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VIEWPOINTS

Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward

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Human immunodeficiency virus (HIV)–associated neurocognitive disorders (HAND) criteria are frequently used to describe cognitive impairment in persons living with HIV (PLWH) across diverse populations globally. These criteria typically find 20–60% of PLWH meet criteria for HAND, which does not tally with clinical observations in the modern era that cognitive disorders present relatively infrequently. Most with HAND have asymptomatic neurocognitive impairment; however, the significance of low cognitive test performance without symptoms is uncertain. Methods underlying HAND criteria carry a false-positive rate that can exceed 20%. Comorbidities, education, and complex socioeconomic factors can influence cognitive test performance, further increasing the potential for misclassification. We propose a new framework to characterize cognitive impairment in PLWH that requires a clinical history and acknowledges the multifactorial nature of low cognitive test performance. This framework is intended to be applicable across diverse populations globally, be more aligned with clinical observations, and more closely represent HIV brain pathology.

Keywords. HIV-associated neurocognitive disorders; HAND; cognitive impairment; criteria.

The most frequently used criteria for cognitive impairment in persons living with human immunodeficiency virus (PLWH) are the human immunodeficiency virus (HIV)–associated neurocognitive disorders (HAND) criteria, developed in 2007 by a working group formed by the US National Institute of Mental Health and National Institute of Neurological Diseases and Stroke (sometimes referred to as the Frascati criteria after the Italian town in which they were formulated) [1]. The HAND criteria were intended for use in research, but the terminology has become widely used to refer to clinical burden of disease [2–5]. Several authors have expressed that the HAND criteria may not be appropriate for the modern era [3, 6–13].

HAND criteria typically characterize 20–60% of PLWH with a cognitive disorder, with some studies describing rates as high as 70–90% [4, 5]. A recent meta-analysis of global studies showed a HAND prevalence of 43% (range, 11–92%) [5]. These figures do not tally with clinical observations that cognitive impairment presents rarely in PLWH in the modern era, usually in those with viral nonsuppression or significant comorbidities. A recent UK study showed a 3.2% prevalence of cognitive impairment when diagnosed clinically [14].

Prior to HAND were the 1991 American Academy of Neurology criteria [15], which defined HIV-associated dementia (HAD) and HIV-associated minor cognitive/motor disorder. These criteria stated that cognitive deficits causing mild impairment to activities of daily living 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 [15]. The 2007 HAND criteria moved away from this by including an Asymptomatic Neurocognitive Impairment (ANI) category, whereby the minimum criteria for cognitive disorder were met by low performance on cognitive tests when compared with a control population matched for certain parameters (namely, age, sex, ethnicity, and years of education) [1]. In the modern era, most of those classified as HAND have ANI with no evidence of functional limitation [5]. The clinical relevance of the ANI category is unclear and most clinical guidelines have moved away from recommending screening for this [16].

By definition, HAND is due to the direct effect of HIV. However, performing poorly on cognitive tests without functional impairment (ie, ANI) does not always reflect the direct effect of HIV on the brain, particularly in populations with a high prevalence of socioeconomic stressors and inequalities, low educational attainment, and comorbid conditions. The statistical methods underlying ANI lead to a high false-positive rate; over

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20% of cognitively normal HIV-negative control subjects can be defined as impaired based on the current approach [8, 12].

When HAND criteria were developed the frequency of cognitive disorders was such that an algorithm that was simple to apply and reduced the need for clinical assessments was appealing. Now that viral suppression is more common, antiretroviral therapy (ART) less toxic, and the relative contribution of comorbid/lifestyle factors has increased, a full clinical assessment has become essential. Here we review the current criteria as applied to diverse settings in the modern era and propose a new framework to describe cognitive impairment in PLWH.

FACTORS AFFECTING PERFORMANCE ON COGNITIVE TESTS

Performance on cognitive tests among PLWH is influenced by 3 main factors, as described below and illustrated in Figure 1.

