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# Low Incidence and Brief Duration of Gastrointestinal Adverse Events with Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Over 96 Weeks: Post hoc Analyses of AMBER and EMERALD

**Keith Dunn[1], Bryan Baugh[2], Nika Bejou[1], Donghan Luo[3], Jennifer Campbell[1], Sareh Seyedkazemi[1], and David Anderson[1]**

**Abstract**

Gastrointestinal intolerance has been associated with ritonavir-boosted protease inhibitors. This post hoc analysis evaluated gastrointestinal adverse events of interest (AEOIs; diarrhea, nausea, abdominal discomfort, flatulence [MedDRAv21]) through Wk96 among patients enrolled in the phase 3 AMBER (treatment-naïve) and EMERALD (virologically suppressed) studies of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg. 362 and 763 patients initiated D/C/F/TAF in AMBER and EMERALD, respectively. All D/C/F/TAF-related gastrointestinal AEOIs were grade 1/2 in severity; none were serious. Across studies, incidence of D/C/F/TAF-related diarrhea and nausea were each ≤5% in Wk1 (≤1% post-Wk2); prevalence of each decreased to <5% post-Wk2. In each study, there was 1 case of D/C/F/TAF-related abdominal discomfort during Wk1 and none thereafter. Incidence of D/C/F/TAF-related flatulence was <1% throughout. Median duration of D/C/F/TAF-related gastrointestinal AEOIs was 16.5 (AMBER) and 8.5 (EMERALD) days. In conclusion, in treatment-naïve and virologically suppressed patients, incidences and prevalences of D/C/F/TAF-related gastrointestinal AEOIs were low and tended to present early.

**Keywords**

darunavir/cobicistat/emtricitabine/tenofovir alafenamide, gastrointestinal, adverse events, tolerability, HIV-1

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## Introduction

Gastrointestinal (GI) intolerance in people with human immunodeficiency virus (HIV)–1 has been associated with ritonavir-boosted protease inhibitors (PIs).[1–3] Ritonavir was originally developed as a standalone PI at high doses but has primarily been used as a low-dose pharmacokinetic booster for other PIs since its approval to improve side effect profiles and decrease pill burden.[1,3] Despite being used at lower doses, GI-associated symptoms remained a challenge with ritonavir.[3–6]

GI tolerability varies across boosted PI–based regimens, with relatively better tolerability with once-daily darunavir/ritonavir and once-daily atazanavir/ritonavir versus lopinavir/ritonavir,[2,4–6] possibly attributed to lower daily doses of ritonavir with darunavir and atazanavir. In one study of treatment-naïve patients initiating once-daily darunavir/ritonavir 800/100 mg or lopinavir/ritonavir 800/200 mg (total daily dose), patients receiving darunavir/ritonavir had a lower incidence of treatment-related grade 2–4 diarrhea (4% vs 10%) and nausea (2% vs 3%) than patients receiving lopinavir/ritonavir at Week 48.[7] These observations suggest consideration of specific boosted PI–based

[1] Janssen Scientific Affairs, LLC, Titusville, NJ, USA
[2] Janssen Research & Development, LLC, Raritan, NJ, USA
[3] Janssen Research & Development, LLC, Titusville, NJ, USA

**Corresponding Author:**
David Anderson, Janssen Scientific Affairs, LLC,
1125 Trenton-Harbourton Road, Titusville, NJ 08560 USA.
Email: DAnder20@its.jnj.com

regimens is important, particularly as they have evolved over time. In 2015, the requirement for ritonavir was obviated with the approval of a fixed-dose combination of once-daily darunavir/cobicistat 800/150 mg.[8]

Cobicistat is a selective, potent cytochrome P450 3A inhibitor without anti-HIV activity but with a chemical profile that allows for coformulation with other agents.[9] Most recently, in 2018, the once-daily, single-tablet regimen darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg was approved.[10] As this combination includes a different chemical agent than ritonavir, the resulting tolerability profile of cobicistat combined with darunavir is unique from that observed when boosting with ritonavir. Accordingly, as the most commonly used PI-based regimen today, D/C/F/TAF was studied in this post hoc analysis of the AMBER and EMERALD trials to evaluate the GI tolerability of this formulation in both treatment-naïve and treatment-experienced, virologically suppressed patients over 96 weeks.[11–14]

