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Psychiatric Symptoms in Patients Receiving Dolutegravir

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Introduction: Psychiatric symptoms (PSs) are reported to occur frequently in people living with HIV and may be associated with specific antiretrovirals. We analyzed PSs observed with dolutegravir (DTG) and other frequently prescribed anchor drugs.

Methods: Selected PSs (insomnia, anxiety, depression, and suicidality) occurring in HIV-positive patients during DTG treatment across 5 randomized clinical trials (3 double-blind), in the Observational Pharmaco-Epidemiology Research & Analysis (OPERA) cohort, and among cases spontaneously reported to ViiV Healthcare were analyzed.

Results: In clinical trials, PSs were reported at low and similar rates in patients receiving DTG or comparators [atazanavir, darunavir, efavirenz, or raltegravir (RAL)]. Insomnia was most commonly reported. The highest rates were observed in SINGLE (DTG 17%, efavirenz 12%), with consistently lower rates in the other trials (DTG: 3%–8% versus comparator: 3%–7%). More efavirenz-treated patients withdrew because of PSs than patients treated with other anchor drugs. In OPERA, history of PSs at baseline was lowest in efavirenz-treated patients compared with patients treated with DTG, RAL, or darunavir. Despite baseline differences, prevalence and incidence during treatment were similar across the 4 anchor drugs. Withdrawal rates for PSs were lowest for DTG (0%–0.6%) and highest for RAL (0%–2.5%). Spontaneously reported events were similar in nature to clinical trial data.

Conclusions: Analysis of 3 different data sources shows that, similar to other frequently prescribed anchor drugs to treat HIV infection, PSs are also reported in DTG-treated patients. These events are reported with low frequency and rarely necessitate DTG discontinuation.

Key Words: dolutegravir, antiretroviral therapy, insomnia, anxiety, depression, suicide

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INTRODUCTION

The integrase strand transfer inhibitor (INSTI) class of antiretroviral drugs used to treat HIV-1 infection includes raltegravir (RAL), elvitegravir, and dolutegravir (DTG). Clinical studies using INSTIs have demonstrated 80%–90% efficacy in HIV-positive, antiretroviral therapy (ART)-naive patients.[1] The INSTIs have also demonstrated favorable safety and tolerability,[2] are recommended options for patients initiating ART,[3–6] and are often used in switch strategies for patients with tolerability issues.[2,7] They show similar rates of adverse events (AEs), with nausea, diarrhea, and headache reported most commonly.[7–9] These AEs have been shown to be mild to moderate in severity and are not typically associated with treatment discontinuation. Psychiatric symptoms (PSs) have been reported in patients treated with INSTI class drugs but typically occur less frequently than in patients treated with efavirenz.[9,10]

PSs are substantially more frequent among persons living with HIV (PLWH; anxiety 28%, depression up to 48%, insomnia 29%–73%)[11–15] compared with the general population (anxiety 7.3%, depression 5%–10%, and insomnia 3.6%–18%).[11,12,15–17] The rate of suicide for PLWH has been reported to be up to 8 times higher than that of the general population.[18,19] A systematic review of studies published between 1989 and 2008 showed a prevalence of 27% (range 4%–78%) for suicidal ideation among PLWH.[20] Although the underlying pathogenesis of PS in PLWH remains elusive, several factors have been proposed. The etiology is likely multifactorial, including immune activation due to HIV disease, antiretroviral toxicities, stigma from living with HIV, and lifestyle factors, such as drug and alcohol use, which may be higher in PLWH compared with control

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populations.[15,21–23] Although antiretroviral therapy improves survival and reduces morbidity in PLWH, PSs may be associated with certain antiretroviral agents.[10,24]

High background rates of psychiatric conditions among PLWH and the likely multifactorial pathogenesis make it challenging to assess the relationship between PSs and specific antiretroviral therapies. The objectives of this analysis are to provide insight into the frequency and characteristics of PSs that have been reported in patients treated with DTG-based regimens using new data sources, including aggregated data from ViiV Healthcare clinical trials, the Observational Pharmaco-Epidemiology Research & Analysis (OPERA)[25] cohort, and cases spontaneously reported to ViiV Healthcare; and put these findings in the context of results for other anchor drugs.

