Invited Review

Cognitive Impairment in people living with HIV in the ART era: A Review

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Abstract

Background: Cognitive disorders are a common issue impacting those liv- ing with human immunodeficiency virus (HIV). Effective antiretroviral treat- ment has lessened the severity but not the frequency of these impairments. Such deficits reduce quality of life and present a significant challenge to clinicians in the context of an ageing HIV population with a growing num- ber of comorbidities.

Sources of data: This review is based on recent published literature in the field of HIV-associated cognitive impairment (HAND).

Areas of agreement: The pathogenesis of HAND is multifactorial and can be categorized into HIV viral factors, antiretroviral factors and individual factors. The risk factors associated with HAND are well documented.

Areas of controversy: The prevalence of HAND in HIV populations varies and is dependent on populations studied and assessment batteries used. Disease progression is poorly understood and has important implication for screening programmes. The relative contribution of pathogenic mechanisms causing HAND is unclear, but recent papers point to inflam- mation as a significant contributor.

Growing areas: The role of psychiatric diseases, such as depression, in the development and maintenance of HAND has recently been examined and requires clinical consideration. Furthermore, as the HIV population ages, its clinical management faces new challenges.
Areas timely for developing research: Identifying biomarkers for HAND which are practical in a clinical setting and utilizing new imaging technologies to better monitor diagnosis and disease progression. Furthermore, the development of therapeutics targeting inflammation appears of increasing importance.

Key words: HIV, MRI, HAND

Introduction

In the UK over 100,000 or 0.16% of the population are chronically infected with human immunodeficiency virus (HIV) and over 6000 new cases are seen each year. The advent of effective combination antiretroviral (cART) has revolutionized the treatment of HIV and led to dramatic reductions in the incidence and prevalence of acquired immune deficiency syndrome (AIDS)-related illnesses and HIV-associated central nervous system (CNS)-opportunistic infections. Prior to the widespread use of cART, over 50% of people living with HIV (PLWH) experienced severe cognitive impairments before death. In the era of potent cART, HIV-associated dementia (HAD) is rare; however, neurocognitive impairment is a common problem impacting quality of life and medication adherence. Changes in the natural history of HIV-associated brain diseases present clinicians with significant challenges; as the HIV population ages, comorbidities are likely to compound problems and increase the prevalence of cognitive impairments. Whilst HAND stands for HIV-associated neurocognitive dysfunction, this term denotes a method of classification as well as a more general description of the clinical syndrome; thus, for the purpose of this review, when using the term HAND we are referring to HIV-associated cognitive impairment. Research has shown the pathogenesis of HIV-associated cognitive impairment (HAND) to be multifactorial with numerous factors associated with development risk. However, understanding the interactions between pathogenic mechanisms and their influences on disease progression in the context of ageing is unclear and remains an essential clinical question to allow the guided targeting of effective treatment. Promising assessment methods, sensitive enough to quantify and monitor its course, are emerging from biomarkers in plasma and cerebrospinal fluid (CSF) and the use of neuroimaging techniques.

Clinical presentation and patient profile

HAND in the era of cART differs substantially from what was observed in the pre-cART era. The classic descriptions of AIDS–dementia complex were characterized by a progressive subcortical dementia with prominent degeneration of cognitive and motor functions. In contrast, the clinical neuropsychological presentation of HAND, in the era of effective cART, shows a more subtle subcortical involvement and a cortical involvement which appears influenced by age. A comparative analysis examining PLWH from pre- and post-eras found that impairments in motor skills, cognitive speed and verbal fluency predominated in the pre-cART era, whereas executive function dominates impairments seen today. An important issue clinicians facing is the relative increase of neurodegenerative disorders seen as a function of age, in the HIV population, and how to distinguish ‘true HAND’ from other conditions. This is addressed later in the review. These executive function impairments have been shown to effect working memory, attention and prospective memory, or the ability to ‘remember to remember’. The impact of this is a reduction in quality of life, lower levels of medication adherence (which may jeopardize both the long-term effectiveness of treatment for the individual and increase risk of onward transmission), increased unemployment and lowered life expectancy. In addition, the profile of PLWH living with HAND is likely to further compound the impact of this disease; older aged individuals, with a heightened risk
for depression and living with other comorbidities. Loneliness and social isolation are two major psychosocial consequences for PLWH, with older adults perceiving less social support, greater isolation and lower social functioning than their younger HIV-positive counterparts. Ageing with HIV would appear to create a synergistic state, whereby increased comorbidities, such as cardiovascular disease, diabetes or depression likely contribute to, and maintain HAND.

