CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY DOSING: WEEK 48 RESULTS FROM THE ATLAS-2M STUDY

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- Paul Benn is an employee of ViiV Healthcare

ATLAS-2M Introduction

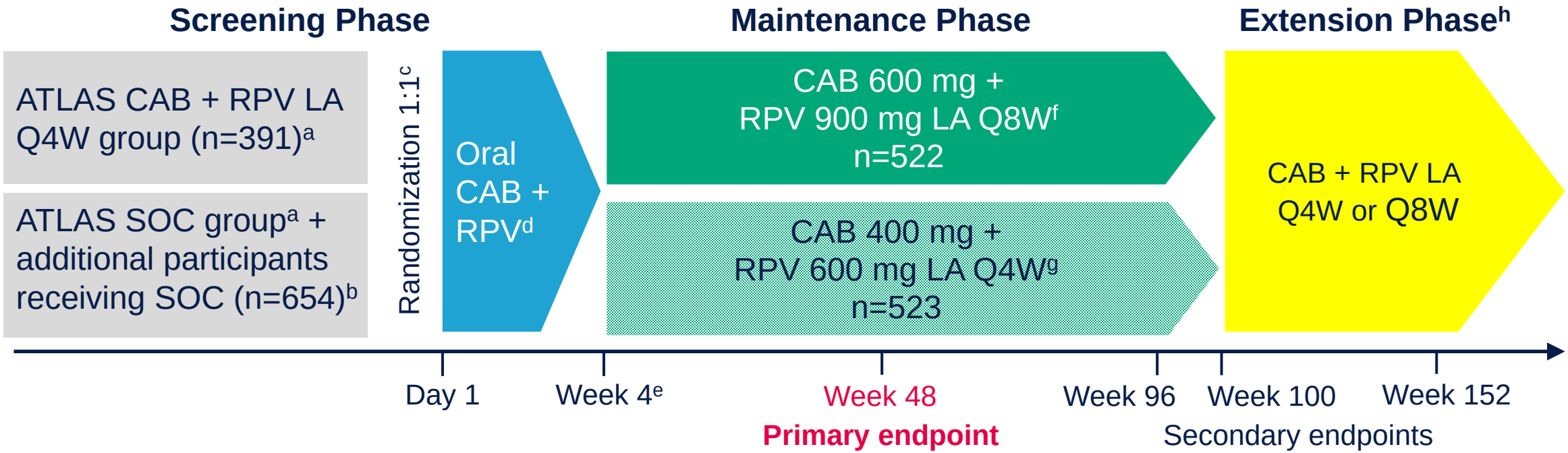
- There is a need for more convenient, less frequent treatment to help address remaining challenges around stigma, pill burden, drug/food interactions, and adherence associated with daily oral HIV treatment in people living with HIV
- Cabotegravir, an INSTI, and rilpivirine, an NNRTI, are currently under development as a long-acting, injectable, 2-drug regimen for the maintenance of virologic suppression in people living with HIV
- The ATLAS[1] and FLAIR[2] phase 3 randomized controlled trials have shown that CAB + RPV LA, dosed intramuscularly every 4 weeks, was noninferior to daily oral 3-drug ART in the maintenance of virologic suppression in people living with HIV
- Longer-term phase 2 data (LATTE-2)[3] provide the rationale to investigate whether an Q8W dosing interval is noninferior to Q4W dosing

ART, antiretroviral therapy; CAB, cabotegravir; INSTI, integrase stand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

1. Swindells et al. *N Engl J Med*. In press. 2. Orkin et al. *N Engl J Med*. In press. 3. Margolis et al. *Lancet*. 2017;390:1499-1510.

ATLAS-2M Study Design

Phase 3, randomized, multi-center, parallel-group, noninferiority, open-label study



IM, intramuscular; ITT-E, intent-to-treat–exposed; LA, long-acting; SOC, standard of care. [a]Participants from ATLAS must have been taking CAB + RPV LA Q4W or a current ART regimen through at least Week 52 with HIV-1 RNA <50 c/mL at screening. [b]Participants receiving SOC not from ATLAS must have been taking an uninterrupted ART regimen ≥6 mo prescreening with ≥2 HIV-1 RNA measurements <50 c/mL in the 12 mo prescreening (one between 12 and 6 mo and one ≤6 mo of screening). Exclusion criteria: history of virologic failure or evidence of viral resistance. [c]Randomization stratified by prior CAB + RPV exposure. [d]Except those from ATLAS on LA therapy. [e]Tolerability in participants on oral lead-in ART assessed at Week 4. [f]After oral lead-in period, participants in the Q8W group received intramuscular injections at Weeks 4 and 8, then Q8W thereafter. [g]In participants in the Q4W group with oral lead-in, first LA dose was CAB 600 mg + RPV 900 mg. [h]Optional extension phase to continue randomized CAB + RPV LA Q4W or Q8W at Week 100.

