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Efficacy and safety of long-acting cabotegravir and rilpivirine in adults with adherence or engagement challenges in sub-Saharan Africa: the IMPALA trial 96-week results

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Background and study rationale

- In East & Southern Africa, ~1 million people on oral antiretorviral therapy (ART) remain unsuppressed.[1]
- Inconsistent ART adherence contributes to the 630,000 HIV-related deaths and increasingly contributes to the 1.3 million transmission events per year globally.[1,2,3]
- Long-acting (LA) cabotegravir (CAB) + rilpivirine (RPV) is now recommended by WHO as a suppressed switch option, but availability remains limited.
- In a meta-analysis of 6 RCTs, LA CAB + RPV had equivalent efficacy to oral ART (91.5% versus 91.4% with VL<50 c/ml at 48 weeks).[4] This included a single study from Africa – the CARES trial. At week 96, the CARES trial demonstrated that 97% (247/255) in the LA group and 97% (250/257) in the oral ART group had VL <50 c/mL (difference −0.4%; 95% confidence interval −3.1% to 2.0%).[5]
- **Week 48 primary outcome results from the phase 3b IMPALA trial showed:** 91% (244/268) in the LA CAB + RPV group and 89% (240/269) in the oral ART group had VL <50 c/ml (difference +1.9%; 95% confidence interval −3.1% to 6.9%). Demonstrating non-inferiority.

Methods

Phase 3b, open-label, non-inferiority trial (NCT05546242)
7 sites: Uganda, Kenya, South Africa

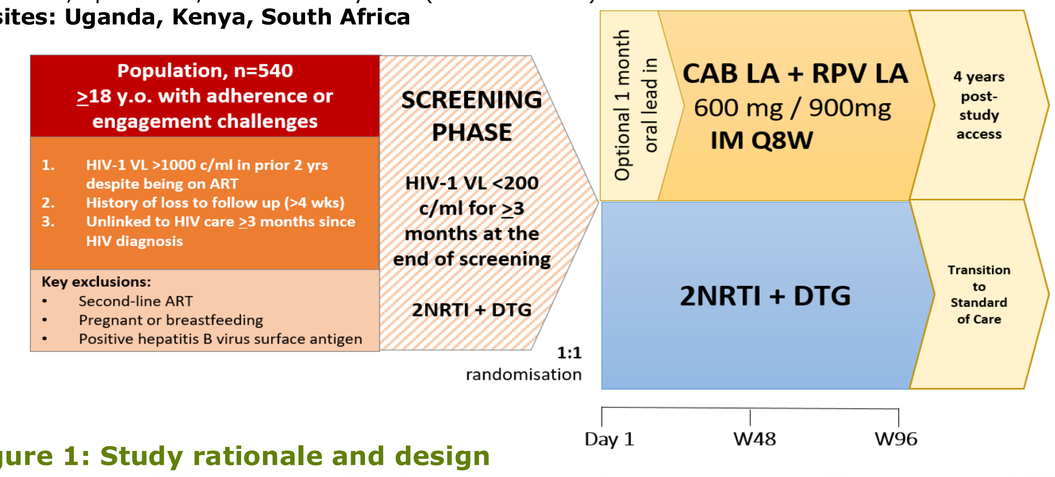


Figure 1: Study rationale and design

CAB = cabotegravir; DTG = dolutegravir; HIV-1 VL = human immunodeficiency virus 1 viral load; IM = intramuscular; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; Q8W = 8-weekly dosing; RPV = rilpivirine.
Participants on the LA arm received their first injection at month 1. HIV-1 VL is tested 4 times in year 1 and 2 times in year 2.