METHODS

Clinical Trials

This is an analysis of phase III clinical trials that investigated DTG 50 mg once daily in adults and had at least 48 weeks of data as of April 2016, which includes the SPRING-2, FLAMINGO, SINGLE, ARIA, and SAILING studies. Design details for each study have been previously described.[26–30] Briefly, in all 5 studies, patients were randomized 1:1 to receive either DTG- or comparator-containing treatment [RAL in SPRING-2 and SAILING, efavirenz (EFV)/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) in SINGLE, darunavir + ritonavir (DRV/r) in FLAMINGO, and atazanavir + ritonavir (ATV/r) in ARIA]. In 4 of the studies, DTG was administered as the single active preparation, whereas in the ARIA study, the fixed-dose combination tablet of abacavir (ABC)/DTG/lamivudine (3TC) was used. SPRING-2, SINGLE, and SAILING were all double-blind double-dummy controlled trials. Patients in SAILING had been treated with ART (not including INSTIs), had documented resistance to 2 or more antiretroviral drug classes, and had background therapy (BT) with 1–2 fully active agents.[27] Patients in the other 4 trials were ART naive. For SPRING-2 and FLAMINGO, BT in each arm was ABC/3TC or TDF/FTC; BT for DTG-treated patients in SINGLE was ABC/3TC, and BT was TDF/FTC for ATV/r-treated patients in ARIA. All patients treated with ABC-containing regimens were negative for the *HLA-B*5701* allele.[26–30] For all 5 studies, ethics committee approval was obtained at all participating centers in accordance with the principles of the 2008 Declaration of Helsinki. Each patient provided written informed consent before undergoing study procedures.

In all these clinical trials, PSs were captured through AE and serious AE reporting after baseline at scheduled study visits.[26–30]

All Medical Dictionary for Regulatory Activities (MedDRA) preferred terms used to code psychiatric AEs in clinical trials were examined, and company safety physicians grouped related terms to describe 4 main PS categories: insomnia, anxiety, depression, and suicidality. The category insomnia included the terms insomnia, initial insomnia, terminal insomnia, and middle insomnia. The category anxiety included the terms anxiety and anxiety disorder. The category depression included the terms depression, major depression, depressed mood, depressive symptom, and bipolar disorder. The category suicidality included suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior. For each category, the incidence, intensity, and action taken with the study drug were examined. An in-depth case review was performed for every patient with suicidality to determine additional information about the nature of the event (s), psychiatric history, and other risk factors.

OPERA Cohort

Using electronic medical record data from the OPERA database, 6347 HIV-positive patients were identified who initiated DTG-, EFV-, RAL- or DRV-based regimens (commonly prescribed anchor drugs) regardless of previous ART treatment from January 1, 2013 (the first year DTG was marketed) through April 30, 2016. Patients were observed from the start of these regimens until the first of the following censoring events: discontinuation of the agent of interest, cessation of continuous clinical activity, death, or study end. Patients exposed to any of the drugs of interest before the observation period were excluded. The endpoints included diagnoses consistent with anxiety, depression, insomnia, and suicidality identified from the medical record and event time to onset (TTO) calculated from treatment initiation to first occurrence of a PS. Patient demographics and clinical characteristics, including history of psychiatric conditions, were examined.

Spontaneously Reported Cases

Spontaneously reported postmarketing cases of PSs in patients treated with either DTG or ABC/DTG/3TC were identified from the ViiV Healthcare Global Safety Database (OASIS, based on Oracle Argus Safety 2013; Oracle Corporation, Redwood Shores, CA) through February 29, 2016. The same MedDRA preferred terms applied to the clinical trial data were used, and cases were grouped into the same 4 PS categories for analysis. The TTO for the event, drug action taken, and event outcome were examined for cases in which this information was available. For patients with depression or suicidality, a case review was performed to assess characteristics such as history of depression/suicidality and presence of other ongoing risk factors.

Because it is not possible to estimate the true incidence of an event from spontaneous data, reporting rates were calculated for the 4 PS categories using estimated exposure from DTG and ABC/DTG/3TC sales data, which provide an indication of reporting frequencies. Rates were calculated as the number of spontaneously reported cases during an estimated 124,737 patient-years (PY) of exposure to DTG and 62,045 PY of exposure to ABC/DTG/3TC and are expressed as the number of cases per 1000 PY. For these calculations, a data cut-off date of December 31, 2015 was used to identify relevant cases from the Global Safety Database, which corresponds with the most current available sales data at the time of this analysis.

RESULTS

PSs in Clinical Trials

Reporting rates for each of the 4 PS categories were low and similar across the 5 clinical trials (N = 3353; DTG, n = 1672; comparator, n = 1681) and between individual treatment groups, except for insomnia in the SINGLE study. For each of the 4 PS categories, most patients developed single episodes, and with few exceptions, TTO was >28 days across trials/treatment groups. There were no discernible patterns for any observable differences in anxiety, depression, and suicidality among trials or treatment groups in terms of median TTO; proportion of AEs considered drug related, serious (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/A959), or of grade 3–4 intensity by reporting investigators; or AEs resulting in treatment withdrawal. A higher number of EFV-treated patients were withdrawn as a result of a PS [15/419 (4%)] compared with the other anchor drugs [Table 1; <1% for DTG (4/1672) and RAL (3/773), 0 for DRV and ATV]. Most cases in all 4 categories either resolved or improved across trials/treatment groups (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/A959).

