Measuring neurocognitive impairment in virally suppressed HIV: HIV-associated neurocognitive disorders, HIV-associated brain injury problems and solutions

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Purpose of review
To discuss neurocognition measurement in view of current controversies in HIV-associated neurocognitive disorders (HAND).

Recent findings
The HAND criteria have been criticised for several reasons with some proposing alternative criteria and terminology, HIV-associated brain injury (HABI). The following concerns have been raised: the legacy effect from past ineffective therapy is not included, the adoption of an asymptomatic neurocognitive impairment (ANI) stage, including liberal neuropsychological test cut-offs overestimate neurocognitive impairment (NCI), and that NCI with viral suppression is still related to HIV rather than the effect of either legacy and/or comorbidities. However, the legacy effect cannot be easily identified, the HAND criteria have been inappropriately used, and there is increasing evidence that low level HIV replication is important in virally suppressed HAND, though likely mitigated in some by resilience factors. Potential solutions to addressing these within the HAND framework will be proposed.

Summary
The HAND framework is still useful but it must be put in clinical context. ANI should be considered a research category pending further clarification of its clinical utility. Further work is needed to identify and quantify the legacy effect/ongoing NCI, as well as the nature of resilience.

Keywords
cognitive dysfunctions, HIV-associated brain injury, HIV-associated neurocognitive disorders, HIV, viral suppression

CONTROVERSIES IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDER AND HIV-ASSOCIATED BRAIN INJURY

HIV-associated neurocognitive disorders (HAND) [1] criteria and their implementation have been criticised with some researchers advocating an alternative framework HIV-associated brain injury (HABI) [2▪]. We consider HAND to be still a valuable term and framework [3▪,4▪]. HAND does not attribute the disorder to HIV but remains neutral hence "associated" in the title. Further, it recognises that there may be several neurocognitive disorders, hence the pleural. The lack of direct attribution to HIV was deliberate as people with HIV (PWH) had and continue to have illnesses that variably contribute to or confound their NCI [5]. *The extent to which such illnesses interact and amplify the effect of HIV as partial or full contributors was and still is unclear*. The HAND framework is still useful though recognising that the following quite reasonable issues have triggered the HABI proposal: the legacy effect from past partly effective antiretroviral therapy (ART), the identification of an asymptomatic neurocognitive impairment (ANI) stage including liberal cut-offs for abnormality on neuropsychological testing leading to high rates of impairment, and the fact that HIV can now be so

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KEY POINTS

- Measuring NCI remains a cornerstone of the evaluation of HAND and the issue of false positives is an issue that is transdiagnostic.
- Placed in the context of a comprehensive clinical review, it is possible to reduce misclassification of NCI and carefully document the extent of functional impact.
- Apart from HIV disease factors, contributing preexisting or de-novo co-occurring conditions, and resilience factors should be considered during the clinical assessment.
- ANI and MCI have overlapping features and epidemiology and should be further considered in research settings as the original HAND criteria were designed for research purpose.
- Active brain injury will be better understood if research continues to include ANI, but in clinical practice evidence of functional impairment should take precedence.
- Current data suggest a model of HAND whereby there is gradually accumulating damage over prolonged periods with implications for biomarkers, trials and patient management.

well controlled with ART that HIV RNA is below detection limits which by the HABI framework raises the proposition that NCI with undetectable viral RNA must be a legacy effect or the consequence of comorbidities. Each of these will be discussed in the following sections. A solution will be proposed along with a HAND model that has direct implications for clinical management, biomarkers and trials.

THE LEGACY EFFECT

By the HABI framework, NCI may be a result of a legacy effect [2▪] from an earlier time when less effective ART was used. Such a concept is not new and indeed was a consequence of the analyses of the abacavir AIDS dementia trial over 25 years ago [6]. It should be acknowledged, however, that there is no consensus on how to define "legacy". Furthermore, the most comprehensive studies have shown that sociodemographic and other clinical characteristics cannot be easily dissociated from a legacy effect on neurocognition [7]. Therefore, legacy should be perhaps more correctly termed "legacies" because they are likely multifactorial and include HIV, treatment and non-HIV effects as well as complex viral host genetics and dementia genetics. The field would therefore strongly benefit from a better conceptualisation, operationalisation and quantification of legacies.

