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Differentiating HIV-Associated Neurocognitive Disorders from Alzheimer's Disease: an Emerging Issue in Geriatric Neuro HIV

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Abstract

Purpose of Review—To examine characteristics that may distinguish HIV-associated Neurocognitive Disorder (HAND) from early Alzheimer's disease (AD)

Recent Findings—CSF AD biomarkers are perturbed in HIV, yet these alterations may be limited to settings of advanced dementia or unsuppressed plasma HIV RNA. Neuropsychological testing will require extensive batteries to maximize utility. Structural imaging is limited for early AD detection in the setting of HIV, but proper studies are absent. While positron emission tomography (PET) amyloid imaging has altered the landscape of differential diagnosis for age-associated neurodegenerative disorders, costs are prohibitive.

Summary—Risk for delayed AD diagnosis in the aging HIV-infected population is now among the most pressing issues in geriatric neuro HIV. While clinical, imaging, and biomarker characterization of AD is extensively defined, fewer data define characteristics of HAND in the setting of suppressed plasma HIV RNA. Data needed to inform the phenotype of AD in the setting of HIV are equally few.

Keywords

HIV; HAND; Alzheimer's disease; cognitive impairment; biomarkers; neurodegeneration

Introduction

In 2012, over one quarter of people living with HIV in the United States were above the age of 55.[1] By 2017, these older HIV-infected patients will turn 60, entering an age where Alzheimer's Disease (AD) becomes a critical diagnostic differential underlying their cognitive impairment. Given known parkinsonian features for HIV, neurodegenerative disorders in the Parkinson's disease spectrum (e.g. Parkinson's' Disease Dementia (PDD), Progressive Supranuclear Palsy (PSP), Lewy Body dementia (LBD)) are also pertinent to consider in proper cognitive care of aging HIV patients.[2, 3]Excluding HIV-associated Neurocognitive Disorder (HAND) from the differential diagnosis for most (presumably HIV-uninfected) patients attending memory clinics can be achieved easily with a serologic test for HIV.[4] Here, the diagnosis of AD is largely dependent on clinical history, exclusion

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of other causes and supplemented by biomarkers. This clinical algorithm for AD, employing neurological, cognitive and behavioral information, remains largely untested in patients living with HIV, up to 50% of whom suffer from cognitive syndromes in the setting of HIV. As the HIV-infected population is reaching geriatric ages, differentiating HAND from early stage AD thus avoiding delayed AD diagnosis is becoming one of the most pressing geriatric neuro HIV issues.[4-7]

This challenge is exacerbated by more recent evidence that HAND, remains frequent despite plasma HIV RNA suppression in an era of more tolerable combination antiretroviral therapies (cART).[4, 8-11]Symptoms are typically mild and fluctuant rather than relentlessly progressive as seen in AD.[12] Indeed, HIV-associated dementia (HAD) among treated patients is rare, a clear signal that progression may be valuable in distinguishing HAND from AD. However, it may take years to differentiate the relentless progression that is core to AD from the inherent fluctuation of HAND, thus, risking a delayed AD diagnosis in the setting of HIV. In the current era, nearly 70% of HAND is unrecognized by the participant, thus termed Asymptomatic Neurocognitive Impairment.[8, 13, 14] Similarly, insight is frequently impaired in AD, making the reliance on self-reported symptom patterns risky for the diagnosis of either entity and challenging for use in differential diagnosis.[15] This is further confounded by less frequent access to reliable proxy informants in HIV.[16]HAND nosology, developed a decade ago, primarily focuses on neuropsychological test performance, but extensive studies document a HAND phenotype that includes cognitive, motor and behavioral features, again providing options to extend the specificity of HAND nosology as it might relate to age-associated neurodegenerative disorders like AD.[4] Aligning currently HAND criteria to be more consistent with the comprehensive guidelines of these age-associated neurodegenerative disorders could add value for the emerging older HIV-infected population.

The extant literature is limited by most HAND data captured among middle-aged or younger participant groups, thus less pertinent to age groups, particularly over 70, where background AD risk is apparent. These studies often include participants who have mixed degrees of viral suppression, less pertinent to the current era where most adherent patients can achieve plasma viral suppression. A further confound is that these studies were completed during variable cART eras, sometimes including individual exposure to antiretroviral medications thought to have higher degrees of neurotoxicity.[17] Contributions to impairment in the setting of HIV are broad and complex, including comorbidities and possible contributions from both past but not progressive brain injury (e.g. smaller brain size compared to controls, static cognitive deficits) and superimposed ongoing injury (e.g. progressive atrophy and cognitive fluctuation despite viral suppression).[18]

The current work aims to examine existing publications to suggest areas where additional guidance to the HAND nosology may be valuable in differential diagnosis in order to decrease risk for delayed AD diagnosis, and improve the health of this expanding population of patients.

Neuropathology of HIV in the current era and overlap with AD pathology

The neuropathology of HIV has changed substantially with suppressive cART and the neuropathological signature of HAND in the setting of viral suppression has not been fully elucidated.[19] Indeed, the classically described pathology of perivascular macrophages and microglial nodules is not commonly seen in a cART era autopsy series and, when present, the more phenotypically 'HIV-like' pathology is linked to detectability of plasma HIV RNA.[20] A more recent series observed nonspecific histological findings in older HIV-infected patients (n=28; median age at death: 56 years) on cART with low or undetectable plasma HIV RNA, that included infarcts and areas of ischemia, hemorrhage and large vessel atherosclerosis as the most common brain pathologies.[21] Some have called for a complete re-examination of pathological mechanisms in the era of viral suppression.[19]

