Cognitive impairment in people with HIV: consensus recommendations for a new approach.

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ABSTRACT

Current approaches to classify cognitive impairment in people with HIV (PWH) may overestimate disease burden and can lead to ambiguity around disease mechanisms. The 2007 criteria for HIV-associated neurocognitive disorders (HAND), sometimes called the *Frascati criteria*, can falsely classify over 20% of cognitively normal individuals as impaired. Minimum criteria for HAND are met based on performance on cognitive tests alone, which may not be appropriate for populations with diverse educational and socioeconomic backgrounds. Imprecise phenotyping can limit mechanistic research, biomarker discovery and treatment trials. Importantly, overestimation of cognitive impairment risks creating fear among PWH, and worsening stigma and discrimination towards them. In response we established an International HIV-Cognition Working Group, which is globally representative and involves the community of PWH. We reached consensus on six recommendations towards a new approach, intended to focus discussion and debate going forward. We propose the conceptual separation of HIV-associated brain injury (which can be active or the legacy of pre-treatment damage) from other causes of brain injury occurring in PWH. We suggest moving away from a quantitative neuropsychological approach towards an emphasis on clinical context. Our recommendations are intended to better represent the changing profile of cognitive impairment in PWH in diverse global settings and provide a clearer framework of classification for clinical management and research studies.

INTRODUCTION

The most frequently used criteria for cognitive impairment in people with HIV (PWH) are the HIV–associated neurocognitive disorders (HAND) criteria, developed in 2007 by a working group convened by the United States National Institute of Mental Health.[1] The HAND criteria (sometimes referred to as the *Frascati criteria*) were intended to harmonise research methodology allowing comparisons across diverse study settings. Although originally intended for use in research, the terminology has become widely used to refer to clinical burden of cognitive impairment.[2] HAND criteria have been successful in providing a consistent system of classification in global research studies for 15 years.

The spectrum of HIV disease has changed dramatically in recent years; the majority of PWH globally are now virally supressed on effective antiretroviral therapy and life expectancy approaches that of uninfected cohorts.[3,4] Minimum criteria for HAND are met based on cognitive test performance compared to HIV-negative populations without the need for a clinical assessment of cognitive status. Several authors have argued that this approach overestimates disease burden and that HAND criteria are not appropriate for the modern era.[5-11]

Criticism of the HAND criteria centres on three main points, as recently outlined by authors from our group.[12] Firstly, the statistical approach applied to cognitive data has the potential for a very high false positive rate: over 20% of cognitively normal HIV-negative control participants are defined as impaired based on the current approach.[8,10] Secondly, cognitive test performance is strongly influenced by complex educational, cultural and socioeconomic factors which can interact with HIV risk such that low cognitive test performance may not correspond to a pathological state.[13,14] Thirdly, in the modern era of effective ART and an ageing population of PWH, cognitive impairment in PWH is frequently multifactorial, hence not synonymous with the direct effect of HIV on the brain and not best described as 'HIV-associated' which implies a degree of causation.[15,16]

HAND criteria typically classify 20–60% (and sometimes up to 90%) of PWH as cognitively impairmed,[2,14,17] which does not seem to align with clinical observations that cognitive impairment in PWH presents less frequently in the modern era, and then usually in the context of absent/ineffective antiretroviral therapy, significant comorbidities or as a legacy of damage caused by CNS HIV replication occurring before effective antiretroviral therapy.[18-20] Lack of diagnostic precision risks hampering clinical trials for cognitive impairment and biomarker discovery. Misclassification impacts power to detect differences risking type-one error in clinical trials.[21]

Additionally, a label of cognitive impairment can impact self-esteem, confidence, and fears for future health.[22] Overestimation of cognitive impairment may risk creating fear among PWH and worsen stigma and discrimination towards them.[23] For example, PWH in the United Kingdom were denied the opportunity to become airline pilots due to concerns over the development of cognitive impairment. Following a campaign by a pilot living with HIV, the UK Civil Aviation Authority recently changed their rules to reflect the improved HIV-outcomes of the modern ART era, allowing pilots with HIV to work alongside their HIV-negative colleagues.[24]

Conversely, underestimation or misclassification of cognitive impairment in PWH risks missing cases and preventing access to care. Cognitive impairment is an important complication of HIV with far reaching consequences on quality of life.[22] It is crucial that approaches to

diagnosis and classification of cognitive impairment reflect the modern spectrum of disease so that prognostic information is accurate and those affected can receive the help they need. The original HAND publication of 2007 acknowledged several of these potential methodological issues. It recommended strongly that their criteria be field tested and further refined going forward.[1]

METHODS

In response to the issues described above, we established an International HIV-Cognition Working Group. The broad aim of the group was to propose improvements to the diagnostic approach to cognitive impairment in PWH to reflect changes in the spectrum of HIV disease in the modern antiretroviral era. We intended to produce specific recommendations around key issues to focus discussion and help the field move forward.

