P168

Drug-Related Neuropsychiatric Adverse Events Across Phase 3/3b Studies of Long-Acting Cabotegravir + Rilpivirine Through Week 48

Emilie Elliot[1], Paula Teichner[2], Samia Dakhia[1], Joseph W. Polli[2], Parul Patel[2], Louise Garside[3], Sri Byrapuneni[4], Shanker Thiagarajah[5], Ronald D'Amico[2], Rodica Van Solingen-Ristea[6], Eileen Birmingham[7], Bryan Baugh[8], Jean van Wyk[1]

[1]ViiV Healthcare, Brentford, United Kingdom; [2]ViiV Healthcare, Research Triangle Park, NC, United States; [3]PHASTAR, Macclesfield, United Kingdom; [4]Parexel International, Research Triangle Park, NC, United States; [5]GSK, London, United Kingdom; [6]Janssen Research & Development, Beerse, Belgium; [7]Janssen Research & Development LLC, Raritan, NJ, United States; [8]Janssen Research & Development, Titusville, NJ, United States

Key Takeaways

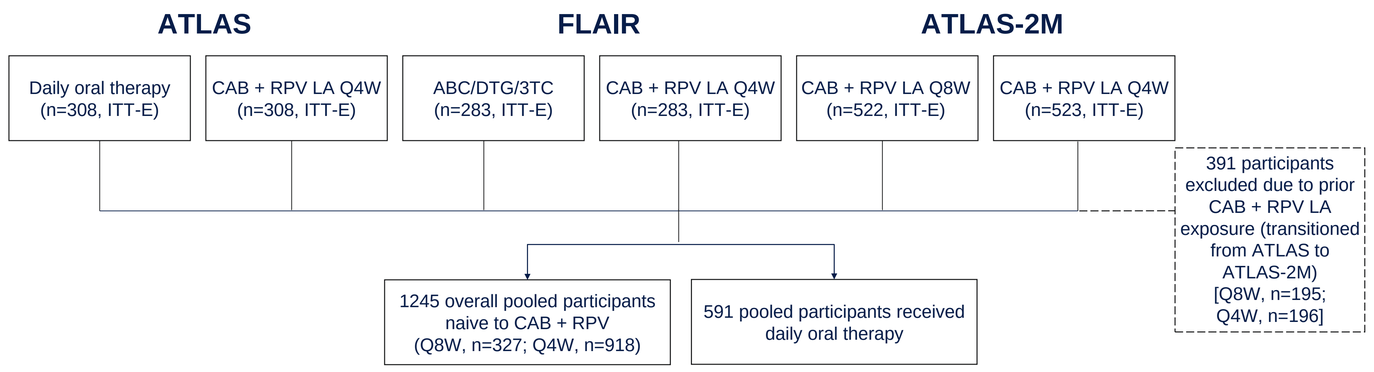
- **This *post hoc* analysis summarizes drug-related neuropsychiatric adverse events (NPAEs) in participants in the ATLAS, FLAIR, and ATLAS-2M Phase 3/3b studies.**
- **Overall, drug-related NPAEs were reported in 9% of participants receiving cabotegravir + rilpivirine long-acting (CAB + RPV LA) through 48 weeks; most drug-related NPAEs were mild to moderate in severity, with few Grade 3 events and few leading to treatment withdrawal.**
- **The NPAE safety profile presented supports the use of CAB + RPV LA as a complete regimen for the maintenance treatment of HIV-1.**

