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MAJOR ARTICLE

Randomized Trial Evaluating the Neurotoxicity of Dolutegravir/Abacavir/Lamivudine and Its Reversibility After Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: GESIDA 9016

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Background. Despite evidence shown of dolutegravir (DTG)-related neurotoxicity, which may be more common when combined with abacavir (ABC), its reversibility has not been explored in a clinical trial.

Methods. We conducted a randomized, multicenter, open-label, pilot trial to evaluate the reversibility of patient-reported neuropsychiatric symptoms, developed or worsened on DTG/ABC/lamivudine (DTG/ABC/3TC), in virologically suppressed patients switched to cobicistat-boosted-elvitegravir/emtricitabine/tenofovir-alafenamide (EVG/COBI/FTC/TAF). Participants were randomized to immediate switch (baseline) or to defer switch (week 4), and then all completed 24 weeks of follow up on EVG/COBI/FTC/TAF. At each visit, participants completed Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression (HAD) scales and were interviewed about 11 neuropsychiatric symptoms potentially related with DTG through a questionnaire. At baseline and at the end of follow up, they also performed neurocognitive testing. Our primary objective was to compare changes in neuropsychiatric symptoms and PSQI and HAD scales between arms at week 4. Secondary objectives were to evaluate changes in neuropsychiatric symptoms and PSQI and HAD scales at weeks 4, 12, and 24 after switching to EVG/COBI/FTC/TAF and in neurocognitive performance and magnetic resonance imaging biomarkers at end of follow up.

Results. Thirty-eight participants were included. Study arms were similar at baseline. At week 4, neuropsychiatric symptoms and PSQI and HAD scores remained unchanged in participants receiving DTG/ABC/3TC and improved significantly in participants receiving EVG/COBI/FTC/TAF. These significant improvements were also observed at weeks 4, 12, and 24 after all participants switched to EVG/COBI/FTC/TAF. In addition, global neurocognitive performance improved (NPZ-7) after switching to EVG/COBI/FTC/TAF.

Conclusions. Neuropsychiatric symptoms in patients on DTG/ABC/3TC could resolve or improve after switching to EVG/COBI/FTC/TAF.

Keywords. clinical trial; CNS; dolutegravir; neurotoxicity.

Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) is a recommended regimen for the treatment of human immunodeficiency virus (HIV) infection [1]. In clinical trials, this combination showed a good profile of tolerability with low rates of neuropsychiatric adverse events [2–4]. However, after years of use in clinical practice, DTG/ABC/3TC has been associated in several European cohort studies with the development or worsening of neuropsychiatric symptoms and with rates of discontinuation up to 5.6% due to neuropsychiatric symptoms [5–10]. In addition, a recent meta-analysis of randomized clinical trials confirmed higher risk of insomnia with DTG (6.1%) versus other antiretrovirals (4.5%), including efavirenz (EFV) [11].

Although the association between DTG/ABC/3TC use seems likely to develop or worsen neuropsychiatric symptoms, several questions remained unanswered. (1) Does DTG/ABC/3TC cause these neuropsychiatric symptoms? (2) Are these symptoms reversible after DTG/ABC/3TC cessation? (3) What is the mechanism for this neurotoxicity? (4) Are pre-existing conditions predictors of this toxicity?

Our study focused on evaluating the first 2 of these unanswered questions, and we developed a randomized, open-label, pilot clinical trial to assess the reversibility of neuropsychiatric

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symptoms after switching DTG/ABC/3TC to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF). To explore the potential mechanism related to DTG/ABC/3TC neurotoxicity, our study also included a substudy of magnetic resonance imaging (MRI) of the brain that still remains under evaluation for future outcomes.

METHODS

Design

This randomized (1:1), multisite, open-label, pilot trial was designed to provide evidence for the potential reversibility of neuropsychiatric adverse events as well as patient-reported symptoms of insomnia, depression, and anxiety detected in patients treated with DTG/ABC/3TC after switching to EVG/COBI/FTC/TAF.

