# Working HAND in HAND: Central nervous system complications in people with HIV

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Dear Editor:

In looking back, in 2005 leading investigators met in Frascati, Italy to help devise new research criteria for defining HIV associated neurocognitive disorders (HAND). These criteria were not published until 2007 [1]. Revised nomenclature were established to define milder impairment: asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND). Both were defined by impaired performance on neuropsychological tests compared to demographically-corrected norms (at least 1 standard deviation below mean normative scores in 2 separate domains), with cognitive impairment accompanied by mild interference in daily functioning defined as MND and ANI defined by impairments in cognitive performance without overt interference in activities of daily living.

While cognitive impairment persists despite modern suppressive combination antiretroviral therapy (cART), significant heterogeneity exists in their clinical presentation [2-6]. Two individuals can meet criteria for HAND with different patterns of impairment (e.g., memory and learning, motor and learning, etc). Such heterogeneity introduces a barrier to identifying the underlying neurobiological mechanisms of the clinical presentation as the mechanisms may differ across PWH. In addition, PWH who meet criteria for cognitive impairment often meet criteria for both internalizing (major depressive disorder, anxiety disorders, and post-traumatic stress disorder (PTSD)) and externalizing disorders (substance use disorders-SUD) [7, 8]. These CNS comorbidities bring into question whether we should be focused on the disorders themselves or to focus on identifying common dimensions underlying these comorbidities.

We are at a point where the underlying pathophysiology of these complications remains elusive, often multifactorial, and no effective therapies exist to reverse the cognitive deficits that are still observed despite cART. As a field and as noted by Nightingale et al. [9], we are at an important juncture that requires the community to perform a thorough re-examination of current definitions and approaches (e.g. role for neuropsychological performance testing and various self-report measures); and to strongly consider emerging alternative approaches that also integrate psychiatric complications (e.g., depression, anxiety, PTSD, apathy), neurobiological features (e.g., neuroimaging measures of brain structure and function) and cerebrospinal fluid (CSF)/plasma biomarkers (e.g., neuroinflammatory and neurodegenerative markers) to identify Biotypes in persons with HIV (PWH). When evaluating if a PWH for cognitive impairment multiple domains (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care) need to be evaluated within a patient but, when possible, also reliably verified by an informant in order to elicit meaningful change from prior levels of functioning. In addition, multiple comorbidities (e.g., substance use disorders, cardiovascular disease) as well as social and structural determinants of health (e.g., environmental factors, stigma, trauma) can also affect CNS outcomes. It is important to identify and cluster the heterogeneity of cognitive impairment and other psychiatric conditions seen in PWH in order to develop more personalized therapies. Novel approaches that integrate multi-dimensional data and tools such as artificial intelligence-based learning algorithms that incorporate multiple biomarkers will be needed.

We can learn from the paths that have been taken for other neurodegenerative (including Alzheimer's disease and vascular cognitive impairment) and neuro-inflammatory (e.g. multiple sclerosis) diseases as well as the field of psychiatry that has transitioned over the past decade to conceptualizing mental health disorders transdiagnostically. The successful

integration of multiple modalities to stage an individual will allow us to understand the neurobiology of the disease and will directly influence future therapies.

Just as our thought leaders in the field have met in the past to devise an updated approach, we need to work as a community to determine the best current approach to move forward as a field in order to better help PWH and their families both in the United States and internationally. A series of meetings will be conducted starting in the Fall of 2021 in collaboration with the National Institute of Mental Health (NIMH), Division of AIDS Research (DAR) to understand etiology-based heterogeneity and identify biotypes in PWH. We think this will be a great forum to bring the community together, constructively revise the current criteria, and build consensus to continue to provide the best care that will continue to improve the lives of PWH.

Potential Conflicts of Interest:

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