The group was initiated by the HIV Mental Health Research Unit at the University of Cape Town and follows our recent HAND critique.[12] The group was intended to be globally representative, hence preference was given to those based in low-and middle-income countries with high HIV prevalence. In high-income countries, members were invited in approximately equal numbers from Europe and the USA. We aimed to include people with direct clinical experience working with PWH, as well as leading researchers in the field. Representatives were invited from the community of PWH in both high- and low-income settings.

Twenty-five invites were extended. Three declined and two withdrew after initially accepting, citing time commitments. Of the remaining 20 members, 9 (45%) are based in low-and middle-income countries in the global south. Members include academics and clinicians from neurology, psychiatry, neuropsychology and HIV/infectious disease, as well as three community representatives.

Working group meetings were held virtually. The framework laid out in the recent HAND critique was used as a starting point for discussion,[12] with the specific aims to outline an approach which is: i) applicable clinically as well as in research, ii) appropriate for diverse populations of PWH globally, iii) applicable in low- as well as high-resource settings, and iv) reduces the risk of fear, stigma and discrimination for PWH. Members participated in videoconference discussions and engaged further via the group email chain. Based on this, a manuscript draft was prepared by SN and distributed to the group for comment and further input. Multiple iterations of the manuscript were reviewed, revised, and redistributed. Additional smaller meetings were held virtually or in-person at international conferences, the outcome of which was subsequently shared for discussion with the wider group. This iterative process continued until broad consensus was reached on all points by all working group members.

This led to the six recommendations outlined below. These should be interpreted as representing the consensus opinion of a diverse group of experts rather than being a definitive new set of criteria. Further validation and a broader consensus within the field will be required to define and implement definitive new criteria for cognitive impairment in PWH.

RECOMMENDATIONS

Neuropathology

Recommendation 1: HIV-associated brain injury should be considered as one cause of cognitive impairment alongside other potential causes of brain injury occurring in PWH

In the modern era, cognitive impairment is frequently multifactorial, with one cause being the direct effect of HIV on the brain.[15,19] To distinguish this from other causes of brain injury in PWH, we recommend the term HIV-associated brain injury (HABI) be used to refer to damage caused directly by HIV. Other causes of brain injury include a variety of comorbidities and medication effects (table 1).[19,25] We recommend that HABI should be conceptually separated from other causes of brain injury, while accepting that in practice this can be difficult to do with certainty, that several causes can coexist, and that clinical manifestations can lead to overlapping symptoms and signs. Nevertheless, we feel that separating the concept of HABI from all-cause cognitive impairment in PWH reduces ambiguity in terminology and facilitates examination of brain injury mechanisms.

HAND is defined as being caused by HIV, at least in part.[1] HAND criteria do acknowledge that PWH are potentially vulnerable to cognitive effects from other conditions. When present they term these to be either 'contributing' or 'confounding'. Confounding conditions are considered to represent an alternative diagnosis and not HAND. The implication is that HAND is caused by HIV, with other conditions contributing to this HIV-effect where present. This framing may have been appropriate when brain injury caused by HIV was frequent, but may not be appropriate now that HIV clinical care has improved so dramatically worldwide.

We recommend that cognitive impairment in PWH represents all potential causes of brain injury, regardless of whether HABI may be the cause or even contributing in any given case. Moving to a classification that considers multiple causes of cognitive impairment is aimed at more accurately representing changes to the clinical burden of disease and facilitating the study of more representative samples in research.

There are parallels with Mild Cognitive Impairment (MCI) in the field of Alzheimer's disease. The underlying pathology associated with MCI is heterogenous and the majority do not go on to develop Alzheimer's disease.[26] Biomarkers have been identified which reliably predict which of those with MCI have underlying Alzheimer's pathology compared to other causes, and can be used to predict progression to Alzheimer's disease.[27] The comparable situation in PWH is to distinguish which of those with cognitive impairment have underlying HABI versus other causes. This distinction is more difficult with HABI compared to MCI as, in contrast to Alzheimer's disease, HABI does not generally progress to a marked dementia syndrome in those receiving suppressive antiretroviral therapy.[28]

