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The Intersection of Cognitive Ability and HIV: A Review of the State of the Nursing Science

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Abstract

Neurocognitive problems have been endemic to the HIV epidemic since its beginning. Four decades later, these problems persist, but currently, they are attributed to HIV-induced inflammation, the long-term effects of combination antiretroviral therapy, lifestyle (i.e., physical activity, drug use), psychiatric, and age-associated comorbidities (i.e., heart disease, hypertension). In many cases, persons living with HIV (PLWH) may develop cognitive problems as a function of accelerated or accentuated normal aging and lifestyle rather than HIV itself. Nonetheless, such cognitive impairments can interfere with HIV care, including medication adherence and attending clinic appointments. With more than half of PLWH 50 years and older, and 30%–50% of all PLWH meeting the criteria for HIV-associated neurocognitive disorder, those aging with HIV may be more vulnerable to developing cognitive problems. This state of the science article provides an overview of current issues and provides implications for practice, policy, and research to promote successful cognitive functioning in PLWH.

Key words: cognitive deficits, cognitive reserve, cognitive training, HIV-associated neurocognitive disorder, neuroplasticity

Since the introduction of effective antiretroviral therapy, the demographics of persons living with HIV (PLWH) have changed dramatically. Treatment advances have allowed people to live and age with HIV. In the United States and dependent areas in 2018, nearly 51% of people living with HIV were 50 years and older (CDC, 2018); by 2030, 70% of PLWH will be 50 years and older (Wing, 2016).

Fortunately, with a better functioning immune system and more controlled viral replication, the neurological burden in this population has decreased. Yet, due to the development of age-related comorbidities known to affect brain health, those aging with HIV may become especially vulnerable to developing more rapid and severe cognitive impairments; as such, this is being closely examined in the neuroAIDS literature (Cody & Vance, 2016).

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The intersection of cognition and HIV is an important topic for nurses and health care. After nearly 40 years of this epidemic, the cognitive and neurological circumstances for people living and aging with HIV have changed. The purpose of this article is to provide an overview of the current HIV cognitive science as it relates to nursing research and practice. The first section reviews epidemiological perspectives on how cognitive impairment is defined and how it affects the care continuum. The second section provides an overview of approaches to mitigate cognitive impairment and decline among PLWH, specifically cognitive decline as a symptom of reduced brain reserve. The third section posits nursing clinical implications. Finally, we conclude with future consideration of the nursing science surrounding cognitive impairment as a symptom.

Epidemiological Perspective

In the mid to late 1990s, combination antiretroviral therapy (cART) was introduced and significantly suppressed viral replication. With improved immune system function, less progression to AIDS, and fewer opportunistic infections of the brain, there were fewer cases of HIV-associated dementia (HAD). These improved treatment outcomes necessitated an update of the nosology of HIV-associated cognitive impairment.

Definitions of Cognitive Impairment

In 2007, a group of neuroAIDS experts convened in Frascati, Italy, to update this nosology. Under the rubric named HIV-Associated Neurocognitive Disorders, or

HAND, these experts defined three categories of increasing cognitive and functional severity, known as the Frascati criteria. The categories included (a) asymptomatic neurocognitive impairment (ANI), (b) mild neurocognitive disorder (MND), and (c) HAD (Antinori et al., 2007). To determine HAND, other potential causes of cognitive impairment (i.e., major depressive disorder, substance dependence, heart failure) are first ruled out. In addition, cognitive impairment is determined by evaluating at least five cognitive domains (e.g., executive functioning, verbal learning). Norm-based (e.g., age and education) cognitive performance measures are used to evaluate the presence of cognitive impairment. A diagnosis of ANI is given if there is a score 1 *SD* below the adjusted mean in two or more cognitive domains. For a diagnosis of MND, the same criteria for ANI are met and the cognitive impairment interferes with everyday functioning (e.g., instrumental activities of daily living). A diagnosis of HAD is given if two or more cognitive domains are scored 2 *SD*s below the demographically adjusted mean and the impairments interfere with everyday functioning. Using these criteria, estimates of the prevalence of HAND fluctuate across studies. In a study with 1,555 PLWH from the CNS HIV Anti-Retroviral Therapy Effect Research cohort (49% Black, 39% White, 9% Hispanic, and 3% Other), approximately 30%–50% had HAND, with 21%–30% having ANI, 5%–20% having NMD, and 2% having HAD (Heaton et al., 2010).

In 2016, an international HAND task force of neuroAIDS experts concluded that despite the utility of this HAND nosology, it has inherent problems (Cysique et al., 2017). First, although other dementias and neurodegenerative diseases are progressive, a diagnosis of HAND does not necessarily imply progressive deterioration over time. In fact, several studies indicate that cognitive recovery is common and, over time, there is considerable variation in the cognitive ability of PLWH (Vance, Lee, et al., 2019). In the CNS HIV Anti-Retroviral Therapy Effect Research cohort (44% Black, 43% White, 11% Hispanic, and 2% Other), which follows PLWH every 6 months on laboratory, medical, and neurocognitive measures, researchers observed in 436 PLWH over 16–72 months (mean, 35), using normed cognitive measures, that 60.8% remained stable, 22.7% declined, and 16.5% improved (Heaton et al., 2015).

Second, measurement issues may lead to misclassification of HAND. A variety of cognitive assessments used across studies may overestimate or underestimate the prevalence/severity of HAND and may vary in their ability to detect cognitive problems. These assessments are also prone to testing error (i.e., human error in administration), practice effects, circadian influences (e.g., alertness of the PLWH), cultural bias, and unrepresentative normative data (Vance, Lee, et al., 2019).

