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Cognitive Impairment Among Older Individuals with HIV Infection

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Abstract The introduction of combination antiretroviral therapy (CART) has led to a dramatic increase in the survival of HIV seropositive (HIV+) individuals and an aging HIV+ population with over 50 % of HIV+ persons in the USA now over the age of 50. Cognitive impairment is common across the lifespan in HIV but is twice as common among older HIV+ adults. HIV itself may lead to HIV-associated neurocognitive disorders, but cardiovascular risk factors may also contribute to cognitive impairment in older HIV+ adults. Abnormal amyloid deposition in brains of HIV+ individuals at autopsy may also indicate a role of accelerated aging and early-onset Alzheimer disease. We review the evidence to support these three mechanisms of cognitive impairment in HIV+ individuals. Regardless of etiology, cognitive impairment has significant impact on the everyday functioning and quality of life of older HIV+ adults.

Keywords HIV · Aging · Neurocognitive impairment · HIV-associated neurocognitive disorders · Frailty

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Introduction

The introduction of combination antiretroviral therapy (CART) in 1996 has resulted in a dramatic decrease in the mortality associated with human immunodeficiency virus (HIV) infection so that HIV seropositive (HIV+) individuals receiving CART now have nearly normal life expectancies [1]. As a result, in 2015, more than 50 % of all HIV+ individuals in the USA are older adults, defined as those greater than 50 years of age [2, 3]. In Sub-Saharan Africa, where 70 % of the global HIV+ population resides, 3 million (14 %) of the 21 million HIV+ people are older adults, and this number is expected to rise with more widespread distribution of CART and resultant increasing life expectancies [4]. In the USA, older adults also account for 15 % of new HIV diagnoses and 35 % of all deaths among HIV+ individuals [5]. HIV infection leads to an earlier onset and increased comorbidities involving the heart, liver, kidney, bone, endocrine system, and immune system, and more than 75 % of older HIV+ adults die from non-HIV related causes [6, 7]. These data suggest that cognitive impairment, which is common in the setting of HIV infection, could also have an earlier age of onset in HIV+ individuals and that the causes of cognitive impairment in older HIV+ individuals may overlap with the causes of cognitive impairment among older HIV seronegative (HIV−) individuals.

A variety of etiologies for cognitive impairment in older HIV+ individuals have been proposed. HIV-associated neurocognitive disorder (HAND) is characterized by deficits in executive functioning, psychomotor speed, and memory performance and is attributed to the effects of HIV in the central nervous system (CNS) [8]. HAND is common throughout the lifespan of HIV+ individuals and is more frequently seen in older HIV+ adults [9]. Multiple studies have demonstrated persistent ongoing systemic and CNS inflammation in HIV+ individuals, and this may accelerate aging-

related processes including cerebrovascular disease and Alzheimer disease (AD) [6]. As a result, cognitive impairment among older HIV+ individuals may also be due to effects from HIV-associated small vessel cerebrovascular disease or potentially the earlier onset of neurodegenerative diseases such as AD.

This review will focus on these three potential causes for cognitive impairment in older HIV+ individuals. We will review the clinical characteristics of HAND, specifically focusing on its presentation over the age of 50 years. We will also discuss cerebrovascular disease as a potential cause for the cognitive impairment in older HIV+ individuals. Finally, we will summarize the evidence for abnormal amyloid processing in HIV infection and discuss whether AD could be a potential cause of cognitive impairment in older HIV+ individuals. In addition, we will briefly discuss potential consequences of cognitive impairment of any etiology in older HIV+ adults focusing specifically on a potential association with frailty.

