

Changes in Quality of Sleep, Mood, and Other Neuropsychiatric Symptoms After Switching Dolutegravir/Lamivudine/Abacavir to Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Randomized Study of People With Human Immunodeficiency Virus With Poor Sleep Quality: GESIDA 10418

Alfonso Cabello-Úbeda,¹ Alicia González Baeza,² Jesús Troya García,^{3,6} Sara de La Fuente Moral,⁴ María Novella Mena,⁵ Adriana Pinto Martínez,⁶ Rafael Micán,⁷ Miguel Górgolas,¹ Guillermo Cuevas Tascón,^{3,6} Alberto Díaz de Santiago,⁴ José Sanz Moreno,⁵ David Rial Crestelo,⁶ Carmen Busca Arenzana,⁷ José Ignacio Bernardino Serna,^{7,8} Mariana Díaz Almirón,⁸ Joanna Cano,⁷ Herminia Esteban,⁹ and Ignacio Pérez-Valero¹⁰

¹División de Enfermedades Infecciosas, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, ²Departamento de Psicobiología, Facultad de Psicología, Universidad Autónoma de Madrid, Madrid, Spain, ³Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain, ⁴Servicio de Medicina Interna, Hospital Universitario Puerta de Hierro, Majadahonda, Spain, ⁵Servicio de Medicina Interna, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain, ⁶Fundación de Investigación i-12, Madrid, Spain, ⁷Servicio de Medicina Interna, Hospital Universitario La Paz—IDIPAZ, Madrid, Spain, ⁸Unidad de Bioestadística, Instituto de Investigación Biomédica Hospital La Paz (IDIPAZ), Madrid, Spain, ⁹Fundación SEIMC-GESIDA, Madrid, Spain, and ¹⁰Servicio de Enfermedades Infecciosas, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III (CIBERINFEC, ISCIII), Córdoba, Spain

Background. Although switching antiretroviral therapy (ART) in people with human immunodeficiency virus experiencing insomnia due to dolutegravir-related neurotoxicity is well founded upon evidence, there is a lack of proof in regard to the outcome of stopping dolutegravir-based ART in people without insomnia but reporting poor sleep quality.

Methods. This is a randomized, multicenter, open-label study to evaluate the reversibility of patient-reported sleep disturbances in patients on dolutegravir/lamivudine/abacavir without insomnia after switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. The participants were randomized to switch ART at baseline or at week 4 and then completed 8 weeks of darunavir/cobicistat/emtricitabine/tenofovir alafenamide. Our primary objective was to compare changes in sleep quality between arms at week 4. Secondary objectives were to compare changes in mood and neuropsychiatric symptoms (NS) at week 4 and 4 and 8 weeks after switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. The participants completed a survey, including the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression scale (HADS), and specific questions to explore NS, at each visit to assess those objectives.

Results. We included 72 participants. The results show that study arms were similar at baseline; however, at week 4, PSQI scores remained unchanged with dolutegravir/lamivudine/abacavir, whereas patients improved significantly after switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. Similar differences between arms were also observed in HADS and NS changes. At weeks 4 and 8 after all participants switched to darunavir/cobicistat/emtricitabine/tenofovir alafenamide, we have observed significant improvements in PSQI and HAD scores and in NS.

Conclusions. In patients reporting subclinical sleep disturbances without insomnia, switching from dolutegravir/lamivudine/abacavir to darunavir/cobicistat/emtricitabine/tenofovir alafenamide was associated with better sleep quality and improvements in mood and NS.

Keywords. clinical trial; CNS; darunavir; dolutegravir; neurotoxicity.

Received 03 May 2022; editorial decision 01 July 2022; accepted 01 July 2022; published online 6 August 2022

Correspondence: I. Pérez-Valero, MD, Servicio de Enfermedades Infecciosas, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III (CIBERINFEC, ISCIII), Córdoba, Spain, Avda. Menéndez Pidal, s/n, 14004 Córdoba, Spain (ignacio.perez.valero.sspa@juntadeandalucia.es).

Open Forum Infectious Diseases®

© The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
<https://doi.org/10.1093/ofid/ofac345>

In some cases, the use of dolutegravir/lamivudine/abacavir (DTG/3TC/ABC) seems to be associated with the development or worsening of neuropsychiatric symptoms [1]. Several previous cohorts have reported higher rates of DTG/3TC/ABC discontinuation due to neuropsychiatric symptoms [2–6]. A meta-analysis of randomized clinical trials reported a higher risk of developing insomnia with DTG (6.1%) than with other antiretrovirals (4.5%) [7]. In addition, a clinical trial designed to evaluate DTG/3TC/ABC neurotoxicity and its reversibility, which includes virologically suppress people with human immunodeficiency virus (PWH) reporting neuropsychiatric symptoms

after starting DTG/3TC/ABC, revealed improvements in sleep, mood, and neuropsychiatric symptoms after switching from DTG/3TC/ABC to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) [8].

Several studies have explored the pathogenesis behind the development or worsening of neuropsychiatric symptoms that some PWH have after starting DTG-based therapies. In rats, DTG/3TC/ABC seems to increase the excitability of pyramidal neurons in the medial prefrontal cortex, a region associated with sleep, mood, and stress regulation [9]. Regardless of whether this or another process could be the underlying mechanism of DTG-related neurotoxicity, there are several factors that seem to be associated with its development, such as female gender, older age, higher dolutegravir concentrations, a SLC22A2 gene variant in the organic cation transporter-2 (OCT-2), or the concomitant use of ABC with DTG [3, 10,11].

