Le Infezioni in Medicina, n. 4, 488-494, 2023
10.53854/liim-3104-7

Central nervous system and neuropsychiatric disturbances in people living with HIV

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Article received 10 October 2023; accepted 21 November 2023

SUMMARY

CNS/NP disturbances are common in PLWH and still represent one of the major concerns in the modern HIV era.
With an increasingly aging population, the spectrum of these manifestations depends on several factors, such as HIV direct activity in the CNS, the type of antiretroviral therapy, comorbidities and age-associated decline in neurocognition.
When selecting an appropriate ARV regimen for PLWH, it is important to discuss the perception and impact of CNS/NP disturbances in the patient's quality of life.
The rapidly evolving progress in antiretroviral development encourages the possibility of having minimally toxic molecules with even better CNS tolerability profiles in the future. Different studies have shown how in both ARV-naive and virologically suppressed adults, BIC-based regimen is associated with significantly lower bothersome CNS/NP symptoms when compared to DTG-based regimen.
In conclusion, BIC-based regimen is an interesting option for all types of PLWH, especially among ARV-experienced patients with previous exposure to either EFV or DTG (or both) that may suffer from bothersome CNS/NP disturbances associated with antiretroviral therapy.

Keywords: Neuropsychiatric disturbances; PLWH; efavirenz; dolutegravir.

INTRODUCTION

Since the beginning of the epidemic in the 1980s, approximately 84 million people world-wide have become infected with human immunodeficiency virus (HIV) and around 40 million people have died of HIV; according to the most recent data, roughly 38 million people were living with HIV at the end of 2021, making it one of the most challenging epidemics of all times [1]. The story of HIV has changed dramatically over the years due to the approval of different antiretroviral (ARV) therapies, which have become extremely potent in inhibiting viral replication and preventing progression towards acquired immunodeficiency syndrome (AIDS); although PLWH can now lead a normal life with an estimated life-expectancy comparable to those without HIV infection, clinicians have to deal more frequently with the consequences of ceaseless HIV-related chronic inflammation and ARV-related side effects, including most often disturbances of the central nervous system (CNS) and neuropsychiatric (NP) disorders [2, 3]. These events, which include a wide range of signs and symptoms, have great impact on the global health of the HIV population, which has become older and more comorbid over the years and is therefore more prone to decline in neurocognitive functions *per se*: the presence of chronic, degenerative diseases and polypharmacy overall hazes the clinical scenario and makes it difficult to discriminate between CNS/NP manifestations straightly linked to HIV/ARV or to the overall clinical characteristics of the patients [4]. Nevertheless, several studies suggest that CNS/NP disorders are overall more frequent

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in PLWH than the general population, with an incidence of roughly 20-40% versus 5-10% in HIV-negative individuals, especially in women. Among these conditions, depression and anxiety are the most frequent ones and, at the same time, most often underdiagnosed or attributed to other causes [5-7].

Before the advent of ART, HIV-related neurologic diseases (including active viral replication in the CNS, CNS opportunistic infections, HIV-related sensory polyneuropathy and others) developed in most infected patients, with different studies reporting up to 30-50% incidence of such complications [8]. This scenario has changed dramatically with the introduction of antiretrovirals, with currently most CNS/NP disturbances attributable to HIV-associated neurocognitive disorder (HAND) and ART-related side effects [9]. CNS opportunistic infections are heterogenous and may range from a wide variety of clinical, radiological, and laboratory scenarios [10]. The diagnosis of these conditions is usually challenging as they are now less common in high-income countries, where the overall incidence of these events has greatly decreased [11]. Conversely, in low-income regions of the world where the access to ART is limited, certain CNS opportunistic infections, such as tuberculous and cryptococcal meningitis, remain significant contributors to morbidity and mortality for PLWH [12].

CNS/NP disturbances in PLWH are complex and the exact neuropathogenetic mechanisms are often challenging to highlight: usually, several intertwined factors coexist. For example, low CD4+ T cells count, unknown HIV status and poor drug compliance have great impact on the development of CNS/NP disturbances in PLWH and are significantly associated with development of CNS opportunistic infections, cerebrospinal fluid (CSF) viral escape, chronic cerebrovascular disease and HAND [13]. Furthermore, even in experienced patients under optimal antiretroviral therapy and acceptable viro-immunological conditions, it is unclear whether the CNS serves as a source and niche of perpetual neuroinflammation that contributes to the development of CNS/NP disturbances [14]. The discussion of the complex neuroimmunology of HIV goes beyond the scope of this review, which will focus on the most common causes of CNS/NP disturbances in PLWH in regions with prompt access to ARVs.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)