HIV-Associated Neurocognitive Disorder

HAND represents a spectrum of neurocognitive impairment that includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). HAND is diagnosed using criteria based on both formal neuropsychological testing and functional status assessments, and each successive HAND stage is categorized by both worsening neurocognitive deficits and greater functional impairment (Table 1) [10]. ANI is characterized by mild to moderate deficits on neuropsychological testing without any corresponding functional status deficits. MND includes mild to moderate neuropsychological and functional status deficits, and HAD is characterized by severe neuropsychological and functional status impairment. Clinically, HAND is characterized by executive dysfunction, memory impairment, and motor dysfunction [8, 11••]. Neurocognitive abnormalities include prominent disruption of executive function, multitasking, impulse control, and judgment as well as psychomotor slowing and memory encoding and retrieval. Motor dysfunction commonly includes bradykinesia, coordination abnormalities, and gait imbalance.

The prevalence of all forms of HAND is approximately 40–50 % and remains unchanged since the pre-CART era, making HAND the third most common cause of cognitive impairment globally; however, the frequency of ANI has increased and the frequency of HAD has drastically decreased in CART-treated individuals [12]. Whereas HAD was present in 20 % of participants enrolled in the Multicenter AIDS Cohort Study (MACS) prior to 1991, it was found in only 5 % of participants enrolled between 2001 and 2003 [13•, 14]. ANI now accounts for approximately 70 % of all forms of HAND [12]. Importantly, HAD was previously a progressive and fatal condition in untreated HIV+ persons and was primarily seen in advanced HIV disease stages [15]. In the majority of CART-treated HIV+ individuals today, HAND is typically not progressive. A 4-year study of 197 CART-treated individuals demonstrated that 77 % remained neurocognitively stable with only 13 % deteriorating to a more severe form of HAND and 10 % improving to a less severe stage [16••]. In addition, neurocognitive impairment is now more common in medically asymptomatic HIV disease stages with less severe immunosuppression [17].

Clinical characteristics of and risk factors for HAND have also changed in the CART era. Whereas deficits in motor skills and psychomotor speed were more commonly found in the pre-CART era, learning/memory and executive function deficits are more commonly seen today [17]. Degree of current immunosuppression, estimated duration of HIV infection, and viral suppression in the cerebrospinal fluid (CSF) were risk factors for HAND in the pre-CART era, but are not significant current risk factors for HAND [17]. On the contrary, nadir CD4 count remains a risk factor for HAND, even in virally suppressed patients on CART, and clinically defined AIDS is associated with an earlier onset of mild cognitive impairment [12, 17–19]. Cognitive reserve may also be an important factor in decreasing the risk of HAND as cognitive impairment was found in 38 % of HIV+ participants in the MACS study with less than a high school education compared to only 17 % of HIV+ participants with at least a high school education [13•].

Older age is also increasingly recognized as an important risk factor for HAND [20]. In a study of 202 HIV+ adults in the Hawaii Aging with HIV-1 Cohort, older HIV+ adults (defined as greater than age 50 years) were more than three times

Table 1 Diagnostic criteria for HIV-associated neurocognitive disorders based on Frascati criteria [10]

HAND stage	Neurocognitive testing results	Functional status assessments
Asymptomatic neurocognitive impairment (ANI)	≥1 SD below the mean in ≥2 cognitive domains	No impairment
Mild neurocognitive disorder (MND)	≥1 SD below the mean in ≥2 cognitive domains	Mild to moderate impairment
HIV-associated dementia (HAD)	≥2 SD below the mean in ≥2 cognitive domains	Moderate to severe impairment

as likely as their younger HIV+ counterparts (defined as age 20–39 years) to meet criteria for HAD after adjusting for other known HAD risk factors [21]. In the MACS cohort, HIV+ participants ≥60 years old were four times more likely than those <40 years old to meet criteria for HAD (8 vs. <2 %), although no significant difference was seen in the rates of all stages of HAND or in rates of progression to worsening HAND stage [16••]. Older age has also been identified as a risk factor for cognitive impairment in several South African cohorts [22, 23]. On the contrary, early results from the University of California San Francisco Over 60 Cohort demonstrated similar rates of all HAND stages when compared to HIV+ participants <60 years old [24]. This cohort had higher levels of CART adherence than other longitudinal cohorts, however, and a survivorship bias may also account for these discrepancies. Further investigation with larger and longer longitudinal studies is needed to further clarify whether older age is truly a risk factor for HAND and, if so, via what pathophysiologic mechanisms age confers an increased risk.

