LONG-TERM PATIENT ADHERENCE AND MANAGEMENT OF TREATMENT INTERRUPTIONS WITH LONG-ACTING INJECTABLE CABOTEGRAVIR + RILPIVIRINE FOR MAINTENANCE THERAPY IN PHASE 2B/3 STUDIES

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Introduction

- Adherence to daily oral antiretroviral therapy (ART) is an important factor in maintaining virologic suppression, but it may be impacted by stigma, disclosure concerns, pill fatigue, and the daily reminder of living with HIV
- Cabotegravir (CAB) and rilpivirine (RPV) are in development as a novel long-acting (LA) regimen for the maintenance of virologic suppression in people living with HIV-1 as an alternative to daily oral ART
- Two pivotal phase III studies, FLAIR* and ATLAS,† demonstrated noninferior efficacy of CAB + RPV LA vs continuing current antiretroviral regimen (CAR) for the primary endpoint of HIV-1 RNA ≥50 copies/mL, with high levels of adherence observed through 48 weeks[1,2] High levels of adherence were also seen in the phase II LATTE-2 study‡ through 96 weeks of treatment[3,4]
- Here we report long-term participant adherence to dosing schedules, and the outcomes after use of oral CAB + RPV to cover planned missed injections, for participants in the FLAIR phase III study through Week 96§ and in the LATTE-2 Phase 2b study through Week 256

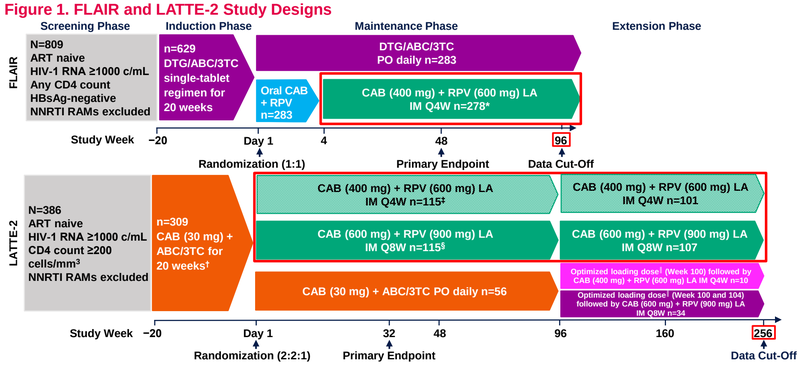
*NCT02938520. †NCT02951052. ‡NCT02120352. §Long-term participant adherence to CAB + RPV LA from ATLAS not reported due to the large number of participants who transitioned to the ATLAS-2M study (NCT03299049).

Methods

- FLAIR and LATTE-2 are ongoing, multicenter, parallel-arm, open-label studies evaluating CAB + RPV LA for the maintenance of virologic suppression (HIV-1 RNA <50 copies/mL; Figure 1)
- Both studies comprised an Induction Phase and Maintenance Phase
  - Induction Phase: ART-naive participants received oral dolutegravir/abacavir/lamivudine* (DTG/ABC/3TC; FLAIR) or oral CAB plus abacavir/lamivudine (LATTE-2)
  - Maintenance Phase: participants achieving virologic suppression during the Induction Phase (HIV-1 RNA <50 copies/mL) were randomized to either CAB + RPV LA or to continue their oral treatment
- During the Maintenance Phase, injections were scheduled every 4 weeks (Q4W; FLAIR and LATTE-2) or every 8 weeks (Q8W; LATTE-2 only) with a ±7-day dosing window† from the projected dosing date‡
- Adherence to CAB + RPV LA was calculated as the number of on-time injection visits divided by the number of expected dosing visits through the period of follow-up§
- Daily oral dosing (CAB 30 mg + RPV 25 mg) to cover planned missed injections was permitted to enable dosing flexibility for planned absences from a clinical site (eg, vacation/travel), after approval by a medical monitor
- Injection visits outside the prespecified window and missed injection visits with or without use of oral dosing were characterized

*If any participant had toxicity or intolerability in association with DTG/ABC/3TC, a single switch to an approved alternative background nucleoside reverse transcriptase inhibitor (NRTI) was permitted. Participants who were positive for HLA-B*5701 received DTG plus 2 alternative non-ABC NRTIs instead of DTG/ABC/3TC. †Dosing window: −7 days for the second and third injections, and ±7 days thereafter. ‡Projected dosing date is relative to date of first injection at Week 4b. §The cut-off dates for these analyses predate the 2020 COVID-19 pandemic.