Insomnia was the most commonly reported PS. The highest rates were reported in SINGLE [DTG, 71/414 (17%); EFV, 52/419 (12%)], with consistently lower rates reported in the other 4 trials (SPRING-2: DTG 6%, RAL 5%; SAILING: DTG 3%, RAL 4%; FLAMINGO: DTG 8%, DRV/r 7%; ARIA: DTG 4%, ATV/r 3%). The SINGLE study reported the highest proportion of insomnia cases considered drug related by reporting investigators [DTG, 43/71 (61%); EFV, 28/52 (54%)] and the shortest median TTO [DTG, 16.0 days (1.0–72.0); EFV, 30 days (2.0–218.0)]. Four grade 3–4 insomnia cases occurred in DTG-treated patients and 0 in the comparator groups; none were considered serious (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/A959). Two DTG-treated patients withdrew across trials because of insomnia compared with 4 treated with EFV/TDF/FTC in SINGLE (Table 1).

Depression was reported for numerically more patients treated with EFV/TDF/FTC in SINGLE [44/419 (11%)] than for other treatment groups/trials. The proportion of depression cases considered drug related by reporting investigators was highest in both treatment groups for SINGLE compared with the other 4 trials; this was also true for anxiety cases in the EFV-treated patients. A small proportion of either anxiety or depression cases were considered serious (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/A959) or of grade 3–4 intensity. SINGLE was the only study in which patients withdrew due to anxiety (EFV, n = 4) or depression (DTG, n = 1; EFV, n = 6; Table 1).

Suicidality, including suicidal ideation, attempted suicide, and self-injurious behavior, occurred in 1% of patients across trials/treatment groups (DTG, 20/1672; comparator, 20/1681), and was considered drug related in 2/20 of the DTG-treated patients and 5/20 of the comparator-treated patients (Table 1). Two patients, 1 treated with DTG and 1 with RAL, completed suicide. One separate, nonfatal case of suicidality with DTG and 3 additional nonfatal cases with comparators led to treatment withdrawal. Most cases resolved or improved across all trials (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/A959). Of the 20 reported cases of suicidality in DTG-treated patients, 19 (95%) had a psychiatric history at baseline consistent with an increased risk for suicide, including a history of suicidal ideation (n = 2), suicide attempts (n = 6), depression/bipolar disorder (n = 8), or other psychiatric conditions not further specified (n = 3). The one DTG-treated patient with no psychiatric history who attempted suicide did so on day 899; the event was associated with emotional triggers and considered unrelated to study drug. Of the 20 cases of suicidality in comparator-treated patients, 16 (80%) had a psychiatric history at baseline, with a similar pattern as observed for DTG, 2 had socioeconomic triggers, and 2 had no obvious underlying risk factors. The DTG-treated patient who completed suicide was male, of unknown age, and had a medical history of bipolar disorder requiring treatment, suicidal ideation, and suicide attempt. The RAL-treated patient who completed suicide was also male, aged 22 years, and had no reported underlying risk factors or triggers. Neither case of completed suicide was considered drug related.

PSs in the OPERA Cohort

Differences existed in the baseline characteristics of patients treated with the 4 anchor drugs (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/A959). The EFV-treated patients had the lowest proportion of treatment-experienced patients, whereas higher similar proportions were seen for the other regimens. Median follow-up time was similar among the regimens at approximately 15 months.

History of anxiety, depression, or insomnia was highest in DTG-treated patients and lowest in EFV-treated patients. Despite this, the prevalence of anxiety, depression, and insomnia was similar across all 4 anchor drugs, except for a higher prevalence of anxiety and depression in RAL-treated patients and a lower prevalence of insomnia in DRV-treated patients (Table 2). Treatment discontinuations for these symptoms were generally lowest for DTG-treated patients (range 0.1%–0.6%), with the exception of insomnia which was also low for both DRV-treated (0.5%) and RAL-treated (0.7%) patients (DTG, 0.6%). In patients without a history of these psychiatric conditions at baseline, the incidence of anxiety, depression, and insomnia was similar across all 4 anchor drugs. However, treatment discontinuations for these symptoms were lowest for DTG-treated patients (range 0.1%–0.3% compared with a range of 0.5%–1.1% for the other 3 anchor drugs).

History of suicidality at baseline (0.2%–0.5%) and subsequent prevalence and incidence were low and similar for all drugs (0.1%–0.2%). Only one patient in the cohort discontinued because of suicidality (EFV-treated).

Kaplan–Meier plots demonstrated no difference in TTO among patients treated with the 4 anchor drug regimens when all 4 PS categories were pooled; however, DTG had a longer TTO for depression and DRV had a longer TTO for insomnia (Fig. 1).

