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Central nervous system disorders in HIV-infected individuals using distinct antiretroviral drugs

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Abstract

Neuropsychiatric disorders and central nervous system-related symptoms are very common in people with HIV and can have a very negative impact on their quality of life and worsen the prognosis of the disease. These disorders are multifactorial in origin, but may be triggered or worsened by the use of certain antiretroviral treatments. This paper reviews the epidemiology of neuropsychiatric disorders and symptoms in people with HIV, the recommendations and tools available for their early assessment, as well as the neurotoxicity of the main families of antiretroviral (ARV) drugs. It is important to focus on improvement towards the detection of these disorders during the first evaluation or patient follow-up, aimed at improving quality of life. Because of the central nervous system neurotoxicity profile of different antiretroviral drugs, proactive assessment of neuropsychiatric disorders and symptoms prior to treatment start and during follow-up is necessary.

Key words

Anti-HIV agents. Drug-related side effects and adverse reactions. Neurocognitive disorders. Psychophysiologic disorders. Neuropsychological tests.

Introduction

The prevalence of neuropsychiatric disorders is higher in patients with HIV (PLHIV) than in the general population[1–3]. The spectrum of neuropsychiatric disorders includes a wide range of pathologies such as cognitive disorders, mood and anxiety disorders[4,5]. The high prevalence of these disorders in HIV-infected persons is related to a wide variety of factors including direct effects of the virus, pre-existing psychiatric conditions, personal responses to HIV diagnosis, adaptation to the disease, social stigma, substance use, etc.[1,3]. In addition, certain antiretroviral treatments may also lead to neuropsychiatric disorders or worsen pre-existing disorders such as insomnia, headache, fatigue, etc. These disorders can impair the quality of life of HIV-positive patients.[6,7].

This paper addresses the importance of neuropsychiatric disorders and symptoms in people with HIV, highlighting the need for early assessment of these symptoms and, in parallel, to evaluate the ARV therapy of choice according to the neurotoxicity profiles of the available drugs.

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Prevalence of neuropsychiatric disorders and symptoms in people living with HIV

The most commonly diagnosed neuropsychiatric disorders in PLHIV are depressive disorders[3,5]. It is estimated that between 27% and 83% of patients have or may develop a depressive disorder during their lifetime [5]. The spectrum of this pathology ranges from organic affective disorder (depression caused by another illness), adaptive disorder with depressive mood, to major depressive disorder or dysthymic disorder[5]. The presence of depressive disorder in PLHIV has been associated with poorer infection control (delayed ART initiation, poor adherence or loss to follow-up) and increased morbidity and mortality[3].

Anxiety is another very common problem. It is estimated that 22-47% of PLHIV have or will experience anxiety in their lifetime. In these people, as with depressive disorders, anxiety is associated with a significant decrease in quality of life and problems in managing their infection (delayed ART initiation, poor adherence or loss to follow-up)[3,5].

Other disorders to consider are manic syndrome, which can appear in 8% of patients, psychotic syndromes, with a prevalence of 0.5-15%, or personality disorders whose prevalence can reach 25%, the most common being antisocial, borderline, histrionic and narcissistic disorders[3,5].

On the other hand, the diagnosis and experience of a chronic illness such as HIV can trigger adaptive emotional responses that result in alterations of some physiological functions. Some of the most relevant are sleep disturbances, fatigue, sexual function and appetite disorders[3]. Insomnia is the most prevalent sleep disorder in PLHIV. The prevalence of insomnia in PLHIV is estimated to be 29% to 97%, much higher than the 10% prevalence in the general population[8]. It is a multifactorial phenomenon involving biological, psychological and psychosocial factors that may be enhanced by ART (antiretroviral therapy)[3,6,9]. Fatigue is another common symptom reported by HIV patients. Its prevalence may be around 33% to 88%[10]. Another important symptom, related to the neurological sphere, is headache, which is the most common form of pain reported among HIV patients[11]. Its prevalence can be as high as 38-61%[11].

Psychoactive substance use is also common among PLHIV. In most cases, such use is occasional and sporadic and is not associated with health problems. However, an escalation in the use of these drugs is clearly detrimental to the health of patients and can lead to a neuropsychiatric substance use disorder[3].

