Effect of Long-Acting Cabotegravir Plus Rilpivirine on Weight

Summary

ATLAS, FLAIR, ATLAS-2M

- A median increase from baseline in weight of 1.5 kg was reported among patients receiving long-acting cabotegravir plus rilpivirine (CAB + RPV LA) in the pooled analysis of ATLAS and FLAIR at Week 48.[1-3]
- A median increase from baseline in weight of 1.0 kg was reported among patients receiving CAB + RPV LA in ATLAS-2M at Week 48.[1,4,5]
- In a pooled analysis of all phase 3 trials, patients in the CAB + RPV LA arms had an approximately 1.2 kg increase in weight compared to an increase of 1.0 kg in the comparator arm at Week 48.[6]
- Another 48 week pooled analysis of ATLAS, FLAIR and ATLAS-2M which stratified patients by BMI (< 30 kg/m^2 or ≥ 30 kg/m^2) showed high and comparable virologic suppression rates between BMI categories. No participant with high BMI as the only baseline factor met confirmed virologic failure criterion. Use of 2-inch needles resulted in higher median cabotegravir trough concentrations for participants with BMI ≥30 kg/m^2.[7]

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- At Month 12, median changes in weight and body mass index from baseline were minimal and comparable between treatment groups in the SOLAR trial.[8]
- Important Safety Information can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

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ATLAS, FLAIR, ATLAS-2M

Change in weight was evaluated in the phase 3 clinical trials for CAB + RPV LA when used in virologically suppressed patients with HIV-1.[6,9,10]

ATLAS and FLAIR 48 Week Results

Table 1. Median (Q1,Q3) Change From Baseline in Weight (kg) at Week 48 in ATLAS and FLAIR[1-3]

	ATLAS		FLAIR		Pooled	
	CAB + RPV LA* (N = 308)	CAR (N = 308)	CAB + RPV LA* (N = 283)	CAR (N = 283)	CAB + RPV LA* (N = 591)	CAR (N = 591)
Week 48	+1.8 (-0.3, 4.9) (n = 179)	+0.3 (-1.6, 2.5) (n = 291)	+1.3 (-1, 5) (n = 262)	+1.5 (-1, 3.9) (n = 263)	+1.5 (n = 441)	+1 (n = 554)

*CAB + RPV LA was administered once-monthly

CAB + RPV LA = long-acting cabotegravir and rilpivirine; CAR = current antiretroviral regimen

ATLAS and FLAIR Extension Phases

After Week 48, patients enrolled in ATLAS were given the opportunity to switch to ATLAS-2M or switch to (CAR arm)/continue with monthly CAB + RPV LA in the extension phase of the study.[11] Fifty-two people opted to remain in ATLAS (23 patients on CAB + RPV LA from day 1 through Week 96 and 29 patients who switched from the CAR arm after study Week 48 with data from Weeks 52 through 96) and 502 transitioned to ATLAS-2M.

FLAIR continued through Week 100 as a comparative trial and beyond Week 100 to Week 124 as an open-label extension phase where all patients were potentially eligible to transition to treatment with CAB + RPV LA.[12]

Body weight increased during the extension phases of both ATLAS and FLAIR. See Table 2.

Table 2. Median (Q1, Q3) Change from Baseline in Weight (kg) During the Extension Phase in ATLAS and FLAIR [11,12]

	ATLAS		FLAIR	
	CAB + RPV LA	Switch	CAB + RPV LA	CAR
Week 96	+2.1 (-1.0, 5.0) (n = 23)	+1.1 (0.0, 3.1) (n = 29)	+2.0 (-0.7, 6.0) (n = 283)	+2.0 (-0.9, 5.0) (n = 283)

ATLAS-2M

Table 3. Median (Q1,Q3) Change From Baseline in Weight (kg) in ATLAS-2M[1,4,5]

	Every 8 Week Group (N = 522)	Every 4 Week Group (N = 523)
Week 48	+1.0 (-1.0, 3.2) (n = 494)	+1.0 (-1.0, 3.0) (n = 490)
Week 96	+1.8 (-1.0, 5.0) (n = 475)	+1.3 (-1.5, 4.0) (n = 470)
Week 152	+2.0 (-0.6, 6.0) (n = 439)	+1.65 (-1.2, 5.0) (n = 443)