Although scientific evidence supports that switching DTG/3TC/ABC to a regimen with a better neurotoxic profile would help to improve symptoms in PWH who complain about insomnia, mood disorders, or neuropsychiatric symptoms [1–8], we do not know whether PWH treated with DTG/3TC/ABC and not complaining about neuropsychiatric symptoms would improve their quality of sleep, mood, and/or neuropsychiatric status if they switched antiretroviral therapy (ART) to a regimen with a more favorable neurotoxic profile.

To explore this possibility in virologically suppress PWH not complaining of insomnia but with poor quality of sleep, we developed a randomized, open-label, multisite, clinical trial that evaluated whether switching from DTG/3TC/ABC to another ART such as darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF), a regimen with a non-neurotoxic profile, could help to improve the quality of sleep of these patients as well as their mood and neuropsychiatric status.

METHODS

Design

The DETOX study included 2 consecutive design phases. In phase one, participants who reported poor quality of sleep in the Pittsburgh Sleep Quality Index (PSQI) were randomized to switch at baseline from DTG/3TC/ABC to DRV/COBI/FTC/TAF (immediate switch arm) or to continue 4 weeks with DTG/3TC/ABC and then switch to DRV/COBI/FTC/TAF (deferred switch arm). In phase 2, participants from both arms completed 8 weeks of follow-up after their switch to DRV/COBI/FTC/TAF.

Patient Consent Statement

Written informed consent was obtained from all study participants. Study protocol was approved by the ethics committees of each institution and by the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS). The protocol

was registered at <https://eudract.ema.europa.eu> (identifier 2018-001158-82).

Participants

Individuals eligible for screening included PWH (1) without major neuropsychiatric comorbidities (major depression with psychotic symptoms or suicidal ideation, drug abuse/dependence, dementia, or psychosis), (2) receiving DTG/3TC/ABC for at least 4 weeks, (3) under virological suppression (human immunodeficiency virus [HIV] ribonucleic acid [RNA] <50 copies/mL for >12 weeks), (4) with poor quality of sleep (PSQI score >5), and (5) not complaining of insomnia. Of these, we enrolled those willing to participate in the study who could receive DRV/COBI/FTC/TAF and complete all study procedures. We excluded pregnant women, nursing women, or women of childbearing age who do not agree to use an adequate birth control method, and candidates with active central nervous system (CNS) infections or illnesses that may interfere with the study procedures.

Interventions

The study included visits at baseline and weeks 4 and 8 for participants assigned to the immediate switch arm and at baseline and weeks 4, 8, and 12 for participants assigned to the deferred switch arm. In addition to the conventional procedures of HIV clinical trials, participants completed 3 patient-reported outcome (PRO) questionnaires at each visit: the PSQI, the Hospital Anxiety and Depression scale (HADS), and a neuropsychiatric symptoms score (defined as DETOX score) obtained by adding the severity grade (0, none; 1, mild; 2, moderate; and 3, severe) reported in the 11 neurological and psychiatric symptoms included in the US Division of AIDS table for grading the severity of adverse events [12]. The first 2 questionnaires have been validated for their use in PWH and can be widely used for assessing sleep and mood disturbances [13–15], whereas the third questionnaire has been used as a valid tool in several clinical trials to evaluate ART-related neurotoxicity [8, 16].

Objectives

Our primary objective was to compare changes in the quality of sleep, measured with the PSQI, from baseline to week 4 between study arms. Secondary objectives were as follows: (1) to compare changes in patient-reported neuropsychiatric symptoms detected and quantified, using the HADS and DETOX questionnaires, from baseline to week 4 between study arms; (2) to evaluate changes in the quality of sleep and in patient-reported neuropsychiatric symptoms detected and quantified, using the HADS and DETOX questionnaires, 4 and 8 weeks after switching to DRV/COBI/FTC/TAF (pooled data from both arms); and (3) to evaluate the efficacy (proportion of participants who maintain HIV RNA <50 copies/mL)

and safety (proportion of participants who develop any adverse event) after switching to DRV/COBI/FTC/TAF.

Sample Size

To calculate the sample size for this study, we used unpublished estimations obtained from PWH enrolled in La Paz Hospital cohort who completed a PSQI questionnaire before and after switching from DTG/3TC/ABC to another ART, due to the lack of pre-existing data published estimating the presence and reversibility of sleep disturbances in PWH treated with DTG/3TC/ABC. Based on those observations, we estimated that change of the PSQI score will be >15% after switching DTG/3TC/ABC to DRV/COBI/FTC/TAF. Therefore, we calculated that a sample size of 55 participants per arm would be enough to demonstrate differences between study arms, assuming that study discontinuations would be ≤8%, with type I and II errors of 0.05 and 0.2.

Statistical Methods

Absolute frequencies or percentages displayed qualitative variables, quantitative variables with normal distribution as means, standard deviations (SDs) or standard errors (SEs), and quantitative variables without normal distribution as medians and interquartile ranges. Comparisons among baseline demographic and clinical characteristics between the 2 arms were done using Student *t* (for independent samples), χ^2 , and Mann-Whitney *U* tests.

Primary Analyses

The primary analysis was calculated using the Student *t* test for independent samples, after converting raw results on the PSQI scores to a normalized (0–100) scale, for the intent-to-treat (ITT) and on-treatment (OT) populations. The ITT analyses included all participants who provided PSQI outcome data at baseline and week 4, whereas the OT analyses included all participants who remained on the regimen to which they had been randomized through week 4.

