

# Impact of Patient and Viral Factors on Virologic Outcome with Long-Acting Cabotegravir and Rilpivirine in Phase 3 Trials (ATLAS, FLAIR, and ATLAS-2M)

## Summary

### Week 48 Results

- A post hoc multivariable analysis (MVA) showed that 4 factors were associated with confirmed virologic failure (CVF) through Week 48 in FLAIR, ATLAS, and ATLAS-2M:
  - RPV resistance-associated mutations (RAMs) at baseline
  - Post-hoc RPV  $C_{min}$  at Week 8
  - HIV-1 subtype A6/A1 at baseline
  - Body mass index (BMI) at baseline
- A post hoc baseline factors analysis (BFA) showed that there is an increased risk of CVF if 2 or more baseline factors (among RPV RAMs, HIV-1 subtype A6/A1, and BMI  $\geq 30$  kg/m<sup>2</sup>) are present.
  - The rate of CVF among patients with no or 1 factor present was <0.5%

### Beyond Week 48

- Using data through the of study for FLAIR (Week 124), ATLAS (Week 96), and ATLAS-2M (Week 152) the MVA was updated and revealed the following factors associated with CVF:
  - RPV RAMs at baseline
  - HIV-1 subtype A6/A1 at baseline
  - Predicted log<sub>2</sub> cabotegravir and rilpivirine troughs at Week 44
  - Predicted log<sub>2</sub> cabotegravir trough at Week 4
- The updated BFA confirmed the results of the BFA conducted at Week 48
- Important Safety Information can be found in the [Prescribing Information](#) and can also be accessed from the [Our HIV Medicines](#) section of [viihealthcare.com/us](http://viihealthcare.com/us).

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## BACKGROUND

Overall in Phase 3 trials reported to date, CAB + RPV LA maintained virologic suppression in 94% (1531/1636) through Week 48.<sup>1</sup> Despite high levels of adherence with the medicines, the rate of CVF (defined as 2 consecutive HIV-1 RNA  $\geq 200$  copies/mL) was 1-2%. For more information about the efficacy and safety of monthly CAB + RPV LA reported in ATLAS and FLAIR please click [here](#). For more information about the efficacy and safety of CAB + RPV LA administered every 2 months in ATLAS-2M please click [here](#).

## MULTIVARIABLE ANALYSES

### Week 48

The objective of this post hoc MVA was to provide an understanding of potential factors associated with CVF through Week 48 among patients receiving CAB + RPV LA in ATLAS, FLAIR, and ATLAS-2M.<sup>1</sup> A logistic regression model was used to assess the influence of 10 covariables suspected to contribute to virologic outcomes and included:

- CAB trough at Week 8  $\leq 25^{\text{th}}$  percentile ( $\leq Q_1$ )
- RPV trough at Week 8  $\leq Q_1$
- HIV-1 subtype A6/A1
- Baseline L74I
- Baseline integrase (IN) mutation
- Baseline RPV RAMs
- Baseline non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation
- Female at birth
- BMI  $\geq 30$  kg/m<sup>2</sup>
- Every-8-week dosing of CAB + RPV LA

### Results

Patients were included if they were naïve to CAB + RPV LA (n=1039).<sup>1</sup> Patients (n=597) were excluded from the analysis if they were not naïve to CAB + RPV LA (n=391), had not received CAB + RPV LA (n=22), or had missing data (n=184).

Seventeen patients met the criteria for CVF through Week 48.<sup>1</sup> Of these, 13 patients were included in the MVA. Four patients were excluded from the analysis.

See Table 1 below for a listing of the 10 potential factors among the 13 patients included in the analysis.<sup>1</sup> As can be seen, 12 of the 13 patients had 2 or more factors present.

It should also be noted that there was a high degree of correlation between the presence of L74I (integrase polymorphism) and HIV-1 subtype A6/A1 (see Table 2 below).<sup>1</sup> In this analysis, the presence of L74I only appears to be relevant in the context of HIV-1 subtype A6/A1. Among this group of patients, the rate of CVF was 6.6% (7/106). There were no (0/14) CVFs in patients with HIV-1 subtype A6/A1 and without L74I. Among patients with L74I and HIV-1 subtype B, the most prevalent subtype in North American and Western Europe, there were no CVFs.