The DREAM study included 2 consecutive phases. In the first phase, participants were randomized to switch DTG/ABC/3TC to EVG/COBI/FTC/TAF at baseline (immediate switch arm) versus delayed switching at week 4 (deferred switch arm). In the second phase, all participants continued EVG/COBI/FTC/TAF for 24 weeks. We adopted this design because it allowed us to compare the effects of continued versus discontinued DTG/ABC/3TC on neuropsychiatric symptoms while minimizing exposure to DTG/ABC/3TC.

Patient Consent Statement

Study procedures were approved by the ethics committees of each institution. Written informed consent was obtained from all study participants. The protocol was registered at https://eudract.ema.europa.eu (identifier 2016-004646-29).

Participants

Potential candidates to participate in the study were identified at each site by the anamnesis during their regular HIV follow-up appointments. Individuals eligible for screening were virologically suppressed (HIV ribonucleic acid [RNA] <50 copies/mL for >12 weeks) HIV-infected participants treated with DTG/ABC/3TC who developed new neuropsychiatric symptoms or worsening of existing symptoms after starting this regimen. We enrolled those without major central nervous system (CNS) comorbidities (active CNS infections, dementia, developmental CNS disabilities or fulfilling DSM-5 criteria for psychosis, major depression with psychotic symptoms, or suicidal ideation, or a substance use disorder) who could perform all the study procedures and whose virus was fully susceptible to the components of EVG/COBI/FTC/TAF.

Interventions

The study included visits at baseline and weeks 4, 12, and 24 for participants assigned to the immediate switch arm and at weeks 4, 8, 16, and 28 for participants assigned to the deferred switch arm. In addition to conventional HIV management procedures for HIV clinical trials, participants completed 3 patient-reported outcome questionnaires at each visit: (1) a neuropsychiatric symptoms score reported by 11 neurological and psychiatric symptoms, included in the US Division of AIDS table for grading the severity of adverse events, was obtained by adding the severity grade (0, none; 1, mild; 2, moderate; and 3, severe) that we named DTG/ABC/3TC-RElated Adverse events Monitoring (DREAM) score [12]; (2) the Hospital Anxiety and Depression scale (HADS) [13]; and (3) the Pittsburgh Sleep Quality Index (PSQI) [14]. The HADS and PSQI questionnaires are well validated tools for evaluating symptoms of anxiety, depression, and sleep disturbances in people with HIV, whereas the DREAM score was previously used for monitoring the reversibility of EFV-related neurotoxicity [15].

In addition, at baseline and at the end of follow up, all participants also performed a comprehensive battery of 14 tests validated and recommended to evaluate neurocognitive performance in people with HIV in Spain [16] and a 3-Tesla MRI to evaluate changes in the structure and functionality of their brains.

Objectives

Our primary objective was to compare changes in the severity of neuropsychiatric adverse events (DREAM questionnaire) as well as patient-reported symptoms of anxiety, depression, and insomnia (HADS and PSQI questionnaires) from baseline to week 4 between study arms.

Our secondary objectives were as follows: (1) to evaluate changes in the severity of neuropsychiatric adverse events (DREAM score) and self-reported neuropsychiatric symptomatic (HADS and PSQI scores) along with the proportion of patients experiencing moderate to severe (grade 2–3) events in each neuropsychiatric item included in the DREAM questionnaire in 4, 12, and 24 weeks after switching to EVG/COBI/FTC/TAF (pooled data from both arms); (2) to evaluate the proportion of participants who develop virologic failure (HIV RNA determination >50 copies/mL in repeated samples) after 24 weeks of switching to EVG/COBI/FTC/TAF; and (3) to evaluate changes in neurocognitive performance between baseline and week 24.

The study also included as an exploratory objective to assess changes in brain structure and functionality biomarkers measured by brain MRI. Due to the large amount of MRI data available, we decided to report results for this objective as an independent paper.

Sample Size

To calculate the sample size for this study, due to the lack of existing data with DTG/ABC/3TC, we based our estimation in the change observed in a score, equivalent to the DREAM score, after EFV discontinuation in neurosymptomatic patients [15]. We calculated that a sample size of 64 participants would be

enough to demonstrate >20% differences in the change of the DREAM score between study arms, assuming that study discontinuations would be <10%, with type I and II errors of 0.05 and 0.2.