Introduction

- CAB + RPV LA administered monthly[1,2] or every 2 months[3] is the first and only complete LA regimen recommended by treatment guidelines for the maintenance of virologic suppression in people living with HIV-1.[4,5]
- In Phase 3/3b trials, CAB + RPV LA dosed every 4 weeks (Q4W) was noninferior to daily oral antiretroviral therapy (ART) and CAB + RPV LA dosed every 8 weeks (Q8W) was noninferior to Q4W through 152 weeks.[1–3,6,7]
- NPAEs have been reported with antiretrovirals including integrase strand transfer inhibitors (INSTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[8,9]
  - NPAEs listed in the CAB + RPV LA product label include headache, dizziness, somnolence, vasovagal reactions (injection-related), depression, anxiety, abnormal dreams, insomnia, poor-quality sleep, and depressed mood.[10–13]
- This *post hoc* analysis provides information on drug-related NPAEs in participants in the ATLAS (NCT02951052), FLAIR (NCT02938520), and ATLAS-2M (NCT03299049) Phase 3/3b studies in order to contextualize labeled NPAEs.

Methods

Figure 1. Participants Analyzed



3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Data from CAB + RPV–naive participants in the open-label switch studies ATLAS, FLAIR, and ATLAS-2M were pooled (**Figure 1**).
- Incidence and characteristics of NPAEs (most commonly reported or of special interest) through Week 48 were summarized.
- Adverse events (AEs) were classified as drug-related or non-drug-related following assessment by investigators during the trials according to study protocols.
- Results beyond Week 48 for FLAIR (Week 124) and ATLAS-2M (Week 152) are also briefly described.

Results

Table 1. Baseline Characteristics From the Pooled ATLAS, FLAIR, and ATLAS-2M Studies

ITT-E population	CAB + RPV LA Q8W (n=327)	CAB + RPV LA Q4W (n=918)	Daily oral therapy* (n=591)
Median age (range), years	41 (20–83)	39 (19–74)	38 (18–82)
Female sex at birth, n (%)	73 (22)	237 (26)	168 (28)
Race, n (%)			
White	238 (73)	686 (75)	408 (69)
Black or African American	57 (17)	154 (17)	133 (23)
Other races	32 (10)	78 (8)	48 (8)
Pre-switch ART regimen, n (%)			
INSTI-based	136 (42)	526 (57)	382 (65)
EFV-based	83 (25)	170 (19)	105 (18)
NNRTI-based	151 (46)	311 (34)	155 (26)
Psychiatric medication use at baseline	56 (17)	147 (16)	102 (17)
History of substance abuse	22 (7)	107 (12)	61 (10)

*Participants receiving DTG-based regimen (FLAIR, n=283) or INSTI-, NNRTI-, or PI-based oral comparator therapy (ATLAS, n=308). †FLAIR participants continued induction therapy (DTG-based) and ATLAS participants continued the daily oral therapy they entered the study on. ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- In total, 1245 participants were randomized to switch to CAB + RPV LA, dosed Q8W (n=327) or Q4W (n=918), and 591 continued daily oral therapy† (ATLAS and FLAIR studies only).
- Baseline characteristics were comparable between treatment groups (**Table 1**).

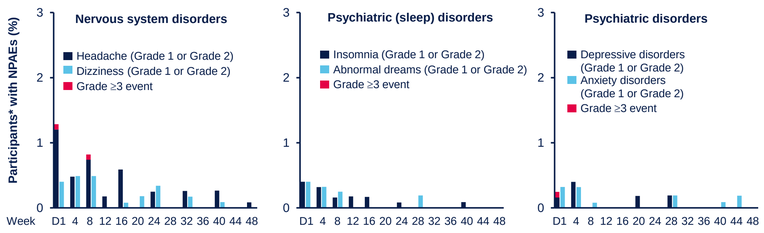
Table 2. NPAEs Through Week 48 by Treatment Regimen

