

Effect of Dolutegravir compared to Darunavir/Cobicistat, both with Tenofovir Disoproxil Fumarate/Emtricitabine, On the severity of neuropsychiatric effects at 24 weeks of treatment in people living with HIV and baseline neuropsychiatric disorders with no prior antiretroviral therapy experience (MORFEO)

José Antonio Mata-Marín

Hospital de Infectología "Dr Daniel Méndez Hernández" National Medical Center "La Raza", Instituto Mexicano del Seguro Social

Ana Luz Cano-Díaz

ana.knodiaz@gmail.com

Hospital de Infectología "Dr Daniel Méndez Hernández" National Medical Center "La Raza", Instituto Mexicano del Seguro Social

Emily Itzel Pecero-García

Hospital de Infectología "Dr Daniel Méndez Hernández" National Medical Center "La Raza", Instituto Mexicano del Seguro Social

Mara Soraya Rodríguez-Evaristo

Hospital de Infectología "Dr Daniel Méndez Hernández" National Medical Center "La Raza", Instituto Mexicano del Seguro Social

Paola Edith Padilla-Noguera

Universidad Nacional Autónoma de México

Mitzi Daniela Ramírez-Ramírez

Universidad Nacional Autónoma de México

Marco Antonio Cruz-León

Universidad Nacional Autónoma de México

Diana Martínez-López

Universidad Nacional Autónoma de México

Ericka Nelly Pompa-Mera

Hospital de Infectología "Dr Daniel Méndez Hernández" National Medical Center "La Raza", Instituto Mexicano del Seguro Social

Jesús Enrique Gaytán-Martínez

Hospital de Infectología “Dr Daniel Méndez Hernández” National Medical Center “La Raza”, Instituto Mexicano del Seguro Social

Research Article

Keywords: Adverse events, psychiatric safety, virological efficacy, mental health disorders in PLWH.

Posted Date: October 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11169472/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Neuropsychiatric adverse events (NPAEs) associated with dolutegravir (DTG) represent a challenge for clinical retention in people living with HIV (PWH), particularly among those with pre-existing mental health conditions. We aimed to compare the psychiatric safety, tolerability, and virological efficacy of DTG versus darunavir/cobicistat (DRV/c), both combined with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), in treatment-naïve adults with baseline neuropsychiatric vulnerabilities.

Methods

MORFEO was a phase IV, randomized, open-label, active-controlled trial conducted in Mexico. Naïve adult males presenting with baseline vulnerabilities across standardized scales (ISI, PHQ-9, HADS, PSQI) were assigned (1:1) to DTG vs DRV/c + TDF/FTC for 24 weeks. Longitudinal psychometric trajectories, virological suppression (RNA HIV-1 < 50 copies/mL), safety, and predictors of discontinuation were evaluated.

Results

Fifty-three male participants were randomized. Allocation to DTG (RR = 2.23, 95% CI: 1.62–3.07; $P = 0.023$) and severe baseline insomnia (ISI ≥ 15 : RR = 9.6, 95% CI: 1.04–90.1; $P = 0.031$) independently predicted treatment discontinuation. Intragroup repeated-measures analyses showed that DRV/c conferred broad, sustained stabilization across all psychometric domains, including depressive symptoms (HADS-D: $P < 0.001$), sleep duration ($P = 0.031$), and daytime dysfunction ($P = 0.044$). Conversely, the DTG arm failed to achieve significant improvements in HADS-D, sleep duration, or daytime dysfunction.

Conclusions

In treatment-naïve PWH with baseline neuropsychiatric vulnerabilities, both regimens achieved high, comparable 24-week virological suppression and reduced general distress. However, DRV/c showed a more uniform longitudinal stabilization across depressive symptoms, sleep duration, and daytime functioning, alongside fewer discontinuations than DTG. Baseline mental health screening is essential to tailor initial ART and safeguard treatment retention.

Trial registration

Background

The management of human immunodeficiency virus (HIV) infection has undergone a paradigmatic evolution with the advent of combination antiretroviral therapy (ART), achieving sustained viral suppression and a dramatic improvement in life expectancy (1). In contemporary international guidelines, integrase strand transfer inhibitors (INSTIs), such as dolutegravir (DTG), have established themselves as first-line components due to their high genetic barrier, rapid plasma viral load clearance, and a favorable drug interaction profile (2). However, the widespread adoption of INSTI-based regimens in real-world clinical practice has revealed an unforeseen incidence of neuropsychiatric adverse events (NPAEs), which substantially compromise the quality of life and treatment adherence in people living with HIV (PLWH) (3). These effects frequently include insomnia, anxiety, generalized depression and, critically alarming, suicidal ideation or the exacerbation of pre-existing emotional labilities (4). The variability reported in the scientific literature suggests that the real-world impact of these neuropsychiatric manifestations differs significantly between controlled clinical trials and real-world observational populations (5).

Several cohort and meta-analyses studies have described the central nervous system toxicity associated with DTG compared to other therapeutic classes. In this context, INSTIs exhibit variable penetration into brain tissue and can induce direct neurotoxicity mechanisms via mitochondrial dysfunction and oxidative stress in astrocytic models (6). Furthermore, clinical investigations have emphasized that the discontinuation of DTG-based regimens due to central nervous system toxicity is significantly higher than originally reported in drug registration trials, particularly among female patients and older adults (7, 8, 9). For their part, Mata-Marín and cols. (10) have evidenced the high prevalence of underlying mental health disorders in PLWH prior to initiating antiretroviral therapy in the Latin American epidemiological context. These observations raise the imperative need to meticulously evaluate each patient's baseline mental health profile to optimize initial regimen selection (11).

In light of the concerns surrounding INSTI use, regimens based on boosted protease inhibitors (PI/b), such as darunavir with cobicistat (DRV/c) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) as Doravirine (DOR), offer a robust therapeutic alternative in complex psychiatric scenarios (11). Unlike INSTIs, DRV/c or DOR/Lamivudine/Tenofovir (DOR/3TC/TDF) regimens show distinct biological interactions that rarely induce sleep-wake cycle disorders or acute mood destabilization (12). Nonetheless, the concurrent use of nucleoside reverse transcriptase inhibitors, such as the fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), introduces additional variables due to the potential risk of renal tubular toxicity and alterations in bone mineral density (13). Despite these well-documented metabolic effects, the cognitive and psychic stability conferred by the DRV/c regimen may outweigh peripheral risks in selected populations with pre-existing baseline psychiatric symptomatology (14).

Clinical decision-making in antiretroviral therapy-naïve patients who already present with prior neuropsychiatric symptomatology remains a critical challenge that is rarely addressed in large-scale randomized clinical trials. Current scientific literature highlights a clear dichotomy between virological efficacy and comprehensive patient tolerability, emphasizing the urgency of controlled and targeted clinical studies in this vulnerable population (15). Accurately understanding the underlying pathophysiological mechanisms, early discontinuation rates, and the actual need for concomitant pharmacological interventions—such as antidepressants or anxiolytics—is indispensable to guide future therapeutic guidelines (16, 17). The rigorous analysis of standardized clinical scales for depression, anxiety, and insomnia at 12 and 24 weeks provides an objective scientific foundation to delineate the true impact of these antiretroviral strategies on the patient's mental health (18). In this study, we compared the psychiatric safety, tolerability, and virological efficacy of DTG versus darunavir/cobicistat (DRV/c), both combined with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), in treatment-naïve adults with baseline neuropsychiatric symptomatology.

