Monthly Long-Acting Cabotegravir and Rilpivirine Is Noninferior to Oral ART as Maintenance Therapy for HIV-1 Infection: Week 48 Pooled Analysis From the Phase III ATLAS and FLAIR Studies

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ET Overton,[1] C Orkin,[2] S Swindells,[3] K Arasteh,[4] MG Hernández-Mora,[5] V Pokrovsky,[6] P-M Girard,[7] S Oka,[8] J-F Andrade-Villanueva,[9] GJ Richmond,[10] G Rizzardini,[11] A Baumgarten,[12] M Del Mar Masia,[13] G Latiff,[14] S Griffith,[15] CM Harrington,[15] KJ Hudson,[15] M St. Clair,[15] C Talarico,[15] V Van Eygen,[16] R D'Amico,[15] JM Mrus,[15] S Wu,[17] K Chow,[18] J Roberts,[18] S Vanveggel,[16] DA Margolis,[15] P Williams,[16] W Parys,[16] K Smith,[15] WR Spreen,[15] M Shields[19,*]

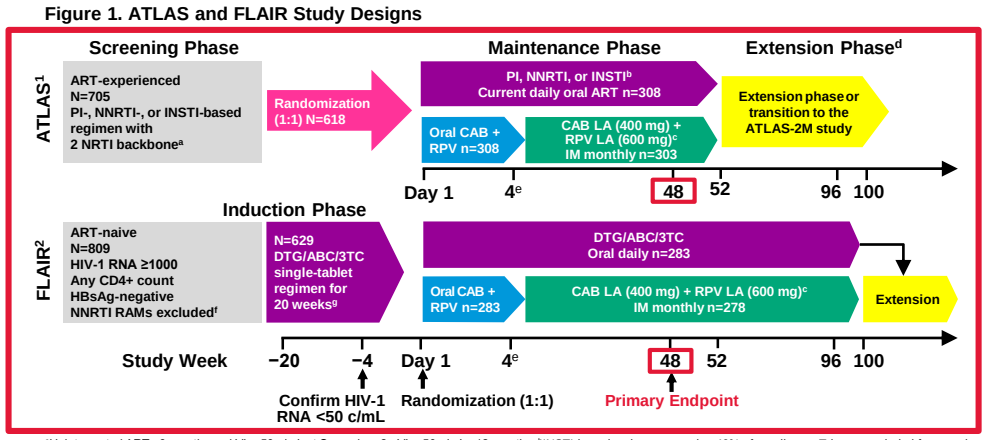
[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Queen Mary University, London, UK; [3]University of Nebraska Medical Center, Omaha, NE, USA; [4]EPIMED GmbH, Berlin, Germany; [5]Fundación Jiménez Díaz, Madrid, Spain; [6]Central Research Institute of Epidemiology, Moscow, Russia; [7]Hôpital Saint Antoine, Paris, France; [8]National Center for Global Health and Medicine, Tokyo, Japan; [9]University of Guadalajara, Guadalajara, Mexico; [10]Broward Health Medical Center, Fort Lauderdale, FL, USA; [11]Fatebenefratelli Sacco Hospital, Milan, Italy; [12]MIB Infectious Disease Medical Center, Berlin, Germany; [13]Hospital General de Elche, Alicante, Spain; [14]Maxwell Centre, Durban, South Africa; [15]ViiV Healthcare, Research Triangle Park, NC, USA; [16]Janssen Research & Development, Beerse, Belgium; [17]GlaxoSmithKline, Collegeville, PA, USA; [18]GlaxoSmithKline, Mississauga, ON, Canada; [19]Taylor Square Private Clinic, Sydney, NSW, Australia

**Presenting on behalf of the authors.*

Introduction

- Despite the success of daily oral therapy, considerable interest exists in long-acting (LA) treatment options for HIV-1 infection
- ATLAS[1] (NCT02951052) and FLAIR[2] (NCT02938520) are 2 randomized, open-label, international phase III studies evaluating the switch to monthly IM injections (Figure 1)

