Trial design and enrolment characteristics of LATA (Long-Acting Treatment in Adolescents): a randomised, open-label, non-inferiority, 96-week trial evaluating the virological efficacy, safety, acceptability and quality-of-life of the dual long-acting injectable regimen (CAB/RPV) compared to daily oral therapy (DTG based TDF or TAF with 3TC or FTC backbone) in virologically suppressed adolescents living with HIV-1 infection, aged 12 to <20 years, in Sub-Saharan Africa.

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Abstract

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Background

Alternatives to daily oral antiretroviral therapy (ART) are important for adolescents living with HIV (ALHIV) to improve adherence and outcomes. Long-Acting-injectable (LAI) cabotegravir/rilpivirine (CAB/RPV) has demonstrated excellent efficacy and safety and strong patient preference in adult trials.

Methods

LATA is an on-going randomised, open-label, 96-week, non-inferiority trial evaluating the efficacy, safety and acceptability of LAI CAB/RPV vs. daily oral therapy with tenofovir (disoproxil fumarate or alafenamide)/lamivudine/dolutegravir (TLD). Participants are virologically suppressed ALHIV aged 12-<20 years in Kenya/South Africa/Uganda/Zimbabwe. Randomisation was 1:1 to LAI CAB/RPV given once every 8 weeks (after optional oral lead-in) or daily oral TLD. The primary outcome is confirmed (two consecutive) viral load ≥50 copies/mL by 96-weeks. Viral loads are measured every 24 weeks. The trial employs the Smooth Away From the Expected (SAFE) non-inferiority frontier, where the non-inferiority margin depends on the observed event rate in the control arm. Secondary outcomes include confirmed viral load ≥200 copies/mL by 96-weeks, HIV resistance, safety, patient-reported outcomes and cost-effectiveness. LAI participants return to oral ART at confirmed viral load ≥200 copies/mL; LAI participants who become pregnant are given the choice to continue on LAI or to switch back to daily oral ART, with optional pharmacokinetic sampling during pregnancy and post-partum in both groups. Enrolment of 476 ALHIV completed in April 2024. Results will be reported in 2026.

Conclusion

LATA is the first trial reporting on the efficacy, safety and acceptability of LAI CAB/RPV in ALHIV, enrolled in Sub-Saharan Africa, using a programmatic approach to viral load testing.

Trial registration: This trial has been registered with ClinicalTrials.gov (NCT05154747)

Background

Globally in 2023, an estimated 1.5 million adolescents (10-19 years) were living with HIV (ALHIV), with close to 90% in sub-Saharan Africa (SSA)(1, 2). Adolescents have poorer treatment outcomes including higher loss to follow-up, lower treatment adherence, poorer virological suppression and higher mortality than adults living with HIV(3-5). Some ART adherence challenges for adolescents relate to fear of disclosure associated with carrying/taking oral medication, HIV stigma, relative lack of power in decision making, and the burden of secrecy(6).

Long-acting injectable (LAI) cabotegravir (CAB) and rilpivirine (RPV), administered every one or two months, demonstrated non-inferior efficacy and safety compared to daily oral ART in licensing trials in virologically suppressed adults (Table 1, (7-9)). The regimen was licensed as a switch strategy for adults virologically suppressed on oral ART by the EMA (2020) and the FDA (2021)(10, 11), and subsequently approved down to 12 years of age(12, 13) following the MOCHA trial (Table 1, (14, 15)). Durability beyond 96 weeks has now also been demonstrated(16-19). In July 2025 the World Health Organization (WHO) recommended LAI CAB/RPV as an alternative switching option for adults and adolescents with undetectable viral load (VL)(20).

In these trials, viral loads were measured at each injection visit, which would be unsustainable in low- and middle-income country (LMIC) settings. The CARES trial, which enrolled 512 adult participants in Africa, demonstrated non-inferiority of LAI once every 8 weeks to oral ART at both week 48 and 96, using a programmatic approach to VL testing (once every 6 months)(21, 22). While there are concerns about the high prevalence of NNRTI resistance in sub-Saharan Africa, the frequency of injections and need for cold-chain storage, the CARES trial demonstrated that even when NNRTI resistance was detected at baseline using proviral DNA, LAI CAB/RPV performed incredibly well.

Evidence is growing to support the use of LAI in individuals who have adherence difficulties and a history of viraemia. The African-based IMPALA(23) and US-based LATITUDE(24) trials demonstrated non-inferiority of LAI, given once every 8 weeks and monthly respectively, versus oral ART at 48-weeks among those virologically suppressed but with a recent history of raised VL or poor engagement in care. In addition, the AFINAty study, assessing LAI for youth living with HIV in Cape Town, South Africa, who were suppressed at enrolment or suppressed on oral ART over 24 weeks following viraemia or new ART initiation, demonstrated that in a community-based setting at week 48, 124/130 (96.9%) on LAI were suppressed (<50 copies/mL) with 98% retention(25). A meta-analysis assessing the efficacy of starting LAI in adults with current viraemia concluded that LAI

CAB/RPV could offer a therapeutic option for viraemic patients, provided adherence to injection schedules is supported(26).

Injectable ART represents an exciting and novel approach to ART delivery, however there are several unknowns relevant to its use in ALHIV in SSA including: efficacy with a programmatic approach to viral load monitoring, acceptability of clinic visits once every 8 weeks (where standard-of-care is now every 12-weeks or less), acceptability of LAIs administered by site staff, side-effect profile including injection site reactions, safety and pharmacokinetics (PK) of LAI CAB/RPV in pregnancy and breastfeeding, and safety of being exposed to two integrase inhibitors (INSTI) at therapeutic levels when those developing tuberculosis (TB) switch to oral dolutegravir-containing ART but still have residual, declining levels of CAB/RPV.

The LATA trial is the largest randomised trial of LAI CAB/RPV compared to daily oral ART in ALHIV who are virologically suppressed, and the only trial in this population in SSA. LATA is being conducted by the BREATHER Plus Consortium alongside a second trial in the same population evaluating short-cycle therapy with weekends off DTG-based triple therapy (BREATHER Plus)(27, 28). Both trials together will inform on novel approaches to ART in ALHIV in SSA.

This paper provides an overview of the key design elements of the LATA trial including description of the methodology used, the study population and their enrolment characteristics, Investigational Medicinal Products, trial procedures, safety management, endpoints, sample size and statistical analysis.

127 **Table 1: Previous trials evaluating efficacy of long-acting injectable CAB/RPV in people living with HIV who are virologically suppressed**