Diffuse rather than the AD-specific neuritic amyloid plaques, were noted in brains of HIV-infected patients during the era preceding cART.[22] These plaques were noted in the temporal lobes including hippocampus and frontal lobes and their frequency was associated with age and HIV status.[22] The implication of diffuse plaques to AD risk is less clear, sometimes found in the brain of cognitively healthy elders.[23] Several studies noted an increase amyloid staining with longer durations of cART, particularly with protease inhibitor use.[24-26] A longer HIV duration similarly predicted increased staining, but CD4 cell count did not. [24] Most amyloid was found to be intracellular and when extracellular plaques were identified, they were most often noted in perivascular regions.[25, 26] Age and HIV were similarly associated with higher intraneuronal amyloid staining by Xu et al.[6]

By contrast, others found no evidence for premature amyloid deposit in cognitively unimpaired HIV-infected participants, but noted an increase in hyperphoshorylated tau (p-tau) in the hippocampus and increased ubiquitin staining in concert with decreased synaptic protein staining, suggesting an increased synaptic and dendritic damage in the cART era.[27, 28] However, the work by Gelman et al. included only 10/25 cases over 60 years and viral load suppression was not uniform, thus making the clinical implications of these findings less clear.[28] Several studies indicate increased amyloid deposition in older HIV-infected individuals with one study showing elevated levels of both amyloid and α-synuclein among older HIV-infected subjects (age range: 50-76) with mean log CSF HIV RNA of 2.64 compared to age-matched controls.[6, 25, 26, 28-30] In one study, cART treated cases had diffuse plaques while cART-naïve HAD cases demonstrated only intraneural amyloid staining.[6] While the implications of these pathology studies are less clear as it relates to AD risk, nearly all show perturbation of amyloid pathways.

Chronic inflammation is likely contributing to these changes, but, *in vitro* studies also confirm that HIV neurotoxic proteins can disrupt different steps of the amyloid pathways.[31]The disruption of the blood-brain barrier (BBB), hypothesized to occur early in the HIV infection, is also known to play a role in brain amyloid homeostasis.[32] HIV protein gp120 promotes amyloid aggregation by triggering a pathological cascade resulting in axonal injury or inducing microglial activation, altering transcription and cleavage of amyloid precursor protein (APP).[31, 33, 34] Alterations of APP cleavage products have also been described in HAD patients.[35, 36] The protein *tat* has been shown to promote amyloid

accumulation by inhibiting neprilysin, a proteolytic enzyme that prevents amyloid accumulation, or altering endolysosome structure and function.[31, 34, 37, 38]

Apolipoprotein E (ApoE) impacts amyloid metabolism and the ApoE ε4 isoform is a known genetic risk factor for AD.[39] Controversy remains as to whether ApoE ε4 is associated with susceptibility to cognitive impairment with more consistency among studies examining older HIV-infected participants.[40, 41] In HIV-infected participants over age 60, negative associations between ApoE ε4 carrier status and clinical measures of cognitive functioning, brain atrophy and white matter (WM) integrity were noted.[42] In another study ApoE ε4 was found to moderate the expression of amyloid in HAND subjects, although the authors failed to find a direct association between ApoE ε4 carrier status and HAND.[43] Similarly, autopsy findings showed that the presence of diffuse amyloid plaques was associated with HAND among ApoE ε4 carriers, but not in non-ε4 carriers, suggesting that ApoE isoforms differently moderate the association between amyloid aggregation and HAND.[44]

A recent *in vivo* PET imaging study using a novel microglial activation marker provides insight into the pathology of HAND in the era of suppressed plasma HIV RNA. Microglia-driven inflammation was investigated via the expression of translocator protein (TSPO) in 12 cognitively asymptomatic and healthy HIV-infected participants on effective cART with suppressed plasma and CSF HIV RNA.[45] Increased binding of the TSPO radiotracer was noted in HIV compared to controls particularly in parietal and occipital regions and in basal ganglia. Increased TSPO binding in the hippocampus, amygdala and thalamus was associated with worse neuropsychological performance on tests of verbal and visual memory.[45] In AD, TSPO levels increase over the course of disease, possibly serving as a marker of disease progression, demonstrating potential parallels across diseases.[46]

Taken together these studies document the need for better characterization of HAND pathogenesis among suppressed patients. Commonalities in some neuropathogenic mechanisms could increase brain vulnerability of elders living with HIV, that, along with reduced brain reserve (e.g. atrophy), could predispose to more frequent or more rapid course of AD.

Insight from the Clinical Presentation

Research diagnosis of HAND relies on poor performance documented on neuropsychological tests from any of five to seven cognitive domains.[4] The absence of neuropsychological testing pattern specificity inherent in this nosology limits its utility in differential diagnosis from age-associated neurodegenerative disorders, an issue that was not as paramount 10 years ago, when the criteria were established. Instead, a supplemental table provides guidance for excluding the most common confounding or contributing conditions in younger age, such as depression, traumatic brain injury, substance use disorder, opportunistic brain infections and Hepatitis C.[4] This lack of specificity contrasts with diagnostic guidelines for common age-associated neurodegenerative conditions, where emphasis is placed on strengths and weaknesses in cognitive testing performance, the presence or absence of behavioral, affective, or motor findings, and select atrophy on brain

imaging. A guidance defining likely patterns in these cognitive, behavioral and motor spheres could aid in differential diagnosis of older patients living with HIV.

