Published in final edited form as:
Semin Neurol. 2014 February ; 34(1): 27–34. doi:10.1055/s-0034-1372340.

HIV and Aging: Effects on the Central Nervous System

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Abstract

With the introduction of combination antiretroviral therapy, many human immunodeficiency virus-positive (HIV+) individuals are reaching advanced age. The proportion of people living with HIV older than 50 years already exceeds 50% in many communities, and is expected to reach this level nationally by 2015. HIV and aging are independently associated with neuropathological changes, but their concurrence may have a more deleterious effect on the central nervous system (CNS). Published data about neurocognitive and neuroimaging markers of HIV and aging are reviewed. Putative factors contributing to neurocognitive impairment and neuroimaging changes in the aging HIV+ brain, such as metabolic disturbances, cardiovascular risk factors, immune senescence, and neuroinflammation, are described. The possible relationship between HIV and some markers of Alzheimer's disease is presented. Current research findings emphasize multiple mechanisms related to HIV and combination antiretroviral therapy that compromise CNS structure and function with advancing age.

Keywords

human immunodeficiency virus; aging; neurocognitive; neuroimaging; metabolic syndrome

Aging with HIV: A Rapidly Growing Population

With over 33 million infected individuals, HIV is one of the largest single infectious causes of neurologic disease worldwide. The development and application of combination antiretroviral therapy (cART) for HIV has allowed many infected persons to live to an older age. In addition, HIV transmission and incident infections are increasing among older adults, who in turn have a greater risk to develop cognitive impairment.[1,2] The Centers for Disease Control (CDC; Atlanta, GA) estimates that by 2015, half of all people living with HIV infection in the United States will be 50 years of age or older (www.cdc.gov/hiv/topics/over50) and in many localities this threshold has already been exceeded. Therefore, there is an urgent clinical need to better delineate neurologic complications and treatment in HIV+

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individuals who are living longer, including those with sustained virologic suppression and immune reconstitution on cART.[3]

HIV and Abnormal Aging: Convergent Pathophysiological Mechanisms

HIV and aging are independently associated with neuropathological changes (e.g., reduced synaptodendritic complexity, abnormal protein deposition in the brain) and impaired neurocognitive function. Furthermore, their concurrence may have additive or synergistic effects on the CNS,[4] as is the case for general major medical comorbidities.[5] Mechanisms of neural injury in aging with HIV may include persistent inflammation, oxidative stress, metabolic disturbances, cardiovascular risk factors, immune senescence, disorders of protein processing,[6–8] and age-related changes in the pharmacology of antiretrovirals (ARVs), which may worsen their neurotoxicity.[9–11]

Neurocognitive impairment, along with its associated disability and reduced quality-of-life, remains highly prevalent despite reductions in the most severe form of brain disease, HIV-associated dementia (HAD). The CNS HIV Anti-retroviral Therapy Effects Research (CHARTER) study (2010) found a 47% prevalence of HIV-associated neurocognitive disorders (HAND) in a diverse sample of 1,555 individuals who were on cART, most of them experiencing mild (33%) or moderately severe (12%) forms.[12] The term HIV-associated neurocognitive disorders (HAND) encompasses three subclassifications: asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD). The current gold standard for case definition of HAND is an international expert consensus document often referred to as the Frascati Criteria.[13] These criteria integrate objective neuropsychological performance, information about changes in functional status, and neurocognitive comorbidities such as developmental learning disabilities and brain injury from other causes. Individuals with confounding comorbidities sufficient to explain their compared neurocognitive performance are not eligible for a diagnosis of HAND. To further summarize the diagnostic criteria, all categories require impairment in at least two ability domains. Asymptomatic neurocognitive impairment (ANI) is assigned when there is no accompanying functional decline. Mild neurocognitive disorder (MND) is assigned when both neuropsychological and everyday functioning deficits are in the mild to moderate range. Criteria for the most severe form, HAD, are met when cognitive deficits are moderate to severe and there is substantial functional impairment.

As older age is a risk factor for HAND and also for non-HIV-related cognitive deficits, cognitive impairment presenting in an older HIV-infected individual represents a true clinical conundrum.[14] Potential contributing factors, such as reversible endocrine disturbances, nutritional deficiencies, and others must be explored, and in some instances the roles of cerebrovascular disease or neurodegenerative disorders such as Alzheimer’s disease (AD) need to be considered. Other disorders known to have an impact on cognitive functions (e.g., hepatitis C virus coinfection, substance abuse) may interact with age as well.[15,16]

We review below published data about neurocognitive and imaging markers of HIV and aging. Though not exhaustive, the discussion addresses some of the putative factors contributing to neurocognitive imaging changes, such as metabolic disturbances, cardiovascular risk factors and neuroinflammation. Available data about the possible relationship between HIV and AD are described.

Neurocognitive Impairment in HIV and Aging

Two decades of research have demonstrated that HIV+ individuals can show impaired cognitive abilities in several domains, including learning, memory, speed of information processing, working memory, executive functions, and motor skills. There is growing evidence that HIV and aging may amplify each other's adverse impacts on cognition. Initial reports from the Hawaii Aging with HIV Cohort indicated twice the rate of HIV-associated dementia (HAD) in older versus younger individuals.[17] Similar findings were described by Becker et al.[18] Cherner et al[19] reported that HIV+ older participants with detectable cerebrospinal fluid (CSF) viral load had twice the prevalence of neurocognitive impairment compared with those without detectable virus.

