*Invited Review*

# Neurocognition and the Aging Brain in People With HIV: Implications for Screening

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*The introduction of effective antiretroviral therapy (ART) has converted HIV infection from a lethal disease to a manageable chronic condition for most people. The drastic improvement in life expectancy of people with HIV has led to an expansion of the aging population of people with HIV globally. Recent research indicates that people with HIV on suppressive ART still sustain persistent, albeit alleviated, systemic and cerebral immune activation that can facilitate age-related causes of cognitive impairment (CI), including neurodegenerative and cerebrovascular diseases. Although HIV-associated neurocognitive disorder remains prevalent in older people with HIV on suppressive ART, the co-occurrence of other age-related causes of CI makes the investigation and management of CI more challenging. More importantly, it remains unknown if the neuropsychiatric manifestations of HIV-associated neurocognitive disorder are modified by the presence of age-related causes of CI, such as Alzheimer disease, and vice versa. This article will review findings regarding the interaction between HIV-1 infection and age-related comorbidities, namely atherosclerosis and neurodegenerative diseases, followed by cognitive outcomes of people with HIV in longitudinal studies. Cognitive symptoms of people with HIV on stable ART will be discussed. The review will go through the latest recommendations for cognitive screening in different HIV management guidelines, as well as the usefulness of various screening tools in the setting of stable viral suppression.*

**Keywords:** neurocognition, HIV, screening, HAND, cognitive impairment, aging

## Introduction

The availability of effective antiretroviral therapy (ART) has converted HIV infection from a lethal disease to a manageable chronic condition. People with HIV on stable and suppressive ART now enjoy a life expectancy comparable to HIV-uninfected populations. This drastic change in longevity has given rise to an upsurge of populations of aging people with HIV. Globally, around one-fifth of people with HIV are age 50 years or older, and the frequency of people with HIV age 50 years or older in the United States has been greater than 50% for many years. This demographic change has led to a shift in the focus of medical care and research from the management of immunodeficiency and opportunistic infection to that of noncommunicable diseases, particularly age-related comorbidities.

Cognitive impairment (CI) has been one of the more common complications among people with HIV since the pre-ART era. Before the availability of ART, AIDS dementia complex (ADC) was commonly seen in people with HIV of advanced immunodeficiency. In the current era, the frequency of HIV-associated dementia (HAD), an equivalent diagnosis to ADC, but employing the contemporary "Frascati" research criteria for HIV-associated neurocognitive disorder (HAND),[1] has dropped from about 15% to less than 5%, particularly among those on suppressive ART. Despite this, milder forms of HAND, namely asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), remain common and range from 30% to 60% in studies with people with HIV on ART. However, these figures were largely based on samples of younger individuals. The prevalence and incidence of CI are likely to rise with aging, when other age-related causes of CI, namely neurodegenerative diseases and cerebrovascular diseases, unfold.

In younger people with HIV, the diagnosis of HAND is largely based on the exclusion of other etiologies. In older people with HIV, the co-occurrence of other age-related causes of CI could make the investigation and management of CI more challenging. In particular, existing studies support a view that HIV infection could lead to premature and accelerated cognitive aging among those who are older now and who have had an extensive duration with HIV, sometimes without suppression of HIV RNA.[2] Moreover, it remains unknown if the neuropsychiatric manifestations of HAND are modified by age-related causes of CI, and vice versa. Cognitive screening tools that work well for common neurodegenerative diseases may not have the same performance characteristics among people with HIV given the frequent cognitive inefficiency related to HIV, which can lead to abnormalities in testing performance across multiple domains. Furthermore, there is growing concern that incomplete immune recovery and persistent inflammation in people with HIV on suppressive ART could potentially fuel age-related

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processes, including atherosclerosis and neurodegenerative diseases.

## Vascular Diseases in People With HIV in the ART Era

In the past, vascular dementia was narrowly defined as the cognitive decline seen after a documented stroke. More recent research highlights the important relationship between vascular pathology and cognitive decline.[3] Indeed, over 75% of aging brains show evidence of vascular pathology at autopsy, and both Alzheimer disease (AD) and vascular pathologies are key predictors of CI in the elderly. Cerebral small vessel disease has been associated with HAND in people with HIV. Compared with individuals without HIV, people with HIV have about 2-fold increased relative risk (RR) of coronary artery disease and 3-fold increased RR of stroke. In a systematic review of 80 longitudinal cardiovascular disease (CVD) studies, the global burden of HIV-associated CVD has tripled over the past 2 decades,[4] highlighting the persistent threat of CVD in people with HIV in the ART era. Data from Denmark and the United States suggest that people with HIV have a 1.6-fold to 2-fold increased risk of stroke compared with individuals without HIV, after adjustment of confounding factors.