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ATLAS-2M 48-Week Endpoints

- **Primary endpoint**
  - Proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
    - Noninferiority margin of 4%
- **Key secondary endpoint**
  - Proportion of participants with HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E)
- **Additional secondary endpoints**
  - Safety and tolerability
  - Incidence of confirmed virologic failure
  - Incidence of viral resistance in participants experiencing CVF
  - Participants' treatment preference for LA regimen
- **Randomization was stratified by prior CAB + RPV exposure**

AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intent-to-treat exposed; LA, long-acting; RPV, rilpivirine.

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ATLAS-2M Baseline Characteristics (ITT-E Population)

Parameter	Q8W n=522	Q4W n=523	Total N=1045*
Prior exposure to CAB + RPV, n (%)			
None	327 (63)	327 (63)	654 (63)
1–24 weeks	69 (13)	68 (13)	137 (13)
>24 weeks	126 (24)	128 (24)	254 (24)
Median age (range), years	42 (20–83)	42 (19–75)	42 (19–83)
Age ≥50 years, n (%)	143 (27)	139 (27)	282 (27)
Female (sex at birth), n (%)	137 (26)	143 (27)	280 (27)
Female (participant-reported gender), 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)
Median body mass index (IQR), kg/m^2	26 (23–29)	26 (23–29)	26 (23–29)
≥30, n (%)	113 (22)	98 (19)	211 (20)
Median CD4 count (IQR)	642 (499–827)	688 (523–878)	661 (508–849)

*1049 participants were randomized. However, 4 participants did not receive study drug and therefore were not part of the ITT-E population.

CAB, cabotegravir; IQR, interquartile range; ITT-E, intent-to-treat exposed; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

