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HIV-associated neurocognitive disorders in Africa: challenges, peculiarities, and future directions

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Abstract

The impact of Human Immunodeficiency Virus (HIV) on neurocognition in Africa is a pressing public health issue, with profound implications for both individual well-being and healthcare systems across the continent. This narrative review aims to elucidate the intricate relationship between HIV infection and neurocognitive function, particularly focusing on HIV-associated neurocognitive disorders (HAND), the effects of antiretroviral therapy (ART), and neuropathological changes. Evidence from Africa emphasizes the variability in the prevalence of neurocognitive impairment among people living with HIV. For instance, a meta-analysis showed that Central and South Africa had the highest pooled prevalence of neurocognitive impairment (NCI) (49.33%), followed by East Africa (45.04%) and West Africa (42.40%). These differences may reflect varying ART coverage, healthcare infrastructure, and the prevalence of co-infections like tuberculosis highlighting the importance of region-specific interventions and support services tailored to local contexts. Furthermore, challenges such as late diagnosis, methodological variations, treatment non-adherence, and limited access to specialized care exacerbate the burden of neurocognitive impairment in this setting. Addressing the complex intersection of HIV and neurocognition in Africa requires a multifaceted approach involving various stakeholders, including healthcare providers, policymakers, researchers, and community organizations. Enhancing awareness, education, and capacity- building initiatives can improve early detection and management of neurocognitive disorders among individuals living with HIV. Moreover, investment in infrastructure and resources for neurocognitive care, including diagnostic tools and rehabilitation services, is essential to meet the growing needs of this population. Additionally, promoting research collaboration and knowledge exchange is important for advancing our understanding of HIV-related neurocognitive impairment and developing evidence-based interventions. By fostering partnerships between academia, healthcare institutions, and governmental agencies, we can facilitate the translation of research findings into policy and practice, ultimately improving outcomes and quality of life for individuals affected by HAND in Africa.

Keywords HIV/AIDS, Neurocognition, Africa, Antiretroviral therapy

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Introduction

Human Immunodeficiency Virus (HIV) is a global pandemic affecting millions worldwide, with a profound impact on public health and society. Beyond its well-documented effects on the immune system, HIV is increasingly recognized as a neurotropic virus capable of infiltrating the brain leading to a spectrum of neurocognitive impairments collectively termed HIV-associated neurocognitive disorder (HAND) [1, 2]. This condition encompasses a range of cognitive deficits, from asymptomatic neurocognitive impairment to mild neurocognitive disorder and, in severe cases, frank dementia, significantly impacting the quality of life and functional abilities of affected individuals [3].

In the context of Africa, where the burden of HIV/AIDS is disproportionately high, neurocognitive impairments associated with HIV/AIDS represent a critical public health issue [3–5]. The impact of HAND extends beyond individual health outcomes, influencing transmission dynamics, treatment outcomes, and overall disease burden. Addressing the intersection of HIV/AIDS and neurocognition is therefore paramount for improving clinical care, enhancing quality of life, and reducing the burden of HIV/AIDS in Africa.

This narrative review aims to provide a comprehensive overview of the impact of HIV on neurocognition in Africa, synthesizing existing literature on the epidemiology, pathophysiology and challenges peculiar to Africa. By elucidating the multifaceted relationship between HIV/AIDS and neurocognitive impairments, this review seeks to inform healthcare professionals, researchers, policymakers, and other stakeholders involved in the care and management of HIV-infected individuals in Africa.

Epidemiology of HIV-related neurocognitive disorders

A meta-analysis was conducted to determine the prevalence of neurocognitive impairment (NCI) among people living with HIV across Africa. A total of 22 studies were included in the final analysis, encompassing data from various regions and employing different study designs and assessment tools [6–21]. The pooled prevalence of NCI among HIV-positive individuals in Africa was found to be 45.15% (95% CI: 36.86, 53.43), indicating a substantial burden of neurocognitive impairment within this population. Significant heterogeneity was observed across studies (I^2 = 100%, p-value 0.001), highlighting the diverse nature of NCI prevalence estimates within the African context [10, 22].

