Implementazione delle terapie LA a livello globale: quali prospettive

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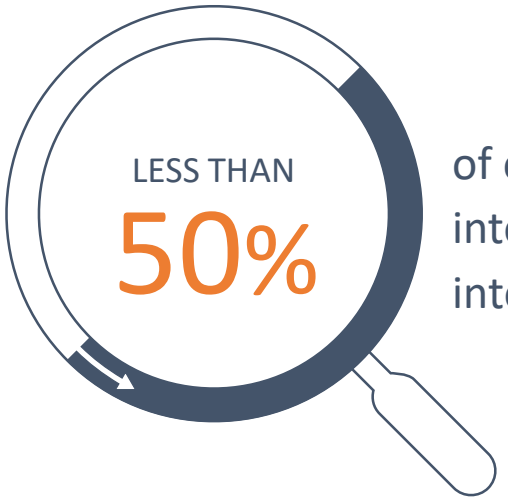
Implementation science is the study of translating innovative scientific discoveries to routine clinical practice



of evidence-based interventions get into general use[1]

ONLY
20%
of medical research dollars make a public health impact[1]

Implementation research aims to address potential barriers to the adoption of new healthcare practices in real-world settings[2]

1. Bauer MS, et al. Psychiatry Res 2020;283:112376
2. Schillinger D. Series: UCSF Clinical and Translational Science Institute Resource Manuals and Guides to Community-Engaged Research, 2010

There are several key differences between clinical and implementation research

	Clinical research[1,2] Preclinical, efficacy, effectiveness, safety research	**Implementation research**[1,2]
Study aim	Superiority, non-inferiority	Implementation strategy to improve uptake
Intervention(s)	Drug, procedure, therapy, programme	Organisational practice change, facilitation
Primary outcome(s) for HIV	VL suppression, change in CD4+ T cells, AEs	Adoption, acceptability, fidelity, sustainability
Units of analysis and randomisation	Patient	Clinician, team, facility and patient (secondary)

AE, adverse event; **CD4+,** cluster of differentiation 4-positive

1. Bauer MS, et al. Psychiatry Res 2020;283:112376
2. Curran G, et al. Med Care 2012;50:217–26

Implementation science outcomes indicate whether a strategy has had an impact

Common implementation science outcomes include:[1,2]

Adoption
Are people using it?

Fidelity
Are people using it as intended?

Reach
Are people willing to participate?

Sustainability
Does the new practice become standard procedure?

Implementation outcomes can also serve as intermediate outcomes for treatment effectiveness and quality of care[1]

- **1.** Proctor E, et al. Adm Policy Ment Health 2011;38:65–76
- **2.** Chaudoir SR, et al. Implement Sci. 2013;8:22

What should clinics consider for implementing CAB + RPV LA?

Key considerations for implementation planning in CARISEL:*

How the medication gets to the clinic

Space for the injection administration

The ideal number of injections/day in clinic

Personnel (including sick and holiday coverage)

The impact of medication collection on appointment time

The impact of pharmacy hours on injection appointments

The process for vial differentiation

*Each clinic undertook planning activities to support implementation in their clinics, although when directly asked, not all identified formally creating an implementation plan at the start of the study

Olalla J, et al. BHIVA 2022. Poster 008

Clinical Infectious Diseases
MAJOR ARTICLE

Perspectives of People With Human Immunodeficiency Virus on Implementing Long-acting Cabotegravir Plus Rilpivirine in Clinics and Community Settings in the United Kingdom: Results From the Antisexist, Antiracist, Antiageist Implementing Long-acting Novel Antiretrovirals Study

Chloe Orkin,[1,2] Rosalie Hayes,[3] Joanne Haviland,[4] Yuk Lam Wong,[4] Kyle Ring,[1,2] Vanessa Apea,[2,3] Bakita Kasadha,[5] Emily Clarke,[6] Ruth Byrne,[7] Julie Fox,[8,9] Tristan J. Barber,[10,11] Amanda Clarke,[12] and Sara Paparini[3]; For the ILANA study Group (Sadna Ullah, Nishat Halim, Chikondi Mwendera, James Hand)

[1]SHARE Collaborative, Blizard Institute, Queen Mary University of London, London, United Kingdom; [2]HIV/GUM Directorate, Barts Health NHS Trust, London, United Kingdom; [3]SHARE Collaborative, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom; [4]Pragmatic Clinical Trials Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom; [5]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom; [6]Axess Sexual Health, Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom; [7]St Stephen's Centre, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [8]School of Immunology & Microbial Sciences, Kings College London, London, United Kingdom; [9]Infection and Immunity, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [10]Ian Charleson Day Centre, Royal Free London NHS Foundation Trust, London, United Kingdom; [11]Institute for Global Health, University College London, London, United Kingdom; and [12]The Lawson Unit, University Hospitals Sussex NHS Foundation Trust, Brighton, United Kingdom

Introduction. The equity-focused Implementing Long-Acting Novel Antiretrovirals study evaluated feasibility, acceptability, appropriateness of delivering on-label 2-monthly cabotegravir and rilpivirine (CAB + RPV) injections for human immunodeficiency virus (HIV)-1 therapy in clinics and community settings.

Methods. The study, which mandated inclusive recruitment, was conducted May–December 2022 at 6 UK sites. Injections were delivered in clinic (month [M] 1–6) and in clinic or community setting according to patient choice (M6–12). Surveys were completed at baseline, M4, and M12 using validated measures for feasibility (FIM), acceptability (AIM), and appropriateness (IAM). Primary endpoint: proportion of participants agreeing that the injection and community setting were feasible (FIM ≥4) at M12. Fourteen participants completed interviews at baseline and M12.

Results. Community settings offered by sites included: home visits (n = 3), HIV support organizations (n = 2), and community clinic (n = 1). Of 114 participants, 54% were female, 70% racially minoritized, and 40% aged ≥50 years. A total of 27/114 chose to receive injections in community settings. FIM/AIM/IAM scores at M12 were high for the injection (79.0–87.4%) and lower for the community setting (44.2–47.4%) overall. Subgroup analyses indicated differences in scores by gender and ethnicity. Among those who attended the community, FIM/AIM/IAM scores for the community setting at M12 were high (73.1–80.8%). Concerns about stigma, inconvenience, and losing access to trusted clinicians negatively influenced perceptions of receiving injections at community settings, amongst other factors.

