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Interactions between aging and NeuroAIDS

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Abstract

Purpose of review—To summarize recent advances in aging and neuroAIDS by reviewing relevant articles from the preceding eighteen months from PubMed and PsycINFO databases.

Recent findings—The success of combination antiretroviral therapy (cART) has led to aging of the HIV-infected population, which in turn contributes to the prevalence of HIV-associated neurocognitive disorder (HAND). Biomedical advances continue to clarify the pathophysiology of HAND despite effective cART, including chronic inflammatory and neurovascular etiologies. In recent months, associations between HAND and non-neurological medical diseases have been identified, as well as linkage to neuroimaging in those aging with HIV. Developing effective screening tools to detect impairment remains an important scientific gap, while promoting factors associated with successful cognitive aging is emerging as a possible means of enhancing quality of life.

Summary—A greater understanding of HAND pathophysiology among treated subjects with suppressed virus will aid in explaining the high prevalence of HAND despite effective cART and allow for development of novel targeted interventions. Neuroimaging and other biomarkers show promise in discerning HAND from age-associated cognitive disorders. Effective screening tools remain critically needed. Together, this work will inform promising strategies needed to address issues pertinent to an expanding group of older patients living with HIV.

Keywords

HIV; AIDS; cognition; neurology; aging

Introduction

Infection with HIV has become a manageable, chronic illness for most patients with access to combination antiretroviral therapy (cART). Consequently, the number of older people living with HIV (PLWH) has increased substantially. More than one-half of U.S. HIV/AIDS

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cases will be over age 50 by 2015 and these demographic trends extend to resource-limited setting, including sub-Saharan Africa. (1, 2) Despite treatment advancements, between 35–50% of PLWH suffer from HIV-associated neurocognitive disorders (HAND). (3, 4) In the current era, HAND is defined by the 2007 “Frascati” guidelines as one of three conditions. The two milder diseases are Asymptomatic Neurocognitive Impairment (ANI), with a prevalence of 30–35% and accounting for up to 70% of people with HAND and Mild Neurocognitive Disorder (MND), with a prevalence of 20–25%. HIV-associated dementia (HAD) is a severe form of impairment, based on neuropsychological testing and the degree to which it impacts daily function, and has a prevalence of 2–3%. (4, 5)

The presence of deficits that impact daily function differentiate ANI from both MND and HAD. However, a pilot study of 24 HIV-infected men (age >60) and 10 seronegative controls noted that ANI subjects rated their ability to perform objective measures on a functional task to be normal, despite poor performance when measured objectively and despite neuropsychological testing deficits that were comparable to MND cases. (6) The authors conclude that involvement of frontal-striatal circuits in HIV neuropathology may contribute to deficits in insight leading to a bias that ANI captures a subset of cognitively impaired individuals who have deficits in self-awareness or less proximal objective informants. A recent analysis of 84 Kenyan PLWH also found limitations in the nomenclature, noting that the “Frascati” criteria may lead to a high frequency of false-positive diagnoses, particularly in resource-limited settings, resulting in an overestimation of prevalence; however, the study did not report use of local normative data and the sample size was small. (7

Identifying effective screening tests for ANI and MND remains challenging. Among 1,580 PLWH recruited from 6 U.S. academic sites, the HIV Dementia Scale (HDS) demonstrated low diagnostic classification accuracy (66% sensitivity, 61% specificity) using a modified raw cut point of 14. (8)** Similar findings were reported from a meta-analyses, in which the HDS and its derivate form, the International HIV Dementia Scale (IDHS), showed poor and moderate sensitivity, respectively, to detect HAND. (9) The Alzheimer Disease-8 (AD-8) and the Montreal Cognitive Assessment (MoCA) are also poor for the detection of HAND, based on a study of 200 subjects (mean age = 43 years) where the authors identified a sensitivity of 61% and 63% for AD-8 and MoCA, respectively. (10) Among individuals over age 60 (n=67), using cut point of 25 had only 72% sensitivity and 67% specificity for HAND. (11) One group noted that the combination of the Controlled Oral Word Association Test and both parts A and B of the Trail Making Test were associated with cognitive impairment established from a larger battery; however, few subjects were tested (n=106) and validation remains necessary. (12) Together, these recent studies highlight continued gaps in screening for HAND in the current era.

