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Psychiatric outcomes observed in patients living with HIV using six common core antiretrovirals in the Observational Pharmaco-Epidemiology Research and Analysis database

Ricky Hsu, Jennifer Fusco, Cassidy Henegar, Karam Mounzer, Michael Wohlfeiler, Vani Vannappagari, Michael Aboud, Lloyd Curtis and Gregory Fusco

Abstract

Background: Psychiatric outcomes are common among people living with HIV and may be associated with specific antiretroviral use. We evaluated the occurrence of psychiatric outcomes in patients taking dolutegravir (DTG)-containing regimens compared with five other core agents.

Methods: Patients in the OPERA database prescribed regimens based on DTG, efavirenz (EFV), raltegravir (RAL), darunavir (DRV), rilpivirine (RPV), or elvitegravir (EVG) for the first time between 1 January 2013 and 31 December 2015 were analyzed. Psychiatric outcomes included diagnoses of anxiety, depression, insomnia, or suicidality during core agent exposure. Multivariable Cox analysis models were used to assess time to psychiatric outcomes between core agents stratified by psychiatric history, with DTG as the referent.

Results: A total of 13,261 patients initiated a regimen of interest (DTG: 2783; RAL: 979; EVG: 3895, EFV: 1746, RPV: 1921, DRV: 1937). Psychiatric history was common, with varied prevalence across groups (DTG 38%, EFV 24%, RAL 40%, DRV 34%, RPV 29%, EVG 31%). Among patients without a psychiatric history, the likelihood of a psychiatric outcome during follow up did not differ between DTG and the other core agents. Among patients with a psychiatric history, risk during follow up for patients taking DTG was equivalent (*versus* RPV), marginally reduced (*versus* RAL and EFV), or reduced (*versus* EVG and DRV).

Conclusions: In a large cohort of HIV+ patients in care, patients with a psychiatric history appeared channeled towards drugs with known favorable psychiatric safety profiles, including DTG. Despite this, DTG exposure was not associated with an increased risk of psychiatric outcomes during follow up in patients with or without a psychiatric history.

Keywords: antiretroviral therapy, HIV, integrase strand transfer inhibitors, psychiatric outcomes

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Correspondence to:
Jennifer Fusco
Epividian, Inc., 4505 Emperor Blvd, Suite 220, Durham, NC 27703, USA
jennifer.fusco@epividian.com

Ricky Hsu
AIDS Healthcare Foundation, New York, NY, USA, and New York University Langone Medical Center, New York, NY, USA

Cassidy Henegar
ViiV Healthcare, Research Triangle Park, NC, USA

Karam Mounzer
Philadelphia FIGHT, Philadelphia, PA, USA

Michael Wohlfeiler
AIDS Healthcare Foundation, Miami, FL, USA

Vani Vannappagari
ViiV Healthcare, Research Triangle Park, NC, USA

Michael Aboud
ViiV Healthcare, London, UK

Lloyd Curtis
GlaxoSmithKline, London, UK

Gregory Fusco
Epividian, Inc., Durham, NC, USA

Introduction

Recently, there have been published reports from observational settings of dolutegravir (DTG) discontinuations due to the development of neuropsychiatric side effects at higher than expected rates based on clinical trial data.[1–3] DTG belongs to the integrase strand transfer inhibitor (INSTI) drug class, which also includes elvitegravir (EVG) and raltegravir (RAL). INSTIs are highly potent with favorable safety profiles and are commonly used in both treatment-naïve and treatment-experienced patients switching from other drug

classes due to tolerability issues.[4,5] In clinical trials, DTG demonstrated low frequencies of psychiatric adverse events with no elevated risk relative to comparator groups.[6]

The development of psychiatric symptoms has long been attributed to exposure to specific antiretroviral therapy (ART) medications. In particular, efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been associated with neuropsychiatric side effects (including vivid dreams, insomnia, and mood changes) in up to 50% of patients initiating the drug in clinical trial and clinical practice settings.[7,8] While most symptoms are mild or moderate, and resolve within a few weeks of therapy, more serious side effects, such as depression and suicidal ideation can occur.[9–12] Central nervous system side effects have been reported less commonly for other antiretrovirals, including rilpivirine (RPV) and RAL, in addition to DTG.[13–17]

Mental health conditions are substantially more prevalent in people living with HIV compared with the general population, and are the most common comorbidities in HIV.[18,19] Depression affects up to 50% of HIV-infected individuals, while 28% experience anxiety and 29–73% report insomnia.[20–24] HIV infection is also associated with increased risk for suicidal ideation or attempt.[25,26] Identifying and addressing psychological comorbidities among patients with HIV is critical; these conditions are associated with negative clinical outcomes, including reduced adherence to ART, faster disease progression, and increased mortality.[27–30]

The objective of this analysis was to assess the risk of psychiatric outcomes in patients taking DTG relative to other commonly prescribed core agents, while addressing previous psychiatric medical history, in a large cohort of HIV-infected patients in the USA.

