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HOT TOPIC

An Overview of HIV-associated Neurocognitive Disorder in South Africa

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Abstract

Purpose of Review It is well established that South Africa has the highest prevalence of human immunodeficiency virus (HIV) worldwide. The increasing widespread availability of combination antiretroviral therapy (cART) has improved the life-expectancy of people living with HIV. cART has dramatically reduced morbidity, however many people living with HIV continue to experience central nervous system (CNS) complications including neuropsychiatric conditions such as depression, anxiety, and neurocognitive disorders.

Recent Findings The pathological effects of HIV on the CNS have not been well elucidated. There are limited studies focusing on the prevalence, screening, and treatment strategies of HIV-associated neurocognitive disorder (HAND) in South Africa. The few studies included in this review indicate that the prevalence of HAND may be higher than estimated. In addition, only a limited number of cases have been reported. This may be due to a lack of registry, screening tools, expertise, and awareness.

Summary This review aimed to provide an overview of HAND in South Africa including prevalence, screening, and current treatment strategies. Whether South Africa has the necessary and effective screening tools remains to be determined; however, HAND screening should be mandated for all HIV-infected individuals. cART remains the mainstay treatment of HAND, currently there are no alternative treatment strategies other than adjuvant therapies. In addition, it is yet to be established whether cART plays a role in the development of HAND.

Keywords Human immunodeficiency virus · Central nervous system · Neurocognitive impairment · HIV-associated neurocognitive disorder · Dementia

Introduction

It is well established that South Africa has a highest prevalence of human immunodeficiency virus (HIV) worldwide with approximately 8 million people living with HIV [1]. However, due to the availability and accessibility of combination antiretroviral therapy (cART), people living with HIV tend to have a longer lifespan. It has been reported that cART can achieve potent, long-term suppression of HIV plasma viremia and increase the life expectancy of people living with HIV [2]. cART has dramatically transformed the scope of HIV from an incurable disease to a chronic treatable disease [3], with the life expectancy of people living with HIV having increased to that of uninfected counterparts. Unfortunately, with an increase in life expectancy and as the HIV-1 infection progresses, secondary problems associated with HIV and the chronic use of cART have been observed such as cardiovascular, renal, osteological, and central nervous system (CNS) problems [4]. These complications may be caused by several factors including a long-term inflammatory response, the HIV infection itself, cART-related adverse events, host genetics, socioeconomic factors, and a combination thereof [3]. However, this review will focus on HIV-associated CNS complications, specifically neurocognitive disorder. This narrative review aimed to determine the prevalence of HIV-associated neurocognitive disorder (HAND) in South Africa including current screening and treatment approaches. Given the high prevalence of HIV in the country, it is possible that the prevalence of HAND may also be increased.

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The Effect of HIV on the Central Nervous System

It is well known that HIV is neuroinvasive and neurovirulent [5], thus it can infect the CNS and cause neurological impairment. HIV neuroinvasion occurs early after primary infection but persists throughout the disease course. It has been reported that HIV can be detected in the CNS days after infection, and has been associated with cognitive, neurological, and mental health complications [6]. HIV may enter the CNS either directly or as "trojan passenger" via the trafficking of infected monocytes, macrophages, and/or $CD4^+$ T-cells across the blood–brain barrier (BBB), thus it may enter as a cell associated virus [7]. Immune cells such as monocytes, macrophages and $CD4^+$ T-cells are known to be trafficked across the BBB into the brain during routine surveillance [8, 9]. However, since they are infected with HIV, they proceed to infect the local cells of the CNS [8]. In addition, HIV has been shown to disrupt the integrity of the BBB by altering protein expression and post-translationally modifying proteins critical to maintaining tight junctions of the endothelial cells [8]. It has also been reported that HIV viral infection stimulates the production of proteins such as matrix metalloproteinases that alter the integrity of the BBB and induce leukocyte transmigration from the peripheral circulation across the BBB into the brain [7, 10]. Furthermore, lymphocytes can also enter the brain through the meningeal lymphatic system and activate inflammatory pathways to permeabilise the vessels and cross the vessel walls into the CNS [11]. However, the exact mechanisms by which HIV crosses the BBB and enters the CNS are not well understood. Once in the brain, HIV has been shown to infect glial cells such as microglia and astrocytes through direct infection mediated by $CD4^+$ T-cells/chemokine fusion of HIV glycoprotein (gp120) in the case of microglia or through endocytosis for astrocytes [11]. Following entry of the virus, viral reverse transcriptase generates a deoxyribonucleic acid (DNA) copy of the viral ribonucleic acid (RNA), which together with a pre-integration complex is actively transported into the nucleus allowing it to infect non-dividing cells of the CNS [12].