Numerous potential pathological mechanisms may underlie HABI, including persistent immune activation, blood-brain barrier dysfunction and more direct virus-induced neurotoxicity. Neuronal damage may be mediated by both immune active molecules and HIV products and involve several mechanisms including oxidative stress, metabolic changes, glutamate dysregulation and N-methyl-D-aspartate (NMDA) excitotoxity.[29-31] Of note, HABI differs slightly from the existing terms HIV-encephalopathy and HIV-encephalitis. The former refers to a predominantly subcortical cognitive-motor syndrome (also known as HIV-associated dementia) which is an acquired immunodeficiency syndrome (AIDS)-defining condition, and the latter to the histopathological correlate of multinucleated giant cells and microglial nodules.[32] While these continue to occur, particularly in those with untreated or advanced HIV disease, they may no longer represent the prominent neuropathology of HABI

in the modern ART era. For example of 20 people diagnosed with HIV-associated dementia in life, only one had histopathological evidence of HIV-encephalitis at post-mortem.[33] Our proposed term HABI is intended to encompass any mechanism of brain injury caused directly by HIV, including those previously described by the terms HIV-encephalopathy/encephalitis.

HIV-associated brain injury (HABI) - see figure 1
Legacy HABI: Inactive brain injury from pre-treatment damage.
Active HABI: Ongoing brain injury leading to clinical or radiological progression
Other causes of brain injury
Previous or ongoing CNS infections (e.g. neurosyphilis, CNS tuberculosis, CNS toxoplasmosis, CNS cryptococcosis, progressive multifocal leukoencephalopathy)
Cerebrovascular disease
Traumatic brain injury
Neurodegenerative disorders such as Alzheimer's disease
Other non-HIV related neurological condition (e.g. multiple sclerosis or uncontrolled epilepsy)
Developmental disability
Nutritional deficiencies (e.g. vitamin B12, niacin)
Coinfections (including syphilis and hepatitis C)
Hazardous alcohol use
Substance misuse
Antiretroviral CNS neurotoxicity

Table 1. Potential causes of brain injury in PWH. *This is not an exhaustive list as any neuropathological process can potentially affect PWH. CNS: central nervous system*

Recommendation 2: HABI should be differentiated based on HIV RNA suppression and the activity of pathology

HABI can occur in PWH with untreated, or incompletely treated, HIV infection.[34,35] In such cases the focus should be on systemic HIV viral control.[25,36-38]

In the modern era the majority of PWH globally are virally supressed on effective ART and as a result are largely protected from progressive HIV disease.[3] As such, defining the risk of HABI causing progressive disease in those with HIV RNA suppression is particularly important. Current evidence is conflicted as to how commonly HIV causes cognitive impairment in this group,[2,28] and whether this represents a progressive or static process.[39-43] To reduce ambiguity in this area, we recommend that HABI is subdivided into legacy and active HABI based on progression (figure 1). This differentiation is important as treatment and prognosis

differ.[25,38] Of note, legacy and active HABI may coexist as the latter may occur on a background of the former.

Legacy HABI

Central nervous system (CNS) damage due to HABI that is irreversible, or only partially reversible, can be sustained during periods of untreated HIV infection, particularly during advanced immunosuppression.[20] This has been referred to as the legacy effect and represents brain injury that may have occurred prior to the individual initiating ART. For adults with vertically acquired HIV, the concept of legacy HABI would include sequalae from the effects of HIV infection on the developing brain.[44] Legacy effects are inactive and permanent, hence not amenable to treatment. Subclinical legacy HABI may lower cognitive reserve, increasing vulnerability to cognitive impairment from other causes, eg. in older age.[45-47]

Active HABI

Active HABI in this context represents evidence of sustained clinical or radiological progression over time, beyond that expected for normal ageing or the variability in cognitive performance testing, with careful exclusion of alternative causes.

Progression in the context of HIV RNA suppression in plasma should prompt CSF examination for CSF HIV RNA escape.[37,38] Definitions of CSF HIV RNA escape vary, but consensus is that this refers to the presence of HIV RNA in CSF when not in plasma, or at a higher level in CSF than in plasma.[48] CSF escape can indicate compartmentalised HIV replication in the CNS resulting from low treatment potency in the intrathecal compartment due to ART resistance, less effective/older ART regimens, or low adherence, leading to varying presentations including rapidly progressive neurological disease and diffuse white matter signal abnormality on MRI.[49,50] CSF escape may be becoming less common with modern ART.[51] It can be treated with ART directed to CSF resistance profiles. It is important to note that CSF HIV RNA escape can be transient and asymptomatic.[49] Low levels of HIV RNA in CSF may not necessarily be the cause for active neuropathology and its presence should not be taken as definitive evidence of CNS compartmentalised HIV. However, in the presence of clinically active disease CSF HIV RNA should be investigated and, if present, treated in the first instance.[52]

