3rd Long-Acting HIV Treatment and Prevention Conference

15 September 2026 | Johannesburg

Progress towards bringing long-acting antiretrovirals to children and adolescents: New formulations and drug delivery development

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THE PROGRESSION: ADDRESSING NEEDS, ASPIRING FOR MORE IN LONG-ACTING AR FOR CHILDREN

THE NEED

ADDRESSING FUNDAMENTAL DEMANDS

Current Limitations & Resource Scarcity

Daily Regimen Stress

Adherence Fatigue

Complex Dosing Logistics

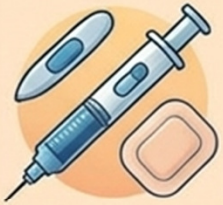
Healthcare Access Barriers for Families

Fragmented Data and Outdated Systems

THE DREAM

VISUALIZING IDEAL SOLUTIONS

Conceptual Long-Acting Breakthroughs



Long-Acting Injectable (LAI) & Transdermal Delivery

Integrated, Child-Friendly Delivery Points

Optimized! "medication-release" system Drug Release

Universal, Equitable Access to LA-ART

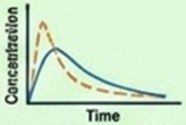
THE REALITY

NAVICATING CURRENT PROGRESS

Development and Implementation Challenges

Infrastructure for administration and delivery of LA-ART

Ongoing Clinical Trials for Pediatric Formulations



Improved Paediatric PK Models

Pharma Manufacturing and Scaling Hurdles

Infrastructure and Implementation Challenges

Integrating New into Existing Health Systems

THE FUTURE

ACHIEVING SUSTAINABLE PROGRESS

Optimization for Thriving Pediatric Health

Holistic Care and Integrated Wellness Programs

Enhanced Quality of Life and Normal Daily Activities

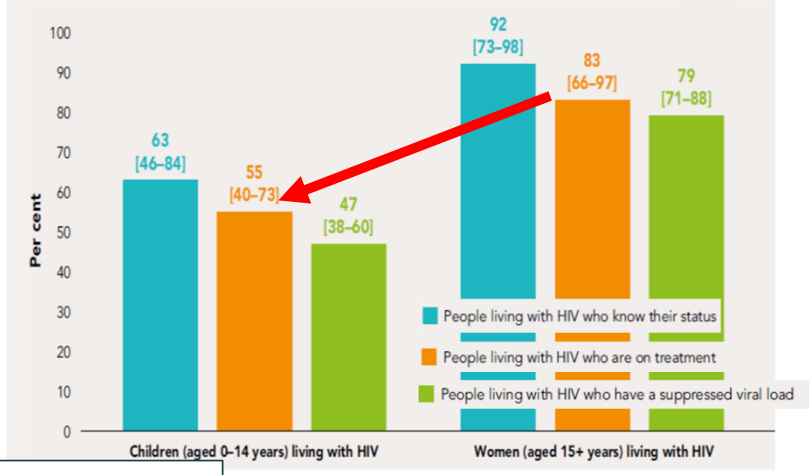
Future-Proof Pediatric ART and Sustained Viral Suppression

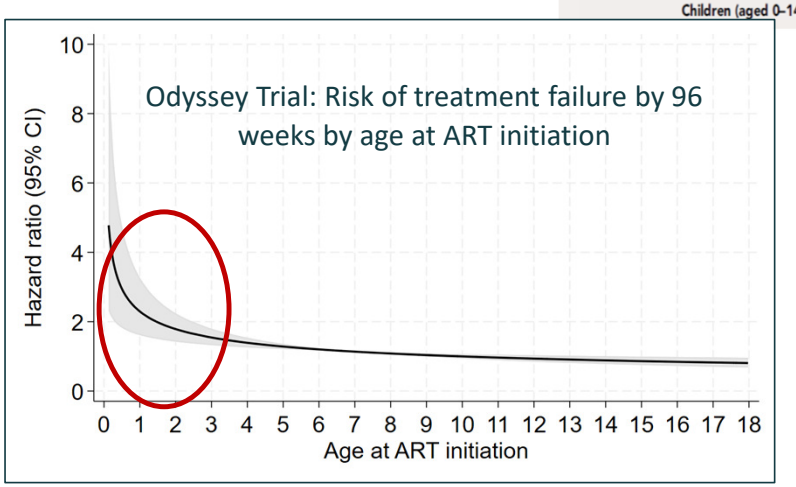
THE NEED → THE DREAM → THE REALITY → THE FUTURE

Need: Children and adolescents

- Children <15 years continue to experience poorer outcomes across the treatment cascade compared to adults

- In RCT settings, the risk of treatment failure decreases with increasing age independently of baseline CD4% and viral load
- **Unique challenges facing children and adolescents:**
  - Lack of palatable child-friendly fixed dose formulations
  - Caregiver-led adherence
  - Life-long toxicity
  - Disclosure and stigma
  - Mental health challenges
  - Adolescent-specific
    - Transition to adult/self-care
    - Emerging SRH needs
    - Autonomy vs adherence

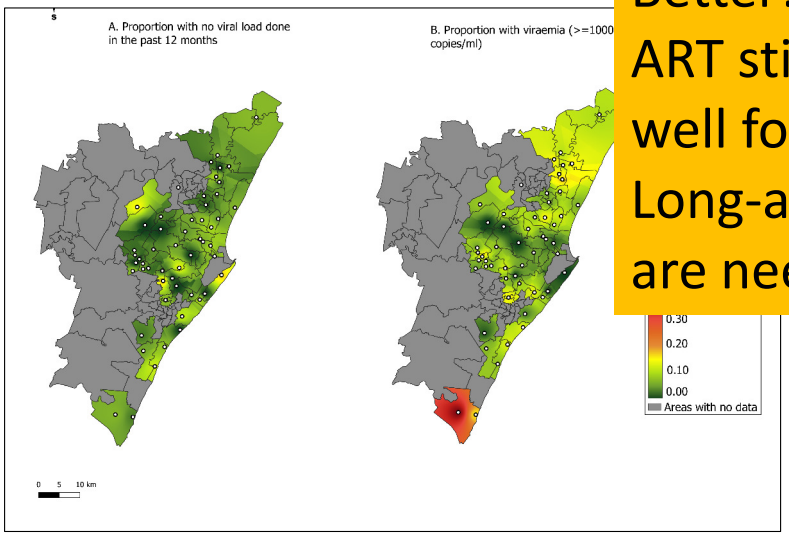




UNAIDS Global AIDS Update - 2025 (https://aidsinfo.unaids.org/), Wyncoll J, CID, 10 April 2026 (https://doi.org/10.1093/cid/ciag232)

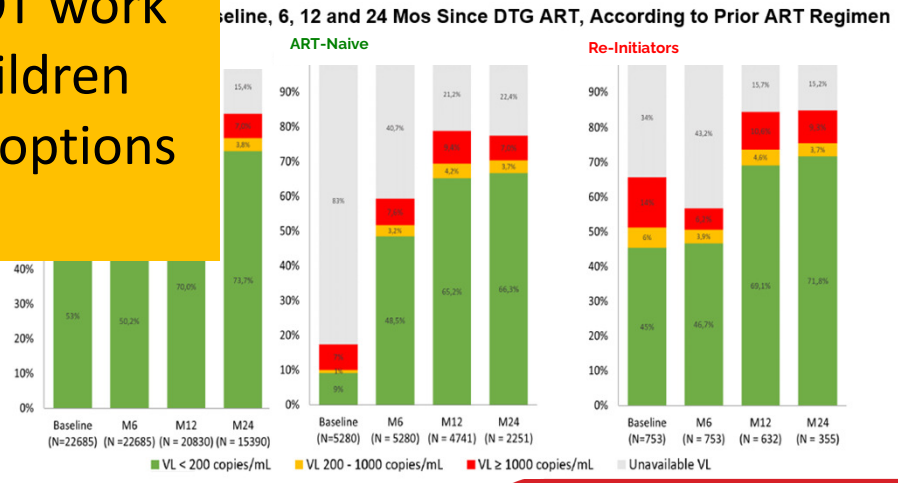
Rapid transition to Dolutegravir

- **KwaZulu-Natal** within 1 year of introduction:
  - **100% (3379)** were transitioned to DTG
  - **94% (3180)** had a recent HIV VL
  - **90% (2877)** viral suppression (<1000c/mL) at 12 months



Better! But daily oral ART still does NOT work well for many children Long-acting ART options are needed