Material and methods

Study design and patients

The MORFEO study was designed as a phase IV, open-label, randomized, parallel-group, active-controlled, monocentric clinical trial conducted at the HIV Clinic of the Hospital de Infectología, Centro Médico Nacional "La Raza," Instituto Mexicano del Seguro Social (IMSS) in Mexico City, Mexico. The trial aimed to evaluate longitudinal changes in standardized neuropsychiatric scales over a 24-week therapeutic period.

Eligible participants consisted of adult patients (≥ 18 years of age) with documented human immunodeficiency virus type 1 (HIV-1) infection who were completely naïve to combination antiretroviral therapy (cART). To ensure adequate organ function and baseline physical safety prior to exposure, an estimated glomerular filtration rate (eGFR) $> 60 \text{ mL/min}$ was strictly required. Candidate patients had to present clear evidence of baseline neuropsychiatric vulnerabilities, verified by specific scoring thresholds across a comprehensive battery of validated psychometric instruments. Patients meeting at least two of the following criteria at the screening phase included: an Insomnia Severity Index (ISI) score above 8; a Patient Health Questionnaire-9 (PHQ-9) score above 9; a Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) score above 11; a Hospital Anxiety and Depression Scale-Depression subscale (HADS-D) score above 11; or Pittsburgh Sleep Quality Index (PSQI) score above 5.

Patients with any of the following criteria at the screening phase were excluded from enrollment: active use of antidepressants or anxiolytic pharmacotherapy prior to ART initiation; known hypersensitivity or formal medical contraindications to second-generation INSTIs or boosted PIs; active coinfection with the hepatitis C virus (HCV); or the baseline documentation of major resistance mutations to any component of the selected antiretroviral regimens.

Participants were withdrawn prior to the final analysis if they formally withdrew their informed consent, lost their institutional social security rights, experienced severe drug-related toxicities necessitating treatment suspension, or developed active tuberculosis or other acute opportunistic infections requiring modification of the background ART.

Randomization

Participants were assigned to one of the two active therapeutic arms using a simple, unrestricted randomization paradigm (1:1 ratio). Treatment assignment was performed utilizing an automated, secure digital allocation platform (MEDSHARING: Randomizer for Clinical Trials) to ensure strict allocation concealment. Due to the open-label nature of the trial, necessitated by the distinct administrative multi-tablet presentations within the institutional formulary, neither the investigators nor the patients were masked to the assigned drug regimen after allocation.

Procedures

At the baseline visit (week 0), comprehensive demographic data, clinical history, smoking and alcohol habits, and recreational drug use histories were systematically documented. Standardized laboratory assessments were performed, including the quantification of plasma HIV-1 RNA viral load by real-time reverse transcription polymerase chain reaction (RT-qPCR), absolute CD4 + T-lymphocyte counts via flow cytometry, and baseline biochemical profiles. Prior to the administration of the first dose of ART, all participants underwent a comprehensive, mandatory baseline evaluation by the specialized hospital psychiatry service. Baseline neuropsychiatric vulnerabilities included: severe depressive symptoms (HADS D ≥ 11 or PHQ-9 ≥ 15 points), anxiety (HADS A ≥ 11 points), suicidality (answer 9 of PHQ-9 ≥ 1 point), and poor sleep quality measured by PSQI ≥ 8 points.

Patients randomized to the experimental arm received a second-generation INSTI-based regimen consisting of dolutegravir (50\ :mg once daily) co-administered with a fixed-dose combination of tenofovir disoproxil fumarate (300\ :mg) and emtricitabine (200\ :mg) (DTG + TDF/FTC). Patients randomized to the active control group received a boosted protease inhibitor-based regimen consisting of darunavir (800\ :mg) co-formulated with cobicistat (150\ :mg) once daily, combined with the same fixed-dose nucleoside backbone of tenofovir disoproxil fumarate and emtricitabine (DRV/c + TDF/FTC). Both regimens utilized drugs provided directly through the standard institutional formulary of the IMSS.

Longitudinal follow-up was performed at weeks 4 and 12 post-initiation. At each clinical intersection, patients completed a standardized battery of supervised, self-reported psychometric questionnaires to monitor the evolution of neuropsychiatric symptoms:

1. **Insomnia Severity Index (ISI)**: A 7-item instrument insomnia scored from 0 to 4 per item (range 0–28) measuring the severity of sleep-onset, maintenance, and early awakening difficulties.
2. **Patient Health Questionnaire-9 (PHQ-9)**: A 9-item tool reflecting the DSM-5 diagnostic criteria for major depressive disorder, graded from 0 to 3 per item to quantify depressive symptom severity.
3. **Hospital Anxiety and Depression Scale (HADS)**: A 14-item scale divided into two distinct 7-item subscales (HADS-A and HADS-D) scored from 0 to 3 per item to specifically detect clinically significant states of anxiety and depression in somatically ill patients.
4. **Pittsburgh Sleep Quality Index (PSQI)**: A 19-item questionnaire evaluating seven clinical domains of sleep components over a 1-month recall period, generating a global score where ≥ 8 points represented severe sleep disturbances.

Adherence, development of clinical adverse events, and changes in concurrent medication—with particular focus on the emergent need for exogenous psychotropic drugs such as antidepressants or anxiolytics—were systematically captured. Any participant exhibiting a substantial clinical worsening on the psychometric scales or reporting significant distress was immediately referred for prioritized psychiatric intervention. In the event of intolerable or severe central nervous system toxicities, an immediate modification of the antiretroviral regimen was executed as a safety mandate.

Outcomes

The primary objective of the study was to evaluate the longitudinal change in standardized neuropsychiatric severity scale scores (specifically ISI, PHQ-9, HADS-A, HADS-D, and PSQI) from baseline to week 12 and 24 of continuous antiretroviral therapy.

Secondary clinical outcomes included:

- The absolute proportion of patients requiring a treatment modification or discontinuation due to drug-related toxicities or virological criteria within 24 weeks.
- The identification of independent baseline demographic, behavioral, or viro-immunological risk factors associated with significant changes in neuropsychiatric scale scores.
- The incidence of patients developing severe, clinically meaningful categories of insomnia ($\text{ISI} \geq 15$), depression ($\text{PHQ-9} \geq 15$), or pathological anxiety/depression (HADS subscales ≥ 11) at the end of follow-up.
- Virological efficacy, defined as the proportion of patients achieving plasma HIV-1 RNA < 50 copies/mL at week 12 and 24, alongside immunologic recovery measured by the absolute gain in CD4 + T-cell counts.

Statistical analysis

The total sample size was calculated using the standard formula for comparing two parallel samples of equal size. Assuming an alpha error of 0.05, a statistical power of 80% ($\beta = 0.20$), and a prespecified 20%

attrition rate during the short-term follow-up period, the initial required sample size of 80 randomized individuals.

All statistical procedures were performed using IBM SPSS Statistics software version 20.0. Descriptive analytics involved calculating percentages and absolute frequencies for categorical data. Quantitative variables will first undergo formal normality testing utilizing the Kolmogorov-Smirnov test. Normally distributed continuous parameters were expressed as means with standard deviations ($\pm$ SD), whereas non-normally distributed metrics were summarized as medians with interquartile ranges (IQRs).