In a pooled analysis of ATLAS, FLAIR, and ATLAS-2M, 13.2% and 0.6% of patients overall experienced an upward change in BMI category at 48 Weeks from normal to overweight or normal to obese, respectively.[6]

Table 4. Pooled Weight Change by Treatment Regimen from Baseline to Week 48 in ATLAS, FLAIR, and ATLAS-2M[6]

	CAB + RPV LA Q4W (n = 918)	CAB + RPV LA Q8W (n = 327)	CAR (n = 591)
Median (range) weight change (kg)	1.2 (-27.5, 40.9)	1.25 (-16.0, 22.2)	1.0 (-28.0, 39.0)
Proportion of patients with ≥10% weight increase (%)	8	5	7
Median (range) BMI change (kg/m^2)	0.4 (-9.9, 14.3)	0.42 (-4.8, 7.3)	0.35 (-8.2, 13.7)
Proportion of patients with upward shift in BMI resulting in obesity (%)	3.9	4.1	4.7

CAB + RPV LA = long-acting cabotegravir and rilpivirine; CAR = current antiretroviral regimen; BMI = body mass index; Q4W = every 4 weeks; Q8W = every 8 weeks

ATLAS, FLAIR, ATLAS-2M Pooled Analysis Through 48 Weeks

Efficacy, safety, and pharmacokinetics of CAB + RPV LA through Week 48 were evaluated among participants receiving CAB + RPV LA in the ATLAS, FLAIR, and ATLAS-2M studies.[7] Participants were stratified by dosing regimen (Q8W vs. Q4W) and BMI category (lower, < 30 kg/m^2; higher, ≥ 30 kg/m^2). Of the 1,245 participants randomized to receive CAB + RPV LA, 213 (17%) had a BMI ≥30 kg/m2 at baseline

Across both dosing regimens, 93–94% of participants with BMI < 30 kg/m^2 and 92% with BMI ≥ 30 kg/m^2 had HIV-1 RNA < 50 copies/mL. CVF events were uncommon across all three studies (n=13/1245; 5 in the lower BMI group and 8 in the higher BMI group). Among 153 participants with BMI ≥ 30 kg/m^2 as the only baseline factor, none met CVF criterion.[7]

BMI categories did not affect cabotegravir or rilpivirine trough levels, which remained above PA-IC_{90} targets. Median trough levels tended to be lower in patients with baseline BMI ≥ 30 kg/m^2; however, this trend disappeared by Week 48. Higher cabotegravir trough levels were observed in participants in the higher BMI cohort who utilized longer 2-in needles. Longer 2-inch needles are recommended for participants with BMI ≥ 30 kg/m^2 to ensure appropriate administration into gluteal muscle.[7]

Through 48 weeks, adverse events leading to study withdrawal occurred in 2-3% of participants in the low BMI group and < 1% in the high BMI group. Most ISRs were classified as mild to moderate in severity and decreased in incidence over time.[7]

ATLAS-2M and FLAIR Pooled Analysis Through 96 Weeks

Weight changes through 96 weeks were evaluated in a pooled analysis of patients receiving CAB + RPV LA every 4 or 8 weeks (Q4W or Q8W, n = 937) or daily oral therapy (ABC/DTC/3TC, n = 283) in the ATLAS-2M and FLAIR studies, respectively.[13]

Baseline demographics were comparable between groups.[13] In patients receiving CAB + RPV LA, the median age was 39 years, 23% were female (sex at birth), and 16% were Black or African American. Overall, 33% of patients receiving CAB + RPV LA were overweight and 16% were obese at baseline.

Though Week 96, there were comparable minor median weight changes between CAB + RPV LA and daily oral therapy.[13] See Table 5 for mean weight changes from baseline. Black/African American patients in both groups experienced the most increase in weight.