TABLE 1. Characteristics of PSs* That Occurred During DTG Clinical Trials

	SPRING-2 ART Naive Double-Blind 96 wk		FLAMINGO ART Naive Open-Label 96 wk		SINGLE ART Naive Double-Blind† 144 wk	
Cases	**DTG + 2NRTIs‡ (n = 411)**	**RAL + 2NRTIs‡ (n = 411)**	**DTG + 2NRTIs‡ (n = 242)**	**DRV/r + 2NRTIs‡ (n = 242)**	**DTG + ABC/ 3TC (n = 414)**	**EFV/TDF/FTC (n = 419)**
Insomnia, n (%) [No. of Events]	25 (6) [25]	20 (5) [21]	20 (8) [22]	16 (7) [17]	71 (17) [80]	52 (12) [55]
TTO, median (IQR), d	98.0 (57.0–223.0)	83.0 (25.5–247.0)	104.0 (5.5–236.0)	12.5 (1.0–141.0)	16.0 (1.0–72.0)	30.0 (2.0–218.0)
Drug related, n (%)	6/25 (24)	3/20 (15)	4/20 (20)	5/16 (31)	43/71 (61)	28/52 (54)
Severe or grade 3/4, n (%)	0	0	0	0	3/71 (4)	0
Led to withdrawal, n (%)	0	0	0	0	1/71 (1)	4/52 (8)
Anxiety, n (%) [No. of Events]	17 (4) [17]	23 (6) [25]	13 (5) [13]	9 (4) [9]	28 (7) [30]	30 (7) [38]
TTO, median (IQR), d	66.0 (57.0–278.0)	217.0 (89.0–303.0)	253.0 (66.0–360.0)	129.0 (21.0–265.0)	265.0 (93.5–574.5)	120.0 (2.0–160.0)
Drug related, n (%)	1/17 (6)	2/23 (9)	1/13 (8)	0	4/28 (14)	11/30 (37)
Severe or grade 3/4, n (%)	1/17 (6)	0	0	0	0	3/30 (10)
Led to withdrawal, n (%)	0	0	0	0	0	4/30 (13)
Depression, n (%) [No. of Events]	29 (7) [30]	21 (5) [21]	16 (7) [19]	12 (5) [13]	35 (8) [42]	44 (11) [52]
TTO, median (IQR), d	226.0 (113.0–311.0)	249.0 (85.0–337.0)	167.5 (83.5–275.5)	234.0 (66.5–483.0)	148.0 (34.0–316.0)	135.0 (40.5–272.5)
Drug related, n (%)	1/29 (3)	2/21 (10)	0	0	13/35 (37)	19/44 (43)
Severe or grade 3/4, n (%)	1/29 (3)	1/21 (5)	3/16 (19)	1/12 (8)	5/35 (14)	8/44 (18)
Led to withdrawal, n (%)	0	0	0	0	1/35 (3)	6/44 (14)
Suicidality, n (%) [No. of Events]	4 (<1) [4]	6 (1) [8]	4 (2) [4]	1 (<1) [1]	3 (<1) [3]	7 (2) [7]
TTO, median (IQR), d	212.5 (102.0–296.0)	320.0 (260.0–385.0)	331.0 (275.0–504.0)	204.0 (204.0–204.0)	332.0 (43.0–410.0)	173.0 (55.0–330.0)
Drug related, n (%)	0	0	1/4 (25)	0	0	4/7 (57)
Severe or grade 3/4, n (%)	3/4 (75)	5/6 (83)	3/4 (75)	0	2/3 (67)	5/7 (71)
Led to withdrawal, n (%)	0	2/6 (33)	1/4 (25)	0	0	1/7 (14)

	ARIA ART Naive Open-Label 48 wk		SAILING ART Experienced Double-Blind 48 wk			
Cases	**ABC/DTG/3TC (n = 248)**	**ATV/r + TDF/FTC (n = 247)**	**DTG + ISBR (n = 357)**	**RAL + ISBR (n = 362)**	**Total DTG (n = 1672)**	**Total Comparator Arms (n = 1681)**
Insomnia, n (%) [No. of Events]	10 (4) [10]	8 (3) [8]	12 (3) [12]	14 (4) [15]	138 (8) [149]	110 (7) [116]
TTO, median (IQR), d	34.5 (8.0–71.0)	158.0 (27.5–241.0)	77.0 (29.0–178.0)	72.5 (42.0–90.0)	NA	NA
Drug related, n (%)	5/10 (50)	1/8 (13)	0	6/14 (43)	58/138 (42)	43/110 (39)
Severe or grade 3/4, n (%)	1/10 (10)	0	0	0	4/138 (3)	0
Led to withdrawal, n (%)	1/10 (10)	0	0	0	2/138 (1)	4/110 (4)
Anxiety, n (%) [No. of Events]	5 (2) [5]	8 (3) [8]	5 (1) [5]	6 (2) [6]	68 (4) [70]	76 (5) [86]
TTO, median (IQR), d	99.0 (85.0–144.0)	122.0 (35.5–224.5)	171.0 (84.0–208.0)	75.5 (33.0–313.0)	NA	NA
Drug related, n (%)	0	1/8 (13)	0	2/6 (33)	6/68 (9)	16/76 (21)
Severe or grade 3/4, n (%)	0	2/8 (25)	0	0	1/68 (1)	5/76 (7)
Led to withdrawal, n (%)	0	0	0	0	0	4/76 (5)
Depression, n (%) [No. of Events]	9 (4) [9]	11 (4) [12]§	11 (3) [15]	9 (2) [10]	100 (6) [115]	97 (6) [108]
TTO, median (IQR), d	218.0 (169.0–270.0)	146.0 (108.0–249.0)	147.0 (85.0–176.0)	138.0 (43.0–203.0)	NA	NA
Drug related, n (%)	1/9 (11)	1/11 (9)	0	0	15/100 (15)	22/97 (23)
Severe or grade 3/4, n (%)	0	1/11 (9)	2/11 (18)	2/9 (22)	11/100 (11)	13/97 (13)
Led to withdrawal, n (%)	0	0	0	0	1/100 (1)	6/97 (6)
Suicidality, n (%) [No. of Events]	3 (1) [3]	4 (2) [4]	6 (2) [8]	2 (<1) [3]	20 (1) [22]	20 (1) [23]
TTO, median (IQR), d	88.0 (1.0–325.0)	105.0 (75.5–211.0)	79.5 (32.0–147.0)	55.5 (9.0–102.0)	NA	NA
Drug related, n (%)	1/3 (33)	0	0	1/2 (50)	2/20 (10)	5/20 (25)
Severe or grade 3/4, n (%)	0	1/4 (25)	4/6 (67)	2/2 (100)	12/20 (60)	13/20 (65)
Led to withdrawal, n (%)	0	0	0	1/2 (50)	1/20 (5)	4/20 (20)

