CABOTEGRAVIR + RILPIVIRINE LONG-ACTING AS HIV-1 MAINTENANCE THERAPY: ATLAS WEEK 96 RESULTS

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Introduction

- Long-acting (LA) injectable therapies have the potential to address some challenges associated with daily oral antiretroviral therapy (ART), e.g. pill fatigue, drug/food interactions, stigma and suboptimal adherence.
- Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), have been developed as an LA, injectable, two-drug regimen for the maintenance of virologic suppression.
- The ATLAS (NCT02951052) and FLAIR (NCT02938520) Phase 3 randomised controlled trials have previously demonstrated that monthly intramuscular (IM) CAB + RPV LA is noninferior to daily oral ART in the maintenance of virologic suppression over a period of 48 weeks.[1,2]
- We present results from the Extension Phase of ATLAS, reporting data for participants switched from the comparator arm to CAB + RPV LA at the conclusion of the Maintenance Phase and longer-term outcomes for participants randomised to CAB + RPV LA at the start of the Maintenance Phase.
- As a majority of study participants elected to rollover to the ATLAS-2M study (NCT03299049), this analysis encompasses the results from participants' time on study within the ATLAS Extension Phase through Week 96.

Objective and Endpoints

Objective

- To establish noninferior antiviral activity of monthly IM CAB + RPV LA vs. continuing current antiretroviral regimen (CAR) in ART-experienced participants.

Endpoints Assessed at Week 96

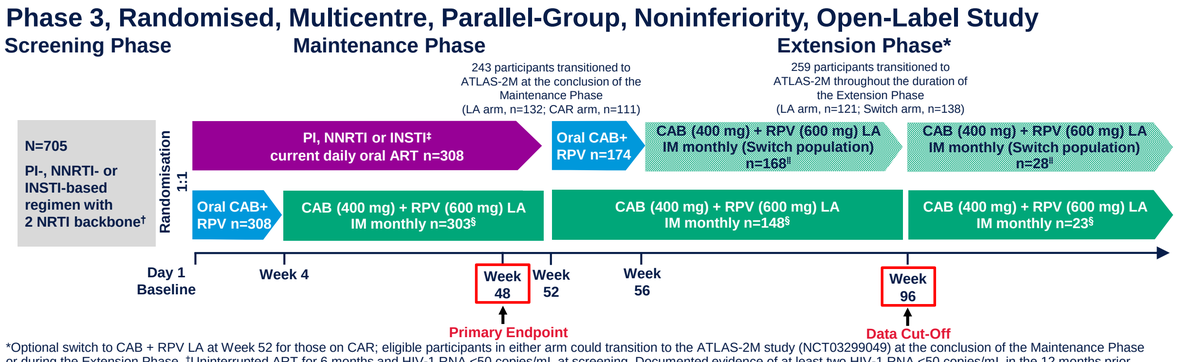
- For participants randomised to CAB + RPV LA at Day 1 (intention-to-treat exposed [ITT-E]) and for participants electing to transition to CAB + RPV LA from CAR in the Extension Phase (Switch population):
  - Proportion with HIV-1 RNA ≥50 copies/mL at Week 96
  - Proportion with HIV-1 RNA <50 copies/mL at Week 96
  - Incidence of confirmed virologic failure (CVF; two consecutive HIV-1 RNA ≥200 copies/mL)
  - Safety and tolerability (including injection site reactions [ISRs])
  - CAB and RPV pharmacokinetics
  - Patient-reported outcomes (PROs).

Methods

Study Design

- ATLAS is a randomised, multicentre, parallel-group, open-label Phase 3 study designed to assess the efficacy, safety and tolerability of IM CAB + RPV LA given monthly for the maintenance of virologic suppression following a switch from CAR in ART-experienced adults living with HIV-1 (**Figure 1**).
- Participants were randomised (1:1) to either continue their current ART (CAR arm) or switch to LA therapy (LA arm) for the duration of the 52-week Maintenance Phase.
- Participants could then either withdraw, enter the Extension Phase of ATLAS or transition to the ATLAS-2M study.
- Participants entering the Extension Phase at Week 52 either continued CAB + RPV LA therapy (LA arm) or switched from CAR to CAB + RPV LA (Switch arm).

