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

P083

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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 1 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+/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[1,2]
- Non-inferiority of CAB + RPV LA administered Q2M IM to Q1M IM through Week 152 was demonstrated in the phase 3b ATLAS-2M study,[3] 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[5]
  - 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+/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

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 aged ≥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-2M), or treatment naive (FLAIR)
- Participants were given IM injections of CAB LA 600 mg + RPV LA 900 mg Q2M (ATLAS-2M Q2M IM group) or CAB LA 400 mg + RPV LA 600 mg Q1M (ATLAS-2M and FLAIR Q1M IM groups) as maintenance doses or remained on current antiretroviral regimen (FLAIR ABC/DTG/3TC group)
  - CAB + RPV LA–naive participants received a 4-week oral lead-in of daily CAB 30 mg + RPV 25 mg
- This exploratory study quantitatively and qualitatively analyzed plasma HIV-1 RNA samples from participants from baseline through Week 96 in the FLAIR study and from baseline through Week 152 in the ATLAS-2M study
  - Quantitative blips and qualitative TD/TND outcomes were assessed using Abbott RealTime HIV-1 assay (Abbott Molecular Inc, Des Plaines, IL), low-copy HIV-1 RNA (<2 c/mL) was assessed using bioMONTR Labs HIV-1 SuperLow Assay (Research Triangle Park, NC), and lymphocyte subsets were assessed using flow cytometry (Q2 Solutions, Durham, NC)

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
  - In the ATLAS-2M Q2M IM and Q1M IM groups, 11/522 (2%) and 2/523 (<1%) participants met CVF criteria through Week 152, respectively
    - Most CVFs in ATLAS-2M occurred by Week 48 (10/13 [77%]); 12/13 participants resuppressed on alternative treatment regimens (1 participant was non-adherent to a protease inhibitor–based regimen)
  - In FLAIR, 4/283 (1%) participants in the Q1M IM group and 4/283 (1%) in the ABC/DTG/3TC group met CVF criteria through Week 96
    - In the FLAIR Q1M IM group, 1 participant had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test; upon re-initiation of oral therapy, a suspected virologic failure was confirmed

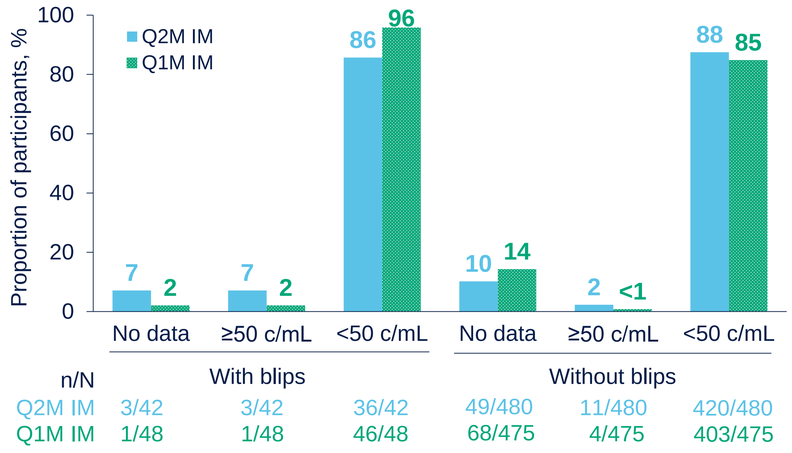
Table 1. Participants With Blips and/or CVF at Week 152 (ATLAS-2M; ITT-E) or Week 96 (FLAIR; ITT-E)

	ATLAS-2M (Week 152)		FLAIR (Week 96)	
Parameter, n/N (%)	**Q2M IM**	**Q1M IM**	**Q1M IM**	**ABC/DTG/3TC**
Participants with blips[a]	42/522 (8)	48/523 (9)	45/283 (16)	48/283 (17)
CVF[b] in participants with blips	1/42 (2)[c]	0/48	0/45	1/48 (2)

CVF, confirmed virologic failure; IM, intramuscular; Q1M, monthly dosing. [a]Defined as HIV-1 RNA values between 50 to <200 c/mL and adjacent HIV-1 RNA values <50 c/mL. [b]Defined as 2 consecutive HIV-1 RNA ≥200 c/mL.[3,4] [c]Participant met CVF criteria at Week 24.

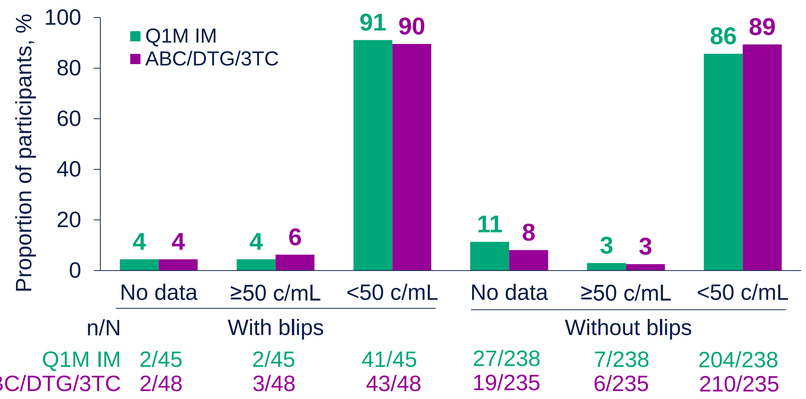
- At Week 152 in ATLAS-2M and Week 96 in FLAIR, the proportions of participants with HIV-1 RNA <50 c/mL were generally similar between treatment groups, regardless of whether participants had blips
  - Few participants with HIV-1 RNA blips had viral loads ≥50 c/mL

