UC San Diego

UC San Diego Previously Published Works

Title

The current understanding of overlap between characteristics of HIV-associated neurocognitive disorders and Alzheimer's disease.

Permalink

<https://escholarship.org/uc/item/70q4v4s6>

Journal

Journal of neurovirology, 25(5)

ISSN

1355-0284

Authors

Rubin, Leah H
Sundermann, Erin E
Moore, David J

Publication Date

2019-10-01

DOI

10.1007/s13365-018-0702-9

Peer reviewed

The current understanding of overlap between characteristics of HIV-associated neurocognitive disorders and Alzheimer's disease

Leah H. Rubin^{1,2} · Erin E. Sundermann³ · David J. Moore³

Received: 10 October 2018 / Revised: 4 November 2018 / Accepted: 13 November 2018
© Journal of NeuroVirology, Inc. 2019

Abstract

The advent of effective antiretroviral medications (ARVs) has led to an aging of the HIV population with approximately 50% of people with HIV (PWH) being over the age of 50 years. Neurocognitive complications, typically known as HIV-associated neurocognitive disorders (HAND), persist in the era of ARVs and, in addition to risk of HAND, older PWH are also at risk for age-associated, neurodegenerative disorders including Alzheimer's disease (AD). It has been postulated that risk for AD may be greater among PWH due to potential compounding effects of HIV and aging on mechanisms of neural insult. We are now faced with the challenge of disentangling AD from HAND, which has important prognostic and treatment implications given the more rapidly debilitating trajectory of AD. Herein, we review the evidence to date demonstrating both parallels and differences in the profiles of HAND and AD. We specifically address similarities and difference of AD and HAND as it relates to (1) neuropsychological profiles (cross-sectional/longitudinal), (2) AD-associated neuropathological features as evidenced from neuropathological, cerebrospinal fluid and neuroimaging assessments, (3) biological mechanisms underlying cortical amyloid deposition, (4) parallels in mechanisms of neural insult, and (5) common risk factors. Our current understanding of the similarities and dissimilarities of AD and HAND should be further delineated and leveraged in the development of differential diagnostic methods that will allow for the early identification of AD and more suitable and effective treatment interventions among graying PWH.

Keywords HIV · Alzheimer's disease · Cognitive impairment · HAND

Public health significance—aging and age-associated disorders among PWH

With increased effectiveness of antiretrovirals (ARVs), HIV has shifted from a deadly disease with an aggressive time course to a chronic disease with increased longevity. Presently, one half of people living with HIV (PWH) in the USA are over 50 years of age and life expectancy among ARV-treated adults is

approaching that of the general population (Antiretroviral Therapy Cohort 2017; CDC 2017; Lohse et al. 2007; May and Ingle 2011). The “graying of the HIV epidemic” has introduced new challenges including increasing rates of age and inflammation-related comorbidities including central nervous system (CNS) complications. Currently, one of the most common CNS complications is HIV-associated neurocognitive disorders (HAND) (Antinori et al. 2007). Rates of the milder forms of HAND, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) persist, if not increased in the post-ARV era (Heaton et al. 2010). With increased survival of older PWH, there is an increased likelihood that some will also suffer from common age-associated disorders including neurodegenerative dementias and their precursor stage, mild cognitive impairment (MCI). Because Alzheimer's disease (AD) is the most common dementing condition, this review focuses specifically on AD, which includes both MCI and Alzheimer's-type dementia.

Older PWH may be particularly at risk for age-associated, neurodegenerative diseases including AD given evidence of synergistic effects of HIV and aging on the brain (Hodes et al.

Leah H. Rubin and Erin E. Sundermann equally contributed to this work.

✉ Erin E. Sundermann
esundermann@einstein.yu.edu

¹ Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

² Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

³ Department of Psychiatry, University of California, San Diego (UCSD) School of Medicine, La Jolla, CA, USA

2016; Van Epps and Kalayjian 2017). Some evidence suggests premature or accelerated aging phenotypes among PWH (Stoff et al. 2017). For example, age-associated conditions appear 5–10 years earlier in PWH versus the general population (Deeks 2011; Deeks and Phillips 2009; Durand et al. 2017). Using an epigenetic prediction of age based on DNA methylation levels, PWH demonstrate accelerated aging of 7.4 years in brain tissue and 5 years in peripheral blood versus HIV-uninfected (HIV-) persons (Horvath and Levine 2015). Further supporting accelerated aging among PWH, Sheppard et al. (2017) demonstrated that neurocognitive performance in older PWH (aged 50–65) was worse than age-matched HIV-adults but similar to older (≥ 65 years) HIV-adults.

Evidence of PWH with AD

Presently, evidence of a probable/possible AD diagnosis in PWH, either alone or in conjunction with HAND, is derived mostly from case studies (Morgello et al. 2018; Tripathi et al. 2016; Turner et al. 2016). In the case of a 71-year-old man living with HIV for 14 years, an AD-like profile was indicated by clinical, neuropsychological, and neuroimaging assessments (Turner et al. 2016). His family reported that he had mild short-term memory problems for the past 5 years with insidious onset and a noticeable decline in the past 3 years. He also demonstrated similar alterations in resting-state functional connectivity as seen in HIV-individuals with MCI ($n = 8$) or mild Alzheimer's-type dementia ($n = 14$) versus 42 age-matched cognitively normal individuals. Moreover, [18F]florbetaben positron emission tomography (PET) imaging demonstrated marked cortical amyloid- β ($A\beta_{42}$) plaque deposits, a hallmark neuropathological characteristic of AD (Turner et al. 2016). In a second case, a 70-year-old woman presented with memory complaints. PET imaging detected abnormal phosphorylation of the tau protein (p-tau) in the women, which leads to another AD neuropathological hallmark, neurofibrillary tangles (Tripathi et al. 2016). Recently, two virally-suppressed female cases (52 and 81 years old) demonstrated AD neuropathology and age-related tau astroglial pathology. Consistent with AD, the 52-year-old demonstrated severe learning, memory, and daily function impairment; however, the 81-year-old was managing all activities of daily living (Morgello et al. 2018). One clinical study demonstrated that PWH were over seven times more likely to meet diagnostic criteria for MCI than HIV-individuals (Sheppard et al. 2015). Importantly, MCI diagnosis was associated with older age and mild declines in activities of daily living but not with HIV-related clinical factors.

The minimal evidence of PWH with diagnosed possible/probable AD may be an artifact of the fact that most cohorts of PWH are middle aged rather than older. The majority of large-scale, longitudinal, cohort studies including the Women's

Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS) have focused on mid-life (~ 40 years old) or younger. Large-scale data will continue to emerge over the next decade with continued follow-up of MACS and WIHS individuals into their 50s and 60s. Also, multiple prospective, cohort studies with a focus on aging among PWH have commenced including the Veterans Aging Cohort Study, the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY), and a 12-year follow-up study of individuals enrolled in CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study. As more PWH reach an age where they are at risk for traditional dementias, clinicians should assess for AD in older PWH, and researchers will benefit from prioritizing longitudinal studies of older PWH measuring AD-related markers.

Importance of distinguishing between HAND and AD

Given that half of PWH are over 50 years old (CDC 2017) and $\sim 45\%$ of PWH are diagnosed with HAND (Heaton et al. 2010), it is possible that a considerable proportion of these individuals are on an AD trajectory, but are erroneously presumed to have HAND given their HIV diagnosis. Clinicians and researchers are faced with a new challenge of distinguishing between early signs of AD and mild forms of HAND. Typical protocols for diagnosing AD including neurocognitive, neurological, and neuroimaging assessments have not yet been tested in the context of PWH. Distinguishing between AD and HAND is important for both clinical and experimental reasons. Clinically, the more degenerative profile of AD requires different life planning and treatment options versus the HAND profile in which neurocognitive impairment (NCI) is typically more stable (Milanini and Valcour 2017). A delayed AD diagnosis in PWH would limit the opportunity to intervene early in the course of AD when interventions are most effective and life planning can be better implemented. Experimentally, the identification of AD among PWH will lead to more accurate prevalence estimates of HAND and will improve studies examining biomarker, imaging, and genetic correlates of HAND.

Parallels and differences in profiles of HAND and AD

Table 1 provides a summary of the evidence outlined below and builds upon a previously-published summary of features differentiating HAND from AD in (Milanini and Valcour 2017).

