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Review

Neuropsychiatric sequelae of medication non-adherence in people living with HIV

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Abstract: Non-adherence to anti-retroviral therapy (cART) among people living with HIV/AIDS (PLWHA) is complex, multifactorial, and leads to increases in viral load, immunosuppression, and HIV burden related to direct CNS virulence and cART re-initiation (i.e., immune reconstitution syndrome). Among behavioral disturbances, which may become long-lasting without proper treatment, major depressive disorder, generalized anxiety disorder, schizophrenia, and bipolar spectrum disorders are frequent, as well as exacerbation of other premorbid underlying psychiatric conditions, such as post-traumatic stress disorder (PTSD) and substance use and related conditions, not to mention neurocognitive disorders that are encompassed under the umbrella term of HIV-Associated Neurocognitive Disorders (HAND). In this review, we summarized the neuropsychiatric sequelae of medication non-adherence in PLWHA by utilizing two clinical vignettes to illustrate how syndemic factors may interact and lead to unique presentations.

Keywords: HIV-associated dementia; anti-retroviral agents; medication adherence; neurocognitive disorders; psychiatric disorders

Abbreviations: ADC: AIDS Dementia Complex; AIDS: Acquired immunodeficiency syndrome; ANI: Asymptomatic neurocognitive impairment; ATP: Adenosine triphosphate; cART: combination anti-retroviral therapy; CNS: Central nervous system; GAD: Generalized anxiety disorder; HAD: HIV-associated dementia; HAND: HIV-associated neurocognitive disorders; HCL-32: Hypomania

checklist 32; HIV: Human Immunodeficiency Virus; IL-1β: Interleukin-1beta; KYN/TRP: Kynurenine-to-tryptophan ratio; MoCA: Montreal Cognitive Assessment; MiND: Minor neurocognitive disorder; NNRTI: Nonnucleoside reverse transcriptase inhibitor; NRTIs: Nucleoside analog reverse transcriptase inhibitors; PI: Protease inhibitor; PLWHA: People living with HIV/AIDS; PHQ-9: Patient Health Questionnaire; PTSD: Post Traumatic Stress Disorder; TNF-α: Tumor necrosis factor-alpha; TSH: Thyroid-stimulating hormone

1. Introduction

The human immunodeficiency virus (HIV) and its associated acquired immunodeficiency syndrome (AIDS) were first described in 1981 in the United States, and global spread was quick. By the late 20th century, HIV/AIDS became a major global health challenge. Nearly 38 million people are currently infected, and an average of one million die yearly from AIDS-related illnesses [1].

The widespread use of combined anti-retroviral therapy (cART), a combination of at least three drugs that includes either a protease inhibitor (PI) or a non-nucleoside-analog reverse-transcriptase inhibitor (NNRTI) and two nucleoside-analog reverse-transcriptase inhibitors (NRTIs), has substantially improved the prognosis of PLWHA [2], with a more recent increase in the use of integrase and fusion inhibitors as part of cART treatments [3]. In the USA, one in two patients had a Medicaid claim for at least one neuropsychiatric event 6 months after initiation of cART [4], while the prevalence of neurocognitive impairment in PLWHA ranges from 11.5 to 73.6% [5] with the presence of major neurocognitive disorder in 1–5% of those exposed to cART in developing countries with similar global trends [6]. When used consistently, cART is highly effective and leads to HIV suppression, improving immune function and significantly reducing the risk of developing AIDS. However, cART is not curative, and its discontinuation invariably leads to re-detectable viral loads within weeks [7].

Barriers to cART adherence vary across demographics. Lifestyle factors and cognitive symptoms play a role, especially in more complex cART regimens [8]. Depression is also a frequent barrier, as well as alcohol and other substance use disorders. In addition, societal stigma and health service-related barriers commonly limit cART adherence.

Although HIV is known for its direct impact on the cellular immune system through the depletion of infected CD4 lymphocytes, it also has a broad impact on the CNS via direct neurotoxic substances and inflammatory cytokines released by glial cells.

HIV-associated neurocognitive disorders (HAND) are a group of cognitive disturbances with varying levels of functional decline, mood, and impulse control manifestations, especially in patients non-adherent to cART or whose regimen was delayed, which can predispose them to a range of opportunistic infections comprising neuro-AIDS.