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



n/N	With blips			Without blips		
Q2M IM	3/42	3/42	36/42	49/480	11/480	420/480
Q1M IM	1/48	1/48	46/48	68/475	4/475	403/475

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



n/N	With blips			Without blips		
Q1M IM	2/45	2/45	41/45	27/238	7/238	204/238
ABC/DTG/3TC	2/48	3/48	43/48	19/235	6/235	210/235

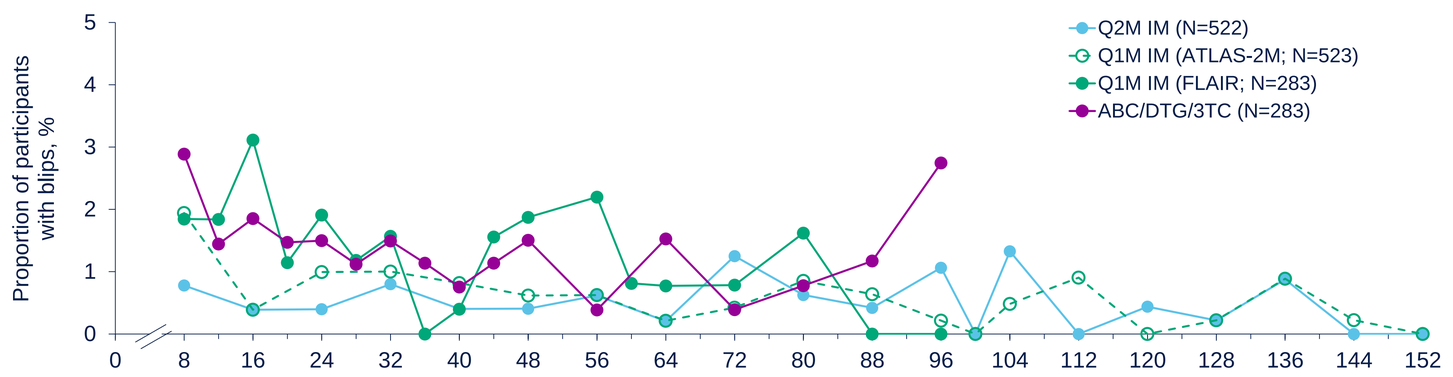
IM, intramuscular; Q1M, monthly dosing. Blips are defined as HIV-1 RNA values between 50 to <200 c/mL and adjacent HIV-1 RNA values <50 c/mL.

- Proportions of participants with blips were consistently <4% of participants with available data across all studies and treatment groups at any time point

Low-Level Viremia Outcomes

- In each scheduled visit window, >70% of participants had HIV-1 RNA <40 c/mL and qualitative TND outcomes across all studies and treatment groups
- The proportion of participants with HIV-1 RNA <2 c/mL was comparable between groups through Week 152 in ATLAS-2M and between groups through Week 96 in FLAIR

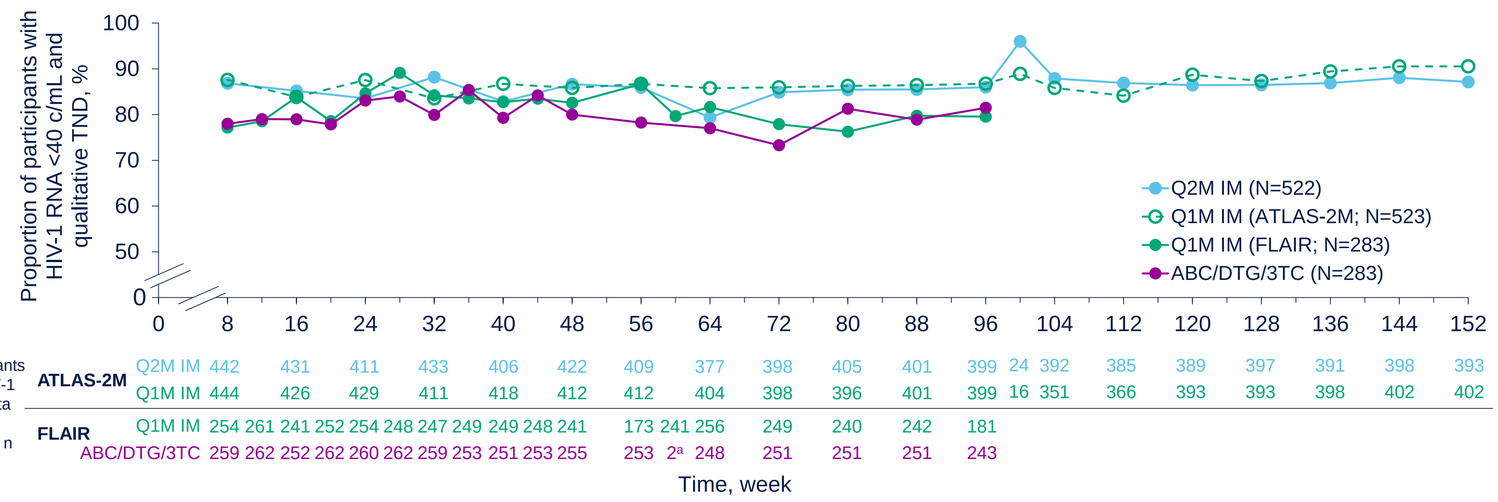
Figure 3. Proportion of Participants With Blips by Visit (ITT-E)



