Expanded Multivariable Models to Assist Patient Selection for Long-Acting Cabotegravir + Rilpivirine Treatment: Clinical Utility of a Combination of Patient, Drug Concentration, and Viral Factors Associated With Virologic Failure Over 152 Weeks

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- We thank everyone who has contributed to the success of these studies: all study participants and their families; the ATLAS, FLAIR, and ATLAS-2M clinical investigators and their staff; and the ViiV Healthcare, GlaxoSmithKline, and Janssen Pharmaceuticals study team members.
Introduction

- Cabotegravir (CAB) + rilpivirine (RPV) dosed monthly or every 2 months is the first complete long-acting (LA) injectable regimen recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression\(^1,2\)

- Confirmed virologic failure (CVF)* on CAB + RPV LA therapy occurred in 1% (n=19/1651) of participants in Phase 3/3b clinical trials through 48 weeks, with few instances (n=4/1651) thereafter\(^3–5\)

- In a multivariable analysis (MVA), the presence of ≥2 baseline factors (pre-existing RPV resistance-associated mutations [RAMs],\(^†\) HIV-1 subtype A6/A1,\(^‡\) and/or body mass index [BMI] ≥30 kg/m\(^2\)) was associated with increased CVF risk in the first year of CAB + RPV LA therapy\(^6\)

- Post hoc MVAs exploring predictors of CVF were expanded to include data beyond Week 48, and to incorporate additional factors and participants

*Two consecutive measurements of plasma HIV-1 RNA ≥200 copies/mL. \(^1\)Pre-existing RPV RAMs (IAS–USA 2019) were evaluated retrospectively from archived pro-viral DNA in ATLAS and ATLAS-2M, and from plasma RNA in FLAIR.\(^7\)

\(^\text{See Jeffrey JL, et al. for further characterization of subtype A6/A1.}^\)

\(^\text{FLAIR (NCT02938520); ATLAS (NCT02951052); ATLAS-2M (NCT03293049).}^\)

\(^\text{BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; MVA, multivariable analysis; RAM, resistance-associated mutation; RPV, rilpivirine.}^\)


Methodology: Expanded Study Population (Two Steps)

- Study participant data were pooled from FLAIR through Week 124, ATLAS through Week 96, and ATLAS-2M through Week 152 for two separate model analyses to predict CVF risk:
  - MVA for covariates present at baseline and post-baseline
  - BFA for covariates present at baseline only

- Once significant factors were identified, the virologic outcomes were summarized for participants with significant factors according to combinations of these key factors for the total population (N=1651)

**Multivariable analysis (MVA)**
- N=1224 complete records from participants exposed to only Q4W or Q8W

**Baseline factors analysis (BFA)**
- N=1363 complete records from participants exposed to only Q4W or Q8W

Pooled ATLAS/FLAIR/ATLAS-2M
N=1651 unique participants with up to 3 years* on study

- 19 participants with CVF who were exposed to only Q4W or Q8W†
  - N=1129 Q4W only; 11 CVFs
  - N=327 Q8W only; 8 CVFs

- N=1292/1651 with non-missing information on selected baseline and post-baseline factors
- N=1431/1651 participants with non-missing information on selected baseline factors

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*Participants who rolled over from ATLAS to ATLAS-2M with prior exposure had up to 5 years of exposure to CAB + RPV LA.
†A participant in FLAIR was excluded because CVF occurred prior to receiving LA injection (withdrawn due to false-positive pregnancy test); thus, this participant was excluded from the MVA analysis because there was no LA PK data.
‡An additional 126 participants who received Q4W prior to transitioning to ATLAS-2M were also included in the Single Regimen Population as Q4W (N=1255).