This article reviews common neuropsychiatric sequelae related to cART non-adherence by utilizing two clinical vignettes to illustrate how syndemic factors may interact and lead to unique presentations.

2. Materials and methods

Two clinical vignettes will discuss the biopsychosocial aspects of cART non-adherence in a resource-rich and resource-poor setting, respectively. We reviewed the available literature on Medline for relevant articles on June 5th, 2022, using the search terms HIV and cART or anti-retroviral and

non-adherence. Three hundred thirty-two articles were identified, and 34 were included in this study to address issues identified in the clinical vignettes.

2.1. Case 1

A 32-year-old married woman living in a remote rural municipality in Northeast Brazil was evaluated in a local government primary care clinic and immediately started on cART following local government guidelines. Education was provided on her condition, treatment duration, efficacy, adverse reactions, and the need for safe sex practices, nutrition changes, and contraception.

She could not read or write and had limited access to transportation, issues that were addressed by relying on her neighbor for support. However, as her neighbor moved to a different city, she serially lost multiple follow-up appointments and became non-adherent to her cART regimen. After two years of sub-optimal cART adherence, her cousin noted that she moved slower than usual and was more confused and forgetful. She was then brought for an evaluation at the local primary care clinic, which referred her to a specialized ambulatory center to treat a suspected case of HAND. During workup, she was found to have both folate and vitamin B12 deficiencies. However, her cognitive symptoms significantly improved 6 months after restarting her cART, repleting the vitamin deficiencies, and connecting her to the local food bank.

2.2. Case 2

A 45-year-old executive at a prominent IT firm was diagnosed with HIV several months earlier during a workup for fatigue-associated diarrhea. Given his busy schedule, he decided to plan a vacation month "to take care of everything medically," as deadlines at work required him to postpone appointments multiple times. However, during one of his task force meetings, he could not remember the highlights of a critical project, became tremulous, and had difficulties typing, which prompted his colleagues to recommend a medical leave "to get checked up". His partner then applied for medical leave and scheduled a telehealth appointment with a private HIV specialist. On further workup, he was found to have a reactivation of neurosyphilis predisposed by steroids he took a month ago to treat an upper respiratory infection and his highly stressful lifestyle. His symptoms were mainly resolved two months later with the proper initiation of cART and three weeks of intramuscular Penicillin G benzathine.

3. Results and discussion

3.1. Reasons for cART non-adherence

The advent of combination anti-retroviral therapy (cART) has drastically decreased the progression to AIDS and mortality among PLWHA, who now have a much-improved quality of life and near-normal life expectancy, to the point now that HIV is viewed as a chronic disease rather than a terminal illness [9]. While it may be challenging to accurately measure it in the short-term, adherence rates below 80% usually culminate with detectable viral load [10], and strategies for earlier identification of non-adherence, such as using visual analog scales, have been tried.

The most frequent reasons for cART non-adherence may be grouped into five themes: Social support, Self-identity, Poverty, Coping, and Health Systems (Figure 1):