Fig. 1 depicts overall cognitive performance in both HIV− and HIV+ individuals from age 20–70 years studied by Grant and Heaton at the HIV Neurobehavioral Research Center (HNRC) in San Diego. Average scaled scores on a range of neuropsychological tests were used to measure overall cognitive performance. In addition to a main effect of HIV, represented by the vertical distance between the fitted regression lines, an age-effect can also be appreciated, represented by the downward slope of the lines for both HIV− and HIV +. Most importantly, the slope of the regression line for those with HIV is more steeply negative, so that the average gap between HIV+ and HIV− increases with age. Thus, the deleterious effects of age on cognitive performance are amplified in HIV. Consistent with this, aging and HIV also show synergistic deleterious effects on measures of everyday functioning.[20] Global neuropsychological impairment is a particularly strong and significant predictor of functional disability in older HIV+.

Cognitive dispersion is conceptualized as increased intra-individual variability across test measures. It has been found to increase with advanced aging, and to be more prevalent among individuals with concomitant cognitive dysfunction.[21] Older HIV+ individuals exhibit greater dispersion in performance on a broad battery of cognitive tasks.[22] This finding is interpreted as reflecting accelerated aging in HIV. Older HIV+ individuals are at particular risk for impairment in executive functioning, psychomotor speed, and episodic memory.[12] Several studies have demonstrated significant interactions between serostatus and age for psychomotor speed[16,23,24] and executive functioning.[25] The Multicenter AIDS Cohort Study (MACS), a repeated measures design with 5-years follow-up, found a significant interaction among serostatus, age, and time of assessment on a measure of executive functioning.[25] As neuropsychological testing was done each 6 months, practice effects were controlled. Among the seronegative individuals, there was not an effect of age on longitudinal performance. By contrast, middle aged and older HIV+ individuals exhibited a significant decline over time.

Cysique et al[26] showed significant independent effects of serostatus and age in the expected direction, but not evidence of a synergistic or interaction effect between these factors. In addition, they found a trend for a quadratic interaction between age and serostatus, where HIV+ individuals tended to show a sudden precipitous drop in cognitive performance in the impaired range with advanced age. This trending effect remained after controlling for plasma viral load. Although most evidence suggests that age may exert a more deleterious effect on the HIV-infected brain, not all investigators find evidence of interactions.[27,28] Limited interactions were reported in a cross-sectional analysis of the Hawaii Aging with HIV Cohort for attention and timed gait.[29]

Neuroimaging

Neuroimaging changes that are particularly prominent in association with aging in HIV include brain atrophy, elevations in abnormal white matter signal on magnetic resonance imaging (MRI), and changes in neurovascular coupling as indicated by both resting and activation-induced changes in blood-oxygen-level dependent (BOLD) signal on functional magnetic resonance imaging (fMRI). We summarize below research findings according to each specific technique.

Structural MRI

HIV-infected individuals show more structural abnormalities on MRI than expected by normal aging. Voxel-based morphometry studies (VBM) have reported independent effects of HIV and aging, but some suggest premature aging in HIV. Becker et al[30] found age and HIV effects on gray (GM) and white matter (WM). Specifically, age-related GM atrophy was found in inferior frontal and superior temporal regions, as well as medial temporal and cingulate areas. HIV-related GM atrophy was more extended, including posterior and inferior temporal lobes, parietal lobes, and cerebellum. WM atrophy was associated primarily with age. Older individuals displayed a loss of periventricular, frontal, and temporal WM. These results were partly replicated in a work of Towgood et al,[31] who also noted volume reduction in the medial and superior frontal regions related to HIV infection. In the same vein, Ances et al[32] reported a significant volume reduction in several subcortical areas (amygdala, caudate, and corpus callosum) related to HIV, as well as a decrease in caudate volume related to aging.

Smaller volumes of the anterior cingulate cortex were related to an estimated older age at HIV infection.[33] Progressive changes in brain volumetrics were indicated indirectly by Stout et al,[34] who found an inverse relationship between severity of infection according to CDC criteria and brain volumes in WM and caudate nucleus, as well as a direct relation with cerebrospinal fluid volume. Chang et al[35] found a significant interaction among HIV-status, apolipoprotein E ε4 allele (APOEε4), and age. Younger HIV+ APOEε4 carriers exhibited brain volume loss to a degree similar to that of older HIV+ in both the putamen and the right cerebral WM. These authors interpreted the volume loss in younger HIV+APOEε4 carriers as premature aging.

Diffusion Tensor Imaging Studies

Abnormal white matter is characterized by reductions in fractional anisotropy (FA) and increases in mean diffusion (MD), both of them reflecting microstructural damage. In HIV+ individuals, diffusion tensor imaging studies (DTI) studies have found widespread abnormalities in several regions, mostly subcortical WM, corpus callosum, and frontal WM.[36]

HIV+ individuals showed greater temporal changes on DTI when compared with HIV-seronegative controls in a repeated measures design with one-year follow-up.[37] At baseline, HIV+ individuals had significantly higher MD in the frontal WM and lower FA in the parietal WM. After 1 year, HIV+ individuals exhibited a MD increase in frontal and parietal WM, putamen, as well as the genu of the corpus callosum. A relationship between age and changes on diffusion was observed in most brain regions. However, it was significant only for the controls. By contrast, Towgood et al[31] failed to obtain a significant serostatus effect on several measures of diffusivity in a cross-sectional study, although a significant aging effect was observed in several brain regions including frontotemporal WM. The lack of significance of serostatus was explained as related to the early and asymptomatic stage at which HIV+ individuals were evaluated and the difficulty of detecting subtle white matter alterations.