Table 1 Summary of evidence for biological and neurocognitive profiles associated with cognitively normal, HAND and aMCI/AD diagnoses

Normal (Reference)	HAND	aMCI/AD
Biofluids		
Higher CSF A β 42	Intermediate CSF A β 42 (Brew and Letendre 2008; Brew et al. 2005; Clifford et al. 2009; Krut et al. 2013)	Lower CSF A β 42 (Brew and Letendre 2008; Clifford et al. 2009; Rosenmann 2012)
Lower CSF p-tau	Lower CSF p-tau (Clifford et al. 2009; Gisslen et al. 2009; Krut et al. 2013; Peterson et al. 2014)	Highest CSF p-tau (Brew et al. 2005; Clifford et al. 2009; Rosenmann 2012)
Lower plasma CCL2, TNF- α , IL-6, MCP-1, quinolinic acid	Higher plasma CCL2, TNF- α , IL-6, MCP-1, quinolinic acid (Giunta et al. 2008; Guillemain et al. 2005; Sokolova et al. 2009; Town et al. 2008)	Higher plasma CCL2, TNF- α , IL-6, MCP-1, quinolinic acid (Galimberti et al. 2006; Liao et al. 2016; Streit et al. 2004; Tarkowski et al. 2003)
Lower CSF levels of Ng and NfL	Downregulation of Ng mRNA among those with high viral loads (Duskova et al. 2013). Elevated CSF levels of NfL (Abdulle et al. 2007; Jessen et al. 2014; Mellgren et al. 2007; Peterson et al. 2014)	Elevated CSF/plasma levels of Ng (Janelidze et al. 2016; Tarawneh et al. 2016; Wellington et al. 2016) and NfL (Abu-Rumeileh et al. 2018; Bacioglu et al. 2016; Gisslen et al. 2016)
Neuroimaging - PET		
No/minimal A β 42 plaque burden as detected by PET	No/minimal A β 42 plaque burden as detected by PET (Ances et al. 2012; Ances et al. 2010)	High A β 42 plaque burden as detected by PET (Thal et al. 2014; Valotassiou et al. 2018)
No/minimal tau burden as detected by tau PET	Unknown	High tau burden as detected by tau PET (Thal et al. 2014; Valotassiou et al. 2018)
Neuroimaging - MRI		
Age-related levels of cerebral atrophy predominantly in sensorimotor and visual cortices (Bakkour et al. 2013)	Pronounced cerebral atrophy, with early changes in basal ganglia and frontal regions (Bonnet et al. 2013; Cohen et al. 2010; Masters and Ances 2014; Zhang et al. 2016)	Pronounced cerebral atrophy, with early changes in the mesial temporal lobe regions (Braak et al. 1998; Braskie et al. 2013; Vernooij and Smits 2012)
Neuropathology		
Lower rates of A β 42	Intermediate rates of A β 42 (Achim et al. 2009; Aksenov et al. 2010; Cohen et al. 2015; Esiri et al. 1998; Gelman and Schuenke 2004; Green et al. 2005; Rempel and Pulliam 2005; Xu and Ikezu 2009)	Higher rates of A β 42 (Thal et al. 2014)
Lower rates of p-tau	Higher rates of p-tau (Anthony et al. 2006; Patrick et al. 2011)	Higher rates of p-tau (Thal et al. 2014)
Neuropsychological		
Normal recall & recognition performance	Poor recall but normal recognition performance (Becker et al. 1995; Peavy et al. 1994; White et al. 1997)	Poor recall and recognition performance (Joubert et al. 2016; Petersen et al. 1999; Salmon 2012)
Minimal memory and functional decline	Minimal memory and functional decline (Antinori et al. 2007; Brouillette et al. 2016; Sacktor et al. 2016)	Accelerated memory and functional decline (Grober et al. 2008; Karr et al. 2018; Wilson et al. 2011)
Psychiatric features	Depression, anxiety, sleep disorders (Chaponda et al. 2018; Kamat et al. 2016; Lowther et al. 2014)	Depression, apathy, aggression, anxiety, sleep disorders (Cortes et al. 2018; Zhao et al. 2016)

Neuropsychological profiles

Amnesic MCI (aMCI) is the MCI subtype that is specifically associated with increased risk of progression to Alzheimer's-type dementia (Petersen 2004; Petersen et al. 1999). There is considerable overlap in the neuropsychological profiles of aMCI and the milder forms of HAND. Both conditions are defined by mild impairment (neuropsychological scores 1–1.5 SD below normative mean) and with none-to-mild difficulties

in everyday function. aMCI is characterized specifically by episodic memory deficits (Petersen et al. 1999) and although the domains impacted by HAND vary, memory (e.g., delayed recall) is one of the domains most impaired in PWH currently (Heaton et al. 2011; Rubin et al. 2017).

There are also important differences between aMCI and HAND that may allow us to better distinguish the conditions including the type and trajectory of memory deficits. For example, aMCI is characterized by hippocampal-based

encoding, storage and rapid forgetting deficits that are observed on memory recall and recognition tests (Petersen et al. 1999). Conversely, evidence suggests a more “subcortical” pattern of NCI in HAND including processing speed, executive function, and memory retrieval deficits but relatively normal memory storage and retention in the pre (i.e., impaired recall but intact recognition) (Becker et al. 1995; Peavy et al. 1994; White et al. 1997) and post-ARV era (Scott et al. 2011); although not always (Maki et al. 2015; Tierney et al. 2018). This cortical versus sub-cortical distinction was recently evidenced in a study where a combination of six neuropsychological tests discriminated aMCI from mild HAND with 86% accuracy (Milanini et al. 2016). HAND was distinguished from aMCI by better performance on the recognition subtest of the California Verbal Learning Test and the Digits Backward Test (working memory), and worse performance on the Mini Mental State Exam (global function), Trails A (attention), Trails B (executive function), and Digit Symbol (processing speed). Additionally, longitudinal studies indicate differing trajectories of NCI among persons with HAND versus aMCI. Specifically, among virally suppressed PWH, HAND is typically characterized by mild cognitive deficits fluctuating across and within affected domains (Brouillette et al. 2016; Sacktor et al. 2016) rather than the rapidly progressive declines typically observed in aMCI. Although these differences allow for opportunities to disentangle aMCI and HAND, conventional diagnostic approaches, without experienced clinical interpretation, are not sensitive to profiles and trajectories of domain-specific impairment.

AD-associated neuropathological features in HIV

Neuropathology studies

Studies suggest commonalities in the neuropathological processes underlying AD and HAND. The hallmark pathological characteristics of AD, A β ₄₂ plaques, and neurofibrillary tangles are observed in normal aging (Sjogren et al. 2001); however, excessive plaque and tangle burden is indicative of disease pathology. A β ₄₂ plaque deposition is an initial event in the AD trajectory that can occur more than a decade before clinical symptoms (Bateman et al. 2012; Morris and Price 2001). A β ₄₂ plaque deposits are also observed in the brains of HIV+ post-mortem cases, particularly older cases (Achim et al. 2009; Aksenov et al. 2010; Esiri et al. 1998; Gelman and Schuenke 2004; Green et al. 2005; Rempel and Pulliam 2005; Xu and Ikezu 2009), and the degree of deposition increases with age (Esiri et al. 1998; Xu and Ikezu 2009) suggesting that A β ₄₂ pathology may contribute to accelerated aging or AD risk in PWH. Similar to AD, plaque deposition is found in mid-temporal and frontal lobe regions in PWH (Esiri et al.

1998); however, the deposition appears to a greater extent in AD versus HIV (Cohen et al. 2015). A β ₄₂ plaque type and deposition pattern also differs between HIV and AD. Whereas A β ₄₂ plaques in AD are predominantly neuritic, associated with abnormal neural/glial function and deposited extracellularly, the plaques in HIV are typically “diffuse” and deposited intracellularly (e.g., neuronal soma and axonal tracks) (Brew et al. 2009; Brew and Letendre 2008; Everall et al. 2009; Green et al. 2005). These plaque differences do not necessarily discriminate AD from HAND-related neuropathology given that diffuse plaques are thought to be the precursor to neuritic plaques and they are consistently observed in Down’s Syndrome patients who inevitably develop AD if their lifespan allows (Brew and Letendre 2008). Thus, it is unclear whether the intraneuronal, diffuse plaques in HIV are associated with AD but manifest differently in the context of HIV or whether they reflect a different disease process.