Moreover, we must not forget that HIV infection itself triggers direct damage to the central nervous system. The development of HIV-associated neurocognitive disorders (HAND) leads to a progressive loss of function that can be associated with a poorer quality of life and life expectancy[3]. Although this was a very common complication in the past, early use of ART has led to a marked decrease in its prevalence. However, despite this decline, we may still have values of 20-40% in PLHIV who may still suffer from HAND[3,12]. Likewise, early diagnosis and treatment of neuropsychiatric disorders is particularly important given that their presence has been associated with poorer infection control, more risk behaviours for HIV transmission, more HIV-associated symptomatology, higher rates of hospitalisation, poorer quality of life and poorer survival rates[3].

All of these central nervous system-related adverse events resulting from HIV infection itself and from some ART may enhance cognitive deficits associated with ageing per se. In addition, the increase in life expectancy associated with ART use will mean that the number of PLHIV diagnosed with age-related dementia may increase significantly in the coming years[3].

Many of these neuropsychological and cognitive-related disorders and symptoms may be due to or may be exacerbated by the use of certain antiretroviral (ARV) drugs[6,7]. The relationship between a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV), and CNS-related adverse events has been previously described and is well known. However, the involvement of other drugs in the integrase inhibitor (INI) family, such as DTG and bictegravir (BIC), in this same symptomatology is gradually becoming known. It was already described in clinical development and has been corroborated in real-life studies, but also nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) can be associated with neuropsychiatric disorders, mainly due to mitochondrial toxicity, or INIs, especially dolutegravir (DTG), which in real-life studies is associated with more neuropsychiatric adverse events (NPAEs) than previously described in clinical trials[6,13].

Screening for neuropsychiatric disorders and symptoms in HIV-positive people

Early diagnosis and correct management of these neuropsychiatric disorders and ART-associated NPAEs in PLHIV is essential, not only because they impair quality of life, but also because mental health problems

in HIV-infected patients can have a negative influence on treatment adherence and disease prognosis [1,3].

Therefore, screening for all these disorders and symptoms is recommended in the initial assessment and during follow-up of PLHIV [3]. The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) AIDS Study Group (GeSIDA) published recommendations in 2020 based on a comprehensive literature review that can be used for early diagnosis and optimal management of these disorders[3]. Its main recommendations emphasise the importance of screening for neuropsychiatric disorders and symptoms in people living with HIV (Table 1)[3].

These guidelines recommend that the assessment of all PLHIV should include[3]: 1) An assessment of family and personal history of mental illness and personal history of substance use, 2) An assessment of appearance, behaviour, thinking, language, critical judgement, anxiety and depression, cognitive complaints (attention, memory and executive functions), motor skills and sensory perception, and 3) An assessment of work, family and social status[3].

Furthermore, the existence of ART-associated neurotoxicity should be suspected in any patient who reports the onset or worsening of neuropsychiatric or cognitive symptoms following the initiation of a new ART; provided that no other aetiologies are identified that could justify them. There is controversy about whether the identification of ART-associated symptoms should be reactive or proactive. Reactive approaches underestimate ART neurotoxicity and, therefore, some experts recommend a more proactive approach that includes, in addition to anamnesis, the use of some patient-reported symptom questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI) or The Hospital Anxiety and Depression Scale (HADS). Regarding the use of complementary tests, so far none has proven to be useful for the diagnosis of ART neurotoxicity[3].

Table 2 shows the most useful surveys and tools for assessing neuropsychiatric disorders and symptoms in HIV patients [3,9,14–25]. Furthermore, proper management of CNS pathology in HIV patients requires a multidisciplinary approach involving infectious diseases/internal medicine, psychology, psychiatry and, when necessary, nursing professionals[3].

Neuropsychiatric effects of antiretroviral drugs

ARV drugs can cause CNS neurotoxicity directly, through neuronal stress mechanisms secondary to ARV exposure, or through indirect mechanisms such as increased cardiovascular risk, dyslipidaemia and accelerated neuro-ageing due to reduced telomerase activity[3,12]. However, not all ARVs have the same mechanism of action and neurotoxicity profile[3]. The most relevant NPAEs associated with the main ARV families are summarised below.

Nucleoside/nucleotide analog reverse-transcriptase inhibitors (NARTIs or NRTIs)

In the past, NARTI neurotoxicity was thought to be limited to the peripheral nervous system, but accumulating evidence now shows that these treatments can also be associated with CNS disorders[6]. Mitochondrial toxicity is the main cause of direct neurotoxicity that has been associated with this ARV family[3,26,27]. It has been suggested that this toxicity may contribute to the development of HAND[6]. The degree of mitochondrial toxicity among NRTIs is didanosine (ddI)> stavudine (d4T) >> lamivudine (3TC)> tenofovir disoproxil fumarate (TDF) ≥ emtricitabine (FTC) ≥ AZT ≥ abacavir (ABC)[6].

