EPB183

Week 96 Weight and Lipid Changes From Baseline Among Participants Receiving Cabotegravir + Rilpivirine Long-Acting or Comparator Therapy in the ATLAS-2M and FLAIR Studies

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Key Takeaways

- **We present longer-term weight and lipid changes for participants receiving cabotegravir + rilpivirine long-acting (CAB + RPV LA) or daily oral therapy (abacavir/dolutegravir/lamivudine [ABC/DTG/3TC]) through Week 96 of the Phase 3/3b ATLAS-2M and FLAIR studies.**
- **Longer-term weight, body mass index (BMI), and lipid changes were minor and comparable between participants receiving CAB + RPV LA and daily oral therapy, supporting the use of CAB + RPV LA dosed monthly or every 2 months as a complete regimen for the maintenance of HIV-1 virologic suppression in adults.**

Introduction

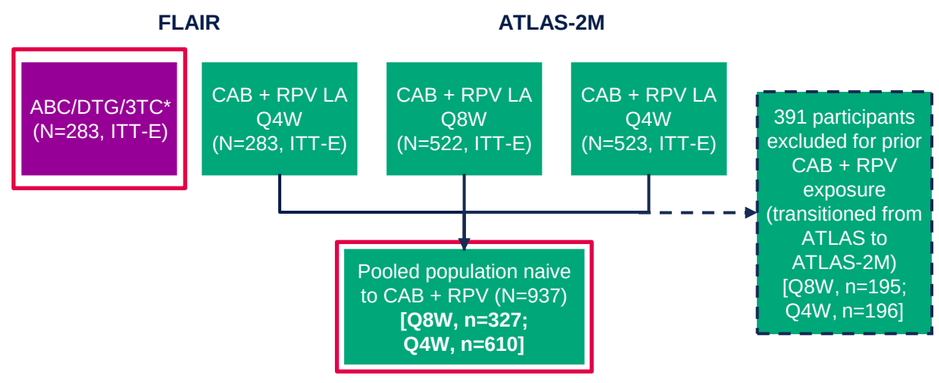
- Weight gain and metabolic alterations have been reported with integrase strand transfer inhibitor (INSTI)- and tenofovir alafenamide (TAF)-based antiretroviral regimens.[1–3]
- Multiple associations with weight gain have been described, including immune status, TAF use, female sex, Black race, and pre-existing comorbidities.[1,4]
- CAB, an INSTI, plus RPV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a complete LA regimen recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression.[5–7]
- In pooled Phase 3/3b studies, weight and lipid changes were modest in participants receiving CAB + RPV LA or daily oral therapy through Week 48.[8]
- Here, we present weight and lipid changes from baseline to Week 96 in the FLAIR* and ATLAS-2M† studies.

*NCT02938520. †NCT03299049.

Methods

- Data were pooled for participants receiving CAB + RPV LA every 4 or 8 weeks (Q4W or Q8W, n=937) or daily oral therapy (ABC/DTG/3TC, n=283) through 96 weeks in the FLAIR and ATLAS-2M studies (**Figure 1**).
  - FLAIR participants were antiretroviral naive at study entry and underwent induction with ABC/DTG/3TC for 20 weeks, and were subsequently randomized to receive either CAB + RPV LA Q4W or continue daily oral therapy if their HIV-1 RNA was <50 copies/mL.
  - ATLAS-2M participants were antiretroviral experienced and virologically suppressed on comparator oral therapy before being randomized to receive either CAB + RPV LA Q4W or Q8W.
    - ATLAS-2M participants who transitioned from the Phase 3 ATLAS study with prior exposure to CAB + RPV were excluded to ensure all participants had only 96 weeks of follow-up.
- The following parameters were assessed at baseline, Week 48, and Week 96:
  - Change in weight and BMI.
  - Lipids, including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.
  - Proportion with ≥10% weight increase from baseline, overall and by baseline subgroup.

