COMMENTARY

Need to Revise Frascati Criteria for HIV-Associated Neurocognitive Disorders to Improve Relevance for Diverse Global Populations

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Abstract

Worldwide, cognitive impairment is a frequent complication of HIV, and few treatments are available. Existing diagnostic criteria for cognitive disorders associated with HIV have limited diagnostic accuracy, hampering biomarker and therapeutic development. Furthermore, these criteria are not linked to clinically meaningful outcomes, limiting utility in clinical settings. Limitations in diagnostic accuracy are most pronounced in resource-limited settings where the burden of HIV is greatest, largely because of heavy reliance on neuropsychological testing with limited cross-cultural validity. Accurate and clinically meaningful diagnostic criteria validated in diverse populations will improve research and clinical care for cognitively impaired people living with HIV globally.

HIV: History and Current Burden

The first case definitions for AIDS were developed in 1982.[1] Only 5 years later, in 1987, the first antiretroviral drug, zidovudine, was approved by the U.S. Food and Drug Administration after a trial lasting approximately 19 weeks and antiretroviral therapy (ART) rapidly became available in resource rich settings. However, it took another decade of grass-roots political advocacy before ART first became available in Africa when the United Nations endorsed the 2001 Declaration of Commitment on HIV/AIDS.[1,2] By 2001, there were 40 million people living with HIV (PWH)/AIDS, of whom 28.5 million (71%) were living in sub-Saharan Africa without access to ART.[3] Over the subsequent 2 decades, there was tremendous progress in scaling up HIV care and treatment in resource limited settings. In 2020, of 37.7 million PWH worldwide, 27.5 million were taking ART; gaps were greater among the 1.7 million children living with HIV of whom less than half were taking ART.[4]

Globally, mild cognitive impairment associated with HIV may affect around 50% of PWH, and moderate to severe impairment may affect between 2% and 25%.[5-10] Importantly, cognitive development is also affected in pediatric HIV, where infants and young children with HIV do not perform, as well as their HIV-exposed or HIV uninfected peers.[11-14] ART remains the mainstay of treatment for HIV-associated cognitive disorders in both adults and children.[15] As ART has become more widely available, the prevalence of HIV-associated cognitive impairment has generally decreased,[16-18] yet at an individual level, it remains an important source of morbidity for PWH.

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Brief History of Diagnostic Criteria for Cognitive Disorders in HIV

In 1986, shortly after the first U.S. cases of what now is known to be HIV/AIDS were described, Dr. Richard Price and colleagues at Memorial Sloan Kettering first defined and described the AIDS Dementia Complex (ADC), a progressive dementia with associated motor and other neurologic findings.[19] This led to the development of the Memorial Sloan Kettering ADC scale which was largely used to describe the clinical stages of the disease. Some years later, in 1991, a working group of the American Academy of Neurology came together to begin to categorize the vast array of clinical manifestations of HIV in the nervous system and which first began to define milder manifestations of HIV in the nervous system. These were later codified in the Frascati criteria for HIV-associated neurocognitive disorders (HAND) in 2007.[20]

Discussion

Strengths and Weaknesses of the Frascati Criteria

Over the past decade, the Frascati criteria have been incredibly useful to define the epidemiology and trajectories of HAND in a standard fashion across observational and clinical trial cohorts and document the changes observed as we entered the HAART era. However, the Frascati criteria have also been criticized. Frascati criteria threshold scores for mild impairment may result in "false positive" diagnoses and bias to the null in studies of association, hampering efforts to validate biomarkers and develop therapeutics.[21,22] Furthermore, reliance on neuropsychological tests developed for U.S. and European populations may introduce bias in assessments of diverse global populations.[23] Importantly, issues with bias in neuropsychological tests have been described for the assessment of other dementias globally.[24]

Although cognitive complaints are frequent among PWH, mild forms of HAND as defined by the Frascati criteria have had limited impact on patient-centered clinical and functional outcomes.[25] Providers, particularly in resource-limited settings, highlight concerns about increasing stigma and psychological distress among PWH by receiving diagnoses of mild impairment without a clear understanding of the prognosis. Thus, despite patient need, assessment of cognitive complaints has not been widely implemented in clinical settings, especially in resource-limited settings where the burden of HIV is greatest.

Practical Implications

Clinically relevant and accurate diagnostic criteria for cognitive disorders in HIV are critical to advance research and improve clinical care for PWH. Although the field has identified promising biomarkers, therapies, and interventions, limited diagnostic accuracy in cognitive outcome measures impedes further development. Linking diagnostic criteria to clinically meaningful and patient-centered outcomes will enable early identification and intervention for PWH with cognitive disorders in clinical settings.

Unanswered Questions

Because performance on neuropsychological tests varies regarding education, literacy, cultural context, and comfort with technology and the testing process itself, a key research priority for the field is the development of culturally appropriate assessment methods validated in diverse global populations, particularly in resource-limited settings with high HIV burden. Furthermore, neuropsychological tests alone cannot discriminate between HIV-associated pathology and other comorbid brain injuries common among PWH such as traumatic brain injury, brain infections, stroke, and mental health and psychiatric disorders. Thus, development of biomarkers reflective of HIV-related pathophysiology remains an urgent need. Finally, new treatments specific to the effects of HIV on the nervous system are critical to improve outcomes for PWH.

Next Steps for the Field

New diagnostic criteria for HAND should be clinically relevant, valid among diverse populations, and, when appropriate and feasible, incorporate imaging and emerging biomarkers that identify HIV-specific pathology, such as active viral replication in the CNS. Finally, prospective validation to ensure diagnostic criteria aligns with clinically meaningful and patient-centered outcomes is essential to ensure that novel therapies or interventions positively affect the lives of PWH, especially those living in resource-limited settings.

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