Figure 1. Study Design



*Optional switch to CAB + RPV LA at Week 52 for those on CAR; eligible participants in either arm could transition to the ATLAS-2M study (NCT03299049) at the conclusion of the Maintenance Phase or during the Extension Phase. †Uninterrupted ART for 6 months and HIV-1 RNA <50 copies/mL at screening. Documented evidence of at least two HIV-1 RNA <50 copies/mL in the 12 months prior to screening. ‡INSTI-based regimen capped at 40% of enrolment; abacavir/dolutegravir/lamivudine excluded from study. §Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB LA (400 mg) and RPV LA (600 mg) injections every 4 weeks. ‖Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 56. From Week 60 onwards, participants received CAB LA (400 mg) and RPV LA (600 mg) injections every 4 weeks. ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral therapy; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine.

Results

- Baseline characteristics were similar between the LA and CAR arms at baseline (Day 1) (**Table 1**).

Table 1. Baseline Characteristics: ITT-E Population

Parameter	LA arm n=308	CAR arm n=308	Total N=616
Age, median (range) years	40 (21–74)	43 (18–82)	42 (18–82)
Age ≥50 years, n (%)	66 (21)	96 (31)	162 (26)
Female (sex at birth), n (%)	99 (32)	104 (34)	203 (33)
Race, n (%)			
White	214 (69)	207 (67)	421 (68)
Black or African American	62 (20)	77 (25)	139 (23)
Other	32 (10)	24 (8)	56 (9)
Body mass index, median (range) kg/m^2	26 (15–51)	26 (18–58)	26 (15–58)
CD4+ cell count, median (range) cells/mm^3	654 (185–1903)	653 (150–2543)	653 (150–2543)
Duration of prior ART, median (range) years	4 (1–19)	4 (1–21)	4 (1–21)
Total treatment satisfaction score (HIVTSQs), mean (standard deviation)	55.25 (9.14)	55.40 (8.68)	–
Baseline third ART agent class, n (%)			
NNRTI	155 (50)	155 (50)	310 (50)
INSTI	102 (33)	99 (32)	201 (33)
PI	51 (17)	54 (18)	105 (17)

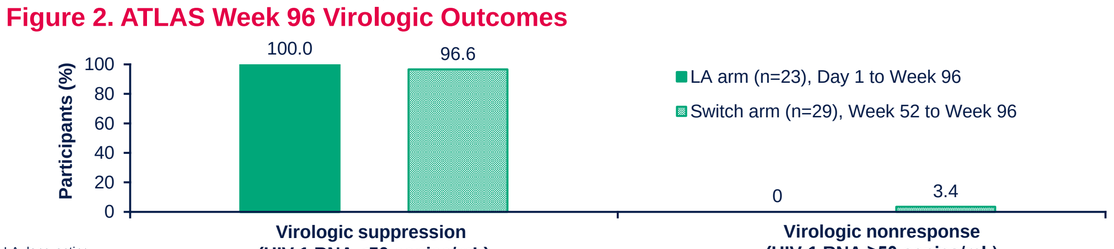
ART, antiretroviral therapy; CAR, current antiretroviral therapy; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Participant Disposition

- Of the participants who completed the Maintenance Phase (LA arm, n=282; CAR arm, n=290), almost all decided to remain on/switch to LA therapy.
  - In total, 243 participants transitioned to ATLAS-2M at the conclusion of the Maintenance Phase (LA arm, n=132; CAR arm, n=111).
  - Overall, 174 CAR arm participants elected to switch to CAB + RPV LA and 148 LA arm participants chose to continue CAB + RPV LA in the Extension Phase.
  - Only 7 participants chose to discontinue treatment (LA arm, n=2; CAR arm, n=5).
- Throughout the Extension Phase, as participants became eligible, most chose to transition to ATLAS-2M (LA arm, n=121; Switch arm, n=138) and few participants withdrew (LA arm, n=4*; Switch arm, n=8†).
- This left 52‡ participants in the ATLAS study for inclusion in the Week 96 data analysis (LA arm, n=23; Switch arm, n=29).

