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Resolution of neuropsychiatric adverse events after switching to a doravirine-based regimen in the open-label extensions of the DRIVE-AHEAD and DRIVE-FORWARD trials

Graeme Moyle[1]; Hong Wan[2]; Fanxia Meng[2]; Rebeca M. Plank[2]; Peter Sklar[2a]; Rima Lahoulou[3]

[1]Chelsea & Westminster Hospital, London, United Kingdom; [2]Merck & Co., Inc., Rahway, NJ, USA; [3]MSD France, Puteaux, France

[a]An employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time of the study

Background

- Neuropsychiatric adverse events (NPAEs) have been associated with a number of different antiretrovirals
- For the integrase inhibitors dolutegravir and bictegravir, discontinuation due to NPAEs was higher in real-life settings than in randomized controlled trials
  - In a retrospective cohort study, 5.6% of 1073 participants had discontinued dolutegravir within 12 months because of NPAEs, a significantly higher rate than that found for elvitegravir or raltegravir[1]
  - In a retrospective analysis, 31 (3.3%) of 943 participants had discontinued the fixed-dose combination of bictegravir with emtricitabine (FTC) and tenofovir alafenamide because of NPAEs after a median follow-up of 6.2 months[2]
- For efavirenz (EFV), a non–nucleoside reverse transcriptase inhibitor (NNRTI), NPAEs are the most common types of side effects, occurring in 40%-60% of participants, and are the main reason for switching to a different therapy[3]
- Doravirine (DOR), a next-generation NNRTI, does not significantly interact in vitro with known neurotransmitter receptors[4] and has demonstrated a favorable NPAE profile in clinical trials (**Table 1**)
  - In the DRIVE-AHEAD phase 3 trial, participants receiving the fixed combination of DOR with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) as first-line therapy had a significantly lower rate of NPAEs (26.4%) at week 96 than participants who received EFV/FTC/TDF (58.5%)[5]
  - In the DRIVE-FORWARD phase 3 trial, the rate of NPAEs at week 96 was similar for participants receiving DOR with 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs, 15.7%) and those receiving ritonavir-boosted darunavir (DRV/r) with 2 NRTIs (18.8%) [data on file]

Table 1. Most common NPAEs during double-blind phase of DRIVE-AHEAD and DRIVE-FORWARD (weeks 0-96)

	DRIVE-AHEAD		DRIVE-FORWARD	
	DOR/3TC/TDF (N = 364)	EFV/FTC/TDF (N = 364)	DOR + 2 NRTIs (N = 383)	DRV/r + 2 NRTIs (N = 383)
Participants with 1 or more NPAEs	96 (26.4)	213 (58.5)	60 (15.7)	72 (18.8)
Sleep disorders and disturbances	**51 (14.0)**	**100 (27.5)**	**34 (8.9)**	**30 (7.8)**
Abnormal dreams	18 (4.9)	44 (12.1)	5 (1.3)	3 (0.8)
Insomnia	25 (6.9)	38 (10.4)	18 (4.7)	20 (5.2)
Nightmare	12 (3.3)	18 (4.9)	2 (0.5)	5 (1.3)
Sleep disorder	5 (1.4)	12 (3.3)	11 (2.9)	4 (1.0)
Dizziness	**37 (10.2)**	**139 (38.2)**	**20 (5.2)**	**19 (5.0)**
Depression and related disorders	**19 (5.2)**	**27 (7.4)**	**12 (3.1)**	**22 (5.7)**
Depressed mood	6 (1.6)	8 (2.2)	3 (0.8)	2 (0.5)
Depression	9 (2.5)	13 (3.6)	8 (2.1)	15 (3.9)
Altered sensorium	**18 (4.9)**	**31 (8.5)**	**4 (1.0)**	**15 (3.9)**
Lethargy	2 (0.5)	0	0	6 (1.6)
Somnolence	13 (3.6)	28 (7.7)	3 (0.8)	6 (1.6)
Psychosis and psychotic disorders	**2 (0.5)**	**5 (1.4)**	**1 (0.3)**	**1 (0.3)**
Headache[a]	**57 (15.7)**	**56 (15.4)**	**57 (14.9)**	**46 (12.0)**

3TC, lamivudine; ABC, abacavir; AE, adverse event; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; QD, once daily; TDF, tenofovir disoproxil fumarate.