Third, the HAND diagnosis serves more as a classification for research than for clinical diagnosis; HAND diagnoses are based on assessments conducted by trained psychometrists and computerized algorithms, and they lack a clinical judgment component. Moreover, there is no standard of care to treat HAND (Vance et al., 2013; Saylor et al., 2016), making it questionable to give such diagnostic labels to PLWH, thereby causing undue stress. In a cognitive training study of 109 participants (87% Black, 11.8% White, and 1.2% Hispanic) who met the criteria for HAND, Vance, Jensen, et al. (2019) informed participants by letter that they met the probable diagnosis of HAND. Weeks later, participants were asked how they reacted to this diagnostic information. A thematic analysis of their responses revealed that most people (57.7%) perceived this diagnosis as a "confirmation" of their suspicion that something was wrong. Others also indicated the following reactions to the HAND diagnosis: (a) finding the diagnosis "Unexpected" (22.4%); (b) feeling "Anxiety" (14.1%), "Concern" (23.5%), and/or "Sadness" (3.5%); (c) a "Desire to Improve" (61.2%) their cognitive abilities and "Seek Knowledge" (12.9%) about this; and (d) "No Reaction" (7.1%) or "Not Concerned" (31.8%). Although the responses were generally positive, an awareness that one's cognitive abilities are in jeopardy may also create distress, as demonstrated in the Alzheimer's literature (Stites et al., 2017).

Fourth, using the criteria for HAND, one must eliminate other potential etiologies of cognitive impairment, such as heart disease, hypercholesterolemia, diabetes, hypertension, and renal and liver disease; however, this is challenging because people are more likely to develop such comorbidities as they age with HIV (Vance, Lee, et al., 2019). In fact, legacy and cohort effects further complicate efforts to disentangle the singular effect of HIV on cognition. Many older cART regimens are known to be neurotoxic (Cohen et al., 2015); perhaps for those treated with such regimens, this exposure may have detrimentally influenced their cognition later in life, thus creating a legacy effect. Likewise, nearly 25% of those with HIV in the United States are also coinfected with hepatitis C; this combination synergistically compromises brain health and cognition more than HIV or hepatitis alone (Barokar et al., 2019). Yet for many, hepatitis C is now curable, so those diagnosed with HAND may no longer meet the criteria for HAND after being cured of their hepatitis C (Asselah et al., 2018) and may experience a boost in their cognition.

Fifth, as we witness the graying of the epidemic, age-related cognitive impairment will naturally become an issue for PLWH because it is for those without HIV (Cody & Vance, 2016). Other diagnostic approaches, such as the more universally, less stigmatizing, standard diagnostic of mild cognitive impairment (MCI), considered a preclinical stage of dementia, may be an alternative classification. Similar to the neuropsychological criteria used to diagnosis HAND, MCI is diagnosed when a person performed less than 1.5 *SD* below his/her norm-based mean (education and age) in one or more cognitive domains (Petersen, 2011). Indeed, emerging work has demonstrated that the MCI operationalization shows utility in PLWH, showing overlap with ANI, and that PLWH were more than seven times more likely to be classified with MCI than their seronegative counterparts (Sheppard et al., 2015).

Demographics and HIV-Associated Neurocognitive Disorders/ Neurocognitive Impairment

Further complicating efforts to understand the etiology and prevalence of cognitive symptoms among PLWH, disparities among racial minorities with HIV in cognitive problems may exist. In the broader aging literature, racial disparities in cognitive outcomes, including Alzheimer disease and related dementias, are well-documented (Lines & Wiener, 2014; Potter et al., 2009; Tang et al., 2001). Less research has examined racial disparities in HAND, but some evidence suggests that minorities are at a greater risk for HAND, particularly African American/Black individuals (Cross et al., 2013). Indeed, many of the risk factors for HAND are more prevalent in Black PLWH, such as disease severity (Reif et al., 2017); social comorbidities such as low education, poverty, and trauma (Tedaldi et al., 2015); cardiometabolic disorders such as hypertension and diabetes (Graham, 2015); and psychiatric comorbidities such as depression and substance use disorders. Unfortunately, despite the higher burden of HIV among Black PLWH, and their higher rates of HAND risk factors, very little work has focused on disparities in HAND among this population.

A larger body of work has demonstrated ethnic differences in cognitive outcomes in Hispanic/Latino PLWH (Heaton et al., 2015; Marquine et al., 2018; Mindt et al., 2014; Wojna et al., 2006). This research suggests that cognitive disorders may be more prevalent in Latinx PLWH than non-Hispanic Whites, with disease severity and educational factors emerging as potential mechanisms. As mentioned above, further complicating the understanding of racial disparities in HAND, as well as the prevalence of HAND in general, are issues with representativeness of normative data, as well as the need to consider the influence of quality of education rather than simply years of education in minority populations (Arentoft et al., 2015; Manly et al., 2011).

Recent evidence also indicates that men and women may have differential rates and patterns of neurocognitive impairment (Rubin et al., 2019). Although many studies were underpowered to reliably measure sex differences in cognitive impairment, a few have met this objective, showing evidence that women living with HIV may have greater neurocognitive impairment than men living with HIV. Moreover, this difference may be especially pronounced in the domains of memory, speed of information processing, and motor function (Maki et al., 2018; Sundermann et al., 2018). Further research is needed to understand these potential differences as they relate to comorbidities and hormonal/biological factors (Rubin et al., 2019).

Approaches to Mitigating Cognitive Impairment and Decline Among Persons Living With HIV

Cognitive impairment and cognitive complaints are manifestations of HIV pathology, comorbid health conditions, multiple lifestyle factors, genetic and environmental influences, or, more likely, a combination of these. Currently, there is no standard of care to treat cognitive complaints or HAND, likely because there is no single unified cause or mechanism by which PLWH experience such cognitive problems (Saylor et al., 2016). Yet, a number of practical and evidence-based recommendations suggested in the literature, often with evidence derived from the aging neuroscience literature (Vance, Fazeli, et al., 2019), may be applicable. These include cognitive training, physical exercise, treatment of psychiatric and other health comorbidities, diet, and education for brain health.

