Use of D/C/F/TAF With Neurologic/Psychiatric Comorbidities: AMBER Subgroup Analysis

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CONCLUSIONS

- **In AMBER, the presence of baseline NPCs did not preclude high virologic response rates**
- Among D/C/F/TAF-related AEs, the majority were grade 1 in severity and none were serious
  - **There was no added risk of study discontinuation due to study drug–related AEs in participants with baseline NPCs**
  - **Participants with baseline NPCs did not experience a higher incidence of new-onset neurologic or psychiatric AEs related to D/C/F/TAF**
- **Patients with NPCs are predisposed to ART toxicities, particularly neurologic or psychiatric AEs, and may be at risk for suboptimal treatment adherence. Findings from this analysis suggest that D/C/F/TAF is a good option to consider for such patients when selecting an initial ART regimen**

INTRODUCTION

- Individuals living with human immunodeficiency virus (HIV)–1 are more likely than the general population to experience neurologic and/or psychiatric comorbidities (NPCs), such as depression, anxiety, and insomnia[1-4]
- The presence of NPCs is associated with poor retention in care and suboptimal antiretroviral therapy (ART) adherence, which can lead to the development of resistance, disease progression, regimen discontinuation, and an increased risk of mortality[5]
- To improve adherence, guidelines from the United States Department of Health and Human Services (US DHHS) recommend selecting an ART regimen that has a low pill burden and is well tolerated; if suboptimal adherence is a concern, a regimen with a high genetic barrier to resistance, such as a boosted darunavir (DRV)–based regimen, should be used[5]
  - US DHHS guidelines also state that, for patients with NPCs, symptoms may be exacerbated by integrase inhibitors or select non-nucleoside reverse transcriptase inhibitors[5]
- In the phase 3 AMBER study, treatment-naïve participants were randomized to initiate either darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg or a control regimen (DRV/cobicistat [COBI] + emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF])[6]
  - This subgroup analysis examined the prevalence of pre-existing NPCs among participants in AMBER, as well as outcomes for participants with and without baseline NPCs

OBJECTIVES

- To assess efficacy and safety in the AMBER study over 48 weeks in participants with and without baseline NPCs
- To evaluate the disposition of participants with and without baseline NPCs after 48 weeks

METHODS

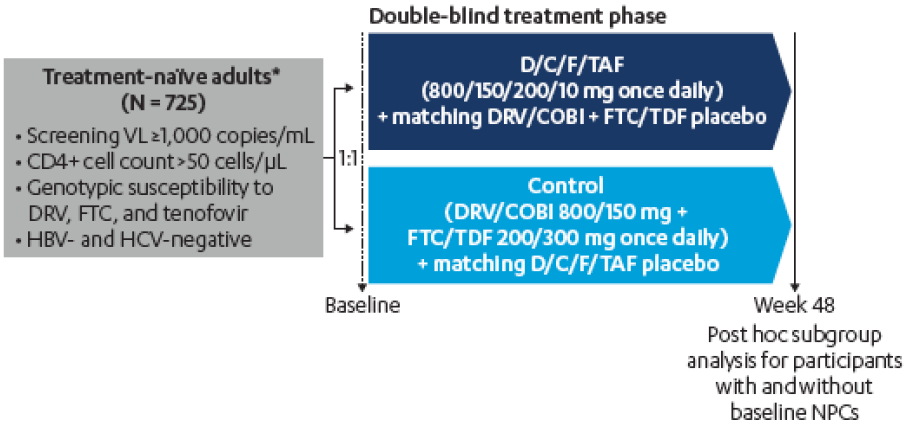
Study Design

- AMBER (ClinicalTrials.gov Identifier: NCT02431247) was a phase 3, randomized study that enrolled treatment-naïve adults with HIV-1 infection to initiate either D/C/F/TAF or a control regimen (**Figure 1**)[6]
  - No exclusion criteria explicitly limited enrollment of participants with baseline NPCs

Analyses

- The primary objective of this analysis was to assess the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 (intent-to-treat [ITT] US Food and Drug Administration [FDA] snapshot)
- Safety was assessed by adverse events (AEs), serious adverse events (SAEs), grade 3 or 4 AEs, discontinuations due to AEs, and new onset or worsening of NPCs through Week 48

Figure 1. AMBER study design.



VL, viral load; HBV, hepatitis B virus; HCV, hepatitis C virus.
*Participants were stratified by VL (≤ or >100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/µL) at screening prior to randomization.

