Aging and Apolipoprotein E in HIV Infection

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Abstract
With the implementation of increasingly effective antiretroviral therapy (ART) over the past three decades, individuals infected with HIV live a much longer life. HIV infection is no longer a terminal but rather a chronic disease. However, the lifespan of infected individuals remains shorter than that of their uninfected peers. Even with ART, HIV infection may potentiate “premature” aging. Organ-associated disease and systemic syndromes that occur in treated HIV-infection are like that of older, uninfected individuals. Brain aging may manifest as structural changes or neurocognitive impairment that are beyond the chronological age. The spectrum of neurological, cognitive, and motor deficiencies, currently described as HIV-associated neurocognitive disorders (HAND), may reflect earlier onset of mechanisms common to HIV infection and aging (accelerated aging). HAND could also reflect the neurological impact of HIV infection superimposed on comorbidities linked to age and chronic inflammation, leading to a higher prevalence of neurocognitive impairment across the age span (accentuated aging). In addition, apolipoprotein E (ApoE), one of the most influential host risk factors for developing Alzheimer’s disease, has been implicated in the development of HAND. But studies differ as to whether ApoE is relevant, and whether age and ApoE interact to impair brain function in the HIV-infected patient. What is clear is that HIV-infected individuals are living longer with HIV, and therefore factors related to aging and health need to be examined in the context of current, effective ART. This review addresses the recent evidence for the influence of aging and ApoE on HIV-associated neurocognitive impairment.

Keywords Human immunodeficiency virus · Neurocognitive impairment · Aging · Apolipoprotein E

Introduction
In the early 1980s, HIV infection resulted in a devastating illness that led to an array of opportunistic infections and malignancies, and eventually to death within a short number of years after diagnosis. With the advent of antiretroviral therapy (ART), HIV replication has been suppressed in the majority of patients to circulating viral levels that are undetectable with our current assays. HIV infection is now a chronic state with a prolonged survival since, when effective, ART has all but eliminated early mortality. According to the CDC, 45% of Americans with diagnosed HIV infection are 50 years of age or older (https://www.cdc.gov/hiv/group/age/olderamericans/index.html). By the end of 2014, this number had reached 428,724 people. It is likely that the majority of these individuals were infected at an earlier age and survived the disease for years; the new infections as recorded for 2015 by the CDC were 6725 and some of them may be newly diagnosed but not newly acquired. In fact, in 2014, 40% of people who were above the age of 55 had AIDS when diagnosed (https://www.cdc.gov/hiv/group/age/olderamericans/index.html). Recent studies predict that an infected 20-year-old with CD4+ lymphocyte levels above 350 cells/μl 1 year after starting ART may live as long as 78 years, which is similar to the life span of an uninfected individual. But this is a best case scenario and many factors are likely to reduce this predicted survival (Antiretroviral Therapy Cohort Collaboration 2017). The aging HIV-infected population now requires medical intervention for both management of HIV infection itself and management of disorders that typically accompany older age, that are HIV-associated, non-AIDS (HANA) conditions (Gualdali et al. 2011; High et al. 2012). In the current era, ART-treated infected individuals are affected by comorbidities that are common in uninfected aging populations, including organ diseases affecting the heart (Freiberg et al. 2013; Currier et al. 2008; Triant 2012, 2014; Triant et al.
2007), the kidney and liver (Joshi et al. 2011; Joshi and Liu 2000; Kovari et al. 2013), the bones (Schouten et al. 2014), or the brain (Kaul et al. 2005) as well as non-AIDS-defining cancers (Dubrow et al. 2012), as reviewed by (Grulich et al. 2011). HANA comorbidities and systemic geriatric syndromes (multimorbidity, polypharmacy, frailty, falls) are more prevalent in HIV-infected populations than in uninfected populations of similar age. This raises the question of whether HIV infection accelerates or accentuates aging itself, as reviewed in (Pathai et al. 2014). Accelerated aging is the result of HIV infection acting through pathways and mechanisms common to aging. For example, age-related immunological senescence, typical of the elderly, is also manifested in the HIV-infected population (Appay and Sauce 2017), driven by immuno-inflammatory mechanisms that are similar in HIV infection and aging (reviewed in Bhattacharya et al. 2012). Accentuated aging is the result of HIV infection acting as an additional risk factor for chronic disorders associated with aging; thus, the prevalence of the disorder is increased in the HIV-infected population across the age span. Pathai et al. propose that HIV-related acceleration versus accentuation of aging is probably organ and disease/condition specific. Immune system changes more clearly reflect accelerated aging (e.g., immune senescence). Specific end-organ diseases during HIV infection present a more complex picture, but several suggest accentuated aging, e.g., cardiovascular disease, diabetes mellitus, or bone fractures (Pathai et al. 2014). Given that nervous system aging is impacted by intrinsic changes as well as other organ pathologies (e.g., cardiovascular), HIV infection can be expected to potentiate both accelerated and accentuated neurological aging.

Neurocognitive impairment (NCI) is among the persistent, even growing clinical challenges associated with aging in the treated HIV-infected population (McArthur and Brew 2010; McArthur et al. 2010). NCI persists in ART-treated populations (Heaton et al. 2011; Sacktor et al. 2016; Simioni et al. 2010), and is likely the clinical manifestation of underlying cellular mechanisms driving HIV neuropathogenesis despite suppression of circulating viral load. As early as 8 days after the suspected time of infection (Valcour et al. 2012), HIV can be detected in the cerebrospinal fluid (CSF) and rapidly enters the brain within 15 days after infection (Davis et al. 1992). Brain invasion presumably results from a Trojan horse mechanism like that initially proposed to describe neuroinvasion by Visna virus after infection of peripheral monocytes (Peluso et al. 1985). HIV-infected monocytes reach the brain across the blood–brain barrier and differentiate into macrophages, which increases virus replication dramatically. Macrophages, together with microglia and to some extent astrocytes, constitute the principal population of cells supporting HIV replication in the brain (Liu et al. 2004; Thompson et al. 2011) and drive the neuropathogenesis of neurological disease. Potential mechanisms of neuropathogenesis include direct neurotoxicity by the HIV proteins Tat (Buscemi et al. 2007; Fan and He 2016; Fields et al. 2015; Rahimian and He 2016; Sabatier et al. 1991) and gp120 (Bachis et al. 2006; Bachis et al. 2012; Mocchetti et al. 2012; Nosheny et al. 2006; Reddy et al. 2012; Wenzel et al. 2017; Zhou et al. 2017), and the pro-inflammatory milieu generated by factors released by infected and/or immune-activated microglia and astrocytes (Faisser et al. 2014; Wu et al. 2015; Zenon et al. 2015). HIV replication in the central nervous system (CNS) is clinically associated with a spectrum of neurological abnormalities collectively known as HAND (HIV-associated neurological disorders) and subdivided into asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD) (reviewed by Wendelken and Valcour 2012). The severe neurological deficits of HAD were more prevalent before the advent of ART. Numerous reports have chronicled these severe neurological deficits acquired by infected individuals in the 1980s and 1990s. But with the advent of ART, the spectrum of neurological disease has shifted over the past two decades towards a more chronic NCI encompassed by ANI and MND (McArthur et al. 2010), and that has similarities to cognitive impairments seen in uninfected aging populations that are affected by host genetic factors (e.g., apolipoprotein E) and acquired organ-related or systemic conditions (e.g., vascular disease). Accordingly, this review will focus primarily on neurological disorders described over the past two decades in studies of the ART-treated populations living and aging with HIV infection.

Neurocognitive changes and chronic HIV infection: accelerated or accentuated aging

There remains debate on the relationship between aging and HIV-associated neurocognitive impairment (Bhatia et al. 2012; Pathai et al. 2013; Sheppard et al. 2017). But numerous studies over the past two and a half decades, conducted with relatively large HIV-infected cohorts and age-matched seronegative (SN) controls, overall suggest that both accelerated and accentuated aging may affect the neurological course of HIV infection (Table 1).