Table 1. Per-Patient Accounting of Covariates Included in the Multivariable Analysis<sup>1</sup>

Study	Patient ID	CAB C <sub>min</sub> ≤Q1	RPV C <sub>min</sub> ≤Q1	HIV-1 Subtype A6/A1	Baseline L74I	Baseline IN Mutation	Baseline RPV Mutation	Baseline NNRTI Mutation	Female at Birth	BMI ≥30 kg/m <sup>2</sup>	Q8W Dosing
ATLAS-2M	1										
ATLAS-2M	2										
ATLAS	3										
ATLAS	4										
FLAIR	5										
FLAIR	6										
FLAIR	7										
ATLAS-2M	8										
ATLAS-2M	9										
ATLAS	10										
ATLAS-2M	11										
ATLAS-2M	12										
ATLAS-2M	13										

CAB = cabotegravir; C<sub>min</sub> = trough concentration at prior to Week 8 administration of CAB + RPV LA (4 weeks following first injections); Q1 = 25<sup>th</sup> percentile; RPV = rilpivirine; IN = integrase; NNRTI = non-nucleoside reverse transcriptase inhibitor; BMI = body mass index; Q8W = every-8-week dosing

Table 2. Proportion of Patients with CVF with and without L74I Across HIV-1 Subtypes<sup>1</sup>

Subtype	With L74I		Without L74I	
	n/N (%)	95% CI	n/N (%)	95% CI
A6/A1	7/106 (6.6)	2.7 to 13.1	0/14	0.0 to 23.2
A other	0/4	0.0 to 60.2	0/13	0.0 to 24.7
C	1/7 (14.3)	0.4 to 57.9	0/70	0.0 to 5.1
B	0/41	0.0 to 8.6	4/714 (0.6)	0.2 to 1.4
Other	0/5	0.0 to 52.2	1/65 (1.5)	0.0 to 8.3
Total	8/163 (4.9)	2.1 to 9.4	5/876 (0.6)	0.2 to 1.3

CVF = confirmed virologic failure; CI = confidence interval

Four factors were associated with an increased risk of CVF.<sup>1</sup> See Table 3 below for details. Of note, there was no association between female gender at birth or every-8-week dosing and CVF.

It is important to note that the magnitude of the odds ratio in Table 3 below does not show that there is a causal relationship between certain covariables and CVF; it shows the strength of the association.<sup>1</sup>

**Table 3. Strength of Association of the Covariables and CVF through Week 48<sup>1</sup>**

Covariable	Odds Ratio* (95% CI)	P value
<b>RPV RAMs at baseline<sup>†</sup></b>	37.24 (8.44 to >99)	<0.001
<b>Log<sub>2</sub> of post hoc Week 8 RPV C<sub>min</sub></b>	4.17 (1.59 to 11.11)	0.004
<b>Baseline HIV-1 subtype A6/A1</b>	6.59 (1.82 to 25.26)	0.005
<b>BMI at baseline</b>	1.13 (1.03 to 1.25)	0.014
<b>Pre-specified IN mutation (excluding L74I non-M mixture) at baseline<sup>‡</sup></b>	0.11 (0.01 to 0.83)	0.029
<b>Log<sub>2</sub> of post hoc Week 8 CAB C<sub>min</sub></b>	Not significant	
<b>Female at birth</b>	Not significant	
<b>Q8W dosing</b>	Not significant	
<b>L74I (non-M mixture) polymorphism at baseline</b>	Not significant	
<b>NNRTI RAMs (excluding RPV RAMs) at baseline</b>	Not significant	

\*Odds ratios (ORs), 95% penalised profile CIs and penalised likelihood ratio p-values are provided. Covariates with p<0.05 in the final backwards elimination model are presented. CAB and RPV PK parameters were log<sub>2</sub>-transformed; therefore, the corresponding ORs are per halving of each variable.

<sup>†</sup>Identified per the IAS-USA 2019 list of mutations.

<sup>‡</sup>Identified per the IAS-USA list of mutations associated with resistance to bictegravir, CAB, dolutegravir, elvitegravir or raltegravir and observed mutations during in vitro passage of dolutegravir or seen in a previous dolutegravir study (NCT01328041) in INSTI-experienced subjects.

