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Pathogenesis of age-related HIV neurodegeneration

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Abstract

People over the age of 50 are the fastest growing segment of the HIV-infected population in the USA. Although antiretroviral therapy has remarkable success controlling the systemic HIV infection, HIV-associated neurocognitive disorder (HAND) prevalence has increased or remained the same among this group, and cognitive deficits appear more severe in aged patients with HIV. The mechanisms of HAND in the aged population are not completely understood; a leading hypothesis is that aged individuals with HIV might be at higher risk of developing Alzheimer's disease (AD) or one of the AD-related dementias (ADRD). There are a number of mechanisms through which chronic HIV disease alone or in combination with antiretroviral therapy and other comorbidities (e.g., drug use, hepatitis C virus (HCV)) might be contributing to HAND in individuals over the age of 50 years, including (1) overlapping pathogenic mechanisms between HIV and aging (e.g., decreased proteostasis, DNA damage, chronic inflammation, epigenetics, vascular), which could lead to accelerated cellular aging and neurodegeneration and/or (2) by promoting pathways involved in AD/ADRD neuropathogenesis (e.g., triggering amyloid β, Tau, or α-synuclein accumulation). In this manuscript, we will review some of the potential common mechanisms involved and evidence in favor and against a role of AD/ADRD in HAND.

Keywords Aging · Alzheimer's disease · HIV-associated cognitive impairment · Neurodegeneration

Introduction

There is a global trend toward a rise of HIV among older adults. In 2013, the Center for Disease Control (CDC) estimated that 42% of Americans living with HIV were at least 50 years, 25% were at least 55 years old, and 6% were at least 65 years old (CDC 2018). With longer life expectancy, individuals living with chronic HIV are at greater risk of developing age-related metabolic, cardiovascular, neoplastic, and neurodegenerative disorders. Common neurodegenerative disorders of the aging population leading to severe neurological and psychiatric impairment include Alzheimer's disease (AD), Lewy body disease (LBD), vascular cognitive impairment-dementia (VCID), and frontotemporal dementia (FTD). It is estimated that in the USA alone approximately 5.3 million people age 65 or older live with AD and that by the year 2050, this number will triple (Hebert et al. 2013). Considerable overlap among these disorders is observed, in particular in those with advanced age (Boyle et al. 2018; Robinson et al. 2018).

Alzheimer's disease is the sixth most common cause of death in the USA and AD and related dementing disorders (ADRD) including LBD, FTD, and VCID are the only top causes of death for which no prevention or cure is currently available (Alzheimer's Association 2013). For this reason, the USA and other countries have developed national plans to address this public health emergency (International 2016; Secretary and Evaluation 2016). In 2011, the US Congress signed into law the National Alzheimer's Project Act (NAPA) (Public Law 111-375). The Act called for the creation of a National Plan to Address AD/ADRD and one of its major goals is to accelerate the development of treatments that would prevent, halt, or reverse the course of AD/ADRD by the year 2025. In support of the National Plan, the US Congress has appropriated over two billion dollars to NIA/NIH to advance the research agenda to date.

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The key to developing such treatments resides in better understanding the mechanisms of neurodegeneration and thereby developing disease-modifying therapeutics. The neurodegenerative process is characterized by the progressive accumulation of proteins (including the formation of inclusions and trans-cellular propagation), damage of selective synaptic circuitries leading to neuronal loss, neuroinflammation with astrogliosis and microgliosis, myelin degradation, and vascular alterations. In view of the genetic and neuropathological evidence, research in AD/ADRD has focused on better understanding the abnormal accumulation of proteins with amyloid properties (beta pleated sheets) in the brain. However, there is growing evidence that age-related factors also play a key role. For example in AD, Aβ, and Tau accumulate in the neocortex and hippocampus (Crews and Masliah 2010), while in LBD, which represents an heterogeneous group of disorders that includes Parkinson's disease (PD), PD dementia (PDD), and dementia with Lewy bodies (DLB) (Donaghy and McKeith 2014; McKeith et al. 2004; McKeith 2000). The neuronal protein α-synuclein (α-syn) accumulates in the cortical striato-nigral system and other subcortical nuclei (Goedert et al. 2001; Spillantini 1999).In FTD, either Tau or TDP-43 aggregates are found in multiple cortical regions (Ferrari et al. 2011; Goedert et al. 2012). Moreover, in FTD cases with the GGGGCC expansion mutation located in intron 1 of the C9ORF72 gene, there is an accumulation of TDP43 and repeat-associated non-ATG (RAN) translation proteins (Zu et al. 2013) in the affected brain regions. In addition, it is now evident that α-syn accumulates in the amygdala in AD (Winslow et al. 2014) and TDP-43 aggregates are found in the limbic system in AD, DLB (Arai et al. 2009) and hippocampal sclerosis in older affected individuals (James et al. 2016; Murray et al. 2014). In VCID, there is ischemic micro-vessel disease that can be accompanied by accumulation of amyloid (Vinters et al. 2018).

The mechanisms leading to proteinopathy in these disorders (progressive accumulation of Aβ, Tau, α-syn, and TDP-43) is not completely understood, however, evidence supports the hypothesis that genetic and environmental factors might result in an imbalance in the rates of synthesis, aggregation, and clearance of these proteins resulting in the generation of toxic oligomers, protofibrils, and fibrils with amyloid characteristics that could propagate from cell to cell in a prion-like fashion (Valera et al. 2016). The contribution of AD/ADRD to the neurocognitive impairment in older individuals with HIV is not fully understood. In this manuscript, we will review some of the potential common mechanisms involved and evidence in favor and against a role of AD/ADRD in HIV-associated neurocognitive disorders (HAND).

