et al. IAS 2025; Kigali, Rwanda. Poster EP0178 **4.** Pozniak et al. IAS 2025; Kigali, Rwanda. Poster EP0171 **5.** Gistand. CROI 2025. Abstr 185. **6.** John M, et al. HIV Medicine 2024.

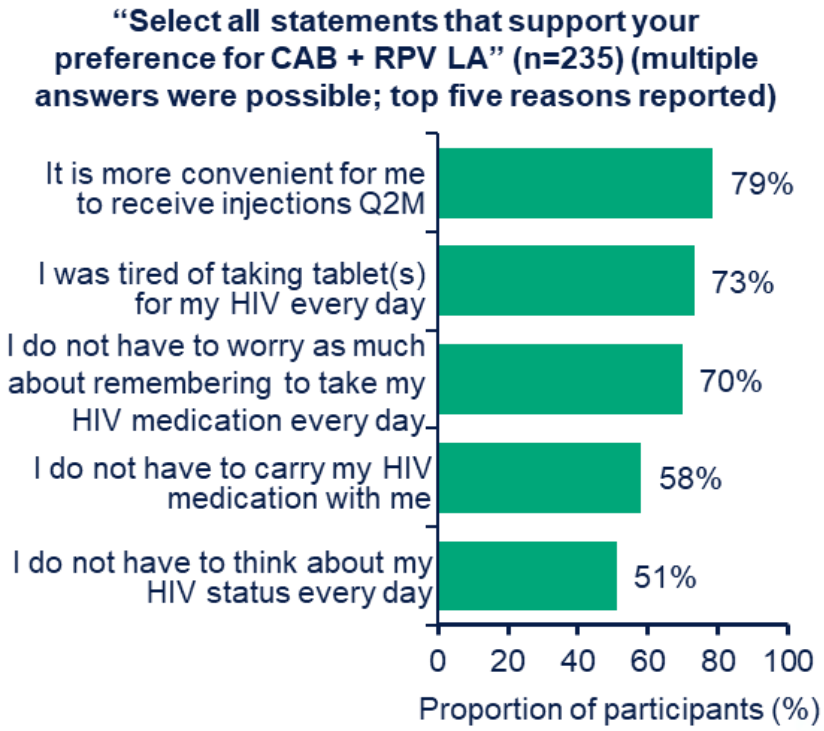
Adherence and preference

CARLOS 24 month

- Multicenter Germany, prospective, n=351, 2QM,
- all suppressed switch







. Wyen et al. IAS 2025; Kigali, Rwanda. Poster TUPEB035.