Formerly known as AIDS-dementia complex, HAND comprehends a spectrum of neurocognitive disorders associated with HIV, ranging from asymptomatic/mildly symptomatic to severe and debilitating forms of dementia with significant impact on the patient's quality of life. The exact mechanisms for HAND to occur are still to be fully dilucidated, but an interplay of elements (such as HIV *per se*, HIV-related systemic and CNS inflammation, HIV cross penetration through the blood-brain barrier acting as a reservoir for replication) appears to be a major determinant in the pathogenesis of these events. Interestingly, this spectrum of disorders may ensue in both HIV-uncontrolled and HIV-controlled individuals, with different risk factors contributing to its development [15]. In HIV-uncontrolled individuals, a longer duration of untreated actively replicating infection, a lower nadir of CD4+ T-cells count, higher HIV baseline viral loads and AIDS-defining illnesses have been recognized as risk factors, whereas HIV-controlled individuals tend to suffer from HAND because of a global longer duration of HIV infection (regardless of viro-immunological status), pharmacotherapy and polymorbidity. Clinically, HAND can manifest as cognitive, behavioral and/or motor dysfunction. Symptoms are heterogenous, and may range from memory impairment, lack of concentration and attention, apathy, social withdrawal, and loss of interest in different activities. Although heterogenous, HAND does not include concrete signs of cortical dysfunction such as apraxia, aphasia, diplopia, hyposthenia, and others: the presence of these signs and symptoms may hint differential diagnosis. Detailed neuropsychological evaluations, along with different tests and scales, are fundamental to establish a diagnosis of HAND and to assess its evolution over time. Neurocognitive impairment is often diagnosed despite ART, and several studies have reported some degree of neurocognitive dysfunction attributable to HAND in up to 50% of PLWH, with most cases being either mild or asymptomatic thanks to the effects of ART; interestingly, the incidence of severe HIV-associated dementia is decreasing and plays a less important role nowadays than it used to [16]. Latest highly effective treatment regimens ensure long-term vi-

rological success, therefore virally suppressed PLWH are unlikely to show severe cognitive deterioration with stable HIV infection. Nonetheless, the prevalence of older and comorbid PLWH is increasing; thus, it is reasonable to hypothesize that the burden of HAND will increase in the next future.

THE ROLE OF EFAVIRENZ IN CNS/NP DISTURBANCES

Efavirenz (EFV), the third approved non-nucleoside reverse transcriptase inhibitor (NNRTI), has certainly been the most investigated antiretroviral as far as CNS/NP disturbances in ARV-treated PLWH are concerned. EFV-based regimen has been one of the most prescribed treatment for many years, due to its high efficacy in limiting viral replication by binding non-competitively to viral reverse transcriptase and altering enzyme conformation and function: important clinical trials established its effectiveness in the initial treatment of HIV-infected individuals, showing potent and durable virological suppression and convenient once-daily administration [17]. Notwithstanding its optimal pharmacokinetic profile, EFV-induced neurological toxicity soon surged in clinical practice as some of the most common – if not the most common – adverse events related to its use. The spectrum of EFV-induced toxicity varies extensively, with both neurological (namely vivid dreams, dizziness, insomnia), neuropsychiatric (impaired concentration, lack of attention and focus, irritability) and psychiatric (hallucinations, anxiety, depression, suicidality) effects [18]. These adverse events occur in up to half of patients taking EFV and usually (but not always) resolve after several weeks of drug administration [19]. Although some sort of tolerance develops in most patients, EFV-based regimen has been gradually discontinued with the advent of new molecules for the management of HIV, both because of the patients' will to discontinue such therapy and because of the established role of EFV in determining long-term neurotoxicity. The ability of EFV to induce long-term and persistent cognitive impairment regardless of ARV switch has been demonstrated, thereby posing a significant concern in an ageing population with, as already mentioned, a significant prevalence of HAND and inevitable risk of neurocognitive decline [20]. Albeit well established, the exact mechanisms at the basis of EFV-induced CNS disturbances haven't been fully elucidated yet: it appears that its main metabolite, 8-hydroxy-efavirenz, acts as a neurotoxin in a dose-dependent manner, generating oxidative stress and consequently mitochondrial dysfunction at neuronal level, which can manifest through a variety of clinical scenarios. Other possible mechanisms, such as altered calcium homeostasis, decreases in brain creatinine kinase, mitochondrial damage, increases in brain inflammatory cytokines and involvement of the cannabinoid system have been suggested, too [21]. Although some studies have demonstrated that lower doses of EFV appear safe in maintaining adequately suppressed HIV viral loads and may exert less toxicity from a neuronal point of view, the approval of new, highly effective molecules with a much safer CNS profile has discouraged EFV use [22]. For instance, data from four ACTG trials on antiretroviral-naïve participants randomized to either EFV-containing or EFV-free (with either a protease inhibitor or a 3-nucleoside regimen) were analyzed for risk of suicidality (defined as suicidal ideation and attempted or completed suicide): results showed that the initial treatment with EFV was associated with a 2-fold risk of suicidality compared to an EFV-free regimen [23]. Likewise, the discontinuation of EFV-based regimen in favor of novel molecules may furthermore improve different aspects of neurocognition, such as sleep quality, anxiety and depression. For instance, switching from EFV to bictegravir (BIC)-based regimen appears to improve psychiatric symptoms and sleep quality at 48 weeks after EFV discontinuation [24]. In a population with an already high rate of neuropsychiatric disorders, minimizing the possibility of amplifying such conditions becomes not only a choice but also good clinical practice: choosing a less impacting molecule not only improves patient's wellbeing but also favors adherence and compliance, paving the way for a more personalized approach in the choice of ART regimen. Despite the remarkable efficacy of the drug, this peculiar neurotoxicity and the advent of new antiretroviral drugs characterized by lower toxicity has determined the progressive exit of EFV from the recommended regimens in the main international therapeutic guidelines of high-income countries [25, 26].