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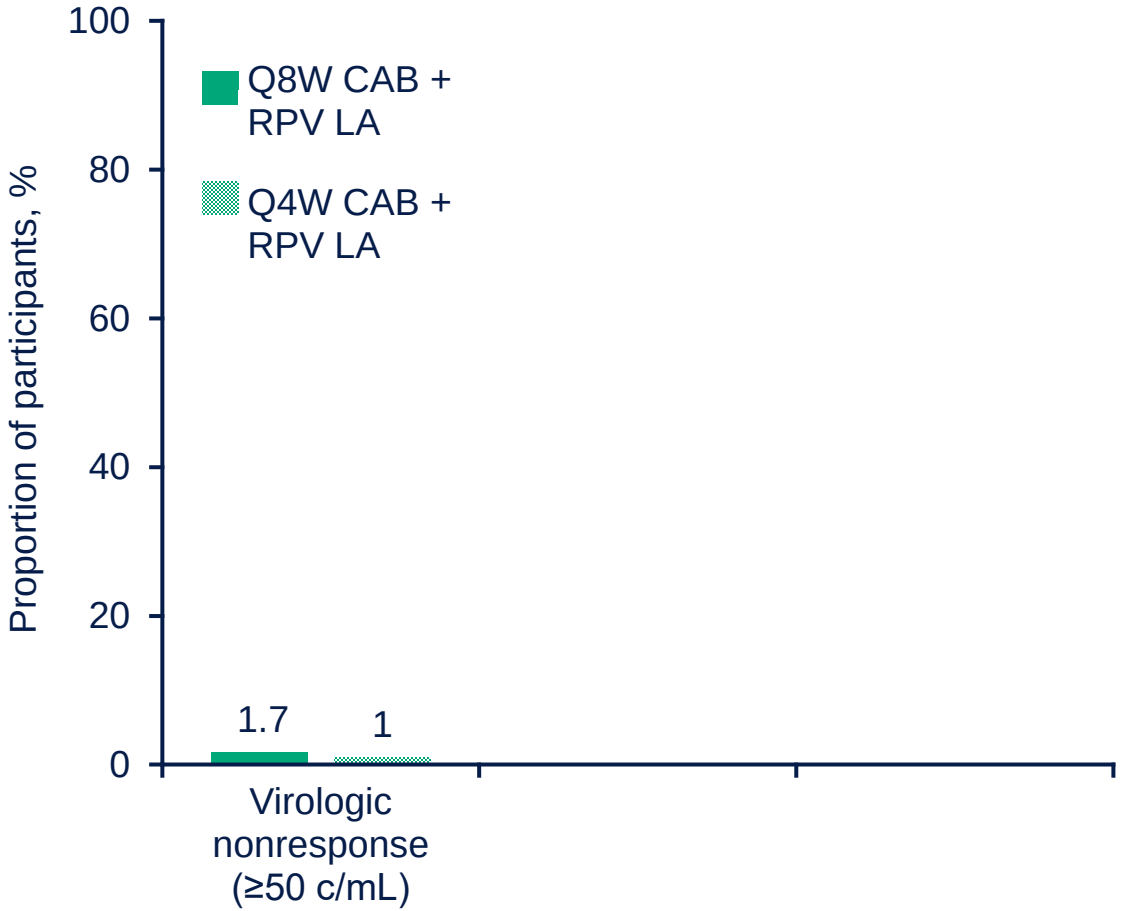
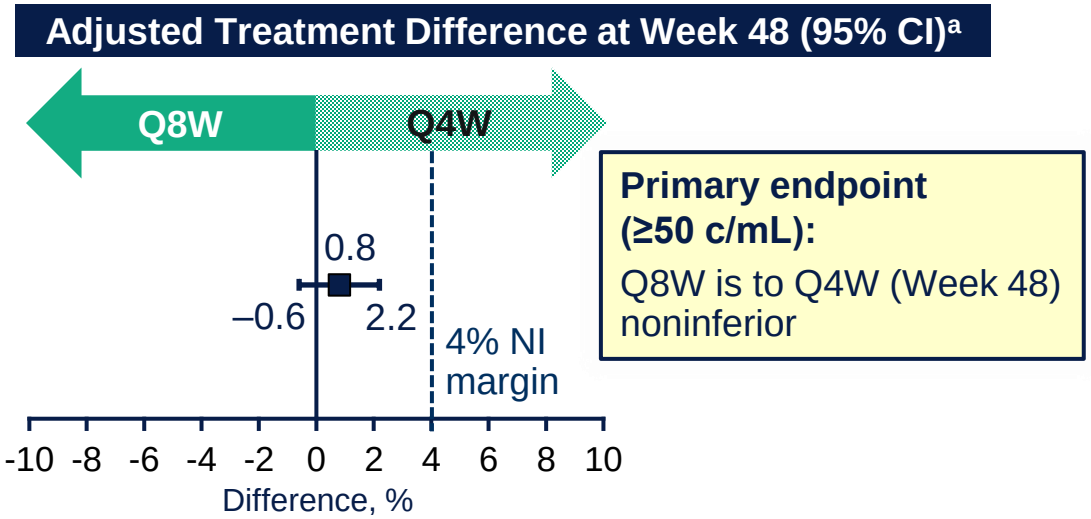
ATLAS-2M Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints





Primary endpoint (≥50 c/mL):
Q8W is to Q4W (Week 48) noninferior

CMH, Cochran–Mantel–Haenszel; LA, long acting; NI, noninferiority.