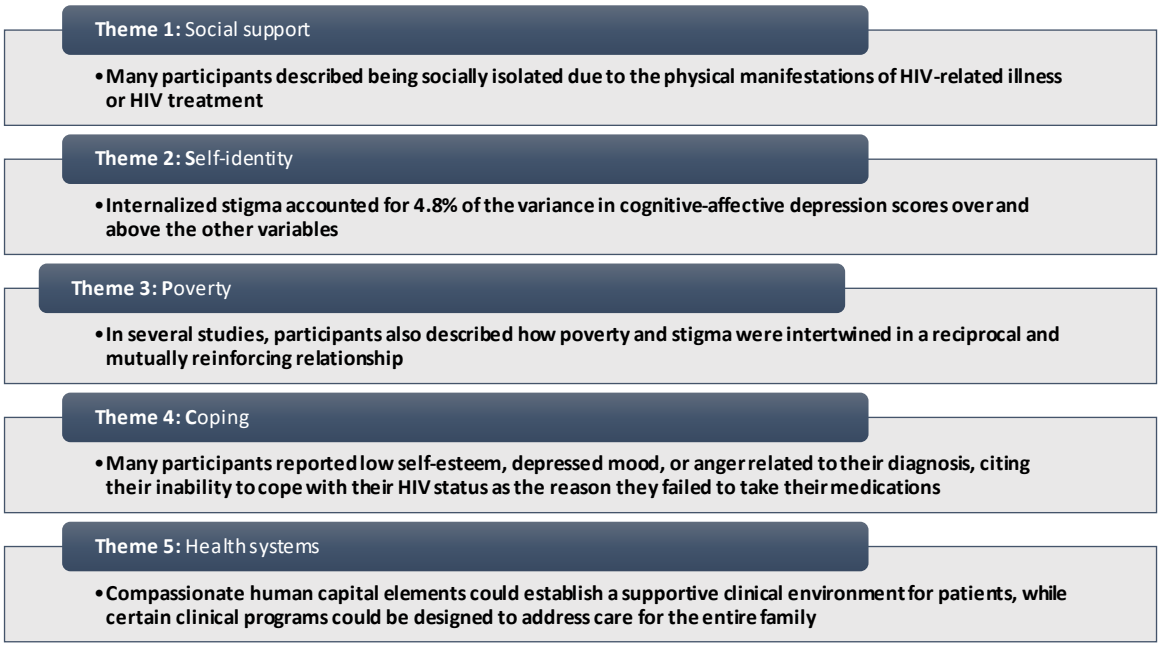

Figure 1. Five themes for cART-non-adherence. Adapted from [8,10].

3.2. Pathophysiology of HIV Associated Neurocognitive Disorders (HAND)

It is well known that the CNS is one of the target organs where HIV can be detected soon after primary infection [11]. HIV preferentially spreads to the basal nuclei and hippocampus, to a lesser extent in the mid-frontal cortex's cortex and cerebellar grey matter. Magnetic resonance imaging studies typically demonstrate cortical and central atrophy with a corresponding ventricular enlargement [12]. These findings typically correlate with neuropsychiatric dysfunction of the frontal-subcortical regions (Figure 2) [13].

In 1986, Navia et al. described neuropathologic changes in AIDS Dementia Complex (ADC), including generalized atrophy, leukoencephalopathy, microglial nodules suggestive of viral encephalitis, and multinucleated giant cells that seem to be directly infected by HIV-1 [14]. However, the exact pathogenesis of how HIV infects the CNS is largely debated. One hypothesis, the "Trojan horse" theory, proposes that the virus enters the CNS through infected monocytes or CD4+ T lymphocytes [15].

Once in the CNS, HIV-1 leads to neurotoxicity, neurodegeneration, and chronic activation of the inflammatory response. This mechanism may also result from immunosuppression, which predisposes to opportunistic infections and CNS neoplasms [16]. HIV also broadly infects macrophages, microglia, and, to some degree, astrocytes, even though they do not primarily support viral replication. Neurotoxic viral proteins are shed by the virus, released by infected cells, and can cause direct neuronal injury [17].