Older age has been linked to greater diffusivity in widespread white matter regions in HIV-infected individuals.[38] In addition, decreased FA was observed in global frontal WM, temporal WM regions (fusiform, inferior gyrus, banks of the superior sulcus and insular cortex), and parietal WM (supra-marginal gyrus, superior and inferior cortices). In this study, several clinical variables were related to the pattern of diffusivity, primarily HCV coinfection. Because increased diffusion may reflect elevated inflammation, some of these results point to greater neuroinflammation in the HIV aging brain.

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (MRS) detects cerebral biomarkers that reflect region-specific glial and neuronal changes. The most investigated brain metabolites are *myo*-inositol (MI) and choline compounds (CHO), both of which are elevated in disorders with chronic inflammation and glial activation. In addition, total creatine (CR), which is involved in energy metabolism, N-acetylaspartate (NAA) as a neuronal marker, and glutamate and glutamine (Glu, Glx) are also utilized. In HIV+ individuals, proton MRS has revealed several metabolite abnormalities, such as decreased NAA/CR in individuals with HAD, elevations in MI/Cr, etc.,[39,40] but few studies have addressed aging and HIV.

Chang et al[41] in a multicenter study assessed the metabolite pattern of HIV-associated brain injury related to cognitive impairment (AIDS dementia complex–ADC–vs. neuroasymptomatic) and also the effect of age (cutpoint of 40 years old). They found that HIV and aging have similar effects on certain metabolites. Higher Cho/Cr and MI/Cr in the basal ganglia, and higher Cho/Cr and lower NAA/Cr in the frontal WM were associated with both serostatus and aging. After controlling for the effect of age, a continuum of metabolite changes appeared from cognitively asymptomatic HIV+ individuals to those with ADC.

Progression in cognitive impairment was related to increases in MI/Cr and Cho/Cr in the basal ganglia, and both increase in Cho/Cr, but also with a decrease in NA/Cr in the frontal WM.

Indirect information regarding the effect of age on HIV+ individuals is provided by a more recent study of Harezlak et al,[42] which partly replicated these findings. HIV+ effects were reported as increases in MI/Cr and Cho/Cr in all brain regions evaluated (basal ganglia, frontal WM, and mid-frontal cortex). In addition, a significant age effect was found for Glx/Cr, MI/ Cr, and NAA/Cr. HIV+ and HIV− experienced a similar decline in NAA/Cr in the midfrontal cortex as age increased. Interestingly, a significant interaction between HIV serostatus and age was found with respect to MI/Cr in the frontal WM. In seronegative individuals, the ratio was unchanged, but in neuroasymptomatic HIV+ the ratio increased with age. In HIV+ with at least mild neurocognitive disorder, the MI/Cr decreased with age, suggesting a threshold level of inflammation that is reached in the early stages of HIV infection. Cysique et al[43] found a synergistic effect between age and serostatus. Decreased NAA/unsuppressed water signal in frontal WM was associated with older age, particularly in the HIV+ group. Ernst et al[44] reported a glutamate concentration decline with aging in parietal gray matter, and a trend in frontal gray matter and basal ganglia. In addition, a trend for lower brain glutamate levels was found in the parietal and frontal cortex in HIV+ individuals, more pronounced in individuals with cognitive impairment. Taken together, these results again suggest a premature aging effect on brain processes of HIV+ through an exacerbation of neuroinflammation and augmented neuronal injury.

Functional Neuroimaging Studies

fMRI, a noninvasive method to study brain metabolic demands, is based on BOLD changes in cortical regions that occur during specific tasks.[45] In addition, data can also be acquired on the resting state. In HIV+ individuals, fMRI studies based on attention or working memory tasks have shown a greater load-dependent activation than HIV− individuals.[41]

In a study by Thomas et al,[46] additive effects of HIV and aging were observed on resting-state functional-connectivity MRI measures of default mode and salience networks, which are thought to be most affected by age and neurodegenerative processes. Resting-state functional connectivity was diminished in intra- (default mode, salience, and executive control) and internetwork (default mode-dorsal attention) connections in HIV+ individuals, suggesting a diminished efficiency in the processing and integration of various external and internal stimuli. In addition, effects of aging and HIV appeared to partially overlap. Older age was associated with decreases in intranetwork (default mode and salience) and internetwork (default mode-salience) connectivity. Ances et al[47] also reported independent effects of aging and HIV serostatus on cerebral blood flow, in producing significant reductions at baseline and increased abnormality with functional tasks. An inverse pattern was found when considering functional BOLD signals related to age and HIV. In their study, the fMRI measures of any given HIV+ individual were equivalent to those of a control individual 15–20 years older.

