Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy: ATLAS Week 48 Results

P012

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Introduction

- In a randomized, phase IIb, open-label study of treatment-naive adults with HIV-1 infection (LATTE-2), long-acting (LA) cabotegravir (CAB) + rilpivirine (RPV) LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years[1]
- ATLAS is an ongoing phase III, randomized, open-label study designed to establish whether switching to monthly intramuscular (IM) injections of CAB LA + RPV LA is noninferior to continuing current 3-drug oral antiretroviral therapy (ART) in virologically suppressed adults with HIV-1 infection

Methods

- Eligible participants (pts) had HIV-1 RNA <50 c/mL for ≥6 months without virologic failure on oral regimens of 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 integrase strand transfer inhibitor (INSTI), non-NRTI (NNRTI), or protease inhibitor
- Pts were randomly (1:1) assigned to continue their current ART regimen (CAR) or switch to CAB LA + RPV LA
  - CAB LA + RPV LA pts received oral CAB 30 mg + RPV 25 mg once daily for 4 weeks, then single 3-mL loading doses of CAB LA 600 mg (200 mg/mL) and RPV LA 900 mg (300 mg/mL) by IM injection, followed by 2-mL IM injections every 4±1 weeks of CAB LA 400 mg and RPV LA 600 mg
  - At Week 52, pts receiving CAR had the option to switch to CAB LA + RPV LA by transitioning to the ATLAS-2M study (extension phase)
- The primary endpoint was HIV-1 RNA ≥50 c/mL at Week 48 (US Food and Drug Administration snapshot algorithm, 6% noninferiority margin)
- Select secondary endpoints included HIV-1 RNA <50 c/mL at Week 48 (−10% noninferiority margin), viral resistance in the setting of confirmed virologic failure (2 consecutive HIV-1 RNA measurements ≥200 c/mL), safety and tolerability, and patient-reported outcomes (HIV Treatment Satisfaction Questionnaire, status version [HIVTSQs], and single-item question for patient-reported preference)

Results

- 616 pts initiated treatment (308 in each group; Table 1)

Table 1. Baseline Characteristics

Parameter	Participants, n (%) CAB LA + RPV LA (n=308)	CAR (n=308)	Total (N=616)
Median age (range), y	40 (21-74)	43 (18-82)	42 (18-82)
Age ≥50 y, n (%)	66 (21)	96 (31)	162 (26)
Female, n (%)	99 (32)	104 (34)	203 (33)
Race/Ethnicity, n (%)			
White	214 (69)	207 (67)	421 (68)
Black/African American	62 (20)	77 (25)	139 (23)
Other	32 (10)	24 (8)	56 (9)
Median body mass index (range), kg/m^2	26 (15-51)	26 (18-58)	26 (15-58)
Median CD4+ cell count (range), cells/mm^3	654 (185-1903)	653 (150-2543)	653 (150-2543)
Median duration of prior ART (range), y	4 (1-19)	4 (1-21)	4 (1-21)
Baseline third ART agent class, n (%)[a]			
NNRTI	155 (50)	155 (50)	310 (50)
INSTI	102 (33)	99 (32)	201 (33)
PI	51 (17)	54 (18)	105 (17)

CAR, current ART regimen; LA, long-acting. [a]Common backbone regimens included FTC/TDF (LA 60% vs CAR 56%), FTC/TAF (LA 16% vs CAR 17%), and ABC/3TC (LA 13% vs CAR 13%).

Virologic Snapshot Outcomes for Week 48 for Intention to Treat–Exposed

- 5 pts (1.6%) receiving CAB LA + RPV LA and 3 (1.0%) receiving CAR had HIV RNA ≥50 c/mL, meeting noninferiority criteria for the primary endpoint (adjusted treatment difference 0.6 [95% confidence interval: −1.2 to 2.5]; Figure)
  - Of the pts with HIV-1 RNA ≥50 c/mL in the CAB LA + RPV LA and CAR groups, respectively, 1 (0.3%) and 1 (0.3%) had data in the window not below the threshold; 3 (1.0%) and 2 (0.6%) discontinued the study due to lack of efficacy; and 1 (0.3%) and 0 discontinued for another reason while not below the threshold
  - 18 pts (5.8%) in the CAB LA + RPV LA and 11 (3.6%) in the CAR group did not have virologic data, with the primary reason being study discontinuation due to adverse events (AEs) followed by discontinuation for other reasons