Participants with HIV-1 RNA data in visit window, n																								
ATLAS-2M	Q2M IM	514	514	503	500	496	493	487	483	480	479	476	470	26	452	449	456	460	457	454	454
	Q1M IM	515	513	503	499	490	487	481	473	473	470	470	469	19	414	442	446	454	451	449	445
FLAIR	Q1M IM	271	272	257	262	262	254	255	255	251	257	267	182	246	259	255	247	249	248		
	ABC/DTG/3TC	277	277	270	272	267	268	268	264	265	264	266	259	3[a]	262	256	258	256	255		

IM, intramuscular; Q1M, monthly dosing. Blips are defined as HIV-1 RNA values between 50 to <200 c/mL and adjacent HIV-1 RNA values <50 c/mL. Week 8 is the first maintenance week; Weeks 0-4 are the induction period. [a]Week 60 was not a scheduled HIV-1 RNA assessment visit for participants in the ABC/DTG/3TC group; 0/3 ABC/DTG/3TC participants with HIV-1 RNA data had a blip at Week 60 (not plotted above).

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



Participants with HIV-1 RNA data in visit window, n																								
ATLAS-2M	Q2M IM	442	431	411	433	406	422	409	377	398	405	401	399	24	392	385	389	397	391	398	393
	Q1M IM	444	426	429	411	418	412	412	404	398	396	401	399	16	351	366	393	393	398	402	402
FLAIR	Q1M IM	254	261	241	252	254	248	247	249	249	248	241	173	241	256	249	240	242	181		
	ABC/DTG/3TC	259	262	252	262	260	262	259	253	251	253	255	253	2[a]	248	251	251	251	243		

IM, intramuscular; TND, target not detected; Q1M, monthly dosing. Blips are defined as HIV-1 RNA values between 50 to <200 c/mL and adjacent HIV-1 RNA values <50 c/mL. Week 8 is the first maintenance week; Weeks 0-4 are the induction period. [a]Week 60 was not a scheduled HIV-1 RNA assessment visit for participants in the ABC/DTG/3TC group; 1/2 (50%) ABC/DTG/3TC participants with HIV-1 RNA data at Week 60 had HIV-1 RNA <40 c/mL and qualitative TND (not plotted above).

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

- CD4+/CD8+ ratios were similar at individual study visits between treatment groups and in those with vs without blips
- Mean (SD) ratios in the Q2M IM and Q1M IM groups in ATLAS-2M increased from baseline to Week 152 (with blips: 0.93 [0.48] to 1.09 [0.58] and 1.21 [0.63] to 1.38 [0.81], respectively; without blips, 1.07 [0.51] to 1.14 [0.53] and 1.11 [0.61] to 1.23 [0.70], respectively)
- Mean (SD) ratios in the Q1M IM and ABC/DTG/3TC groups in FLAIR increased from baseline to Week 96 (with blips: 0.78 [0.45] to 1.08 [0.57] and 0.75 [0.43] to 0.97 [0.56], respectively; without blips, 0.83 [0.41] to 1.12 [0.50] and 0.84 [0.41] to 1.08 [0.47], respectively)

Conclusions

- The proportion of participants with HIV-1 RNA blips, TND, HIV-1 RNA <2 c/mL, and mean CD4+/CD8+ ratio (with and without blips) was similar between the Q2M IM and Q1M IM CAB + RPV LA groups through Week 152 in ATLAS-2M and between the Q1M IM CAB + RPV LA and oral ABC/DTG/3TC groups through Week 96 in FLAIR
- The number of CVFs in ATLAS-2M and FLAIR is low and the presence of HIV-1 RNA blips was not associated with CVF development through Week 152 and Week 96, respectively
  - Of the 17 total CVFs on CAB + RPV LA, only 1 had a transient blip; these data and the overall rate of blips being similar support that blips alone do not identify those at risk of CVF
- These data support the robustness of CAB + RPV LA for the maintenance of virologic suppression in PWH

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References: 1. Cabenuva [prescribing information]. ViiV Healthcare; 2022. **2.** Panel on Antiretroviral Guidelines for Adults and Adolescents. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed August 22, 2022. **3.** Overton et al. CROI 2022; Virtual. Poster 479. **4.** Orkin et al. *Lancet HIV*. 2021;8:e185-e196. **5.** Talarico et al. IDWeek™ 2020; Virtual. Poster 1021.

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