The research examining p-tau and neurofibrillary tangles PWH is sparse. In one neuropathological study, higher p-tau levels were found specifically in the frontal cortex tissue of 8 PWH with HIV encephalitis (HIVE) versus 8 PWH without HIVE (Patrick et al. 2011), although, in the ARV era, HIVE is generally less common and has shifted from a subacute, rapidly progressive condition with subcortical pathology to a more chronic and mild condition with cortical pathology (Achim et al. 2009; Brew 2004). In the HIVE cases, p-tau levels were positively correlated with the expression of CDK5 and p35; kinases that contribute to atypical phosphorylation of neural substrates and neuronal death when abnormally activated. In another study, elevated levels of p-tau were observed in the hippocampus of 29 HIV+ cases compared to seven age-matched, HIV-cases with the highest levels reported in ARV-treated cases (Anthony et al. 2006).

Cerebrospinal fluid and neuroimaging studies

Changes in A β ₄₂ and p-tau can be measured in the cerebrospinal fluid (CSF) and by PET imaging as an early surrogate marker of pathology. Lower levels of CSF A β ₄₂ indicate greater cortical deposition of A β ₄₂ plaques (Fagan et al. 2006; Roe et al. 2013), whereas higher levels of CSF p-tau indicate greater p-tau in the brain. The literature regarding CSF levels of A β ₄₂ in PWH is equivocal with some reporting no differences between HIV-individuals and ARV-treated (Ances et al. 2012) or non ARV-treated PWH (Gisslen et al. 2009) or both (Steinbrink et al. 2013), whereas other studies conducted in the post-ARV era report reductions in CSF A β ₄₂ levels in PWH with HAND versus HIV-individuals although treatment information was unavailable in some (Brew and Letendre 2008; Brew et al. 2005; Clifford et al. 2009; Krut et al. 2013). In one study comparing HIV-individuals with Alzheimer’s-type dementia ($n = 20$) and without NCI ($n = 20$) and HIV+ individuals with AIDS Dementia Complex

(ADC, another term for HAD; $n = 87$) and without NCI ($n = 30$), CSF A β_{42} levels in those with ADC were lower than both HIV+ and HIV-participants without NCI and comparable to the HIV-Alzheimer's-type dementia patients (Brew et al. 2005). Disparate findings may be due to small samples and differences in age and severity of HAND whereby A β_{42} is more common among older PWH with moderate-to-severe impairment. Fewer studies use amyloid PET imaging to detect A β_{42} plaques in PWH and, in contrast to CSF findings, these post-ARV era studies report no evidence of elevated extracellular amyloid fibrillar deposits in PWH that are cognitively normal (Ances et al. 2010) or have HAND (Ances et al. 2012; Ances et al. 2010). Disparities between CSF and PET findings of A β_{42} deposition may reflect the differences in A β_{42} plaque characteristics and deposition in HAND versus AD. Pittsburgh Compound B (PiB) PET measures the extracellular fibrillar deposits that are common to AD, and thus may not detect the deposits in HIV that are typically intracellular and diffuse (Anthony et al. 2006; Green et al. 2005; Rempel and Pulliam 2005). Although it is unclear if or how the A β_{42} plaques in PWH relate to AD pathological mechanisms, these studies suggest that altered amyloid metabolism is common to AD and HIV.

In contrast to the neuropathological finding in HIVE cases (Patrick et al. 2011), most studies examining CSF levels of p-tau do not report elevated levels in PLWH versus HIV-individuals (Clifford et al. 2009; Gisslen et al. 2009; Krut et al. 2013; Peterson et al. 2014) although inconsistencies exist (Brew et al. 2005). Studies included comparisons among older and younger HIV-individuals with and without AD and older and younger PWH that were either neuroasymptomatic and untreated, ARV-treated, or diagnosed with HAND (Gisslen et al. 2009; Krut et al. 2013; Peterson et al. 2014). Conversely, Brew et al. (2005) found that patients with ADC had CSF p-tau levels that were higher than PWH and HIV-participants without NCI and comparable to HIV-AD patients. Disparate results may be due to differences in the age range, severity of HAND, time period when cases were gathered, and treatment history of study samples. The detection of cortical tau tangles via PET has yet to be examined in HIV except in the aforementioned case study of the 70-year-old patient with HIVE. Consistent with neuropathological findings in HIVE (Patrick et al. 2011), the patient demonstrated p-tau in the periventricular and deep white matter brain regions (Tripathi et al. 2016). Taken together, these limited findings suggest that p-tau may be a shared pathologic process specifically between AD and HIVE.

AD is also characterized by markers of cellular and synaptic integrity. Neurogranin (Ng) is a marker of synaptic loss (Wellington et al. 2016) shows elevated CSF levels in the early stages of AD relative to normal controls and other types of dementias including subcortically-characterized dementias (Janelidze et al. 2016; Tarawneh et al. 2016; Wellington et al.

2016). Biofluid levels of Ng has not been examined in relation to HAND; however, Ng mRNA was found to be significantly downregulated in PBMCs of PWH with high viral loads compared to demographically-matched, HIV-controls (Duskova et al. 2013). Elevated CSF levels of neurofilament light (NfL) is a marker of axonal injury that has been reported in multiple types of neurodegenerative disorders including AD (Abu-Rumeileh et al. 2018; Bacioglu et al. 2016; Gisslen et al. 2016), and HAND (Abdulle et al. 2007; Jessen et al. 2014; Mellgren et al. 2007; Peterson et al. 2014).

Cell death and brain atrophy are also neuropathologic characteristics of AD particularly in the temporal lobe and other cortical structures (Braak et al. 1998; Braskie et al. 2013; Vernooij and Smits 2012). Brain atrophy is also associated with HAND (Bonnet et al. 2013; Cohen et al. 2010; Masters and Ances 2014). Machine learning approaches demonstrate utility in distinguishing HAND from MCI among older (aged 60–70 years) PWH and HIV-individuals using brain morphometry data (Zhang et al. 2016). Consistent with the cortical-(AD) versus subcortical-based (HAND) dementia distinction, the combination of volume estimates that best distinguished HAND from MCI in the post-ARV era was in cortical and subcortical brain regions that subserve episodic memory, executive function, and fine motor tasks including medial orbitofrontal cortex, precuneus, inferior temporal gyrus, cerebellum, and parahippocampal volume (Zhang et al. 2016).

Biological mechanisms underlying cortical A β_{42} deposition in HIV versus AD

Although cortical A β_{42} deposition is found in both AD and older PWH, the mechanism underlying the deposition may differ in HIV and AD. Whereas AD is predominantly an auto “proteopathic” neurodegenerative disorder (Jucker and Walker 2011) initiated by misfolding and aggregation of the A β_{42} and tau protein in neurons (Jucker and Walker 2011; Maccioni et al. 2001), HIV infection represents an environmental insult to neurons. In HIV, several steps in the synthesis and clearance of A β_{42} are disrupted by viral proteins and blood-brain barrier (BBB) compromise (Andras and Toborek 2013; Ortega and Ances 2014). For instance, the viral protein gp120 alters transcription of the amyloid precursor protein (APP) by triggering neural injury and microglial activation (Mocchetti et al. 2014; Ortega and Ances 2014; Rahimian and He 2017). The viral protein Tat promotes A β_{42} aggregation by inhibiting neprilysin, the primary enzyme in A β_{42} degradation (Kim et al. 2013; Ortega and Ances 2014; Rahimian and He 2017; Rempel and Pulliam 2005). Increases in cortical A β_{42} deposition are also associated with longer durations of ARVs, particularly with protease inhibitors (Achim et al. 2009; Green et al. 2005; Rempel and Pulliam 2005). Certain ARVs such as protease inhibitors and

efavirenz inhibit the expression of P-glycoprotein expression, which contributes to the clearance of A β ₄₂ from the brain (Giunta et al. 2008; Lam et al. 2001). Evidence of a shared precursor step to cortical A β ₄₂ deposition in HAND and AD lies in the β -site A β precursor protein cleaving enzyme 1 (BACE1) and 2 (BACE2), a beta-secretase enzyme that cleaves APP and can lead to an overproduction of A β ₄₂ oligomers that aggregate into plaques (Vassar et al. 1999). Elevated levels of BACE enzymatic activity are found in all AD stages (Holler et al. 2012; Johnston et al. 2005; Yang et al. 2003). Similarly, studies report elevated levels of BACE1 enzymatic activity, A β ₄₂ oligomers (Stern et al. 2018) and BACE2 gene expression (Borjabad and Volsky 2012) in the brains of HIV cases. Findings implicate BACE as a common mechanism underlying AD and HAND A β ₄₂ deposition and highlight its broad therapeutic potential.