Figure 1. Participants Analyzed



*Participants with HLA-B*5701 positivity or tolerability issues with ABC received FTC + TDF, FTC + TAF, or 3TC/TDF.
3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; DTG, dolutegravir; FTC, emtricitabine; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Results

Table 1. Baseline Demographics and Characteristics*

ITT-E population	Pooled Q8W arm (ATLAS-2M only) (n=327)	Pooled Q4W arm (FLAIR and ATLAS-2M) (n=610)	ABC/DTG/3TC† (FLAIR only) (n=283)
Median age (range), years	41 (20–83)	37 (19–68)	34 (18–68)
Female sex at birth, n (%)	73 (22)	138 (23)	64 (23)
Transgender female, n (%)	2 (<1)	4 (<1)	0
Race, n (%)			
Black or African American	57 (17)	92 (15)	56 (20)
White	239 (73)	472 (77)	203 (72)
Asian	17 (5)	24 (4)	15 (5)
Other	14 (4)	22 (4)	9 (3)
BMI (kg/m^2), median (IQR)	25.3 (22.7–28.6)	24.8 (22.5–27.7)	24.0 (21.8–27.1)
Weight (kg), median (IQR)	77.0 (68.0–87.0)	76.0 (67.0–85.4)	74.0 (64.5–83.7)
Pre-switch ART regimen, n (%)			
INI-based	136 (42)	424 (70)	283 (100)
NNRTI-based	151 (46)	156 (26)	N/A
PI-based	40 (12)	30 (5)	N/A
Pre-switch TAF, n (%)	99 (3)	113 (19)	3 (1)
Pre-switch TDF, n (%)	151 (46)	148 (24)	11 (4)
CD4 count at baseline (cells/mm^3), median (IQR)	643 (496–849)	572 (411–778)	453 (323–604)

*Participants in FLAIR were ART naive and underwent induction with ABC/DTG/3TC for 20 weeks. Baseline for FLAIR refers to induction phase baseline (Week –20), prior to participants receiving ABC/DTG/3TC for 20 weeks; participants in ATLAS-2M were ART experienced and virologically suppressed prior to entering the study.
†14 participants received DTG + two non-ABC nucleoside reverse transcriptase inhibitors due to HLA-B*5701 positivity or tolerability issues with ABC.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; INI, integrase inhibitor; IQR, interquartile range; ITT-E, intention-to-treat exposed; N/A, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- In participants receiving CAB + RPV LA, the median age was 39 years, 23% were female (sex at birth), and 16% were of Black or African American race (**Table 1**), comparable to participants receiving daily oral therapy.

Table 2. Pertinent Baseline Metabolic Parameters, Medical History, and Co-medications History

ITT-E population	Pooled Q8W arm (ATLAS-2M only) (n=327)	Pooled Q4W arm (FLAIR and ATLAS-2M) (n=610)	ABC/DTG/3TC (FLAIR only) (n=283)
BMI category, n (%)*			
Underweight (<18.5 kg/m^2)	4 (1)	11 (2)	10 (4)
Normal (18.5–<25 kg/m^2)	151 (46)	309 (51)	160 (57)
Overweight (≥25–<30 kg/m^2)	113 (35)	198 (32)	76 (27)
Obese (≥30 kg/m^2)	59 (18)	92 (15)	37 (13)
Baseline lipids, median (range)†			
TG (mmol/L)	1.23 (0.21–8.30)	1.14 (0.36–10.60)	1.12 (0.30–4.88)
TC (mmol/L)	4.75 (2.00–8.45)	4.60 (2.30–8.50)	4.40 (2.05–9.50)
LDL (mmol/L)	2.75 (0.98–5.77)	2.64 (0.67–5.60)	2.45 (0.60–5.86)
HDL (mmol/L)	1.30 (0.50–2.90)	1.25 (0.10–3.30)	1.25 (0.60–3.00)
TC/HDL ratio	3.45 (1.21–10.73)	3.48 (1.45–26.00)	3.50 (1.66–9.50)
Relevant medical history, n (%)*			
Hypertension	51 (16)	56 (9)	22 (8)
Diabetes	11 (3)	15 (2)	5 (2)
Relevant co-medications, n (%)†			
Anti-hypertensives	6 (12)	13 (13)	3 (13)
Anti-diabetes	8 (16)	11 (11)	4 (17)
Anti-lipids	31 (63)	53 (54)	8 (35)
SSRIs	9 (18)	30 (31)	8 (35)
Anti-psychotics	4 (8)	5 (5)	3 (13)

*Participants in FLAIR were ART naive and underwent induction with ABC/DTG/3TC for 20 weeks. Baseline BMI category and relevant medical history for FLAIR refers to induction phase baseline (Week –20), prior to participants receiving ABC/DTG/3TC for 20 weeks; participants in ATLAS-2M were ART experienced and virologically suppressed prior to entering the study.
†Baseline lipid and co-medication values for participants from FLAIR represent maintenance baseline, after the 20-week induction period on ABC/DTG/3TC. Participants in ATLAS-2M were ART experienced and virologically suppressed prior to entering the study.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; HDL, high-density lipoproteins; ITT-E, intention-to-treat exposed; LDL, low-density lipoproteins; Q4W, every 4 weeks; Q8W, every 8 weeks; SSRI, selective serotonin reuptake inhibitor; TC, total cholesterol; TG, triglycerides.