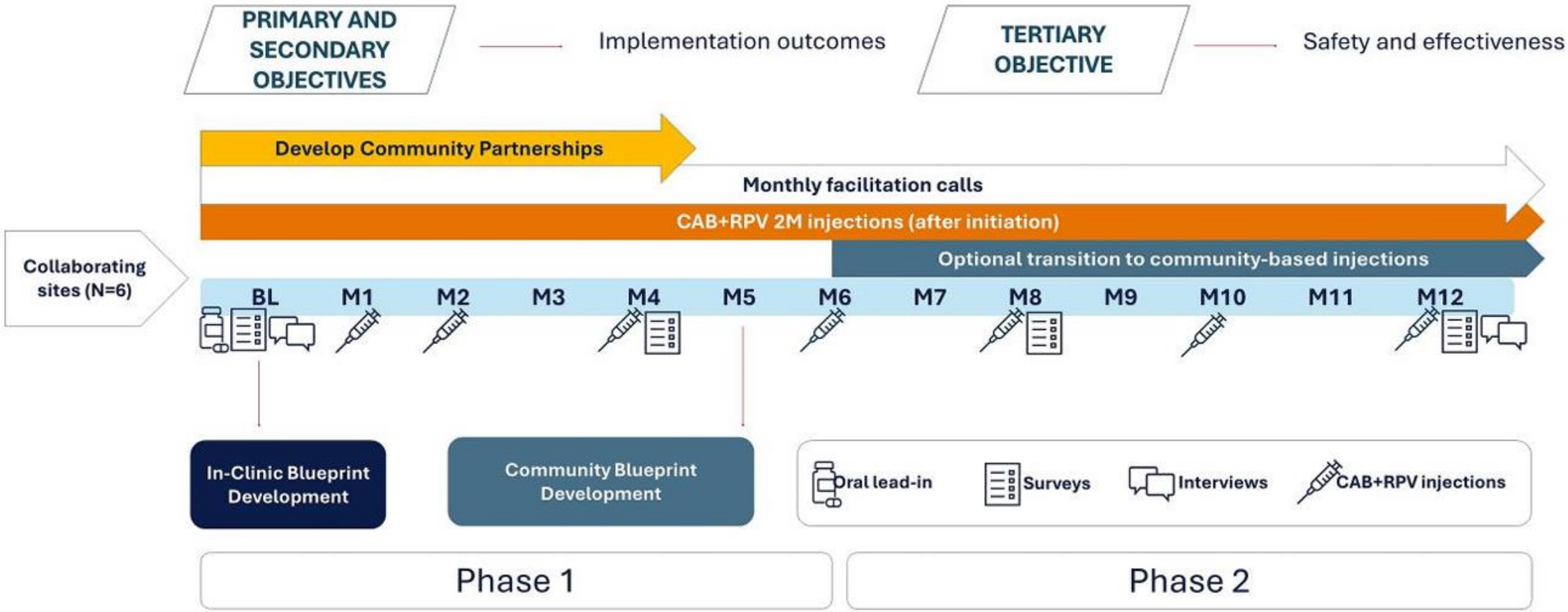
Conclusions. CAB + RPV injections were considered highly feasible, acceptable, and appropriate; however, few chose community delivery. Those that chose community delivery found it highly acceptable and feasible. Further exploration of CAB + RPV delivery in alternative community sites not offered (eg, primary care, pharmacies) is warranted.

ClinicalTrials.gov. NCT05294159

Keywords. cabotegravir; rilpivirine; long-acting injectable; implementation science; inclusive protocol.

Clin Infect Dis. 2024 Oct 28:ciae523.

ILANA – STUDY DESIGN



Clin Infect Dis. 2024 Oct 28:ciae523.

- Women and Black people reported smaller increases in treatment satisfaction and found CAB + RPV less feasible and appropriate compared to men and non-Black people, respectively

- Participant responses overall indicated lower acceptability, feasibility, and appropriateness for community delivery of CAB + RPV.

- Interview findings indicated that for many participants, switching to a new setting provoked concerns about HIV stigma and confidentiality

Clin Infect Dis. 2024 Oct 28:ciae523.

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Barriers to Uptake of Long-Acting Antiretroviral Products for Treatment and Prevention of HIV in Low- and Middle-Income Countries (LMICs)

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Long-acting injectable antiretroviral therapy (LA ART) has been found to be non-inferior to daily oral ART in phase 3 clinical trials and is poised to soon enter routine clinical care. This treatment modality has the potential to address many barriers to daily oral ART adherence among people living with human immunodeficiency virus (HIV) and for HIV Pre-Exposure prevention. Data from the Patient Reported Outcomes (PROs) showed high rates of satisfaction, acceptability, tolerability and preference for the LA regimen, compared with the daily oral treatment. Once LA ART is available, access and uptake will be limited because of current knowledge gaps in the use of these agents and multiple challenges many specific to low-income and middle-income countries, where the epidemic is most concentrated and HIV prevention and treatment options are limited. These gaps will lead to multiple systems-level and individual-level barriers to implementation. Anticipating and addressing these gaps and barriers will help fulfill the promise of these agents against the pandemic.

Table 1. Barriers to Uptake of Long-Acting Injectable Antiretroviral Therapy for HIV Treatment and Prevention in LMICs

Knowledge Gaps in Implementing Long-Acting ART
Evidence for WHO to incorporate long-acting ART in global treatment guidelines
Efficacy and safety data in diverse populations in LMICs
Efficacy and safety of treatment administered using a feasible monitoring strategy in a public health approach
Representative patient values and perceptions in LMICs
Lack of complementary studies in LMICs to inform operational issues, efficacy feasibility, and cost-effectiveness
Health Systems Challenges
High cost of CAB/RPV LA
Complex manufacturing platforms for LA products that may not be amenable to cheaper generics production
Cost-effectiveness information to inform policy decisions on adoption of LA ART
Need for steady supply chains for the injectable forms of ART and supplies like needles
Development of resistance to LA ART (preexisting NNRTI resistance, CAB "tail" with very short half-life of RPV)
Appropriate and trained personnel are required for programing, administering injections and care of post-injection complications
Suitable and adequate physical space to administer gluteal injections, along with administrative and registration tasks
Adequate physical space to store the drugs at the required temperature (RPV requires a cold chain)
Implementation Challenges
Patient selection for eligible population requiring viral load testing which is not readily accessible
Higher number of user visits given more frequent visits with LA ART
Feasibility of CAB LA for large PrEP programs in LMIC currently delivered by lay providers
Current lack of possibility for self-injection such as thigh muscle or subcutaneous injection
Service delivery platforms and decentralized care (including mobile health units) to deliver LA and cater for more frequent healthcare visits
Synchronization of every 8-wk CAB-LA injection schedule with testing frequency of HIV in PrEP
Handling various patterns of CAB-LA and switch between oral PrEP (initiation, discontinuation, and reinitiation/reload)
Delay in diagnosis of PrEP breakthrough infection by conventional HIV testing approach and need for HIV RNA assays which is more expensive
Additional requirements include management of biological risk waste
Individual-Level Challenges to Implementing Long-Acting ART
Adherence to injection visits and injection reminder approaches in absence of pills
Short- and long-term side effects including injection site reactions
Added cost to clients and healthcare system with more frequent visits with LA compared with oral ART
Patient preference and acceptability of injection based therapy in LMICs

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; LMIC, lower and middle income countries; NNRTI, non-nucleoside reverse transcriptase inhibitor; PrEP, preexposure prophylaxis; RPV, rilpivirine; WHO, World Health Organization.