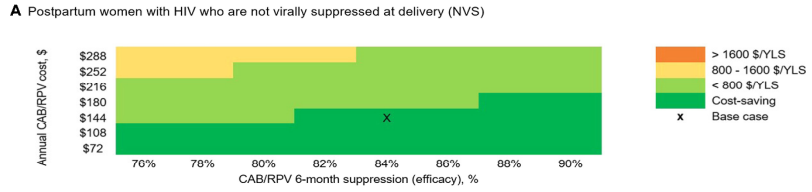
- **Global IeDE cohort**: >60,000 children with HIV 2% died, 23% LTFU, 6% stopped DTG
  - **Overall, 73% had a HIV VL <200c/mL at 24 months**
  - Viral suppression at 24 months On ART prior 73.7%
  - [illegible]3%
  - [illegible]ors 71.8%

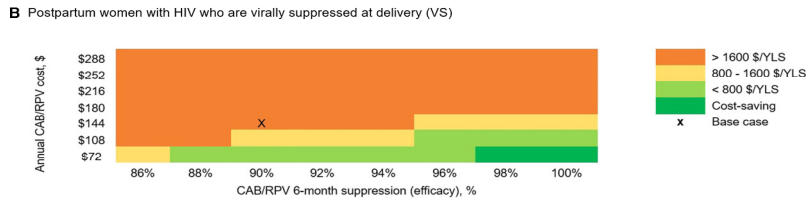


Unpublished, Hlabisa M, Dame J et al. CROI February 2026, Denver, CO # 860

Need: Protecting Mothers and their infants post partum

- Despite improved maternal coverage and viral suppression with daily oral ART
  - High rates of HIV vertical transmission persist
  - Increasing proportion of new paediatric infections occurring during the postnatal period
- Retention in care and viral suppression fall post delivery
- Long-acting ART (LA ART) strategies have the potential to simplify options for women post partum and for post-natal prophylaxis during breastfeeding



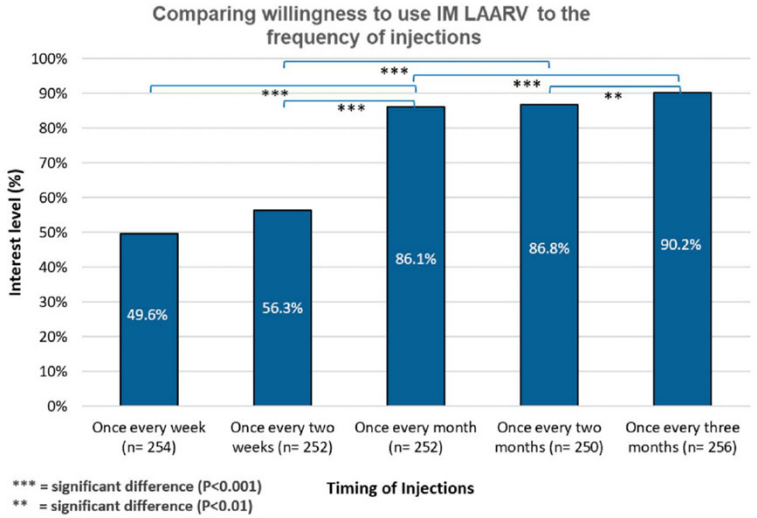


Phillips. 2014 Oct 8;17(1):19242;. Tewari, J Infect Dis, Volume 233, Issue 1, 15 January 2026

Need: Youth are interested in LA ART

- Cross-sectional focus group discussions with caregivers, adolescents and healthcare workers in KwaZulu-Natal, South Africa.
- LA-ART assessed as highly useful, anticipating **reduced pill burden, greater privacy, and improved adherence**
- Concerns about **injection pain, potential side effects, and proper administration.**
- Importance of education, provider support, and stigma reduction for uptake and sustained use.

- Cross-sectional survey of 303 youth living with HIV at 4 clinics in the United States
- Perinatal and non-perinatal infections



Bergham.S, unpublished, Weld ED, et al. JAIDS. 2019. PMID: 30418298.

The Dream

Dosing Interval

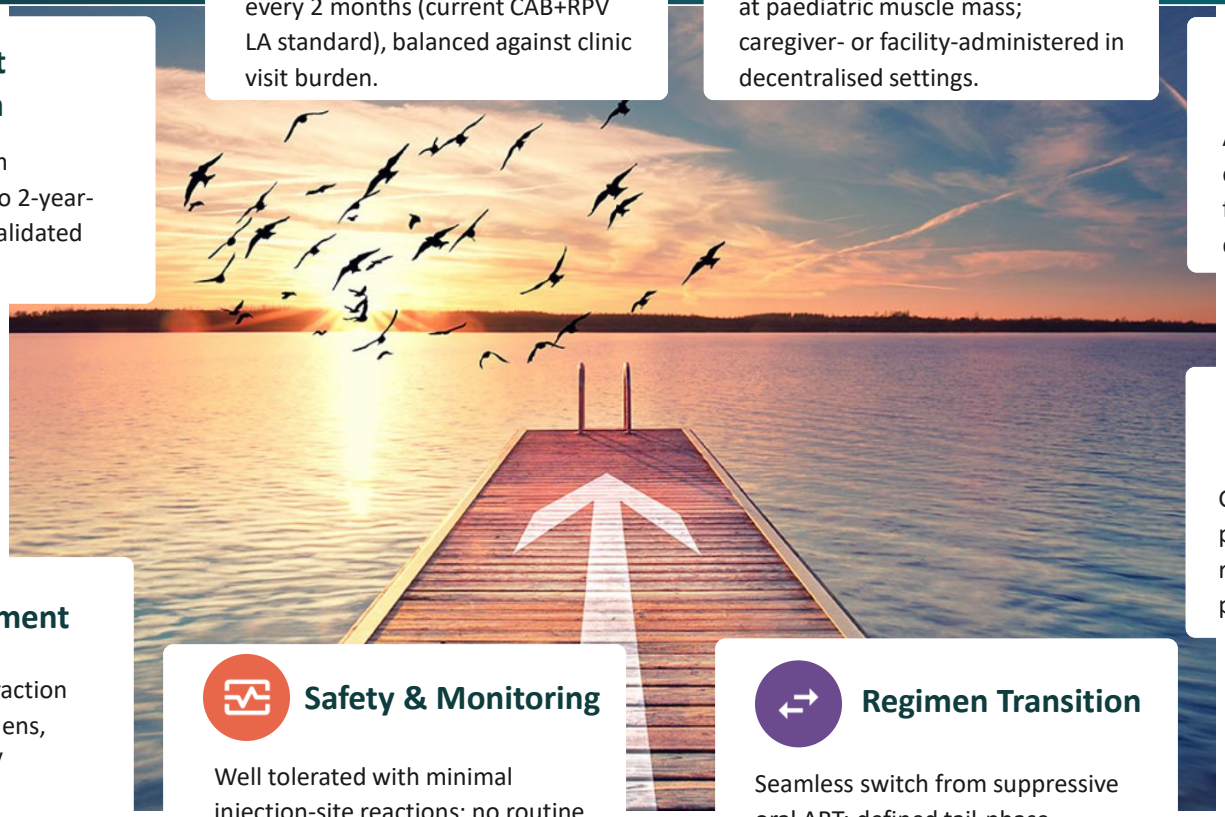
Ideal: every 4-6 months. Acceptable: every 2 months (current CAB+RPV LA standard), balanced against clinic visit burden.

Administration

Low-volume IM injection tolerable at paediatric muscle mass; caregiver- or facility-administered in decentralised settings.

Age & Weight De-escalation

Stepwise PK bridging from adolescents (12+) down to 2-year-olds, with dosing bands validated across low body weights.



Storage & Cold Chain

Ambient-stable formulation; no cold chain requirement to remain feasible for LMIC primary-care delivery.

Access & Affordability

Generic-ready manufacturing pathway and multi-source supply to reach LMIC paediatric HIV programmes at scale.

TB Co-treatment

No clinically significant interaction with rifampicin-based regimens, given high paediatric TB-HIV overlap.