Neuropsychological deficits among older HIV-infected adults

The risk for cognitive impairment has been consistently linked to advancing age, but the degree to which synergistic (interaction) or additive effects occur remains controversial. One recent study of 162 adults reported main effects for age and HIV on measures of processing speed and a timed measure of everyday functioning, but interaction effects were not seen.

(13) Conversely, a longitudinal study suggested that HIV by age interaction effect may exists using longitudinal data; however, effects were only identified on one test of verbal memory, few individuals were over age 55 (n=23) and only 36% of their cohort had longitudinal data. (14) More research is needed to understand this issue more clearly.

Confirmation of deficits in memory and executive functioning was recently described in older PLWH. On a task of temporal order memory (recalling the order that stimuli have been experienced), one report noted inefficiency in PLWH over age 50 (n=50) compared to age-matched controls. (15)* By virtue of frequent comorbidities seen in their HIV-infected group, non-HIV contributions should be considered. A separate group noted 4.8-fold higher odds of memory deficits in age over 50 (n=32) compared to under 50 (n=74). (16) They noted that classically described HIV predictors of HAND were not associated with memory deficits and that their sample had a high rate of substance abuse, limiting generalizability.

Cognitive disorders adversely impact everyday functioning. Using a driving simulator with 26 adults aged 41–67 years, older age was associated with poorer driving and both visual attention and visual processing speed were associated with reaction time. (17)* In a separate study, older PLWH (n= 58, age ≥50) were less efficient and slower on a route-planning virtual city task compared to younger PLWH (n=21, age <40) and, among older subjects, attention and visuospatial abilities maximally predicted impaired driving performance. (18) Together, these studies emphasize persistent deficits associated with HIV in the current era and provide a window of potential to impact meaningful aspects of everyday function.

HAND pathophysiology

It is increasingly clear that HAND is heterogeneous, with contributions from HIV-specific, HIV-related, and non-HIV mechanisms; and that this is particularly important among older individuals. (19)** Treatment with cART has allowed more individuals to age with HIV, revealing that viral suppression alone is not sufficient to eradicate HAND and exposing gaps in our knowledge needed to design the next phase of targeted interventions. Since most PLWH who have access to and adherence to cART can maintain viral suppression, optimal studies will investigate mechanisms in such subjects, rather than mixed populations of individuals with and without detectable plasma HIV RNA; but use of mixed populations, possibly associated with mixed pathologies, remains a weakness of many studies.

Knowledge that immune activation persists despite effective cART provides insight into why HAND can occur despite viral suppression. Plasma soluble CD163, an indicator of HIV-induced monocyte-macrophage system activation and also a correlate to vascular inflammation, was higher in PLWH with an impaired global deficit score (GDS) compared to age-matched, HIV-uninfected controls and despite suppression of plasma HIV RNA. (20) Higher levels in plasma were also noted in subjects with MND compared to those with ANI, a pattern not seen in CSF.

Another study of post-menopausal women compared the soluble factors of immune activation in virally suppressed, HIV-infected and uninfected subjects, theorizing that increased microbial translocation related to HIV damage of intestinal mucosa contributes to an inflammatory state. (21) They found that HIV was associated with increased serum

markers of monocyte-macrophage system activation (sCD14, sCD163), T-cell activation (sCD25), and microbial translation (lipopolysaccharide (LPS)) in plasma. In an exploratory study completed by a different group, HIV-infected individuals on cART with stable or progressive HAND were found to have elevated plasma IFN-α-2b, IL-6, and sIL-2R, when compared to HIV-infected subjects on cART with improved or without HAND and to healthy controls. (22)* The authors highlight the importance of controlling for age, medical comorbidities including obesity, substance abuse, HCV and cytomegalovirus (CMV), as they can influence inflammatory biomarker levels.