Methods

Subjects for this analysis were identified in the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) database, which includes prospectively captured routine clinical data from HIV-infected patients treated at 79 outpatient clinical sites in the USA. At the time of data freeze (9 February 2017), the OPERA database included records from 74,933 HIV-infected patients. The OPERA database includes comprehensive patient-level information from electronic health records, including diagnoses, clinical history, medication, laboratory, and demographic information. The OPERA database, in compliance with the Health Insurance Portability and AccountabilityAct and the Health Information Technology for Economic and Clinical Health Act regulations; cleans, categorizes, and aggregates anonymized data for research purposes. The OPERA database receives annual institutional review board (IRB) approval from Advarra IRB, including a waiver of informed consent and authorization for use of protected health information.

HIV-infected patients prescribed ART regimens containing one of six common core agents from the INSTI (DTG, RAL, EVG), NNRTI (EFV, RPV), or protease inhibitor (PI) (darunavir [DRV]) drug classes for the first time between 1 January 2013 and 31 December 2015 were included in the analysis; 2013 was the first year that DTG was marketed.

The first regimen containing a drug of interest within this window was selected. Patients exposed to any of the core agents prior to the observation period were excluded, and regimens had to be initiated while the patient was actively followed in the OPERA database. Patients taking more than one core agent simultaneously were excluded. No other restrictions were placed on drug components of eligible ART regimens.

Patients were followed from the first prescription date of the regimen containing the core agent until the earliest of either discontinuation of the core agent of interest, loss to follow up, death, or study end (31 December 2016). By selecting patients only through 31 December 2015, everyone included in the analysis had the potential for at least one year of follow up. Loss to follow up was defined as having no clinic contact for 12 months or longer; these patients were censored 12 months after their last contact.

The primary endpoints for this analysis were diagnoses consistent with four specific psychiatric outcomes: anxiety, depression, insomnia, and suicidality during core agent exposure. Electronic health records were queried using text string and ICD-9/10 code for diagnosis titles consistent with a list of 63 neuropsychiatric outcomes gathered from previous DTG clinical studies, identifying diagnoses in patients' histories as well as during core agent exposure. Due to significant

overlap, some of the outcomes were collapsed (e.g. major depressive disorder was combined with adjustment disorder with depression and bipolar disorder with severe depressed episode). All outcomes observed in greater than 2% of the exposure groups were considered for inclusion in the study plus suicide which resulted in the four outcome categories. Anxiety included diagnoses titles with 'anxiety' or 'anxiety disorder'. Depression included diagnoses with 'depression', 'major depression', 'depressed mood', 'depressive symptom', or 'bipolar'. Insomnia included diagnoses with 'insomnia', 'initial insomnia', 'middle insomnia' or 'terminal insomnia'. Suicidality included diagnoses with 'suicide', 'suicide attempt', 'suicidal ideation', 'completed suicide', 'intentional self-injury', or 'self-injurious behavior'. Patients with more than one psychiatric outcome were counted in both. For example, patients with a diagnosis of anxiety with depression were counted in both depression and anxiety.

Demographic and clinical characteristics were evaluated at initiation of the regimen of interest. Psychiatric history included diagnoses occurring at any time prior to or at baseline.

Both prevalent and incident psychiatric outcomes were assessed. All diagnoses occurring during the follow-up period were included in prevalence estimates, regardless of whether the patient had a psychiatric history prior to baseline. Incident psychiatric outcomes included only new diagnoses after baseline, excluding events in patients with psychiatric history prior to baseline. Incident psychiatric outcomes were a subset of the prevalent psychiatric outcomes. Event time to onset was calculated as time from regimen initiation to first report of a psychiatric outcome during the follow-up period. Discontinuation of core agents within 14 days of reported psychiatric outcomes was evaluated.

Baseline characteristics and outcome frequencies were characterized using standard descriptive statistics. Chi-square tests were used to compare categorical variables and Wilcoxon rank-sum tests for continuous variables by category; for tests, pairwise comparisons between DTG and each other drug of interest were made. To account for multiple comparisons between DTG and each drug, the Sidak correction was applied, resulting in an adjusted alpha level for significance of 0.01. Time to discontinuation following a psychiatric outcome was compared by core agent using Kaplan–Meier survival analysis and logrank tests.

Cox proportional hazards models were used to estimate the effect of the core agent on time to first psychiatric outcome. Time to the pooled outcome (any of the four psychiatric outcomes) was modeled. For variables for which stratified estimates would be qualitatively meaningful, effect measure modification was evaluated by considering the exposure–outcome relationship at each level of a third variable using a product interaction term between the exposure and the potential effect modifier.

Each analysis considered confounding by family psychiatric history, age, sex, race, low socioeconomic status (defined as receiving AIDS Drug Assistance Program/Ryan White or Medicaid coverage), history of a comorbid condition at baseline (diagnosis of cardiovascular disease, cancer, endocrine disorders, liver disease, osteoporosis, peripheral neuropathy, renal disease, or hypertension), and history of substance abuse. These variables were selected from substantive knowledge of factors potentially associated with both the core agent prescribed and development of psychiatric outcomes. Age was modeled as a continuous variable using restricted cubic splines.