Neuropsychological studies dating back to the previous decade did indicate that age is a risk factor for HIV-associated NCI (Sacktor et al. 2007; Valcour et al. 2004a). Valcour et al. (Valcour et al. 2011; Valcour et al. 2004a; Valcour et al. 2004b) studied the Hawaii Aging with HIV-1 Cohort (HAHC), a longitudinal, prospective cohort that has included hundreds of subjects, including those older than 50 years of age and younger than 40 years, with carefully matched SN controls. Their earlier study (Valcour et al. 2004a) that did not include SN individuals used neuropsychology testing and neurobehavioral data to designate diagnoses by a consensus panel that included neurologists and neuropsychologists. The study identified a twofold increased risk
Table 1  Studies on neurological manifestations of HIV and aging

| Publication | Study population | Measures | Findings |
|-------------|------------------|----------|----------|
| Valcour et al. (2004a) | Hawaii Aging with HIV Cohort (HAHC) HIV+ n = 202 > 50 years n = 106 67% on ART < 50 years n = 96 78% on ART | Longitudinal cohort Neuropsychological tests | Twofold risk for HAD associated with age < 50 years |
| Becker et al. (2004) | HIV+ n = 290 age 34.3 years 17% on ART SN n = 124 age 38.3 years | Neuropsychological tests | Neurocognitive disorders more prevalent in the HIV+ group older than 50 years than in the younger group. HIV viral load at entry was higher in individuals who later developed cognitive dysfunction |
| Chang et al. (2004) | HIV+ n = 100 61 with AIDS dementia complex Asymptomatic n = 39 7% naïve to ART 93% on ART SN n = 37 Stratified for age > 40 years (overall median) | MRS: glial (myoinositol, MI to creatine, Cr) and neuronal (N-acetyl compound, NA, to creatine, CR) metabolites | HIV+ had higher glial metabolites in white matter Elevated MI in white matter is early in HIV disease, before cognitive decline Dementia is associated with lower neuronal marker in frontal white matter HIV infection and aging had additive effects on glial metabolites in basal ganglia and white matter Lower NA in frontal white matter of younger HIV+ (< 40 years); this may reflect greater inflammatory response Elevated glial metabolite (MI) persisted across the age span |
| Sacktor et al. (2007) | HIV+ n = 254 > 50 years n = 133 80% on ART 20–39 years n = 121 67% on ART | Neuropsychological tests - Verbal and visual memory - Verbal fluency - Psychomotor speed | Age associated with poorer performance in tests with dementia |
| Chang et al. (2008) | HIV+ n = 100 age 47.4 years SN n = 32 age 46.7 years | Neuropsychological tests DTI measured at entry and after 1 year | HIV+ had higher mean diffusivity of genu of corpus callosum compared to SN after 1 year This was associated with lower cognitive performance |
| Woods et al. (2010) | HIV+ n = 35 age 40 years 71.4% on ART SN n = 20 HIV+ ≥ 50 years n = 48 75% on ART SN ≥ 50 years n = 15 | Prospective memory tests | Additive effects of aging and HIV infection on event-based prospective memory. The poorest performers were HIV-infected, older individuals |
| Valcour et al. (2011) | Hawaii Aging with HIV Cohort (HAHC) HIV+ n = 136 73% on ART HIV+ < 40 years old n = 110 75% on ART SN > 50 years n = 106 SN < 40 years n = 98 | Neuropsychological tests | No correlation between age and neuropsychological performance |
| Scott et al. (2011) | HIV+ n = 24 age 40 years 66.7% on ART SN ≤ 40 years n = 24 HIV+ ≥ 50 years old n = 48 75% on ART SN ≥ 50 years old n = 20 | Neuropsychological testing - Episodic learning and memory - Executive functions - Visuoconstruction | All three measures were affected by aging HIV infection affected verbal learning and memory |
| Ances et al. (2012) | HIV+ n = 26 age 40 years HIV+ HAART naïve n = 26 | Neuropsychological tests - Memory - Psychomotor speed - Executive function | HIV+ performed worse in neurological tests than SN HIV+ had reduced brain volumes in some but not all brain regions compared to SN HAART did not affect these measures |
for HAD in patients greater than 50 years of age. In a follow-up report published 7 years later and using a slightly larger cohort of HIV-infected individuals from the same HAHC cohort with age-matched SN controls, there was limited evidence for any correlation between age and neuropsychological performance (Valcour et al. 2011). The differences in results between the two studies were attributed to the use in the latter study of models that included interaction variables and means and frequency of poor performance on neuropsychological tests, instead of cutoff points defining neurological impairment. In addition, a carefully selected control group of matched SN individuals helped normalize the data for

### Table 1 (continued)

| Publication | Study population | Measures | Findings |
|-------------|------------------|----------|----------|
| Sheppard et al. (2015) | Neurocognitively normal \( n = 146 \), tested at entry and 14 months \( n = 27 \) HIV+ ≤ 40 years \( n = 24 \) SN ≤ 40 years \( n = 24 \) HIV+ ≥ 50 years \( n = 56 \) SN ≥ 50 years \( n = 39 \) | Neuroimaging: Brain volume | HIV and age were independent correlates of lower brain volumes |
| Marquine et al. (2014, 2016) | Veterans Aging Cohort Study (VACS) Longitudinal study (up to 6 years follow-up) HIV+ \( n = 655 \), age 42.5 years 61% on ART \( n = 392 \) with no baseline impairment | Neuropsychological tests & VACS Index (composite marker of disease in HIV+, marker of all-cause mortality) Neurocognitive testing | VACS Index associated with risk for worse global neurocognitive performance (2014) With time, increasing VACS Index was associated with higher risk of developing neurocognitive impairment in individuals who had normal tests at baseline (2016) |
| Avci et al. (2016) | Younger \( n = 125 \) HIV+ ≤ 40 years \( n = 77 \) 84% on ART SN ≤ 40 years \( n = 48 \) Older \( n = 189 \) HIV+ ≥ 50 years \( n = 112 \) 90.2% on ART SN ≥ 50 years \( n = 77 \) | Tests of prospective memory (PM) -Memory for Intentions Screening Test (MIST) -Naturalistic PM task -Prospective and retrospective memory questionnaire (PRMQ) | Effects of aging vary by cue type and delay interval on the MIST Effect of HIV on the MIST varies per cue type and delay interval HIV disease interacts with age on naturalistic PM task -HIV+ older perform equal to HIV+ younger and SN younger -SN older perform better than others |
| Cole et al. (2017) | HIV+ \( n = 162 \) All on ART SN \( n = 105 \) Ages 45–80 years | Brain-PAD (brain predicted age difference score) based on MR neuroimaging Cognitive testing | Brain-PAD score higher in HIV+ Higher brain-PAD score associated with poorer cognitive performance PAD score not associated with age, duration of infection |
| Strain et al. (2017) | HIV+ \( n = 92 \) age 49.1 years SN \( n = 66 \) age 38.6 years | Diffusion basis spectral imaging (DBSI): cellularity | Diffuse increases in cellularity in brains of HIV+ compared to SN Cellularity declined with age in HIV+, but not significant when corrected for sex, duration of ART No difference in NP test performance between HIV+ and SN |

**ART** antiretroviral treatment

*Age values are mean ages unless otherwise specified as median or age range*
comorbidities that are found in the aged population independently of HIV infection. Sacktor et al. (2007) compared neuropsychological test performance between 133 older (≥ 50 years) versus 121 younger (20–39 years) HIV-infected individuals, with or without NCI or dementia. They found that age was associated with lower performance in domains including memory, executive functions, and fine motor skills. It was unclear whether the differences were the result of age or age-associated comorbidities since the study did not include an age-matched HIV SN population. Using the Veterans Aging Cohort Study (VACS), Marquine et al. (Marquine, Montoya et al., 2016; Marquine, Umlauf et al. 2014) examined the risk for global NCI in HIV-infected individuals that had been scored by the VACS Index, a risk index that combines age, HIV biomarkers (e.g., viral load and CD4 count), and non-HIV factors that take into account HANA. The VACS Index had been validated as a marker of all-cause mortality in this cohort. Using 601 participants (mean age 41.9 years, overall range 18–76 years, age 50–64 years n = 95, age ≥ 65 years n = 13), the VACS Index was associated with risk for concurrent global NCI (Marquine et al. 2014), particularly with older age. In a longitudinal study following 655 HIV-infected participants (mean age 42.5 years, range 18–70 years) for up to 6 years, baseline VACS Index scores were not significantly associated with incident NCI in demographics-adjusted analyses. But time-dependent analyses showed that increases in VACS Index scores were significantly associated with worse global and domain neurocognitive performance and higher risk of developing neurocognitive deficits among patients who had normal neurocognitive tests at baseline (Marquine et al. 2016). While the VACS cohort and the VACS index provided a well-characterized study population and risk marker (VACS Index) for longitudinal study of NCI in HIV infection, the cohort was still relatively young, with mean age < 50 years of age.