HIV neuropathogenesis in the antiretroviral era

It is estimated that there are over 30 million people living with HIV worldwide and in the US, the aging population represents one of the fastest growing population with HIV (Scott et al. 2011). A considerable proportion of patients with HIV, especially those with advancing age, develop cognitive impairment that can range from mild to severe disruptions, which jointly are now denominated as HAND (Morgan et al. 2012). In the pre-highly active antiretroviral therapy (HAART) era, it was recognized that HIV can penetrate the blood-brain barrier (BBB) resulting in HIV encephalitis (HIVE) that could manifest clinically as HAND, which manifests as dementia at the extreme end of the spectrum (Crews et al. 2009; Ellis et al. 2007; Morgello 2018; Sillman et al. 2018) (Fig. 1a). At the time, neurological manifestations were also reported in patients with HIV, which were usually the result of opportunistic infections (Fig. 1b).

In the central nervous system (CNS), macrophages and microglial cells have been identified as a primary reservoir for HIV infection (Gendelman et al. 1997; Gonzalez-Scarano and Martin-Garcia 2005; Haas et al. 2000; Wiley et al. 1996) with productive infection also detected in astrocytes (Carroll-Anzinger and Al-Harthi 2006). In the pre-HAART era, classical HIVE (Morgello 2018; Sillman et al. 2018) was characterized by the presence of microglial nodules, multinucleated giant cells (MNGC), severe astrogliosis, myelin loss (Budka et al. 1991), neurodegenerative pathology with synaptic-dendritic damage (Everall et al. 1999), and selective loss of calbindin and excitatory neurons in the neocortex, hippocampus, and striatum (Masliah et al. 1995) (Fig. 1).

Modern treatments with HAART resulted in HIV suppression and immune recovery; consequently the pathology of HIVE has shifted from subcortical regions towards a cortical pattern (Brew 2004; Soontornniyomkij et al. 2018) and from a subacute, rapidly progressive disorder to a more subtle, chronic neurodegenerative process (Everall et al. 2005; Xu and Ikezu 2009) (Fig. 1b). Viral levels in the CNS are lower or undetectable and neuropathologically, these patients usually show diffuse astrogliosis, some microglial nodules, white matter alterations, and vascular changes with peri-vascular lymphocytic infiltration; however, MNGC are not present (Desplats et al. 2013; Fields et al. 2013) (Fig. 1b).

In spite of the successful use of HAART to control systemic HIV infections, the prevalence of mild to moderate HAND (Budka et al. 1987; Cherner et al. 2007; Gendelman et al. 1997; Heaton et al. 2010; Wiley and Achim 1994) has remained the same or increased (Heaton et al. 2011a; Joska et al. 2010). In particular, among people over the age of 50, age and HIV synergize to worsen cognitive performance (Morgan et al. 2012). The mechanisms of neurodegeneration in HAND are not completely understood; however, a number of studies have proposed that HIV proteins such as gp120, Tat, and nef activate neuro-inflammatory and apoptotic pathways (Kaul et al. 2001), dysregulate calcium homeostasis by abnormally activating glutamate receptors (Lipton 1994; Nath et al. 2000), promote oxidative stress (Nath 2002; Norman et al.
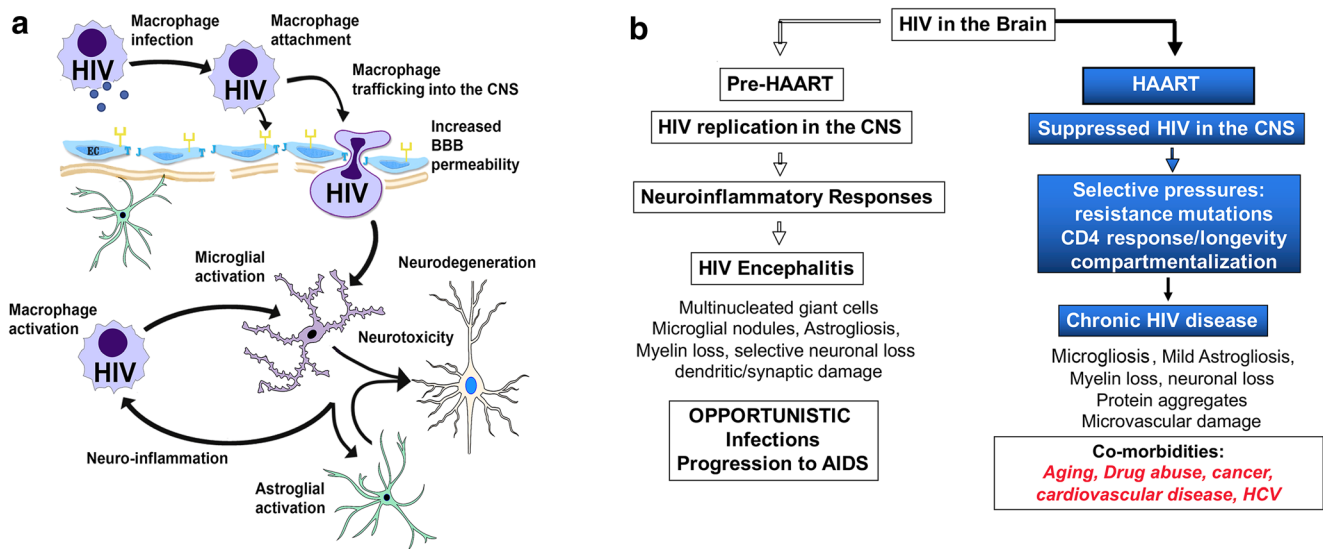
Fig. 1 Mechanisms of neurodegeneration in HIV-associated neurocognitive disorders (HAND) in the pre- and highly active antiretroviral (HAART) eras. **a** Schematic representation of mechanisms leading to HIV encephalitis and neurodegeneration initiating with trafficking of HIV-infected macrophages through an injured blood-brain barrier followed by activation and infection of microglial and astroglial cells resulting in neurotoxicity and inflammation with synapto-dendritic damage and selective neuronal damage. **b** In the pre-HAART era, HIV CNS pathology was characterized by the presence of microglial nodules, multinucleated giant cells, severe astrogliosis, myelin loss, and neurodegenerative pathology accompanied by opportunistic infections. Modern treatments with HAART results in HIV suppression and immune recovery; the pathology has shifted to a more subtle, chronic neurodegenerative process with lower or undetectable HIV in the CNS and diffuse astrogliosis, some microglial nodules, white matter alterations and vascular changes accompanied by comorbid conditions associated with aging

