HIV-1 RNA BLIPS AND LOW-LEVEL REPLICATION DURING PHASE III/IIIB CABOTEGRAVIR + RILPIVIRINE LONG-ACTING STUDIES ARE SIMILAR TO ORAL 3-DRUG THERAPY AND NOT ASSOCIATED WITH WEEK 48 VIROLOGIC OUTCOME

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Introduction

- Findings from phase III/IIIb studies demonstrated that long-acting (LA) cabotegravir (CAB) + rilpivirine (RPV) dosed every 4 weeks (Q4W) was noninferior to current antiretroviral (ART) regimen (CAR; FLAIR[1] and ATLAS[2]), and dosing every 8 weeks (Q8W) was noninferior to Q4W (ATLAS-2M[3]) through Week 48
- Presence of transient, elevated HIV-1 RNA levels as a predictor for durability of ART is of clinical interest,[4] but the clinical relevance of such HIV-1 RNA blips is unknown[5]
- This analysis evaluates the robustness of antiviral potency of CAB LA + RPV LA using these measures (Table 1):
  - Number of participants with HIV-1 RNA blips overall and at individual study visits
  - Qualitative detection of HIV-1 RNA
  - HIV-1 RNA low-copy analysis
  - Presence or absence of HIV-1 RNA blips in participants with HIV-1 RNA <50 c/mL at Week 48 (Snapshot analysis)

Methods

Study Design

- FLAIR (ClinicalTrials.gov identifier: NCT02938520), ATLAS (ClinicalTrials.gov identifier: NCT02951052), and ATLAS-2M (ClinicalTrials.gov identifier: NCT03299049) are phase III/IIIb, randomized (1:1), open-label studies designed to assess antiviral activity and safety of intramuscular (IM) CAB + RPV LA (Q4W or Q8W)
- Eligible participants were adults (aged ≥18 years) with HIV-1 infection who were treatment naive (FLAIR) or had no history of virologic failure to ART (ATLAS and ATLAS-2M) and HIV-1 RNA <50 c/mL before randomization
- All participants who had not previously taken CAB + RPV LA received a 4-week oral lead-in of CAB 30 mg + RPV 25 mg once daily to assess individual tolerability prior to receiving LA injections
- Participants were given IM injections of CAB LA 400 mg + RPV LA 600 mg Q4W (FLAIR/ATLAS/ATLAS-2M Q4W group) or CAB LA 600 mg + RPV LA 900 mg Q8W (ATLAS-2M Q8W group) as maintenance doses or remained on CAR

Endpoints and Assessments

- Plasma samples were collected at study visits to quantitatively and qualitatively analyze HIV-1 RNA (Table 1)

Table 1. Outcome Definitions

Outcome	Definition	Assay	Assessment
Blip	HIV-1 RNA 50 to <200 c/mL with adjacent values <50 c/mL[4]	Abbott RealTime HIV-1 Assay	BL to Week 48
TD/TND	Qualitative outcome for HIV-1 RNA <40 c/mL	Abbott RealTime HIV-1 Assay	BL to Week 48
Low copy	HIV-1 RNA <2 c/mL limit of detection[6]	bioMONTR Labs HIV-1 SuperLow Assay	BL and Week 48

BL, Baseline; TD, target detected; TND, target not detected.

Results

Participant Disposition and Baseline Characteristics

- Demographic characteristics of the FLAIR, ATLAS, and ATLAS-2M study participants were generally similar between treatment groups and have been previously presented[1-3]

Blip Outcomes

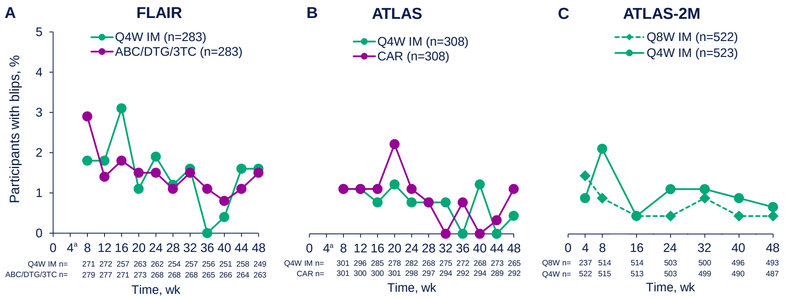
- Overall, proportions of participants with HIV-1 RNA blips were similar in the Q4W CAB + RPV LA and CAR groups in FLAIR and ATLAS and in the Q4W and Q8W CAB + RPV LA groups in ATLAS-2M (Table 2)
  - Blip rate was higher in treatment-naive participants from FLAIR vs treatment-experienced participants from either treatment group in ATLAS and ATLAS-2M

Table 2. Participants With Increased Viral Load: Intention-to-Treat–Exposed Populations

	FLAIR		ATLAS		ATLAS-2M	
Parameter, n (%)	Q4W IM (n=283)	ABC/DTG/3TC (n=283)	Q4W IM (n=308)	CAR (n=308)	Q8W IM (n=522)	Q4W IM (n=523)
Blip	36 (13)	37 (13)	18 (6)	22 (7)	18 (3)	29 (6)
≥2 consecutive viral loads ≥50 to <200 c/mL	6 (2)	4 (1)	0 (0)	6 (2)	2 (<1)	4 (<1)

- Proportions of participants with HIV-1 RNA blips were similar for each study week and consistently occurred in <5% of participants with available HIV-1 RNA data (Figure 1)