**Nosology and diagnosis of HAND**

HAND refers to a spectrum of neurocognitive impairments that consists of asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HAD. The principal methodology used to define HAND is the Frascati criteria. This involves neuropsychiatric testing of the following domains: attention and working memory; language and verbal fluency; executive function and abstraction; speed of processing; memory (inc. learning and recall); and sensory-perceptual and motor skill. HAND is defined when two or more of these neuropsychological domains are more than one standard deviation below normative test scores and the extent to which daily functions are impacted (this is examined via self-report or functional assessment). Cognitive impairments must be acquired and not resultant of comorbidities. This in practice is extremely difficult as multifactorial causes are seen in most clinical cohorts. Distinction between ANI and MND is ascertained using self-report functional assessments, whereby MND is diagnosed if cognitive impairments interfere with daily functioning (and ANI is diagnosis if it does not).

**How prevalent is HAND among the HIV-positive population?**

HIV-associated CNS disease is a major public health issue in many resource-poor countries; however in this review, focus is applied only to HAND where access to cART is available. The prevalence rate of HAND in PLWH varies widely depending on sources used and appears dependent on the populations studied and approaches used. Rates as high as 52% have been reported. However a significant problem effecting prevalence estimates is the lack of sensitivity and specificity provided by the neuropsychological tests available; indeed, concerns that Frascati criteria classification overestimates prevalence rates of HAND are well acknowledged. Indeed, in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (which reported HAND prevalence at 52%), 33% of patients without confounding comorbidities were diagnosed with ANI. Whilst acknowledging this is a significant problem for PLWH on cART, Gisslen et al. find the definition of ANI to be far from stringent, resulting in 16–21% of the population being classified as abnormal—this they argue is an unacceptably high false-positive rate and likely contributes to overinflated perceptions of HAND prevalence.

The most stringent estimate of prevalence to date comes from the Pharmacokinetic and Clinical Observations in People over Fifty (POPPY) study in the UK, here the authors sought to compare the agreement of different diagnostic criteria used in HAND. Age- and education-adjusted test scores were determined if subjects met the following three main definitions of cognitive impairment employed in HAND diagnosis, namely, the Frascati criteria, the global deficit score and the multivariate normative comparison method. The authors found 14% of individuals were classified as cognitively impaired by all three definitions, and 28% met criteria for classification on one or two of these diagnostic criteria. Based on the conservatism demonstrated in this study, it provides compelling evidence that prevalence rates lie somewhere around this 14–28%.

**Is HAND a progressive disease?**

Prior to the use of cART in the mid-1990s, HAD was a progressive neurocognitive disorder resulting in death within a few months. With the induction of cART, rates of survival after HAD improved and milder forms of cognitive impairment were more commonly reported. Whether this continues to be a progressive neurologic syndrome, as it was in the pre-cART era, is an important question, particularly given that PLWH are living longer and thus likely
to experience age-associated conditions which in turn can increase risk of cognitive impairment. A recent longitudinal study found a diagnosis of MND and HAD was not progressive in 70% of individuals with virologic suppression over a 4-year period. For those with a diagnosis of ANI, 29% showed progression to MND or HAD, while 58% remained neurologically stable and 13% showed improvements. The CHARTER study showed that patients with a diagnosis of ANI at baseline were two to six times more likely to exhibit symptomatic HAND in the 3-year follow-up period than those who showed no neurocognitive impairments at baseline. These studies would appear to suggest that HAND is stable in the majority of those experiencing it. Further studies are needed to evaluate the temporal progression of HAND over longer time periods to enable the potential contributions of comorbid conditions to be determined. It is worth noting, however that a recent meta-analysis of structural brain changes following HIV infection has shown grey and white matter atrophy, as well as subcortical atrophy in well-treated PLWH. Other studies employing markers, CSF markers of inflammation and active axonal injury also indicate continued CNS injury. This again points to the issue of neuropsychological tests lacking sensitivity and emphasizes a need for biological markers.