CD8 encephalitis is a severe inflammatory disorder with T-lymphocytic infiltration into the brain leading to swelling and raised intracranial pressure which can be fatal.[31] CD8 encephalitis typically occurs in those on ART and can be associated with a number of triggers including CSF HIV RNA escape and immune reconstitution inflammatory syndrome (IRIS), suggesting some overlap between these conditions.[31,53] It is responsive to corticosteroids.[54]

An IRIS can occur in the weeks to months following initiation of ART, which can affect the brain in the absence of opportunistic pathogen.[31,55] This is thought to be due to an immune response directed at HIV viral reservoirs in the brain and has been associated with CSF HIV RNA escape.[55,56] As with CD8 encephalitis, a severe, potentially fatal, T-cell encephalitis with brain oedema occurs which can respond to immune modulation with corticosteroids.[57] IRIS directed at opportunistic pathogens in the brain (viral, fungal, bacterial, or parasitic) are considered secondary effects and not part of HABI.

Outside the uncommon scenarios of CD8 encephalitis and CNS IRIS described above, it has not been definitively shown that HIV can cause a progressive cognitive syndrome in the context of sustained HIV RNA suppression in both plasma and CSF. However, there are a number of mechanisms proposed for this to occur including HIV protein-associated

encephalopathy, ongoing CNS HIV replication below the threshold of detection, and a neuroinflammatory process established during legacy damage that persists after effective HIV control with ART.[29-31] The 2013 consensus report from the MIND Exchange project concluded that: "It is not possible from existing data to conclude whether patients with successful treatment (ie, plasma HIV RNA <50 copies/mL) are at risk of progression [of cognitive impairment]".[37] Since that time several studies have examined this question, with some suggesting that active HABI can occur in this context,[39,58] particularly in ageing cohorts,[42,59,60] while others have shown reassuring longitudinal outcome data,[20,40,43] falling rates of impairment,[28,61] cognitive deterioration associated with comorbidities rather than HIV factors,[19] and ageing trajectories similar to lifestyle matched controls.[41] This remains a critical question to answer so that PWH can have accurate prognostic information and those at risk can be targeted.

Raised biomarkers without brain injury

Some CSF, plasma and imaging biomarkers used in research can indicate potentially active processes in the brain despite viral suppression and stable cognition.[39,58,62-65] Examples include diffusor tensor imaging and functional MRI, and various CSF biomarkers of immune activation and neuronal damage.[66] While such markers may indicate ongoing inflammation, it is not clear to what extent this has a clinical correlate or represents an injurious process versus subclinical effects or a healing process in response to prior damage.[25] Some imaging and biomarkers change with age and can be raised in comorbid and lifestyle matched HIV-negative controls.[67] As such, we recommend that abnormalities indicated by such markers should not be considered definitive evidence of an active injurious process, unless demonstrated to correspond to clinical or radiological progression as described above. This distinction is not intended to undermine the potential importance of such abnormalities, but to acknowledge the difference between a research finding of concern and definitive evidence of clinical effect.

If a biomarker is demonstrated to consistently correspond to clinical or radiological progression, this could be used as evidence of active HABI. This is similar to CSF amyloid and tau proteins validated to predict progression to Alzheimer's disease.[27] One biomarker that may be useful in this context is CSF neurofilament light chain, a robust and sensitive marker of neuronal injury.[68] Research is needed to investigate the use of neurofilament light chain as a biomarker for active HABI in those with sustained HIV RNA suppression. It should be noted that neurofilament light chain is not specific for HABI versus other causes of brain injury, hence other causes should be carefully excluded.

It remains possible that neuroinflammation indicated by raised biomarkers may cause an active process of neuronal dysfunction without progressive injury. This could lower cognition in a stable or fluctuant way without sustained progression, akin to a metabolic encephalopathy. Supporting this, some CSF and imaging biomarkers have been correlated with clinical outcomes, however associations have been inconsistent and generally weak.[66,69] Trials of anti-inflammatory and neuroprotective compounds aimed at improving cognition have not shown clinical effect.[70-73] Research is needed to determine whether an active (ie. potentially amenable to treatment) but non-progressive process can occur in those with sustained suppression of HIV RNA. If shown to occur, this would warrant a third HABI subtype.

