Cognitive screening considerations for psychosocial clinical trials on HIV, aging, and cognition

Abstract

Cognitive impairment is a common comorbidity among individuals aging with HIV, which can be an extreme source of stress and anxiety for many. Psychosocial interventions have the potential to alleviate symptoms associated with cognitive impairment and help improve the quality of life of people with HIV as the continue to age; these interventions are in the infancy of development and require further testing via clinical trials. The slow development of interventions may be partially attributed to a common trend of requiring a formal HIV-Associated Neurocognitive Disorder (HAND) diagnosis to qualify for psychosocial clinical trials. HAND is diagnosed through intensive, time-consuming tests, and still many cases of HAND remain undiagnosed, misdiagnosed, or misclassified due the limitations of the assessment process. This commentary suggests an alternate method of screening for cognitive impairments through the use of a brief, low-barrier assessment, alongside validity considerations. Such alternate screening may improve enrollment and completion rates in psychosocial clinical trials for people aging with HIV and cognitive impairment, by removing the burden of extensive testing that is commonly associated with a HAND diagnosis from clinical trial eligibility, while still providing valuable insight into individuals' cognitive functioning.

Keywords

Aging; Cognitive Screening; HIV-Associated Neurocognitive Disorder; Psychosocial Trials

Cognitive Impairment and Aging with HIV

Cognitive impairment is a significant comorbidity for people aging with HIV. Although commonly ascribed to HIV-Associated Neurocognitive Disorder (HAND), other potential causes include Alzheimer's and other dementias, depression, substance use, polypharmacy, and ischemic brain injury for which minimal effective biomedical treatments exist.[1] Changes in cognition—such as memory loss and decreased speed-of-processing—can result in increased stress and anxiety and decreased ability to cope and manage daily activities.[2] The associated stress and anxiety could be ameliorated by psychosocial (e.g., mindfulness, cognitive training) and compensatory (e.g., note-taking, reminder systems) strategies.[3] Yet, there have been few psychosocial intervention trials to address HIV, aging, and cognition.[3] Psychosocial interventions refer to facilitated therapies such as mutual aid, mindfulness, and brain training activities.[4] The lack of studies in this area may partly be due to an overdependence on a diagnosis of HAND as an entry criterion.[3] Both HAND's definition and its intensive, time-consuming screening are controversial[5], thereby limiting study feasibility. Distinguishing HAND from other causes of cognitive dysfunction is not always possible.

Regardless of the underlying diagnosis, psychosocial interventions may provide symptomatic relief. Employing a brief neurocognitive assessment as entry criteria for psychosocial clinical trials for HIV and cognition—instead of HAND screening and similar to brief neurocognitive screens as clinical trial entry criteria applied in the general population[6]—could mitigate potential difficulties of enrolling people aging with HIV into clinical trials for psychosocial interventions, and potentially allow for enrollment of more people aging with HIV who have cognitive impairment.

Receiving a HAND Diagnosis

Dementia directly related to HIV replication in the brain is most commonly diagnosed as HIV-Associated Neurocognitive Disorder. Cognitive impairment is thought to result from HIV penetrating the blood-brain barrier and causing structural damage to fronto-striatial-thalamatory circuits in the brain. Early in the epidemic, an estimated ~30-50% of the HIV-positive population were affected to some degree by HAND during their lifetime.[1] HAND's incidence is decreased with the earlier initiation of antiretroviral therapy.[7,8] One characteristic distinguishing HAND from most other cognitive impairments is that people living with HIV may experience mild-to-moderate impairment in their 40s and 50s in contrast to the general population typically at similar risk in their 60s and beyond.[9,10] Aside from this notable difference, HAND may present similarly to other cognitive impairments, impairing domains of functioning, such as speed-of-processing, memory, and executive functioning.[1,10] From the perspective of people aging with HIV, impairments in these domains—including difficulty adhering to medication, maintaining employment, keeping medical and other appointments, and remaining socially active—make daily life more difficult.[11] People aging with HIV and affected by HAND can experience fear and worry about being perceived as 'losing their mind', loss of autonomy and reliance on supportive services to continue living in the community, and/or the risk, and associated impact, of further impairment on their lives.[11]