Identifying those at highest risk for symptomatic decline may offer an opportunity to modify treatment to delay progression. While this area remains contentious, regular screening of PLWH is recommended. The British HIV Association (BHIVA) states patients should be screened annually, although they do not specify which methods should be used or which populations to target. The clinical applicability of ANI remains debatable as evidence pointing to deterioration is not clear-cut and for a diagnosis to be of value an effective intervention should be present. Given no effective interventions, aside from cART, exist for ANI, the benefits of screening are contentious. Contrary to this, those in favour of screening argue that identification allows individuals to mitigate or control the risk factors associated with HAND, adjust treatment regimens and monitor progression more closely.

Pathogenesis of HAND

The mechanisms underlying the development of HAND in PLWH are multifactorial. It is not caused by a 1D, direct pathogenetic event, but instead via multidimensional and complex immunopathological processes which are controlled by viral, cART and individual factors and likely mediated by one’s cognitive reserve. The concept of a cognitive reserve postulates that the stronger and more sophisticated one’s synaptodendritic neuron connections are the more neurological insults one can manage. Indeed, this is theorized as a dynamic process with exposure to positive and negative life events moderating it across lifespan. Findings that the majority of individuals (within the longitudinal studies’ period) remain cognitively stable and in some cases improve, add credence to the idea that cognitive reserve, specifically low reserve, play a role in the development of HAND via malleable neuroplasticity.

Viral factors

HIV enters the brain quickly after initial exposure via infected monocytes and lymphocytes crossing the blood–brain barrier and establishes itself in microglia, perivascular macrophages and possibly astrocytes. Indirect neurotoxicity is caused by the proteins of the HIV virus, such as the glycoprotein gp120 and the regulatory protein Tat as well as neurotoxins resulting from the chronic sustained immune response.

One important and well-documented clinical pathogenic mechanism of HAND is the so-called ‘legacy effect’. This is a consequence of long-term chronic HIV infection, where neuronal damage which was triggered prior to the initiation of cART may not be fully reversible. Investigators attempting to mitigate the legacy effect have hypothesized that the avoidance of a low nadir CD4+ lymphocyte count (the lowest CD4 cell count recorded in a patient) together with initiating cART, at the earliest stage of HIV disease, a reduction in incidence of HAND may be seen. The strategic timing of antiretroviral treatment (START) study has examined the difference between the effects of immediate versus deferred cART on neuropsychological test
performances in PLWH with CD4+ cells counts >500 cells/μl and found no difference. This suggests that there is no neurological advantage for immediate cART initiation in asymptomatic patients. Current guidelines recommend the initiation of cART in PLWH with clinically overt cognitive symptomatology. This is regarded as related to HIV disease regardless of CD4+ lymphocyte count.

As one might expect, sequelae from previous CNS opportunistic infections, such as encephalitis, also appear to have a legacy effect. Such neurological insults can be linked to a traumatic brain injury, reducing one’s cognitive reserve and thus forming a risk factor for the development of HAND.

HIV RNA found in cerebrospinal fluid is closely correlated with HIV RNA in plasma, and replication of HIV in the CNS is frequently linked to treatment failure. The occurrence of detectable HIV RNA in CSF when undetectable in plasma is termed CSF viral escape. Studies have shown groups of patients who present with neurocognitive impairments attributed to HIV RNA CNS infection and detectable CSF viral load, even though plasma viraemia is suppressed. CSF viral escape is documented in around 2–10% of patients. In some of these cases, HIV strains isolated in the CNS are documented to show patterns of drug-associated resistance mutations different to those seen in the plasma compartment. CSF viral escape might be related to establishments of viral reservoirs which occur during advanced immunosuppression and appear responsive to cART to varying extents. In untreated patients in the pre-ART era, high levels of HIV RNA in the CSF were associated with HAD. Evidence suggests that changing cART for a regimen which reaches greater concentrations in the CSF is effective in controlling CSF escape and in some cases improves symptoms of HAND. Whilst CSF viral escape is associated with neuroinflammation, the extent to which it causes HAND and is a relevant cognitive impairment correlate in asymptomatic CSF escape remains less well understood. In practice, if CSF escape is detected, cART is switched (this switch is based on the resistance genotype of virus in the CSF) and a lumbar puncture, 6 weeks following change, is employed to monitor its impact.