HIV infection likely modifies atherosclerosis, one of the most important contributors of cerebrovascular diseases. Structurally, noncalcified coronary plaques are more prevalent in people with HIV than in individuals without HIV. Recent research highlights the association between atherosclerosis, persistent systemic immune dysregulation, and HIV reservoir. Monocyte/macrophage activation, denoted by elevated levels of plasma sCD14 and sCD163, and reversed CD4/CD8 ratio, a marker of T-cell dysregulation, is associated with atherosclerosis in people with HIV. Both conditions persist despite viral suppression.

HIV-encoded proteins, including transactivator of transcription (Tat), negative factor (Nef), and envelope protein gp120, are linked to inflammation, endothelial dysfunction, and endothelin-1 production.[5] Notably, the HIV reservoir is still able to produce HIV-encoded proteins through low-level transcription during plasma viral suppression. Increased microbial translocation in the gut, which persists during HIV suppression, serves as an important potential contributor to atherosclerosis, even among HIV-uninfected populations.[6] Apart from abnormal vascular wall inflammation detected by vascular positron emission tomography (PET) imaging, preclinical atherosclerotic changes of small-to-medium–sized intracranial arteries were readily detected in people with HIV within the first 6 years of HIV infection in autopsy,[7] suggesting that ART reduces inflammation but does not resolve arterial remodeling.

The elevated risk of atherosclerosis in treated people with HIV thus leads to the hypothesis that HAND persistence in the ART era might originate from vascular diseases.[8] In studies to date, HIV serostatus inconsistently serves as an independent risk factor linking atherosclerosis and CI. Nonetheless, HIV serostatus is strongly associated with metabolic risk factors of atherosclerosis, namely diabetes and hyperlipidemia. Future studies could clarify whether HIV infection is an independent risk factor of atherosclerosis and examine the longitudinal impact of atherosclerosis on the burden of vascular pathology and cognitive function in people with HIV.

## HIV Infection and Neurodegenerative Diseases

In HIV-uninfected populations, systemic inflammation is a predictor of age-related cognitive decline. Systemic inflammatory scores built from levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, and iron predicted longitudinal cognitive outcomes in older adults. In another study, a combination of blood fibrinogen, white blood cell count, von Willebrand factor, and factor VIII, and CRP at midlife was predictive to cognitive change over 20 years. In people with HIV, recent research has indicated the persistence of cerebral inflammation despite suppressive ART, evidenced by elevated inflammatory and neuronal injury markers in the cerebrospinal fluid (CSF), abnormal central nervous system (CNS) metabolites in magnetic resonance spectroscopy, and abnormal activation signal in brain PET scans us ing macrophage/microglia-specific ligands. Moreover, elevated immune activation markers were associated with impaired cerebral white matter (WM) integrity, represented by lower fractional anisotropy and higher mean diffusivity in diffusion tensor imaging, in people with HIV. The latter was linked to worse cognitive speed and executive functions, and worse global cognitive performance.[9]

Whether persistent cerebral inflammation might accelerate or augment the cognitive symptoms among those with underlying neurodegenerative disease, such as AD and Parkinson disease (PD), remains inconclusive. Although there are reports that some people with HIV and CI have alterations of CSF biomarkers of AD including beta-amyloid and tau levels, recent PET studies do not show major differences in amyloid deposition stratified by HIV serostatus or HAND severity. However, no study to date compares the progression of cognitive decline or the change in AD-related biomarkers in AD-positive individuals with and without concomitant HIV infection. To date, only a handful of case reports have described diverse neuropsychiatric manifestations of individuals with HIV who presented with AD; some of them were pathologically confirmed.