Interestingly, analyses from the Hawaii cohort found that the effects of aging and HIV on neuropsychological test performance appear to be independent of each other [25]. In the MACS cohort, older HIV+ participants demonstrated a longitudinal decline in performance on tests of psychomotor speed compared to stable performance that was seen in younger HIV+ persons, suggesting that age was an additional risk factor for impairment independent of HIV status [26]. However, in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, aging and HIV infection appeared to have synergistic effects on both cognitive and functional status with older HIV+ individuals showing more significant declines in both a summary measure of neuropsychological testing performance [27, 28] and basic and instrumental activities of daily living compared to HIV+ adults <40 years old [29]. In the same cohort, aging had additive negative effects with HIV on physical functioning and general health perceptions, and aging had a significant interaction with HIV infection on emotional functioning.

Other HAND risk factors and manifestations have been demonstrated to vary by age group as well. In the Hawaii cohort, CD4 nadir remained a risk factor for HAD [30], and depressive symptoms were found to increase the risk of neurocognitive impairment in younger HIV+ participants but not in older participants [31]. Clinically, aging was found to exacerbate the development of extrapyramidal motor findings associated with HAND [32]. Of note, cognitive reserve may be especially important in older HIV+ adults as a different cohort found that cognitive reserve appeared to decrease the risk of cognitive impairment in older HIV+ individuals even more than their younger counterparts [33].

Given the frequency of HAND across all ages and indications that it is even more common and more likely to be present in its most severe form among older HIV+ adults, special consideration is needed when treating older HIV+ persons in a clinical setting. While some older HIV+ adults acquired HIV infection at an older age, many have lived with HIV for many years, including in the pre-treatment era. Therefore, they likely have been exposed to longer periods of viremia and chronic immune activation and may have been treated with more neurotoxic medications, such as stavudine, which are less commonly used today [34]. In addition, older HIV+ adults are more likely to have delayed times to diagnosis of their HIV infection and may experience more social isolation than their younger counterparts [34].

Cerebrovascular Disease

The impact of age on risk of HAND is likely confounded by the increased prevalence of cardiovascular risk factors among older adults as these factors have been linked to an increased risk of cognitive impairment in HIV+ persons. For example, diabetes and insulin resistance were significantly associated with dementia in older HIV+ adults in the Hawaii cohort [35]. In the MACS, both diabetes and pre-diabetes (defined as a fasting blood glucose between 100 and 125 mg/dL or hemoglobin A1c 5.7–6.4 %) were associated with worse neuropsychological test performance across multiple domains [unpublished data]. Furthermore, in this sub-population of the MACS, HIV status was not a significant predictor of cognitive impairment in multivariate models suggesting that metabolic status might be a more important predictor of cognitive impairment among HIV+ persons in the CART era. This finding was recently replicated in a smaller study of 122 MACS participants in which diabetes was correlated with the rate of brain atrophy (as measured by an increase in size of the cerebrospinal fluid compartment), but HIV status and other cardiovascular risk factors, including hypertension and urine protein/creatinine ratio, were not risk factors [36••].