In addition to mitochondrial toxicity, other pathways of CNS damage by NRTIs have been described, such as abacavir-associated increased astrocyte endoplasmic reticulum stress (ABC) or the possible amyloidogenic effect of AZT, 3TC or ABC, especially when associated with indinavir, by inhibiting the phagocytosis of extracellular beta-amyloid by microglia[28,29]. Tenofovir alafenamide (TAF) is a prodrug of tenofovir and a component of many modern ART regimens. Because of the higher intracellular concentration of TAF, some authors suggest that it may be associated with greater neurotoxicity than TDF[6].

From the point of view of indirect neurotoxicity, renal toxicity from TDF or cerebrovascular toxicity from ABC could promote cognitive impairment in PLHIV[3].

Non-nucleoside reverse transcriptase inhibitor

EFV is the NNRTI with the highest reported CNS toxicity[3,6]. The toxicity caused by EFV is due to both direct exposure to the drug and its main metabolite, 8-hydroxy-efavirenz, which has no antiretroviral activity but is more neurotoxic than the drug itself[30]. Cytochrome P450 2B6 (CYP2B6) is the main enzyme catalysing the formation of 8-hydroxy-efavirenz, and certain genetic polymorphisms in CYP2B6 can lead to increased exposure to this metabolite and in-

Table 1. Summary of recommendations for screening PLHIV for neuropsychiatric disorders

Disorder	Recommendations
ART neurotoxicity	– Diagnosis of ART neurotoxicity is primarily clinical. – ART-associated neurotoxicity should be suspected following the onset of neuropsychiatric symptoms or worsening of pre-existing symptoms. – The use of patient self-reported symptom questionnaires could be useful for early identification and monitoring of ART-associated neurotoxicity.
Depression	– Screen for depression, using validated scales such as HADS, in all PLHIV at the time of diagnosis and annually or biannually thereafter. – When the screening result is positive, the diagnosis could be confirmed in the consultation using a semi-structured interview such as the MINI. – Ruling out an organic origin of the depressive symptoms (complete blood test with thyroid hormones, folate and vitamin B12). – Brain imaging scans should only be indicated when organic origin is suspected. – When depressive symptoms are detected (new or an aggravation of existing ones), it is always recommended to evaluate suicidal ideation and, if detected, to activate an urgent patient assessment circuit by psychiatry.
Anxiety	– Screen for anxiety and depression, using validated scales such as HADS, in all PLHIV at the time of diagnosis and annually or biannually thereafter. – When the result of the anxiety screening is positive, the diagnosis could be confirmed in the consultation by applying a semi-structured interview such as the MINI.
Personality disorders	– Suicide or self-harm risk should be assessed and patient should be referred for treatment (psychotherapy and symptomatic pharmacotherapy) to a mental health specialist.
Manic or psychotic disorder	– When a manic or psychotic disorder of recent onset is detected, urgent assessment and treatment by psychiatry is recommended, as well as ruling out an organic origin of the disorder (delirium, cognitive impairment, substance or drug use such as efavirenz, central nervous system diseases, etc.)
Sleep disorders	– Screening for sleep disorders by means of anamnesis at each medical visit and on an annual or biannual basis using scales such as the PSQI.
Sexual dysfunction	– Perform screening for sexual dysfunction, by means of anamnesis, on an annual basis.
Eating disorders	– In the event of any significant change in appetite, it is recommended, among other measures, to screen for anxious-depressive disorders.
Substance use	– Regular assessment of substance use is recommended, either through anamnesis and/or using validated scales such as the DUDIT or AUDI
HAND	– Identification of cognitive complaint should be done proactively at diagnosis and at least once every 1-2 years. – Routine use of screening instruments for HAND is not recommended. – In centres with limited access to neuropsychological diagnosis of HAND, screening instruments may be useful, in patients with cognitive complaints, to establish criteria for referral to other centres with diagnostic capacity. – Regarding available screening instruments, those with sensitivities and specificities >70%, validated in the population studied (such as the NEU Screen in the case of the Spanish population), should be preferred. – Whenever the existence of HAND is suspected, a regular neuropsychological assessment is recommended.
Age-related dementia	– In patients over 60 years of age with neurocognitive impairment, complementary tests (brain MRI, beta-amyloid levels, TAU and phospho-TAU in CSF +/- PET) should be performed to rule out the existence of age-related dementia.