	Study	Year Published	End points	Results
PAST RANDOMISED CLINICAL TRIALS OF LAI CAB/RPV VS. ORAL ART CONDUCTED IN ADULTS WHO ARE VIROLOGICALLY SUPPRESSED				
1	**ATLAS** (Week 48 results(7)): Randomised, open label, phase 3, non-inferiority trial comparing LAI CAB/RPV administered intramuscularly every 4 weeks vs. standard oral ART therapy in adults living with HIV who are virologically suppressed. All LAI arm did OLI for 4 weeks. N=618.	2020	(i) VL ≥50 copies/ml by week 48 (primary endpoint, non-inferiority margin 6%, FDA snapshot) (ii) VL <50 copies/ml by week 48 (non-inferiority margin 10%, FDA snapshot) (iii) CVF to week 48 (two consecutive VL ≥200 copies/ml)	(i) VL ≥50 LAI 1.6% (5/308); oral 1.0% (3/308); adjusted difference (LAI-oral) -0.6% (95% CI-1.2, 2.5); non-inferiority of LAI demonstrated (ii) VL <50 LAI 92.5% (285/308); oral 95.5% (294/308); adjusted difference (LAI-oral) -3.0% (95% CI -6.7, 0.7); non-inferiority of LAI demonstrated (iii) CVF Criteria met in 3 LAI participants and 4 in oral therapy group
2	**ATLAS-2M** (Week 48 results(8), Week 96 results(16), Week 152 results(17)): Randomised, open label, phase 3b, non-inferiority trial comparing LAI CAB/RPV administered intramuscularly every 8 weeks (Q8W) vs. every 4 weeks (Q4W) in adults living with HIV who are virologically suppressed. All participants with no previous	2020, 2021, 2023	(i) VL ≥50 copies/ml by week 48 (primary endpoint, non-inferiority margin 4%) and 96 (extended follow-up, non-inferiority margin 4%) and 152 (all FDA snapshot) (ii) VL<50 copies/ml by week 48, 96 (both non-inferiority margin -10%) and 152 weeks (all FDA snapshot) (iii) CVF to week 48, 96, 152 (two consecutive VL ≥200 copies/ml)	(i) VL≥50 Week 48: Q8W 2% (9/522); Q4W 1% (5/523); adjusted difference (Q8W-Q4W) 0.8% (95% CI -0.6, 2.2); non-inferiority of Q8W demonstrated Week 96: Q8W 2% (11/522); Q4W 1% (6/532); adjusted difference (Q8W-Q4W) 1.0% (95% CI -0.6, 2.5); non-inferiority of Q8W demonstrated

	CAB/RPV exposure did OLI for 4 weeks. N=1045.			Week 152: Q8W 2.7% (14/522); Q4W 1.0% (5/523); adjusted difference 1.7% (95% CI 0.1, 3.3) (ii) VL <50 Week 48: Q8W 94% (492/522); Q4W 93% (489/523); adjusted difference (Q8W-Q4W) 0.8% (95% CI -2.1, 3.7); non-inferiority of Q8W demonstrated Week 96: Q8W 91% (475/522); Q4W 90% (472/523); adjusted difference (Q8W-Q4W) 0.8% (95% CI -2.8, 4.3); non-inferiority of Q8W demonstrated Week 152: Q8W 87.4% (456/522); Q4W 85.9% (449/523); adjusted difference 1.5% (95% CI -2.6, 5.6) (iii) CVF Week 48: Q8W 1.5% (8/522); Q4W 0.4% (2/523) Week 96: Q8W 1.7% (9/522); Q4W 0.4% (2/523) Week 152: Q8W 2.3% (12/522); Q4W 0.4% (2/523)
3	**FLAIR STUDY** (Week 48 results(9), Week 96 results(18), Week 124 results(19)):	2020, 2021	(i) VL ≥50 copies/ml at week 48 (primary endpoint, non-inferiority margin 6%)) and week 96 and 124 (all FDA snapshot)	(i) VL ≥50 Week 48: LAI 2.1% (6/283); oral 2.5% (7/283; adjusted difference (LAI-oral) -0.4% (95% CI -2.8, 2.1); non-inferiority demonstrated

	Randomised, phase 3, open label study investigating whether switching to LAI CAB/RPV is non-inferior to daily dolutegravir, abacavir and lamivudine in adults living with HIV who had started oral ART in the previous 20 weeks and were virologically suppressed. All LAI arm did OLI for 4 weeks. N=566. At week 100: 232 (92%) oral ART participants who were suppressed at week 96 transitioned to LAI in the extension phase (111 in the direct-to-injection group and 121 in the oral lead in group).		(ii) VL <50 copies/ml at week 48 (non-inferiority margin -10%) and week 96 and 124 (all FDA snapshot) (iii) CVF to week 48, 96, 124 (two consecutive VL ≥200 copies/ml)	Week 96: LAI 3% (9/283); oral 3% (9/283); adjusted difference (LAI-oral) 0.0% (95% CI -2.9, 2.9) Week 124: randomised LAI group 5% (14/283); oral ART to direct-to-injection LAI 1% (1/111) and oral ART to LAI with OLI 1% (1/121) (ii) VL <50 Week 48: LAI 93.6% (265/283); oral 93.3% (264/283); adjusted difference (LAI-oral) 0.4% (95% CI -3.7, 4.5); non-inferiority demonstrated Week 96: LAI 87% (245/283); oral 89% (245/283); adjusted difference (LAI-oral) -2.8% (95% CI -8.2, 2.5) Week 124: randomised LAI group 80% (227/283); oral ART to direct-to-injection LAI 99% (110/111) and oral ART to LAI with OLI 93% (113/121) (iii) CVF Week 48: LAI 1.4% (4/283); oral 1.1% (3/283) Week 96: LAI 1.4% (4/283); oral 1.4% (4/283) Week 124, during extension phase: LAI 0.4% (1/283); oral ART to direct-to-injection LAI 0.9% (1/111) and oral ART to LAI with OLI 0% (0/121)

4	**SOLAR STUDY** (12 months results(29)): Randomised, open label, phase 3b, non-inferiority trial, assessing the efficacy, safety and tolerability of switching to LAI CAB/RPV vs. continuing fixed dose bictegravir, emtrictabine and tenofovir alafenamide in adults living with HIV who were virologically suppressed. 39% of LAI arm elected to do OLI for 4 weeks. N=687.	2023	(i) VL ≥50 copies/ml by month 11 (if no OLI)/12 (if OLI, control arm) (primary endpoint, FDA snapshot, non-inferiority margin 4%) (ii) VL <50 copies/ml by month 11/12 (FDA snapshot, non-inferiority margin -12%) (iii) CVF to month 11/12 (two consecutive plasma HIV-1 RNA measurements ≥200 copies per mL)	(i) VL ≥50 LAI 1% (5/447); oral <1% (1/223); adjusted difference (LAI-oral) 0.7% (95% CI -0.7, 2.0); non-inferiority demonstrated (ii) VL <50 LAI 90% (403/447; oral 93% (207/223); adjusted difference (LAI-oral) -2.7 (-7.0, 1.7); non-inferiority demonstrated (iii) CVF LAI <1% (2/447); oral 0% (0/223)
5	**CARES STUDY** (Week 48 results(21), Week 96 results(22)): Randomised, open label, non-inferiority trial, assessing whether switching to LAI CAB/RPV every 8 weeks is non-inferior to daily oral therapy in adults living with HIV in Africa who were virologically suppressed. 84% of LAI arm elected to do OLI for 4 weeks. N=512.	2024, 2025	(i) VL <50 copies/ml by week 48 and 96 (primary endpoint, FDA snapshot, non-inferiority margin -10%). (ii) CVF to week 48 and 96 (two consecutive values of at least 200 copies per mL, non-inferiority margin 4%) (iii) VL ≥50 copies/ml by week 48 and 96 (FDA snapshot, non-inferiority margin 4%)) (iv) VL<200 copies/ml by week 48 (FDA snapshot)	(i) VL <50 Week 48: LAI 96% (246/255); oral 97% (250/257); adjusted difference (LAI-oral) -0.8% (95% CI -3.7, 2.3); non-inferiority demonstrated Week 96: LAI 96.9% (247/255); oral 97.3% (250/257); adjusted difference (LAI-oral) -0.4% (95% CI -3.1, 2.0); non-inferiority demonstrated (ii) CVF Week 48: LAI 1% (2/255); oral 0% (0/257); adjusted difference (LAI-oral) 0.8% (95% CI-0.7, 2.8); non-inferiority demonstrated Week 96: LAI 1.6% (4/255); oral 0% (0/257); adjusted difference (LAI-oral) 1.6% (95% CI 0.4, 4.2)