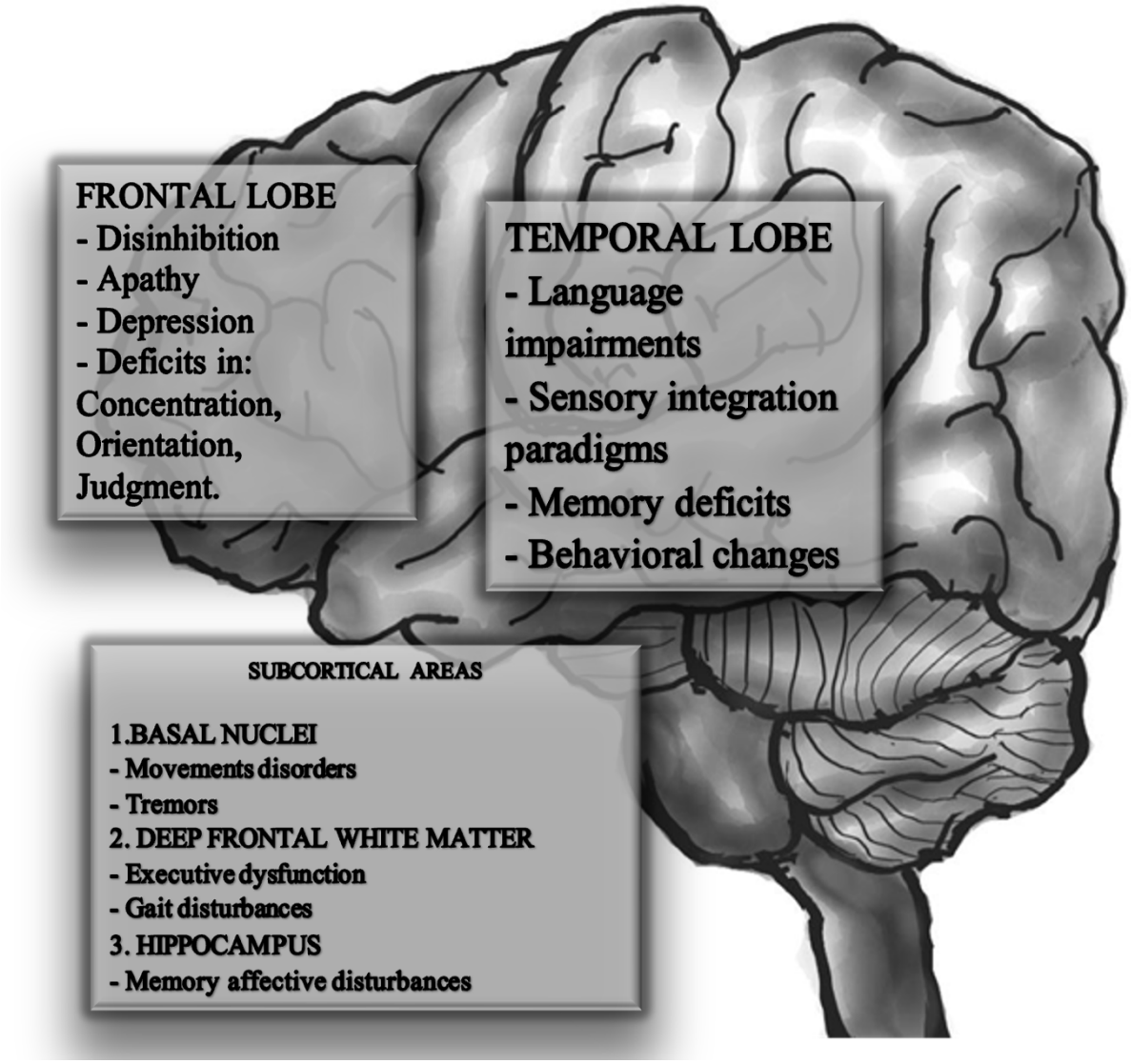

Figure 2. Key brain regions affected by untreated or undertreated HIV infection.

Neuroinflammatory processes in HAND are regulated by perivascular macrophages, microglia, and astrocytes, which release neurotoxic substances and inflammatory cytokines upon immune activation or viral infection, such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), ATP, arachidonate, and the excitatory amino acids, glutamate, quinoline, and cysteine. At the same time, astrocytes also release glutamate and nitric oxide radicals, which predispose to altered neuronal function, injury, and apoptosis [18].

These neurotoxic processes highlight how host-immune responses lead to largely heterogeneous manifestations of HAND [19]. Therefore, it is crucial to rule out other contributing causes that may induce neurocognitive deterioration in the context of delirium while also considering risk factors that can influence HAND severity [20]. These include high serum or CSF HIV viral load, low CD4 nadir, low educational level, advanced age, anemia, illicit drug use, and female sex.

Additionally, several chronic diseases can contribute to neurocognitive dysfunction and present with delirium or primary motor dysfunction, such as traumatic brain injury, developmental disorders,

CNS opportunistic infections, medications with CNS effects, cardiovascular diseases, diabetes, and metabolic problems. Laboratory testing of vitamin B12, folate level, TSH, syphilis, hepatitis C, and vitamin B1 is indicated to rule out other neurocognitive causes [21]. Table 1 describes clinical neuropsychiatric sequelae and contributing factors of medication non-adherence in PLWHA, while the influence of aging in the new onset and progression of neurobehavioral symptoms was reviewed elsewhere [22].

Table 1. Neuropsychiatric sequelae of medication non-adherence in PLWHA.

