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A neuropathologic diagnosis of Alzheimer's disease in an older adult with HIV-associated neurocognitive disorder

Joanna Hellmuth, MD, MHS¹, Benedetta Milanini, PhD¹, Eliezer Masliah, MD^{2,*}, Maria Carmela Tartaglia, MD³, Miranda B. Dunlop, MD⁴, David J. Moore, PhD⁵, Shireen Javandel¹, Saskia DeVaughn¹, and Victor Valcour, MD, PhD¹

¹Memory and Aging Center, Department of Neurology, University of California, San Francisco

²Departments of Neurosciences and Pathology, University of California, San Diego

³University of Toronto, Tanz Centre for Research in Neurodegenerative Diseases

⁴Department of Internal Medicine, University of California, San Francisco

⁵University of California, San Diego, Department of Psychiatry

Abstract

We discuss the challenges associated with diagnosing neurodegenerative disorders in older adults living with HIV, illustrated through a case report where neurologic co-diagnosis of Alzheimer's disease (AD) and HIV-associated Neurocognitive Disorder (HAND) are considered. The patient was followed and evaluated for over four years and underwent post-mortem neuropathologic evaluation. Further work is needed to identify diagnostic tests that can adequately distinguish HAND from early stage neurodegenerative disorders among older adults living with HIV and cognitive changes.

Keywords

HIV-associated neurocognitive disorder; Alzheimer's disease; Neuropathology; Dementia; Neuropsychological testing

Introduction

The US population of people living with HIV (PLWH) is now aging, with over 25% who are age 55 or older (CDC, 2018). Accurately diagnosing cognitive disorders in this group is an emerging challenge, as 30–50% of PLWH have HIV-associated Neurocognitive Disorder (HAND), which can occur despite maintaining undetectable plasma HIV RNA levels ('viral load') (Heaton *et al.*, 2010; Eden *et al.*, 2016). At the same time, these older individuals are at risk for developing age-associated neurodegenerative diseases, the most common of which is Alzheimer's disease (AD). There are few data available to inform the accurate differentiation of HAND from neurodegenerative processes such as AD (Milanini &

Corresponding author: Joanna Hellmuth, MD, MHS; Joanna.Hellmuth@ucsf.edu; telephone: 415-514-2384.

*Current address, Division of Neurosciences, NIA/NIH

Valcour, 2017). Nuanced clinical features, including neurological findings and neuropsychological testing performance may aid physicians in this diagnosis. Biologic testing for AD can be challenging to interpret in the setting of HIV. Additionally, there are unique management issues for older PLWH with cognitive impairment. We describe an older adult who presented with untreated HIV infection and cognitive impairment who, on autopsy, was found to have Braak stage VI Alzheimer's disease neuropathology.

Case presentation

A 79-year-old right-handed man with a diagnosis of HIV infection presented to our memory disorders clinic in 2008 for cognitive changes. He initially reported a year of short-term memory difficulties, with increased challenges managing finances, an episode of getting lost, and motor slowing noted when writing and hiking. HIV infection was diagnosed 14 months prior when he had a plasma viral load of 46,028 copies/mL and CD4 count of 209 cells/mm³ (Figure 1). At his first neurology clinic visit, he had not yet initiated antiretroviral therapy (ART). It was suspected that he had been infected more than 10 years prior based on a risk behavior inventory and a history of unprotected sex with men. Relevant past medical history included hypertension, hyperlipidemia, coronary artery disease with non-ST elevated myocardial infarction (NSTEMI), severe asymptomatic aortic stenosis, mild normocytic anemia of chronic disease, and treated prostate adenocarcinoma. Medications at that time included aspirin, atenolol, lisinopril, atorvastatin, donepezil, and trimethoprim/sulfamethoxazole. He had obtained a Bachelor's degree in law and accounting and had worked in the field until he retired in his 60s. He reported no history of smoking, and had approximately one drink of alcohol per week, and was living alone. Other than a brother who developed AD in his late 70s, he had no other family history of neurologic disease.

His heart rate was 56 beats per minute and blood pressure was 128/80. His general examination revealed a loud systolic ejection murmur. His neurologic examination was notable for bradyphrenia, hypomimia, hypophonia, elevated right upper extremity tone, moderately slowed rapid alternating movements, mild hyperreflexia in the lower extremities, and gait instability. On the Mini-Mental State Exam (MMSE), the patient scored 16/30, with poor verbal short-term memory, impaired attention and working memory, difficulty with confrontation naming, impaired executive functioning, with relatively intact visuospatial skills. A one-hour neuropsychological evaluation documented substantial difficulties in multiple cognitive domains including verbal and visual episodic memory, language, attention, executive functions and manual dexterity, although he demonstrated intact visuospatial functioning (Table 1). Laboratory tests indicated recent normal TSH and non-reactive RPR. A clinical suspicion for AD was noted and he had been started on donepezil prior to our evaluation. The patient was diagnosed with HIV-Associated Dementia (HAD), the most severe form of HAND, and a MRI brain was ordered (Antinori et al., 2007). It was recommended he initiate ART. While a high central nervous system penetration/effectiveness (CPE) combination was considered, he was soon started on emtricitabine, tenofovir, and efavirenz due to the simplicity of one pill per day regimen.