2008), deplete neurotrophic factors (Fields et al. 2014; Mocchetti et al. 2008) and cause vascular damage (Soontornniyomkij et al. 2014) (Fig. 1a). Remarkably, recent studies have shown that regardless of effective CNS viral suppression with HAART, neurotoxic HIV proteins, such as Tat, are persistently expressed in the brain of HIV-infected individuals (Johnson et al. 2013). Moreover, we have shown that with HAART antiretroviral therapy, prolonged viral suppression might be associated with epigenetic alterations mediated by transcription factors that suppress HIV such as BCL11b potentially resulting in chronic neuroinflammation (Desplats et al. 2013).

In older individuals with HIV, additional mechanisms intrinsic to the aging process such as defective proteostasis, altered stress response, epigenetic alterations, macromolecular damage, cellular senescence, inflammation, and stem cell deficits might be also at play (Fig. 2). Together, these mechanisms are thought to be the corner-stones of aging and are studied under the umbrella of geroscience (Kennedy et al. 2014; Sierra 2016). Interestingly, brain aging and neuronal damage in individuals with chronic HIV infection are aggravated, but in contrast, early HAART treatment ameliorates brain aging in well-controlled HIV infection (Boban et al. 2018) (Fig. 2). Thus, most of our understanding of HIV neuropathogenesis is largely based on clinical outcomes that were predominantly seen in the era preceding the development of antiretroviral therapy. Moreover, the majority of basic neuro-HIV research has focused on evaluating neuronal damage in the context of active viral replication and outcomes related to HIVE. However, it is critical to examine neuronal impairment caused by HIV in the context of viral suppression and antiretroviral therapies. There is an urgent need to bridge the gap between pathogenesis research and observed clinical outcomes. As a result of a major demographic shift in the HIV-infected population in the USA, there is also a critical need to better define the underlying pathophysiology of neurodegenerative processes, neurological complications, and neurocognitive decline accompanying HIV during the course of aging.

Common mechanisms of neurodegeneration in aging and HIV

With the advent of HAART, HIV disease has transitioned from a subacute, rapidly progressive condition to a slowly advancing, chronic disorder in which the aging processes synergize with the pathogenic mechanisms driven by HIV in the CNS (Fig. 1b). Remarkably, cellular and molecular mechanisms involved in the aging process including defective proteostasis, mitochondrial abnormalities, epigenetic alterations, DNA damage, cellular senescence, and stem cell defects have also been also shown to be driven by HIV, leading to the concept that HIV might accelerate the aging process or hijack aging mechanisms (Fig. 2). Increased effects of aging in the brain in HAART treated HIV cases can be predicted using
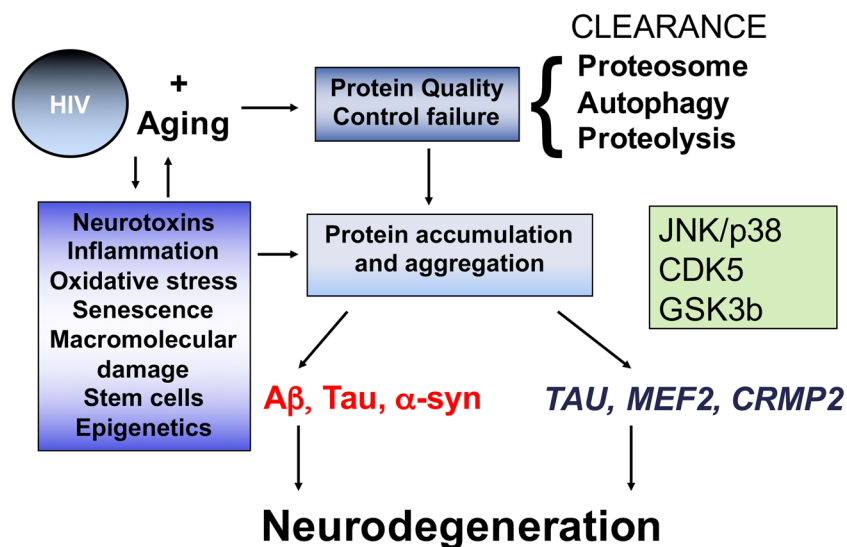
Fig. 2 Potential mechanisms of neurodegeneration in HIV and aging. Common pathways involved in aging and chronic HIV disease in the CNS might interact leading to neurodegeneration. Such mechanisms include defective proteostasis (e.g., altered proteasome, proteolysis, autophagy), mitochondrial abnormalities, epigenetic alterations, DNA damage, cell senescence, neuroinflammation, oxidative stress, and stem cell defects. Together, these alterations might lead to abnormal protein accumulation (Aβ, Tau, α-synuclein) and hyperactivation of signaling pathways (e.g., CDK5, JNK) involved in neuronal damage