Figure 1. ATLAS and FLAIR Study Designs



[a]Uninterrupted ART ≥6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months. [b]INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study. [c]Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up. [d]Optional switch to CAB + RPV LA at Week 52 for those on CAR. [e]Participants received initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onward, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks. [f]NNRTI RAMs, but not K103N, were exclusionary. [g]DTG + 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

Objective

- To establish noninferior antiviral activity of monthly IM CAB + RPV LA vs continuing current antiretroviral regimen (CAR) in treatment-experienced (ATLAS) and previously treatment-naive (FLAIR) participants

Methods

- The primary endpoint was the proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 using the US Food and Drug Administration Snapshot algorithm (4% noninferiority margin on difference between arms)
- Secondary endpoints included HIV-1 RNA <50 c/mL at Week 48 (Snapshot), safety and tolerability, treatment satisfaction and preference, and a resistance analysis of confirmed virologic failure (CVF)

Results

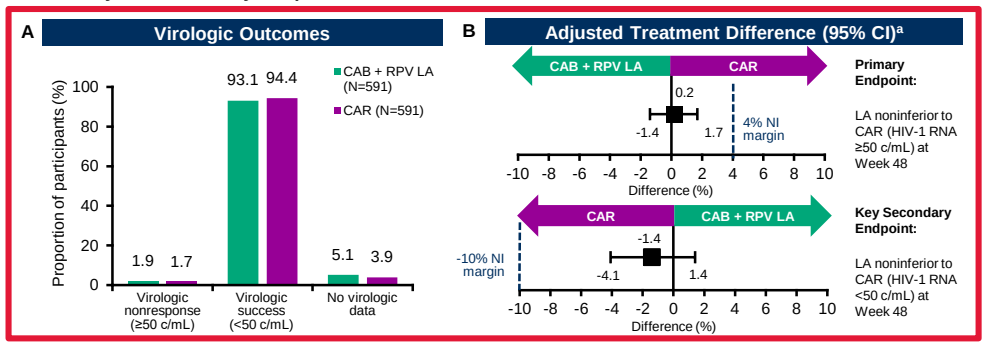
Table 1. Baseline Characteristics: ITT-E Population

Characteristic	CAB + RPV LA N=591	CAR N=591
Age, median (range), y	38 (19-74)	38 (18-82)
Age ≥50 y, n (%)	99 (17)	125 (21)
Female, n (%)	162 (27)	168 (28)
Race, n (%)		
White	430 (73)	408 (69)
Black/African American	109 (18)	133 (23)
Other	52 (9)	50 (8)
Median body mass index (range), kg/m^2	24.9 (15.3-50.9)	24.8 (12.6-57.7)
Median CD4+ cell count (IQR), cells/mm^3	645 (487-824)	641 (480-821)
HIV-1–HCV coinfection, n (%)	42 (7)	40 (7)

Baseline for FLAIR was Day 1 (maintenance phase).

- At Week 48, 93.1% (550/591) of participants in the CAB + RPV LA arm and 94.4% (558/591) in the CAR arm had HIV-1 RNA <50 c/mL (Snapshot; intention-to-treat–exposed population; Figure 2)
- Proportions of participants with HIV-1 RNA ≥50 c/mL were similar between the CAB + RPV LA (1.9% [11/591]) and CAR arms (1.7% [10/591])
- Proportion of participants discontinuing due to an adverse event (AE) was 3.2% (19/591) in the CAB + RPV LA arm compared with 1.2% (7/591) in the CAR arm

Figure 2. (A) Virologic Snapshot Outcomes at Week 48 for ITT-E and (B) Noninferiority Achieved for Primary and Secondary Endpoints



ITT-E, intention-to-treat–exposed; LA, long-acting; NI, noninferiority. [a]Adjusted for sex and baseline third agent class.