The potential role of long-acting injectable cabotegravir–rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis

Andrew N Phillips, Loveleen Bansi-Matharu, Valentina Cambiano, Peter Ehrenkranz, Celicia Serenata, Francois Venter, Sarah Pett, Charles Flexner, Andreas Jahn, Paul Revill, Geoff P Garnett

Research in context

Evidence before this study

The use of a combination of the integrase inhibitor, cabotegravir, and the non-nucleoside reverse transcriptase inhibitor, rilpivirine, in long-acting injectable form as an antiretroviral treatment option in sub-Saharan Africa is being considered. Modelling can help to inform potential policies for its introduction. We searched Web of Science, with no restrictions on language, using the search terms "cabotegravir" AND (list of countries in sub-Saharan Africa) on June 30, 2020, and identified one modelling study that has considered the cost-effectiveness of the introduction of such treatment in adolescents in the context of Kenya, and found that this could be cost-effective if associated with an additional annual cost of US$89 or less.

Added value of this study

We used an existing individual-based model of HIV to consider the predicted effects and cost-effectiveness of the introduction of monthly injectable cabotegravir–rilpivirine. We considered drug resistance to cabotegravir and rilpivirine, cross resistance with oral drugs of the same classes, and the long tail of cabotegravir drug concentrations in people who stop attending for monthly injections.

Implications of all the available evidence

Injectable cabotegravir–rilpivirine offers potential benefits; however, its introduction needs to be carefully targeted to individuals who might otherwise have suboptimal adherence to ART and studied in pilot implementation projects to ascertain if it is likely to be a cost-effective option.

Lancet Glob Health 2021; 9: e620–27

	Implementation in all people on ART (n=333 setting scenarios)	Implementation in people with a recently measured viral load of >1000 copies per mL (n=334 setting scenarios)	Implementation in people with a recently measured viral load of <1000 copies per mL (n=333 setting scenarios)
Percentage of people on ART on injectable CTG-RPV, %	99% (99 to 99; 97 to 100)	26% (25 to 27; 13 to 44)	86% (86 to 87; 75 to 94)
People starting injectable CTG-RPV			
Percentage with viral load >1000 copies per mL*, %	40% (39 to 41; 26 to 56)	69% (68 to 71; 52 to 81)	4% (3 to 4; 1 to 7)
Percentage for whom first-line ART failed†, %	13% (0·12 to 0·13; 0·05 to 0·23)	25% (24 to 26; 13 to 38)	7% (6 to 7; 2 to 18)
Percentage with integrase inhibitor resistance, %	2% (2 to 2; 0 to 4)	7% (6 to 7; 2 to 13)	1% (0·01 to 0·02; 0·00 to 0·04)
Percentage with non-nucleoside reverse transcriptase inhibitor resistance, %	24% (23 to 26; 11 to 46)	38% (37 to 40; 18 to 59)	18% (17 to 20; 7 to 39)
Percentage male, %	40% (40 to 41; 34 to 48)	46% (45 to 47; 38 to 55)	39% (39 to 40; 33 to 46)
Percentage aged <25 years, %	5% (5 to 6; 1 to 12)	3% (3 to 4; 1 to 8)	5% (4 to 5; 1 to 10)
Introduction of injectable CTG-RPV *vs* no introduction			
Difference in proportion of people with suboptimal drug concentrations (ie, <80% adherence to oral therapy) among people who started injectable cabotegravir-rilpivirine, %	+8·0% (7·1 to 8·8; 0·0 to 19·5)	+11·7% (10·3 to 2·6; 0·0 to 26·8)	+7·4% (6·5 to 8·3; 1·2 to 18·0)
Difference in proportion of people with a viral load of <1000 copies per mL among people on ART, %	+5·3% (4·8 to 5·7; 1·0 to 14·4)	+4·1% (3·7 to 4·4; 0·7 to 11·2)	+3·0% (2·7 to 3·3; 0·4 to 8·5)
Difference in AIDS-related mortality among people with HIV, per 100 person-years	−0·19 (−0·21 to −0·16; −0·68 to 0·08	−0·17 (−0·19 to −0·15; −0·54 to −0·01)	−0·05 (−0·06 to −0·04; −0·28 to 0·11)
Difference in proportion of people with HIV with integrase inhibitor resistance, %	+0·8% (0·5 to 1·2; −3·0 to 6·0)	−0·4% (−0·5 to −0·3; −2·1 to 0·9)	+1·0% (0·7 to 1·2; −2·0 to 4·7)
Difference in proportion of people with HIV with non-nucleoside reverse transcriptase inhibitor resistance, %	+4·3% (4·1 to 4·5; 1·9 to 7·7)	+1·5% (1·3 to 1·6; 0·2 to 3·8)	+3·4% (3·3 to 3·6; 1·5 to 6·2)
Difference in HIV incidence in people aged 15–49 years, per 100 person-years	−0·04 (−0·05 to −0·03; −0·14 to 0·04	−0·02 (−0·02 to −0·01; −0·10 to 0·06)	−0·02 (−0·03 to −0·01; −0·10 to 0·04)
DALYs averted, per year over 10 years	30 400 (27 300 to 33 400; 400 to 91 800	17 900 (15 700 to 20 000; −3200 to 54 800)	16 700 (15 000 to 18 500; −2800 to 47 600)
Difference in cost, US$ million per year over 10 years (with discounting at 3% per annum)	+42·9 (40·2 to 45·6; 9·0 to 86·5)	+5·4 (4·6 to 6·2; −4·9 to 18·7)	+42·5 (39·8 to 45·1; 10·1 to 83·9)
Net DALYs averted, per year over 10 years‡	−55 500 (−60 400 to −50 500; −135 000 to 7100)	7100 (4700 to 9600); −18 000 to 54 800)	−68 200 (−72 900 to −63 500; −143 600 to −10 700)
Median cost per DALY averted (90% range)	$1638 (390 to 59 524)	$404 (dominant to dominated)	$2808 (794 to dominated)
Difference in proportion of setting scenarios in which injectable CTG-RPV is cost-effective, % (95% CI)	7% (5 to 11)	59% (53 to 64)	2% (0 to 3)

Data are mean (95% CI; 90% range) over 10 years, unless otherwise indicated. Percentage values are absolute (ie, percentage with CTG-RPV − percentage without CTG-RPV). ART=antiretroviral therapy. CTG-RPV=cabotegravir-rilpivirine. DALY=disability-adjusted life-year. *Proportion of all initiations of injectable CTG-RPV over the 10 year period for which the most recent viral load was >1000 copies per mL, as opposed to the calculation of this proportion for each 3 month period in the 10 years and then taking the mean. This is important for this regimen in all people on ART because there are many initiations of injectable CTG-RPV in the first period (when the proportion of people with a most recent viral load of >1000 copies per mL is low), and few subsequent initiations that are all in people initiating ART for the first time (hence, viral load is >1000 copies per mL in almost all cases). Because we model true viral load, this is the actual viral load of the person and is not necessarily measured, whereas a clinic would only know a person's viral load if it was measured. †These patients fulfilled the first-line failure or switch criteria. ‡Difference in DALYs ÷ (difference in costs/cost-effectiveness threshold).