Statistical Methods

Qualitative variables were reported as absolute frequencies or percentages, quantitative variables with normal distribution were reported as means, and standard deviations and quantitative variables without normal distribution were reported as medians and interquartile ranges. Comparisons of baseline demographic and clinical characteristics between the 2 arms were done using Student *t* tests for independent samples and χ^2 and Mann-Whitney *U* tests.

Primary Analyses

Primary analyses were calculated using the Student *t* test for independent samples, after converting raw results on the DREAM, HADS, and PSQI scores to a normalized (0–100) scale, for the intent-to-treat (ITT) and on-treatment (OT) populations. The ITT analysis included all participants who provided DREAM, HADS, and PSQI outcome data at week 4, whereas the OT analysis included all participants who remained on the regimen to which they had been randomized through week 4. A sensitivity analysis, to confirm that score changes associated with the type of therapy received, was also performed using analysis of covariance model adjusting for baseline score and therapy.

Secondary Analyses

Secondary analyses were performed on the ITT subset. Generalized estimated equation (GEE) models were used to estimate the effect of switching antiretroviral therapy (ART) on changes observed in normalized results of the DREAM, HADS, and PSQI scores and in the proportion of patients reporting moderate to severe adverse events in each neuropsychiatric item included in the DREAM questionnaire over time (weeks 4, 12, and 24). Differences between baseline and week 24 in each neurocognitive domain, global neurocognitive performance (GDS and NPZ-7), and brain volumes were analyzed using the Student *t* test for paired samples.

RESULTS

Accrual to the study began at 7 sites in April 2017. During the following year, accrual was not on a trajectory to meet the planned goals, mainly because clinicians of most candidates who developed neuropsychiatric symptoms after starting DTG/ABC/3TC decided to switch DTG/ABC/3TC to another regimen, before the enrollment period started. In addition, some patients reporting neuropsychiatric symptoms after starting DTG/ABC/3TC refused to enroll in a study that might require continuing DTG/ABC/3TC for 4 additional weeks. In April 2018, at the end of the recruitment period, accrual was not reached, and the data safety monitoring board recommended that the study be terminated, because completing accrual and achieving the study goals in a reasonable time frame were judged to be improbable.

As shown in the CONSORT diagram (Figure 1), 51 individuals were screened. Of these, 38 (74.5%) met selection criteria and were randomized: 19 on each study arm. At week 4, all participants continued in the trial, contributing to primary ITT analyses. At week 12, a participant switched from EVG/COBI/FTC/TAF to FTC/TAF + raltegravir to avoid drug-drug interactions with chemsex drugs, and another participant, also a chemsex user, was lost to follow up after completing week 12. Therefore, 37 participants contributed to the secondary ITT analyses.

Table 1 provides the entry characteristics of the 38 participants enrolled in the trial. Both arms were well balanced concerning demographic, disease variables, neuropsychiatric adverse events, and self-reported neuropsychiatric symptoms.