Intragroup longitudinal analysis comparing psychometric score changes from baseline to weeks 4, 12, and 24 were conducted using the paired Student's *t*-test for parametric data or the Wilcoxon signed-rank test for non-parametric structures. Intergroup comparisons between the DTG + TDF/FTC and DRV/c + TDF/FTC arms regarding quantitative psychometric scores were evaluated via the independent Student's *T*-test or the Mann-Whitney *U*-test, as appropriate. Proportions of clinical outcomes and categorical scale conversions were analyzed using the Chi-squared test or Fisher's exact test. Predictors of antiretroviral discontinuation due to neuropsychiatric adverse events were evaluated using univariate cross-tabulations. Relative risks (RRs) and corresponding 95% confidence intervals (95% CIs) were estimated. Between-group categorical comparisons were assessed using Fisher's exact test to accommodate sparse data distributions. Due to the low overall number of discontinuation events ($n = 6$) and sparse-data separation across treatment arms, standard multivariable logistic regression via maximum likelihood was precluded to prevent small-sample bias, non-convergence, and inflated standard errors. Statistical significance was established at a two-tailed $P < 0.05$.

Although the initial protocol-defined sample size target was 80 participants (40 per arm), the trial was prematurely discontinued after randomizing 53 patients (DTG + TDF/FTC, $n = 27$; DRV/c + TDF/FTC, $n = 26$). Recruitment challenges arose from the stringent baseline psychometric threshold requirements and patient reluctance to initiate multi-tablet regimens given the widespread availability of single-tablet regimens (STRs) in clinical practice. Furthermore, enrollment was closed early in consideration of participant safety following an imbalance in premature treatment discontinuations driven by emergent neuropsychiatric adverse events within the dolutegravir arm. With an effective sample size of 53 individuals, the post-hoc achieved statistical power to detect moderate-to-large longitudinal effect across the primary psychometric endpoints was approximately 62%–65% at a two-tailed alpha of 0.05.

Results

Participants characteristics

A total of **65** treatment-naïve adult patients living with HIV-1 were screened, and **53** were formally randomized and allocated to either the DTG + TDF/FTC arm, $n = 27$ (50.9%) or the DRV/c + TDF/FTC arm, $n = 26$ (49.1%). Baseline demographic, behavioral, and clinical characteristics were well-balanced across both therapeutic groups, with no statistically significant differences observed (all $P > 0.05$).

The overall study population exhibited a mean age of 27 (± 6) years old, and biological sex at birth was male in all the participants.

At enrollment, the median baseline CD4 + T-lymphocyte count was 303 (IQR 167–404) cells/ μ L, and the median plasma HIV-1 RNA viral load was 31470 (IQR 8280-107987). According to the CDC clinical staging classification, 21 (39.6%) patients presented at Stage 1, 24 (45.2%) at Stage 2, and 8 (15%) at Stage 3.

Per inclusion criteria, all enrolled participants demonstrated baseline neuropsychiatric vulnerabilities, fulfilling at least two standardized psychometric scale entry thresholds. The mean baseline scores for the entire cohort were 12 (± 3) for the Insomnia Severity Index (ISI), 13 (± 5) for the Patient Health Questionnaire-9 (PHQ-9), 10 (± 3) for the HADS-A, 8 (± 3) for the HADS-D and 10 (± 3) for PSQI. No significant baseline intergroup imbalances were detected regarding specific neuropsychiatric indicators or psychiatric comorbidities ($P > 0.05$) (Table 1).

Table 1
Baseline Characteristics (N = 53)

Variable	DRV/c + TDF/FTC n = 26	DTG + TDF/FTC n = 27	P value
Age (years); mean (SD)	28.6 (7.2)	26.1 (4.6)	0.288
Ethnicity; n (%)			
Latin American	26 (100%)	27 (100%)	
Weight (kg); median (IQR)	66.0 (59.2–71.3)	62.9 (57.4–69.9)	0.135
Total cholesterol (mg/dL); median (IQR)	137.0 (127.0-182.5)	125.0 (111.0-147.0)	0.028
HDL-cholesterol (mg/dL); median (IQR)	39.0 (32.5–45.5)	38.0 (28.0–43.0)	0.193
Tryglicerides (mg/dL); median (IQR)	117.5 (62.5)	132.5 (88.9)	0.965
Glucose (mg/dL); median (IQR)	87.0 (80.0-90.5)	87.0 (82.0–90.0)	0.986
Creatinine (mg/dL); median (IQR)	0.89 (0.77–0.94)	0.87 (0.79–0.96)	0.915
AST (IU/dL); median (IQR)	29.0 (24.5–39.0)	27.0 (23.0–40.0)	0.922
ALT (IU/dL); mean (SD)	31.5 (14.2)	35.7 (29.2)	0.557
GGT (IU/dL); mean (SD)	32.1 (26.7)	29.8 (25.6)	0.932
CD4 + cells count; median (IQR)	297.0 (164.5-406.2)	303.0 (165.0-419.0)	0.838
HIV-1 RNA viral load (copies/mL); median (IQR)	63,543 (18,589 – 117,911)	23,417 (4,756 – 98,301)	0.130
Neuropsychiatric comorbidities			
HADS A; median (IQR)	11.0 (6.7–13.0)	11 (9.0–13.0)	0.610
HADS D; median (IQR)	9.0 (7.2–11.0)	8.0 (6.0–10.0)	0.124
ISI; median (IQR)	12.0 (10.0–17.0)	12.0 (9.0–16.0)	0.377
PHQ-9; median (IQR)	13.5 (8.0-16.2)	14.0 (9.0–18.0)	0.515
IQR: interquartile ranges; SD: standard deviation; kg: kilograms; mg: milligrams; IU: international units; dL: deciliter; mL: milliliter; HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; DRV/c: darunavir/cobicistat; DTG: dolutegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine. HIV: human immunodeficiency virus; RNA: viral load.			
*Mann Whitney U-test			
**Student T test			
***Chi Square test			

Variable	DRV/c + TDF/FTC n = 26	DTG + TDF/FTC n = 27	P value
Suicidality (PHQ-9); n (%)	9 (34%)	15 (55%)	0.170
PSQI; median (IQR)	10.5 (8.0–13.0)	10.0 (8.0–13.0)	0.971
Sleep quality; median (IQR)	2 (1–2)	1 (1–2)	0.575
Sleep latency; median (IQR)	1 (1–2)	2 (1–3)	0.919
Sleep duration; median (IQR)	1 (1–2)	2 (1–2)	0.196
Habitual sleep efficiency; median (IQR)	0 (0–2)	0 (0–1)	0.866
Sleep disturbance; median (IQR)	2 (1–2)	2 (1–2)	0.866
Use of sleeping medication; median (IQR)	0 (0–1.25)	0 (0–1)	0.949
Daytime dysfunction; median (IQR)	2 (1–2)	2 (1–2)	0.666
IQR: interquartile ranges; SD: standard deviation; kg: kilograms; mg: milligrams; IU: international units; dL: deciliter; mL: milliliter; HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; DRV/c: darunavir/cobicistat; DTG: dolutegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine. HIV: human immunodeficiency virus; RNA: viral load.			
*Mann Whitney U-test			
**Student T test			
***Chi Square test			

Virological outcomes

At week 12, the proportion of participants achieving plasma HIV-1 RNA suppression (< 50 copies/mL) was 22/27 (81%) in the DTG + TDF/FTC arm and 14/26 (53%) in the DRV/c + TDF/FTC arm ($P = 0.031$). At the definitive week 24 landmark, virological suppression by *Per* protocol analysis was in 20/21 (95.2%) in the DTG + TDF/FTC arm and 23/25 (92%) in the DRV/c + TDF/FTC arm ($P = 1.0$). Two patients in the DTG arm discontinued prior to week 24: one was lost to follow-up without virological data, and one requested a switch to a single-tablet regimen.

