Virologic Failure and Treatment-Emergent Resistance in Patients Treated with Long-Acting Cabotegravir Plus Rilpivirine

Summary

- Treatment-emergent genotypic resistance with reduced phenotypic susceptibility to cabotegravir and/or rilpivirine has been reported infrequently in clinical trials evaluating oral and long-acting cabotegravir plus rilpivirine (*Cabenuva*, CAB + RPV LA).
- Important Safety Information and Boxed Warning can be found in the Prescribing Information and can also be accessed from the Our HIV Medicines section of viivhealthcare.com/us

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LATTE

Study Design

In LATTE, antiretroviral naïve patients were randomized to 1 of 3 doses of oral CAB (10 mg, 30 mg, or 60 mg) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 24 weeks followed by maintenance therapy with oral CAB plus RPV.[1] After Week 96, all patients who remained in the open label phase were switched to CAB 30 mg plus RPV for the remainder of their time on study.

Patients were excluded from LATTE if they had any major antiretroviral resistance-associated mutations detected at screening or if known from any historical resistance tests.[1]

For more information on the study design of LATTE please click here.

Protocol-Defined Virologic Failure (PDVF)

Suspected protocol-defined virologic failures were confirmed with a first and a repeat plasma HIV-1 RNA measurement 2–4 weeks apart.[1] A **virologic non-response** was defined as a reduction of <1 $\log_{10}$ copies/mL in plasma HIV-1 RNA by week 4, or two consecutive plasma HIV-1 RNA levels of 200 copies/mL after week 16. **Virologic rebound** was indicated by ≥200 copies/mL of HIV-1 RNA after previous suppression to <200 copies per mL, or two consecutive plasma HIV-1 RNA measurements that showed an increase of greater than 0·5 $\log_{10}$ copies/mL in plasma HIV-1 RNA from the nadir value on study, with the lowest HIV-1 RNA value of ≥200 copies/mL.

A total of 8 patients met the criteria of PDVF through Week 312 (see Table 1 below).[2] Six of these patients were PDVF through Week 144 and 2 occurred from Week 144 through Week 312.

Of the 8 patients, 3 had treatment-emergent INSTI resistance associated mutations detected and 5 had treatment-emergent NNRTI resistance associated mutations.[2] See Table 1 below.

Table 1. Patients from LATTE Who Were PDVF through Week 312[2]

Subject ID	CAB Arm	Week of PDVF	INSTI RAMs	CAB Fold Change	NNRTI RAMs	RPV Fold Change
16	10 mg	48	Q148R	3.08	E138Q	1.83
462	10 mg	180	G140A, Q148R, E138K	116	K101E	21
206	10 mg	132	None	N/A	K101E, M230M/L	12
413	10 mg	60	None	N/A	K101K/E, E138E/A	4.6
601	30 mg	36	Assay Failed	N/A	None	N/A
393	10 mg	108	None	N/A	None	N/A
111	30 mg	132	None	N/A	None	N/A
472	60 mg	264	G140S, Q148R	9.84	K101K/E, E138E/K	1.77

CAB = cabotegravir; INSTI = integrase strand-transfer inhibitor; RAMs = treatment-emergent resistance-associated mutations; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; NR = not reported; N/A = not applicable

LATTE-2

Study Design

Patients were excluded from LATTE-2 if they had any major antiretroviral resistance-associated mutations detected at screening or if known from any historical resistance tests.[3]

For more information on the study design of LATTE-2 please click here.

Protocol-Defined Virologic Failure (PDVF)

PDVF was defined as having 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL.[3]

Through Week 160, there were 2 PDVFs; both in the CAB + RPV LA every 8 weeks arm.[4] In 1 of these patients, reduced susceptibility to CAB and RPV was reported.[3] This patient had a HIV-1 RNA of 463 copies/mL at Week 48 that was confirmed (205 copies/mL) 7 days later.[5] At PDVF, virus from this patient had treatment-emergent NNRTI resistance mutations (K103N, E138G, and K238T) and displayed phenotypic resistance to RPV (fold-change [FC]=3.34), delavirdine (FC=max), efavirenz (FC=48), and nevirapine (FC=max). This virus also had the treatment-emergent INSTI resistance mutation Q148R accompanied by phenotypic resistance to CAB (FC=5.06), raltegravir (FC=29), and elvitegravir (FC=138). The virus remained susceptible to etravirine (FC=1.91) and dolutegravir (FC=1.38).