## Neurocognitive Outcomes in People With HIV on Suppressive ART

HIV enters the CNS within days after transmission. Impaired cognitive performance and depression symptoms are frequent among individuals who were recently infected during acute HIV. Without ART, cognitive deficits often develop and progress in a pattern that some have described as "subcortical," affecting psychomotor speed, information processing, executive function, and working memory, in addition to the

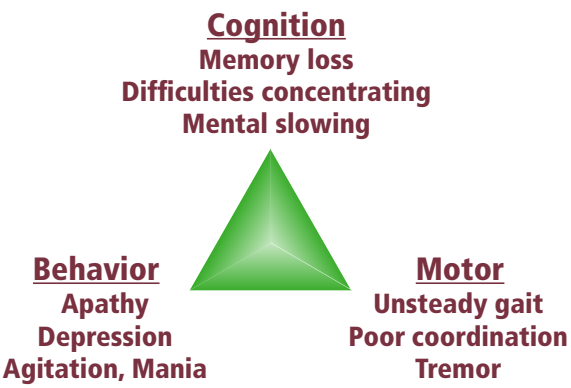


**Figure.** Clinical symptoms seen in the setting of HIV. Although individuals with HIV often present with memory complaints, careful questioning often identifies challenges with attention and concentration, as well as symptoms in the motor and behavioral domains.

psychiatric symptoms (Figure). In the pre-ART era, CI in people with HIV predominantly affected motor skills, cognitive speed, and verbal fluency, whereas those with HAND in the ART era demonstrate an increased association with memory (learning) and executive function deficits.[10] Women with HIV on suppressive ART share a similar profile of cognitive deficits. In a study with 239 middle-aged, virally suppressed women, participants with HIV scored lower in tasks involving learning, memory, attention, working memory, and fluency than HIV-uninfected controls. Two European cohort studies (COBRA [Comorbidity in Relation to AIDS] and POPPY [Pharmacokinetic and Clinical Observations in People Over Fifty]) targeting middle-aged people with HIV on suppressive ART showed worse performance in attention, executive function, psychomotor speed, and verbal learning than matched HIV-uninfected controls. Taken together, these studies revealed a mixed pattern of subcortical and cortical cognitive findings among aging people with HIV in the ART era. Clinically, poor memory may be the most common complaint of people with HIV with CI, despite testing that reveals learning inefficiency, attentional deficits, and executive challenges rather than deficits in encoding new memories. Closer inspection of the actual symptoms may reveal a mix of symptoms, including attentional deficits such as rereading of information to understand it and better recall with cues, as well as working memory and executive function challenges revealed through symptoms of difficulty in holding memory during multitasking.

The stability of cognitive function post-ART is another focus of HAND research. In an initial report from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort that included 226 cognitively normal and 121 participants with ANI, those with ANI demonstrated a 2-fold to 6-fold increased risk of becoming symptomatic compared with cognitively normal participants at follow-up. In the MACS (Multicenter AIDS Cohort Study) investigation, the frequency of HAND increased from 25% to 31% among 197 individuals with HIV after 5 years of follow-up between 2007 and 2012. During the study period, 77% of the participants remained at the same stage, 13% deteriorated, and 10% improved. However, the 2 studies were limited by participants' inconsistent treatment and virus suppression status.

A follow-up cognitive trajectory analysis from the CHARTER cohort revealed that participants with declining cognitive trajectory were older, had worse baseline cognitive performance, and had a longer duration of HIV infection. In an Australia-based longitudinal study with 96 people with HIV on suppressive ART, only 16% showed cognitive decline over the study period of 18 months: 13% had either a history of HAND or baseline CI, compared with 3% who had neither condition. The rate of cognitive decline is similarly low in cohort studies of middle-aged people with HIV. A recent report from the HAILO (Long-term Follow-up of Older HIV-Infected Adults in the ACTG: Addressing Issues of Aging, HIV Infection, and Inflammation) study, which included 929 people with HIV at a median age of 51 years, identified CI in 16% of the participants at study baseline, whereas the development of CI over 3 years was 6%. A longitudinal report from the COBRA study revealed generally stable cognitive performance in virally suppressed people with HIV in comparison with the HIV-uninfected control over 2 years.

Longitudinal studies also shed light on the stability of different cognitive domains in people with HIV on suppressive ART. In the trajectory study of CHARTER, executive and motor functions, examined by the Trail Making Test B and the dominant hand grooved pegboard test, were the most common domains with decline over time. In contrast, no participant showed a decline in performing tasks related to verbal fluency (letter and category) and memory recall (verbal and nonverbal). Among virally suppressed people with HIV, subclinical decline in psychomotor speed and executive functioning were reported in the Australian cohort study, whereas a greater decline in motor skills was reported in the WIHS (Women's Interagency HIV Study) investigation that compared women who are virally suppressed and women without HIV. In short, longitudinal studies confirm the higher risk of cognitive decline in those with pre-existing CI or history of HAND; however, the rate of advanced impairment seen in dementia remains very small. In contrast, people with HIV without pre-existing CI or history of HAND demonstrated stable cognitive performance after suppressive ART. Among cognitive domains, declines in executive, motor, and psychomotor functions are the most common. In the authors' experiences, cognitive statuses of people with HIV suffering from concomitant HAND and AD usually deteriorate over 2 to 3 years, whereas cognitive statuses of those with HAND alone fluctuate without persistent decline.

