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Update on neurological complications of HIV

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Abstract

Purpose of review: The prevalence of neurological complications among people with HIV (PWH) is expected to increase as PWH live longer due to increased access to antiretroviral treatment (ART). This review provides updates to the understanding of the neurological sequelae, including neurocognitive impairment, neuropathy, neurological opportunistic infections, and others, which are crucial for improving care and outcomes of PWH.

Recent findings: Recent literature highlights several key themes: the pathophysiology of HIV-related neuronal damage involving HIV proteins (gp120, Nef) and neuroinflammation; the role of aging in exacerbating neurological complications; the high prevalence of HIV-associated neurocognitive disorders (HAND) and Alzheimer's disease-related dementias (AD/ADRD) among PWH; the importance of neurocognitive screening tools like IHDS and MoCA; and the identification of biomarkers and neuroimaging techniques for early detection and monitoring of HAND.

Summary: The findings highlight the need for comprehensive healthcare strategies to manage neurological complications in PWH, including targeted interventions for high-risk groups, improved diagnostic tools, and tailored treatments. It is important for clinicians and researchers to develop effective approaches to mitigate the impact of HIV on brain health and improve quality of life for PWH.

Keywords

central nervous system opportunistic infection; HIV-associated neurocognitive disorder; HIV-associated neuropathy; neurological complications HIV; people with HIV

INTRODUCTION

The number of people with HIV (PWH) worldwide in 2023 was nearly 40 million people with 1.3 million new infections in that year [1]. With improved access to antiretroviral treatment (ART), PWH are living longer increasing the risk of developing aging-related comorbidities [2], including cardiovascular disease, osteoporosis, and neurological sequelae, including neurocognitive impairment, neuropathy, cerebrovascular disease and others.

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Conflicts of interest
There are no conflicts of interest.

Neurological sequelae in HIV may affect up to 50% of PWH on stable ART [3]. These neurological complications may be due to direct effect of HIV or the neuroimmune response to HIV and ART neurological toxicity [4]. In this article, recent updates on neurological complications of HIV, including an update on pathophysiological mechanisms, biomarkers of disease activity and comorbidity prevalence and management, are described. Table 1 describes a summary of the sub-topics covered in this manuscript.

PATHOPHYSIOLOGY OF NEUROLOGICAL COMPLICATIONS OF HIV

Mechanisms of neuronal damage

Several recent studies have studied pathophysiological mechanisms of neurological sequelae in HIV, including how HIV envelope glycoprotein gp120, as well as neuroinflammation, may directly lead to neuronal damage. One study determined whether gp120 is present in the central nervous system (CNS) of PWH both before and after ART. This study found gp120 mRNA in the caudate nucleus and identified gp120 peptides in the cerebrospinal fluid (CSF) of PWH on ART, but not in people without HIV (PWoH), suggesting that gp120 is expressed and released by infected cells despite ART, potentially contributing to the neuropathogenesis of HIV-associated neurocognitive disorder (HAND) [5]. Another HIV protein Nef plays an important role in HIV pathogenesis. A study using a murine model found that Nef contributes to neuroinflammation and neuronal injury, primarily through microglial targeting and demyelination, suggesting that Nef may also serve as a potential target for HIV-NCI pathogenesis [6].

The inflammatory effect of macrophages and microglia has been linked to neuronal damage in HIV. One study assessed cognitive function and monocyte transmigration in 56 PWH on stable ART; those with HAND had significantly increased CD14⁺CD16⁺ monocyte transmigration compared to those with normal cognition, demonstrating that these monocytes may serve as targets for therapeutic interventions in virally-suppressed PWH [7]. The neuroprotective effects of some potential treatment targets have recently been investigated. C16, a PKR inhibitor that suppresses cell proliferation, was shown to have activity against gp120-induced cognitive impairment in vitro and in vivo; C16 improved short-term memory in rats, reduced neuronal damage, suggesting C16 may have protective mechanism against cognitive impairment stimulated by gp120 [8]. These pathophysiological studies have

AGING-RELATED NEUROLOGICAL COMPLICATIONS OF HIV

A recent Position Paper developed by the NeuroHIV and Aging Advocacy Group was published highlighting a multidimensional strategy to protect and enhance brain health in older adults with HIV, focused on prevention, early detection, and management of neurocognitive disorders, including barriers to healthcare and government resources, health literacy, discrimination, and disparities to care. The authors emphasized the importance of developing comprehensive healthcare responses, establishing stigma-free HIV and healthy aging clinics and raising awareness about cognitive health issues affecting PWH [9[■]].