These earlier studies highlighted the need for a carefully matched SN control population in studies where neurocognitive performance may be associated with aging but may also be impacted by other health and lifestyle factors such as alcohol or tobacco use. More recent neuropsychological studies, reported in the current decade, suggest that age and HIV infection have an additive impact on neurocognitive performance, with younger HIV-infected individuals performing comparably to older SN individuals in neurocognitive tests, suggestive of accelerated aging (Avci et al. 2016; Scott et al. 2011; Woods et al. 2010). Sheppard et al. (2015) started with a group of cognitively normal individuals and tested their neurocognitive performance approximately 14 months later. Younger individuals were < 40 years of age, and older were > 50 years of age. In a study population of 146, 63 were SN. This study found that HIV seropositivity was a correlate of developing neurocognitive deficiencies in follow-up tests, but age was not. Interestingly, SN individuals with hepatitis C virus (HCV) infection were more likely to develop neurological abnormalities, but HCV infection was not a factor in the HIV-seropositive group. Sheppard et al. (2017) subsequently investigated accelerated neurocognitive aging by testing older HIV-infected individuals (aged 50–65 years) against age-matched SN and much older (“older old,” ≥ 65 years) SN controls. Using clinical measures of attention, the investigators found that the HIV-infected group performed more poorly than the age-matched SN but were similar to the much older SN controls with respect to auditory attention. The differences suggested both accentuated and accelerated aging. However, the investigators did not observe similar changes in other neurocognitive domains, including episodic memory, language, or executive functions.

In addition to neurocognitive tests, brain imaging methods have been used to correlate brain structure or metabolism with cognitive function in the aging HIV-infected population (reviewed in Holt et al. 2012). Magnetic resonance (MR)-based structural studies have shown brain cortical atrophy and/or subcortical regional volumetric loss in HIV-infected individuals, volume loss that is greater than age-related and independent of HAND status. Normal aging is an independent factor contributing to brain atrophy in the frontal and temporal lobe gray matter and white matter. But HIV infection and aging may independently contribute to regional brain volume loss, particularly in subcortical regions, even with ART-managed infection (Ances et al. 2012; Chang et al. 2011), as reviewed in Holt et al. (2012). In HIV-infected subjects, specific subcortical brain regions, e.g., the putamen, have shown volume loss across the age span (Chang et al. 2011), which Chang termed a “legacy effect” (Chang 2018). While early and persistent brain volume loss during HIV infection could reflect accentuated aging, it may also be the result of the “legacy” of accumulated disease effects such as chronic neural inflammation and oxidative stress over time. Alternatively, other subcortical regions, e.g., the corpus callosum, have shown increased volume loss with age, suggesting accelerated aging. MR diffusion tensor imaging (DTI) detected increased mean diffusivity of the genu of the corpus callosum over 1 year in a cohort of 39 clinically and cognitively stable HIV-infected subjects (mean age 47.4 years) compared to 32 SN controls (mean age 46.7 years), suggesting greater than age-related inflammatory changes occurred in that region (Chang et al. 2008). In a subsequent study, Strain et al. (2017) used diffusion basis spectral imaging (DBSI)-derived cellularity as a measure of restricted water diffusion associated with inflammation in the brain. Their study cohort included 92 virologically suppressed HIV-infected subjects on stable ART regimens (mean age 49.1 years) and 66 SN controls (mean age 38.6 years). Diffuse increases in cellularity were present in the brains of HIV-infected individuals compared to SN control subjects. Similar diffuse increases in cellularity were seen in an age-sex matched subset of 40 HIV-
infected and 40 SN control subjects. Considering all study subjects, cellularity declined with age in the HIV-infected group but not the SN controls. However, after adjustment for sex and duration of ART (mean 10.3 ± 7.1 years), this inverse relationship between cellularity and age was not significant. Neuropsychology test performance was not significantly different between HIV-infected versus SN controls tested for memory, psychomotor speed, or executive function. Strain et al. concluded that DBSI-derived cellularity is a particularly sensitive brain imaging measure, revealing diffuse inflammation in HIV-infected subjects regardless of cognitive impairment and even with effective viral suppression by ART. In a study of 48 older (age > 50 years) HIV-infected subjects and 25 SN controls, Sacktor (2018) measured brain amyloid deposition by positron emission tomography (PET) using the [18F] AV-45 tracer. The subjects were stratified by (1) serostatus, (2) HAND status (HIV-infected only), and (3) decade of life. Comparing the HIV-infected to the SN, there was significant increased global and regional tracer uptake only in the HIV subjects aged 50–59 compared to SN aged 50–59. No significant differences were detected between HIV-infected and SN subjects aged 60–69. There were no differences in median global or regional uptake when HIV-infected subjects were stratified by HAND stage. Neuropsychological testing did not find any correlation between cognitive impairment and the higher amyloid deposition in the HIV-infected aged 50–59 subgroup. Sacktor noted that the age-specific increase in amyloid deposition could suggest a “pre-clinical” stage of HIV-related neurocognitive disease, but there is as yet insufficient evidence for this, and further longitudinal imaging and cognitive testing of the age groups are warranted by this initial study (Sacktor 2018).

These structural studies support the notion of premature brain aging in the patient living with HIV infection. To better quantitate this, Cole et al. developed a “brain predicted age” from T1-weighted MRI scans of 2001 healthy individuals aged between 18 and 90 years, analyzing gray matter and white matter images together to quantify the normal whole brain (Cole et al. 2017). Using these normals, the investigators created a reference plot of brain-predicted age (years) versus chronological age (years), then went on to generate brain-predicted age difference (brain-PAD) scores by subtracting chronological age from the imaging-determined brain-predicted age. In 162 HIV-seropositive versus 105 “highly comparable” SN controls, the HIV-seropositive individuals with undetectable viral loads after at least a year of ART had higher brain-PAD scores, and therefore had “older” brains, by about 2.15 years. In addition, higher brain-PAD scores were associated with poorer cognitive performance. Interestingly, PAD scores did not interact with chronological age or duration of infection. The authors interpreted these results as favoring accentuated rather than accelerated structural aging in the HIV-infected brain.

Within the past two decades, proton MR spectroscopy (MRS) has been used to study neurometabolite levels in different brain regions of individuals with AIDS dementia complex (ADC) versus neuroasymptomatic HIV infection versus SN controls. Extensive data from both ART-naïve and primarily ART-treated subjects have indicated that advancing cognitive impairment is associated with significantly increasing glial metabolite MI/tCr (myoinositol-to-total creatine) or Cho/tCr (choline-to-total creatine) ratios in the basal ganglia and frontal white matter. This suggests glial activation and increased inflammation. With symptomatic neurocognitive impairment, neuronal metabolite NA/tCr (N-acetyl aspartate-to-total creatine) ratios are decreased, suggesting neuronal loss even at younger (< 40 years) age (Chang L 2012; Chang et al. 2004; Ernst and Chang 2004). HIV-infected subjects with symptomatic neurocognitive impairment also had lower NA/tCr ratios in the frontal white matter. Symptomatic neurocognitive impairment in HIV-infected subjects has correlated with the highest levels of MI/tCr and Cho/tCr in the basal ganglia across age groups (< versus ≥ 40 years), as compared to neuroasymptomatic HIV-infected subjects. And, in neuroasymptomatic subjects < 40 years old, HIV infection associated with higher MI/tCr and Cho/tCr ratios in basal ganglia compared to age-matched SN controls. The young neuroasymptomatic HIV-infected subjects’ ratios were like those of older (≥ 40 years) SN subjects. These patterns have suggested that there may be greater inflammatory response in younger HIV-infected subjects, but glial activation (with elevated MI in the frontal white matter) persists across the age span (Chang et al. 2004). MRS study of slightly older (median age 40–45 years) and ART-treated subjects showed MI/tCr increased with age in mildly cognitively impaired subjects but decreased with age in more severe brain disease such as ADC (Harezlak et al. 2011). This pattern may reflect an increase in microglia-driven inflammation in mildly impaired subjects, an accentuated aging effect, but premature microglial inflammatory senescence in advanced brain disease, e.g., accelerated aging (Holt et al. 2012). MRS study of glutamate found levels were lower even in younger HIV-infected subjects, similar to those of SN controls 10 years older (Ernst et al. 2010). Lower brain glutamate was associated with worsening cognitive deficits. Thus, while interpretation in some cases is complicated by the cross-sectional nature of the studies, brain metabolite data in HIV-infected subjects suggests features of both accentuated and accelerated aging effects leading to premature brain aging.