Confirmed virological failure (defined as two consecutive HIV-1 RNA measurements ≥ 50 copies/mL) occurred in 1/27 (3.7%) patients in the DTG group and 2/26 (7.6%) patients in the DRV/c group within 24 weeks. Among those meeting virological failure criteria, emergent resistance mutations were not detected via genotypic testing.

Immunologic recovery, at week 12, CD4 + cells count in DTG + TDF/FTC group the median of CD4 + cells count was 613 (IQR 370–787) cells/ μ L and in the DRV/c + TDF/FTC group was 439 (IQR 332–666) (P = 0.206); and median CD4 + cells count at 24 weeks for DTG was 603 (IQR 504–729) cells/ μ L vs. 533 (IQR 383–810) cells/ μ L in the DRV/c group (P = 0.565)

Neuropsychiatric Outcomes

Longitudinal cross-sectional comparisons between the two treatment groups revealed similar median scores across all standardized psychometric instruments at weeks 4, 12, and 24 (all P > 0.05) (Table 2).

Table 2
Comparison between both antiretroviral regimen at 24 weeks

Variable	DRV/c + TDF/FTC n = 25	DTG + TDF/FTC n = 21	P value*
Weight (kg); median (IQR)	69.7 (58.5–75.1)	63.1 (54.1–71.4)	0.119
Total cholesterol (mg/dL); median (IQR)	154.0 (134.0-184.9)	138.0 (120.0-155.5)	0.165
HDL-cholesterol (mg/dL); median (IQR)	41.0 (33.0–46.0)	35.0 (32.2–42.7)	0.304
Tryglicerides (mg/dL); mean (±SD)**	130.7 (97.0)	141.0 (114.3)	0.418
Glucose (mg/dL); mean (±SD)**	90.0 (14.1)	86.8 (5.7)	0.617
Creatinine (mg/dL); median (IQR)	0.96 (0.85-1.0)	1.0 (0.96–1.1)	0.126
AST (IU/dL); median (IQR)	24.0 (20.0–27.0)	31.0 (28.0-42.5)	0.008
ALT (IU/dL); mean (±SD)**	32.3 (30.5)	43.5 (29.4)	0.032
GGT (IU/dL); mean (±SD)**	37.4 (40.0)	28.6 (20.7)	0.509
CD4 + cells count; median (IQR)	533 (383–810)	603 (504–729)	0.565
HIV-1 RNA viral load < 50 copies; n (%)***	23 (92%)	20 (95.2%)	1.0
HADS A; median (IQR)	5.0 (1.5–10.0)	8 (3.5–10.5)	0.294
HADS D; median (IQR)	3.0 (1.0–6.0)	4.0 (1.5-9.0)	0.346
ISI; median (IQR)	5.0 (2.5–9.5)	7 (2.0–12.0)	0.228
PHQ-9; median (IQR)	3.0 (2.0–7.0)	5.0 (2.0-12.5)	0.259
PSQI; median (IQR)	5.5 (5.0–8.0)	6.0 (4.5–10.0)	0.390
Sleep quality; median (IQR)	1 (0–1)	1 (1–1)	0.146
Sleep latency; median (IQR)	1 (0–2)	1 (0–2)	0.905
IQR: interquartile ranges; SD: standard deviation; kg: kilograms; mg: milligrams; IU: international units; dL: deciliter; mL: milliliter; HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; DRV/c: darunavir/cobicistat; DTG: dolutegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine. HIV: human immunodeficiency virus; RNA: viral load.			
*Mann Whitney U-test			
**Student T test			
***Chi Square test			

Variable	DRV/c + TDF/FTC n = 25	DTG + TDF/FTC n = 21	P value*
Sleep duration; median (IQR)	1 (0–2)	1 (1–2)	0.165
Habitual sleep efficiency; median (IQR)	0 (0–1)	0 (0–1)	0.671
Sleep disturbance; median (IQR)	1 (1–1)	1 (1–1)	0.577
Use of sleeping medication; median (IQR)	0 (0–2)	0 (0–0.7)	0.263
Daytime dysfunction; median (IQR)	1 (1–2)	1 (1–2)	0.933
IQR: interquartile ranges; SD: standard deviation; kg: kilograms; mg: milligrams; IU: international units; dL: deciliter; mL: milliliter; HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; DRV/c: darunavir/cobicistat; DTG: dolutegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine. HIV: human immunodeficiency virus; RNA: viral load.			
*Mann Whitney U-test			
**Student T test			
***Chi Square test			

Intragroup repeated-measures Friedman analyses demonstrated marked differences in symptom trajectories over the 24-week period:

DRV/c + TDF/FTC: Displayed statistically significant, continuous reductions across almost all neuropsychiatric domains from baseline to week 24, including HADS-A (mean rank: 3.00 to 1.79; $P < 0.001$), HADS-D (3.33 to 1.90; $P < 0.001$), ISI (3.27 to 1.79; $P < 0.001$), PHQ-9 (3.40 to 1.73; $P < 0.001$), and global PSQI (3.40 to 1.96; $P < 0.001$), as well as subjective sleep quality ($P < 0.001$), sleep latency ($p = 0.002$), sleep duration ($P = 0.031$), sleep disturbances ($P < 0.001$), and daytime dysfunction ($P = 0.044$) (Table 3).

Table 3

Evaluation of NPS questionnaires from baseline, 4, 12 and 24 weeks DRV/c + TDF/FTC (N = 53)

Variable	Baseline	4 Weeks	12 Weeks	24 Weeks	P value*
	Mean Rank	Mean Rank	Mean Rank	Mean Rank	
HADS A	3.0	3.04	2.17	1.79	< 0.001
HADS D	3.33	2.63	2.13	1.90	< 0.001
ISI	3.27	2.69	2.25	1.79	< 0.001
PHQ 9	3.40	2.52	2.35	1.73	< 0.001
PSQI	3.40	2.46	2.18	1.96	< 0.001
Sleep quality	3.10	2.63	2.23	2.04	< 0.001
Sleep latency	3.04	2.75	2.13	2.08	0.002
Sleep duration	2.88	2.75	2.19	2.17	0.031
Habitual sleep efficiency	2.44	2.73	2.48	2.35	0.539
Sleep disturbance	3.23	2.52	2.15	2.10	< 0.001
Use of sleeping medication	2.52	2.19	2.62	2.67	0.267
Daytime dysfunction	2.98	2.38	2.33	2.21	0.044
Evaluation of NPS questionnaires from baseline, 4, 12 and 24 weeks DTG + TDF/FTC (N = 53)					
Variable	Baseline	4 Weeks	12 Weeks	24 Weeks	P value*
	Mean Rank	Mean Rank	Mean Rank	Mean Rank	
HADS A	3.19	2.58	2.40	1.83	0.003
HADS D	2.96	2.33	2.58	2.13	0.116
ISI	3.21	2.88	2.10	1.81	< 0.001
PHQ 9	3.25	2.73	2.31	1.71	< 0.001
PSQI	3.08	2.77	2.33	1.81	0.002
Sleep quality	2.70	2.85	2.24	2.22	0.036
Sleep latency	3.02	2.35	2.30	2.33	0.042
Sleep duration	2.74	2.59	2.43	2.24	0.401
HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9.					
*Friedman					