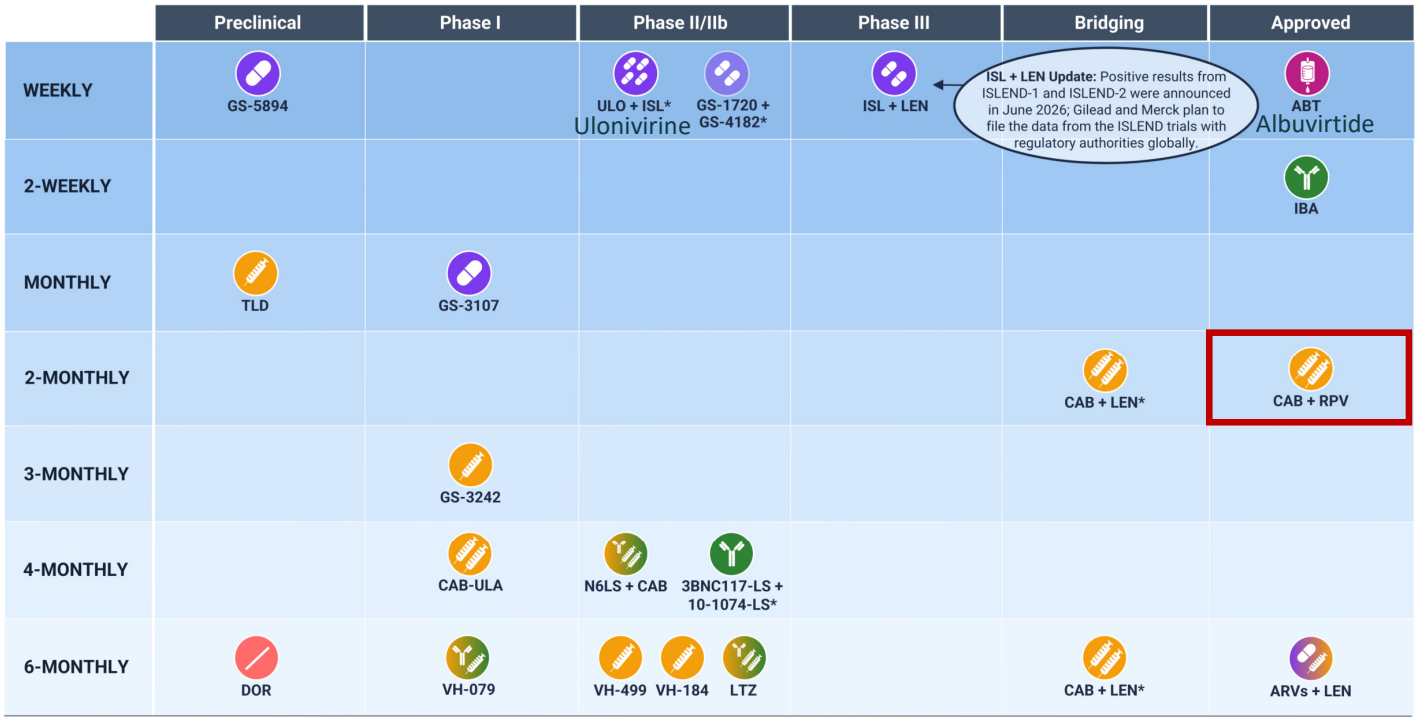
Safety & Monitoring

Well tolerated with minimal injection-site reactions; no routine laboratory monitoring required post-initiation.

Regimen Transition

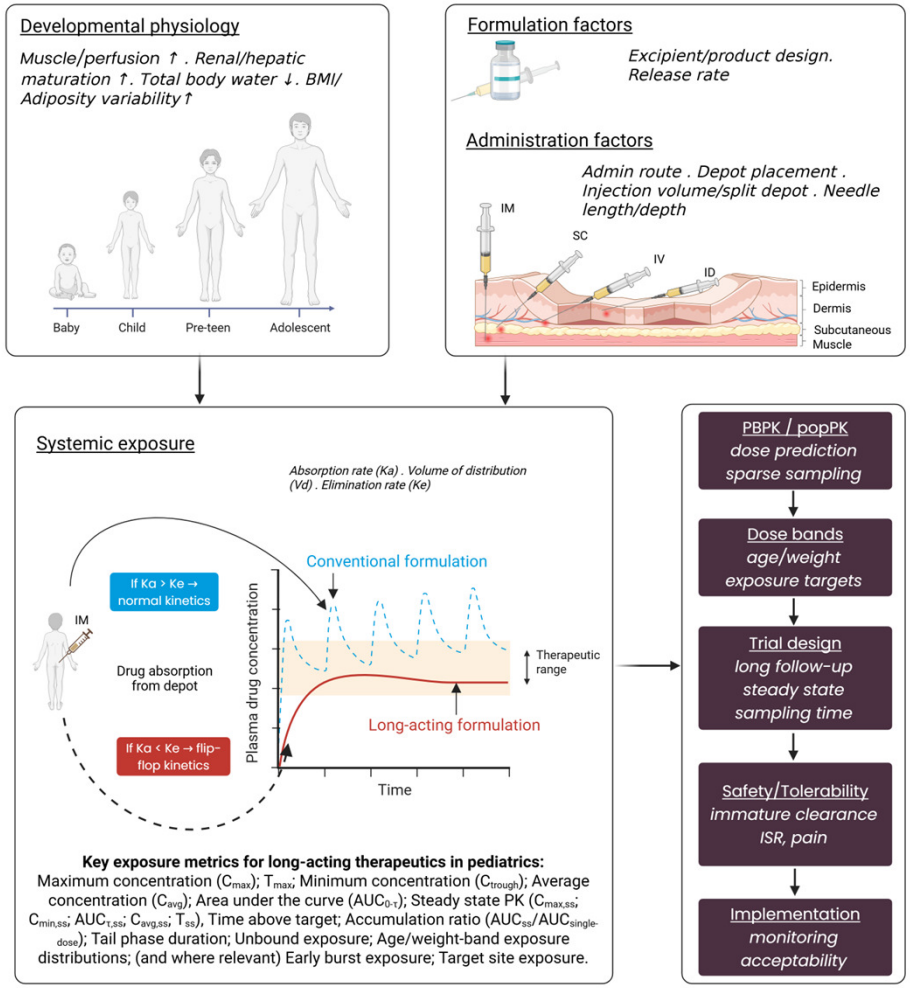
Seamless switch from suppressive oral ART; defined tail-phase resistance mitigation on discontinuation.

Dream: LA-ART Pipeline



https://avac.org/resource/infographic/long-acting-hiv-treatment-pipeline/

Key considerations



The Reality

Drug	Age/ Weight	US FDA Approved Indication	WHO guidelines
Cabotegravir – Rilpivrine [CABENUVA]	≥12 years ≥ 35 kg	"…to replace the current antiretroviral regimen in those who are **virologically suppressed** (HIV-1 RNA <50 copies/mL) on a **stable antiretroviral regimen** with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.	Long-acting injectable cabotegravir + rilpivirine (CAB+RPV) can be used as an alternative switching option in adults and adolescents who have an undetectable HIV viral load on oral ART and no active hepatitis B infection.
Lenacapavir [SUNLENCA]	Adults	"… in heavily **treatment-experienced adults with multidrug resistant HIV-1 infection** failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.	

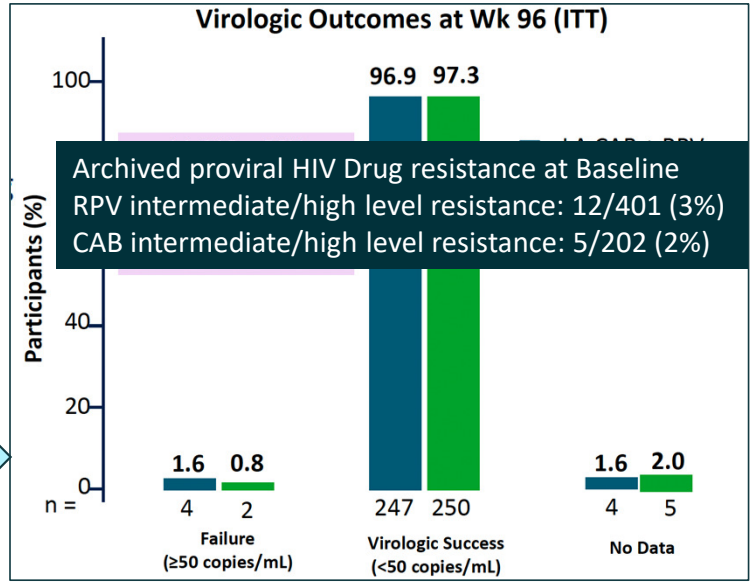
https://www.accessdata.fda.gov/

WHO updated recommendations on HIV clinical management: recommendations for a public health approach. Geneva: World Health Organization; 2025.

