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The Evolution of Assessing Central Nervous System Complications in Human Immunodeficiency Virus: Where Do We Go From Here?

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In this fifth decade of the human immunodeficiency virus (HIV) epidemic, central nervous system (CNS) complications including cognitive impairment and mental health remain a burden for people with HIV (PWH) on antiretroviral therapy. Despite the persistence of these complications, which often co-occur, the underlying pathophysiology remains elusive and consequently treatments remain limited. To continue to grow our understanding of the underlying mechanisms of CNS complications among PWH, there is a need to reexamine our current approaches, which are now more than 2 decades old. At the 2021 National Institutes of Health–sponsored meeting on Biotypes of CNS Complications in PWH, the Neurobehavioral Working Group addressed the following: (1) challenges inherent to determining CNS complications; (2) heterogeneity in CNS complications; and (3) problems and solutions for examining integrated biotypes. The review below provides a summary of the main points presented and discussed by the Neurobehavioral Working Group at the meeting.

Keywords. cognitive dysfunction; comorbidity; human immunodeficiency virus; neuropsychological testing; psychosocial factors.

Evolution of the Assessment of CNS Complications in HIV

Historically, the field of neuroHIV (human immunodeficiency virus [HIV] neurology) has focused primarily on one particular CNS complication, cognitive impairment, as there was strong evidence that objective cognitive impairment via performance on neuropsychological tests was evident in multiple cognitive domains and was observed across all stages of HIV disease (eg, medically asymptomatic, symptomatic, and AIDS) [1]. The AIDS Task Force of the American Academy of Neurology (AAN) convened initially in 1991 and again in 1996 and outlined guidelines for CNS complications. At this time, the AAN criteria included cognitive impairment, motor dysfunction, and psychiatric or psychosocial functions (motivation, emotional control, social behavior), however no guidance was provided on how to measure and operationalize these constructs. Although the AAN criteria had clinical utility, the criteria for CNS complications were updated in 2007 [2] as the clinical presentation and severity of CNS complications changed due to the advent of effective antiretroviral therapy (ART). Among people with HIV (PWH) who had access to ART, the more severe forms of cognitive impairment were becoming rarer and the presence of milder forms of cognitive impairment increased in PWH. However, these shifts were not universal, as patient populations in underserved nations did not benefit as uniformly. In parallel, in most countries PWH increasingly included a more diverse range of people with greater socioeconomic vulnerabilities as well as complex mental health issues. Then with increased survival on stable ART, a greater prevalence of age-related comorbidities is shown in PWH. In light of the changing epidemiology whereby PWH have multiple CNS complications and numerous medical comorbidities, our group critically reviewed the current approach to diagnose HIV-associated neurocognitive disorder (HAND) (the Frascati criteria [2]) and several ways of measuring cognitive impairment including clinical rating [3], Global Deficit Scores [4], and multivariate normative comparison (MNC). In addition, we discuss the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) framework as an approach for not

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only improving our understanding of CNS complications more broadly (cognitive impairment and mental health issues) but also its clinical utility. This is important as multimorbidity is prevalent in PWH and cognition cannot be assessed and measured in a vacuum.

Frascati Criteria Approach

The 2007 HAND diagnostic criteria, also known as the Frascati criteria [5], outline standards for detecting and staging cognitive impairment among PWH. In brief, using these criteria, HAND is classified as either asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), or HIV-associated dementia (HAD). One benefit of this approach is that cognitive impairment in PWH follows other neurological nomenclatures for mild, moderate, and severe deficits. Additionally, their clinical significance can be classified using a clinical rating approach as in a standard neuropsychological assessment. Thus, this system operationalizes a neuropsychological approach to determining deficits at the earliest possible presentation (ie, ANI), while also specifying mild deficits with interferences in instrumental activities of daily living (IADL) (ie, MND), followed by more severe presentations of cognitive and functional impairment (ie, HAD). The 2007 HAND criteria also provide clear definitions of the level of cognitive impairment required against normative data. These criteria also offered guidelines for considering the effects of confounding psychiatric or medical conditions on cognitive health and classified these as incidental, contributing, or confounding.