Four sensitivity analyses were conducted. For the first, a psychiatric history at baseline of any of the four diagnoses of interest resulted in a psychiatric outcome during follow up classified as prevalent; in the primary analysis, only a psychiatric history at baseline of the same diagnosis (e.g. depression history and depression during follow up) resulted in a prevalent psychiatric outcome. In the second, records for medications commonly prescribed for each psychiatric outcome were used in addition to diagnosis titles to identify both baseline psychiatric history and psychiatric outcomes during follow up. For the third sensitivity analysis, the rate of discontinuation was evaluated within 42 days of a recorded diagnosis, rather than 14 days, to capture delayed discontinuations. Discontinuation windows of 14 days and 42 days were selected based on input from clinical advisors. For the fourth sensitivity analysis, person-time was censored after 31 January 2016, thus excluding any psychiatric outcomes recorded after the Conference on Retroviruses and Opportunistic Infections 2016, where unexpectedly high rates of psychiatric events with DTG were first reported.[31]

Results

Between 1 January 2013 and 31 December 2015, 13,261 patients initiated a regimen containing a core agent of interest, including 58% taking an INSTI (DTG: 2783; RAL: 979; EVG: 3895), 28% taking an NNRTI (EFV: 1746; RPV: 1921), and 15% taking a PI (DRV: 1937). Demographic and clinical characteristics assessed at baseline varied between patients taking DTG and patients taking other core agents (Table 1). Patients taking RAL-based and DRV-based regimens were older (median: 48 years and 44 years, respectively) than patients on DTG (42 years), while patients on RPV- (34 years) and EVG-containing regimens (35 years) tended to be younger. More patients prescribed a DTG-based regimen (47%) had a history of other chronic conditions at baseline compared with those on RPV- (33%), EVG- (31%), and EFV-based regimens (33%); comorbidities were more common in patients taking RAL-based regimens (55%). Patients taking RPV, EVG, and EFV were also less likely than those taking DTG to have experienced an AIDS-defining illness prior to regimen initiation. Substance abuse was most common among patients on DTG- (16%) and DRV-containing regimens (15%). At baseline, patients receiving DTG (60%) were less likely to be treatment naïve than patients initiating any of the other core agents; patients initiating EFV-containing regimens were overwhelmingly treatment naïve (94%).

Psychiatric history at baseline was common, with varying prevalence across treatment groups (Figure 1). Depression was the most common of the four diagnoses. Patients prescribed DTG were more likely to have a history of depression (29%) than patients prescribed EVG (22%), EFV (16%), and RPV (21%); depression history was similarly prevalent in patients taking RAL (29%) and DRV (26%). Patients taking DTG were also more likely to have a history of anxiety relative to patients taking EFV, RPV, and DRV; they were also more likely to have a history of insomnia relative to patients taking EVG, EFV and RPV. History of suicidality was rare, occurring in 0.5% or less of patients in all treatment groups, and did not differ significantly across core agents.

For prevalent psychiatric outcomes, which included both new and recurrent outcomes during follow up, patients on DTG were less likely to experience anxiety compared with patients taking EVG, but not compared with patients taking other core agents (Figure 2a). There was no difference in prevalent depression or prevalent insomnia between core agents.

There were fewer incident outcomes for all psychiatric outcomes except suicidality, which was rare for both prevalent and incident measures (Figure 2b). The proportions of patients experiencing anxiety, depression, and insomnia outcomes for the first time were similar across treatment groups. The only observed statistically significant differences were slightly higher rates of depression in patients taking EVG and RPV.

Treatment discontinuations within 14 days of prevalent depression diagnoses were significantly less frequent for patients taking DTG (0.4%) compared with other core agents, except EVG. Patients taking DTG were also less likely to discontinue following anxiety diagnoses (0.3%) compared with patients taking RAL or DRV, and less likely to discontinue after insomnia diagnoses (0.4%) compared with patients taking EFV; discontinuation rates with other core agents were comparable for anxiety and insomnia. Discontinuation within 14 days of an incident psychiatric outcome was uncommon ($\leqslant 1.0\%$) across drugs and conditions, particularly in patients taking DTG (depression: 0.1%; anxiety: 0.2%; insomnia: 0.3%) (see Supplemental Materials).

Kaplan–Meier estimates and logrank tests indicated statistically significant global differences between core agents in time to incident psychiatric outcomes followed by a discontinuation within 14 days ($p < 0.0001$) (Figure 3). Within the first 1000 days after core agent initiations, 0.5% of patients taking DTG had a psychiatric outcome followed by discontinuation (EVG: 0.7%, RPV: 0.8%, DRV: 1.2%, RAL: 1.4%, EFV 2.2%).