Secondary Analyses

Secondary analyses were performed on the ITT subset. Generalized estimated equation (GEE) models were used to estimate the effect of switching ART on changes observed in normalized results of the PSQI, HADS, and DETOX scores and in the proportion of participants reporting (1) moderate-severe adverse events versus non-mild adverse events and (2) any adverse event versus asymptomatic in each neuropsychiatric item included in the DETOX questionnaire over time (weeks 4 and 8). Results from GEE models were adjusted for multiple comparisons using Bonferroni.

RESULTS

Accrual to the study began at 6 sites in January 2019. Accrual was slower than planned, mainly because several potential candidates simplified to other therapies or refused to enroll in the

study due to an increase in scheduled visits compared with their usual clinical routine. In March 2020, the safety monitoring board recommended stopping the accrual before it was reached, due to the coronavirus disease 2019 (COVID-19) pandemic.

As shown in the CONSORT diagram (Supplementary Figure 1), 78 individuals were screened. Of these, 72 (92.3%) met criteria and were randomized: 37 to the immediate switch arm and 35 to the deferred switch arm. At week 4, all continued in the trial, except 3 participants from the immediate switch arm who abandoned the trial (COVID-19 pneumonia, consent withdrawal, and loss of follow-up), contributing to primary ITT analyses. After switching to DRV/COBI/FTC/TAF, 3 participants abandoned the study before the end of follow-up (2 due to loss of follow-up and 1 due to gastrointestinal intolerance). Therefore, 66 participants contributed to the secondary ITT analyses.

Baseline Characteristic

Table 1 provides entry characteristics of the 72 participants enrolled in the trial. Both arms were well balanced across demographic and disease variables, except for the higher proportions of illicit drug use observed in the immediate switch arm (40.5% vs 17.1%; *P* = .023).

Table 1. Baseline Characteristics

Variable	Delayed Switch ^a Arm n = 35	Immediate Switch ^a Arm n = 37	<i>P</i> Value
Age, mean (SD)	46.1 (10.5)	48.4 (11.5)	.379
Gender: male, n (%)	29 (82.9)	32 (86.5)	.669
Ethnicity: Caucasian, n (%)	26 (74.3)	28 (75.7)	.915
Toxic habits ^b , n (%)	20 (57.1)	24 (64.9)	.502
Illicit drug use, n (%)	6 (17.1)	15 (40.5)	.023^c
Years since HIV diagnosis, mean (SD)	12.2 (10.3)	13.1 (10.3)	.720
Years of HIV undetectability, mean (SD)	5.3 (5.0)	5.56 (4.0)	.798
Years on DTG/3TC/ABC, mean (SD)	3.1 (1.6)	2.7 (1.25)	.205
CD4 nadir, mean (SD)	358 (232.5)	230 (215)	.482
Previous AIDS diagnosis, n (%)	5 (14.3)	7 (18.9)	.598
Current CD4 cell count, mean (SD)	727.4 (315.7)	611.1 (190.9)	.067
Positive anxiety screen: HADs, n (%)	21 (60)	19 (51.4)	.424
Positive depression screen: HADs, n (%)	10 (28.6)	7 (18.9)	.307

Abbreviations: ABC, abacavir; AIDS, acquired immune deficiency syndrome; DTG, dolutegravir; HAD, Hospital Anxiety and Depression scale; HIV, human immunodeficiency virus; SD, standard deviation; 3TC, lamivudine.

^aSwitch from dolutegravir/lamivudine/abacavir to darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

^bToxic habits: tobacco, daily alcohol, or illicit drug consumption.

^cBold text: Statistically significant result.

Five participants reported neuropsychiatric concomitant medication at baseline: 1 took benzodiazepines as treatment for anxiety (lorazepam 1 mg), 2 took antidepressants for depression (mirtazapine 30 mg and paroxetine 20 mg), and another 2 took antidepressants and benzodiazepines in combination for anxiety depressive disorders (bromazepam 1.5 mg with escitalopram 10 mg and lorazepam 1 mg with mirtazapine 15 mg). Thirteen participants were treated with lipid-lowering agents at baseline (10 atorvastatin, 1 pitavastatin, 1 pravastatin, and 1 gemfibrozil).

Quality of Sleep

Figure 1 includes the results of the PSQI scores in each study arm at baseline and at week 4 for the ITT population. From baseline to week 4, participants who switched to DRV/COBI/FTC/TAF experienced significant improvements in the PSQI score compared with participants continuing on DTG/3TC/ABC (mean \pm SD change: -18.0 ± 16.2 vs -3.3 ± 11.4 ; $P < .001$). Similar results were observed in the OT population and after adjusting by the proportion of illicit drug use in each study arm ($P = .004$).

Figure 2 includes the proportion of participants reporting moderate or severe disturbances in the PSQI components in

each study arm at baseline and at week 4 (ITT population). From baseline to week 4, participants who switched to DRV/COBI/FTC/TAF experienced a significant decrease in the proportion of moderate to severe disturbances in the following PSQI components compared with participants who continued on DTG/3TC/ABC: sleep quality (%decrease: 64.6% vs 7.1%; $P = .007$), sleep latency (36.6% vs 0.0%, $P = .045$), and habitual sleep efficiency (59.8% vs 16.5%, $P = .034$). A trend was also observed in the sleep duration PSQI component (58.3% vs 21.8%, $P = .055$). A nonstatistical significant decrease, but of a magnitude clinically relevant, was also observed in the use of medication for sleep component (21.4% decrease in the DRV/COBI/FTC/TAF arm vs 15.6% increase in the DTG/3TC/ABC arm; $P = .131$). Similar results were observed for the OT population.