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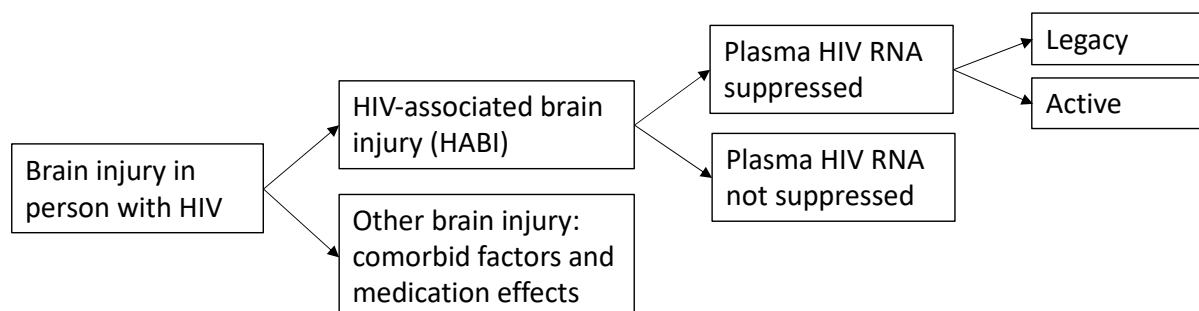
Figure 1. Brain injury in PWH.
Legacy HABI: Inactive brain injury from pre-treatment damage.
Active HABI: Ongoing brain injury leading to clinical and/or radiological progression.

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Interpreting cognitive test results

Recommendation 3: Low performance on cognitive tests should not be labelled as cognitive impairment without clinical context

Cognitive testing is an important element of assessment in someone suspected of having cognitive impairment. While cognitive scores are appealing as an objective measure of neuronal function, results vary widely depending on a number of non-biological factors such as educational background and socioeconomic status.[13,14] Indeed this issue was stressed in the original HAND criteria publication.[1] As an example, the average score on the Montreal Cognitive Assessment (MoCA) in a study of a healthy, HIV-negative, cognitively unimpaired population in a low-income area of Cape Town was 21.7 out of 30,[74] whereas in the North American population for which the MoCA was developed a normal score is considered to be 26–30. These differences do not imply impaired cognition *per se*, but rather that performance on these tests can be culture-bound and vary substantially in groups with different educational and sociodemographic backgrounds.

In research studies, cognitive scores are typically compared to normative control populations. These comparisons can be improved by the collection of normative data from populations with similar demographics to the measured population of PWH (e.g. similar age, sex, ethnicity, and years of education are recommended in the HAND criteria), or by controlling for these factors in established normative data sets with regression-based techniques.[75] These approaches have several limitations. Firstly, studies have demonstrated wide variation in normative data between and within countries,[76] and it would be impractical to develop extensive normative data for each setting in which PWH reside. Secondly, it is difficult to match for all lifestyle and comorbid factors associated with HIV status. Thirdly, in some areas HIV acquisition is associated with poverty and lower education,[77,78] increasing the likelihood that a person with HIV will return lower test scores than the average for their population.

In clinical practice, these factors are taken into account by neuropsychologists and clinicians with experience in cognitive testing who use cut-offs appropriate for their population, or consider the subjective interpretation of an individual's performance based on educational background and estimates of premorbid functioning. In research studies this is often not practical and can be considered too subjective, hence comparisons with normative control scores are made.

The HAND criteria define statistical methodology to determine cut-offs for cognitive performance in PWH compared to normative controls.[1] Cognitive performance within a particular domain must fall more than one standard deviation (SD) below the normative average for that domain to be considered impaired. This threshold must be crossed in two or more cognitive domains for a classification of HAND. Several other statistical approaches to define cognitive impairment have also been used as alternatives to the HAND criteria. These include the Global Deficit Score, Multivariate Normative Comparison, Novel Multivariate Method and the 'Gisslén criteria'.[8,25] Some methods can be applied in several different ways (discussed under recommendation 4 below) which results in the potential for large variation in the statistical methodology used to define cognitive impairment in PWH. The size of the group classified as impaired can vary widely with different methods. For example, when 20 different methods were applied to a clinical cohort in South Africa, the rate of cognitive impairment ranged from 20% to 97%.[79] As such, an individual can be classified as impaired by one statistical method and not impaired by another.

Another issue is that cognitive scores can fluctuate in an individual over time.[80] Minor variation around domain cut-offs can have large effects on binary classifications.[81] As such, an individual on the margin of impairment can be classified as impaired at one timepoint and then not impaired at a different timepoint. This is reflected in longitudinal studies, where fluctuation between groups is frequently observed.[1,82]

For these reasons, we suggest that cross-sectional quantitative neuropsychological approaches alone are limited as a method of determining impairment in diverse populations. No tool is a perfect indicator of neuronal function and any statistical method of dichotomisation based on cognitive performance will be to some extent arbitrary. It is extremely difficult to perfectly match a normative population to factors associated with HIV acquisition in all settings. While it can be useful to determine a group at the lower end of the cognitive spectrum, we recommend that they be classified as having low cognitive performance rather than diagnosed with cognitive impairment, unless there is supporting information in other areas (see recommendation 5 below).

