Gastrointestinal (GI) Adverse Events With Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Through Week 96: An AMBER Post Hoc Analysis

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INTRODUCTION

- Ritonavir-boosted protease inhibitors (PIs) have been associated with GI intolerance, such as diarrhea and nausea, that tends to be transient[1]
- D/C/F/TAF 800/150/200/10 mg is the only available PI-based single-tablet regimen and removes the need for ritonavir as the boosting agent
- In the phase 3 AMBER study, treatment-naïve adults with human immunodeficiency virus (HIV)–1 infection were randomized to initiate either D/C/F/TAF or darunavir (D)/cobicistat (C) + emtricitabine (F)/tenofovir disoproxil fumarate (TDF)[2]
  - This post hoc analysis evaluated GI tolerability in AMBER

OBJECTIVES

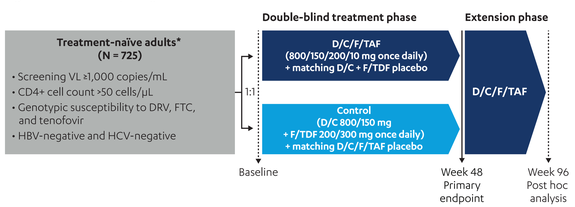
- To assess the incidence, prevalence, and duration of GI adverse events of interest (AEOIs) in the AMBER study over 96 weeks
- To evaluate the percentage of patients receiving concomitant medication for treatment of GI AEOIs through Week 96

METHODS

Study Design

- The AMBER (ClinicalTrials.gov Identifier: NCT02431247) study design[2,3] is summarized in **Figure 1**

Figure 1. AMBER study design.



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

Analyses

- The primary objective of this post hoc analysis was to assess the incidence, prevalence, and duration of GI AEOIs through Week 96
- GI AEOIs were defined using *Medical Dictionary for Regulatory Activities* (MedDRA) v21 preferred terms of diarrhea, nausea, abdominal discomfort, and flatulence
- Related GI AEOIs were those assessed by the investigator to be very likely, probably, or possibly related to study drug
- Incidence and prevalence were evaluated at weekly intervals during the first month and monthly thereafter
- Duration was reported for D/C/F/TAF-related GI AEOIs through Week 96
  - Only patients whose events had start and stop dates were included in duration calculations
- Concomitant medications were evaluated based on the percentage of patients who received such a medication for the treatment of a GI AEOI through Week 96

RESULTS

Patient Population

- Among 725 patients in AMBER, 362 were randomized to D/C/F/TAF and 363 to D/C + F/TDF (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics

	D/C/F/TAF (n = 362)	D/C + F/TDF (n = 363)
Demographic		
Age, median (IQR), y	34 (27-42)	34 (27-42)
Male, n (%)	318 (88)	322 (89)
Race, n (%)		
White	300 (83)	300 (83)
Black/African American	40 (11)	40 (11)
Other	22 (6)	23 (6)
Clinical		
HIV-1 RNA ≤100,000 copies/mL, n (%)	60 (17)	70 (19)
CD4+ cell count <200 cells/µL, n (%)	22 (6)	29 (8)

IQR, interquartile range.

Incidence and Prevalence of GI AEOIs Over Time

- Through Week 96, the incidence and prevalence of D/C/F/TAF-related GI AEOIs remained low (**Figures 2** and **3**)
  - During Week 1, the incidences of D/C/F/TAF-related diarrhea and nausea were each 5% and subsequently decreased to ≤1% starting at Week 2
  - Starting at Week 2, the prevalences of D/C/F/TAF-related diarrhea and nausea both decreased to <5%
  - Only 1 case of D/C/F/TAF-related abdominal discomfort occurred, and it was reported at Week 1
  - From Week 1 through Week 96, the incidence of D/C/F/TAF-related flatulence was <1%

Figure 2. Incidence of D/C/F/TAF-related GI AEOIs over time.