Cognitive Training

Cognitive training programs are a collection of mental exercises, usually administered via computer, to improve cognition or remediate cognition negatively affected by disease or injury. In many studies, participants engage in 10–20 hr of exercises with the goal of improving a specific cognitive ability or overall cognitive functioning

(Vance, Lee, et al., 2019). Generally, these exercises become increasingly difficult, thereby challenging the brain to strengthen the efficiency of cognitive processing via a process called neuroplasticity (Vance, Lee, et al., 2019). Simply, neuroplasticity is the brain's ability to adapt to exposure to stimuli, in this case cognitive training, and form new and stronger connections between neurons to support cognitive function (Vance, McDougall, et al., 2014). Studies in older adults without HIV demonstrate the efficacy of such cognitive training protocols, with some transfer effect toward improved instrumental activities of daily living and quality of life (Vance, Fazeli, et al., 2019).

In a systematic review of 13 studies investigating cognitive training in PLWH, Vance, Fazeli, et al. (2019) found that cognitive ability can be moderately improved in the domain that was targeted (i.e., working memory, attention, and speed of processing); however, most of the studies had small sample sizes, limiting their reliability and generalizability. Of interest, one case comparison study examined three participants with HAND who either received 10 or 20 hr of speed of processing training or 10 hr of sham cognitive training; the participant who received 20 hr of speed of processing training no longer met the criteria for HAND at posttest (Hossain et al., 2017). This finding is encouraging but is in need of a larger replication study. Fortunately, in a substantial sample (n = 2,802) of older adults without HIV, Edwards et al. (2017) found that those who received 10 hr of speed of processing training experienced a 29% risk reduction of dementia over a 10-year period compared with a no-contact control group. Given the low cost and low risk of cognitive training programs, such approaches represent a feasible strategy to protect cognition as PLWH age. Furthermore, because such cognitive training can be self-administered on one's home computer, such a therapeutic delivery is convenient and ideal for those experiencing high levels of HIV stigma, have transportation or caregiving challenges, or live in remote areas who may not be able to easily attend a clinic for such cognitive training.

Physical Exercise

A growing body of literature suggests that physical activity is protective and can promote better brain health in the general population (e.g., Blondell et al., 2014; Carvalho et al., 2014). The mechanisms may be direct or indirect. Directly, physical activity may promote better cognitive function via mechanisms such as increased blood flow to the brain (Barnes, 2015). Indirectly, physical activity may promote better brain function by reducing comorbidities (e.g., vascular diseases such as diabetes and hypertension) and stress (e.g., increased nitric oxide and decreased vascular reactivity; Barnes, 2015). While the optimal dose and frequency of physical activity to promote better cognitive function is not fully understood, it is likely that consistent, multicomponent (e.g., aerobic and strength training) exercise is the most beneficial (Barnes, 2015). Furthermore, physical activity behaviors throughout early life are protective of cognition in late life (Nyberg et al., 2014).

In PLWH, there is relatively less research on this topic, yet existing literature (Dufour et al., 2013; Fazeli et al., 2015; Henry & Moore, 2016; Quigley et al., 2019) suggests equally promising protective effects. This is an important area of HIV research, given that PLWH engage in lower levels of physical activity than other populations with a chronic illness (Vancampfort et al., 2018). Several cross-sectional studies have shown, even using simple self-report measures, that greater levels of physical activity are associated with better cognitive performance as well as daily functioning in PLWH (e.g., Dufour et al., 2013; Fazeli et al., 2015; Quigley et al., 2019). Longitudinal observational work also supports this finding in PLWH (Dufour et al., 2018).

Emerging research has begun to explore physical activity interventions in PLWH. Henry and Moore (2016) used text messages to monitor and encourage physical activity over 16 weeks in 21 PLWH (n = 11 intervention [7 of 11 (63.6%) White], n = 10 control [6 of 10 (60%) White]). The preliminary feasibility findings showed that adherence to the text messaging was high, which included reporting pedometer readings. Participants also reported that the encouraging texts, such as milestone achievement messages, facilitated engaging in physical activity. A recent review supported the benefit of physical activity for protecting cognitive functioning in PLWH; however, intervention studies only showed positive benefits on self-reported cognitive function (Quigley et al., 2019). This suggests that more studies are needed to examine the broad effects of physical activity on cognitive outcomes in PLWH using rigorous methods and more comprehensive cognitive measures.

Thus, research supports physical activity as a viable way to protect and promote cognitive health in PLWH. Yet there may be barriers to facilitating such behaviors in this population. Several barriers to physical activity in PLWH have been shown, including HIV symptoms such as neuropathy and lipoatrophy, pain, depression, opportunistic infections, HIV medication effects, and fatigue, whereas physical activity facilitators that have been found include self-monitoring, family support, self-efficacy, and more perceived benefits (Montoya et al., 2015; Vancampfort et al., 2018). More observational as well as interventional work is needed to understand the physical activity behaviors in PLWH as well as the association between physical activity and brain health in this population, using rigorous assessment methods that consider the influence of unique surrounding factors in PLWH (e.g., medications, inflammation, and frailty).

Treatment of Psychiatric/Mental Health Comorbidities

Several personal and psychosocial factors influence cognition in those with and without HIV that may be more prevalent among PLWH. A systematic review by Lowther et al. (2014) that included both domestic and international studies indicated that negative affective factors are often more prevalent in PLWH, including loneliness (point prevalence 46%), depression (point prevalence 33%), and anxiety (point prevalence 28%; Lowther et al., 2014). In a nationally representative sample, the prevalence of major depression among PLWH was about three times that of the general population and was associated with differences in annual household incomes between the two populations (Do et al., 2014).