In the second phase of the study, 8 weeks after all participants switched to DRV/COBI/FTC/TAF, we observed progressive improvements in the PSQI score (Figure 3) and a significant decrease in moderate to severe disturbances in the following PSQI components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, and daytime dysfunction (Table 2).

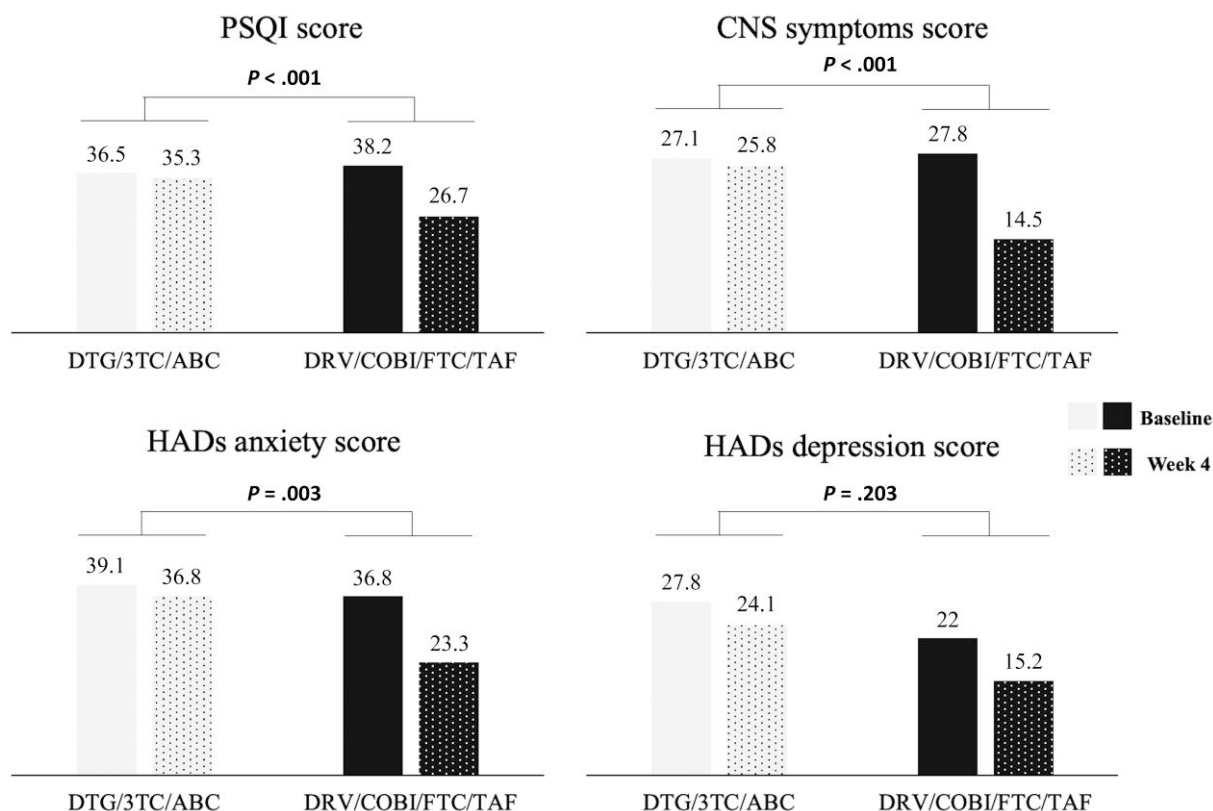


Figure 1. Baseline and week 4 results of the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression scale (HADS) anxiety and depression subscales, and the central nervous system (CNS) symptoms scores in each study arm, for the intention-to-treat population. ABC, abacavir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine.

Mood and Neuropsychiatric Symptoms

Figure 1 includes the results of the HADS and DETOX scores in each study arm at baseline and at week 4. From baseline to week 4, participants who switched to DRV/COBI/FTC/TAF experienced significant improvements in self-reported scores of neuropsychiatric symptoms and anxiety compared with

participants continuing on DTG/3TC/ABC (DETOX changes: -13.7 ± 13.3 vs -1.3 ± 8.6 , $P < .001$; HAD anxiety subscale changes: -14 ± 16.9 vs -1.9 ± 15.6 , $P = .003$). No differences were observed in the self-reported score of depression (HAD depression subscale changes: -5.8 ± 11.1 vs 1.8 ± 10.8 , $P = .041$).