Comparisons can be made with the diagnosis of MCI in the field of Alzheimer's disease. Statistical cut-offs for low cognitive performance in MCI vary between 1, 1.5 and 2 SD, resulting in wide variation in MCI prevalence depending on method.[83] Less stringent definitions using 1 SD are generally not favoured as they have a higher false positive rate,[84] fail to show an association with medial temporal atrophy and APOE genotype,[85] and have greater degrees of diagnostic instability over time (ie. an individual fluctuating between a classification of MCI and normal over time).[83] The potential for false classification of MCI is mitigated by the requirement of symptomatology, in contrast to HAND for which symptoms are not a requirement (see recommendation 6).

It should be stressed that isolated low cognitive performance, although not meeting our proposed criteria for cognitive impairment, may have clinical and research significance. Individuals with low cognitive performance represent an important group to study. Subclinical impairment and/or a lower cognitive reserve may increase vulnerability to other brain injury, which is particularly important as the population of PWH ages.[45-47]

It is important to note that those at the lower end of the spectrum of cognitive performance may be more likely to have lower levels of education and lower socioeconomic status as well as different comorbid and lifestyle factors.[86,87] As such this group may have worse health

related outcomes *per se* and outcomes associated with low cognitive performance should be interpreted in this context.[88]

Recommendation 4: When interpreting cognitive data, the false classification rate should be considered

As stated above, HAND criteria define impairment as performance at least one SD below normative average in at least two cognitive domains.[1] If population performance is normally distributed, then approximately 16% of scores on each test will fall more than one SD below the mean. This means that a sizable proportion of a cognitively unimpaired population will be falsely classified as impaired based on the statistical approach. This false classification rate depends on the number of domains measured, the number of tests used per domain, and the relationships between different tests, but is typically in excess of 20% and can rise to over 70% if enough tests are employed.[9,10,80]

As also mentioned above, there are several other statistical approaches to determine cut-offs for cognitive performance in PWH compared to normative controls.[8,25] Some methods are more stringent than others, with improved false positive rates generally at the expense of decreased sensitivity. Some methods can be applied in several different ways, for example when more than one test is used per domain to improve accuracy, domain impairment for HAND can be determined by one test being positive, both tests being positive, or by the average domain T-score. These variations can alter the false classification rate quite dramatically.[80,81]

It is important to consider the false classification rate when interpreting study findings: a study reporting low performance on cognitive tests in 30% of a population has a different interpretation when the false classification rate is known to be 25% compared to 2.5%. Currently, the false classification rate is rarely acknowledged or reported in studies reporting HAND prevalence.[11] Tools which can be used to help estimate the false classification rate for different statistical methodologies should be expanded.[8]

There are alternative approaches to handling cognitive data in research studies which do not lead to false classification in this way. One is to longitudinally assess trajectory of cognitive performance, rather than apply dichotomisation cross-sectionally. Here fluctuation in cognitive performance and practice effects must be taken into account.[80,89] Another approach is to use cognitive performance as a continuous variable, rather than apply a statistical cut-off. The use of continuous variables assesses the full spectrum of cognition and provides greater statistical power than the comparison of proportions below a cut-off.[81]

Diagnosing cognitive impairment in PWH

Recommendation 5: A research classification of cognitive impairment in PWH should consider a combination of cognitive symptoms, low performance on cognitive testing, and abnormality on neurological investigations

Assessment for cognitive impairment broadly falls into three areas: clinical history, performance on cognitive testing, and the results of neurological investigations. Each area has strengths and weaknesses if used alone to determine cognitive impairment (table 2). The presence of cognitive symptoms is clinically important, but is a subjective measure and

reporting of symptoms varies between settings (see recommendation 6). The results of cognitive testing can be more objective, but are strongly influenced by complex educational and socioeconomic factors and must be interpreted in the context of the background of the individual or population studied (as discussed in recommendation 3). Evidence of brain injury on neurological investigation such as neuroimaging is the most objective measure of pathology, but abnormalities can represent subclinical damage and tests are not universally available or accessible in low-resource settings. In addition, neurological investigations can be insensitive for some causes of brain injury, including for HABI, and the absence of abnormality evident on routine investigations does not exclude there being brain injury present.[50]

As such we propose that a classification of cognitive impairment in research can be made if there are abnormalities in at least two of these three areas. Using this pragmatic approach, someone with low cognitive performance would be considered to have cognitive impairment if there was supporting evidence of symptoms and/or brain injury. Similarly, someone with cognitive symptoms and evidence of brain injury would be considered to have cognitive impairment, even if cognitive performance did not fall below a threshold (and hence would not be have been classified as HAND), for example due to a higher pre-morbid function and/or cognitive reserve.