In addition, HIV establish reservoirs of proviral DNA in infected cells can persist indefinitely despite cART [13]. The CNS is specifically suited to carrying functionally latent viral genomes, in addition to being populated with HIV susceptible cells that carry HIV receptors and coreceptors including macrophages and astrocytes [14, 15]. In addition, the brain constitutes a typical anatomical site that has poor drug penetration and reduced immune surveillance as it is compartmentalised and protected by the BBB [16]. As HIV enters the brain, an inflammatory response is activated that can be overstimulated resulting in neurological complications. The HIV reservoirs including microglia, macrophages, and astrocytes promote a prolonged inflammatory state that can result in neuronal dysregulation and cell death [11]. Thus, the presence of HIV in the brain may disrupt the health and normal functioning of nerve cells resulting from inflammation mediated damage of the brain region involved in learning, memory, and information processing [10]. This can result in symptoms associated with neurological dysfunction such as memory loss and neuropathy.

Although cART has dramatically reduced CNS morbidity, many people living with HIV continue to experience CNS complications such as depression, anxiety, and other neuropsychiatric problems [6]. Despite the effectiveness of cART in the reduction of CNS morbidity, neurocognitive impairment still occurs in approximately 20 – 30% of people living with HIV and is an ongoing problem [4, 17]. Since cART needs to be taken lifelong by people living with HIV, it may have chronic adverse effects which may further contribute to CNS dysfunction. However, it has been challenging to distinguish between the direct effects of cART and those of the HIV virus. Thus, the underlying mechanisms by which cART may result in CNS dysfunction are not well elucidated. The most common primary HIV-associated CNS disorders include HIV-associated dementia (HAD) and its antecedent syndrome, minor neurocognitive disorder which are collectively termed HAND [17].

HIV-Associated Neurocognitive Disorder

HIV-associated neurocognitive disorder (HAND) is a collective term for a group of neurocognitive dysfunctions that are associated with HIV infection [18, 19]. Based on Frascati criteria, these neurocognitive dysfunctions are categorised into three stages based on the severity of the disease i.e., asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [19–21]. Asymptomatic neurocognitive impairment is defined by a neuropsychological test performance at least one standard deviation (SD) below the mean on standardised neuropsychological tests as compared with demographic controls, and in at least two specific cognitive areas [18, 22]. However, cognitive impairment does not interfere with daily activities. The diagnostic criteria of MND is the same as ANI; however, it includes mild interference with daily activities, whereas HAD includes impairment in cognitive test performance by at least two SD below the mean in two or more cognitive areas and marked interference with daily activities in addition to at least one SD below the mean in neuropsychological tests [18, 23]. In addition, there may be secondary neurocognitive disorders that can accompany

coinfections, cerebrovascular disease, malnutrition, and treatment-related disorders [24]. The morphological hallmarks of HAND includes HIV encephalitis (characterised by disseminated infiltrates of lymphocytes, macrophages, and multinucleated giant cells), and HIV leukoencephalopathy (characterised by bilateral diffuse loss of myelin in the hemispheric white matter alongside astrocytosis and microglial infiltration) [22]. The risk factors for HAND include host factors (genetic predisposition, metabolic disorders, aging, vascular disease, anaemia, and malnutrition), HIV disease factors (AIDS, immune activation, HIV subtype, neuroadaptation, and drug resistance), and comorbidity factors (stimulant use, hepatitis C viral infection, and depression) [24]. As previously mentioned, neurological disorders may be caused by three main mechanisms in patients living with HIV i.e., a direct HIV infection, opportunistic processes due to loss of cell mediated immunity, and inflammation or autoimmunity [25]. The neuropathogenesis of HAND is initiated and driven by HIV invasion and replication within the brain parenchyma, through productive infection of brain perivascular macrophages and endogenous microglia, and astrocytes [18]. Although HAND may have several clinical features including cortical neurocognitive deficits due to long-term manifestation, its predominant clinical feature is subcortical dementia [21]. Once HIV enters the brain, it causes neuropathological changes in the basal ganglia and white matter, leading to subcortical dementia with deficits in memory, concentration, attention, and executive functions [21].