The 5 categories of NPAEs (shown in bold text) were predefined. Specific terms included for each category were based on MedDRA 20.0. A participant with multiple AEs within a category is counted a single time for that category.

Doravirine 100 mg QD and darunavir 800 mg + ritonavir 100 mg QD were administered with FTC/TDF or ABC/3TC.

[a]Headache was not included in the predefined NPAE categories and is not included in the total number of participants with 1 or more NPAEs.

Data shown as n (%).

Objectives

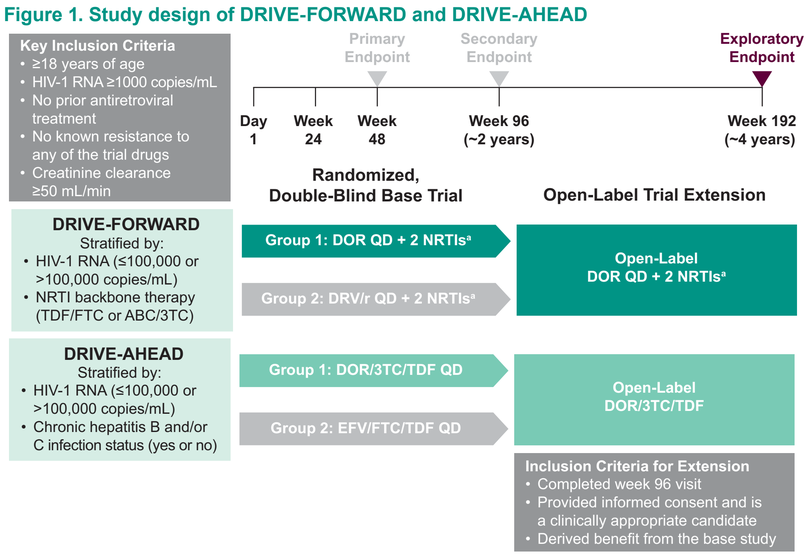
- To examine NPAEs in participants who switched to a DOR-based regimen in the open-label extensions of the DRIVE-AHEAD and DRIVE-FORWARD studies, focusing on resolution of NPAEs that remained ongoing from the double-blind phase, and onset and resolution of new NPAEs after switching to a DOR-based regimen

Methods

Study design and population

- DRIVE-FORWARD (NCT02275780) and DRIVE-AHEAD (NCT02403674) were randomized, double-blind, active-controlled, noninferiority trials in adults with previously untreated HIV-1 (**Figure 1**)
  - Participants were randomly assigned to a DOR regimen (DOR/3TC/TDF or DOR with 2 NRTIs) or the comparator regimen (EFV/FTC/TDF or DRV/r with 2 NRTIs) for 96 weeks of double-blind treatment
  - Upon completing the double-blind phase, eligible participants in the comparator groups could switch to the study-specific DOR-based regimen for 96 weeks in an open-label study extension

Figure 1. Study design of DRIVE-FORWARD and DRIVE-AHEAD

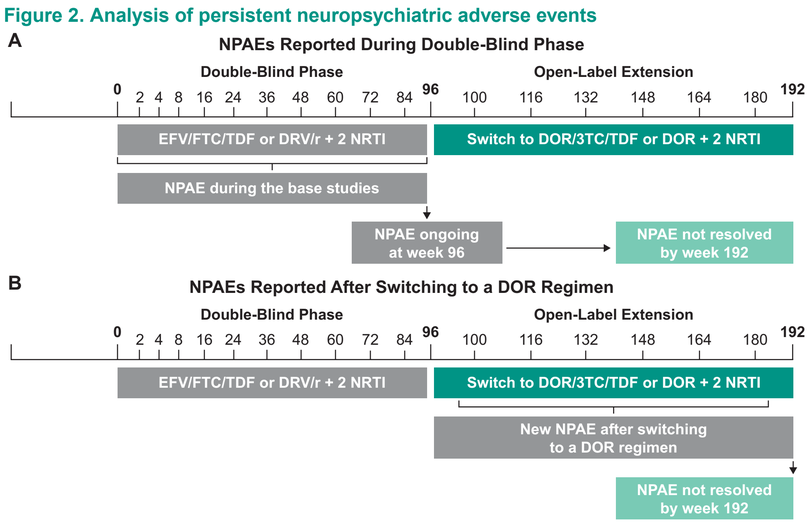


3TC, lamivudine; ABC, abacavir; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; QD, once daily.