- Overall, 33% of participants receiving CAB + RPV LA were overweight and 16% were obese at baseline (**Table 2**); this was generally comparable between arms.
- Lipid-lowering agents and SSRIs were the most common reported co-medications across treatment arms at baseline.
  - SSRI use was higher in the daily oral therapy arm vs. the CAB + RPV LA arms (29% vs. 24%, respectively).

Figure 2. Change in Weight From Baseline*

Figure 2A. Median Weight Change (kg) by Regimen

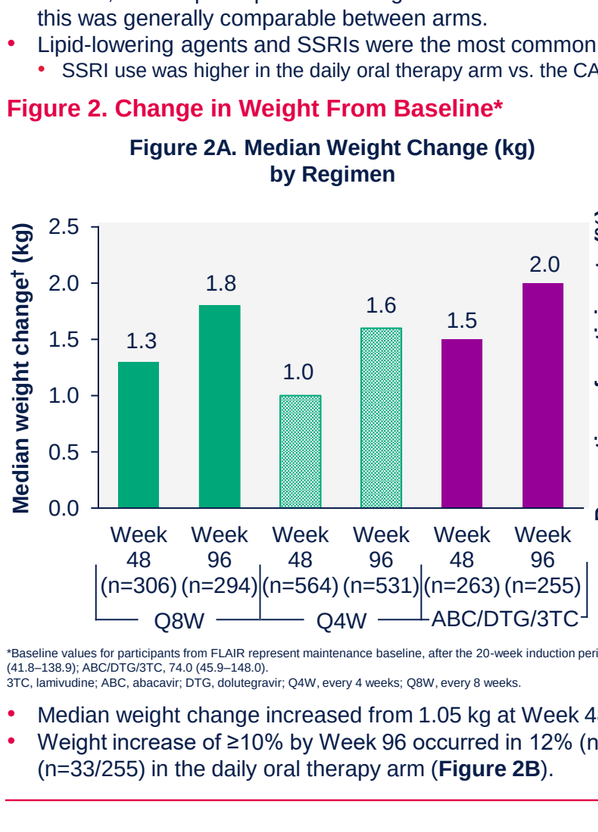
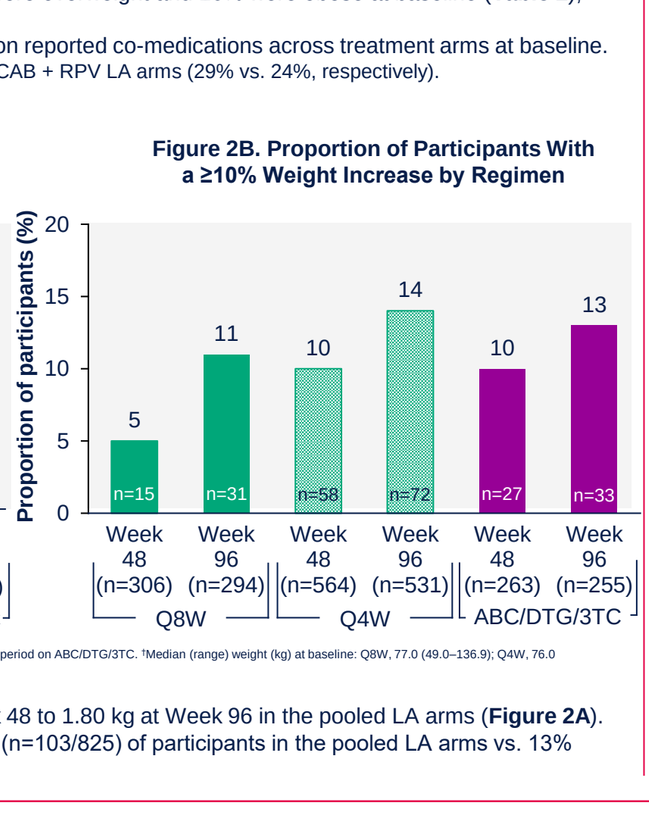