## Methods

### Study Designs

In the phase 3 AMBER study (ClinicalTrials.gov Identifier: NCT02431247), treatment-naïve adults with HIV-1 infection were randomized (1:1) to initiate either D/C/F/TAF or darunavir/cobicistat 800/150 mg + emtricitabine/tenofovir disoproxil fumarate (TDF) 200/300 mg (control regimen) for 48 weeks. In the phase 3 EMERALD study (NCT02269917), treatment-experienced, virologically suppressed adults with HIV-1 infection were randomized (2:1) to switch to D/C/F/TAF or continue their boosted PI (atazanavir and ritonavir, atazanavir and cobicistat, darunavir and ritonavir, darunavir and cobicistat, or lopinavir and ritonavir) + emtricitabine/TDF regimen for 48 weeks. In both AMBER and EMERALD, all patients received D/C/F/TAF in an extension phase through Week 96. Detailed methods have been published.[11–14]

### Analyses

The primary objective of this post hoc analysis was to assess the incidence, prevalence, and duration of GI adverse events (AEs), as well as the percentage of patients receiving a concomitant medication for treatment of GI AEs, through 48 and 96 weeks from baseline for patients enrolled in AMBER and EMERALD. For both studies, analyses were performed in the intent-to-treat population, and D/C/F/TAF arm data were evaluated through Week 96 while control arm data were evaluated through Week 48. Diarrhea, nausea, abdominal discomfort, and flatulence were identified as GI AEs of interest (AEOIs) based on the most common GI AEs observed with previous darunavir-based regimens[15] and defined using *Medical Dictionary for Regulatory Activities* v21 preferred terms. Related GI AEOIs were those evaluated by the investigator to be very likely, probably, or possibly related to study drug. Incidence and prevalence were assessed at weekly intervals during the first month and every month thereafter. Duration was reported for D/C/F/TAF-related GI AEOIs for patients whose AEs had start and stop dates through Week 96.

### Ethical Approval and Informed Consent

AMBER and EMERALD were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocols and amendments were approved by local or central institutional review boards or independent ethics committees, and all participants provided written informed consent prior to enrollment in the studies.

## Results

### Incidence, Prevalence, and Severity of Study Drug–Related GI AEOIs Over Time

In AMBER, 362 patients were randomized to initiate D/C/F/TAF and 363 patients were randomized to initiate darunavir/cobicistat + emtricitabine/TDF in the control arm. Through Week 48, 14% of patients receiving D/C/F/TAF and 19% of patients in the control arm experienced a study drug–related GI AEOI. In both the D/C/F/TAF arm (through Week 96) and the control arm (through Week 48), all study drug–related GI AEOIs were grade 1 or 2 in severity and no serious events were reported.

During Week 1 in AMBER, the incidence of D/C/F/TAF-related diarrhea and nausea was each 5% and decreased to ≤1% after Week 2 (Figure 1A). The prevalence of D/C/F/TAF-related diarrhea decreased to <5% starting at Week 2, and the prevalence of D/C/F/TAF-related nausea decreased to <3% starting at Week 2 and to <1% by Week 5. Only 1 case of D/C/F/TAF-related abdominal discomfort was reported and it was during Week 1. The incidence of D/C/F/TAF-related flatulence was <1% from Week 1 through Week 96. The incidence and prevalence of each study drug–related GI AEOI in the control arm through Week 48 were comparable to those in the D/C/F/TAF arm.

In EMERALD, 763 patients were randomized to switch to D/C/F/TAF and 378 patients were randomized to continue their boosted PI + emtricitabine/TDF regimen in the control arm. Through Week 48, 3% of patients receiving D/C/F/TAF and 1% of patients in the control arm experienced a study drug–related GI AEOI. In both the D/C/F/TAF arm (through Week 96) and the control arm (through Week 48), all study drug–related GI AEOIs were grade 1 or 2 in severity and no serious events were reported.