A longitudinal design performed by Ernst et al[48] showed different patterns of brain activation changes in HIV+ individuals when compared with controls, suggesting a more

deleterious effect of aging in HIV+ individuals. At baseline, HIV+ individuals were significantly different in the pattern of activation only on the more difficult task, with a greater activation in the right prefrontal cortex, medial frontal gyrus, and cerebellar tonsil/occipital lobe. One year later, HIV+ individuals did not show the decrease in the pattern of activation observed in controls, likely reflecting impaired learning in HIV+ individuals. Furthermore, HIV+ individuals displayed further increases in activation (in all levels of difficulty), primarily in the right prefrontal, posterior parietal cortices, and the bilateral cerebellum. As performance between measurements was unchanged, it was hypothesized that HIV-infected brains compensate for reduced efficiency at the expense of greater activation. A synergistic effect of HIV and aging was reported by Chang et al[49] with the same visual task. The authors compared three groups of individuals, HIV−, HIV+ without cognitive impairment, and HIV+ with a HAND diagnosis. Again, groups differed in the pattern of brain activation. HIV+ individuals exhibited a complex response with aging. HIV+ individuals without cognitive impairment showed age-dependent increases in activation on the simplest tasks, yet they exhibited load-dependent decreases (right temporal lobe) instead of the normal increased activation with the most difficult tasks. In addition, their performance declined on the most complex task, likely reflecting exhausted reserve capacity. Otherwise, aging HIV+ individuals with HAND showed an age-dependent decline in brain activation patterns, suggesting a diminished reserve capacity for compensation in this group. Thus, functional studies suggest additive or synergistic effects of HIV and aging on brain activation abnormalities.

Metabolic Syndrome

Emerging findings demonstrate that metabolic syndrome (MetS) and vascular risk factors contribute to abnormal neurocognitive function in aging HIV-infected individuals on cART. Individuals with HIV infection have been shown to develop MetS prematurely. For example, Krishnan et al[50] studied over 2,500 HIV+ individuals, all of whom were ART-naïve at baseline. Individuals were randomized to a triple nucleoside reverse transcriptase inhibitor (RTI) regimen, a nonnucleoside (NNRTI)-based regimen, a PI-based regimen, or an NNRTI/PI combination. MetS was defined according to conventional criteria as three or more of the following conditions: increased waist circumference, hypertension, dyslipidemia (high triglycerides, low HDL cholesterol), and fasting hyperglycemia or diabetes mellitus (DM). At ART initiation, 20% of participants met criteria for MetS. During follow-up averaging about 3 years, an additional 478 cases developed incident MetS, comprising 27% of those who were initially MetS-free. Significantly elevated independent hazards for MetS were seen for older age, higher baseline body mass index, lower CD4+ lymphocytes, higher viral loads, and use of PI-based ART.

A unifying hypothesis put forth to explain the clustering of MetS components is abnormal deposition of intra-abdominal or visceral fat. Shown to occur in many HIV-infected individuals, accumulated visceral fat is also predisposed to become inflamed. This occurs when the phenotype of local tissue macrophages, which is normally anti-inflammatory (M2), switches to an inflammatory (M1) phenotype, likely under the influence of HIV-related immune activation and microbial translocation. The resulting inflamed adipose tissue produces cytokines and alters its production of hormones such as leptin and adiponectin,

resulting in the downstream metabolic disturbances of insulin resistance, diabetes mellitus, hypertension, hyperlipidemia, and endothelial dysfunction. These disturbances in turn can directly impact the ability of the neurovascular unit to appropriately and dynamically regulate local blood flow, affecting brain delivery of oxygen and nutrients, as well as removal of wastes and toxins.

Although MetS has been associated with ischemic stroke in HIV,[51] it also is a likely contributor to cognitive decline even in the absence of stroke. The link between cognitive impairment and MetS was originally demonstrated for insulin resistance and diabetes.[52,53] However, several groups subsequently replicated and extended these findings. Though not exhaustive, Table 1 lists many of these studies, which generally support that these risk factors are associated with impaired cognition in HIV-infected individuals, including those with durable virologic suppression on cART. One study specifically focused on the role of visceral adiposity.[54] Neurocognitive impairment in this sample was statistically significantly associated with greater weight circumference, a surrogate for visceral adiposity, but not with elevated body mass index more generally.

Recent neuroimaging studies addressing the effects of MetS on structural volumetry or functional brain integrity in aging HIV+ individuals have yielded mixed results.[30,43] For instance, Nakamoto et al[55] in a small sample of older HIV+ individuals found marginal correlations between the presence of cardiovascular risk factors (abnormal glucose metabolism) and abnormalities in DTI (microstructural alterations in caudate and hippocampus). However, the number of such studies is still limited.

Biomarkers of Neurodegenerative Diseases

To date, there is not enough evidence to establish a link between HIV and some neurodegenerative disorders as Alzheimer's disease (AD). However, several laboratories are investigating whether the expression and progression of neurodegenerative diseases may be facilitated by HIV.[56] Some reports indicate an increase of amyloid burden in long-term HIV infection,[57] which seems to be greater in individuals on cART.[6] Additionally, similarities between changes in CSF markers and other characteristics of AD have been reported.[58,59] However, there are also negative findings.[60–62] Results have been mixed also for the role of APOEε4.[62,63] Some data from the University of California San Francisco (UCSF) HIV Over 60 Cohort study indicated that APOEε4 carriers showed greater deficits in global, psychomotor, and executive tests after controlling for HIV-related variables.[63] Older HIV+ carriers of APOEε4 exhibited more compromise in networks connections than the noncarriers.[64] In contrast, Morgan et al[65] found no association between APOEε4 carrier status and HAND in a large sample. Therefore, the impact of APOEε4 and alterations in the processing of amyloid and synuclein or neurodegeneration in older HIV-infected individuals is still a matter of debate and needs to be clarified by further studies.[65–67]