Figure 1. FLAIR and LATTE-2 Study Designs

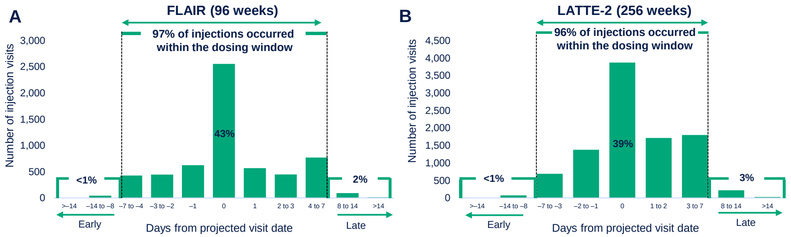


Red boxes indicate the dosing arms included in the current analysis. *Participants received initial loading doses of CAB LA 600 mg and RPV LA 900 mg at Week 4. Beginning at Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections Q4W. †RPV 25 mg was added at Week −4 for the remainder of the Induction Phase. ‡Participants received initial loading doses of CAB LA 800 mg and RPV LA 600 mg on Day 1. Beginning at Week 4, participants received CAB LA 400 mg and RPV LA 600 mg Q4W. §Participants received initial loading doses of CAB LA 800 mg and RPV LA 900 mg on Day 1. At Week 4, participants received CAB LA 600 mg only. Beginning at Week 8, participants received CAB LA 600 mg + RPV LA 900 mg injections Q8W. ‖Optimized loading dose: CAB LA 600 mg + RPV LA 900 mg. 3TC, lamivudine; ART, antiretroviral therapy; ABC, abacavir; CAB, cabotegravir; DTG, dolutegravir; HBsAg, hepatitis B surface antigen; IM, intramuscular; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PO, oral regimen; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

Results

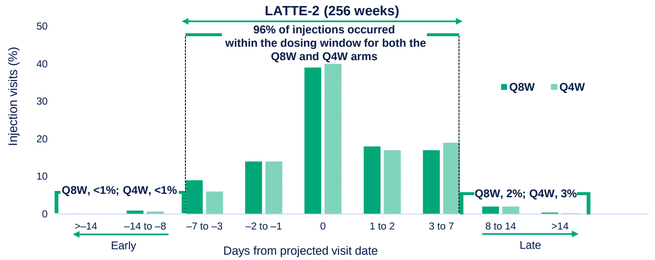
- Of 6005 expected injection visits through Week 96 in FLAIR, 97% of injections were given within the allowed ±7-day dosing window, with 43% on the projected dosing date (Figure 2A)
  - 45 (<1%) injection visits were early and 107 (2%) were late
- Adherence to 9803 expected injection visits in LATTE-2 through Week 256 was similarly high, with 96% of injections given within the allowed ±7-day dosing window and 39% on the projected dosing date (Figure 2B)
  - 80 (<1%) injection visits were early and 247 (3%) were late

Figure 2. Long-Term Adherence to Injection Visits



- In LATTE-2, adherence to the treatment regimen was comparable between the Q8W and Q4W arms, with 39% and 40% of injections given on the projected dosing date, respectively (Figure 3)

Figure 3. Similar Rates of Adherence in LATTE-2 by Dosing Regimen



Q4W, every 4 weeks; Q8W, every 8 weeks.