Altering the criteria for cognitive impairment in this way is not intended to undermine the importance of an isolated abnormality in any one area. It should be emphasised that such cases, while not meeting criteria for cognitive impairment, may still represent a group with clinical and research significance. Our recommendation is simply to alter the terminology used to describe these groups. Those previously defined as having Asymptomatic Neurocognitive Impairment (part of HAND and hence a neurocognitive disorder) would be referred to as having 'low performance on cognitive tests'. They would not be considered to have cognitive impairment unless there was supportive evidence of abnormality from another area.

Area	Assessment	Strengths	Weaknesses
Cognitive symptoms	Clinical assessment (ideally with observer account)	Clinically relevant	Subjective. Can be insensitive to subtle/early brain injury.
Low cognitive performance	Cognitive testing	More objective	Affected by non-biological factors
Evidence of brain injury (HABI or other)	Neurological investigations	Most objective for pathology	Investigations can be insensitive, thresholds for abnormality are not well defined, abnormalities may not have clinical correlate, and access varies between settings.

Table 2. *Areas of assessment for cognitive impairment.*

Recommendation 6: Cognitive symptoms should refer to any change in cognition that has been noticed by the individual or an observer, whether or not this impacts daily functioning.

Cognitive symptoms are an important aspect of assessment of someone at risk of cognitive impairment. We recommend a subtly different use of the term 'symptom' from that applied in the HAND criteria. HAND criteria define symptomatic impairment as a change in activities of daily living (ADLs) resulting from cognitive issues. In the modern era, cognitive symptoms in PWH have generally become milder.[28] Symptoms such as forgetfulness or difficulty concentrating may significantly impact an individual's quality of life and ability to work, but may not be severe enough to limit ADLs.[22] This is similar to the diagnosis of MCI in the field of Alzheimer's disease, for which cognitive change should be noticeable but not yet have significant impact on ADLs.[90]

Cognitive symptoms are inherently subjective. Some cultures may be reluctant to acknowledge cognitive issues and some languages have limited vocabulary for cognitive complaints.[91,92] Furthermore, cognitive dysfunction can impair insight, decreasing the chances of difficulties being reported.[93] Where available, an observer account (for example a collateral history from a partner, family member or carer) can improve accuracy in this area and form part of criteria for MCI.[94] It is important that consent is gained as the observer account can include sensitive information. Any reported difficulties with ADLs on functional scales should be confirmed as related to cognitive issues rather than physical disability, intercurrent illness, psychological factors, or fatigue.

Cognitive symptoms can be transient and reactive to psychological stressors or life events.[95,96] Symptoms can be more common in those with depression, which may be due to over-reporting or potentially due to shared biological mechanisms of neuroinflammation.[97-99] Where uncertainly arises, repeated assessments over longer periods may be needed. Rapidly evolving symptoms should trigger urgent investigation for CNS opportunistic infection, CD8 encephalitis, more fulminant presentations of symptomatic CSF HIV RNA escape, or neurological disorders unrelated to HIV infection.[49,55]

Discussion and potential limitations

Our recommendations differ from the HAND criteria in two main ways: firstly, by distinguishing HABI as a separate entity from all-cause cognitive impairment, and secondly by recommending a clinical assessment for a label of cognitive impairment to be applied. While perhaps not as appealingly simple as the HAND classification, our approach represents the complexity of assessing cognitive impairment in PWH in the modern era. To apply this approach in clinical settings would require no additional measures beyond recommended standard of care. Assessment of a person suspected of having cognitive issues should, at a minimum, involve a clinical history, ideally with an observer account, backed up with a cognitive measure. Assessment for brain injury depends on available local resources, and detailed neurological investigations are not essential for this classification.

Historically, not all research studies have collected the information necessary to diagnose cognitive impairment in this way. We feel that collecting a clinical history and objective markers of brain injury is important to conduct research with relevance to PWH outcomes and concerns. Studies assessing individual areas in isolation without a clinical history (for example, a study of cross-sectional cognitive performance or neuroimaging) may provide

useful mechanistic information, but we suggest should avoid reporting rates of cognitive impairment and making assumptions about the cause. Measures interpreted without clinical context have been shown to have poor inter-rater agreement for assigning the aetiology of cognitive impairment, even in advanced HIV disease, due to myriad comorbidities.[100]

While we highlight issues with the HAND criteria and its potential to overestimate prevalence, our approach should not be interpreted as implying that cognitive impairment is no longer an issue in PWH. Cognitive impairment remains a critically important complication of HIV with multiple causes. It can have profound impacts on many aspects functioning and of quality of life.[22] Cognitive issues may become even more important as the population of PWH ages. It is crucial we have a robust set of criteria to focus research and ensure those at risk are identified and receive the help they need.