AUDIT: Alcohol Use Disorders Identification Test; DUDIT: Drug Use Disorders Identification Test; HADS: The Hospital Anxiety and Depression Scale; CSF: cerebrospinal fluid; MINI: Mini International Neuropsychiatric Interview; PET: positron emission tomography; PSQI: Pittsburgh Sleep Quality Index; MRI: magnetic resonance imaging; ART: antiretroviral therapy; HAND: HIV-associated neurocognitive disorders; PLHIV: people living with HIV.

Table 2. Main tools available for the assessment of neuropsychiatric disorders in PLHIV

Disorder	Tools	Number of items	Available at
Depression	HADS	14 (7 anxiety and 7 depression)	https://eprovide.mapi-trust.org/instruments/hospital-anxiety-and-depression-scale
	PHQ9	9	https://patient.info/doctor/patienthealth-questionnaire-phq-9
	CES-D	20	https://cesd-r.com/
	MINI	Semi-structured interview	https://harmresearch.org/index.php/mini-international-neuropsychiatric-interview-mini/
Anxiety	HADS	14 (7 anxiety and 7 depression)	https://eprovide.mapi-trust.org/instruments/hospital-anxiety-and-depression-scale
	GAD-7	7	https://patient.info/doctor/generalised-anxiety-disorder-assessment-gad-7
	HAMA	14	https://www.mdcalc.com/hamilton-anxiety-scale
Sleep disorders	PSQI	19	https://www.sleep.pitt.edu/instruments
	Insomnia severity index	7	https://eprovide.mapi-trust.org/instruments/insomnia-severity-index
Substance Abuse	DUDIT	11	https://www.emcdda.europa.eu/drugs-library/drug-use-disorders-identification-test-dudit_en
Alcohol abuse	AUDIT	10	https://auditscreen.org/
HAND	NEU Screen	3 neuropsychological tests	https://www.flsida.org/es/blog/neu-screen

HAND: HIV-associated neurocognitive disorders; HADS: The Hospital Anxiety and Depression Scale; PHQ9: Patient Health Questionnaire-9; CES-D: Center for Epidemiologic Studies Depression Scale; MINI: Mini International Neuropsychiatric Interview; GAD-7: General Anxiety Disorder- 7; HAMA: Hamilton Anxiety Rating Scale; PSQI: Pittsburgh Sleep Quality Index; DUDIT: Drug Use Disorders Identification Test; AUDIT: Alcohol Use Disorders Identification Test.

creased neurotoxicity[30]. The mechanism by which EFV-associated neurotoxicity occurs is not entirely clear[6]. Among other mechanisms, neurotoxicity could be mediated by increased oxidative stress and subsequent mitochondrial dysfunction, as is the case with NRTIs[31].

Clinically speaking, the adverse effect traditionally associated with EFV is vivid dreams, although it has been associated with numerous neurological (dizziness, insomnia, headache, impaired concentration) and psychiatric (paranoia, hallucinations, anxiety, mania and depression) adverse effects. These adverse effects occur in more than half of all patients taking EFV and, although they are usually resolved after several weeks, in some patients they may persist longer after withdrawal of the drug[6].

The neurotoxic potential of other NNRTIs is highly variable, although it is less common, has been less studied and has fewer clinical implications than EFV neurotoxicity[6]. Nevirapine is the NNRTI associated with the greatest toxicity following EFV[6]. Rilpivirine (RPV), compared to EFV, results in fewer NPAEs and fewer treatment discontinuations for this reason. Grade 2-4 NPAEs such as dizziness have been reported in 8% of patients (vs. 26% with EFV), or abnormal dreams/nightmares in 8% of patients (vs. 13% with EFV)[32]. Similarly, fewer NPAEs have been reported with doravirine (DOR) than with EFV, but their frequency also remains remarkable[9]. Thus, in the DRIVE-AHEAD clinical trial, NPAEs were analysed as a pre-specified variable including: dizziness, sleep disturbances, sensory disturbances, depression and

suicidal ideation/self-harm, psychosis and psychotic disturbances. At 96 weeks, NPAEs were less frequent for DOR/3TC/TDF than for EFV/FTC/TDF, but their proportion was still highly significant (26.4% vs. 58.5%)[33].