Table 5. Pooled Weight Changes by Treatment Regimen from Baseline to Week 96 in FLAIR and ATLAS-2M[13]

	CAB + RPV LA Q4W		CAB + RPV LA Q8W		ABC/DTG/3TC	
	48 Week	**96 Week**	**48 Week**	**96 Week**	**48 Week**	**96 Week**
Median (IQR) weight at baseline (kg)	76.0 (67 – 85.4)		77.0 (68 - 87)		74.0 (64.5 – 83.7)	
	n = 564	n = 531	n = 306	n = 294	n = 263	n = 255
Median weight change (kg) from baseline	1.0	1.6	1.3	1.8	1.5	2.0
Proportion of patients with ≥10% weight increase (%)	10	14	5	11	10	13
Median (IQR) BMI at baseline (kg)	24.8 (22.5 – 27.7)		25.3 (22.7 – 28.6)		24.0 (21.8 – 27.1)	
	n = 610	n = 531	n = 327	n = 294	n = 283	n = 255
Median BMI change (kg/m^2)	0.4	0.5	0.4	0.6	0.5	0.6
Proportion of patients with upward shift in BMI resulting in obesity (%, n)	4 (27) (n = 610)		4 (13) (n = 327)		4 (11) (n = 283)	

CAB + RPV LA = long-acting cabotegravir and rilpivirine; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; BMI = body mass index; Q4W = every 4 weeks; Q8W = every 8 weeks

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Changes in body weight and body mass index (BMI) category were assessed from baseline (Day 1) to Month 12.[8] At baseline, 59% of patients randomized to receive CAB + RPV LA Q2M were overweight or obese compared with 64% randomized to continue BIC/FTC/TAF.

See Table 6 for pertinent baseline parameters.

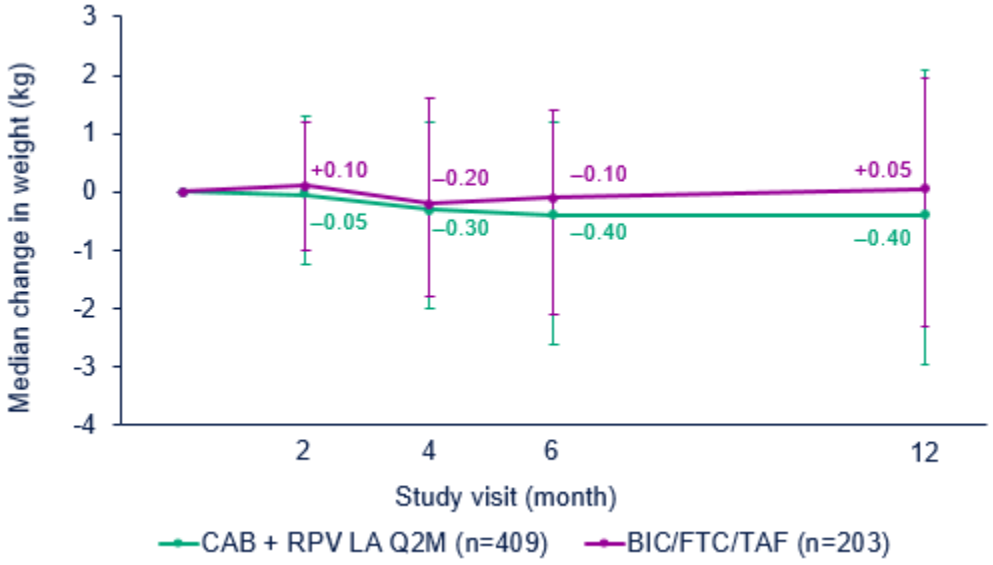
Table 6. Pertinent Baseline Parameters[8]

Parameter	**CAB + RPV LA Q2M (n = 454)**	**BIC/FTC/TAF (n = 227)**
Weight (kg), median (IQR)	81.3 (70.7–91.8)	79.0 (69.4–91.7)
BMI (kg/m^2), median (IQR)	26.0 (23.2–29.3)	25.4 (23.6–29.6)
BMI ≥ 30 kg/m^2	97 (21)	52 (23)
BMI Category, n (%)		
Underweight (< 18.5 kg/m^2)	8 (2)	3 (1)
Normal (18 - < 25 kg/m^2)	175 (39)	94 (41)
Overweight (25 - < 30 kg/m^2)	174 (38)	78 (34)
Obese (≥ 30 kg/m^2)	97 (21)	52 (23)
Relevant Medical History		
Hypertension	48 (11)	26 (12)
Diabetes	19 (4)	7 (3)

BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir; BMI = body mass index; CAB + RPV LA = long-acting cabotegravir and rilpivirine; Q2M = every 2 months

Changes in weight and BMI were minor and comparable between CAB + RPV LA Q2M and BIC/FTC/TAF through Month 12.[8] At Month 12, median (IQR) change in weight in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg and +0.05 (-2.30, +1.95) kg in the BIC/FTC/TAF group. See Figure 1.