Other cardiovascular disease factors have also been linked to risk of cognitive impairment among HIV+ persons. In the cardiovascular disease sub-study of the MACS, carotid intima media thickness was significantly associated with slower psychomotor speed and poorer memory test performance [37]. In the CHARTER cohort, waist circumference, which was used as a proxy for central obesity, was associated with cognitive impairment, whereas there was no association between cognitive impairment and body mass index (BMI) [38]. Of note, diabetes was associated with cognitive impairment only in participants >55 years old in this study. In another analysis of the CHARTER cohort, significant interactions between age and systolic blood pressure, BMI, and cholesterol were found suggesting that vascular risk factors may contribute to the disproportionate reduction in neurocognitive performance that is seen among older HIV+ individuals. Finally, in the recent Strategic Timing of Antiretroviral Therapy (START) trial,

worse neurocognitive test performance among >600 HIV+ CART-naïve adults with CD4 counts >500 cells/μL was associated with older age, diabetes, and higher Framingham risk score, a clinical scale based on cardiovascular disease risk factors [39••].

The relationship between cardiovascular risk factors and cognitive impairment in HIV is especially important as it appears the detrimental effect of cardiovascular risk factors on cognition can be at least partially attenuated with treatment. In a study of 98 HIV+ individuals, cardiovascular risk factors were associated with slower processing speed on neuropsychological testing. Furthermore, when compared to participants with cardiovascular disease risk factors being treated with medications, those participants with untreated risk factors demonstrated poorer performance on tests of processing speed, learning and memory, and executive function [40].

Alzheimer Disease

Early-onset AD has also been proposed as a mechanism of cognitive impairment in HIV+ individuals based on several lines of research and putative pathophysiologic mechanisms. Autopsy studies are one such line of research that has provided evidence for the theory for a role of AD in HIV-associated cognitive impairment. In 1998, Esiri et al. first reported increased amyloid deposition in the brains of AIDS patients when compared to HIV− age-matched control brains, and this difference was even more striking in younger individuals [41]. These findings were extended in 2005, with results from a study of 162 brains collected at AIDS autopsies that demonstrated significant amyloid deposition in HIV+ brains [42]. Deposition was significantly increased in older individuals and in CART-treated individuals. Interestingly, while the classic pathologic finding in AD is extracellular neuritic amyloid plaques, amyloid deposition in the HIV+ brains was diffuse, non-neuritic, and often intraneuronal. These findings suggest that HIV infection may lead to early aging with resultant increased deposition of amyloid in the brain which may be enough to cause cognitive impairment.

CSF abnormalities in HIV+ persons with HAND are also similar to those of AD. Clifford et al. reported that CSF levels of amyloid-beta-42 (Aβ42), which is reduced in AD, were significantly lower in HIV+ adults with HAND compared to age-matched healthy controls and cognitively normal HIV+ individuals and were similar to levels seen in subjects with AD [43]. Reduced Aβ42 was also seen in HIV+ adults with HAD in another cohort of 121 HIV+ and 20 AD patients [44]. The latter cohort also found elevated levels of total and phosphorylated tau in the CSF of HIV+ persons with HAD, a finding that is also present in AD. This finding of elevated levels of total and phosphorylated tau has been replicated in several other cohorts [45, 46•]. However, these findings have not been consistent across all cohorts [43, 46•, 47•] which may be the result of heterogeneity in the populations being assessed.

Imaging studies using methods employed in AD to identify increased amyloid deposition in the brains of HIV+ participants have been unrevealing thus far. For example, positron emission tomography (PET) studies using the tracer 11-C Pittsburgh Compound (11C-PIB) have been shown to identify regions of amyloid deposition in patients with AD [48]. However, increased PIB uptake was not found in studies of cognitively unimpaired HIV+ persons [49] or in HIV+ adults with HAND [50]. Of note, participants in these studies were less than 60 years old, so this may account at least partially for the negative findings. Further research using larger cohorts of HIV+ adults >60 years old and age-matched controls are needed to determine whether imaging modalities such as these can be used as surrogate markers for amyloid deposition in HIV+ persons in order to assess whether amyloid burden correlates with neurocognitive impairment in older HIV+ adults.