ITT-E population, n (%)	CAB + RPV LA Q8W + Q4W pooled (n=1245)	Daily oral therapy (n=591)
Participants with AEs (excluding ISRs)	1035 (83)	444 (75)
Participants with NPAEs	319 (26)	104 (18)
Participants with drug-related AEs (excluding ISRs)	335 (27)	35 (6)
Participants with drug-related NPAEs	111 (9)	14 (2)
Grade 3*†	4 (<1)	1 (<1)
Serious	0	1 (<1)
Leading to withdrawal	10 (<1)	3 (<1)
Drug-related NPAEs occurring in ≥5 participants‡		
Nervous system disorders		
Headache	41 (3)	4 (<1)
Dizziness	23 (2)	1 (<1)
Psychiatric disorders		
Insomnia	15 (1)	1 (<1)
Abnormal dreams	12 (<1)	2 (<1)
Anxiety disorders§	11 (<1)	3 (<1)
Depressive disorders‖	10 (<1)	1 (<1)
Suicidal ideation/behavior¶	1 (<1)	1 (<1)
Other (of potential interest)		
Seizures/seizure-like events	0	0

*There were no Grade 4 or 5 NPAEs. †CAB + RPV LA: headache (n=2); depression (n=1); sleep disorders (n=1). Daily oral therapy: depression (n=1). ‡Occurred in ≥5 participants except for the suicidal ideation/behavior category. §Includes the following recorded terms: anxiety, anxiety disorder, nervousness, and panic attack. ‖Includes the following recorded terms: depression, depressed mood, and adjustment disorder with depressed mood. ¶Includes the following recorded terms: depression suicidal and suicidal ideation.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; ITT-E, intention-to-treat exposed; LA, long-acting; NPAE, neuropsychiatric adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- In total, 9% (n=111/1245) of participants reported drug-related NPAEs, of which 96% (n=107/111) reported Grade 1 or 2 events (**Table 2**).
- Headache was reported in 3% (n=41/1245) of participants in the LA arm, with insomnia and abnormal dreams both occurring in ≤1% (n=15/1245 and n=12/1245, respectively) of participants.
- No participants experienced drug-related Grade 4, Grade 5, or serious NPAEs in the LA arm.
- Withdrawal due to drug-related NPAEs occurred in <1% (n=10/1245) of participants in the LA arm, and was similar to the oral therapy arm (<1%, n=3/591).

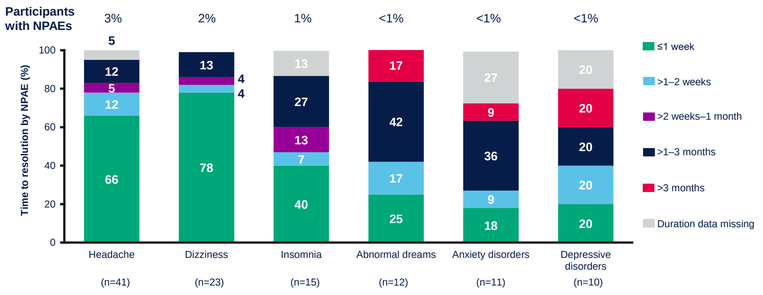
Figure 2. Incidence of Drug-Related NPAEs Occurring in ≥5 Participants Receiving CAB + RPV LA Through Week 48



*Day 1, n=1245; W4, n=1237; W8, n=1217; W12, n=568; W16, n=1185; W20, n=542; W24, n=1194; W28, n=523; W32, n=1152; W36, n=530; W40, n=1130; W44, n=533; W48, n=1159. Number of participants decreases at W12, W20, W28, W36, and W44 due to Q8W dosing regimen.
CAB, cabotegravir; D, day; LA, long-acting; NPAE, neuropsychiatric adverse event; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

- Most drug-related NPAEs were Grade 1 or 2 in severity.
- Drug-related NPAEs occurred infrequently (<2% at each time point), with more frequent reporting at Week 4, 8, and 12 compared with later time points (**Figure 2**).

Figure 3. Duration of Drug-Related NPAEs Occurring in ≥5 Participants Receiving CAB + RPV LA Through Week 48



CAB, cabotegravir; LA, long-acting; NPAE, neuropsychiatric adverse event; RPV, rilpivirine.