Within two months of starting ART, his plasma viral load had decreased to 89 copies/mL with a CD4 count of 249 cells/mm³ (Figure 1). Within four months of initiating ART, his

plasma viral load was undetectable and remained undetectable. At this point the patient felt cognitively sharper and was brighter in affect, although short-term memory difficulties persisted. The patient had a low-normal vitamin B12 of 359 ng/L with an elevated methylmalonic acid of 0.6 Umol/L leading to B12 oral supplementation. A MRI of the brain without contrast revealed mild to moderate atrophy including mesial temporal atrophy bilaterally, as well as mild bilateral temporal, dorsal, and posterior atrophy (Figure 2a). He had mild periventricular white matter changes. Given persistent cognitive deficits and good adherence to medications, his ART regimen was switched to have a higher CPE with nevirapine, lamivudine, and zidovudine.

Six weeks after changing his ART regimen, he experienced lightheadedness and decreased exercise tolerance and was found to have a severe macrocytic anemia (hemoglobin 6.9 g/dL, hematocrit 9.6%), attributed to zidovudine (Walker *et al.*, 1988). He was hospitalized and transfused with two units of blood. The zidovudine was then replaced with abacavir.

Nine months after his initial evaluation, now age 80, his cognitive impairment persisted despite undetectable plasma HIV RNA levels. He was writing information down he did not want to forget and did not recall his hospitalization and blood transfusion. A neurologic exam found persistent parkinsonism, new en bloc turning and apraxia bilaterally. Neuropsychological testing with the Montreal Cognitive Assessment (MoCA) revealed marked dysfunction in the executive and memory domains with a total score of 10/30. On measures of manual dexterity his performance was still below the expectations despite being relatively stable compared to the first assessment (Figure 3a). He was diagnosed with HAD and possible AD. Donepezil was continued and a caregiver became involved.

In the coming months, he noted difficulty controlling his left foot movements, and had a fall leading to a hand fracture. A friend noted he was not able to recognize family members in a picture. Adult Protective Services (APS) became involved, and the patient relayed he was the victim of elder sexual abuse perpetrated by a stranger on the street. The evaluation determined he did not know how to contact the police, identify correct change, or perform simple math. The APS-initiated neuropsychology report found an improved MMSE of 19/30 with impaired attention, verbal memory, confrontation naming, with preserved visuospatial functioning. It was determined he did not possess capacity for financial or medical decision making.

In the coming months, he showed slight improvements in addition to his MMSE score. He was found to have less hypomimia, with normal tone in the upper extremities, and a brisk, more stable gait. He still required caregiver assistance at home, but was more independent with tasks such as laundry. One year after initial presentation, his MoCA improved to 16/30 despite still revealing poor performance on naming, memory, attention, language, and the clock draw task (Figure 3b). The improvement in his cognitive functioning as compared to baseline was attributed to the plasma viral suppression of HIV. There were plans to perform a lumbar puncture (LP) to check cerebrospinal fluid (CSF) HIV RNA levels, however, the patient did not show for this appointment. At age 81, 21 months after initial presentation, there were additional concerns of the patient being a victim of elder sexual abuse, requiring an evaluation for sexually transmitted diseases (negative RPR, urine Chlamydia DNA,

urethral gonococcus culture and Gram stain). Repeat neurologic examination revealed improved parkinsonism with normal tone, small amplitude rapid alternating movements now with good speed, normal heel tapping, and brisk ambulation without instability. A repeat MoCA showed relative stability at 15/30. An LP was performed revealing undetectable CSF HIV RNA (<75 copies/mL) with a normal white blood cells, normal glucose, and an elevated CSF protein of 61 mg/dL.

By two years after initial presentation, at age 81, the patient now had 24-hour supervision. He was able to hike daily but his neurologic exam revealed slowness in upper extremity rapid alternating movements. On MMSE, he earned a score of 6/30, indicating a significant decline to severe dementia. He evidenced profound impairment on tests of visual memory, language and visuo-constructional skills (Table 1; Figure 3c). Escitalopram had been started for apathy. Later that year at age 82, he again displayed masked facies, now with flat affect, apraxia, mild bradykinesia and slow gait. Repeat MMSE was 5/30. In the following months, he had more hesitations in speech and his gait became wide-based. His CD4 cell count was above 600. A MRI of the brain repeated three years after his initial scan revealed progressive atrophy in the bilateral frontal lobes, mesial and superior temporal lobes, parietal and occipital lobes, with moderately progressive periventricular white matter changes (Figure 2b).