Thus, HAND most prominently affects the neurocognitive domains and cognitive activities including memory, learning, attention, information processing, problem solving, decision making, and executive functioning [20]. There are two proposed pathogenic mechanisms of neuronal apoptosis that may result in HAND i.e., cytokine release from astrocytes in response to infection of the CNS by HIV, and direct neural damage by HIV proteins [26]. Although several mechanisms involved have been studied, the pathogenesis of HAND is complex and multifactorial and not well understood. HAND is known to predispose people living with HIV to poor treatment adherence, unsafe sex, substance abuse, alcohol addiction, loss to follow-up, and poor quality of life [27].

Prevalence and Incidence of HIV-associated Neurocognitive Disorder in South Africa

Neurocognitive impairments are common among people living with HIV with approximately 30 – 50% of people affected globally despite progress with cART [21, 28]. HAND can develop in almost any stage of HIV infection; however, it is more common in late stages of infection [29]. Based on comprehensive neuropsychological assessments, the prevalence of any neuropsychological impairment in South Africa ranges from 25—80% [30], with HAND estimated to be approximately 23.5% [28]. However, this is just an estimate and does not accurately represent the prevalence of HAND in South Africa. With an increase in prevalence of HIV, additional studies investigating HAND need to be conducted to fully understand it in South African context.

Currently, there is a limited number of studies reporting the incidence of HAND in South Africa despite the increased prevalence of HIV. Those with reported incidences are mostly single institute studies with a limited number of participants. However, there appears to be several studies conducted in other Sub-Saharan African countries such as Malawi, Zambia, Nigeria, and Uganda. In this review, eight studies that reported a prevalence or incidence of HAND from 2007—2021 in South Africa were included. A recent study conducted by Narsi and colleagues in 2021 investigated the neuropsychological performance status of naïve HIV-positive individuals [30]. In this study, 211 participants were included of which 82.5% showed evidence of neuropsychological impairment with a mean international HIV dementia scale (IHDS) score of 8.42 (1.96) (Table 1) [30]. In

Table 1 Studies reporting the prevalence or incidence of HAND in South Africa. IHDS, international HIV Dementia Scale; NPI, neuropsychological impairment; NCI, neurocognitive impairment; HAND, HIV associated neurocognitive disorder; ANI, asymptomatic neurocognitive impairment; MND, mild neurocognitive disorder; SD, standard deviation

Author	Type of HIV-NCD	Sample size	IHDS/CSID/SD	Prevalence (%)	cART
Narsi et al. 2021 [30]	NPI	211	IHDS (mean): 8.42 (1.92)	82.5	No
Kobayashi et al. 2021 [31]	NCI	850	Not reported	6.1 (Incidence)	Yes
Joska et al. 2019 [32]	Dementia	1320	CSID: 6.77 (2.37)	18.2	Yes
Phillips et al. 2019 [33]	Dementia	247	IHDS (mean): 9.33 (1.51)	42	Yes
Mogambery et al. 2017 [26]	HAND	146	IHDS (mean): 9	53	Yes
Goodkin et al. 2014 [34]	NCI	70	IHDS (mean): ANI/MND 9.82 (1.49), HAND 9.40 (2.09)	42.9	Yes
Robbins et al. 2011 [35]	Dementia	65	IHDS: 8.58 (1.98)	80	Yes
Modi et al. 2007 [36]	Dementia	193	Not reported	38	Yes