neuroimaging. Recent studies have shown that age exacerbates HIV-associated white matter abnormalities and loss of fronto-subcortical white matter integrity (Seider et al. 2016). In contrast, a more recent study found that the extent of increased brain aging related to cognitive deficits. However, predicted brain age difference did not correlate with chronological age or duration of HIV infection, suggesting that HIV disease may accentuate rather than accelerate brain aging (Cole et al. 2017). Moreover, it has been proposed that some of the mechanisms of action of antiretroviral drugs, such as reverse transcription, protease inhibition, and metabolic effects, may also contribute to this cascade (Soontornniyomkij et al. 2018).

In terms of epigenetic alterations, recent studies have investigated DNA methylation (Levine et al. 2016) using the Illumina Infinium Human Methylation 450 K platform, to study biological aging in HIV+ brains. The purpose behind these studies was to compare biological age, determined via the epigenetic clock, with chronological age to obtain a measure of age acceleration, which was then compared between those with HAND and neurocognitively normal individuals. The normal control and HAND groups did not differ with regard to demographical, pathological, or virologic measures. HAND was associated with accelerated aging relative to neurocognitively normal individuals, with an average relative acceleration of 3.5 years. These results suggest that the increased risk of a neurocognitive disorder due to HIV might be mediated by an epigenetic aging mechanism (Levine et al. 2016).

The role of stem cell alterations in aging and neuro-HIV is not completely clear given that neurogenesis in the adult human CNS is a subject of debate (Kuhn et al. 2018). However, alterations in adult neurogenesis have been noted in the hippocampus of HIV-infected individuals and could be related to HAND (Ferrell and Giunta 2014). Similarly, in vitro studies have shown that HIV proteins such as Tat and gp120 (Avraham et al. 2015) arrest proliferation and development of neuro-stem cells (Mishra et al. 2010; Yao et al. 2012). In vitro neuronal precursor cell (NPC)-derived neurosphere assays showed that Tat-containing conditioned media from astrocytes or recombinant Tat protein inhibited NPC proliferation and migration and altered NPC differentiation (Fan et al. 2016). In vivo studies in conditional tg mice have suggested similar results. For example, in the doxycycline-inducible and astrocyte-specific HIV-1 Tat tg mice (iTat), Tat expression in glial cells resulted in a reduction in the numbers and maturation of neuron progenitor cells (NPCs) in mouse hippocampus. This occurs via a mechanism involving Notch signaling since the Notch signaling inhibitor N-[N-(3,5-difluorophenacetyl)-l-alanyl]-S-phenylglycine t-butyl ester (DAPT) rescued the neurogenesis defects in the iTat mice (Fan et al. 2016); this may be a possible therapeutic approach for HAND in the aging population.

Another interesting process in which HIV and aging might overlap is disruption of proteostasis, a protein quality control mechanism involved in protein folding and clearance of protein aggregates (Fig. 2). The protein clearance pathway includes mechanisms such as direct degradation of proteins by proteases, the proteasome, or via lysosomal pathways such as autophagy (Cuervo 2004). Studies in the brains of patients with HIV, as well as in vitro work have shown that HIV proteins like Tat and gp120 could inhibit proteases such as

neprilysin and IDE that degrade amyloid beta protein (Pulliam 2009). These studies have also shown widespread alterations in components of the proteasomal machinery leading to synaptic alterations (Nguyen et al. 2010). Moreover, recent studies have shown that HIV proteins (e.g., Tat, gp120, and nef) might interfere with protein quality control and clearance pathways such as autophagy (Alirezaei et al. 2008a; Alirezaei et al. 2008b; Fields et al. 2015a; Fields et al. 2013; Zhou et al. 2011) (Fig. 2).

Autophagy is a complex process that involves nucleation, initiation, elongation, and termination proteins. Initially, a phagophore forms and develops into the autophagosome, a double-membrane sac that delivers cytoplasmic material to the lysosomal compartment for degradation (Codogno et al. 2012). Deficits in autophagy have been described in AD (Nixon et al. 2005; Pickford et al. 2008), Parkinson's disease (PD) (Crews et al. 2010; Cuervo et al. 2004) and other aging-related disorders (Cuervo 2004). Specifically, the autophagy nucleation protein beclin-1 and closure protein light chain (LC) 3 have been implicated in human disease (Crews et al. 2010; Gozuacik and Kimchi 2004; Jaeger and Wyss-Coray 2010). Similarly, neurodegeneration has been linked to defects in autophagy in patients with HIV (Alirezaei et al. 2008a, b; Fields et al. 2013, 2015a; Zhou et al. 2011) (Fig. 2).