Nevertheless, at present, discerning cognitive impairment due to HIV vs comorbidities remains a challenge because comorbidities can preclude attribution to the observed impairment and functional limitations to HIV disease. Several studies have demonstrated large effects of these comorbidities on cognitive function in PWH [6–10]. However, in the absence of a biomarker for HIV-associated neurocognitive impairment in treated people, it is unclear how some of those comorbidities may not be themselves related to the chronic presence of HIV in the body (eg, cardiovascular diseases are more prevalent in PWH even when accounting for traditional risk factors). Such heterogeneity introduces a barrier to understanding the underlying pathology of CNS complications among PWH and may hinder the treatments for addressing CNS complications.

Additional challenges of the Frascati approach include that the diagnostic criteria rely on an optimal characterization of everyday functioning to distinguish between ANI and MND. Unlike the cognitive criteria, the process of operationalizing IADL effects is difficult, especially in clinical settings, a challenge that has plagued other neurologic conditions. Second, for non-neuropsychologists, errors are often made in the application of cutoff scores in determining cognitive impairment, suggesting that improvements may be needed for wider implementation [11]. While there is evidence that the use of standard cutoffs (eg, 1 standard deviation below the mean of demographically corrected scores) within the context of clinical ratings provides good sensitivity and specificity to cognitive impairment vs comorbidities in PWH [12], multivariate cutoffs and global score approaches may better address the issue of intercorrelations among tests and help to avoid type I errors (false positives). An additional consideration, size and type of battery, can affect clinical ratings, yet recommendations for examination allow for a breadth of combinations of assessments for different ability domains [11]. Third, the removal of psychiatric symptoms as a predictor in the HAND 2007 criteria vs its previous versions, the 1991 and 1996 AAN criteria, warrants reconsideration.

Global Deficit Score Approach

The GDS is a scoring method for global impairment and an algorithmic rendition of the clinical rating approach [4]. It is slightly more conservative (ie, less likely to identify a person as impaired) than the clinical approach. One benefit of the GDS is that it is easier to implement in research than clinical ratings, especially for non-neuropsychologists. Additionally, the GDS avoids the issue of multiple comparisons within the test battery, thus increasing protection against type I errors (false positives). Conversely, as is the case with clinical ratings, one of the disadvantages of the GDS is that this approach can produce different results depending on the test battery size. Nevertheless, there is evidence that the GDS can provide robust impairment estimates with at least 6 different neuropsychological tests [11]. Yet, aspects of performance that may have clinical relevance, such as heterogeneity at the individual test level, are lost with this approach. Again, the consideration of other CNS complications as part of the outcome warrants consideration.

Additionally, the GDS avoids the problem of multiple comparisons, and the cutoff can be selected to determine the probability of a "false positive" result. The standard cutoff of 0.50 indicates that the person averaged at least mild impairment on at least half of the tests that were administered. This cutoff was chosen with the understanding that (1) there is overlap between cognitive performance of people with well-documented CNS disorders and those without any known risks of such disorders, and (2) since both false-positive and false-negative errors are undesirable, it is best to seek a balance between false positives and false negatives. Published data indicate that the "standard" GDS cutoff provides and optimal balance between false positives and false negatives, although one could easily amend the cutoff if there were justification for emphasizing specificity over sensitivity [13]. In the case of HIV-associated CNS disorders, the workgroup did not recognize justification for altering the GDS standard cutoff of 0.50 that best balances sensitivity and specificity.