HIV-associated neurocognitive disorders/brain injury

HAND [or HIV-associated brain injury (HABI)] is a common complication of aging with HIV. One recent study analyzed neurocognitive function in virally suppressed PWH in Chennai, India and found that 71% of all virally-suppressed PWH on stable ART had asymptomatic neurocognitive impairment using the International HIV Dementia Scale [10]. Longitudinal cognitive trajectories in PWH have also been characterized. One study assessed longitudinal cognitive profiles of South African women with HIV compared to those without, finding significant group differences in learning and attention/working memory at baseline, and both groups showed improved cognition over time [11]. The association between risk of Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) among PWH has been previously studied, but bur risk factors for AD/ADRD in PWH have been inadequately studied. One recent study found that 5% of the population had AD/ADRD, with a higher likelihood among older adults, males, and those with encephalopathy. This suggests that targeted interventions for AD/ADRD may be necessary for these particular groups who may be at higher risk for AD/ADRD [12].

Risk factors for HAND/HABI

Identifying risk factors for HAND/HABI, either protective or leading to greater risk of HAND/HABI, remains important. One study found that positive psychological factors, such as higher internal strengths were associated with better neurocognitive outcomes, including learning, memory, and higher socioemotional support was linked to better processing and psychomotor speed [13]. Another study examined the relationships between HAND, HIV care engagement, and functional disability among older men living with HIV and substance use. Findings indicated that poorer cognitive performance was associated with more missed HIV care appointments and greater functional disability, highlighting the need for increased neuropsychological assessments and interventions to improve HIV care engagement and mitigate substance use in this population [14]. Mental health also plays an important role in HAND/HABI. For example, one study assessed neurocognitive impairment, depression, and anxiety in HIV-infected individuals in Azerbaijani penitentiary institutions, finding high prevalence rates of HIV-associated neurocognitive disorder (72.7%), depression (72%), and anxiety (67%), highlighting that targeted interventions to address the mental health needs of incarcerated PWH are needed [15].

Polypharmacy may play a significant role in HAND. One recent study used structural equation modeling to examine how comorbidity, polypharmacy, and anticholinergic/sedative burden impact cognitive ability, perceived cognitive deficits, and physical frailty in 824 older PWH. Results demonstrated that anticholinergic and sedatives negatively impacted cognitive ability and frailty, suggesting that polypharmacy reduction could help improve cognitive impairment and frailty in older PWH [16]. Similarly, another study investigated the relationship between medication-related metrics, depressive symptoms, and neurocognitive performance in 491 PWH on ART and found that the use of benzodiazepines, opiates, and anticholinergic drugs was associated with worse neurocognitive and mood outcomes, suggesting that modifying or deprescribing these medications may be beneficial [17].

Neurocognitive screening

Harmonization of neurocognitive batteries and tests to accurately detect HAND in asymptomatic or mild stages is of increasing interest. One recent study from Italy compared cognitive impairment assessments in PWH using the International HIV Dementia Scale (IHDS), HIV Dementia Scale-Italian Version, and Montreal Cognitive Assessment (MoCA), and found that the IHDS and MoCA were useful for detecting HAND in outpatient settings, but MoCA was found to be a more comprehensive assessment for HAND screening [18]. Another study developed demographically-corrected South African normative data for an HAND/HABI-focused neuropsychological test battery for local language speakers and compared its utility to internal standardization norms and US published norms. The newly-developed norms were more sensitive to cognitive impairment in PWH, highlighting the importance of using population-appropriate norms for effective neuropsychological assessment in low- and middle-income countries [19].