By age 83 he found it harder to get out of a chair and had a fall while hiking. His walking remained bradykinetic and he was unable to perform tandem gait. He noticed unusual movements in his legs stimulated by putting on his socks that otherwise did not interfere with activities, and was referred for further evaluation. He was diagnosed with stimulus sensitive myoclonus and was also noted to have bilateral agrophesthesia and difficulty with two-point discrimination on the left side.

Weeks prior to his 84th birthday, he was hospitalized for syncope and was found to have another NSTEMI. An echocardiogram confirmed known severe aortic stenosis, which was symptomatic. He was started on clopidogrel. Less than two months later, he was seen for his final neurology visit, where he displayed dense amnesia. Eight days later he had substernal chest pain and shortness of breath, and was again hospitalized for an NSTEMI with troponin peak at 12.9 ug/L. He had critical symptomatic aortic stenosis with pulmonary congestion, and an aortic valve repair was not consistent with his goals of care. He entered hospice care. Due to new renal insufficiency, lamivudine and abacavir were discontinued, and replaced with raltegravir and emtricitabine. He died four days later.

Neuropathology

The patient and surrogate decision maker had consented to a post-mortem neuropathologic evaluation, which was performed at the California NeuroAIDS Tissue Network, a site within the National NeuroAIDS Tissue Consortium. Gross examination of the brain revealed a weight of 590 grams. The cerebral hemispheres displayed significant atrophy of the frontal, parietal, and temporal regions. There was moderate atrophy of the cortical gray ribbon, hippocampus, basal ganglia, thalamus, and cerebellum with ventricular dilatation and normal white matter. There was normal pigmentation in the substantia nigra and the locus

ceruleus. Hematoxylin and eosin stain revealed gliosis in the neocortex with diminished neuronal populations. The anterior entorhinal cortex showed loss of neurons in the layer II and thioflavin-S stain revealed abundant tangles. The anterior hippocampus was poorly populated by neurons and displayed astrogliosis. Immunohistochemical analysis with an anti-beta amyloid antibody and PHF-1 antibody for phosphorylated tau were positive for plaques and tangles consistent with Braak Stage VI. There were no Lewy bodies or glial cytoplasmic inclusions. There were no microglial nodules or multinucleated giant cells. The final neuropathologic diagnosis was severe Alzheimer's disease (Figure 2c-d).

Discussion

We present the case of a 79-year-old man with untreated HIV infection and progressive cognitive changes that improved after ART initiation, but the subsequently declined despite viral suppression. He ultimately received a neuropathologic diagnosis of AD. While this case illustrates the challenges of forming diagnoses for cognitive dysfunction in older PLWH, it also raises questions about how to best apply the HAND criteria in an older population.

A review of his neurologic exam findings supports the pathologic diagnosis of AD. Notably, he developed apraxia nine months into his presentation and later, agraphesthesia. Both of these findings point to parietal cortical involvement seen in a neurodegenerative process such as AD (Ahmed, Baker, Thompson, Husain & Butler, 2016). However, his fluctuating extrapyramidal motor symptoms suggests this patient also had CNS involvement of HIV. The parkinsonism improved with ART initiation, but ultimately had a fluctuating course, a hallmark of HAND (Heaton *et al.*, 2015). Mild parkinsonism is relatively common in older PLWH, (Valcour *et al.*, 2008), but less so in people with early AD where it typically presents without fluctuation (Snowden, Bowen, Hughes & Larson, 1995; Horvath, Burkhard, Herrmann, Bouras & Kövari, 2014). His development of stimulus sensitive myoclonus later in his course has been separately described in HIV and AD (Kojovic, Cordivari & Bhatia, 2011).

The possible co-diagnosis of AD and HAND is supported by his neuropsychological performance over time. AD is commonly characterized by substantial and early involvement in the hippocampal region of the brain, producing a prominent amnesic profile on cognitive testing due to deficits in encoding, as evidenced by failure to benefit from cueing (Weintraub, Wicklund & Salmon, 2012; Delis *et al.*, 1995). On initial testing, this patient had a poor delayed recall score on the California Verbal Learning Test (0/9) with no substantial benefit from cueing. In fact, were it not for his diagnosis of untreated HIV, he likely would have received an AD diagnosis based on this testing performance. Memory deficits are also common in HAND, although these often reflect learning inefficiency rather than a pure amnesic disorder, as demonstrated by normal or near normal recognition ability (Heaton *et al.*, 2011; Ciccarelli *et al.*, 2012; Clifford & Ances, 2013; Murji *et al.*, 2003). The patient initially performed in the normal range on the recognition tasks of visual and verbal memory, a memory profile that suggests subcortical dysfunction observed in HAND (Woods, Moore, Weber & Grant, 2009). At his first visit, the patient also demonstrated intact visuospatial abilities, which is consistent with the findings of relatively preserved