Antiretroviral factors
Evidence regarding the role antiretroviral neurotoxicity may have on cognitive functioning is mixed, although increasing evidence suggests potential neurotoxicity of several antiretroviral medicines in current use. This represents clinically significant neurotoxicity remains debatable. Furthermore, despite laboratory data suggesting effects exist, deciphering the role of antiretroviral neurotoxicity given the dynamics of cognitive functioning apparent in HIV-positive patients is a challenge. For a recent review see the work done by Underwood et al. In clinical practice, cognitive and psychiatric (e.g., insomnia and depression) side effects are commonly reported, suggesting there may be other secondary clinically relevant toxicities from drugs such as Raltegravir or Efavirenz. CART regimens with high CNS penetration-effectiveness (CPE) have been associated with a reduction in patient CSF viral loads and one might expect that if cART was neurotoxic, drugs with greater CNS penetration would be associated with increased levels of cognitive impairment. The evidence for this, however, is again mixed; one large cohort study (n = 51,938) of PLWH who were cART-naïve at consent, found those taking cART with a high CPE had a 74% increase in risk of HAD. However, other studies have reported no effect of cART regimen CPE on neurocognitive performance. The evidence in support of the neurotoxic effect of some cART, has led to the suggestion of a therapeutic window for cART, whereby efficacy and toxicity in the CNS are equiposed. In practice, the most important intervention for HAND is to have plasma viral load below the level of detection, regardless of CPE score—cART is only changed in the presence of CSF escape or patient complaint.

Inflammation
Compelling research suggests that inflammation plays a significant role in triggering events that lead to cognitive dysfunction in HIV infection. Activated monocytes maintain a critical role, both for the initiation of HIV into the brain, via transmigration across the blood–brain barrier, and for latter
establishment of infection within the CNS perivascular macrophages, microglia and astrocytes. While astrocytes do not appear capable of making intact virions, they are able to produce and export proteins such as Tat, Rev and Nef—all of which encourage inflammation and neuronal damage. Inflammation persists even during cART therapy which may impair CNS functioning. While this systemic inflammation is attenuated under cART, ongoing macrophage/monocytic-associated inflammation remains resistant. Interestingly, a recent report found increased brain inflammation is associated with poorer cognitive performance and that inflammatory processes in the brain persist despite effective control of HIV RNA. The ligand, translocator protein ligand (TSPO), adheres to receptors on activated microglial cells and therefore serves as a proxy measure of brain microglial activation which can be examined in vivo using positron emission tomography (PET). Investigators found evidence for a chronically activated brain-innate immune response and elevated blood markers of microbial translocation even though effective control of plasma viraemia was seen, suggesting that neuroinflammation persists despite effective viral suppression which may significantly contribute to HAND. This study contributes to the growing evidence that neuroinflammation plays a significant role in the pathogenesis on HAND. Future longitudinal research is needed to ascertain how increases in correlates of neuroinflammation affect cognitive impairments, and whether they represent markers of risk for progression from asymptomatic to symptomatic.

Patient-related factors and factors associated with an increased risk of HAND

Comorbidities such as cardiovascular disease and diabetes are associated with higher rates of cognitive impairment. The START trial, a large HIV treatment study, found these comorbidities to be among the strongest predictors of cognitive impairment. Furthermore, the CHARTER study found central obesity and diabetes to be important risk factors for HAND in their cohort. Prevalence of cerebrovascular disease increases with age, and in HIV-positive patients, cerebrovascular disease may result from traditional risk factors (i.e. smoking) or can occur from the metabolic and systemic effects of HIV and CART on endothelial function. The prevalence of such non-communicable comorbidities in PLWH will increase as the HIV-positive population ages and may lead to potentially dramatic rises in reports of cognitive impairments. Non-pharmaceutical interventions and awareness campaigns aimed at HIV patients are an important area for development.