- Most neurological AEs (headache and dizziness) resolved in ≤7 days (**Figure 3**); the durations of sleep disorders (insomnia and abnormal dreams) and psychiatric disorders (anxiety and depressive disorders) were more varied.

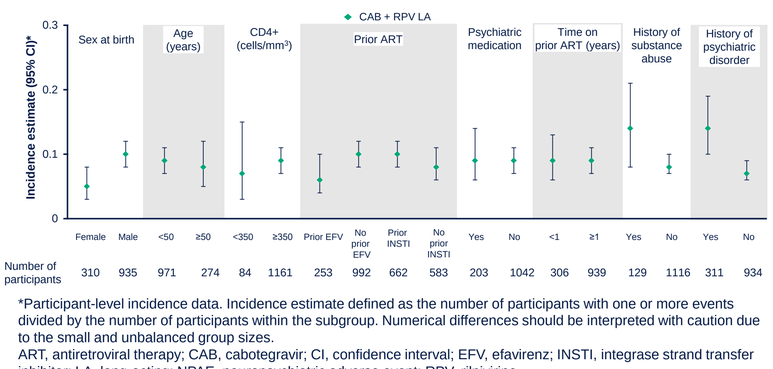
Table 3. Drug-Related NPAEs Leading to Withdrawal Through Week 48*

ITT-E population, n (%)	CAB + RPV LA Q8W + Q4W pooled (n=1245)	Daily oral therapy (n=591)
Participants with drug-related NPAEs leading to withdrawal	10 (<1)	3 (<1)
Nervous system disorders		
Headache	4 (<1)	0
Dizziness	1 (<1)	1 (<1)
Dysarthria	0	1 (<1)
Psychiatric disorders		
Insomnia	1 (<1)	0
Abnormal dreams	2 (<1)	0
Anxiety disorders†	1 (<1)	1 (<1)
Depressive disorders‡	1 (<1)	1 (<1)
Suicidal ideation/behavior§	1 (<1)	1 (<1)
Fear	1 (<1)	0
Sleep disorders	2 (<1)	0
Disturbance in attention	1 (<1)	1 (<1)
Amnesia	0	1 (<1)

***Participants may have had more than one drug-related NPAE leading to withdrawal**. †Includes the following recorded terms: anxiety, anxiety disorder, nervousness, and panic attack. ‡Includes the following recorded terms: depression, depressed mood, and adjustment disorder with depressed mood. §Includes the following recorded terms: depression suicidal and suicidal ideation.
CAB, cabotegravir; LA, long-acting; NPAE, neuropsychiatric adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Withdrawals due to drug-related NPAEs were infrequent (<1%, n=10/1245) (**Table 3**) and most commonly occurred in the first 16 weeks of CAB + RPV LA therapy (n=7/10).
- Most participants (n=6/10) withdrew due to Grade 1 or 2 drug-related NPAEs.

Figure 4. Drug-Related NPAEs for CAB + RPV LA Through Week 48 by Demographics



*Participant-level incidence data. Incidence estimate defined as the number of participants with one or more events divided by the number of participants within the subgroup. Numerical differences should be interpreted with caution due to the small and unbalanced group sizes.
ART, antiretroviral therapy; CAB, cabotegravir; CI, confidence interval; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; LA, long-acting; NPAE, neuropsychiatric adverse event; RPV, rilpivirine.

- For participants receiving CAB + RPV LA, the incidence of drug-related NPAEs was highest for those with a history of psychiatric disorder or substance abuse (**Figure 4**).