## Intraindividual Variability as a Marker of Cognitive Deficit in People With HIV

Apart from persistent, sometimes progressive CI that manifests as persistent cognitive deficits, older people with HIV

who have HAND often report fluctuation in cognitive symptoms, a finding that would not be surprising given the links between inflammation and cognitive performance. Indeed, some studies document fluctuating cognitive performance in people with HIV, as noted in the 2007 Frascati criteria.[1] Such fluctuations may present as periods of normal mental capacities intercalated with days of cloudiness of mind. Occasionally, such cognitive fluctuations may not be captured by a one-off assessment that focuses on mean-level cognitive performance. Recently, cognitive intraindividual variation (IIV) has attracted increased interest in the broader field of neurodegeneration because of its potential in predicting underlying CNS disorders and their progression. Cognitive IIV can be subdivided into inconsistency and dispersion. The former measures variations in cognitive performance across trials within a task or across sessions spanning longer intervals. The latter highlights variations across multiple tasks at a single point in time.

Cognitive IIV increases with age and cognitive decline in HIV-uninfected adults, as well as in those with neurodegenerative diseases including AD and PD. Moreover, it correlates with CSF biomarkers of AD. Cognitive IIV better detects mild cognitive impairment (MCI) and AD, and better predicts cognitive deterioration than mean-level cognitive performance. Structurally, cognitive IIV is correlated with WM integrity of the brain in older adults with or without AD. Cognitive IIV increases with concomitant impairments in attention, memory, and language in the older population, especially attentional lapses and fluctuations in executive control, suggesting that cognitive IIV can arise from interruptions of the grey and white frontal cortex neural network.[11] Given its anatomical proximity to the frontostriatal system compromised by HIV infection, people with HIV may demonstrate abnormal cognitive IIV.

Recent studies support this hypothesis. Cognitive dispersion and variability in accuracy response across trials increased with age and HIV status. Increased cognitive dispersion was associated with worse cognitive performance in a study that included both people with HIV and HIV-uninfected controls. Functionally, increased dispersion in people with HIV predicted worse medication adherence, subsequent dependence in activities of daily living, future cognitive decline, and death after controlling for HAND severity and global cognitive functioning. However, the relationship among cognitive IIV, global cognitive performance, and structural changes of the brain is less clear. In a cross-sectional study, total grey matter volume was inversely associated with cognitive dispersion but was independent of HIV status. In another longitudinal study, participants with HIV showed a greater dispersion than the HIV-uninfected controls despite similar global cognitive test performance. Furthermore, greater dispersion was related to lower fractional anisotropy values in the anterior thalamic radiations and the superior longitudinal fasciculus. Taken together, cognitive IIV appears to be a potential tool for HIV-related cognitive deficits and for age-related CI.

## Current Guidelines and Recommendations for Cognitive Screening in HIV Infection

To date, evidence for and against routine cognitive screening in HIV infection remains inconclusive. The US Preventive Services Task Force (USPSTF) concludes that, among asymptomatic adults without HIV above 65 years old, screening for CI does not show clear evidence of benefit or harm to patients and their caregivers.[12] Although earlier detection and the subsequent intervention of CI could be beneficial to patients and their caregivers, the stress of cognitive screening, the risk of a false-positive result, and the stigma of CI should be carefully balanced. It is important to clarify that these screening recommendations relate to individuals without cognitive symptoms rather than a diagnostic workup that may typically occur among patients presenting with cognitive symptoms.

In the context of the varied cognitive impairment profile in HAND and the uncertain nature of the interaction between HIV infection and aging,