In multivariable analyses, significant interaction was identified between core agent exposure and personal psychiatric history at baseline. Cox models were stratified by baseline psychiatric history to account for this interaction (Table 2). Among patients with no history of anxiety, depression, insomnia, or suicidality when starting the core agent, the likelihood of experiencing a psychiatric outcome during follow up did not appear to differ among patients taking DTG compared with the other drugs of interest. Among patients with a psychiatric history, those taking DTG were less likely to experience another psychiatric outcome compared with patients taking EVG or DRV.

Table 1. Demographic and clinical characteristics measured at initiation of regimen of interest.

	DTG-containing regimens *n* = 2783 *n* (%)	RAL-containing regimens *n* = 979 *n* (%)	*p* value RAL *versus* DTG	EVG-containing regimens *n* = 3895 *n* (%)	*p* value EVG *versus* DTG	EFV-containing regimens *n* = 1746 *n* (%)	*p* value EFV *versus* DTG	RPV-containing regimens *n* = 1921 *n* (%)	*p* value RPV *versus* DTG	DRV-containing regimens *n* = 1937 *n* (%)	*p* value DRV *versus* DTG
Age*	41.8 (29.8, 51.3)	48.3 (39.4, 54.8)	< 0.01	34.7 (26.7, 45.6)	< 0.01	41.3 (30.3, 49.7)	0.10	33.5 (26.3, 45.1)	< 0.01	44.4 (34.1, 51.5)	< 0.01
Sex											
Male	2356 (84.7)	798 (81.5)	0.02	3371 (86.7)	0.02	1529 (87.7)	< 0.01	1543 (80.4)	< 0.01	1537 (79.3)	< 0.01
Female	427 (15.3)	181 (18.5)		519 (13.3)		215 (12.3)		375 (19.6)		400 (20.7)	
Race											
Not African American	1729 (62.1)	684 (69.9)	< 0.01	2338 (60.0)	0.08	1046 (59.9)	0.14	955 (49.7)	< 0.01	1131 (58.4)	< 0.01
African American	1054 (37.9)	295 (30.1)		1557 (40.0)		700 (40.1)		966 (50.3)		806 (41.6)	
Ethnicity											
Not Hispanic	2059 (74.0)	790 (80.7)	< 0.01	2831 (72.7)	0.24	1387 (79.4)	< 0.01	1511 (78.7)	< 0.01	1476 (76.2)	0.08
Hispanic	724 (26.0)	189 (19.3)		1064 (27.3)		359 (20.6)		410 (21.3)		461 (23.8)	
HIV transmission risk											
Not MSM	1404 (50.4)	572 (58.4)	< 0.01	1895 (48.7)	0.15	965 (55.3)	< 0.01	987 (51.4)	0.53	1138 (58.8)	< 0.01
MSM	1379 (49.6)	407 (41.6)		2000 (51.3)		781 (44.7)		934 (48.6)		799 (41.2)	
Low SES	1355 (48.7)	379 (38.7)	< 0.01	1859 (47.7)	0.44	699 (40.0)	< 0.01	813 (42.3)	< 0.01	923 (47.7)	0.48
Substance abuse	448 (16.1)	99 (10.1)	< 0.01	449 (11.5)	< 0.01	170 (9.7)	< 0.01	242 (12.6)	< 0.01	298 (15.4)	0.51
Comorbid disease[$]	1315 (47.3)	534 (54.5)	< 0.01	1222 (31.4)	< 0.01	579 (33.2)	< 0.01	628 (32.7)	< 0.01	900 (46.5)	0.59

(Continued)

Table 1. (Continued)

	DTG-containing regimens $n = 2783$ *n* (%)	RAL-containing regimens $n = 979$ *n* (%)	*p* value RAL *versus* DTG	EVG-containing regimens $n = 3895$ *n* (%)	*p* value EVG *versus* DTG	EFV-containing regimens $n = 1746$ *n* (%)	*p* value EFV *versus* DTG	RPV-containing regimens $n = 1921$ *n* (%)	*p* value RPV *versus* DTG	DRV-containing regimens $n = 1937$ *n* (%)	*p* value DRV *versus* DTG
Family psychiatric history	188 (6.8)	55 (5.6)	< 0.01	174 (4.5)	< 0.01	79 (4.5)	< 0.01	98 (5.1)	< 0.01	106 (5.5)	0.02
ART exposure											
Experienced	1124 (40.4)	334 (34.1)	< 0.01	728 (18.7)	< 0.01	108 (6.2)	< 0.01	317 (16.5)	< 0.01	705 (36.4)	< 0.01
Naïve	1659 (59.6)	645 (65.9)		3167 (81.3)		1638 (93.8)		1604 (83.5)		1232 (63.6)	
ADI at baseline	311 (11.2)	125 (12.8)	0.18	231 (5.9)	< 0.01	81 (4.6)	< 0.01	100 (5.2)	< 0.01	257 (13.3)	0.03
Baseline viral load*‡	4.0 (1.3, 4.8)	1.7 (1.3, 4.4)	< 0.01	4.5 (3.4, 5.0)	< 0.01	3.9 (1.3, 4.9)	0.14	4.0 (2.4, 4.5)	0.05	4.1 (1.5, 5.0)	< 0.01
Baseline CD4 cells/μL*	453 (275, 649)	484 (271, 693)	0.09	418 (260, 598)	< 0.01	468 (298, 684)	0.05	510 (364, 681)	< 0.01	366 (152, 596)	< 0.01