Table 2: **Predicted effects of three implementation approaches for the introduction of injectable CTG-RPV**

- Estimated to be cost effective if delivered 131 $/year
- Less like to be cost effective if the proportion of PWH <1000 cp/mL is high
- Injections every 2 months partially reduce some of the costs
- Key population: adholescents, high risk sexual behaviours and mobile workers
- Increases risk of resistance and no resistance testing planned to be implemented

Lancet Glob Health 2021; 9: e620–27

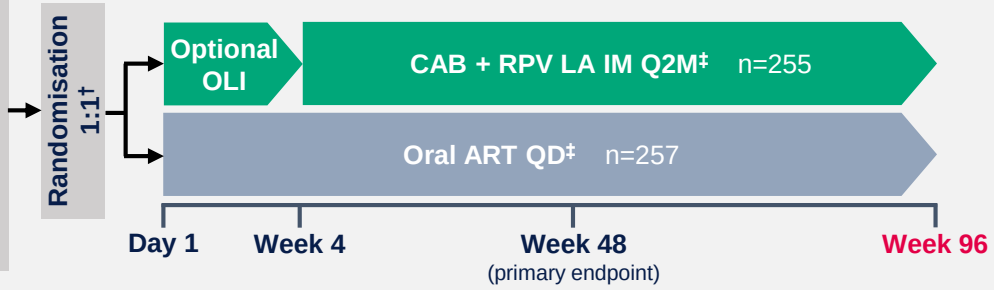
CARES

CAB + RPV LA demonstrates non-inferior long-term efficacy in diverse populations and settings through 2 years, compared to oral ART

Study design and population[1,2]

Inclusion criteria

- Aged ≥18 years
- Receiving ART* for ≥6 months
- No history of treatment failure
- Confirmed VL <50 c/mL



Multi-country RCT completed in Uganda, Kenya and South Africa (N=512):

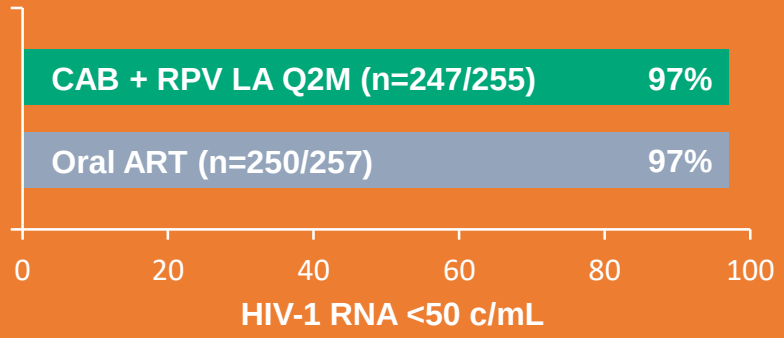
- **Women**: 58%
- **Black** race: 99.6%
- BL **BMI ≥30 kg/m²**: 21%
- **INSTI** use at BL: 92%
- Prior exposure to **NNRTIs**: 74%

Assessed retrospectively at W48:

- **Viral subtype A1**: 55%
- BL archived **RPV RAMs§**: 8%
- BL archived **CAB RAMs§**: 4%

Routine VL monitoring was done at BL, 6, 12, 18 and 24 months

Efficacy[1]



1.6%
4/255

on CAB + RPV LA experienced CVF¶

3 participants had viral sequences available at failure; 3/3 had RAMs to RPV and CAB. 3 resuppressed on DTG/TDF/3TC, 1 died due to HIV-unrelated reason[2]

Adherence, safety, tolerability and PROs[1]

- **High adherence to injections**
  96% (3,142/3,261) of scheduled injections administered within the ±7-day window
- **CAB + RPV LA was well tolerated**
  <1% (2/255) Grade 1–4 AEs led to treatment discontinuation in the CAB + RPV LA arm and 2% (5/257) in the oral ART arm#
- **Strong preference for CAB + RPV LA and significant increase in treatment satisfaction with CAB + RPV LA vs oral ART**
  >99% (243/244) preferred CAB + RPV LA vs oral ART (CAB + RPV LA arm)
  HIVTSQs mean change +27.1 vs +17.9 (p<0.0001), respectively**

See next slide for footnotes and abbreviations

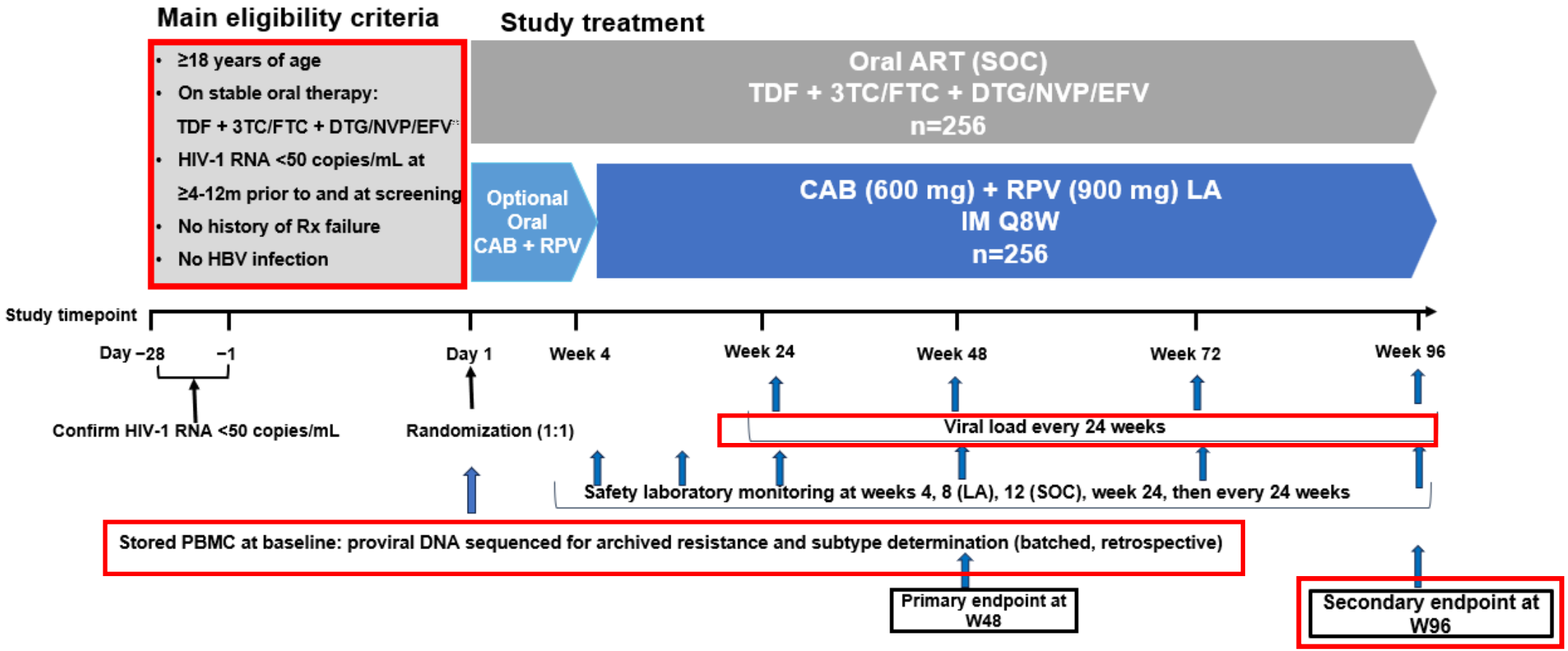
1. Kityo C, et al. CROI 2025. Oral 202
2. Kityo C, et al. Lancet Infect Dis. 2024:S1473-3099(24)00289-5 (and suppl. appendix)