During Week 1 in EMERALD, the incidence of D/C/F/TAF-related diarrhea and nausea was 2% and <1%, respectively, and decreased to ≤0.1% after Week 2 (Figure 1B). Starting at Week 2, the prevalence of D/C/F/TAF-related diarrhea and nausea was each <1%. There was 1 case of D/C/F/TAF-related abdominal discomfort reported during Week 1 and none thereafter. The incidence of D/C/F/TAF-related flatulence was 0.4% at Week 1 and remained <0.1% from Week 2 through Week 96. No new cases of flatulence were reported after Week 3. The

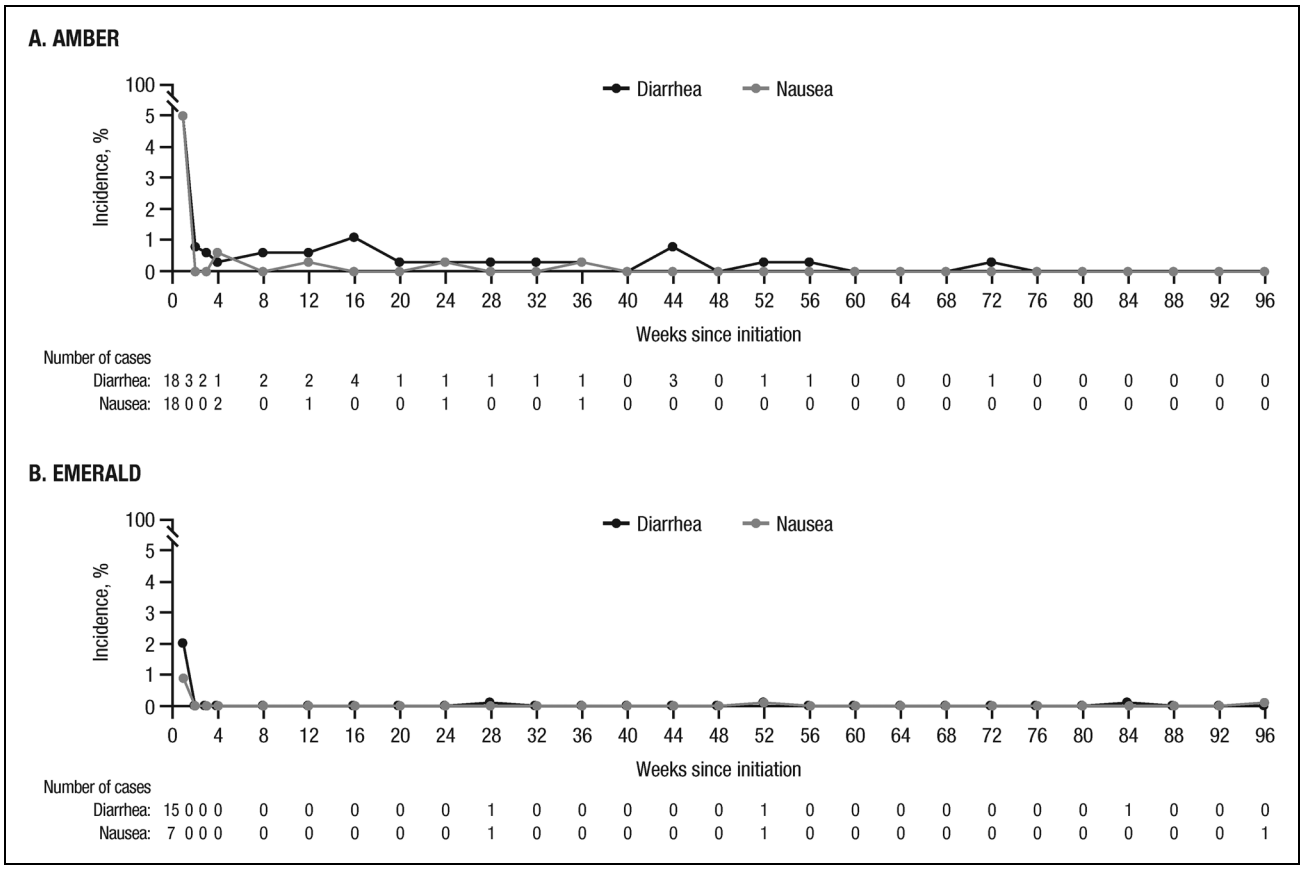


**Figure 1.** Incidence of D/C/F/TAF-related diarrhea and nausea over time.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

incidence and prevalence of each study drug–related GI AEOI in the control arm through Week 48 were comparable to those in the D/C/F/TAF arm.