visuospatial skills in the setting of HAND (Heaton *et al.*, 2011; Clifford *et al.*, 2013). In contrast, AD patients often exhibit deficits in this domain and can be an initial manifestation of the disease (Weintraub *et al.*, 2012; Caine, 2004). By the time of his final neuropsychological assessment, the patient showed substantial visuospatial changes. In terms of language functioning, semantic abilities are usually retained in HAND, in contrast to patients with AD where impairment is in part due to the deterioration in the semantic memory that supports language (Heaton *et al.*, 2011; Weintraub *et al.* 2012). At presentation, our patient had very poor performance on a confrontation naming task. Finally, the patient showed early impairment in fine motor abilities on the Grooved Pegboard task that later progressed. Manual dexterity impairment is common in HIV-related CNS dysfunction.

While the histopathologic diagnosis confirms AD in this case, it does not exclude co-existing HAND. In the current HIV era where ART is accessible and viral suppression can be achieved, HAND tends to have “no specific neuropathology” (Gelman, 2015). This contrasts with the historical findings of diffuse microglial nodules (clusters of activated microglia) in the white and gray matter and perivascular multinucleated giant cells (fused, HIV-infected mononuclear phagocytes) in the central white matter and deep gray structures seen in severe cases of HIV encephalitis (HIVE) and AIDS-related dementia prior to the widespread access to ART. (Bell, 1998; Gelman, 2015).

In terms of clinical management, this man had untreated HIV at presentation with a detectable plasma viral load, indicating that he likely had CNS viral replication and associated inflammation and immune activation. Thus, it is probable that HIV contributed to the initial presentation of his cognitive disorder. Once ART was initiated and his plasma viral load was suppressed, it is notable that his symptoms initially improved, further signifying that HIV likely contributed to his cognitive and motor issues. However, his symptoms then worsened, leading the clinical team to perform a lumbar puncture to exclude CNS escape, a rare condition where the virus replicates in the CNS despite undetectable levels in the plasma (Ferretti, Gisslen, Cinque & Price, 2015). With well-controlled HIV infection, an undetectable CSF HIV RNA and progressive cognitive symptoms, a concurrent neurodegenerative disorder such as AD became more likely.

While there are several features supporting HIV-related CNS involvement in addition to the known AD pathology, it is unclear how the HAND criteria should be applied to this case. Although often employed in clinical settings (Bearden & Meyer, 2016), the 2007 Frascati criteria for HAND were designed for research purposes and do not contain guidelines for considering concomitant neurodegenerative processes that are seen more commonly in older populations (Antinori *et al.*, 2007). Without current guidance, the patient’s clinical diagnosis of possible AD would be a confounding condition where Frascati criteria cannot be applied. Moreover, the existing research criteria provide little clinical guidance on the pattern of cognitive deficits that would add specificity for an HIV etiology, nor do they include biomarker evidence of disease. Together, these core limitations inhibit utility of HAND criteria for differential diagnosis in older PLWH.

Developing additional biologic tests may assist practitioners facing similar diagnostic challenges. While there are no neurodiagnostic tests specific for HAND in PLWH, there

have been considerable gains in the past decade in the biologic diagnosis of AD. CSF biomarkers of AD became clinically available in 2007 and comprise amyloid beta 1–42 (A β 42, a marker of aggregated amyloid deposition when at low levels), phosphorylated tau (P-tau, a component of neurotoxic neurofibrillary tangles), and total-tau (T-tau, a marker of axonal injury). Collectively, these CSF biomarkers of neurodegeneration have 85% sensitivity and 90% specificity for AD (Blennow & Hampel, 2003; Blennow, 2010; Blennow, Mattsson, Schöller, Hansson & Zetterberg, 2015). Unfortunately, this diagnostic panel of AD biomarkers is thought to be altered in neuroinflammatory conditions such as HIV, and there is insufficient published information to understand utility for those who are aging with HIV and achieve viral suppression (Milanini & Valcour, 2017). Some of the existing studies demonstrate low A β 42, similar to that seen in early stage Alzheimer's, while P-tau and T-tau have been shown to be alternately elevated, reduced, or normal compared to healthy adults (Clifford *et al.*, 2009; Brew, Pemberton, Blennow, Wallin & Hagberg, 2005; Abassi *et al.*, 2017; Krut *et al.*, 2016). However, these studies included participants that are not relevant to the clinical questions at hand: primarily younger individuals not at risk for neurodegenerative diseases, those in advanced stages of HAND (i.e. HAD), which comprise a small portion of HAND cases, or those with confounding detectable plasma viral loads. A recent study in adults living with HIV, of whom over 60% had HAND and >95% of whom were virally suppressed, found that low CSF A β 1–42 levels were influenced by APOE ϵ 4 status; (Cysique *et al.*, 2015). Although the participants in this study were older than other published cases, they were younger than the typical age for developing a neurodegenerative disease (mean age of 57 years old), which is notable, as there is known variability of these biomarkers with age (Mattsson *et al.*, 2012). Overall, the existing studies do not provide clinical clarity on the use of CSF AD biomarkers for practitioners caring for aging patients living with HIV at risk for neurodegenerative diseases. CSF biomarkers of Alzheimer's were not obtained in the presented patient due to uncertainty of how any findings would be interpreted and the unlikelihood that the results would alter therapy.