Subgroup analysis was conducted to explore potential sources of variation in NCI prevalence based on regional location, study design, assessment tool used, and year of publication. The results revealed differences in NCI prevalence across regions, with Central and South Africa exhibiting the highest pooled prevalence (49.33%), followed by East Africa (45.04%) and West Africa (42.40%). Variation in study design also influenced NCI prevalence estimates, with case- control and cohort studies reporting a higher prevalence (50.90%) compared to cross-sectional studies (44.24%) [10, 22].

Furthermore, differences were observed in NCI prevalence depending on the assessment tool utilized. Studies employing the Montreal Cognitive Assessment (MoCA), Wechsler Adult Intelligence Scale (WAIS), and Neuropsychological Test Battery (such as Grooved Pegboard test, WAIS-III Digit Symbol Coding, Wisconsin Card Sorting test, Hopkins Verbal Learning test and so on) reported a higher prevalence of NCI (50.70%) compared to those using the International HIV Dementia Scale (IHDS) (48.13%) or Geriatric Depression Scale (GDS) and Frascati criteria (33.46%) [10, 22]. This can likely be attributed to the greater comprehensiveness and sensitivity of the former tools in detecting subtle cognitive impairments across multiple domains, whereas the latter tend to be more limited in scope.

Additionally, the temporal trend in NCI prevalence was examined based on the year of publication. Studies published between 2010 and 2015 reported a slightly higher prevalence of NCI (48.89%) compared to those published between 2016 and 2020 (42.55%) [10, 22].

HIV and the central nervous system (CNS)

HIV infection in the CNS triggers complex neurological dysfunctions without directly infecting neurons. Instead, viral proteins released from infected cells and inflammatory mediators from glial cells contribute to neuronal toxicity. HIV primarily enters the CNS through infected macrophages crossing the blood-brain barrier (BBB) during early infection stages, with microglia and macrophages as primary viral targets (Fig. 1). This process leads to the establishment of viral reservoirs within the CNS, complicating efforts to achieve full viral suppression, even with antiretroviral therapy. The "Trojan horse" mechanism, where infected immune cells facilitate viral entry into the CNS, along with viral proteins like Tat and gp120 that increase BBB permeability, are central to this process. The persistence of HIV within CNS reservoirs is influenced by viral integration into the host genome, reverse transcription, and the establishment of latency, particularly in long-lived cells like microglia and astrocytes [23].

HAND represent the clinical manifestations of HIV's impact on the CNS, ranging from mild cognitive impairment to severe dementia (HAD). The neuropathological effects of HIV include regional neuronal damage, with distinct patterns observed in different brain regions such as the hippocampus and basal ganglia. Molecular mechanisms, including alterations in brain-derived

