Variables Associated With Neuropsychiatric Symptoms in PLWH Receiving Dolutegravir-Based Therapy in Phase III Clinical Trials

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Background

- Neuropsychiatric disorders, including depression, anxiety, and suicidal behavior, occur more frequently in people living with HIV (PLWH) compared with HIV-negative individuals[1]
- Neuropsychiatric adverse events (AEs) are commonly listed in the labels of antiretroviral medications
- In phase III/IIIb trials of dolutegravir (DTG), when compared with raltegravir (RAL), efavirenz (EFV), ritonavir-boosted darunavir (DRV/r), or ritonavir-boosted atazanavir (ATV/r) in treatment-naive PLWH, rates of neuropsychiatric AEs were low, mostly of mild-to-moderate severity, and rarely resulted in treatment discontinuation
- Evolving observational HIV cohort data suggest that neuropsychiatric AEs may result in somewhat higher rates of DTG discontinuation in clinical practice than documented in clinical trials and that this might occur more frequently in women, patients aged >60 years, and those with concomitant abacavir (ABC) use[2-7]
- As DTG is now globally used and has >1,000,000 patient-years of exposure (data on file), continual monitoring of the safety profile is needed

Objectives

- To examine patient-level data from the DTG phase III/IIIb studies to identify variables associated with development of neuropsychiatric AEs
- To determine whether insomnia was a potential precursor to other neuropsychiatric events, neuropsychiatric AEs were categorized according to whether they were preceded by insomnia and analyzed descriptively

Methods

- This meta-analysis included individual patient-level data from ViiV Healthcare–sponsored phase III/IIIb randomized clinical trials of DTG in adult participants (Table 1)

Table 1. Studies Included in Meta-analysis of Neuropsychiatric AEs Reported in Phase III/IIIb Trials of DTG in Adults Infected With HIV-1

Study	Study treatments			Duration, weeks[a]	Study population	DTG (n)	Non-DTG (n)
SINGLE (phase III)[8,b]	DTG + ABC/3TC	vs	EFV/TDF/FTC	144	ART naive	414	419
SPRING-2 (phase III)[9]	DTG + ABC/3TC or TDF/FTC	vs	RAL + ABC/3TC or TDF/FTC	96	Treatment naive	411	411
SAILING (phase III)[10]	DTG + investigator-selected background regimen	vs	RAL + investigator-selected background regimen	48	Integrase inhibitor naive, ART experienced	357	362
ARIA (phase IIIb)[11,b]	DTG/ABC/3TC FDC	vs	ATV/r or TDF/FTC FDC	48	ART-naive women	248	247
FLAMINGO (phase IIIb)[12]	DTG + ABC/3TC or TDF/FTC	vs	DRV/r + ABC/3TC or TDF/FTC	96	Treatment naive	242	242

ABC, abacavir; AE, adverse event; ART, antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; RAL, raltegravir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate. [a]Duration of study data included in meta-analysis. [b]Randomized with respect to ABC therapy.

- Neuropsychiatric AEs included in the analyses were insomnia, anxiety, depression, suicidality, nightmares/abnormal dreams, and headache
- Exposure-adjusted incidence of neuropsychiatric AEs was calculated from frequencies of reported AEs
  - Poisson mixed-effects meta-regression models were used to conduct patient-level and event-level analyses of prespecified variables in a backward selection on the incidence rate of AEs
    - Analysis performed at patient level and event level as patients could have more than one AE
  - Significance level was 10%; 95% CIs were based on exact binomial 2-sided CIs
- The analyses were carried out examining different exposures of interest
  - DTG vs non–DTG-containing current antiretroviral regimen (CAR)
    - Exposed group treated with DTG as part of CAR
    - Comparator group was exposed to non–DTG-containing CAR
    - A single participant could only contribute to one of the exposure categories
  - DTG + ABC vs DTG + non-ABC
  - No adjustments for multiple testing were made
- Variables investigated for association with the development of a neuropsychiatric AE based on cohort data included sex; age; race; region; country; previous psychiatric history; any chronic comorbidity (eg, hepatitis C, diabetes, hypertension); risk factors for HIV acquisition; baseline viral load; CD4 nadir; and body mass index

Results

Participant Characteristics

- Across all 5 studies, 1672 participants received regimens containing DTG, while 1681 received non–DTG-containing regimens (Table 2)
- 930 participants who received DTG also received ABC