a longitudinal study conducted in the Mpumalanga province in 2021, Kobayashi and colleagues reported an incidence of neurocognitive impairment of 6.1% in 850 HIV-positive individuals who were followed-up to an average of 3 and a half years [31]. The largest cross-sectional study to date was conducted by Joska and colleagues in 2019 and investigated the prevalence of HIV infection and its associations with neurocognitive impairment [32]. Joska and colleagues (2019) included 1320 older (mean age of 71.3 years) rural based South Africans. Although the HIV-positive individuals were significantly younger than the HIV-negative individuals, they had higher rates of dementia (18.18 vs 10.68%) (Table 1) [32]. These participants had a Community Screening Interview for Dementia (CSID) score and SD which included measures of memory, orientation, naming, language expression and comprehension of 6.77 (SD = 2.37) [32]. Another study conducted in 2019 investigated HAND in perinatally infected adolescents [33]. In this study, Phillips, and colleagues (2019) reported a HAND prevalence of 42% in a cohort of 247 adolescents with a mean IHDS score and SD of 9.33 (1.51) respectively [33].

Another study that reported on the prevalence of HAND was conducted in 2017 by Mogambery and colleagues [26]. In this study, 146 participants were recruited from a peri-urban HIV clinic. A prevalence of 53% with a mean IHDS score of 9 was reported; however, this was not associated with functional impairment [26]. While assessing the diagnostic utility of the IHDS in 70 participants, Goodkin and colleagues (2014) reported a prevalence of neurocognitive impairment of 42.9% with a mean IHDS score of 9.82 (1.49) (ANI/MND), and 9.40 (2.09) (HAND) [34]. The highest prevalence reported to date was by Robbins and colleagues in 2011. Robbins and colleagues (2011) reported a HAND prevalence of 80% with a mean IHDS score of 8.58 (1.98); however, only 65 participants were included [35]. In this study, an IHDS score of < 10 was significantly associated with a lower CD4 T-cell count (< 200 cells/mL) which suggested that poor immune function may be related to increased neurocognitive impairment [35].

In 2007, Modi and colleagues reported a HAND prevalence of 38% in a cohort of 193 participants and this was significantly correlated with lower CD4 T-cell count of less than 200 cells/mL [36]. Based on these findings, it is evident that the prevalence of HAND is high in South Africa even in the cART era. However, only a few studies investigated the prevalence and pathological effects of HAND in South Africa. The reported studies are mainly single institute studies conducted in selected province, however, they do not by any means reflect the overall incidence of HAND in South Africa. However, they do provide an indication of the prevalence of HAND in South Africa. Based on these findings, the overall prevalence of HAND in the South African population may be high and needs to be investigated further.

Screening and Diagnosis of HAND

The screening of HAND is important for the improvement of clinical outcomes as early interventions can be employed. It has been reported that individuals with lower CD4 + T-cell count are more likely to develop neurocognitive impairment [30]. In addition, it has been shown that neurocognitive impairment develops prior to the initiation of cART [30], which means that it may not be due to the detrimental effects associated with cART. Furthermore, the CNS is one of the first targets of HIV infection, encouraging early assessment of neurocognitive function in all HIV-infected individuals regardless of their CD4 + T-cell count and symptomatic state [37]. Unfortunately, HAND is a highly undiagnosed problem in developing countries including South Africa especially in HIV-infected individuals especially milder forms such as ANI, and MND [3]. A range of tests are available for use in the clinical assessment of neurocognitive function, some of which are quick and simple [3, 22]. HAND can be diagnosed using neurocognitive testing (patient's performance below one SD from the norm in at least two cognitive domains), radiology studies, biochemical analysis (cerebrospinal fluid), and electrophysiological studies (electroencephalogram, somatosensory evoked potential) [22, 23]. However, it should be noted that radiology studies, biochemical analysis, and electrophysiological studies are supportive but not specific.