Biomarkers of HAND/HABI

Various biomarkers of neuronal degeneration and neuroinflammation have been implicated in the pathogenesis of HAND, particularly neurofilament light (NfL), a marker of neuronal degeneration. One study found significant associations between specific CSF biomarkers and CSF NfL levels in PWH, with notable correlations including CSF t-tau, CSF MCP-1, CSF TNF- α , and albumin ratio in untreated PWH, and CSF IL-21 in treated, virally-suppressed PWH [20]. Another study investigated neuronal degeneration in the setting of acute HIV infection in neurologically asymptomatic individuals and the effects of different ART regimens. A significant proportion of participants had abnormal NfL levels in their serum and CSF at baseline, which decreased over time with ART; there was a positive correlation between NfL and HIV RNA levels, suggesting that CNS involvement can occur early in HIV infection and that ART helps reduce biomarkers of neuronal injury, regardless of the specific drug regimen used [21]. A similar study examined changes in serum NfL levels and their association with neuropsychological performance among women living with and without HIV over approximately 8 years. Higher baseline and follow-up serum NfL levels were linked to poorer neuropsychological performance in both groups [22].

Neuroimaging biomarkers, including functional MRI, Positron Emission Tomography (PET) and magnetoencephalography (MEG), may detect early microstructural changes that may serve as biomarkers prior to clinical onset of HAND. One study used functional MRI and found that tensor-valued diffusion encoding metrics were more sensitive than conventional diffusion tensor imaging (DTI) metrics in detecting HIV-associated brain microstructural injury. This measure showed stronger associations with plasma biomarkers of neuronal and microglial injury, as well as cognitive performance, suggesting that tensor-valued diffusion encoding metrics offer heightened sensitivity in detecting subtle changes associated with axonal injury in HIV [23]. Another study used brain FDG-PET and found that high atherosclerotic cardiovascular disease scores were associated with decreased thalamic glucose metabolism, which was associated with neurocognitive decline. Despite significant gray matter loss over the follow-up period, whole brain FDG uptake did not change, suggesting that FDG PET might underestimate neuronal injury compared to structural MRI [24]. High-density magnetoencephalography (MEG) is used to study neural oscillatory

dynamics in HIV. The authors found changes specifically in alpha activity in the cingulo-opercular cortices and gamma activity in the cerebellum. These oscillatory activities were linked to performance on cognitive flexibility tasks, indicating they may play a role in executive function [25]. These neuroimaging techniques may serve as an advanced in vivo biomarker to detect early or subtle structural changes prior to the onset of symptoms of HAND.

HIV-1 CSF ESCAPE

Neurosymptomatic HIV-1 CSF escape (NSE) occurs when PWH who are peripherally-virally-suppressed on ART develop neurological symptoms and have detectable HIV-1 RNA in their CSF. One recent study found that HIV-1 populations in the CSF in NSE were drug-resistant and adapted to CD4⁺ T cell replication, with higher genetic diversity linked to greater CNS inflammation. This suggests that CNS inflammation and injury during NSE may be driven by replication of partially drug-resistant virus in CNS CD4⁺ T cells [26].

HIV-ASSOCIATED PERIPHERAL NEUROPATHY

Peripheral neuropathy (PN) is the most common neurological issue in PWH, often linked to advanced HIV disease and ART. One study found that 86% of PWH had distal sensory polyneuropathy (DSP), with DSP severity correlating significantly with advanced HIV/AIDS stage, but not with CD4⁺ cell count, ART use, BMI, nor hemoglobin levels [27]. Another study investigated the association between DSP signs and symptoms and plasma biomarkers of inflammation and vascular integrity in PWH and PWH, and found that biomarkers of inflammation (sTNFR2 and VCAM-1) and vascular integrity (MMP-2) were independently associated with DSP signs in both groups, suggesting that these alterations may contribute to DSP pathogenesis in PWH through endothelial dysfunction and axonal degeneration [28]. Another study investigated the relationship between brain white matter hyperintensities (WMH) and gait instability in PWH and age-matched PWH over 15 years; longer sway paths were associated with larger WMH volumes in both groups, but these associations were most influenced by age, pedal discrimination and years with HIV infection, which may contribute to frailty and fall risk as PWH age [29]. Another study found that HIV and certain ARTs can compromise mitochondrial function, leading to decreased mitochondrial DNA quantity and increased common deletions, which are linked to DSP in PWH. These findings highlight the need to protect mitochondrial integrity to treat or prevent HIV-associated PN [30].