Table 2. Participant Characteristics

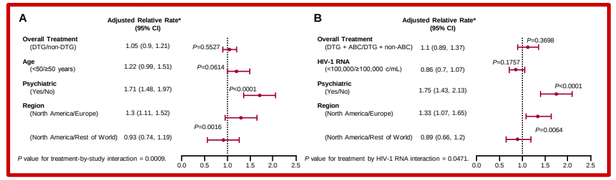
	DTG (N=1672)		Non-DTG (N=1681)	
	n (%)[a]	Participants experiencing neuropsychiatric AEs, n (%)[b]	n (%)[a]	Participants experiencing neuropsychiatric AEs, n (%)[b]
Sex				
Male	1155 (69.1)	309 (26.8)	1150 (68.4)	301 (26.1)
Female	517 (30.9)	121 (23.4)	531 (31.6)	107 (20.2)
Age, y				
<50	1429 (85.5)	379 (26.5)	1436 (85.4)	356 (24.8)
≥50	243 (14.5)	51 (21.0)	245 (14.6)	52 (21.2)
Race				
White	1099 (65.7)	298 (27.1)	1095 (65.1)	266 (24.3)
Other	571 (34.2)	132 (23.1)	584 (34.7)	141 (24.1)
Psychiatric history				
Yes	577 (34.5)	214 (37.1)	589 (35.0)	199 (33.8)
No	1095 (65.5)	216 (19.7)	1092 (65.0)	209 (19.1)
Region				
Europe	793 (47.4)	179 (22.6)	803 (47.8)	171 (21.3)
North America	607 (36.3)	193 (31.8)	619 (36.8)	187 (30.2)
Rest of world	272 (16.3)	58 (21.3)	259 (15.4)	50 (19.3)

AE, adverse event; DTG, dolutegravir. [a]Denominators based on number of participants in each treatment group. [b]Denominators are based on number of participants in each baseline variable category.

Patient-Level Analysis

- Overall, for the Poisson model at the patient level, adjusted estimates (standard error) for neuropsychiatric AE rates per 1000 person-years were 5.26 (0.068) with DTG vs 5.21 (0.07) with non-DTG (adjusted relative rate [aRR], 1.05; 95% CI, 0.9-1.21; *P*=0.55) and 5.4 (0.079) with DTG + ABC vs 5.3 (0.085) with DTG + non-ABC (aRR, 1.1; 95% CI, 0.89-1.37; *P*=0.37)
- For the DTG vs non-DTG analysis, age, psychiatric history, and region were associated with neuropsychiatric AEs, with a significant interaction between treatment and study (Figure 1A)
- For the DTG + ABC vs DTG + non-ABC analysis, HIV-1 RNA, psychiatric history, and region were associated with neuropsychiatric AEs, with a significant interaction between treatment and HIV-1 RNA (*P*=0.0471; Figure 1B)

Figure 1. Patient-Level Analyses of Predictors of Neuropsychiatric AEs Using Poisson Regression for Exposure to (A) DTG vs Non-DTG and (B) DTG + ABC vs DTG + Non-ABC

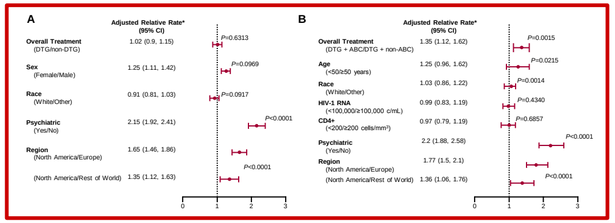


ABC, abacavir; AE, adverse event; DTG, dolutegravir. Prespecified variables included in the Poisson model were sex, age, race, region, country, previous psychiatric history, any chronic comorbidity, HIV acquisition risk factor, history of drug use, baseline viral load, CD4 nadir, and body mass index. *Adjusted estimate rate is per 1000 person-years.

Event-Level Analysis

- At the event level, in the DTG vs non-DTG analysis, psychiatric history, region, race, and sex were associated (Figure 2A)
- In the DTG + ABC vs DTG + non-ABC analysis, overall treatment, HIV-1 RNA, psychiatric history, region, age, race, and CD4 count were associated (Figure 2B)
- The treatment effect was likely driven by the SINGLE study due to the significant interaction between treatment and study

Figure 2. Event-Level Analysis of Predictors of Central Nervous System Events Using Poisson Regression for Exposure to (A) DTG vs Non-DTG and (B) DTG + ABC vs DTG + Non-ABC



ABC, abacavir; DTG, dolutegravir. *Estimates for least squares mean rates are per 100,000 person-years and adjusted relative rates are from the Poisson model. 95% CIs were derived from the same model. For DTG vs non-DTG, *P* values for treatment by race, region, and study interactions were 0.0031, 0.0469, and <0.0001, respectively. For DTG + ABC vs DTG + non-ABC, *P* values for treatment by age, psychiatric history, HIV-1 RNA, CD4+, and study interactions were 0.0045, 0.0664, 0.0205, 0.0119, and 0.0079, respectively.