Amyloid PET is an emerging neuroimaging tool to determine if individuals have amyloid proteins characteristic of AD deposited in cortical brain tissue. A negative amyloid PET scan excludes the possibility of significant AD neuropathology with high specificity, while a positive test reflects true amyloid deposition but not necessarily an inevitable AD diagnosis. Not everyone with PET detectable amyloid deposition in the brain will develop Alzheimer's and there is an increasing occurrence of amyloid deposition by age. By age 80, 40% of healthy adults will have a positive amyloid PET scan (Ossenkoppele *et al.*, JAMA 2015). A study in ten participants living with HIV (mean age 53; 90% on ART) employing a 11C-PiB ligand for amyloid was negative in all individuals, suggesting no increased amyloid PET positivity in those who are middle-aged and living with HIV (Ances *et al.*, 2010). While a negative amyloid PET result is useful to rule out the diagnosis of AD, these scans are not readily accessible currently, as amyloid PET is not presently approved for reimbursement by Medicare and out of pocket costs can range upwards of \$4000 USD. In the presented case, amyloid PET imaging was not a diagnostic option during the lifetime of the patient.

This case adds to the small literature of patients with a neurodegenerative diagnosis in the context of HIV. There are two existing case reports of individuals with HIV diagnosed with AD, both of whom were on long-standing ART with low CSF A β 1–42 levels suggesting

AD (Turner *et al.*, 2016; Mäkitalo *et al.*, 2015). Neither had neuropathologic confirmation of Alzheimer's. One patient presented at age 71, with 14 years of viral suppression and progressive short-term memory issues starting five-year prior who was diagnosed with AD based on a positive amyloid PET scan (Turner *et al.*, 2016). The other published case was in a 63-year-old woman (an age considered to be early onset AD) with at least seven years on ART who developed visuospatial issues, and then progressed to functional impairments (Mäkitalo *et al.*, 2015). She had a strong maternal family history of late-onset Alzheimer's and a lumbar puncture performed five years after presentation revealed an elevated CSF HIV RNA of 221 copies/mL with a plasma level of 46 copies/mL. This suggested CNS escape of HIV, and a change of her ART regimen lead to viral suppression below 50 copies/mL. Much like the presented patient, this case reflects co-involvement of AD and CNS HIV-related causes. In both cases raise the concern of a possible delay in AD diagnosis in the setting of HIV.

Separately, the current case also highlights relevant clinical aspects for older adults living with HIV and cognitive issues. Not uncommon for PLWH, the presented patient experienced social isolation and also limited insight; both limited information about his functional abilities (Herek, Capitanio & Widaman, 2002; Chiao *et al.*, 2013). Indeed, this patient was likely in a moderate clinical stage of Alzheimer's at presentation and more detailed information may have clarified his diagnosis sooner. Relevant to all individuals with cognitive issues, this patient was at an increased risk for abuse. The existing literature on dementia and elder sexual abuse is limited, and identifies women as having the highest vulnerability (Friedman, Avila, Rizvi, Partida & Friedman, 2017). However, there are few if any studies looking at the specific risks for gay or bisexual men with dementia, and the lack of research in this area may have contributed to a lowered perception of his vulnerability. Other considerations unique to managing older adults living with HIV includes the complicating factors of co-morbid medical conditions (Greene, Justice, Lampris & Valcour, 2013). The presented patient experienced a zidovudine-induced anemia, the impact of which was magnified by his coexisting severe aortic stenosis. Unless there is a concern of CNS escape of HIV, the evidence to date does not support adoption of unusual regimens in an effort to improve CPE. These issues illustrate that elders living with HIV and cognitive issues have a unique set of clinical needs and diagnostic issues, and further research is needed in the field to provide optimum care.