CAB/RPV in PLHIV virologically suppressed
Adult data

- FLAIR: CAB/RPV LA in treatment naïve; First put on DTG/ABC/3TC for 20 weeks then LA ART (n=283)
- Atlas: CAB/RPV LA in treatment experienced participants every 4 weeks, on suppressive regimen for 6 months prior to switch (n=308)
- Atlas 2M: CAB/RPV LA in treatment experienced participants every 8 weeks after VS x ≥ 6 months (n=522)
- Solar: CAB/RPV LA every 8 weeks in treatment experienced participants (47% expressed internal or external stigma) switched BIC/TAF/FTC when VS (n=447)
- Cares: CAB/RPV LA every 8 weeks in treatment experienced participants who switched from oral ART in Uganda, Kenya, South Africa (n=512)

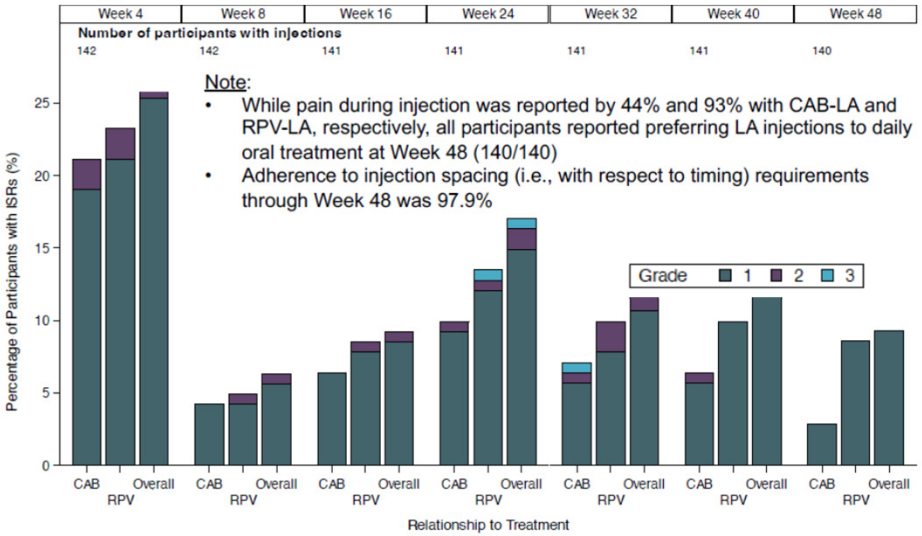
Rate of confirm virological failure ranged from 0.7% at 48 weeks, 0.9-1.6% at 96 weeks and 1.6-2.3% >124weeks



Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023; Ramgopal M. Lancet HIV 2023; Kityo C Lancet ID 2024 & CROI 2025

IMPAACT 2017 (MOCHA)
Data in Adolescents

- 140/144 completed 48 weeks
- No confirmed virologic failures (2 consecutive plasma HIV-1 RNA ≥200 copies/mL) on CAB LA + RPV LA
- Ten participants had viral blips (HIV VL >50 copies/mL; range 53-457 copies/mL) at some point



Injection Site Reactions (ISRs)

- ***12% (196/1,696)*** *of injections had an ISR*
  - *98% were Grade 1/2*
  - *89% resolved within 7 days*
- *At week 48, % reporting ISR*
  - *RPV: 9.3% (13/140)*
  - *CAB: 2.9 % (4/140)*

One discontinued study drug after "anaphylaxis," but independent review classified as severe ISR

Two grade 3/4 abscess attributed to study drugs

NCT03497676

Gaur AH, et al. Lancet HIV. 2026 PMID: 41547359.

IMPAACT 2017 (MOCHA)
Acceptability and tolerability

- Adolescents' most consistent concern was about the location of the injection. *Many expressed **wanting a shot that could be given somewhere other than the buttocks**.*

- Sub-study of Cohort 1 that included 30 on CAB and 25 on RIL

Recognized CAB LA + RPV LA as <u>better for stigma</u>: Not having to worry about people seeing them take their pills (44%) was the most common primary reason for wanting intramuscular ART.

Pain scores (through 12 weeks):

	Cohort 1C (LA-cabotegravir)			Cohort 1R (LA-rilpivirine)			Total		
	Week 4 (n=29)	Week 8 (n=29)	Week 12* (n=8)	Week 4 (n=23)	Week 8 (n=23)	Week 12* (n=13)	Week 4 (n=52)	Week 8 (n=52)	Week 12* (n=21)
No hurt	12 (41%)	9 (31%)	6 (75%)	4 (17%)	3 (13%)	3 (23%)	16 (31%)	12 (23%)	9 (43%)
Hurts little bit	13 (45%)	15 (52%)	1 (13%)	14 (61%)	11 (48%)	4 (31%)	27 (52%)	26 (50%)	5 (24%)
Hurts little more	2 (7%)	4 (14%)	1 (13%)	1 (4%)	6 (26%)	4 (31%)	3 (6%)	10 (19%)	5 (24%)
Hurts even more	2 (7%)	1 (3%)	0	3 (13%)	2 (9%)	2 (15%)	5 (10%)	3 (6%)	2 (10%)
Hurts whole lot	0	0	0	1 (4%)	1 (4%)	0	1 (2%)	1 (2%)	0
Hurts worst	0	0	0	0	0	0	0	0	0

Data are n (%). Percentages might not sum to 100 due to rounding. Answers are verbatim quotations from the questionnaire. The pain during injection questionnaire used a face scale. LA=long-acting injectable. *Only participants enrolled in protocol version 2.0 received a week 12 injection.

Table 3: **Responses to pain during injection questionnaire**

Concerns about <u>clinic attendance</u>: *"Especially for that teenager who's already not liking to be reminded that they're HIV positive. Then actually having to go to the clinic every month would not be necessarily a positive experience for them."*

By Week 48, the odds of reporting "*Hurts a little bit or worse*" decreased by 55% from Week 4 [OR (95% CI): 0.45 (0.29, 0.69)]

At the Week 8, 24, and 48 injections, 97%, 99%, and 100% of participants, respectively, preferred IMI over oral treatment

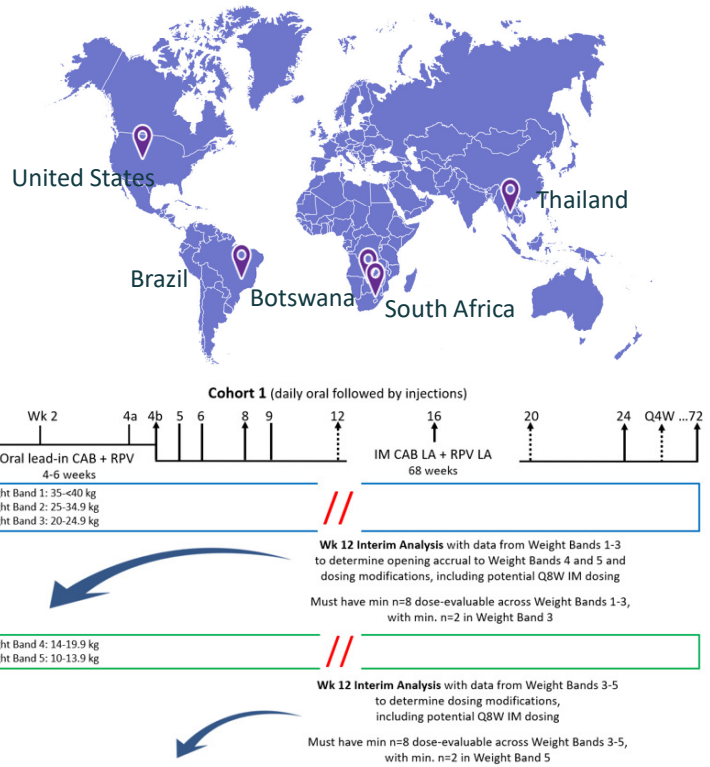
NCT03497676 Lowenthal et al, Lancet HIV. 2024 (PMID: 38538161) and 2026 (PMID: 41547358)

Slide courtesy of Ted Ruel

IMPAACT 2036: CRAYON

Safety and pharmacokinetics of long-acting cabotegravir and rilpivirine in young children 10 to <40 kg

- Interim safety and PK data from first **61 participants**, including first data from children <20 kg.
- Weight-band (WB) dosing: WB1 (35-<40 kg), WB2 (25-<35 kg), WB3 (20-<25 kg), WB4 (14<20 kg) and WB5 (10-<14 kg).
- The median (min, max) age and body weight at entry were **8 years of age** (2, 11) and **22 kg** (10.8, 39.3)
- Intramuscular injection either in **gluteal muscle** or **lateral thigh** (vastus lateralis)



- PO CAB+RPV x 4 wks followed by IM CAB+RPV Q4W in children 10 to <40 kg achieved target CAB and RPV plasma concentrations

Figure 1. Predose CAB (A) and RPV (B) concentrations after IM CAB-LA and RPV-LA: CRAYON/IMPAACT 2036