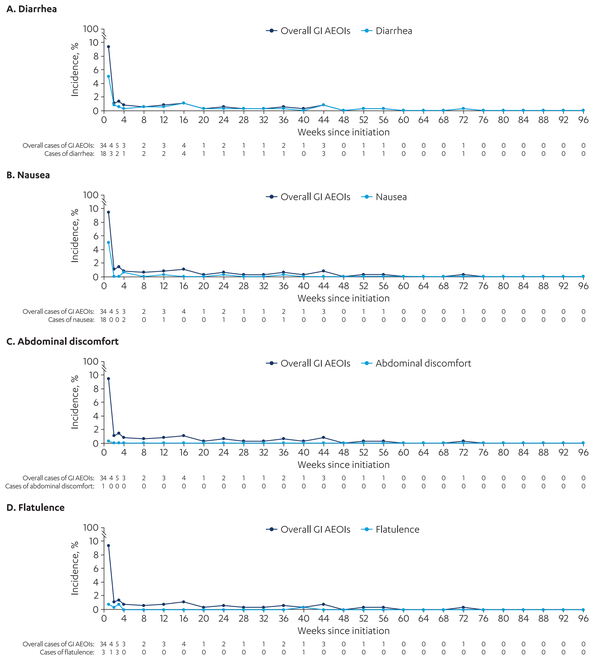
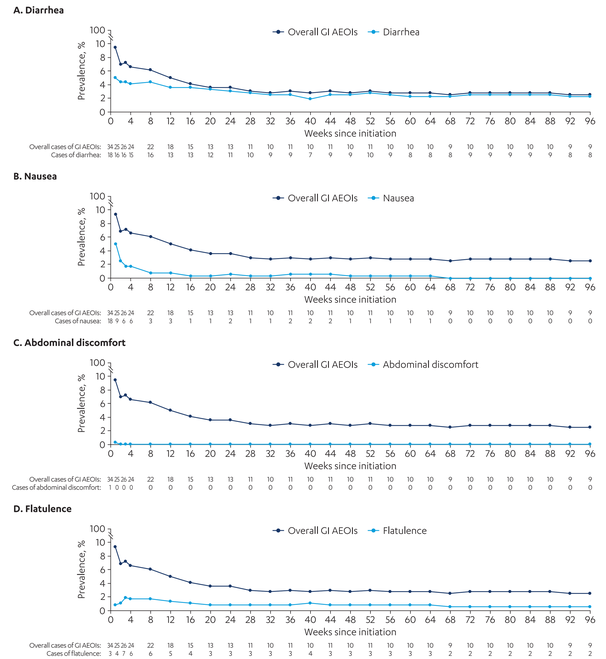


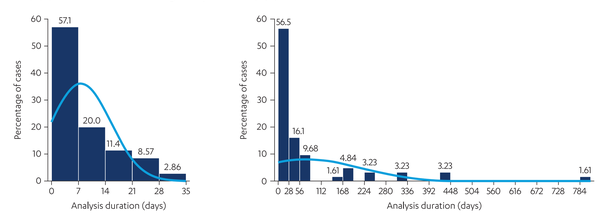
Figure 3. Prevalence of D/C/F/TAF-related GI AEOIs over time.



Duration of GI AEOIs

- Among the 50 patients with a D/C/F/TAF-related GI AEOI, there were 62 events in which the duration could be calculated and results were skewed towards shorter durations (**Figure 4**)
- The median duration was 16.5 days

Figure 4. Distribution of duration of D/C/F/TAF-related GI AEOIs.