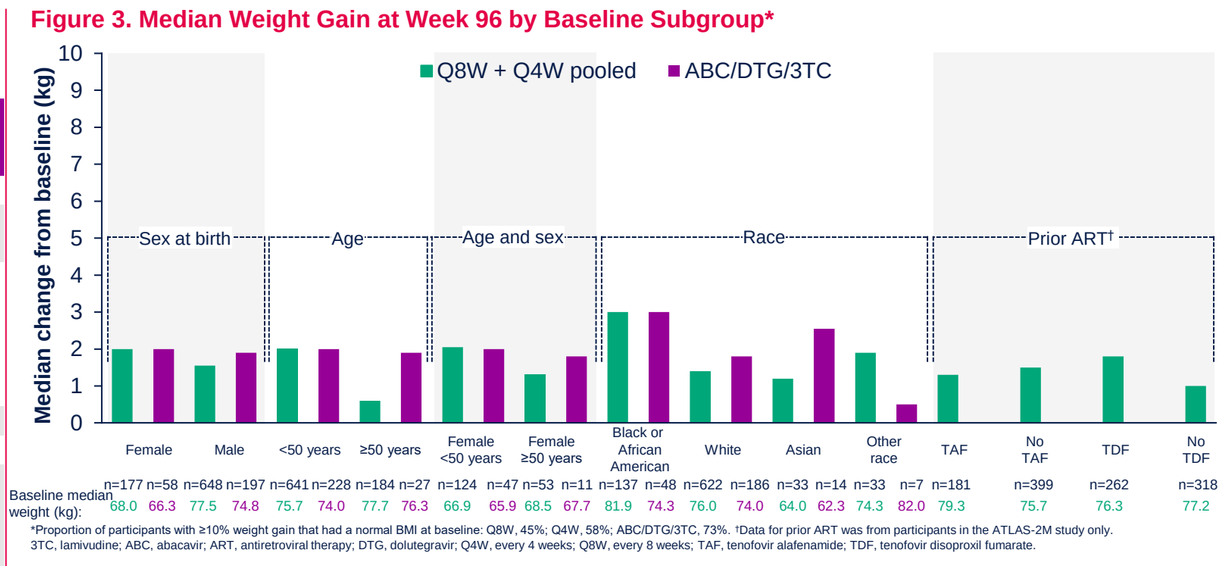
Figure 2B. Proportion of Participants With a ≥10% Weight Increase by Regimen



*Baseline values for participants from FLAIR represent maintenance baseline, after the 20-week induction period on ABC/DTG/3TC. †Median (range) weight (kg) at baseline: Q8W, 77.0 (49.0–136.9); Q4W, 76.0 (41.8–138.9); ABC/DTG/3TC, 74.0 (45.9–148.0).
3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Median weight change increased from 1.05 kg at Week 48 to 1.80 kg at Week 96 in the pooled LA arms (**Figure 2A**).
- Weight increase of ≥10% by Week 96 occurred in 12% (n=103/825) of participants in the pooled LA arms vs. 13% (n=33/255) in the daily oral therapy arm (**Figure 2B**).

Figure 3. Median Weight Gain at Week 96 by Baseline Subgroup*



*Proportion of participants with ≥10% weight gain that had a normal BMI at baseline: Q8W, 45%; Q4W, 58%; ABC/DTG/3TC, 73%. †Data for prior ART was from participants in the ATLAS-2M study only.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; DTG, dolutegravir; Q4W, every 4 weeks; Q8W, every 8 weeks; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- The median weight increased most for participants of Black or African American race in both the pooled LA and daily oral therapy arm, followed by females, participants <50 years, and female participants <50 years (**Figure 3**).

Figure 4. Change in BMI From Baseline

Figure 4A. Median BMI Change (kg/m^2) by Regimen Through Week 96

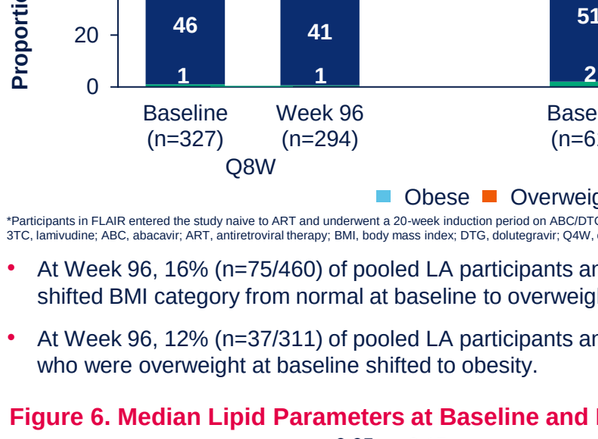
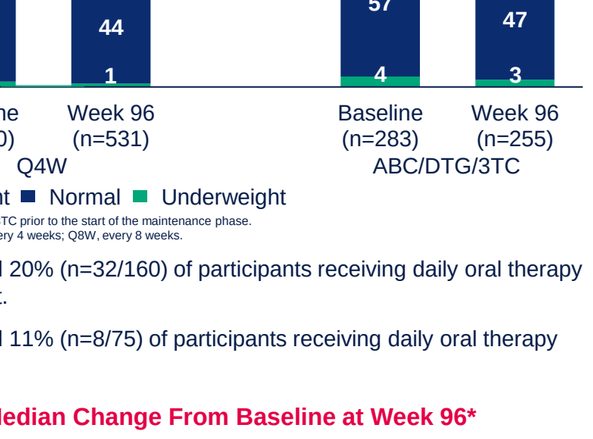


