CABOTEGRAVIR (CAB) + RILPIVIRINE (RPV) EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY: ATLAS-2M STUDY

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**Presenting on behalf of the authors.*

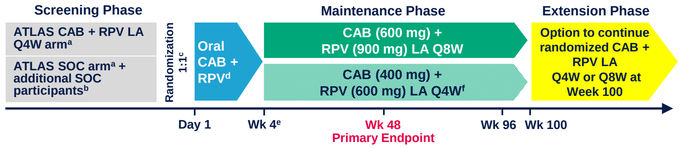
Introduction

- The phase III ATLAS[1] and FLAIR[2] studies demonstrated that intramuscular injection of long-acting (LA) cabotegravir (CAB) + rilpivirine (RPV) administered every 4 weeks (Q4W) was noninferior to daily oral 3-drug antiretroviral therapy (ART) for maintenance of virologic suppression in people living with HIV infection
- The phase III, randomized, open-label ATLAS-2M study was conducted to determine whether CAB + RPV LA administered every 8 weeks (Q8W) is noninferior to Q4W dosing

Methods

- Eligible participants included those from ATLAS who had been taking CAB + RPV LA Q4W or standard of care (SOC) for ≥52 weeks with plasma HIV-1 RNA <50 c/mL at screening and additional SOC participants who were taking an uninterrupted ART regimen for ≥6 months before screening and had ≥2 HIV-1 RNA measurements <50 c/mL within 12 months of screening (Figure 1)
- Primary and key secondary efficacy endpoints were proportion of participants with plasma HIV-1 RNA ≥50 c/mL (noninferiority [NI] margin, 4%) and <50 c/mL (NI margin, −10%), respectively, at Week 48
  - Other secondary endpoints included incidence of confirmed virologic failure (CVF; 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression <200 c/mL), safety, tolerability, and treatment preference

Figure 1. ATLAS-2M Study Design: Phase III, Randomized, Multicenter, Parallel-Group, Noninferiority, Open-Label Study



[a]Participants from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 with HIV-1 RNA <50 c/mL at screening. [b]SOC participants not from ATLAS must have been on an uninterrupted ART regimen ≥6 mo before screening with ≥2 HIV-1 RNA measurements <50 c/mL in the 12 mo before screening (1 between 12 and 6 mo and 1 within 6 mo of screening). Participants were excluded if they had a history of virologic failure or evidence of viral resistance. [c]Randomization was stratified by prior CAB + RPV exposure. [d]Except participants from ATLAS already on LA therapy. [e]Tolerability in participants on oral lead-in treatment was assessed at Week 4. [f]In participants in the Q4W arm who had an oral lead-in, the first LA dose was CAB 600 mg + RPV 900 mg.

Results

- 1045 participants initiated treatment; 391 were from the Q4W group of ATLAS and 654 had previously been treated with SOC (Table 1)

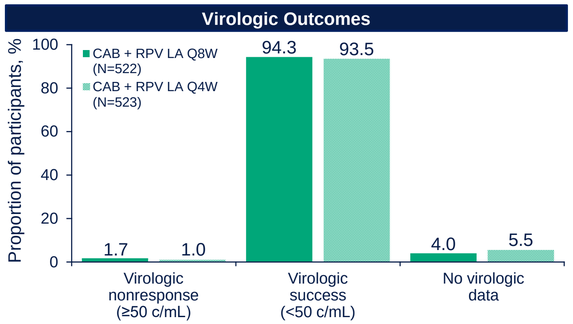
Table 1. Baseline Characteristics (ITT-E Population) Were Well Balanced Between Q8W and Q4W Groups

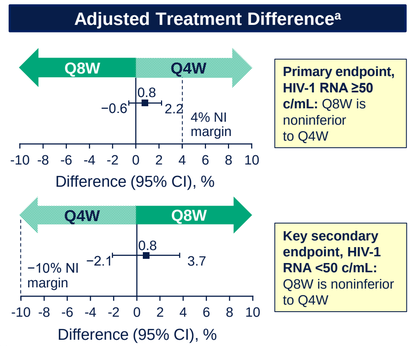
Parameter	Q8W (N=522)	Q4W (N=523)	Total (N=1045)
Age, median (range), y	42 (20-83)	42 (19-75)	42 (19-83)
≥50 y, n (%)	143 (27)	139 (27)	282 (27)
Sex at birth, female, n (%)	137 (26)	143 (27)	280 (27)
Participant-reported gender, female, n (%)	142 (27)	146 (28)	288 (28)
Race, n (%)			
White	370 (71)	393 (75)	763 (73)
Black or African American	101 (19)	90 (17)	191 (18)
Other	51 (10)	40 (8)	91 (9)
BMI, median (IQR), kg/m^2	26 (23-29)	26 (23-29)	26 (23-29)
≥30 kg/m^2, n (%)	113 (22)	98 (19)	211 (20)
CD4 count, median (IQR), cells/mm^3	642 (499-827)	688 (523-878)	661 (508-849)
Prior exposure to CAB + RPV, n (%)			
None	327 (63)	327 (63)	654 (63)
1-24 wk	69 (13)	68 (13)	137 (13)
>24 wk	126 (24)	128 (24)	254 (24)