CVF = confirmed virologic failure; RPV = rilpivirine; RAMs = resistance associated mutations; C<sub>min</sub> = trough concentration; BMI = body mass index; CAB = cabotegravir; Q8W = every-8-week dosing; NNRTI = non-nucleoside reverse transcriptase inhibitor

## Beyond Week 48

The MVA presented above was updated with data through Week 124 from FLAIR, Week 96 from ATLAS, and Week 152 from ATLAS-2M.<sup>2</sup> The pooled analysis includes 1651 patients with up to 3 years on study and 1292 patients with non-missing information on selected baseline and post-baseline factors. There were a total of 19 patients with CVF who were exposed to only every-4-week (n=11) or every-8-week (n=8) CAB + RPV LA. Data is only available for patients who received either every-4-week or every-8-week CAB + RPV LA, but not both.

See Table 4 for the rate of CVF by treatment regimen.

**Table 4. Rates of CVF by Dosing Regimen through End of Study in FLAIR, ATLAS, and ATLAS-2M<sup>2</sup>**

<b>CAB + RPV LA Regimen at CVF</b>				
	<b>Every-4-week Only (N=1129)</b>	<b>Every-8-week Only (N=327)</b>	<b>Switch from every-4-week to every-8-week (N=195)</b>	<b>Overall (N=1651)</b>
<b>CVFs n (%)</b>	11 (1)	8 (2.4)	4 (2.0)	23 (1.4)
<b>Person-years</b>	2621	936	734	4291
<b>Incidence rate/100 person years</b>	0.42	0.85	0.54	0.54
<b>95% CI for incidence rate</b>	(0.21, 0.75)	(0.37, 1.68)	(0.15, 1.40)	(0.34, 0.80)

CAB + RPV LA = long-acting cabotegravir and rilpivirine; CVF = confirmed virologic failure

As seen in the Week 48 MVA, rilpivirine RAMs and HIV-1 subtype A6/A1 remained significant predictors of CVF (see Table 5 below).<sup>2</sup> Predicted cabotegravir and rilpivirine log<sub>2</sub> trough concentrations at Week 44 and predicted cabotegravir log<sub>2</sub> trough at Week 4 were new predictive factors identified. Body mass index and rilpivirine log<sub>2</sub> trough at Week 4 were no longer predictive of CVF.

**Table 5. Strength of Association of the Covariables and CVF through End of Study from FLAIR, ATLAS, and ATLAS-2M<sup>2</sup>**

<b>Covariable</b>	<b>Odds Ratio* (95% CI)</b>	<b>P value</b>
<b>RPV RAMs: Yes/No</b>	25.7 (7.17, 92.2)	<0.0001
<b>HIV-1 subtype A6/A1: Yes/No</b>	15.5 (4.69, 50.9)	<0.0001
<b>Predicted log<sub>2</sub> Week 44 CAB trough*</b>	5.99 (1.94, 18.5)	0.0019
<b>Predicted log<sub>2</sub> Week 44 RPV trough*</b>	4.16 (1.04, 16.7)	0.0441
<b>Predicted log<sub>2</sub> Week 4 CAB trough†</b>	2.20 (1.04, 16.7)	0.0100
<b>BMI at baseline‡</b>	Not significant	
<b>Regimen: every-8-week/every-4-week</b>	Not significant	
<b>Integrase L74I: Yes/No§</b>	Not significant	
<b>Sex at birth: male/female</b>	Not significant	
<b>Other NNRTI RAMs: Yes/No¶</b>	Not significant	
<b>CAB RAMs: Yes/No</b>	Not significant	
<b>Other INSTI RAMs: Yes/No</b>	Not significant	
<b>Predicted log<sub>2</sub> Week 4 RPV trough†</b>	Not significant	

\* After 44 weeks of LA therapy (excludes oral lead-in)

† After 4 weeks of LA therapy (excludes oral lead-in)

‡ BMI was evaluated on a continuous scale

§ Including mixtures except L74I/M

¶ Other NNRTI RAMs were also retained in the final selected model, but not considered statistically significant (p=0.0667)

CVF = confirmed virologic failure; RPV = rilpivirine; RAMs = resistance associated mutations; BMI = body mass index; NNRTI = non-nucleoside reverse transcriptase inhibitor; CAB = cabotegravir; INSTI = integrase strand transfer inhibitor

## BASELINE FACTOR ANALYSES

### Week 48 Results

Of the 4 factors noted above to be associated with CVF through Week 48 in ATLAS, FLAIR, and ATLAS-2M, three (RPV RAMs, HIV-1 subtype A6/A1, and BMI  $\geq 30$  kg/m<sup>2</sup>) may be present at baseline prior to initiation of CAB + RPV LA.<sup>1</sup> Of note, HIV-1 subtype A is primarily found in eastern Europe, central Asia, and east/central Africa.<sup>3</sup>

This analysis showed that there is an increased risk of CVF if 2 or more of these baseline factors are present.<sup>1</sup> The rate of CVF among patients no or 1 factor present was <0.5%. See Table 6 below for details.

