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

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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 4 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.

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”) ( Eden et al., 2016; Heaton et al., 2010). 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 & 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 AD 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 bpm and blood pressure was 128/80. His general examination revealed a loud systolic ejection murmur. His neurologic examination was notable for bradycardia, 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 1-h 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 to 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 2 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 4 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 effect, 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 2(a)). He had mild peryventricular 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 with the first assessment (Figure 3(a)). 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 despite being relatively stable compared with the first assessment (Figure 3(a)). He was diagnosed with HAD and possible AD. Donepezil was continued and a caregiver became involved.

![Figure 1. Trajectory of clinical HIV variables and cognitive functioning overtime.](image-url)
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 3(b)). 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 Chlamydial 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 2 years after initial presentation, at age 81, the patient now had 24-h 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 3(c)). 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 3 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 2(b)).

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 agraphesthesia 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 clopidigrel. Less than 2 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 4 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 g. 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 astroglisis. 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 AD (Figure 2(c-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 9 months into his presentation and later, agraphasthesia. 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 suggest that 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 (Horvath, Burkhard, Herrmann, Bouras, & Kövari, 2014; Snowden, Bowen, Hughes, & Larson, 1995). 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 overtime. AD is commonly characterized by substantial and early involvement in the hippocampal region of the brain, producing a prominent amnestic profile on cognitive testing due to deficits in encoding, as evidenced by failure to benefit from cueing (Delis et al., 1995; Weintraub, Wicklund, & Salmon, 2012). 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, it was 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 amnestic disorder, as demonstrated by normal or near normal recognition ability (Ciccarelli et al., 2012; Clifford & Ances, 2013; Heaton et al., 2011; 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 & Ances, 2013). In contrast, AD patients often exhibit deficits in this domain and can be an initial manifestation of the disease (Caine, 2004; Weintraub et al., 2012). 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 (Aβ42, a marker of aggregated amyloid deposition when at low levels), phosphorylated tau (P-tau, a component of neurototoxic 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, 2010; Blennow & Hampel, 2003; Blennow, Mattsson, Schöll, 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 & Valsour, 2017). Some of the existing studies demonstrate low Aβ42, similar to that seen in early stage AD, while P-tau and T-tau have been shown to be alternately elevated, reduced, or normal compared with healthy adults (Abassi et al., 2017; Brew, Pemberton, Blennow, Wallin, & Hagberg, 2005; Clifford et al., 2009; Krut et al., 2017). 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 Aβ1–42 levels were influenced by APOE ε4 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 AD 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 whether 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 AD 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., 2015). A study in 10 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 Aβ 1–42 levels suggesting AD (Mäkitalo et al., 2015; Turner et al., 2016). Neither had neuropathologic confirmation of AD. One patient presented at age 71, with 14 years of viral suppression and progressive short-term memory issues starting 5-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 7 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 AD and a lumbar puncture performed 5 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 (Chiao et al., 2013; Herek, Capitanio, & Widaman, 2002). Indeed, this patient was likely in a moderate clinical stage of AD 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 include 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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