Limitations of HIV-Associated Neurocognitive Disorder (HAND) Assessments

There is no gold standard for diagnosing HAND.[7] HAND being a diagnosis of exclusion adds to the complexity of the assessment[1,8]. HAND is most commonly diagnosed via a consensus regimen termed Frascati criteria as either asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia, defined below, through a subjective

weighing of evidence from a neuropsychological battery of tests and a review of medical history and potential confounders.[7,8] Frascati criteria for diagnosing HAND includes outcomes of twelve neuropsychological tests (e.g., grooved pegboard test for motor speed, digit span test for attention and working memory) that often take a half day to administer, followed by analysis and a follow-up appointment for results and feedback.[8,12] Further, HAND is only concluded if the criteria for dementia or delirium is not met and if comorbid conditions (i.e., depression, traumatic brain injury) are contributing rather than confounding–often clinician-determined–conditions to the impairment.[7,8]

Neuropsychologists and physicians screen for performance in cognitive domains using tests administered digitally or on paper, with scores compared against normative means from the general population, adjusted for demographic characteristics (e.g., age, education level).[1,7,8,12] Asymptomatic neurocognitive impairment is defined as abnormality (≥ 1 standard deviation below the mean) in two or more cognitive domains, with no self-reported impairment in activities of daily living. Mild neurocognitive disorder is also comprised of abnormality in ≥ 2 cognitive domains, with the addition of mild disruption to daily functioning. HIV-associated dementia is diagnosed when two or more cognitive domains are severely abnormal (≥ 2 standard deviations below the mean) and there is moderate impairment to daily living activities.[7,8] Due to the tests' time-consuming nature, limited access to testing, lack of gold standard guidelines, subjective determination of causation, and subjective assessment of the impact of cognitive impairment on a person's ability to function in daily life, many cases of HAND may be either undiagnosed, misdiagnosed, or misclassified.[13,14]

HAND screening has been well-recognized as a burden by people aging with HIV[11,12] and has poor test-retest reliability.[15] Researchers have investigated briefer and more reliable

HAND screening tests but so far, none have adequately substituted for Frascati criteria.[15] While investigation into improved HAND screening tools is worthwhile, people aging with HIV are in urgent need of psychosocial support for their cognitive health immediately[11,16] and a single study cannot feasibly test diagnostics while simultaneously testing efficacy of an intervention. Further, people aging with HIV face detrimental effects from cognitive concerns and have no specific treatment—biomedical or psychosocial—to alleviate the burden.[3] Further, with the evolution and earlier initiation of antiretroviral therapy, HAND is a less common diagnosis, although cognitive dysfunction remains a significant concern for the aging HIV population.[11,13,14] A brief screen of cognition for entry into a psychosocial trial—with HAND screening as a referral option—may permit clinical trial enrollment for people aging with HIV and cognitive impairment, regardless if they meet the threshold for a HAND diagnosis.

Implications for Clinical Trials

Psychosocial trials for dementia in the general population frequently employ a low-barrier entry condition for cognitive impairment, such as the Mini Mental State Examination or the Montreal Cognitive Assessment.[6] For people aging with HIV, a similarly brief cognitive assessment could partly determine participants' cognitive strengths and deficits. From our perspective as people aging with HIV, clinicians, and researchers who have led exploratory and interventional research for people with HAND[4,16,17]—we propose piloting a thirty-minute neurocognitive assessment that will evaluate learning/memory (Hopkins Verbal Learning Test–Revised [HVLT-R]), psychomotor efficiency (Trail Making Test A [TMT-A] and Wechsler Adult Intelligence Scale III [WAIS-III]—digit symbol), executive functioning/working memory (Trail-Making Test B [TMT-B], Wechsler Memory Scale III [WMS-III]—spatial span and F-A-S test), letter number sequencing, grooved pegboard, and reported difficulties with activities of

daily living.[8,12,18] The HVLT-R possesses excellent construct and content validity for neurocognitive assessments with older adults,[19] and—along with the WAIS-III (digit symbol) and grooved pegboard assessment—serves as valid screening tools for individuals with HIV-related cognitive impairment.[20] The TMT-A and TMT-B are widely used in neurocognitive assessments to gauge cognitive processing and executive functioning, with strong construct validity.[21] Moreover, previous studies[20,22,23] have employed a similar battery of tests to assess cognitive domains commonly affected by HIV (e.g., TMT-A and WAIS-III to evaluate psychomotor processing; TMT-B to evaluate executive functioning; and WMS-III/digit span and WAIS-III/letter-number sequencing to evaluate working memory).