The simple tests are mainly conducted to assess working or short-term memory, attention, interference, and visuoconstruction, while the in-depth testing mainly includes psychomotor speed and abstraction [22]. However, IHDS is also used to assess motor and psychomotor speed. These include the administration of symptom questionnaires to be completed by patients which serves as a baseline tool for the basic assessment of HAND [3]. This is normally followed by a more comprehensive assessment using screening tools such as HIV dementia scale, the international HIV dementia, the Montreal cognitive assessments (MOCA), and mini-mental state examination (MMSE) [3, 38]. Although these tools have been employed in screening for HAND, no individual tool seems to be adequate alone. A study conducted by Joska and colleagues in 2016 showed that a combination of IHDS and Cognitive assessment tool (CAT) (rapid tools) had excellent sensitivity (89%) and specificity (82%) for HIV associated dementia but was poorly specific for the screening of HAND [38].

The screening of HAND needs to be conducted routinely in all HIV clinics. Unfortunately, in a developing country such as South Africa, there may be several challenges that affect the routine diagnosis and reporting of HAND including a lack of training, screening tools, and

HAND awareness. A survey-based study conducted by Gouse and colleagues in 2021 which included 105 health practitioners, showed that only 2% received training for HAND, 45.2% did not know which screening tools to use, and 77.1% lacked expertise [39]. This proves that the lack of HAND screening may be due to a lack of knowledge and expertise of health providers, as well as a lack of screening tools. Training of health providers is vital in improving the screening and management of HAND in South Africa. In addition, screening tools appropriate for the culturally diverse South African population need to be developed.

Current Management and Treatment Approaches for HIV-Associated Neurocognitive Disorders

The treatment of HAND remains challenging due to the multiple mechanisms involved. Currently there is no cure for HAND [40]. However, it is well established that HIV infection of the brain is essential for the development of HAND [41]. Non-pharmacological interventions in individuals with HAND include cognitive and neurological rehabilitation strategies which aims to enhance cognitive function, memory, attention, and problem-solving abilities [42]. In addition, comprehensive support and care also play a vital role in managing HAND. This includes psychoeducation, counselling, social support, and assistance with day-to-day activities with the aim of improving an individual's quality of life. Specific symptoms associated with HAND, such as mood disorders or attention deficits, can be addressed using medication for example, antidepressants which help manage mood disorders, while stimulant medications can help with attention deficits [43]. These treatments target individual symptoms; however, fail to address underlying neurocognitive impairment. While there are different strategies for the management and treatment of HAND, this review will focus on a select few with particular focus on the pharmacotherapy thereof.

The main focus of HAND treatment has been on the suppression of virus replication in the brain using cART [22]. Thus, treatment involves strict compliance with cART to decrease the viral load [40]. However, there have been concerns that cART may not fully control HIV replication in the CNS due to lower drug concentrations [44]. It has been reported that cART treatment for approximately 1 year is associated with modest benefits in neurocognitive functioning particularly attention, processing speed, and executive performance, and this has been correlated with the improvement in $CD4^+$ T-cell counts [37]. The introduction of cART has led to a decrease in the prevalence of HAND from approximately 16% to less than 5% [14, 26]. However, the milder forms of neurocognitive impairments are still prevalent. The prevalence of HAND has been shown to be higher in developing countries as compared to developed countries [27]. However, there are limited studies investigating the prevalence of HAND in South Africa.

In contrast, there have been incidences of cognitive improvement following the discontinuation of cART suggesting cART may be neurotoxic and may be implicated in the development of HAND [45–47]. cART regimens especially nucleoside reverse transcriptase inhibitors (NRTIs) have been shown to be highly neurotoxic, and neuropathology is a major complication of HIV treatment [18, 48]. Some regimens included in cART such as efavirenz, stavudine, zidovudine, and abacavir have been associated with neurological disorders [49]. It has been previously shown that the 8-OH metabolite of efavirenz is a potent neurotoxin [50]. However, there is not enough evidence implicating other regimens.

The pharmacokinetic and pharmacodynamic properties of antiretroviral medications were shown to exhibit differences between the CNS and the systemic circulation leading to the hypothesis that certain drugs may have limited efficacy in the CNS due to reduced drug penetration in the CNS compartment. As a result, the concept of a cART regimen CNS Penetration-Effectiveness (CPE) score was introduced, where a higher score indicates better CNS penetration [51]. Despite several studies utilising this approach, results were inconsistent [52–54]. In addition, although cART regimens may have a higher CPE score, which indicate effectiveness in the treatment of HAND, they may be neurotoxic.