Neuropsychiatric Adverse Events and Symptoms

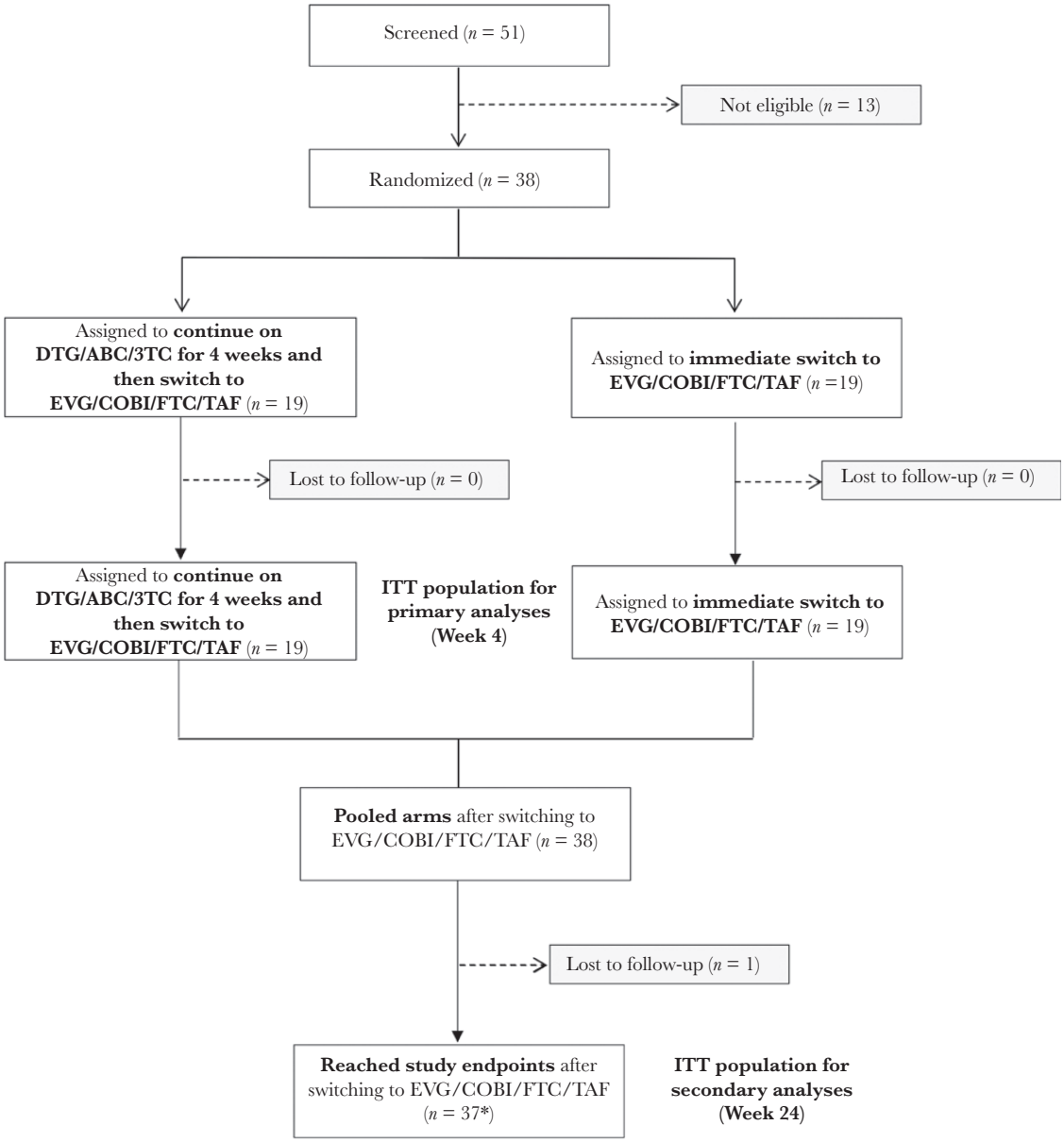
No significant changes in the DREAM score were observed from screening to baseline, either in patient-reported scores of anxiety, depression, or insomnia (DREAM: −1.7 ± 13.1, $P = .313$; HADs anxiety: 2.2 ± 19.81, $P = .362$; HADs depression: 2.9 ± 20.8, $P = .352$; and PSQI: 0.3 ± 18.8, $P = .812$).

Figure 2 includes the results of the DREAM, HADS, and PSQI scores in each study arm at baseline and at week 4. From baseline to week 4, participants who switched to EVG/COBI/FTC/TAF experienced significant improvements in the DREAM score and patient-reported scores of anxiety, depression, and insomnia compared with participants continuing on DTG/ABC/3TC (DREAM change: −14 ± 9.8 vs −1 ± 9.1, $P < .001$; HADs anxiety change: −11.9 ± 16.4 vs −1 ± 9.6, $P = .021$; HADs depression change: −5.8 ± 11.1 vs 1.8 ± 10.8, $P = .041$; PSQI change: −14 ± 13.4 vs −1 ± 12, $P = .008$).