HIV Brain Pathology

In the pre-ART era, HAD occurred frequently in advanced immunosuppression. Neuropathologically, HAD was associated with multinucleated giant cells and microglial nodules; termed HIV-encephalitis. While HIV-encephalitis and HAD are uncommon in the modern era, there are now multiple potential mechanisms by which HIV can damage the brain, some of which may persist on ART in some individuals, although this is not clearly defined. Such mechanisms include compartmentalized HIV, sustained immune activation, oxidative stress, metabolic changes, glutamate dysregulation, neurotoxicity of HIV viral proteins, N-methyl-D-aspartate (NMDA) excitotoxicity, blood–brain barrier rarefication, neurodegeneration, and effects of HIV on endothelium and vascular tissue, a detailed discussion of which is beyond the scope of this review [17]. In this paper we refer to these collectively as HIV brain pathology.

HIV brain pathology can cause impairment in cognitive function but may be asymptomatic. Even in the early studies of HAD (then termed AIDS Dementia Complex) it was noted that one-third of cases of dementia had relatively bland histopathology, whereas histopathological abnormalities were apparent in over half of patients without dementia [18]. In the modern era, it is not infrequent to observe white matter signal changes on neuroimaging in someone without demonstrable cognitive problems who undergoes imaging for another indication.

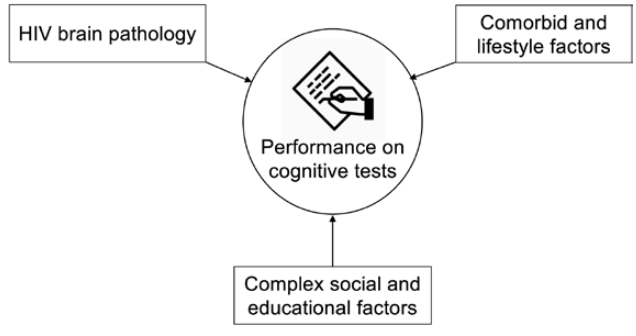

Figure 1. Factors affecting cognitive test performance in persons living with HIV. Abbreviation: HIV, human immunodeficiency virus.

Comorbid and Lifestyle Factors

In the modern era, the etiology of cognitive impairment in PLWH is frequently multifactorial, related to a number of comorbid and lifestyle factors. Such factors can be common in HIV-positive populations and are linked to HAND prevalence. In the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, HAND prevalence ranged from 83% of 239 patients with severe comorbidities to 40% of 843 patients with minimal comorbidities [19]. Comorbidities were common overall, such that even in the group with minimal comorbidities, 71% had a history of drug misuse and 16% had current depression or psychotic disorder.

HAND criteria acknowledge that PLWH not infrequently have complex medical and social histories that may include more than 1 risk factor for cognitive impairment [1]. A strategy to determine the impact of such factors is suggested, classifying them as contributing or confounding, largely based on the history and chronology of impairment. Those with confounding conditions cannot be defined as HAND, whereas those with contributing factors can. In practice, most studies of cognition seek to exclude participants with confounding conditions (ie, clear alternative diagnoses such as neurodegenerative conditions, uncontrolled epilepsy, alcoholism, or severe head injury). Other comorbidities identified within the impaired study population are labeled as "contributing" and a diagnosis of HAND can be made. By definition, HAND is due to the direct effect of HIV on the brain; therefore, a label of HAND assumes that low performance on cognitive tests in a persons living with HIV is caused by HIV, at least in part. In reality, some low cognitive test performance is entirely caused by HIV, some is due to a combination of HIV and comorbid factors, and in some people HIV brain pathology may not be contributing at all. The latter category is likely to become larger as more PLWH are treated with suppressive ART earlier in infection, given that significant central nervous system (CNS) injury is usually associated with more advanced immune deficiency. To label all low performance on cognitive tests in PLWH as a cognitive disorder caused by HIV (excluding the few with a clear alternative "confounding" diagnosis) risks overestimating the extent of HIV brain pathology in this population.