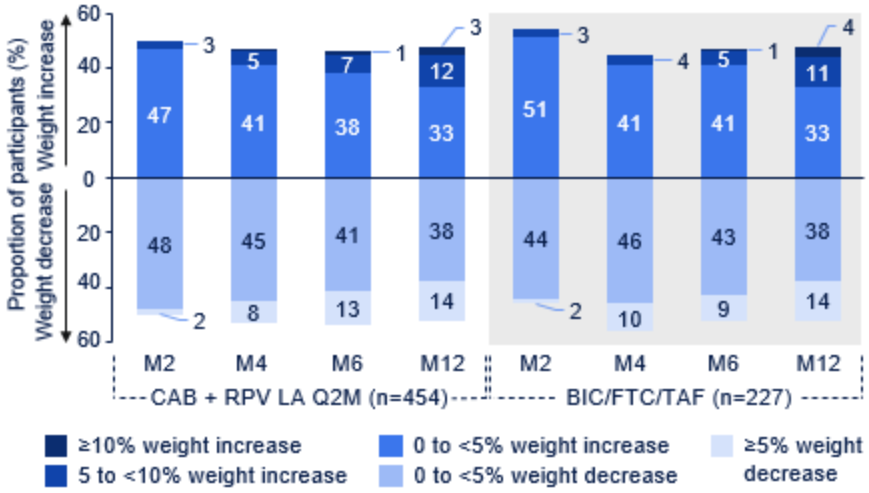
Figure 1. Median (IQR) Change in Weight Through Month 12 by Treatment Regimen[a,8]



a=any participant who started lipid-modifying agents during the study was non-evaluable in anthropometric assessments.
CAB + RPV LA = long acting cabotegravir + rilpivirine; BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir

A weight increase of ≥ 10% by Month 12 occurred in 3% (n = 11/454) of participants in the CAB + RPV LA arm vs. 4% (n = 9/227) in the BIC/FTC/TAF arm.[8] See Figure 2.

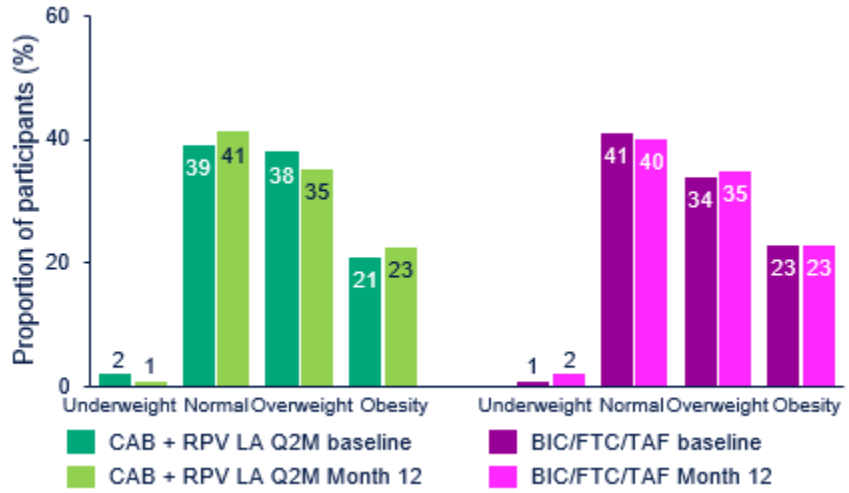
Figure 2. Percent Change in Weight Through Month 12[a,8]



a=any participant who started lipid-modifying agents during the study was non-evaluable in anthropometric assessments.
CAB + RPV LA = long acting cabotegravir + rilpivirine; BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir

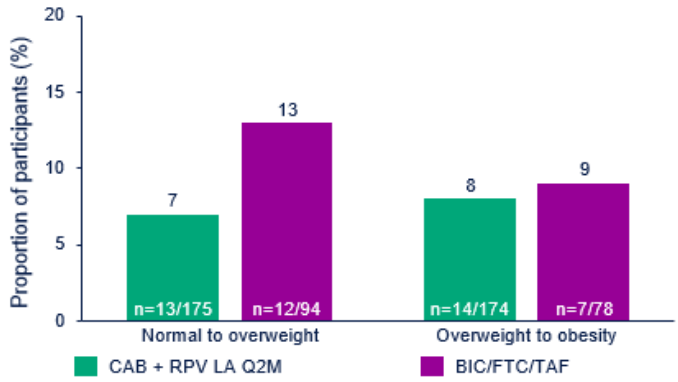
Overall, the proportion of individuals in BMI categories remained similar at Month 12.[8] No participant shifted from normal to obesity or underweight to overweight at Month 12. See Figures 3 and 4.