BFA, baseline factors analysis; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; MVA, multivariable analysis; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
Methods

- Dosing regimen, demographic, viral, and pharmacokinetic (PK) covariates were explored as potential predictors of CVF:
  - Every 4 or 8 week dosing regimen (Q4W or Q8W), sex at birth, baseline BMI, HIV-1 subtype A6/A1, baseline viral factors (integrase L74I, pre-existing RPV RAMs, other NNRTI RAMs, CAB RAMs, and other INSTI RAMs)
  - Population PK model-predicted CAB and RPV trough plasma concentrations after the first injections (Week 4) and after 44 weeks of LA therapy
  - Timing of CVF by regimen was analysed using simple Kaplan-Meier curves, as well as unadjusted incidence rates per 100 person-years (py)
  - Dosing regimen experience was accounted for using “single-regimen” analyses (received either Q4W or Q8W, but not both) and “all-regimen” analyses (inclusive of switching from Q4W to Q8W dosing from ATLAS to ATLAS-2M) (This presentation on the MVA and BFA focuses on single-regimen data only)
  - Poisson regression modeling with variable selection procedures was used to identify significant factors and calculate adjusted CVF incidence rate per 100 py

*Including mixtures excluding L74I/M. †Separate models for CAB and RPV. ‡Week 4 is equivalent to Week 8 in the Phase 3/3b studies for CAB-naive participants who received a 4-week oral lead-in. §At the end of six every 2 month injections, or 11 monthly injections.

BFA, baseline factors analysis; BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; MVA, multivariable analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetics; py, person-years; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.
Most participants remained virologically suppressed up to 3 years on study,\textsuperscript{1–3}† with an overall CVF rate of 1.4%.

Overall unadjusted incidence rate of CVF per 100 py was 0.54, and broadly similar between dosing arms.

The absolute difference between Q4W and Q8W regimens equates to roughly one additional CVF on Q8W over 200 py.

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\textsuperscript{1} Swindells S, et al. AIDS. 2022;36(2):185–194.


\textsuperscript{3} Overton ET, et al. CROI 2022 (Poster H03).

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\textsuperscript{†} Participants who rolled over from ATLAS to ATLAS-2M with prior exposure had up to 5 years of exposure to CAB + RPV LA.

CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; LA, long-acting; py, person-years; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
Multivariable Analysis: RPV RAMs and HIV-1 Subtype A6/A1 Remain Significant Factors, With Predicted CAB and RPV Troughs as Additional Predictive Factors

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Expanded MVA adjusted IRR (95% CI) [p value] n=1224</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV RAMs: Yes/No</td>
<td>25.7 (7.17, 92.2) [&lt;0.0001]</td>
</tr>
<tr>
<td>HIV-1 subtype A6/A1: Yes/No</td>
<td>15.5 (4.69, 50.9) [&lt;0.0001]</td>
</tr>
<tr>
<td>Predicted log$<em>2$ Week 44§ CAB C$</em>{\text{trough}}$ (µg/mL)</td>
<td>5.99 (1.94, 18.5) [0.0019]</td>
</tr>
<tr>
<td>Predicted log$<em>2$ Week 44§ RPV C$</em>{\text{trough}}$ (ng/mL)</td>
<td>4.16 (1.04, 16.7) [0.0441]</td>
</tr>
<tr>
<td>Predicted log$<em>2$ Week 4† CAB C$</em>{\text{trough}}$ (µg/mL)</td>
<td>2.20 (1.21, 4.00) [0.0100]</td>
</tr>
</tbody>
</table>

Baseline BMI (kg/m$^2$)*
Regimen: Q8W/Q4W
Integrase L74I:† Yes/No
Sex at birth: Female/Male
Other NNRTI RAMs: Yes/No‡
CAB RAMs: Yes/No
Other INSTI RAMs: Yes/No
Predicted log$_2$ Week 4§ RPV C$_{\text{trough}}$ (ng/mL) Eliminated from model

- RPV RAMs,¹ HIV-1 subtype A6/A1, predicted CAB trough 4 weeks following initial injections, and predicted CAB and RPV troughs 44 weeks after initial injections were predictive of increased CVF risk.
- RPV RAMs and HIV-1 subtype A6/A1 contributed to a greater extent toward CVF risk compared with predicted RPV and CAB concentrations; dosing regimen was not predictive of CVF risk.
- BMI was not retained, possibly due to correlation with CAB PK.