Parallels in mechanisms of neural insult in HAND and AD

Certain mechanisms of neural injury are common to both HIV and AD as well as aging in general including chronic, low-grade inflammation, immune senescence, mitochondria dysfunction, compromised BBB (Banks 1999; Bowman et al. 2007), and oxidative stress (Lovell and Markesbery 2007; Nath et al. 2008). In a proteomic profiling study in post-mortem HIV+ cases, Zhou et al. (2010) identified 76 differentially-expressed proteins in HIV+ cases with HAD versus without HAD in the post-ART era. Over 90% of the identified proteins also show differential expression patterns in AD, with the large majority reflecting energy metabolism (mitochondria) and signal transduction pathways. Increasing evidence implicates chronic inflammation and immune activation in the accelerated aging and in the development of age-associated, non AIDS conditions, including AD, in PWH. In HIV and AD, chronic inflammation is triggered by activated microglia and astrocytes (Kadiu et al. 2005; Minagar et al. 2002; Ting et al. 2007) and is demonstrated by elevated biofluid levels of inflammatory markers including TNF α , IL6, MCP-1, YKL-40, and quinolinic acid (Giunta et al. 2008; Guillemin et al. 2005; Sokolova et al. 2009; Town et al. 2008). Growing evidence also implicates TREM2 in AD- and HAND-related pathogenic mechanisms likely due to its role in regulating neuroinflammation and in phagocytizing extra-cellular A β plaques. Decreased levels of membrane-enriched TREM2 were found in the brain tissue of HIV+ cases with HAND versus without HAND in the post-cART era (Fields et al. 2018). A meta-analytic study reported higher levels of soluble TREM2 (indicating greater neuroinflammation) in the prodromal AD stages (Liu et al. 2018). In AD, a high A β ₄₂ plaque burden can activate microglia (Bolmont et al. 2008), which results in the release of pro-inflammatory cytokines (Streit et al. 2004)

that contribute to neural dysfunction (Cameron and Landreth 2010; Maezawa et al. 2011; Perry et al. 2010). In HIV, viral proteins, including tat and gp120, trigger an immune response and inflammation through the release of host-derived cytokines and chemokines (Kovalevich and Langford 2012). Monocyte-driven inflammatory markers in particular (e.g., sCD163, sCD14) have been strongly linked to NCI among PWH (Burdo et al. 2013; Imp et al. 2017; Royal et al. 2016). Neuroinflammation is observed even in virally-suppressed PWH (Aukrust et al. 1999). In fact, ARV-treated PWH show high levels of neuroinflammation, particularly in the hippocampus, a brain region that shows early AD-related changes (Anthony et al. 2005; Eden et al. 2007). Furthermore, immune reconstitution syndrome in long-term, ARV-treated PWH involves recovered immune cells attacking previously-acquired opportunistic infections with an excessive inflammatory response that can contribute to AD pathology either directly or indirectly through subsequent conditions such as vasculitis (Gray et al. 2005; Stoll and Schmidt 2003; Stoll and Schmidt 2004). It remains unclear whether the concurrence of HIV, ARVs, and aging leads to compounding inflammatory pathways that make PWH more vulnerable to AD in general and/or to an earlier onset and more rapid trajectory.

Risk factors common to both HAND and AD

Certain demographic, clinical and genetic factors have been independently associated with increased risk of HAND and AD including, but not limited to, older age, vascular abnormalities, neuropsychiatric characteristics, and APOE- ϵ 4 carrier status. First, older age is the strongest risk factor for AD and is also associated with a greater likelihood of HAND (Hardy and Vance 2009; Sacktor et al. 2010; Tan et al. 2013; Valcour et al. 2004; van Gorp et al. 1994; Vance et al. 2011). Germane to potential manifestations of AD, older age (> 50 years) was associated with a 4 to 5 fold increased odds of memory impairment (Tan et al. 2013) among 106 PWH with HAND. Several studies, but not all (Cysique et al. 2011), reported an age by serostatus interaction whereby older age had more deleterious effects on neurocognitive performance in PWH versus HIV-persons (Hardy and Vance 2009; Sacktor et al. 2010; van Gorp et al. 1994; Vance et al. 2011). Second, vascular disorders including hypertension, stroke, diabetes, and obesity are well-established risk factors for AD (Kivipelto et al. 2001; Meng et al. 2014; Qiu and Fratiglioni 2015; Skoog et al. 1996). HIV-related biological mechanisms and ARV medications are associated with hyperlipidemia, insulin resistance, abnormalities in body fat distribution and, in turn, these conditions are associated with a higher likelihood of HAND (Fabbiani et al. 2013; Sattler et al. 2015; Schouten et al. 2016). These vascular conditions are likely linked to AD and HAND through similar mechanisms of inflammation,

insulin resistance, dyslipidemia, and/or oxidative stress (de Bruijn and Ikram 2014; Helzner et al. 2009; Li et al. 2009; Luchsinger et al. 2005), which further obscures whether NCI reflects AD and/or HAND. Third, meta-analytic studies suggest that depression is a strong risk factor for AD (Mega et al. 1996; Mourao et al. 2016; Terracciano et al. 2014). Evidence also suggests that depression is associated with HAND (Bryant et al. 2015; Milanini et al. 2017), particularly learning and memory deficits (Maki et al. 2015). Last, the APOE- ϵ 4 allele is the strongest genetic risk factor for AD and is linked with earlier AD onset and greater degree of cortical A β ₄₂ burden (Morris et al. 2010; Polvikoski et al. 1995). Although not consistently (Joska et al. 2010; Morgan et al. 2013), APOE- ϵ 4 is associated with NCI, brain atrophy, and decreases in white matter integrity in older PWH (Chang et al. 2011; Hoare et al. 2013; Panos et al. 2013; Valcour, 2013; Wendelken et al. 2016); even after controlling for HIV-related disease factors (Valcour 2013). A family history of dementia has also been implicated in the development of HAND (Moore et al. 2011). In a post-mortem study, APOE- ϵ 4 genotype moderated the relationship between the presence of A β ₄₂ plaques and increased likelihood of HAND, whereby this relationship was observed in APOE- ϵ 4 carriers but not in non-carriers (Soontornniyomkij et al. 2012).

In conclusion, the rising rate of older PWH presents a major public health concern for the manifestation and possible exacerbation of AD in the context of HIV infection. Multiple biological and neuropsychological features are common to AD and HAND (e.g., episodic memory deficits, chronic inflammation, A β ₄₂ plaques), and thus present a challenge in identifying AD among PWH. Although NCI observed among PWH is typically classified as HAND because of their HIV disease, the true source of impairment may be AD or a combination of HIV and AD pathologies in a subset of older PWH. Similarly, AD pathological hallmarks have been observed in PWH although their manifestation differs in some ways from AD. Thus, it is unclear whether these pathological processes are associated with HAND or AD. Further complicating matters, certain risk factors are common to AD and HAND and some result from HIV itself or ARVs such as vascular abnormalities and insulin resistance. Research is needed to determine whether these common risk factors and overlapping disease processes interact mechanistically to exacerbate both AD and HAND. There are some known differences (e.g., AD-specific recognition memory deficits, p-tau biomarker) and possibly currently-unexplored differences in the biological and clinical profiles of AD and HAND. Research is warranted to further dissociate these AD and HAND profiles and leverage these differences to develop differential diagnostic procedures that can distinguish these phenotypes. Identifying AD in PWH has vast clinical implications. If AD in PWH is erroneously attributed solely to HAND, then this limits and possibly prevents the opportunity to intervene early in the course of AD

when pharmaceutical and cognitive interventions as well as care, financial and legal planning are most effective and better implemented. Alternatively, the identification of convergent pathophysiological pathways in AD and HAND may represent opportunities for common therapeutic interventions to AD and HAND and other neurodegenerative diseases.