Multivariate Normative Comparison

The MNC is another way of measuring cognitive impairment and is an a priori statistical approach that accounts for high

false discovery rate (FDR) in a comprehensive neuropsychological test battery [14, 15]. Recent analyses suggest that when FDR is set to 5%, the method remains robust against type I error rates (false positives) even in small samples, suggesting that it may be a method of determining cognitive impairment but may result in significantly higher false negatives (ie, missing PWH who have cognitive impairment). However, MNC is not as easily applied as the GDS, although online tools have been developed to facilitate use of the approach [15]. An additional downside is that heterogeneity is lost at the individual test level, as MNC is a global score approach. Like the GDS, the MNC is a measuring tool and there is no evidence that it does better or worse in the context of comorbidities. Moreover, the focus remains on cognitive impairment and excludes other CNS complications.

NIMH Research Domain Criteria Framework

Although Frascati, and its associated clinical rating or the GDS, and MNC are widely used, the current diagnostic procedure and way of measuring cognitive impairment have inherent limitations including poor to moderate reliability with self-report ratings of cognitive symptoms and IADL change [16–19], moderate reliability with clinical ratings methods [3], and in some instances, inflation of false positives [20].

Perhaps, more importantly, as cognitive impairment is not the only CNS complication among PWH, we discussed that an alternative approach for integrating the factors that contribute to CNS complications in PWH more broadly is warranted. Specifically, an alternative approach that can handle both HIV and non-HIV comorbidity and heterogeneity and allow for more nuanced characterization to complement discrete categories (impaired vs unimpaired) may be particularly helpful. The RDoC framework, which is widely used in the field of psychiatry, may also demonstrate utility in neuroHIV given its orientation toward identification of central-peripheral interactions and new targets for neuropathological mechanisms for clinical treatment [21]. The RDoC framework provides an approach to assessing a wide range of psychosocial, demographic, medical, and other factors that may interact with HIV and impact neuropsychological functioning and thus capture the current complex characteristics of PWH. RDoC is a research framework for understanding core constructs (not just cognition) that are designed to align with neurobiological processes, in contrast with disease-specific diagnostic approaches [22]. Adoption of an RDoC framework in assessing CNS complications in PWH has advantages. First, RDoC would encourage the assessment of domains beyond cognition, including those shown to be impaired in PWH, such as social processing [23–26]. Furthermore, the RDoC framework capitalizes on obtaining data from different levels of analysis (eg, behavior, self-report, neuroimaging, molecules)—data that could be examined comprehensively using artificial intelligence methods (eg, machine learning) to generate biotypes that could lead to the development of targeted interventions and treatments to improve CNS complications.

As we look to integrate multidimensional data and more extensive assessments, we must be mindful of the continued need to enhance the clinical relevance of this work (eg, functional impact, treatment), and to best understand the complex interplay between factors. Additionally, participant burden warrants consideration. Novel technologies, including adaptive administration, may help reduce redundancy and participant burden. Combining adaptive assessments with integration of multidimensional data using complex statistical approaches may produce powerful results that match individual neuropathological underpinnings (eg, biotypes). While data-driven approaches have been criticized for allowing interpretation of the data based upon an infinite number of models with several potential solutions that may not be easily replicated, there are continuous improvements for improving the model's robustness (as reviewed in the machine learning workgroup).

HETEROGENEITY IN CNS COMPLICATIONS IN PWH

Heterogeneity is the rule, not the exception, when discussing the clinical presentation and severity of CNS complication in PWH. With respect to cognition, the profile of impairment is variable with deficits in a range of cognitive domains. Studies using statistical clustering techniques demonstrate different patterns of impairment among PWH with some individuals demonstrating global impairment across all domains, whereas other profiles indicate domain-specific impairment commonly in the domains of executive function and episodic memory [27–30]. This heterogeneity is likely exacerbated by the fact that (1) HAND is typically a mild clinical condition in individuals receiving ART, and (2) ongoing HIV pathology [31] is occurring in the context of comorbid medical and psychiatric conditions.