**Molecular markers associated with HIV and aging**

Telomere length is a molecular chromosomal marker that correlates inversely with aging in normal populations. It has also
| Publication | Study population | Measures | Findings |
|-------------|------------------|----------|----------|
| Pathai et al. (2013) | HIV+ n = 236  
\^Age 39 years (35–46)  
68% on ART  
SN n = 250  
age 40 years (35–49) | Telomere length | Shorter telomeres associated with HIV infection and with lower CD4+ cell numbers in ART-treated individuals with undetectable viral loads |
| Zanet et al. (2014) | HIV+ n = 229  
median age 40 years  
92% on ART  
SN n = 166  
median age 38 | Telomere length | Shorter telomeres associated with infection, older age, active HCV infection.  
No correlation with ART |
| Solomon et al. (2014) | HIV+ n = 124  
Treated with darunavir/ritonavir  
n = 63, age 63 years  
Treated with darunavir/ritonavir+ NNRTI  
n = 61, age 40 yrs | Telomere length | No difference in telomere length between patients on darunavir/ritonavir with and without NNRTI |
| Rickabaugh et al. (2015) | Grouped by age and HIV serostatus  
all ART naive  
all groups n = 12  
HIV+ 20–24 years  
SN 20–24 years  
HIV+ 48–56 years  
SN 48–56 years  
HIV+ 27–35 years  
SN 27–35 years  
HIV+ 36–56 years  
SN 36–56 years | DNA methylation | HIV infection accelerated age-associated methylation by 13.7 to 14.7 years |
| Horvath and Levine (2015) | Brain and blood tissues from different sources | DNA methylation | HIV infection increased epigenetic methylation in brain and blood tissue  
Epigenetic age increased 7.4 years in brain  
Epigenetic age increased 5.2 years in blood |

Study population details:
Data set 1: Brain specimens  
HIV+ n = 71, age at death 45.9 years, 91.5% on ART  
SN n = 13, age NS |
Data set 2: Brain specimens  
HIV+ n = 8, age 44 years; SN n = 44, age NS |
Data set 3: Cerebellar samples  
HIV+ n = 8 (same as data set 2); SN n = 12, age NS |
Data set 4: Blood samples  
HIV+ n = 24, age 49 years, no ART information; SN n = 68, age 36 years |
Data set 5: PBMC samples  
HIV+ n = 23, age 45 years; SN n = 69, age 51 years |
Data set 6: PBMC samples  
HIV+ n = 109, age 52 years |
Data set 7: Whole blood  
SN n = 335, age 17–70 years |
Data set 8: Sorted leukocytes  
SN n = 4, age NS |
Data set 9: Sorted blood sets  
SN = 6, age 38 years |
Data set 10: T cells and monocytes  
SN n = 23, age NS |
Data set 11: Sorted blood cells  
SN n = 6, age 36–51 years |
Gross et al. (2016) | Whole blood samples  
HIV+ n = 137  
age 45.7 years | DNA methylation | HIV+ had advanced aging by 4.9 years  
Epigenetic age independent of duration of infection |
been used to investigate aging in the HIV-infected population (Table 2). A study performed in South Africa that included 236 HIV-infected and 250 age-matched SN controls revealed that shorter telomeres were associated with HIV infection. In those infected individuals with undetectable viral loads, shorter telomeres were associated with lower CD4+ lymphocyte numbers (Pathai et al. 2013). Supporting studies by Zanet et al. (2014) have found a correlation between telomere length and HIV infection, age, peak viral loads higher than 100,000 copies/ml, and smoking, but not with ART. Similarly, no changes in rates of telomere shortening were found when HIV-infected individuals were switched from an ART regimen of darunavir/ritonavir supplemented with nonnucleoside reverse transcriptase inhibitor (NNRTI) to darunavir/ritonavir without NNRTI (Solomon et al. 2014). Telomere shortening occurred after seroconversion, but no further shortening was observed with prolonged infection (Leung et al. 2017), possibly suggesting accentuated rather than accelerated aging. Of all the 81,361 DNA methylation CpG sites characteristic of HIV infection, 4338 were also associated with aging, indicating, as expected, that many other processes associated with HIV infection are being modified by methylation.

In addition to telomere length, changes in DNA methylation patterns (the “epigenetic clock”) have been associated with the aging process (Alisch et al. 2012; Bollati et al. 2009) and with medical disease. Two models of age-associated methylation changes have recently been applied to the study of epigenetic aging in HIV infection. Horvath and Levine (2015) compiled methylation data from the blood cells and brain tissue of HIV-infected and uninfected individuals, while Hannum et al. (2013) compiled data from the whole blood cells of uninfected individuals of various ages. Gross et al. applied a combined model that included the age-associated methylation changes compiled by Horvath and Levine (2015) and those compiled by Hannum et al. (2013), and proposed that HIV advances biological aging by 4.9 years and increases mortality by 19% (Gross et al. 2016). Gross et al. adjusted for the different composition of cell types in whole blood from HIV-infected versus normal individuals. Additionally, the HIV-infected population studied was otherwise healthy and on ART, thus avoiding the confounding contributions to aging of medical comorbidities and coinfections. Interestingly, predicted biological age, as measured by the epigenetic clock, was independent of the duration of infection, suggesting an accentuated rather than accelerated aging. Of all the 81,361 DNA methylation CpG sites characteristic of HIV infection, 4338 were also associated with aging, indicating, as expected, that many other processes associated with HIV infection are being modified by methylation. This biological age difference between HIV-infected and uninfected individuals was lower than that published by Rickabaugh and collaborators—close to 14 years (Rickabaugh et al. 2015). Differences between the two studies in the prediction of biological aging due to HIV infection may be due to the use of a different model to calculate epigenetic age. Gross et al. used the average of the above-named two models to calculate epigenetic aging (Horvath and Levine 2015; Hannum et al. 2013), while Rickabaugh et al. used only the Horvath and Levine model. This biological age difference

Table 2 (continued)

| Publication          | Study population | Measures                              | Findings                                      |
|----------------------|------------------|---------------------------------------|-----------------------------------------------|
| Levine et al. (2016) | HIV+ n = 58      | Retrospective analysis of neurocognitive | HAND associated with increased methylation    |
|                      | With HAND n = 43 | tests within 1 year of death           | age of 3.5 years                               |
|                      | age at death 45.7| DNA methylation from post-mortem       | No correlation with global neurocognitive     |
|                      | years 77% on ART| brain                                  | functioning or HAND severity                  |
|                      | Neurocognitively |                                      | Age acceleration correlated with duration      |
|                      | normal n = 15    |                                      | of HIV infection                               |
|                      | age at death 46.5|                                      |                                               |
|                      | years 87% on ART |                                      |                                               |
| Leung et al. (2017)  | 31 IV drug users | Longitudinal blood samples             | Lower telomere length and changes in methylation |
|                      | who seroconverted| -Telomere length                       | patterns within 2 years after seroconversion  |
|                      | to HIV+          | -DNA methylation                       | Telomeres were not further shortened over      |
|                      | age 35.8 years   |                                      | subsequent 2 years                             |
|                      | 22% on ART by    |                                      |                                               |
|                      | last time point  |                                      |                                               |

NS age not specified, PBMC peripheral blood mononuclear cells, ART antiretroviral treatment

*Age values are mean ages unless otherwise specified as median or age range*
may also be due to the fact that, in the Rickabaugh et al. study, samples from antiretroviral-naive individuals were used. An increase in CD4+ lymphocyte numbers is an expected outcome of ART (Kaufmann et al., 2003), and lower CD4+/CD8+ ratios are associated with increased epigenetic aging (Gross et al. 2016). Thus, ART may result in younger age, as measured by the epigenetic clock, due to an increase in CD4+ lymphocyte numbers. In addition, in a 2016 study conducted by Levine et al. (2016), 58 HIV+ individuals were diagnosed with or without HAND within 1 year of their death. Post-mortem brain tissue analysis was used to calculate biological age based on DNA methylation patterns (Horvath and Levine 2015), and determined that individuals with HAND had an increased biological age by a mean of 3.5 years as compared to individuals without HAND. However, as the age of the patient increases, the differences in biological aging between the HAND and the asymptomatic group widened, and increased biological age was associated with length of infection, consistent with accelerated aging. Interestingly, this biological age acceleration did not depend on the severity of HAND symptoms. These results suggest that molecular markers of aging can be used to evaluate the progression of HIV infection. But further longitudinal studies are needed to understand whether some of these molecular markers may herald neurological changes, and thus can be used as markers for earlier therapeutic interventions.