These psychosocial challenges are associated with the hypothalamus–pituitary–adrenal (HPA) axis and neuroplasticity. Studies show that prolonged negative affect activates the HPA axis, stimulating cortisol production that, over time, produces systemic inflammation that can damage the brain and the hippocampus (a vital memory structure of the brain) and impair cognition (Cody & Vance, 2016). Likewise, loneliness and social withdrawal reduce stimulation in the social environment; human interaction is a complex mental activity, and social stimulation is known to be important for healthy brain aging (Pennikilampi et al., 2018). Addressing and treating these negative affective factors may improve cognition. For example, in a sample of 142 older adults without HIV, Victoria et al. (2017) found that pharmacological treatment for depression can improve cognitive function in some patients.

Personal factors such as resilience and grit (i.e., perseverance in achieving a goal or passion) are important in abating the detrimental effects of loneliness, depression, and anxiety. For example, in a cross-sectional study of 120 PLWH and 94 adults without HIV (54.2% White, 19.17% Black, 19.17% Latino, and 7.5% Other), Moore et al. (2018) found that although there was no relationship between grit and cognition in adults without HIV, for PLWH those with high levels of grit experienced less cognitive decline. Similarly, in a sample of 100 mostly (84%) older Black PLWH, Fazeli et al. (2019) found that higher levels of self-reported resilience were significantly associated with better verbal fluency, executive function, learning, working memory, speed of processing, and global cognition. Thus, providing opportunities to help people tap into resilience resources or training/teaching positive coping skills may be key to reduce the psychosomatic and cognitive effects of negative affect but also protect cognitive functioning (Vance et al., 2008).

Treatment of Comorbidities

As PLWH age, an increase in comorbidities is expected, which can weaken physical and cognitive reserve. Several studies have demonstrated that when comorbidities are well-managed, cognitive health improves (Viamonte et al., 2010; Yang et al., 2018). For example, in a sample of 864 older adults (more than 90% White), those with medically treated hypertension had similar cognitive performance compared with those without hypertension (Viamonte et al., 2010). Similarly, in a large sample of 900 men with HIV and 1,149 men without HIV (51.7% White, 37.1% Black, and 6.9% Other with HIV; 64.9% White, 28.2% Black, and 6.9% Other without HIV), Yang et al. (2018) observed that men with diabetes experienced poorer cognitive functioning than those without diabetes. Further, the effect size for poor cognition was largest in men with uncontrolled diabetes (Yang et al., 2018). Managing diabetes and other chronic conditions is clearly a target for promoting successful cognitive aging.

Diet

A healthy diet can prevent or mitigate the negative effects of diabetes, heart disease, renal disease, and other conditions on brain health. Related dietary approaches are being evaluated to protect brain health in HIV and other diseases, such as the ketogenic diet (KD; Kim et al., 2020; Morris et al., 2015) and probiotic supplementation (Ceccarelli et al., 2017; Wilson et al., 2014). Although these dietary approaches are still experimental, their accessibility means that patients may attempt them at home. As such, nurses should be familiar with such approaches to advise patients about their use.

In the neuroscience literature, research suggests that the reduction of carbohydrates and dietary sugars can decrease systemic inflammation and neuroinflammation, thereby protecting brain health, supporting cognition, and possibly reducing the risk of Alzheimer disease and other dementias (Kim et al., 2020;

Morris et al., 2015). By using ketones instead of glucose for energy, the KD is thought to reduce the expression of crucial genes involved in inflammation; increase adenosine triphosphate production and mitochondrial biogenesis; and improve neural antioxidant effects, cerebral perfusion, and brain metabolism (Gasior et al., 2006).

With brain hypometabolism associated with HAND, the KD represents a viable intervention target. In a pilot study of 14 PLWH 50 years or older (85.6% Black, 14.3% White, and 14.3% Native American), Morrison et al. (2020) randomized participants to either (a) KD (low carbohydrate [≤50 g/day]/high-fat diet) or (b) patient choice diet for 12 weeks, followed by a 6-week washout period. A registered dietician selected meals from an 8-day KD menu prepared by a metabolic kitchen, and all meals and snacks were delivered weekly to participants' homes (Morrison et al., 2020). Cognitive assessments were completed at baseline, 12 weeks, and 18 weeks postbaseline. Compared with the control group, the KD group exhibited improvements in processing speed and executive function after 12 weeks of the KD; however, these cognitive improvements diminished after resumption of a normal diet (Morrison et al., 2020). However, a caution of KD is that it may exacerbate hypercholesterolemia as well as kidney and liver disease, conditions for which PLWH are at risk.

Another form of diet/nutrition support for cognition is probiotic supplementation. Microbial translocation (the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites) is exacerbated in PLWH and can create systemic inflammation, which can interfere with brain perfusion and possibly cognition (Wilson et al., 2014). Probiotic supplementation has been suggested as a treatment option. In a pilot study of 10 PLWH (all White), Ceccarelli et al. (2017) administered high-concentration multi-strain probiotic supplementation over a 6-month period. Researchers observed cognitive improvements in visual and verbal learning, memory, verbal fluency, and state-trait anxiety (Ceccarelli et al., 2017). Such effects correspond with the larger scientific literature suggesting support of the gut–brain axis (Michael et al., 2020).

Education About Brain Health

Health literacy, in general, has been shown to influence treatment management (e.g., missed clinic visit, medication adherence) in PLWH (Fazeli, Woods, Chapman, et al., 2020; Fazeli, Woods, Gakumo, et al., 2020; Jones et al., 2013; Waldrop-Valverde et al., 2009; Waldrop-Valverde et al., 2010; Waldrop-Valverde et al., 2018). Much health education has been disseminated to help patients understand how to protect relevant health areas such as heart and bone health; however, it is unclear whether the same type of educational emphasis has been directed toward brain health.