Funding This work was supported by salary support for Dr. E.E. Sundermann from the Interdisciplinary Research Fellowship in NeuroAIDS [R25MH081482].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Abdulle S, Mellgren A, Brew BJ, Cinque P, Hagberg L, Price RW, Rosengren L, Gisslen M (2007) CSF neurofilament protein (NFL)—a marker of active HIV-related neurodegeneration. *J Neurol* 254:1026–1032
- Abu-Rumeileh S, Capellari S, Stanzani-Maserati M, Polisch J, Martinelli P, Caroppo P, Ladogana A, Parchi P (2018) The CSF neurofilament light signature in rapidly progressive neurodegenerative dementias. *Alzheimers Res Ther* 10:3
- Achim CL, Adame A, Dumaop W, Everall IP, Masliah E, Neurobehavioral Research C (2009) Increased accumulation of intraneuronal amyloid beta in HIV-infected patients. *J Neuroimmune Pharmacol* 4:190–199
- Aksenov MY, Aksenova MV, Mactutus CF, Booze RM (2010) HIV-1 protein-mediated amyloidogenesis in rat hippocampal cell cultures. *Neurosci Lett* 475:174–178
- 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* 75:111–115
- Ances BM, Benzinger TL, Christensen JJ, Thomas J, Venkat R, Teshome M, Aldea P, Fagan AM, Holtzman DM, Morris JC, Clifford DB (2012) 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. *Arch Neurol* 69:72–77
- Andras IE, Toborek M (2013) Amyloid beta accumulation in HIV-1-infected brain: the role of the blood brain barrier. *IUBMB Life* 65:43–49
- Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE (2005) Influence of HAART on HIV-related CNS disease and neuroinflammation. *J Neuropathol Exp Neurol* 64:529–536
- Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE (2006) 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* 111:529–538
- 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* 69:1789–1799

- Antiretroviral Therapy Cohort C (2017) Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* 4:e349–e356
- Aukrust P, Muller F, Lien E, Nordoy I, Liabakk NB, Kvale D, Espevik T, Froland SS (1999) Tumor necrosis factor (TNF) system levels in human immunodeficiency virus-infected patients during highly active antiretroviral therapy: persistent TNF activation is associated with virologic and immunologic treatment failure. *J Infect Dis* 179:74–82
- Bacioglu M, Maia LF, Preische O, Schelle J, Apel A, Kaeser SA, Schweighauser M, Eninger T, Lambert M, Pilotto A, Shimshek DR, Neumann U, Kahle PJ, Staufenbiel M, Neumann M, Maetzler W, Kuhle J, Jucker M (2016) Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and in neurodegenerative diseases. *Neuron* 91:56–66
- Bakkour A, Morris JC, Wolk DA, Dickerson BC (2013) The effects of aging and Alzheimer's disease on cerebral cortical anatomy: specificity and differential relationships with cognition. *Neuroimage* 76:332–344
- Banks WA (1999) Physiology and pathology of the blood-brain barrier: implications for microbial pathogenesis, drug delivery and neurodegenerative disorders. *J Neuro-Oncol* 5:538–555
- Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC, Dominantly Inherited Alzheimer N (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 367:795–804
- Becker JT, Caldararo R, Lopez OL, Dew MA, Dorst SK, Banks G (1995) Qualitative features of the memory deficit associated with HIV infection and AIDS: cross-validation of a discriminant function classification scheme. *J Clin Exp Neuropsychol* 17:134–142
- Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME (2008) Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. *J Neurosci* 28:4283–4292
- Bonnet F, Amieva H, Marquant F, Bernard C, Bruyand M, Dauchy FA, Mercie P, Greib C, Richert L, Neau D, Catheline G, Dehail P, Dabis F, Morlat P, Dartigues JF, Chene G, Cohort SCA (2013) Cognitive disorders in HIV-infected patients: are they HIV-related? *AIDS* 27:391–400
- Borjabad A, Volsky DJ (2012) Common transcriptional signatures in brain tissue from patients with HIV-associated neurocognitive disorders, Alzheimer's disease, and multiple sclerosis. *J NeuroImmune Pharmacol* 7:914–926
- Bowman GL, Kaye JA, Moore M, Waichunas D, Carlson NE, Quinn JF (2007) Blood-brain barrier impairment in Alzheimer disease: stability and functional significance. *Neurology* 68:1809–1814
- Braak H, Braak E, Bohl J, Bratzke H (1998) Evolution of Alzheimer's disease related cortical lesions. *J Neural Transm Suppl* 54:97–106
- Braskie MN, Toga AW, Thompson PM (2013) Recent advances in imaging Alzheimer's disease. *J Alzheimers Dis* 33(Suppl 1):S313–S327
- Brew BJ (2004) Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. *AIDS* 18(Suppl 1):S75–S78
- Brew BJ, Letendre SL (2008) Biomarkers of HIV related central nervous system disease. *Int Rev Psychiatry* 20:73–88
- Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L (2005) CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. *Neurology* 65:1490–1492
- Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G (2009) Neurodegeneration and ageing in the HAART era. *J NeuroImmune Pharmacol* 4:163–174
- Brouillette MJ, Yuen T, Fellows LK, Cysique LA, Heaton RK, Mayo NE (2016) Identifying neurocognitive decline at 36 months among HIV-positive participants in the CHARTER cohort using group-based trajectory analysis. *PLoS One* 11:e0155766
- Bryant VE, Whitehead NE, Burrell LE 2nd, Dotson VM, Cook RL, Malloy P, Devlin K, Cohen RA (2015) Depression and apathy among people living with HIV: implications for treatment of HIV associated neurocognitive disorders. *AIDS Behav* 19:1430–1437
- Burdo TH, Weiffenbach A, Woods SP, Letendre S, Ellis RJ, Williams KC (2013) Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *AIDS* 27:1387–1395
- Cameron B, Landreth GE (2010) Inflammation, microglia, and Alzheimer's disease. *Neurobiol Dis* 37:503–509
- CDC (2017) HIV surveillance report, 2016. Centers for Disease Control and Prevention
- Chang L, Andres M, Sadino J, Jiang CS, Nakama H, Miller E, Ernst T (2011) Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. *Neuroimage* 58:1017–1027
- Chaponda M, Aldhouse N, Kroes M, Wild L, Robinson C, Smith A (2018) Systematic review of the prevalence of psychiatric illness and sleep disturbance as co-morbidities of HIV infection in the UK. *Int J STD AIDS* 29:704–713
- 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
- Cohen RA, Harezlak J, Gongvatana A, Buchthal S, Schifitto G, Clark U, Paul R, Taylor M, Thompson P, Tate D, Alger J, Brown M, Zhong J, Campbell T, Singer E, Daar E, McMahon D, Tso Y, Yiannoutsos CT, Navia B, Consortium HIVN (2010) Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *J Neuro-Oncol* 16:435–444
- Cohen RA, Seider TR, Navia B (2015) HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimers Res Ther* 7:37
- Cortes N, Andrade V, Maccioni RB (2018) Behavioral and neuropsychiatric disorders in Alzheimer's disease. *J Alzheimers Dis* 63:899–910
- Cysique LA, Maruff P, Bain MP, Wright E, Brew BJ (2011) HIV and age do not substantially interact in HIV-associated neurocognitive impairment. *J Neuropsychiatry Clin Neurosci* 23:83–89
- de Bruijn RF, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* 12:130
- Deeks SG (2011) HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 62:141–155
- Deeks SG, Phillips AN (2009) HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 338:a3172
- Durand M, Chartrand-Lefebvre C, Baril JG, Trottier S, Trottier B, Harris M, Walmsley S, Conway B, Wong A, Routy JP, Kovacs C, MacPherson PA, Monteith KM, Mansour S, Thanassoulis G, Abrahamowicz M, Zhu Z, Tsoukas C, Ancuta P, Bernard N, Tremblay CL, investigators of the Canadian HIV, Aging Cohort S (2017) The Canadian HIV and aging cohort study—determinants of increased risk of cardio-vascular diseases in HIV-infected individuals: rationale and study protocol. *BMC Infect Dis* 17:611
- Duskova K, Nagilla P, Le HS, Iyer P, Thalamuthu A, Martinson J, Bar-Joseph Z, Buchanan W, Rinaldo C, Ayyavoo V (2013) MicroRNA regulation and its effects on cellular transcriptome in human immunodeficiency virus-1 (HIV-1) infected individuals with distinct viral load and CD4 cell counts. *BMC Infect Dis* 13:250
- Eden A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslen M (2007) Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. *J Infect Dis* 196:1779–1783
- Esiri MM, Biddolph SC, Morris CS (1998) Prevalence of Alzheimer plaques in AIDS. *J Neurol Neurosurg Psychiatry* 65:29–33
- Everall I, Vaida F, Khanlou N, Lazzaretto D, Achim C, Letendre S, Moore D, Ellis R, Cherner M, Gelman B, Morgello S, Singer E, Grant I,