One option used to address this in research studies is to stringently exclude all comorbidities; however, this is not practical given the high rates of comorbidities in PLWH and is not desirable in terms of studying a representative population. Persons living with HIV with comorbidities are highly represented, even more so in those with cognitive impairment, and are a vulnerable group worthy of study. Cognitive impairment from any

cause may impact an individual's ability to function effectively. For example, memory problems may impact ART adherence and executive dysfunction may limit the ability to problem-solve around complex life challenges, creating barriers to full adherence [20].

Complex Social and Educational Factors

In this paper we use the term socioeconomic status (SES) to represent diverse social and economic factors related to income, occupation, social standing, culture, education, and associated indices of social inequality and stressors. In high-income countries HIV tends to disproportionately affect those with lower SES [21], and health outcomes are worse for those at the lower end of the socioeconomic spectrum [22]. In some African settings HIV was associated with greater wealth earlier in the epidemic; however, as the epidemic has evolved this has changed to an association, in general, with poverty, wealth inequality, and lower education [23–25]. Within low-income populations, it is usually the poorer of the poor that are disproportionately affected by HIV. For example, HIV prevalence among 800 women attending a public antenatal clinic in a low-income South African setting was 19–24% in the lowest 2 wealth quintiles compared with 4–8% in the highest; every additional year of education was associated with a 10% reduction in HIV risk [26]. Norming cognitive performance at a lower level for a low-income population does not take into account the diversity within that population and the fact that HIV may not be evenly distributed throughout the socioeconomic spectrum.

The impact of SES on cognitive performance can be such that controls from one setting can have average scores that would be associated with pathology in another. For example, in 1 study the mean score on the Montreal Cognitive Assessment (MoCA) in cognitively unimpaired, healthy, controls without HIV in a low-income peri-urban South African population was 21.7 out of 30 [27]. 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, rather that performance on these tests can be culture-bound and vary substantially in groups with different education and sociodemographic backgrounds.

There is a large literature from non-HIV settings in high-income countries linking low SES with lower performance on cognitive tests, which is thought to be due to a number of educational, cultural, linguistic, and developmental factors, a detailed discussion of which is outside the scope of this review [28]. In clinical practice, these factors are taken into account by neuropsychologists who consider the subjective interpretation of an individual's performance based on educational background and estimates of premorbid functioning.

A large study by Robertson et al [29–31] sought to examine cognitive performance between diverse resource-limited settings. A total of 860 PLWH and 2400 controls were recruited across 11 sites from 7 counties in sub-Saharan Africa, South America, and Asia. Large differences in cognitive test performance were seen between countries, and between sites within the same country. These differences were not due to HIV factors as they were also present in controls without HIV and were not fully explained by comorbidities, as these were excluded or controlled for; rather, they underline the impact of educational and socioeconomic factors between diverse populations.

Studies of PLWH have shown an association of cognitive performance with trauma, economic hardship (ie, food insecurity and low SES), and stress [32, 33]. In a 2015 study of 1521 women in America, 1019 of whom were PLWH, the effect size for HIV status on cognition was very small, accounting for only 0.05–0.09 SD units, far less than the impact of education, age, race, income, and reading level [32].

HAND criteria acknowledge that other factors influence cognitive test scores by stating that cognitive norms should be matched for age, sex, ethnicity, and years of education [1]. Matching for these factors alone may not adequately control for the effect of SES on cognition, particularly in diverse low-income settings. Years of education does not account for quality of education, which can vary widely, or for nonformal education provided at home [34]. In South African Xhosa-speaking adult populations, variations in quality of education have been shown to affect scores on the Wechsler Adult Intelligence Scale by as much as 20 to 30 points [35]. The suggestion to control for ethnicity essentially utilizes this parameter as a crude marker for SES; something that is not appropriate across all settings.