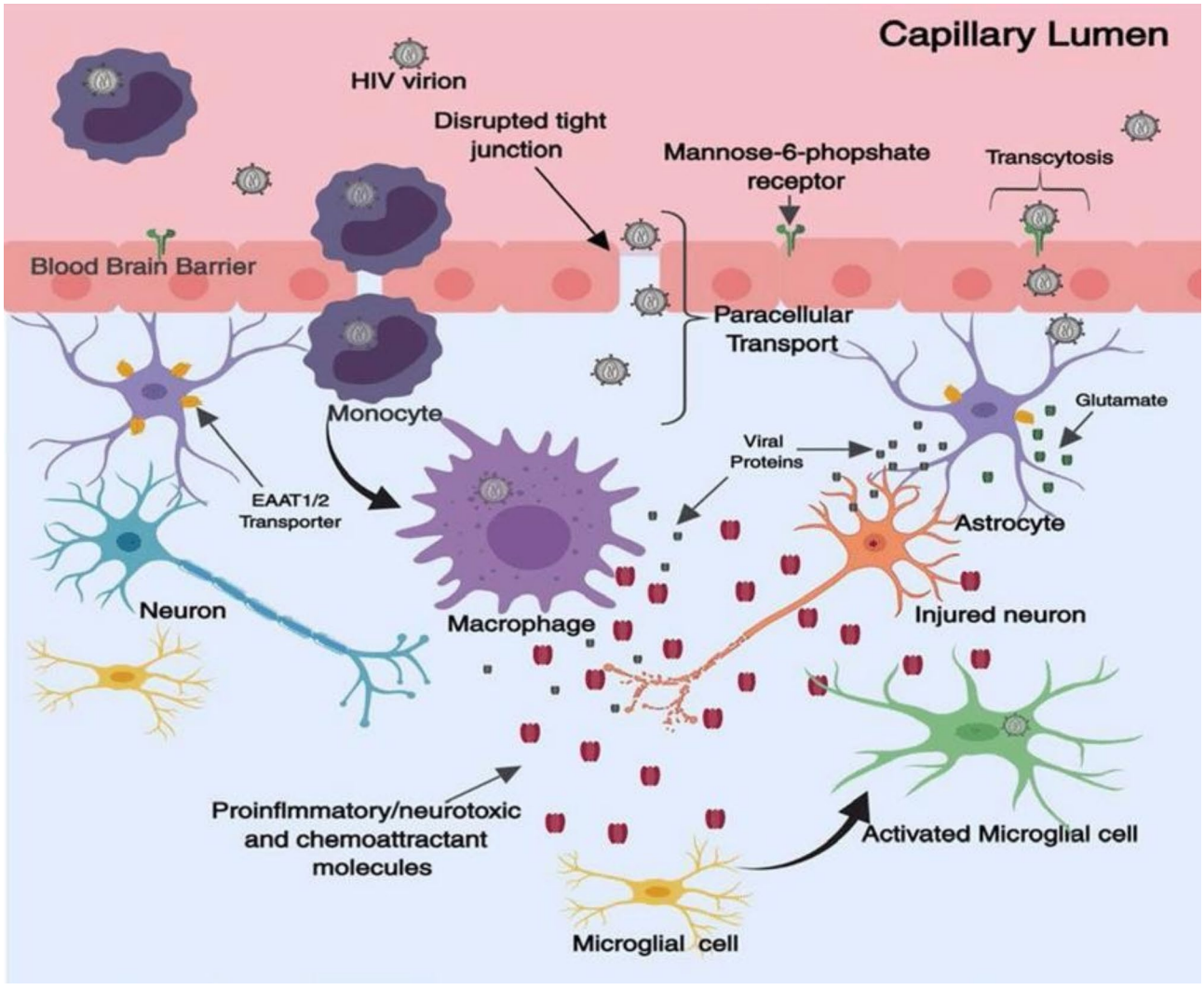

Fig. 1 Neuropathogenesis of HAND [23]

neurotrophic factor (BDNF) levels, play a critical role in the synaptic and dendritic dysfunctions seen in HAND. Decreased BDNF levels, influenced by inflammatory mediators like TNF-α, contribute to the structural and functional deficits characteristic of HAND, including synaptic loss and impaired learning and memory. This complex interplay between viral persistence, neuroinflammation, and neurotrophic factors underpins the broad spectrum of neurocognitive impairments observed in people living with HIV.

Neuropathological changes

The neuropathological changes associated with HAND in Africa present unique challenges due to the distinct HIV subtypes prevalent in the region and the complex interplay of these subtypes with the CNS. Unlike the HIV-1 subtype B, which is common in Western countries, Sub-Saharan Africa primarily deals with subtypes C, G, and CRF_AG [24–27]. These variations may lead to different neurotoxic profiles and immune responses. For instance, the dicysteine motif in the Tat protein of the African HIV subtypes remains intact, promoting monocyte chemotaxis and stimulating microglia and astrocytes to produce inflammatory cytokines. This contrasts with the clade C variants in India, which show a disruption in the same motif, leading to reduced neurocognitive deficits. Moreover, studies in Zambia have shown that clade C infection is associated with reduced microgliosis and astrogliosis, highlighting the possibility of varied immunopathological outcomes between different HIV subtypes [28].