As described by Bougea and colleagues in 2019, several adjuvant pharmacotherapies have been outlined for the management and treatment of HAND; however, only a few have been discussed in this review [55]. One approach to managing HAND involves incorporating maraviroc into the treatment regimen of patients experiencing cognitive impairment. Maraviroc plays a role in neuroinflammation and monocyte activity. This drug was used as an adjunct therapy in virologically suppressed patients and demonstrated some positive outcomes in pilot studies [56, 57]. Minocycline, a tetracycline antibiotic derivative emerged as a promising drug candidate for the treatment of HAND and various other neurodegenerative diseases [58]. Apart from its antibiotic properties, this compound exhibits potential protective as well as anti-inflammatory effects within the CNS. Due to its ability to effectively penetrate the BBB at a significant rate [59, 60], it can be delivered at much lower concentrations in comparison to other medications. Consequently, it has demonstrated neuroprotective effects in numerous neurodegenerative disease models, as well as in cases of traumatic and ischemic brain injuries [61–63].

The use of additional adjunctive medications has also been reported in a study conducted by Simioni and

colleagues in 2013 [64]. Simioni and colleagues (2013) aimed to investigate the efficacy and safety of rivastigmine for HAND in a cohort of long-standing aviremic HIV-positive patients [64]. This randomised, double-blind, placebo-controlled, crossover study was conducted in seventeen, virally suppressed HIV-positive patients with HAND. The patients were assigned either oral rivastigmine (up to 12 mg/day for 20 weeks) followed by placebo (20 weeks), or placebo followed by rivastigmine [64]. The study aimed to assess the efficacy of rivastigmine by evaluating improvements in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and individual neuropsychological scores related to the speedy at which information was processed, attention, executive functioning, and motor skills. Overall, there was no significant difference observed in the primary outcome measure, i.e., the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), following administration of the drug [64]. However, improvements in processing speed were noted with rivastigmine, as demonstrated by the Trail Making Test A ($F_{1,13} = 5.57$, $p = 0.03$) [64]. The authors concluded that rivastigmine seemed to improve psychomotor speed in aviremic HIV-positive patients with HAND however, a larger trial with a better tolerated transdermal form of rivastigmine was recommended [64].

A pilot study conducted by Letendre and colleagues in 2006 investigated the effects of low-dose oral lithium on the neuropsychological performance of individuals diagnosed with HAND [65]. This pilot study was conducted over twelve weeks at a university-based tertiary care center, utilising a single-arm, open-label design [65]. A requirement for the study was that individuals had to be on stable antiretroviral therapy for a minimum of 12 weeks [65]. Of the twenty-one participants screened, 8 met the inclusion and exclusion criteria and were enrolled in the study. An oral administration of lithium was initiated at a daily dose of 300 mg and adjusted to maintain 12-h trough concentrations within the range of 0.4 to 0.8 mEq/l [65]. The global deficit score was used to evaluate global neuropsychological performance. Upon initial assessment, all participants exhibited impaired neuropsychological performance, with the majority having decreased CD4 cell counts (median 292 cells/microl) and HIV RNA levels in plasma below 400 copies/mL (i.e., seven out of eight participants) [65]. The prescribed doses of titrated lithium ranged from 600 to 1200 mg per day. Following the 12-week intervention period, all eight participants demonstrated improved performance, and six participants achieved unimpaired neuropsychological functioning [65]. The findings of the study revealed that the use of lithium led to enhanced neuropsychological performance in cognitively impaired individuals receiving antiretroviral therapy [65].

Memantine, an N-methyl-D-aspartate receptor (NMDAR) antagonist was under investigation in a multicenter trial conducted by Schifitto and colleagues in 2007. Following a 16-week treatment phase, the trial did not show any clinically significant improvement in neuropsychological and behavioural testing performance in HAND patients [66]. However, potential neuroprotective effects were observed in the frontal white matter and parietal cortex of treated individuals using magnetic resonance spectroscopy [66]. The authors concluded that trials with longer durations be designed to further explore the full potential of neuroprotective agents [66].