- NPCs were based on verbatim medical history terms and were coded and defined as those within the Medical Dictionary for Regulatory Activities (MedDRA) v22 entire system organ classes of Nervous System Disorders or Psychiatric Disorders
  - For Psychiatric Disorders, the following high-level group terms were excluded: sexual dysfunctions/disturbances, gender identity disorders, and eating disorders and disturbances
- Descriptive statistics were used

RESULTS

Participant Population and Disposition

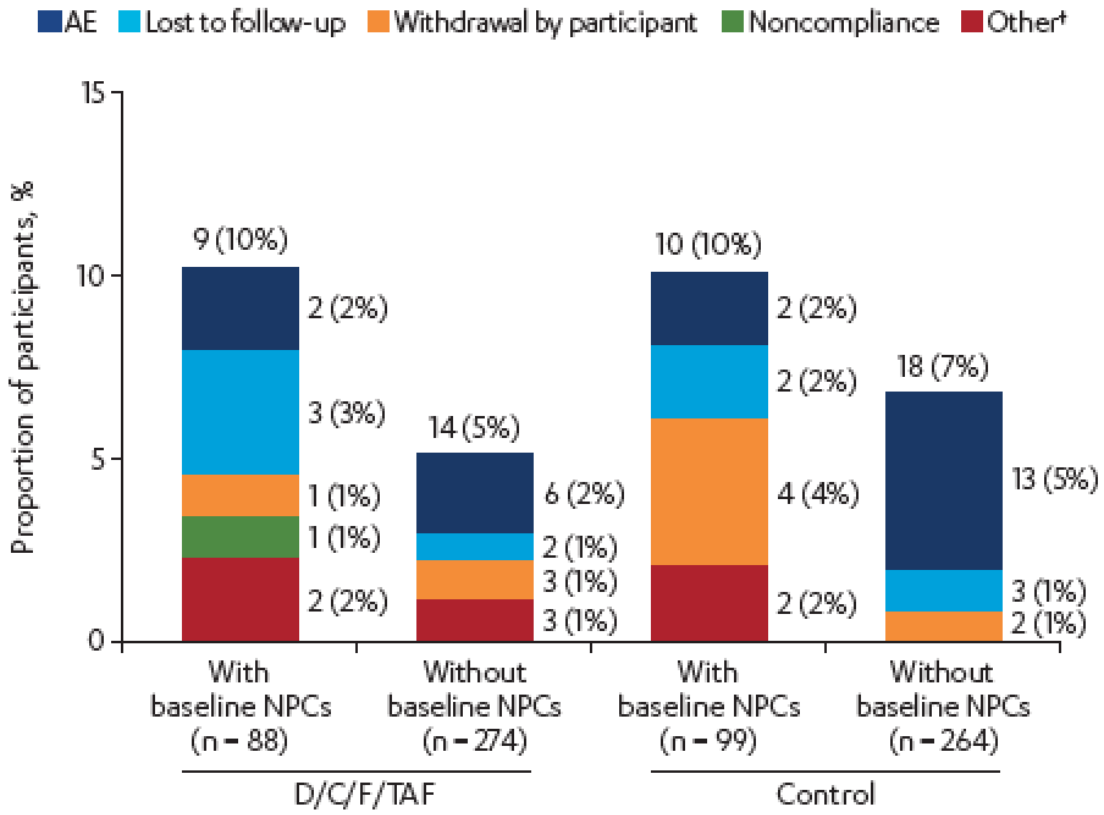
- Among 725 participants in AMBER, the median (interquartile range) age was 34 (27-42) years, 88% of participants were male, and 83% were white (efficacy and safety results from AMBER for subgroups of participants based on age, sex, and race have been reported[6,7])
- Overall, 88 (D/C/F/TAF) and 99 (control) participants had baseline NPCs, and psychiatric comorbidities (125/187 [67%]) were more common than neurologic comorbidities (81/187 [43%]; **Table 1**)
  - The overall most common (>5%) psychiatric comorbidities were depression (31%), anxiety (16%), and insomnia (10%)
  - The overall most common (>5%) neurologic comorbidities were headache (21%) and migraine (7%)
- Participants with baseline NPCs, versus those without, were more likely to be black/African American (32/187 [17%] vs 48/538 [9%]), be female (31/187 [17%] vs 54/538 [10%]), be from North America (70/187 [37%] vs 95/538 [18%]), be drug users (48/187 [26%] vs 75/538 [14%]), and use nicotine (98/187 [52%] vs 243/538 [45%])
- Other baseline characteristics were generally similar for participants with versus without baseline NPCs, including median age (36 vs 33 years), Hispanic/Latino ethnicity (20/187 [11%] vs 75/538 [14%]), and current alcohol use (138/187 [74%] vs 374/538 [70%])
- Participants with versus without baseline NPCs had higher rates of early study discontinuation (D/C/F/TAF, 10% vs 5%; control, 10% vs 7%), which was largely driven by loss to follow-up (**Figure 2**)

