Use of *Cabenuva*, Administered Every Two Months, for HIV-1 Infection

Summary

- Across multiple studies, Cabenuva (long-acting cabotegravir plus rilpivirine [CAB + RPV LA]) every-2-months (Q2M) has demonstrated non-inferior efficacy (based on primary endpoint) in maintaining virologic suppression:
  - SOLAR, compared with bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) at Month 12[1]
    - HIV-1 RNA ≥ 50 copies/mL: 1% vs < 1% (adjusted treatment different [95% CI] 0.7% [-0.7% to 2.0%])[1]
  - CARES, compared with oral antiretroviral therapy (ART) at Week 48[2]
    - HIV-1 RNA < 50 copies/mL: 97% vs 98% (adjusted treatment difference [95% CI] -0.8% [-3.4% to 1.8%])[2]
  - ATLAS-2M, compared with CAB + RPV LA administered every-4-weeks at Weeks 48 and 152
    - HIV-1 RNA ≥ 50 copies/mL: 1.7% vs 1% (Week 48)[3]; 3% vs 1% (Week 152)[4]
- Confirmed virologic failures (CVFs) were infrequent across the studies (Q2M vs comparator):[1-5]
  - SOLAR: 0.4% (n = 2) vs 0 at Month 12[1]
  - CARES: 0.4% (n = 1) vs 0 at Week 48[2]
  - ATLAS-2M: 2% (n = 12) vs 1% (n = 2) at Week 152[4]
- Injection site reactions (ISRs) were the most common adverse event reported, most of which were mild-moderate in severity.[1-5]
- Important Safety Information can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

SOLAR

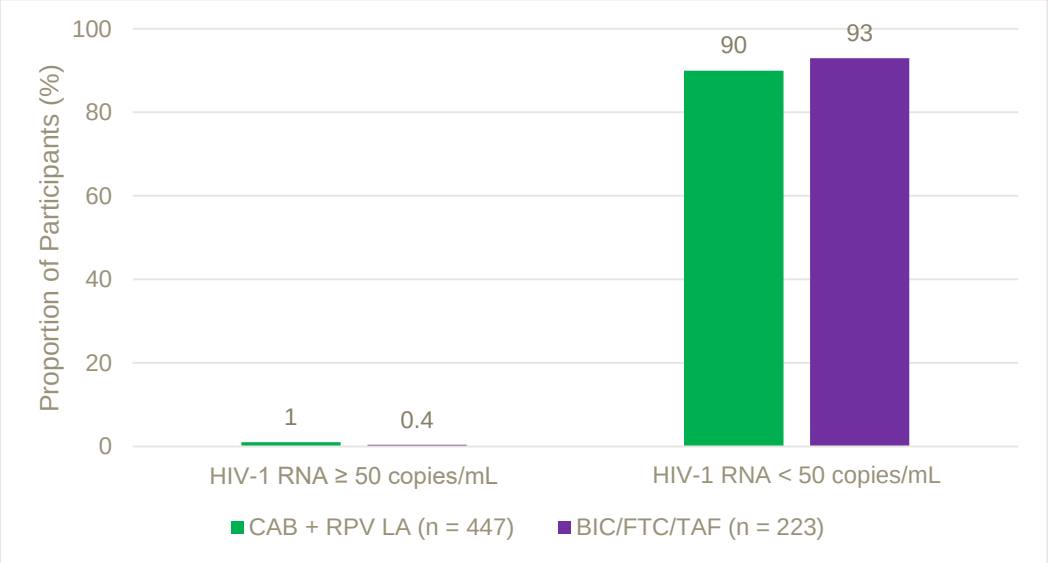
SOLAR (Study 213500) was a Phase 3b, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of CAB + RPV LA administered Q2M compared with oral BIC/FTC/TAF.[1] Adult HIV-1 infected participants must have been on an uninterrupted stable regimen of BIC/FTC/TAF with an undetectable HIV-1 viral load for ≥ 6 months prior to and at screening. Patients were randomized 2:1 to either switch to CAB + RPV LA or continue BIC/FTC/TAF. The use of oral lead-in (OLI) was optional for participants randomized to the CAB + RPV LA arm; the decision to use the OLI was determined by the study participant following informed consent discussions with the investigator. For further information on the SOLAR study, please click here.