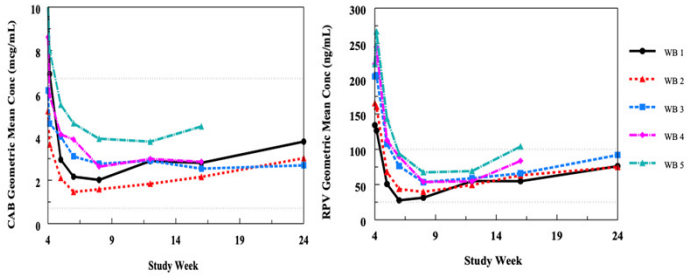


Figure 1 describes the median concentrations by weight-band of IM CAB-LA **(A)** and IM RPV-LA **(B)** and the protocol-defined PK acceptable criteria (minimum and maximum median pre-dose concentrations (.....) evaluated at W12

Protocol defined PK criteria (median W12 trough):
CAB: 0.71-6.7 mcg/mL
RPV: 25-100 ng/mL

Archary M, et al. CROI 2026, Denver, CO Poster #854

IMPAACT 2036: CRAYON

- 6 (10%) children experienced ≥ Grade 3 adverse event (AE), all of which resolved.
- One ≥ Grade 3 AE was drug-related (Grade 3 post-injection reaction). Two additional children had Grade 2 post-injection reactions. All 3 participants continued the study treatment.
- Injection site pain in 28 children (46%) was the most frequent AE.
- No AEs led to treatment discontinuation.

Table 2. Number of participants with Injection site (IS) reactions

Adverse Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
IS pain	24 (39.3)	4 (6.6)	0	28 (45.9)
IS swelling	7 (11.5)	1 (1.6)	0	8 (13.1)
IS erythema	3 (4.9)	0	0	3 (4.9)
IS induration	2 (3.3)	1 (1.6)	0	3 (4.9)
IS nodule	2 (3.3)	0	0	2 (3.3)
IS pruritus	2 (3.3)	0	0	2 (3.3)
IS haematoma	1 (1.6)	0	0	1 (1.6)

Weight Band	Daily Oral Dose (Oral lead-in)	Initial IM Injection	Subsequent IM Injection every four weeks
WB1: 35-<40kg	30mg CAB + 25mg RPV	600mg CAB LA + 900mg RPV LA	400mg CAB LA + 600mg RPV LA
WB2: 25-34.9kg	10mg CAB + 25mg RPV	300mg CAB LA + 600mg RPV LA	200mg CAB LA + 450mg RPV LA
WB3: 20-24.9kg	10mg CAB + 15mg RPV		
WB4: 14-19.9kg	10mg CAB + 12.5mg RPV	300mg CAB LA + 450mg RPV LA	200mg CAB LA + 300mg RPV LA
WB5: 10-13.9kg			

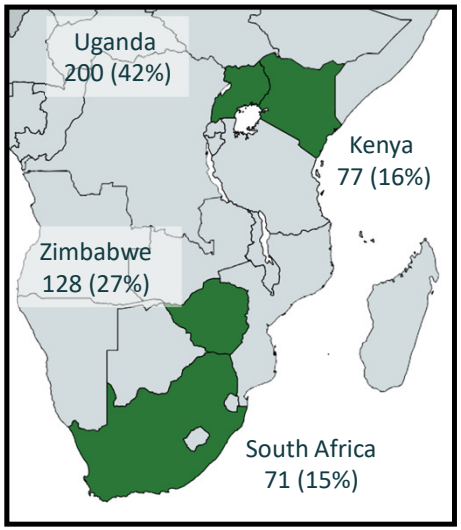
- PO CAB+RPV x 4 wks followed by IM CAB+RPV Q4W in children 10 to <40 kg achieved target CAB and RPV plasma concentrations
- No new safety concerns
- All participants transitioned to IM injection every 8 weeks
- Acceptability and tolerability presented at Paed HIV Workshop, July 2026
- Cohort 2 – fully enrolled (optional oral lead-in)

Archary M, et al. CROI 2026, Denver, CO Poster #854

LATA

A randomised open-label 2-arm 96 week trial in virologically suppressed adolescents aged 12-19 years of age in Sub-Saharan Africa

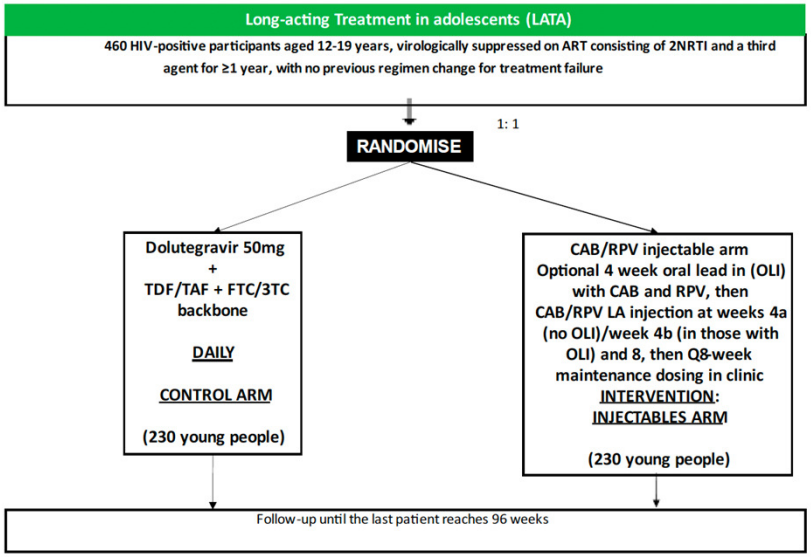
- Non-inferiority trial in Kenya, South Africa, Uganda and Zimbabwe. **Adolescents (12-19 years), with suppressed viral load (VL)<50copies/mL for ≥12 months** on ART and no prior treatment failure
- Randomised to every-8-weeks LAI CAB/RPV [optional oral lead-in (OLI)] or daily oral ART [tenofovir/lamivudine/dolutegravir (TLD)].



Hypothesis: CAB LA + RPV LA therapy will provide non-inferior sustained virological suppression compared to continuous treatment with daily oral ART

476 participants enrolled:

235 **LAI**, 241 **control**



Penta
Child Health Research

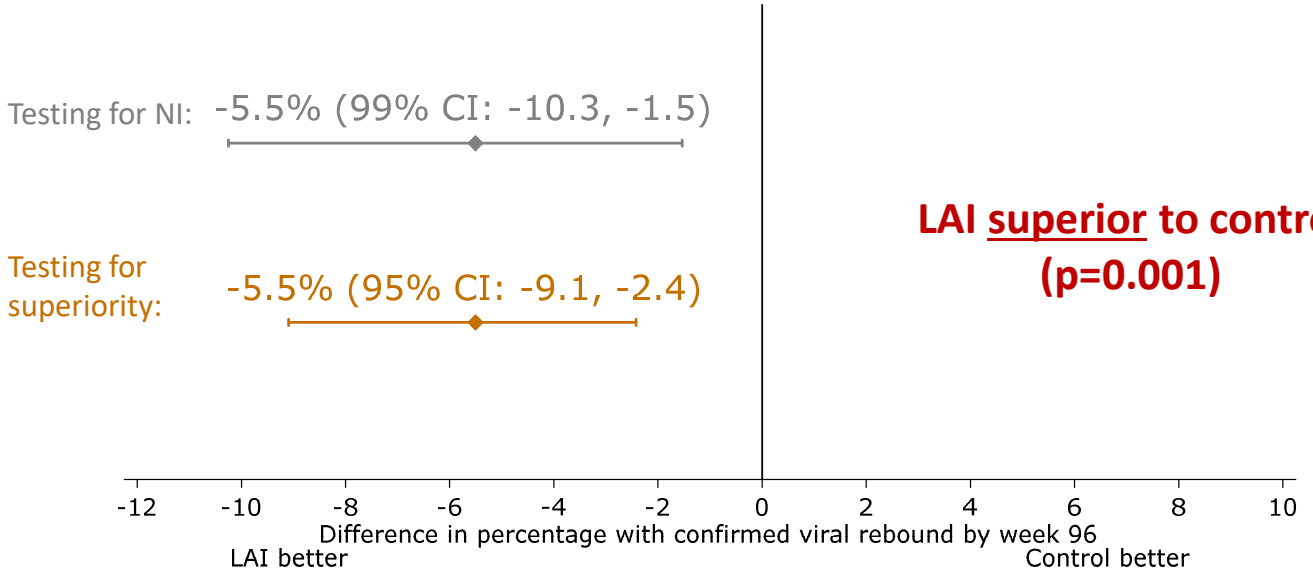
AIDS 2026: Co-Chairs Choice

3rd LA ART Conference

LATA

A randomised open-label 2-arm 96 week trial in virologically suppressed adolescents aged 12-19 years of age in Sub-Saharan Africa

- 2 (0.9%) **LAI** vs. 15 (6.4%) **control** had confirmed viral rebound



LAI superior to control (p=0.001)

- LATA is the **first randomised trial** to compare the efficacy and safety of LAI to oral ART in adolescents.
- Q8W LAI CAB/RPV was **superior** to TLD over 96 weeks, using the primary outcome of confirmed HIV-1 RNA ≥50 copies/mL and FDA snapshot HIV-1 RNA ≥50 copies/mL.
- LAI CAB/RPV was **well tolerated**, with no new safety concerns identified, and was **strongly preferred** by adolescents.