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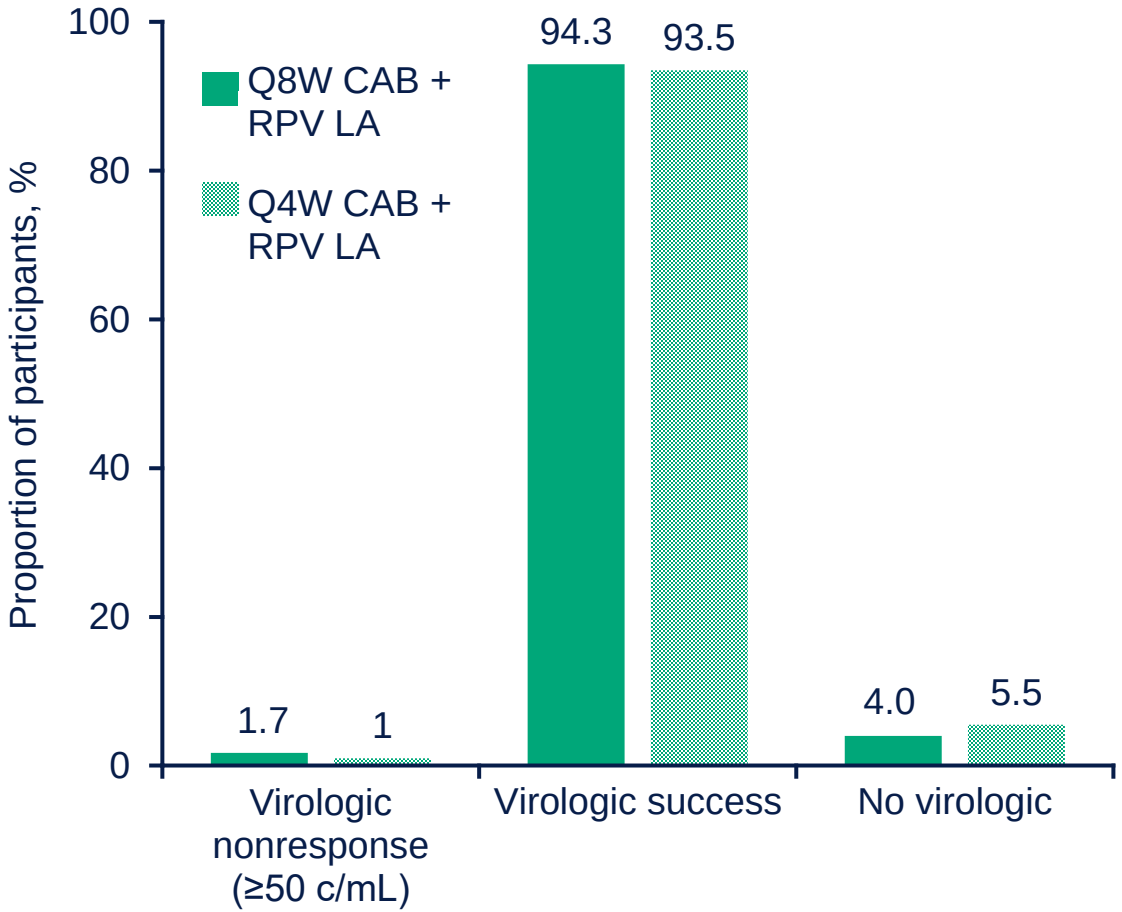
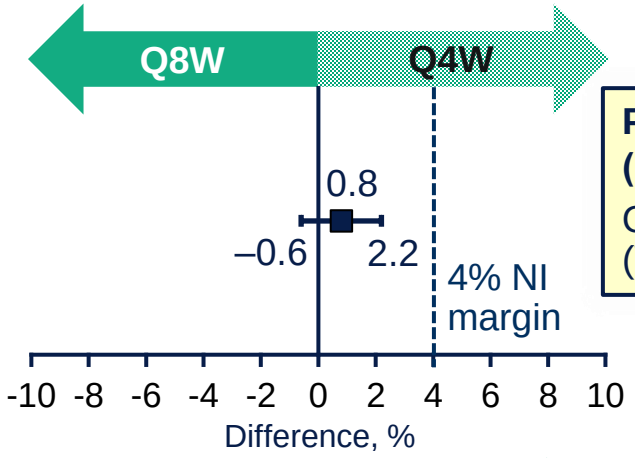
ATLAS-2M Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints



Participant numbers: Q8W, n=522; Q4, n=523.

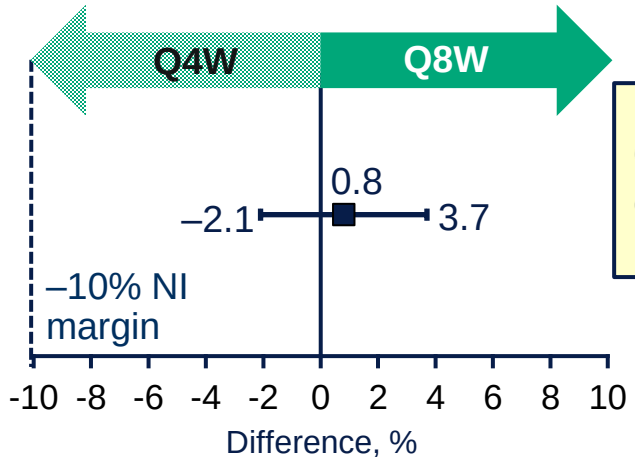
CMH, Cochran–Mantel–Haenszel; LA, long acting; NI, noninferiority.