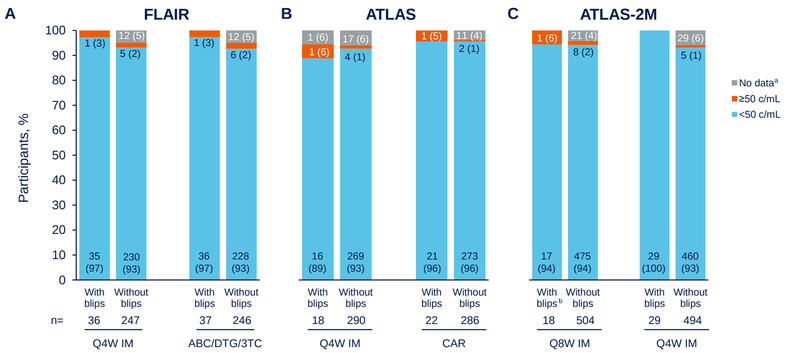
Figure 1. Proportion of Participants With Blips by Visit: Intention-to-Treat–Exposed Populations of (A) FLAIR, (B) ATLAS, and (C) ATLAS-2M



[a]Week 4 data not reported for FLAIR and ATLAS because only participants who received CAB + RPV LA had viral load measured at Week 4 per study protocol.

- Few participants with HIV-1 RNA blips in these trials had HIV-1 RNA ≥50 c/mL at Week 48, and participants with or without blips and HIV-1 RNA <50 c/mL were comparable using the Snapshot algorithm (Figure 2)
- Of 17 participants with confirmed virologic failure (CVF) in CAB + RPV LA groups,[1-3] only 1 had a blip before reaching CVF criteria (2 consecutive HIV-1 RNA measurements ≥200 c/mL)

Figure 2. Snapshot Analysis Outcomes by Presence of Blips in Intention-to-Treat–Exposed Populations of (A) FLAIR, (B) ATLAS, and (C) ATLAS-2M



[a]No virologic data reported due to participant discontinuation for adverse events, deaths, or other events or participant on study but missing data at Week 48. [b]The participant with blips in ATLAS-2M Q8W had CVF.

Qualitative Outcomes for Target Not Detected

- Among participants with plasma HIV-1 RNA <40 c/mL at any timepoint, the majority (>75%) had qualitative outcomes for TND (Figure 3)

HIV-1 Low-Copy Assay Outcomes

- Across treatment groups and studies, the majority of study participants virologically suppressed (HIV-1 RNA <50 c/mL) had plasma HIV-1 RNA <2 c/mL at Baseline and Week 48 (Figure 4)

Figure 3. Proportions of Participants With Plasma HIV-1 RNA <40 c/mL and Target Not Detected by Visit in Intention-to-Treat–Exposed Populations of (A) FLAIR, (B) ATLAS, and (C) ATLAS-2M

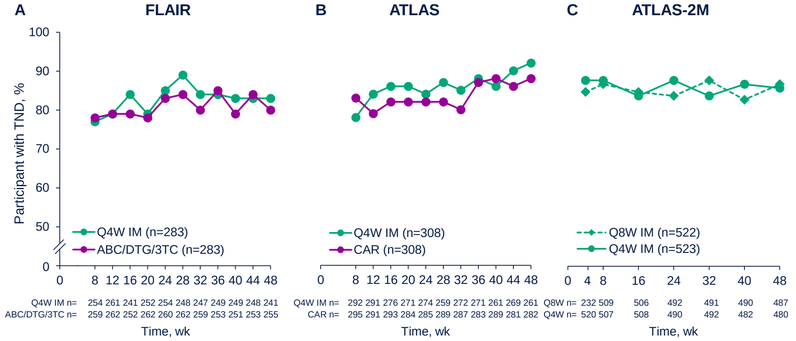
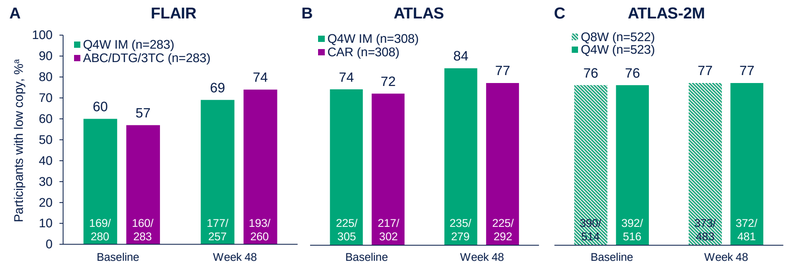


Figure 4. Proportions of Participants With Low (<2 c/mL) Plasma HIV-1 RNA in Intention-to-Treat–Exposed Populations of (A) FLAIR, (B) ATLAS, and (C) ATLAS-2M



Conclusions

- Proportions of participants in phase III/IIIb studies with HIV-1 RNA blips, TND viral load results, and HIV-1 RNA <2 c/mL were similar in the Q4W and Q8W CAB + RPV LA and the oral 3-drug CAR groups through Week 48
- Majority (89%-100%) of participants with HIV-1 RNA blips was virologically suppressed (Snapshot analysis) at Week 48
  - Occurrence of blips through Week 48 did not correlate with Week 48 Snapshot outcomes in any group from phase III studies
- These data further reinforce the potency and robustness of CAB + RPV LA for treatment of HIV-1 infection

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