Twenty-four weeks after all participants switched to EVG/COBI/FTC/TAF, we observed progressive improvements in the DREAM score as well as patient-reported scores of anxiety, depression, and insomnia (Figure 3). We also found significant improvements in the proportion of participants reporting moderate-severe (grade 2–3) neuropsychiatric adverse events in most of items conforming to the DREAM questionnaire 4, 12, and 24 weeks after switching to EVG/COBI/FTC/TAF (Table 2). The GEE models confirm that all of these changes were associated with switch DTG/ABC/3TC to EVG/COBI/FTC/TAF.

Neurocognitive Performance

Supplementary Table S1 includes the results of the neurocognitive assessments performed at baseline and at the end of follow up. We observed significant improvements in global neurocognitive performance (NPZ-7:



* One participant switched therapy to raltegravir + tenofovir disoproxil fumarate/emtricitabine at week 12 due to chemsex use

Figure 1. Subject disposition chart according to CONSORT guidelines

baseline 0.02 ± 0.61—week 24 0.31 ± 0.57; $P = .031$). At baseline, 10 participants (26.3%) fulfilled Frascati criteria for neurocognitive impairment. Of those, 4 (40%) normalized after switching to EVG/COBI/FTC/TAF. A single participant (3.6%) with a normal neurocognitive performance at baseline developed neurocognitive impairment after switching to EVG/COBI/FTC/TAF.

Efficacy and Safety

At the end of follow up, 36 of 38 participants (94.8%) maintained HIV RNA suppression on EVG/COBI/FTC/TAF. During the trial, we did not detect any case of virologic failure or any severe adverse event. After switching to EVG/COBI/FTC/TAF, 16 participants experienced 35 adverse events (30 were grade 1, 3 grade 2, and 2 grade 3). Only 1 was considered ART-related, a case of transient erectile dysfunction (grade 2).

DISCUSSION

Our study demonstrates improvements in CNS adverse events and patient-reported neuropsychiatric symptoms associated with DTG/ABC/3TC when switching to EVG/COBI/FTC/TAF.

Table 1. Baseline Characteristics

Characteristics	Immediate Switch to EVG/COBI/FTC/TAF n = 19	Deferred Switch to E/CF/TAF n = 19
Gender (male), n (%)	19 (100)	18 (94.7)
Ethnicity (Caucasian), n (%)	16 (84.2)	18 (94.7)
Age (years), mean ± SD	40.2 ± 10.1	45.6 ± 8.9
Years since HIV diagnosis, mean ± SD	9.4 ± 9.2	9.0 ± 7.9
Weeks of HIV RNA <50 copies/mL, mean ± SD	235.9 ± 216.3	292.5 ± 257.1
Weeks on DTG/ABC/3TC, mean ± SD	67.1 ± 38.3	83.7 ± 35.3
CD4 nadir (cells/mm^3), mean ± SD	416.05 ± 218.01	412.95 ± 225.52
CD4 cell count (cells/mm^3), mean ± SD	772.0 ± 402.6	748.3 ± 317.6
Glomerular filtrate rate (Chronic Kidney Disease Epidemiology Collaboration), n (%)	92.0 ± 20.2	85.6 ± 14.0
History of illicit drug consumption, n (%)	6 (31.6)	5 (26.3)
History of psychiatric conditions, n (%)	4 (21.1)	5 (26.3)
Neurocognitive impairment, n (%)	5 (26.3)	5 (26.3)

Abbreviations: 3TC, lamivudine; ABC, abacavir; COBI, emtricitabine; DTG, dolutegravir; EVG, elvitegravir; FTC, tenofovir; HIV, human immunodeficiency virus; RNA, ribonucleic acid; SD, standard deviation; TAF, alafenamide.

The magnitude of all these improvements was large, ranging from 35% and 37.7% for symptoms of depression and anxiety to 89% for insomnia.

Our trial supports the association seen in previous cohort studies between neuropsychiatric symptoms and the use of DTG/ABC/3TC [5–10]. The lack of complete reversibility observed in some patients could be explained by the possibility that some symptoms, which are common among people with HIV and in the general population, were unrelated to the medications; however, the possibility of continued CNS side effects resulting from the new regimen cannot be ruled out.