Study Objective

To demonstrate the sustained virologic response and safety of switching virologically suppressed adults to CAB + RPV LA every 8 weeks compared to continuing oral standard-of-care (SOC) in a sub-Saharan African population managed under a Public Health Approach at Week 96

Study Design

Phase 3b, Randomized (1:1), Open-Label, Active-Controlled, Multi-Centre, Parallel-Group, Noninferiority Study



Kityo Mutuluuza et al. CROI 2025; San Francisco, CA. Oral presentation 202.

Outcomes and Analysis

Main outcome:

- Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 96 (FDA snapshot)
- Non-inferiority assessed in the intention-to-treat (ITT) population, 10% NI margin
- Sensitivity analysis done in per-protocol population

Secondary outcomes:

- Proportion of participants with plasma HIV-1 RNA ≥50 copies/mL (FDA Snapshot; ITT, 4% NI margin)
- Proportion of participants with confirmed virologic failure (CVF; 2 consecutive HIV-1 RNA ≥200 copies/mL taken 4-6 weeks apart) [key secondary outcome]
- Safety and tolerability
- Treatment satisfaction

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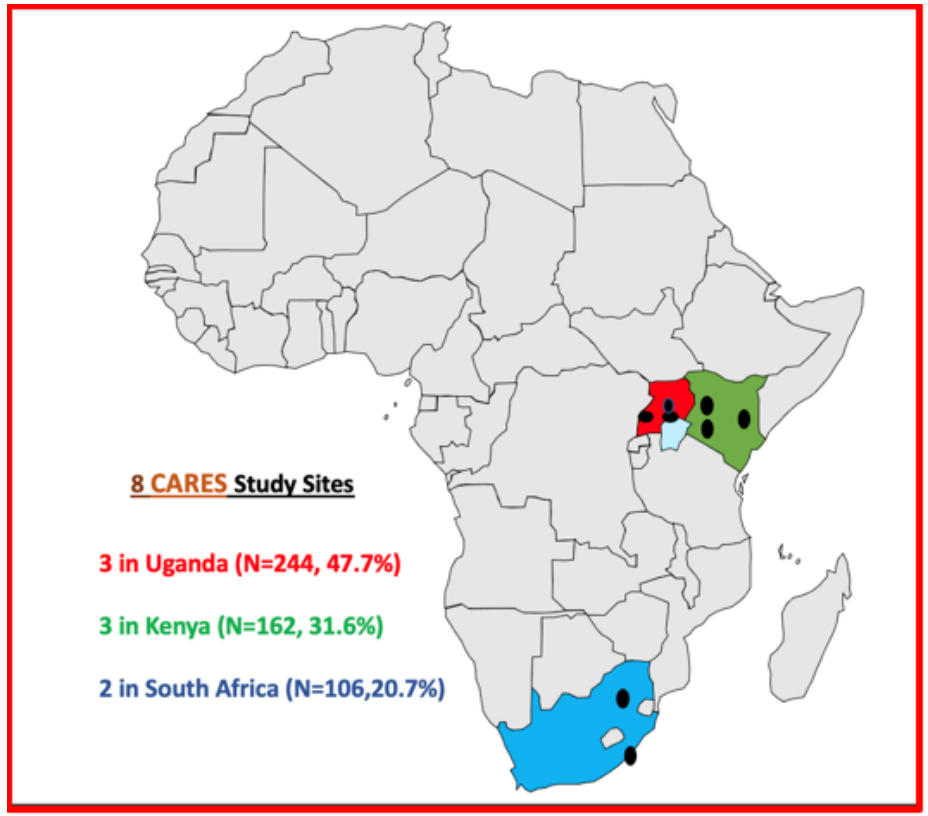
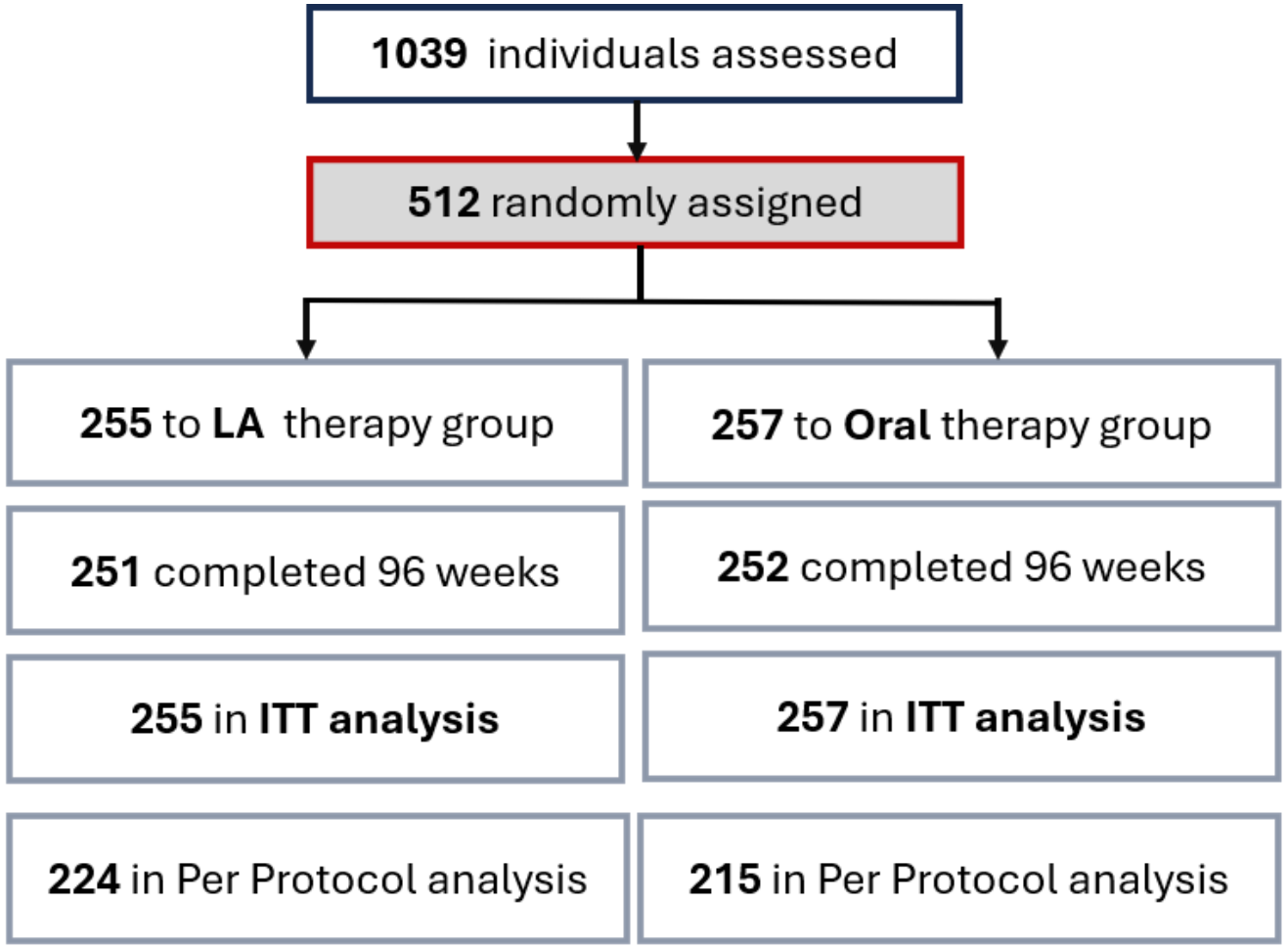
Enrollment and Retention