- For participants receiving CAB + RPV LA, common AEs (≥5%) were nasopharyngitis (18%), headache (12%), upper respiratory tract infection (12%), diarrhea (9%), back pain (7%), influenza (7%), and pyrexia (7%)
- For participants receiving CAB + RPV LA, ISR events occurred with 24.9% (3663/14,682) of injections given, with pain being the most frequently reported (21%); most of these events (99%) were grade 1/2 and most (88%) resolved within ≤7 days; 6 participants withdrew because of ISRs

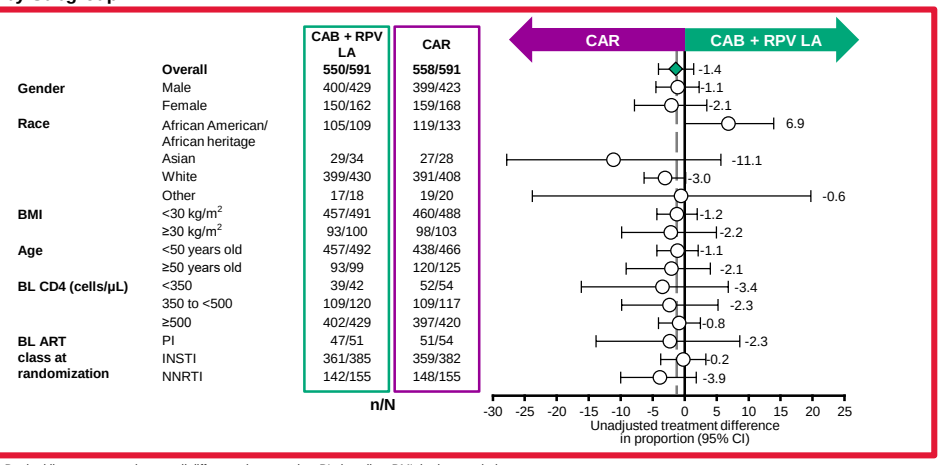
L74I Polymorphism in FLAIR Participants

- Proportion of participants with the L74I substitution at baseline was similar between study arms (CAB + RPV LA, 22% [54/243]; CAR, 20% [47/240])
- Of the 101 participants with the L74I substitution, most were from the Russian Federation (63.4% [64/101])
  - 6.0% (5/84) were from the United States
- L74I was most commonly observed in subtype A (85.7% [60/70])
- Subtype B (67.5% [326/483]) was the most prevalent subtype
- The presence of L74I IN polymorphism had no impact on overall treatment outcomes
  - HIV-1 RNA <50 by Snapshot (Table 4)
  - HIV-1 RNA ≥50 by Snapshot (CAB + RPV LA, 3/54 [5.6%]; CAR, 1/47 [2.1%]; treatment difference, 3.4 [95% CI, −6.8 to 13.5])

Single-Item Question on Participants' Preference at Week 48

- ITT-E population: 88% (523/591) preferred LA; 2% (9/591) preferred daily oral therapy
  - Responding participants: 98% (523/532) preferred the LA regimen over previous oral therapy

Figure 3. Treatment Difference in Proportion (95% CI) Snapshot HIV-1 RNA <50 c/mL at Week 48 by Subgroup



Dashed line represents the overall difference in proportion. BL, baseline; BMI, body mass index.

Table 2. Safety Overview, Excluding ISRs, Through Week 48 in the Maintenance Phase

AE, n (%)	CAB + RPV LA N=591	CAR N=591
Any AE	506 (86)	444 (75)
Any grade 3-5 AE[a]	44 (7)	35 (6)
Any drug-related AE	165 (28)	35 (6)
Any grade 3-5 drug-related AE[a]	8 (1)	1 (<1)
Any AEs leading to withdrawal	17 (3)	9 (2)
Any SAE	24 (4)	25 (4)
SAEs related to study treatment[b]	1 (<1)	1 (<1)

[a]There was 1 (<1%) participant with grade 5 AE in the CAR arm. [b]Serious AEs related to study treatment: LA arm – arthritis; CAR arm – suicidal ideation.