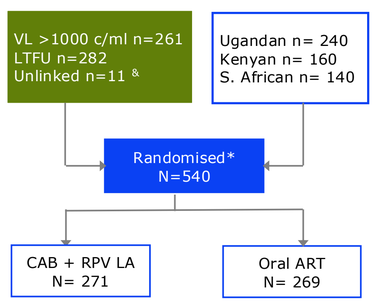
Week 96 Secondary Endpoints

Proportion of participants with **HIV-1 VL <50 c/mL (FDA snapshot algorithm).** *10% NI margin.*
Proportion of participants with virologic non-response **HIV-1 VL ≥50 c/mL** (FDA snapshot). *4% NI margin.*
Proportion of participants with confirmed virological failure (CVF) **HIV-1 VL ≥200 c/mL on 2 consecutive occasions** ~4 weeks apart. *4% NI margin.*
Proportion of participants experiencing **adverse events**
Participant-reported outcomes: quality of life (MOS-HIV, EQ-5D-5L), treatment satisfaction (HIVTSQ) & preference
Pre-specified CVF sensitivity analysis: Proportion with CVF at 200 c/ml OR one HIV-1 VL >1000 c/ml*. *4% NI margin.*

CVF = confirmed virological failure; **The CONSENSUS-LAI Study: Establishing Shared Definitions of Virological Failure and Discontinuation for Long-Acting Injectable Cabotegravir and Rilpivirine Therapy.* Orkin et al. *Lancet HIV. 2025.*

Results

Inclusion and Randomisation



& Participats could meet multiple eligibity criteria
*All particpants had VL<200 prior to randomisation

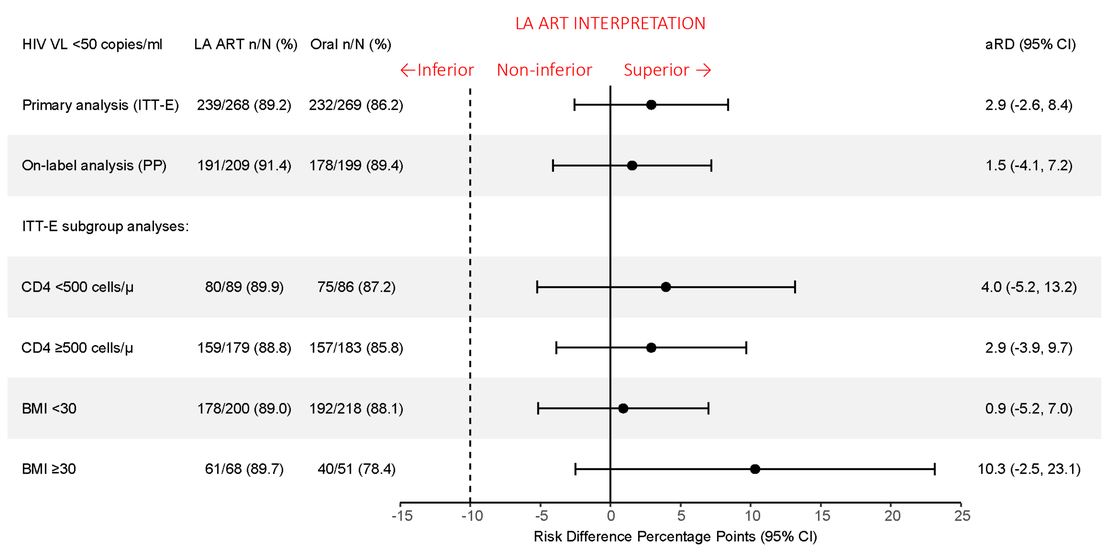
Four withdrawals from study (2 LA, 2 oral)
• 1 participant choice after randomisation to oral arm
• 2 participant choice due to visit schedule (1 oral, 1 LA)
• 1 moved out of area, LA arm

Baseline characteristics

Baseline Characteristics	Total
Age, median years (IQR)	40 (33–48)
Cis-female, n (%)	324 (60)
Black African, n (%)	538 (99.6)
Hepatitis B core antibody positive, n (%)	168 (31.1)
Formal employment, n (%)	96 (17.8)
BMI ≥30, n (%)	120 (22.2)
CD4, median cells/µl (IQR)	629 (453–873)
ART duration, median yrs (IQR)	7.5 (4.6–10.8)
Prior AIDS-defining illness, n (%)	142 (26.3)
Prior exposure to NNRTI, n (%)	411 (78.3)
HIV subtype A1&, n (%)	173 (50.4)
Major RPV RAM& n (%)	18 (5.7)
Major CAB RAM& n (%)	1 (0.3)

BMI = body mass index; IQR = interquartile range; NNRTI = non-nucleoside reverse transcriptase inhibitors; RAM = resistance associated mutation. & next generation sequencing of baseline PBMCs. Results not available at randomization. All variables were well balanced between randomization arms.