				(iii) VL ≥50 Week 48: LAI 3% (7/255); oral 2% (5/257); adjusted difference (LAI-oral) 0.8% (95% CI -1.8, 3.4) Week 96: LAI 1.6% (4/255); oral 0.8% (2/257); adjusted difference (LAI-oral) 0.8% (95% CI -0.7, 3.2) (iv) VL <200 Week 48: LAI 98% (250/255); oral 98% (252/257); adjusted difference (LAI-oral) -0.01% (95% -0.7, 2.8)
PAST CLINICAL TRIALS OF LAI CAB/RPV CONDUCTED IN CHILDREN/ADOLESCENTS				
7	**MOCHA/ IMPAACT 2017**(14, 15): A phase 1/2, open label, non-comparative, dose finding study in adolescents (12-18 years) living with HIV who were virologically suppressed. *Cohort 1* Oral CAB or RPV (4 weeks), followed by 4-weekly or 8-weekly LAI CAB or RPV (12 weeks) while continuing pre-study oral ART. N=55. *Cohort 2*	2024	(i) Assessment of safety measures (ii) PK measures at week 2 for oral CAB or RPV, and week 16 for LAI CAB or RPV (iii) VL <50 copies/ml at each study visit in Cohort 1) and virologic success/failure (</≥50 copies/ml, FDA snapshot) at week 24 in Cohort 2	(i) *Cohort 1* 28/29 (97%, 95% CI 82, 100) of those receiving CAB and 21/23 (91%, 95% CI 72, 99) of those receiving RPV had at least one adverse event None were severe. *Cohort 2* 110 (76%, 95% CI 69, 83) had at least one adverse event; 15 (11%; 6, 7) had at least one adverse event grade ≥3; no drug-related events were serious or led to discontinuation (ii) Concentrations were similar to those in adults.

	Oral CAB and RPV (4 weeks), followed by 8-weekly LAI CAB and RPV (96 weeks) (either newly recruited or continuing from cohort 1). N=144.			(iii) *Cohort 1* Proportion with VL<50 was >90% at each visit in the CAB group, and >95% at each visit in the RPV group *Cohort 2* VL<50: 137/139 (99%, 95% CI 95, 99.8) VL ≥50: 2/139 (1%, 95% CI 0, 5)
ONGOING CLINICAL TRIALS OF LAI CAB/RPV CONDUCTED IN CHILDREN/ADOLESCENTS				
8	**CRAYON TRIAL/IMPAACT 2036**(30, 31): An on-going phase 1/2 study of the safety, tolerability, acceptability, and pharmacokinetics of oral and 4-weekly LAI CAB/ RPV in children living with HIV who are virologically suppressed, aged 2-<12 years of age. N=90.		(i) Pharmacokinetic parameters (ii) Safety: Including proportion experiencing AEs/grade ≥3 AEs/SAEs, occurrence of treatment discontinuation, drug-related safety failure (iii) Virological suppression	The study is on-going, with interim results to week 12 among the 35 participants presented (i) Exposure concentrations comparable to adolescents and adults (ii) 8 (40%) had at least one adverse event, and 1 (5%) had a grade 3 adverse event (iii) Virological suppression maintained in all participants

128 Abbreviations: CVF (Confirmed Virological Failure), ITT (Intention to Treat), NI (Non inferiority), Q8W (Every 8 weeks), Q4W (Every 4 weeks), VL (Viral Load), LAI (Long Acting Injectable).

129 Table 1 presents only virological outcomes for studies in adults and both pharmacokinetic, virological and safety outcomes for studies in children/adolescents.

Methods

Objectives and hypotheses

The LATA trial is evaluating the virological efficacy, safety, acceptability and quality-of-life on the dual LAI regimen (CAB/RPV) compared to daily oral therapy with TLD.

The trial's primary hypothesis is that LAI CAB/RPV will provide non-inferior virological suppression over 96 weeks compared with TLD. The trial's secondary hypothesis is that LAI CAB/RPV will be superior to TLD with respect to secondary outcomes including adherence (days missed of medication or missed injection visits), acceptability, and quality-of-life.

Study design, randomisation, and follow-up

LATA is an open-label, randomised, 96-week, non-inferiority trial in ALHIV who are virologically suppressed in Kenya, Uganda, South Africa and Zimbabwe (https://www.mrcctu.ucl.ac.uk/media/2656/lata-protocol-v10_01-dec-2021_signed.pdf).

ALHIV were randomised (1:1) to LAI CAB/RPV or TLD. Randomisation was stratified by centre and mode of HIV acquisition (vertical or horizontal/other), and lists were prepared using permuted blocks with variable size. Data officers carried out randomisation using a secure electronic system within the trial database.

Study population

The trial enrolled ALHIV, aged between 12 to <20 years and weighing ≥35kg, who were virologically suppressed (HIV-1 RNA <50 copies/mL) for the last year, with no history of treatment failure. Participants had to be on 3-drug ART consisting of a dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone and an anchor drug prior to enrolment. Previous ART substitutions because of toxicity, simplification, changes in guidelines or drug availability were allowed. Participants were confirmed HIV-2 negative in the year prior to screening or between screening and randomisation, because HIV-2 is intrinsically resistant to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class which includes RPV. Hepatitis B surface antigen (SAg) positivity was an exclusion for participation as the withdrawal of tenofovir in the LAI arm could risk a hepatitis B flare. Pregnancy and breastfeeding were exclusion criteria, and females who were sexually-active had to be on highly effective contraception (Appendix A, Supplementary Table 1).

Treatment of participants

Adolescents allocated to the control arm receive the fixed-dose combination, TDF(300mg)/3TC(300mg)/DTG(50mg) (TLD) in line with WHO(32) guidelines. The protocol allows for

Tenofovir Alafenamide Fumarate (TAF)(25mg) instead of TDF, and/or Emtricitabine (FTC)(200mg) instead of Lamivudine (3TC).

Adolescents allocated to the LAI arm continued to receive oral ART for the first 4 weeks, either TLD or oral CAB/RPV (the optional oral lead-in [OLI]), based on clinician and participant/carer-choice; the option for OLI was provided if preferred to ensure tolerance of oral formulations of CAB/RPV before starting LAI. Loading doses of LAI CAB/RPV were then given at weeks 4 and 8, first maintenance dose at week 16, with injections once every 8 weeks thereafter (Table 2). Where a participant in the LAI arm cannot attend a visit on time, oral CAB and RPV is provided as an 8-week supply of oral CAB and RPV as a short-term oral bridging strategy.

