Indirect Comparison of 96-Week Efficacy and Safety of Cabotegravir + Rilpivirine Long-Acting Every 2 Months Versus Dolutegravir/Abacavir/Lamivudine in Suppressed HIV-1–Infected Participants

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Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) is the first complete long-acting (LA) regimen for the maintenance of HIV-1 virologic suppression.[1,2]
- Switching from daily oral antiretroviral therapy (ART) to CAB + RPV LA administered every month (Q1M) has demonstrated non-inferiority in maintaining HIV-1 viral suppression compared with continuing on dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) up to 96 weeks in the pivotal Phase 3 FLAIR study.[3]
- CAB + RPV LA treatment with less frequent dosing of every 2 months (Q2M) was non-inferior in maintaining viral suppression vs. Q1M dosing in the Phase 3b ATLAS-2M study over 96 weeks.[4,5]
- The objective of this analysis was to indirectly compare the efficacy and safety of CAB + RPV LA Q2M vs. DTG/ABC/3TC at 96 weeks.

Methods

- Outcomes for participants receiving CAB + RPV LA every 8 weeks (Q8W) in ATLAS-2M,[5] who switched from integrase inhibitors (INIs) without prior exposure to CAB, were indirectly compared with those who received DTG/ABC/3TC in FLAIR[3] via the common CAB + RPV LA every 4 weeks (Q4W) comparator arm (**Figure 1**).
  - FLAIR and ATLAS-2M were selected for inclusion as, at the time the analysis was conducted, they were the only 96-week Phase 3 studies using the Q4W and Q8W dosing regimens required for comparison.
- Participants included were limited to those with prior INI treatment, as it has been previously identified that initial INI regimens have demonstrated some differences in relative efficacy after switching compared with switching from protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[6,7]
- All indirect comparisons were conducted using the fixed-effect Bucher methodology due to the structure of the network, in accordance with the International Society for Pharmacoeconomics and Outcomes Research guidelines.[8]
- Risk ratios, odds ratios, and relative risks were calculated for each outcome.
- Injection site reactions (ISRs) were excluded from the safety analysis to ensure that the comparisons reflected the difference between the drug therapies vs. the mode of administration (injection vs. oral).

Figure 1. Network of Evidence Included in the Indirect Treatment Comparison (ITC)

*Participants switching from INI, but without prior CAB exposure.
CAB, cabotegravir; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; INI, integrase inhibitor; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- The characteristics of the included studies are shown in **Table 1**.

Table 1. Characteristics of the Phase 3, Multicenter, Open-Label FLAIR and ATLAS-2M Trials

Trial name	Dosing regimen and n	Population	Week 96 outcome (Snapshot)
FLAIR[3]	CAB + RPV LA Q4W (n=283) SoC (DTG/ABC/3TC*) (n=283)	ART naive; suppressed prior to randomization†	Switching to CAB + RPV LA Q4W was non-inferior to continuing DTG/ABC/3TC*
ATLAS-2M[5]	CAB + RPV LA Q4W (n=523) CAB + RPV LA Q8W (n=522)	ART experienced; suppressed prior to randomization	CAB + RPV LA Q8W was non-inferior to CAB + RPV LA Q4W

*If any participant had toxicity or intolerability associated with DTG/ABC/3TC, one switch to an approved alternative background NRTI was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative non-ABC NRTIs instead of DTG/ABC/3TC. †Participants were suppressed on study during a 20-week induction phase with DTG/ABC/3TC prior to randomization. ART, antiretroviral therapy; CAB, cabotegravir; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

Results

Endpoints

- Efficacy endpoints:
  - Virologic non-response defined as the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 96 per the FDA Snapshot algorithm.
  - Virologic suppression defined as the proportion of participants with HIV-1 RNA <50 copies/mL at Week 96 per the FDA Snapshot algorithm.
  - CD4+ cell count change from baseline to Week 96.
- Safety endpoints:
  - Discontinuation due to adverse events (AEs).
  - Overall AEs excluding ISRs.
  - Serious AEs excluding ISRs.
- Baseline characteristics were similar across the populations included in the ITC, as shown in **Table 2**.

Table 2. Baseline Characteristics of the Participants Included in the Analysis

	ATLAS-2M		FLAIR	
Outcome	CAB + RPV LA Q8W (n=136)*	CAB + RPV LA Q4W (n=141)*	CAB + RPV LA Q4W (n=283)	DTG/ABC/3TC (n=283)
Mean age, years	41.2	39.7	35.9	36.0
Male (sex at birth), n (%)	113 (83.1)	118 (83.7)	220 (77.7)	219 (77.4)
Race, n (%)				
White	99 (72.8)	113 (80.1)	216 (76.3)	201 (71.0)
Black or African American	21 (15.4)	19 (13.5)	47 (16.6)	56 (19.8)
Asian	10 (7.4)	7 (5.0)	12 (4.2)	15 (5.3)
Other	6 (4.4)	2 (1.4)	8 (2.8)	11 (3.9)
Ethnicity, n (%)				
Hispanic/Latinx	25 (18.4)	13 (9.2)	28 (9.9)	40 (14.1)
Baseline CD4+ cell count, cells/μL, mean (SD)	707.3 (284.8)	767.9 (294.3)	666.4 (272.1)	645.7 (253.4)

*Participants switching from INI, but without prior CAB exposure.
CAB, cabotegravir; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; INI, integrase inhibitor; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SD, standard deviation.

