OUTCOMES FOR WOMEN RECEIVING LONG-ACTING CABOTEGRAVIR + RILPIVIRINE MONTHLY AND EVERY 2 MONTHS: ATLAS-2M STUDY WEEK 48 RESULTS

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Introduction

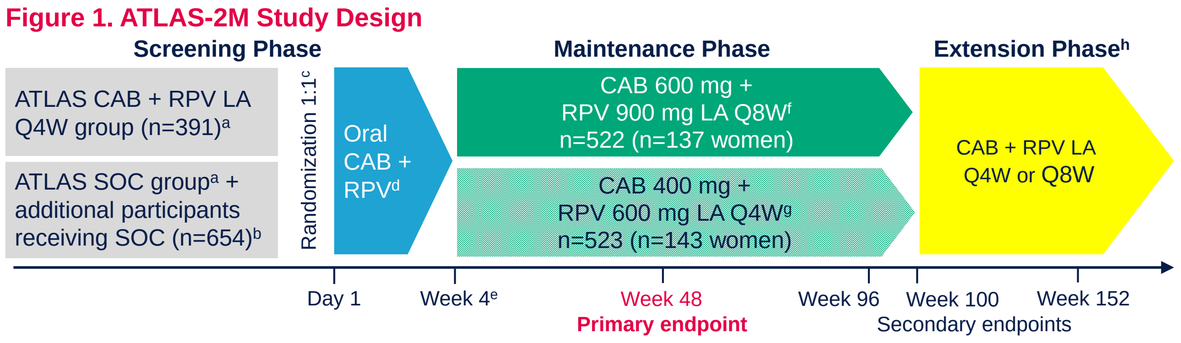
- LA injectable CAB + RPV provides a highly effective ART regimen with the potential to improve treatment convenience, adherence, and quality of life for people living with HIV-1[1]
- CAB + RPV LA Q4W demonstrated noninferiority vs daily oral ART in the phase III ATLAS and FLAIR studies[2,3]
- CAB + RPV LA dosing Q8W demonstrated noninferiority vs Q4W dosing in the ATLAS-2M study for maintenance of virologic suppression[4]
- Although >50% of people living with HIV are women, they are often under-represented in HIV ART clinical trials[5,6]
- This analysis examines the efficacy, safety, and treatment satisfaction outcomes for the women participating in the ATLAS-2M study vs men at Week 48

Methods

Study Design

- Subgroup analyses were performed on the primary and secondary endpoints (Figure 1) of the ATLAS-2M study by sex at birth
  - Differences between Q8W and Q4W groups for women and men in snapshot analyses were based on Cochran–Mantel–Haenszel stratified analysis and adjusted for prior exposure to CAB + RPV

Figure 1. ATLAS-2M Study Design



[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.

Results

Baseline Characteristics

- Baseline characteristics were similar between women and men in Q8W and Q4W groups (Table 1)

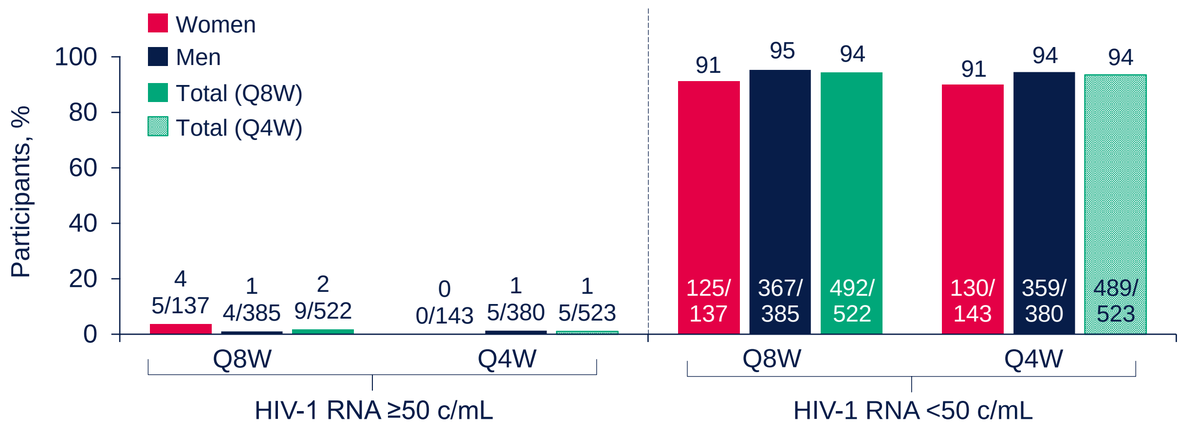
Table 1. Baseline Characteristics (ITT-E Population)

Characteristic	Q8W (N=522) Women	Q8W (N=522) Men	Q4W (N=523) Women	Q4W (N=523) Men
Sex at birth, n (%)	137 (26)	385 (74)	143 (27)	380 (73)
Mean age, y	46	42	44	42
Black/African American, n (%)	52 (38)	49 (13)	54 (38)	36 (9)
BMI, median (IQR), kg/m^2	27 (23-32)	25 (23-28)	27 (23-32)	26 (23-28)
≥30 kg/m^2, n (%)	52 (38)	61 (16)	42 (29)	56 (15)
Prior CAB + RPV exposure, n (%)	64 (47)	131 (34)	68 (48)	128 (34)

