A COMBINATION OF VIRAL AND PARTICIPANT FACTORS INFLUENCE VIROLOGIC OUTCOME TO LONG-ACTING CABOTEGRAVIR + RILPIVIRINE: MULTIVARIABLE AND BASELINE FACTOR ANALYSES ACROSS ATLAS, FLAIR AND ATLAS-2M PHASE 3 STUDIES

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Multivariable Analysis: Introduction

- CAB + RPV LA dosed Q4W in FLAIR[1] and ATLAS,[2] and Q4W/Q8W in ATLAS-2M,[3,4] maintained virologic suppression in 94% (n=1531/1636) of participants across all three Phase 3 studies at Week 48
  - The rates of confirmed virologic failure (CVF)* in the LA arms across the three studies were ~1%
- Understanding predictors of outcome is important for prescribers when considering this novel LA regimen
- In a *post hoc* analysis, we pooled data from the three studies to explore potential factors associated with CVF

*Two consecutive measurements of HIV-1 RNA ≥200 copies/mL.
CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
1. Orkin C, et al. *N Engl J Med.* 2020;382(12):1124–1135. 2. Swindells S, et al. *N Engl J Med.* 2020;382(12):1112–1123.
3. Overton ET, et al. CROI 2020; Boston, Massachusetts; March 8–11, 2020; Presentation 3334.
4. Overton ET, et al. *Lancet*. accepted 2020.

Multivariable Analysis: Methods

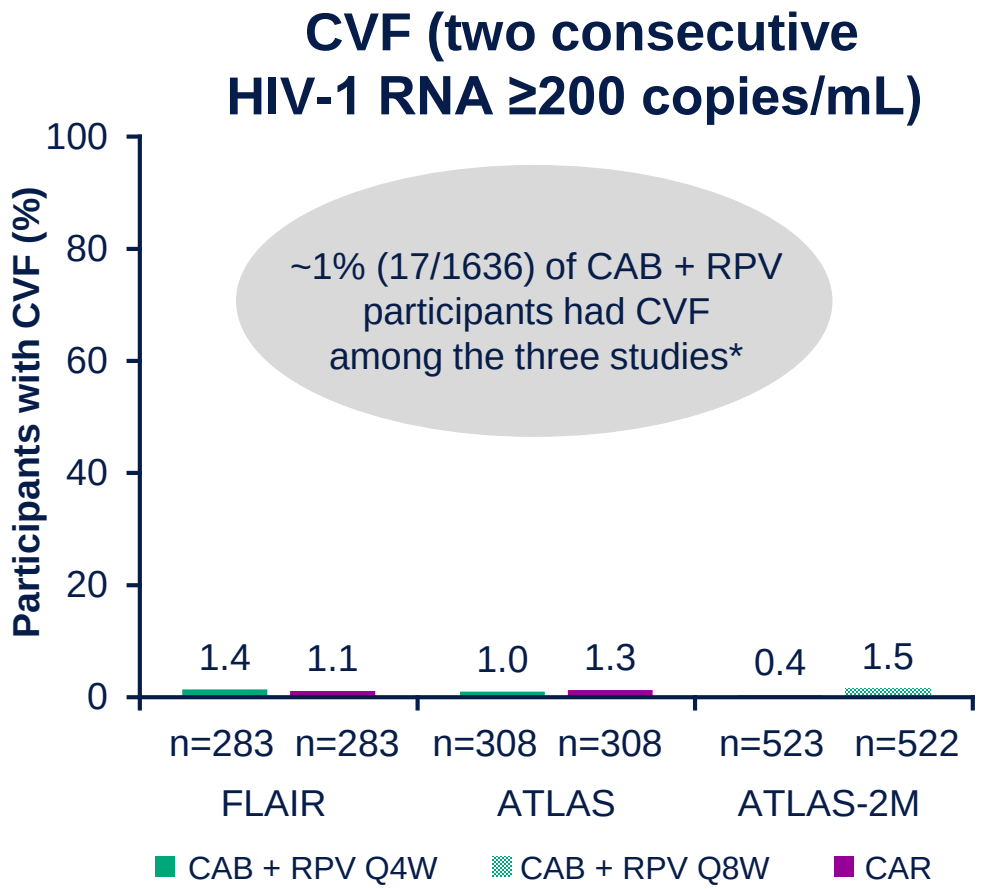
- Potential predictors of virologic outcomes through Week 48 (Q4W or Q8W) from participants naive to CAB + RPV LA from FLAIR, ATLAS and ATLAS-2M (N=1039) were explored in a *post hoc* multivariable analysis
  - Excluded: n=597 (prior exposure to CAB + RPV [n=391]; no LA dosing [n=22]; missing data [n=184])

- A logistic regression model was used to examine the influence of 10 covariates known or suspected to contribute to virologic outcomes, including drug PK and factors impacting drug exposure, key virus characteristics and dosing interval (Q8W vs. Q4W), on the occurrence of CVF
  - Final model obtained using a backwards variable selection procedure:
    - Initial model removed the covariate with the largest p-value (among all with p>0.2) and the model was refitted
    - Process was repeated until no covariate yielded a p-value >0.2

- In a separate analysis, significant factors that were present at baseline were further evaluated to determine if specific combination of factors were more or less likely among CVF cases compared with the presence of a single factor