The legacy theory, which posits that HAND is a result of brain damage before the initiation of combined antiretroviral therapy (cART), is insufficient in the African context, where ongoing neuroinflammation persists despite cART use. Elevated levels of cytokines like IFN-gamma and IL-1 alpha in the cerebrospinal fluid indicate continuous neuroinflammation, which contributes to the neuropathology of HAND in African patients. The

distinct pathophysiology of HAND in Africa, shaped by specific HIV clades and the region's unique clinical and socio-economic environment, emphasizes the need for more localized research and treatment strategies that consider these differences [25, 26].

Neurocognitive disorders in HIV

HAND encompass a range of cognitive impairments that can occur in individuals with HIV-1 infection, including asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [29–31]. HAND arises from the involvement of the central nervous system in HIV-1 infection, leading to various neurological and cognitive impairments. The classification of HAND, based on the Frascati criteria, considers both neurocognitive status and functional ability. ANI is characterized by cognitive impairments in at least two domains without affecting daily activities, while MND involves mild cognitive impairment with some functional decline. HAD, the most severe form, presents with significant cognitive deficits and considerable disruption of daily functioning [29–31]. Despite the use of cART, HAND remains prevalent among people living with HIV, with up to a third of patients experiencing ANI and a smaller percentage diagnosed with MND or HAD.

In Africa, the presentation and management of HAND have unique challenges and implications. The burden of HIV in sub-Saharan Africa is among the highest globally, yet neurocognitive disorders related to HIV often remain underdiagnosed or misclassified due to limited access to specialized care and diagnostic tools. Moreover, cultural perceptions and stigma associated with cognitive impairment may deter individuals from seeking help, exacerbating the impact of these disorders. The high prevalence of comorbid conditions such as malnutrition, tuberculosis, and other infections further complicates the clinical presentation and management of HAND in African settings, potentially leading to higher rates of misdiagnosis or underreporting [29–31].

The introduction of cART has significantly reduced the incidence of HAD, particularly in regions with better access to treatment. However, in many parts of Africa, inconsistent access to cART and delayed treatment initiation mean that HAND continues to present in its more severe forms. Additionally, the neuropathological impact of HIV in African populations may be influenced by genetic diversity and different patterns of co-infections, suggesting a need for more region-specific research and tailored interventions. Addressing HAND in Africa requires a comprehensive approach that includes improving access to cART, enhancing diagnostic capabilities, and integrating mental health services with HIV care to better manage and mitigate the cognitive impacts of the disease.

Impact on specific cognitive domains

The impact of HIV on specific cognitive domains, such as memory, learning, and executive function, may be influenced by several unique factors, including the prevalence of different HIV subtypes and varying access to healthcare resources. Research indicates that subtypes like HIV-1 clade C, prevalent in Sub-Saharan Africa, may have different neuropathological effects compared to clade B, more commonly found in Western countries. This could potentially influence the degree and nature of memory impairments observed in African populations. For example, studies suggest that HIV-related neuroinflammation and neuronal injury in the hippocampus, a region important for memory, might be exacerbated in African settings due to delayed initiation of cART and limited healthcare access, leading to more pronounced memory deficits [32].

Regarding executive function, disruptions in frontal-subcortical circuits critical for goal-directed behavior, planning, and decision-making are similarly observed in African populations living with HIV [32]. However, these impairments may be further complicated by social determinants of health, such as lower educational levels, economic challenges, and stigma associated with HIV, which can exacerbate executive dysfunction. The impact of these deficits on daily functioning, including medication adherence and social relationships, may be more severe in African settings due to these additional challenges, further complicating efforts to manage HIV and reduce its transmission.

Risk factors and vulnerable populations

The risk factors for HAND reflect both the biological impacts of HIV and the socioeconomic challenges prevalent in the region. Sub-Saharan Africa bears a significant burden of neurocognitive impairment due to the high prevalence of HIV/AIDS, compounded by delayed access to ART and the prevalence of advanced symptomatic conditions. Patients in this region often present with severe immunosuppression, marked by low CD4 counts, anemia, and significant weight loss, which are strongly associated with the onset of neurocognitive impairment [18, 26, 33]. Studies have shown that while some findings in African contexts do not establish a clear link between plasma viral load and neurocognitive impairment, others demonstrate that high viral load and low CD4 counts are significant predictors of HAND. Additionally, cerebrospinal fluid (CSF) viral load has emerged as a potential predictor of HAND, emphasizing the importance of early and sustained ART intervention to reduce these risks.