In the first quantitative study to examine brain health literacy in PLWH, Woods et al. (2019) assessed 41 older PLWH and 60 older adults without HIV (total sample 85% Black) on their knowledge of dementia and health literacy. As a group, PLWH had moderately low general knowledge about dementia (Woods et al., 2019). Similarly, in a focus group totaling 30 older African American (70%) and Caucasian (30%) PLWH, Vance et al. (2017b) assessed participants' perception of brain health and cognition. Although participants had some basic knowledge about the importance of being socially, physically, and intellectually active to preserve their brain health and cognition as they age, more detailed knowledge was lacking; furthermore, few reported deliberately engaging in such activities to protect their brain health. Some expressed a passive acceptance that cognitive impairment and dementia were inevitable (Vance et al., 2017b).

In the same sample, Vance et al. (2017a) presented PLWH with a self-administered multimodal cognitive intervention called a cognitive prescription. The modules targeted six areas for behavioral change: physical exercise, intellectual exercise, mood support, sleep hygiene, nutrition, and social engagement (Vance et al., 2017a). These are all areas shown in the neuroscience literature as important to support brain health and cognition (Figure 1). When this intervention was presented in such a structured format, participants remarked that it was a simple and straightforward way to protect and improve cognition (Vance et al., 2017a). Although no studies in the neuroAIDS literature have used such a multimodal cognitive intervention, several studies in the gerontological literature indicated that such an approach was effective in improving and protecting cognition as people age (e.g., The Agewell trial; Clare et al., 2015). Given the ease of this approach, nurses are in a position to provide such basic health information to their patients.

Pharmacological Treatment

So far, there is no direct medical treatment for HAND, although there is emerging evidence that medications and approaches that reduce inflammation may be effective. In a sample of 22 adults with HAND (77.3% Black), Sacktor et al. (2018) randomized participants to receive 24 weeks of (a) paroxetine (a selective serotonin reuptake inhibitor anti-depressant) 20 mg/day, (b)

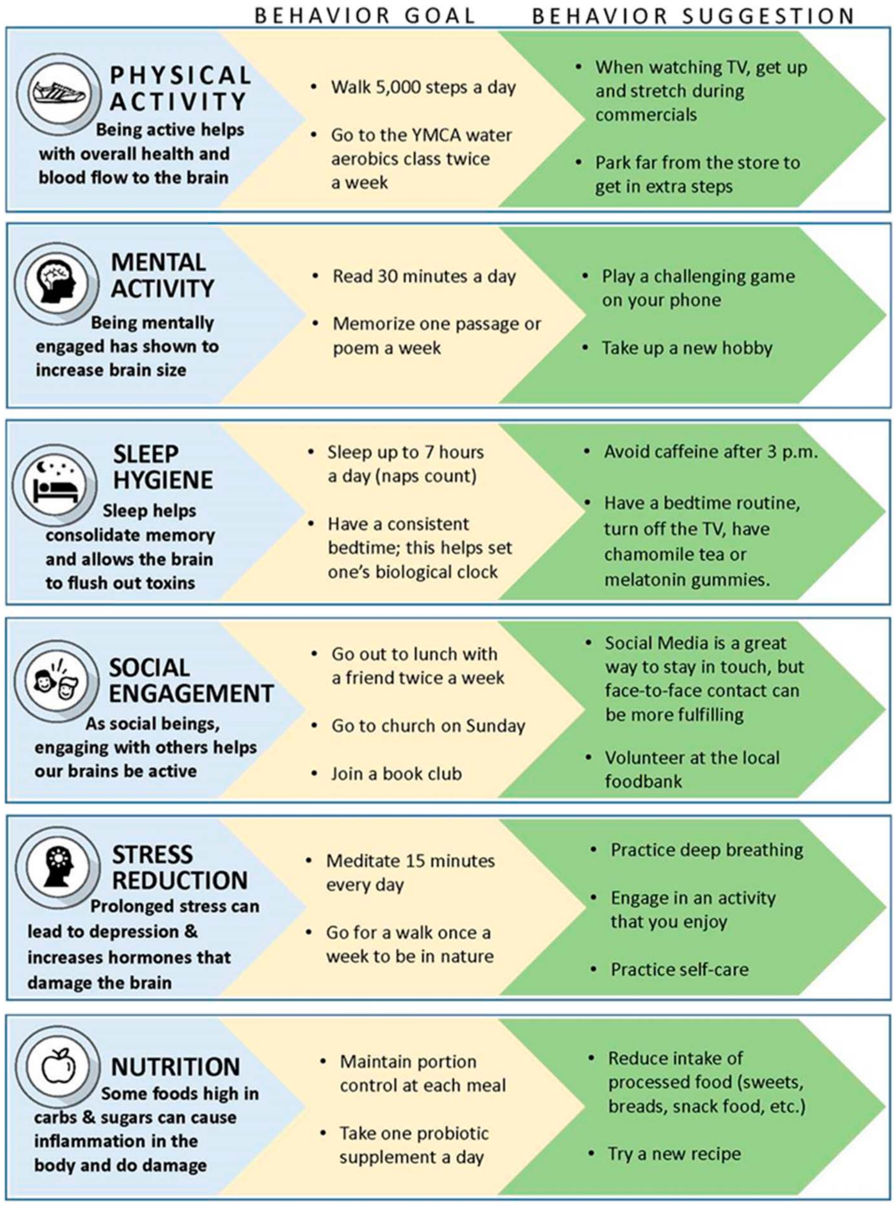

Figure 1. Lifestyle behaviors that can protect cognitive function. This figure is available in color online www.janacnet.org.

fluconazole 100 mg/12 hr, (c) paroxetine and fluconazole, or (d) placebo. Those receiving paroxetine displayed significant cognitive improvement, suggesting that paroxetine may have neuroprotective effects by mitigating oxidative stress-mediated neuronal injury (Sacktor et al., 2018).