*The PS category insomnia included insomnia, initial insomnia, middle insomnia, and terminal insomnia; anxiety included anxiety and anxiety disorder; depression included depression, major depression, depressed mood, depressive symptom, and bipolar disorder; suicidality included suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior.

†Double-blind phase occurred from initiation to week 96 followed by an open-label phase from week 96 to week 144.

‡Background therapy was ABC/3TC or TDF/FTC.

§One additional case of depression has been identified in the ATV/r treatment group after the primary analysis of ARIA; additional details are not currently available.

3TC, lamivudine; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; ISBR, investigator-selected background regimen; NA, not available; TDF, tenofovir disoproxil fumarate; TTO, time to onset (to first occurrence).

TABLE 2. Characteristics of PSs* in the OPERA Cohort

	ART Regimens			
	DTG-Containing (n = 2029)	EFV-Containing (n = 1608)	RAL-Containing (n = 963)	DRV-Containing (n = 1747)
History of diagnoses at baseline, n (%)				
Insomnia	291 (14.3)	124 (7.7)	133 (13.8)	173 (9.9)
Anxiety	345 (17.0)	148 (9.2)	145 (15.1)	216 (12.4)
Depression	656 (32.3)	261 (16.2)	282 (29.3)	465 (26.6)
Suicidality	9 (0.4)	3 (0.2)	4 (0.4)	8 (0.5)
Prevalence of diagnoses during follow-up, n (%)				
Insomnia	157 (7.7)	139 (8.6)	82 (8.5)	96 (5.5)
Discontinued	13 (0.6)	19 (1.2)	7 (0.7)	9 (0.5)
Anxiety	134 (6.6)	110 (6.8)	98 (10.2)	132 (7.6)
Discontinued	7 (0.3)	13 (0.8)	14 (1.5)	20 (1.1)
Depression	205 (10.1)	153 (9.5)	136 (14.1)	204 (11.7)
Discontinued	13 (0.6)	25 (1.6)	24 (2.5)	19 (1.1)
Suicidality	3 (0.1)	3 (0.2)	2 (0.2)	1 (0.1)
Discontinued	0	1 (0.1)	0	0
Incidence of new diagnoses during follow-up, n (%)				
Insomnia	110 (5.4)	110 (6.8)	55 (5.7)	71 (4.1)
Discontinued	6 (0.3)	15 (0.9)	6 (0.6)	8 (0.5)
Anxiety	98 (4.8)	89 (5.5)	64 (6.6)	93 (5.3)
Discontinued	3 (0.1)	10 (0.6)	8 (0.8)	12 (0.7)
Depression	98 (4.8)	104 (6.5)	69 (7.2)	109 (6.2)
Discontinued	5 (0.2)	17 (1.1)	7 (0.7)	12 (0.7)
Suicidality	3 (0.1)	3 (0.2)	2 (0.2)	1 (0.1)
Discontinued	0	1 (0.1)	0	0

*History of PSs (insomnia, anxiety, depression, and suicidality) was determined at the baseline date, defined as the date of regimen prescription. Prevalence of PSs during follow-up includes PS diagnoses that occurred after baseline, regardless of whether the patient had the diagnosis before baseline. Incidence of new PSs during follow-up includes only new PS diagnoses that occurred in patients without a history of the specified PS at or before baseline. Discontinued indicates discontinuation of drug due to the specified PS. The PS category insomnia included insomnia, initial insomnia, middle insomnia, and terminal insomnia; anxiety included anxiety and anxiety disorder; depression included depression, major depression, depressed mood, depressive symptom, and bipolar disorder; suicidality included suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior.