Apolipoprotein E and the aging HIV-infected population

Apolipoprotein E (ApoE) is a small secreted protein involved in cellular lipid and cholesterol transport (Mahley 1988; Mahley and Rall 2000). In the brain, neuronal processes such as synaptogenesis and neurite extension are dependent on a supply of cholesterol and phospholipids, which are transported by ApoE after production and secretion by astrocytes (Boyles et al. 1985; Qiu et al. 2004). Thus, ApoE is vital for neurons; it is involved in neuronal development, migration, and survival. Three isoforms of ApoE exist in the human population, ApoE2, ApoE3, and ApoE4; they differ by the presence or absence of arginine or cysteine residues at amino acid positions 112 and 158. These amino acid substitutions result in distinct structural and functional differences, including binding to lipoproteins and to the ApoE receptor (Hatters et al. 2006; Hauser et al. 2011; Mahley et al. 2009; Yamamoto et al. 2008). Associated with ApoE isoforms E2, E3, and E4 are distinct genetic alleles, ε2, ε3, and ε4, respectively. The most common phenotype is ε3/ε3, with a prevalence of 60–63%, and the least frequent is E2/E2, with a prevalence of only 1% of individuals tested. Approximately 28% of the population carries at least one ε4 allele (reviewed by Mahley 1988).

Apolipoprotein E4 has been characterized as the single most prominent human host risk factor for developing Alzheimer’s disease (Corder et al. 1993; Michaelson 2014). Studies carried out primarily to find predictors of Alzheimer’s disease in aging subjects provide information about the influence of ApoE4 on cognitive function even in the absence of overt dementia and suggest that ApoE4 is associated with lower or longitudinally declining performance in different cognitive domains. In a longitudinal study of 369 educationally and ethnically diverse older adults, ApoE4 carriers had lower baseline scores and faster decline for the cognitive measure Episodic Memory, and ApoE4 was also related to decline of the cognitive measure Executive Function (Mungas et al. 2010). In a cross-sectional study of 105 subjects ≥ 60 years and with normal mental status screening, there was a significant relationship between ApoE4 and worse performance on verbal memory testing using the Word List Memory Immediate Recall (Turan et al. 2015). In a longitudinal study of “relatively high functioning” men and women aged 70 to 79 years (MacArthur Successful Aging Study), initial modest cognitive decline in naming and spatial ability was noted in ApoE4 carriers (Bretsky et al. 2003); by 7 years, ApoE4 carriers were twice as likely to have global cognitive score declines compared to noncarriers (subjects with no ApoE4 allele). In general, the acquisition risk as well as the prevalence risk of mild cognitive impairment have been associated with the ApoE4 allele in aging cohorts (DeCarli et al. 2001; Lipnicki et al. 2017; Roberts et al. 2015). The ApoE effect on cognitive impairment risk may be diminished somewhat by enriched education, which associates with higher frontal and temporal lobe metabolism, independent of amyloid deposition (Arenaza-Urquijo et al. 2015). This implies that the clinical effect of ApoE4 can be delayed or offset by greater cognitive reserve. Interestingly, ApoE genotype also affects survival: ε2 allele carriers live longer than individuals that are homozygous for the ε3 allele, and these live longer than carriers of the ε4 allele (Blanche et al. 2001; Rea et al. 2001; Schachter et al. 1994).

The influence of ApoE phenotype or genotype on the pathogenesis of HAND in HIV infection is controversial; conflicting results have emerged from numerous studies over the past two decades (Table 3). Given its role in neuronal structure and function, any impact of ApoE may be the product of multiple confounding factors, such as age-related effects of HIV infection, antiretroviral therapy, and medical comorbidities. Added to that, the complexity of symptoms that can lead to a diagnosis of HAND may complicate the analysis of possible associations with ApoE.

Based on neuropsychological assessments, no correlation was found between the presence of ApoE4 alleles and HAND or ApoE4 alleles and dementia in relatively large, well-characterized HIV-infected cohorts (Becker et al. 2015; Joska et al. 2010; Morgan et al. 2013). Even though Burt et al. found a correlation between ApoE4/ε4 genotype and faster disease progression to death, they did not find an increased risk for HAD in all ApoE4 carriers (Burt et al. 2008). However, an
Table 3  Studies relating apolipoprotein E (ApoE) to HIV and aging

| Publication                  | Study population                  | Measures                  | Findings                                                                 |
|------------------------------|-----------------------------------|---------------------------|--------------------------------------------------------------------------|
| Dunlop et al. (1997)         | HIV+ autopsied $n=132$            | Neuropsychological testing | No correlation between ApoE genotype and HIV dementia or encephalitis   |
|                              | *Median age = 37 years            | Senile plaques            |                                                                          |
|                              | Zidovudine only ART               | Amyloid deposits          |                                                                          |
|                              |                                  | ApoE genotype             |                                                                          |
| Diaz-Arrastia et al. (2004)  | HIV+ $n=270$, who died of AIDS    | Microscopic pathological exams of spinal cords | No correlation between HIV encephalitis and ApoE genotype |
|                              | most on ART                       | ApoE genotype             |                                                                          |
| Valcour et al. (2004b)       | HIV+ $n=182$, Ages > 50 years     | Neuropsychological tests  | Independent risk of HAD associated with ApoE4 in older but not younger individuals |
|                              | $n=97$, 97% on ART                | ApoE genotype             |                                                                          |
| Burt et al. (2008)           | HIV+ $n=1267$, 369 ApoE4 carriers | Progression to death (survival curves) | Faster progression in ApoE3 noncarriers compared to ApoE3 carriers |
|                              | All accessed ART                  | ApoE genotype             | Fastest progression in ApoE4 homozygotes                                |
|                              | SN $n=1132$, Similar frequency of ApoE4 carriers | Clinical history          | Progression similar in ApoE4 heterozygotes and ApoE4 noncarriers |
|                              | All subjects: age range 18–70 years, 94% male | ApoE genotype             | $e4$ allele did not increase the risk for dementia                      |
| Joska et al. (2010)          | HIV+ $n=144$, age 29.7 years, ART naive | Neurological tests | No correlation between ApoE genotype across different categories of HAND |
|                              | SN $n=50$, age 25.3 years          | ApoE genotype             |                                                                          |
| Andres et al. (2011)         | HIV+ $n=48$, on ART               | CSF ApoE isoform levels   | Overall CSF ApoE levels lower in HIV+ than SN                            |
|                              | 18 (38%) with HAND                | Cognitive tests            | CSF ApoE levels similar in SN$e4+$ compared to SN$e4$                    |
|                              | $e4− < 50$ years $n=33$, Age = 45.8 years | ApoE genotype             | CSF ApoE levels higher in HIV+ $e4+$ compared to HIV+ $e4−$ but were similar to SN levels |
|                              | 3 subjects $e4/e4$ homozygous      |                           | In $e4+$: higher CSF ApoE levels trended to worse learning or memory performance in both HIV+ and SN, but especially in HIV+ |
|                              | SN $n=39$, $e4+$ $n=11$, age 47.2 years |                           |                                                                          |
|                              | $e4− < 28$, age 47.0 years         |                           |                                                                          |
|                              | 0 subjects $e4/e4$ homozygous      |                           |                                                                          |
| Chang et al. (2011)          | HIV+ $n=69$, Approximately 80% on ART | MRI morphometry            | Brain volume:                                                            |
|                              | 29 (42%) with HAND                | Neuropsychological testing | -HIV+ $<SN$                                                             |
|                              | $e4− < 50$ years $n=31$           | ApoE genotype             | -HIV+ $e4+$ had the smallest brain volumes; younger SN $e4+$ had the largest (putamen, cerebral white matter) |
|                              | $e4− < 50$ years $n=16$           |                           | Cognitive performance:                                                    |
|                              | $e4+ < 50$ years $n=11$           | Ruff Figural Fluency Test: | -HIV+ $e4+$ < HIV+ $e4−$ or SN                                          |
|                              | $e4+ < 50$ years $n=11$           | < 50 years SN$e4+$ better than | -memory, learning, attention)                                            |
|                              | SN $n=70$, $e4− < 50$ years $n=32$ | -SN $e4+$ > SN $e4−$ (memory) |                                                                          |
|                              | $e4− < 50$ years $n=22$           | Ruff Figural Fluency Test: |                                                                          |
|                              | $e4+ < 50$ years $n=9$            | < 50 years HIV+ $e4−$ worse than |                                                                          |
|                              | $e4+ < 50$ years $n=7$            | > 50 years: no significant $e4$-related differences in SN or HIV+ groups |                                                                          |
| Jahanshad et al. (2012)      | HIV+ $n=55$, SN $n=30$            | MRI plus DTI tractography  | HIV+ $e4+$ have higher risk of neurodegeneration                          |
|                              | Age matched (60–80 years of age)  | ApoE genotype             | (impaired connectivity), exceeding normal aging                          |
|                              | All on ART                        |                           | Impaired connectivity in HIV+ $e4+$ exacerbated with longer duration of infection |
| Publication | Study population | Measures | Findings |
|-------------|------------------|----------|----------|
| Soontornniyomkij et al. (2012) | HIV+ n = 160 cases from 4 cohorts <br> Aged 27–67 years, median 46 years <br> Frozen brain tissue from 151 <br> SN n = 22 <br> Aged 24–90 years, median 50 years | APOE genotyping n = 151 <br> Immunohistochemistry for Aβ plaques n = 105 <br> Neuropsychological test HAND n = 78 | Probability and abundance of Aβ plaques is higher in Apoε4 carriers <br> Apoε4 and age ≥ 50 years independently predict Aβ plaques <br> Aβ plaques associated with HAND only with HIV+ Apoε4 carriers |
| Morgan et al. (2013) | HIV+ n = 466 <br> Apoε4+ n = 144, age 44.3 years <br> 68% on ART <br> Apoε4− n = 322, age 44 years <br> 69.9% on ART | Neurological tests ApoE genotype | No correlation between Apo ε4 and HAND |
| Hoare et al. (2013) | HIV+ n = 43 <br> ε4+ n = 24 (21 heterozygous and 3 homozygous) <br> Age 29.54 years <br> ε4− n = 19 <br> Age 28.58 years | Neuropsychological tests White matter integrity by DTI ApoE genotype | ε4 allele associated with memory impairment and corpus callosum atrophy |
| Panos et al. (2013) | HIV+ n = 259 <br> ε4+ > 50 years n = 18 <br> ε4+ < 50 years n = 59 <br> ε4− > 50 years n = 39 <br> ε4− < 50 years n = 143 <br> Approximately 84.5% on ART | Neuropsychological testing ApoE genotype | No impact of ε4 on neurocognition in overall cohort <br> HAND diagnosis more prevalent in older HIV+ε4+ than age-matched HIV+ε4− <br> Older HIV+ε4+ showed reduced executive functions, processing speed, independent of disease severity <br> Younger HIV+ε4+ and HIV+ε4− had similar frequency of HAND diagnosis |
| Chang et al. (2014) | HIV+ n = 80 <br> Age 47.3 years <br> ε4+ n = 23, age 47.0 years <br> 91% on ART <br> ε4− n = 57, age 47.4 years <br> 93% on ART <br> SN n = 97 <br> Age 44.7 years <br> ε4+ n = 28, age 45.3 years <br> ε4− n = 69, age 44.5 years | MRS cross-sectional study Neuropsychological testing | HIV+: elevated myoinositol (MI) in frontal WM across the age span <br> SN ε4+: antagonistic pleiotropy for MI ε4+: poor attention and working memory regardless of HIV status <br> HIV ε4+: lowest performance on most cognitive tests across age span |
| Becker et al. (2015) | The Multicenter AIDS Cohort Study (MACS) | Neuropsychological testing Longitudinal analysis Time to impairment Age, Time to death (Cox regression) ApoE genotype | Significant increase in the prevalence of ε4 among non-white subjects (primarily African-American) ApoE genotype not associated with time to cognitive impairment and cognitive outcomes or with time to death ApoE genotype not significantly interacting with HIV to increase risk of death |