Snapshot Outcomes at Week 48

- Proportions of women and men with HIV-1 RNA ≥50 c/mL were similar between groups (adjusted differences [95% CI], 3.5% [0.4 to 6.6] for women and −0.3% [−1.8 to 1.3] for men; Figure 2)
- HIV-1 RNA <50 c/mL was maintained in the majority of women and men in each group (adjusted differences [95% CI], 0.4% [−6.2 to 7.1] for women and 0.8% [−2.3 to 4.0] for men)

Figure 2. Virologic Snapshot Outcomes at Week 48 (ITT-E Population)



Other Virologic Outcomes

- The proportion of women and men with HIV-1 RNA <2 c/mL was similar at baseline and at Week 48 across both groups. At baseline, 81% (109/135) Q8W and 83% (116/139) Q4W of women and 74% (281/379) Q8W and 73% (276/377) Q4W of men had HIV-1 RNA <2 c/mL, respectively. At Week 48, 81% of women (Q8W, 96/119; Q4W, 105/129) and 76% of men (Q8W, 277/364; Q4W, 267/352) in both arms had HIV-1 RNA <2 c/mL

Confirmed Virologic Failure

- 8 (1.5%) and 2 (<1%) participants in the Q8W and Q4W groups had CVF, with 5/8 (Q8W) and 0/2 (Q4W) occurring in women (Table 2)
- On baseline PBMC DNA samples, 3/5 and 1/5 women with CVF had only RPV and both RPV and INSTI RAMs, respectively
- 4/5 women with CVF were subsequently suppressed on oral ART and 1/5 had continued low-level viral replication due to poor adherence on a boosted PI regimen

Table 2. Women Receiving CAB + RPV LA Q8W with CVF[a] at Week 48

Country (HIV-1 subtype)	SVF, wk	VL at SVF/CVF, c/mL	Baseline RAM[7] (PBMC/HIV-1 DNA; Day 1) RT	Baseline RAM[7] (PBMC/HIV-1 DNA; Day 1) IN	SVF timepoint RAM[7] (HIV-1 RNA) RT	SVF timepoint RAM[7] (HIV-1 RNA) IN	Drug sensitivity at SVF, FC[b] RPV	CAB	DTG
South Africa (Complex)	8	267/2355	V108V/I Y181Y/C H221H/Y	None	K103N	None	2.4	1.1	0.9
South Africa (C)	16	938/2374	Y/188Y/F/H/L	G140G/R	Y188L	Q148Q/R N155N/H	6.8	2.6	1.3
Russia (A1)	16	141,132/19,099	None	None	K101E	Q148R	4.7	9.1	1.6
Canada (A1)	24	16,205/874	Y188L P225H	None	Y188L P225H	NA[c]	15.0	NA[c]	NA[c]
Russia (A)	24	211,639/38,015	E138E/A	None	K101E E138A	N155H	2.6	7.0	2.2

FC, fold-change; RAM, resistance-associated mutation; RT, reverse transcriptase; SVF, suspected virologic failure. [a]CVF=2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. [b]Monogram biologic/clinical cutoffs: RPV=2.0, CAB=2.5, DTG=4.0. [c]Integrase analysis failed.

Pharmacokinetics

- CAB and RPV plasma median concentrations in women were generally >1× and 4× PA-IC$_{90}$ values through Week 48 and within the same range as concentrations in men[8]
- Plasma CAB and RPV concentrations for the 5 women with CVF were generally below the population median but within the range of exposures that showed efficacy in most participants

Safety and Tolerability

- Overall AE types were similar between treatment groups and sexes (Table 3)
- Rates of any AE and drug-related AEs were numerically lower in women vs men

Table 3. Summary of AEs, Including ISRs

Event	Q8W (N=522) Women (n=137)	Q8W (N=522) Men (n=385)	Q4W (N=523) Women (n=143)	Q4W (N=523) Men (n=380)
Any AE	116 (85)	357 (93)	125 (87)	357 (94)
Drug-related AE[a]	88 (64)	312 (81)	97 (68)	302 (79)
SAE	6 (4)	21 (5)[b]	6 (4)	13 (3)
Drug related[c]	2 (1)	1 (<1)	1 (<1)	0
AE leading to withdrawal[d]	5 (4)	7 (2)	5 (3)	8 (2)
ISR event/Injection[e,f]	477/2124 (23)	2030/6346 (32)	809/4191 (19)	2343/11,520 (20)
Grade ≥3[f,g]	9 (<1)	34 (1)	9 (<1)	39 (<1)
ISR leading to withdrawal[h]	3 (<1)	8 (<1)	2 (<1)	12 (<1)

[a]High proportion of drug-related AEs associated with ISRs. [b]One fatal SAE not considered drug related. [c]Drug-related SAEs were injection-site abscess, presyncope, acute pancreatitis, and hypersensitivity. [d]Non-ISR AEs leading to withdrawal occurred in 1 participant each, except for fatigue (1 in Q8W and 2 in Q4W), abnormal dreams and hyperhidrosis (2 in Q4W), and acute hepatitis B, headache, presyncope, and pyrexia (1 each in Q8W and Q4W). [e]Most commonly reported ISRs were pain, induration, and nodule formation. [f]Percentages calculated from total injections. [g]No grade 4/5 ISRs were reported. [h]Percentages calculated from total ISR events.