Integrase inhibitors

Evidence of INI-associated neurotoxicity in available in vitro studies is scarce[3,12]. There is evidence that DTG can induce abnormal axonal overgrowth, similar to that produced by EFV, but the clinical relevance of this phenomenon is unclear[3]. There are also in vitro studies indicating that elvitegravir/cobicistat (EVG/c) can induce mitochondrial toxicity, through depolarisation of the membrane potential and generation of free radicals, and excitotoxicity in the form of neuronal degeneration[3].

Although in vitro evidence is scarce, at the clinical level, all INIs have been associated with the development of neuropsychiatric adverse effects[3], so it seems that there may be neurotoxicity phenomena associated with INIs that have not yet been identified[3].

Among the most frequently reported neuropsychiatric effects during INI treatment are headache and insomnia[34]. In clinical trials with raltegravir (RAL), the frequency of both headache and insomnia was <1-4% [34]. Insomnia may be reversible after stopping intake of the drug or, in some cases, may improve by switching to morning dosing schedules[6,35–37]. The spectrum of CNS symptoms associated with INI use also includes dizziness, drowsiness, sleep disorders, anxiety, depression, paraesthesia or difficulties in concentration, and suicidal ideation[13,34].

In clinical trials, the rate of discontinuation of INI treatment due to CNS effects is generally low. However, there are real-life clinical practice studies that suggest a higher frequency of neuropsychiatric symptoms and a higher discontinuation rate than found in clinical trials[6,13]. Hence, in phase 3 clinical trials in naïve patients with DTG[38–44], the discontinuation rate for neuropsychiatric symptoms was generally less than 1% during the first year. However, in real-life studies, the proportion of patients with any NPAE associated with DTG ranges from 5% to 20.6% [9] and discontinuation of DTG for neuropsychiatric adverse effects is mostly above 1%[45–64], being generally around 3.5% [9,13] or higher in the long term[45]. In a Spanish cohort study including 282 DTG-treated patients (16.7% naïve), a treatment discontinuation rate for neuropsychiatric symptoms of 8.2% was observed after a follow-up of 137 weeks [45].

Moreover, evidence from real-life practice suggests that DTG neurotoxicity may be superior to other INIs such as RAL or EVG (Table 3)[34,46,49,52,55–58,62]. In the largest prospective series comparing NPAEs with various INIs (Dat'AIDS cohort) [46], 21,315 patients were included: 6,274 received DTG, 3,421 patients received EVG/c and 11,620 patients received RAL. During a 48-month follow-up, treatment discontinuation occurred in 12.5%, 20.2% and 50.9% of patients treated with DTG, EVG/c and RAL, respectively (p=0.001). NPAE discontinuation occurred in 2.7%, 1.3% and 1.7% of patients treated with DTG, EVG/c and RAL, respectively (p=0.001). In multivariate analysis, NPAE discontinuation was associated with DTG vs. EVG/c (HR: 2.27; 95% CI: 1.63-3.17; p=0.0001) and vs. RAL (HR: 2.46; 95% CI: 2.00-3.40; p=0.0001), in addition to CD4 nadir and prior ART use[46]. Neither sex nor age was associated with treatment discontinuation due to NPAE, which is in line with other studies[52,55,58]. The use of ABC in association with DTG has also been related to an increased risk of discontinuation due to NPAE in some studies[52,60,65]. In a recent retrospective cohort study by the Belgian Research on AIDS and HIV Consortium (BREACH) that included 4,101 DTG-treated patients, treatment discontinuation for NPAE was associated with age older than 50 years, CD4 <350 cells/microliter, concomitant ABC/3TC use and sub-Saharan origin [60]. Discontinuation of DTG treatment has also been associated with the presence of previous psychiatric symptoms[66]. A Spanish retrospective cohort study included 283 patients aged 11-87 years (70% male, 21% naïve) with a median follow-up of 463 days. Sixty-nine patients (24.4%) discontinued DTG treatment; compared to patients who did not discontinue treatment, this group had a higher frequency of psychiatric history (62 vs. 41%; p = 0.002) and a higher frequency of psychotic disorders (8.7 vs. 1.9%; p = 0.008). There was also a tendency to present with depression, anxiety, personality disorder and sleep disorder more frequently, although the differences were not statistically significant. Additionally, patients who discontinued DTG more frequently presented to their primary care physician with psychiatric symptoms (18.8 vs. 8.4%; p = 0.016) and to the emergency department (8.7 vs. 3.3%; p = 0.061) compared to the other group[66].