Proportion of participants with HIV-1 VL <50 c/mL at week 96



ITTe = receiving at least one dose of long-acting investigational drug in the CAB LA+RPV LA arm, or one dose of oral ART in the control arm; NI = non-inferiority; VL = viral load; On-label per protocol (PP) population = excluding participants with drug administration and visit window protocol deviations, and those with a viral load between ≥50 copies/ml and <200 copies/ml at the end of screening. Three participants randomised to LA arm did not initiate LA CAB+RPV and were excluded from ITT-e (1 self-switch to oral dolutegravir-based ART during oral lead in (OLI) phase, 1 rheumatoid arthritis during OLI (unrelated), 1 protocol-defined virological failure before starting LA therapy (first high VL on dolutegravir, repeat on OLI).

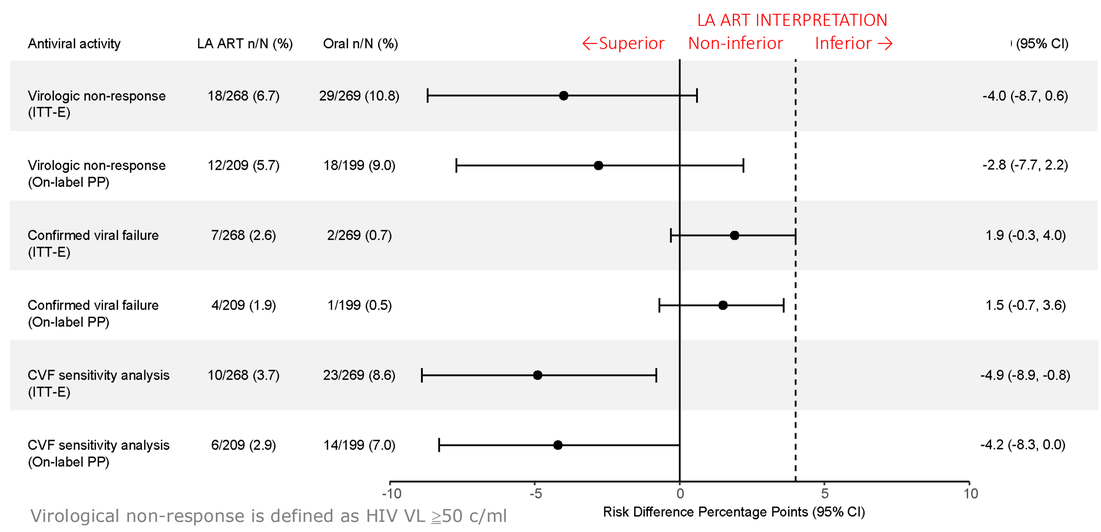
In the intention-to-treat exposed (IIT-E) population, 89.2% (239/268) of participants in the LA arm and 86.2% (232/269) in the oral therapy arm had VL <50 copies/ml at 96 weeks, resulting in a risk difference (RD) of 2.9% [95% confidence interval (CI) -2.6 to 8.4].

Presented at AIDS 2026, the 26th International AIDS Conference

Virological non-response or confirmed virological failure at week 96

Up to week 96, in the IIT-E population, CVF since baseline occurred in:
- 2.6% (7/268) in the LA arm – two new cases after week 48
- 0.7% (2/269) in the oral arm – two new cases after week 48

The two cases of CVF in CAB + RPV LA arm were reported at week 72:
1. No known risk factors for CVF, at baseline L74I, no NNRTI resistance. E138K+Q148R at CVF. Resuppressed on AZT/3TC/ATZ/r.
2. No known risk factors for CVF, baseline INI genotyping did not amplify, no NNRTI resistance. No emergent resistance, resuppressed on once daily tenofovir/lamivudine/dolutegravir.