Cerebrospinal fluid (CSF) biomarkers of HAND have been explored as well. HIV-infected individuals (n= 46, only 36 on cART) compared to unaffected controls had elevated factors indicative of inflammation and glutamate neurotoxicity, as well as markers of abnormal metabolic waste accumulation in ways that overlap with aging. (23) The mixture of individuals on and off cART makes it difficult to interpret the pertinence of this finding for patients with suppressed plasma viral loads. A separate study of individuals off cART identified increased inflammatory CSF IL-8, MCP-1, G-CSF, and IP-10 among those with cognitive impairment. (24

Neurodegenerative and neurovascular disease and HIV

It is increasingly important to understand the relationships between HAND and Alzheimer's disease (AD), the most common neurodegenerative disease of old age. Controversy remains as to whether apolipoprotein E4 (APOE4), a known AD risk factor, increases risk for HAND with past studies supporting and others not supporting correlations and some data suggesting that age may modulate potential associations. A recent substudy of the CHARTER group with 466 relatively younger subjects (mean age = 44 years and 50% with detectable plasma HIV RNA), found no association between the APOE4 allele and HAND. (25

In contrast, greater clarity is emerging around neurovascular factors, increasingly associated with HAND, particularly in older age. HIV infection itself may be an independent risk factor for stroke since the Framingham Risk Score for Stroke (FRS-S) was found to underestimate the stroke risk in this population. (26)** In addition to traditional stroke risk factors, some theorize influence from HIV-mediated mechanisms including increased immune activation, hypercoagulable state, and even the effects of cART. (27

HIV and cART directly influence the neurovasculature. In one study, 32% of middle-aged PLWH had increased carotid intima-media thickness (cIMT), a marker of early atherosclerosis; diabetes, cardiovascular risk factors and cIMT changes were independently linked to poorer cognitive performance. (28) Neuropathological studies substantiate these changes with 47% of 137 autopsy cases examined between 1999 and 2011 having moderate to severe cerebral small vessel disease. (29) The frequency of disease was associated with protease inhibitor (PI) use, suggesting that cohort effect may exist, since cases were captured at a time when PIs with poorer lipid metabolic profiles were in common use and clinicians were gearing up aggressive monitoring and treatment efforts related to lipids. But, this legacy effect may continue to impact HAND in current older PLWH. In a separate study of

brain vessels and compared to HIV-uninfected controls, those with HIV had thinner, more dilated arterial walls indicative of continuous modeling, possibly reflective of preclinical HIV arteriopathy and increased stroke risk. (30) The study was confounded by substantial difference in race between HIV-infected and uninfected groups.

The presence of multimorbidity may predispose to HAND. The Veteran's Administration Index (VACS), a composite measure that includes hematological, renal and hepatic measures as well as hepatitis C and HIV parameters, was found to be associated with a higher rate of global cognitive impairment [OR = 1.21 (1.12 to 1.32)] among 601 individuals (mean age = 42 years), but about one-half had detectable plasma HIV RNA. (31)* Since multimorbidity increases with age, this work may be particularly relevant.

Imaging in HIV and aging

Diffuse cerebral atrophy has been observed in HIV. Distinguishing image characteristics of HIV from that of age-associated neurodegenerative disorders and normal aging remains a critical gap. Investigators in the CHARTER cohort evaluated longitudinal MRIs in comparison to CD4 and viral loads changes noting that larger CD4 recoveries, but not viral suppression, developed increasingly abnormal white matter findings and greater subcortical gray matter volumes. (32) Among HIV-infected subjects over the age of 60 years, reductions in white matter fiber integrity by diffusion tensor imaging (DTI) were found throughout the brain, with particular decreases in the callosum; these changes were exacerbated in subjects who carried one or more APOE4 alleles. (33) A follow-up study of the same individuals noted abnormalities in DTI connectivity associated with HIV. (34

New imaging data provide evidence of persistent CNS inflammation despite viral suppression. The binding of a PET marker of activated microglia, [11C]-PK11195, was analyzed in seven HIV-infected patients on cART without neurologic symptoms, and compared to healthy controls. Clusters of increased binding were seen in HIV compared to controls and image abnormalities were linked to lower executive function. (35)* Using a fermoxytolol contrast agent, a substance readily taken up by circulating monocytes, separate investigators identified a "tram track" appearance on MRI among four older, HIV-infected, and virally suppressed males with HAND, a pattern thought to reflect perivascular monocytes and not seen in one HIV-uninfected control. (36)* Both studies provide intriguing evidence for monocyte-macrophage pathways and microglia involvement in HAND despite cART-era.