Similarly, a recent study noted that HIV-infected elders have higher rate of meeting criteria for Mild Cognitive Impairment (MCI), an intermediate state between typical cognitive aging and dementia.[47, 48] Here, HIV-infected participants (mean age: 57, all on effective cART with undetectable plasma HIV RNA) were seven-times more likely than age-matched controls to meet research criteria for MCI.[48] Two case reports of AD in patients with HIV have been documented, each highlighting the risk for delayed diagnosis and distinguishing factors on neuropsychological testing patterns as well as progression triggering concern for concurrent AD.[5, 49]

In one case, a 63-year-old HIV-infected woman eventually was noted to have a clinical history, neuropsychological profile and CSF biomarkers consistent with AD. She had been diagnosed with HIV seven years earlier, started cART, and maintained plasma HIV RNA <50 copies/ml for approximately five years, with only few minor blips. Her CD4 count had ranged between 800 and 1000 cells/ml with a nadir of 200 cells/ml. She developed cognitive symptoms and, a few years later, neuropsychological assessment revealed abnormal performance in spatial short time memory and spatial episodic memory. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) identified decreased glucose uptake bilaterally in the parietal lobes, in the left anterior singulum and in the right posterior thalamus. In subsequent years, the patient and her family reported worsening memory, irritability and depression. A CSF biomarker pattern was suggestive of AD pathology after a prior CSF examination identified possible CSF escape that was treated without improvement of cognitive symptomatology.[49]

A second case reported a 71-year old man with 14 years of stable HIV infection and consistent cART compliance. His CD4 cell count was between 300-350 copies/ml and plasma HIV RNA was <20 copies/ml. He and his wife reported mild short-term memory starting five years earlier but more pronounced over the prior three years and including difficulties with multitasking and calculations. He required only minimal functional assistance. Family history included AD and parkinsonism dementia. His first neuropsychological assessment revealed impaired performance in processing speed, executive function, language and fine motor abilities. Approximately two years later he underwent a second evaluation demonstrating cognitive decline of working memory and verbal fluency. Brain MRI revealed atrophy and WM abnormalities thought to be consistent with age and FDG-PET showed a mixed pattern of altered metabolism. While CSF biomarkers were equivocal (low Ab_{42}/tau index, consistent with AD and a low phospho-tau, indeterminate for AD), an amyloid PET/CT with florbetaben confirmed a pattern of amyloid deposition consistent with AD, leading the authors to conclude a mixed AD/HAND diagnosis.[5]

In HIV-infected individuals on cART with suppressed HIV RNA, HAND is usually not a progressive condition although longitudinal cognitive changes can be heterogeneous across different neuropsychological measures.[50, 51]Thus, the likelihood of AD may be suggested by progressive cognitive decline, particularly rapid forgetting and confrontational naming

impairment that are less typical of HAND; although, our personal unpublished experience offers that alterations in these cognitive domains can be seen in amyloid PET negative elder HIV+ patients. On neuropsychological testing, HAND has been described to include psychomotor slowing, deficits in concentration and attention, impaired executive functions, poor learning efficiency with retained recognition memory, with sparing of semantic and visuo-spatial abilities.[13, 52] Anterograde amnesia is a clinical hallmark of typical AD where episodic memory deficits are thought to be due to impaired consolidation rather than ineffective retrieval of new information. This is evident in that AD patients fail on both recognition and free recall tasks in contrast to HAND, where recognition is often less impaired, an additional possible distinguishing characteristic from testing patterns.[53]

Although some evidence suggested that the neuropsychological testing phenotype of HAND may have shifted from a subcortical dysfunction towards a more cortical pattern in the cART era, other studies suggest that the combined deleterious effects of HIV and aging on the central nervous system (CNS) do not necessarily manifest as a “cortical” pattern of cognitive impairment.[54-56] Recently, our group has shown that a combination of six cognitive measures can discriminate with 86% accuracy the cognitive phenotypes of mild HAND from that of MCI due to AD.[57] Consistently with published work, our findings largely supported a “subcortical” pattern in HAND characterized by worse performance on tasks of information processing speed and executive functioning. Although longitudinal studies are needed to examine trajectories, these findings, if validated, could be useful in clinical settings to identify those HIV-infected individuals who require closer evaluation and monitoring.

Motor components of HIV-related brain injury are well documented particularly in later stages of dementia, but have also been noted in milder disease.[13, 14, 58] These findings may include changes in gait, poor coordination, and tremor. Patients can develop parkinsonian features, including symmetric bradykinesia and rigidity, but often lack resting tremor and the early presentation of postural instability and gait difficulty.[3] The magnitude of the association of extrapyramidal motor signs depends, in part, on age and cognitive status.[2]In contrast, the neurological exam often lacks these motor findings in early stages of AD. Extrapyramidal signs are seen in only 30% of the cases and resting tremor is uncommon.[59, 60] Gait changes are associated with higher risk for falls and are more frequent in the advanced stages of AD.[59]

Symptoms reporting has substantial limitations in the setting of HIV, notable by the asymptomatic nature of nearly 70% of participants who have objective neuropsychological testing impairment and by a smaller study identifying poor insight into objective measures of functional capabilities.[8, 16] Thus, symptom reporting may be less accurate and less valuable for differential diagnosis. Through proxy reporting, HIV-infected elders over age 60 more frequently experienced agitation, depression, anxiety, apathy, irritability and sleep difficulties compared to health controls, regardless of cognitive status.[61] Similarly, neuropsychiatric symptoms such as apathy, agitation and anxiety affect more that 80% of AD patients during the course of the disease and may be present at the earliest AD stages, while their severity worsens throughout the disease progression.[62-65] Data from HIV-

infected patients with reliable and proximal informants would add greatly to understanding how the symptom and neuropsychiatric presentations of mild disease differs from early AD.

Cerebrospinal Fluid (CSF) biomarkers

In recent years, amyloid and tau based CSF and imaging biomarkers have improved diagnostic accuracy of AD. A typical CSF profile in AD is characterized by decreased levels of amyloid beta and increases of both total tau (t-tau) and p-tau in the absence of substantial inflammation.[66] These findings mirror the abnormal accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles throughout cortical and limbic areas of the brain that are key features of AD neuropathology.