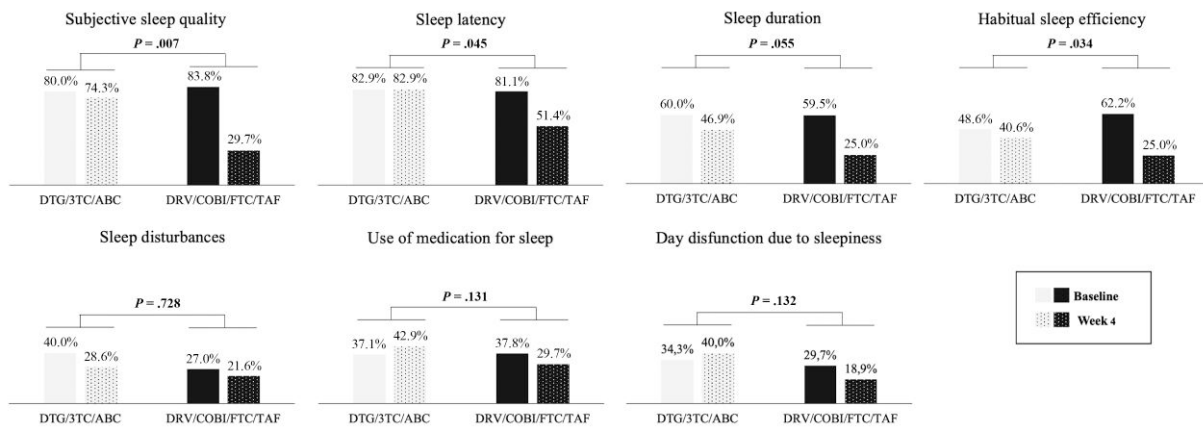


Figure 2. Proportion of participants reporting moderate-severe disturbances in the Pittsburgh Sleep Quality Index components in each study arm at baseline and at week 4 for the intention-to-treat population. ABC, abacavir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine.

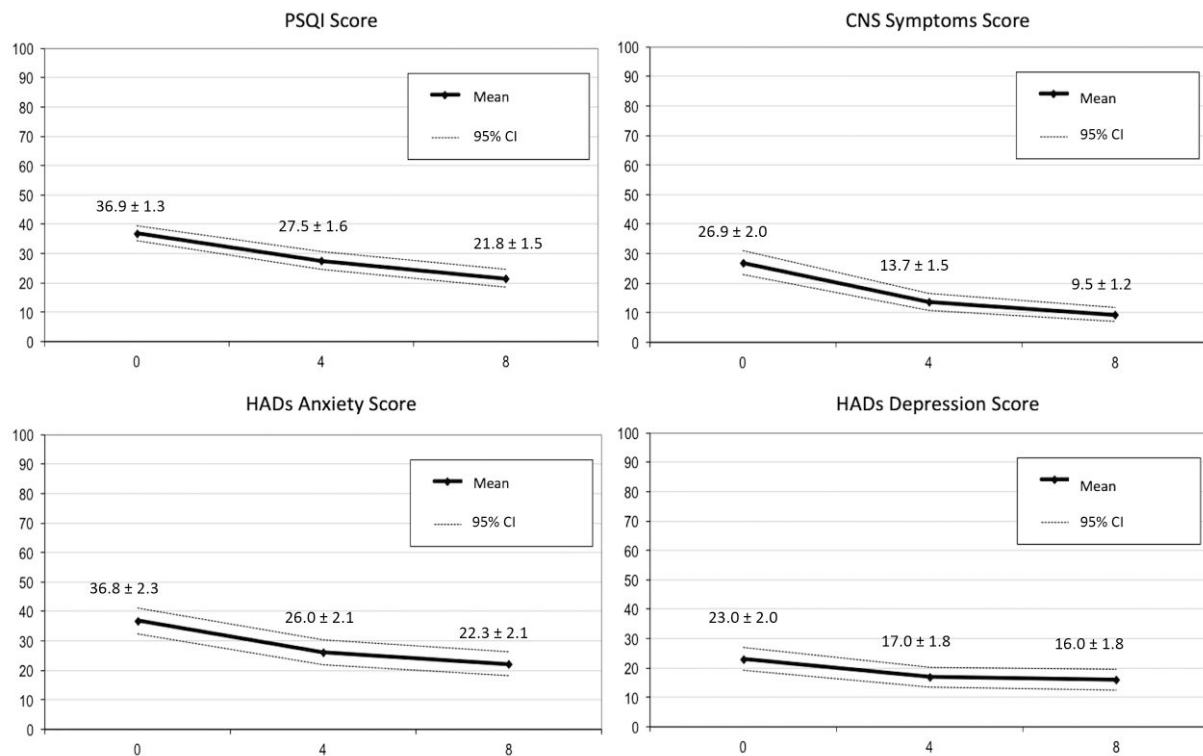


Figure 3. Changes at weeks 4 and 8 of the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression scale (HADS) anxiety and depression subscales, and the central nervous system (CNS) symptoms scores after all participants for the intention-to-treat population switched to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. CI, confidence interval.

Table 2. Changes in the Proportion of Participants Reporting Moderate-Severe Disturbances in the PSQI 4 and 8 Weeks After All Participants Switched to DRV/COBI/FTC/TAF

PSQI component scores	Baseline (n = 69)	Week 4 (n = 66)	Week 8 (n = 66)
Subjective sleep quality, n (%) ^a	54 (78.3)	15 (22.2) ^b	13 (19.7) ^b
Sleep latency, n (%) ^a	56 (81.2)	33 (50) ^b	25 (37.9) ^b
Sleep duration, n (%) ^a	37 (53.6)	19 (28.8) ^b	11 (16.7) ^b
Habitual sleep efficiency, n (%) ^a	36 (52.2)	17 (25.8) ^b	17 (25.8) ^b
Sleep disturbances, n (%)	17 (24.6)	10 (15.2)	7 (11.1)
Use of medication for sleep, n (%)	26 (37.7)	21 (31.8)	14 (21.2)
Day disfunction due to sleepiness, n (%) ^a	22 (31.9)	12 (18.2)	4 (6.1) ^b

Abbreviations: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; PSQI, Pittsburgh Sleep Quality Index; TAF, tenofovir alafenamide.