*Two participants discontinued due to adverse events (AEs), 1 participant discontinued due to protocol deviation and 1 participant withdrew from the study. †One participant discontinued due to an AE, 1 participant discontinued due to the decision of the treating physician, 1 participant discontinued due to lack of efficacy and 5 participants withdrew from the study. ‡One participant who discontinued at Week 92 in the Switch arm was included in the Week 96 data analysis.

Figure 2. ATLAS Week 96 Virologic Outcomes



LA, long-acting.

- The majority of participants who entered the Extension Phase and remained in the study through the Week 96 analysis maintained virologic suppression with CAB + RPV LA (**Figure 2**).
  - Only 1 participant in the Switch arm had HIV-1 RNA ≥50 copies/mL at the Week 96 data analysis (HIV-1 RNA of 173 copies/mL at Week 92).*
- Furthermore, no participants in either treatment arm met the CVF criterion during the Extension Phase.

*Participant discontinued at Week 92 and was included in the Week 96 data analysis.

Table 2. Safety Overview

Outcome, n (%)	Maintenance Phase: LA arm (Day 1 to Week 52) n=308	Maintenance Phase: CAR arm (Day 1 to Week 52) n=308	Extension Phase: LA arm* (Week 52 to Week 96)†	Extension Phase: Switch arm (Week 52 to Week 96)‡
Any AE	294 (95)	220 (71)	1	105
Excluding ISRs	264 (86)	220 (71)	3	76
Any Grade 3/4 AEs	35 (11)	23 (7)	2	7
Excluding ISRs	25 (8)	23 (7)	2	5
Any drug-related AEs	255 (83)	8 (3)	0	79
Drug-related Grade 3/4 AEs	14 (5)	1 (<1)	0	4§
Any serious AEs‖	13 (4)	14 (5)	2	2
Fatal serious AEs	0	1 (<1)¶	0	0
AEs leading to withdrawal	14 (5)	5 (2)	2#	1**

*Values represent the number of new participants with AEs in the LA arm during the Extension Phase. †148 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 23 participants at the Week 96 analysis. ‡174 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 29 participants at the Week 96 analysis. §Grade 3 injection site pain (n=3) and Grade 4 increased lipase (n=1). ‖No serious AEs were classified as related to CAB/RPV. ¶Death was due to a methamphetamine overdose and was considered not related to the study treatment. #Includes acute hepatitis B and fear. **Injection site pain. AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral therapy; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

- Safety data collected during the Extension Phase for the LA and Switch arms were comparable to those collected for the LA arm during the Maintenance Phase (**Table 2**).

Table 3. Common Adverse Events (Excluding ISRs)

Common AEs excluding ISRs (≥5%), n (%)	Maintenance Phase: LA arm (Day 1 to Week 52) n=308	Maintenance Phase: CAR arm (Day 1 to Week 52) n=308	Extension Phase: LA arm* (Week 52 to Week 96)†	Extension Phase: Switch arm (Week 52 to Week 96)‡
Nasopharyngitis	52 (17)	42 (14)	7	10
Headache	34 (11)	17 (6)	1	4
Upper respiratory tract infection	32 (10)	25 (8)	4	2
Diarrhoea	22 (7)	15 (5)	2	6
Fatigue	22 (7)	6 (2)	1	5
Pyrexia	21 (7)	9 (3)	0	6
Back pain	20 (6)	10 (3)	2	2
Influenza	17 (6)	14 (5)	1	8
Cough	16 (5)	14 (5)	2	4
Insomnia	15 (5)	4 (1)	1	0
Respiratory tract infection viral	11 (4)	17 (6)	3	4

*Values represent the number of new participants with AEs in the LA arm during the Extension Phase. †148 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 23 participants at the Week 96 analysis. ‡174 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 29 participants at the Week 96 analysis. AE, adverse event; CAR, current antiretroviral therapy; ISR, injection site reaction; LA, long-acting.

- No new safety signals were identified during the Extension Phase (**Table 3**).
- All non-ISR, drug-related AEs, with the exception of pyrexia and diarrhoea, were reported at a frequency of <1% and were all Grade 1 or 2, except for one Grade 4 AE of increased lipase.