As marijuana becomes more legally accessible in the United States and other parts of the world, its effect on cognitive functioning remains debatable (Saloner et al., 2019). In a recent study of 734 PLWH (58% White) and 123 adults without HIV (81% White), Saloner et al. (2019) found that those who engaged in lifetime cannabis use were protected against cognitive decline (as well as exhibited fewer depressive symptoms and the absence of diabetes). This may be because marijuana use can promote less excitotoxicity of neurons and exhibit anti-inflammatory properties (Marsicano et al., 2003; Rom & Perdisky, 2013).

National Institutes of Health Symptom Science Model

The National Institutes of Health Symptom Science Model (NIH-SSM) was developed to facilitate the identification and measurement of patients' self-reported symptoms to further understand phenotypes, genomic, and other "omics" approaches to identify biological mechanisms and markers of symptoms to better direct interventions (Cashion et al., 2016). The model provides a process that begins with the presentation of a complex symptom, which then undergoes phenotypic characterization. The model then follows identification of biological markers or mechanisms that are then the targets for clinical application.

The evidence presented herein can be organized within the NIH-SSM to guide current knowledge and future research. As explained above, cognitive symptoms among PLWH are complex and include both self-reported complaints and objectively measured impairments. Indeed, one of the unique aspects of cognition, considered as a symptom, is the ability to measure both perceived and objectively measured cognitive functioning. The phenotype of cognitive symptoms, then, can be described as representing an alignment between an individual's perception of function and that individual's objective performance. This alignment is also reflected in the criteria for an MCI diagnosis, which requires both objective and subjective cognitive difficulties (Albert et al., 2011). Yet inclusion of both objective and subjective information does not always occur in PLWH, as studies have shown discrepancies between objective cognitive performance and subjective cognitive complaints among PLWH with affective disorders and metacognitive deficits in awareness (Hinkin et al., 1996; Rourke et al., 1999; Thames et al., 2011).

Additionally, the manifestation of cognitive symptoms is related to an individual's education (and other brain-stimulating activities, indicating that a risk phenotype for the outward expression of cognitive symptoms among PLWH may be more likely among those with low education and conversely, less likely among those with greater education (Stern, 2009). This supports the concept of cognitive reserve, which suggests that more highly educated individuals can tolerate more neuropathology before presenting with impairments (Stern, 2009).

The precise mechanisms causing cognitive symptoms among PLWH are a continued area for research, but the current literature suggests that the mechanisms are multidetermined. Neurotoxic effects of antiretroviral regimens, prolonged stimulation of the HPA axis, and other proinflammatory processes associated with chronic infection are purported to affect the central nervous system and brain function (Chittiprol et al., 2007; Hong & Banks, 2015; Kumar et al., 2003; Underwood et al., 2015). The association of omics (e.g., gut–brain axis, microbiotic dysbiosis) with cognitive symptoms in PLWH is emerging, and it remains unclear whether HIV infection itself or other comorbid conditions, common in PLWH, are associated with cognitive symptoms and the gut–brain axis (Zhang et al., 2019). Cardiovascular and cerebrovascular mechanisms are associated with cognitive symptoms, further suggesting important lifestyle targets to improve those symptoms (Moroni et al., 2018). For PLWH, broadening the NIH-SSM to account for social determinants of health that directly affect these individual-level targets is especially needed, given the disproportionate burden of HIV among marginalized and vulnerable populations (CDC, 2018).

Nursing Clinical Considerations

Nursing Model of Care: Application to Neurocognitive Impairment

Nurses caring for adults living with HIV and neurocognitive impairments should consider both conditions to be chronic and can situate their care and counsel within the Chronic Care Model (Bodenheimer et al., 2002). This classic, widely used model emphasizes patient self-management combined with supportive community resources and policies, health systems, and a prepared and proactive practice team to help guide innovations to improve the quality of (HIV) primary care. Given the state of the science reviewed in this article, nurses and nurse practitioners caring for these patients can glean several key actions to improve the health and well-being of PLWH with neurocognitive disorders.

First, nurses working clinically with these patients should know how to support HIV and neurocognitive self-management. This includes ongoing, preventative education, such as teaching patients the symptoms and risk factors of neurocognitive impairment in PLWH. Frank discussions about how patients' comorbidities, HIV, and lifestyle may influence current and future cognitive functioning can lead to additional discussion about cognitive training, physical activity, diet, and other evidence-based self-management strategies that will promote optimal brain health as this population ages. This discussion should be revisited periodically throughout the duration of patients' engagement with their health care team.

Clinical information systems should be designed and/or adapted to help the health care team to (a) assess neurocognitive symptoms, (b) assess changes in risk status for neurocognitive impairment (e.g., changes in comorbidities), (c) discuss progress in/adherence to neurocognitive self-management strategies, and (d) make specialist referrals and appropriate follow-ups as necessary. The Chronic Care Model also implies that Health Care Delivery System Design and Advanced Practice Nurses should be working at the top of their license to help manage HIV and neurocognitive impairment as chronic conditions. This includes seeing affected patients regularly and being appropriately reimbursed for this complex work. Nurses should also use their experience to advocate for the necessary institutional resources to manage neurocognitive impairments in PLWH within an integrated health care delivery system. This can include obtaining many of the resources and strategies described in this review and adapting them to their local clinic context. Managing neurocognitive impairments in PLWH as intersecting chronic conditions will require the important work of an integrated health care team, in which nurses will have a pivotal role.