CNS OPPORTUNISTIC INFECTIONS IN HIV

Opportunistic CNS infections remain a significant cause of morbidity and mortality in PWH, particularly in resource-limited settings. The DREAMM study aimed to diagnose the causes of HIV-related CNS OIs across Cameroon, Malawi, and Tanzania, and found that the prevalence of cryptococcal meningitis, tuberculous (TB) meningitis, bacterial meningitis, and cerebral toxoplasmosis varied significantly between these countries. Cryptococcal meningitis was the most common infection overall, with high mortality rates, particularly within the first 10 weeks. The study highlights the need for additional epidemiological

data and new interventions to reduce mortality rates posthospital discharge [31]. One study used real-time PCR testing in CSF to identify pathogens, and found that *Toxoplasma gondii* was the most frequently detected pathogen, followed by *Cryptococcus* sp., Epstein-Barr Virus, Cytomegalovirus, Varicella Zoster Virus, and John Cunningham Virus (JCV). Therefore, improvement of access to laboratory diagnostic testing, including PCR testing, in resource-limited settings is needed for early identification and management of CNS OIs in PWH [32]. Another study from western Brazil found that Human Herpesviruses (HHVs), particularly Human Cytomegalovirus and Epstein-Barr Virus (EBV), significantly contribute to neurological diseases like encephalitis and meningitis in PWH which has not been previously thought to lead to high morbidity in HIV [33].

Cryptococcosis also has a high mortality rate in PWH. One study examined survival of 83 PWH with disseminated cryptococcosis over three years, finding that lower plasma levels of interleukin (IL)-1RA and MCP-1 were associated with better survival outcomes. IL-1RA emerged as a key biomarker for predicting long-term survival, suggesting its potential as a therapeutic target in HIV-associated disseminated cryptococcosis [34].

Development of therapeutics for CNS OIs has recently been studied. For example, one study evaluated the use of Pembrolizumab in treating Progressive Multifocal Leukoencephalopathy (PML) in PWH and found that 3 out of 4 patients showed neurological improvement and prolonged survival. Pembrolizumab, combined with ART, led to a significant decrease in PD-1 activity and stabilization of MRI lesions. Despite the small sample size, the results suggest potential benefits of Pembrolizumab, but further investigation is needed [35]. Another study evaluated if adding single high-dose liposomal amphotericin B to standard fluconazole therapy could improve meningitis-free survival in PWH with low cryptococcal antigen (CrAg) titers. Results showed no additional clinical benefit from the combination therapy, with 14.5% of participants experiencing meningitis or death compared to 10.6% with fluconazole alone. Moreover, adverse events were more frequent in the combination therapy group [36]. Similarly, the same group compared mortality rates of daily liposomal amphotericin B and amphotericin B deoxycholate in treating HIV-associated cryptococcal meningitis. Results showed no significant difference in CSF fungal clearance between the two treatments. Mortality at 10 weeks was slightly lower for liposomal amphotericin B but not statistically significant after adjusting for baseline characteristics. Overall, daily liposomal amphotericin B demonstrated similar efficacy to amphotericin B deoxycholate when combined with flucytosine [37].

NEUROLOGICAL COMPLICATIONS OF CHILDREN WITH HIV

Neurological complications are common in children with HIV. One study found that children exposed to HIV and ARTs in utero have a higher incidence of neurodevelopmental disorders compared to the general population, even after adjusting for sociodemographic factors and gestational age. Moreover, exposure to certain ART combinations, like ritonavir-boosted darunavir, was linked to a higher incidence of neurodevelopmental delay, highlighting the importance of ongoing monitoring for children prenatally exposed to HIV and ARTs [38]. One recent study of 148 children with HIV found that 20.9% had peripheral neuropathy. Significant risk factors for peripheral neuropathy were being 15–18 years old,

low BMI for age, recent isoniazid exposure, longer duration of HIV and prior tuberculosis treatment [39].

CONCLUSION

Key developments in the field of neurological HIV have been covered herein. Several emerging research areas in the field of neuroHIV include exploring the mechanisms of neuroinflammation and neurodegeneration in HIV to understand how low-level inflammation may lead to neuronal death and subsequently cognitive decline. The role of the CNS as a reservoir for HIV remains a significant challenge. Understanding how HIV persists in the brain despite ART is crucial for developing effective eradication strategies. Novel biomarkers, including exosome and peroxisomal biomarkers are being identified as potential biomarkers for HAND. Finally, as the population of people living with HIV ages, the interaction between HIV and age-related cognitive decline needs more exploration.