**Table.** Summary of Cognitive Screening Recommendations From Various Guidelines for People With HIV

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| **British HIV Association (BHIVA)[14]** | - All individuals with HIV should have regular screening to identify psychologic support needs<br>- Individuals with HIV should have access to screening for cognitive difficulties within the first 3 months of receiving an HIV diagnosis |
| **European AIDS Clinical Society (EACS)[16]** | Clinicians can make use of a 3-question screening tool for people with HIV who present with cognitive complaints:<br>1. Do you experience frequent memory loss (eg, do you forget the occurrence of special events, even the more recent ones, such as appointments, etc)?<br>2. Do you feel that you are slower when reasoning, planning activities, or solving problems?<br>3. Do you have major difficulties paying attention (eg, to a conversation, book, or film)?<br>Answering "yes" to 1 or more of these questions may suggest the presence of cognitive disorders, although not necessarily linked to HIV. Attending clinicians should consider referral to a neurologist and clinical psychologist for further assessment as appropriate |
| **International Antiviral Society–USA (IAS–USA)[15]** | Periodic assessment of cognitive function using a validated instrument is recommended for people with HIV who are older than 60 years of age |
| **World Health Organization (WHO)[13]** | Routine screening and management for mental health disorders (particularly depression and psychosocial stress) should be provided for people from key populations with HIV in order to optimize health outcomes and improve adherence to antiretroviral therapy |

recommendations about cognitive screening are considerably different and nonspecific in HIV management guidelines (Table). For example, the World Health Organization (WHO)[13] and the British HIV Association (BHIVA)[14] recommend routine screening and management of mental health disorders for key populations of people with HIV to optimize health outcomes and ART adherence. However, the guidelines do not specify the preferred screening tools nor recommend a frequency of screening in asymptomatic people with HIV. Likewise, the IAS–USA guidelines suggest routine assessment of cognitive function every other year using a validated instrument in people with HIV after the age of 60 years, but it does not describe a validated instrument with good performance characteristics. The IAS–USA guidelines[15] note that individuals with progressively worsening symptoms of HAND should be referred to a neurologist for evaluation or to a neuropsychologist for formal neurocognitive testing.

Contrary to the aforementioned guidelines, the European AIDS Clinical Society (EACS) recommends a stepwise approach in tackling cognitive complaints in people with HIV. The EACS v10.0 guidelines[16] recommend evaluating cognitive complaints in people with HIV using a 3-question screen that covers memory loss, mental slowing, and attention difficulties. Positive response in any 1 of the 3 questions warrants further evaluation and referral to a neurologist and neuropsychologist. In a study with mandatory application of the 3-question screen to 974 mostly viral-suppressed people with HIV, around one-fourth of them answered positively to at least 1 of the 3 questions. Among those, half showed CI in formal neuropsychological assessment. The positive and negative predictive values of genuine CI by this approach were 0.35 and 0.7, respectively. Individuals who responded positively to all 3 questions showed an increased risk of underlying depression. Although the EACS approach does not offer satisfactory predictive value to cognitive complaints in people with HIV, it is practical and clinically pragmatic in tackling a mix of neuropsychiatric symptoms in people with HIV and is especially useful in resource-limited settings.

## Available Tools for Cognitive Screening in Aging People With HIV and Cognitive Complaints

Although full neuropsychologic assessment remains the gold standard for diagnosing HAND, it is not readily available in most clinical settings and can be too cumbersome for use in screening. Simple screening tools such as the HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS) have been developed for the detection of the most severe forms of impairment in resource-limited settings. However, their usefulness in the ART era, especially their accuracy in detecting milder forms of HAND, is poor. Based on the recommended cutoff score, HDS is not sensitive to CI in people with HIV on suppressive ART, with a sensitivity and specificity of 24% and 92%, respectively, in the CHARTER cohort. Modifying the raw cutoff score to 14 yielded better sensitivity and specificity of 66% and 61%, respectively.

Similar performance characteristics are noted for the IHDS in the ART era. In the initial validation study, the IHDS demonstrated sensitivity and specificity of 80% and 57%, respectively, in the US cohort, and 80% and 55%, respectively, in the Uganda cohort in identifying HAD. However, in 2 subsequent Africa-based studies, despite around two-thirds of the participants being on ART, 64% and 83% were screened positive by the IHDS, highlighting the likely overestimation of HAD. Moreover, 77% of the HIV-uninfected controls in one of the studies would have been rated as "cognitively impaired" based on a cutoff score of 10 in the IHDS.[17] This figure is well above the reported HAD prevalence of 25% to 31% in Uganda and South Africa using conventional neuropsychologic testing. In a Dutch study with mostly treated people with HIV, combining the IHDS with the EACS 3-question screen showed sensitivity and specificity of 50% and 73%, respectively.