ATLAS AND FLAIR

Study Design

Patients with HIV-1 RNA <50 copies/mL were randomized to receive either long-acting cabotegravir plus rilpivirine (CAB + RPV LA) or continue their current antiretroviral regimen (CAR).[6]

Patients were excluded from ATLAS and FLAIR if they had any evidence of primary resistance based on the presence of any major known integrase strand-transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutation, except for K103N by any historical resistance test result.[7,8]

For additional information on the study design of ATLAS and FLAIR please click here.

Confirmed Virologic Failures

Confirmed virologic failure (CVF), defined as having 2 consecutive HIV-1 RNA ≥200 copies/mL after prior suppression to <200 copies/mL, occurred in 6 patients in the CAB + RPV LA arm (see Table 2) and in 7 in the CAR arm (Table 3).[7-9]

Table 2. Confirmed Virologic Failures in the CAB + RPV LA Arms of ATLAS and FLAIR Through Week 48[6]

Study	Sex, Country, HIV-1 Subtype	Previous ART	RAMs at Baseline		Viral Load at SVF/CVF (copies/ mL)	RAMs at SVF		Drug Suscepti-bility (Fold Change)*
			RT	INSTI		RT	INSTI	
ATLAS	F, Russia, A/A1	3TC, AZT, LPV/r	E138E/ A	None	79,166/ 25,745	E138A	None	**RPV (2.4)** CAB (0.8) DTG (0.9)
	F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	V108V/I, E138K	None	695/ 258	V108V/I, E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)
	M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	None	None	544/ 1841	E138E/K	N155H	**RPV (6.5)** **CAB (2.7)** DTG (1.2)
FLAIR	F, Russia, A1	-	None	None	373/ 456	E138E/A/ K/T	Q148R	**RPV (7.1)** **CAB (5.2)** DTG (1.0)
	M, Russia, A1	-	None	None	287/ 299	K101E	G140R	**RPV (2.6)** **CAB (6.7)** DTG (2.2)
	F, Russia, A1	-	None	None	488/ 440	E138K	Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

*Bolding indicates fold change above the biologic or clinical cutoff for the antiretroviral agent. Biologic cutoffs: rilpivirine (2.0), cabotegravir (2.5). Clinical cutoff: dolutegravir (4.0). Fold Change = IC_{50} patient / IC_{50} reference.

CAB + RPV LA = long acting cabotegravir and rilpivirine; ATLAS = Antiretroviral Therapy Long-Acting Suppression; FLAIR = First Long-Acting HIV Injectable Regimen; RAM = resistance-associated mutation; SVF = suspected virologic failure; ART = antiretroviral therapy; RT = reverse transcriptase; INSTI = integrase strand-transfer inhibitor; CVF = confirmed virologic failure; 3TC = lamivudine; AZT = zidovudine; LPV/r = ritonavir-boosted lopinavir; RPV = rilpivirine; CAB = cabotegravir; DTG = dolutegravir; NVP = nevirapine; ABC = abacavir; FTC = emtricitabine; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; EFV = efavirenz; IC = inhibitory concentration

In ATLAS, an additional patient receiving CAB + RPV LA had suspected virologic failure (SVF) at Week 28 (239 copies/mL) and 40 (249 copies/mL) that was never confirmed.[10] This patient had repeated blips (HIV-1 RNA ≥50 but <200 copies/mL) and was an FDA Snapshot non-responder at Week 48. An NNRTI

mutation, G190G/E, was observed in baseline peripheral blood mononuclear cell (PBMC) viral DNA. At Week 40, no INSTI mutations were detected and the reverse transcriptase and protease assays failed.

In FLAIR, an additional patient receiving CAB + RPV LA was an SVF at Week 12 (231 copies/mL) but was never confirmed.[7] This subject was found to have the INSTI mutation T97A at baseline and at Week 12. This mutation did not cause an increase in the fold-change for any INSTI at either time point.

Of the 6 CVFs in the CAB + RPV LA arms in ATLAS and FLAIR, 5 went on to re-suppress on a subsequent regimen chosen by the investigator.[10,11] Four of the 5 regimens were protease inhibitors [lopinavir/ritonavir n=2), darunavir with ritonavir (n=1), and atazanavir (n=1)] plus 2 nucleoside reverse transcriptase inhibitors. The fifth patient received dolutegravir, abacavir, and lamivudine.