EFV, efavirenz; OPERA, Observational Pharmaco-Epidemiology Research & Analysis.

PSs in Spontaneously Reported Cases

Most spontaneously reported cases were reported by health care providers (>85%). Reporting rates for all PSs in patients treated with DTG or ABC/DTG/3TC were 3.09 and 2.79 per 1000 PY respectively (Table 3). Reporting rates for the 4 specific PS categories were low and comparable between DTG and ABC/DTG/3TC (Table 3), with insomnia most commonly reported (approximately 1 event per 1000 PY for both DTG and ABC/DTG/3TC). Cases of suicidality were reported at <0.25 cases per 1000 PY.

The TTO was reported for approximately one-third of patients with insomnia, anxiety, and depression and was generally <28 days after starting treatment with DTG or ABC/DTG/3TC, although TTO for depression with DTG was typically >28 days. Action taken with drug was reported in 71%–80% of cases for all 4 PS categories and was most often discontinuation (60%–93%). Where event outcome was available (39%–60% of cases), the majority resolved or improved (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/A959).

Anxiety was generally reported with other concurrent psychiatric conditions, most commonly depression; however, insomnia was usually reported as an isolated psychiatric event. In those patients who developed depression whose psychiatric history was known (34/100), approximately 85% had a history of depression before drug initiation. An absence of a history of depressive symptoms was only identified in 3 cases.

Among cases of suicidality with reported TTO (~50%), suicidality typically occurred within 1 month of starting treatment with DTG or ABC/DTG/3TC. In the 40% of suicidality cases for which psychiatric history was available, 16 of the 20 patients had a psychiatric condition before starting treatment. Five patients completed suicide (DTG, n = 4; ABC/DTG/3TC, n = 1). Four of the 5 cases occurred within 6 months of commencing treatment (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/A959). Three of these patients had a history of depression and 1 previously attempted suicide. In the case for which psychiatric history was not available, there was evidence suggesting drug abuse and psychiatric instability when the patient started treatment. The final case involved a 55-year-old man living with HIV for approximately 30 years who had multiple comorbidities; the suicide was considered unrelated to DTG.