Psychiatric sequelae	Neurological sequelae
↑Depression, ↑anxiety disorders, adjustment disorder, grief reaction	CNS opportunistic infections: toxoplasma encephalitis, progressive multifocal leukoencephalopathy (JC virus), cytomegalovirus retinitis, herpes simplex virus retinitis, cryptococcal meningoencephalitis, primary CNS lymphoma, large B-cell lymphoma
↑Manic episodes in bipolar disorder	Cardiovascular and cerebrovascular events: vascular dementia, thrombocytopenia
Worsening of substance use disorders (Especially stimulants/cannabis)	Distal symmetric polyneuropathy
↑PTSD, re-traumatization	Asymptomatic neurocognitive impairment Mild neurocognitive disorder HIV-associated dementia
Psychosis (Hallucinations, disorganization of behavior, delusions)	

Note: ↑ means worsening of that particular symptom.

3.3. Neuropsychiatric consequences of cART non-adherence

3.3.1. Cognition

Case 1 summarizes how biopsychosociocultural scenarios can influence adherence to cART, as poverty, difficulties with transportation, and understanding the complex cART regimen led to lost follow-up for years, finally heralding the emergence of neurocognitive symptoms.

Hinkin et al. showed that executive dysfunction, memory impairment, and distractibility are associated with suboptimal cART adherence, especially among those prescribed complex dosing regimens [23]. Specifically, deficits in prospective memory functioning, particularly on the index of time-based prospective memory, are linked to an increased risk of medication non-adherence independent of general cognitive impairment and psychiatric comorbidity [24].

Mental disorders are further exacerbated by HIV progression and functional impairment in cART non-adherence, with uncontrolled mental illness often resulting in alienation from family and friends and occupational impairment. This was illustrated in Case 2, where an executive initially presented with unspecified diarrhea symptoms and fatigue, only to develop asymptomatic neurocognitive impairment with soft cognitive signs that delayed his connection to proper medical care. This, lastly, resulted in clinical deterioration, stigma, and occupational impairment with a functional decline that would have been historically classified as part of the AIDS Dementia Complex (ADC): a general

denomination for a large spectrum of neurocognitive changes typically seen in people living with HIV. In 2007, Frascati criteria delineated the severity of the clinical manifestations of HAND in three levels: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MiND), and HIV-associated dementia (HAD) [25].

Neurocognitive testing on people living with HIV includes assessment of at least five domains: attention, information processing, language, abstraction/executive functioning, sensory-perceptual skills, simple motor skills, complex perceptual-motor skills, and memory (including learning and recall). ANI presents with soft cognitive signs, such as mild psychomotor retardation or difficulties with short-term recall. In MiND, cognitive decline slightly interferes with instrumental activities of daily living in PLWHA, vastly decreasing their effectiveness at work and social engagement. HAD may occur in about 15–30% of untreated PLWHA [26] and is characterized by attention and concentration deficits, notable psychomotor slowing, and various behavioral disturbances that may lead to death within one year [20].

Various screening instruments can be implemented in the identification of HAND. For example, in busier clinical settings, where time constraints are predominant, the clock drawing test may efficiently gauge declines in executive function, visuospatial skills, concentration, working memory, abstraction, and motor skills. At the same time, the Montreal Cognitive Assessment (MOCA) is the most sensitive test to diagnose HAND and takes an average of thirteen mins for its completion.

Finally, there seems to be a significant role in using mobile apps [27] and telehealth platforms [28] to improve cART adherence in PLWHA. For instance, case 2 illustrates how stigma can contribute to clinical deterioration and delayed diagnosis of neurocognitive symptoms in PLWHA, which could have been mitigated by utilizing a smartphone app to connect with an HIV provider in a time-flexible fashion privately. In addition, simple, cost-efficient strategies, such as text-messaging reminders, have improved adherence to tuberculosis treatment [29], which may occur in PLWHA living in developing countries or those undergoing immunosuppressive treatments.