Summary

An excess of neurocognitive impairment among individuals with HIV infection remains, even with durable virologic suppression on cART. This excess is particularly prominent with advancing age. Neurocognitive domains that are selectively vulnerable in older HIV-

infected persons include speed of information processing and executive function. Neuroimaging changes that are particularly prominent with aging in HIV include brain atrophy, elevations in abnormal white matter signal on MRI, and changes in neurovascular coupling as indicated by both resting and activation-induced changes in BOLD signal on fMRI. Despite effective virologic suppression on antiretroviral therapy, microbial translocation and immune activation persist, and abnormal visceral fat accumulation is frequent. These changes promote metabolic disturbances, such as insulin resistance and hyperlipidemia, which in turn may contribute to neurocognitive decline in aging HIV+ individuals. In addition, immune senescence and inflammation likely influence neurodegeneration in aging HIV-infected individuals. The impact of apolipoprotein ε4 gene status and alterations in the processing of amyloid and synuclein on neurodegeneration in older HIV-infected individuals is a matter of debate. Future research directions should include larger longitudinal studies with truly older individuals.

Acknowledgments

Ronald Ellis is supported by grants from the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), and the National Institute on Drug Abuse (NIDA). Mariana Cherner is supported by grants from NIMH and NIDA.

References

1. Bhaskaran K, Mussini C, Antinori A, et al. CASCADE Collaboration. Changes in the incidence and predictors of human immunodeficiency virusassociated dementia in the era of highly active antiretroviral therapy. Ann Neurol. 2008; 63(2):213–221. [PubMed: 17894380]
2. Brew BJ, Letendre SL. Biomarkers of HIV related central nervous system disease. Int Rev Psychiatry. 2008; 20(1):73–88. [PubMed: 18240064]
3. McArthur JC, Brew BJ. HIV-associated neurocognitive disorders: is there a hidden epidemic? AIDS. 2010; 24(9):1367–1370. [PubMed: 20559041]
4. Soontornniyomkij, V.; Achim, C. Aging. In: Gendelman, HE.; Grant, I.; Everall, PE., et al., editors. The neurology of AIDS. 3rd edition. New York: Oxford Univeristy Press; 2012. p. 567-580.
5. Rodriguez-Penney AT, Iudicello JE, Riggs PK, et al. HIV Neurobehavioral Research Program HNRP Group. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. AIDS Patient Care STDS. 2013; 27(1):5–16. [PubMed: 23305257]
6. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005; 19(4):407–411. [PubMed: 15750394]
7. Khanlou N, Moore DJ, Chana G, et al. HNRC Group. Increased frequency of alpha-synuclein in the substantia nigra in human immunodeficiency virus infection. J Neurovirol. 2009; 15(2):131–138. [PubMed: 19115126]
8. Worm SW, Lundgren JD. The metabolic syndrome in HIV. Best Pract Res Clin Endocrinol Metab. 2011; 25(3):479–486. [PubMed: 21663841]
9. Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology. 2011; 76(16):1403–1409. [PubMed: 21502598]
10. Schweinsburg BC, Taylor MJ, Alhassoon OM, et al. HNRC Group. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol. 2005; 11(4):356–364. [PubMed: 16206458]
11. Liner, J.; Meeker, RB.; Robertson, K. CNS toxicity of antiretroviral drugs; San Francisco, CA. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; 2010 Feb. p. 16-19.