A challenge for early identification of AD in patients living with HIV is the known perturbations of these biomarkers in neuroinflammatory conditions.[5] Inconsistent reports exists regarding CSF amyloid and tau in the setting of HIV, possibly due to discrepancies in participant ages, levels of immunosuppression and viral suppression, cognitive and HIV disease severity as well as inter-laboratory test variations. Current reports note low or normal levels of amyloid, while t-tau and p-tau have been shown to be alternately elevated or reduced. [29, 34, 35, 67-69] One study documented lower CSF amyloid levels in cognitively impaired HIV-infected participants and individuals with mild AD, but not in cognitively normal HIV-infected subjects.[29] They also found that the characteristically elevated CSF tau seen in AD was absent in HAND, leading some to conclude that the common decrease in CSF amyloid compared to unimpaired HIV-infected individuals and AD patients in concert with increased tau levels in AD but not in HAND provides hope for diagnostic clarity between AD and HAND.[29, 35]

In contrast, however, other studies have shown increased CSF t-tau and p-tau concentrations in more advanced stages of HAND.[35, 67] Specifically, one study observed lower levels of CSF amyloid along with increased t-tau in more advanced stages of HIV dementia and p-tau in all dementia cases compared to AD patients and HIV-uninfected controls.[67] These authors also noted that the effect on both CSF amyloid and p-tau were much stronger in the group of individuals over 40 years of age and that amyloid, t-tau, and p-tau did not correlate to conventional markers of disease severity, including CSF HIV RNA, CSF β-2-microglobulin, or neopterin.[67] Given these mixed reports, firm conclusions remain controversial.

Neurofilament protein (NFL) is a major component of myelinated axons and serves as a biomarker of neuronal damage.[34] Some reports indicated NFL as the most sensitive biomarker in detecting neuronal injury compared to biomarkers such as soluble APPs or t-tau, suggesting the presence of CNS axonal damage in HAD individuals, but also in those patients with decreased CD4 cell count.[35, 70] Treatment-induced viral suppression was instead associated with normal or slightly elevated CSF NFL levels.[35] Plasma NFL levels were found to be highly correlated with CSF NFL measurement, thus supporting a more accessible measure of CNS injury.[71] In AD, one study showed that CSF NFL concentration was also elevated compared to controls and MCI and that its concentration was associated with accelerated cognitive decline in MCI.[72] in a case report of AD in HIV,

CSF NFL measurements were slightly higher than in HIV-uninfected subjects with AD, but significantly lower compared to HAD patients.[49] Examination of these inflammatory and AD biomarkers in age-relevant suppressed patients with and without HAND would add greatly to the field.

Neuroimaging

HIV has been characterized by prominent neuroimaging abnormalities in the basal ganglia, thalamus, cerebellum and cortical motor strip.[73-75] These regions undergo notable atrophy, reduced thickness of cortical tissue and shape abnormalities particularly in advances disease (e.g. dementia, AIDS), among incompletely suppressed or untreated cases or in groups with substantial comorbidity (e.g. alcoholism, small-vessel disease or Hepatitis C co-infection) or in older individuals.[76-81] Collectively, the neuroimaging pattern is consistent with that often referred to as a “subcortical” clinical phenotype.[80] Some argue that the presentation of HIV is beginning to involve both subcortical along with cortical structures.[82]

In typical AD, early cortical atrophy affects the medial temporal lobe (i.e. entorhinal cortex and hippocampus) and extends to the rest of the cortex along a temporal-parietal-frontal trajectory, whereas motor regions can be spared until late in the disease.[83] Machine learning techniques are able to distinguish morphometric patterns of HAND (n=15; 94% on cART and 80% with undetectable HIV RNA) from presumed HIV-uninfected participants with a similar degree of cognitive impairment (e.g MCI, n=80) between the ages of 60 and 70 with 90% accuracy.[84] These factors contributing most were from eight brain regions (cerebellum VIIb, cerebellum VIII, precentral gyrus, precuneus, medial orbitofrontal cortex, inferior temporal gyrus, parahippocampal gyrus and superior temporal pole), each described to have volume deficits in HIV or be significant for characterizing the early onset of MCI or predict MCI patients converting to AD.[84] If validated, these findings could support added guidance to the HAND criteria and provide evidence that imaging data are likely to be effective in differentiating HAND from AD in people over age of 60.

Reduced white matter integrity as measured by diffusion tensor imaging (DTI) is seen in older HIV-infected individuals with suppressed plasma HIV RNA.[41, 85-88] One study found widespread white matter abnormalities that correlated with cognitive impairment.[88] In contrast, cardiovascular risk factors and duration of past immune deficiency but not cognitive impairment were found to be associated with white matter injury among men with well controlled HIV infection.[87] Another study investigated white matter abnormalities in 56 HIV-infected elders compared to 31 matched controls reporting widespread fractional anisotropy (FA) decreases and increased mean diffusivity (MD) in areas including the corpus callosum, splenium, body of the genu, tapetum of the corpus callosum, as well as the anterior, superior and posterior corona radiata.[41] Compared to non-demented HIV, HAD patients showed elevated mean and radial diffusivity in parietal WM.[89] To our knowledge no study has directly compared DTI abnormalities among elders with HIV versus MCI or AD patients. In the context of AD, most DTI changes seem to occur in more posterior regions compared to the frontal dominance often described in HIV.[90]