The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), the latter of which has been translated and validated in different languages, are commonly used cognitive screening tools to identify age-related CI in HIV-uninfected adults. MMSE is the most widely used screening tool for AD, but it is not sensitive enough to detect MCI. Without testing executive function and motor skills, MMSE is insensitive to HAND. MoCA evaluates visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation function in an individual; thus, it is potentially useful for aging people with HIV who present with CI driven by HAND, AD, vascular CI, or in combinations. In a study that identified HAND in people with HIV older than 60 years of age, MoCA with an optimized cutoff score of 25/30 or less showed sensitivity and specificity of 72% and 67%, respectively. In a meta-analysis that included 8 cross-sectional studies using MoCA to identify HAND, the authors concluded that a lower threshold than the original cutoff (≤25/30) of MoCA would lower false-positive rates and improve its diagnostic accuracy, but the choice of cutoff always comes with a sensitivity–specificity trade-off.[18]

With the advancement of portable digital devices and their increased penetration into daily activities, including among the elderly, digital cognitive assessment could be a solution to replace conventional neurocognitive assessment, which is labor-intensive and highly skill-dependent. More recently, digital cognitive assessments are being developed as mobile applications (apps) operated on tablets with or without an internet connection. Compared with computer-based assessment, mobile apps operated on tablets offer a better-standardized testing environment, including screen size and output recording using a touchscreen that is timed and scored automatically. With standard in-app instructions, digital cognitive assessments allow the possibility of operation outside the clinic with or without supervision. With careful selection of test modules and cutoff

scores, digital cognitive assessments have demonstrated their usefulness in detecting preclinical AD.[19] NeuroScreen and Cogstate have been tested for validity in detecting HAND in people with HIV, and both showed reasonable sensitivity and specificity in identifying CI in symptomatic and asymptomatic people with HIV. Future research should explore the use of digital cognitive assessments for cognitive screening and assessment.

## Prevention of Cognitive Impairment in Older People With HIV

To date, a number of ART modification theories to improve HAND have been studied, including the application of CNS penetration effectiveness and monocyte efficacy as well as ART intensification by adding an integrase strand transfer inhibitor and maraviroc, a CCR5 antagonist, to the standard 3-drug ART regimen. Nevertheless, there is considerable enthusiasm toward ART simplification to reduce ART-related toxicity. Such an approach could be especially important to older people with HIV at an increased risk of organ failure. The CNS outcomes of these ART modifications were recently reviewed by Handoko and collegues.[20] However, whether proactive adoption of these strategies is beneficial to long-term cognitive stability in asymptomatic people with HIV has not been examined in large-scale studies. In general, modification of ART is not recommended except in the case of symptomatic CSF viral escape, during which clinicians should revise the ART regimen according to the viral resistance profile in the CSF.

Meanwhile, general measures to delay the onset of dementia in HIV-uninfected populations are also essential in HIV care. A recent review of dementia in individuals without HIV pinpoints the importance of modifiable risk factors, including the treatment of hypertension, diabetes, obesity, hearing impairment, and depression, as well as smoking cessation, encouraging physical and social activity, decreasing alcohol consumption, and avoiding traumatic brain injury.[21] The reviewers estimated that these modifiable risk factors could account for up to 40% of dementia worldwide, compared with an estimated AD risk of 7% in those bearing the *apolipoprotein E4* gene. Indeed, an intensified management of these modifiable risk factors is especially important as they are highly prevalent in people with HIV compared with HIV-uninfected populations.

## Conclusion

Despite the improved understanding of neuroHIV, a knowledge gap exists concerning CI in aging people with HIV. Systemic and cerebral inflammation persists, albeit to a lesser extent, in people with HIV after suppressive ART. Current evidence supports that persistent immune activation could facilitate both systemic and cerebral age-related noncommunicable diseases. In the CNS, people with HIV may experience premature aging and accelerated cognitive aging. However, the characteristics of CI in older people with HIV remain less clear, particularly the involved cognitive domains and the speed of progression. Intensified atherosclerosis could make vascular cognitive impairment a predominant component in older people with HIV. The CI of people with HIV may present with fluctuations of cognitive performance that are occasionally overlooked by a one-off cognitive assessment. Moreover, screening tools such as the HDS and IHDS, developed for more severe forms of HAND, are generally insensitive to milder forms of HAND and are unlikely useful in detecting age-related CI. Current HIV management guidelines have diverse recommendations for cognitive screening in older people with HIV, as well as the frequency and the recommended tools. Digital cognitive assessments with reasonable sensitivity to CI allow repeated testing and automatic collection of test performance. They might serve as useful screening tools and potentially fill the gap of unrecognized cognitive fluctuations. Although clinicians treating people with HIV should tailor their services for cognitive symptoms, based on the available resources, priority should be allocated to management of modifiable risk factors of dementia as these factors also impact the prognosis of other age-related noncommunicable diseases.

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