[a]NRTIs were TDF/FTC or ABC/3TC.

- We examined the persistence of NPAEs in participants who switched to a DOR-based regimen for the open-label extensions of DRIVE-AHEAD and DRIVE-FORWARD (**Figure 2A**)
  - NPAEs reported for participants in the comparator groups (EFV/TDF/FTC or DRV/r + 2 NRTI) that remained ongoing at week 96 (end of the double-blind base studies and time point at which participants switched to a DOR-based regimens)
  - Of these ongoing NPAEs, how many were not resolved by week 192 (end of the open-label extensions) after switching to a DOR regimen at week 96
- We examined the new onset of NPAEs after the switch to a DOR regimen (weeks 96-192) and how many of these were not resolved by week 192 (**Figure 2B**)
- 5 categories of NPAEs were predefined: sleep disorders, depression and related disorders (suicide/self-injury), dizziness, altered sensorium, and psychoses/psychotic disorders (based on MedDRA 23.0)
  - Headache was not included in the predefined NPAE categories, but it was a commonly reported nervous system AE in the DRIVE-AHEAD and DRIVE-FORWARD trials (**Table 1**). Therefore, the persistence of headache and new onset of headache after switching to a DOR regimen were examined

Figure 2. Analysis of persistent neuropsychiatric adverse events



3TC, lamivudine; ABC, abacavir; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

NRTIs were TDF/FTC or ABC/3TC.

Results

Participant characteristics

- At the end of the double-blind phase (week 96), 269 participants in DRIVE-AHEAD switched from their original double-blind regimen (EFV/FTC/TDF) to open-label DOR/3TC/TDF, and 233 participants in DRIVE-FORWARD switched from their original double-blind regimen (DRV/r + 2 NRTIs) to open-label DOR + 2 NRTIs
  - Characteristics of the participants who switched to the open-label DOR regimen are shown in **Table 2**
- The incidence of NPAEs reported during the double-blind phase among the participants who switched to a DOR regimen (**Table 2**) was similar to that reported by all randomized participants (**Table 1**): 57.6% vs 58.5% in DRIVE-AHEAD; 17.6% vs 18.8% in DRIVE-FORWARD
  - The incidence of headache during the double-blind phase was also similar among participants who switched to a DOR regimen in the extension to that reported for all randomized participants: 16.4% vs 15.4% in DRIVE-AHEAD; 11.2% vs 12.0% in DRIVE-FORWARD

Table 2. Characteristics of participants who switched to a DOR regimen

	DRIVE-AHEAD	DRIVE-FORWARD
	Switch from EFV/FTC/TDF (N = 269)	Switch from DRV/r + 2 NRTIs (N = 233)
Age, mean (SD), years	32.7 (10.1)	35.6 (10.6)
Male, n (%)	229 (85.1)	205 (88.0)
Race, n (%)		
Asian	50 (18.6)	3 (1.3)
Black or African American	41 (15.2)	45 (19.3)
Multiple	45 (16.7)	0 (0)
Other[a]	5 (1.9)	3 (1.3)
White	128 (47.6)	182 (78.1)
Hispanic or Latino, n (%)	92 (34.2)	52 (22.3)
TDF in regimen, n (%)	269 (100)	203 (87.1)
HIV-1 RNA <50 copies/mL at week 96, n (%)	261 (97.0)	210 (90.1)
CD4+ T-cell count at week 96, median (range), cells/mm^3	613 (85-2043)	641 (149-1507)
NPAEs reported during double-blind phase	155 (57.6)	41 (17.6)
Headache reported during double-blind phase	44 (16.4)	26 (11.2)

3TC, lamivudine; ABC, abacavir; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

NRTIs were TDF/FTC or ABC/3TC.