Some of the neuropsychiatric adverse events attributed to DTG, such as sleep or mood disturbances, are similar to those observed with EFV. Considering that the results observed in our trial were similar to those reported in symptomatic patients who switched from EFV-based ART to other regimens, we cannot exclude the possibility that both drugs may share some similarities in their neurotoxic pathway. An in vitro study of neuronal cultures exposed to different antiretroviral drugs found that both EFV and DTG produced the same pattern

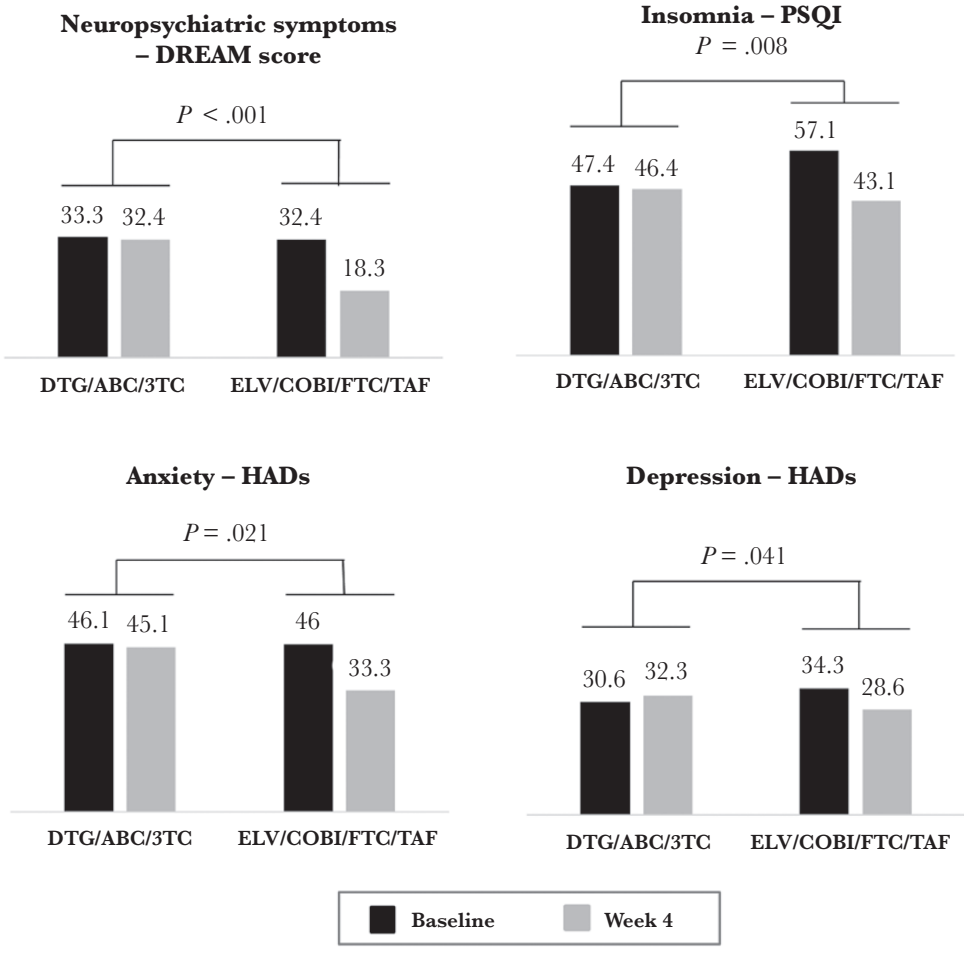
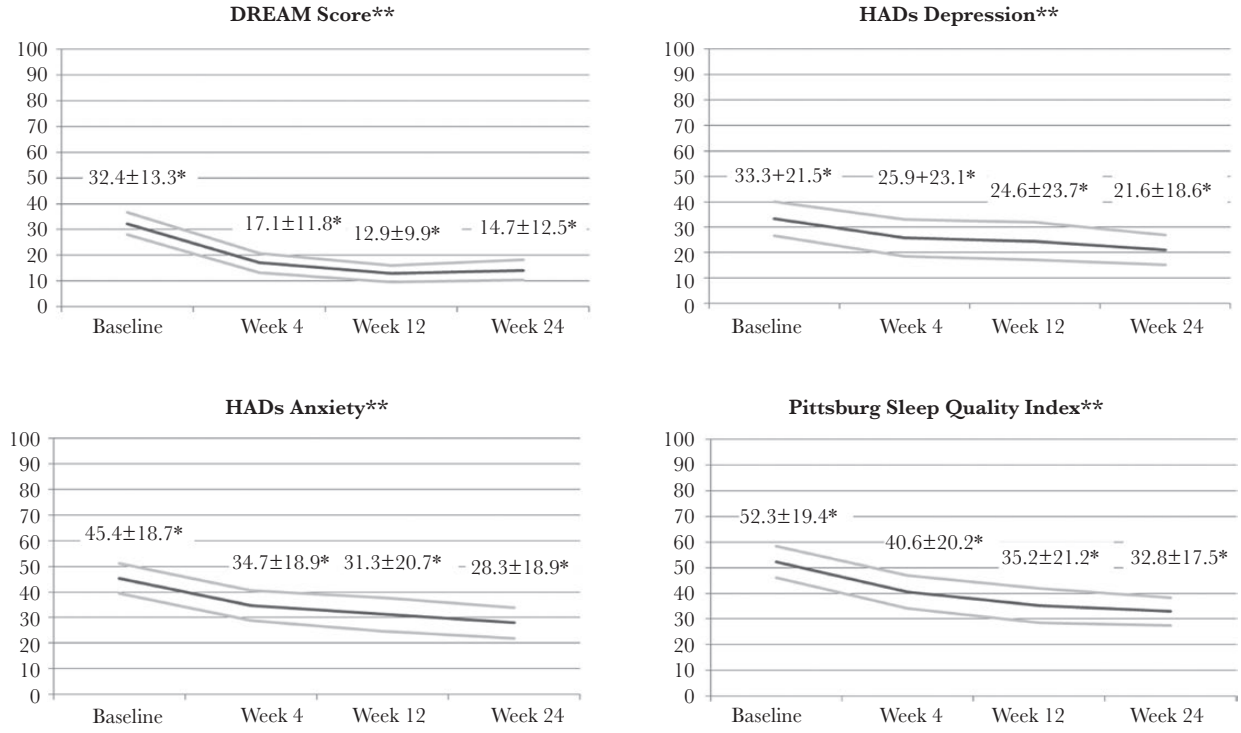