Several potential mechanisms for the increased levels of amyloid in HIV infection have been proposed. In in vitro studies, Tat, a regulatory protein encoded by the HIV genome, has been shown to inhibit neprilysin, one of the major enzymes responsible for degrading Aβ42 [51, 52], and disrupt endolysosome function leading to increased levels of β-amyloid-converting enzyme [53]. In addition, chronic CNS inflammation during HIV infection leads to increased levels of interleukin (IL)-1 and tumor necrosis factor-α (TNFα) which have been shown to upregulate γ-secretase which degrades amyloid precursor protein (APP) into Aβ42 [44, 54]. Finally, the HIV protein Gp120 may also increase Aβ42 production by increasing the association between APP and β-secretase in cell membranes [55].

Impact of Cognitive Impairment in Older HIV+ Adults

Regardless of the etiology, cognitive impairment in older HIV+ adults is important for a variety of reasons. HIV+ adults with neurocognitive impairment perform worse on measures of shopping, cooking, financial management, medication management, and vocational abilities [56] and show worsened CART adherence [57], automobile driving capacity [58], and emotional well-being [31, 59]. Furthermore, absence of objective and subjective neurocognitive impairment has been associated with better mood, more independence in activities of daily living, and better interactions with healthcare providers [60] as well as significantly better mental health-related quality of life [61].

The impact of neurocognitive impairment on frailty is also being increasingly recognized. Frailty is a clinical syndrome

consisting of ≥3 of the following: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity [62]. HIV infection has been associated with earlier onset of frailty, especially in individuals with a history of AIDS, and frailty is independently predictive of falls, worsening mobility, disability, hospitalization, and death [62–65]. Emerging evidence from the MACS cohort indicates that HAND may increase the risk of frailty in HIV+ older adults. In a cross-sectional analysis of 494 HIV+ participants, odds of HAND was increased by 2.2 in frail participants compared to those without frailty, and odds of symptomatic HAND (i.e., MND or HAD) was increased by 3.8 [66••]. A longitudinal analysis of MACS participants found that HIV+ participants with neurocognitive impairment had 73 % increased odds of developing frailty over 6 years of follow-up compared to HIV+ participants without cognitive impairment. Overall, HAND was associated with twice the odds of developing frailty after adjusting for age [66••].

All of these results suggest that cognitive impairment among HIV+ older adults has both relevant clinical and everyday life implications. A diagnosis of HAND is also associated with an increased risk of mortality [67]. Therefore, screening for cognitive impairment should be completed regularly in older HIV+ adults so that those with cognitive impairment can be identified and provided with additional support services to mitigate the adverse effects associated with this condition.

Conclusion

Cognitive impairment is common among all HIV+ individuals, but older HIV+ adults are at even higher risk. The etiology of cognitive impairment in HIV+ persons may be due to direct and indirect effects of HIV itself (i.e., HAND), the consequences of cardiovascular risk factors, accelerated aging with early onset of AD, or a combination of each of these. One hypothetical model (Fig. 1) supposes that the effects of diabetes, hypertension, hyperlipidemia, tobacco use, hepatitis C co-infection, and genetic factors combine to lead to neuropathological damage and decreased cognitive reserve among younger aged HIV+ individuals. Among older aged HIV+ adults, both cerebrovascular disease risk factors and potential effects from neurodegenerative disease such as AD may contribute to neuropathological comorbidity and cognitive impairment. Over time, these factors in combination with the effects of chronic inflammation and immunosenescence, long-term HIV infection, and increased exposure to the toxic effects of antiretroviral drugs lead to symptomatic neurocognitive impairment which has detrimental effects on an individual's everyday functioning.