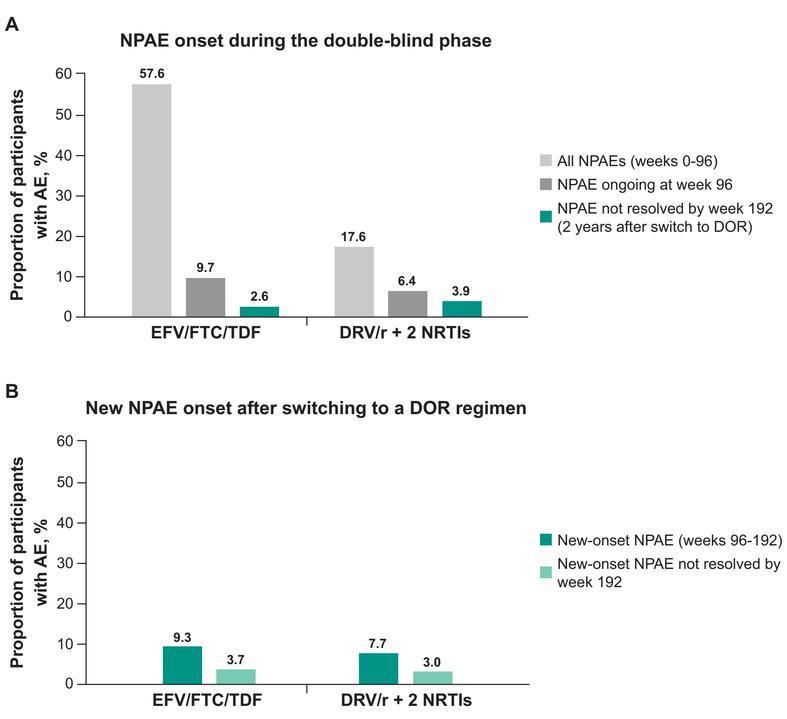
[a]Other race includes multiracial, American Indian, Alaskan native, and Hawaiian/other Pacific Islander.

Data shown as n (%).

Outcomes for NPAEs reported during the double-blind phase

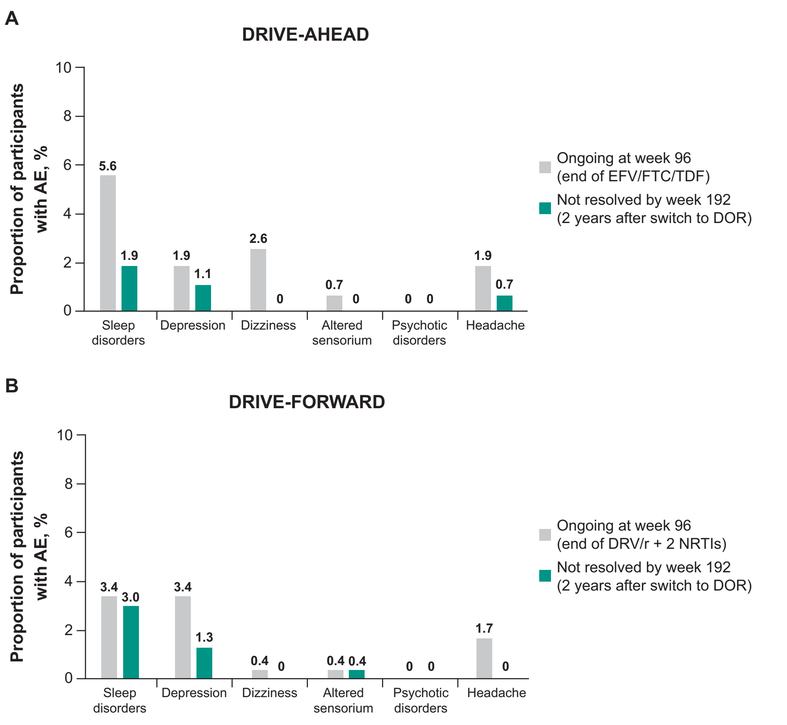
- At the end of the double-blind phase (week 96), NPAEs remained ongoing in 26 of 269 participants (9.7%) on EFV/FTC/TDF and 15 of 233 participants (6.4%) on DRV/r (**Figure 3A**)
- By week 192, these NPAEs were not resolved in 7 participants (2.6%) who switched from EFV/FTC/TDF to DOR/3TC/TDF and in 9 participants (3.9%) who switched from DRV/r + 2 NRTIs to DOR + 2 NRTIs (**Figure 3A**)
- In both studies, the most common NPAEs reported during the double-blind phase that persisted into the extension after switching to a DOR regimen, with an incidence of ≥1%, were sleep disorders and depression (**Figure 4** and **Table 3**)