Using a variety of amyloid-specific ligands, positron-emission tomography (PET) has transformed the landscape of AD diagnostics for challenging cases where a negative scan is thought to have high specificity for lack of AD pathology. The PET tracer ^{11}C-labeled Pittsburgh Compound-B (PIB) specifically binds fibrillar amyloid plaques and can be detected in AD.[91] When compared to symptomatic AD patients, HAND individuals did not show increased fibrillar amyloid concentrations as detected by PIB-PET imaging.[92] However, this study included only five participants with HAND and a mean age of 46 years. Adding to potential diagnostic utility, the current amyloid radioligands lack affinity for more diffuse amyloid plaques characteristic of HIV or for primarily intracellular amyloid concentrations.[31, 92, 93]

In the case report by Turner et al., FDG-PET showed both hypermetabolism in bilateral basal ganglia consistent with HIV and hypometabolism of parietal cortex consistent with AD pathology.[5, 94-96] The amyloid PET/CT with florbetaben confirmed amyloid deposition in the frontal, temporal and parietal lobes bilaterally including the posterior cingulate and precuneus, a pattern consistent with AD.[5] Recently, a case study showed frontal, parietal and temporal hypometabolism on FDG-PET in a 70-year old HIV-infected individual with CD4 cell count of 124 presenting with memory deficits for the 4 months, apraxia and incontinence.[97] The patient also underwent a PET scan with a tau ligand (F-18 THK5117) showing increased tau binding in the periventricular and WM regions.[97] Advances in selective tau tracers for PET imaging have now made possible in vivo exploration of tau pathology in neurodegenerative diseases but not in HIV where this research field is still in its early stages.[98] Both amyloid and tau PET imaging are prohibitively expensive for clinical use despite their potential value in terms of diagnostics.

Concluding remarks

The emerging clinical challenges of an aging HIV-infected population have been recognized for more than a decade, following transformative suppressive therapies. But, the overlap with age-related neurodegenerative disorders is a relatively new clinical issue. Given that AD risk rises exponentially from <1% at age 60 with a doubling of frequency every five years, only recently have sufficient numbers of HIV-infected patients entered these at-risk age ranges. Informing key discriminating factors is curtailed by most published data on HIV pathogenesis stemming from studies that include unsuppressed and, typically, far younger participants. Studies that include age-relevant suppressed participants and methodologies that allow cross-disease comparisons would add greatly to the field.

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References

1. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data - United Sattes and 6 dependent areas - 2013. HIV Surveillance Supplemental Report. 2015
2. Valcour V, et al. Aging exacerbates extrapyramidal motor signs in the era of highly active antiretroviral therapy. J Neurovirol. 2008; 14(5):362–7. [PubMed: 18989814]

3. DeVaughn S, et al. Aging with HIV-1 Infection: Motor Functions, Cognition, and Attention--A Comparison with Parkinson's Disease. Neuropsychol Rev. 2015; 25(4):424–38. [PubMed: 26577508]
4. Antinori A, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–99. [PubMed: 17914061]
5. Turner R, et al. An individual with human immunodeficiency virus, dementia, and central nervous system amyloid deposition. Alzheimer Dis Assoc Disord. 2016; 4:1–5.
6. Xu J, Ikezu T. The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. J Neuroimmune Pharmacol. 2009; 4(2):200–12. [PubMed: 19016329]
7. Becker JT, et al. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS. 2004; 18 Suppl 1:S11–8. [PubMed: 15075493]
8. Heaton RK, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75(23):2087–2096. [PubMed: 21135382]
9. Simioni S, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS. 2010; 24(9):1243–50. [PubMed: 19996937]
10. Nightingale S, et al. Controversies in HIV-associated neurocognitive disorders. Lancet Neurol. 2014; 13(11):1139–51. [PubMed: 25316020]
11. Milanini B, et al. Cognitive reserve and neuropsychological functioning in older HIV-infected people. J Neurovirol. 2016; 22(5):575–583. [PubMed: 26965299]
12. Woods SP, et al. Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychol Rev. 2009; 19(2):152–68. [PubMed: 19462243]
13. Heaton RK, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17(1):3–16. [PubMed: 21174240]
14. Saylor D, et al. HIV-associated neurocognitive disorder - pathogenesis and prospects for treatment. Nat Rev Neurol. 2016; 12(5):309. [PubMed: 27080521]
15. Rosen HJ, et al. Metacognition in the behavioral variant of frontotemporal dementia and Alzheimer's disease. Neuropsychology. 2014; 28(3):436–47. [PubMed: 24548124]
16. Chiao S, et al. Deficits in self-awareness impact the diagnosis of asymptomatic neurocognitive impairment in HIV. AIDS Res Hum Retroviruses. 2013; 29(6):949–56. [PubMed: 23432363]
17. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. J Neurovirol. 2012; 18(5):388–99. [PubMed: 22811264]
18. Clifford K, et al. Progressive brain atrophy despite persistent viral suppression in HIV over age 60. JAIDS. 2017 in press.
19. Gelman BB. Neuropathology of HAND With Suppressive Antiretroviral Therapy: Encephalitis and Neurodegeneration Reconsidered. Curr HIV/AIDS Rep. 2015; 12(2):272–9. [PubMed: 25860316]
20. Hult B, et al. Neurobiology of HIV. Int Rev Psychiatry. 2008; 20(1):3–13. [PubMed: 18240058]
21. Solomon IH, et al. Brain and liver pathology, amyloid deposition, and interferon responses among older HIV-positive patients in the late HAART era. BMC Infect Dis. 2017; 17(1):151. [PubMed: 28212619]
22. Esiri MM, Biddolph SC, Morris CS. Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry. 1998; 65(1):29–33. [PubMed: 9667557]
23. Serrano-Pozo A, et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011; 1(1):a006189. [PubMed: 22229116]
24. Rempel HC, Pulliam L. HIV-1 Tat inhibits neprilysin and elevates amyloid beta. AIDS. 2005; 19(2):127–35. [PubMed: 15668537]
25. Achim CL, et al. Increased accumulation of intraneuronal amyloid beta in HIV-infected patients. J Neuroimmune Pharmacol. 2009; 4(2):190–9. [PubMed: 19288297]
26. Green DA, et al. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005; 19(4):407–11. [PubMed: 15750394]