The patient who did not re-suppress was placed on lopinavir/ritonavir plus lamivudine and zidovudine.[11]

Table 3. Confirmed Virologic Failures in the CAR Arms of ATLAS and FLAIR Through Week 48[6,10,11]

Study	Sex, Country, HIV-1 Subtype	Previous ART	RAMs at Baseline		Viral Load at SVF/CVF (copies/mL)	RAMs at SVF		Drug Susceptibility (Fold Change)
			RT	INSTI		RT	INSTI	
ATLAS	M, Russia, A1	EFV, 3TC, AZT	M184M/I	None	1295/9727	G190S, M184V	None	Assay Failed
	F, US, B	DRV/r, TDF, FTC to EVG/c, TDF, FTC	None	None	524/815	M184I	None	FTC (>97)
	M, US, B	EVG/c, TDF, FTC to EVG/c, TAF, FTC	None	None	339/264	None	None	No change
	M, US, B	EVG/c, TDF, FTC	None	None	392/512	M230M/I	None	No change
FLAIR	F, Russia, A1	-	V179I	I203M	2959/666	V179I	I203M	No change
	M, Spain, B	-	None	None	3044/257	None	None	No change
	M, US, B	-	None	None	7518/2271	None	None	No change

CAR = current antiretroviral regimen; ATLAS = Antiretroviral Therapy Long-Acting Suppression; FLAIR = First Long-Acting HIV Injectable Regimen; RAM = resistance-associated mutation; SVF = suspected virologic failure; ART = antiretroviral therapy; RT = reverse transcriptase; INSTI = integrase strand-transfer inhibitor; CVF = confirmed virologic failure; DRV/r = ritonavir-boosted darunavir; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; EVG/c = cobicistat-boosted elvitegravir; NR = not reported; TAF = tenofovir alafenamide

A key secondary endpoint of ATLAS and FLAIR was to assess the proportion of subjects with CVF at Week 96 (ATLAS and FLAIR) and Week 124 (FLAIR).[12,13]

No participants in either arm met CVF criterion during the extension phase up to Week 96 in the ATLAS trial.[12]

There were no new CVF in the CAB + RPV group between Week 48 and Week 96 in the FLAIR study.[13] One additional patient in the FLAIR study had a CVF between Week 96 and Week 124.[14]

ATLAS-2M

Study Design

Patients with HIV-1 RNA <50 copies/mL were randomized to receive/stay on long-acting cabotegravir plus rilpivirine (CAB + RPV LA) given every 4 weeks or to CAB + RPV LA given every 8 weeks.[15] For more information on the study design of ATLAS-2M please click here.

Confirmed Virologic Failures

Confirmed virologic failure (CVF), defined as having 2 consecutive HIV-1 RNA ≥200 copies/mL after prior suppression to <200 copies/mL, occurred in 8 (1.5%) patients in the every 8 week arm and 2 (0.4%) patients in the every 4 week arm at the 48 week timepoint (see Table 4).[15] Of these 10, 9 patients 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 susceptibility to dolutegravir.

Table 4. Confirmed Virologic Failures in the CAB + RPV LA Arms of ATLAS-2M Through Week 48[15,16]

Study Arm	Country / Gender	HIV Subtype	Prior Duration of CAB + RPV LA	BMI	SVF Timepoint	HIV-1 RNA at SVF / CVF (copies per mL)	Baseline Major RAMs (Pro-Viral DNA)* (day 1)		On-Treatment RAMs		Drug Susceptibility (FC) at SVF†
							NNRTI	IN	NNRTI	IN	
Every 8 Week Arm	S. Africa / Female	C	1-24 weeks	>30	8	267 / 2355	Y181Y/C H221H/Y	None	None	None	**RPV (2.4)** CAB (1.07)
	Spain / Male	B	None	<30	16	737,830 / 259	None	None	None	None	RPV (1.43) CAB (0.63)
	S. Africa / Female	C	None	>30	16	938 / 2374	Y188Y/F/H/L	G140G/R	Y188L	Q148Q/R N155N/H	**RPV (6.8)** **CAB (2.63)**
	Russia / Female	A1	None	>30	16	141,132 / 19,099	None	None	K101E	Q148R	**RPV (4.7)** **CAB (9.1)**
	Canada / Female	A1	None	>30	24	16,205 / 874	Y188L	None	Y188L	Assay Failed	**RPV (15)** CAB (NA)
	US / Male	B	None	>30	24	5687 / 1928	E138A	None	E138A	N155H	**RPV (7.2)** CAB (1.8)
	Russia / Female	A	1-24 weeks	<30	24	211,639 / 38,015	E138E/A	None	K101E E138A	N155H	**RPV (2.6)** **CAB (6.98)**
	Russia / Male	A/A1	1-24 weeks	<30	48	296 / 303	None	None	E138E/K	N155N/H	**RPV (4.2)** CAB (NA)
Every 4 Week Arm	France / Male	B	None	<30	16	121,233 / 173,421	None	None	None	N155N/H	**RPV (>119.2)** CAB (1.8)
	US / Male	B	None	<30	32	9627 / 2234	None	None	K101E M230L	Q148R E138E/K	**RPV (17)** **CAB (4.6)**