EARLY STAGES OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER AND THE OVERLAP WITH MILD COGNITIVE IMPAIRMENT

The original formulation of the HAND criteria [1] emphasised that appropriate normative data had to be used where possible and advised caution where such data were unavailable, representing standard neuropsychological practice. To address such issues, neuropsychologists routinely develop norms for a vast array of tests and update them as often as possible. However, we recognise significant inequalities [8]. Importantly, the 2007 HAND criteria [1] were meant to be used in research settings – hence the term "research" in the title of the original study – rather than in the clinical arena where evidence of functional impairment is to be demonstrated [9]. Unfortunately, the research HAND criteria have been applied to clinical practice without consideration of all these caveats. The criteria introduced a very mild stage of the disorder ANI. This was done to capture the earliest stage of the disorder, as it was underpinned by a small number of autopsy studies [10] that showed significant HIV pathology. However, it was recognised that there would always be a false-positive rate as specificity and sensitivity are inversely related [11]. This stage is similar to the subjective cognitive impairment/mild cognitive impairment (MCI) that is used in Alzheimer's disease and other dementias [4▪]. Just as in ANI, MCI has a significant false positive rate (see below) with some returning to normal on follow-up. This issue will need to be resolved as with ageing, some PWH have MCI [12].

MEASURING NEUROCOGNITION

Measuring neurocognition is important in clinical practice, research and clinical trial settings. Further, accurate clinical characterisation is fundamental to understanding pathogenesis, the development of biomarkers, and management. While self-reported symptoms are valuable, they are strongly influenced by mood and personality [13]. Quantification can be challenging, but standard assessments of everyday function are now available and inclusive of the assessment of more complex activities [14]. This is important especially in the absence of an informant as is often the case in HIV clinics. In this context, neuropsychological testing remains a key component of a HAND evaluation where neurocognition is assessed using standard tests and protocols (including the selection of appropriate normative data). The neuropsychological assessment represents but one of the components of a HAND assessment and should be considered *in association* with all other evaluations as reviewed below. Neuropsychological testing can

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range from simple bedside screens to a medium-size battery (some maybe computerised) to more formal testing that often takes several hours. Standard neuropsychological testing, however, is not routinely available even in high-income countries, posing a major problem in the implementation of the 2007 HAND criteria in clinical practice [15].