98% retention at Week 96



Kityo Mutuluuza et al. CROI 2025; San Francisco, CA. Oral presentation 202.

Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57)	149 (58)	295 (58)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI≥30 kg/m^2, n (%)	57 (22)	51 (20)	108 (21)
Black race, n (%)	254 (>99)	256 (>99)	510 (>99)
Time on first-line ART, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (74)	191 (74)	380 (74)
INSTI regimen at screening	231 (91)	240 (93)	471 (92)
NNRTI regimen at screening	24 (9)	17 (7)	41 (8)
Archived DNA analysis* †			
Viral subtype A1, n/n (%)	116/218 (53)	120/215 (56)	236/433 (55)
RPV resistance mutations, n/n (%)	14/208 (7)	16/193 (8)	30/401 (7)
RPV intermediate/high-level resistance, n/n (%)	4/208 (2)	8/193 (4)	12/401 (3)
CAB resistance mutations, n/n (%)	8/99 (8)	12/103 (12)	20/202 (10)
CAB intermediate/high-level resistance, n/n (%)	3/99 (3)	2/103 (2)	5/202 (2)

*Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline. †Viral subtype, resistance mutations and drug susceptibility were determined using the Los Alamos National Laboratory Panel, IAS-USA 2022 mutations list and Stanford algorithm respectively.

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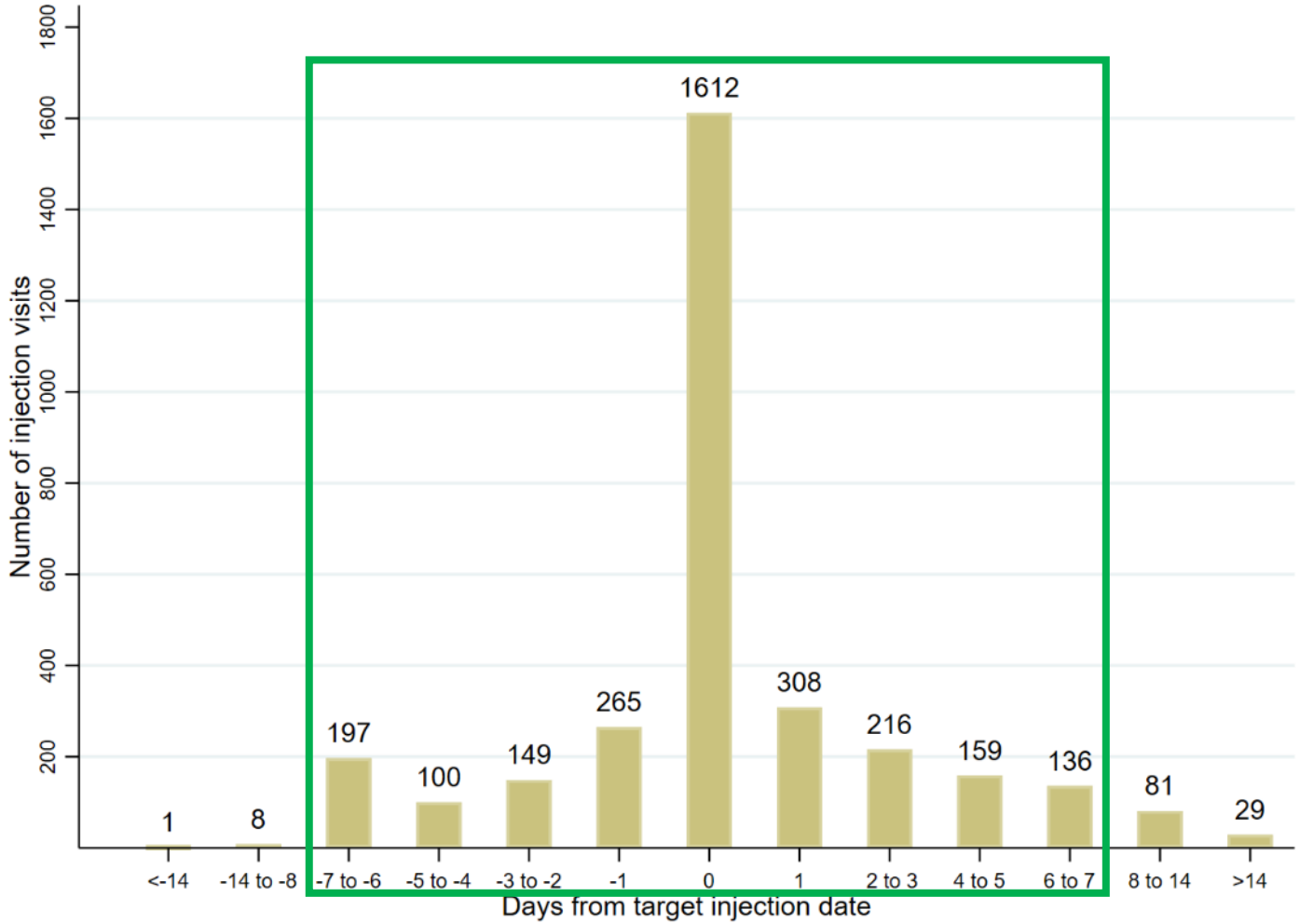
Adherence and Timing of Injections



206 (81.1%) participants received all scheduled injections within the protocol-mandated 7-day window