During our meeting, several factors including ART, HIV disease history, medical comorbidities, substance use, psychosocial determinants of health (eg, trauma and stress exposure across the lifespan), and population-specific sociodemographic factors were discussed as likely contributors to cognitive heterogeneity in PWH. With respect to ART, perhaps most germane to cognitive impairment is the legacy effects of ART drugs with poor CNS penetrability and/or potential neurotoxicity. Some commonly prescribed ARTs (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and integrase inhibitors) may have increased neurotoxicity relative to newer-age protease inhibitors (eg, darunavir), and these newer drugs may be more helpful in their ability to prevent opportunistic disease [32]. Access to early ART affects whether PWH develop AIDS, a major risk factor for cognitive impairment as low nadir CD4 is associated with a greater likelihood of current cognitive impairment [12, 33]. Medical comorbidities such as diabetes, hypertension, obesity, and hepatitis C coinfection and the emergent

severe acute respiratory syndrome coronavirus 2 virus are also likely to contribute to different patterns of cognitive impairment. Notable is that the distribution of comorbidities among PWH vary in part with economic status of the region. In high-income nations, cardiovascular disease and diabetes require special attention due to high incidence and prevalence, in part attributable to lifestyle and environmental factors. Psychosocial determinants of health including access to resources and exposure to trauma and other psychosocial stressors across the lifespan, including gender, were also discussed as contributors to cognitive heterogeneity [34–38]. Despite the complex combination of psychosocial factors that may influence cognition, it is important to consider their contributions to cognition given the disproportionate burden of HIV infection among socioeconomically marginalized populations who are often disproportionately exposed to stigma, discrimination, and poor access to resources [33, 39, 40]. A cross-culturally informed approach using local knowledge from various types of researchers can also be used to address the most relevant factors in a specific context. Population-specific sociodemographic factors that impact but do not reflect brain health were also mentioned including exposure and quality of formal education, quality of acquisition of skills/trade, and other socioeconomic factors. Data regarding the effect of socioeconomic status (SES), racial/ethnic/minoritized status, access to resources, and premorbid intelligence/educational quality on cognitive impairment incidence further underscores the notion of heterogeneity being the rule rather than exception in CNS complications in PWH. Furthermore, few studies among PWH examine change in SES status over the lifespan despite evidence that downward mobility is associated with psychiatric and cognitive dysfunction [33]. Demographic variables, such as age, education, and race/ethnicity, do not fully capture the valence of past and present effects of psychosocial factors on neuropsychological test performance. There are also disparities in the experience of socioenvironmental stressors such as discrimination, trauma, adversity, stigma, conflict, and environmental toxins, as well as differential barriers to accessing health-related resources that should be accounted for in future studies. One of the first steps needed to develop population-specific assessments of psycho-social-environmental factors in PWH is to adopt standardized SES status measures. We must also consider the effects of understudied psychosocial factors (eg, stigma, discrimination) on cognitive impairment and associated distress.

Modern Testing in Cross-Cultural Settings

A critical step forward for the field in cross-cultural assessment among PWH has been the development of population-specific norms that account for setting, education, ethnicity, socioeconomic, cultural, and linguistic factors that impact neuropsychological test performance [41]. These efforts have led to substantial progress in assessing cognitive function in non-Western populations including Asia, sub-Saharan and North Africa, and South America [42–48]. These studies suggest not only that standard neuropsychological test batteries can be implemented across cultural settings, but also that when doing so, rates of cognitive impairment are relatively consistent across samples. However, the challenge remains to develop norms that are population appropriate and that do not bias against racial or ethnic groups. Researchers must also be aware of the regional burden carried by healthcare systems treating PWH as the same systems are typically utilized for cognitive screening and assessment. Further complicating neuropsychological assessment is the need to determine the validity of tests that, culturally and linguistically speaking, assess skills that may not be germane to that population. Efforts are needed to employ an anti-racist lens to cross-cultural studies and to resist the reflexive behavior of considering Western cultural values, assumptions, behaviors, and performance patterns as standard, although awareness of what is the dominant culture in a particular setting will be informative. To ensure this bias is avoided, studies should involve local researchers and individuals from communities whose performance is being evaluated. Once a target language has been selected for adaptation, researchers should familiarize themselves with the guidelines for assessment of linguistically and culturally diverse populations, computer-based and internet-delivering systems, scoring, test analysis, and reporting of test scores, as recommended by professional societies such as the International Test Commission [49–52].