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*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). †After 44 weeks of LA therapy (excludes oral lead-in). *After 4 weeks of LA therapy (excludes oral lead-in). BMI, body mass index; CAB, cabotegravir; CI, confidence interval; C$_{\text{trough}}$, trough concentration; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; IRR, incidence rate ratio; MVA, multivariable analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

A Combination of Baseline RPV RAMs, HIV-1 Subtype A6/A1, and Low Initial Predicted CAB/RPV PK Troughs* Increased the Risk of CVF

<table>
<thead>
<tr>
<th>Factor</th>
<th>CVF, n (%)</th>
<th>HIV-1 RNA &lt;50 copies/mL, n (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No factors</td>
<td>0/664 (0)‡</td>
<td>584/664 (88.0)</td>
</tr>
<tr>
<td>Any one factor</td>
<td>5/396 (1.3)</td>
<td>339/396 (85.6)</td>
</tr>
<tr>
<td>Two or more factors</td>
<td>17/232 (7.3)</td>
<td>190/232 (81.9)</td>
</tr>
<tr>
<td>Three or more factors</td>
<td>8/39 (20.5)</td>
<td>28/39 (71.8)</td>
</tr>
<tr>
<td>TOTAL [95% CI]</td>
<td>22/1292 (1.7)</td>
<td>1113/1292 (86.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three or more factors</td>
<td>20.5%</td>
<td>98.9%</td>
<td>36.4%</td>
<td>97.6%</td>
</tr>
<tr>
<td>Any one factor</td>
<td>1.3%</td>
<td>98.1%</td>
<td>22.7%</td>
<td>69.2%</td>
</tr>
</tbody>
</table>

* CAB/RPV trough concentrations ≤ first quartile 4 weeks after first injections (CAB, 1.2 µg/mL; RPV, 32.6 ng/mL). † Based on the FDA Snapshot algorithm of HIV-1 RNA <50 copies/mL at Week 48 for ATLAS, Week 124 for FLAIR, and Week 152 for ATLAS-2M. ¶ PPV 0%; NPV 96.5%; sensitivity 0%; specificity 47.7%. § After 4 weeks of LA therapy (excludes oral lead-in). ¶ After 44 weeks of LA therapy (excludes oral lead-in).

- To explore how these factors can aid patient selection, retained factors were assessed in combination.
- Initial Week 4§ troughs correlate with Week 44¶ troughs; thus, only Week 4 troughs were included as they are more clinically relevant for a new patient initiating the regimen.
- Sensitivity and specificity of at least three baseline and post-baseline factors is optimal; however, this was observed in only 3% (n=39/1292) of the population.

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Orkin et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Presentation 044
Baseline Factors Analysis: RPV RAMs, HIV-1 Subtype A6/A1, and BMI Remain Significant Baseline Factors Predictive of CVF Risk

- Using an expanded dataset, pre-existing RPV RAMs, HIV-1 subtype A6/A1, and BMI remained significant baseline factors predictive of CVF risk.
- Dosing regimen and integrase L74I were not predictive of CVF risk.
- These results are consistent with those in the original BFA\(^1\).

<table>
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<th>Covariate</th>
<th>Expanded BFA adjusted IRR (95% CI) [p value] n=1363</th>
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<tr>
<td>RPV RAMs: Yes/No</td>
<td>21.7 (5.80, 80.8) [&lt;0.0001]</td>
</tr>
<tr>
<td>HIV-1 subtype A6/A1: Yes/No</td>
<td>12.9 (4.42, 37.5) [&lt;0.0001]</td>
</tr>
<tr>
<td>Baseline BMI (kg/m(^2))*</td>
<td>1.09 (1.00, 1.19) [0.0447]</td>
</tr>
<tr>
<td>Regimen: Q8W/Q4W</td>
<td>Eliminated from model</td>
</tr>
<tr>
<td>Integrase L74I:† Yes/No</td>
<td></td>
</tr>
<tr>
<td>Sex at birth: Female/Male</td>
<td></td>
</tr>
<tr>
<td>Other NNRTI RAMs: Yes/No</td>
<td></td>
</tr>
<tr>
<td>CAB RAMs: Yes/No</td>
<td></td>
</tr>
<tr>
<td>Other INSTI RAMs: Yes/No</td>
<td></td>
</tr>
</tbody>
</table>