Bictegravir (BIC) is the latest INI to be added to the HIV treatment arsenal and data from routine clinical practice are slowly emerging. Cabotegravir will be available soon[9]. The BIC structure is very similar to that

Table 3. Differences in NPAEs with different INSTIs in real-life studies

	Design	n	Naïve patients	Follow-up	Treatments	NPAE-related outcomes	Factors related to treatment discontinuation for NPAE in multivariate analyses
Cuzi et al[46]	Prospective cohort	21.315	12,9%-23,1%	48 months	RAL, EVG/c, DTG	Treatment discontinuation due to NPAE in 2.7%, 1.3% and 1.7% of patients treated with DTG, EVG/c and RAL, respectively (p=0.001).	– NPAE discontinuation was associated with DTG vs. EVG and RAL, CD4 nadir and prior ART use. – Neither sex nor age was associated with an increased risk of NPAE discontinuation.
Llibre et al[58]	Prospective cohort	4.165	37%	48 weeks	RAL, EVG/c, DTG	Discontinuation rates due to NPAE were higher for DTG/ ABC/3TC (2.9 discontinuations/100 patients/year) vs. EVG/c/TDF/FTC (0.8/100 patients/ year) (p = 0.002) and similar to RAL/TDF/ FTC (2.1/100 patients/ year)	– Increased risk of discontinuation due to NPAE with DTG vs. EVG/c. – Female sex, age > 60 years and ABC use were not associated with NPAE discontinuation
Elzi et al[55]	Prospective cohort	4.041	9%-16.8%	>12 months	RAL, DTG	– NPAEs were the most frequently reported AE, being more frequent with DTG (1.7%) than with RAL (0.6%). – Higher rate of treatment discontinuation due to NPAE in the DTG group vs. RAL (1.83/100 patient-years vs. 0.70/100 patient-years, p=0.002.	– Higher risk of NPAE discontinuation with DTG vs RAL. – Neither sex nor age was associated with an increased risk of discontinuation due to NPAE.
Cid-Silva et al[52]	Retrospective cohort	542	NR	287.5 days (median)	EVG/c, DTG	– 10.2% of patients were treated with DTG and 4.5% of those treated with EVG discontinued due to adverse events. For DTG mainly related to neuropsychiatric disorders (70.4%) and for EVG/c to gastrointestinal distress (50%).	– Increased risk of NPAE discontinuation with DTG/ ABC/3TC. – Neither sex nor age was associated with an increased risk of discontinuation due to NPAE.

(Continues)

Table 3. Differences in NPAEs with different INSTIs in real-life studies *(Continued)*

	Design	n	Naïve patients	Follow-up	Treatments	NPAE-related outcomes	Factors related to treatment discontinuation for NPAE in multivariate analyses
Brehm et al[49]	Retrospective cohort	323	32%	360 days (median)	RAL, EVG/c, DTG	In the switch group, NPAEs (depression, vertigo and sleep disorders) occurred more frequently in DTG-treated patients (11%, n = 10) compared to the other 2 INSTI-based regimens (EVG: 2%, n = 1; RAL: 1%, n = 1)	NR
Hoffman et al[56]	Retrospective cohort	1.704	13%-23%	11.5-36.3 months (median)	RAL, EVG/c, DTG	– Estimated NPAE rates leading to discontinuation between 12 and 24 months were 5.6% for DTG, 0.7% for EVG/c and 1.9% for RAL (log rank test: p<0.0001). – The median time between DTG initiation and discontinuation was 3.1 months.	Discontinuation of DTG for NPAE was associated with female sex, age >60 years, and concomitant use of ABC.
Lepik et al[57]	Retrospective cohort	1.344	15%	> 24 months	RAL, EVG/c, DTG	– NPAEs were more frequent with DTG (3.5%) than with EVG/c or RAL (2.8% and 1.6%, respectively), but without statistically significant differences.	NR
Peñafiel et al[62]	Retrospective cohort	1.091	68%	1 year	RAL, EVG/c, DTG	– NPAEs significantly more common with DTG than with RAL or EVG/c. – Nearly all patients who discontinued DTG due to toxicity had experienced NPAEs (88%) in contrast to those discontinuing RAL (35%) or EVG/c (19%) (p = 0.0046). – The most common NPAEs leading to early discontinuation were insomnia, dizziness or headache.	NR