27. Anthony IC, et al. Accelerated Tau deposition in the brains of individuals infected with human immunodeficiency virus-1 before and after the advent of highly active anti-retroviral therapy. Acta Neuropathol. 2006; 111(6):529–38. [PubMed: 16718349]
28. Gelman BB, Schuenke K. Brain aging in acquired immunodeficiency syndrome: increased ubiquitin-protein conjugate is correlated with decreased synaptic protein but not amyloid plaque accumulation. J Neurovirol. 2004; 10(2):98–108. [PubMed: 15204928]
29. Clifford DB, et al. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. Neurology. 2009; 73(23):1982–7. [PubMed: 19907013]
30. Khanlou N, et al. Increased frequency of alpha-synuclein in the substantia nigra in human immunodeficiency virus infection. J Neurovirol. 2009; 15(2):131–8. [PubMed: 19115126]
31. Ortega M, Ances BM. Role of HIV in amyloid metabolism. J Neuroimmune Pharmacol. 2014; 9(4):483–91. [PubMed: 24816714]
32. Andras IE, Toborek M. Amyloid beta accumulation in HIV-1-infected brain: The role of the blood brain barrier. IUBMB Life. 2013; 65(1):43–9. [PubMed: 23225609]
33. Mocchetti I, et al. Human immunodeficiency virus-associated dementia: a link between accumulation of viral proteins and neuronal degeneration. Curr Trends Neurol. 2014; 8:71–85. [PubMed: 26069421]
34. Rahimian P, He JJ. HIV/neuroAIDS biomarkers. Prog Neurobiol. 2016
35. Peterson J, et al. Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. PLoS One. 2014; 9(12):e116081. [PubMed: 25541953]
36. Gisslen M, et al. Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. BMC Neurol. 2009; 9:63. [PubMed: 20028512]
37. Kim J, Yoon JH, Kim YS. HIV-1 Tat interacts with and regulates the localization and processing of amyloid precursor protein. PLoS One. 2013; 8(11):e77972. [PubMed: 24312169]
38. Chen X, H L, Geiger NH, Haughey NJ, Geiger JD. Endolysosome involvement in HIV-1 transactivator protein-induced neuronal amyloid beta production. Neurobiol Aging. 2013; 34(10): 2370–2378. [PubMed: 23673310]
39. Liu CC, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013; 9(2):106–18. [PubMed: 23296339]
40. Valcour V, et al. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. J Neuroimmunol. 2004; 157(1-2):197–202. [PubMed: 15579298]
41. Nir TM, et al. Mapping white matter integrity in elderly people with HIV. Hum Brain Mapp. 2014; 35(3):975–92. [PubMed: 23362139]
42. Wendelken L, J N, Rosen H, Busovaca e, Allen I, Coppola G, Adams C, Rankin K, Milanini B, Clifford K, Wojta K, Nir T, Gutman BA, Thompson PM, Valcour V. ApoE e4 Is Associated With Cognition, Brain Integrity, and Atrophy in HIV Over Age 60. J Acquir Immune Defic Syndr. 2016; 73(4):426–432. [PubMed: 27228100]
43. Cysique LA, et al. APOE epsilon4 moderates abnormal CSF-abeta-42 levels, while neurocognitive impairment is associated with abnormal CSF tau levels in HIV+ individuals - a cross-sectional observational study. BMC Neurol. 2015; 15:51. [PubMed: 25880550]
44. Soontornniyomkij V, M D, Gouaux B, Soontornniyomkij B, Tatro ET, Umlauf A, Masliah E, Levine AJ, Singer EJ, Vinters HV, Gelman BB, Morgello S, Cherner M, Grant I, Achima CL. Cerebral β-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE ε4 carriers. AIDS. 2012; 26(18):2327–2335. [PubMed: 23018443]
45. Vera JH, et al. Neuroinflammation in treated HIV-positive individuals: A TSPO PET study. Neurology. 2016; 86(15):1425–32. [PubMed: 26911637]
46. Kreisl WC, et al. (11)C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016; 44:53–61. [PubMed: 27318133]
47. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004; 256(3):183–94. [PubMed: 15324362]
48. Sheppard DP, et al. Elevated rates of mild cognitive impairment in HIV disease. J Neurovirol. 2015; 21(5):576–84. [PubMed: 26139019]