### *Treatment and Discontinuation due to D/C/F/TAF-Related GI AEOIs*

In AMBER through Week 96, 10 (3%) patients required treatment with a concomitant medication for a D/C/F/TAF-related GI AEOI; 2 patients discontinued before Week 96 due to D/C/F/TAF-related diarrhea (1 patient with grade 2 and 1 patient with grade 1). In EMERALD through Week 96, 6 (1%) patients required treatment with a concomitant medication for a D/C/F/TAF-related GI AEOI; 1 patient discontinued due to D/C/F/TAF-related diarrhea, and 1 patient discontinued due to D/C/F/TAF-related abdominal pain. Across both studies, the most common concomitant medications required were antipropulsives.

### *Duration of D/C/F/TAF-Related GI AEOIs*

Through Week 96, there were 62 events in AMBER for which duration could be calculated (out of 76 events in total) and 28 events in EMERALD for which the duration could be calculated (out of 32 events in total); the median duration of a D/C/F/TAF-related GI AEOI was 16.5 (Figure 2A and B) and 8.5 (Figure 2C and D) days, respectively. In both studies, the results were skewed towards shorter durations.

## Discussion

In this post hoc analysis of the AMBER and EMERALD studies of the most recent darunavir formulation, a favorable GI tolerability profile was observed for D/C/F/TAF. GI tolerability can be a factor when considering an appropriate antiretroviral therapy (ART) regimen across patient populations. Additionally, when selecting an ART regimen, the US Department of Health and Human Services recommends a regimen with a high genetic barrier to resistance, such as a darunavir-based regimen, when suboptimal adherence is suspected or resistance testing is pending or unavailable.[1] Thus, for treatment-naïve patients concerned about potential GI side effects when initiating therapy, D/C/F/TAF may be an appropriate option, as shown in the current report.

Treatment-experienced, virologically suppressed patients may consider switching regimens due to poor tolerability on their current regimen. Tolerability concerns regarding weight