Interestingly, in the brains of patients with HIVE under the age of 50 years and in young transgenic (tg) mice expressing HIV-gp120 protein (gp120 tg) (Toggas et al. 1994) autophagy was upregulated while in the brains of aged patients with HIVE or aged Tat and gp120 tg mice autophagy was downregulated (Fields et al. 2015a; Fields et al. 2013). Moreover, activation of autophagy by beclin-1 gene transfer (Fields et al. 2013) or treatment with rapamycin ameliorated the neurodegenerative phenotype (Fields et al. 2015a). HIV might alter autophagy at various stages including vesicle formation, nucleation, and elongation (Campbell and Spector 2013; Spector and Zhou 2008). The alterations in the autophagy pathway mediated by Tat, gp120, and nef might depend on the cell cycle of HIV, with autophagy upregulation during the initial events and downregulation during the permissive stage of the infection (Campbell and Spector 2013). Nef has been shown to bind beclin-1 blocking the formation of autophagic vacuoles (Kyei et al. 2009) and Tat has been shown to inhibit autophagosome maturation and acidification (Fields et al. 2015a). Likewise, in vivo studies in iTat tg mice showed increased autophagosome accumulation in neurons, altered LC3II levels, and neurodegeneration (Fields et al. 2015a). These effects were reversed by rapamycin treatment. Tat protein may induce autophagosome and lysosome fusion through interaction with LAMP2A leading to abnormal neuronal autophagy function and dysregulated degradation of critical intracellular (Fields et al. 2015a; Fields et al. 2017). Alterations in these protein clearance mechanisms might lead to abnormal accumulation of proteins associated with AD/ADRD,

neuroinflammation, oxidative stress, and mitochondrial alterations (Fig. 2).

Neurodegenerative disorders in aged patients with HAND

With the growth of the aged HIV population in the USA, which already includes over 1 million individuals, there is an urgent need to better understand the contribution of AD and related dementias (e.g., LBD, FTD, and VCID) to HAND and to what extent the HIV-associated neuropathology and AD/ADRD overlap. Moreover, we need to know if HIV in the older population augments the risk for AD/ADRD and to what extent chronic viral suppression, viral silencing, HAART, and comorbidities (e.g., alcohol and drug abuse, HVC) might contribute to increased risk of HAND and AD/ADRD in these individuals. For instance, individuals with a history of alcohol abuse showed the most severe cognitive deficits and older age was also associated with poor cognitive performance (Cohen et al. 2018; Zahr 2018) In this context, in 2018 the National Institute on Aging (NIA) in collaboration with the National Institute of Mental Health (NIMH) and the Office of AIDS Research (OAR) published a call for applications (RFA-AG-18-023) to help address these questions affecting the aging population with HIV in the USA.

Previous studies have shown that HAND could be more persistent and severe in the older population (Becker et al. 2004; Heaton et al. 2011b; Valcour and Paul 2006). For example, it has been shown that subjective cognitive impairment (SCI) may be a predictor of more severe neurocognitive impairment. Among HIV+ individuals, SCI was associated with lower performance-based learning and delayed memory scores and worsening global everyday functioning, indicating an increased risk for developing major neurocognitive disorders as these HIV+ individuals age (Sheppard et al. 2018). Moreover, a recent study showed that HIV-infected individuals over the age of 60 years who have at least one ApoE ε4 allele displayed more severe HAND and evidence of brain atrophy by MRI suggesting an age-related exacerbation of HIV-related pathology (Wendelken et al. 2016). This is consistent with previous studies showing that the presence of ApoE ε4 allele predicted the presence of amyloid plaques and cognitive impairment in HIV patients (Soontornniyomkij et al. 2012). A recent study has reviewed the evidence for the influence of aging and ApoE status on HIV-associated neurocognitive impairment; they conclude that HIV-infected individuals are clearly living longer with HIV, and therefore factors related to aging need to be investigated in the context of effective HAART (Geffin and McCarthy 2018a; Geffin and McCarthy 2018b).

There are a number of mechanisms through which chronic HIV disease alone or in combination with antiretroviral

therapy and other co-morbidities (e.g., drug use, HCV) might be contributing to HAND in older individuals, including (1) synergy between overlapping pathogenic mechanisms involving HIV and aging that could lead to accelerated cellular aging and neuronal cell death and/or (2) by promoting pathways involved in AD/ADRD neuropathogenesis (e.g., triggering Aβ protein, Tau of α-syn accumulation) (Figs. 2 and 3). These two pathways can act independently or cooperatively leading to neurodegeneration of selective populations and HAND in the aging population. In the previous section, we described some of the common mechanisms involving chronic HIV disease and aging including decreased proteostasis, DNA damage, chronic inflammation, and epigenetic dysregulation (Levine et al. 2016) that could lead to neurodegeneration (Fig. 2). Moreover, abnormal functioning of clearance pathways including proteolysis (Pulliam 2009), proteasome (Nguyen et al. 2010), and autophagy (Zhou et al. 2011) might result in accumulation of Aβ (Achim et al. 2009), α-syn (Ebrahimi-Fakhari et al. 2011; Everall et al. 2009; Khanlou et al. 2009), and Tau proteins (Patrick et al. 2011) in aged patients with HIV (Fig. 2).

