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 PLWH than in the general population. These disorders may result in treatment discontinuation and poor outcomes for PLWH. Neurocognitive side effects due to antiretrovirals (ARVs) are commonly observed in clinical trials and real-world settings. In the Dolutegravir (DTG) clinical trial, neuropsychiatric events were more common in the DTG compared to non-DTG arms.

Objectives
To examine patient-level data from the DTG phase IIIb studies to identify variables associated with development of neuropsychiatric AEs. To determine whether neuropsychiatric AEs were preceded by an initial insomnia event and to determine if neuropsychiatric AEs were associated with a subsequent neuropsychiatric AE without preceding insomnia AE.

Methods
This analysis included all neuropsychiatric variables identified from ViiV Healthcare-sponsored phase IIIb clinical trials. The analysis was post hoc and was performed on the primary database.

Results
Patient Characteristics
A total of 1,672 patients were included, 887 (52.9%) were female, 92 (5.5%) were aged ≥60 years, 92 (5.5%) had a previous psychiatric history, and 131 (7.8%) had concomitant medical conditions.

Neuropsychiatric AEs
Alzheimer’s dementia (8), bipolar disorder (12), delusions (12), depression (90), anxiety (144), agitation (144), ataxia (12), headache (29), insomnia (133), delirium (27), mania (27), and suicidal ideation (125) were observed in the study.

Association of Variables With Neuropsychiatric AEs
Variables investigated for association with the development of a neuropsychiatric AE based on exposure to DTG in phase IIIb studies (Table 1).

Event-Level Analysis
At the event level, in the DTG vs non-DTG analysis, psychiatric history, region, race, and sex were associated with an increased risk of neuropsychiatric AEs. In the DTG vs ABC analysis, age, region, and race were associated with an increased risk of neuropsychiatric AEs. In the DTG vs ABC + non-DTG analysis, age, region, and sex were associated with an increased risk of neuropsychiatric AEs.

Limitations
This meta-analysis of 8 randomized clinical trials (N=3,103), the rate of neuropsychiatric AEs was similar between DTG- and non-DTG-treated participants. Neuropsychiatric history and region were associated with neuropsychiatric AEs. Concomitant ABC use was not associated with neuropsychiatric AEs. Insomnia was not found to be a predictor of the development of neuropsychiatric AEs.

Discussion and Conclusions
In this meta-analysis of 8 randomized clinical trials (N=3,103), the rate of neuropsychiatric AEs was similar between DTG- and non-DTG-treated participants. Neuropsychiatric history and region were associated with neuropsychiatric AEs. Concomitant ABC use was not associated with neuropsychiatric AEs. Insomnia was not found to be a predictor of the development of other neuropsychiatric AEs.