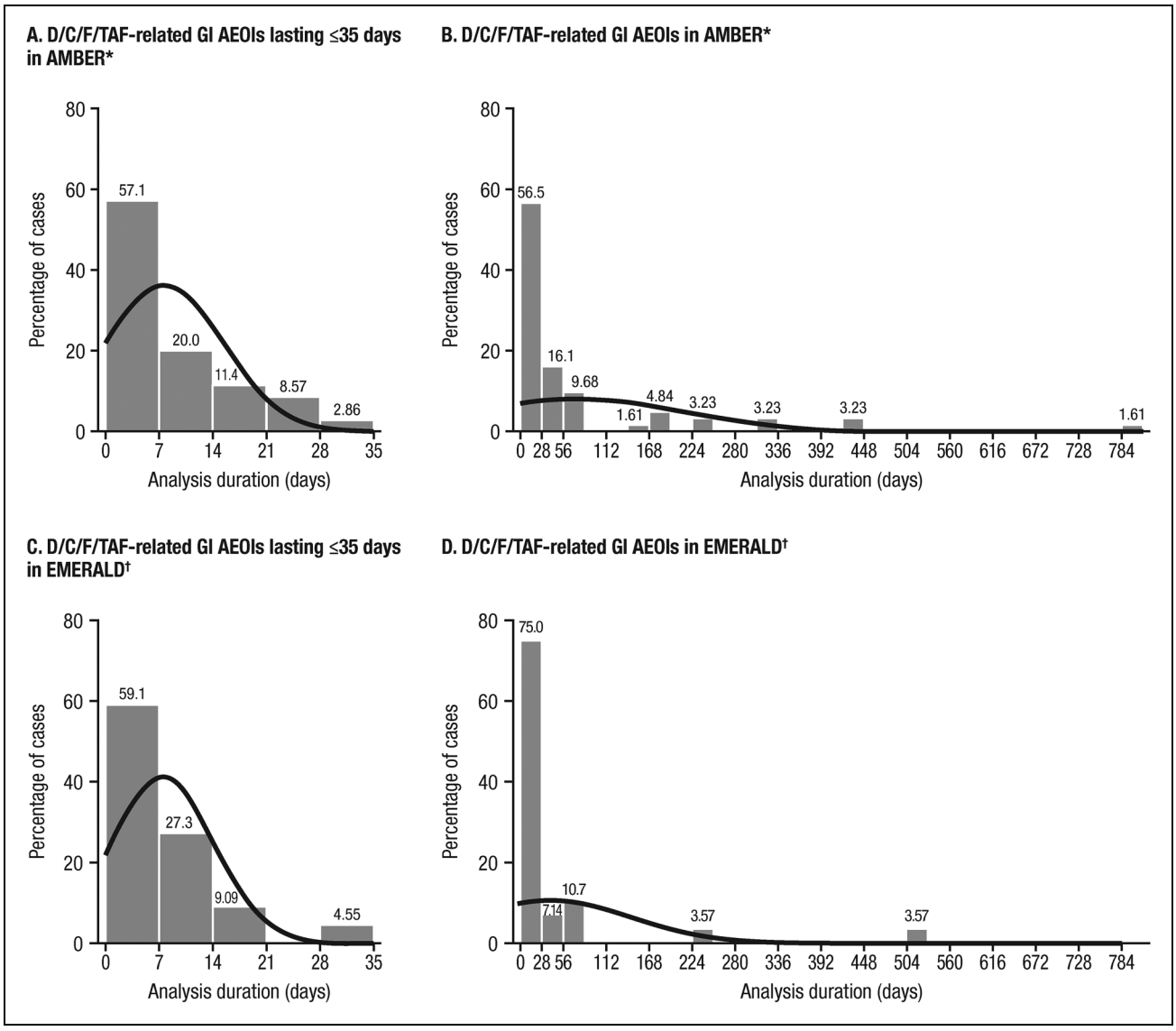


**Figure 2.** Distribution of duration of D/C/F/TAF-related GI AEOIs.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; GI, gastrointestinal; AEOI, adverse event of interest.
*In AMBER, 50 patients had a D/C/F/TAF-related GI AEOI; there were 76 events in total, and duration could be calculated for 62 of these events.
†In EMERALD, 26 patients had a D/C/F/TAF-related GI AEOI; there were 32 events in total, and duration could be calculated for 28 of these events.

gain and neuropsychiatric AEs, mainly with integrase inhibitors, have recently been recognized.[1,16–20] Given the favorable GI tolerability profile of D/C/F/TAF and the low risk of weight gain and neuropsychiatric AEs[14,21–23] with its use, D/C/F/TAF may serve as an important option for patients experiencing these AEs and considering switching to a new regimen. Moreover, for both treatment-experienced, virologically suppressed and treatment-naïve patients, the GI tolerability of D/C/F/TAF is generally consistent with that of commonly used integrase inhibitor–based regimens.[18,24–28] For example, Stellbrink et al reported GI AEs in 9% and 14% of treatment-naïve patients receiving bictegravir or dolutegravir regimens, respectively.[18]

Overall, findings from the current analysis suggest prompt resolution of D/C/F/TAF-related GI AEOIs among the few treatment-naïve and virologically suppressed patients who experienced such an event. The perception of GI intolerance as a barrier to this regimen, largely based on older formulations and dosing schema, may not be in proportion to the reality of actual patient experience.

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## Data Availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: J. Campbell, S. Seyedkazemi, and D. Anderson are employees of Janssen Scientific Affairs, LLC. K. Dunn and N. Bejou are former employees of Janssen Scientific Affairs, LLC. B. Baugh and D. Luo are employees of Janssen Research & Development, LLC. All authors may be stockholders of Johnson & Johnson.

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## ORCID iD

David Anderson https://orcid.org/0000-0002-6584-1666

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