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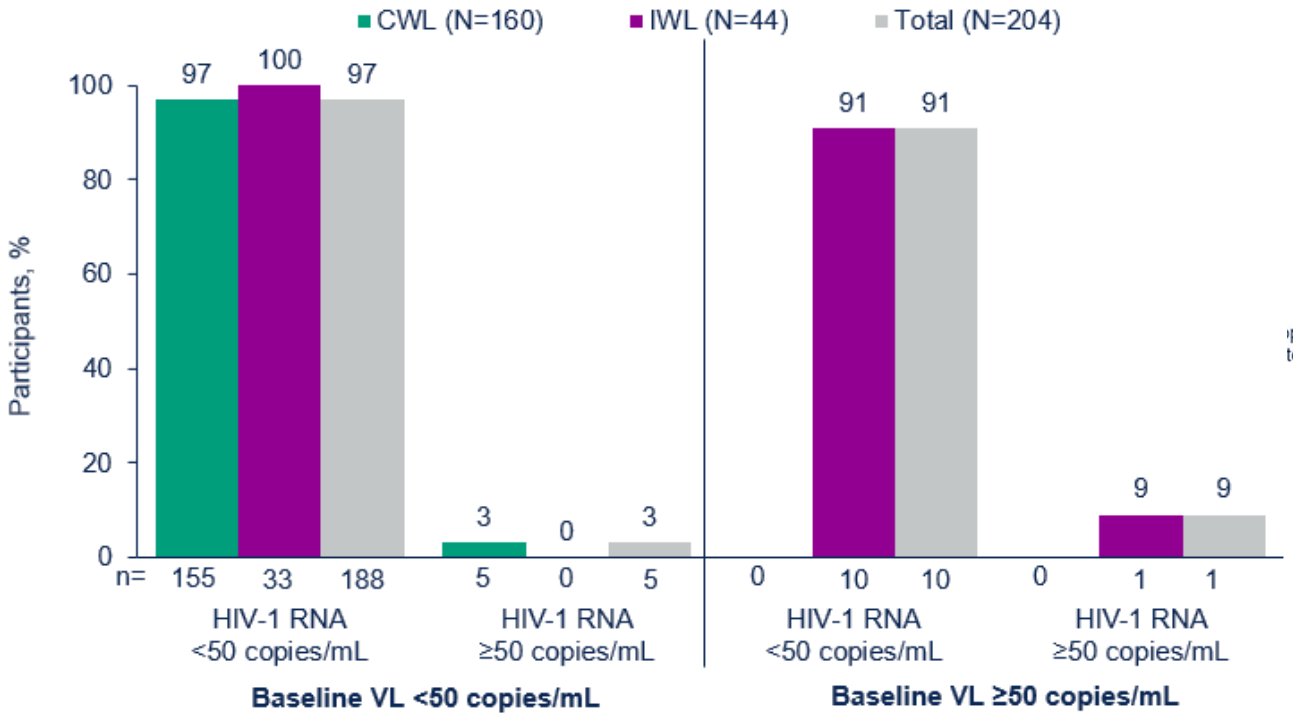
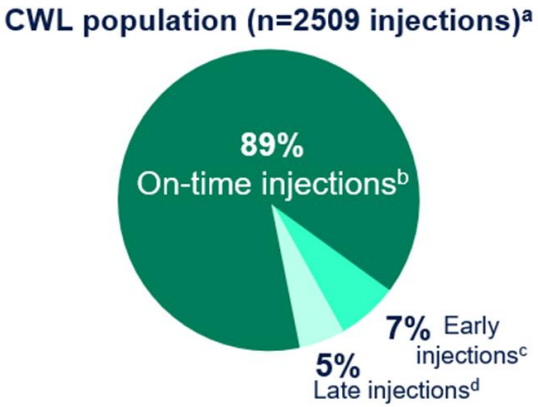
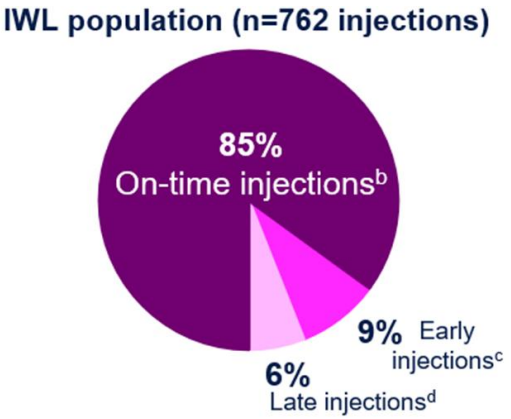
Adherence and preference

- BEYOND, 24 month
  - United States (27 sites), HCP report, n=308,
  - 24% 'IWL'
  - 98% 2QM,2% 1QM



VL, viral load. [a]Population with VL data at both baseline and Month 24.





portions in the CWL group total 101%. [b]On-time injections: within ±7 days from the target treatment date. [c]Early injections: >7 days before the te. [d]Late injections: >7 days after the target treatment date.

****Consistent preference for LA CAB+RPV vs oral SOC across all RCTs and RW studies >90%**

Blick et al. IAS 2025; Kigali, Rwanda. Poster EP0178.

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Safety and Tolerability

Frequently reported adverse reactions include:

Frequency	Adverse events		Effects on laboratory tests
Very Common (≥1/10)	• Headache • **Injection site reactions (ISRs)-Grade 1-2** • Pyrexia		Small, non-progressive increases in total bilirubin were observed with treatment with CABENUVA. These changes are not considered clinically relevant as they likely reflect competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1) Elevated transaminases (ALT/AST) were observed in subjects receiving CABENUVA during the clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects had transaminase elevations attributed to suspected drug-related hepatotoxicity
Common (≥1/100 and <1/10)	• Abdominal pain/ discomfort • Abnormal dreams • Anxiety • Asthenia • Depression/ depressed mood • Diarrhoea • Dizziness	• Fatigue • Flatulence • Insomnia • Malaise • Myalgia • Nausea • Rash • Vomiting • Weight increase	