For example, autopsy studies have shown accumulation of Aβ deposits forming diffuse plaques in the frontal cortex and hippocampus of aged HIV cases (Achim et al. 2009) (Fig. 3a), increased intra-neuronal granular Aβ immunoreactivity associated with lysosomes and axons (Green et al. 2005), intra-neuronal phosphorylated Tau aggregates mimicking pre-tangles (Patrick et al. 2011) (Fig. 3b), and α-syn accumulating in the striato-nigral system forming Lewy body-like inclusions and dystrophic neurites (Ebrahimi-Fakhari et al. 2011; Everall et al. 2009; Khanlou et al. 2009) (Fig. 3c) in aged patients with HIV. Consistent with these findings, immunoblot analysis of frontal cortex samples from young (less than 50 years old) and older patients with HIV showed that Aβ accumulates as a dimer (Fig. 3d, e) while α-syn accumulates as monomers and trimers (Fig. 3d, f). Older HIV cases displaying Aβ, Tau, or α-syn protein accumulation often display clinical features of HAND, as well as motor deficits, but no definitive correlation between the severity of the pathology and the neurological alterations have been found. The strongest microanatomical correlate to the cognitive impairment seen in aged patients with HIV is the extent of the damage to synapses and dendrites in the neocortex and hippocampus (Levine et al. 2016; Moore et al. 2006). In addition to the parenchymal diffuse amyloid deposits, congophilic amyloid angiopathy (CAA) has been reported in 6.7% of older HIV cases and in 4.5% of 22 controls, always in association with Aβ plaques and with ApoE ε4 predicting amyloid deposition and HAND (Soontornniyomkij et al. 2012). In terms of the amyloid deposits in these cases, it is worth mentioning that they resemble lesions found in early stages of AD but are not sufficient to meet criteria of AD/ADRD, with the exception of a few cases (Fig. 3a). For instance, we recently reported the case of a 79-year-old man with HIV who presented with short-term memory deficits, increased challenges managing finances, an episode of getting lost, and motor slowing when writing and walking. HIV infection was diagnosed 14 months prior (Hellmuth et al. 2018). He was treated with HAART and had some initial memory improvements however his cognitive impairment re-appeared despite undetectable plasma HIV RNA levels. He developed worsening cognitive status consistent with dementia and parkinsonism and died 4 years after the initial diagnosis of HIV due to cardiovascular failure caused by aortic stenosis (Hellmuth et al. 2018). Neuropathologically, there was severe cerebral atrophy, neuronal loss, and gliosis in the neocortex, hippocampus and *substantia nigra* with abundant plaques and tangles to warrant the diagnosis of AD, consistent with Braak stage VI. There were no Lewy bodies, glial cytoplasmic inclusions, TDP43 inclusions, microglial nodules, or multinucleated giant cells (Hellmuth et al. 2018). Thus, a case like this raises the question as to what extent the AD neuropathology was the source of HAND and if this patient already had pre-clinical AD and the HIV infection merely accelerated or exacerbated AD. Moreover, one could argue that this was a classical AD case in an aged individual in which HIV had no contribution. The rapid progression, severity, and closeness of the onset of neurological alterations and HIV seropositivity argue against this possibility. In a more recent study from the Manhattan HIV Brain Bank, the autopsy results in two aged individuals treated with HAART and virally suppressed were reported. One showed AD neuropathology and age-related Tau astrogliopathy (ARTAG). She was homozygous for APOE ε3/ε3. The second also displayed ARTAG and cerebral congophilic angiopathy. She was an APOE ε3/ε4 heterozygote. They conclude that in aged individuals in the setting of HIV, AD neuropathology may occur with or without symptomatic cognitive dysfunction (Morgello 2018).