12. Heaton RK, Clifford DB, Franklin DR Jr, et al. CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75(23):2087–2096. [PubMed: 21135382]
13. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–1799. [PubMed: 17914061]
14. Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis. 2013; 56(7):1004–1017. [PubMed: 23175555]
15. Bhatia R, Ryscavage P, Taiwo B. Accelerated aging and human immunodeficiency virus infection: emerging challenges of growing older in the era of successful antiretroviral therapy. J Neurovirol. 2012; 18(4):247–255. [PubMed: 22205585]
16. Hardy DJ, Vance DE. The neuropsychology of HIV/AIDS in older adults. Neuropsychol Rev. 2009; 19(2):263–272. [PubMed: 19247836]
17. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. Neurology. 2004; 63(5):822–827. [PubMed: 15365130]
18. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS. 2004; 18(Suppl 1):S11–S18. [PubMed: 15075493]
19. Cherner M, Ellis RJ, Lazzaretto D, et al. HIV Neurobehavioral Research Center Group. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. AIDS. 2004; 18(Suppl 1):S27–S34. [PubMed: 15075495]
20. Morgan EE, Iudicello JE, Weber E, et al. HIV Neurobehavioral Research Program (HNRP) Group. Synergistic effects of HIV infection and older age on daily functioning. J Acquir Immune Defic Syndr. 2012; 61(3):341–348. [PubMed: 22878422]
21. MacDonald SW, Hultsch DF, Dixon RA. Performance variability is related to change in cognition: evidence from the Victoria Longitudinal Study. Psychol Aging. 2003; 18(3):510–523. [PubMed: 14518812]
22. Morgan EE, Woods SP, Delano-Wood L, Bondi MW, Grant I. HIV Neurobehavioral Research Program (HNRP) Group. Intraindividual variability in HIV infection: evidence for greater neurocognitive dispersion in older HIV seropositive adults. Neuropsychology. 2011; 25(5):645–654. [PubMed: 21574712]
23. van Gorp WG, Miller EN, Marcotte TD, et al. The relationship between age and cognitive impairment in HIV-1 infection: findings from the Multicenter AIDS Cohort Study and a clinical cohort. Neurology. 1994; 44(5):929–935. [PubMed: 8190299]
24. Vance DE, Wadley VG, Crowe MG, Raper JL, Ball KK. Cognitive and everyday functioning in older and younger adults with and without HIV. Clin Gerontol. 2011; 34(5):413–426. [PubMed: 22563140]
25. Sacktor N, Skolasky RL, Cox C, et al. Multicenter AIDS Cohort Study (MACS). Longitudinal psychomotor speed performance in human immunodeficiency virus-seropositive individuals: impact of age and serostatus. J Neurovirol. 2010; 16(5):335–341. [PubMed: 20726699]
26. Cysique LA, Maruff P, Bain MP, Wright E, Brew BJ. HIV and age do not substantially interact in HIV-associated neurocognitive impairment. J Neuropsychiatry Clin Neurosci. 2011; 23(1):83–89. [PubMed: 21304143]
27. Wilkie FL, Goodkin K, Khamis I, et al. Cognitive functioning in younger and older HIV-1-infected adults. J Acquir Immune Defic Syndr. 2003; 33(Suppl 2):S93–S105. [PubMed: 12853858]
28. Onen NF, Overton ET, Seyfried W, et al. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. HIV Clin Trials. 2010; 11(2):100–109. [PubMed: 20542846]
29. Valcour V, Paul R, Neuhaus J, Shikuma C. The effects of age and HIV on neuropsychological performance. J Int Neuropsychol Soc. 2011; 17(1):190–195. [PubMed: 21144102]
30. Becker JT, Maruca V, Kingsley LA, et al. Multicenter AIDS Cohort Study. Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology. 2012; 54(2):113–121. [PubMed: 21424708]

31. Towgood KJ, Pitkanen M, Kulasegaram R, et al. Mapping the brain in younger and older asymptomatic HIV-1 men: frontal volume changes in the absence of other cortical or diffusion tensor abnormalities. Cortex. 2012; 48(2):230–241. [PubMed: 21481856]
32. Ances BM, Ortega M, Vaida F, Heaps J, Paul R. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr. 2012; 59(5):469–477. [PubMed: 22269799]
33. Pfefferbaum A, Rosenbloom MJ, Sassoon SA, et al. Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. Biol Psychiatry. 2012; 72(5):361–370. [PubMed: 22458948]
34. Stout JC, Ellis RJ, Jernigan TL, et al. HIV Neurobehavioral Research Center Group. Progressive cerebral volume loss in human immunodeficiency virus infection: a longitudinal volumetric magnetic resonance imaging study. Arch Neurol. 1998; 55(2):161–168. [PubMed: 9482357]
35. Chang L, Andres M, Sadino J, et al. Impact of apolipoprotein E ε4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage. 2011; 58(4):1017–1027. [PubMed: 21803164]
36. Chen Y, An H, Zhu H, et al. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. Neuroimage. 2009; 47(4):1154–1162. [PubMed: 19376246]
37. Chang L, Wong V, Nakama H, et al. Greater than age-related changes in brain diffusion of HIV patients after 1 year. J Neuro-immune Pharmacol. 2008; 3(4):265–274.
38. Gongvatana A, Cohen RA, Correia S, et al. Clinical contributors to cerebral white matter integrity in HIV-infected individuals. J Neurovirol. 2011; 17(5):477–486. [PubMed: 21965122]
39. Chang L, Ernst T, Leonido-Yee M, et al. Highly active antiretroviral therapy reverses brain metabolite abnormalities in mild HIV dementia. Neurology. 1999; 53(4):782–789. [PubMed: 10489041]
40. Holt JL, Kraft-Terry SD, Chang L. Neuroimaging studies of the aging HIV-1-infected brain. J Neurovirol. 2012; 18(4):291–302. [PubMed: 22653528]
41. Chang L, Lee PL, Yiannoutsos CT, et al. HIV MRS Consortium. A multicenter in vivo proton-MRS study of HIV-associated dementia and its relationship to age. Neuroimage. 2004; 23(4): 1336–1347. [PubMed: 15589098]
42. Harezlak J, Buchthal S, Taylor M, et al. HIV Neuroimaging Consortium. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. AIDS. 2011; 25(5):625–633. [PubMed: 21297425]
43. Cysique LA, Moffat K, Moore DM, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. PLoS ONE. 2013; 8(4):e61738. [PubMed: 23620788]
44. Ernst T, Jiang CS, Nakama H, Buchthal S, Chang L. Lower brain glutamate is associated with cognitive deficits in HIV patients: a new mechanism for HIV-associated neurocognitive disorder. J Magn Reson Imaging. 2010; 32(5):1045–1053. [PubMed: 21031507]
45. Orringer DA, Vago DR, Golby AJ. Clinical applications and future directions of functional MRI. Semin Neurol. 2012; 32(4):466–475. [PubMed: 23361489]
46. Thomas JB, Brier MR, Snyder AZ, Vaida FF, Ances BM. Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. Neurology. 2013; 80(13):1186–1193. [PubMed: 23446675]
47. Ances BM, Vaida F, Yeh MJ, et al. HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. J Infect Dis. 2010; 201(3):336–340. [PubMed: 20047503]
48. Ernst T, Yakupov R, Nakama H, et al. Declined neural efficiency in cognitively stable human immunodeficiency virus patients. Ann Neurol. 2009; 65(3):316–325. [PubMed: 19334060]
49. Chang L, Holt JL, Yakupov R, Jiang CS, Ernst T. Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. Neurobiol Aging. 2013; 34(4):1240–1253. [PubMed: 23158761]