*Post-hoc analysis of peripheral blood mononuclear cell (PBMC) HIV-1 DNA

†Bolding indicates fold change above the biologic or clinical cutoff for the antiretroviral agent. Biologic cutoffs: rilpivirine (2.0), cabotegravir (2.5). Fold Change = IC_{50} patient / IC_{50} reference. Reduced susceptibility was determined from the clinical cut-offs or biological cutoffs used in PhenoSense GT or PhenoSense Integrase assays by Monogram Biosciences.

SVF = suspected virologic failure; RAM = resistance-associated mutation; NNRTI = non-nucleoside reverse transcriptase inhibitor; IN = integrase; RPV = rilpivirine; CAB = cabotegravir; FC = fold-change in IC50 compared to wild-type virus

One additional participant, who was in the Q8W arm, met the CVF criterion between Week 48 and 96.[17] NNRTI RAM K103N and RPV RAM Y181C were detected at virologic failure in the plasma sample and retrospectively at baseline in the PBMC sample. No INSTI RAMs were present at virologic failure in the plasma sample or in the baseline PBMC sample.

A summary of CVFs through Week 152 can be found in Table 5 below. In total, through Week 152, 13 participants (every-8-week arm, 11 [2%]; every-4-week arm, 2 [<1%]) had CVF. [18] Of the 13 CVFs, 12 re-suppressed on alternative ART (one participant was non-adherent to protease inhibitor-based ART). Two participants, both in the every-8-week arm, met the CVF criterion between Week 96 and 152.

One participant, who met CVF criterion at Week 112, was a German male with a BMI <30 kg/m², subtype B and a viral load of 24,221 copies/mL at failure.[18] The other participant, who met CVF criterion at Week 120, was a Russian male with a BMI <30 kg/m², subtype A6 and a viral load of 59,467 copies/mL at failure. Neither had RAMs at baseline; however, the participant with A6 subtype had L74I integrase (IN) polymorphism at baseline. Both had treatment-emergent RAMs to CAB (Q148R) and RPV (E138A+Y181Y/C; E138A+M230M/L), and both resuppressed on an alternate regimen.

An additional participant was identified as having non-protocol defined virologic failure at Week 48 (Q8W).[18] The participant had subtype A1, with RPV RAM E138K and IN mutation S230S/R observed at withdrawal; no RAMs to RPV or INIs were present at baseline; the participant resuppressed on an alternate regimen.

Table 5. Summary of CVFs through Week 152 in ATLAS-2M[18]

Regimen	N	CVFs N (%)	CVFs with RPV RAMs*	RPV RAMs at Failure	CVFs with INSTI RAMs*	INSTI RAMs at Failure
Q8W	522	11 (2)	9/11	K101E, E138E/K, E138A, Y188L, Y181C*, M230M/L	7/11	Q148R,* N155H*
Q4W	523	2 (<1)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

*or mixture

CVF = confirmed virologic failure; RPV = rilpivirine; RAMs = resistance-associated mutations; INSTI = integrase strand-transfer inhibitor; Q8W = every 8 week arm; Q4W = every 4 week arm

SOLAR

SOLAR (**S**witch **O**nto **L**ong-**A**cting **R**egimen) is an ongoing Phase 3b, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study to assess the antiviral activity and safety of *Cabenuva* (long-acting cabotegravir + rilpivirine, CAB + RPV LA) administered every 2 months (Q2M) compared with daily oral bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). For further information on the SOLAR study, please click here.