- ISRs per injection tended to be lower in women vs men, and the proportion of participants with ISRs generally decreased over time through Week 48 in both sexes (Figure 3)
  - 98% of ISRs were grade 1/2 with a median duration of 3 days in both treatment groups
- Adherence rates to injection visits within the allowable ±7-day window were 98% overall, 99% in women, and 98% in men

Figure 3. Proportion of Women and Men Reporting ISRs Over Time

Study week:

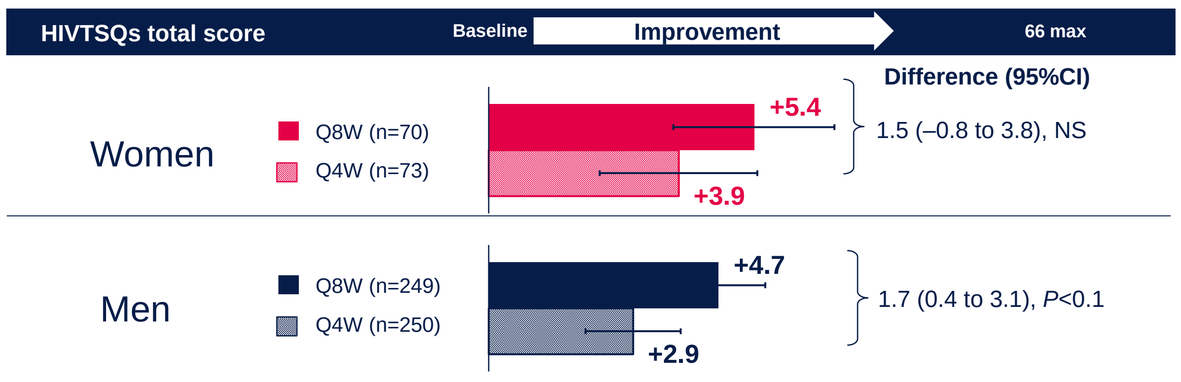
	Day 1	4[a]	8	12	16	20	24	28	32	36	40	44	48
Q8W Women	64	70	134		132		129		126		125		123
Q8W Men	130	252	380		379		373		370		370		370
Q4W Women	68	138	138	138	136	134	134	134	132	130	130	129	130
Q4W Men	128	377	377	375	372	368	369	368	367	362	361	361	358

Bars represent incidence of onset ISR-related AEs relative to the most recent IM injection visit. [a]Initial injection for participants transitioning from an oral lead-in occurred at Week 4.

Patient-Reported Outcomes

- Women and men with no prior CAB + RPV LA exposure reported improvement from baseline in treatment satisfaction at Week 48 (Figure 4)
  - Treatment satisfaction for women and men with prior CAB + RPV exposure was high at baseline and remained high through Week 48

Figure 4. Mean Change From Baseline in HIVTSQs Total Score[a] at Week 48 in Women and Men Without Prior CAB + RPV LA Exposure



[a]Adjusted for baseline score, age, and race. Error bars show 95% CI.

- Participants with no prior CAB + RPV LA exposure reported increases from baseline in treatment acceptance (mean changes from baseline at Week 48, 6.0 vs 9.4 [women] and 7.1 vs 4.6 [men]) in Q8W vs Q4W, respectively
  - Men and women with prior CAB + RPV exposures maintained high treatment acceptance scores over time through Week 48
- The majority of women in Q8W group with prior CAB + RPV exposure preferred Q8W dosing (56/64 [88%]) vs Q4W (5/64 [8%]) and oral (1/64 [2%]) dosing
  - Increased convenience/ease to integrate into daily life was cited as a key benefit for Q8W in 73% (41/56)

Conclusions

- CAB + RPV LA Q8W and Q4W demonstrated high and similar rates of efficacy in women and men[4]
- Rates of CVF were low and similar for women and men; 4/5 CVFs in women (Q8W) had archived preexisting resistance
  - Multivariable analysis across ATLAS, FLAIR, and ATLAS-2M phase III studies (n=1039) suggests that reasons for CVF are multifactorial and that ≥2 baseline factors (baseline RPV RAMs, subtypes A1/A6, and BMI ≥30 kg/m^2) were associated with an increased risk of CVF
  - Female sex at birth and Q4W or Q8W dosing had no significant association with CVF in this analysis[9]
- Q8W and Q4W dosing were generally well tolerated among women, with treatment discontinuations due to ISRs being low among both women and men
- Treatment satisfaction was high with Q8W and Q4W LA dosing for both sexes, with women expressing preference for Q8W compared with Q4W and daily oral dosing[10]
- These results support the therapeutic potential of CAB + RPV LA Q8W in women

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