49. Makitalo S, et al. The cerebrospinal fluid biomarker profile in an HIV-infected subject with Alzheimer's disease. AIDS Res Ther. 2015; 12:23. [PubMed: 26175795]
50. Sacktor N, et al. Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology. 2016; 86(4):334–40. [PubMed: 26718568]
51. Brouillette MJ, et al. Identifying Neurocognitive Decline at 36 Months among HIV-Positive Participants in the CHARTER Cohort Using Group-Based Trajectory Analysis. PLoS One. 2016; 11(5):e0155766. [PubMed: 27191850]
52. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013; 13(11): 976–86. [PubMed: 24156898]
53. Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med. 2012; 2(4):a006171. [PubMed: 22474609]
54. Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J Neurovirol. 2004; 10(6):350–7. [PubMed: 15765806]
55. Scott JC, et al. Neurocognitive consequences of HIV infection in older adults: an evaluation of the “cortical” hypothesis. AIDS Behav. 2011; 15(6):1187–96. [PubMed: 20865313]
56. Ciccarelli N, et al. Verbal list learning and memory profiles in HIV-infected adults, Alzheimer's disease, and Parkinson's disease: An evaluation of the “cortical hypothesis” of NeuroAIDS. Appl Neuropsychol Adult. 2016:1–10.
57. Milanini, B., A, I., Javandel, S., Joanna, H., Paul, R., Valcour, V. International Society of NeuroVirology. Vol. 2016. Toronto, Canada: 2016 Oct 25-28. Discriminant analysis of neuropsychological testing differentiates HIV-Associated Neurocogntive Disorder from Mild Cognitive Impairment due to Alzheimer's disease.
58. Ances BM, Ellis RJ. Dementia and neurocognitive disorders due to HIV-1 infection. Semin Neurol. 2007; 27(1):86–92. [PubMed: 17226745]
59. Tarawneh R, Holtzman DM. The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med. 2012; 2(5):a006148. [PubMed: 22553492]
60. Scarmeas N, et al. Motor signs during the course of Alzheimer disease. Neurology. 2004; 63(6): 975–82. [PubMed: 15452286]
61. Milanini B, et al. Psychiatric symptom burden in older people living with HIV with and without cognitive impairment: the UCSF HIV over 60 cohort study. AIDS Care. 2017:1–8.
62. Mega MS, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology. 1996; 46(1):130–5. [PubMed: 8559361]
63. Cummings JL. Alzheimer's disease. N Engl J Med. 2004; 351(1):56–67. [PubMed: 15229308]
64. M FM, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's disease, and its relationship with cognitive impairment. Curr Alzheimer Res. 2010; 7(6):517–26. [PubMed: 20455862]
65. Boublay N, Schott AM, Krolak-Salmon P. Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. Eur J Neurol. 2016; 23(10):1500–9. [PubMed: 27435186]
66. Krut JJ, P R, Zetterberg H, Fuchs D, Hagberg L, Yilmaz A, Cinque P, Nilsson S, Gisslén M. No support for premature central nervous system aging in HIV-1 when measured by cerebrospinal fluid phosphorylated tau (p-tau). Virulence. 2016
67. Brew BJ, et al. CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. Neurology. 2005; 65(9):1490–2. [PubMed: 16275845]
68. Peluso MJ, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. J Infect Dis. 2013; 207(11):1703–12. [PubMed: 23460748]
69. Krut JJ, et al. Cerebrospinal fluid Alzheimer's biomarker profiles in CNS infections. J Neurol. 2013; 260(2):620–6. [PubMed: 23052602]
70. Krut JJ, M T, Price RW, Hagberg L, Fuchs D, Rosengren L, Nilsson S, Zetterberg H, Gisslén M. Biomarker Evidence of Axonal Injury in Neuroasymptomatic HIV-1 Patients. PLoS One. 2014; 9(2)

71. Gisslen M, et al. Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study. EBioMedicine. 2016; 3:135–40. [PubMed: 26870824]
72. Zetterberg H, et al. Association of Cerebrospinal Fluid Neurofilament Light Concentration With Alzheimer Disease Progression. JAMA Neurol. 2016; 73(1):60–7. [PubMed: 26524180]
73. Gongvatana A, et al. White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. J Neurovirol. 2009; 15(2):187–95. [PubMed: 19306228]
74. Thompson PM, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. Proc Natl Acad Sci U S A. 2005; 102(43):15647–52. [PubMed: 16227428]
75. Klunder AD, C M, Dutton RA, Lee SE, Toga AW, Lopez OL, Aizenstein HJ, Becker JT, Thompson PM. Mapping cerebellar degeneration in HIV/AIDS. Neuroreport. 2008; 19(17):1655–1659. [PubMed: 18806691]
76. Pfefferbaum A, 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):361–70. [PubMed: 22458948]
77. Kallianpur KJ, et al. Peripheral blood HIV DNA is associated with atrophy of cerebellar and subcortical gray matter. Neurology. 2013; 80(19):1792–9. [PubMed: 23596064]
78. McMurtray A, et al. Small-vessel vascular disease in human immunodeficiency virus infection: the Hawaii aging with HIV cohort study. Cerebrovasc Dis. 2007; 24(2-3):236–41. [PubMed: 17630484]
79. Jernigan TL, et al. Clinical factors related to brain structure in HIV: the CHARTER study. J Neurovirol. 2011; 17(3):248–57. [PubMed: 21544705]
80. Ances BM, et al. Independent effects of HIV, aging, and HAART on brain volumetric measures. J Acquir Immune Defic Syndr. 2012; 59(5):469–77. [PubMed: 22269799]
81. Becker JT, et al. Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology. 2012; 54(2):113–21. [PubMed: 21424708]
82. Clark US, Cohen RA. Brain dysfunction in the era of combination antiretroviral therapy: implications for the treatment of the aging population of HIV-infected individuals. Curr Opin Investig Drugs. 2010; 11(8):884–900.
83. Pini L, et al. Brain atrophy in Alzheimer's Disease and aging. Ageing Res Rev. 2016; 30:25–48. [PubMed: 26827786]
84. Zhang Y, et al. Extracting patterns of morphometry distinguishing HIV associated neurodegeneration from mild cognitive impairment via group cardinality constrained classification. Hum Brain Mapp. 2016; 37(12):4523–4538. [PubMed: 27489003]
85. Soontornniyomkij V, et al. HIV protease inhibitor exposure predicts cerebral small vessel disease. AIDS. 2014
86. Watson C, et al. White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV. J Neurovirol. 2017; 23(3):422–429. [PubMed: 28101804]
87. Su T, et al. White matter structure alterations in HIV-1-infected men with sustained suppression of viraemia on treatment. AIDS. 2016; 30(2):311–22. [PubMed: 26691551]
88. Underwood J, et al. Grey and white matter abnormalities in treated HIV-disease and their relationship to cognitive function. Clin Infect Dis. 2017
89. Chen Y, et al. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. Neuroimage. 2009; 47(4):1154–62. [PubMed: 19376246]
90. Stebbins GT, Murphy CM. Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. Behav Neurol. 2009; 21(1):39–49. [PubMed: 19847044]
91. Rabinovici GD, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. Neurology. 2011; 77(23):2034–42. [PubMed: 22131541]
92. Ances BM, et al. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. Arch Neurol. 2012; 69(1):72–7. [PubMed: 22232345]