The prevalence of HAND is also notably higher among individuals in Africa who do not receive ART or who experience interruptions in their treatment. This issue is exacerbated by the limited access to healthcare and ART in many parts of the continent, increasing the vulnerability of these populations to neurocognitive decline. Unlike in developed countries, where metabolic and age-related comorbidities are prominent risk factors, in Africa, risk factors are more closely tied to immunological status, age, education, and socioeconomic conditions. Lower levels of education, often linked to lower cognitive reserve [34], are associated with an increased risk of HAND, highlighting the critical role of education in mitigating the impact of HIV on cognitive function. Additionally, co-existing psychiatric conditions, such as depression and anxiety, as well as substance use, including alcohol and other drugs, are significant contributors to the development of HAND in African populations [33]. Moreover, individuals in WHO Clinical Staging 3 and 4, particularly those aged 40 years and above, are at a heightened risk, underscoring the importance of targeted interventions for these vulnerable groups. Finally, socioeconomic factors such as low income, unemployment, and poor social support further exacerbate the risk of neurocognitive impairment, making it essential to address these broader social determinants to effectively manage and prevent HAND in the African context.

Challenges and future directions

In Africa, addressing HAND involves unique challenges due to the continent's diverse healthcare landscape. The heterogeneity in neurocognitive profiles, influenced by varying levels of HIV treatment, co-infections, and healthcare access, complicates diagnosis and research. Additionally, the absence of standardized diagnostic criteria, methodological variability, and difficulties in conducting longitudinal studies further hinder progress. Socioeconomic and cultural factors, such as stigma and disparities in healthcare access, also impact research participation and patient management.

To advance understanding and management of HAND in Africa, several key areas warrant focus. Biomarker discovery is important, with efforts needed to identify biomarkers relevant to African populations and consider prevalent co-infections and genetic variations. Precision medicine approaches should be adapted to local contexts, with an emphasis on developing cost-effective genetic testing and personalized treatment plans. Innovative therapeutic interventions must be feasible within the African setting, prioritizing affordable and practical solutions.

Technology-based interventions offer promising solutions for enhancing access to cognitive rehabilitation, particularly through mobile health applications and telemedicine. Finally, promoting multidisciplinary collaborations among local researchers, international experts, and community stakeholders is essential for advancing research, standardizing practices, and integrating findings into national health policies. By addressing these tailored challenges and focusing on localized solutions, the management of HAND in Africa can be significantly improved.

Conclusion

Healthcare providers need to be aware of the complexities of HAND and the importance of early detection and intervention. Standardized diagnostic criteria and assessment protocols should be implemented to ensure consistency in diagnosis and treatment across healthcare settings. Moreover, culturally sensitive approaches are essential to address disparities in access to care and research participation among diverse populations affected by HIV.

Policymakers play a important role in supporting research initiatives and implementing policies that facilitate multidisciplinary collaborations and the translation of research findings into clinical practice. By prioritizing funding and resources for research on HAND, policymakers can contribute to advancements in diagnosis, treatment, and care for individuals living with HIV.

Researchers should continue to explore emerging research areas and collaborate across disciplines to further our understanding of HAND.

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BBB	Blood Brain Barrier
BDNF	Brain Derived Neurotrophic Factor
cART	Combined Antiretroviral Therapy
CNS	Central Nervous System
GDS	Geriatric Depression Scale
HAD	HIV Associated Dementia
HAND	HIV Associated Neurocognitive Disorders
HIV	Human Immunodeficiency Virus
IHDS	International HIV Dementia Scale
MND	Mild Neurocognitive Disorder
MoCA	Montreal Cognitive Assessment
NCI	Neurocognitive Impairment
TNF-α	Tumor Necrotic Factor-alpha
WAIS	Wechsler Adult Intelligence Scale

Author contributions

T.O conceptualized the study. T.O, E.O, D.O, O.O, F.M were involved in the abstract and full paper screening. All authors wrote the first and final drafts. All authors read and approved the final manuscript.

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Data availability

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Declarations

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