- Masliah E, National Neuro ATC (2009) Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. *J Neuro-Oncol* 15:360–370
- Fabbiani M, Ciccarelli N, Tana M, Farina S, Baldonero E, Di Cristo V, Colafigli M, Tamburrini E, Cauda R, Silveri MC, Grima P, Di Giambenedetto S (2013) Cardiovascular risk factors and carotid intima-media thickness are associated with lower cognitive performance in HIV-infected patients. *HIV Med* 14:136–144
- Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, LaRossa GN, Spinner ML, Klunk WE, Mathis CA, DeKosky ST, Morris JC, Holtzman DM (2006) Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann Neurol* 59:512–519
- Fields JA, Spencer B, Swinton M, Qvale EM, Marquine MJ, Alexeeva A, Gough S, Soontornniyomkij B, Valera E, Masliah E, Achim CL, Desplats P (2018) Alterations in brain TREM2 and amyloid-beta levels are associated with neurocognitive impairment in HIV-infected persons on antiretroviral therapy. *J Neurochem*
- Galimberti D, Fenoglio C, Lovati C, Venturelli E, Guidi I, Corra B, Scalabrini D, Clerici F, Mariani C, Bresolin N, Scarpini E (2006) Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. *Neurobiol Aging* 27:1763–1768
- Gelman BB, Schuenke K (2004) Brain aging in acquired immunodeficiency syndrome: increased ubiquitin-protein conjugate is correlated with decreased synaptic protein but not amyloid plaque accumulation. *J Neuro-Oncol* 10:98–108
- Gisslen M, Krut J, Andreasson U, Blennow K, Cinque P, Brew BJ, Spudich S, Hagberg L, Rosengren L, Price RW, Zetterberg H (2009) Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. *BMC Neurol* 9:63
- Gisslen M, Price RW, Andreasson U, Norgren N, Nilsson S, Hagberg L, Fuchs D, Spudich S, Blennow K, Zetterberg H (2016) Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: a cross-sectional study. *EBioMedicine* 3:135–140
- Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, Town T, Tan J (2008) Inflammaging as a prodrome to Alzheimer's disease. *J Neuroinflammation* 5:51
- Gray F, Bazille C, Adle-Biassette H, Mikol J, Moulignier A, Scaravilli F (2005) Central nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral treatment. *J Neuro-Oncol* 11(Suppl 3):16–22
- Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL (2005) Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS* 19:407–411
- Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C (2008) Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J Int Neuropsychol Soc* 14:266–278
- Guillemin GJ, Kerr SJ, Brew BJ (2005) Involvement of quinolinic acid in AIDS dementia complex. *Neurotox Res* 7:103–123
- Hardy DJ, Vance DE (2009) The neuropsychology of HIV/AIDS in older adults. *Neuropsychol Rev* 19:263–272
- Heaton RK, Clifford DB, Franklin DR Jr, 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 (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology* 75:2087–2096
- 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, Group C, Group H (2011) HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neuro-Oncol* 17:3–16
- Helzner EP, Luchsinger JA, Scarmeas N, Cosentino S, Brickman AM, Glymour MM, Stern Y (2009) Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol* 66:343–348
- Hoare J, Westgarth-Taylor J, Fouche JP, Combrinck M, Spottiswoode B, Stein DJ, Joska JA (2013) Relationship between apolipoprotein E4 genotype and white matter integrity in HIV-positive young adults in South Africa. *Eur Arch Psychiatry Clin Neurosci* 263:189–195
- Hodes RJ, Sierra F, Austad SN, Epel E, Neigh GN, Erlandson KM, Schafer MJ, LeBrasseur NK, Wiley C, Campisi J, Sehl ME, Scalia R, Eguchi S, Kasinath BS, Halter JB, Cohen HJ, Demark-Wahnefried W, Ahles TA, Barzilai N, Hurria A, Hunt PW (2016) Disease drivers of aging. *Ann N Y Acad Sci* 1386:45–68
- Holler CJ, Webb RL, Laux AL, Beckett TL, Niedowicz DM, Ahmed RR, Liu Y, Simmons CR, Dowling AL, Spinelli A, Khurgel M, Estus S, Head E, Hersh LB, Murphy MP (2012) BACE2 expression increases in human neurodegenerative disease. *Am J Pathol* 180:337–350
- Horvath S, Levine AJ (2015) HIV-1 infection accelerates age according to the epigenetic clock. *J Infect Dis* 212:1563–1573
- Imp BM, Rubin LH, Tien PC, Plankey MW, Golub ET, French AL, Valcour VG (2017) Monocyte activation is associated with worse cognitive performance in HIV-infected women with virologic suppression. *J Infect Dis* 215:114–121
- Janelidze S, Hertze J, Zetterberg H, Landqvist Waldo M, Santillo A, Blennow K, Hansson O (2016) Cerebrospinal fluid neurogranin and YKL-40 as biomarkers of Alzheimer's disease. *Ann Clin Transl Neurol* 3:12–20
- Jessen H, Allen TM, Streeck H (2014) How a single patient influenced HIV research—15-year follow-up. *N Engl J Med* 370:682–683
- Johnston JA, Liu WW, Todd SA, Coulson DT, Murphy S, Irvine GB, Passmore AP (2005) Expression and activity of beta-site amyloid precursor protein cleaving enzyme in Alzheimer's disease. *Biochem Soc Trans* 33:1096–1100
- Joska JA, Combrinck M, Valcour VG, Hoare J, Leisegang F, Mahne AC, Myer L, Stein DJ (2010) Association between apolipoprotein E4 genotype and human immunodeficiency virus-associated dementia in younger adults starting antiretroviral therapy in South Africa. *J Neuro-Oncol* 16:377–383
- Joubert S, Gour N, Guedj E, Didic M, Gueriot C, Koric L, Ranjeva JP, Felician O, Guye M, Ceccaldi M (2016) Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. *Cortex* 74:217–232
- Jucker M, Walker LC (2011) Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann Neurol* 70:532–540
- Kadiu I, Glanzner JG, Kipnis J, Gendelman HE, Thomas MP (2005) Mononuclear phagocytes in the pathogenesis of neurodegenerative diseases. *Neurotox Res* 8:25–50
- Kamat R, Doyle KL, Iudicello JE, Morgan EE, Morris S, Smith DM, Little SJ, Grant I, Woods SP, Translational Methamphetamine ARCG (2016) Neurobehavioral disturbances during acute and early HIV infection. *Cogn Behav Neurol* 29:1–10
- Karr JE, Graham RB, Hofer SM, Muniz-Terrera G (2018) When does cognitive decline begin? A systematic review of change point studies on accelerated decline in cognitive and neurological outcomes preceding mild cognitive impairment, dementia, and death. *Psychol Aging* 33:195–218
- Kim J, Yoon JH, Kim YS (2013) HIV-1 Tat interacts with and regulates the localization and processing of amyloid precursor protein. *PLoS One* 8:e77972
- Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A (2001) Midlife

- vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322:1447–1451
- Kovalevich J, Langford D (2012) Neuronal toxicity in HIV CNS disease. *Future Virol* 7:687–698
- Krut JJ, Zetterberg H, Blennow K, Cinque P, Hagberg L, Price RW, Studahl M, Gisslen M (2013) Cerebrospinal fluid Alzheimer's biomarker profiles in CNS infections. *J Neurol* 260:620–626
- Lam FC, Liu R, Lu P, Shapiro AB, Renoir JM, Sharom FJ, Reiner PB (2001) Beta-amyloid efflux mediated by p-glycoprotein. *J Neurochem* 76:1121–1128
- Li L, Zhang X, Yang D, Luo G, Chen S, Le W (2009) Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. *Neurobiol Aging* 30:1091–1098
- Liao Y, Qi XL, Cao Y, Yu WF, Ravid R, Winblad B, Pei JJ, Guan ZZ (2016) Elevations in the levels of NF-kappaB and inflammatory chemotactic factors in the brains with Alzheimer's disease—one mechanism may involve alpha3 nicotinic acetylcholine receptor. *Curr Alzheimer Res* 13:1290–1301
- Liu D, Cao B, Zhao Y, Huang H, McIntyre RS, Rosenblat JD, Zhou H (2018) Soluble TREM2 changes during the clinical course of Alzheimer's disease: a meta-analysis. *Neurosci Lett* 686:10–16
- Lohse N, Hansen AB, Gerstoft J, Obel N (2007) Improved survival in HIV-infected persons: consequences and perspectives. *J Antimicrob Chemother* 60:461–463
- Lovell MA, Markesbery WR (2007) Oxidative damage in mild cognitive impairment and early Alzheimer's disease. *J Neurosci Res* 85:3036–3040
- Lowther K, Selman L, Harding R, Higginson IJ (2014) Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): a systematic review. *Int J Nurs Stud* 51:1171–1189
- Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R (2005) Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 65:545–551
- Maccioni RB, Munoz JP, Barbeito L (2001) The molecular bases of Alzheimer's disease and other neurodegenerative disorders. *Arch Med Res* 32:367–381
- Maezawa I, Zimin PI, Wulff H, Jin LW (2011) Amyloid-beta protein oligomer at low nanomolar concentrations activates microglia and induces microglial neurotoxicity. *J Biol Chem* 286:3693–3706
- Maki PM, Rubin LH, Valcour V, Martin E, Crystal H, Young M, Weber KM, Manly J, Richardson J, Alden C, Anastos K (2015) Cognitive function in women with HIV: findings from the Women's Interagency HIV Study. *Neurology* 84:231–240
- Masters MC, Ances BM (2014) Role of neuroimaging in HIV-associated neurocognitive disorders. *Semin Neurol* 34:89–102
- May MT, Ingle SM (2011) Life expectancy of HIV-positive adults: a review. *Sex Health* 8:526–533
- Mega MS, Cummings JL, Fiorello T, Gombin J (1996) The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 46:130–135
- Mellgren A, Price RW, Hagberg L, Rosengren L, Brew BJ, Gisslen M (2007) Antiretroviral treatment reduces increased CSF neurofilament protein (NFL) in HIV-1 infection. *Neurology* 69:1536–1541
- Meng XF, Yu JT, Wang HF, Tan MS, Wang C, Tan CC, Tan L (2014) Midlife vascular risk factors and the risk of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 42:1295–1310
- Milanini B, Valcour V (2017) Differentiating HIV-associated neurocognitive disorders from Alzheimer's disease: an emerging issue in geriatric NeuroHIV. *Curr HIV/AIDS Rep* 14:123–132
- Milanini B AI, Javandel S, Joanna H, Paul R, Valcour V (2016). Discriminant analysis of neuropsychological testing differentiates HIV-associated neurocognitive disorder from mild cognitive impairment due to Alzheimer's disease. In: International Society of NeuroVirology: Toronto, Canada
- Milanini B, Catella S, Perkovich B, Esmaeili-Firidouni P, Wendelken L, Paul R, Greene M, Ketelle R, Valcour V (2017) Psychiatric symptom burden in older people living with HIV with and without cognitive impairment: the UCSF HIV over 60 cohort study. *AIDS Care* 29:1178–1185
- Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C (2002) The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *J Neurol Sci* 202:13–23
- Mocchetti I, Bachis A, Esposito G, Turner SR, Taraballi F, Tasciotti E, Paige M, Avdoshina V (2014) Human immunodeficiency virus-associated dementia: a link between accumulation of viral proteins and neuronal degeneration. *Curr Trends Neurol* 8:71–85
- Moore DJ, Arce M, Moseley S, McCutchan JA, Marquie-Beck J, Franklin DR, Vaida F, Achim CL, McArthur J, Morgello S, Simpson DM, Gelman BB, Collier AC, Marra CM, Clifford DB, Heaton RK, Grant I, Charter G, Group H (2011) Family history of dementia predicts worse neuropsychological functioning among HIV-infected persons. *J Neuropsychiatry Clin Neurosci* 23:316–323
- Morgan EE, Woods SP, Letendre SL, Franklin DR, Bloss C, Goate A, Heaton RK, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Ellis RJ, Abramson I, Gamst A, Fennema-Notestine C, Smith DM, Grant I, Vaida F, Clifford DB, Group CHATER (2013) Apolipoprotein E4 genotype does not increase risk of HIV-associated neurocognitive disorders. *J Neuro-Oncol* 19:150–156
- Morgello S, Jacobs M, Murray J, Byrd D, Neibart E, Mintz L, Meloni G, Chon C, Cray J (2018) Alzheimer's disease neuropathology may not predict functional impairment in HIV: a report of two individuals. *J Neuro-Oncol*
- Morris JC, Price JL (2001) Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci* 17:101–118
- Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* 67:122–131
- Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS (2016) Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. *Int J Geriatr Psychiatry* 31:905–911
- Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J (2008) Evolution of HIV dementia with HIV infection. *Int Rev Psychiatry* 20:25–31
- Ortega M, Ances BM (2014) Role of HIV in amyloid metabolism. *J NeuroImmune Pharmacol* 9:483–491
- Panos SE, Hinkin CH, Singer EJ, Thames AD, Patel SM, Sinsheimer JS, Del Re AC, Gelman BB, Morgello S, Moore DJ, Levine AJ (2013) Apolipoprotein-E genotype and human immunodeficiency virus-associated neurocognitive disorder: the modulating effects of older age and disease severity. *Neurobehav HIV Med* 5:11–22
- Patrick C, Crews L, Desplats P, Dumaop W, Rockenstein E, Achim CL, Overall IP, Masliah E (2011) Increased CDK5 expression in HIV encephalitis contributes to neurodegeneration via tau phosphorylation and is reversed with Roscovitine. *Am J Pathol* 178:1646–1661
- Peavy G, Jacobs D, Salmon DP, Butters N, Delis DC, Taylor M, Massman P, Stout JC, Heindel WC, Kirson D et al (1994) Verbal memory performance of patients with human immunodeficiency virus infection: evidence of subcortical dysfunction. The HNRC Group *J Clin Exp Neuropsychol* 16:508–523
- Perry VH, Nicoll JA, Holmes C (2010) Microglia in neurodegenerative disease. *Nat Rev Neurol* 6:193–201
- Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* 256:183–194
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 56:303–308