Pairwise comparisons between DTG and each other core agent made using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables; $p < 0.01$ considered statistically significant after adjusting for multiple comparisons.
*Median (interquartile range). $Diagnosis prior to baseline of cardiovascular disease, cancer, endocrine disorders, liver disease, osteoporosis, peripheral neuropathy, renal disease, or hypertension, ‡Log10 copies/mL. ADI, AIDS defining illness ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; DRV, darunavir; MSM, men who have sex with men; RAL, raltegravir; RPV, rilpivirine; SES, socioeconomic status (defined as AIDS Drug Assistance Program/Ryan White or Medicaid participation).

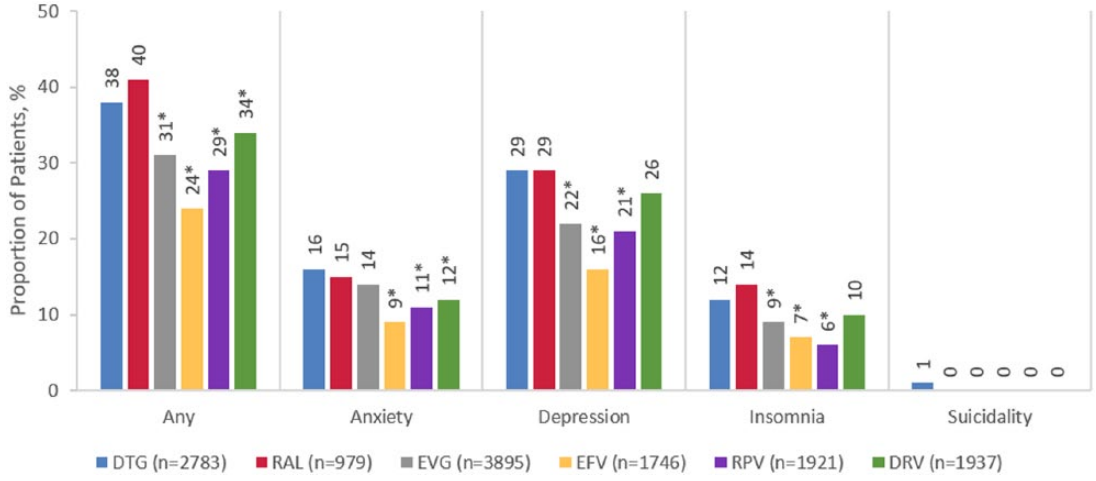

Figure 1. Psychiatric history[a] at baseline by antiretroviral therapy regimens containing core agents of interest.
Pairwise comparisons between DTG and each other core agent made using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables; *$p < 0.01$ considered statistically significant after adjusting for multiple comparisons.
[a]Psychiatric history at baseline = diagnosis of anxiety, depression, insomnia, and/or suicidality on or before first day of core agent exposure. DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; RAL, raltegravir; RPV, rilpivirine.

Each of the sensitivity analyses conducted changed the number of events observed (psychiatric outcomes and discontinuations) but did not result in differences in trends between core agents or in the main conclusions from the primary analysis (see Supplemental Materials).

Discussion

In a large cohort of HIV+ patients in care in the USA, psychiatric history prior to treatment initiation with one of six common core agents was common (32%). Baseline psychiatric history differed between drugs, with patients prescribed RAL- and DTG-based regimens more likely to have a history of the psychiatric outcomes of interest. Despite the larger proportion of patients prescribed DTG with a psychiatric history, neither prevalent nor incident outcomes during follow up were elevated among patients taking DTG compared with patients taking the other drugs of interest. Discontinuations of DTG following psychiatric outcomes were infrequent and typically occurred less often than for other core agents.

Other real-world evaluations of psychiatric adverse events associated with DTG are limited. Kheloufi and colleagues were the first to report anxiety and depression in patients taking DTG outside of clinical trials.[1] Four cases were observed, including two patients with a history of depression. In all four cases, symptoms began within the first month of treatment with DTG, resolving shortly after stopping the drug for three patients discontinuing DTG. de Boer and colleagues evaluated the frequency of DTG discontinuation and reason for stopping among all patients starting DTG at treatment centers in The Netherlands (n = 556).[2] In total, 85 patients stopped taking DTG, including 31(5.6%) who discontinued due to insomnia and sleep disturbances, and 24(4.3%) who switched due to neuropsychiatric symptoms, including anxiety, depression, and psychosis. While the relative impact of some patient characteristics on discontinuation were evaluated, prior history of sleep disorders or neuropsychiatric diagnoses among the patients who discontinued were not reported. Discontinuations were not evaluated for other core agents.

