Indirect Treatment Comparison of 48-Week Efficacy and Safety of Cabotegravir + Rilpivirine Long-Acting Every 2 Months to Bictegravir/Emtricitabine/Tenofovir Alafenamide in Suppressed HIV-1–Infected Participants

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Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) is the first complete long-acting (LA) regimen recommended by treatment guidelines[1] for the maintenance of HIV-1 virologic suppression.
- Switching from daily oral antiretroviral therapy (ART) to CAB + RPV LA administered every month (Q1M) has demonstrated noninferiority in viral suppression vs. a range of daily oral standard of care (SoC) antiretroviral regimens, including tenofovir alafenamide–based regimens, in two pivotal Phase 3 clinical trials (ATLAS[2] [NCT02951052] and FLAIR[3] [NCT02938520]).
- CAB + RPV LA treatment with less frequent dosing of every 2 months (Q2M) was noninferior in maintaining viral suppression vs. Q1M dosing in the Phase 3b ATLAS-2M study (NCT03299049).[4]
- Bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) was not available at the time of study initiation and therefore was not included in the SoC arms of ATLAS and FLAIR.
- The objective of this analysis was to indirectly compare the efficacy and safety of CAB + RPV LA Q2M vs. BIC/FTC/TAF after 48 weeks of treatment.

Methods

Systematic Literature Review (SLR)

- A previously published SLR, based on searches in PubMed, Embase, and Cochrane databases,[5] was used to identify published randomized controlled trials evaluating the efficacy and/or safety of treatment regimens examined in virologically suppressed HIV-infected participants switching treatment.
- Two studies meeting these criteria were identified as appropriate to facilitate indirect comparison to BIC/FTC/TAF (GS-US-380-1844[6] and GS-US-380-4030[7]).

Indirect Treatment Comparison (ITC) Methods

- Outcomes for participants receiving CAB + RPV LA every 8 weeks (Q8W) in ATLAS-2M with prior integrase inhibitor (INI) exposure, but without prior exposure to CAB, were indirectly compared with those with prior INI exposure in ATLAS and FLAIR via the common CAB + RPV LA every 4 weeks (Q4W) comparator arm. This result was then indirectly compared with BIC/FTC/TAF users in the GS-US-380-1844[6] and GS-US-380-4030[7] studies via the INI comparator (**Figure 1**).
- Participants included were limited to prior INI users, 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).[8,9]
- 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 (ISPOR) guidelines.[10]
- Risk ratios, odds ratios, and relative risks were calculated for each efficacy outcome.
- Injection site reactions (ISRs) were excluded from the safety analysis to ensure that the comparisons reflect the differences between the drug therapies vs. the mode of administration (injection vs. oral).

Endpoints

- Efficacy endpoints:
  - Virologic non-response defined as the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48 per the FDA Snapshot algorithm.
  - Virologic suppression defined as the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 per the FDA Snapshot algorithm.
  - CD4+ cell count change from baseline to Week 48.
- Safety endpoints:
  - Discontinuation due to adverse events (AEs).
  - Overall AEs excluding ISRs.
  - Serious AEs excluding ISRs.

Figure 1. Network of Evidence Included in the ITC

*Participants switching from INI, but without prior CAB exposure.

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

Table 1. Study Characteristics of the Included Trials

Trial Name/ID	Dosing Regimen and n	Population	Primary Outcome (Snapshot at Week 48)
ATLAS[2]	CAB + RPV LA Q4W (n=308) SoC (any)* (n=308)	ART experienced; suppressed prior to randomization	Switching to CAB + RPV LA Q4W was noninferior to continuing SoC
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 noninferior to continuing DTG/ABC/3TC†
ATLAS-2M[4]	CAB + RPV LA Q4W (n=523) CAB + RPV LA Q8W (n=522)	ART experienced; suppressed prior to randomization	CAB + RPV LA Q8W was noninferior to CAB + RPV LA Q4W
GS-US-380-1844[6]	BIC/FTC/TAF (n=282) DTG/ABC/3TC (n=281)	ART experienced; suppressed prior to randomization	BIC/FTC/TAF was noninferior to continuing DTG/ABC/3TC
GS-US-380-4030[7]	BIC/FTC/TAF (n=284) DTG + FTC/TAF (n=281)	ART experienced; suppressed prior to randomization	BIC/FTC/TAF was noninferior to continuing DTG + FTC/TAF

*Acceptable regimens included two NRTIs plus one of: an INI, an NNRTI, a boosted PI, or unboosted atazanavir.
†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.
3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor.

Results

- Baseline characteristics across these studies were similar, as shown in **Table 2**.
- Efficacy and safety data used for the ITC are presented in **Table 3**.

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

	ATLAS-2M		ATLAS/FLAIR		GS-US-380-1844/ GS-US-380-4030	
Outcome	CAB + RPV LA Q8W (n=136)*†	CAB + RPV LA Q4W (n=141)*†	CAB + RPV LA Q4W pooled (n=385)*†	INI-based pooled (n=382)†	Pooled DTG-based regimen (n=562)†	Pooled BIC/FTC/TAF (n=566)†
Mean age, years	41.2	39.7	37.2	37.4	47.0	38.0
Male (sex at birth), n (%)	113 (83.1)	118 (83.7)	304 (79.0)	299 (78.3)	492 (87.5)	492 (86.9)
Race, n (%)						
White	99 (72.8)	113 (80.1)	295 (76.6)	274 (71.7)	401 (71.4)	406 (71.7)
Black or African American	21 (15.4)	19 (13.5)	58 (15.1)	73 (19.1)	123 (21.9)	127 (22.4)
Asian	10 (7.4)	7 (5.0)	22 (5.7)	21 (5.5)	12 (2.1)	12 (2.1)
Other	6 (4.4)	2 (1.4)	10 (2.6)	14 (3.7)	26 (4.6)	21 (3.7)
Ethnicity, n (%)						
Hispanic/Latinx	25 (18.4)	13 (9.2)	43 (11.2)	54 (14.1)	101 (18.0)	107 (18.9)
Baseline CD4+ cell count, cells/μL, mean (SD)‡	707.3 (284.8)	767.9 (294.3)	683.7 (396.7)	670.2 (401.3)	1352.3 (414.6)	1463.1 (432.3)