Overall, 447 participants were randomized to the CAB + RPV LA arm and 223 participants to the BIC/FTC/TAF arm.[1] Median age in both arms was 37 years and median body mass index (BMI) was 26

kg/m² in the CAB + RPV LA arm and 25.4 kg/m² in the BIC/FTC/TAF arm; most participants were male (CAB + RPV LA, 83%; BIC/FTC/TAF, 82%) and White (69% and 70%).

At Month 12, non-inferior efficacy of CAB + RPV LA vs BIC/FTC/TAF was demonstrated for the proportion of participants with HIV-1 RNA ≥ 50 copies/mL (adjusted treatment different [95% CI] 0.7% [-0.7% to 2.0%]).[1] The upper bound of 95% CI for the adjusted treatment difference between CAB + RPV LA Q2M and BIC/FTC/TAF was less than the pre-defined non-inferiority margin of 4%. Additionally, the proportion of participants with HIV-1 RNA < 50 copies/mL was similar between groups (adjusted treatment different [95% CI] -2.7% [-7.0% to 1.7%]). See Figure 1 for additional details. Among participants with no virologic data, the incidence of AEs leading to withdrawal was low, and discontinuations for other reasons were similar between the CAB + RPV LA and BIC/FTC/TAF groups.

Figure 1. SOLAR Virologic Outcomes at Month 12 (mITT-E Population)[1]



CVF was defined by two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL.[1] Through Month 12 in the mITT-E Population, 2 (0.4%) participants receiving CAB + RPV LA in the mITT-E population met the CVF criterion; no participants in the BIC/FTC/TAF arm met the CVF criterion. One additional participant receiving CAB + RPV LA in the ITT-E population met CVF criterion through Month 12.

Excluding ISRs, adverse events and serious adverse events were similar between groups; however, non-ISR drug-related adverse events were reported more frequently in the CAB + RPV LA arm (90 [20%] participants) compared with the BIC/FTC/TAF arm (2 [< 1%] participants).[1]

CARES

CARES is a randomized, open-label, multicenter, Phase 3b, non-inferiority study of virologically-suppressed adults to compare switching to CAB + RPV LA with continuing on first-line ART in sub-Saharan Africa.[2] Patients were randomized (1:1) to receive either every-8-week CAB + RPV LA (with optional OLI) or oral ART (tenofovir disoproxil fumarate [TDF] plus FTC or lamivudine, plus either dolutegravir [DTG], efavirenz, or nevirapine). Eligible patients must have been on stable oral ART, with no history of treatment failure, no history of hepatitis B virus infection, and HIV-1 RNA < 50 copies/mL for at least 4–12 months prior to and at screening. Viral load and safety monitoring was performed every 6 months from randomization. Study sites were located in Uganda, Kenya, and South Africa.

The primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL, based on the ITT population, at Week 48 (10% non-inferiority margin).[2] Other endpoints assessed included the

proportion of participants with virologic suppression (HIV-1 RNA ≥ 50 copies/mL, 4% non-inferiority margin), incidence of CVF (defined as 2 consecutive HIV-1 RNA ≥ 200 copies/mL, 4–6 weeks apart), and safety.

A total of 512 participants were randomized, 255 to the CAB + RPV LA arm and 257 to the oral ART arm.[2] See Table 1 for additional details on select baseline characteristics. Most patients had prior non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure.