Co-infections also represent an important risk factor for cognitive impairment. PLWH who are co-infected with hepatitis C show an increased risk of cognitive impairment compared to those infected with HIV alone. Likewise, PLWH with previous infection with syphilis or showing antibody concentrations of cytomegalovirus seem to show deficits in cognitive functioning. It is of note that the effects seen here on cognitive impairment may be due to the inflammatory responses within the nervous system caused by the neurological injury. Lifestyle factors such as smoking, alcohol use and recreational drug use are frequent issues reported in PLWH. Whilst these are likely to impact cognitive functioning, they also contribute to the pathogenesis of other diseases associated with cognitive decline such as a cardiovascular disease. Furthermore, such issues may too increase peripheral inflammatory responses resulting in neuroinflammation.

How does depression affect HAND?

One area currently receiving increased attention is the role of depression on cognitive impairment in PLWH. Depression is the most prevalent psychiatric problem seen in PLWH, with reports suggesting it is up to three times higher than in the general population and seen in over 50% in HIV outpatients. Understanding the role depression plays in HAND is complicated by its prevalence and its presentation. Depression has, previously, been termed as ‘pseudodementia’ because it mimics cognitive impairments and can cause executive dysfunction, short-term memory loss, inattention and apathy in its sufferers.
This was addressed during the POPPY study, where investigators found that the poorer cognitive performance seen in PLWH (matched for age and lifestyle factors) was, in part, mediated by the greater prevalence of depressive symptoms reported. And interestingly, differences in cognitive performance between HIV-negative individuals and PLWH (age-matched) were attenuated when depressive symptoms were accounted for. The findings from this study indicate depression to be a confounding factor in the association between HIV and cognitive function.

The relationship between HIV and depression is likely to be bidirectional and multifactorial and of bio-psychosocial aetiology. Psychologically and socially the impact of being diagnosed with HIV is well documented: stigma, isolation and discrimination are not uncommon, and all of which may cause depressive symptoms. Depression may in turn, lead to a lack of interest, apathy, poor attention and impaired short-term memory which will likely affect any cognitive testing. Furthermore, research examining the biological effects of HIV on depression suggests that HIV replication in the CNS causes depression through modifications in brain structure, somatostatin dysregulation and increased inflammatory cytokines. It has been theorized that depression is likely to cause chronic, low-grade inflammation and cell-mediated immune activation. Therefore, depression and cognitive impairment may represent a unique manifestation of the same underlying pathological process. This is due to direct and indirect effects of HIV replication in the CNS and may be due to the same underlying pathological processes.

This represents an important area for research—indeed, understanding the biological consequences of HIV in the brain on mood and cognitive impairment is extremely important. Findings from a recent meta-analysis shows that across 95 independent samples, depression was significantly \((P < 0.0001)\) associated with non-adherence to cART. Given that adherence to medication is essential to the long-term health of the PLWH and to the prevention of HIV transmission, this represents an important area for future research.

Current management of depression in HIV relies primarily on antidepressant treatment, with responses at a level equivocal to depressed patients without HIV. Open-label trials of sertraline, fluoxetine and paroxetine, across different stages of HIV illness, reported response rates between 70% and 90%, and all medication were tolerated well. Clinicians are reminded, however, that PLWH are potentially more sensitive to side effects and antidepressants should be started at a subtherapeutic dosage and raised as required. Furthermore, the clinical significance of some interactions between antidepressants and cART have not been well established, therefore close monitoring and dose adjustment may be necessary.