SOLUTIONS: A TIERED-APPROACH TO THE HIV-ASSOCIATED NEUROCOGNITIVE DISORDER ASSESSMENT

Given the constraints of resources both in time and personnel, it is suggested that a tiered approach be adopted as previously outlined [16,17]. Briefly, clinical assessment by a medical doctor first (centring clinical practice on a clinical review and laboratory examination as previously proposed [15]) with targeted questions regarding cognition corroborated by a partner/friend/chosen family when possible. The questions themselves should go beyond simple one-line issues to focused questions with demonstration of neurocognitive and functional decline across a longitudinal timeframe (i.e., significant decline compared to best previous level). These include de novo and increased frequency of symptoms such as losing track of the conversation, having to keep lists, slowed reading, and word finding difficulties. The use of standard instruments to evaluate subjective neurocognitive symptoms for this stage of the clinical assessment will assist. As HIV involvement of the brain is often accompanied by motor and behavioural disturbances, questions addressing these should be included. These are slowing, and inaccuracy of dexterity, for example with computer keystrokes, sloppy handwriting, gait slowing and imbalance. Behavioural symptoms include social withdrawal and apathy without the inner feeling of sadness, or/and anhedonia more typical of depression. Such an approach reflects the subcortical nature of the disorder which is evident at all stages though in the earlier milder phases these are less common [17]. This is especially true in the era of virally suppressive ART which has rendered brain involvement in general milder and less clearly subcortical at least from a neurological standpoint [17]. The clinical assessment can then be complemented by attention to risk factors such as a low nadir $CD4^+$ cell count, anaemia, glucose intolerance, vascular risk, duration of HIV disease, age more than 50 and previous poor adherence to ART [17] [here we assume that current viral load is suppressed both in the plasma and the cerebrospinal fluid (CSF)]. At present, how these factors should be combined to give an overall risk score is not clear, nor is it apparent as to whether there should be any weighting of one over another save for poor ART adherence. Nonetheless, the greater number and severity of these factors the more likely HAND. The next tier then is some form of quantifiable neurocognitive evaluation. Bedside tests such as the mini mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are attractive because of ease of use and brevity. However, neither is particularly sensitive and certainly not specific for HAND, especially the MMSE. The MoCA has gained popularity largely because of its frequent use in the context of COVID-19. Nonetheless, its limitations must be appreciated: it fails to identify psychomotor slowing, a key feature of HAND and is more weighted towards cortical impairment, a feature not characteristic of HAND. At a practical level then, test combinations such as the NPZ4 or a well validated computerised screen can be considered. If this is not possible then the MoCA can be used but *in combination* with the aforementioned targeted clinical assessment. Older tests such as the international HIV dementia scale are better suited to the more severe form of HAND. Such a clinical review *must* be complemented by appropriate investigations including neuroimaging.

ISSUES TO CONSIDER AND SOLUTIONS

There are several significant issues with the use of such cognitive screens, however. First, the "cut point" for abnormality is a balance between identifying early disease with some false positives versus later disease with virtually no false positives, while considering the comprehensiveness of the screen, and the demographics of the person evaluated [18]. The issue is not unique to HIV; it is a common problem throughout medicine. Indeed, it is perhaps best exemplified by MCI which is widely accepted but which is known to have a variable false-positive rate depending upon the potential presence of other illnesses acting as partial or full contributors and on the timing of assessment. MCI patients can return to normal with longer follow-up. Indeed, one study found that only approximately 10% in a cohort whose mean age was 74 progressed to definite clinically significant impairment with annual assessments [19]. Second, there is the issue of reliability of cognitive screens when used repeatedly [20]. Interwoven with this problem is that of the practice effect, that is the improvement in test performance when the same tests are repeated within a short time frame. This can be minimised by the use of alternate forms of the tests, which is easier to achieve for computerised screens [20]. In clinical practice, a reliable change index corrected for practice effect can be used [19], however, a more comprehensive neuropsychological assessment is required [11].

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MANAGEMENT POST-HIV-ASSOCIATED NEUROCOGNITIVE DISORDER DETERMINATION: ACTIVE DISEASE

Once NCI and functional impact have been identified and graded, the next issue is the evaluation of what reflects current ongoing/active disease [17], the converse of what has been termed the legacy effect. This is a "thorny" problem which is yet to be resolved. There is no clinical or laboratory measure that can assess the presence or severity of active NCI. Recency of symptoms would seem to be a good measure of active disease but how recent? Must it be in the last twelve months or shorter? However, stability of neurocognitive or functional symptoms or even lack of symptoms does not necessarily indicate lack of active disease, as there may be compensatory mechanisms keeping the active injury in check until a tipping point is reached. In the context of ART, active disease may depend on the duration of HIV infection as well as duration of detectable viral load pre-ART. Indeed, stable NCI does not necessarily mean the process is "burnt out", a simmering pot is an analogy [21]. Clarification of this issue is critical for patient management. Nonetheless, at a practical level, it would be reasonable to conclude that a legacy effect is operating when the symptoms have been stable for several years.