- Efficacy and safety data used for the ITC are presented in **Table 3**.

Table 3. Week 96 Efficacy and Safety Data of the Treatment Regimens From the Studies Included in the ITC

	ATLAS-2M		FLAIR	
Outcome	CAB + RPV LA Q8W (n=136)*	CAB + RPV LA Q4W (n=141)*	CAB + RPV LA Q4W (n=283)	DTG/ABC/3TC (n=283)
Snapshot outcomes				
HIV-1 RNA ≥50 copies/mL, n (%)	3 (2.2)	2 (1.4)	9 (3.2)	9 (3.2)
HIV-1 RNA <50 copies/mL, n (%)	120 (88.2)	117 (83.0)	245 (86.6)	253 (89.4)
No virologic data in Week 96 window, n (%)	13 (9.6)	22 (15.6)	29 (10.2)	21 (7.4)
Other efficacy outcomes				
CD4+ cell count change from baseline, cells/μL, mean (SD)	23.7 (170.6)	8.7 (196.2)	114.1 (205.2)	64.3 (180.3)
Safety outcomes				
Discontinuation due to AEs, n (%)	9 (6.6)	9 (6.4)	14 (4.9)	4 (1.4)
AEs (excluding ISRs), n (%)	120 (88.2)	134 (95.0)	264 (93.3)	242 (85.5)
Serious AEs (excluding ISRs), n (%)	12 (8.8)	6 (4.3)	24 (8.5)	22 (7.8)

*Participants switching from INI, but without prior CAB exposure.
AE, adverse event; CAB, cabotegravir; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; INI, integrase inhibitor; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SD, standard deviation.

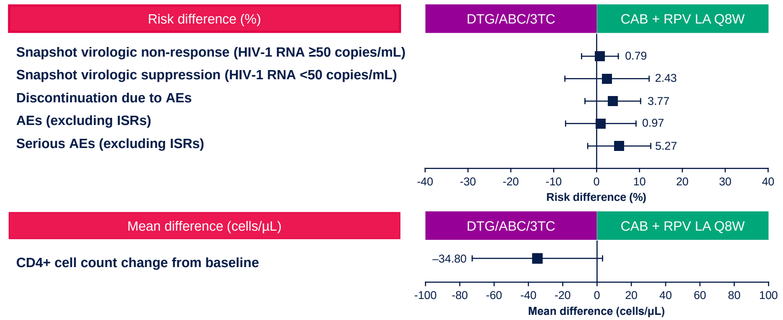
- No statistically significant differences were observed in any of the key efficacy or safety outcomes analyzed for CAB + RPV LA Q8W compared with DTG/ABC/3TC at Week 96 (**Table 4/Figure 2**).

Table 4. ITC Results: Efficacy and Safety of CAB + RPV LA Q8W Compared With DTG/ABC/3TC

	Comparative effect measure (95% CI) CAB + RPV LA Q8W vs. DTG/ABC/3TC at Week 96		
	Relative risk	Odds ratio	Risk difference, %
Virologic non-response (HIV-1 RNA ≥50 copies/mL)	1.56 (0.21, 11.41)	1.57 (0.20, 11.99)	0.79 (–3.49, 5.06)
Virologic suppression (HIV-1 RNA <50 copies/mL)	1.03 (0.92, 1.15)	1.18 (0.50, 2.76)	2.43 (–7.39, 12.25)
Discontinuation due to AEs	3.63 (0.88, 14.96)	3.77 (0.86, 16.49)	3.77 (–2.71, 10.25)
AE (excluding ISRs)	1.01 (0.92, 1.11)	0.92 (0.31, 2.73)	0.97 (–7.24, 9.19)
Serious AEs (excluding ISRs)	2.26 (0.75, 6.80)	2.39 (0.74, 7.76)	5.27 (–2.08, 12.63)
			Mean difference
CD4+ cell count change from baseline (cells/μL)			–34.80 (–72.80, 3.20)

AE, adverse event; CAB, cabotegravir; CI, confidence interval; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; ISR, injection site reaction; LA, long-acting; Q8W, every 8 weeks; RPV, rilpivirine.

Figure 2. Difference (95% CI) for CAB + RPV LA Q8W vs. DTG/ABC/3TC at Week 96



AE, adverse event; CAB, cabotegravir; CI, confidence interval; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; ISR, injection site reaction; LA, long-acting; Q8W, every 8 weeks; RPV, rilpivirine.

Conclusions

- These ITC results suggest that the selected efficacy and safety outcomes of switching from DTG/ABC/3TC to CAB + RPV LA Q2M are statistically not different from continuing DTG/ABC/3TC treatment.
- Results from the ITC support the therapeutic value of CAB + RPV LA dosed Q2M for virologically suppressed people living with HIV-1 who seek an alternative treatment option to daily oral ART.

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