HIV-1 RNA Blips, Low-Level Viral Replication, and Mean CD4+/CD8+ Ratio During Phase 3/3b Cabotegravir + Rilpivirine Long-Acting Studies Up to 152 Weeks of Therapy

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Key Takeaways
- An exploratory analysis compared low-level viremia and lymphocyte outcomes in virologically suppressed people with HIV (PWH) receiving either long-acting cabotegravir + rilpivirine (CAB + RPV LA) intramuscular injections every 2 months (Q2M IM), CAB + RPV LA injections every month (Q1M IM), or daily oral abacavir/dolutegravir/lamivudine (ABC/DTG/3TC).
- Low and comparable numbers of “blips” of temporarily increased viral load were experienced by participants receiving Q2M IM, Q1M IM, and ABC/DTG/3TC across study visits in ATLAS-2M and FLAIR; blips were not associated with virologic failure and did not affect overall proportions maintaining virologic suppression.
- Long-acting Q2M IM and Q1M IM HIV-1 RNA blip, low-level viremia (HIV-1 RNA <40 c/mL), and target not detected (TND), and/or HIV-1 RNA <2 c/mL, and CD4+ and CD8+ ratio outcomes were similar to those with daily oral ABC/DTG/3TC through at least 96 weeks.

Introduction
- CAB + RPV LA is the only long-acting therapy approved for maintenance of viral suppression in PWH who are already virologically suppressed.3
- Non-inferiority of CAB + RPV LA administered Q2M IM or Q1M IM through Week 152 was demonstrated in the phase 3b ATLAS-2M study,1 and non-inferiority of CAB + RPV LA administered Q1M IM to daily oral ABC/DTG/3TC through Week 96 was demonstrated in the phase 3 FLAIR study.4
- Week 48 study data showed that the proportion of participants with HIV-1 RNA blips (single HIV-1 RNA values between 50 to <200 c/mL with adjacent values <50 c/mL), TND, and HIV-1 RNA <2 c/mL were similar in the CAB + RPV LA Q2M IM and Q1M IM and daily oral ABC/DTG/3TC groups.2
- Blips were not associated with developing confirmed virologic failure (CVF), defined as ≥2 consecutive HIV-1 RNA >200 c/mL.
- Here we report HIV-1 RNA blip, TND, HIV-1 RNA <2 c/mL, and CD4+ and CD8+ ratio data and the impact of HIV-1 RNA blips on CVF through Week 96 in the FLAIR study and Week 152 in the ATLAS-2M study.

Results
- The proportion of participants with at least 1 HIV-1 blip was similar between the CAB + RPV LA Q2M IM and Q1M IM groups at Week 152 in ATLAS-2M and between the Q1M IM CAB + RPV LA and ABC/DTG/3TC groups at Week 96 in FLAIR.5
- In the ATLAS-2M Q2M IM and Q1M IM groups, 11/522 (2%) and 5/523 (1%) participants met CVF criteria through Week 152, respectively.1
- Most CVF in the Q1M IM CAB + RPV LA group occurred between Weeks 19-23 (71%) of participants who experienced on-treatment adverse events (1 participant was non-adherent to a previous protease inhibitor-based regimen).2
- In FLAIR, 4/202 (1%) participants in the Q1M IM group and 4/283 (1%) in the ABC/DTG/3TC group met CVF criteria through Week 96.9
- In the FLAIR Q1M IM group, 1 participant had a CAB/RPV virus detected due to a false-positive pregnancy test upon induction of oral therapy; a suspected virologic failure was confirmed.9

Table 1. Participants With Blips and/or CVF at Week 152 (ATLAS-2M; ITT-E) or Week 96 (FLAIR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
<th>CAB (196)</th>
<th>ABC/DTG/3TC (200)</th>
<th>CAB (197)</th>
<th>ABC/DTG/3TC (199)</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>392/396</td>
<td>392/396</td>
<td>392/396</td>
<td>392/396</td>
<td></td>
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<tr>
<td>With blips</td>
<td>22/46</td>
<td>22/46</td>
<td>22/46</td>
<td>22/46</td>
<td></td>
</tr>
<tr>
<td>Without blips</td>
<td>370/370</td>
<td>370/370</td>
<td>370/370</td>
<td>370/370</td>
<td></td>
</tr>
</tbody>
</table>

- At Week 152 in ATLAS-2M and Week 96 in FLAIR, the proportions of participants with HIV-1 RNA <50 c/mL were generally similar between study groups, regardless of whether participants had blips.
- Few participants with HIV-1 RNA blips had viral loads >200 c/mL.

Figure 1. Snapshot Outcomes by Presence of Blips in ATLAS-2M at Week 152 (ITT-E)

Figure 2. Snapshot Outcomes by Presence of Blips in FLAIR at Week 96 (ITT-E)

Methods
- ATLAS-2M and FLAIR are phase 3b and 3, respectively, randomized (1:1), open-label studies assessing efficacy and safety of CAB + RPV LA Q2M IM or Q1M IM; the primary endpoint of each was the proportion of participants with HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E).
- Eligible participants were ≥18 years with HIV-1 and were either virologically suppressed (HIV-1 RNA <50 c/mL at randomization with no history of virologic failure (ATLAS-3M), or treatment naïve (FLAIR).
- Participants were given IM injections of CAB LA 600 mg + RPV LA 900 mg Q2M IM (ATLAS-2M group) or CAB LA 400 mg + RPV LA 600 mg Q1M IM (ATLAS-2M group) as maintenance doses or remained on current antiretroviral regimen (FLAIR ABC/DTG/3TC group).
- CAB + RPV LA-naïve participants received a 4-week lead-in of daily CAB 30 mg + RPV 25 mg.
- This exploratory study quantitatively and qualitatively analyzed plasma HIV-1 RNA samples from participants baseline through Week 96 in the FLAIR study and from baseline through Week 152 in the ATLAS-2M study.
- Quantitative HIV-1 RNA values between 50 to <200 c/mL and adjacent HIV-1 RNA values <50 c/mL were continuously <4% of participants with HIV-1 RNA >40 c/mL.
- Participants with HIV-1 RNA <40 c/mL and qualitative TND (not plotted above) were assessed using Abbott RealTime HIV-1 assay (Abbott Molecular Inc, Des Plaines, IL, USA) on every available sample through Week 96 in FLAIR and Week 152 in ATLAS-2M. Study baseline samples were assessed using Linea HIV-1 Super Assay (Research Triangle Park, NC). Lymphocyte subsets were assessed using flow cytometry (Q2 Solutions, Durham, NC).

Figure 3. Proportion of Participants With Blips by Visit (ITT-E)

Figure 4. Proportion of Participants With HIV-1 RNA <40 c/mL and Qualitative Target Not Detected by Visit (ITT-E)

Figure 5. Proportion of Participants With Low-Copy (<2 c/mL) Plasma HIV-1 RNA (ITT-E)

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