Table 2: Treatment schedule in the injectable arm

WEEKS 0 TO 4	WEEK 4A	WEEK 4B	WEEK 8	WEEK 16	WEEK 24 ONWARDS
OLI[a] CAB (30mg) + RPV (25mg) with a meal	LFTs performed, to confirm within normal limits	1st loading dose of CAB 600mg and RPV 900mg	2nd loading dose of CAB 600mg and RPV 900mg	1st maintenance dose CAB 600mg and RPV 900mg	Maintenance dose CAB 600mg and RPV 900mg every 8 weeks
NON-OLI DTG + TDF/TAF + 3TC/FTC	1st loading dose of CAB 600mg and RPV 900mg		2nd loading dose of CAB 600mg and RPV 900mg	1st maintenance dose CAB 600mg and RPV 900mg	Maintenance dose CAB 600mg and RPV 900mg every 8 weeks

Abbreviations: 3TC (Lamivudine), CAB (Cabotegravir), DTG (Dolutegravir), FTC (Emtricitabine), LFTs (Liver Function Tests), OLI (Oral Lead In), RPV (Rilpivirine), TAF (Tenofovir Alafenamide Fumarate), TDF (Tenofovir Disoproxil Fumarate)

[a]**Rationale for optional OLI**: The rationale for OLI was the original anxiety about drug induced liver injury (DILI), but after an analysis in FLAIR and ATLAS, where DILI was not reported, it became optional both in FLAIR and ATLAS, and subsequent trials. Therefore, OLI was optional in LATA. In those opting to have the 4-week OLI in the LATA trial, they received 4 weeks of daily oral cabotegravir and rilpivirine with a meal. Subsequently, the first doses of CAB/RPV LAI were received at week 4B, predicated upon tolerating the oral CAB/RPV and having week 4A LFTs within acceptable limits. In sites with rapid turnaround time for LFTs, the week 4A and 4B visit could be conducted on the same day.

Timing of injections: Injections at week 8 should be given 3 weeks – 4weeks+1 day after those at week 4A/B; injections at week 16 should be given 7 weeks-8 weeks+1 day after those at week 8; injections at weeks 24 onwards should be given 7-9 weeks after the previous injections

Primary and secondary outcomes

The primary outcome is confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50 copies/mL) by week 96, chosen as an objective and clinically relevant measure of the loss of virologic suppression. Secondary outcomes are listed in Table 3, and include confirmed HIV-RNA

≥200 copies/mL, which is used as the threshold for return from LAI CAB/RPV to oral ART (see 'Criteria for discontinuing or modifying allocated interventions').

Table 3: Primary and secondary outcome measures

Primary outcome
i) Proportion of participants with confirmed virological rebound (2 consecutive plasma HIV-RNA ≥50 copies/mL) at any time up to the 96-week assessment.
Secondary outcomes
A) EFFICACY
(i) Proportion of participants with HIV-RNA ≥50 copies/mL at 48 and 96 weeks using a modified FDA snapshot algorithm
(ii) Proportion of participants with HIV-RNA ≥1000 copies/mL (confirmed) by week 96
(iii) Proportion of participants with HIV-RNA ≥200 copies/mL (confirmed) by week 96
(iv) The number and type of HIV mutations (reverse transcriptase and integrase) in participants with confirmed virological rebound
(v) HIV-RNA <50 copies/mL at 24, 48 and 96 weeks
B) SAFETY
(i) Change in toxicity profile including change in metabolic parameters (lipids, HbA1c, phosphate), liver function tests (ALT), renal function (eGFR) from baseline to 96 weeks; change in anthropometric measures, including weight, from baseline to 48 and 96 weeks
(ii) Time to any new or recurrent WHO stage 3 or WHO stage 4 event or death
(iii) Incidence of serious, grade 3, 4 and 5, and treatment-modifying (of any grade) adverse events
(iv) Proportion of participants with any change from assigned ART regimen
(v) Change in CD4+ and CD8+ T-cell count from baseline to 48 and 96 weeks
(vi) LA group only: incidence of injection site reactions of any grade
C) PATIENT-REPORTED OUTCOMES
(i) Adherence (days missed of oral medication and/or missed scheduled injection visits), acceptability, wellbeing and neuropsychiatric problems (e.g. depression, anxiety and sleep disturbance)
(ii) LAI group only: perception of injection*
(iii) Healthcare resource utilisation (as a sub-study outcome)
(iv) Health-related quality-of-life (as a sub-study outcome)
(v) Perception of body shape using Stunkard (33) figure rating scales (as a sub-study outcome)

Abbreviations: ALT (Alanine Aminotransferase), ART (Antiretroviral Therapy), CD4 (Cluster of Differentiation 4), CD8 (Cluster of Differentiation 8), eGFR (Estimated Glomerular Filtration), LAI (Long Acting Injectables), FDA (Food and Drug Administration), HIV (Human Immunodeficiency Virus), RNA (Ribonucleic Acid), T-cel, (Thymus cell), WHO (World Health Organization)

*This questionnaire was the same as that used in the registrational trials FLAIR and ATLAS, to allow for direct comparison with findings in adults

Sample size

Non-inferiority of LAI ART will be assessed by the difference between the CAB/RPV LAI and control groups in the estimated proportion of participants with viral rebound by week 96.

The LATA trial was designed with a fixed non-inferiority margin of 10%. At the design stage it was estimated a total of 460 participants (230 per group) would provide 90% power, 2-sided alpha of 5%, to demonstrate non-inferiority of LAI CAB/RPV vs. oral ART, assuming 11% of participants met the

primary endpoint of confirmed HIV-RNA ≥50 copies/mL by the 96-week assessment in both groups and allowing for 10% loss to follow-up. Assumptions for the sample size calculations were made based on the BREATHER results on efavirenz-based regimens(34).

To ensure interpretability of results in the event of a lower-than estimated risk of viral rebound in the control arm, prior to trial opening, the Smooth Away From Expected (SAFE) frontier was adopted(35). Provided that the observed rate of confirmed viral rebound in the oral ART arm is ≥9%, a 95% two-sided confidence interval for the difference in confirmed viral rebound between LAI CAB/RPV and oral ART will be computed and a 10% non-inferiority margin will be used. If the observed rate of confirmed viral rebound in the oral ART arm is <9%, a 99% two-sided confidence interval will be computed and the non-inferiority margin will be modified as shown in Appendix A, Supplementary Table 2.

Study procedures

Participants were seen at screening, enrolment, week 4A (LAI arm only), week 4B (LAI arm on OLI), week 8 and every 8 weeks thereafter until the end of follow up (Table 4). Liver biochemistry was assessed prior to administering LAI and then closely monitored at the beginning of the trial (week 0, 4A (OLI group), 8, 16) for early detection of potential drug induced liver injury (DILI) among patients receiving CAB/RPV.

Pregnancy testing is conducted at every scheduled visit among females post menarche and sexually-active adolescent females are required to use highly effective contraception. If pregnancy does occur in a participant on LAI, they may choose to remain on LAI. Participants who become pregnant on oral ART are managed according to local guidelines. Under protocol v1.0 additional VL testing was done in the 2nd and 3rd trimester for those on LAI and as per local guidelines for those on oral ART; following implementation of protocol v2.0 (August 2025) VL testing was done at all scheduled visits in pregnant participants in both arms.

Plasma HIV-1 VL is measured at screening (to confirm eligibility) and at weeks 24, 48, 72 and 96 (and every 24 weeks thereafter), similar to standard-of-care in participating countries. Participants who have a VL ≥50 copies/mL are brought back to clinic for confirmatory testing within the ±4 week (±6 under protocol v2.0) testing window for the scheduled visit. At the end of the trial, stored plasma taken at the time of rebound will be used for retrospective resistance testing in participants who have met the primary outcome.

During follow-up, hepatitis B vaccination has been made available for those without evidence of receipt of the 3-vaccine schedule in infancy, to align with good clinical practice.

Participants will be followed up until the last enrolled participant reaches 96 weeks.