More longitudinal studies are needed to understand the long-term effects of HIV on the brain and cognitive function. Finally, addressing disparities in access to neurological care for people with HIV, particularly in low- and middle-income countries, is crucial. Advancements in neuroHIV research are leading to an improved understanding of the mechanisms, diagnosis and treatment of neurological complications in people living with HIV.

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KEY POINTS

- The findings underscore the need for comprehensive healthcare strategies to manage neurological complications in people with HIV (PWH), including targeted interventions for high-risk groups, improved diagnostic tools, and tailored treatments.
- Recent literature highlights several key themes: the pathophysiology of HIV-related neuronal damage involving HIV proteins (gp120, Nef) and neuroinflammation; the role of aging in exacerbating neurological complications.
- Identification of biomarkers and neuroimaging techniques for early detection and monitoring of HAND is needed.

Table 1. Summary of recent updates in topics related to neurological complications of HIV

Updates	Subtopics	Key points
Pathophysiology of neurological complications	Mechanisms of neuronal damage	New studies on HIV proteins (gp120, Nef) and neuroinflammatory markers contribute to neuronal damage [5,6]
	Monocyte transmigration	Increased CD14 ⁺ CD16 ⁺ monocyte transmigration is linked to neurocognitive impairment [7]
HIV-associated neurocognitive disorders (HAND)	Brain health in older adults	Multidimensional strategies for prevention, early detection, and management of neurocognitive disorders were discussed including updated diagnostic criteria for HABI [9,19]
	Identified risk factors for HAND/HABI	The following risk factors have been identified across various studies as increasing the risk of HAND/HABI: lower internal strengths (poor coping skills), low socioeconomic status, substance use, depression, polypharmacy, physical frailty and other chronic comorbid conditions [13–17]
	Alzheimer's disease and related dementias (AD/ADRD)	Higher risk of AD/ADRD among PWH who are older adults, men, or had encephalopathy [12]
	Impact of polypharmacy	Benzodiazepines, opiates, anticholinergic drugs were linked to worse cognitive and mood outcomes among PWH [16]
	Normative data	The importance of population-appropriate norms for effective neuropsychological assessments were identified [19]
	Neurodegeneration biomarkers	Several elevated levels of CSF biomarkers (NFL, t-tau, MCP-1, TNF- α) were identified as significantly associated with HAND [20,21,22]
HIV-1 CSF Escape	Neuroimaging biomarkers	Tensor-valued diffusion encoding metrics, FDG PET, MEG were useful imaging markers of HAND/HABI [24,25]
	Neurosymptomatic HIV-1 CSF escape (NSE)	Drug-resistant HIV-1 populations in CSF were drug-resistant but adapted to CD ⁺ T cell replication; higher genetic diversity linked to greater CNS inflammation [26]
HIV-associated peripheral neuropathy	Prevalence and risk factors	Significant risk factors for neuropathy in HIV included older age, higher BMI and HIV illness duration, advanced HIV disease, certain antiretroviral treatments [27–30]
CNS opportunistic infections	Prevalence and mortality rates	Cryptococcal meningitis, tuberculous meningitis, bacterial meningitis, cerebral toxoplasmosis were CNS opportunistic infections identified as having high mortality rates among PWH [31,34]
	Diagnostic approaches	Importance of molecular diagnosis for accurate pathogen identification was stressed in one study [32]
Treatments of CNS OIs	Antifungal therapies	Adding single high-dose liposomal amphotericin B to standard fluconazole therapy in PWH with low CrAg titers did not improve meningitis-free survival and led to more adverse events compared to fluconazole alone [36]
Neurological complications in children with HIV	Peripheral neuropathy	Significant risk factors for peripheral neuropathy were being 15–18 years old, low BMI for age, recent isoniazid exposure, longer duration of HIV and prior tuberculosis treatment [39]
	Neurodevelopmental disorders	Children exposed to HIV and ARTs (i.e. ritonavir-boosted darunavir) in utero had a higher risk of neurodevelopmental disorders [38]