Variable	Baseline	4 Weeks	12 Weeks	24 Weeks	P value*
	Mean Rank	Mean Rank	Mean Rank	Mean Rank	
Habitual sleep efficiency	2.20	2.87	2.61	2.33	0.111
Sleep disturbance	2.93	2.63	2.11	2.33	0.012
Use of sleeping medication	2.59	2.48	2.74	2.20	0.186
Daytime dysfunction	2.78	2.57	2.46	2.2	0.335
HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9.					
*Friedman					

DTG + TDF/FTC: Showed significant improvements over time in HADS-A (mean rank: 3.19 to 1.83; $P=0.003$), ISI (3.21 to 1.81; $P<0.001$), PHQ-9 (3.25 to 1.71; $P<0.001$), and global PSQI (3.08 to 1.81; $P=0.002$), as well as subjective sleep quality ($P=0.0036$), sleep latency ($P=0.042$), and sleep disturbances ($P=0.012$). However, the reduction in depressive symptoms on the HADS-D scale failed to reach statistical significance across 24 weeks in this arm (mean rank: 2.96 to 2.13; $P=0.116$), and sleep duration ($P=0.401$) and daytime dysfunction ($P=0.335$) did not significantly improve (Table 3).

In the risk analysis for study discontinuation/dropout, severe baseline insomnia ($ISI \geq 15$) was identified as a strong predictor of treatment abandonment (Relative Risk [RR] = 9.68, 95% CI: 1.04–90.1; $P=0.031$). In addition, allocation to DTG + TDF/FTC was associated with a significantly higher risk of treatment discontinuation compared to DRV/c + TDF/FTC (RR = 2.23, 95% CI: 1.62–3.07; $P=0.023$). In contrast, baseline severe depressive symptoms, anxiety, suicidal ideation, poor baseline sleep quality, and age ≥ 40 years were not significantly associated with study dropout (Table 4). Owing to the limited absolute number of events and quasi-complete data separation, a multivariable logistic regression model could not achieve stable convergence; thus, univariate associations are reported as exploratory findings.

Table 4
Risk factors for discontinuation at 24 weeks of follow up

Variable	RR	IC95%	P value*
HADS A $\geq$ 11 at baseline	1.76	0.293–10.5	0.678
HADS D $\geq$ 11 at baseline	1.85	0.29–11.5	0.608
ISI $\geq$ 15 at baseline	9.68	1.04–90.1	0.031
PHQ 9 $\geq$ 15 at baseline	1.23	0.22–6.78	1.0
Suicidality baseline	1.23	0.22–6.78	1.0
PSQI $\geq$ 8 at baseline	1.0	0.10–10.2	1.0
DTG-based regimen	2.23	1.62–3.07	0.023
Age $\geq$ 40 years old	1.04	0.98–1.10	1.0
HADS: Hospital Anxiety and Depression Scale (D: depression; A: anxiety); ISI: Insomnia Severity Index; PHQ-9: Patient Health Questionnaire-9; DTG: Dolutegravir.			
*Chi Square Test or Fisher exact Test			

Safety and Tolerability

During early follow-up (week 4), at least one adverse event (AE) was experienced by 81.5% (n = 22) of patients in the DTG arm and 92.3% (n = 24) in the DRV/c arm (Table 5). Gastrointestinal events were more frequent with DRV/c at week 4 (80.8% [n = 21] vs. 44.4% [n = 12]), as were mucocutaneous manifestations (53.8% [n = 14] vs. 18.5% [n = 5]), whereas neurological AEs occurred in 55.6% (n = 15) of DTG-treated patients vs. 46.2% (n = 12) of DRV/c-treated patients. Individual adverse event reporting showed no statistically significant differences between regimens, although abdominal distension tended to be more common with DTG (25.9% [n = 7] vs. 7.6% [n = 2]; $P = 0.059$).

Table 5
Adverse events

Any adverse events	DRV/c + TDF/FTC	DTG + TDF/FTC:
	n = 26	n = 27
	24 (92%)	22 (81%)
Systemic adverse event	8 (30%)	10 (37%)
Neurological adverse event	12 (46%)	15 (55%)
Cardiovascular adverse event	6 (23%)	6 (22%)
Respiratory adverse event	9 (34%)	10 (37%)
Gastrointestinal adverse event	21 (80%)	12 (44%)
Genitourinary adverse event	5 (19%)	2 (7.4%)
Mucocutaneous adverse event	14 (53%)	5 (18%)
Musculoskeletal adverse event	7 (26%)	3 (11%)
DRV/c: darunavir/cobicistat; DTG: dolutegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine.		

Regarding laboratory safety at week 24, median serum creatinine remained stable (1.0 [0.96–1.1] mg/dL in DTG vs. 0.96 [0.85–1.0] mg/dL in DRV/c; $P = 0.126$). Serum lipid fractions and glucose levels showed no between-group differences at 24 weeks ($P > 0.05$). However, transaminase levels were significantly higher in the DTG group at week 24: median AST was 31.0 U/L (IQR 28.0–42.5) vs. 24.0 U/L (20.0–27.0; $P = 0.008$), and mean ALT was 43.4 ± 29.4 U/L vs. 32.3 ± 30.5 U/L ($P = 0.032$) (Table 2).

Discussion

The primary findings of the MORFEO trial offer nuanced insights into how initial antiretroviral selection interacts with pre-existing emotional vulnerabilities in newly diagnosed individuals. In this clinical setting, both therapeutic strategies provided therapeutic benefit, driving noticeable reductions in overall anxiety, insomnia, and depressive severity over 24 weeks. Nevertheless, the longitudinal symptom trajectories unfolded differently between arms. While participants on DRV/c + TDF/FTC experienced a uniform, sustained improvement encompassing depressive symptoms (HADS-D) and restorative sleep parameters (sleep duration and daytime dysfunction), the DTG arm exhibited a more fragmented recovery, failing to demonstrate significant statistical gains in daytime alertness or residual low mood. When combined with the heightened discontinuation risk observed in the DTG group and the profound vulnerability posed by severe baseline insomnia, these results highlight that treating HIV in the context of distress involves delicate trade-offs between rapid virological clearance and holistic psychological well-being.