97% of 3,261 scheduled injections within protocol-mandated 7-day window

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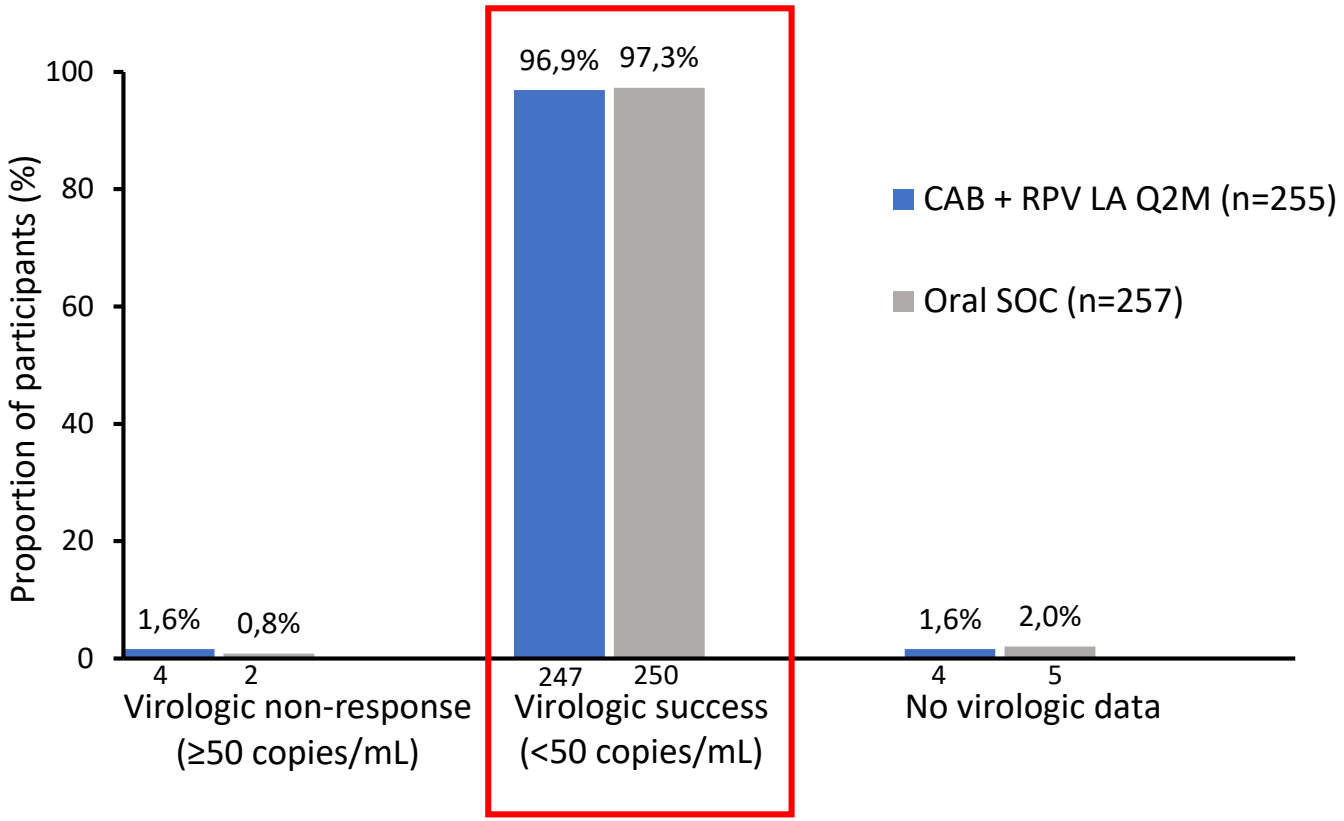
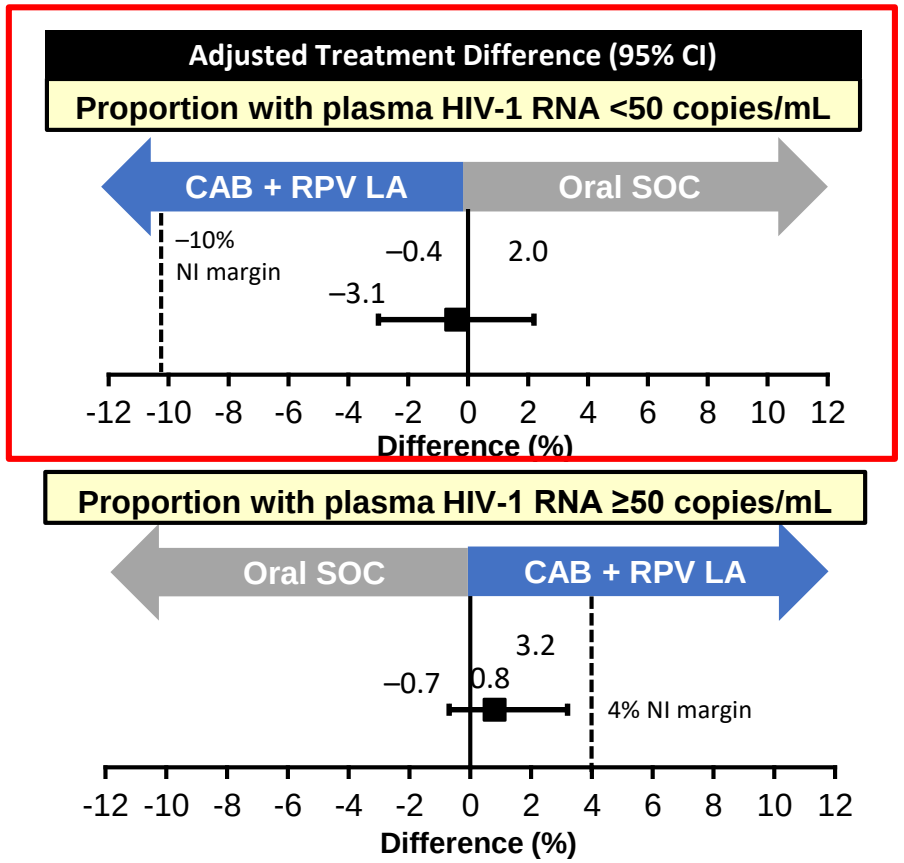
Virologic Outcomes at Week 96 (ITT)





Primary outcome - proportion with plasma HIV-1 RNA <50 copies/mL:

- Main analysis (ITT): adjusted difference -0.4% (95% CI, −3.1 to 2.0), **meeting the non-inferiority criterion**
- Sensitivity analysis (per-protocol): adjusted difference -1.3% (95% CI, -4.2 to -0.1) **confirming non-inferiority**

Kityo Mutuluuza et al. CROI 2025; San Francisco, CA. Oral presentation 202.

Participants With Virological Failure

Confirmed virological failure (VL ≥ 200 copies/ml x 2)	CAB + RPV LA 4 (1.6%)	Oral ART 0	Difference (95% CI) 1.6% (0.4 to 4.2)

	Participant 1	Participant 2	Participant 3	Participant 4
At confirmed virological failure				
Week of failure	48	48	**72**	**72**
Viral load, copies/ml	8,608 and 1612	44,984, no repeat	798 and 563	259 and 16,161
RPV mutations (level) ††	V108I, E138K (intermediate)	K103N/S, V106V/A, E138A, M230M/L (high)	Test Failed	E138A (low)
CAB mutations (level CAB, DTG) ††*	E92E/V, N155H, L74M (intermed., potential low)	G118R (high, high)	Test Failed	Q148R (M50I) (high, low)
At baseline				
RPV mutations (level) †	Nil	K103N/S, E138A (low)	E138K (low)	Nil
CAB mutations (level) †	L74M (low)	Nil	Test Failed	Nil
Viral subtype †	A1	D	A1	C
BMI, kg/m^2	25.9	22.0	22.2	19.9

*Participants 1,3 and 4 resuppressed on TLD. ††RNA sequencing performed on plasma collected at confirmed virologic failure. Interpreted using Stanford algorithm. †Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline.