Table 1. Select Baseline Characteristics[2]

	CAB + RPV LA (n = 255)	Oral ART (n = 257)
Female sex, n (%)	146 (57)	149 (58)
Age, median (IQR), years	43 (36–51)	42 (35–49)
BMI ≥ 30 kg/m^2, n (%)	57 (22)	51 (20)
Black race, n (%)	254 (> 99)	256 (> 99)
Prior exposure to NNRTI, n (%)	189 (74)	191 (74)
INSTI at screening	231 (91)	240 (93)
NNRTI at screening	24 (9)	17 (7)
Archived DNA analysis*		
Subtype A1, n/n (%)	119/213 (56)	115/201 (57)
RPV resistance mutations, n/n (%)	25/200 (13)	26/177 (15)
RPV intermediate/high-level resistance, n/n (%)	17/200 (9)	21/177 (12)
CAB resistance mutations, n/n (%)	15/95 (16)	14/85 (17)
CAB intermediate/high-level resistance, n/n (%)	10/95 (11)	5/85 (6)

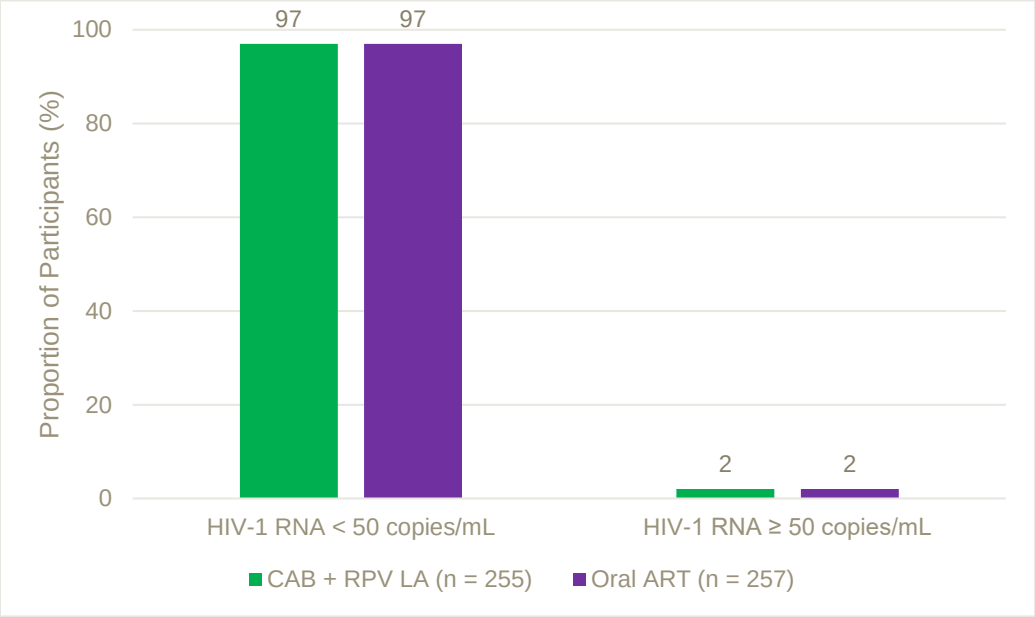
*Archived DNA analysis performed retrospectively from baseline samples; resistance level determined using Stanford algorithm

ART = antiretroviral therapy; BMI = body mass index; CAB + RPV LA = long-acting cabotegravir plus rilpivirine; INSTI = integrase strand-transfer inhibitor; IQR = interquartile range; NNRTI = non-nucleoside reverse transcriptase inhibitor

Overall, 96% of injection visits were on-time; 83% of participants received all scheduled injections within a 7-day window.[2]

Non-inferiority of CAB + RPV LA to oral ART was met in the ITT population (adjusted treatment difference [95% CI] -0.5% [-3.4% to 2.4%]).[2] See Figure 2 for additional details.

Figure 2. CARES Virologic Outcomes at Week 48 (ITT Population)[2]



CVF occurred in one participant in the CAB + RPV LA arm (0.4%) compared with none in the oral ART arm.[2] One additional patient in the CAB + RPV LA arm had virological failure, but this was unconfirmed as the participant died prior to retesting. See Table 2 for additional details.