Unfortunately, no pharmacologic agents have been shown to specifically improve cognitive functioning in HIV+ persons other than CART which has led to a remarkable decrease in the frequency of and mortality associated with HAD. Therefore, all older HIV+ individuals should be treated with

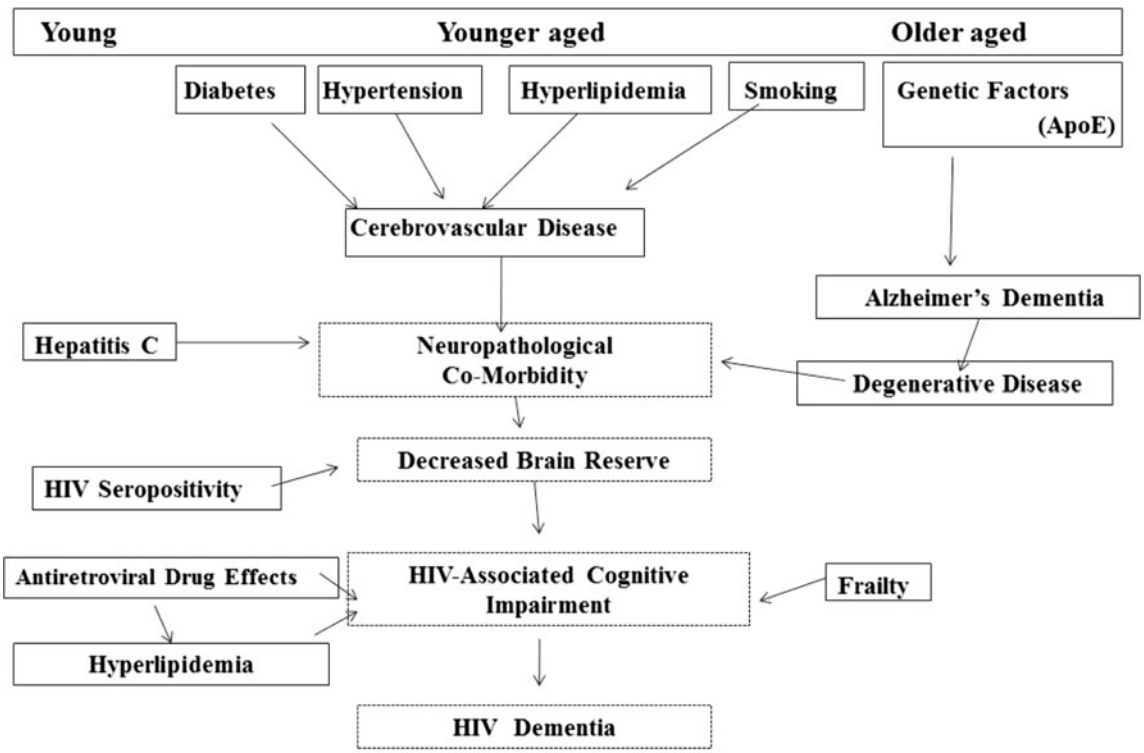

Fig. 1 Proposed model of the development of HIV-associated neurocognitive impairment and HIV-associated dementia

CART, especially in light of the recent START trial which showed that early initiation of ART regardless of CD4 count reduced the incidence of AIDS and non-AIDS related adverse events [68]. Given the evidence that treated cardiovascular risk factors may lead to lesser degrees of cognitive impairment than untreated risk factors, it is also reasonable to treat older HIV+ persons with cardiovascular risk factors with aspirin and a cholesterol-lowering statin medication as is clinically indicated for their cardiovascular risk factors. Finally, it is possible that there is also a role for cholinesterase inhibitors and/or memantine in HIV+ adults in their 7th or 8th decade of life, but this has not been evaluated in a clinical trial. Future studies are needed to evaluate these treatments for AD specifically in older HIV+ patients.

Unlike many other neurological complications of HIV which have become significantly less common in the CART era, cognitive impairment continues to be an important neurological complication in HIV+ individuals on CART with suppressed viral replication. As the HIV+ population ages, the burden of cognitive impairment will likely continue to increase, so further research into its prevention and treatment is urgently needed.

Compliance with Ethical Standards

Conflict of Interest Deanna Saylor and Ned Sacktor declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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