MANAGEMENT POST-HIV-ASSOCIATED NEUROCOGNITIVE DISORDER DETERMINATION: CONTRIBUTORS TO ACTIVE DISEASE

Another aspect that requires evaluation once neurocognitive and functional impairments have been established is the extent (incidental, contribution, or confounding) to which impairments may be driven by preexisting or new co-occurring illnesses (e.g., mental health, and cerebrovascular disease) or/and life stressors (i.e., financial stress, social isolation with ageing) or/and lifestyle (alcohol and substance use). At all levels of the clinical review and associated examinations (neuropsychology, laboratory and neuroimaging), this can be very difficult to determine if preexisting or concurrent conditions have overlapping similarities in neurocognitive and functional impairment profiles. It is therefore essential to include accurate assessment of such conditions to help guide more precise attribution of deficit causation, while recognising the uncertainties when appropriate. It should also be appreciated that such preexisting or concurrent conditions may be actually compounding HIV-driven disease analogous to what is suspected in Alzheimer's disease [22]. Nonetheless, it is biologically plausible that the chronic inflammation associated with vascular disease may "kindle" low-level HIV replication and amplify HIV-driven brain disease [23].

RESILIENCE

The concept of resilience should be further explored in HAND [24]. This is an area of further research but again it is biologically plausible that the factors important in resilience against diseases such as Alzheimer's disease (dementia risk reduction factors) are likely important in the assessment of HAND. These include mediterranean diet, exercise, brain training, social engagement, the trait of resilience, lower level of health disparities, and so on. Ideally these should be quantified and be able to be incorporated into a single score acknowledging that it is unknown whether some factors should be weighted more than others in the context of HAND.

FUTURE DIRECTIONS: IMPLICATIONS FOR CLINICAL TRIALS

There is an increasing requirement from regulatory bodies such as the Food and Drug Administration in the USA to have a minimal clinically significant difference as a measure in serial testing within a trial setting to establish the efficacy of a particular intervention in Alzheimer's disease. The delineation of this metric in the context of HAND clinical trials is yet to be established. A corollary of this is the functional impact of impairment which is typically more rigorously determined during a neuropsychological assessment [25]. Investigators in other fields such as Alzheimer's disease have used a combination of cognitive and functional scales such as the CDR sum of boxes and the ADAS-COG to assess efficacy of an intervention. In fact, the CDR sum of boxes is most often the primary outcome in Alzheimer's disease trials. Here again, work is needed in HAND to determine what outcomes should be chosen.

FUTURE DIRECTIONS: ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT AND MILD COGNITIVE IMPAIRMENT

The biological basis for ANI still requires understanding and so it should be included as a research category but not for clinical use [26]. In some, it was underpinned by HIV encephalitis [10] and others by neuroimaging changes [24]. Currently, its identification is best suited to formal neuropsychological testing in the context of research noting that it will have a false positive rate of approximately 16% [1] similar to MCI. Indeed, Taylor and Heaton [25] found that a neuropsychological test score of one standard deviation below the mean represented the best cut-off

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value for distinguishing between neurologically healthy and neurologically ill people, recognising the issue of false positivity [26]. Two test scores in the same cognitive domain below one standard deviation may lessen the false positive rate to approximately 5% [27] Nonetheless, there is not an agreed precise definition of MCI beyond the broad NIA-AA criteria [28] where there must be impairment in at least one of the cognitive domains of attention, memory, language, visuospatial skills, and executive function. Noteworthy is that no particular tests are specified and impairment can be one or one and a half standard deviations below the demographically corrected norm. The DSM-5 has social cognition as an additional domain and the ICD-11 criteria are essentially those of DSM-5. Salari *et al.*[29] found the global prevalence of MCI in the geriatric population (above 65 years) to be 23.7%, while a Norwegian study observed that MCI in people over 70 years of age was 35.6% [30]. Thus, even the well accepted construct of MCI does not have strict definitional criteria and has relatively high rates of impairment, some of which may well be false positives. Interestingly, rates of 25–35% of HAND in the virally suppressed have been found in studies using standard neuropsychological tests and appropriate normative data [11].