^aSignificant changes were observed in the linear model.

^bSignificant change from baseline to that setpoint.

Eight weeks after all participants switched to DRV/COBI/FTC/TAF, we observed progressive improvements in the DETOX score and in HADS scores of anxiety and depression (Figure 3). We also observed significant improvements in the proportion of participants reporting sleep disturbances, abnormal dreams, asthenia or fatigue, and impaired concentration in the DETOX questionnaire at week 4 and in all the items of the questionnaire, except hallucinations and suicidality, at week 8 after all participants switched to DRV/COBI/FTC/TAF (Table 3). Longitudinal GEE models confirmed that all these changes were associated with the effect of switching from DTG/3TC/ABC to DRV/COBI/FTC/TAF.

Efficacy and Safety

At the end of follow-up, 61 of 66 participants (92.4%) maintained HIV RNA suppression below 50 copies/mL on DRV/

Table 3. Changes in the Proportion of Participants Reporting any Symptom in the Neuropsychiatric Items Conforming the DETOX Questionnaire, 4 and 8 Weeks After All Participants Switched to DRV/COBI/FTC/TAF

Neuropsychiatric items	Baseline (n = 69)	Week 4/8 (n = 66)	Week 8/12 (n = 66)
Sleep disturbances ^a , n (%) ^b	65 (94.2)	32 (48.5) ^c	26 (39.4) ^c
Abnormal dreams, n (%) ^b	45 (65.2)	14 (21.2) ^c	13 (19.7) ^c
Dizziness, n (%) ^b	23 (33.3)	12 (18.2)	6 (9.1) ^c
Headache, n (%) ^b	30 (43.5)	17 (25.8)	15 (22.7) ^c
Impaired concentration, n (%) ^b	37 (53.6)	20 (30.3) ^c	14 (21.2) ^c
Nervousness or irritability, n (%) ^b	45 (65.2)	32 (48.5)	28 (42.4) ^c
Asthenia or fatigue, n (%) ^b	52 (75.4)	32 (49.2) ^c	24 (36.4) ^c
Symptoms of anxiety, n (%) ^b	43 (62.3)	29 (43.9)	22 (33.3) ^a
Symptoms of depression, n (%) ^b	32 (46.4)	21 (31.8)	12 (18.2) ^a
Hallucinations, n (%)	4 (5.8)	3 (4.6)	1 (1.6)
Suicidality, n (%)	4 (5.8)	3 (6.1)	1 (3.0)

Abbreviations: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; TAF, tenofovir alafenamide.

^aDefinition: sleep abnormalities not fulfilling the diagnostic criteria for insomnia.

^bSignificant change over time associated with antiretroviral therapy switch (linear generalized estimated equation [GEE] model).

^cSignificant change from baseline to the setpoint (adjusted GEE model).

COBI/FTC/TAF and 5 participants experienced blips. We did not detect any case of virologic failure during the trial.

After switching to DRV/COBI/FTC/TAF, 26 participants experienced approximately 46 adverse events (36 grade 1 and 10 grade 2). Of those adverse events, 11 were CNS adverse events (5 headaches, 2 anxiety, 2 insomnia, 1 depression, and 1 dizziness) and 10 were ART related (4 dyslipidaemia, 3 gastrointestinal intolerance, 2 headaches, and 1 facial edema). One ART-related adverse event (nausea) led to DRV/COBI/FTC/TAF discontinuation. An additional participant experienced an unrelated serious adverse event (radius and ulna open fracture).

Four participants (36.4%) of those reporting CNS adverse events experienced resolution of their symptoms during the study (3 headaches and 1 dizziness), and in 7 the adverse event continued at the end of follow-up. Three participants started CNS medication after switching to DRV/COBI/FTC/TAF (1 started vortioxetine 5 mg once a day at day 18 due to depression, 1 started on demand lorazepam 1 mg at day 26 due to insomnia, and 1 started bromazepam 1.5 mg twice a day at day 15 due to anxiety). Nobody had to start or intensify their lipid-lowering therapy after switching to DRV/COBI/FTC/TAF.

Weight and the CD4⁺ cell count remained stable during all follow-up periods (weight change [kg] at week 8 [mean ± SE]: 0.1 ± 0.34, *P* = 1; CD4⁺ cell count change: 36.8 ± 18.5, *P* = .14). Significant increases in total cholesterol (before switching [mean ± SE]: 181.2 ± 3.5 mg/dL; week 4 after switching: 200.7 ± 4.2 mg/dL; week 8 after switching: 203.8 ± 4 mg/dL; *P* < .001 [changes from baseline to week 8]), low-density lipoprotein cholesterol (before switching: 109.4 ± 2.7 mg/dL; week 4 after switching: 124.2 ± 3.6 mg/dL; week 8 after switching: 125.4 ± 3.3 mg/dL; *P* < .001 [changes from baseline to week 8]), and triglycerides (before switching: 132.9 ± 10.5 mg/dL; week 4 after switching: 160.9 ± 10.5 mg/dL; week 8 after switching: 157.8 ± 9.6 mg/dL; *P* = .021 [changes from baseline to week 8]) were observed. Levels of HDL cholesterol remained stable during follow-up (before switching [mean ± SE]: 47.1 ± 1.5 mg/dL; week 4 after switching: 47.4 ± 1.5 mg/dL; week 8 after switching: 47.4 ± 1.4 mg/dL; *P* = 1 [changes from baseline to week 8]).