Table 2. Participants with Virologic Failure[2]

	Participant with confirmed virologic failure	Participant with unconfirmed virologic failure
HIV-1 RNA at Week 48, copies/mL	4608	44,984
Delayed injections	No	No
Sex	Female	Female
Baseline BMI, kg/m^2	25.9	22
HIV-1 subtype	A1	D
Resistance mutations* (level of resistance**)		
Baseline†	none	K103N/S, E138A (RPV low)
Failure		
NNRTI	V108I, E138K, V179L (RPV high)	K103N/S, V106V/A, E138A (RPV low)
INSTI	E92E/V, N155H, L74M (CAB intermediate, DTG none)	G118R (CAB high, DTG intermediate)
Outcome	Re-suppressed on TDF/3TC/DTG once daily	Died before retest (HIV-unrelated cause)

*NNRTI or INSTI mutations

**Resistance level determined using Stanford algorithm

†Retrospective testing on archived viral DNA

3TC = lamivudine; BMI = body mass index; CAB = cabotegravir; DTG = dolutegravir; INSTI = integrase strand-transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

Any adverse event was reported in 86% (220/255) and 63% (161/257) of participants in the CAB + RPV LA and oral ART arms, respectively.[2] Excluding ISRs, adverse events occurred in 71% and 63% of participants, respectively; 1 participant in the CAB + RPV LA arm and 3 in the oral ART arm discontinued due to an adverse event. Grade 3 adverse events occurred in 9% and 4% of participants, respectively; 1% were deemed as drug-related in each arm (CAB + RPV LA: injection-site nodule, increased LDL cholesterol, proteinuria; oral ART: decreased estimated glomerular filtration rate, increased blood glucose).

Most ISRs were grade 1 (63%) or grade 2 (10%) in severity; 1 grade 3 ISR was reported (injection-site sterile abscess leading to treatment discontinuation).[2] The most common ISRs were pain (72%), swelling (8%), and nodule (5%).

ATLAS-2M

ATLAS-2M was a phase 3b, randomized, multicenter, open-label, parallel-group, non-inferiority study which evaluated the efficacy, safety, and tolerability of CAB + RPV LA administered every-8-weeks compared with every-4-weeks in HIV-1-infected adults who were virologically suppressed.[3]

Overall, 1045 participants were enrolled in the study; 522 participants in the every-8-week arm and 523 in the every-4-week arm.[3] Median age was 42 years, most participants were male (74% in the every-8-week arm vs 73% in the every-4-wek arm) and White (71% vs 75%). Median BMI in both arms was 26 kg/m^2. In either group, 63% had no prior exposure to CAB + RPV LA, 13% had 1–24 weeks of exposure, and 24% had > 24 weeks of exposure. Most patients had an prior INSTI (64% [every-8-week] vs 65% [every-4-week]) or NNRTI (70% vs 73%) exposure.

Week 48 Results

Efficacy

Through Week 48, CAB + RPV LA administered every-8-weeks was found to be non-inferior to CAB + RPV LA administered every-4-weeks.[3] The proportion of participants with HIV-1 RNA ≥ 50 copies/mL was 1.7% (9/522) in the every-8-week arm compared with 1% (5/523) in the every-4-week arm (adjusted treatment difference [95% CI] 0.8% [-0.6% to 2.2%]). Similar results were seen for the proportion of participants with HIV-1 RNA < 50 copies/mL (94.3% [492/522] vs 93.5% [489/523]; adjusted treatment difference [95% CI] 0.8% [-2.1% to 3.7%]).

Confirmed Virologic Failures

CVF, defined as having 2 consecutive HIV-1 RNA ≥ 200 copies/mL after prior suppression to < 200 copies/mL, occurred in 8 (1.5%) participants in the every-8-week arm and 2 (0.4%) participants in the every-4-week arm.[3] Of the 10, 9 participants re-suppressed on an oral antiretroviral regimen chosen by the investigator. The patient who did not re-suppress was non-adherent to a protease inhibitor-based regimen. Virus from all CVFs retained phenotypic susceptibility to dolutegravir.