Successful Cognitive Aging

In the setting of HIV, higher cognitive reserve, defined as the ability to maintain cognitive functioning despite brain damage, is associated with lower rates of cognitive impairment and decreased dependence in tasks of everyday functioning. (37, 38) These theories provide hope for interventions that may preserve cognition for vulnerable aging PLWH. In a recent study using a visual attention tasks with increased task difficulty (attentional load), investigators found that HIV-uninfected controls (n = 36) and HIV-infected subjects without HAND (n = 37) were able to compensate for declining neural efficiency with age; whereas

older HIV-infected individuals with HAND (n = 29) were unable to fully compensate or activate the reserve network, thus resulting in poorer performance. (39

In a separate study, higher cognitive reserve was associated with less apathy among 116 PLWH (66% female, mean age = 52, 91% on cART). (40) The association was stable across all age groups (range age 22–79) and was stronger for participants with lower nadir CD4 counts. In another study of 70 younger (≤40 years) and 107 older (≥50 years) HIV-infected adults compared to age-matched HIV-uninfected younger (n = 48) and older (n = 77) controls, additive effects of age and HIV were identified in relation to successful cognitive aging, operationalized as the absence of both performance-based neurocognitive deficits and self-reported symptoms. (41)* Higher cognitive reserve (e.g. education, intellectual ability) was the only significant correlate to successful cognitive aging.

By promoting factors associated with successful cognitive aging, quality of life could be improved. Interventions addressing cognitive impairment may decrease the demand for social services. (42) Based on the principles of neuroplasticity, cognitive remediation therapies are designed to extend cognitive abilities in a certain domain through repetitive exercise. In a recent study of 22 middle-aged and older HIV-infected adults with deficits in speed of processing and everyday functioning, benefits from cognitive training were identified; however, more research is needed given the small sample studied. (43

Exercise, a modifiable lifestyle behavior, may influence the frequency of HAND. Among 335 subjects (aged 20 to 79), self-reported recent engagement in exercise was inversely associated with global cognitive impairment. (44) Similarly, the relationship between aerobic fitness, measured by VO_2 peak, and cognitive impairment was explored in a group of 37 HIV-infected individuals above age 50 and on cART. (45) Higher aerobic fitness was associated with better cognitive performance, extending to domains of language, memory and visual perception (n=37) and subjects with greater VO_2 peak values were less likely to have MND or HAD. Future longitudinal studies are warranted to address the causality of these findings.

Conclusions

Despite a rapidly aging HIV epidemic in both resource-limited and rich settings, our understanding of important contributors to cognitive decline among HIV-infected elders is incomplete. Existing data support contributions from HIV-related factors, particularly those associated with immune activation and inflammation; but there is increasing awareness of contributions from comorbid conditions, particularly metabolic derangements and cerebrovascular disease. Since most patients with access to cART can achieve suppression of plasma HIV RNA, studies that investigate HAND in groups with suppressed viral loads are most informative, but these continue to be infrequent in the existing literature. Encouraging work identifies cognitive reserve and exercise to potentially protect from the effects of HAND.

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Bullet point summary

- The HIV-infected population is aging worldwide; in the U.S. over 50% of HIV-infected patients will be over the age of 50 by 2015
- Between 35–50% of HIV-infected patients meet criteria for HIV-associated Neurocognitive Disorder (HAND) and several groups have demonstrated persistent HAND despite up to 5 years of suppressive therapy with cART
- There is little evidence that the effects of HIV and aging interact with regard to neuropsychological testing.
- Cerebrovascular disease is an important comorbidity related to cognitive health in aging HIV-infected patients
- Multiple lines of evidence demonstrate continued immune activation and/or inflammation despite suppression of HIV RNA in plasma and providing a mechanistic link to cognitive impairment despite cART.