93. Ances BM, C J, Teshome M, Taylor J, Xiong C, Aldea P, Fagan AM, Holtzman DM, Morris JC, Mintun MA, Clifford DB. Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. Neurology. 2010; 75(2):111–115. [PubMed: 20534887]

94. Sathekge M, McFarren A, Dadachova E. Role of nuclear medicine in neuro HIV: PET, SPECT, and beyond. Nucl Med Commun. 2014; 35(8):792–6. [PubMed: 24781008]

95. Ishii K. PET approaches for diagnosis of dementia. AJNR Am J Neuroradiol. 2014; 35(11):2030–8. [PubMed: 23945233]

96. Vera JH, et al. PET brain imaging in HIV-associated neurocognitive disorders (HAND) in the era of combination antiretroviral therapy. Eur J Nucl Med Mol Imaging. 2017; 44(5):895–902. [PubMed: 28058461]

97. Tripathi M, et al. HIV encephalitis with subcortical tau deposition: imaging pathology in vivo using F-18 THK 5117. Eur J Nucl Med Mol Imaging. 2016; 43(13):2456–2457. [PubMed: 27488858]

98. Dani M, Brooks DJ, Edison P. Tau imaging in neurodegenerative diseases. Eur J Nucl Med Mol Imaging. 2016; 43(6):1139–50. [PubMed: 26572762]

Table 1

Summary of key features differentiating HAND from Alzheimer's disease. Note, references available on line as supplemental material, accessable at XXX

	HIV	Alzheimer's Disease (AD)
Neuropsychological Profile		
Neurocognitive dysfunction	Retrieval deficit Slowness Attention Executive dysfunction Focal cognitive impairment Fluctuating and variable course	Learning and consolidation deficit Visuospatial deficit Semantic memory Global cognitive deficit Progressive decline
Motor component	Motor slowing Loss of coordination Gait imbalance Sometimes initial manifestation Most prominent in advanced stages	Increased muscle tone Myoclonus in severe cases Gait disorders with risk for falls Most prominent in advanced stages
Behavioral manifestation	Apathy Depression Agitation Anxiety	Depression Apathy Agitation Delusion and hallucinations in advanced stage
Neuroimaging		
DTI	Widespread WM aberrations Initial frontal abnormalities Abnormalities correlate with viral load Frontal WM, parietal WM, caudate, splenium, genu, putamen, globus pallidus, thalamus	Early hippocampal changes WM changes extensively described in the cingulum bundle, uncinated fasciculus, corpus callous, anterior commissure and superior longitudinal fasciculus Increased MD in hippocampus, temporal lobe, posterior cingulum and more posterior regions
MRI	Smaller global cerebral volume Early reductions in basal ganglia and frontal lobe volumes WM loss primarily periventricular and frontal Atrophy rates correlate with age and plasma HIV RNA	Increased rates of cerebral atrophy Mesial temporal lobe atrophy Pronounced hyppocampal atrophy Early white matter changes
PiB PET	No PiB binding in cognitively unimpaired individuals with low CSF amyloid levels No PiB binding in HAND patients compared to AD	Early changes in posterior association cortex High uptake found in the prefrontal cortex, precuneus, and posterior cingulate cortex followed by lateral parietal, lateral temporal cortex and striatum Correlate withApoEε4 carrier status
Neuropathology		
Aβ Beta-amyloid	Decreased (especially in HAD or early infection) or normal levels in CSF Diffuse extracellular plaques Primarily intracellular Primarily concentrated in frontal lobe and basal ganglia	Decreased levels in CSF Neuritic plaques Initially concentrated in the entorhinal cortex and hippocampus Primarily extracellular
Tau pathology	Normal or increased t-tau levels and normal p-tau levels in CSF Accelerated deposition of p-tau in the hippocampus and entorhinal cortex	Increased t-tau and p-tau levels in CSF Early accumulation in entorhinal cortex, then spreading to the hippocampus and cerebral cortex
APP	Decreased soluble forms of APP in HAD	Higher concentrations of soluble APPs in MCI-AD
NFL	Increased in HAD patients Positive association with plasma HIV RNA Negative association with CD4 Significantly associated with monocyte activation markers	Moderately elevated especially light NF
Neurotrophic Factors		
BDNF/GDNF	Reduced BDNF levels Decreased GDNF levels in HAD	Decreased BDNF levels Reduced BDNF levels in MCI patients Changes correlate with cognitive dysfunction

	HIV	Alzheimer's Disease (AD)
		Depleted GDNF levels
Genetics		
ApoEε4	Cognitive dysfunction Reduced white matter integrity Cerebral atrophy Disease progression Age modulated	Consistent elevated risk factor for cognitive impairment Higher risk for Aβ aggregation Accelerated longitudinal memory decline Risk factor for cardiovascular disease

Abbreviations: WM: white matter; MD: mean diffusivity; HAD: HIV-associated dementia