Figure 2. Comparison of neuropsychiatric symptoms among participants who switched to ELV/COBI/FTC/TAF or continued on DTG/3TC/ABC at baseline and week 4. Symptoms were self-reported by participants using the DREAM score, the Hospital Anxiety and Depression Scale and the Pittsburg Sleep Quality Index.



* Significant changes at this timepoint from baseline (all *P* values <.0015)
** Significant changes in the longitudinal model (all *P* values <.001)

Figure 3. Changes in neuropsychiatric symptoms after switching from DTG/ABC/3TC to ELV/COBI/FTC/TAF. Symptoms were self-reported by participants using the DREAM score, the Hospital Anxiety and Depression Scale and the Pittsburg Sleep Quality Index.

of neurotoxicity, neurite outgrowth, which supports this hypothesis [17]. However, further in vitro and in vivo studies are needed to evaluate this possibility.

There is a previous in vitro report suggesting that ABC/3TC had a worse neurotoxic profile compared with tenofovir disoproxil fumarate/FTC (TDF/FTC), and at least 1 cohort study found higher rates of discontinuation of DTG-based ART when combined with ABC/3TC [7, 18]. Because all participants in this trial used ABC/3TC in combination with DTG, we cannot determine whether the observed clinical improvements were due to discontinuation of DTG, ABC, or both. Based on the results of the patient-reported questionnaires from GS 380–1489 [2], GS 380–1490 [3], and GS 380–1844 [4] clinical trials, which found better neuropsychiatric outcomes with bictegravir (BIC) when the backbone of DTG was ABC/3TC (GS 380–1489 and GS 380–1844) [19] and not when it was TAF/FTC (GS 380–1490), we estimate that the benefits observed in our study were the result of the discontinuation of both drugs. Further studies with ABC-free DTG combinations would help to clarify the real dimension of DTG-related potential neurotoxicity.