**HAND and the challenges associated with ageing**

Increased life expectancy in the HIV population has brought the challenges of geriatric medicine to HIV clinical care. This increasing longevity in PLWH and the accompanying attenuation of cognitive reserve seen in older adults means the burden of cognitive impairment is likely to increase. An important question facing clinicians in this field is whether neurodegeneration is a possible contributor for HAND and linked to this question is whether HIV infection causes accelerated cognitive ageing. A recent review examined behavioural and neuroimaging studies which sought to address this question and found 11 studies in favour of accelerated neurological ageing and 9 against. Likewise, longitudinal studies examining this have also reported mixed results, with some finding evidence for interacting effects of HIV infection on ageing and other reporting no effects of HIV infection and age on cognitive decline. A recent, methodologically rigorous report using longitudinal assessment of cognitive performance and quantitative magnetic resonance imaging (MRI) found main effects of HIV status and age group on longitudinal change in cognitive performance and change over time in mean diffusivity using diffusion tensor imaging. This supports the notion that HIV infection leads to accelerated cognitive ageing, and that there is a statistically significant HIV status by age group interaction.
interaction for change in overall cognition. Thus, a HIV-positive status and older age are risk factors for worsening global cognitive performance. Of interest however is that the interactions documented could not be explained by the imaging findings, as no significant interactions were evidenced from any of the imaging metrics. The authors suggest further work is needed to examine other biological mechanisms, such as metabolic factors or treatment effects, which could explain the cognitive performance changes seen in HIV-positive patients. Of interest, a recent report argues against accelerated brain ageing, instead finding evidence of accentuated brain ageing in virologically suppressed PLWH. Using structural neuroimaging, Cole et al. found evidence of increased apparent brain ageing, the magnitude of which related to neuropsychological performance across multiple cognitive domains. However, predicted brain age did not correlate with chronological age or duration of HIV infection, thus suggesting HIV disease does not accelerate the rate of age-associated brain atrophy. Instead, HIV is accentuating age-related changes in brain structure, driving atrophy in brain regions that normally change with advancing age. A longitudinal study supports this, finding that PLWH receiving successful treatment are not at greater risk of age-related brain changes or cognitive decline over a 2-year period, when compared to matched HIV-negative controls. Whilst the PLWH had significantly worse overall cognitive performance, lower grey matter volume, higher white matter hyperintensity load and great brain-predicted age differences at baseline, differences in longitudinal rates of change in brain structure or function between the two groups were absent. The authors suggest the deficits observed are the result of a historical pathological process (such as direct pathogenic effect of HIV on CNS or the initial immune response to the infection) rather than ongoing pathological processes. Whilst these latterly mentioned studies may provide reassurance for PLWH, further work is needed to elucidate the effects of HIV infection on brain ageing. Importantly, these studies did not examine other HIV-related factors such as antiretroviral toxicity, lifestyle factors and other comorbidities and future studies need to employ other imaging modalities to better model differential patterns of brain ageing in PLWH.

A second question challenging clinicians is the differentiation of HAND from other dementias of ageing, such as Alzheimer’s disease (AD). Furthermore, the relationship between HIV infection/treatment and AD is unknown and may constitute an important risk factor. Remarkably, the first case of AD in a HIV-positive patient was only reported recently. This report suggests that progressive dementia in PLWH may be due to HAND, AD or both. For the PLWH examined in this report, the physicians suggest a mixed dementia, and that CNS HIV infection did not prelude Ab/amyloid deposition. However, they suggest HIV infection may be a risk factor for AD due to the neurological ‘assaults’ of neuroinflammation, accelerated CNS ageing and attenuated cognitive reserve.

Interestingly, a recent report found no evidence of amyloid burden in HIV-positive patients and like a number of other studies reported no association between the apolipoprotein E (APOE4) genotype (considered a significant risk factor for the development of AD) and HAND. Interestingly however, they did find evidence to suggest the APOE4 genotype moderates the expression of CSF Aβ1-42, a CSF biomarker consistent with increased risk of Alzheimer’s, in PLWH with HAND. A second finding from this report was that higher levels of CSF p-tau and t-tau were associated with the current neurocognitive impairment in middle-aged HIV-positive patients. This is not seen in normal ageing and may represent a marker for greater risk of current HAND. As aforementioned, a role for cART is also possible with antiretroviral medications having been demonstrated to disrupt microglial phagocytosis of b-amyloid and lead to greater production by neurons in vitro. However, other studies have not reported this effect. Overall, understanding the potential interactions between HAND and AD pathologies resulting in dementia, including the impact of cART, remains unclear (Table 1).
Biomarkers and findings from Neuroimaging