Figure 4B. Proportion of Participants‡ With an Upward BMI Shift Resulting in Obesity



*BMI (kg/m^2) range: Q8W W48, –4.8, 7.3; W96, –5.8, 7.5. Q4W W48, –9.9, 9.6; W96, –8.9, 10.3. ABC/DTG/3TC W48, –8.2, 9.7; W96, –5.9, 12.7. †Median (range) BMI (kg/m^2) at baseline: Q8W, 25.26 (17.8–46.0); Q4W, 24.81 (16.6–54.0); ABC/DTG/3TC, 24.00 (16.2–47.4). ‡Includes those classified as normal and overweight. Includes underweight participants had an upward shift resulting in obesity.
3TC, lamivudine; ABC, abacavir; BMI, body mass index; DTG, dolutegravir; Q4W, every 4 weeks; Q8W, every 8 weeks; W, week.

- Median change in BMI from baseline was 0.5 kg/m^2 vs. 0.6 kg/m^2 in the pooled LA arms vs. the daily oral therapy arm, respectively, through Week 96 (**Figure 4A**).
- At Week 96, 4% (n=40/937) of pooled LA participants and 4% (n=11/283) of participants receiving daily oral therapy had an upward shift in BMI category resulting in obesity (**Figure 4B**).

Figure 5. Changes in BMI Category Through Week 96*

*Participants in FLAIR entered the study naive to ART and underwent a 20-week induction period on ABC/DTG/3TC prior to the start of the maintenance phase.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; Q4W, every 4 weeks; Q8W, every 8 weeks.

- At Week 96, 16% (n=75/460) of pooled LA participants and 20% (n=32/160) of participants receiving daily oral therapy shifted BMI category from normal at baseline to overweight.
- At Week 96, 12% (n=37/311) of pooled LA participants and 11% (n=8/75) of participants receiving daily oral therapy who were overweight at baseline shifted to obesity.

Figure 6. Median Lipid Parameters at Baseline and Median Change From Baseline at Week 96*

*Proportion of participants reporting anti-lipids: Q8W, 63%; Q4W, 54%; ABC/DTG/3TC: 35%. SSRIs: Q8W, 18%; Q4W, 31%; ABC/DTG/3TC, 35%.
3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; HDL, high-density lipoproteins; LDL, low-density lipoproteins; Q4W, every 4 weeks; Q8W, every 8 weeks; SSRI, selective serotonin reuptake inhibitor; TC, total cholesterol; TG, triglycerides.

- Changes in laboratory values for total cholesterol, HDL cholesterol, LDL cholesterol, and TC/HDL ratio were similar between treatment groups, and not clinically relevant (**Figure 6**).

Conclusions

- Median weight changes were minor and comparable between CAB + RPV LA and daily oral therapy participants at Week 96.
- Weight increases of ≥10% and upward BMI shifts were uncommon, with no significant lipid changes observed.
  - The largest median weight gain was observed in participants of Black or African American race, consistent with previously published data,[1] followed by female participants, participants aged under 50 years, and female participants aged under 50 years.
- Across the CAB development program, weight data were collected as per routine clinical practice across study sites, warranting future exploration with comprehensive and standardized weight and metabolic data collection.
- CAB + RPV LA dosed Q8W and Q4W demonstrated an overall favorable weight and lipid profile through 96 weeks, supporting its use for maintenance HIV-1 treatment in adults with HIV.

Acknowledgments: The authors thank everyone who has contributed to the success of FLAIR and ATLAS-2M, all study participants and their families, and the clinical investigators and their staff. This analysis was funded by ViiV Healthcare.

Editorial assistance was provided by Poppie Cooper of Scimentum (Nucleus Global), with funding provided by ViiV Healthcare.

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