Study population details:  
Cohort 1 (enrolled 1984 to 1985 and 1987 and 1991)  
\( n = 3411 \) with ApoE genotype: HIV+ n = 1224, SN n = 2187  
Mean ages all subjects: Apoε4− non-white 32.09 years, Apoε4+ non-white 32.14 years, Apoε4− white 33.79 years, Apoε4+ white 33.55 years  
No ART  
Cohort 2 (enrolled 2001 to 2003)  
\( n = 864 \) with ApoE genotype: HIV+ n = 465, SN n = 399  
Mean ages all subjects: Apoε4− non-white 38.29 years, Apoε4+ non-white 39.02 years, Apoε4− white 36.78 years,
earlier prospective study of a HIV-infected cohort with mean absolute CD4+ cell counts of approximately 350/mm³, “sufficient to avoid opportunistic infection” (Corder et al. 1998), reported a statistically significant excess of cognitive impairment symptoms and peripheral neuropathy in individuals with the ApoE4 isoform, some of whom had been treated with zidovudine ART.

Other studies have reported that the ε4 allele is associated with cognitive impairment in the context of HIV infection. In a cross-sectional study of 43 treatment naïve, young (≤ 35 years) HIV-infected adults in South Africa, Hoare and collaborators (2013) found that immediate and delayed verbal recall, determined by the Hopkins Verbal Learning Test-revised (HVLT-R), was significantly impaired in the 24 subjects with at least one ApoE4 allele compared to 19 subjects with no ApoE4 allele. Additionally, brain imaging with DTI detected atrophy of the corpus callosum in the ApoE4 carriers compared to the noncarriers. The investigators further stratified the study cohort into three groups: ApoE4 homozygotes (n = 3), ApoE4 heterozygotes (n = 24), and noncarriers (n = 19). Kruskal-Wallis tests of HVLT-R performed among the three groups produced a significant result, suggesting that verbal learning performance differed significantly across the three groups. While direct pairwise comparisons were not reported, the mean values of HVLT-R performance were lowest in the ApoE4 homozygous group, implying an ε4 allele dose effect, though interpretation is limited by the small number of homozygous ApoE4 subjects. The homozygous ApoE4 subjects also showed worsened corpus callosal atrophy compared to other subjects. Of note, all these patients were infected with clade C HIV-1, rather than the clade B HIV-1 infection of other reported cohorts. Chang et al. (2011) studied 139 “relatively young” subjects (average age < 50 years) by morphometry of MRI images to evaluate brain volumes (see below) as well as neuropsychological testing and ApoE genotyping (Chang et al. 2011). Their cohort included 69 HIV-infected and 70 SN subjects divided into four subject groups: HIV-infected ApoE4 carriers, HIV-infected noncarriers, SN ApoE4 carriers, SN noncarriers. The HIV-infected and SN subject groups had similar ages and prevalence of the ApoE4 allele; 29 (42%) of HIV-infected subjects had HAND while 4 (6%) of SN controls had cognitive deficits “comparable to HAND.” Chang et al. did observe poorer cognitive performance (verbal fluency, learning, executive function, memory) in HIV-infected ApoE4 carriers compared to HIV-infected noncarriers and SN controls. In contrast, SN ApoE4 carriers scored significantly higher on verbal learning and memory testing compared to SN noncarriers. When subjects were divided into younger (<50 years) versus older (≥50 years) subgroups, there was no significant ApoE4 effect in older HIV-infected or SN subjects, rather the ApoE4 effect was seen in younger subjects. In a study that estimated brain ApoE exposure as measured by ApoE levels in CSF, Andres et al. (2011) found that CSF ApoE levels were lower in HIV-infected versus healthy SN controls (mean age approximately 47–49 years). However, HIV-infected ApoE4 carriers had higher CSF ApoE levels, comparable to those of the SN controls, and the higher levels correlated with lower cognitive performance (HIV Dementia Scale and Global Cognitive Score). The investigators described this as a negative “dose-dependent” effect of CSF ApoE on cognition in HIV-infected ApoE4 carriers. Even SN ApoE4 carriers tended to an inverse relationship between CSF ApoE level and performance on tests related to learning, memory, and speed of processing. By contrast, in HIV-infected ApoE4 noncarriers, higher CSF ApoE levels tended to better performance on processing speed and executive functioning tests. But, there was no significant relationship between global cognitive scores and CSF ApoE level in either HIV-infected or SN without an ApoE4 allele. Thus, the effect of CSF ApoE levels in noncarriers was inconclusive.

The seemingly contradictory findings regarding the influence of the ApoE4 allele on cognitive performance in these HIV-infected cohorts may be due, at least in part, to an age dependence of the ApoE4 effect. Indeed, some studies have

### Table 3 (continued)

| Publication          | Study population | Measures | Findings |
|----------------------|------------------|----------|----------|
| Wendelken et al. (2016) | HIV+ n = 87, Ages 60–84 years, 76 with ApoE genotype | Neuropsychological testing, Brain MRI and DTI, ApoE genotype | At least 1 ε4 allele associated with poorer cognitive test scores (executive function), reduced brain white matter integrity and brain atrophy (corpus callosum, thalamus) |

ART antiretroviral treatment, Aβ amyloid beta

*Age values are mean ages unless otherwise specified as median or age range
found an age differential of the ApoE4 effect when subjects older than 50–60 years were analyzed separately, while the “negative” studies examined aggregate cohorts less than 65 years of age (noted in Becker et al. 2015). In their study of the HAHC, Valcour et al. hypothesized that, since the association between Alzheimer’s disease and the ApoE4 allele was more pronounced in elderly patients, any association between the ApoE4 allele and neurocognitive decline may also manifest preferentially in older HIV-infected patients. In their cohort of 182 HIV-infected participants, 97 were older than 50 years. Only in this older group was there an independent increased risk (odds ratio) for HAD associated with at least one ε4 allele, even after controlling for diabetes status and age (Valcour et al. 2004a; Valcour et al. 2004b). Panos et al. (2013) studied 259 HIV-infected subjects with average age of 43 years in both ApoE4 carriers and noncarriers. While there was no impact of the ApoE4 allele on neurocognitive functioning in the overall cohort, the older (≥ 50 years) ApoE4 carriers showed a significantly disproportionate risk (odds ratio = 13.14) for diagnosis of HAND compared with age-matched ApoE4 noncarriers. In the cognitive domains of executive functions and information processing speed, older ApoE4 carriers showed reduced performance, independent of disease severity (CD4+ cell count and duration of HIV infection). The younger ApoE4 carriers and ApoE4 noncarriers had a similar frequency of HAND diagnoses (odds ratio = 0.80).