Late Injections

- For late injections (after the +7-day dosing window: FLAIR, 107 late injections; LATTE-2, 247 late injections):
  - The mean number of days outside the +7-day window was 5 days (range: 1–21) for FLAIR and 3 days (range: 1–15) for LATTE-2, with the majority (313/354, 88%) administered within 1–7 days after the projected +7-day dosing window (Table 1)

Table 1. Late Injections Outside of the +7-Day Dosing Window

Number of days outside dosing window	Late injection visits (combined)
1-7 days	313/15,808 (2%)
>7 days	41/15,808 (<1%)

In FLAIR and LATTE-2, no participant with an injection visit outside of the +7-day dosing window met the confirmed virologic failure (CVF) criterion*

*Two consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL.

Missed Injections and Oral Dosing

- Across FLAIR and LATTE-2 combined, 18 participants had a total of 31 missed injection visits out of 15,808 total planned visits
  - Of these, 30/31 (97%) missed injection visits were covered with oral CAB + RPV therapy*
- **All participants who bridged planned missed visits with oral CAB + oral RPV therapy maintained HIV-1 RNA <50 copies/mL at the time they resumed LA dosing and at the end of the study period (Table 2)**
- In those participants who used oral CAB + RPV for planned treatment interruptions, most used oral dosing to cover single dosing visits; 3 participants (all from LATTE-2) repeated use of oral therapy on ≥2 separate occasions

*One participant who missed an injection visit at Week 32 without oral CAB + RPV therapy (dosing interrupted due to acute hepatitis A) continued LA therapy at Week 36 and viral suppression was maintained.

Table 2. Oral Dosing for Planned Missed Visits Maintained Viral Suppression

Participant no.	Study	Treatment regimen	Injection visit(s) covered by oral therapy (Study Week)	Duration of oral therapy (days)	Viral load at restart of LA regimen (copies/mL)	Viral load at data cut-off (copies/mL)
1	FLAIR	Q4W	48	29	<50	<50
2	FLAIR	Q4W	68	26	<50	<50
3	FLAIR	Q4W	96	30	<50	<50*
4	FLAIR	Q4W	16 and 20	61	<50	<50
5	FLAIR	Q4W	60	35	<50	<50
6	FLAIR	Q4W	92	29	<50	<50
7	FLAIR	Q4W	48	20	<50	<50
8	FLAIR	Q4W	52	36	<50	<50
9	FLAIR	Q4W	72	28	<50	<50
10	LATTE-2	Q4W	112, 188, 204, 208, 232, 236, and 256†	224	<50	<50‡
11	LATTE-2	Q4W	224, 228, 232, and 236§	116	<50	<50
12	LATTE-2	Q8W	40 and 248	105	<50	<50
13	LATTE-2	Q8W	24	56	<50	<50
14	LATTE-2	Q4W	196	28	<50	<50
15	LATTE-2	Q4W	64 and 120	50	<50	<50
16	LATTE-2	Q4W	40	27	<50	<50
17	LATTE-2	Q4W	80 and 84	56	<50	<50

*Week 108 data (next visit with data after cut-off). Participant missing data at Week 96. †Participant 10 missed multiple visits due to frequent work travel. ‡Week 272 data (next visit with data after cut-off). Participant missing data at Week 256. §Participant 11 missed 4 injection visits due to a prolonged psychiatric hospitalization (approved by medical monitor), and resumed CAB + RPV LA post-hospitalization. CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Conclusions

- Participants maintained high levels of long-term adherence to CAB + RPV LA dosed Q4W or Q8W, through 2 to 5 years of follow-up, with 97% of injections given within the ±7-day dosing window in the FLAIR and LATTE-2 studies
- No participant with a late injection outside the +7-day dosing window met the CVF criterion
- Over 2 to 5 years of follow-up, few participants used oral therapy to cover a planned missed visit, with most using oral CAB + RPV to cover a single injection interval
- The use of oral CAB + RPV therapy to bridge planned missed injection visits provided an effective strategy to maintain virologic suppression during short periods of LA treatment interruption

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References: 1. Swindells et al. *N Engl J Med.* 2020;382:1112-1123. **2.** Orkin et al. *N Engl J Med.* 2020;382:1124-1135. **3.** Margolis et al. *Lancet.* 2017;390:1499-1510. **4.** Sutton et al. AIDS 2018; Amsterdam, Netherlands; July 23-27, 2018. Poster THPEB084.