With respect to secondary outcomes, distinct safety, metabolic, and viro-immunological profiles emerged between the two strategies. While DTG + TDF/FTC demonstrated significantly faster plasma viral load clearance at week 12 compared to DRV/c + TDF/FTC (81.5% vs. 53.8%, $P = 0.031$) virological suppression rates converged by week 24 in the *per protocol* analysis (95.2% vs. 92.0%, $p = 1.0$), with comparable immune reconstitution and zero emergent resistance mutations in both groups. However, systemic and organ-specific tolerability differed markedly. Patients receiving DTG exhibited a higher frequency of neurological adverse events throughout the study (55.6% vs. 46.2% at week 4, and 42% vs. 28% at week 24) and developed significantly higher transaminase elevations at week 24 (AST: median 31.0 vs. 24.0 U/L, $P = 0.008$), ALT: mean 43.5 ± 29 . vs. 32.3 ± 30.5 U/L $P = 0.032$). Conversely, DRV/c was associated with a higher burden of gastrointestinal events, particularly during early treatment (80.8% vs. 44.4% at week 4).

Collectively, these primary and secondary findings delineate a fundamental clinical trade-off in the management of psychiatric-vulnerable, treatment-naïve individuals. While DTG delivers rapid early virological clearance, this kinetic advantage is counterbalanced by an increased risk of neurological complaints, transaminase elevations, incomplete resolution of depressive and diurnal sleep disturbances, and a higher risk of premature treatment abandonment. In contrast, darunavir/cobicistat provides robust mid-term virological efficacy and a superior multidimensional psychiatric stabilization across sleep and mood parameters, with its primary clinical drawback confined to manageable, early gastrointestinal adverse effects.

The higher rate of treatment discontinuation observed with DTG ($RR = 2.23$) and the profound vulnerability conferred by severe baseline insomnia ($ISI \geq 15$, $RR = 9.68$) closely mirror real-world European cohort data, where dolutegravir-associated neuropsychiatric adverse events and discontinuations were significantly higher than initially reported in registrational randomized trials (19). Initial clinical trials systematically excluded individuals with active psychiatric symptomatology, masking the true real-world impact of second-generation INSTIs in vulnerable populations. In contrast, observational studies by Hoffmann et al. and de Boer et al. documented elevated rates of insomnia, anxiety, and depression leading to premature DTG discontinuation, particularly when baseline psychiatric factors were unmasked (4). Mechanistically, preclinical and pharmacogenetic evaluations have demonstrated that DTG inhibits organic cation transporter 2 (OCT2/SLC22A2) and induces oxidative stress in central astrocytes, disrupting monoamine neurotransmitter clearance and explaining the persistence of diurnal dysfunction and residual depressive symptoms observed in our DTG cohort (20).

Conversely, the multidimensional psychiatric and sleep stabilization achieved with DRV/c + TDF/FTC aligns with previous interventional switch studies. In the randomized GESIDA 10418 trial, Cabello-Úbeda et al. reported significant improvements in sleep quality (PSQI) and anxiety/depressive symptoms (HADS) after switching suppressed individuals with poor sleep from DTG-based regimens to a boosted darunavir combination (14). Similarly, Mata-Marín et al. demonstrated rapid reversibility of insomnia and mood disturbances when transitioning patients with INSTI-related neuropsychiatric toxicities to DRV/c or doravirine (11). While the double-blind MIND trial in long-term stable tolerators found comparable

psychiatric safety between continuing DTG and switching to BIC/FTC/TAF, MORFEO evaluated treatment-naïve individuals with active baseline distress. In this naïve setting, DRV/c proved protective against mood destabilization, reinforcing observational evidence from Fabbiani et al. regarding the robust clinical durability and favorable central nervous system tolerability of darunavir-based therapies (7, 21).

This study has several limitations that warrant careful consideration. First, the final sample size was restricted to 53 participants rather than the prespecified target of 80, which inevitably constrained the statistical power to detect subtle intergroup differences across secondary endpoints. Several interrelated operational and clinical factors accounted for this premature study termination. The rigorous eligibility requiring patients to fulfill at least two high-severity score thresholds across five distinct psychometric scales prior to starting ART, substantially narrowed the recruitment yield. Additionally, patient hesitancy toward multi-tablet regimens posed a barrier to enrollment and retention, as most treatment-naïve individuals expressed a strong preference for co-formulated STRs. Crucially, the trial was halted early on clinical and safety grounds due to a higher-than-expected rate of premature treatment discontinuations secondary to acute neuropsychiatric adverse events within the DTG-containing arm. While this early termination reflects real-world clinical challenges in managing this vulnerable subgroup, our findings regarding differential discontinuation risks and intragroup trajectory dynamics should be interpreted within this constrained statistical framework and replicated in larger multicenter cohorts. Second, all enrolled participants were biologically male, precluding direct extrapolation of these findings to cisgender or transgender women, who have historically exhibited higher rates of INSTI-related neuropsychiatric intolerance. Third, the open-label design mandated by the administrative multi-tablet presentations within the institutional formulary could theoretically introduce reporting bias, although the utilization of standardized, self-administered psychometric instruments mitigated subjective investigator interference. Furthermore, while severe baseline insomnia and DTG assignment were identified as significant risk factors for treatment discontinuation in univariate analyses, the small absolute number of discontinuation events ($n = 6$) resulted in sparse-data separation, precluding robust multivariable adjustment via standard maximum likelihood methods. These risk estimates should therefore be interpreted as exploratory associations that warrant validation in larger, multicenter cohorts.

Notwithstanding these limitations, MORFEO possesses substantial strengths. It represents the first randomized clinical trial in Latin America specifically designed to evaluate the psychiatric and virological impact of first-line antiretroviral regimens exclusively in treatment-naïve individuals harboring predefined baseline mental health vulnerabilities. Furthermore, the study utilized a comprehensive, prospective battery of five validated psychometric instruments across multiple longitudinal timepoints (weeks 4, 12, and 24), paired with multidisciplinary psychiatric baseline screening and active adverse event tracking, providing an objective phenotypic characterization of sleep and mood trajectories in a historically underrepresented clinical population.

From a clinical and public health perspective, these findings emphasize the imperative need to incorporate systematic, baseline neuropsychiatric screening into routine HIV clinical practice prior to ART initiation. Rather than relying on a generalized first-line paradigm, initial antiretroviral selection should be individualized based on baseline psychiatric risk. For patients presenting with clinically significant baseline insomnia or mood disorders, boosted protease inhibitors such as darunavir/cobicistat provide a reliable pharmacological strategy that ensures robust virological control while minimizing the risk of treatment abandonment and psychiatric exacerbation. Future multicenter trials with larger sample sizes are needed, including single-tablet regimens, gender-diverse cohorts, and longer follow-up. This would allow for the assessment of whether long-acting regimens or integrase inhibitor-sparing options (including doravirine) offer comparable psychiatric benefits in treatment-naïve populations.

In conclusion, while both DTG + TDF/FTC and DRV/c + TDF/FTC secured high and comparable virological suppression at 24 weeks, their impact on the lived psychological experience of participants diverged. Both regimens alleviated general distress, yet DRV/c supported a more harmonious, multidimensional stabilization across persistent depressive symptoms, sleep architecture, and daytime vitality, while offering greater treatment retention. Conversely, starting DTG in the presence of marked insomnia or affective symptoms was accompanied by a tangible risk of early discontinuation and residual daytime fatigue. Managing HIV involves caring for the whole person rather than solely clearing plasma viremia; incorporating brief, compassionate neuropsychiatric screening prior to ART initiation empowers clinicians to tailor therapy thoughtfully, safeguarding mental equilibrium from the very first dose.