For further information on CVFs and development of resistance, please click here.

Safety

Excluding ISRs, 77% and 84% of participants in the every-8-week arm and the every-4-week arm, respectively, experienced at least 1 adverse event.[3] Serious adverse events were reported in 5% and 4% of participants, respectively; discontinuations due to drug-related adverse events were low (2% in each arm). In each arm, 83% of adverse events were categorized as grades 1 or 2.

Proportion of participants who experienced an ISR was 76% in the every-8-week group and 75% in the every-4-week group.[3] The majority of ISRs in both groups were grade 1 or 2 in severity (98%); the median

duration of ISRs was 3 days in both groups, with 86% resolving within 7 days. ISRs were mostly reported at treatment initiation and reports of ISRs tended to decrease over time.

For further information on ISRs in the ATLAS-2M study, please click here.

Week 152 Results

Efficacy

Through Week 152, the proportion of participants with HIV-1 RNA ≥ 50 copies/mL in the every-8-week and every-4-week arms was 3% (14/522) and 1% (5/523), respectively (adjusted treatment difference [95% CI] 1.7% [0.1%–3.3%]).[4] Proportion of participants with HIV-1 RNA < 50 copies/mL continued to be similar between the two groups (87% [456/522] vs 86% [449/523]; adjusted treatment difference [95% CI] 1.5 [-2.6 to 5.6]).

Confirmed Virologic Failures

Through Week 152, 14 participants (every-8-week arm, 12 [2%]; every-4-week arm, 2 [< 1%]) had CVF. Of the 14 CVFs, 13 re-suppressed on alternative ART (one participant was non-adherent to protease inhibitor-based ART).[4] Two participants, both in the every-8-week arm, met the CVF criterion between Week 96 and 152.

For further information on CVFs and development of resistance, please click here.

Safety

Drug-related adverse events occurred in 82% of participants in each arm through Week 152.[4] Non-ISR drug-related adverse events were reported in 27% and 32%, respectively. Drug-related adverse events leading to participant withdrawal occurred in 2% in the every-8-week arm and 3% in the every-4-week arm. Most adverse events were grade 1 or 2 in severity (84%).

Through Week 152, ISRs were mild to moderate in severity (99%); there were no Grade 4/5 ISRs.[4] Four participants withdrew due to injection-related reasons between Week 96 and Week 152, due to injection intolerability. Reports of ISRs decreased over 48 weeks and remained consistent through Week 152.

CARISEL STUDY: AN IMPLEMENTATION STUDY IN EUROPEAN SETTINGS

CARISEL was a Phase 3b, multicenter, open-label, hybrid type III implementation-effectiveness trial that included 430 virologically suppressed participants who switched from daily oral therapy to CAB + RPV LA dosed Q2M.[5] At Month 12, 87% (373/430 [95% CI 83.2–89.8]) of participants remained virologically suppressed (HIV-1 RNA < 50 copies/mL, FDA Snapshot algorithm, ITT-E); 0.7% (3/430 [95% CI 0.1–2.0]) had an HIV-1 RNA ≥ 50 copies/mL. These clinical outcomes were consistent regardless of implementation support and clinical infrastructure at the HCP clinics/practices.[6]

One patient (0.23%) met CVF criterion (two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL) at Month 10 with a viral load of 1861 copies/mL.[5] RPV resistance-associated mutation (RAMs) were present at failure (E138A + M230L); no INSTI RAMs were detected. E138A was detected at baseline retrospectively at the time of failure. One other patient had suspected virologic failure (SVF) (HIV-1 RNA ≥ 200 copies/mL) at Month 4 and resuppressed upon retest, followed by a second SVF event at the last visit prior to withdrawal. RPV RAM E138K and INSTI RAMs N155N/S were detected at the first SVF. No baseline resistance was detected retrospectively at the time of failure.

Adverse events were similar to what have been reported with CAB + RPV LA in other Phase 3 clinical studies.[5]

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

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