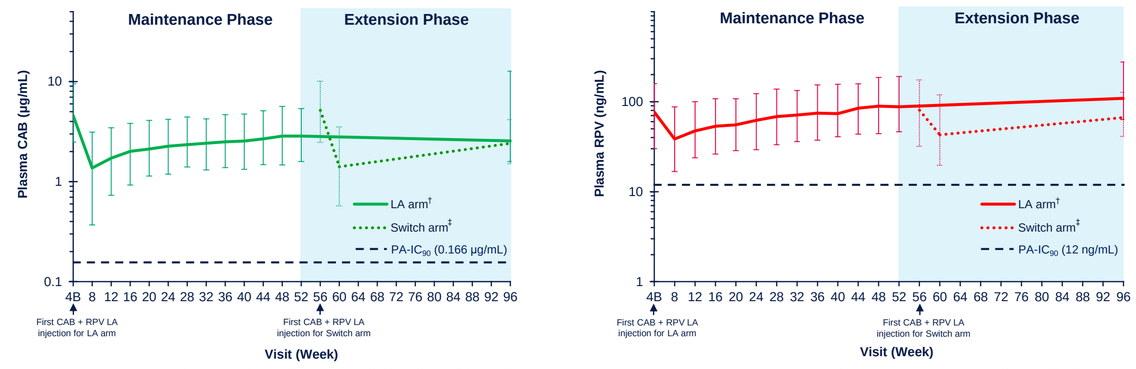
Table 4. Injection Site Reactions

Outcome	Maintenance Phase: LA arm (Day 1 to Week 52) n=308	Extension Phase: LA arm (Week 52 to Week 96)*	Extension Phase: Switch arm (Week 52 to Week 96)†
Number of injections	6978	1363	1264
ISR events, n (% of total injections)	1460 (20.9)	154 (11.3)	238 (18.8)
Grade 1 – mild	1156 (16.6)	134 (9.8)	184 (14.6)
Grade 2 – moderate	283 (4.1)	20 (1.5)	51 (4.0)
Grade 3 – severe	21 (<1)	0	3 (<1)
ISR events (most frequent), n (% of total injections)			
Pain	1208 (17.3)	120 (8.8)	207 (16.4)
Induration	54 (<1)	8 (<1)	14 (1.1)
Nodule	54 (<1)	7 (<1)	3 (<1)
Swelling	48 (<1)	2 (<1)	4 (<1)
Erythema	38 (<1)	2 (<1)	0
Bruising	14 (<1)	0	1 (<1)
Pruritus	12 (<1)	14 (1.0)	3 (<1)
Median duration of ISR events, days	3	3	3
Number of participant withdrawals due to ISR events	4	0	1

*148 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 23 participants at the Week 96 analysis. †174 participants entered the Extension Phase; however, this number deteriorated throughout the study leaving 29 participants at the Week 96 analysis. ISR, injection site reaction; LA, long-acting.

- The frequency and severity of ISR AEs during the Extension Phase in the Switch arm were consistent with results observed in the LA arm during the Maintenance Phase (**Table 4**).
- During the Extension Phase, across both treatment arms, the majority of ISR events were Grade 1 or Grade 2 (>99%, 389/392), with a median duration of 3 days, and led to 1 participant withdrawal.

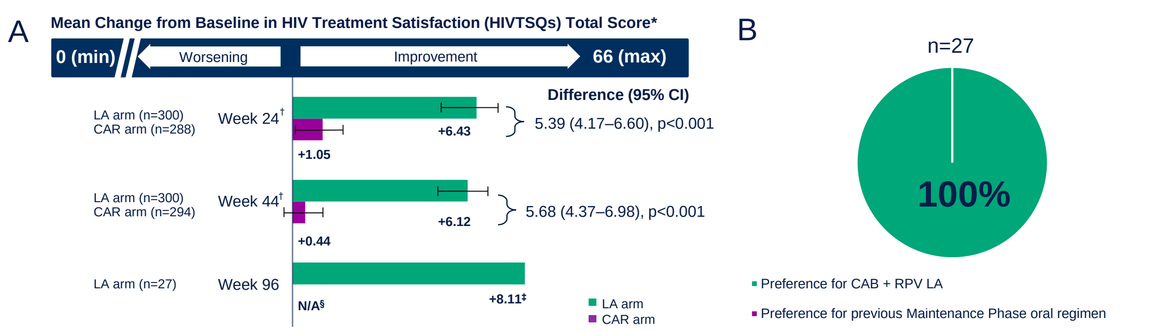
Figure 3. Plasma CAB and RPV Trough Concentrations*



