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COMMENTARY

More Than Two HANDs to Tango

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Abstract Developing a validated tool for the rapid and efficient assessment of cognitive functioning in HIV-infected patients in a typical outpatient clinical setting has been an unmet goal of HIV research since the recognition of the syndrome of HIV-associated dementia (HAD) nearly 20 years ago. In this issue of JNIP Cross et al. report the application of the International HIV Dementia Scale (IHDS) in a U.S.-based urban outpatient clinic to evaluate its utility as a substitute for the more time- and effort-demanding formalized testing criteria known as the Frascati criteria that was developed in 2007 to define the syndrome of HIV-associated neurocognitive disorders (HAND). In this study an unselected cohort of 507 individuals (68 % African American) that were assessed using the IHDS in a cross-sectional study revealed a 41 % prevalence of cognitive impairment (labeled 'symptomatic HAND') that was associated with African American race, older age, unemployment, education level, and depression. While the associations between cognitive impairment and older age, education, unemployment status and depression in HIV-infected patients are not surprising, the association with African American ancestry and cognitive impairment in the setting of HIV infection is a novel finding of this study. This commentary discusses several important issues raised by the study, including the pitfalls of assessing cognitive functioning with rapid screening tools, cognitive testing criteria, normative testing control groups, accounting for HAND co-morbidity factors, considerations for clinical trials assessing HAND, and selective population vulnerability to HAND.

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This study (Cross et al. 2013) clearly addresses several extremely important issues and raises important questions: how can health-care professionals efficiently determine a patient's cognitive status during a routine clinical office visit to ultimately formulate appropriate treatment plans? And, are African Americans at a higher risk for cognitive impairment associated with HIV infection? This begs an earnest discussion in the field that should now follow. The points for discussion are not that the IHDS and the HAND diagnostic criteria can be cross-validated, but whether the IHDS, or some variant thereof, can adequately substitute for HAND diagnostic criteria in a routine clinical practice, and particularly in African American populations. How does one effectively evaluate HV-infected patients with co-morbidity conditions for cognitive testing in such a setting? How does one invoke HIV as a causative agent in mediating cognitive impairment in such individuals? Can the IHDS be used as a screening (not diagnostic) tool for cognitive impairment in a resource-limiting setting where neuropsychological testing is not routinely available?

To fully evaluate and appreciate the implication of this study the clarity of the metrics for assigning cognitive dysfunction must be appreciated. The application of the term 'HAND' should conform to the Frascati diagnostic criteria of Antinori et al. (2007). The need to assess the prevalence of HAND in this population was a short fall of the study. Indeed, cognitive dysfunction was determined using the specific criteria of the IHDS, which are distinct from the Frascati criteria. Among the 41 % of individuals found to be impaired by IHDS criteria (labeled 'symptomatic HAND') in the current study, the true prevalence of HAND sub-groups in this cohort, and whether these cohorts necessarily define the syndrome of HAND was unclear. For validation of the IHDS as a surrogate for the group of diagnostic criteria for HAND, the

diagnosis of HAND must first be confirmed, including sub-group analysis, to determine the functional relevance of the IHDS assessment. To their credit, the authors clearly recognize this limitation in their study. Furthermore, it is not clear what percentage of the 41 % had functional impairment in their activities of daily living (ADLs) that define the HAND sub-group with functional impairment (Woods et al. 2009) The article could appropriately be entitled *'Identifying risk factors for cognitive impairment in HIV-infected individuals using the International HIV Dementia Scale'*.

Another point to consider is that this study was designed to address cognitive assessments in a routine clinical setting, few patient exclusion criteria were applied, which further distinguishes this study from others. Thus, while the study truly complements other studies, it does not substitute for more rigidly-controlled neuroAIDS treatment outcome studies, such as those developed through the AIDS Clinical Trials Group consortium for testing candidate neuroprotective drug therapies (Sacktor et al. 2011; Schifitto et al. 2007a, b; Marra et al. 2009; Schifitto et al. 2009). Although this complicates the interpretation and data analysis, this study nonetheless ascertains data that likely have intrinsic value for determining the at-large problem that practicing clinicians face daily. Certainly, scientific rigor must be applied to determine the significance of the findings. Among the critical questions to ask are what is the control group against which demographically-defined test groups are measured? First, if African-American ancestry is presented as a risk factor for HIV-associated cognitive dysfunction, can one confirm that HIV infection presents a higher risk for cognitive dysfunction in African-Americans evaluated in this clinical setting than in the white/Caucasian group similarly evaluated? Are African-Americans more vulnerable to damaging effects of CNS HIV infection? Does the IHDS have demographically-adjusted normative scoring for African-Americans to determine this?

Second, another obvious question is how these results compare with previous studies of risk factors for HIV cognitive impairment. The most generally accepted biomarker for increased risk for developing cognitive impairment in HIV infected individuals is the historical CD4 T lymphocyte nadir (Heaton et al. 2011; Ellis et al. 2011), which approached but did not reach statistical significance in this study. Nonetheless, the comparison in this study is probably informative, when one considers that a largely unselected patient population was studied. The authors mention other 'traditional' risk factors for cognitive impairment, including age, race, education, depression, and income level. Each of these has been suggested as a risk factor for HAND in previously published studies, which also suggests that this study indeed reflects several validated associations, even though the correlation with CD4 nadir was not significant.

Of course, the conclusion that African-American ancestry is a significant risk factor for HAND will surely and appropriately prompt robust discussions. The authors cite other published studies that suggest that co-morbidities within the African-American population, such as a metabolic syndrome of cardiovascular disease and diabetes, might account for increased risk for cognitive impairment independent of HIV infection. Whether the putative independent risk of HIV infection for cognitive impairment in African Americans suggested in this study reflects the high risk of metabolic syndrome in HIV-infected African Americans is presented as a possibility. Both cardiovascular disease and diabetes are more prevalent in HIV-infected individuals (Samaras 2012; Boccara and Cohen 2003), but whether HIV infection alone is a particularly stronger risk factor for cognitive impairment in African-Americans will clearly require further detailed study.