There are several potential limitations to our proposed approach. Firstly, our recommendations suggest a clinical assessment to determine clinically meaningful impairment - this can be difficult to transfer to the research environment. In many low-resource settings, standardised cognitive measures are applied by local-language speaking research assistants without the medical or neuropsychology training to obtain a detailed history.[17] Although this presents challenges, a clinical assessment forms part of inclusion criteria for studies of other diseases, including in PWH in low-resource settings.[101] A clinical history was a requirement of the 1991 American Academy of Neurology criteria for HIV-associated dementia and HIV-associated minor cognitive/motor disorder which stated that mild cognitive deficits should be verified by a reliable history, when possible from an informant, to ensure the timing and nature of impairment are consistent with HIV as a cause of the impairment.[102] The 2007 HAND criteria moved away from this by creating the category of Asymptomatic Neurocognitive Impairment (ANI).[1] The intention was that ANI would represent a pre-clinical stage of impairment that may be amenable to treatment. However the fact ANI is based on cognitive performance alone, without clinical correlate or other evidence of brain injury, may limit the ability of ANI to reliably identify a pathological phenotype. To facilitate the collection of clinical assessments in research, tools are needed that can distinguish cognitive limitations from physical/mental health issues and include collection of an observer account. Such tools exist in the non-HIV field; for example the Community Screening Instrument for Dementia (CSID) includes a cognitive assessment, functional measures and an observer account, and has been used across diverse settings globally.[103]

Secondly, sensitivity to detect cognitive impairment, based on the overlap of at least two areas of assessment (recommendation 5), would differ depending on method. For example, the size of the group with brain injury would vary depending on whether neuroimaging was available, and if so whether MRI or CT was used. Although imperfect, this mirrors the clinical situation where sensitivity to detect disease is lower when access to investigations is reduced. We propose this as a pragmatic alternative to HAND which considers clinical context. It is perhaps the most speculative of our recommendation and we suggest it is validated against clinical diagnosis compared with existing approaches.

Thirdly, the term HABI is coined to refer to a significant degree of brain injury as a direct result of HIV, but what constitutes significant injury in this context is to some extent subjective. HIV enters the brain early in infection and it is difficult to exclude HABI on some level in all PWH.[29] Furthermore, the separation between HABI and other causes of brain injury may not be completely distinct. For example, cerebrovascular disease can be exacerbated by HIV-

associated endothelial dysfunction and/or antiretroviral effects.[104] There is evidence indicating that HIV interacts with substance abuse to compound the injurious effects on the brain.[105] Nevertheless, we feel it is useful to distinguish injury which is caused directly by HIV (ie. HABI), from indirect or combined effects (which would not be described as HABI).

Fourthly, there is no universal biomarker for HABI. Although a combination of investigations and clinical context can diagnose HABI, particularly when severe (eg. during advanced immunosuppression) or when rapidly progressive (eg. symptomatic CSF escape), no single imaging or CSF biomarker of HABI has been identified for all stages and types of HABI that is robust enough for clinical use.[69] This may in part be because the phenotype of those described as having HAND is insufficiently precise to allow accurate identification of complex mechanisms. As discussed, HAND can encompass a mixture of different pathologies and include individuals without true cognitive impairment. As a result, any genuine association between biomarkers and cognitive impairment due to HABI may be diluted by the inclusion of individuals without this condition. Conceptually separating HABI from low cognitive performance is intended to improve clarity in this area. It should be noted that this issue is not unique to HABI; many other causes of brain injury have no definitive test and rely on clinical judgment in the context of history, risk factors and investigation findings. We feel that, although not always straightforward, it is important to attempt to identify the relative contribution HABI makes to cognitive impairment as treatment for HIV becomes more effective and widespread, so that PWH can better understand their risk of this condition and treatments can be tailored to the cause.

CONCLUSIONS

We outline a series of recommendations reflecting the consensus opinion of our diverse group. These recommendations are intended to drive discussion and debate towards the development of new criteria for cognitive impairment in PWH. Our recommendations will require assessment, validation, refinement, and a broader consensus within the field. More detail will be needed in several areas including which cognitive tools to use in different settings, which statistical methods to apply to determine low cognitive performance, how best to obtain a history of cognitive symptoms, which functional scales are appropriate for different settings, how to determine severity, and how to interpret investigations for HABI. Overall, our approach is intended to better represent the changing profile of cognitive impairment in PWH in diverse global settings and provide a clearer framework of classification for clinical management and research studies.

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