Other neuropathological features associated with HIV that might explain HAND in the older population includes neuroinflammation, synaptic and dendritic degeneration, and vascular disease. Interestingly, in spite the fact that HIV levels in the brains of older individuals were lower compared to younger cases with HIVE, the levels of astrogliosis, microgliosis, and synaptic-dendritic degeneration were greater in HIV cases over 50 years of age (Fields et al. 2013). Patients with HIV and motor alterations have also been shown to display degeneration of the striato-nigral system, while those with HAND display degeneration of pyramidal (Crews et al. 2009) and inhibitory neurons in the neocortex and hippocampus (Everall et al. 1999), age might exacerbate this phenotype. Similarly, other studies have concluded that gliosis and cerebrovascular disease are common brain pathologies among older HIV+ patients in the late HAART era and that cerebrovascular disease, interferon responses, and neuroinflammation are likely factors contributing to brain aging and HAND in older HIV+ patients on current HAART regimens (Solomon et al. 2017). However,
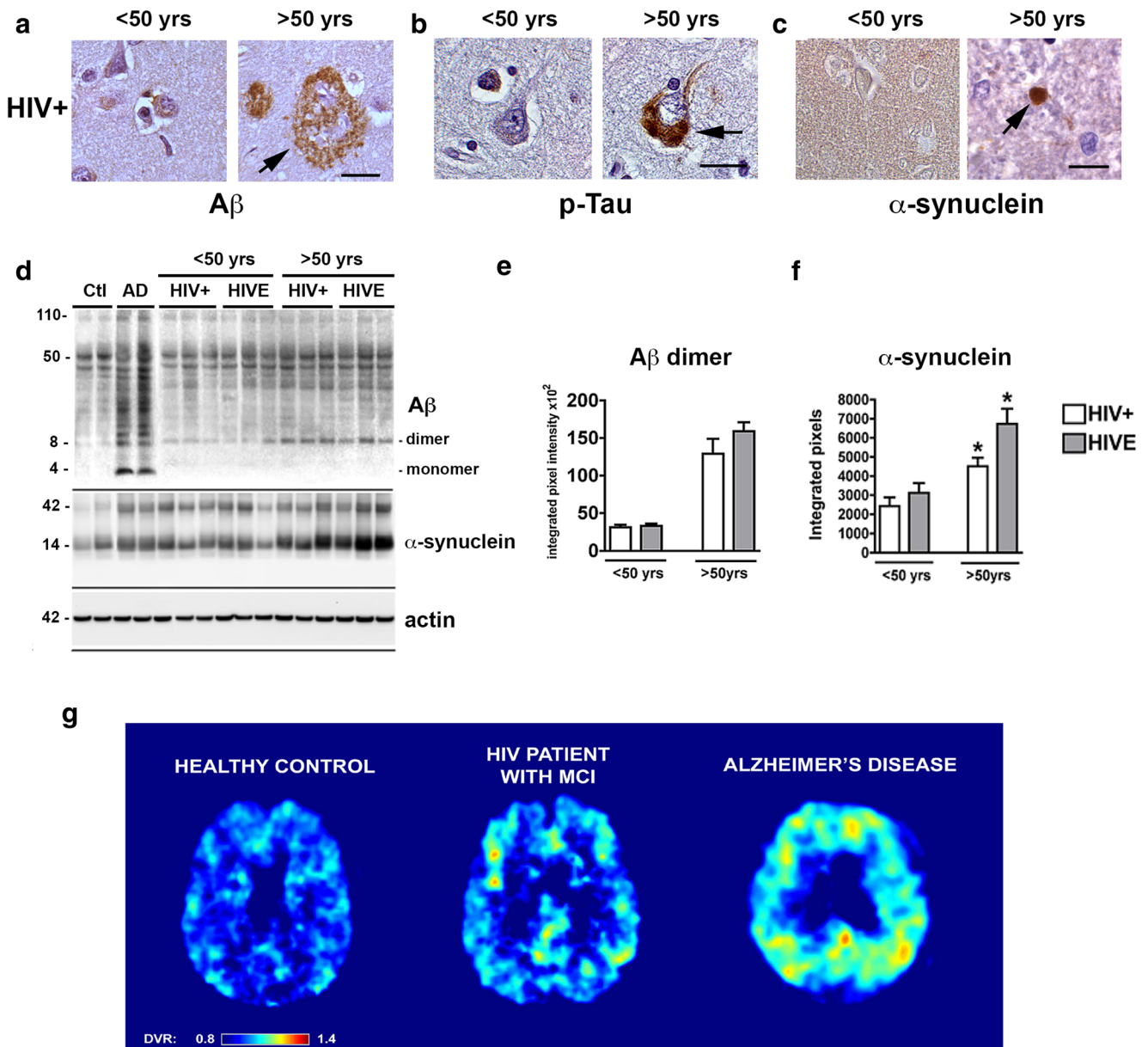
Fig. 3 Brain proteinopathy in aging and HIV. With aging in an individual with chronic HIV disease protein aggregates involved in AD/ADRD might abnormally accumulate. **a** Representative images of the frontal cortex immunostained with an antibody against Aβ (4G8) from an HIV+ case under 50 years of age showing no amyloid deposition while an older case shows plaque-like lesion. **b** Frontal cortex immunostained with an antibody against p-Tau (PHF-1) from HIV+ case under 50 years of age showing no neuronal alterations while an older case shows tangle-like lesion; **c** temporal cortex immunostained with an antibody against alpha-synuclein (SYN1) from HIV+ case under 50 years of age showing neuropil immunoreactivity while an older case shows Lewy-like dystrophic neurites (Bar = 10 μm). **d** Representative immunoblot analysis with the frontal cortex fractioned from control, AD and HIV+ cases under and over the age of 50 years. Samples from the frontal cortex were fractioned by ultracentrifugation and the membrane fractions ran in SDS-PAGE gels followed by blotting onto nitrocellulose membranes. Compared to controls in AD cases there was a considerable accumulation of monomers and multimers at various molecular weights, in older HIV cases Aβ dimers, as well as α-synuclein monomer and trimers appear to accumulate. **e**, **f** Image analysis corrected to actin for levels of Aβ dimers and α-synuclein (n = 3 cases per group). **g** Representative FDDNP parametric PET images from normal control, HIV+ case with mild cognitive impairment (MCI) or Alzheimer's disease. The analysis of FDDNP scans was performed for frames between 15 and 85 min using Logan graphical analysis with cerebellum as reference region. The resulting distribution volume ratios (DVR) were used to generate the DVR parametric images. The DVR values have been color-coded in such a way that all values below DVR 0.8 are shown as dark blue and all values above DVR 1.4 are shown as dark red. The DVR values between are shown in colors of a rainbow as shown on the color bar at the bottom of the image. The control shown is a 43-year-old female with MMSE score 30. The HIV patient with MCI is a 45-year-old male. The AD patient is an 81-year-old female with MMSE score 15. The images shown are transaxial cuts slightly above the basal ganglia so that posterior cingulate gyrus is visible. The frontal lobe is at the top and parietal lobe is at the bottom. The AD case shows high levels of FDDNP binding (high DVR values) throughout the neocortex, most prominently in parietal and frontal cortices and in posterior cingulate. The control case has a uniformly low level of FDDNP binding (low DVR) throughout the cortex. The HIV cases show a limited number of isolated areas with medium to high level of FDDNP binding in prefrontal areas, in posterior and anterior cingulate gyri, and asymmetrically in the parietal lobe

unlike other studies (Green et al. 2005; Rempel and Pulliam 2005), the study by Solomon and colleagues did not find a correlation between aging and amyloid deposition in their autopsy series (Solomon et al. 2017).