In studies using pathological outcome measures, ApoE genotype did not correlate with neuropathological findings of HIV encephalitis or vacuolar myelopathy in earlier studies of AIDS patients (Diaz-Arrastia et al. 2004; Dunlop et al. 1997). But a more recent clinicopathological study of prospective cohorts including 160 HIV-infected patients found that the ApoE4 allele and older age (≥ 50 years) were independent factors associating with cortical (mid-frontal gyrus) amyloid-beta (Aβ) plaques (Soontornniyomkij et al. 2012). Plaques were diffuse and rarely associated with phospho-Tau immunoactivity, and thus more characteristic of aging, not symptomatic Alzheimer’s disease. The ApoE4 allele was associated with the abundance of cerebral Aβ plaques, which is consistent with neuropathology in cognitively normal aging (Morris et al. 2010). But when considering the clinical data for the HIV-infected patients, there was an association between cerebral Aβ deposition and manifestation of HAND in the ApoE4 carriers, but not the noncarriers. This result had parallels to a study of 408 “cognitively normal,” uninfected older adults (median age 79 years) in whom Aβ plaque load was measured by PET scan with [11C] Pittsburgh compound B (PiB) (Kantarci et al. 2012). The global cortical Aβ load was increased in ApoE4 carriers, and greater Aβ load was associated with worse cognitive performance on testing for memory, attention, language, and visual processing. This association was strongest in the ApoE4 carriers compared to other ApoE genotypes. Both studies suggest that ApoE4 associated with greater cerebral Aβ load which in turn associated with poorer cognitive performance on testing. But in the HIV-infected cohort studied by Soontornniyomkij et al. (2012), symptomatic cognitive performance deficit occurred at a younger age, with HAND detected at median age of 44 years. In the uninfected, “cognitively normal” older adults studied by Kantarci et al., the cognitive performance decline was measured at median age 79 years. Although the two studies use different measures of Aβ load, their comparative results imply that HIV infection can accelerate cognitive aging in individuals who carry the ApoE4 allele.

Neuroimaging studies have also been used to examine the influence of ApoE4 on brain structure and metabolism in aging HIV infection. In a sample of older HIV-infected subjects aged 60–84, the presence of at least one ApoE4 allele was associated with decreased executive functioning on cognitive testing, with reduced brain white matter integrity, and with brain atrophy most prominent in the posterior corpus callosum and thalamus, as measured by MRI with DTI imaging (Wendelken et al. 2016). This cross-sectional study did not include SN controls but compared ApoE4 carriers to noncarriers. In a study using combined MRI-based cortical parcellations plus DTI tractography, brain degeneration beyond that expected for normal aging was found in HIV-infected ApoE4 carriers between 60 and 80 years of age, as compared to age-matched SN (Jahanshad et al. 2012). Brain degeneration was assessed by mapping white matter connections between cortical regions of the brain. The study revealed that older HIV-infected ApoE4 carriers have a higher risk of impaired connectivity, particularly involving the temporal and parietal regions of the brain. Interestingly, interruptions in brain networks were exacerbated with longer duration of infection, implying an accelerated effect of HIV and ApoE4 on biological aging. The study by Chang and collaborators that used morphometry of MRI images to evaluate brain volumes (Chang et al. 2011) showed that global cerebral volumes were larger in SN individuals and smaller in the HIV-infected (−4.8%, p < 0.001). The largest brain volumes were found in younger (<50 years) SN ApoE4 carriers, while the smallest were found in the HIV-infected ApoE4 carriers. Significant HIV status and ApoE4 effects on brain volume were evident in multiple brain regions: the right amygdala, right pallidum, left thalamus, left cerebellar white matter, bilateral cerebral white matter, right cerebral cortex, and global cerebral volume. When the imaging data were stratified for age, all older ApoE4 carriers (HIV-infected and SN ≥ 50 years) had smaller brain volumes than noncarriers. However, younger (<50 years) SN ApoE4 carriers had larger brain volumes, larger than both younger SN without the ApoE4 allele and the older SN ApoE4 carriers. The younger (<50 years) HIV-infected ApoE4 carriers showed atrophy particularly in the putamen and right cerebral white matter, when compared to the younger HIV-infected noncarriers; but this relative brain volume
loss was not seen when comparing older HIV-infected ApoE4 carriers versus noncarriers. All SN and the HIV-infected noncarriers showed age-related volume decline in putamen and thalamus, while HIV-infected ApoE4 carriers did not, possibly because these structures had already atrophied at a younger age in those subjects (Chang et al. 2011). Thus, the presence of the ApoE4 allele appeared to accelerate aging in these HIV-infected ApoE4 carriers with respect to volume decline in certain brain regions. As noted above, the group of HIV-infected ApoE4 carriers also showed worse cognitive performance, and this was regardless of HAND diagnosis. The SN ApoE4 controls showed better memory, more so in the younger subjects. The investigators interpreted these findings as a demonstration of antagonistic pleiotropy by the ApoE4 allele, with a beneficial effect on younger but not older SN individuals, reflecting a differential impact of the ApoE4 allele during different life stages (Tuminello and Han 2011). However, a negative impact of the ApoE4 allele is seen much earlier in the HIV-infected subjects, suggesting an accelerated aging effect. A subsequent study using MRS (Chang et al. 2014) showed antagonistic pleiotropic effects of the ApoE4 allele on the frontal lobe white matter myo-inositol, the marker for glial activation and neuroinflammation, in the SN subjects. Myo-inositol increased with age in all SN subjects, but with a lower initial value (at approximately age 25 years) and subsequent steeper slope between ages 25–70 years in the SN ApoE4 carriers compared to SN noncarriers. This suggests SN ApoE4 carriers have relatively less frontal lobe neuroinflammation at a young age, but “catch up” or even surpass the noncarriers at an older age, consistent with antagonistic pleiotropy. In HIV-infected subjects, frontal white matter myo-inositol was increased across the age span, regardless of ApoE genotype, suggesting that HIV infection attenuated the antagonistic pleiotropic effect of ApoE4 on neuroinflammation. As antagonistic pleiotropy by the ApoE4 allele can produce counterintuitive findings in SN ApoE4 carriers, it may be another factor underlying seemingly contradictory findings on the influence of the ApoE4 allele in studies of HIV-infected versus SN subjects, particularly if clinical studies do not have adequate younger and older age representation in both the HIV-infected and SN control groups.