3.3.2. Mood disorders

Depression is the most common neuropsychiatric condition associated with HIV infection. Studies consistently find prevalence rates of about 30% for depression amongst PLWHA [30–33]. Ciesla JA et al. conducted a large-scale meta-analysis showing that depression prevalence in people living with HIV is twice as high as in the general population [1]. HIV may render people susceptible to depression via direct neurotoxic mechanisms, neurotransmitter, metabolic, and inflammatory dysfunction. Changes in immunometabolism of tryptophan, including the kynurenine-to-tryptophan ratio (KYN/TRP), were linked to depressive symptoms amongst PLWHA [34], and overlapping features between depression and cognitive disturbances may be challenging to distinguish. For instance, apathy is frequently present in chronic inflammatory conditions, and HIV infection is known to lead to accelerated aging and long-lasting higher levels of inflammation. Both depression and neurocognitive disorders can lead to worsening apathy [35], which may be particularly difficult to treat. Chronic exposure to HIV-1 seems to lead to an overall deficit of dopamine that may help explain apathy [36], which opens the venue for dopamine modulation when targeting this symptom via dopamine reuptake inhibitors, such as Bupropion or stimulants in selected cases [37].

Mania is often observed in PLWHA, especially in more advanced cases non-adherent to cART. Hypomanic or manic syndromes typically present with impulsivity, manifesting as hypersexual

behavior and increased drug use, synergistically leading to increased HIV transmission behaviors [38]. Mania may also occur as part of a premorbid bipolar disorder (primary mania) or be secondary to the effects of HIV infection in the CNS, treatments offered for HIV infection, or other secondary CNS infections [39], also known as secondary mania. Among practical screening tools utilized to identify suspected cases of bipolar disorder, the hypomania checklist (HCL-32) was an accurate way to detect type II bipolar disorder [40], while the Patient Health Questionnaire (PHQ-9) can be utilized both to identify depression and monitor treatment response longitudinally, being its shorter version (PHQ-2) a time-efficient way for nurses to at least pinpoint the presence of depressive mood/hopelessness and anhedonia. General principles on treatment options for these neuropsychiatric manifestations were described elsewhere [35].

3.3.3. Psychotic disorders

Psychotic disorders can be classified into primary (e.g., schizophrenia, schizoaffective disorder) or secondary (e.g., psychosis caused by a medical condition such as HIV infection). For example, patients with schizophrenia are at increased risk for HIV infection due to poor impulse control, impaired judgment, substance abuse, and other high-risk sexual behaviors that include unprotected sex, sex for money, and drugs [38].

3.3.4. Substance use disorders

Studies have shown a high prevalence of substance abuse among PLWHA, with an estimated lifetime rate of 40–50% [41]. Substance use has been linked to higher rates of HAD and HIV mania than non-drug users [42]. It has been shown that intravenous drug users with HAD do less on cART than non-drug users [43], while substance use is a known risk factor for cART non-adherence.

3.3.5. Anxiety and trauma-related disorders

The prevalence of generalized anxiety disorder (GAD) is increased in PLWHA compared to the general population [23], while up to a third of them may meet the criteria for adjustment disorder in either symptomatic or asymptomatic stages of HIV infection [44].

Post-traumatic stress disorder (PTSD) is also more prevalent in PLWHA, which may share common neurobiological mechanisms [45], especially as HIV can render individuals vulnerable to victimization and other traumatic experiences when presenting in the context of syndemic substance use and related disorders. Conversely, trauma unrelated to PTSD often predisposes people to engage in high-risk behaviors that can lead to subsequent HIV infection, which can be an independent stressor requiring targeted mental health responses [46].

4. Conclusions

Once a diagnosis of HIV is made and cART is initiated, healthcare providers need to consider biopsychosociocultural aspects to individualize their treatment approach, improve patient satisfaction, quality of life, and foster increased adherence. In addition, mental disorders and high-risk behaviors must also be considered in the context of syndemic presentations, especially as they often either lead

to or are worsened by cART non-adherence, which may be considered a biofeedback marker that tracks treatment quality. Finally, the prevention and modulation of CNS neuroinflammation remain a vital aspect of HIV infection that may lead to a panoply of cognitive disturbances encompassed in the umbrella term of HAND.

Multiple mechanisms contribute to neuropsychiatric sequelae in people living with HIV, and coordinated interventions in a multidisciplinary team need to be strategically employed to achieve treatment success. Early detection of non-adherent patients is essential so that treatment teams can identify barriers to continued care and prevent the progression of AIDS and its associated multiorgan illness.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare no conflict of interest in this paper.

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