Penta Child Health Research

AIDS 2026: Co-Chairs Choice

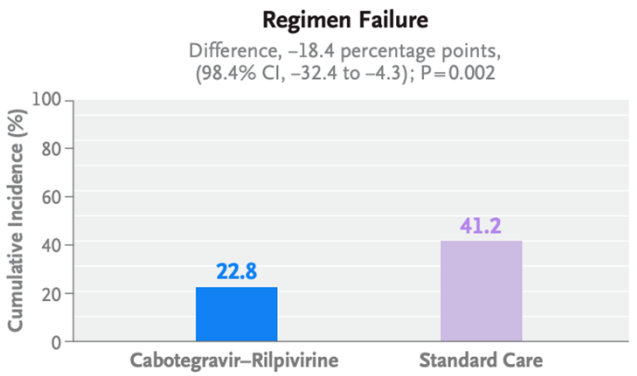
3rd LA ART Conference

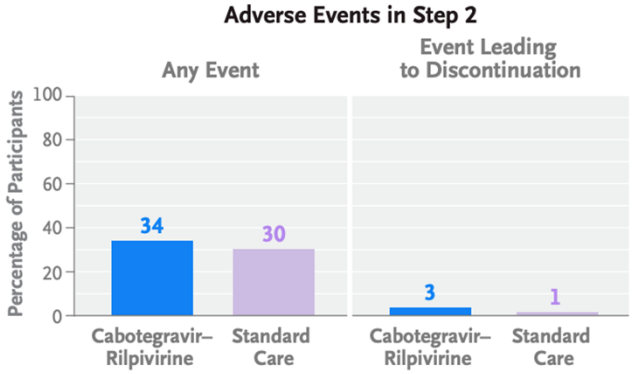
CAB/RPV in PLHIV virologically Unsuppressed Adult data: LATITUDE

Open-label, randomized trial involving persons with HIV who had inadequate adherence to ART (a persistent HIV-1 RNA level of >200c/mL or loss to follow-up).

Step 1: Up to 24 weeks of adherence support, conditional economic incentives, and standard care with oral ART

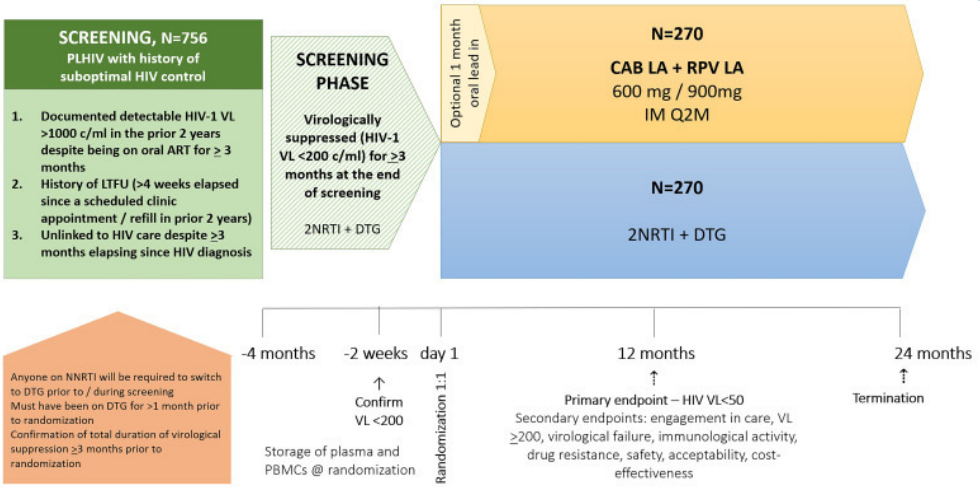
Step 2: If HIV-1 RNA level ≤200 c/mL randomly assigned in a 1:1 ratio to either continue standard care or switch to monthly injections of long-acting cabotegravir plus rilpivirine with or without oral lead-in therapy

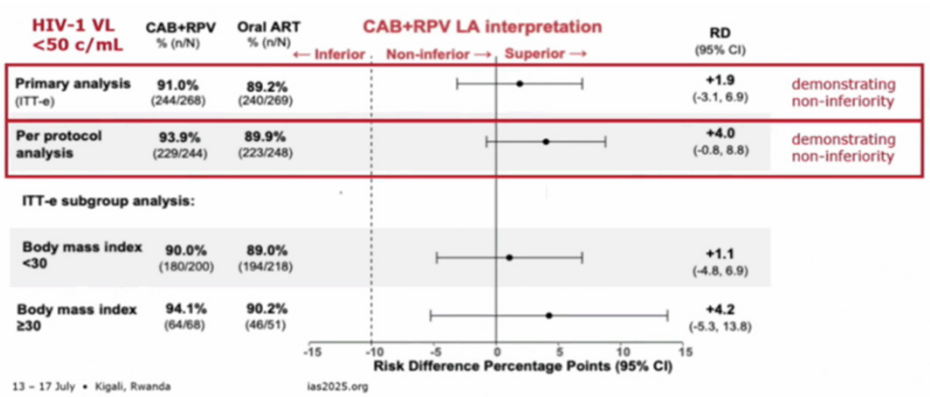




Rana AL, NEJM, Feb 18, 2026, Vol. 394 No 9

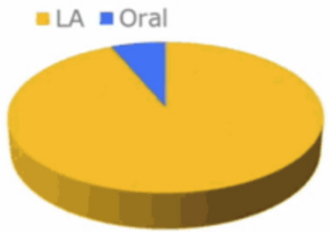
Adult data: IMPALA





Randomised 540 participants (Uganda, Kenya and S Africa)
HIV VL <200 c/mL at randomisation
217 CAB LA + RPV LA
267 Oral ART

Treatment preference:
249/266 (94%) participants who switched to CAB + RPV LA preferred it to oral therapy



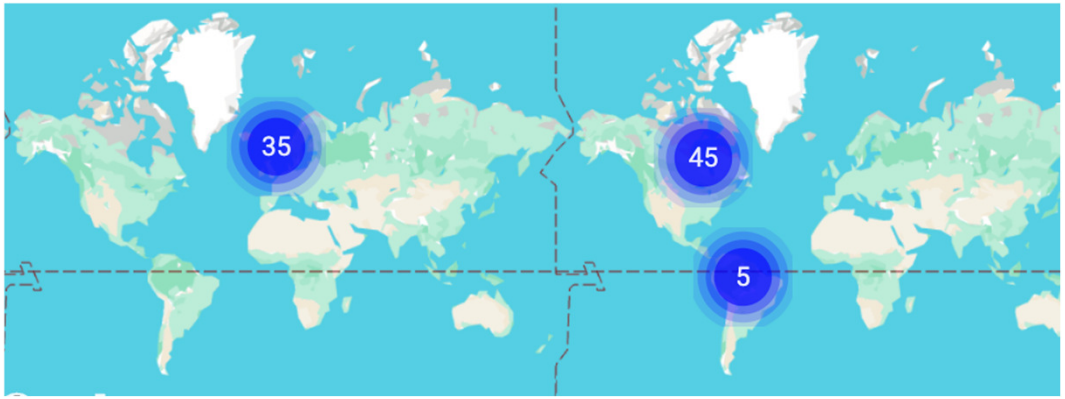
Privacy and stigma reduction were major factors

Cresswell F, IAS 2025

Adult and Adolescents: CROWN

- Randomised study of long-acting cabotegravir + rilpivirine vs. daily oral therapy in people with adherence challenges and detectable virus.
- Unlike LATITUDE, which included a virologic suppression phase, CROWN evaluates the regimen directly in individuals who are not yet suppressed