**ApoE4 and HIV infection: potential mechanisms of interaction**

Studies in rodent models or mammalian cell cultures have produced diverse molecular mechanisms that illustrate a differential effect of ApoE4 on neural cells and the brain, and the potential for interaction with HIV infection (Supplementary Table S1). Rodent models have used targeted replacement (TR) mice, which are transgenic animals generated by microinjecting the human ApoE gene (either ApoE2, e3, or e4) into single-celled embryos fertilized by APOE knockout males. These mice are then backbred with ApoE knockout mice to generate heterozygous mice for human ApoE gene but lacking the mouse ApoE. Continuous breeding of heterozygous mice is performed to generate homozygous human ApoE mice. ApoE expression is driven by a human ApoE promoter with a pattern that is similar to that of ApoE in humans (Xu et al. 1996). These mice, “humanized” for ApoE expression, reproduced differential ApoE4 effects on such processes as dendritic complexity (Dumanis et al. 2009), innate neuroimmune responses (Vitek et al. 2009), neuronal regeneration following innate immune inflammation (Maezawa et al. 2006c), or neuronal responses to traumatic brain injury (TBI) (Crawford et al. 2009; Sabo et al. 2000). Primary microglia cultures from TR ApoE mice stimulated with lipopolysaccharide (LPS) displayed an isoform-dependent innate immune activation that was highest with TR ApoE4 and dependent on p38MAPK signaling (Maezawa et al. 2006b), but the primary astrocytes from these mice showed lower levels of secreted inflammatory cytokines, attributed to differences in NF-kB signaling (Maezawa et al. 2006a). In vivo stimulation of innate immunity by intracerebroventricular LPS injection of TR ApoE mice resulted in loss of dendrite length in hippocampal neurons after 24 h, similar for all three ApoE isoforms. However, recovery of dendrite length over the subsequent 48 h was ApoE isoform dependent, and TR ApoE4 mice did not display any observable dendrite regeneration (Maezawa et al. 2006c). In a study of controlled impact TBI, rodents expressing the human ApoE4 died more frequently, while the ApoE4 survivors showed worse cognitive function and decreased neurite growth compared to TR mice expressing human ApoE3 protein or no human ApoE (Buttini et al. 1999; Sabo et al. 2000). After TBI, ApoE3 and ApoE4 mice showed differences in gene expression profiles from both cortex and hippocampus (Crawford et al. 2009), and the differences suggested a “loss of reparative function rather than a gain of negative function” in the presence of ApoE4. Recent studies using human neural cell cultures underscore the potential for repressive effects of ApoE4 on gene transcription. In a study using human neuroblastoma and human glioblastoma cells, transfection with ApoE3 and ApoE4 expression vectors demonstrated that ApoE4 interacted with certain specific gene promoters, reducing transcription, and reducing the mRNA levels for these genes (Theendakara et al. 2016). This implied a capacity for ApoE4 to function as a transcriptional repressor. To identify specific effects of ApoE isoforms on neurons in the context of HIV infection, human neuronal lineage progenitor cells with the ApoE3/e3 genotype were differentiated in culture with added HIV or control supernatants and individual recombinant ApoE isoform proteins rApoE3 or rApoE4. While addition of rApoE3 resulted in discrete changes in gene expression, addition of rApoE4 resulted in the downregulation of 85 genes, half of which involved processes associated with neurogenesis, an effect that was
magnified in the presence of HIV (Geffin et al. 2017). Both of these studies used a strategy of altering the ApoE phenotype in human neural cells in culture, producing a common outcome of depressed differential gene expression associated with the ApoE4 phenotype compared to the ApoE3 phenotype.

ApoE4 may also interact directly with HIV proteins or infected cells to increase the net neurotoxic effects of neural infection. In an in vitro study using neuronal cultures derived from 54 different human fetal brain specimens, neurotoxicity, measured by decreased mitochondrial potential, was observed in cells exposed to gp120 plus Tat or Tat plus morphine. Cultures with the ApoE3/ε4 or ApoE4/ε4 genotypes were significantly more susceptible to toxic effects, with a threefold increase in neurotoxicity detected in the ApoE4/ε4 cells exposed to gp120 plus Tat (Turchan-Cholewo et al. 2006). Indeed, tat protein, binds to the neuronal lipoprotein receptor LRP1, which can inhibit uptake and clearance of ApoE4, effectively prolonging its circulation in the neuron’s microenvironment. Viral gp120 may affect ApoE binding at the cell surface, as suggested by data showing that added rApoE4 but not rApoE3-enhanced HIV-target lymphoid cell fusion and increased cell susceptibility to HIV infection (Burt et al. 2008). ApoE4 may also augment the impact of HIV infection on Aβ beta production (Pulliam 2009) and further accelerate the impact of aging on the HIV-Aβ dynamic.

Conclusions

Now, well into the third decade of the use of increasingly effective ART, HIV infection is not a death sentence when adequately diagnosed and treated. HIV-infected individuals will live longer, often into the seventh or eighth decades of life. HIV infection has become a chronic medical and neurological disorder. As such, it is now a disorder that must be included in the differential diagnosis during clinical assessment of NCI in the older patient. While the severe dementia of HAD is far less prevalent, varying degrees of NCI are more prevalent in the HIV-infected population. Neuropsychological symptoms of NCI are variable among and within individuals (Hines et al. 2016), but an extensive body of neuropsychological evidence suggests that the infected person is cognitively older than a seronegative person of similar age and medical health. With effective ART, the clinical course of HAND likely reflects the compound effects of age-related decline in neurocognitive reserve (Chang et al. 2013), genetic factors, medical comorbidities, and treatment efficacy all superimposed on the underlying HIV infection. Paraclinical evidence, e.g., neuropathology or brain imaging studies, indicates that premature aging of the brain may be present even before neurocognitive symptoms. Age and HIV infection together impact brain volume loss, deposition of Aβ, and metabolic markers reflecting glial or neuronal function. Premature brain aging is likely a combination of accentuated and accelerated aging effects. Accentuated aging would be evident throughout the time course of infection, such as the higher brain-PAD scores reflecting structurally older brains (Cole et al. 2017), or the older biological age, independent of duration of infection, measured by epigenetic DNA methylation (Gross et al. 2016). Accelerated aging would be increasingly evident with age, such as the time-related changes manifest in DTI patterns of the corpus callosum genu (Chang et al. 2008).

The experimental evidence supporting the concept of premature brain aging in HIV infection has been confounded by the relatively young age of study cohorts, particularly in the pre-ART and early ART eras. Moreover, SN controls were not consistently matched for medical comorbidities or health risk factors which are common to aging. As studies advanced into the second and third decades of the ART era, improved survival produced HIV-infected study populations that were better stratified into younger and older subgroups, roughly ≤ or ≥ 50 years, with corresponding age-matched SN groups that are also controlled for medical comorbidities. The introduction of much older study subjects, roughly ≥ 65 years, has clarified the recognition that cognitive performance in younger HIV-infected individuals is similar to that of much older SN individuals, a finding that suggests accelerated aging. Neuropsychological testing and neuroimaging modalities have proved sensitive enough to detect abnormalities that are “pre-clinical” or “paraclinical,” i.e., present in HIV-infected individuals who are neuroasymptomatic. Overall, the evidence from more than three decades of studies support the concept of HIV infection as increasing the risk for premature brain aging, manifested by cognitive impairment or brain volume loss. But HIV infection does not cause either pre-clinical or symptomatic Alzheimer’s disease in the aging patient, and that distinction must be considered in clinical assessments of patients who present with cognitive complaints.

ApoE4 is emerging as a factor influencing cognitive function in normal aging, showing differential effects across the lifespan, or “antagonistic pleiotropy.” These effects may be beneficial in younger individuals but pathological in older individuals. Neuroimaging studies indicate that brain structural and metabolic parameters decline at relatively younger ages in HIV-infected ApoE4 carriers. To this point, Chang and collaborators have presented compelling evidence that suggests that HIV infection negates the potentially beneficial effects of antagonistic pleiotropy on cognition, brain volume, or frontal white matter inflammation in younger ApoE4 carriers (Chang et al. 2011; Chang et al. 2014). But overall, neuropsychological studies of HIV-infected cohorts have produced conflicting results regarding the impact of ApoE4 or the ApoE4 allele on the course of cognition. Neuropsychological performance in HIV-infected subjects is a very complex outcome measure that is confounded by the individual’s age, medical comorbidities, genetic influences, and within-person variability (Hines et al.
and the ApoE4 phenotype may potentiate a B expression profiles after HIV exposure (Geffin et al. 2017), ments have demonstrated effects of ApoE4 on neuronal gene mechanisms of interaction between ApoE4 and HIV proteins significance. There is non-clinical data to model potential data show trends for interaction but do not achieve statistical ective function neurogenesis at the gene expression level. In particular, ApoE4 may be capable of direct transcriptional repression for some genes (Theendakara et al. 2016). If ApoE4 impairs expression of genes related to neural repair or neuronal complexity, then its effects on the brain would be compounded by HIV infection and aging, leading ultimately to diminished cognitive reserve. Together, the clinical and non-clinical data of the current ART era do provide sufficient basis to implicate ApoE4 carrier status as an additional longitudinal risk factor for premature brain aging in HIV infection. If the impact of the ApoE4 allele on brain aging and cognitive reserve can be better predicted is to its predictive value, then ApoE genotype may inform cognitive risk assessment and treatment planning for the aging HIV-infected patient. Thus, as the aging HIV-infected population grows, so does the need for further longitudinal studies of these patients, studies which include extended age ranges, both clinical and paraclinical outcome measures, and ApoE genotyping and stratification. Given the low frequency of the ApoE4 allele in the general population, such study designs present statistical challenges that would probably necessitate multicenter involvement. But ultimately, such studies can ex- tend our understanding of cognitive reserve not only in aging HIV-infected but also in normal controls, and thus lead to better health care for the aging population.

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Compliance with ethical standards

This review is based entirely on published work indexed by PubMed (National Library of Medicine). No personal communications or unpublished findings were considered in the preparation of this review.

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

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