Declarations

Ethical considerations

The study protocol, comprehensive data collection instruments, and informed consent forms were reviewed and formally approved by the Local Health Research Committee No. 3502 at the “La Raza” National Medical Center, IMSS. The trial was granted the Institutional Review Board institutional registry number R-2024-3502-142. The committee operates under international COFEPRIS registry number 18 CI 09 002 001 and CONBIOETICA registry number 09 CEI 027 2017101. Furthermore, the study was registered prospectively in the international clinical trials database ClinicalTrials.gov with the identifier NCT06787976 (Protocol Acronym: MORFEO).

The trial was conducted in strict adherence to the ethical principles governing human medical research stipulated in the Declaration of Helsinki (originally formulated in 1964 and revised in Tokyo 1975, Venice 1983, and Hong Kong 1989), the International Ethical Guidelines for Health-related Research Involving Humans established by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP).

According to the Mexican General Health Law, this project was classified under Category III (Research with risk greater than minimum) due to the active allocation of pharmacological agents. Clinical justification was sustained by the fact that both therapeutic strategies represented standard first-line options fully recommended by national and international HIV treatment guidelines, ensuring that no patient was deprived of optimal clinical care.

Voluntary participation was secured through the execution of a written informed consent process, signed by the patient and two witnesses. The principal investigator was mandated to maintain three original copies of each signed consent document: one integrated into the patient's physical clinical chart, one given directly to the participant, and one archived securely by the research group for a minimum period of 5 years post-study completion. Patient data confidentiality was strictly preserved; data extraction utilized anonymized, alphanumeric patient codes, and all results will be presented in an aggregate format, entirely preventing the identification of individual participants.

Not applicable. This manuscript does not contain any individual patient details, images, or videos.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors declare that they have no competing financial or non-financial interests.

No external funding was received for this research. All laboratory tests and data collection were carried out using the internal resources and facilities of the Hospital de Infectología, Centro Médico Nacional 'La Raza'.

Conceptualization, A.L.C.-D., and J.A.M.-M.; methodology, M.S. R-E., A.L.C.-D and J.A.M.-M.; software, P.E.P.-N., M-D.R-R., M..C.-L., D.M-López; validation, A.L.C.-D., and J.A.M.-M.; formal analysis, J.A.M.-M.; investigation, A.L.C.-D., J.A.M.-M., E.N.P.-M., P.E.P.-N., and J.E.G.-M.; resources, O.H.-L., A.L.C.-D., M.S. R-E. writing—original draft preparation, J.A.M.-M.; writing—review and editing, E.N.P.-M., J.E.G.-M., A.L.C.-D, P.E.P.-N., M.S. R-E supervision, A.L.C.-D. and J.A.M.-M.; project administration, A.L.C.-D., J.A.M, M.S. R-E, P.E.P.-N., M-D.R-R., M..C.-L., D.M-López and J.E.G.-M., visualization, A.L.C.-D., M.S. R-E, P.E.P-N and J.A.M.-M.; funding acquisition, A.L.C.-D., and J.A.M.-M.

All authors have read and agreed to the published version of the manuscript

The authors gratefully acknowledge the invaluable participation of the patients enrolled in the MORFEO trial. We also wish to thank the MORFEO study group, investigators, and operational staff across all participating sites for their rigorous dedication and essential contributions to data collection and study management.

Author Contribution

Conceptualization, A.L.C.-D., and J.A.M.-M.; methodology, M.S. R-E., A.L.C.-D and J.A.M.-M.; software, P.E.P.-N., M-D.R-R., M..C.-L., D.M-López; validation, A.L.C.-D., and J.A.M.-M.; formal analysis, J.A.M.-M.; investigation, A.L.C.-D., J.A.M.-M., E.N.P.-M., P.E.P.-N., and J.E.G.-M.; resources, O.H.-L., A.L.C.-D., M.S. R-E. writing—original draft preparation, J.A.M.-M.; writing—review and editing, E.N.P.-M., J.E.G.-M., A.L.C.-D, P.E.P.-N., M.S. R-E supervision, A.L.C.-D. and J.A.M.-M.; project administration, A.L.C.-D., J.A.M., M.S. R-E, P.E.P.-N., M-D.R-R., M..C.-L., D.M-López and J.E.G.-M., visualization, A.L.C.-D., M.S. R-E , P.E.P-N and J.A.M.-M.; funding acquisition, A.L.C.-D., and J.A.M.-M. All authors have read and agreed to the published version of the manuscript

Acknowledgement

The authors gratefully acknowledge the invaluable participation of the patients enrolled in the MORFEO trial. We also wish to thank the MORFEO study group, investigators, and operational staff across all participating sites for their rigorous dedication and essential contributions to data collection and study management.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Ghosh AK. Four decades of continuing innovations in the development of antiretroviral therapy for HIV/AIDS: Progress to date and future challenges. *Glob Health Med.* 2023;5(4):194–8. 10.35772/ghm.2023.01013. . PMID: 37655189; PMCID: PMC10461327.
2. Zhao AV, Crutchley RD, Guduru RC, Ton K, Lam T, Min AC. A clinical review of HIV integrase strand transfer inhibitors (INSTIs) for the prevention and treatment of HIV-1 infection. *Retrovirology.* 2022;19(1):22. 10.1186/s12977-022-00608-1. . PMID: 36273165; PMCID: PMC9588231.
3. Hoffmann C, Libre JM. Neuropsychiatric Adverse Events with Dolutegravir and Other Integrase Strand Transfer Inhibitors. *AIDS Rev.* 2019;21(1):4–10. 10.24875/AIDSRev.19000023. PMID: 30899113.
4. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, Wyen C. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med.* 2017;18(1):56–63. 10.1111/hiv.12468. . Epub 2016 Nov 10. PMID: 27860104.
5. de Boer MG, van Holten N, Oryszczyn JE, Dorama W, Moha DA, Brinkman K. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *AIDS.* 2016;30(18):2831–2834. doi: 10.1097/QAD.0000000000001279. PMID: 27824625.