Table 4: Trial Assessment Schedule

Assessment required	Screening	W0 (Randomisation)	W4a (LAI only)	W4b (LA with OLI)	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80	W88	W96	Further follow-up	Close-out visit
Signed informed consent/assent	X	Confirm																
Clinical assessment [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 8 weeks	X
Vitals signs [2]		X			X		X			X						X	Every 48 weeks	X
Dispense IMP/receipt of LAI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 8 weeks	
Laboratory Assessments																		
Pregnancy test (urine)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 8 weeks	X
HIV-1 RNA VL [4]	X						X			X			X			X	Every 24 weeks	X
HBsAg screening	X																	
Biochemistry [5]	X	X	X[a]		X	X				X						X	Every 48 weeks	
Lipids (same draw as biochemistry)		X														X		
HIV-1 and HIV-2 test[b]		X																
HbA1c		X								X						X		
Haematology [6]		X								X						X	Every 48 weeks	
T-cell lymphocyte subsets (same draw as haematology) [7]		X								X						X	Every 48 weeks	
Storage of Samples																		
Mandatory plasma storage [8]		X	X		X[c]	X[c]	X			X			X			X	Every 24 weeks	X
Optional plasma storage [9]		X								X			X			X		
Optional urine storage [9]		X														X		
Sparse PK plasma			X				X			X			X			X		
Intensive PK plasma [10]							X	X										
Other Assessments																		
C-SSRS questionnaire	X	X			X		X			X			X			X	Every 48 weeks	X
Mood survey		X			X		X			X			X			X	Every 48 weeks	X
Acceptability (HATQoL) questionnaire		X			X		X			X						X	Every 48 weeks	X
EQ5D		X					X			X						X		X
Adherence assessment [11]					X	X	X	X	X	X	X	X	X	X	X	X	Every 8 weeks	X
Stunkard figure rating scale [12]		X					X			X						X	Every 48 weeks	X
BIA		X								X						X		
Perception of injection[c]					X	X	X	X	X	X	X	X	X	X	X	X	Every 8 weeks	X
Health economics questionnaire						X						X						

[a]Only for LA participants with OLI

[b]May be done as a point-of-care test at the site and hence not involve the laboratory

[c]Only for LAI participants, on LAI injectables

[1] Clinical assessment includes medical and ART history, clinical examination, paediatric WHO staging for HIV and adverse events (starting from week 0).

[2] Vital signs includes weight, height, resting pulse, sitting blood pressure, waist/hip circumference.
[3] Only for female participants who have reached menarche.
[4] Additional VL is required if any VL ≥50 copies/mL or if treatment failure suspected. Note that participants on LAI with two consecutive VL ≥200 copies/mL must return to oral ART. Under protocol v2.0, all pregnant participants must have a VL at the following timepoints:

- When the pregnancy is first identified
- 8-weekly during pregnancy (at trial visits)
- At 34-36 weeks gestation (if not already done as part of 8-weekly VLs)

[5] Biochemistry: urea, creatinine, albumin, alanine transaminase, aspartate transaminase, bilirubin.
[6] Haematology: haemoglobin, red blood cells, white blood cells, lymphocytes, neutrophils, platelets.
[7] CD3+, CD4+, CD8+ T-lymphocyte percentage and absolute, total lymphocyte count.
[8] Plasma samples stored for possible retrospective VL testing or resistance testing. Additionally, a plasma sample is stored at unscheduled visits if treatment failure is suspected (all trial participants).
[9] Only for participants who have provided additional consented/assented for the optional storage samples.
[10] Only in 20 LAI group participants with additional consent, with trough samples at t=0 (immediately before the LA injectables are administered) at week 24, then week 24+3d, week 24+7d, week 24+28d, week 24+56d(= week 32 visit).
[11] For those on oral ART, pill count (except week 0) and adherence questionnaire.
[12] Only for participants who have provided additional consent to take part in the metabolic sub-study, only conducted in Uganda and Zimbabwe.

Abbreviations: BIA (Bioelectrical Impedance Analysis), CD4 (Cluster of Differentiation 4), CD8 (Cluster of Differentiation 8),C-SSRS (Columbia Suicide Severity Rating Scale), HATQoL (HIV/AIDS Targeted Quality of Life), HbA1c (haemoglobin A1c), HBsAg (Hepatitis B Surface Antigen, HIV (Human Immunodeficiency Virus), LAI (Long-Acting Injectables), OLI (Oral Lead In), PK (Pharmacokinetics), RNA (Ribonucleic Acid), T-cell (Thymus cell), VL (Viral Load), WHO (World Health Organization)

Questionnaires

The trial utilises participant/carer questionnaires to evaluate participant adherence to treatment (in participants on oral ART) and acceptability of study medicines, mood and sleep, suicidal ideation and behaviour and health-related quality of life (Appendix C). All questionnaires have been translated to local languages. In the LAI arm, participant's perception of injection is also captured, utilising the same questionnaire as licensing trials in adults.

Criteria for discontinuing or modifying allocated interventions

Confirmed virological rebound

If a participant on LAI has two consecutive HIV-1 RNA ≥200 copies/mL, they must return to oral ART, with choice of regimen determined by the treating clinician (which may include DTG or may require an alternative third agent).

Participants in both arms (at/after return to oral ART in the injectable arm) who experience treatment failure should be treated according to WHO/country-guidelines, which currently advise a second-line regimen may be required where a patient has had adherence counselling and their HIV-RNA is confirmed ≥1000 copies/mL.

Intent to become pregnant

Adolescent girls on LAI who are sexually-active and no longer wish to use effective contraception must be switched back to oral ART.

Adverse events, including TB, DILI and hepatitis B

If a participant on LAI CAB/RPV is diagnosed with acute hepatitis B they should return to tenofovir-containing ART. A participant on LAI CAB/RPV who develops incident TB should cease LAI CAB/RPV and take TLD) until 14 days after last rifampicin dose; they may then restart LAI CAB/RPV but will need to receive loading doses again. All participants with TB on TLD take total daily DTG dose 100mg.

In both arms, a participant must discontinue trial drugs in case of DILI (criteria in Appendix A, Supplementary Table 3), and may discontinue in case of drug toxicity, intercurrent illness, or any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion. Any change of treatment will be made according to local guidelines.

Safety management

Reportable AEs in the trial include Serious Adverse Events (SAE), clinical grade 3/4 and clinically significant (as determined by investigator) laboratory grade 3/4 AEs, WHO stage 3/4 events, ART-

modifying AEs of any grade, and any suicidal ideation that includes method, intent or plan or any suicidal behaviour. At clinic visits, AEs are screened for using a symptom checklist, completing a clinical assessment, review of laboratory results and completing a suicidality assessment as per the trial schedule. AEs are graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events(36).

Pregnancies and suspected cases of DILI are reported as Notable Events (NE). Participants with AEs are followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Pregnancies are followed up to completion, with infants followed up to 4-6 weeks post birth; in Uganda regulatory authorities require follow-up to 18 months of age for infants born to women on LAI.

Both SAEs and NEs are reported to Sponsor within expedited timelines. SAEs are reported to regulatory agencies as per national requirements. Pregnancies are reported to the Antiretroviral Pregnancy Register(37).

Participants on LAI injectables will be followed for safety (SAEs and NEs) for minimum 12 months after their last injections.

Strategies to improve adherence/ visit attendance

Robust scheduling of visits has been implemented to maximise timely visit attendance. Among those on oral ART, adherence is checked by trial nurse/pharmacist pill count and short participant self-administered adherence questionnaires. Participants may receive continuous adherence counselling as per site standard of care.