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References

- Abassi M, Morawski BM, Nakigozi G, Nakasujja N, Kong X, Meya DB, Robertson K, Gray R, Wawer MJ, Sacktor N, Boulware DR. (2017) Cerebrospinal fluid biomarkers and HIV-associated neurocognitive disorders in HIV-infected individuals in Rakai, Uganda. *J Neurovirol.*, 23(3):369–375. doi: 10.1007/s13365-016-0505-9. [PubMed: 27995575]
- Ahmed S, Baker I, Thompson S, Husain M, Butler CR. (2016). Utility of testing for apraxia and associated features in dementia. *J Neurol Neurosurg Psychiatry*, 87(11):1158–1162. [PubMed: 27251676]

- Ances BM, Christensen JJ, Teshome M, Taylor J, Xiong C, Aldea P, Fagan AM, Holtzman DM, Morris JC, Mintun MA, Clifford DB. (2010). Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. *Neurology*, 75(2):111–5. doi: 10.1212/WNL.0b013e3181e7b66e. [PubMed: 20534887]
- Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, 69(18):1789–99. [PubMed: 17914061]
- Bearden DR, Meyer AC. (2016). Should the Frascati criteria for HIV-associated neurocognitive disorders be used in children? *Neurology*, 87(1):17–8. doi: 10.1212/WNL.0000000000002785. [PubMed: 27206721]
- Bell JE. (1998). The neuropathology of adult HIV infection. *Rev Neurol (Paris)*, 154(12):816–829. [PubMed: 9932303]
- Blennow K, Hampel H. (2003). CSF markers for incipient Alzheimer's disease. *Lancet Neurol*, 2(10):605–13. [PubMed: 14505582]
- Blennow K (2010). Biomarkers in Alzheimer's disease drug development. *Nat Med.*, 16(11):1218–22. [PubMed: 21052077]
- Blennow K, Mattsson N, Schöll M, Hansson O, Zetterberg H. (2015). Amyloid biomarkers in Alzheimer's disease. *Trends Pharmacol Sci.*, 36(5):297–309. [PubMed: 25840462]
- Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L. (2005) CSF amyloid β 42 and tau levels correlate with AIDS dementia complex. *Neurology*, 65:1490–1492. [PubMed: 16275845]
- Caine D. (2004). Posterior cortical atrophy: a review of the literature. *Neurocase*, 10(5):382–385. doi: 10.1080/13554790490892239 [PubMed: 15788276]
- CDC 2017 HIV Among People Aged 50 and Over, viewed 27 February 2018, <https://www.cdc.gov/hiv/group/age/olderamericans/>
- Chiao S, Rosen HJ, Nicolas K, Wendelken LA, Alcantar O, Rankin KP, Miller B, Valcour V. (2013). Deficits in self-awareness impact the diagnosis of asymptomatic neurocognitive impairment in HIV. *AIDS Res Hum Retrovir*, 29(6):949–56. [PubMed: 23432363]
- Ciccarelli N, Fabbiani M, Baldonero E, Fanti I, Cauda R, Di Giambenedetto S, Silveri MC. (2012). Effect of aging and human immunodeficiency virus infection on cognitive abilities. *J Am Geriatr Soc.*, 60(11):2048–2055. doi: 10.1111/j.1532-5415.2012.04213.x. [PubMed: 23110543]
- Clifford DB, Fagan AM, Holtzman DM, Morris JC, Teshome M, Shah AR, Kauwe JS. (2009) CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. *Neurology*, 73:1982–1987. [PubMed: 19907013]
- Clifford DB, Ances BM. (2013). HIV-associated neurocognitive disorder. *Lancet Infect Dis.*, 13(11):976–986. doi: 10.1016/S1473-3099(13)70269-X. [PubMed: 24156898]
- Cysique LA, Hewitt T, Croitoru-Lamourey J, Taddei K, Martins RN, Chew CS, Davies NN, Price P, Brew BJ. (2015). APOE ϵ 4 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.*, 15:51. doi: 10.1186/s12883-015-0298-0. [PubMed: 25880550]
- Delis D, Peavy G, Heaton R, Butters N, Salmon D, Taylor M, Stout J, Mehta P, Ryan L, White D, Atkinson JH, Chandler JL, McCutchan JA, Grant I HNRC Group. (1995). Do patients with HIV-associated minor/motor disorder exhibit a "subcortical" memory profile? Evidence using the California Verbal Learning Test. *Assessment*, 2(2):151–156.
- Eden A, Marcotte TD, Heaton RK, Nilsson S, Zetterberg H, Fuchs D, Franklin D, Price RW, Grant I, Letendre SL, Gisslen M. (2016). Increased Intrathecal Immune Activation in Virally Suppressed HIV-1 Infected Patients with Neurocognitive Impairment. *PLoS One*, 11(6):e0157160. [PubMed: 27295036]
- Ferretti F, Gisslen M, Cinque P, Price RW. (2015). Cerebrospinal Fluid HIV Escape from Antiretroviral Therapy. *Curr HIV/AIDS Rep.*, 12(2):280–8. doi: 10.1007/s11904-015-0267-7. [PubMed: 25860317]