Monitoring Cognitive Function

It is considered standard of care to monitor for cognitive functioning in HIV-infected patients. As they age, patients may comment about normal age-related cognitive complaints (e.g., forgetfulness), which is an opportunity to inquire about health factors (i.e., substance use, depression/anxiety, missed dosages of medication, management of comorbidities, functional loss) that contribute to such complaints and intervene if necessary. Cognitive complaints may not reflect actual cognitive impairment, as some patients may be unaware of their own diminishing cognitive abilities; that is why it is helpful to ask about functional loss in areas such as driving, keeping medical appointments, and adhering to medication schedules. If cognitive impairment is suspected, patients should be administered a global cognitive screen such as the Montreal Cognitive Assessment (Nasreddine et al., 2005) or the NEUrocognitive Screen (Prats et al., 2019) annually, documenting any progression (Prats et al., 2019). If concerns mount, referrals to a psychologist or neurologist are recommended.

Neurocognitive Impairment and Medication Adherence

Medication adherence is essential for effective treatment of HIV. Adhering to cART medication regimens requires an array of cognitive skills, including memory, planning, organization, and attention, which can be negatively affected by HIV. Research has supported the relationship between neurocognitive skills and adherence to cART. For example, Ettenhofer et al. (2009) tested reciprocal relationships with neurocognitive impairment and medication adherence over 6 months and found that both executive function and learning/memory strongly predicted medication adherence levels over this period. Reciprocally, higher levels of adherence were predictive of a range of brain functions including processing speed, attention, executive function, and motor function. Thaler et al. (2015) demonstrated that the pattern and dispersion of neurocognitive deficits was also related to adherence; persons who had more varied domains affected were more likely to have lower adherence.

Others (Anderson et al., 2015; Cook et al., 2014; Waldrop-Valverde et al., 2010) have documented the role of additional characteristics influencing the association of adherence and HIV-associated cognitive impairment. Low health literacy may worsen the effects of neurocognitive impairment on health behaviors such as medication adherence and understanding medication instructions. Among PLWH with low health literacy, neurocognitive impairment was associated with self-efficacy for taking medications and health-related decision making but not among those with adequate health literacy (Fazeli, Woods, Chapman, et al., 2020). In addition, co-occurring drug use alongside neurocognitive impairment and low health literacy confers considerable risk for poor management of one's HIV regimen (Waldrop-Valverde et al., 2008). Among a group of former and current injecting drug users, baseline cognition, active cocaine use, and changes in medication adherence over 6 months were associated with worsening neurocognitive impairment. This group also showed a worsening of adherence over time (Anderson et al., 2015).

Older PLWH are at higher risk for neurocognitive impairment than their younger counterparts. In a sample of 431 adults with HIV (66.36% Black, 16.47% White, and 17.17% Other), Ettenhofer et al. (2009) reported that, although older adults ($>$50 years of age, $n = 79$, 65.82% Black, 18.99% White, and 15.19% Other) had better medication adherence, neurocognitive impairment was associated with lower adherence among older adults only, suggesting that neurocognitive impairment may be an especially important risk factor for low medication adherence among the growing aging PLWH population. Similarly, Caballero et al. (2019) found poorer executive and psychomotor speed test performance to correlate with lower medication adherence among PLWH 65 years old and older (78% White, 19% Black, and 3% Other).

Although less well-studied, retention in care has also been associated with neurocognitive impairment. In a sample of 191 adults (83% Black, 11% Latino, and 6% Other), Waldrop-Valverde et al. (2014) showed that among PLWH with lower levels of social support, neurocognitive impairment was associated with a greater proportion of missed HIV care visits.

Cognitive Dysfunction and Clinical Communication

Communication with patients during clinical encounters may be affected by neurocognitive dysfunction. Poor attention and working memory can lead to problems in following conversations, tuning out distractions, and understanding and retaining instructions (McCabe et al., 2007). Individuals with these cognitive challenges may appear to be unmotivated to follow instructions and manage their care when, in fact, the underlying issue is an inability, rather than an unwillingness, to adhere to treatment.

Given the high prevalence of MCI among PLWH, clinicians are encouraged to consider this as a risk factor for poor HIV self-management. Screening assessments, as mentioned above, can provide valuable information to guide patient interactions and can facilitate effective communication and improved self-management. For example, among patients who may have attention and working memory challenges, clinicians can improve accurate understanding of medication instructions (or other health enhancing information) by using the teach-back method (DeWalt et al., 2010; Johnson et al., 2013; Roett & Coleman, 2013). The teach-back method involves breaking down instructions into straightforward "chunks" of information, stating them orally to the patient, and then asking the patient to repeat back what they understood the instructions to be. Nonjudgmental statements to assess understanding, such as, "Now, I want to be sure I was clear in my explanation. Please tell me how you are going to take this medicine when you get home," are useful for prompting patients to explain their knowledge in their own words. If the patient misstates a portion of the instructions, the clinician then repeats that portion and again asks the patient to state their knowledge in their own words.

Patients who have problems with prospective memory, or "remembering to remember," may struggle with remembering to take a dose of medication or attend a clinical appointment. Linking these behaviors to everyday routines that are habitual and well-established (e.g., placing the pill bottle next to the coffee pot so that the medicine is taken with their morning cup of coffee) can be effective ways to compensate for their memory deficits. For patients with cognitive dysfunction, it is especially important to identify upcoming changes in routines associated with travel or other disruptions. Preplanning provides the opportunity to build new behaviors and strategies that can maintain health-enhancing behaviors.