PROPOSED NEW FRAMEWORK TO CHARACTERIZE COGNITIVE IMPAIRMENT IN PERSONS LIVING WITH HIV

We propose a new framework to describe cognitive impairment in PLWH for use in research and applicable to clinical settings. Changes are in 3 main areas, described below. The key differences between this framework and HAND criteria are summarized in Table 1.

Clinical History

We suggest that a research classification of cognitive impairment in PLWH should not be made on the basis of cross-sectional performance on cognitive tests but take into account a clinical history of cognitive symptoms, the trajectory of decline, and estimates of premorbid functioning. Although this may be time consuming and present logistical challenges, it more closely reflects the real-world scenario and will generate prevalence figures that more meaningfully reflect the extent of clinically significant cognitive impairment. We suggest that studies that do not have the resources to characterize cognitive impairment in this way should not report prevalence, but rather describe a spectrum of cognitive performance.

Table 1. Summary of Key Differences Between HAND Criteria and Our Proposed Framework

	HAND: Existing Criteria	Cognitive Impairment in PLWH: Proposed New Framework
Definition	A cognitive disorder caused by the direct effect of HIV on the brain	Symptomatic cognitive impairment from any cause in a persons living with HIV
Proportion with asymptomatic impairment	Most	None
Diagnosis	Based on performance on cognitive tests compared to matched controls	Based on clinical history, including observer account where possible
Low cognitive test performance without symptoms	Termed ANI, which is part of HAND and hence labeled a cognitive disorder	Described as "low performance on cognitive tests," which is not part of cognitive impairment
Comorbidities	Divided into confounding (not HAND) and contributing	Comorbid factors specified alongside relative contribution of HIV brain disease

Abbreviations: ANI, asymptomatic neurocognitive impairment; HAND, HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus; PLWH, persons living with HIV.

This is aligned with the concept of mild cognitive impairment (MCI) in the non-HIV field. MCI describes the stage between the expected cognitive decline of normal aging and dementia such as Alzheimer disease. Criteria for MCI require that the change in cognition is recognized by the affected individual or observers, as well as objective impairment in 1 or more cognitive domains [36]. MCI can be caused by Alzheimer pathology, non-Alzheimer pathology (such as cerebrovascular disease), or both.

Low Performance on Cognitive Tests

Newer statistical methods of defining cognitive impairment cutoffs have been developed, aimed at improving the accuracy of diagnosis in research studies. These include the Global Deficit Score criteria, a Multivariate Normative Comparison score, and revisions to the HAND criteria (referred to as the Gisslén criteria) [13]. These have lower false-positive rates than HAND criteria; however, any method that involves applying statistical techniques to dichotomize cognitive test scores involves a cutoff for normality that can be somewhat arbitrary. As such, we suggest that those with cognitive performance below a given cutoff, but without evidence of symptoms, should be described as having "low performance on cognitive tests," rather than cognitive impairment or HAND. It should be acknowledged that the clinical significance of this group is uncertain, the association with HIV brain pathology is unclear, and that the proportion falling into this category varies substantially with statistical method applied [8].

In research studies we suggest that, where possible, cognition in those with low performance on cognitive tests should be analyzed as a continuous variable rather than apply a statistical cutoff. This is for 2 reasons: first, the use of continuous variables assesses the full spectrum of cognition and provides greater statistical power than the comparison of proportions below a cutoff with a dichotomous outcome; second, it is difficult to define a meaningful cutoff based purely on cognitive performance. When analyzing cognitive scores in this way, SES factors should be controlled for as closely as possible using regression-based techniques.

In clinical practice, those with asymptomatic low performance on cognitive tests would only be identified by screening of asymptomatic individuals, which is not currently recommended [16].