ABC: abacavir; DTG: dolutegravir; EVG/c: cobicistat-boosted elvitegravir; AE: adverse events; NPAE: neuropsychiatric adverse events; RAL: raltegravir; 3TC: lamivudine.

of DTG and shares many of its clinical features[67]. In clinical trials with BIC, the treatment discontinuation rate for NPAE is between 0-1%, both in studies in naïve patients[68,69] and in previously treated patients[70–74]. Among the most frequently reported NPAEs are headache (5-18% of patients), fatigue (9-11%) and insomnia (3-8%)[9]. The treatment discontinuation rate for NPAE and the NPAE profile is very similar in studies comparing BIC with regimens including DTG[68,69,73,74]. Interestingly, in a treatment switching study in women with undetectable viral load[71] and a similar study in patients aged 65 years or older[72,9].

Regarding real-life experience with BIC, there are data that suggest that, as with DTG, BIC use may be associated with a higher rate of NPAE than shown in clinical trials[9,75]. In a retrospective analysis, 943 patients were evaluated, who switched from a regimen primarily with DTG or EVG/c to BIC/FTC/TAF. After a median follow-up of 6.2 months, 3.3% of patients had discontinued treatment due to NPAE. The existence of prior depression was predictive of NPAE-related discontinuation of BIC, while discontinuation was not related to pre-existing DTG intolerance. The BIC discontinuation rate for NAEP was similar to that reported in a cohort study of 1,043 patients on DTG treatment[75]. Likewise, another cohort study included 786 patients with undetectable viral load who were switched to a regimen that included an INI: 524 patients on DTG/ABC/3TC and 262 patients on BIC/FTC/TAF. After 24 weeks of follow-up, treatment discontinuation due to NPAE was similar in the BIC or DTG group[76]. Conversely, a pilot study in 109 patients showed that switching from EFV/FTC/TDF to BIC/FTC/TAF was associated with a significant improvement in psychiatric symptoms and sleep disorders, which was expected, given the high neurotoxic profile of EFV. Neurocognitive performance remained substantially stable, although a slight decrease in global cognitive status, as measured by the neuropsychological z score (NPZ-12), and a decrease in certain specific domains (mental flexibility, working memory and memory) were observed[77].

Cabotegravir is a new INI approved as a simplifying treatment in combination with RPV administered as a long-acting injectable every 4 to 8 weeks[9]. In clinical trials, very few cases of discontinuation due to NPAE have been reported[9,78-81]. Real-life studies are required to verify whether the risk of discontinuation due to NPAE is low, as suggested by clinical trials, or higher than expected as with other INIs.

Protease inhibitors

The results of protease inhibitor (PI) neurotoxicity studies in vitro and in animals show large differences depending on the type of PI[6]. Some of the unused PIs such as lopinavir, ritonavir or amprenavir have demonstrated neurotoxic potential in vitro. Conversely, in an in vitro study, darunavir (DRV) did not produce mitochondrial toxicity in rat neurons at clinically relevant concentrations, unlike EFV[82]. Similarly, in an animal study, DRV was not associated with toxicity at the neuroglial level unlike lopinavir[83].

In clinical trials, DRV has also demonstrated a good safety profile at the CNS level[84,85]. In the AMBER study comparing DRV/c/FTC/TAF vs. DRV/c + FTC/TDF in 725 patients, there were no drug-related NPAE events greater than 5% in either arm. There were also no treatment discontinuations due to NPAE in any of the analysed groups[85]. The FLAMINGO study compared DTG versus DRV in 484 patients (242 in each arm). In this study, severe NPAE occurred in 2% with DTG and <1% with DRV. There was a higher proportion of headache (15% vs. 10%) and depression (5% vs. 2%) with DTG compared to DRV[84].