Figure 3. Overall summary of NPAEs



AE, adverse event; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

Figure 4. Persistence of specific NPAEs with onset during double-blind phase



AE, adverse event; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

Table 3. Persistence of specific NPAEs with onset during double-blind phase that persisted after switching to a DOR regimen in the extension

	DRIVE-AHEAD		DRIVE-FORWARD	
	Switch from EFV/FTC/TDF (N = 269)		Switch from DRV/r + 2 NRTIs (N = 233)	
	Ongoing at week 96	Not resolved by week 192	Ongoing at week 96	Not resolved by week 192
All persisting NPAEs	**26 (9.7)**	**7 (2.6)**	**15 (6.4)**	**9 (3.9)**
Sleep disorders and disturbances	**15 (5.6)**	**5 (1.9)**	**8 (3.4)**	**7 (3.0)**
Abnormal dreams	8 (3.0)	3 (1.1)	0	0
Insomnia	4 (1.5)	1 (0.4)	6 (2.6)	5 (2.1)
Sleep disorder	2 (0.7)	1 (0.4)	2 (0.9)	2 (0.9)
Nightmares	1 (0.4)	0	0	0
Depression and related disorders	**5 (1.9)**	**3 (1.1)**	**8 (3.4)**	**3 (1.3)**
Depression	4 (1.5)	2 (0.7)	5 (2.1)	2 (0.9)
Depressed mood	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)
Suicidal ideation	0	0	1 (0.4)	0
Dizziness	**7 (2.6)**	**0**	**1 (0.4)**	**0**
Altered sensorium	**2 (0.7)**	**0**	**1 (0.4)**	**1 (0.4)**
Lethargy	0	0	1 (0.4)	1 (0.4)
Somnolence	1 (0.4)	0	0	0
Syncope	1 (0.4)	0	0	0
Psychosis and psychotic disorders	**0**	**0**	**0**	**0**
Headache[a]	**5 (1.9)**	**2 (0.7)**	**4 (1.7)**	**0**

AE, adverse event; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

The 5 categories of NPAEs were predefined. Specific terms included for each category were based on MedDRA 23.0. A participant with multiple AEs within a category is counted a single time for that category.

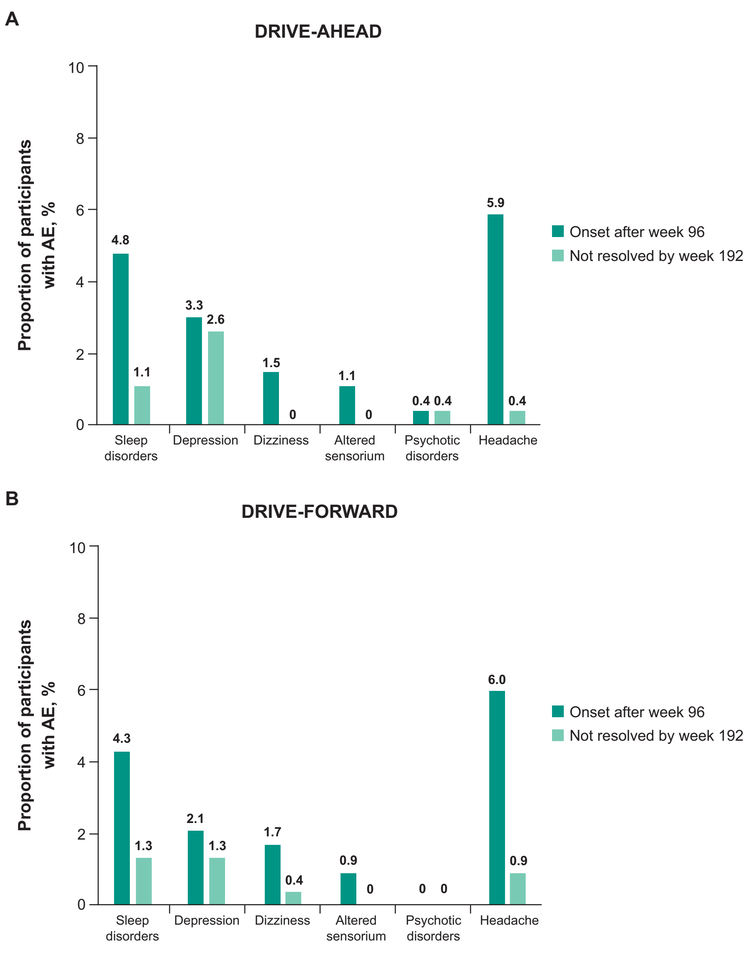
[a]Headache was not included in the predefined NPAE categories and is not included in the total number of participants with persisting NPAEs.