Sub studies

The **Social science sub-study** will quantitatively and qualitatively assess adherence to visit schedules and daily oral ART (days missed medication (control group), injection visits attended on time, number of episodes of oral bridging (LAI group)), acceptability, and overall well-being among trial participants. Some participants from Uganda and South Africa will be invited to participate in focus group discussions and longitudinal in-depth interviews.

The **Neuropsychiatric toxicity sub-study** will assess and compare neuropsychiatric toxicities, including depression, suicidality, anxiety and sleep disturbance longitudinally between randomised groups. A short tool, The Mood Survey Questionnaire (MSQ) (Appendix C, Figure S3), and the Columbia-Suicide Severity Rating Scale (C-SSRS) are administered longitudinally to identify mental health issues. The MSQ was developed at study inception as a quick and easy to administer tool and its sensitivity and specificity in identifying issues in a sample of participants will be assessed, by

comparison with the Patient Health Questionnaire-9 (PHQ-9) for depression, the Generalized Anxiety Disorder-7 (GAD-7) for anxiety and a Sleep survey questionnaire (Appendix C, Figure S4).

The **Metabolic sub-study** will assess anthropometrics, HbA1c, lipids and participant-reported body-shape perception (using the Stunkard figure rating scale) longitudinally and evaluate differences between arms. Additionally, in a subset of sites, bioelectrical impedance measurements will be collected.

The **Health economics sub-study** will assesses the costs and cost-effectiveness of LAI CAB/RPV vs. oral ART. Costs will be measured from a health system perspective including drugs, clinic visits and hospitalisations. Detailed resource use and costing of the delivery of injectables will be undertaken with consideration of implications for wider roll out to ensure evidence produced is useful for policy makers. Outcomes will be measured in quality-adjusted life-years (QALY), using the EQ-5D, to allow comparison with other interventions. Cost-effectiveness will be assessed using incremental cost-effectiveness ratios and incremental net health benefits and compared to appropriate country specific cost-effectiveness thresholds.

Pharmacology sub-studies, which will use a specifically developed assay(38), will involve:

a. Intensive PK: in the LAI group to validate the existing PK model in this population. A minimum of 20 participants will have 5 PK samples taken at/between week 24 and week 32 (week 24 (pre-injection trough sample), week 24 +3 days, week 24 +7 days, week 24 +28 days, week 24 +56 days (trough sample pre week 32 injection).

b. Incident pregnancy: among pregnant participants, CAB/RPV plasma concentrations will be assessed during pregnancy, delivery (maternal and cord blood) and post-partum, both in those who remain on CAB/RPV and those who return to oral ART (to assess the LAI tail in pregnancy). Infant plasma and breastmilk concentrations will also be assessed where the mother remains on CAB/RPV.

c. Incident TB: return to oral DTG-based ART is mandatory following incident TB; PK sampling will be undertaken to obtain data on the declining levels of LAI CAB/RPV during treatment with rifampicin-based TB treatment.

d. LAI Group with OLI: a single trough PK sample at week 4A for those opting for OLI, stored for subsequent analysis of those with virological rebound.

e. Sparse PK Sub-study: samples collected at weeks 24, 48, 72 and 96, pre-injection in the LAI arm and 6-24 hours after last ART intake in the control arm. A case-control design will be used to explore relationships between drug exposure and each of virological response and neuropsychiatric toxicity.

Data management

The trial database is programmed in OpenClinica and access is controlled. To protect confidentiality, participants were assigned a trial identification number and a random three-letter code. The database has programmed checks for eligibility, ranges and missing data. Additional consistency checks are performed by trial statisticians. AEs are coded using Medical Dictionary for Regulatory Activities v25.0.

Statistical analysis plan

The complete Statistical Analysis Plan is provided in Appendix E. For the primary analysis, the two treatment groups will be compared in the intention-to-treat population (ITT). The comparison will be of the cumulative probability of virological rebound by week 96. To allow for censoring, the survival curve for each combination of strata and randomised group will be calculated using a Cox model adjusting for stratification factors (as appropriate) and randomised group. The average cumulative failure function for each randomised group will be estimated by standardisation(39) as a weighted average of the corresponding stratum-specific cumulative failure functions, with weights equal to the prevalence of that stratum in the total ITT population. The difference in the probability of viral rebound will then be estimated by the average difference across strata by week 96. A 2-sided bias-corrected 95% or 99% confidence interval (CI) (Appendix A, Supplementary Table 2) for the difference in the probability of virological rebound by week 96 (LAI CAB/RPV – oral ART) will be calculated using appropriate (bias-corrected) percentiles of the bootstrap estimates. LAI CAB/RPV will be considered non-inferior to oral ART if the upper limit of the 95% or 99% CI of the difference LAI CAB/RPV -control is less than the selected non-inferiority margin (Appendix A, Supplementary Table 2). If non-inferiority is demonstrated, we will test for superiority of LAI CAB/RPV vs. oral ART (2-sided p=0.05). For analysis of the primary outcome and other virological outcomes, except for the FDA snapshot analysis, multiple imputation will be applied if either of the following is met: 5% of all HIV-1 RNA measurements at scheduled visits are missing or 10% of confirmatory HIV-1 RNA measurements are missing.

Secondary outcome measures will be compared for superiority using appropriate statistical methods in the ITT population.

An on-treatment (often referred to as per-protocol) analysis of the primary outcome will be conducted excluding any participants who did not meet all eligibility criteria. Follow-up will be censored in participants who had a break >7 days while on oral ART, took OLI incorrectly, started LAI late, received a scheduled LAI injection late without oral bridging (Table 2), or changed ART (excluding changes between oral and LAI CAB/RPV for oral bridging of <60 days). No interim analyses, beyond Independent Data Monitoring Committee (IDMC) data review, are planned.

Trial oversight

The trial oversight committees are detailed below:

1. **The IDMC** are independent experts who review interim analyses of accumulating data by trial arm. The IDMC will advise the Trial Steering Committee (TSC) if the trial should be stopped for safety or other reasons.
2. **The TSC** are members from The BREATHER Plus Consortium plus independent members, including independent Chair and Patient and Public Involvement (PPI) contributors. The TSC provides overall supervision for the trial.
3. **The BREATHER Plus Consortium,** responsible for the day-to-day running and management of the trial, comprises the BREATHER Plus Trial Chief Investigator (Chair), the LATA Chief Investigator, site Principal Investigators, co-investigators and trial managers, sub-study leads, members of the Medical Research Council Clinical Trials Unit (CTU) at UCL and PPI coordinators.
4. **Trial Management Teams (TMTs) at MRC CTU at UCL and sites** conduct the trial and ensure regulatory processes are followed.