Based on CABENUVA PI

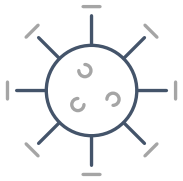
Virological Failure

CVF rate in RCTs (n=1651) up to 152 weeks- 1.4%[1],
RWD (CARLOS, CARISEL, SOLAR, and CUSTOMIZE)- VF rate 0-2%

Three Baseline Factors:
RPV RAMs, Subtype A6/A1, and BMI ≥30 kg/m²

Baseline Factors (Number)	Virologic Suppression, n (%)[b]	CVF, n (%)[c]
0	844/970 (87.0)	4/970 (0.4)[d]
1	343/404 (84.9)	8/404 (2.0)[e]
≥2	44/57 (77.2)	11/57 (19.3)[f]
TOTAL	1231/1431 (86.0)	23/1431 (1.6)
(95% CI)	(84.1–87.8)	(1.0–2.4)
		18/1224 (1.47)[j]

1.Orkin C, et al. Clin Infec Dis 2023;77:1423–31

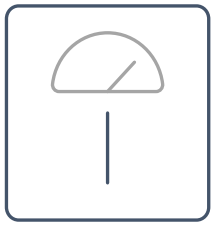


HIV-subtype A1/A6

*Dominant risk (69.5%) of CVF reported in RCTs
*A6 prevalent in Russian trial sites, **Rare in Australia** (<1%)
*CARES[2] - *Subtype A1 in 55% of study cohort.

Archived RPV DRMs

*True RPV and INSTI DRMs likely important
*May include minor/singleton mutations
*proviral genotyping uncertain benefit



BMI ≥30 kg/m²

*CARES[2] :21% BMI>30
*Excluding subtype and DRMs BMI NOT associated with CVF
*likely only relevant if other risk factor is present
* May act as surrogate for higher skin to muscle thickness[3]

2.Kityo. CROI 2025. Abstr 202. 3 Tan B et al. IAS 2024

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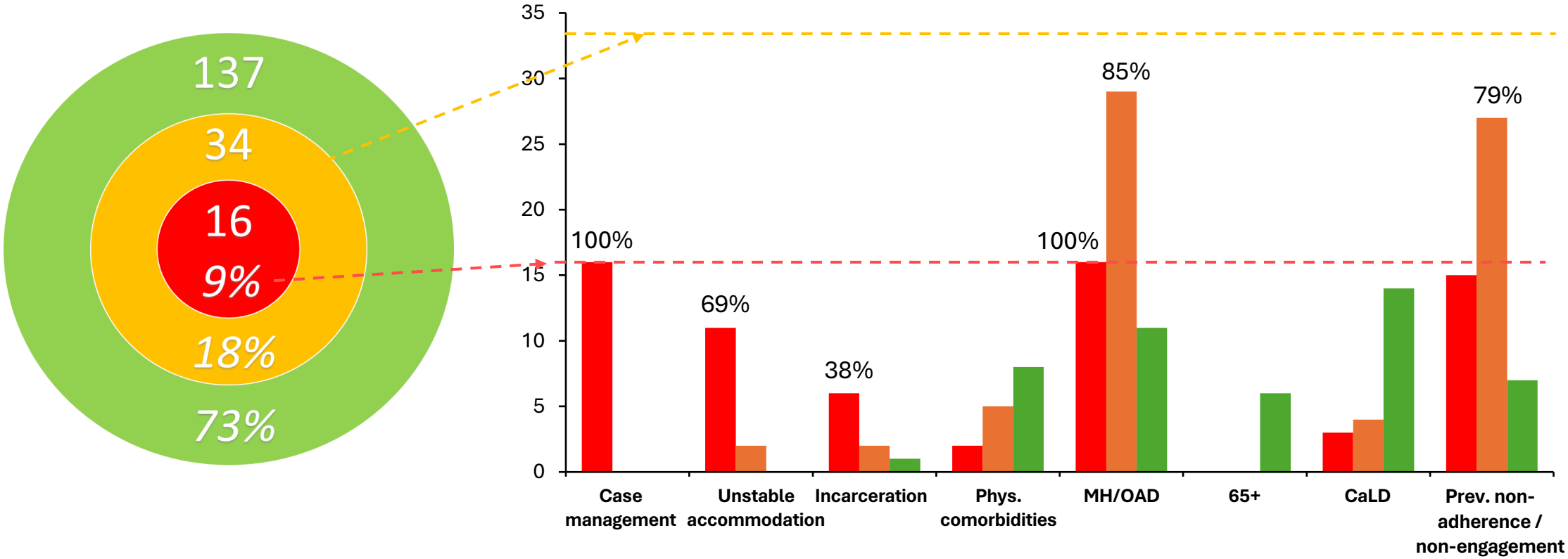
'Hard-to-reach' and vulnerable populations