Differences in discontinuation rates due to adverse events, including neuropsychiatric toxicity, were compared between INSTIs (DTG, RAL, EVG/c) in a multicenter Spanish cohort.[3] A total of 2021 patients were evaluated, including 792 starting DTG with ABC/3TC and 81 starting DTG with TDF/3TC; patients taking DTG/ABC/3TC experienced 17 discontinuations due to neurotoxicity (incidence rate ratio [IR], 95% confidence interval [CI]: 3.1, 1.8–4.9), while patients taking DTG/TDF/FTC experienced zero (IR, 95% CI: 0.0, 0.0–7.0). Multivariable analyses indicated increased rates of discontinuation due to neurotoxicity between DTG and RAL (hazard ratio

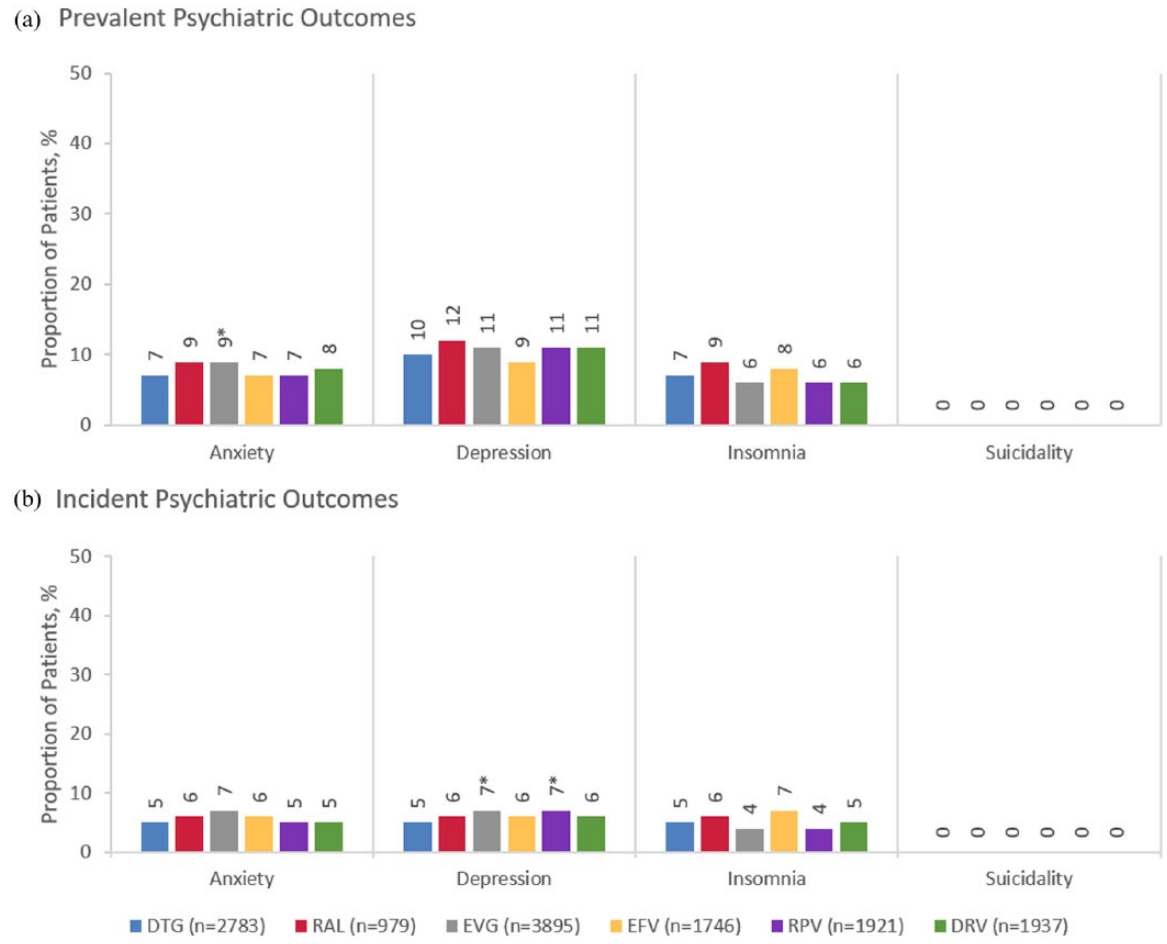

Figure 2. Prevalent[a] and incident[b] psychiatric outcomes at baseline and during follow up on antiretroviral therapy regimens containing core agents of interest.
Pairwise comparisons between DTG and each other core agent made using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables; *$p < 0.01$ considered statistically significant after adjusting for multiple comparisons.
Discontinuation evaluated within 14 days of diagnosis being reported in medical record.
[a]Prevalent psychiatric outcome = diagnosis of anxiety, depression, insomnia, and/or suicidality with or without a history of the same diagnosis at baseline. [b]Incident psychiatric outcome = new diagnoses of anxiety, depression, insomnia, and/or suicidality in the absence of a history of the same diagnosis at baseline. DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; RAL, raltegravir; RPV, rilpivirine.