Table 4. NPAEs for CAB + RPV LA Beyond Week 48

ITT-E population, n (%)	FLAIR* Week 0–48 (n=283)	FLAIR* Week 48–124 (participants with new events)† (n=283)	ATLAS-2M‡ Week 0–48 (n=1045)	ATLAS-2M‡ Week 48–152 (participants with new events)† (n=1045)
Participants with AEs (excluding ISRs)	246 (87)	25 (9)	844 (81)	115 (11)
Participant with NPAEs	84 (30)	41 (14)	224 (21)	196 (19)
Participants with drug-related AEs (excluding ISRs)	79 (28)	23 (8)	234 (22)	75 (7)
Participants with drug-related NPAEs	28 (10)	13 (5)	68 (7)	22 (2)
Grade 3§‖	1 (<1)	0	3 (<1)	2 (<1)
Serious	0	0	1 (<1)	0
Leading to withdrawal	0	2 (<1)	9 (<1)	0

*FLAIR participants received CAB + RPV LA dosed Q4W. †Participants having events with onset during FLAIR Week 48–124 and ATLAS-2M Week 48–152 with no events in the Week 0–48 period. ‡ATLAS-2M participants received CAB + RPV LA dosed Q8W (n=327) or Q4W (n=327). §There were no Grade 4 or 5 NPAEs. ‖FLAIR: poor-quality sleep, n=1. ATLAS-2M: depression, n=1; presyncope, n=2; disturbance in attention, n=1; autonomic nervous system disorder, n=1. AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; NPAE, neuropsychiatric adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- 13 (5%) participants in FLAIR and 22 (2%) in ATLAS-2M had newly reported drug-related NPAEs after Week 48; of these, 94% (n=33/35) were Grade 1 or 2 (**Table 4**).
- After Week 48, the most frequent newly reported drug-related NPAEs were dizziness, headache, and depressed mood for FLAIR, and headache, dizziness, and presyncope for ATLAS-2M.

Conclusions

- Overall, drug-related NPAEs were reported in 9% of participants receiving CAB + RPV LA, with headache (3%) and dizziness (2%) most frequently reported.
- Most drug-related NPAEs were mild to moderate in severity, with few Grade 3 events and few events leading to treatment withdrawal.
- There were no drug-related NPAEs reported as serious by investigators for participants receiving CAB + RPV LA through Week 48.
- The most common drug-related NPAEs occurred earlier in treatment, with a generally lower incidence thereafter, and resolved during the study.
- Drug-related NPAEs were among factors taken into consideration for labeling for CAB + RPV LA; the NPAE profile supports the safety of CAB + RPV LA as a complete regimen for the maintenance treatment of HIV-1.

Acknowledgments: This analysis was funded by ViiV Healthcare. The authors thank everyone who contributed to the success of ATLAS, FLAIR, and ATLAS-2M, all study participants and their families, and the clinical investigators and their staff. Editorial assistance was provided by Poppie Cooper of Scimentum (Nucleus Global), with funding provided by ViiV Healthcare.

References: 1. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123. **2.** Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135. **3.** Overton ET, et al. *Lancet*. 2020;396(10267):1994–2005. **4.** U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://clinicalinfo.hiv.gov/en/guidelines. Accessed September 2022. **5.** Saag MS, et al. *JAMA*. 2020;324(16):1651–1669. **6.** Orkin C, et al. *Lancet HIV*. 2021;8(4):e185–e196. **7.** Overton T, et al. CROI 2022 (Poster 479). **8.** Kolakowska A, et al. *Curr Treat Options Infect Dis*. 2019;11(14):372–387. **9.** Senneker T, et al. *Curr Opin HIV AIDS*. 2021;16(6):309–320. **10.** ViiV Healthcare. Cabenuva PI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf. Accessed September 2022. **11.** Rekambys PI. Available from: https://www.ema.europa.eu/en/documents/product-information/rekambys-epar-product-information_en.pdf. Accessed September 2022. **12.** Vocabria PI. Available from: https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf. Accessed September 2022.

Presenting author: Emilie Elliot; emilie.x.elliot@viivhealthcare.com

This content was acquired following an unsolicited medical information enquiry by a healthcare professional. Always consult the product information for your country, before prescribing a ViiV medicine. ViiV does not recommend the use of our medicines outside the terms of their licence. In some cases, the scientific Information requested and downloaded may relate to the use of our medicine(s) outside of their license.