Table 1. Summary of Baseline NPCs by Preferred Term*

Disorders, n (%)	D/C/F/TAF (n = 88)	Control (n = 99)	Total (n = 187)
Psychiatric	56 (64)	69 (70)	125 (67)
Depression	31 (35)	27 (27)	58 (31)
Anxiety	16 (18)	14 (14)	30 (16)
Insomnia	6 (7)	13 (13)	19 (10)
Attention deficit/hyperactivity disorder	2 (2)	7 (7)	9 (5)
Sleep disorder	8 (9)	1 (1)	9 (5)
Tobacco abuse	3 (3)	5 (5)	8 (4)
Bipolar disorder	0	6 (6)	6 (3)
Adjustment disorder	1 (1)	3 (3)	4 (2)
Alcohol abuse	1 (1)	2 (2)	3 (2)
Borderline personality disorder	1 (1)	2 (2)	3 (2)
Panic attack	1 (1)	2 (2)	3 (2)
Cyclothymic disorder	1 (1)	1 (1)	2 (1)
Drug dependence	1 (1)	1 (1)	2 (1)
Social anxiety disorder	0	2 (2)	2 (1)
Nervous system	38 (43)	43 (43)	81 (43)
Headache	18 (20)	21 (21)	39 (21)
Migraine	5 (6)	8 (8)	13 (7)
Autonomic nervous system imbalance	2 (2)	2 (2)	4 (2)
Tension headache	2 (2)	2 (2)	4 (2)
Paresthesia	2 (2)	1 (1)	3 (2)
Epilepsy	2 (2)	0	2 (1)

*Preferred terms that were reported in 1 participant in the total population are excluded.

Figure 2. Disposition of participants with early study discontinuation through Week 48.*



*Percentages within each bar may not sum to the total due to rounding.
†"Other" includes physician decision, death, and other reasons.

Table 2. Virologic Response at Week 48 (ITT-FDA Snapshot)

Response category, n (%) [95% CI]	D/C/F/TAF		Control	
	With baseline NPCs (n = 88)	Without baseline NPCs (n = 274)	With baseline NPCs (n = 99)	Without baseline NPCs (n = 264)
Virologic response (HIV-1 RNA <50 copies/mL)	76 (86) [77; 93]	255 (93) [89; 96]	84 (85) [76; 91]	237 (90) [85; 93]
Virologic failure	6 (7) [3; 14]	10 (4) [2; 7]	3 (3) [1; 9]	9 (3) [2; 6]
HIV-1 RNA ≥50 copies/mL	3 (3) [1; 10]	6 (2) [1; 5]	3 (3) [1; 9]	6 (2) [1; 5]
Leading to study discontinuation	0	1 (<1) [0; 2]	0	0
Discontinuation due to other reasons with last available HIV-1 RNA ≥50 copies/mL	3 (3) [1; 10]	3 (1) [0; 3]	0	3 (1) [0; 3]
No VL data	6 (7) [3; 14]	9 (3) [2; 6]	12 (12) [6; 20]	18 (7) [4; 11]
Discontinuation due to AE/death	2 (2) [0; 8]	6 (2) [1; 5]	3 (3) [1; 9]	13 (5) [3; 8]
Discontinuation due to other reasons with last available HIV-1 RNA <50 copies/mL (or missing)	3 (3) [1; 10]	1 (<1) [0; 2]	7 (7) [3; 14]	2 (1) [0; 3]
Missing data during window but on study	1 (1) [0; 6]	2 (1) [0; 3]	2 (2) [0; 7]	3 (1) [0; 3]

CI, confidence interval.