Figure 3. BMI Categories at Baseline and Month 12[8]



CAB + RPV LA = long acting cabotegravir + rilpivirine; BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir; Q2M = every 2 months

Figure 4. Proportion of Participants with an Upward BMI Shift Resulting in Overweight or Obesity[8]



CAB + RPV LA = long acting cabotegravir + rilpivirine; BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir; Q2M = every 2 months

A separate analysis evaluated weight changes in females (sex at birth) from SOLAR.[14] Overall, 79 female participants were randomized to receive CAB+RPV LA and 41 were randomized to continue BIC/FTC/TAF (18% [n = 120/681]). Median (IQR) change in BMI from baseline to Month 12 was –0.26 kg/m2 (–1.20, 0.26) and – 0.11 kg/m2 (–1.45, 0.57) in the CAB + RPV LA and BIC/FTC/TAF arms, respectively. Upward shifts in BMI at Month 12 were seen in one participant receiving CAB + RPV LA (moving from underweight at baseline to normal), and two participants receiving BIC/FTC/TAF (both moving from overweight at baseline to obese).

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Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

REFERENCES

1. ViiV Healthcare, Module 5.3.5.3, Integrated Summary of Safety for cabotegravir, version 2.0, March 29, 2019.
2. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med*. 2020;382(12):1112-1123. doi:http://dx.doi.org/10.1056/NEJMoa1904398.
3. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. *N Engl J Med*. 2020;382(12):1124-1135. doi:http://dx.doi.org/10.1056/NEJMoa1909512.
4. Jaeger H, Overton E, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet 2021;8(11):E679-E689. DOI:https://www.doi.org/10.1016/S2352-3018(21)00185-5.
5. Data on File. ATLAS-2M (Study 207966). .
6. Patel P, et al. Weight and lipid changes in phase 3 cabotegravir and rilpivirine long-acting trials. Presented at CROI 2021, March 6-10, 2021, Virtual Event. Science Spotlight.
7. Elliot E, et al. Efficacy and Safety Outcomes by BMI Category Over 48 Weeks in Phase 3/3b Cabotegravir and Rilpivirine Long-Acting Trials. Presented at the 18th European AIDS Conference (EACS), October 27-30, 2021, Online & London, United Kingdom. Best Poster Presentation.
8. Tan D, et al. Weight and Metabolic Changes With Cabotegravir + Rilpivirine Long-Acting or Bictegravir/Emtricitabine/Tenofovir Alafenamide. Presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI), February 19-22, 2023, Seattle, Washington. Oral Presentation.
9. ClinicalTrials.gov identifier NCT02938520. Available at: https://ClinicalTrials.gov/show/NCT02938520.
10. ClinicalTrials.gov identifier NCT02951052. Available at: https://ClinicalTrials.gov/show/NCT02951052.
11. Swindells S, Lutz T, van Zyl L, et al. Long-acting cabotegravir + rilpivirine for HIV-1 treatment: ATLAS week 96 results. *AIDS (London, England)*. 2021. doi:http://dx.doi.org/10.1097/QAD.0000000000003025.
12. Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV*. 2021;8(4):e185-e196. doi:http://dx.doi.org/10.1016/S2352-3018(20)30340-4.
13. Patel P, et al. Week 96 weight and lipid changes from baseline among participants receiving cabotegravir and rilpivirine long-acting or comparator therapy in the ATLAS-2M and FLAIR studies. Presented at AIDS 2022, July 29-August 2, 2022, Montreal, Canada, and virtually. E-poster. EPB183.
14. Patel P, et al. Weight and Body Mass Index Changes in Women Receiving Cabotegravir + Rilpivirine Long-Acting or Bictegravir in the SOLAR Study. Presented at BHIVA Spring Conference 2023, April 24-26, 2023, Gateshead, UK. Poster.