- Health inequity impacts the HIV care continuum, especially retention in care[1]
  - Greater morbidity and mortality
  - Key barrier to eliminating HIV transmission
  - Perpetuates and reinforces ongoing HIV stigma and health inequity

- Clinical strategies to combat inequity[2,3]
  - Patient navigation, care coordination and case management
  - Financial incentives for ART adherence
  - Tolerable, convenient ART with high barrier to resistance
    - **Long-acting therapy** [3,4]

1. Del Rio C. Top Antivir Med. 2016 ;24(2):86-89. 2.Metsch LR et al. JAMA. 2016 Jul 12;316(2):156-70.3. Rana A. CROI, abstract 212, 2024.4. Taub S et al. Expert Opin Drug Saf 2022; 21:517–24.

Factors affecting/reflecting engagement with care



MH, mental health

Images and unpublished data supplied by Dr N Nolan, Royal Perth Hospital

IMPALA: High, non-inferior efficacy and preference for CAB + RPV LA among a diverse population with suboptimal HIV control

Study design and population[1]

Inclusion criteria

- Aged ≥18 years
- Recent VL >1,000 c/mL and/or poor engagement in care*

Screening

HIV-RNA <200 c/mL for ≥3 months at the end of screening

Randomisation 1:1

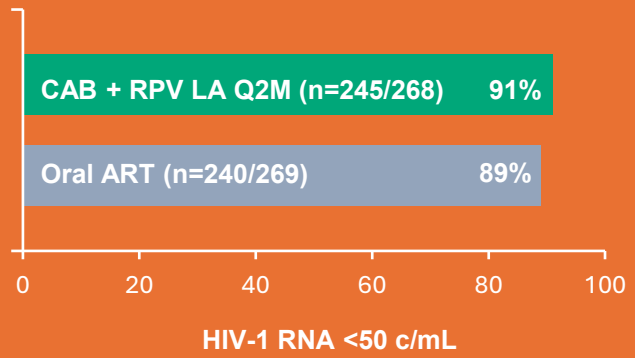
- CAB + RPV LA Q2M n=268
- Oral ART QD n=269

Day 1 — Week 48 (primary endpoint) — Week 96

Multi-country RCT completed in Uganda, Kenya and South Africa (N=540)[1,2]:

- **Female**: 60%
- **Median (IQR) age:** 40 (33–48) years
- **Black** race: 99.6%
- **Prior NNRTI exposure:** 78%
- **HBV:** 7.8% had evidence of vaccine-mediated immunity§

Efficacy[1]



1.5% 4/268

on CAB + RPV LA experienced CVF† with NNRTI and/or INSTI resistance

1.9% (5/268) experienced CVF on CAB+RPV LA; 4 resuppressed on TLD, 1 on LPV/r + TDF/FTC. No CVFs occurred in the oral ART arm.