THE ROLE OF INTEGRASE STRAND TRANSFER INHIBITORS (INSTI) IN CNS/NP DISTURBANCES

Integrase strand transfer inhibitors (INSTI) are one of the most potent, efficacious and safest class of antiretrovirals for the management of HIV infection. With the first agent of the class being raltegravir (RAL), the approval of other drugs, including dolutegravir (DTG), elvitegravir (EVG), bictegravir (BIC) and cabotegravir (CAB) has gradually changed the story of ARV tolerability for PLWH. Currently, the most commonly used INSTIs include DTG (often co-formulated with either 3TC or RPV) and BIC (co-formulated with FTC/TAF); RAL-based regimen is still used in certain conditions (e.g., pregnancy), whereas EVG use is increasingly discouraged because of its co-formulation with cobicistat, generating problems in terms of drug-drug interactions [25]. CAB has only been recently approved as a long-acting therapy, thus data on its use are still very scarce. As a class, INSTIs are safe and generally well-tolerated, although CNS/NP disturbances have also been described for this class and have been documented in clinical practice, especially for DTG and, to a lesser extent, for RAL.

Although present, the entity and extent of CNS disturbances with RAL administration remains somewhat limited and less significantly impacting on the patients' quality of life than other antiretrovirals. The exact mechanisms through which RAL generates neurotoxicity are currently unknown; *in vitro* studies suggest RAL induces the production of reactive oxygen species in astrocytes, although not at clinically relevant concentrations: therefore, the exact dynamics underlying RAL-related CNS/NP disturbances are yet to be elucidated [21]. Studies have shown optimal tolerability profile and, in clinical trials, RAL administration showed a similar incidence of CNS/NP disturbances when compared to placebo and a lower incidence when compared to EFV [27]. Real world data on CNS/NP disturbances associated to RAL exposure are discordant, with huge intervariability among the different analyzed cohorts. While certain studies report very few CNS/NP adverse events, others report a much higher incidence, which goes up to 10%: the disparity among the different populations needs further study to correctly identify the safety and tolerability profile of RAL as far as CNS/NP disturbances are concerned [28, 29]. Contrariwise, DTG is more often associated to development of CNS/NP disturbances, and among INSTIs, it is responsible for the higher rates of ARV discontinuation due to neuropsychiatric effects [30]. The most prevalent CNS/NP disturbances associated with DTG use vary from sleep disturbances, insomnia, anxiety, dizziness, headache and depression: these events are usually mild to moderate but may have a significant impact on the patient's quality of life, up to the point of inducing drug discontinuation [31]. Similarly to RAL, the exact mechanisms leading to DTG-induced CNS/NP disturbances are not fully understood [21]. While initial randomized clinical trials (both in treatment-naïve and treatment-experienced individuals) reported a low incidence of neuropsychiatric disturbances, data from large cohort studies have instead demonstrated higher rates of these events, which were responsible for DTG-regimen discontinuation [32]. These studies have shown that DTG-related CNS/NP disturbances peak during the first two years of drug administration, resulting into high rates of ARV discontinuation: this phenomenon becomes anecdotal and sporadic with persistent exposure to the drug, possibly suggesting some sort of tolerance developing with continuous administration [33, 34]. Interestingly, younger and ARV-naïve patients appear to be at higher risk of developing CNS/NP disturbances than older and ARV-experienced patients, conceivably due to an intrinsic fragility and reluctance towards the diagnosis of HIV infection. The relative risk appears furthermore much higher with pre-existing neuropsychiatric conditions: since DTG-regimen is one of the most frequently prescribed antiretroviral as suggested by international guidelines, a careful assessment of pre-existing clinical risk conditions becomes of paramount importance and must be carefully considered when offering antiretroviral therapy.