Adjusted Treatment Difference at Week 48 (95% CI)[a]



Primary endpoint (≥50 c/mL):

Q8W is noninferior to Q4W (Week 48)



Key secondary endpoint (<50 c/mL):

Q8W is noninferior to Q4W (Week 48)

[a]Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 wk, 1-24 wk, >24 wk).

ATLAS-2M Snapshot Outcomes at Week 48 (ITT-E Population)

Snapshot outcome, ITT-E, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 c/mL at Week 48	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL at Week 48	9 (1.7)	5 (1.0)
Data in window not <50 c/mL	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reasons while not <50 c/mL	0	1 (0.2)
No virologic data	21 (4.0)	29 (5.5)
Discontinued for AE or death	9 (1.7)*	13 (2.5)†
Discontinued for other reasons	12 (2.3)‡	16 (3.1)§

*Discontinuations for AEs (event level) include Q8W: Injection-site pain (n=2), injection-site abscess, injection-site discomfort, skin lesion, fatigue, acute hepatitis B, asthenia, presyncope, pancreatitis acute, headache, rash maculo-papular (all n=1). †Q4W: injection-site pain (n=11), abnormal dreams (n=2), injection-site swelling (n=2), hyperhidrosis (n=2), fatigue (n=2), injection site nodule, influenza, headache, acute hepatitis B, dizziness, glioblastoma, allergic reaction, transaminase increase, depression, chills, insomnia, myalgia, nausea, presyncope, pyrexia, sleep disorder, disturbance in attention (all n=1). ‡Q8W: Withdrawal by participant (n=4), investigator decision (n=4), lost to follow-up (n=2), protocol deviation (n=1), lack of efficacy (n=1). §Q4W: Withdrawal by participant (n=12), protocol-specified withdrawal criteria met (pregnancy) (n=3), protocol deviation (n=1).

AE, adverse event; ITT-E, intent-to-treat–exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

ATLAS-2M: Summary of Confirmed Virologic Failures

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs Observed at Failure	CVFs with IN RAMs*	IN RAMs Observed at Failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

- Post hoc baseline PBMC HIV-1 DNA results for Q8W arm:
  - 5/8 CVFs had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1/8 CVFs had a pre-existing 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 re-suppressed on fully active oral HAART (1/10 non-compliance on PI-based ART)
  - All CVFs retained phenotypic sensitivity to dolutegravir

*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. †Or mixture. ART, antiretroviral therapy; CVF, confirmed virologic failure; HAART, highly active antiretroviral therapy; IN, integrase; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

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ATLAS-2M Safety and Tolerability Was Similar Between Q8W and Q4W Dosing Arms: AEs Excluding ISRs

	Q8W (n=522) n (%)	Q4W (n=523) n (%)
Any AE	403 (77)	441 (84)
Drug-related AEs	109 (21)	125 (24)
Any grade ≥3	29 (6)	30 (6)
Drug-related grade ≥3	4 (<1)	5 (<1)
AEs leading to withdrawal	8 (2)	10 (2)
Drug-related AEs leading to withdrawal	5 (<1)	8 (2)
Any SAE	26 (5)	19 (4)
Drug-related SAEs*	2 (<1)	1 (<1)
Fatal SAEs†	1 (<1)	0
Drug-related fatal SAEs	0	0