Virological non-response is defined as HIV VL ≧50 c/ml

Safety

Safety outcomes were comparable between study arms. Adverse events, excluding injection site reactions, occurred in 96.3% (261/271) of participants on LA therapy and 95.2% (256/269) on oral therapy (RD 1.2%, 95%CI -2.2 to 4.5). Serious adverse events were reported by 7.7% (21/271) of participants on LA and 6.7% (18/269) on oral therapy (RD 1.1%, 95%CI -3.3 to 5.4). There were no serious injection site reactions (ISRs) or discontinuations due to ISRs.

Participants with ≥1 AE	CAB+RPV LA (N=271)	Oral ART (N=269)	aRD (95% CI)
Any (grade 1-4), n (%)			
- Excluding ISRs	261 (96.3)	256 (95.2)	1.2% (-2.2% to 4.5%)
- Lab abnormalities	212 (78.2)	228 (84.8)	
- Related*, excluding ISRs	56 (20.7)	65 (24.2)	
- Discontinuations due to AEs&	7 (2.6)	2 (0.7)	
- Drug-related discontinuations$	2 (0.7)	1 (0.4)	
Grade 3 and above, n (%)			
Related, excluding ISRs^	47 (17.3)	53 (19.7)	-2.4% (-8.7% to 4.0%)
Serious AEs, n (%)	21 (7.7)	18 (6.7)	1.1% (-3.3% to 5.4%)

aDR = adjusted risk difference; AE = adverse event; CI = confidence interval; ISR = injection site reaction

Pregnancies at week 96

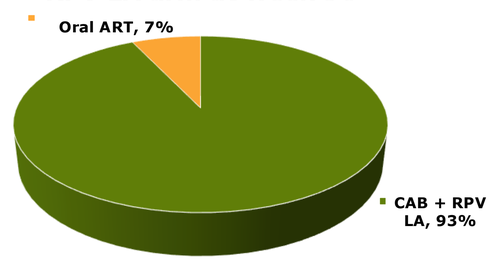
Twenty-nine pregnancies occurred, 15 on LA and 14 on oral therapy. All 15 women in the LA arm consented to remain on CAB + RPV LAI during the pregnancy. There were 7 lives births from women on CAB + RPV LA and all infants were HIV DNA/RNA-negative.

	CAB + RPV LA	Oral ART
Total	15	14
Elective/therapeutic termination	5	4
Miscarriage	3	1
Ongoing	0	1*
Live births	7	8
Infant HIV status	**7 (100%) negative**	**8 (100%) negative**

Patient-reported outcome measures at week 96

Treatment satisfaction:
- Mean treatment satisfaction score increased in both arms compared to baseline but more so on CAB+RPV LA.
- Mean between arm difference was +2.07 (95% CI, 1.19 to 2.96, P<0.001) favouring the LA CAB+RPV arm.

Treatment preference in CAB + RPV LA arm at week 96



Conclusion

Two-monthly CAB+RPV LA continued to be non-inferior at 96 weeks in an African population with prior adherence or engagement challenges. These results were achieved without baseline resistance testing, in line with the African public health approach.

There were a total of seven confirmed virological failure events on CAB+RPV LA by week 96, including two after week 48. The frequency of CVF was 2.6% in the CAB + RPV LA compared to 0.7% on oral DTG-based ART. All participants with CVF in the LA arm resuppressed on oral ART.

Overall, there were fewer participants with episodes of clinically-significant viraemia (instance of viral load >1000 copies/ml or CVF) on CAB+RPV LA, which is a relevant consideration for transmission: 3.7% of participants on CAB + RPV LA, versus 8.6% on oral ART using the CONSENSUS-LAI definition[6].

CAB+RPV LA was well tolerated, safe, and preferred by 93% in the LA arm.

Long-acting HIV treatment has an important role as a management option in people who struggle with daily pill-taking in Africa.

Acknowledgements

- Participants
- Study teams and collaborators
- Community Advisory Boards
- Regulatory authorities
- Independent Data and Safety Monitoring Committee
- Trial Steering Committee

References

[1]UNAIDS. 2024; [2]Moolla H. *AIDS,* 2024; [3]Johnson LF. *J Aquir Immune Def Sydr.* 2022; [4]Manalu SBPS, *JAC.* 2025; [5]Kityo C, *Lancet ID.* 2024; [6]Orkin, Lancet HIV 2025.

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AIDS 2026 26–31 July