**Table 6. Relationship Between the Presence of Baseline Factors and CVF or HIV-1 RNA <50 copies/mL at Week 48<sup>1</sup>**

	Proportion of Patients with CVF n/N (%)	Proportion of Patients with HIV-1 RNA <50 copies/mL n/N (%)
<b>None of the 3 baseline factors</b>	3/732 (0.41)	694/732 (94.8)
<b>Any 1 of the baseline factors</b>	1/272 (0.37)	261/272 (96)
HIV-1 Subtype A6/A1 alone	1/95 (1.1)	90/95 (94.7)
BMI $\geq 30$ kg/m <sup>2</sup> alone	0/153 (0)	147/153 (96.1)
RPV RAMs alone	0/24 (0)	24/24 (100)
<b>At least 2 of the baseline factors</b>	9/35 (25.7)	25/35 (71.4)
RPV RAMs + Subtype A6/A1	1/3 (33.3)	2/3 (66.7)
RPV RAMS + BMI $\geq 30$ kg/m <sup>2</sup>	3/10 (30)	7/10 (70)
Subtype A6/A1 + BMI $\geq 30$ kg/m <sup>2</sup>	4/21 (19)	16/21 (76.2)
<b>All 3 baseline factors</b>	1/1 (100)	0/1 (0)
<b>Total, n/N (%)</b>	13/1039 (1.25) [95% CI 0.67, 2.13]	980/1039 (94.3) [95% CI 92.74, 95.65]
CVF = confirmed virologic failure; BMI = body mass index; RPV = rilpivirine; RAMs = resistance-associated mutations		

### Beyond Week 48

The BFA presented above was updated with data through Week 124 from FLAIR, Week 96 from ATLAS, and Week 152 from ATLAS-2M.<sup>2</sup> The pooled analysis includes 1651 patients with up to 3 years on study and 1431 with non-missing information on selected baseline factors. There were a total of 19 patients with CVF who were exposed to only every-4-week (n=11) or every-8-week (n=8) CAB + RPV LA. Data is only available for patients who received either every-4-week or every-8-week CAB + RPV LA, but not both.

The updated analysis confirmed the results of the BFA conducted at Week 48.<sup>2</sup> See Tables 7 and 8 below.

**Table 7. Strength of Association of the Covariables and CVF through End of Study from FLAIR, ATLAS, and ATLAS-2M<sup>2</sup>**

Covariable	Odds Ratio* (95% CI)	P value
<b>RPV RAMs: Yes/No</b>	21.7 (5.80, 80.8)	<0.0001
<b>HIV-1 subtype A6/A1: Yes/No</b>	12.9 (4.42, 37.5)	<0.0001
<b>BMI at baseline</b>	1.09 (1.00, 1.19)	0.0447
<b>Regimen: every-8-week/every-4-week</b>	Not significant	
<b>Integrase L74I: Yes/No</b>	Not significant	
<b>Sex at birth: male/female</b>	Not significant	
<b>Other NNRTI RAMs: Yes/No</b>	Not significant	
<b>CAB RAMs: Yes/No</b>	Not significant	
<b>Other INSTI RAMs: Yes/No</b>	Not significant	

CVF = confirmed virologic failure; RPV = rilpivirine; RAMs = resistance associated mutations; BMI = body mass index; CAB = cabotegravir; NNRTI = non-nucleoside reverse transcriptase inhibitor; INSTI = integrase strand transfer inhibitor

**Table 8. Relationship Between the Presence of Baseline Factors and CVF or HIV-1 RNA <50 copies/mL through End of Study in FLAIR, ATLAS, and ATLAS-2M<sup>2</sup>**

Factors at Baseline	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
<b>No baseline factors</b>	4/970 (0.4)	844/970 (87)
<b>Any 1 baseline factor</b>	8/404 (2.0)	343/404 (85)
<b>≥2 factors</b>	11/57 (19)	44/57 (77)
<b>Total, n/N (%)</b>	23/1431 (1.6)	1231/1431 (86)
<b>95% CI</b>	1.0, 2.4	84.1, 88

CVF = confirmed virologic failure

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## REFERENCES

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