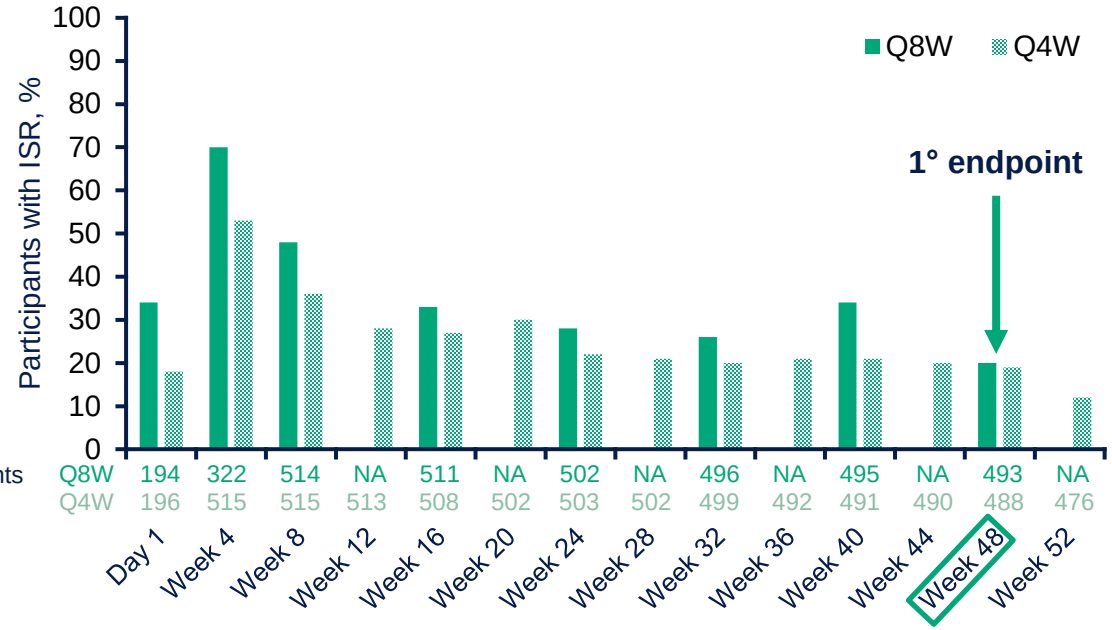
*Drug-related SAEs were presyncope and acute pancreatitis in the Q8W group and allergic reaction in the Q4W group. †The fatal SAE was sepsis. The death was not considered related to study drug. A further participant died during screening (did not receive study drug).

- AEs were similar between the Q8W and Q4W dosing arms
- Overall, 96% of drug-related AEs were grade 1-2
- Drug-related AEs led to withdrawal in 5 participants in the Q8W arm and 8 in the Q4W arm

AE, adverse event; ISR, injection-site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

ATLAS-2M Injection-Site Reactions

Overall ISRs



Note: Day 1 only included participants with prior CAB + RPV exposure due to the oral lead-in phase.

Outcome, n (%), ITT-E	Q8W (n=522)	Q4W (n=523)
Number of injections	8470	15,711
Number of ISR events (events/injections)*	2507 (30)	3152 (20)
Grade ≥3 – severe†	43 (<1)	48 (<1)
ISRs‡		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)
Withdrawals due to injection-related reasons, participant n (%)§	6 (1)	11 (2)

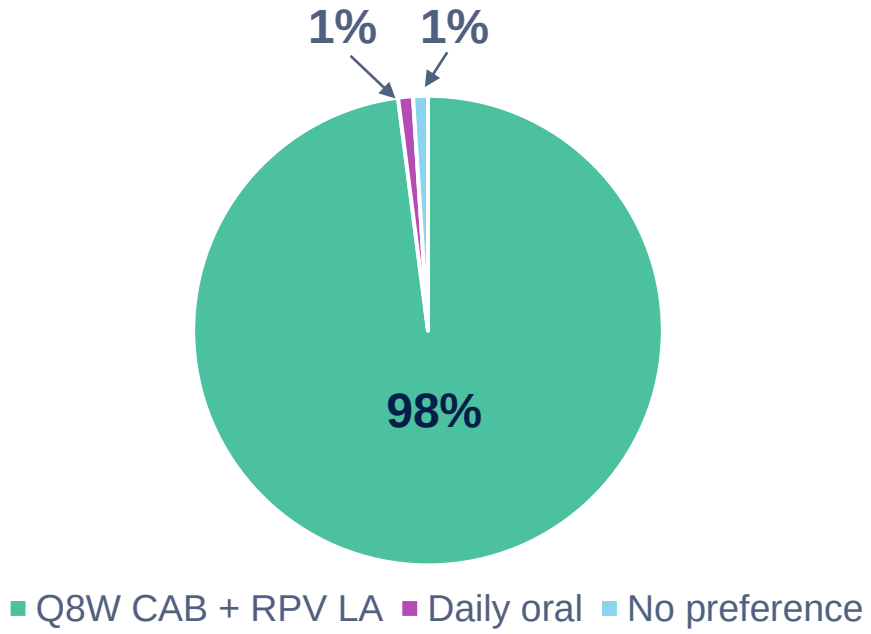
*All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR. †There were no grade 4 or grade 5 ISRs. ‡ISRs occurring in >1% of injections in either the Q4W or Q8W arms are shown. §Q8W: 5 participants had an ISR leading 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.