DISCUSSION

The DETOX trial demonstrated that switching DTG/3TC/ABC to DRV/COBI/FTC/TAF, in PWH describing poor quality of sleep without insomnia complaints, was associated with better sleep quality. Specifically, we observed a significant reduction in moderate to severe symptoms in the following sleep components: subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, and daytime dysfunction. A reduction, without achieving statistical significance but of a magnitude

clinically relevant, was also observed in the use of medication for sleep component. In addition, we also detected significant improvements in self-reported mood and neuropsychiatric symptomatology.

Our results reinforced the association between the use of DTG and the presence of sleep disturbances and insomnia seen by Hill et al [7] in their meta-analysis of DTG phase 3 clinical trials. In PWH reporting insomnia and neuropsychiatric adverse events, we confirmed the partial reversibility of those adverse events observed in several cohorts and in the DREAM trial after switching DTG/3TC/ABC to another regimen [2–6, 8]. In addition, in people without insomnia, we show for the first time that switching DTG/3TC/ABC to another ART (DRV/COBI/FTC/TAF) was associated with a reduction in sleep disturbances, with an improvement in the quality of sleep.

Our study is significant because it is the first clinical trial designed to evaluate subclinical ART-related neurotoxicity that provides benefits in the CNS-related subclinical symptomatology after switching from a higher neurotoxic regimen to a lower neurotoxic regimen. Previous clinical trials, such as the strategy-nucleoside reverse-transcriptase inhibitor [17] or the GS-US-380-1844 [18], show improvements in self-reported neuropsychiatric symptoms after switching from regimens, including neurotoxic drugs (efavirenz [EFV]/FTC/tenofovir disoproxil fumarate [TDF] or DTG/3TC/ABC) to a lower neurotoxic regimen (EVG/COBI/FTC/TDF or bictegravir/FTC/TAF). The main findings of our study is that all of our participants had subclinical neurotoxicity (sleep disturbances) but not clinical neurotoxicity (insomnia).

Based on previous evidence, some HIV clinical guidelines recommend a switch to neurotoxic drugs (EFV and DTG) in PWH who complain of neuropsychiatric adverse events, but not in PWH who report subclinical CNS disturbances, such as poor quality of sleep, due to a lack of evidence [19,20]. We believe our study adds new evidence that would lead to changes in clinical guideline recommendations about the role of neurotoxic ART in PWH reporting subclinical CNS disturbances.

In our study, all of the participants received DTG/3TC/ABC and switched all the regimens. Therefore, we cannot determine whether the observed clinical and subclinical improvements were due to discontinuation of DTG, 3TC/ABC, or both. Considering that 3TC/ABC has demonstrated a worse neurotoxic profile in vitro than FTC/TDF [21], and in some studies this has been identified as an independent risk factor for DTG-based ART discontinuation [3], it is likely that the benefits observed in our study were the result of switching all of the regimens and not only DTG.

Chronic sleep abnormalities are risk factors for mood disorders and cognitive complaints, whereas disturbed sleep seems to be a key symptom of mental disturbances [22]. Therefore, due to the bidirectional flow between sleep and psychiatric disorders, we cannot establish whether switching from DTG/3TC/

ABC to DRV/COBI/FTC/TAF has a direct impact on sleep, mood, or neuropsychiatric symptoms. The fact that sleep disturbances improved faster than mood disturbances after switching ART could suggest a direct effect on sleep.

In concordance with previous reports [3, 5, 8], we observed significant improvements but not complete reversibility of all the neuropsychiatric symptoms detected. This could be explained due to a relatively short period of observation (8 weeks) or due to the possibility that some of these disturbances, which are common among PWH and in the general population, could be unrelated to the medications; however, the chance of continued neurotoxicity from the new regimen cannot be completely ruled out. Another potential explanation could be that part of DTG/3TC/ABC-related neurotoxicity was irreversible. It is unfortunate that the current evidence is unable to confirm or reject this possibility.

No virologic failures occurred in the study after switching to DRV/COBI/FTC/TAF, and only 1 participant had to discontinue the study due to adverse events. Our clinical trial is the first that has evaluated the efficacy and safety of switching from an integrase inhibitor-based ART to DRV/COBI/FTC/TAF. The sample size of our study does not allow us to draw definitive conclusions about efficacy or safety; however, it seems that switching from DTG/3TC/ABC to DRV/COBI/FTC/TAF could be effective and safe.

Our study has important limitations. First, accrual was not completed. We believe this had no influence on our results because the post hoc power calculated for our study to demonstrate differences in score changes between study arms was 99.8%. Second, the study had an open-label design. We cannot exclude the possibility that some improvements in sleep quality were due to a placebo effect resulting from a positive expectation of the switch. However, this seems unlikely considering that participants were not reporting insomnia when entering the trial. Third, the study had a shorter follow-up than previous studies evaluating ART-related neurotoxicity. We do not know the long-term evolution of symptomatic changes observed after switching to DRV/COBI/FTC/TAF, and, based on the results of studies with a similar design but with a larger follow up [8, 16–18], we do not expect long-term changes of tendency in symptomatic results.