50. Krishnan S, Schouten JT, Atkinson B, et al. Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-naive HIV-infected individuals. J Acquir Immune Defic Syndr. 2012; 61(3):381–389. [PubMed: 22828718]
51. Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. Stroke. 2008; 39(1):30–35. [PubMed: 18063821]
52. Valcour VG, Sacktor NC, Paul RH, et al. Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging with HIV cohort. J Acquir Immune Defic Syndr. 2006; 43(4):405–410. [PubMed: 17099311]
53. Valcour VG, Shikuma CM, Shiramizu BT, et al. Diabetes, insulin resistance, and dementia among HIV-1-infected patients. J Acquir Immune Defic Syndr. 2005; 38(1):31–36. [PubMed: 15608521]
54. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. CHARTER Group. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology. 2012; 78(7):485–492. [PubMed: 22330412]
55. Nakamoto BK, Jahanshad N, McMurtray A, et al. Cerebrovascular risk factors and brain microstructural abnormalities on diffusion tensor images in HIV-infected individuals. J Neurovirol. 2012; 18(4):303–312. [PubMed: 22585287]
56. Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G. Neurodegeneration and ageing in the HAART era. J Neuroimmune Pharmacol. 2009; 4(2):163–174. [PubMed: 19067177]
57. Rempel HC, Pulliam L. HIV-1 Tat inhibits neprilysin and elevates amyloid beta. AIDS. 2005; 19(2):127–135. [PubMed: 15668537]
58. Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L. CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. Neurology. 2005; 65(9):1490–1492. [PubMed: 16275845]
59. Clifford DB, Fagan AM, Holtzman DM, et al. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. Neurology. 2009; 73(23):1982–1987. [PubMed: 19907013]
60. Gisslén M, Krut J, Andreasson U, et al. Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. BMC Neurol. 2009; 9:63. [PubMed: 20028512]
61. Ances BM, Christensen JJ, Teshome M, et al. Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. Neurology. 2010; 75(2):111–115. [PubMed: 20534887]
62. Ances BM, Benzinger TL, Christensen JJ, et al. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. Arch Neurol. 2012; 69(1):72–77. [PubMed: 22232345]
63. Valcour VG. HIV, aging, and cognition: emerging issues. Top Antivir Med. 2013; 21(3):119–123. [PubMed: 23981600]
64. Jahanshad N, Valcour VG, Nir TM, et al. Disrupted brain networks in the aging HIV+ population. Brain Connect. 2012; 2(6):335–344. [PubMed: 23240599]
65. Morgan EE, Woods SP, Letendre SL, et al. CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Group. Apolipoprotein E4 genotype does not increase risk of HIV-associated neurocognitive disorders. J Neurovirol. 2013; 19(2):150–156. [PubMed: 23408335]
66. Kuhlmann I, Minihane AM, Huebbe P, Nebel A, Rimbach G. Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: a literature review. Lipids Health Dis. 2010; 9:8. [PubMed: 20109174]
67. Wendelken LA, Valcour V. Impact of HIV and aging on neuropsychological function. J Neurovirol. 2012; 18(4):256–263. [PubMed: 22528478]
68. Becker JT, Kingsley L, Mullen J, et al. Multicenter AIDS Cohort Study. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. Neurology. 2009; 73(16):1292–1299. [PubMed: 19841381]
69. Wright EJ, Grund B, Robertson K, et al. INSIGHT SMART Study Group. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology. 2010; 75(10):864–873. [PubMed: 20702792]
70. Foley J, Ettenhofer M, Wright MJ, et al. Neurocognitive functioning in HIV-1 infection: effects of cerebrovascular risk factors and age. Clin Neuropsychol. 2010; 24(2):265–285. [PubMed: 20162495]

71. Fabbiani M, Ciccarelli N, Tana M, et al. Cardiovascular risk factors and carotid intimamedia thickness are associated with lower cognitive performance in HIV-infected patients. HIV Med. 2013; 14(3):136–144. [PubMed: 22994586]