- 24,181 injections were administered in total
  - <2% of participants discontinued due to injection-related reasons
- 98% (5568/5659) of ISRs were grade 1-2, with a median duration of 3 days in both arms

AE, adverse event; ISR, injection-site reaction; ITT-E, intent-to-treat–exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

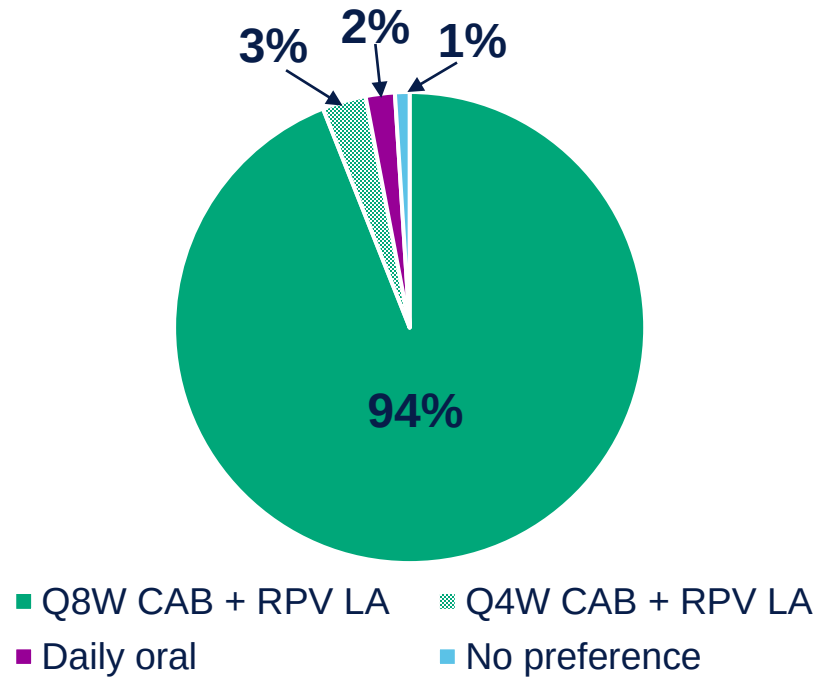
ATLAS-2M: Majority of Participants Preferred Q8W Dosing

Participants in Q8W arm from SOC (no prior Q4W experience)*



*306 participants responded to the preference question.

Participants in Q8W arm with prior Q4W experience in ATLAS†



†191 participants responded to the preference question.

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. Percentages are calculated out of those participants with recorded response to the preference.

CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care.

ATLAS-2M Week 48 Conclusions

- **Q8W dosing of CAB + RPV LA was highly efficacious and noninferior to Q4W dosing**
  - Virologic non-response (≥50 c/mL) was infrequent and similar between the two arms
  - Virologic suppression was maintained in 94.3% and 93.5% of those in the Q8W and Q4W arms, respectively
  - The rate of confirmed virologic failure was low overall (1%)
- **CAB + RPV LA was well tolerated with a comparable safety profile between arms**
  - ISRs were mostly Grade 1–2 (98%) with a median duration of 3 days
- **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**
- **CAB + RPV LA, dosed every 2 months, is an innovative and effective treatment for maintenance of virologic suppression in people living with HIV**

CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

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  - All study participants and their families
  - The ATLAS 2M clinical investigators and their staff in Australia, Argentina, Canada, France, Germany, Italy, Mexico, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, and the United States

Argentina
Cahn
Cassetti
Lupo
Porteiro

Australia
Baker
Bloch
Roth
Shields

Canada
Angel
Baril
Smith
Trottier
Wong
de Pokomandy

France
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