Snapshot Outcomes at Week 48

- 9 (1.7%) participants receiving CAB + RPV LA Q8W and 5 (1.0%) receiving CAB + RPV Q4W had HIV-1 RNA ≥50 c/mL (adjusted treatment difference, 0.8 [95% confidence interval: −0.6 to 2.2]; Figure 2), meeting the NI criteria for the primary endpoint
  - Of these participants in the Q8W and Q4W arms, respectively, 3 (0.6%) and 2 (0.4%) had data in window not <50 c/mL, 6 (1.1%) and 2 (0.4%) discontinued due to lack of efficacy, and 0 and 1 (0.2%) discontinued for other reasons while not <50 c/mL
- 21 (4.0%) participants in the Q8W arm and 29 (5.5%) in the Q4W arm had no virologic data, with discontinuations primarily for reasons not related to adverse events (AEs)

Figure 2. ATLAS-2M Virologic Snapshot Outcomes at Week 48 for ITT-E Population: Noninferiority Achieved for Primary and Key Secondary Endpoints





[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for prior exposure to CAB + RPV (0 wk, 1-24 wk, >24 wk).

Virologic Failure

- 8 (1.5%) participants receiving CAB + RPV LA Q8W and 2 (0.4%) receiving Q4W had CVF (Table 2)

Table 2. Rate of Confirmed Virologic Failure Was Low Overall

	n	CVFs n (%)	CVFs with RPV RAMs[a]	RPV RAMs observed at failure	CVFs with IN RAMs[a]	IN RAMs observed at failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,[b] N155H[b]
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

[a]For those with observed RAMs at failure: 6/6 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5); CVF definition: 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. [b]Or mixture.

- Post hoc baseline peripheral blood mononuclear cell HIV-1 DNA results for Q8W arm:
  - 5/8 CVFs had preexisting major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1/8 CVFs had a preexisting major IN RAM (G140G/R)
  - 5/8 CVFs had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype)
- 9/10 CVFs resuppressed on fully active oral HAART (1/10 noncompliance on PI-based ART)
  - All CVFs retained phenotypic sensitivity to dolutegravir

Adverse Events

- The majority (98% [n/N=5568/5659]) of injection-site reactions (ISRs) were grade 1/2, with a median duration of 3 days in both arms (Table 3)

Table 3. Most Injection-Site Reactions Were Grade 1/2 and Were Well Tolerated

Outcome, n (%), ITT-E	Q8W (N=522)	Q4W (N=523)
Number of injections	8470	15,711
ISR event (event/injection)[a]	2507 (30)	3152 (20)
Grade ≥3 – severe[b]	43 (<1)	48 (<1)
ISR[c]		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)
Withdrawal due to injection-related reasons[d]	6 (1)	11 (2)

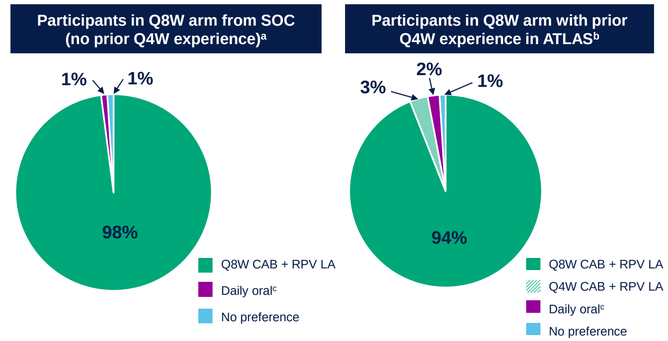
A single injection could result in >1 ISR. [a]All event-level ISR percentages are calculated from the total number of injections. [b]There were no grade 4/5 ISRs. [c]ISRs occurring in >1% of injections in either the Q4W or Q8W arms are shown. [d]Q8W: 5 participants had an ISR leading to withdrawal and 1 participant withdrew consent from the study due to injection intolerability; Q4W: 5 participants had an ISR leading to withdrawal and 6 participants withdrew consent from the study due to injection intolerability.

- Non-ISR AEs (≥10%) were similar between the Q8W and Q4W arms (91% and 92%, respectively), and 96% of drug-related AEs were grade 1/2
  - Nasopharyngitis and upper respiratory tract infection were the most frequent
- Of the AEs leading to withdrawal, 5 (<1%) in the Q8W arm and 8 (2%) in the Q4W arm were drug related
- No drug-related fatal AEs were observed in either dosing arm

Participant Preference

- 98% of participants who responded to the preference question (300/306) with no prior CAB + RPV LA Q4W experience preferred CAB + RPV LA Q8W over daily CAB + RPV oral therapy (Figure 3)

Figure 3. ATLAS-2M: Majority of Participants Preferred Q8W Dosing



[a]306 participants responded to the preference question. [b]191 participants responded to the preference question. Percentages are calculated out of those participants with recorded response to the preference question. [c]Daily oral therapy refers to CAB + RPV oral therapy that was received during the oral lead-in period for either this study or the ATLAS study.

Conclusions

- Q8W dosing of CAB + RPV LA was highly effective and noninferior to Q4W dosing
  - Virologic nonresponse (≥50 c/mL) was infrequent and similar between the 2 groups
  - Virologic suppression was maintained in 94.3% and 93.5% of those in the Q8W and Q4W arms, respectively
  - Rate of CVF was low overall (1%)
- CAB + RPV LA was well tolerated with a comparable safety profile between groups
- 98% of participants preferred Q8W dosing of CAB + RPV LA treatment over oral therapy, and Q8W dosing was preferred by 94% of participants with prior Q4W experience
- Overall, CAB + RPV LA dosed every 2 months is an innovative and effective treatment for maintenance of virologic suppression in people living with HIV infection

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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.