The problem of validating a rapid and simple diagnostic approach for identifying HIV-infected individuals at risk for HAND in 2013 directly depends on the features of cognitive impairment in the setting of anti-retroviral therapy (ART), and at least indirectly on the pathological substrate of brain damage in such individuals. HIV encephalitis is now distinctly uncommon, in contrast to the pre-ART era, and HIV-associated brain injury likely develops more chronically in a setting of smoldering low-level activation and inflammation (Gelman et al. 2013; Everall et al. 2009). A major gap in our understanding of HAND (as strictly defined by Frascati criteria) and its risk factors in the era of ART is the relative contribution of virus replication in the brain. Many patients receiving cART and having the diagnosis of HAND have sustained suppression of peripheral viral load, which raises the question as to how much the virus is now contributing to HAND in such patients (Heaton et al. 2011. It is therefore getting increasingly difficult to confirm progressive cognitive impairment due to HIV infection per se and thus identify patients for whom neuroprotective therapies in addition to ART might be helpful. It must be noted that the benefit of prolonged lifespan due to ART also increases risk for age-associated neurodegeneration risk factors. Paradoxically despite sustained suppression of virus replication, chronic immune activation in the CNS and systemic compartments persist and is linked to chronic disease progression (Burdo et al. 2013; Deeks 2011; Pulliam et al. 1997; Ancuta et al. 2008; Kraft-Terry et al. 2009). Furthermore, sustained ART treatment is often associated with 'blips' of virus replication and probably fluctuating levels of tissue inflammation, which in turn, may have cumulative damaging effects on the host (Havlir et al. 2001).

Adding further complexity is the fact that HAND is often accompanied by many co-morbidity factors such as Hepatitis C infection, substance abuse, and medical conditions associated with ART usage including hyperlipidemia, beta amyloid deposition, medications used for controlling depression and anxiety, all of which individually or in co-operation contribute to the development and progression of HAND, which is emerging as a multifactorial

syndrome. In an immunocompetent host receiving ART virus replication probably plays but a small contributing role in this disorder. Additional additive factors such as types of ART regimens, immunological, genetic and psychosocial entities as well as brain injury prior to ART could also contribute to the severity of cognitive dysfunction, thereby making it difficult to dissociate the effects of HIV from other factors. A subset of patients receiving cART also go on to develop a fulminant immune reconstitution syndrome, which can contribute further to brain injury. A recent review by Alfahad & Nath (2013) is an elegant update on the current thoughts on HAND.

An urgent need therefore exists in the field to develop a universally agreed-upon clinical testing of day-to-day functioning of patients for use in the clinics (Blackstone et al. 2012a). The existing tests that are available are based upon self-reporting and can be confounded in the context of psychiatric or socioeconomic factors (Blackstone et al. 2012b). More recently there has been a report on Computer Assessment of Mild Cognitive Impairment (CAMCI), a computer-based screening tool that includes performance-based measures of functional impairment (Rosenthal et al. 2013). While the advantages of neurosychological battery as the gold standard for diagnosis of HAND cannot be disputed, its lack of availability in resource-limiting settings where the burgeoning burden of HIV infection prevails remains a serious concern. Moreover, the exclusion criteria followed during this testing makes it difficult to assess the effects of depression and pre-existing cognitive impairment as modulators of the disease. Having said that, in the absence of any other universal HAND testing, neurospyschological testing does remain the gold standard for the diagnosis of HAND. Nonetheless, obtaining normative neurospsychological test data for multifactorial disease such as HAND with its comorbid confounds also continues to be a challenge. Along with this, there is a critical need for identifying risk factors that might predominate in particular subpopulations at risk for HAND, such as African-Americans, as suggested by this current study. Understanding the true prevalence of HAND and associated risk factors in patient subpopulations can guide development of more effective neuroprotective therapies in such populations. A recent review by Kamminga et al. (2013) addresses the various strengths and weaknesses of the existing tests for detection of HAND. Taken together, the dilemma exists of the availability of comprehensive neuropsychological testing available to the elite few versus the use of IHDS and other such tests for rapid screening of cognitive dysfunction targeted to a larger population in the clinics. Such rapid tests could be a means to identify symptomatic impairment and its progression longitudinally in patients.

In summary, it must be emphasized that HAND is evolving as a more complex entity and this therefore warrants urgent investigations in the field aimed at development of sophisticated diagnostic tools coupled with neuroimaging studies that are appropriate for vulnerable patient populations in order to define the natural history and test neuroprotective therapies. Additionally, the diffuse nature of the disease that is known to target various regions of the brain makes it a problem for developing animal models to study the disease pathophysiology and to develop effective neuroprotective therapies. However, developing and validating novel rodent and non-human primate models of HAND is still critical for understanding the disease pathogenesis and testing potential therapeutics (Fox and Gendelman 2012). Furthermore, testing neuroprotective drug efficacy against HAND also requires the study of non-HIV-infected, at-risk human control groups sharing co-morbidity factors with HIV-infected subjects to properly determine the relative contribution of HIV and other factors to the genesis of HAND and the response to drugs. Because patients with HAND continue to live long on cART, diseases of the aging are now more common in individuals with HAND it is imperative that such factors are also accounted for in clinical studies. Because HAND presents a major burden to many individuals living with HIV, efforts aimed at both diagnosing and preventing HAND to improve the quality of life of such individuals should be a healthcare priority.

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Conflict of interest The authors declare that they have no conflict of interest.

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