Efficacy

- Overall, high rates of virologic response (85%-93%) were achieved across treatment arms regardless of baseline NPCs; however, participants with baseline NPCs had numerically lower response rates in both arms of the study (**Table 2**)
  - For comparisons of both baseline NPCs (with vs without) and treatment arms (control vs D/C/F/TAF), differences in virologic response rates were due, in large part, to higher rates of having no VL data in the window
- Among participants with baseline NPCs, none experienced virologic failure leading to discontinuation
- No participants discontinued due to a lack of efficacy or developed DRV, primary protease inhibitor, or tenofovir resistance-associated mutations

Safety

- The majority of study drug–related AEs across both treatment arms were grade 1 in severity, and no SAEs related to D/C/F/TAF were reported; there were low rates of discontinuation due to AEs related to study drug regardless of baseline NPCs (**Table 3**)
- Participants with versus without baseline NPCs reported a higher incidence of new or worsening neurologic and/or psychiatric AEs overall; however, they did not experience a higher incidence of neurologic or psychiatric AEs related to D/C/F/TAF
  - The specific neurologic and psychiatric study drug–related AEs reported during the study are shown in **Figure 3**

- No participants with baseline NPCs reported D/C/F/TAF-related neurologic or psychiatric AEs that were ≥grade 2 in severity. Of the study drug–related AEs that were ≥grade 2, the most frequent (≥2% of participants) were as follows:
  - D/C/F/TAF arm with baseline NPCs: diarrhea (2%), rash (2%), and maculopapular rash (2%)
  - D/C/F/TAF arm without baseline NPCs: no events met this threshold
  - Control arm with baseline NPCs: diarrhea (4%), nausea (3%), rash (2%), and headache (2%)
  - Control arm without baseline NPCs: nausea (3%), diarrhea (2%), and rash (2%)

Figure 3. Study drug–related neurologic and psychiatric AEs (specific terms).*

D/C/F/TAF		Control	
With baseline NPCs (n = 88)	**Without baseline NPCs (n = 274)**	**With baseline NPCs (n = 99)**	**Without baseline NPCs (n = 264)**
• **Neurologic† (n = 4)** – Headache (n = 1) – Dizziness exertional (n = 1) – Dizziness postural (n = 1) – Disturbance in attention (n = 1) – Dizziness (n = 1) – Somnolence (n = 1) • **Psychiatric‡ (n = 1)** – Listless (n = 1) – Restlessness (n = 1)	• **Neurologic† (n = 13)** – Headache (n = 11) – Dizziness (n = 1) – Dizziness postural (n = 1) – Somnolence (n = 2) • **Psychiatric‡ (n = 8)** – Insomnia (n = 4) – Depression (n = 2) – Sleep disorder (n = 1) – Abnormal dreams (n = 2)	• **Neurologic† (n = 5)** – Headache (n = 3) – Dizziness postural (n = 1) – Somnolence (n = 1) • **Psychiatric‡ (n = 1)** – Insomnia (n = 1)	• **Neurologic† (n = 8)** – Headache (n = 3) – Dizziness (n = 1) – Hypoesthesia (n = 2) – Somnolence (n = 2) • **Psychiatric‡ (n = 3)** – Insomnia (n = 1) – Abnormal dreams (n = 1) – Mood altered (n = 1)

*The n values represent numbers of participants, not events. A single participant may have reported >1 neurologic or psychiatric study drug–related AE.
†System organ class of Nervous System Disorders.
‡System organ class of Psychiatric Disorders.

Table 3. Summary of AEs Through Week 48

AEs, n (%)	D/C/F/TAF		Control	
	With baseline NPCs (n = 88)	Without baseline NPCs (n = 274)	With baseline NPCs (n = 99)	Without baseline NPCs (n = 264)
Any related	36 (41)	90 (33)	43 (43)	108 (41)
Any related serious	0	0	2 (2)	4 (2)
Any related ≥grade 2	12 (14)	31 (11)	17 (17)	38 (14)
Any related leading to discontinuation of study drug	2 (2)	5 (2)	2 (2)	12 (5)
Any neurologic*	18 (20)	47 (17)	20 (20)	28 (11)
Related†	4 (5)	13 (5)	5 (5)	8 (3)
≥Grade 2	0	2 (1)	3 (3)	2 (1)
Any psychiatric‡	17 (19)	26 (9)	19 (19)	18 (7)
Related†	1 (1)	8 (3)	1 (1)	3 (1)
≥Grade 2	0	1 (<1)	0	1 (<1)

*System organ class of Nervous System Disorders.
†See Figure 3 for a list of the reported AEs.
‡System organ class of Psychiatric Disorders.

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