Patient and Public Involvement

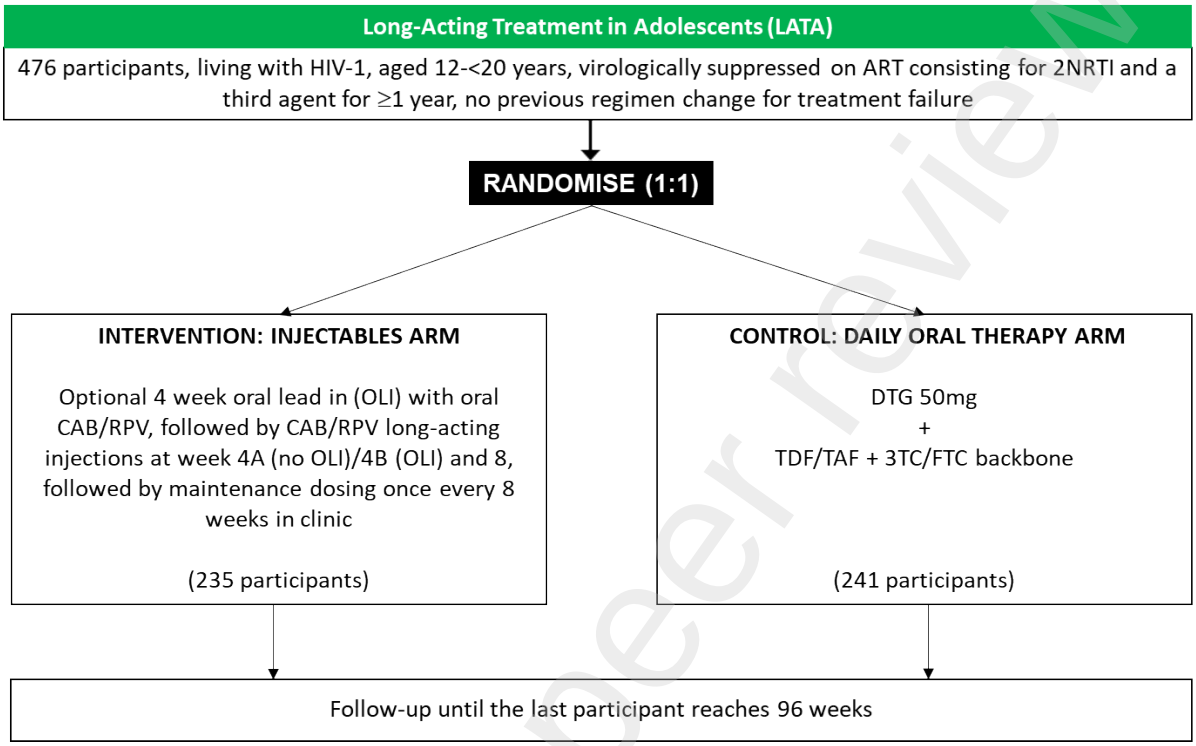
ALHIV are involved in the trial through Youth Trial Boards (YTBs) in South Africa, Uganda, Zimbabwe, Kenya and the UK and local Community Advisory Boards. YTBs consist of young people aged 14-19 years living with HIV. The aim of the YTBs is to ensure the voices of ALHIV are heard, and they contribute meaningfully to the development, delivery and dissemination of paediatric clinical trials. YTB members were provided training on the study. The YTB developed participant-friendly information tools including a video and infographic trial summary, used alongside the patient information sheet to support informed consent and recruitment. Two former YTB members are non-voting independent members on the TSC. YTB members participate in discussions about the trial, will be involved in results interpretation and promote trial findings within their communities, to ensure LATA is conducted and communicated in a way that is relevant and acceptable to ALHIV.

Current status of the trial

Participant enrolment commenced on the 22 June 2023 and a total of 476 participants were enrolled by 15 April 2024 (Figure 1). Follow-up is ongoing, with close-out visits planned between 19 January and 15 March 2026. Table 5 describes characteristics at enrolment. Median age was 16.5 years (IQR 14.8-18.1); 54% participants are female. Most (98%) had vertically acquired HIV. Most participants

were on DTG at trial entry (n=474, 99%), among whom median time on DTG was 3.5 years (2.8-4.2). 40% of participants opted to do OLI.

Figure 1: **LATA Trial Schema**



Abbreviations: 3TC (Lamivudine), ART (Antiretroviral Therapy), CAB (Cabotegravir), DTG (Dolutegravir), FTC (Emtricitabine), HIV (Human Immunodeficiency Virus), NRTI (Nucleoside/Nucleotide Reverse Transcriptase Inhibitors), OLI (Oral Lead In), RPV (Rilpivirine), TAF (Tenofovir Alafenamide Fumarate), TDF (Tenofovir Disoproxil Fumarate)

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	Summary (N=476)
Country	
Kenya	77 (16%)
South Africa	71 (15%)
Uganda	200 (42%)
Zimbabwe	128 (27%)
Age, years	16.5 [14.8, 18.1]
Sex	
Male	220 (46%)
Female	256 (54%)
Ethnicity	
Asian	2 (0.4%)
Black	474 (99.6%)
BMI-for-age z-score[1]	-0.3 [-0.9, 0.4]
Weight, kg	50.0 [44.3, 55.9]
Mode of HIV acquisition	
Vertical	466 (98%)
Horizontal/other[2]	10 (2%)
WHO clinical stage	
Stage 1	245 (51%)
Stage 2	99 (21%)
Stage 3	113 (24%)
Stage 4	19 (4%)
Time since HIV diagnosis, years	12.6 [10.0, 15.3]
Age at ART initiation, years	4.3 [1.9, 8.3]
Time since ART initiation, years	11.7 [8.5, 14.1]
Time on DTG at trial entry, years[3]	3.5 [2.8, 4.2]
Regimen at trial entry	
TDF/3TC/DTG	473 (99.4%)
ABC/3TC/DTG	1 (0.2%)
ABC/3TC/RPV	1 (0.2%)
TDF/3TC/EFV	1 (0.2%)
CD4+ T-cell count, cells/μl[4]	832 [653, 1034]
CD4+:CD8+ ratio[4]	1.3 [1.0, 1.6]
Haemoglobin, g/dL[4]	13.2 [12.0, 14.4]
eGFR, ml/min[4]	115 [101, 134]
HbA1c, mmol/mol[4]	36 [32, 38]
Total cholesterol:HDL cholesterol ratio[4]	3.0 [2.6, 3.6]

Results presented are 'n (%)' or 'median [IQR]'

[1]BMI-for-age z-score calculated using British 1990 Reference data (available 0-23 years) for standardisation

[2]Among 10 participants in the horizontal/other stratum: 3 acquired HIV through sexual contact, 1 through suspected malicious infection via blood, and mode of acquisition was unknown for 6.

[3]Two participants not on DTG-based regimen at trial entry contribute 0 years to summary of time on DTG at entry

[4]Missing data for: CD4+ T-cell (n=3), CD4+:CD8+ ratio (n=3), haemoglobin (n=6), eGFR (n=2), HbA1c (n=2), total cholesterol: HDL cholesterol ratio (n=3)

Abbreviations: 3TC (Lamivudine), ABC (Abacavir), ART (Antiretroviral therapy), BMI (Body Mass Index), CD4 (Cluster of Differentiation 4), CD8 (Cluster of Differentiation 8), DTG (Dolutegravir), EFV (Efavirenz), eGFR (Estimated Glomerular Filtration Rate), HbA1c (haemoglobin A1c), HDL (High-density Lipoprotein), HIV (Human Immunodeficiency Virus), RPV (Rilpivirine), T-cell (Thymus cell), TAF (Tenofovir Alafenamide Fumarate), TDF (Tenofovir Disoproxil Fumarate), WHO (World Health Organization)

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Discussion

LATA is an ongoing trial evaluating the LAI CAB/RPV regimen in SSA in ALHIV who are virologically suppressed. LATA will assess whether LAI CAB/RPV administered once every 8 weeks provides non-inferior virological suppression compared to daily oral DTG-based ART with a tenofovir and lamivudine/emtricitabine backbone over 96 weeks.