[aHR], 95% CI: 3.2, 1.12, 9.0), and DTG and EVG (aHR, 95%: 4.9, 1.6, 15.5), but results were based on a small number of events. The authors reported a higher proportion of DTG-exposed patients with a history of the same symptoms during prior regimens (DTG/ABC/3TC: 82%; RAL: 48%; EVG: 38%) but did not account for symptom history when evaluating discontinuation.

Given the higher prevalence of psychiatric comorbidities in HIV-infected individuals compared with the general population, and frequent history of psychiatric diagnoses among those experiencing adverse events in available observational analyses, accounting for baseline psychiatric history appears key to understanding the risk of related events during follow up. This is the first observational analysis capturing and incorporating specific psychiatric diagnoses prior to drug exposure when assessing the effect of core agents on psychiatric outcomes.

In the OPERA cohort, patients prescribed EFV were the least likely to have pre-existing psychiatric history, while patients placed on DTG and RAL were the most likely to have a psychiatric history. This may reflect channeling bias, in which clinicians place patients with the greatest perceived risk for adverse psychiatric events on ART medications believed to have better tolerability. INSTIs have a demonstrated potency and favorable safety profile;

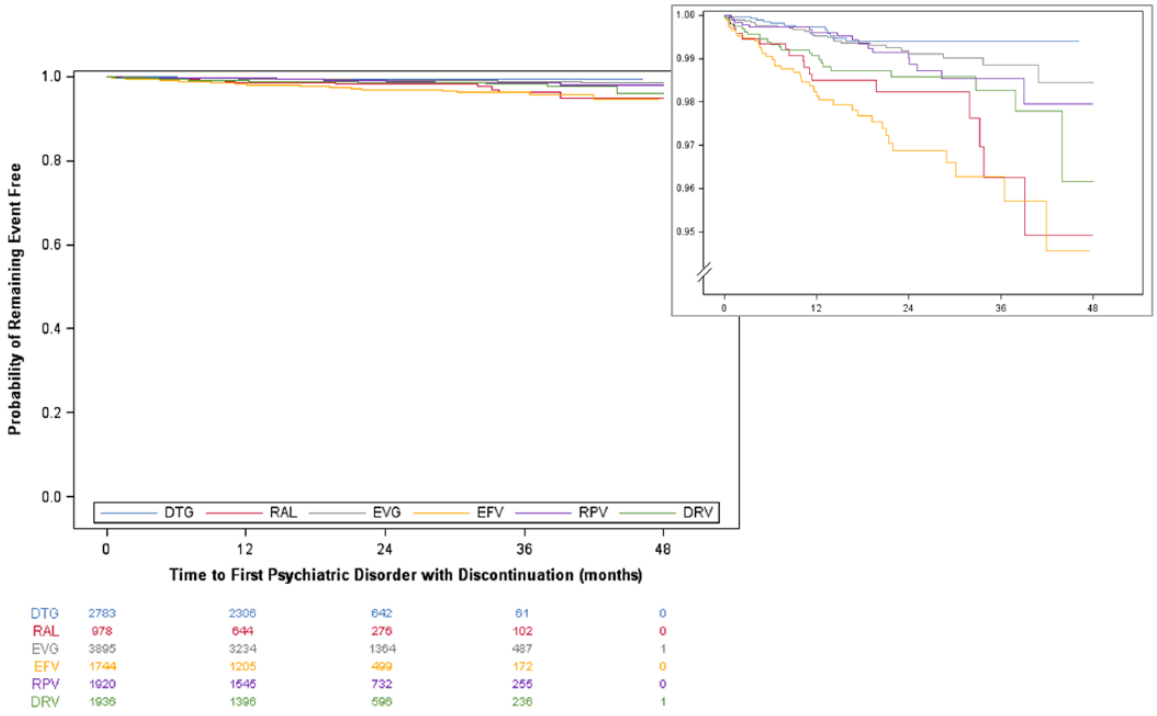

Figure 3. Kaplan–Meier estimates of time to first psychiatric diagnosis with discontinuation among patients with no history of psychiatric symptoms (with enlargement of drug-specific curves).
Event (discontinuation following a psychiatric outcome) time distributions compared between core agents using logrank test. Global *p* value indicates significant differences between core agents. Time measured as days from core agent initiation.
DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; RAL, raltegravir; RPV, rilpivirine.

Table 2. Association between antiretroviral therapy regimen core agent and occurrence of psychiatric outcomes, stratified by psychiatric history.