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Safety: Adverse Events (Week 96)

Participants with at least 1 AE, n (%)	**CAB + RPV LA (n=255)**	**Oral ART (SOC) (n=257)**	**Difference (95% CI)**
Grade ≥3 AE	41 (16)	22 (9)	7.5 (1.9 to 13.2)
Related to study drug *	5 (2)	4 (2)	0.4 (-1.9 to 2.7)
Serious adverse event	12 (5)	9 (4)	1.2 (-2.2 to 4.6)
Any (grade 1-4) AE	230 (90)	185 (72)	18.2 (11.6 to 24.8)
Excluding injection-site reactions	202 (79)	185 (72)	7.2 (-0.2 to 14.6)
Leading to study drug discontinuation **	2 (<1)	5 (2)	-0.8 (-2.6 to 1.1)

*Grade ≥3 AEs considered to be at least possibly related to study drug were:

- Injection-site nodule (1), increased LDL (2), increased triglycerides (1) and proteinuria (1) in the CAB + RPV LA arm
- Decreased eGFR (2), increased AST (1), and increased blood glucose (1) in the oral ART SOC arm

**Grade 1-4 AEs leading to study drug discontinuation were:

- Injection-site sterile abscess (1) and lung adenocarcinoma (1) in the CAB + RPV LA arm
- Decreased eGFR (1), increased blood glucose (1), increased AST (1), and osteoporosis (2) in the oral ART SOC arm

Injection Site Reactions (Week 96)

	Grade 1	Grade 2	Grade 3
Any ISR, n (%)	164 (64)	32 (13)	1 (<1)
Pain	163 (64)	29 (11)	0 (0)
Swelling	17 (7)	3 (1)	0
Nodule	16 (6)	1 (<1)	1 (<1)
Erythema	3 (1)	1 (<1)	0
Induration	1 (<1)	1 (<1)	0
Rash	1 (<1)	0	0
Pruritus	3 (1)	0	0
Discharge	0	1 (<1)	0
Abscess	0	2 (1)	0

- Most ISRs were grade 1 or 2; only 1 grade 3; none were grade 4
- Only 1 (injection-site sterile abscess) led to treatment discontinuation

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Treatment Satisfaction and Preference

	CAB + RPV LA (n=253)	Oral ART (SOC) (n=255)	Adjusted mean difference (95% CI)	P value
HIVTSQc at Week 96	**27.1 ± 11.2**	**17.9 ± 18.6**	**9.6 (7.5 to 11.8)**	**<0.0001**

- Assessed by HIV Treatment Satisfaction Questionnaire change version (HIVTSQc)
- Treatment satisfaction increased to a greater extent in participants who switched to CAB + RPV LA vs. those who continued oral ART at Week 96

Over **99% (243/244**) of participants **on LA** preferred long-acting therapy over daily oral treatment at Week 96

Conclusions

At Week 96, CAB + RPV LA every 8 weeks:

✓ **Had high efficacy:**

- 97% had VL suppression < 50 copies/mL; non-inferior to oral ART (SOC)
- 1.6% had CVF (4 participants); three re-suppressed after switch to tenofovir, lamivudine, dolutegravir
- This was achieved in the public health approach with sparse viral load monitoring; and despite population with high rates of obesity; prior NNRTI exposure; different subtypes (majority A1)

✓ **Had a good safety profile and was well tolerated:**

- 2% had severe (≥ grade 3) AE related to study medication; 5% serious Aes
- Injection site reactions were mainly Grade 1-2; only 1 leading to discontinuation

✓ **Increased treatment satisfaction:**

- Greater increase in satisfaction score in participants who switched to CAB + RPV LA versus those continuing oral SOC

Overall conclusion:

This demonstration of safety and efficacy of CAB + RPV LA in extended follow up provides essential information for discussing a potential role for LA in treatment programs in sub-Saharan Africa using the public health approach

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Clinical Infectious Diseases

IDSA FEATURES

Policy Recommendations to Support Equitable Access to Long-Acting Injectables for Human Immunodeficiency Virus Prevention and Treatment: A Policy Paper of the Infectious Diseases Society of America and the HIV Medicine Association

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Long-acting injectables (LAIs) for HIV prevention and treatment could dramatically improve health outcomes and health equity for people with HIV and those who could benefit from pre-exposure prophylaxis. Despite widespread acceptability and demand by providers and potential users of LAIs, implementation has been extremely limited since the introduction of cabotegravir/rilpivirine, the first LAI for HIV treatment, in January 2021, and long-acting cabotegravir, the first LAI for HIV prevention, in December 2021. We report results of a provider survey, conducted by the HIV Medicine Association, which identified LAI implementation barriers related to health insurance processes, staffing and administrative support, drug costs and acquisition, and access for individuals who are uninsured. We provide policy recommendations to address those barriers and facilitate broad and equitable access to LAIs for HIV prevention and treatment, which will be necessary to achieve the goals of the US Ending the HIV Epidemic initiative.

Keywords. antiretroviral agents; pre-exposure prophylaxis; health policy; cabotegravir; lenacapavir.

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The long wait for long-acting HIV prevention and treatment formulations

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Large randomised studies of new long-acting medications for the prevention and treatment of HIV have shown high effectiveness and acceptability. Although modelling studies indicate these agents could be fundamental in HIV elimination, coordination of their entry into health-care markets is crucial, especially in low-income and middle-income countries with high HIV prevalence, where coordination is low despite UNAIDS flagging that global HIV targets will not be met. Research and implementation projects are tightly controlled by originator pharmaceutical companies, with only a small percentage of eligible people living with or affected by HIV benefiting from these projects. WHO, financial donors, manufacturers, and governments need to consider urgent coordinated action from stakeholders worldwide, akin to the successful introduction of dolutegravir into treatment programmes across low-income and middle-income countries. Without this immediate coordination, large-scale access to long-acting agents for HIV will be delayed, potentially extending into the 2030s. This delay is unacceptable considering the established global HIV targets.

Conclusions

- Long-acting antiretrovirals are perhaps the **greatest advance in HIV care** in over a decade and provide **great promise** towards achieving global **HIV prevention and control** programme targets
- Current long-acting agents remain **unavailable or cost-prohibitive across much of the globe**
- If action from the broader HIV community is stagnant, the **populations who are most in need** of these long-acting agents are **unlikely to receive any benefit until well into the 2030s**, resulting in a **large number of preventable HIV infections**
- **Coordination** by international agencies, with assistance from relevant financial donors and stakeholders, will be needed in the **complex research and access programmes** required to provide **wide scale use** of these indispensable products to people living with HIV or affected by HIV

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