HIV Brain Pathology

We suggest that HIV brain pathology should be differentiated conceptually from cognitive test performance to reflect the multifactorial nature of this condition in the era of effective ART. A separate definition should be developed for HIV brain pathology applicable to research and clinical settings, pivoting on neuroimaging findings, biomarkers, trajectory of symptoms, and/or demonstrated decline in cognitive test performance in relation to acquisition of HIV.

HIV brain pathology and comorbidities should be considered separate overlapping entities, whereby HIV brain pathology has variable contributions to cognitive impairment and it is possible to have cognitive impairment without evidence of HIV brain pathology. In research, such comorbidities should be listed as specifiers where possible—for example, psychiatric illness, ART neurotoxicity, nutritional and vitamin deficiencies, age-related cognitive deficits, neurodegenerative conditions, cerebrovascular disease, head injury, previous CNS infections, birth trauma, and lifestyle factors such as alcoholism and substance misuse. Where this is not possible they can be labeled as "multifactorial" or due to "undetermined factors."

DISCUSSION

Our assertion that the HAND criteria risk overestimating the extent of cognitive disorders in PLWH should not be mistaken for a view that we do not believe HIV brain pathology and cognitive impairment in PLWH to be important or widespread. It is clear that HIV has distinct neuropathological effects that may not always be apparent clinically and may have important implications for an aging population. ART coverage is not universal, and many remain at risk of uncontrolled disease. Compartmentalization of HIV in the CNS occurs, and

the fulminant syndromes observed are likely to be the tip of the iceberg [9]. The fact that cognitive impairment in PLWH is multifactorial does not detract from its impact on the individual or the potential for functional effects on daily living, economic viability, and ART adherence, nor the importance of fully understanding this entity and developing interventions to reduce its impact. While some of those with asymptomatic low performance on cognitive tests may fall on the spectrum of normality, others may have subtle neuropathology or a lower cognitive reserve conferring a greater vulnerability to cognitive impairment. Identifying biomarkers or imaging signatures to differentiate these 2 groups will be essential. Furthermore, while our framework excludes this group from a label of cognitive impairment, it aims to improve their study by analyzing cognition as a continuous variable to provide greater statistical power. This is important as ANI forms the majority of HAND in most research studies.

Cognitive impairment is a much-feared complication and can be stigmatized. Persons living with HIV are an already marginalized population who risk additional discrimination if cognitive impairment is perceived to be common among this group. Our proposed framework is intended to more robustly define cognitive impairment to give more meaningful prevalence figures and avoid those with asymptomatic low performance on cognitive tests being labeled as having a cognitive disorder.

There are limitations to an approach that focuses on symptomatology for diagnosis. People with cognitive impairment can lack insight into their symptoms, and depressed people are more likely to report symptoms regardless of objective function. Our recommendation of an observer account is aimed at addressing this. However, this may pose additional challenges as PLWH do not always disclose their status to those close to them and some visit the clinic alone. In many low-resource settings, standardized cognitive measures are applied by local-language-speaking research assistants without the medical or neuropsychology training to obtain a detailed history [4]. As such, there is a need for objective measures of acquired symptoms for use in research settings.

Accurate identification of HIV brain pathology may be difficult as no biomarker has yet been validated for this purpose. This is particularly true for low-resource settings where access to neuroimaging can be scarce. In many cases, a diagnosis of HIV brain pathology would rely on the trajectory of symptoms and exclusion of other illnesses. This might necessitate a possible/probable/definite hierarchy. Nevertheless, we feel that such classification is realistic and achievable in a low-resource research setting, more accurately reflects the true nature of the problem, and is more aligned to the clinical scenario.

We hope this framework will lead to the development of new consensus criteria to classify cognitive impairment in PLWH, appropriate for the modern era of widespread effective ART. Based on this framework we feel it is achievable to develop criteria for diverse global populations that are applicable to both research and clinical settings. The development of such criteria will require further refinement and validation of our framework and the involvement of different clinical specialities, academic disciplines, and geographic regions, as well as the wider community of PLWH.

Note

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