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. The MORFEO trial

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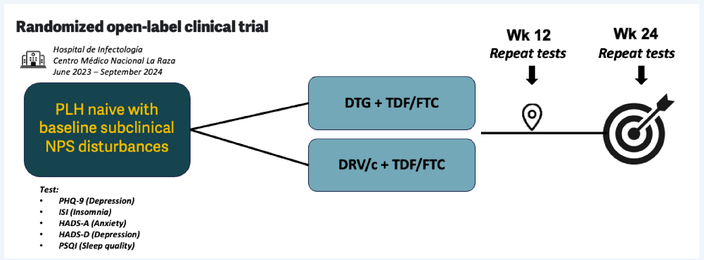
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BACKGROUND

Integrase strand transfer inhibitors (INSTIs) are linked to neuropsychiatric adverse events (NPS). This study aimed to evaluate changes in NPS in antiretroviral therapy (ART)-naïve people living with HIV (PWH) who reported baseline NPS symptoms and initiated treatment with either Dolutegravir (DTG) or Darunavir/Cobicistat (DRV/c), both combined with Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC).

METHODS

Methods: A randomized, open-label clinical trial was conducted at the Hospital de Infectología, Centro Médico Nacional “La Raza” from June 2023 to December 2024 (ClinicalTrials.gov Identifier: NCT06787976). The study assessed changes in NPS scales for depression, anxiety, insomnia, and sleep quality in PWH starting ART with either DTG or DRV/c, both paired with TDF/FTC. All participants underwent psychiatric evaluation before initiating ART. Discontinuation was considered if patients experienced exacerbation of NPS symptoms associated with adverse events by DAIDS grade ≥2. NPS scores were compared at baseline, 12 and 24 weeks.



DTG was associated with a higher risk of ART discontinuation and the need for psychiatric intervention.

RESULTS

The study enrolled 55 male patients, with 27 (49.1%) assigned to DRV/c and 28 (50.9%) to DTG. The median age was 26 years (IQR 23-29), baseline CD4+ count was 303 cells/μL (IQR 171-485), and baseline HIV-1 RNA was 4.4 log10 copies/mL (IQR 3.9-4.9) (Table 1). Before ART initiation, 14 patients (25.5%) reported suicidal thoughts. In the DTG group, 8 patients (28.6%) discontinued ART due to new-onset suicidality and worsening NPS symptoms.

Both groups showed significant reductions in NPS scores at 24 weeks compared to baseline. No significant differences were found in the scales (Table 2). During the 24-week period, 17 participants (60.7%) in the DTG group required antidepressant treatment, compared to 5 (18.5%) in the DRV/c group (p=0.110). DTG was associated with a higher risk of ART discontinuation (RR 4.3, 95% CI 1.00-18, p=0.026) and the need for psychiatric intervention (RR 2.4, 95% CI 1.09-5.37, p=0.019). The study was terminated early for ethical reasons.

Table 1. Baseline characteristics of the studied population.

Characteristic	DTG + TDF/FTC N=28	DRV + TDF/FTC N=27	p
Age, median,(IQR) years	25 (23-34)	26 (23-34)	0.937
CD4+, median (IQR) cells/mm3	275 (163-469)	303 (162-480)	0.739
VIH-1 Viral load, median (IQR), log_{10}	4.4 (3.9-4.9)	4.4 (3.7-4.7)	0.848
ART discontinuation, n (%)	8 (29.6%)	2 (7%)	0.135
Basal PHQ-9, median (IQR), score	16 (10-19)	15 (11-17)	0.224
Basal ISI, median, (IQR), score	12 (9-16)	13 (10-17)	0.067
Basal HADS-A, median (IQR), score	10 (8-12)	11 (8-13)	0.105
Basal HADS-D, median (IQR), score	7 (5-10)	11 (10-17)	0.079
Basal PSQI, median (IQR), score	10 (8-13)	10 (8-13)	0.297

Table 2. Comparison of scores at 12 weeks

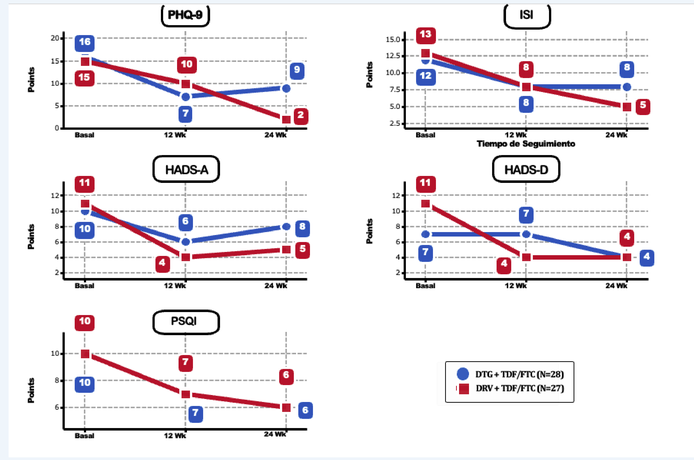
Parameter	DTG + TDF/FTC N=28	DRV + TDF/FTC N=27	p
PHQ-9 12 weeks, median (IQR), score	7 (4-11)	10 (6-13)	0.072
ISI 12 weeks, median, (IQR), puntos	8 (5-14)	8 (2-12)	0.876
HADS-A 12 weeks, median (IQR), score	6 (3-9)	4 (2-9)	**0.032**
HADS-D 12 weeks, median (IQR), score	7 (3-9)	4 (2-9)	0.428
PSQI 12 weeks, median (IQR), score	7 (5-11)	7 (3-10)	0.740

Table 3. Comparison of scores at 24 weeks

Parameter	DTG + TDF/FTC N=28	DRV + TDF/FTC N=27	p
PHQ-9 24 weeks, median (IQR), score	9 (3-13)	2 (2-8)	0.095
ISI 24 weeks, median, (IQR), puntos	8 (2-12)	5 (2-8)	0.778
HADS-A 24 weeks, median (IQR), score	8 (4-11)	5 (2-11)	0.352
HADS-D 24 weeks, median (IQR), score	4 (2-9)	4 (1-7)	0.411
PSQI 24 weeks, median (IQR), score	6 (5-8)	6 (5-10)	0.931

CONCLUSIONS

DTG was linked to higher rates of ART discontinuation due to worsening NPS, including new-onset suicidality and greater need for psychiatric intervention, such as antidepressants. The study was terminated early for ethical reasons due to these adverse outcomes in the DTG arm.



Summary

In this trial, designed to evaluate the worsening of neuropsychiatric symptoms in patients with subclinical abnormalities, no significant differences were found on the assessment scales. However, DTG was associated with a higher risk of ART discontinuation and a greater need for psychiatric intervention compared with DRV/c. Given the clinical relevance of this latter finding, the study was terminated early.