*Median (5th and 95th percentile) concentration–time data for CAB (left) and RPV (right) following monthly LA administration. Values for Week 4B for the LA arm and Week 52 for the Switch arm represent oral dosing concentrations. †Timepoint, n (CAB/RPV): Week 4B, n=259/258; Week 8, n=252/251; Week 12, n=261; Week 16, n=248/247; Week 20, n=233; Week 24, n=234/231; Week 28, n=232; Week 32, n=219/218; Week 36, n=209; Week 40, n=209/208; Week 44, n=221/223; Week 48, n=217/216; Week 52, n=215/214; Week 96, n=19. ‡Timepoint, n (CAB/RPV): Week 56, n=149; Week 60, n=127; Week 96, n=24. CAB, cabotegravir; LA, long-acting; PA-IC$_{90}$, protein-adjusted concentration required for 90% inhibition; RPV, rilpivirine.

- Week 96 median CAB concentrations were comparable between the LA and Switch arms, consistent with an achievement of steady state for CAB after 44 weeks of injections (**Figure 3**).
- Week 96 median RPV concentrations were higher in the LA arm (after 23 IM injections) than the Switch arm (after 10 IM injections). This suggests some limited further accumulation of RPV in the second year of injections, in line with the half-life of RPV LA.

Figure 4. Treatment Satisfaction (A) and Participant Preference (B)



*LA arm: baseline, n=302; CAR arm: baseline, n=298. †Adjusted mean change from baseline; adjusted for baseline score, sex at birth, age, race (white, non-white) and baseline third agent class (INSTI, PI, NNRTI). Error bars show 95% confidence interval. ‡Unadjusted variables. No statistical analysis was carried out due to significantly reduced sample size. §CAR arm participants transitioned to LA therapy during the Extension Phase. CAB, cabotegravir; CAR, current antiretroviral therapy; CI, confidence interval; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine.

- Overall treatment satisfaction for LA arm participants remained at a high level through Week 96, with large improvements from baseline across all timepoints (**Figure 4A**).
- For participants in the Switch arm, similar improvements from Extension Baseline were observed in overall treatment satisfaction at Week 96 (mean HIVTSQs total score [SD]: Extension Baseline [n=174], 54.66 [10.72]; Week 96 [n=35], 59.20 [12.77]).
  - Due to the small sample size at Week 96, only a descriptive analysis of the results was pre-planned.
  - Withdrawal assessments following Week 48 (for the LA arm) and Extension Baseline (for the Switch arm) are included in the Week 96 analysis.
  - The results are consistent with the results from the Week 48 analysis.
- At Week 96, 100% (27/27) of participants in the Switch arm responding to the questionnaire selected CAB + RPV LA as their preferred regimen compared with the daily oral treatment they had been receiving during the Maintenance Phase (**Figure 4B**).

Conclusions

- Most participants chose to continue/switch to LA therapy in ATLAS or ATLAS-2M, with few participants choosing to withdraw.
- Monthly injectable CAB + RPV LA maintained virologic suppression in the majority of participants at the Week 96 data analysis. There were no CVFs reported throughout the Extension Phase.
- Treatment satisfaction and preference for the LA regimen remained high among study participants.
- These longer-term efficacy, safety and tolerability, pharmacokinetic and PRO data complement the positive results collected at Week 48 and support the therapeutic potential of CAB + RPV LA for people living with HIV-1.

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References: 1. Swindells S, et al. *N Engl J Med.* 2020;382(12):1112–1123. 2. Orkin C, et al. *N Engl J Med.* 2020;382(12):1124–1135.

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