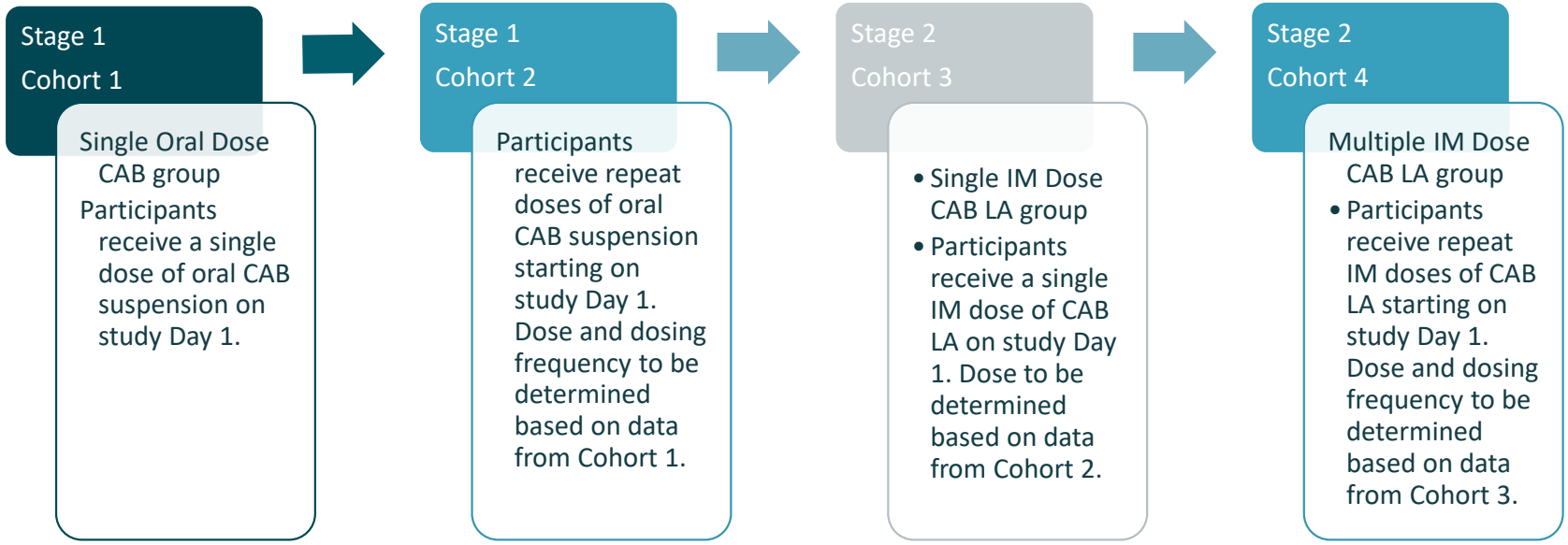
- 89 locations (North and South America, Europe
- Target enrolment: 332 Adults and adolescents >12years and >35kg



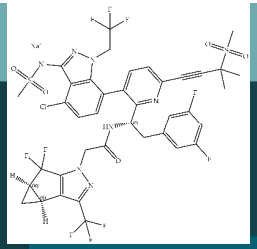
NCT06694805

Cabotegravir for Neonates Exposed to HIV-1: "CABNATE"

A Phase 1/2 Study of the Safety, Tolerability, and Pharmacokinetics of Cabotegravir in Neonates Exposed to HIV-1



https://clinicaltrials.gov/study/NCT07275606



Lenacapavir

Trial	Population	Adolescents?	Regimen
Prevention			
Purpose 1	Cisgender women age 16-25 years	**2.6% (n=56/2138) age 16 or 17**	LEN
Purpose 2	Men and gender diverse age 16+yrs	**34% (n=752/1431) were 16 to 25**	LEN
Treatment			
Capella	12+ yrs, stable failing (≥400 c/mL) for ≥ 8 weeks, with resistance to ≥ 2 ARVs from ≥ 3 of 4 classes	**None (n=60, lowest age 23 years)**	LEN + "failing" regimen
GS-US-200-6712	TE adolescents and children with HIV-1 < 18 years of age and weighing at least 35 kg	**Ongoing**	LEN + "failing" regimen

Approved for prevention among **adolescents and adults** age 12 and ≥ 35 kg

Approved for treatment **of adults** with MDR HIV

Same dosing for all, with oral overlap for first 2 days, and then q 6-months (q 26 weeks) from the date of the last injection +/-2 weeks …

Bekker NEJM 2024 PMID: 39046157; Kelly NEJM 2025 PMID: 39602624; Segal-maura NEJM 2022. PMID: 35544387

Slide courtesy of Ted Ruel

Cabotegravir and Lenacapavir

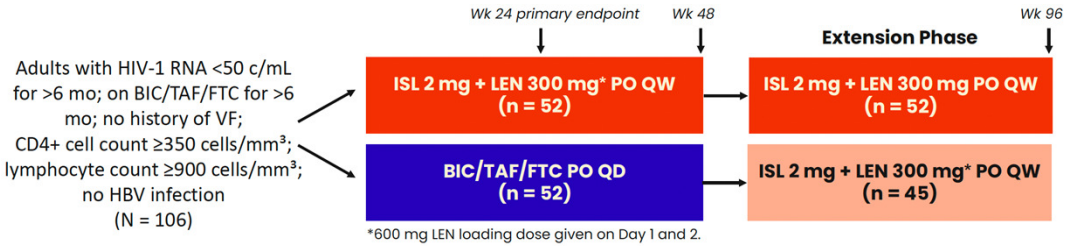
- Marriage of convenience in patients with suspected NNRTI resistance
  - Case series: 34 adults with suspected NNRTI resistance – LEN SC + CAB LA/RPV LA (IMI) – 94% (32/34) achieved viral suppression at 8 weeks (4-16)
  - Cohort: 50 adults with documented NNRTI and INSTi resistance – 31 on LEN/CAB LA and 15 LEN SC + CAB LA/RPV LA (IMI) – viral suppression increased from 44% to 97.5% at 140 weeks

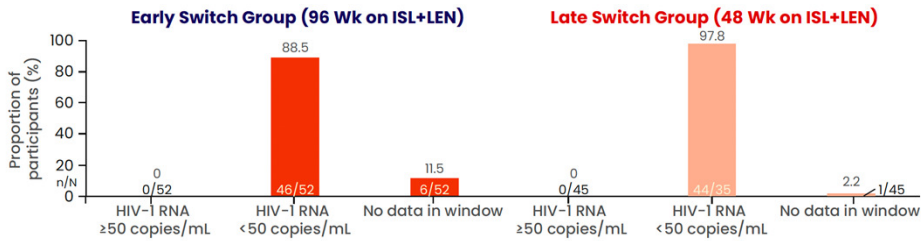
- Planned studies in adults by ACTG (may include adolescents)
  - A5431-PALACE: Small trial (n=38) in PLHIV on ART experiencing adherence challenges/virologically unsuppressed with NNRTI resistance
  - A5433- LANCET: Phase III treatment trial in adults and adolescents ≥16 years, virologically-unsuppressed, planned in LMIC setting

Gandhi M, OFID, 2024, Gistand NL, Poster 582, CROI 2026

The Future
Long-acting oral ART

- Once weekly ISL (NRTTIs) + LEN: Open-labeled, active control, randomized, phase 2 study in adults with virologically suppressed HIV





- Ulonivirine+ Islatravir (ULN+ISL)

- GS-1720 + GS-4182

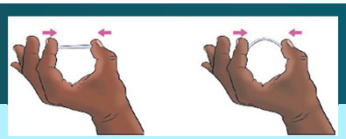
Colson. CROI 2026. Abstr 516.