Although DTG does appear to be linked to these events, the absolute number and frequency of CNS/NP disturbances are lower when compared to EFV-exposure. Moreover, while DTG appears to be more often linked to disturbances in the sleep cycle, suicidal intentions and other neurocognitive impairment are seldomly reported [35]. Considering also its viro-immunological superiority, a DTG-based regimen represents a more valid, safer and tolerable option with respect to an EFV-based one

as far as CNS/NP disturbances are concerned [36]. Bictegravir (BIC), one of the most recently developed INSTIs, is currently recommended by international guidelines as first choice for the treatment of HIV infection due to its optimal pharmacokinetics, practical single-tablet regimen formulation and excellent tolerability profile, with very few side effects reported in clinical trials. Among the explored adverse events associated to BIC exposure, CNS/NP disturbances are scarcely observed, questioning whether these events are class-related or, perhaps, molecule-related. Different studies have shown how in both ARV-naïve and virologically suppressed adults, BIC-based regimen is associated with significantly lower bothersome CNS/NP symptoms when compared to DTG-based regimen, favoring switch from the latter and better adherence to the former [37, 38]. Sleep disturbances and neuropsychiatric symptoms of depression have also been shown to rapidly wane when switching from DTG to BIC, making it apparently free from CNS/NP disturbances of all kinds among INSTIs [39]. However, considering the heterogeneity of the HIV-infected population and the relatively early introduction of BIC among modern antiretrovirals, it is still precocious to draw such conclusions, and real-world data focusing on CNS/NP disturbances in daily-life settings are mandatory to verify its long-term tolerability and safety profile [40]. These characteristics, however, make BIC an interesting option for all types of PLWH, especially among ARV-experienced patients with previous exposure to either EFV or DTG (or both) that may suffer from bothersome CNS/NP disturbances associated with antiretroviral therapy.

THE PATIENT'S PERSPECTIVE ON CNS/NP DISTURBANCES

When selecting an appropriate ARV regimen for PLWH, it is important to discuss the perception and impact of CNS/NP disturbances in the patient's quality of life. In previous years, where HIV-infection was much less manageable than it is nowadays, the side effects associated to ARV exposure, including CNS/NP disturbances, might have seem a reasonable compromise to deal with HIV and be able to maintain a desirable virological suppression, preventing progression towards AIDS. As of today, however, the selection of a more tailored ARV regimen has become one of the cornerstones of modern HIV-therapy: choosing the appropriate regimen according to the needs of the different patients living with HIV has become one of the most important suggestions by international guidelines [25, 26]. As suggested in different works, PLWH's perspectives often differ from those of clinicians: while certain aspects of neurocognition can be objective to both patients and clinicians (e.g., insomnia), some other important features are often either misdiagnosed or undervalued because of their subjective nature, making it hard to estimate the real incidence of these events in the HIV-infected population [41, 42]. A huge proportion of mental health conditions in PLWH is in fact underdiagnosed and, consequently, undertreated: PLWH are undoubtedly more prone to develop mental health conditions compared to HIV-negative individuals [7]. Social stigma, sociodemographic factors, a low educational level, and the feeling of belonging to a minority group predict lower likelihood of using mental health services, and this in turn has an impact on ART-adherence and HIV management [43]. All considered, it is mandatory to acknowledge these aspects in clinical practice when dealing with CNS/NP disturbances in PLWH: as ART becomes more precise and tailored to the patient, the same should account for integrated mental health services, which should be customized to the specific needs of patients, particularly for vulnerable populations in resource-constrained settings.

CONCLUSIONS

CNS/NP disturbances are common in PLWH and still represent one of the major concerns in the modern HIV era. With an increasingly aging population, the spectrum of these manifestations depends on several factors, such as HIV direct activity in the CNS, the type of antiretroviral therapy, comorbidities and age-associated decline in neurocognition. Diagnosing these conditions can be particularly challenging for clinicians, as huge interpersonal variability and low self-perception of these conditions exist. The rapidly evolving progress in antiretroviral development encourages the possibility of having minimally toxic molecules with even better CNS tolerability profiles in the future. For the time being, real-world data and observational studies, notwithstanding their caveats,

can provide more information about the most widely used antiretrovirals and can serve as useful tools for even better management of CNS/NP disturbances.

Conflict of interets
The authors declare no conflict of interests.

Funding
The authors declare no external funding was provided to support the writing of the article.

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