CAB, cabotegravir CVF, confirmed virologic failure; LA, long-acting; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Multivariable Analysis: Participant, Baseline Virus and PK Factors Explored in Relation to CVF Outcome Through Week 48



Factors explored in the MVA:

- CAB and RPV PK (i.e. initial trough concentrations at Week 8) and pre-existing resistance mutations,† adjusting for the following covariates:
  - Sex at birth
  - BMI
  - HIV-1 subtype
  - Q4W and Q8W regimen

*13 of 17 participants who met the CVF criterion were CAB + RPV naive at study entry and received at least one LA injection were included in the multivariable analysis; three participants with CVF were excluded as they rolled over from ATLAS. An additional participant in FLAIR was excluded because CVF occurred prior to receiving LA injection (withdrawn due to false-positive pregnancy test).
†Pre-existing INSTI, as well as L74I polymorphism, RPV and NNRTI RAMs (observed in plasma or peripheral blood mononuclear cells).
BMI, body mass index (kg/m^2); CAB, cabotegravir; CAR, current antiretroviral regimen; CVF, confirmed virologic failure; LA, long-acting; MVA, multivariable analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

Multivariable Analysis: The Majority of CVFs* had Multiple Potential Factors

Study	ID	CAB PK† ≤Q1	RPV PK† ≤Q1	Subtype A6/A1	Baseline IN L74I‡	Baseline INSTI mutation	Baseline RPV RAM	Baseline NNRTI RAM	Female at birth	BMI ≥30	Q8W
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							√			

*13 of 17 participants who met the CVF criterion were CAB + RPV naive at study entry and received at least one dose of CAB + RPV LA.
†CAB and RPV PK refer to Week 8 trough concentrations (4 weeks following first injection).
‡Baseline L74I IN polymorphism excluding M mixtures.
BMI, body mass index (kg/m^2); CAB, cabotegravir; CVF, confirmed virologic failure; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; Q1, 1st quartile; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

Multivariable Analysis: Contribution of Integrase Polymorphism L74I Within HIV-1 Subtype A6/A1

Number of CVF participants with and without L74I across HIV-1 subtypes

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

- L74I INSTI polymorphism was highly correlated with subtype A6/A1
- The presence of the L74I polymorphism did not influence outcomes in subtype B + L74I (n=0/41 with CVF), while fewer data exist for subtype C + L74I (n=1/7 with CVF)

CI, confidence interval; CVF, confirmed virologic failure. INSTI, integrase strand transfer inhibitor.

Multivariable Analysis: Four Factors Were Associated With an Increased Odds Ratio of CVF, Three Are Baseline Factors

Parameter	Final Model OR (95% CI), p-value*
RPV RAM(s) at baseline†	37.24 (8.44–>99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59–11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82–25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03–1.25), p=0.014
Pre-specified INSTI mutation (excluding L74I non-M mixture) at baseline‡	0.11 (0.01–0.83), p=0.029
Log_2 of *post hoc* Week 8 CAB trough concentration	Not significant
Female at birth	Not significant
Q8W regimen	Not significant
L74I (non-M mixture) INSTI polymorphism at baseline	Not significant
NNRTI RAM(s) (excluding RPV RAMs) at baseline‡	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_2-transformed; therefore, the corresponding ORs are per halving of each variable.
†Identified per the IAS–USA 2019 list of mutations.[1]
‡Identified per the IAS–USA list of mutations associated with resistance to bictegravir, CAB, dolutegravir, elvitegravir or raltegravir[1] and observed mutations during *in vitro* passage of dolutegravir or seen in a previous dolutegravir study (NCT01328041) in INSTI-experienced subjects.
BMI, body mass index (kg/m^2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

1. Wensing AM, et al. *Top Antivir Med.* 2019;27(3):111–121.

Multivariable Analysis: A Combination of Baseline RPV RAMs*, Subtype A6/A1 or BMI ≥30 Modestly Increased the Risk of Virologic Failure

Factor	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
No baseline factors	3/732 (0.41)	694/732 (95)
Any one baseline factor	1/272 (0.37)	261/272 (96)
Two or more baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1039 (1.3) [0.67–2.13]	980/1039 (94) [92.74–95.65]

- Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

*Identified per the IAS–USA 2019 list of mutations.[1]
BMI, body mass index (kg/m2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; LA, long-acting; NPV, negative predictive values; PPV, positive predictive values; RAM, resistance-associated mutation; RPV, rilpivirine.
1. Wensing AM, et al. *Top Antivir Med.* 2019;27(3):111–121.

Multivariable Analysis: Conclusions

- CAB + RPV Q4W and Q8W regimens provide comparable, high rates of efficacy
  - 94% of participants in this large pooled dataset maintained viral suppression over 48 weeks
- CVF is an infrequent multifactorial event (~1%)
  - CVF influenced by the presence of at least 2 baseline factors: RPV RAMs, BMI ≥30, HIV-1 subtype A6/A1
  - Week 48 CVF rate was <0.5% when 0 or 1 baseline factor was present
  - While low RPV trough concentrations were observed in some CVFs, this rarely occurred without other predictive factors
- These findings should be contextualized with the high overall success rates and participants' preference for CAB + RPV LA, and may inform prescribers when considering this novel LA regimen

BMI, body mass index (kg/m^2); CAB, cabotegravir; CVF, confirmed virologic failure; IN, integrase; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RAMs, resistance-associated mutations; RPV, rilpivirine.