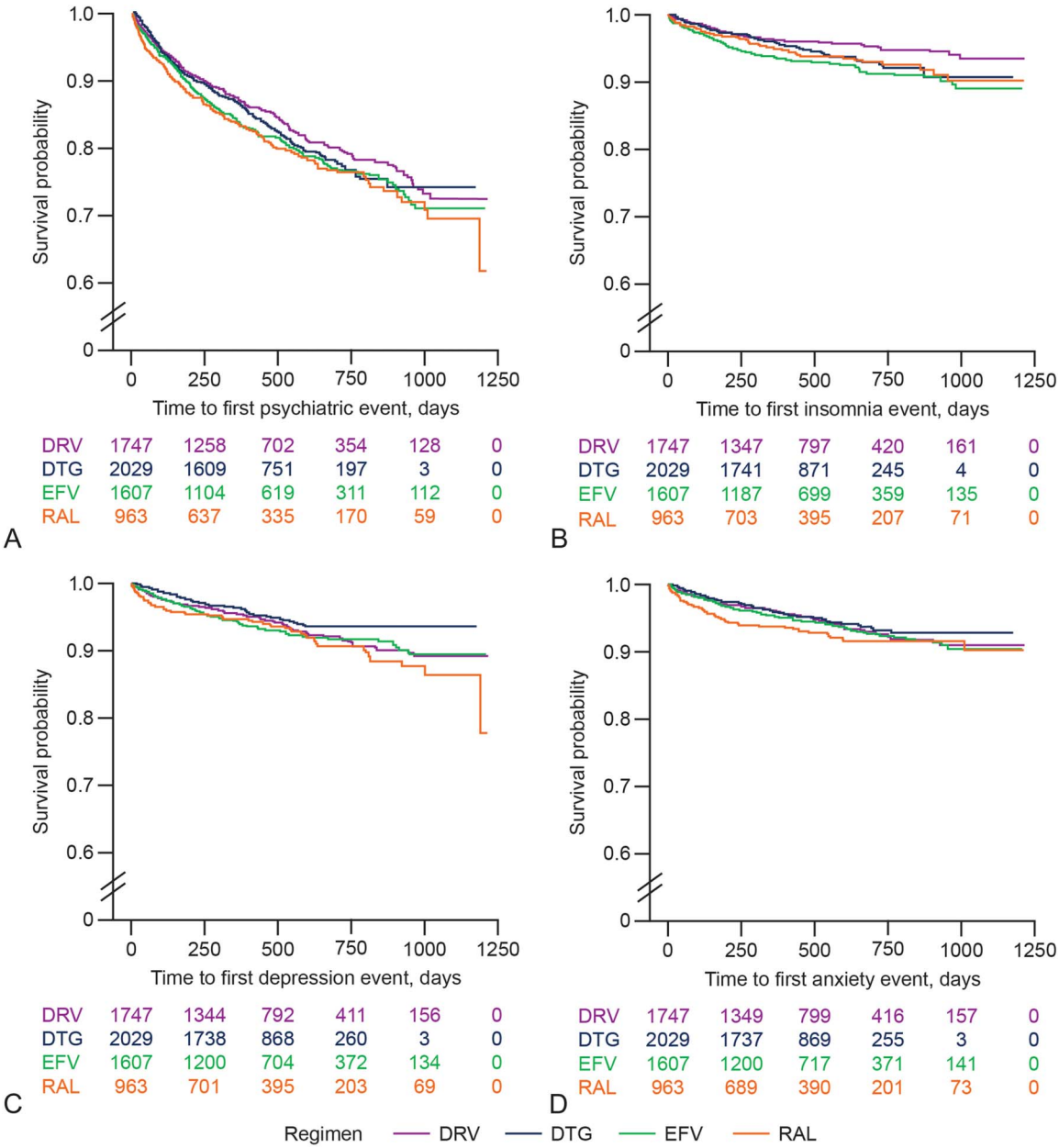

FIGURE 1. TTO of first (A) psychiatric event, (B) insomnia event, (C) depression event, and (D) anxiety event in patients treated with DTG-, RAL-, EFV-, and DRV-containing regimens in the OPERA cohort with number of subjects at risk January 1, 2013–April 30, 2015. EFV, efavirenz; OPERA, Observational Pharmaco-Epidemiology Research & Analysis.

DISCUSSION

It is recognized that PSs may be underreported for several reasons, including patients lacking awareness of the symptoms or denial of symptoms due to a lack of insight or stigma. There are reports in the literature linking ART to the occurrence or exacerbation of PSs, including depression, although this may only have been evident many years after these drugs were first marketed.[31] Given the limitations of the data sources, it is important that there is continued vigilance both by the marketing authorization holders and the scientific community to more accurately describe the safety profiles of marketed drugs, especially during the initial years postmarketing.

This analysis was conducted to characterize PSs occurring in patients during HIV-1 treatment with DTG compared with other recommended anchor drugs. PSs are more prevalent in the HIV-infected population than in the general population[11] and, given other confounders present, are difficult to associate with specific antiretroviral therapies. Because of the nature of the data collected, this article looks at PSs rather than formal psychiatric diagnoses, and the relationship between these varies with the data source. However, clinical trial patients displaying

TABLE 3. Spontaneous Reporting Rates of PSs* Among Patients Treated With DTG or ABC/DTG/3TC Through December 31, 2015

Cases per 1000 PY (No of Events)	DTG (124,737 PY)	ABC/DTG/3TC (62,045 PY)
All PSs SOC	3.09 (385)	2.79 (173)
PS category		
Depression	0.46 (57)	0.50 (31)
Anxiety	0.23 (29)	0.55 (34)
Insomnia	1.23 (154)	1.11 (69)
Suicidality	0.25 (31)	0.16 (10)

*All PSs included all event terms in the MedDRA Psychiatric Disorders System Order Class (SOC). The PS category insomnia included insomnia, initial insomnia, middle insomnia, and terminal insomnia; anxiety included anxiety and anxiety disorder; depression included depression, major depression, depressed mood, depressive symptom, and bipolar disorder; suicidality included suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior.

ABC/DTG/3TC, abacavir/dolutegravir/lamivudine; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Order Class.

serious PSs such as severe depression or suicidal ideation were generally referred to a psychiatrist to seek a formal diagnosis. Analysis of data from these diverse sources (ie, clinical trials, the observational pharmacoepidemiological data, and spontaneously reported AEs) uses the strength of each source, leading to several observations. The individual PSs occurred at a low frequency in patients treated with DTG in clinical trials and the OPERA cohort, and spontaneous reporting rates were low in the context of estimated PY of exposure. The most frequently reported events (ie, insomnia, anxiety, and depression) were generally mild to moderate in intensity. Discontinuation rates due to PSs were low in DTG-treated patients in clinical trials and the OPERA cohort, and where outcome information was available (eg, in clinical trials) events typically resolved or improved on continued treatment. In spontaneously reported cases, discontinuation rates were higher, which could be influenced by the limitations of spontaneous reporting discussed below (eg, reporting bias). The OPERA cohort data may represent the real-world setting more accurately than data from spontaneous reporting because of the low discontinuation rates and the ability to calculate incidence rates based on known denominators. None of the patients in the clinical trials were also in the OPERA cohort.