No virologic failures occurred in the study after switching to EVG/COBI/FTC/TAF, and none of the patients had to

Table 2. Changes in the Proportion of Participants Reporting Moderate-Severe Neuropsychiatric Adverse Events (Grade 2–3) Between Baseline to Week 24

Neuropsychiatric Symptoms	Baseline (n = 38)	Week 4 (n = 38)	Week 12 (n = 38)	Week 24 (n = 37)
Insomnia, (%)	73.7	34.2[a]	18.4[a]	8.1[a]
Abnormal dreams, (%)	31.6	13.2[a]	5.3[a]	8.1[a]
Impaired concentration, (%)	57.9	21.1[a]	13.2[a]	16.1[a]
Nervousness or irritability, (%)	47.4	15.8[a]	10.5[a]	10.8[a]
Asthenia or fatigue, (%)	55.3	26.3[a]	21.1[a]	24.3[a]
Symptoms of anxiety, (%)	42.1	18.4[a]	7.9[a]	10.8[a]
Symptoms of depression, (%)	34.2	18.4[a]	5.3[a]	13.5[a]
Suicidality, (%)	8	0	0	0

[a]Significant differences from baseline.

discontinue the study due to adverse events. These findings were similar to those reported in previous clinical trials after switching to EVG/COBI/FTC/TAF from TDF/FTC and ABC/3TC-based regimens in virologically suppressed patients and theoretically fully sensitive to EVG/COBI/FTC/TAF [20, 21]. Our study results cannot necessarily be extrapolated to patients with detectable viremia or previous resistance mutations.

Our study has important limitations. First, accrual was not completed. We believe this did not influence our results because the post hoc power calculated for our study to demonstrate differences in score changes between study arms was 98.9%. Second, our study only included symptomatic patients; therefore, a regression to the mean effect bias cannot be ruled out. We believe this would be unlikely because of the delayed switch comparator arm. Third, although the study was open to male and female participants of all ages, only 1 woman and 2 men over 60 years old were enrolled. Thus, we are not able to assess the effect of switching from DTG/ABC/3TC to EVG/COBI/FTC/TAF in symptomatic women and people over 60. Considering the existence of data suggesting higher rates of neuropsychiatric symptoms in women and older people receiving DTG/ABC/3TC than in young and middle age men, we believe that further studies in women and people over 60 evaluating the potential neuropsychiatric adverse events profile of DTG/ABC/3TC are necessary.

Another limitation of the study was its open-label design. We cannot exclude the possibility that some of the large improvement in symptoms was due to a placebo effect resulting from a positive expectation of the switch. The mild worsening observed from week 12 to week 24 in some of the symptoms that composed the DREAM score (Table 2) supports the existence of a placebo effect but of mild magnitude. Further analyses of neuroimaging data collected for the study will help to determine the potential relevance of this potential placebo effect. If neuroimaging markers improve after switching DTG/ABC/3TC to EVG/COBI/FTC/TAF, this possibility will be unlikely.

CONCLUSIONS

In conclusion, it seems that neuropsychiatric symptoms observed in some patients on DTG/ABC/3TC could be true side effects of this combination based on their rapid reversibility. We have also observed that they are not class effects, because they improved or resolved with a switch to another integrase inhibitor-based regimen. These findings increase our understanding of DTG-related neurotoxicity. However, some other important questions remain unanswered, such as the underlying mechanism of DTG neurotoxicity, the neuropsychiatric adverse events profile of DTG-based regimens without ABC, or the reversibility of neuropsychiatric symptoms after switching to BIC/FTC/TAF.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. I. P. V., A. C., P. R., S. D. L. F.-M., I. S., M. J. V., M. G., G. C., A. D. D. S., and J. J. G. G. have served as consultant to and/or have received research grants from Gilead Sciences, ViiV, Janssen Cilag, and MSD. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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