Data shown as n (%).

New-onset NPAEs reported after switching to a DOR regimen

- After switching to a DOR regimen, new-onset NPAEs were reported by 25 of 269 participants (9.3%) who switched from EFV/FTC/TDF and 18 of 233 (7.7%) who switched from DRV/r + 2 NRTIs (**Figure 3B**)
- By the end of treatment, these NPAEs were not resolved in 10 (3.7%) participants who switched from EFV/FTC/TDF and 7 (3.0%) who switched from DRV/r + 2 NRTIs (**Figure 3B**)
- In both studies, the most commonly reported NPAEs with new onset after switching to a DOR regimen and that persisted at week 192, with an incidence of ≥1%, were sleep disorders and depression (**Figure 5** and **Table 4**)

Figure 5. Specific new NPAEs with onset after switching to a DOR regimen



AE, adverse event; DOR, doravirine; NPAE, neuropsychiatric adverse event.

Table 4. Specific new NPAEs with onset after switching to a DOR regimen

	DRIVE-AHEAD		DRIVE-FORWARD	
	Switch from EFV/FTC/TDF (N = 269)		Switch from DRV/r + 2 NRTIs (N = 233)	
	Onset after week 96	Not resolved by week 192	Onset after week 96	Not resolved by week 192
All new-onset NPAEs	**25 (9.3)**	**10 (3.7)**	**18 (7.7)**	**7 (3.0)**
Sleep disorders and disturbances	**13 (4.8)**	**3 (1.1)**	**10 (4.3)**	**3 (1.3)**
Abnormal dreams	2 (0.7)	0	0	0
Insomnia	11 (4.1)	3 (1.1)	6 (2.6)	3 (1.3)
Nightmare	0	0	2 (0.9)	0
Sleep disorder	0	0	2 (0.9)	0
Depression and related disorders	**9 (3.3)**	**7 (2.6)**	**5 (2.1)**	**3 (1.3)**
Depressed mood	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Depression	5 (1.9)	4 (1.5)	2 (0.9)	1 (0.4)
Depressive symptom	1 (0.4)	1 (0.4)	0	0
Major depression	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)
Suicidal ideation	1 (0.4)	0	0	0
Dizziness	**4 (1.5)**	**0**	**4 (1.7)**	**1 (0.4)**
Altered sensorium	**3 (1.1)**	**0**	**2 (0.9)**	**0**
Lethargy	1 (0.4)	0	0	0
Somnolence	2 (0.7)	0	2 (0.9)	0
Psychosis and psychotic disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Schizophrenia	1 (0.4)	1 (0.4)	0	0
Headache[a]	**16 (5.9)**	**1 (0.4)**	**14 (6.0)**	**2 (0.9)**

AE, adverse event; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NPAE, neuropsychiatric adverse event; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

Specific terms included for each category were based on MedDRA 23.0. A participant with multiple AEs within a category is counted a single time for that category.

[a]Headache was not included in the predefined NPAE categories and is not included in the total number of participants with new-onset NPAEs.

Data shown as n (%).

Conclusions

- The majority of participants (19/26 [73.1%]) with ongoing NPAEs while receiving EFV/FTC/TDF experienced resolution after switching to DOR/3TC/TDF
  - The similar rate of NPAEs with DOR- and darunavir-based regimens may represent the generalized background rate for these events
- Incidence of new NPAEs was lower after switching to an open-label DOR-based regimen from EFV (9.3%) or DRV/r (7.7%) than during initial double-blind treatment with a DOR-based regimen in DRIVE-AHEAD (26.4%) or DRIVE-FORWARD (15.7%)
- Overall, NPAEs persisted in only 3%-4% of participants at 2 years after switching to a DOR-based regimen in both trials

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