The most frequently reported drug-related PS was insomnia, occurring in 3.5% of patients treated with DTG in clinical trials, which led to withdrawal in only 2 patients. Insomnia was also the most common spontaneously reported PS (1.23 cases per 1000 PY in DTG-treated patients, 1.11 cases per 1000 PY in ABC/DTG/3TC-treated patients). However, in the OPERA cohort, both prevalence and new incidence of insomnia after treatment were similar to anxiety and depression for all 4 anchor drugs. The incidence of insomnia for patients treated with DTG was reproducibly low (3%–8%) and similar to INSTI and protease inhibitor (PI) comparators in 4 of the 5 clinical trials, with the SINGLE trial being an obvious outlier.

EFV/TDF/FTC was the double-blind comparator in SINGLE, and because the adverse drug–reaction profile for EFV includes a high incidence of psychiatric events, HCPs may have monitored patients more closely for PSs and been more likely to report such events during this trial. Patients may also have been more likely to report such symptoms knowing that there was a 50% chance that they were randomized to EFV. A similar finding was previously observed in the 2 double-blind, registrational clinical trials for RAL in which higher reporting rates for insomnia and abnormal dreams were observed in STARTMRK, which had an EFV comparator group, compared with BENCHMRK, which did not.[32]

Clinical trials are a valuable data source because they enable controlled comparisons between treatment groups with consistent baseline characteristics, clinical care, and safety assessments. In the 5 clinical trials we examined, frequencies of PSs were low with DTG and similar to the comparator groups, with the exception of insomnia in SINGLE, and most patients developed a single episode. Among DTG-treated patients who experienced PSs, few were considered grade 3–4 intensity or reported as serious, and most DTG-treated patients (95%) who experienced suicidality had a history of psychiatric conditions.

Using OPERA data that included 98% of all DTG data allowed PSs to be assessed in patients in a real-world setting and allowed all drugs of interest to be compared starting from the same date and for the same follow-up period. Data for EFV, RAL, and DRV before DTG was introduced in 2013 were consistent with the data set used in this study (data not shown). These results support conclusions from the clinical trial data that the frequency of PSs associated with DTG was generally low and similar to that of other anchor drugs, and most similar to DRV. Patients treated with EFV had the lowest prevalence of PSs at baseline (before medication was initiated), which suggests that in the real-world setting physicians may be preferentially prescribing INSTIs and DRV rather than EFV to treat patients with a history of psychiatric events. Despite this potential channeling bias, the prevalence, incidence, and withdrawal rates of PSs with DTG remained low compared with patients treated with the other anchor drugs, including EFV.

There were no new PSs reported spontaneously that had not been seen in clinical trials. The PSs with the highest incidence in clinical trials were also the most common in spontaneously reported cases. Most insomnia, anxiety, and depression cases were nonserious. The serious cases of depression and suicidality shared similar characteristics to those observed in clinical trials including a history of depression or other PSs in 80% of cases for which this information was reported.

Although our analysis used the most robust data sources available, each has limitations. Patients enrolled in clinical trials are screened to meet specific inclusion criteria and therefore might not accurately represent real-world populations. Background rates of psychiatric conditions may differ between patients enrolled in clinical trials and the real-world population. In resource-rich settings, patients without health care insurance may not have access to ART without being in a clinical trial, and in resource-limited settings, participation in a clinical trial may be the only way to obtain access to ART. In both scenarios, both patients and investigators may be reluctant to report side effects because

they know the patients could be removed from the study. A strength of the clinical trial data is that the 5 trials analyzed were randomized, and 3 were double-blind studies, which accounted for approximately 70% of the clinical trial population. Although open-label trials provide less robust data, there were no obvious differences among all the trials.

The OPERA cohort is a large, diverse, real-world patient population, although limited to US patients, so it is unclear if conclusions can be extrapolated to cohorts from other countries. Diagnoses are prospectively captured by health care providers in electronic medical records; however, PSs may be underreported because mild events may be recorded as symptoms instead of diagnoses. Like any observational cohort study, unknown residual confounding factors cannot be ruled out, and causality between antiretrovirals and events cannot be proven. Conclusions based on the OPERA data may be limited by the relatively short follow-up periods (ie, ~15 months), although the follow-up period should be sufficient to detect drug-related events. A detailed future publication of these OPERA data is planned.

Analyses of spontaneously reported cases have several limitations, including underreporting (because reporting is voluntary); retrospective and variable quality data for meaningful causality assessments (eg, often missing concomitant medications, medical history, drug action taken, and event outcome); lack of denominator data biases (eg, no control group, preferential reporting of unusual or serious events, and adverse outcomes); and definitive causality statements against suspect drugs are not often provided.[33,34]

Despite these limitations, the consistency of data from the clinical trials, the OPERA cohort, and spontaneously reported cases support the reliability of the conclusions.

The analysis of 3 different data sources shows that, similar to other frequently prescribed anchor drugs to treat HIV infection, PSs are also reported in DTG-treated patients. These events are reported with low frequency and most are generally mild to moderate in intensity, nonserious (with the exception of suicidality), and rarely necessitate DTG discontinuation.

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