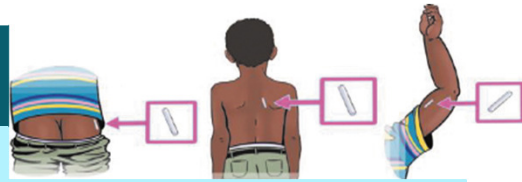
The Future
Long-acting injectable ART

- **Ultra-long CAB+RPV (4-monthy)**
  - CUATRO: phase III study in adults and adolescents ≥12 years (4%), virologically-suppressed, started (EU-CT 2024-518511-19-00)
- **LAI INSTIs under evaluation:**
  - GS-3242 (Phase 1/2) dosed every 4-6 months
  - VH-310 (Phase ½) dosed every 6 months – Prodrug of CAB
  - VH-184 (Phase 1/2) dosed every 6 months – 3rd generation INSTI
- **LAI Capsid Inhibitors**
  - VH-499 (Phase 1) dosing potentially every 6 months
- **LA ARVs + bNAbs**
  - Ultra LA (VH-184 or VH-499) + N6LS (ViiV),
  - LEN + teropavimab and zinlirvimab (Gilead)

CROI 2026: Gupta (174), Hansen (521),Back (176), Underwood (554), Thakkar (175)

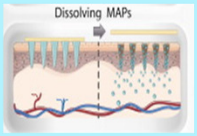
Alternative Delivery Methods





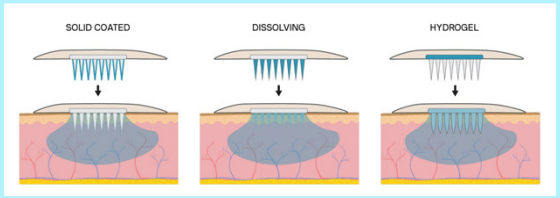
Implants:

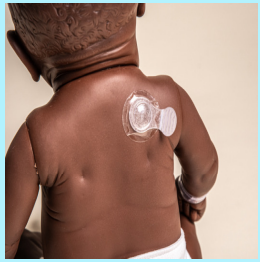
- Dosing: months to years, small size (discreet)
- Key barriers: site reactions, adult studies show suboptimal tolerability

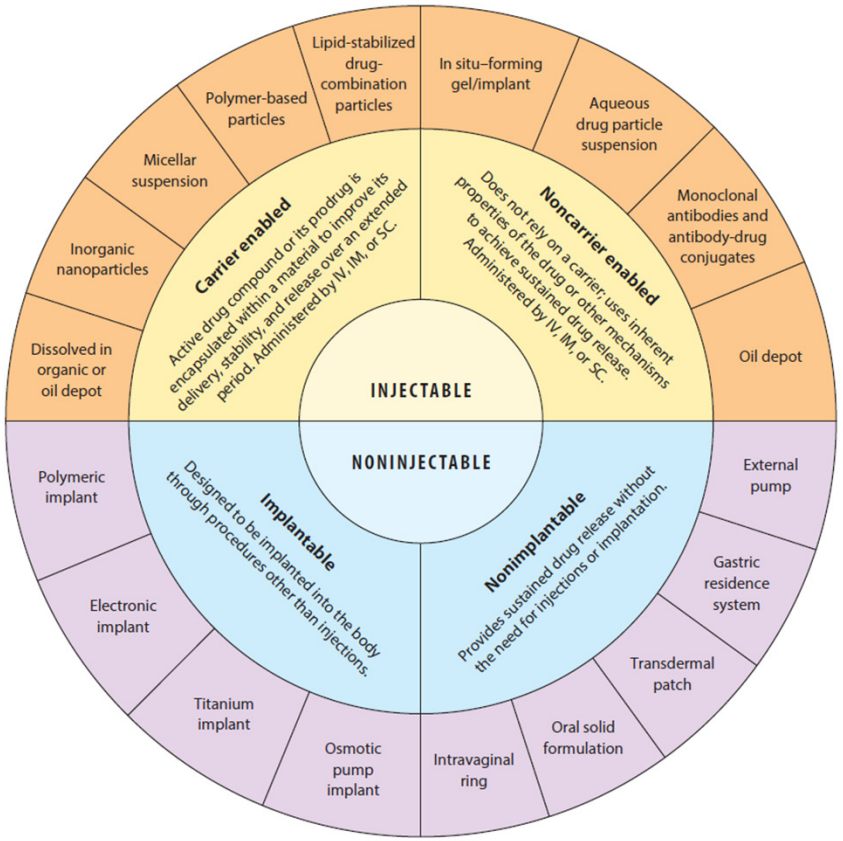


Micro-array patches (MAPS):

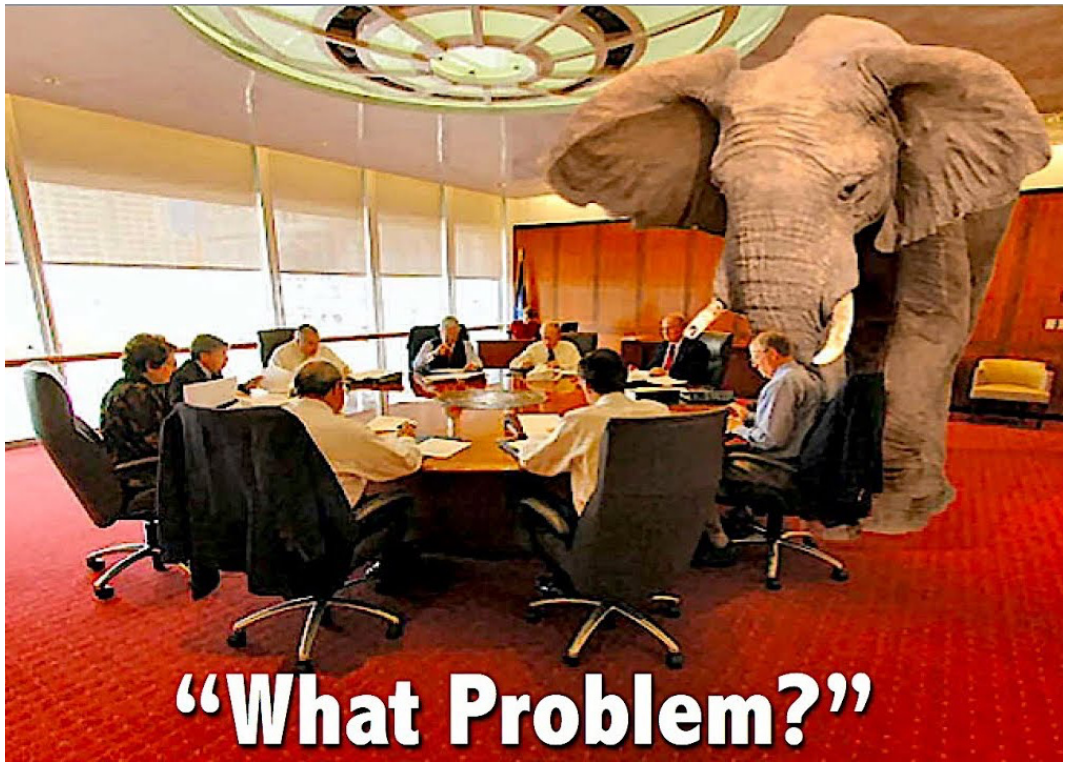
- **Intradermal delivery systems**
- **Preclinical animal studies and PBPK modelling (CAB, RPV, LEN, ISL)**
- **Pediatric ARV MAP has high acceptability and high usability among caregivers, community health workers, health care providers, and decision-makers in two high-HIV-burden settings, South Africa and Uganda.**







Elephant in the room: Funding and Implementation



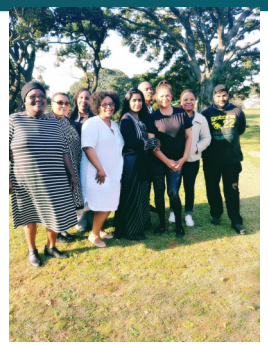
- Inequality in access:
  - In-country Registration
  - Supply
  - Cost
- Lack of sustainable implementation strategy
- Funding constraints for HIV programs

Conclusion

- Long-acting formulations can potentially simplify treatment of HIV in children and adolescents by addressing adherence challenges.
- Rich pipe-line of new paediatric formulations and drug delivery development but progress has been slow
- Equitable access in LMIC remains a concern
- To ensure ongoing drug development in a shrinking paediatric treatment market:
  - Merging of treatment and prevention regimens
  - Evaluation of drugs in adolescents during Phase 3 adult trials will ensure easier access to new formulations

Thank you

- Children and adolescents living with HIV and their carers
- Colleagues and investigators who helped me with the data and shared slides
  - Ted Ruel
  - Anna Turkova
  - CRAYON study team
  - LATA study team
  - ECF CTU: Rosie Mngqibisa, Rejoice Mosia, Tiyara Armugam and team
  - ORCHID study team: Anushka Naidoo, Gabriele Cromhout, Lee Sewnarain and team
  - INTSHA-VIP/AHRI team: Thobekile Sibaya and team
  - Refine/AHRI Team


Supporting Institutions

KWAZULU-NATAL PROVINCE HEALTH REPUBLIC OF SOUTH AFRICA

AHRI AFRICA HEALTH RESEARCH INSTITUTE

UNIVERSITY OF KWAZULU-NATAL INYUVESI YAKWAZULU-NATALI

CAPRISA

ENHANCING CARE FOUNDATION

Funding

NIHR | National Institute for Health and Care Research

saMRC advancinglife

ELMA

NIH National Institute of Allergy and Infectious Diseases

NIH National Institute of Mental Health

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.