- When comparing results of the patient- and event-level analyses, psychiatric history and region were consistently associated with central nervous system events (Table 3)

Table 3. Variables Associated With Central Nervous System Events in Patient- and Event-Level Analyses (*P*<0.10)

Exposure	Patient-level analysis	Event-level analysis
DTG vs non-DTG	Age (years)	Sex
	Psychiatric history Region	Psychiatric history Region
		Race
DTG + ABC vs DTG + non-ABC		Overall treatment
	HIV-1 RNA (c/mL) Psychiatric history Region	HIV-1 RNA (c/mL) Psychiatric history Region
		Age (years) Race CD4+ (cells/mm^3)

ABC, abacavir; DTG, dolutegravir.

Association of Insomnia With Subsequent Neuropsychiatric AEs

- Proportions of participants reporting no neuropsychiatric AEs or 1 neuropsychiatric AE were comparable in the DTG and non-DTG groups (Table 4)
- Comparable proportions of participants in the 2 groups reported neuropsychiatric AEs that were not preceded by an initial insomnia event
- Small and comparable proportions of participants in both groups experienced neuropsychiatric AEs after their first insomnia AE

Table 4. Neuropsychiatric AEs in Participants With and Without Exposure to DTG

	DTG n (%) (N=1672)	Non-DTG n (%) (N=1681)	Difference, % (95% CI)[a]
Participants without neuropsychiatric AEs	1242 (74.3)	1273 (75.7)	-1.45 (-4.38, 1.48)
Participants reporting only one neuropsychiatric AE	310 (18.5)	278 (16.5)	2.00 (-0.57, 4.58)
Insomnia	77 (4.6)	59 (3.5)	1.10 (-0.24, 2.43)
Anxiety	30 (1.8)	29 (1.7)	0.07 (-0.82, 0.96)
Bipolar	1 (0.1)	0 (0)	0.06 (-0.06, 0.18)
Headache	146 (8.7)	143 (8.5)	0.23 (-1.67, 2.13)
Suicidal	11 (0.7)	6 (0.4)	0.30 (-0.18, 0.78)
Participants reporting neuropsychiatric AE without preceding insomnia AE	384 (23.0)	378 (22.5)	0.48 (-2.36, 3.32)
Insomnia	92 (5.5)	78 (4.6)	0.86 (-0.62, 2.35)
Anxiety	54 (3.2)	66 (3.9)	-0.70 (-1.95, 0.56)
Bipolar	3 (0.2)	0 (0)	0.18 (-0.02, 0.38)
Headache	202 (12.1)	204 (12.1)	-0.05 (-2.26, 2.15)
Suicidal	17 (1.0)	17 (1.0)	0.01 (-0.67, 0.68)
Participants reporting first insomnia AE with subsequent neuropsychiatric AE	37 (2.2)	25 (1.5)	0.73 (-0.19, 1.64)
Insomnia	7 (0.4)	8 (0.5)	-0.06 (-0.51, 0.39)
Anxiety	13 (0.8)	7 (0.4)	0.36 (-0.16, 0.88)
Bipolar	0 (0)	1 (0.1)	-0.06 (-0.18, 0.06)
Headache	22 (1.3)	10 (0.6)	0.72 (0.06, 1.38)
Suicidal	2 (0.1)	0 (0)	0.12 (-0.05, 0.29)

AE, adverse event; DTG, dolutegravir. [a]95% CI based on the Wald test.

Limitations

- As the clinical trials were not specifically designed to evaluate neuropsychiatric outcomes, the collection of additional variables associated with neuropsychiatric AEs may not have been incorporated in the original study protocols; there was no additional adjudication for neuropsychiatric AEs for the current meta-analysis
- Because of the small number of events, the post–neuropsychiatric event follow-up time is expected to have a limited effect on the overall exposure
- The absence of any effect may be a result of the size, and therefore power, of the study and not the lack of a relationship between variables associated with neuropsychiatric AEs and outcome; the results should be treated as exploratory and interpreted with caution

Discussion and Conclusions

- In this meta-analysis of 5 randomized clinical trials (N=3353), the rate of neuropsychiatric AEs was similar between DTG- and non–DTG-treated participants
- Psychiatric history and region were associated with neuropsychiatric AEs
- Concomitant ABC use was not associated with neuropsychiatric AEs
- Insomnia was not found to be a precursor to the development of other neuropsychiatric AEs

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