Assessing older PLWH with cognitive impairment when they show signs of AD, HAND or both remains a significant challenge. Validated pathophysiological biomarkers represent a clinical imperative, if we seek to more accurately monitor the diagnosis, progression and treatment of the disease(s). Moreover, the identification of a quantitative laboratory-based biological marker, which preludes ANI and identifies a preclinical stage, would open up treatment avenues for the earliest stages of cognitive impairment and likely has the greatest impact on outcome. Furthermore, understanding the relationship between HIV, HAND and AD will help unlock research avenues and treatment possibilities. For example, antiamyloid and other therapies used for MCI and AD may also prove effectiveness in older PLWH; however, HIV infection is invariably exclusionary for clinical trials testing new therapeutics.

Amyloid PET neuroimaging represents an efficacious tool for distinguishing the putative neuropathologies of HAND, whether this is HIV-related, amyloid-related, or both. Few studies have utilized this tool to date, with those that have reporting no amyloid depositions in individuals with HAND, however, the oldest individual scanned was 67 years old. Longitudinal studies, with older aged, and aged-matched, HIV-positive patients are required to better define interactions between HIV and AD.

Of recent interest is research detailing the potential efficacy of neurofilament light chain proteins (NFL) in the identification of neuronal injury. Previously, this was shown to be a reliable, age-sensitive marker of neuronal injury across a variety of brain regions.
of neurodegenerative conditions, including HIV, and was found to be elevated in ANI or MND. Recent research has found plasma NFL correlates highly ($r = 0.89$, $P < 0.0001$) with CSF NFL. These patterns of NFL changes were almost identical in plasma and CSF, and both exhibited similar age-related increases in concentrations for HAD, MND and ANI, while avoiding the need for a lumber puncture.\textsuperscript{70} This is likely to prove a valuable tool, in both clinical and research settings, for the evaluation of ongoing CNS injury in PLWH.

Brain imaging has so far provided fascinating, non-invasive insights into the brain’s structure, neurochemistry, metabolism and function which occurs due to HIV infection. It is a crucial tool used in clinical practice to assist in the diagnosis and description of neurological problems associated with HIV, and particularly helpful for excluding other pathologies (e.g. cerebrovascular disease).\textsuperscript{22} Within the research field, novel imaging techniques have greatly improved our understanding of the neuro-pathogenesis associated with HAND. Structural imaging was utilized heavily in the pre-cART era, with findings showing subcortical cerebral atrophy\textsuperscript{71} and other white matter changes of uncertain significance. In more recent years, regional volumetric analysis has been employed to investigate progressive degeneration. An interesting study, utilizing a whole-brain approach, showed subcortically weighted topography was associated with HIV status-accentuated age-related volume loss; and in HIV-positive patients, cortical topography correlated with neurocognitive function and nadir CD4, while subcortical volume loss was correlated with current viral load,\textsuperscript{3} suggesting that observed volumetric changes in PLWH likely reflect both previous virus history and current viral status.

The use of functional MRI (fMRI) in studies is a rapidly expanding approach for those wishing to investigate cognitive impairments in HIV. fMRI is extremely sensitive to changes observed in pathological brain processes and allows the temporal mapping and comparison of underlying brain function circuitry. A recent review paper found differences in activation between PLWH and HIV-negative individuals across multiple domains (i.e. attention, working memory and executive functioning). PLWH showed hyperactivation on task-related brain areas (frontostriatal system) despite showing equivocal performance (compared to HIV-negative participants) on all tasks; however, task performance was degraded as task difficulty increased. Hyperactivation is theorized to be due to the so-called brain reserve theory, whereby more neural effort is required to achieve the same behavioural results\textsuperscript{72} and provides good supportive evidence for the idea that one’s cognitive reserve plays a role in the expression of cognitive impairment.