Non-inferiority, safety and preference[1,2]

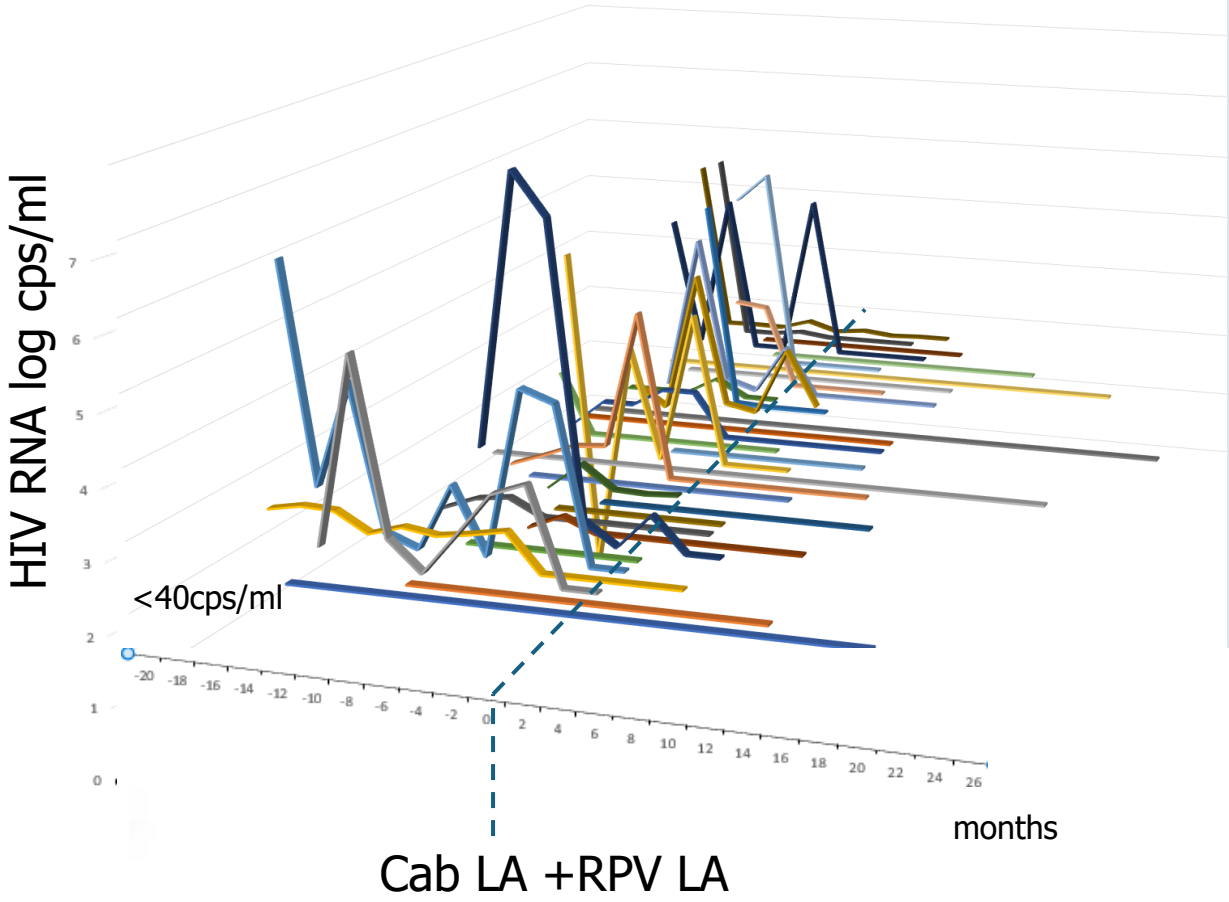
- **CAB + RPV LA was non-inferior to DTG-based ART**
  (91% [245/268] vs 89% [240/269]; risk difference 2.3%, 95% CI: -2.7–7.2)
- **When VF was defined as a single VL >1,000 c/mL, CAB + RPV LA was superior to oral ART**
  (2.6% [7/268] vs 6.7% [18/269]; risk difference -4.1%, 95% CI: -7.7–0.6)
- **High adherence to injections**
  98% of 2159 injections given in window
- **CAB+RPV LA was well tolerated,** with few (n=1) Grade 3 drug-related AEs
  No Hepatitis B reactivations detected.
- **Strong preference for CAB + RPV LA vs prior oral ART**
  91% of participants on CAB + RPV LA preferred LA to oral ART