6. Jakimiuk A, Piechal A, Wiercińska-Drapało A, Nowaczyk A, Mirowska-Guzel D. Central nervous system disorders after use of dolutegravir: evidence from preclinical and clinical studies. *Pharmacol Rep.* 2023;75(5):1138–51. 10.1007/s43440-023-00515-y. . Epub 2023 Aug 21. PMID: 37605102; PMCID: PMC10539422.
7. Fabbiani M, Masini M, Rossetti B, Ciccullo A, Borghi V, Lagi F, Capetti A, Colafigli M, Panza F, Baldin G, Mussini C, Sterrantino G, Farinacci D, Montagnani F, Tumbarello M, Di Giambenedetto S. Efficacy and Durability of Dolutegravir- or Darunavir-Based Regimens in ART-Naïve AIDS- or Late-Presenting HIV-Infected Patients. *Viruses.* 2023;15(5):1123. 10.3390/v15051123. . PMID: 37243208; PMCID: PMC10224150.
8. Hu FH, Liu P, Jia YJ, Ge MW, Shen LT, Xia XP, Chen HL. Prevalence of mental health problems in people living with HIV: a systematic review and meta-analysis. *Psychol Health Med.* 2025;30(3):397–413. Epub 2024 Nov 6. PMID: 39504439.
9. Lang R, Hogan B, Zhu J, McArthur K, Lee J, Zandi P, Nestadt P, Silverberg MJ, Parcesepe AM, Cook JA, Gill MJ, Grelotti D, Closson K, Lima VD, Goulet J, Horberg MA, Gebo KA, Camoens RM, Rebeiro PF, Nijhawan AE, McGinnis K, Eron J, Althoff KN, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). of the International Epidemiologic Databases to Evaluate AIDS (IeDEA). The prevalence of mental health disorders in people with HIV and the effects on the HIV care continuum. *AIDS.* 2023;37(2):259–69. Epub 2022 Nov 10. PMID: 36541638; PMCID: PMC9782734.
10. Mata-Marín JA, Juárez-Contreras CA, Rodríguez-Evaristo MS, Martínez-Carrizales OC, Pompa-Mera E, Chaparro Sánchez A, Triana-González S, Cano-Díaz AL, Gaytán-Martínez JE. Reversibility of Neuropsychiatric Adverse Events after Switching to Darunavir/Cobicistat or Doravirine in Men on INSTI-Based Regimen. *Viruses.* 2024;16(7):1083. 10.3390/v16071083. . PMID: 39066245; PMCID: PMC11281698.
11. Huang B, Younger A, Gallant MP, O'Grady TJ. Depressive Symptoms and HIV Viral Suppression: A Systematic Review and Meta-analysis. *AIDS Behav.* 2025;29(3):870–83. 10.1007/s10461-024-04571-0. . Epub 2024 Dec 18. PMID: 39690344; PMCID: PMC11830644.
12. Moyle G, Meng F, Wan H, Sklar P, Plank RM, Lahoulou R. Brief Report: Resolution of Neuropsychiatric Adverse Events After Switching to a Doravirine-Based Regimen in the Open-Label Extensions of the DRIVE-AHEAD and DRIVE-FORWARD Trials. *J Acquir Immune Defic Syndr.* 2025;99(1):81–6. PMID: 39748155; PMCID: PMC11970612.
13. Karabay O, Vatan A, Ucar A, Yilmaz I, Balta NC, Kanturk A, Dumlu R, Cag Y, Caskurlu H, Şik MT, Otman ZA, Balci U, Senbayrak S, Akhan S, Deniz MT, Yekenkurul D, Ince N, Tunca B, Cakirca TD, Bastug A, Erkorkmaz U, Guclu E. Long-term metabolic and safety profiles of tenofovir alafenamide and tenofovir disoproxil fumarate in ART-naïve people living with HIV: a multicenter retrospective study using a mixed-effects model. *BMC Pharmacol Toxicol.* 2025;26(1):164. 10.1186/s40360-025-01003-0. . PMID: 41088309; PMCID: PMC12523089.
14. Cabello-Úbeda A, Baeza AG, García JT, de La Fuente Moral S, Mena MN, Martínez AP, Micán R, Górgolas M, Tascón GC, de Santiago AD, Morerno JS, Crestelo DR, Arenzana CB, Serna JIB, Almirón

- MD, Cano J, Esteban H, Pérez-Valero I. 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. *Open Forum Infect Dis*. 2022;9(9):ofac345. 10.1093/ofid/ofac345. PMID: 36147597; PMCID: PMC9487706.
15. Lang R, Hogan B, Zhu J, McArthur K, Lee J, Zandi P, Nestadt P, Silverberg MJ, Parcesepe AM, Cook JA, Gill MJ, Grelotti D, Closson K, Lima VD, Goulet J, Horberg MA, Gebo KA, Camoens RM, Rebeiro PF, Nijhawan AE, McGinnis K, Eron J, Althoff KN, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). of the International Epidemiologic Databases to Evaluate AIDS (IeDEA). The prevalence of mental health disorders in people with HIV and the effects on the HIV care continuum. *AIDS*. 2023;37(2):259–69. Epub 2022 Nov 10. PMID: 36541638; PMCID: PMC9782734.
 16. Cusato J, Borghetti A, Teti E, Milesi M, Tettoni MC, Bonora S, Trunfio M, D'Avolio A, Compagno M, Di Giambenedetto S, Di Perri G, Calcagno A. Dolutegravir Discontinuation for Neuropsychiatric Symptoms in People Living with HIV and Their Outcomes after Treatment Change: A Pharmacogenetic Study. *Metabolites*. 2022;12(12):1202. 10.3390/metabo12121202. . PMID: 36557240; PMCID: PMC9781993.
 17. Borghetti A, Calcagno A, Lombardi F, Cusato J, Belmonti S, D'Avolio A, Ciccarelli N, La Monica S, Colafigli M, Delle Donne V, De Marco R, Tamburrini E, Visconti E, Di Perri G, De Luca A, Bonora S, Di Giambenedetto S. SLC22A2 variants and dolutegravir levels correlate with psychiatric symptoms in persons with HIV. *J Antimicrob Chemother*. 2019;74(4):1035–1043. 10.1093/jac/dky508. PMID: 30561642.
 18. Chanie GS, Belachew EA, Seid AM, Limenh LW, Mitku ML, Beyna AT, Mengesha AK, Melese M, Esubalew D, Gela YY, Ayenew W, Simegn W. Patients reported neuropsychiatric adverse events and associated factors among PLHIV patients receiving DTG-based regimen antiretroviral therapy real-life clinical practice in Ethiopia: multi center cross-sectional study. *BMC Psychiatry*. 2025;25(1):383. 10.1186/s12888-025-06820-5. . PMID: 40241041; PMCID: PMC12004852.
 19. Cuzin L, Pugliese P, Katlama C, Bani-Sadr F, Ferry T, Rey D, Lourenco J, Bregigeton S, Allavena C, Reynes J, Cabié A, Dat, 'AIDS Study Group. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. *J Antimicrob Chemother*. 2019;74(3):754–760. 10.1093/jac/dky497. PMID: 30534993.
 20. Cusato J, Borghetti A, Teti E, Milesi M, Tettoni MC, Bonora S, Trunfio M, D'Avolio A, Compagno M, Di Giambenedetto S, Di Perri G, Calcagno A. Dolutegravir Discontinuation for Neuropsychiatric Symptoms in People Living with HIV and Their Outcomes after Treatment Change: A Pharmacogenetic Study. *Metabolites*. 2022;12(12):1202. 10.3390/metabo12121202. . PMID: 36557240; PMCID: PMC9781993.
 21. Perez-Valero I, Corona Mata D, Crussells Canales MJ, Velasco Arribas M, Mican Rivera R, Ryan P, Navarrete-Lorite MN, Tiraboschi J, Barrado-Cuchillo J, Molero Bonilla M, Artigues Serra F, Mena de Cea A, de la Fuente Moral S, Perez Stachowski X, Garcia Fraile LJ, Diaz Almidon M, Gil P, Ferreira

Tata C, Rivero Juarez A, Rivero A. Safety and tolerability of switching to bictegravir/emtricitabine/tenofovir alafenamide versus continuing dolutegravir/lamivudine in people living with HIV with neuropsychiatric comorbidities: Week 24 and 48 results from the Management of INSTI-associated Neuropsychiatric Disorders (MIND) clinical trial. *Int J Antimicrob Agents*. 2026;67(8):107825. 10.1016/j.ijantimicag.2026.107825. . Epub 2026 Apr 27. PMID: 42055353.