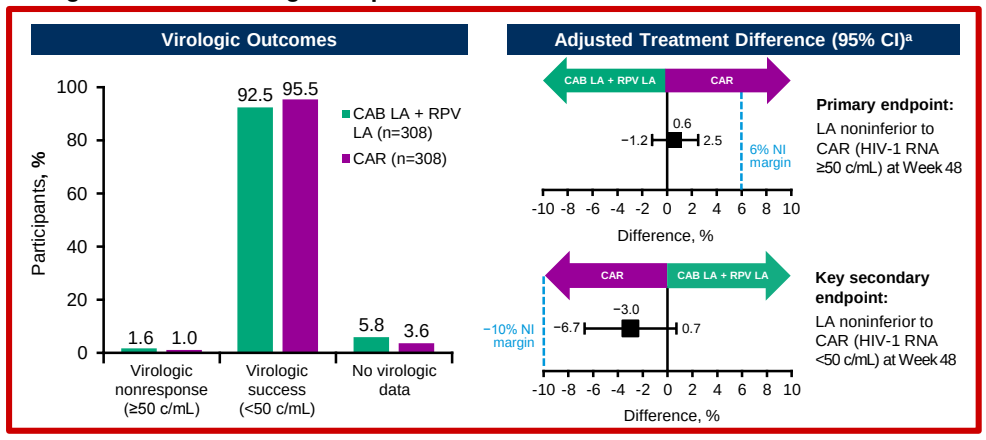
Virologic Failure

- 3 CAB LA + RPV LA and 4 CAR pts had confirmed virologic failure
  - 2 of 3 pts in the CAB LA + RPV LA group had no “on treatment” resistance mutations; 1 pt had “on treatment” NNRTI- and INSTI-resistance associated mutations (E138E/K and N155H) at failure that were not seen in peripheral blood mononuclear cells at baseline
  - Plasma CAB and RPV concentrations at the time of failure were below the population means but within the range for the vast majority of individuals who maintained virologic suppression

Plasma CAB and RPV Concentrations

- Plasma concentrations through 48 weeks with IM CAB LA + RPV LA were comparable with those observed during efficacious oral regimens

Figure. ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E.



CAR, current antiretroviral regimen; LA, long-acting; NI, noninferiority. NI of LA to CAR was achieved for the primary and secondary endpoints at 48 weeks of HIV-1 RNA ≥50 c/mL and <50 c/mL, respectively. [a]Adjusted for sex and baseline third agent class.

Adverse Events

- In pts receiving CAB LA + RPV LA, 231 (75%) had injection-site pain
  - The majority (99%; 1439/1460) of injection-site reactions (ISRs) were grade 1/2; most (88%) resolved within ≤7 days; and 4 pts (1%) withdrew from the study as a result
- 84/88 (95%) of CAB LA + RPV LA pts with any drug-related event (excluding ISRs) had a maximum grade 1/2 AE (Table 2)
  - No cases of drug-related serious AEs, drug hypersensitivity, or drug-induced liver injury were observed in the CAB LA + RPV LA group

Table 2. Adverse Events (Excluding ISRs)

Adverse event	Participants, n (%) CAB LA + RPV LA (n=308)	CAR (n=308)
AE (≥10%), n (%)		
Any event (per participant)	264 (86)	220 (71)
Nasopharyngitis	52 (17)	42 (14)
Upper respiratory tract infection	32 (10)	25 (8)
Headache	34 (11)	17 (6)
Drug-related AE (≥3%), n (%)		
Any event (per participant)	88 (29)	8 (3)
Fatigue	11 (4)	0
Pyrexia	11 (4)	0
Headache	11 (4)	0
Nausea	11 (4)	0
All AEs leading to withdrawal[a]	10 (3)	5 (2)

CAR, current antiretroviral regimen; ISR, injection-site reaction; LA, long-acting. [a]AEs leading to withdrawal: LA arm (n), hepatitis A (2); acute hepatitis B (1); acute hepatitis C (1); headache (1); suicidal depression (1); memory impairment (1); diarrhea/nausea/headache (1); asthenia and myalgia (1); anxiety (1); CAR arm (n), colitis (1); increased blood creatinine (1); fatal methamphetamine overdose (1); renal impairment (1); anxiety disorder/depression/suicidal ideation (1).

Participant Satisfaction (HIVTSQs)

- Increases from baseline to Weeks 24 and 44 in treatment satisfaction were significantly greater in pts receiving CAB LA + RPV LA compared with pts receiving CAR (P<0.001)
- A singe-item preference survey showed that 97% (266/273) of responding pts receiving the CAB LA + RPV LA regimen preferred LA over their previous oral regimen

Conclusions

- Monthly CAB LA + RPV LA was noninferior to 3-drug oral CAR at Week 48 per Snapshot
  - Low rate of HIV-1 RNA ≥50 c/mL: 1.6% vs 1.0%
  - HIV-1 RNA <50 c/mL: 92.5% vs 95.5%
- Confirmed virologic failure rate was low (1.0%) across both treatment arms
- ISRs were mostly grade 1/2 and short lived with few associated discontinuations
- Grade 3/4 and serious AEs were infrequent in both arms
- A significantly greater increase in treatment satisfaction was reported with the CAB LA + RPV LA regimen over time vs CAR
- Overall, these results support the therapeutic potential of monthly CAB LA + RPV LA

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Reference: 1. Margolis DA, Garcia JG, Stellbrink H-J, et al. Safety, efficacy and durability of long-acting cabotegravir (CAB) and rilpivirine (RPV) as two-drug IM maintenance therapy for HIV-1 infection: LATTE-2 Week 160 results. HIV Glasgow 2018. Glasgow, UK. Poster 118.