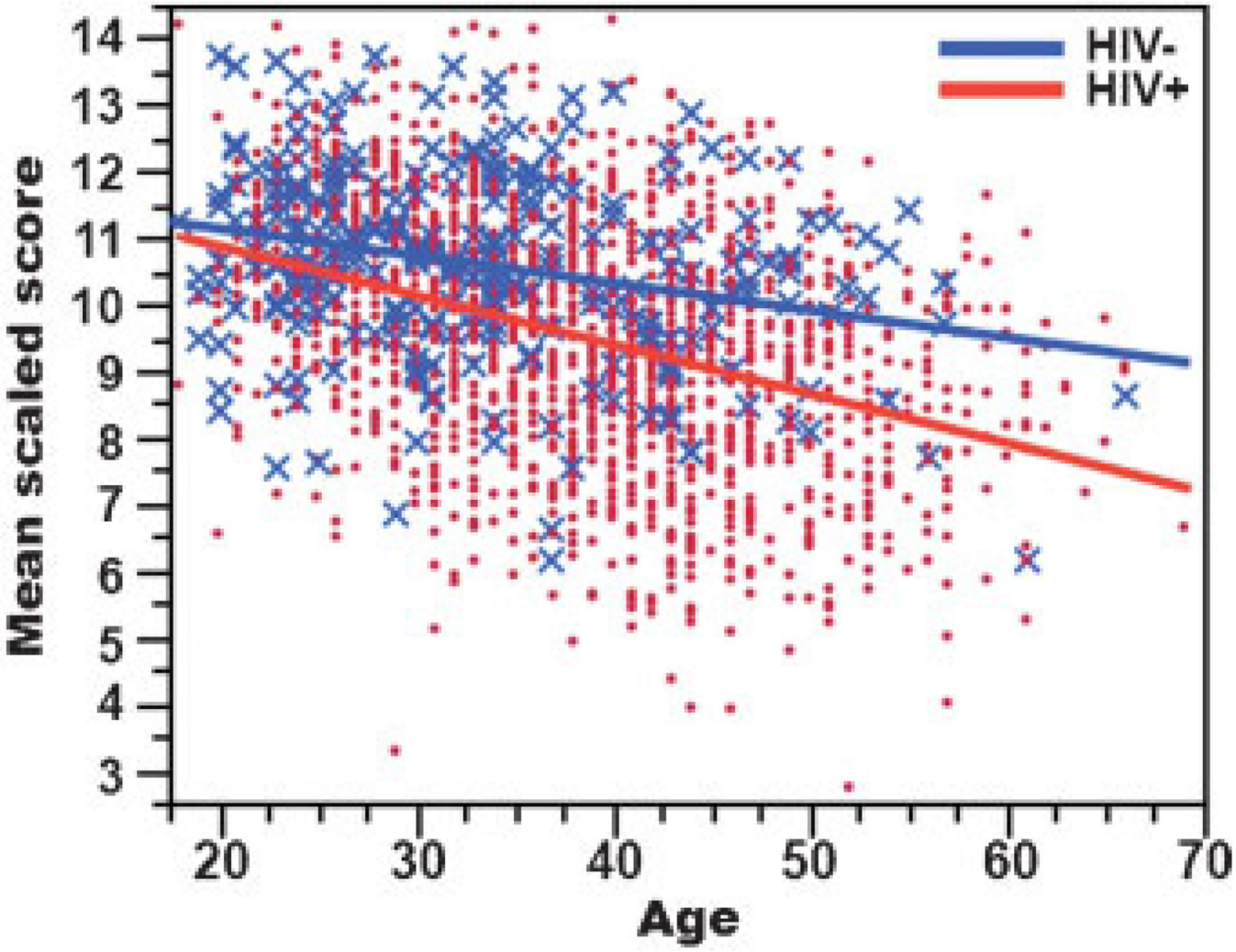

Fig. 1.

Interaction between age and human immunodeficiency virus (HIV) serostatus on mean-scaled scores across a battery of neuropsychological tests. The gap between HIV+ and HIV− individuals increases with age.

Table 1

Cross-sectional findings on vascular/metabolic risk and neurocognitive impairment in HIV

Study	Sample	Demo-graphics	Predictors	Outcomes	Key findings
Valcour et al, 2005, 2006[52,53]	203 HIV+	82% men 20–76 yr	DM self-report or glucose >125	Learning, memory, SIP, executive, motor speed, attention	DM assoc with HAD (adjusted for other vascular risk factors)
Becker et al, 2009[68]	428 HIV+ 207 HIV−	100% men 40–65 yr	Coronary artery calcium, cIMT, lipids, DM, GFR	Learning, memory, executive, psychomotor speed	Worse cIMT & GFR assoc → ↓ PM speed
Wright et al, 2010[69]	292 HIV+	58% men 30–50 years	Prior CVD, HTN, ↑ cholesterol	psychomotor speed, executive, SIP	CVD, HTN, cholesterol → ↓ cognition
Foley et al, 2010[70]	98 HIV+	81% men 30–65 years 70% AA	Self-report DM, HTN, Ml, CHF	Learning, memory, executive, motor, attention, working memory	CV risk→ ↓ processing speed
Fabbiani et al, 2012[71]	245 HIV+	76% men 30–60 years 94% cART	cIMT, vascular comorbidities (obesity, lipids)	Learning, memory, executive, psychomotor speed	DM + cIMT → ↓ cognition
McCutchan et al, 2012[54]	130 HIV+	85% men	BMI.WC, DM, HTN, lipids	Learning, memory, executive, motor, attention, SIP	↑ WC → ↓ cognition

Abbreviations: AA, African American; cART, combination antiretroviral therapy; CHF, congestive heart failure; cIMT, carotid intima-media thickness; CV, cardiovascular; DM, diabetes mellitus; GRF, glomerular filtration rate; HIV, human immunodeficiency virus; HTN, hypertension; SIP, speeded information processing; WC, waist circumference.