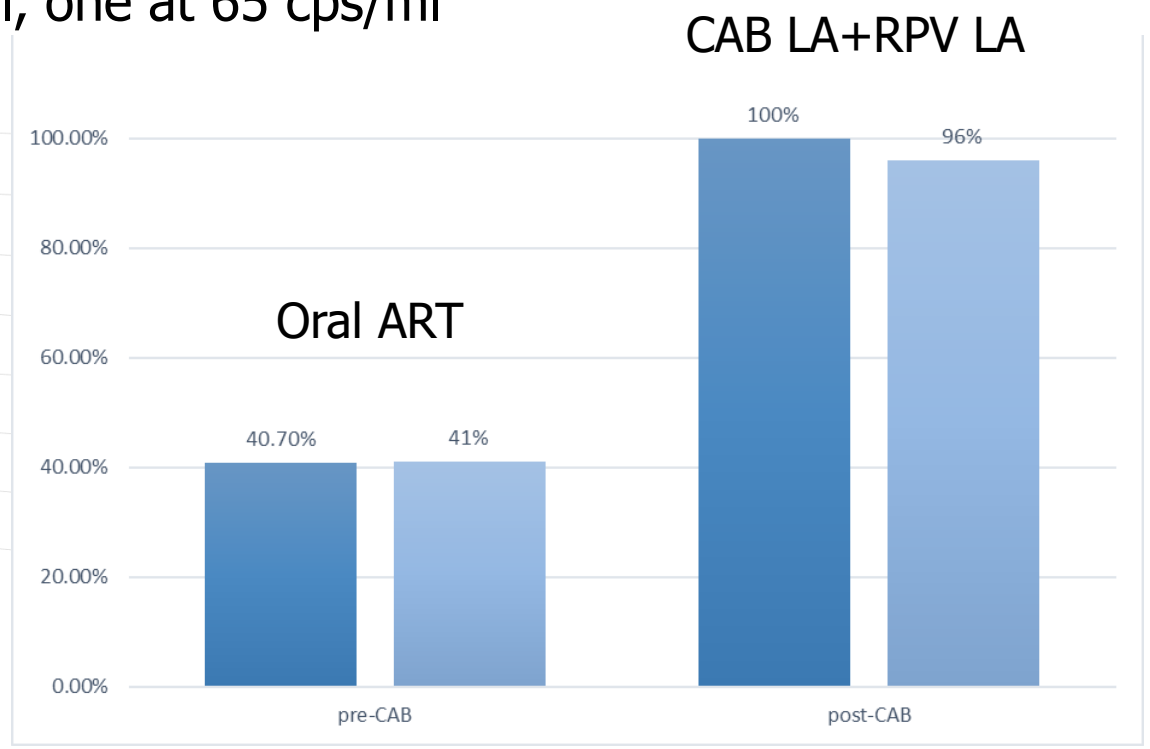
*Poor engagement in care defined as history of LTFU (>4 weeks) or unlinked to HIV care despite ≥3 months since HIV diagnosis; †CVF defined as two consecutive HIV-1 RNA ≥200 c/mL; §.Hep B-related reasons precluded 84 (9.9%) from randomization [29 (3.4%), active hepatitis B; 55 (6.5%), prior infection but no immunity]

1. Cresswell FV, et al. IAS 2025. Abstract OAB0106LB
2. Bahemuka U, et al. IAS 2025. Oral OAB01

HIV suppression on CAB LA+ RPV LA

- At July 2024, 32 of 33 had viral load <40cps/ml, one at 65 cps/ml
- No virological failures





Sustained VL <200cps/ml over 12 months

Two consecutive VL<40cps/ml

Sustained VL <200cps/ml over 12 months

Two consecutive VL<40cps/ml

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Conclusions and data gaps

- RWE for CAB/RPV strongly supports the option of LA ART in PWH who are medically eligible
  - Comparable to results of phase 3 RCTs
  - Highly effective, safe and tolerable,
  - Improves QoL and provides patient choice and preference
  - Durable
- Remaining data gaps
  - Implementation in diverse health care settings
    - Understanding remaining barriers to implementation and improving equity of access
    - Primary and community-based care, nurse-led, pharmacist-led, scale-up
    - Rural and remote populations
    - Vulnerable, hard to reach, baseline viremia
  - Genomic and pharmacokinetic correlates of rare CVF
  - Implementing future LA options- lenacapavir, ISL, BNabs