- Peterson J, Gisslen M, Zetterberg H, Fuchs D, Shacklett BL, Hagberg L, Yiannoutsos CT, Spudis SS, Price RW (2014) Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. *PLoS One* 9:e116081
- Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, Niinisto L, Halonen P, Kontula K (1995) Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. *N Engl J Med* 333:1242–1247
- Qiu C, Fratiglioni L (2015) A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol* 12:267–277
- Rahimian P, He JJ (2017) HIV/neuroAIDS biomarkers. *Prog Neurobiol* 157:117–132
- Rempel HC, Pulliam L (2005) HIV-1 Tat inhibits neprilysin and elevates amyloid beta. *AIDS* 19:127–135
- Roe CM, Fagan AM, Grant EA, Hassenstab J, Moulder KL, Maue Dreyfus D, Sutphen CL, Benzinger TL, Mintun MA, Holtzman DM, Morris JC (2013) Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology* 80:1784–1791
- Rosenmann H (2012) CSF biomarkers for amyloid and tau pathology in Alzheimer's disease. *J Mol Neurosci* 47:1–14
- Royal W 3rd, Cherner M, Burdo TH, Umlauf A, Letendre SL, Jumare J, Abimiku A, Alabi P, Alkali N, Bwala S, Okwuasaba K, Eyzaguirre LM, Akolo C, Guo M, Williams KC, Blattner WA (2016) Associations between cognition, gender and monocyte activation among HIV infected individuals in Nigeria. *PLoS One* 11:e0147182
- Rubin LH, Maki PM, Springer G, Benning L, Anastos K, Gustafson D, Villacres MC, Jiang X, Adimora AA, Waldrop-Valverde D, Vance DE, Bolivar H, Alden C, Martin EM, Valcour VG, Women's Interagency HIVS (2017) Cognitive trajectories over 4 years among HIV-infected women with optimal viral suppression. *Neurology* 89:1594–1603
- Sacktor N, Skolasky RL, Cox C, Selnes O, Becker JT, Cohen B, Martin E, Miller EN, Multicenter ACS (2010) Longitudinal psychomotor speed performance in human immunodeficiency virus-seropositive individuals: impact of age and serostatus. *J Neuro-Oncol* 16:335–341
- Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, Ragin A, Levine A, Miller E (2016) Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. *Neurology* 86:334–340
- Salmon DP (2012) Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. *Curr Top Behav Neurosci* 10:187–212
- Sattler FR, He J, Letendre S, Wilson C, Sanders C, Heaton R, Ellis R, Franklin D, Aldrovandi G, Marra CM, Clifford D, Morgello S, Grant I, McCutchan JA, Group C (2015) Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. *J Acquir Immune Defic Syndr* 68:281–288
- Schouten J, Su T, Wit FW, Kootstra NA, Caan MW, Geurtsen GJ, Schmand BA, Stolte IG, Prins M, Majoie CB, Portegies P, Reiss P, Group AGS (2016) Determinants of reduced cognitive performance in HIV-1-infected middle-aged men on combination antiretroviral therapy. *AIDS* 30:1027–1038
- Scott JC, Woods SP, Carey CL, Weber E, Bondi MW, Grant I, Group HIVNRC (2011) Neurocognitive consequences of HIV infection in older adults: an evaluation of the “cortical” hypothesis. *AIDS Behav* 15:1187–1196
- Sheppard DP, Woods SP, Bondi MW, Gilbert PE, Massman PJ, Doyle KL, Group HIVNRP (2015) Does older age confer an increased risk of incident neurocognitive disorders among persons living with HIV disease? *Clin Neuropsychol* 29:656–677
- Sheppard DP, Iudicello JE, Morgan EE et al (2017) Accelerated and accentuated neurocognitive aging in HIV infection. *J Neurovirol* 23(3):492–500
- Sjogren M, Vanderstichele H, Agren H, Zachrisson O, Edsbacke M, Wikkelso C, Skoog I, Wallin A, Wahlund LO, Marcusson J, Nagga K, Andreasen N, Davidsson P, Vanmechelen E, Blennow K (2001) Tau and Aβ42 in cerebrospinal fluid from healthy adults 21–93 years of age: establishment of reference values. *Clin Chem* 47:1776–1781
- Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A (1996) 15-year longitudinal study of blood pressure and dementia. *Lancet* 347:1141–1145
- Sokolova A, Hill MD, Rahimi F, Warden LA, Halliday GM, Shepherd CE (2009) Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. *Brain Pathol* 19:392–398
- Soontornniyomkij V, Moore DJ, Gouaux B, Soontornniyomkij B, Tatro ET, Umlauf A, Masliah E, Levine AJ, Singer EJ, Vinters HV, Gelman BB, Morgello S, Cherner M, Grant I, Achim CL (2012) Cerebral beta-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE ε4 carriers. *AIDS* 26:2327–2335
- Steinbrink F, Evers S, Buerke B, Young P, Arendt G, Koutsilieri E, Reichelt D, Lohmann H, Husstedt IW, German Competence Network HA (2013) Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. *Eur J Neurol* 20:420–428
- Stern AL, Ghura S, Gannon PJ, Akay-Espinoza C, Phan JM, Yee AC, Vassar R, Gelman BB, Kolson DL, Jordan-Sciutto KL (2018) BACE1 mediates HIV-associated and excitotoxic neuronal damage through an APP-dependent mechanism. *J Neurosci* 38:4288–4300
- Stoff DM, Goodkin K, Jeste D, Marquine M (2017) Redefining aging in HIV infection using phenotypes. *Curr HIV/AIDS Rep* 14:184–199
- Stoll M, Schmidt RE (2003) Immune restoration inflammatory syndromes: the dark side of successful antiretroviral treatment. *Curr Infect Dis Rep* 5:266–276
- Stoll M, Schmidt RE (2004) Immune restoration inflammatory syndromes: apparently paradoxical clinical events after the initiation of HAART. *Curr HIV/AIDS Rep* 1:122–127
- Streit WJ, Mrak RE, Griffin WS (2004) Microglia and neuroinflammation: a pathological perspective. *J Neuroinflammation* 1:14
- Tan IL, Smith BR, Hammond E, Vombrock-Roosa H, Creighton J, Selnes O, McArthur JC, Sacktor N (2013) Older individuals with HIV infection have greater memory deficits than younger individuals. *J Neuro-Oncol* 19:531–536
- Tarawneh R, D'Angelo G, Crimmins D, Herries E, Griest T, Fagan AM, Zipfel GJ, Ladenson JH, Morris JC, Holtzman DM (2016) Diagnostic and prognostic utility of the synaptic marker neurogranin in Alzheimer disease. *JAMA Neurol* 73:561–571
- Tarkowski E, Andreasen N, Tarkowski A, Blennow K (2003) Intrathecal inflammation precedes development of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 74:1200–1205
- Terracciano A, Sutin AR, An Y, O'Brien RJ, Ferrucci L, Zonderman AB, Resnick SM (2014) Personality and risk of Alzheimer's disease: new data and meta-analysis. *Alzheimers Dement* 10:179–186
- Thal DR, Attems J, Ewers M (2014) Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. *J Alzheimers Dis* 42(Suppl 4):S421–S429
- Tierney S, Woods SP, Verduzco M, Beltran J, Massman PJ, Hasbun R (2018) Semantic memory in HIV-associated neurocognitive disorders: an evaluation of the “cortical” versus “subcortical” hypothesis. *Arch Clin Neuropsychol* 33:406–416
- Ting KK, Brew B, Guillemin G (2007) The involvement of astrocytes and kynurenine pathway in Alzheimer's disease. *Neurotox Res* 12:247–262
- Town T, Laouar Y, Pittenger C, Mori T, Szekely CA, Tan J, Duman RS, Flavell RA (2008) Blocking TGF-β-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. *Nat Med* 14:681–687

- Tripathi M, Yadav S, Kumar V, Kumar R, Tripathi M, Gaikwad S, Kumar P, Bal C (2016) HIV encephalitis with subcortical tau deposition: imaging pathology in vivo using F-18 THK 5117. *Eur J Nucl Med Mol Imaging* 43:2456–2457
- 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
- Valcour VG (2013) HIV, aging, and cognition: emerging issues. *Top Antivir Med* 21:119–123
- Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, Holck P, Grove J, Sacktor N (2004) Higher frequency of dementia in older HIV-1 individuals: the Hawaii aging with HIV-1 cohort. *Neurology* 63:822–827
- Valotassiou V, Malamitsi J, Papatriantafyllou J, Dardiotis E, Tsougos I, Psimadas D, Alexiou S, Hadjigeorgiou G, Georgoulas P (2018) SPECT and PET imaging in Alzheimer's disease. *Ann Nucl Med* 32:583–593
- Van Epps P, Kalayjian RC (2017) Human immunodeficiency virus and aging in the era of effective antiretroviral therapy. *Infect Dis Clin N Am* 31:791–810
- van Gorp WG, Miller EN, Marcotte TD, Dixon W, Paz D, Selnes O, Wesch J, Becker JT, Hinkin CH, Mitrushina M et al (1994) The relationship between age and cognitive impairment in HIV-1 infection: findings from the multicenter AIDS cohort study and a clinical cohort. *Neurology* 44:929–935
- Vance DE, Wadley VG, Crowe MG, Raper JL, Ball KK (2011) Cognitive and everyday functioning in older and younger adults with and without HIV. *Clin Gerontol* 34:413–426
- Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M (1999) Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 286:735–741
- Vernooij MW, Smits M (2012) Structural neuroimaging in aging and Alzheimer's disease. *Neuroimaging Clin N Am* 22:33–55 vii–viii
- Wellington H, Paterson RW, Portelius E, Tomqvist U, Magdalinou N, Fox NC, Blennow K, Schott JM, Zetterberg H (2016) Increased CSF neurogranin concentration is specific to Alzheimer disease. *Neurology* 86:829–835
- Wendelken LA, Jahanshad N, Rosen HJ, Busovaca E, Allen I, Coppola G, Adams C, Rankin KP, Milanini B, Clifford K, Wojta K, Nir TM, Gutman BA, Thompson PM, Valcour V (2016) ApoE epsilon4 is associated with cognition, brain integrity, and atrophy in HIV over age 60. *J Acquir Immune Defic Syndr* 73:426–432
- White DA, Taylor MJ, Butters N, Mack C, Salmon DP, Peavy G, Ryan L, Heaton RK, Atkinson JH, Chandler JL, Grant I (1997) Memory for verbal information in individuals with HIV-associated dementia complex. HNRC Group. *J Clin Exp Neuropsychol* 19:357–366
- Wilson RS, Leurgans SE, Boyle PA, Bennett DA (2011) Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch Neurol* 68:351–356
- Xu J, Ikezu T (2009) The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. *J NeuroImmune Pharmacol* 4:200–212
- Yang LB, Lindholm K, Yan R, Citron M, Xia W, Yang XL, Beach T, Sue L, Wong P, Price D, Li R, Shen Y (2003) Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease. *Nat Med* 9:3–4
- Zhang Y, Kwon D, Esmaceli-Firidouni P, Pfefferbaum A, Sullivan EV, Javitz H, Valcour V, Pohl KM (2016) Extracting patterns of morphometry distinguishing HIV associated neurodegeneration from mild cognitive impairment via group cardinality constrained classification. *Hum Brain Mapp* 37:4523–4538
- Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Xu W, Li JQ, Wang J, Lai TJ, Yu JT (2016) The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J Affect Disord* 190:264–271
- Zhou L, Diefenbach E, Crossett B, Tran SL, Ng T, Rizos H, Rua R, Wang B, Kapur A, Gandhi K, Brew BJ, Saksena NK (2010) First evidence of overlaps between HIV-associated dementia (HAD) and non-viral neurodegenerative diseases: proteomic analysis of the frontal cortex from HIV+ patients with and without dementia. *Mol Neurodegener* 5:27