Overview of GI AEOIs

- Through Week 48, 14% of patients receiving D/C/F/TAF versus 19% of patients receiving D/C + F/TDF experienced a study drug–related GI AEOI (**Table 2**)
  - Regardless of study arm, all GI AEOIs were grade 1 or 2 in severity and no serious adverse events were reported
- Ten (3%) patients required treatment with a concomitant medication for a D/C/F/TAF-related GI AEOI
- Two (1%) patients discontinued before Week 96 due to a D/C/F/TAF-related GI AEOI
  - Both patients discontinued due to D/C/F/TAF-related diarrhea; 1 patient had grade 2 diarrhea and 1 patient had grade 1 diarrhea

Table 2. Incidence of Study Drug–related GI AEOIs*

AE, n (%)	D/C/F/TAF Baseline to Week 48 (n = 362)	D/C/F/TAF Baseline to Week 96 (n = 362)	D/C + F/TDF Baseline to Week 48 (n = 363)
Any GI AEOI	50 (14)	54 (15)	68 (19)
Diarrhea†	31 (9)	34 (9)	40 (11)
Grade 1	26 (7)	29 (8)	32 (9)
Grade 2	7 (2)	7 (2)	8 (2)
Nausea†	20 (6)	20 (6)	36 (10)
Grade 1	17 (5)	17 (5)	29 (8)
Grade 2	3 (1)	3 (1)	10 (3)
Abdominal discomfort	1 (<1)	2 (1)	1 (<1)
Grade 1	1 (<1)	2 (1)	1 (<1)
Grade 2	0	0	0
Flatulence	7 (2)	7 (2)	2 (1)
Grade 1	6 (2)	6 (2)	2 (1)
Grade 2	1 (<1)	1 (<1)	0

AE, adverse event; IV, intravenous.
*For each patient, AEs of different severity are reported separately (ie, a single patient could have both a grade 1 event and grade 2 event for the same GI AEOI). Thus, the sum of patients with grade 1 and 2 AEs may be larger than the total.
†Severity was defined as follows: grade 1 (mild), transient or intermittent episodes of unformed stools OR increase of <3 stools over baseline per 24-hour period; grade 2 (moderate), persistent episodes of unformed to watery stools OR increase of 4 to 6 stools over baseline per 24-hour period; grade 3 (severe), increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated; grade 4 (potentially life-threatening), life-threatening consequences (eg, hypotensive shock).
‡Severity was defined as follows: grade 1 (mild), transient (<24 hours) or intermittent AND no or minimal interference with oral intake; grade 2 (moderate), persistent nausea resulting in decreased oral intake for 24 to 48 hours; grade 3 (severe), persistent nausea resulting in minimal oral intake for >48 hours OR rehydration indicated (eg, IV fluids); grade 4 (potentially life-threatening), life-threatening consequences (eg, hypotensive shock).

CONCLUSIONS

- **In treatment-naïve patients, the incidences and prevalences of D/C/F/TAF-related GI AEOIs were low and tended to present early in the study and rapidly decrease thereafter**
  - **The incidence of D/C/F/TAF-related diarrhea was ≤1% starting at Week 2**
  - **The median duration of D/C/F/TAF-related GI AEOIs was 16.5 days**
- **Of the 14.9% (54/362) of patients who experienced a D/C/F/TAF-related GI AEOI through Week 96, 3% required treatment with a concomitant medication and all were grade 1 or 2 in severity**
- **Overall, the GI profile of D/C/F/TAF was favorable, demonstrating adverse events most typically of short duration and mild grade. Numerically better tolerability was also shown relative to the older formulation of D/C + F/TDF, and overall, this profile challenges commonly-held perceptions of boosted PI GI tolerability**

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed September 4, 2020.
2. Eron J, et al. *AIDS*. 2018;32(11):1431-1442.
3. Orkin C, et al. *AIDS*. 2020;34(5):707-718.

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DISCLOSURES

This study was sponsored by Janssen Scientific Affairs, LLC. KD, BB, NB, DL, JC, and DA are employees of Janssen and may be stockholders in Johnson & Johnson.

KD, BB, NB, JC, and DA contributed to the analysis and interpretation of the data. DL contributed to the statistical analysis and interpretation of the data. All authors contributed to the drafting of this poster and approved the final version.

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