In terms of potential interactions between HIV and AD/ADRD pathways (Fig. 2), recent studies have shown that HIV proteins in addition to interacting with aging-related pathways might also interfere with the APP metabolism and Tau phosphorylation and aggregation. For example, Tat, nef, and gp120 interact with Lamp2 and Beclin-1 interfering with autophagy leading to Aβ, Tau, and a-syn accumulation (Campbell et al. 2015; Fields et al. 2015a; Fields et al. 2013). Moreover, Tat blocks neprilysin—an Aβ-degrading enzyme resulting in reduced clearance of Aβ and abnormal accumulation (Daily et al. 2006; Rempel and Pulliam 2005). In addition, Tat interacts with Aβ, promoting Aβ fibrillation, misfolding, and aggregation, with Aβ and Tat co-localizing in amyloid plaques of aged patients with HAND and in double transgenic Tat and APP mice (Hategan et al. 2017). Moreover, APP binds the HIV-1 Gag polyprotein, retains it in lipid rafts and blocks HIV-1 production. Gag could also enhance secretase-dependent cleavage of APP, leading to increased synthesis of toxic Aβ that promotes degeneration of cortical neurons, which can be prevented by γ-secretase inhibitor treatment (Chai et al. 2017). HIV proteins such as Tat and gp120 activate signaling pathways that lead to Tau phosphorylation and toxicity, among them most remarkably GSK3β and the cyclin-dependent kinase [CDK] 5, a member of the Ser/Thr CDK family involved in cell migration, angiogenesis, neurogenesis, and synaptic plasticity. Tat, via calcium dysregulation, promotes calpain-1 cleavage of p35 to p25, which in turn hyper-activates CDK5 resulting in abnormal phosphorylation of downstream targets such as Tau, collapsin response mediator protein-2 [CRMP2], doublecortin [DCX] (Fields et al. 2015b; Patrick et al. 2011) (Fig. 2).

Together these clinicopathological and mechanistic studies illustrate the complexity of understanding both the relationship and the differences between HAND and AD/ADRD in the context of aging. In this regard, considerable efforts are underway to understand the natural history of HAND (Alakkas et al. 2018) and a potential relationship with AD/ADRD (Milanini and Valcour 2017) by identifying novel biomarkers. In the AD field, with the support of the NIA and the Alzheimer's Association efforts are underway to evaluate a biomarker-based framework for the diagnosis of AD (Jack et al 2018). Biomarkers were grouped into Aβ, pathologic Tau, and neurodegeneration [AT(N)]. This ATN system groups different biomarkers (imaging and biofluids) by the pathologic process each measure.

In the field of aging and HIV, there have been efforts to evaluate the usefulness of these ATN biomarkers to differentiate HAND and AD. Previous studies have analyzed levels of Aβ, Tau, and neurofilament light protein (NF-L) in cerebrospinal fluid (CSF) and other fluids. Some studies have found that the CSF biomarker profile in aged HAND patients was similar to the profile typically found in patients with AD who are HIV-negative with increased t-Tau and p-Tau, a decreased level of Aβ42 and normal levels of NF-L, sAPPα, and sAPPβ (Makitalo et al. 2015). Reduced levels of Aβ42 have been confirmed by other independent studies in aged patients with HAND with a family history of dementia (Fazeli et al. 2016). In similarity with other studies, APOE ε4 genotype was not directly associated with HAND but correlated with CSF levels of Aβ1–42. However, in this study, the majority of participants increased CSF p-Tau levels were associated with current neurocognitive impairment (Cysique et al. 2015). A more recent study also found that amyloid metabolism was influenced by HIV infection in a subtype-dependent manner. Aβ-42 levels were lower in HIV1-C than B, suggesting that there may be greater deposition of Aβ-42 in HIV1-C. These individuals also showed increase p-Tau in CSF. The authors concluded that differences between HIV and AD in the patterns of Aβ and Tau biomarkers suggest that CNS HIV infection and AD may not share some of the same mechanisms of neuronal injury (de Almeida et al. 2018). Assessment of CSF biomarkers may be a valuable tool for clinicians to distinguish between HAND and AD.

The results of positron emission tomography (PET) imaging studies to detect Aβ in HIV cases with cognitive impartment have been controversial. For instance, in middle-aged HIV-positive participants, even with HAND, no evidence of increased (11)C-PiB uptake indicative of amyloid deposition similar to AD was detected, while typical AD cases showed extensive (11)C-PiB uptake. They concluded that similar studies in older participants with HAND and longitudinal studies are needed (Ances et al. 2012). In contrast, a more recent study in an older individual with HAND (Turner et al. 2016) showed abnormalities in the brain by MRI and PET-FDG, Aβ, and p-Tau were found in the CSF and an amyloid PET/CT with [18F] florbetaben showed extensive cortical radiotracer deposition. We have more recently imaged with [18F] FDDN ((2-(1-{6-[(2-fluoroethyl(methyl)amino]-2-naphthyl}ethylidene)malononitrile) PET in a few patients with HIV who also have cognitive impairments and found increased tracer retention in the neocortex when compared to healthy control but to a lesser extent than what is typically seen in AD (Fig. 3g). It has been proposed that while (11)C-PiB might detect more compact late stage deposits the FDDN might detect looser earlier stage deposits. In terms of Tau in HAND, currently no PET-Tau imaging studies have been performed; however, as indicated above, there are some studies that have shown accumulation of p-Tau in cortical neurons (Anthony et al. 2006; Patrick et al. 2011) in HAND and increased levels in CSF. Although some controversial results have been reported in CSF, a comprehensive review (Brown et al. 2014) concluded that those maintained on long-term

HAART may develop Tau pathology beyond the extent seen in the studies reviewed herein and overtime may then reach the threshold for clinical manifestation.

In summary, most of these studies have investigated the contribution of AD to HAND; however, it is likely that other disorders such as DLB and VICD might be contributing factors, and future studies will be needed to elucidate the extent to which each disorder contributes to AD.

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