	Patients without a psychiatric history			Patients with a psychiatric history		
	Events –any psychiatric outcome *n* (%)	**Crude HR (95% CI)**	**Multivariable* HR (95% CI)**	**Events – any psychiatric outcome *n* (%)**	**Crude HR (95% CI)**	**Multivariable* HR (95% CI)**
DTG	241 (13.9)	1.	1.	248 (23.6)		1.
RAL	100 (17.1)	1.36 (1.08, 1.72)	1.18 (0.90, 1.53)	110 (28.0)	1.29 (1.03, 1.62)	1.26 (0.99, 1.61)
EVG	418 (15.5)	1.03 (0.88, 1.21)	1.08 (0.91, 1.27)	350 (29.1)	1.26 (1.07, 1.48)	1.33 (1.12, 1.59)
EFV	212 (15.9)	1.20 (1.00, 1.44)	0.99 (0.81, 1.22)	116 (28.0)	1.34 (1.07, 1.67)	1.26 (0.98, 1.61)
RPV	203 (14.9)	0.96 (080, 1.16)	0.95 (0.77, 1.16)	136 (24.5)	1.03 (0.83, 1.27)	0.99 (0.78, 1.25)
DRV	155 (12.1)	0.87 (0.71, 1.06)	0.85 (0.68, 1.05)	205 (31.2)	1.41 (1.17, 1.70)	1.46 (1.20, 1.79)

*Crude and multivariable Cox proportional hazards models with DTG as the referent; multivariable models adjusted for: family psychiatric history, age at initiation (continuous), sex, race, low socioeconomic status (defined as AIDS Drug Assistance Program/Ryan White or Medicaid participation), comorbid conditions at baseline, and history of substance abuse.
CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; HR, hazard ratio; RAL, raltegravir; RPV, rilpivirine.

there also may be less concern about drug–drug interactions among patients taking medications for neuropsychiatric or other comorbid conditions. Patients taking DTG and RAL, in addition to DRV, also were most likely to have other chronic illnesses at baseline.

Multivariable regression results from this analysis suggest that for patients starting a core agent of interest without a history of depression, anxiety, insomnia, or suicidality, the likelihood of developing one of these outcomes during follow up was equivalent in patients prescribed DTG relative to patients prescribed any of the other core agents. For patients with a psychiatric history, those taking a DTG-based regimen were less likely to experience a psychiatric outcome during follow up compared with patients prescribed EVG or DRV, and marginally less likely than patients prescribed RAL or EFV.

The decreased or comparable occurrence of psychiatric outcomes among patients exposed to DTG and other core agents observed in the OPERA cohort is in agreement with trial data.[32–35] In response to the case reports of new and exacerbated psychiatric conditions among patients on INSTIs, the US Food and Drug Administration conducted a meta-analysis of phase III trials of treatment-naïve patients, comparing patients taking an INSTI (RAL, EVG, or DTG) with patients taking EFV or a boosted PI (atazanavir or DRV).[36] Overall risk differences were estimated using data from five trials, with results indicating similar risk of neuropsychiatric adverse events for INSTIs relative to PIs and EFV, with a trend towards lower risk with INSTIs relative to EFV.

This analysis has the advantage of a large sample size in each treatment group. Compared with other large data resources, including claims data,[37] electronic health record data allows for more accurate capture of history of specific diagnoses. The OPERA cohort, in general, is a representative sample of the HIV population in care in the USA (7% of all US patients active in care are represented in the database). Several sensitivity analyses were conducted, strengthening the conclusions drawn from the main results.

Limitations of this analysis included inability to assess severity of psychiatric diagnoses at baseline or during follow up using diagnosis title searches. Reported events might also be biased towards more severe psychiatric outcomes, with mild events potentially not reported by the patient or not recorded as a diagnosis. It is therefore impossible to know if some discontinuations were caused by psychiatric symptoms that were not recorded in the patient's electronic health records by the care provider. Rare psychiatric outcomes such as psychosis were not included in this analysis thus the results are generalizable to more common conditions only. In addition, as with other data sources reflecting routine clinical care, evaluation was not consistent among patients, with variation in follow up and reporting at the discretion of the patients and providers.

This analysis indicates no elevated risk of psychiatric outcomes in patients prescribed DTG, and in fact suggests a potential protective effect among patients with a psychiatric history channeled towards DTG. Although psychiatric outcomes severe enough to warrant discontinuation were infrequent and the risk was not higher in patients taking DTG, providers should remain vigilant for psychiatric side effects regardless of ART regimen given the association between HIV disease, HIV treatment, and psychiatric adverse events.

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Conflict of interest statement

RH has received research support from Gilead Sciences, and has served as a consultant and received lecture honoraria from Gilead Sciences, ViiV Healthcare, Bristol-Myers Squibb, and Merck & Co. JF and GF are employees of Epividian; Epividian has received grants from ViiV Healthcare during the conduct of this study and outside of the submitted work. CH, VV, and MA are employees of ViiV Healthcare. LC is an employee of GlaxoSmithKline. KM has received research support from Gilead Sciences, ViiV Healthcare, Merck & Co. and Janssen, and has served as a consultant and received lecture honoraria from Gilead Sciences, ViiV Healthcare, Merck & Co., and Janssen. MW has no conflicts to declare.

ORCID iD

Jennifer Fusco https://orcid.org/0000-0003-1556-811X

Supplemental Material

Supplemental Material for this article is available online.

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