Cognitive Remediation and Compensatory Strategies

For many aging PLWH, cognitive rehabilitation efforts to maintain or improve cognitive abilities may not be possible due to irreversible neural damage. As such, it is important to be able to compensate for such cognitive impairments. Fortunately, the cognitive rehabilitation literature is replete with compensatory techniques and strategies (Vance et al., 2013; Vance, Lee, et al., 2019). Although beyond the scope of this article, such strategies include spaced retrieval method, chunking, and levels of processing—all methods shown to help people with memory loss retain targeted information (e.g., when to take medications). There are also low-tech (e.g., pill box to remember medication) and high-tech (e.g., digital calendar to manage appointments) cognitive compensatory strategies that may be effective. When appropriate, referrals to a psychologist or occupational therapist are recommended.

Next Steps: Future Considerations for Nursing Science

Role of Technology

Technology-based platforms are of growing interest to health care providers because they offer an alternative to traditional neurocognitive screening and performance tests that require highly trained providers to administer, score, and interpret results, which may not be feasible in clinical settings. As a result, delays in diagnosis and treatment planning can occur in PLWH (Ances & Hammoud, 2014).

Although many digital platforms are available, mobile HIV-associated cognitive impairment screening apps, e.g., Neuroscreen (Robbins et al., 2018), are one pertinent example. These digital screeners automatically time and score performances via a built-in neurocognitive battery that can be administered outside the clinic. It is important that, these apps account for special considerations (e.g., language barriers, audio–visual functions for hearing impaired and/or low-literacy persons) and adjust scores based on sociodemographic characteristics. These user-friendly operating systems minimize the training needed to administer and report results, which could help streamline detection of cognitive impairments and treatment planning (Robbins et al., 2018). Similarly, virtual reality (VR) may be able to address ecological limitations of neurocognitive performance testing. One such example is the Virtual Reality Functional Capacity Assessment Tool, which may be more sensitive to HIV-associated cognitive and functional impairments in comparison with neurocognitive batteries (Iudicello et al., 2019). The strength of VR relates to its ability to measure complex cognitive function (e.g., multitasking, social domain function) by simulating "real-world" and individualized stressors (e.g., discrimination) that are harder to capture and less sensitive to detection in routine clinical or research settings.

Other technological platforms demonstrating clinical promise are biofeedback and neurofeedback systems that measure central–autonomic nervous system function (e.g., heart rate variability, brain waves, cognitive-domain blood flow). Research using these devices suggests associations between central–autonomic dysfunction and cognitive impairments, coexisting medical and psychiatric comorbidities, and increased mortality in PLWH (Jang et al., 2019; McIntosh, 2016). Biofeedback and neurofeedback devices can be combined with other clinical measures for earlier detection of cognitive impairment and to evaluate treatment response in real time. Much like mobile apps and VR, biofeedback and neurofeedback systems are more accessible and feasible for use in consumer, clinical, and research arenas. Furthermore, accompanying software analyzes physiological information and can provide clinical indices for easier interpretation. Most importantly, these platforms (and others) can be fully integrated with existing telehealth technology already being used in health care settings, which allows for a more individualized and comprehensive approach to patient care.

The integrative capacity of these technologies is germane to nursing, particularly with the increasing utilization of telehealth as a surrogate for in-person patient care delivery (i.e., screening, assessing, diagnosing, and treating). Of note, although these technological advances have considerable promise, it will be important to establish their psychometric properties (e.g., reliability and validity) in all PLWH before their first-line use in clinical settings.

Global Concerns

Persons living with HIV are aging worldwide, suggesting that issues of successful cognitive aging are a global priority. Nurses and nursing allies will need to be familiar with cognitive issues because they can increase dependence and increase needs for caregiving. Yet, as many PLWH age, many will likely find themselves providing self-care as they cope with their own cognitive impairment.

Globally, the synergistic effect of HIV and aging will increase HAND in regional populations affected with a variety of HIV clades (Sacktor et al., 2009; Thakur et al., 2019; Tyor et al., 2013). A clade refers to a subtype of HIV that has evolved from an earlier form of HIV. Although studies differ on precisely which clades confer greater risk than others, most researchers agree that Clades D and B are more neurotoxic than Clades A and C (Mishra et al., 2008; Sacktor et al., 2019; Tyor et al., 2013). This suggests that in regions where Clades D and B occur (i.e., North Africa, the Americas, Australia, and Europe), PLWH may experience greater prevalence and severity of cognitive impairment as they age than PLWH in regions where Clades C (i.e., South Africa, India); F, G, H, J, and K (Central Africa); and BC recombinant (i.e., China and Southeast Asia) occur.

Conclusion

Cognitive health is an essential component of successful aging. Without it, one's autonomy, health, and quality of life are jeopardized. As PLWH age, successful cognitive aging may be a challenge for some. Nurses and allied health care professionals can address these challenges by: (a) providing routine cognitive screening with patients; (b) monitoring risk factors for cognitive impairment; (c) providing education to patients to protect brain health and cognition; (d) intervening on medical causes of cognitive impairment; and (e) offering remediation techniques to compensate for cognitive impairment. Despite some research indicating that the cognitive vulnerability due to HIV may not be as dramatic as once thought (Pedersen et al., 2013), the large number of aging PLWH with age-related cognitive impairments will remain a growing concern.

Disclosures

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Author Contributions

All authors have contributed to (a) the conception and design of the work, (b) with each author assigned certain sections to write based on their expertise, (c) all provided revision and final approval of the article, and (d) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Key Considerations

- As PLWH age, evidence suggests many may be at risk of developing cognitive impairments; thus, cognitive screening is a necessary component of standard practice.
- Given the impact cognition exerts on everyday functioning including self-care, medication adherence, health literacy, and quality of life, protecting cognition in PLWH as they age remains an important focus for nursing practice and research.
- Neuroprotective factors such as physical exercise, cognitive training, and management of psychiatric/mental health and physical comorbidities can support brain health and function.
- PLWH may not understand how to protect their brain health as they age; therefore, education on brain health to promote successful cognitive aging is recommended.

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