There is a need to determine validity of this briefer screen. We propose validating the brief screen by establishing *known-groups validity*—a form of construct validity, in which the instrument is shown to discriminate between two groups known to vary on the variable(s) of interest.[24] Between-subjects statistical analyses (e.g., independent samples t-test; ANOVA) may be used to provide evidence of known-groups validity. In this context, the brief screen may be administered to individuals who have received a diagnosis of HAND, as well as a control group of individuals randomly selected and matched for key demographic variables, who have previously undergone neurocognitive screening but who were not diagnosed with HAND or another neurocognitive disorder. If analyses reveal statistically significant differences between the two groups' responses, this would support the known-groups validity of the brief screen. Practically, validation of this screening tool would be most feasible and appropriate within a current HAND clinical trial. Previous studies have utilized a similar method to validate different brief neurocognitive assessments in the general population, and this validation study would mirror acceptable estimates of sensitivity as 0.85 and specificity as 0.80.[25-27]

The primary limitation of a brief screen is that it cannot provide a conclusive diagnosis of any cognitive impairment among participants. The brief screen serves a descriptive rather than diagnostic purpose, seeking to provide sufficient information about a person's cognitive concerns in order for the individual to enter a clinical trial for psychosocial intervention. To mitigate this limitation, we propose that participants be offered a referral to HAND screening upon conclusion of the psychosocial clinical trial. As an additional limitation, the brief screen does not contain all components of HAND screening, instead offering an abbreviated battery of tests; compared to the more extensive Frascati criteria, the brief screen does not provide the same wealth or depth of information about participants' cognitive impairment. Furthermore, the brief screen does not consider the etiologies of HAND and other neurocognitive disorders, and thus does not provide data about pathophysiology to inform targeted therapeutic interventions. A further limitation to broadening clinical trial eligibility in this manner could be variable efficacy based on cognitive impairment etiology. However, psychosocial clinical trials for cognitive impairment in the general population have not reported this problem with briefer screens; this could be due to the nature of psychosocial trials for cognitive impairment being that the intervention's primary focus is not on cognition but rather on the associated stress, anxiety, and quality of life, whereby the discrete diagnosis may not be a significant limitation.[28-30] The brief screen also does not provide specific information about participants' clinical improvements in cognition, which are unlikely to change in a psychosocial clinical trial. Likelier change outcomes from psychosocial clinical trials of HIV and cognitive impairment are stress, anxiety, and depression.

Despite these limitations, we believe that the brief screen has implications for facilitating participant enrolment—and lessening pre-intervention attrition—in psychosocial clinical trials for people aging with HIV and cognitive impairment, therefore increasing clinical trial access for

this population. In the literature, we noted that several clinical trials focused on HAND reported significant rates of pre-intervention attrition.[31-36] One clinical trial testing cognitive rehabilitation therapy in people living with HIV found that 49.6% (59/119) who met the criteria for HAND then declined to be randomized into the trial.[31] Another computer-delivered cognitive training RCT found 25.4% (14/55) of participants receiving a Mild Neurocognitive Disorder HAND diagnosis chose not to continue with randomization.[36] While these studies do not report reasons for post-screening, pre-randomization attrition beyond participants choosing not to participate, these dropoff rates are higher than the 5-10% post-screening, pre-randomization attrition rate frequently reported in psychosocial clinical trials that employ a brief screen for cognitive impairment in the general population.[37] We contend that the brief screen has strong potential to facilitate participant recruitment, enrolment, and randomization (and ameliorate attrition rates) for clinical trials focused on psychosocially remediating cognitive impairment among people living with HIV, as the brief screen can mitigate the barrier of intensive testing for individuals who may not have the motivation or capacity to undergo complex testing.

The purpose of this briefer screen would not be diagnostic – such an aim would require a discrete study – rather, testing the feasibility and acceptability of this approach could result in a briefer cognitive screen that would still provide sufficient insight into the person's cognitive concerns to determine eligibility and categorize a study sample for clinical trials of psychosocial interventions.

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