CONCLUSIONS

In conclusion, we observed that PWH not complaining of insomnia could improve their quality of sleep, mood, and other neuropsychiatric disturbances after switching from DTG/3TC/ABC to DRV/COBI/FTC/TAF. These results suggest a potential benefit of switching regimens with a documented neurotoxic profile, such as DTG/3TC/ABC, to other regimens with a safer neurotoxic profile, such as DRV/COBI/FTC/TAF, even in PWH not complaining of neuropsychiatric disorders or

adverse events. Our findings may be helpful for establishing clinical recommendations about the management of subclinical neurotoxicity in PWH.

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.

Acknowledgments

We thank all participants and families who participated in this study, all the clinical and research staff from the participating institutions, the members of Fundación SEIMC-GESIDA involved in the study, and the statistician team of Hospital La Paz Institute for Health Research (IDIPAZ).

Financial support. This work was funded by an unrestricted grant from Janssen Cilag S.A (Spain).

Potential conflicts of interest. A. C.-U., J. T. G., S. d. L. F. M., M. N. M., A. P. M., R. M., M. G., G. C. T., A. D. d. S., J. S. M., D. R. C., C. B. A., J. I. B. S., and I. P.-V. 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.

References

- Cailhol J, Rouyer C, Alloui C, Jeantils V. Dolutegravir and neuropsychiatric adverse events: a continuing debate. *AIDS* 2017; 31:2023–4. <https://doi.org/10.1097/QAD.0000000000001596>
- Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. *AIDS* 2017; 31:1853–8. <https://doi.org/10.1097/QAD.0000000000001590>
- Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med* 2017; 18:56–63. <https://doi.org/10.1111/hiv.12468>
- Peñafliel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother* 2017; 72:1752–9. <https://doi.org/10.1093/jac/dkx053>
- Libre JM, Montoliu A, Miró JM, et al. Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. *HIV Med* 2019; 20:237–47. <https://doi.org/10.1111/hiv.12710>
- Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. *J Antimicrob Chemother* 2019; 74:754–60. <https://doi.org/10.1093/jac/dky497>
- Hill AM, Mitchell N, Hughes S, Pozniak AL. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials. *Curr Opin HIV AIDS* 2018; 13:102–11. <https://doi.org/10.1097/COH.0000000000000445>
- Pérez-Valero I, Cabello A, Ryan P, et al. Randomized trial evaluating the neurotoxicity of dolutegravir/abacavir/lamivudine and its reversibility after switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide: GESIDA 9016. *Open Forum Infect Dis* 2020; 7:ofaa482. <https://doi.org/10.1093/ofid/ofaa482>
- Chen L, Al-Harhi L, Hu XT. Triumeq increases excitability of pyramidal neurons in the medial prefrontal cortex by facilitating voltage-gated Ca²⁺ channel function. *Front Pharmacol* 2021; 11:617149. <https://doi.org/10.3389/fphar.2020.617149>
- Borghetti A, Calcagno A, Lombardi F, et al. SLC22A2 variants and dolutegravir levels correlate with psychiatric symptoms in persons with HIV. *J Antimicrob Chemother* 2019; 74:1035–43. <https://doi.org/10.1093/jac/dky508>
- Calcagno A, Moltó J, Borghetti A, et al. Older age is associated with higher dolutegravir exposure in plasma and cerebrospinal fluid of people living with HIV. *Clin Pharmacokinet* 2021; 60:103–9. <https://doi.org/10.1007/s40262-020-00916-9>
- U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf. Accessed 10 June 2021.
- Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry* 2003; 25:277–83. [https://doi.org/10.1016/S0163-8343\(03\)00043-4](https://doi.org/10.1016/S0163-8343(03)00043-4)
- Tomfohr LM, Schweizer CA, Dimsdale JE, Loredó JS. Psychometric characteristics of the Pittsburgh sleep quality index in English speaking non-Hispanic whites and English and Spanish speaking Hispanics of Mexican descent. *J Clin Sleep Med* 2013; 9:61–6. <https://doi.org/10.5664/jcsm.2342>
- Robertson K, Bayon C, Molina JM, et al. Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in western Europe and Canada. *AIDS Care* 2014; 26:1555–61. <https://doi.org/10.1080/09540121.2014.936813>
- Waters L, Fisher M, Winston A, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS* 2011; 25:65–71. <https://doi.org/10.1097/QAD.0b013e328341685b>
- Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority clinical trial. *Lancet Infect Dis* 2014; 14:590–9. [https://doi.org/10.1016/S1473-3099\(14\)70796-0](https://doi.org/10.1016/S1473-3099(14)70796-0)
- Wohl D, Clarke A, Maggiolo F, et al. Patients-reported symptoms over 48 weeks among participants in randomized, double-blind, phase III non-inferiority trials of adults with HIV on co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus co-formulated abacavir, dolutegravir, and lamivudine. *Patient* 2018; 11:561–73. <https://doi.org/10.1007/s40271-018-0322-8>
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf>. Accessed 10 June 2021.
- Panel de expertos de GESIDA y Plan Nacional sobre el SIDA. [Documento de consenso de GESIDA/Plan Nacional sobre el SIDA respect al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. GESIDA 2020.] Available at: https://gesida-seimc.org/wp-content/uploads/2020/07/TAR_GUIA_GESIDA_2020_COMPLETA_Julio.pdf. Accessed 10 June 2021.
- Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *J Neurovirol* 2012; 18:388–99. <https://doi.org/10.1007/s13365-012-0120-3>
- Hombali A, Seow E, Yuan Q, et al. Prevalence and correlates of sleep disorder symptoms in psychiatric disorders. *Psychiatry Res* 2019; 279:116–22. <https://doi.org/10.1016/j.psychres.2018.07.009>