Confirmed virologic failure (CVF) was defined by two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to <200 copies/mL. Through Month 12 in the mITT-E Population, 2 (0.4%) participants receiving CAB + RPV LA in the mITT-E population CAB + RPV LA arm met the CVF criterion. [19] See Table 6.

Table 6. Summary of Participants Randomized to CAB + RPV LA with Confirmed Virologic Failures at Month 12[19]

Patient	Sex, Country, BMI at baseline, Subtype	RAMs at Baseline		Viral Load at SVF/CVF (copies/ mL)	RAMs at SVF Fold-Change		Comment
Participants with CVF in the mITT-E Population							
1	Male, Italy, 21.5 kg/m^2, Subtype B	RPV	none	SVF Month 6: 1327	RPV	M230L RPV FC=3.2	Received BIC/FTC/TAF prior to enrollment; resuppressed on D/C/F/TAF following long-term follow-up
		INSTI	none	CVF Retest: 1409	INSTI	Q148R CAB FC=3.1	
2	Male, Spain, 22.9 kg/m^2, Subtype AE	RPV	None	SVF Month 11: 6348	RVP	K101E RPV FC=1.9	Received ABC/3TC/DTG and BIC/FTC/FAF prior to enrollment; resuppressed on BIC/FTC/TAF and D/C/F/TAF during long-term follow-up
		INSTI	G140G/R	CVF Retest: 419	INSTI	G118R CAB FC=8.4	
Participant with CVF in the ITT-E Population							
3[a]	Male, USA, 30.5 kg/m^2, Subtype failed; HIV subtype C at Month 3	RPV	Assay Failed	SVF Month 3: 3797	RPV	E138E/K, Y181Y/C RPV FC=4.2	Excluded due to protocol deviation
		INSTI	Assay Failed	CVF Retest: 928	INSTI	Assay Failed	

a=Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INSTI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site.

ABC/3TC/DTG = abacavir/lamivudine/dolutegravir; ART = antiretroviral therapy; BIC/FTC/TAF = bictegravir/emtricitabine/tenofovir; BMI = body mass index; CVF = confirmed virologic failure; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FC = fold change; INSTI = integrase inhibitor; RAM = resistance-associated mutation; RPV = rilpivirine; SVF = suspected virologic failure

COMPASSIONATE USE PROGRAM

Physicians could request compassionate use (CU) of CAB + RPV LA through an expanded access program.[20] Criteria for granting requests included the need for parenteral therapy, advanced disease, absence of key mutations associated with resistance to CAB or RPV, and established retention in care.

Patients were required to take 1 month of oral CAB and RPV unless their underlying condition precluded the use or oral medication.[20]

All patients received a one-time initiation doses of CAB 600 mg and RPV 900 mg followed by an every 4 week maintenance doses of CAB 400 mg and RPV 600 mg.[20]

There were 5 patients with incomplete virologic responses that led to withdrawal. Their information can be found in Table 7 below.

Table 7. Patients with Incomplete Virologic Responses Leading to Withdrawal[20]

	Patient 9	Patient 18	Patient 22	Patient 34	Patient 35
HIV-1 RNA at CU start (copies/mL)	<40	61,600	32,000	205,000	1,639,794

HIV-1 RNA at failure (copies/mL)	55 (blip); repeat <40	N/A	799	186,972	66,000
Mutations at CU start		RT: M184V, K219E, E138G	RT: K238K/R, E138G		RT: K103N
Mutations at failure	IN: G118G/R	RT: E138E/K	RT: E138G, M230L IN: Q148R, N155H	RT: K101E, Y181Y/C	RT: Y181C, K219N
Outcome	Switched to DRV/r + TAF/FTC	Added DRV/c to CAB + RPV LA	Switched to DRV/r + TAF/FTC	Switched to DRV/r + TDF/FTC	Switched to DRV/c + TAF/FTC
Most recent HIV-1 RNA and CD4+ T-cell count	<40 copies/mL 2 weeks after switch	13,300 copies/mL and 220 cells/mm^3	1170 copies/mL	18,000 copies/mL and 170 cells/mm^3	41 copies/mL

CU = compassionate use; RT = reverse transcriptase; IN = integrase; DRV/r = ritonavir-boosted darunavir; TAF/FTC = tenofovir alafenamide/emtricitabine; DRV/c = cobicistat-boosted darunavir; CAB + RPV LA = long-acting cabotegravir and rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

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