- Friedman LS, Avila S, Rizvi T, Partida R, Friedman D. (2017). Physical Abuse of Elderly Adults: Victim Characteristics and Determinants of Revictimization. *J Am Geriatr Soc.*, 65(7):1420–1426. doi: 10.1111/jgs.14794. [PubMed: 28485492]
- Gelman BB. (2015). Neuropathology of HAND with suppressive antiretroviral therapy: encephalitis and neurodegeneration reconsidered. *Curr HIV/AIDS Rep*, 12(2):272–9. doi: 10.1007/s11904-015-0266-8. [PubMed: 25860316]
- Greene M, Justice AC, Lampiris HW, Valcour V. (2013). Management of human immunodeficiency virus infection in advanced age. *JAMA*, 309(13):1397–405. doi: 10.1001/jama.2013.2963. [PubMed: 23549585]
- Heaton RK, Clifford DB, Franklin J, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*, 75(23):2087–2096. doi: 10.1212/WNL.0b013e318200d727. [PubMed: 21135382]
- Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group; HNRC Group. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*, 17(1):3–16. doi: 10.1007/s13365-010-0006-1. [PubMed: 21174240]
- Heaton RK, Franklin Dr, Jr, Deutsch R, Letendre S, Ellis RJ, Casaletto K, Marquine MJ, Woods SP, Vaida F, Atkinson JH, Marcotte TD, McCutchan JA, Collier AC, Marra CM, Clifford DB, Gelman BB, Sactor N, Morgello S, Simpson DM, Abramson I, Gamst AC, Fennema-Notestine C, Smith DM, Grant I CHARTER Group. (2016). Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis*, 60(3): 473–480.
- Herek GM, Capitanio JP, Widaman KF. (2002). HIV-related stigma and knowledge in the United States: prevalence and trends, 1991–1999. *Am J Public Health*, 92(3):371–7. [PubMed: 11867313]
- Horvath J, Burkhard PR, Herrmann FR, Bouras C, Kövari E. (2014). Neuropathology of parkinsonism in patients with pure Alzheimer's disease. *J Alzheimers Dis.*, 39(1):115–20. doi: 10.3233/JAD-131289. [PubMed: 24121968]
- Kojovic M, Cordivari C, Bhatia K. (2011). Myoclonic disorders: a practical approach for diagnosis and treatment. *Ther Adv Neurol Disord*, 4(1):47–62. doi: 10.1177/1756285610395653. [PubMed: 21339907]
- Krut JJ, Price RW, Zetterberg H, Fuchs D, Hagberg L, Yilmaz A, Cinque P, Nilsson S, Gisslén M. (2017). No support for premature central nervous system aging in HIV-1 when measured by cerebrospinal fluid phosphorylated tau (p-tau). *Virulence*, 8(5):599–604. doi: 10.1080/21505594.2016.1212155. [PubMed: 27435879]
- Mäkitalo S, Mellgren Å, Borgh E, Kilander L, Skillbäck T, Zetterberg H, Gisslén M. (2015). The cerebrospinal fluid biomarker profile in an HIV-infected subject with Alzheimer's disease. *AIDS Res Ther.*, 12:23. doi: 10.1186/s12981-015-0063-x. [PubMed: 26175795]
- Mattsson N, Rosén E, Hansson O, Andreasen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M, Rich K, Kaiser E, Verbeek MM, Olde Rikkert M, Tsolaki M, Mulugeta E, Aarsland D, Visser PJ, Schröder J, Marcusson J, de Leon M, Hampel H, Scheltens P, Wallin A, Eriksdotter-Jönhagen M, Minthon L, Winblad B, Blennow K, Zetterberg H. (2012). Age and diagnostic performance of Alzheimer disease CSF biomarkers. *Neurology*, 78(7):468–76. doi: 10.1212/WNL.0b013e3182477eed. [PubMed: 22302554]
- Milanini B and Valcour V. (2017). Differentiating HIV-associated neurocognitive disorders from Alzheimer's disease: an emerging issue in geriatric neuroHIV. *Curr HIV/AIDS Rep*, 14(4): 123–132. [PubMed: 28779301]
- Murji S, Rourke SB, Donders J, Carter SL, Shore D, Rourke BP. (2003). Theoretically derived CVLT subtypes in HIV-1 infection: internal and external validation. *J Int Neuropsychol Soc*, 9(1):1–16. [PubMed: 12570353]

- Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BN, Scheltens P, Visser PJ; Amyloid PET Study Group, Verfaillie SC, Zwan MD, Adriaanse SM, Lammertsma AA, Barkhof F, Jagust WJ, Miller BL, Rosen HJ, Landau SM, Villemagne VL, Rowe CC, Lee DY, Na DL, Seo SW, Sarazin M, Roe CM, Sabri O, Barthel H, Koglin N, Hodges J, Leyton CE, Vandenberghe R, van Laere K, Drzezga A, Forster S, Grimmer T, Sánchez-Juan P, Carril JM, Mok V, Camus V, Klunk WE, Cohen AD, Meyer PT, Hellwig S, Newberg A, Frederiksen KS, Fleisher AS, Mintun MA, Wolk DA, Nordberg A, Rinne JO, Chételat G, Lleo A, Blesa R, Fortea J, Madsen K, Rodrigue KM, Brooks DJ. (2015). Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA*, 313(19):1939–49. doi: 10.1001/jama.2015.4669. [PubMed: 25988463]
- Snowden MB, Bowen JD, Hughes J, Larson EB. (1995). Study of Alzheimer's dementia patients with parkinsonian features. *J Geriatr Psychiatry Neurol.*, 8(3):154–8. [PubMed: 7576038]
- Turner RS, Chadwick M, Horton WA, Simon GL, Jiang X, Esposito G. (2016). An individual with human immunodeficiency virus, dementia, and central nervous system amyloid deposition. *Alzheimers Dement (Amst)*, 4:1–5. doi: 10.1016/j.dadm.2016.03.009. [PubMed: 27489872]
- Valcour V, Watters MR, Williams AE, Sacktor N, McMurtray A, Shikuma C. (2008). Aging exacerbates extrapyramidal motor signs in the era of highly active antiretroviral therapy. *J Neurovirol*, 14(5):362–367. doi: 10.1080/13550280802216494. [PubMed: 18989814]
- Walker RE, Parker RI, Kovacs JA, Masur H, Lane HC, Carelton S, Kirk LE, Grainick HR, Fauci AS. (1988). Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine. *Ann Intern Med*, 108(3): 372–376. [PubMed: 3422548]
- Weintraub S, Wicklund AH, Salmon DP. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med*, 2(4):a006171. doi: 10.1101/cshperspect.a006171. [PubMed: 22474609]
- Woods SP, Moore DJ, Weber E, Grant I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev*, 19(2):152–168. doi: 10.1007/s11065-009-9102-5. [PubMed: 19462243]

Figure 1.
Trajectory of clinical HIV variables and cognitive functioning over time. MMSE=Mini-Mental State Exam.

Figure 2.

Neuroimaging, gross brain pathology, and neuropathology. (a) First MRI brain, age 79; coronal T2 FLAIR, no T1 image was available; orientation is radiologic; (b) Second MRI brain, age 82; coronal T1; (c) coronal gross pathologic specimen of the brain upon autopsy; (d) Immunohistochemistry showing frontal cortex parenchymal staining for phosphorylated tau in neurofibrillary tangles and amyloid beta 1–42 as a part of neuritic plaques, indicative of advanced stage Alzheimer's disease neuropathology.

Figure 3.

Neuropsychological testing showing fine motor function and visuospatial abilities over time.

(a) Grooved pegboard task of timed fine motor abilities, showing fluctuating non-dominant hand performance and progressively decline in the dominant hand (no non-dominant hand data at last time point due to patient injury). (b) Visuospatial tasks from the Montreal Cognitive Assessment (MoCA) at age 80, displaying relatively preserved cube copy with evidence of tremors, and disorganized clock draw omitting details. (c) Benson figure copy several years later at age 82, showing a distorted figure reflecting impaired visual abilities.

Table 1.

Comparison of neuropsychological testing performance over time. CVLT=California Verbal Learning Test; VOSP=Visual Object and Space Perception battery; CATS Face Matching=Comprehensive Affect Testing System Face Matching. Some data could not be obtained due to low cognitive status, and is reflected by “–” in the table.

Cognitive domain	Test	Age 79, first visit	Age 81, 20 months later
<i>Global</i>	Mini-Mental State Exam	16	6
<i>Memory</i>	9-item CVLT, delayed recall	0/9	-
	CVLT, recognition	5/9	-
	Benson figure recall	6/17	0/17
<i>Language</i>	Boston Naming Test—Short Form	5/15	2/15
	Category fluency (words/minute)	5	2
	Lexical fluency (words/minute)	2	-
	Sentence comprehension	3/5	-
	Word comprehension	14/16	6/16
	Sentence repetition	3/5	1/5
<i>Attention & working memory</i>	CVLT, registration trial 1	0/9	-
	Digits forward	5	-
	Digit backward	2	-
<i>Executive functions</i>	Design fluency	4	-
	Modified Trails	120 [“]	-
<i>Psychomotor speed</i>	Grooved Pegboard (dominant/non-dominant hand)	115 [“] /142 [“]	175 [“] / *
<i>Visuospatial</i>	Benson figure copy	16/17	12/17
	VOSP	10/10	-
	CATS Face Matching	11/12	-
	Basic math problems	4/5	2/5
<i>Mood status</i>	Geriatric Depression Scale	10/30	-

* Tests exploring fine motor abilities not administered at this visit due to hand injury. Data not included for APS-initiated neuropsychological testing, as raw scores were not available.