**Management**

Cognitive impairment in PLWH is well evidenced, complex and presents a significant clinical issue to the services caring for these patients. General practitioners examining the PLWH, who themselves, their family or their caregiver have complained of cognitive difficulties, must perform an evaluation to find out more. First, it needs to be ascertained whether there are confounding conditions such as drug or alcohol abuses, cardiovascular issues or psychiatric problems. If it is deemed not to be related to these neurological risk factors or these are now being optimally managed, and the issue still exists, then the general practitioner must establish if the patient genuinely has a cognitive impairment. An objective neuropsychological examination (which includes tests exploring domains of fluency, speed of information processing, executive functions, verbal and visual learning and memory, attention/working memory, motor skills plus assessment of daily functioning) such as the Montreal Cognitive Assessment, Addenbrooke Cognitive Examination or Mini-Mental State Examination should be employed (whichever is standard for the practice). It is important to note that neurocognitive impairment is defined by impairment in cognitive function on a neuropsychological test when performance is compared to appropriate age-and-education matched controls. If an impairment is detected, due to the complexity of the patient, then referral should be made to a HIV physician and neuropsychology, who will at a minimum conduct a neurological
assessment, brain MRI and CSF examination. These are required to exclude other pathologies and to further characterize HAND by including assessment of CSF HIV viral load level (CSF escape) and if needed, evidence for genotypic drug resistance in paired CSF and plasma samples. A diagnosis of HAND would be given at this point as long as additional causes of neurocognitive impairment other than HIV can be excluded. If a patient is not currently taking cART, then this should be started, and consideration paid to inclusion of potentially CNS-active drugs (i.e. higher CPE score). If the patient is on cART and CSF escape is evidenced, recommendation is to optimize cART by CSF and plasma genotypic drug resistance testing and switch to a cART of a higher CPE. If there is no evidence of CSF escape, clinicians are still recommended to switch ART; however, other risk factors must again be reconsidered.

In practice, it is certainly problematic that there are few recommendations on how to follow-up and manage patients with evidenced cognitive impairment and treated HIV. Furthermore, there are no recommendations on how to address the clinical, social and psychological needs of HIV patients with progressive memory loss and early dementia, regardless of cognitive impairment pathology. In practice, the patient will often be referred to multiple services (e.g. local memory clinics, general neurology services, HIV clinics and mental health/psychology services) adding to the complexity, reducing efficiency and increasing economic and social burden. A recent movement garnering attention is the advent of specialist memory clinics for patients with HIV. The Orange Clinic run by Brighton and Sussex University Hospital Trust provides expert, multidisciplinary assessment, management and advice on care for PLWH with cognitive problems. Over the course of 1 day, patients who are referred will be assessed by a HIV physician, HIV clinical nurse specialist, dementia specialist, neuropsychologist, clinical psychologist who will, in collaboration, provide a diagnosis (when possible) and develop a management plan—which may include further investigation, referral to other specialty services, i.e. neurology/psychiatry needs for support in the community and therapeutic interventions such as memory enhancement strategies or CBT. Clinics such as this provide a clear pathway for general practitioners concerned and uncertain about the cognitive impairments reported/evidenced by their patient. Indeed, given the HIV virus, antiretroviral, impact of inflammation, comorbidities and lifestyle risk factors all potentially contributing to the pathogenesis of HAND, specialist memory clinics are ideally placed to streamline treatment for those PLWH experiencing cognitive impairment.

**Conclusion**

HAND represent an important and ongoing challenge for clinicians caring for PLWH. Likely caused by multiple, dynamic factors including immune-mediated factors (such as monocyte/microglial activation); neurotoxicity of cART; infectious and non-infectious comorbidities; lifestyle factors and psychiatric illnesses. Treating patients with HAND is only further complicated by increases in life expectancy which has brought the issues of geriatric care to the already complex field. New imaging techniques hold great promise for better probing the diagnosis, aetiology and development of cognitive impairments and will inform treatment. Furthermore, the effects of HAND on quality of life, economic independence, medication adherence and mortality (even for mild cognitive impairment) make the development of clear, well-evidenced treatment pathways a clinical necessity.

**Conflict of interest statement**

The authors have no potential conflicts of interest.

**Disclosures**

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Authors’ contributions
KA and JV contributed to design and drafting of the manuscript. All authors read and approved the final manuscript.

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