Table 3. ATLAS and FLAIR Confirmed Virologic Failures[a]: CAB + RPV LA Arm

Study	Sex, country, HIV-1 subtype	Previous CAR	Baseline RAMs[b] RT	Baseline RAMs[b] INSTI	Viral load at SVF/ CVF, c/mL	SVF Timepoint RAMs RT	SVF Timepoint RAMs INSTI[c]	Drug sensitivity at SVF (fold change)[d]
ATLAS	F, Russia, A/A1	3TC, AZT, LPV/r	E138E/ A	None	79,166/ 25,745	E138A	None	**RPV (2.4)** CAB (0.8) DTG (0.9)
	F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	V108V/ I E138K	None	695/258	V108I E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)
	M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	None	None	544/1841	E138E/ K	N155H	**RPV (6.5)** **CAB (2.7)** DTG (1.2)
FLAIR[e]	F, Russia, A1	—	None	None	373/456	E138E/ A/K/T	Q148R	**RPV (7.1)** **CAB (5.2)** DTG (1.0)
	M, Russia, A1	—	None	None	287/299	K101E	G140R	**RPV (2.6)** **CAB (6.7)** DTG (2.2)
	F, Russia, A1	—	None	None	488/440	E138K	Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

[a]In the CAR arm, there were 7 CVFs. In ATLAS, there were 4 CVFs in the CAR arm, where RT mutations M184I, M184V+G190S, and M230M/I were detected in HIV-1 RNA samples from 1 participant each, and 1 had no mutations. In FLAIR, there were 3/4 CVFs in the CAR arm without treatment-emergent resistance mutations or phenotypic changes. [b]Baseline RAMs were determined using DNA for ATLAS and RNA for FLAIR. [c]L74I was present at baseline in 5/6 participants and is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity. [d]Monogram biological cutoffs are: RPV=2.0, CAB=2.5, and the Monogram clinical cutoff for DTG=4.0. [e]FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and, upon reinitiation of oral therapy, had suspected virologic failure that was confirmed.

Table 4. Effect of L74I on Virologic Suppression at Week 48 in FLAIR Participants

L74I polymorphism at induction BL	Treatment	HIV-1 RNA <50 c/mL/ total assessed, n (%)	Difference in proportion (95% CI)[a]
Yes	CAB + RPV LA	50/54 (93)	−1.0 (−12.7 to 11.0)
	CAR	44/47 (94)	
No	CAB + RPV LA	177/189 (94)	0.4 (−4.9 to 5.6)
	CAR	180/193 (93)	

BL, baseline. [a]Difference (unadjusted): Proportion on CAB + RPV LA – proportion on CAR.

Conclusions

- Monthly injections of CAB + RPV LA were noninferior to daily oral CAR for key virologic endpoints at Week 48
  - Primary and secondary outcomes in ATLAS[1] and FLAIR[2] analyzed separately were similar to the results in the pooled analysis
- Low CVF (1.2%) was seen across both treatment arms
- ISRs in the LA arm were common but mainly grade 1 or 2, with few associated discontinuations
- L74I polymorphism alone had no impact on overall efficacy among FLAIR participants; future research on the interplay between L74I and HIV subtype is ongoing
- The LA regimen was preferred over CAR among those who received CAB + RPV LA
- Overall, ATLAS and FLAIR show that CAB + RPV LA offers individuals with HIV-1 infection a well-tolerated, novel, long-acting 2-drug regimen without an increased risk of virologic failure

Acknowledgments: We thank everyone who has contributed to the success of the study, including all study participants and their families, the FLAIR and ATLAS clinical investigators, and their staff. ATLAS and FLAIR are funded by ViiV Healthcare and Janssen R&D. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare. Data included in this poster have been previously presented in full at the 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico. Poster MOPEB257.

References: 1. Swindells et al. CROI 2019; Seattle, WA. Abstract 1475. **2.** Orkin et al. CROI 2019; Seattle, WA. Abstract 3947.