Furthermore, DRV can improve NPAEs in patients on INI treatment such as DTG even in patients who do not spontaneously report neuropsychiatric symptoms[86]. In the DETOX study, switching from DTG/ABC/3TC to DRV/c/FTC/TAF was associated with significant improvements in sleep quality and anxiety scores after four and eight weeks of switching. What is important about this phase 4 study, which included 732 patients, is that patients did not report NPAE while they had an undetectable viral load on DTG/ABC/3TC. Various tools were used to measure CNS symptomatology such as the sleep quality scale (PSQI), the hospital anxiety and depression scale (HAD anxiety score and HAD depression score), and a CNS AE score (CNS AE). At baseline, 37 patients were switched to DRV/c/FTC/TAF and followed up for 8 weeks. Another 35 patients continued with DTG/ABC/3TC for 4 weeks and then switched to DRV/c/FTC/TAF until completing 8 weeks of treatment with this regimen. After 4 weeks, a reduction in PSQI, HAD and CNS AE scores was observed compared to patients who had not made the treatment switch. These improvements were even greater at 8 weeks, when both groups completed 8 weeks of follow-up (Figure 1). The authors conclude that switching from DTG/ABC/3TC to DRV/c/FTC/TAF in patients with no CNS symptomatology at baseline is associated with an

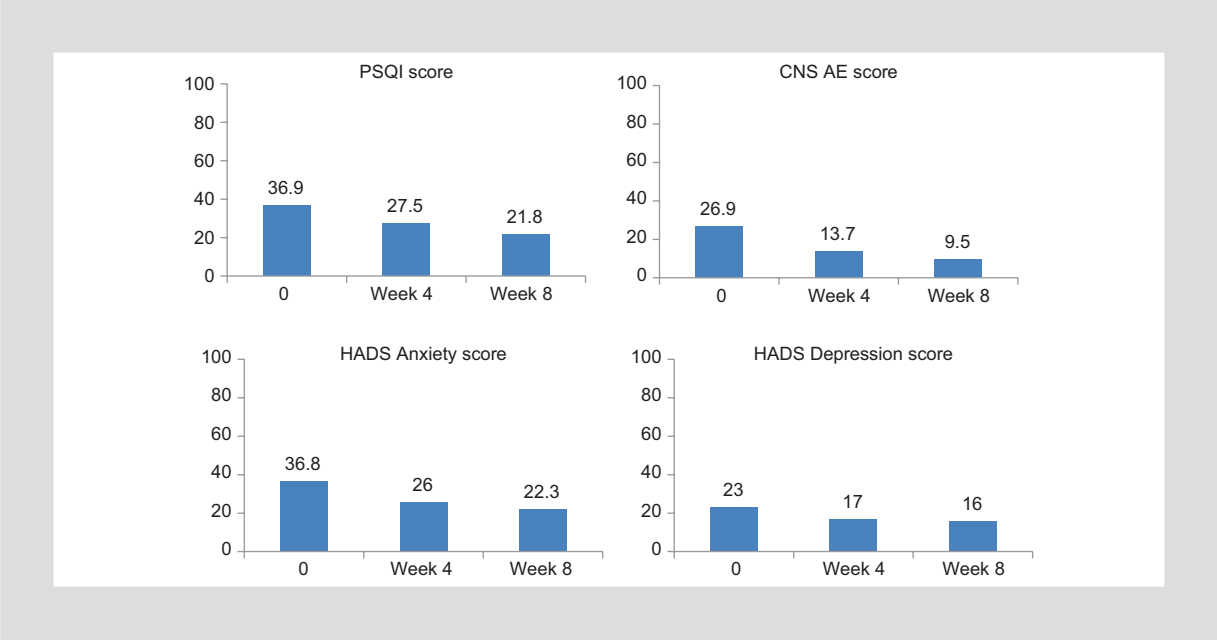

Figure 1. *DETOX Study: changes in PSQI score, HADS Anxiety score, HADS Depression score and CNS AE score after switching DTG/ABC/3TC to DRV/c/FTC/TAF. AE: Adverse events; CNS: central nervous system; HADS: The Hospital Anxiety and Depression Scale; PSQI: Pittsburgh Sleep Quality Index.*

improvement in sleep quality and self-reported neuropsychiatric symptomatology[86].

Conclusions

Neuropsychiatric disorders and ARV-associated NPAEs are very common in PLHIV and can negatively affect their quality of life and worsen the prognosis of the disease[3,6]. A proactive approach to detecting these disorders is necessary in the initial assessment of PLHIV and during follow-up. ART-associated neurotoxicity should be suspected in any patient who reports the onset or worsening of neuropsychiatric or cognitive symptoms after initiation of a new ART, as long as other aetiologies are not identified[3,6]. The occurrence of CNS adverse events is associated with some ARV drugs more than others, with the INI family currently being the most represented in this pathology[6]. In real-life studies, INIs may be associated with a higher prevalence of NPAEs than described in clinical trials[6,13]. Latest generation PIs such as DRV appear to have a more favourable profile in this regard[84,86].

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