A study conducted by the Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders in 1997 investigated the effects of a lipophilic antioxidant, OPC-14117 in alleviating toxic interactions between HIV-infected macrophages and neurons [67]. In this double-blind, placebo-controlled, randomised clinical trial, the safety and tolerability of the investigational drug, OPC-14117 (240 mg per day) was tested [67]. The study involved 30 patients, with cognitive impairment which was assessed using a neuropsychological test [67]. The main objective of the study was to assess the tolerability of a drug by determining the number of participants that were able to successfully complete the study on their assigned dosage of the investigational drug [67]. Overall, there was a trend indicating improvement in cognitive test scores however, this was not statistically significant [67]. These findings indicated that the antioxidant was well-tolerated in patients [67]. In addition, the results strongly suggested that a larger trial be conducted to investigate the impact of OPC-14117 on cognitive performance in patients with HIV [67].

In a parallel group, 2×2 factorial design, randomized double-blind, placebo-controlled trial conducted by the Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders (1998), the effects of deprenyl (monoamine oxidase B inhibitor and putative anti-apoptotic agent) and thioctic acid (antioxidant) was assessed in 36 patients with HIV-associated cognitive impairment [68]. Results showed that deprenyl and thioctic acid were found to be well-tolerated, with only a few adverse events reported [68]. Patients who received deprenyl demonstrated significant improvement in verbal memory tests compared to those who did not receive deprenyl [68]. Treatment with thioctic acid failed to improve cognitive functioning [68]. These findings suggest that deprenyl treatment may lead to cognitive enhancement in individuals with mild HIV-associated cognitive impairment, while thioctic acid does not appear to provide any cognitive benefits [68]. The study concluded by recommending a larger efficacy trial be initiated to determine the long-term effects of deprenyl on cognitive performance in HIV-infected patients [68].

Integrase strand transfer inhibitors (INSTIs) are currently employed as initial cART along with a combination of two nucleoside reverse transcriptase inhibitors (NRTIs)

and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor. In South Africa, the first-line treatments for HAND include NRTIs such as lamivudine and stavudine [69]. Among the NNRTIs, there are nevirapine and efavirenz [69].

Despite numerous studies on adjuvant therapies for the management and treatment of HAND, there have been mixed results due to its complex pathogenesis, heterogeneity in conditions, the ability of drugs to penetrate the BBB, as well as variability in treatment responses to name but a few. In addition, determining which cART regimens and combinations thereof are best suited for the prevention and treatment of HAND or how to treat patients who are on cART remains unclear [22]. As such additional studies investigating ideal and effective combination cART regimen, alternative HAND treatment strategies in both cART naïve and experienced individuals, as well as adjuvant therapies are required. Apart from the existing treatment methods discussed, researchers are exploring novel agents and delivery routes [58]. Notably, recent successes in delivering trophic factors such as insulin, IGF-1, and neurotrophin to the CNS have sparked interest in their potential as neuroprotective agents against HIV-related damage. Intranasal delivery (IND) of neurotrophin, insulin, and IGF-1 has emerged as a promising therapeutic technique, capable of potentially reducing the damage associated with stroke and the memory decline seen in HAND, Alzheimer's disease, or diabetes-related conditions [58].

Conclusion

Although several studies reported a decrease in the prevalence of HAND in the cART era, the incidence of NCI is still evident. There are limited studies focusing on the prevalence of HAND in South Africa. The few studies included in this review indicate that the prevalence of HAND may be higher in South Africa than estimated. In addition, only a limited number of cases have been reported. This may be due to a lack of registry, screening tools, expertise, and awareness. Ideally, HAND should be included as part of the routine diagnosis for all HIV infected individuals regardless of the treatment status i.e., naïve and cART experienced. Whether South Africa has the necessary and effective screening tools remains to be determined; however, HAND screening should be mandated for all HIV-infected individuals. The mainstay treatment of HAND remains to be cART, and currently there is no alternative treatment strategies. However, there are several adjuvant pharmacotherapies that have been implemented in other countries for the management and treatment of HAND which can be adopted in South Africa. The role of cART in the development of HAND is yet to be established.

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Compliance with Ethical Standards

Competing Interests The authors declare no competing interests.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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