*BMI was evaluated on a continuous scale; IRR is per one unit increase in kg/m\(^2\). The IRR for BMI ≥30 kg/m\(^2\) was 3.97, p=0.01. †Including mixtures except L74I/M.

BFA, baseline factors analysis; BMI, body mass index; CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; IRR, incidence rate ratio; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

A Combination of Baseline RPV RAMs, HIV-1 Subtype A6/A1, or BMI ≥30 kg/m² Increased the Risk of Virologic Failure

<table>
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<th>Factor</th>
<th>CVF, n (%)</th>
<th>HIV-1 RNA &lt;50 copies/mL, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No baseline factors</td>
<td>4/970 (0.4)†</td>
<td>844/970 (87.0)</td>
</tr>
<tr>
<td>Any one baseline factor</td>
<td>8/404 (2.0)‡</td>
<td>343/404 (84.9)</td>
</tr>
<tr>
<td>Two or more baseline factors</td>
<td>11/57 (19.3)</td>
<td>44/57 (77.2)</td>
</tr>
<tr>
<td>TOTAL [95% CI]</td>
<td>23/1431 (1.6) [1.0%, 2.4%]</td>
<td>1231/1431 (86.0) [84.1%, 87.8%]</td>
</tr>
</tbody>
</table>

*Based on the FDA Snapshot algorithm of HIV-1 RNA <50 copies/mL at Week 48 for ATLAS, Week 124 for FLAIR, and Week 152 for ATLAS-2M. †PPV 0.4%; NPV 95.9%; sensitivity 17.4%; specificity 31.4%. ‡Driven primarily by RPV RAMs and HIV-1 subtype A6/A1, not BMI. CVF occurred in 3.2% (n=131) of those with RPV RAMs only, 3.8% (n=6157) of those with HIV-1 subtype A6/A1 only, and 0.5% (n=1216) of those with BMI ≥30 kg/m² only. BMI, body mass index; CI, confidence interval; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; NPV, negative predictive value; PPV, positive predictive value; RAM, resistance-associated mutation; RPV, rilpivirine.

- The presence of no or one baseline factors is associated with a low risk of failure
- CVF occurred in 0.5% (n=1/216) of participants with BMI ≥30 kg/m² as their only baseline factor
- Sensitivity and specificity of at least two baseline factors is optimal, and was of similar predictive value as at least three baseline and post-baseline factors (i.e., PK data)
Conclusions

• Over 3 years on CAB + RPV LA in Phase 3/3b trials, CVF occurred in 1.4% (n=23/1651) of participants, with an unadjusted CVF incidence rate of approximately 1 per 200 py

• Dosing regimen (Q8W/Q4W), sex at birth, CAB/other INSTI RAMs, and other NNRTI RAMs had no significant association with CVF in either single-regimen model

• In the expanded MVA, pre-existing RPV RAMs and HIV-1 subtype A6/A1 remained the most significant factors predictive of CVF risk. Predicted CAB and RPV troughs (and not baseline BMI ≥30 kg/m²) were additional factors retained

• The presence of ≥3 factors did not improve prediction of CVF beyond the presence of a combination of ≥2 baseline factors

• The presence of a combination of ≥2 baseline factors (pre-existing RPV RAMs, HIV-1 subtype A6/A1, and/or BMI ≥30 kg/m²) increased CVF rate consistent with prior analyses

• Overall, these results inform and help contextualize appropriate use of this novel LA treatment option

Future communications will present the all-regimen models including Q4W → Q8W participants

BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; LA, long-acting; MVA, multivariable analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; py, person-years; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.
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