There is further more recent evidence for the importance of ANI as a likely subclinical stage, but this still remains at a research level. Restricted focal brain atrophy has been shown in PWH with ANI who were virally suppressed [31], and other neuroimaging abnormalities [32], with functional changes preceding structural changes [33]. More generally, other studies have shown persistent cell-associated DNA and RNA [34,35], low-level replication of HIV despite viral suppression producing whole virus [36] or viral components [37], including gp120 [38▪▪], or tat [39▪▪]. The latter has been shown to correlate with NCI (manuscript under review).

A NEW MODEL OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

Given that HAND in the context of viral suppression still occurs even with appropriate norms and without potential confounding or compounding factors, and that there is ongoing low level HIV transcription with products that are proinflammatory and neurotoxic [37,38▪▪,39▪▪,40,41▪▪,42,43], it is proposed that HAND is a continuously dynamic process with slowly accumulating damage over prolonged periods. Further, at any one time point, there will be variably active disease superimposed upon accumulating irreversible damage (see Fig. 1). At present, there is no method by which to identify and quantify such irreversible damage. This has significant implications for biomarkers, clinical trials, and individual patient management: as per the figure, early systemic HIV disease is likely to have a lower amount of irreversible damage and a sizeable active component of potentially reversible damage while later in HIV disease the reverse will be true. Consequently, clinical trials and biomarkers targeting active disease will struggle to have a "positive" result if there is a significant irreversible cognitive deficit and the trial arms are not balanced for such a deficit. Furthermore, clinical trial and indeed biomarker results at one time will not be the same at later time points, when there is a sizeable irreversible deficit. This problem can

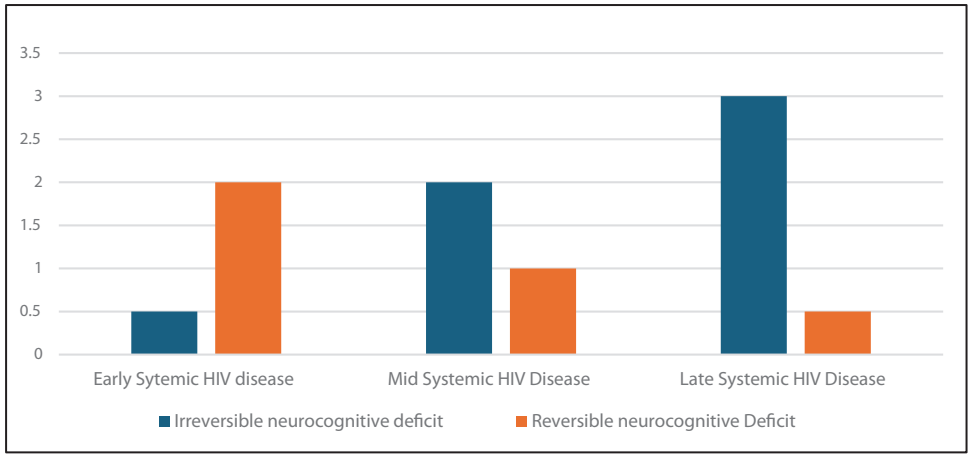

FIGURE 1. Simplified model of HAND and reversible deficit (active disease). The y-axis represents odds of contributing irreversible and reversible neurocognitive deficits to HAND and the x-axis represents the time course of systemic HIV disease. This can be influenced by HIV factors such as duration of viral suppression, CD4+ cell count nadir, and so on as well as host factors related to resilience.

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only be addressed by quantification of the irreversible deficit.

CONCLUSION

For both pathogenesis studies and clinical management, it is important to appreciate that HAND (like any other neurological condition) will be associated with false positives and will often have a mix of potential causes. The proposed tiered-clinical review should significantly minimise false positives. At this stage, ANI should not be diagnosed at a clinical level but rather at a research level, as there is good evolving evidence that some have active brain injury. The more accurately potential contributors of neurocognitive and functional impairments are detailed along with HIV and resilience factors the better the understanding of potential pathogenetic pathways and the better focused clinical management will be.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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