The design is pragmatic, aiming to inform routine care use of LAIs in ALHIV in Africa. First, VL monitoring is once every 24-weeks in line with most African clinical guidelines. Second, while contraception is required in sexually-active girls, participants who become pregnant while receiving LAIs are offered the choice to remain on their LAIs, following additional informed consent, respecting their right to choose and following the WHO framework for inclusive research in pregnant and breastfeeding women(40). This contrasts with LAI CAB/RPV registrational trials which mandated return to oral ART in pregnancy and thus LATA will contribute data on maternal and infant safety on LAIs. Third, OLI was optional. Last, we screened for hepatitis B, using hepatitis B surface antigen alone, accepting that hepatitis B core antibody testing is not widely available in LMIC settings. It is noteworthy that in CARES, 366/1039 people(21) were excluded from participation on the basis of hepatitis B core antibody positivity alone. We plan to explore the percentage of LATA participants with evidence of hepatitis B exposure (core and surface antibody positive) and evidence of hepatitis B reactivation when switched to LAI CAB/RPV, using HBV DNA on stored samples; this risk is considered to be low(41). We have also facilitated hepatitis B vaccination in both arms during follow-up for participants who missed their infant vaccination or had not completed the full course.

LATA includes several important sub-studies. Social science, neuropsychiatric, metabolic and PK sub-studies will provide valuable information on how participants, their families and staff feel about LAI, the toxicity profile in ALHIV, the metabolic consequences of discontinuation of tenofovir in the LAI arm, and PK will inform in the particular groups of interest, including pregnant ALHIV. Provision of LAI is planned for a further 2 years beyond the end of the trial in those in the LAI arm doing well and wishing to remain on them.

Limitations

We selected a highly adherent patient population, who were virologically suppressed, potentially limiting generalisability to a less adherent, INSTI-naïve and/or viraemic population, who might also benefit from injectable ART.

The target was to recruit ≥30% of participants with horizontally acquired HIV, however this was not achieved despite sites implementing strategies such as reaching out to sexual health services. While

there is no reason to believe that adolescents acquiring HIV horizontally would respond differently to LAI in terms of virological outcomes, there might be differences in regard to other outcomes.

Conclusions

The LATA trial will show whether the injectable combination of CAB/RPV is as efficacious, safe and acceptable as daily oral therapy in ALHIV in SSA, using a programmatic approach. It is hoped that lessons learned in the LATA trial will inform the use of LAI combinations in ALHIV.

Abbreviations

3TC: Lamivudine

AE: Adverse event

ALHIV: Adolescent living with HIV

ART: Antiretroviral therapy

ARV: Antiretroviral

BMI: Body Mass Index

CAB: Cabotegravir

CI: Confidence interval

C-SSRS: Columbia-Suicide Severity Rating Scale

CTU: Clinical Trials Unit

DNA: deoxyribonucleic acid

DTG: Dolutegravir

eCRF: electronic Case Report Form

eGFR: estimated Glomerular Filtration Rate

EQ5D: EuroQol-5 Dimension

FDC: Fixed dose combination

FTC: Emtricitabine

GCP: Good Clinical Practice

HATQoL: HIV/AIDS targeted quality of life

HbA1c: Haemoglobin A1c/glycosylated Haemoglobin

HBSAg: Hepatitis B surface antigen

HDL: High-density lipoprotein

HIV/HIV-1: Human Immunodeficiency Virus or Human Immunodeficiency Virus-1

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IDMC: Independent Data Monitoring Committee

IMP: Investigational medicinal product

INSTI: Strand transfer Integrase inhibitor

IQR: Interquartile range

ITT: Intention-to-treat

LAI: Long-Acting Injectable

LATA: Long-Acting Treatment in Adolescents: A randomised, open-label, two-arm, 96-week trial in virologically suppressed HIV-1-positive adolescents aged 12-19 years of age in sub-Saharan Africa

MRC: Medical Research Council

MRC CTU at UCL: Medical Research Council Clinical Trials Unit at University College London

NI: Non-inferiority

NRTI: Nucleoside reverse transcriptase inhibitor

NNRTI: Non-nucleoside reverse transcriptase inhibitor

PK: Pharmacokinetic

PPI: Patient and Public Involvement

RNA: Ribonucleic acid

RPV: Rilpivirine

SAE: Serious adverse event

TAF: Tenofovir alafenamide fumarate

TB: Tuberculosis

T-cell: Thymus cell

TDF: Tenofovir disoproxil fumarate

TLD: Fixed dose combination of TDF, 3TC, DTG

TMT: Trial Management Team

TSC: Trial Steering Committee

UCL: University College London

VL: HIV Viral load

WHO: World Health Organization

YTB: Youth Trial Board

Declarations

Ethics approval and consent to participate

This study is being carried out in accordance with the principles of GCP as laid down by the ICH topic E6 (R2), the Declaration of Helsinki 2013 and applicable national regulations. This trial (Protocol v1.0, which was used from the start of the trial) was approved by Research Ethics Committees, Institutional Review Boards and by all required regulatory authorities in each of the participating countries.

Uganda: Joint Clinical Research Centre Institutional Review Board/Research Ethics Committee (JCRC 2022–28, 26 Aug 2022), Uganda National Council of Science and Technology (HS2515ES, 16 Mar 2023), and the National Drug Authority (CTC 0222/2023; 20 Apr 2023).

South Africa: Pharma Ethics (220324586; 18 Oct 2022) and South African Health Products Regulatory Authority (20221018; 12 Dec 2022).

Kenya: Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (IREC/294/2022; 16 Feb 2023) and Kenya Pharmacy and Poisons Board (PPB/ECCT/23/05/07/2023(301); 11 Sep 2023).

Zimbabwe: Medicines Control Authority of Zimbabwe (B/279/5/652/2022, 16 Dec 2022), Medical Research Council of Zimbabwe (MRCZ/A/2926, 19 Sep 2022), Joint Research Ethics Committee (313/2022, 03 Oct 2022).

Important protocol modifications (e.g. changes to eligibility criteria, outcomes, analyses) will be sent to the above committees.

Participants are enrolled in the trial after giving an informed consent for those 18 years and above; and parent's or legal guardian's informed consent, and assent for those below 18 years. Adolescents who reach the age of consent while on the trial will re-confirm their continued participation by signing the informed consent form. Participants and Parents/legal guardians of the participants eligible for participation in the sub studies (neuropsychiatric, PK, Social science) give an additional consent; whereas children give assent if applicable. Parents and children also give consents and assents, respectively, for storage of the samples for analyses specified in the protocol and patient information sheets, and for future research studies. Informed consent in the trial is taken by a site PI or a trained member of the trial team who have been delegated this activity. See Appendix D for model patient information and informed consent forms given to families.

Availability of data and materials

The LATA trial data are held at MRC CTU at UCL, which encourages optimal use of data by employing acontrolled access approach to data sharing (http://www.ctu.mrc.ac.uk/our_research/datasharing/), incorporating a transparent and robust system to review requests and provide secure data access consistent with the relevant ethics committee approvals. We will consider all requests for data sharing, which can be initiated by contacting the corresponding author or through the URL: https://www.ctu.mrc.ac.uk/our-research/other-research-policy/data-sharing/application-process/

Competing interests

SLP declares grant funding paid to her University from the National Institutes of Health, Gilead Sciences, Janssen-Cilag, ViiV Healthcare, none of which are competing interests for LATA.

Funding

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APPENDIX A: Supplementary Tables

APPENDIX B: BREATHER Plus/LATA Consortium Members and Oversight Committees

APPENDIX C: LATA Participant Questionnaires

APPENDIX D: LATA Participant Information Sheet Master Template

APPENDIX E: LATA Statistical Analysis Plan

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