*Participants with prior CAB exposure were excluded. †Included only participants who were receiving INI at study baseline. ‡ATLAS/FLAIR and GS-US-380-1844/GS-US-380-4030 CD4+ cell count SDs are pooled. SD, standard deviation.

Table 3. Week 48 Efficacy and Safety Data of the Treatment Regimens From the Studies Included in the ITC

	ATLAS-2M		ATLAS/FLAIR		GS-US-380-1844/ GS-US-380-4030	
Outcome	CAB + RPV LA Q8W (n=136)*†	CAB + RPV LA Q4W (n=141)*†	CAB + RPV LA Q4W pooled (n=385)*†	INI-based pooled (n=382)†	Pooled DTG-based regimen (n=562)†	Pooled BIC/FTC/TAF (n=566)†
Snapshot outcomes						
HIV-1 RNA ≥50 copies/mL, n (%)	3 (2.2)	2 (1.4)	6 (1.6)	9 (2.4)	4 (0.7)	4 (0.7)
HIV-1 RNA <50 copies/mL, n (%)	127 (93.4)	126 (89.4)	361 (93.8)	359 (94.0)	523 (93.1)	529 (93.5)
Other efficacy outcomes						
Mean CD4+ cell count change from baseline (SD), cells/μL	4.5 (154.7)	–30.6 (183.2)	24.1 (275.5)	65.7 (272.7)	20.0 (244.5)	–6.4 (254.9)
Safety outcomes						
Discontinued due to AEs, n (%)	4 (2.9)	7 (5.0)	15 (3.9)	4 (1.0)	8 (1.4)	12 (2.1)
AEs (excluding ISRs), n (%)	112 (82.4)	125 (88.7)	330 (85.7)	293 (76.7)	468 (83.3)	461 (81.4)
Serious AEs (excluding ISRs), n (%)	10 (7.4)	3 (2.1)	21 (5.5)	16 (4.2)	41 (7.3)	45 (8.0)

*Participants with prior CAB exposure were excluded. †Included only participants who were receiving INI at study baseline.

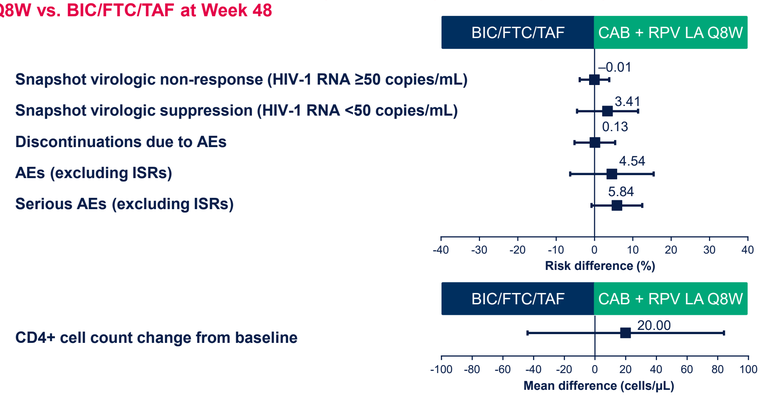
- No significant differences were observed in any of the key efficacy or safety outcomes analyzed for CAB + RPV LA Q8W compared with BIC/FTC/TAF at Week 48 (**Table 4/Figure 2**).

Table 4. ITC Results: Efficacy and Safety of CAB + RPV LA Q8W Compared With BIC/FTC/TAF

	Comparative Effect Measure (95% CI) CAB + RPV LA Q8W vs. BIC/FTC/TAF at Week 48		
	Relative risk	Odds ratio	Risk difference, %
Virologic non-response (HIV-1 RNA ≥50 copies/mL)	1.04 (0.09, 12.25)	1.04 (0.08, 12.70)	–0.01 (–3.84, 3.83)
Virologic suppression (HIV-1 RNA <50 copies/mL)	1.04 (0.95, 1.13)	1.52 (0.48, 4.77)	3.41 (–4.56, 11.37)
Discontinuations due to AEs	1.48 (0.23, 9.45)	1.48 (0.22, 9.93)	0.13 (–5.17, 5.43)
AEs (excluding ISRs)	1.06 (0.93, 1.21)	1.24 (0.54, 2.84)	4.54 (–6.34, 15.42)
Serious AEs (excluding ISRs)	4.13 (0.94, 18.06)	4.39 (0.94, 20.40)	5.84 (–0.77, 12.45)
			Mean difference
CD4+ cell count change from baseline (cells/μL)			20.00 (–43.98, 83.99)

CI, confidence interval.

Figure 2. Risk (Upper Panel) and Mean (Lower Panel) Difference (95% CI) for CAB + RPV LA Q8W vs. BIC/FTC/TAF at Week 48



Conclusions

- These ITC results indicate that the efficacy and safety of switching to CAB + RPV LA Q2M is statistically not different from BIC/FTC/TAF.
- 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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