To advance efforts to develop population-specific assessments, the specific tests need to be evaluated for their reliability and validity across sites and population-specific normative standards should be developed and used unless there is good evidence of generalizability of certain norms across certain groups. These efforts have shown promise thanks to leveraging of technology to provide training, certify examiners, and facilitate quality assurance across sites where neuropsychological testing occurs in clinical populations [43, 53]. Additional testing administration considerations, data and analytic considerations, and validation considerations are provided in Table 1. Regardless of the mode of assessment, researchers should not assume that comorbidities have a uniform and homogeneous impact on HAND across all populations nor across all racial and/or ethnic groups within a population. Importantly, the proposed approach could determine in which factors are more or less important in a given subset of individuals with HIV (eg, among a specific gender).

CHALLENGES AND SOLUTIONS FOR BIOTYPES OF CNS COMPLICATIONS IN PWH

Given the heterogeneity in CNS complications among PWH, there are several challenges in moving the field of neuroHIV forward. One challenge is determining what constructs need

Table 1. Administrative, Data and Analytic, and Validation Considerations for Standardizing Neuropsychological Test Batteries for the Assessment of Human Immunodeficiency Virus–Associated Neurocognitive Impairment

Consideration	Domain
Computerized assessment with adaptive testing	Administration
Online questionnaires to reduce time spent doing testing	Administration
Use of tele-neuropsychology and self-administered test	Administration
Recruit help of open science and associated data coding to be able to make things cheaper and at the same time collect a lot of normative data	Data and analytic
Data simulation and bootstrap may be used to enhance estimates generated when using normative data	Data and analytic
Temporal variability of cognitive function prediction can be improved by incorporating baseline level of cognitive impairment	Data and analytic
Incorporate patient self-report measures and perspective more fully into assessments, even at a research level	Data and analytic
Harmonization is essential at the testing, norming, scoring, and analytic levels	Data and analytic
Longitudinal data may be used to identify a cross-sectional normative cohort of individuals who have not progressed toward cognitive decline	Validation
In longitudinal assessment, people who have stable disease can be added to the comparative group in addition to healthy HIV-negative controls	Validation
Use of cross-cultural frameworks to develop infinite test versions in various languages and cultures	Validation
Large sample sizes are needed and can be created via data sharing	Validation

Abbreviation: HIV, human immunodeficiency virus.

Table 2. Sample Battery With Common Domain-Specific Assessments of Cognition Used to Assess Human Immunodeficiency Virus–Associated Neurocognitive Impairment

Domain	Measure
Executive function	Stroop
	Trail Making B
	Wisconsin Card Sorting
	Digit span
Attention/working memory	Letter-number sequencing
	CalCap
	Paced Serial Addition Test
Fluency	Controlled Oral Word Association Test
	Animal fluency
	Action fluency
Verbal learning and memory	Hopkins Verbal Learning Test–Revised
	Rey Auditory Verbal Learning Test
Spatial learning and memory	Rey Osterreith
	Brief Visuospatial Memory Test
	Spatial span
Visuospatial	Line orientation
Information processing speed	Symbol digit
	Digit symbol
	Symbol search
	Trail Making A
Motor skills	Grooved pegboard
	Finger-tapping test
	Gait speed

to be assessed to facilitate the identification of biotypes of CNS complications in PWH. Considering the existing large datasets (The MACS/WIHS Combined Cohort Study, The CNS HIV Antiretroviral Therapy Effects Research study, etc) and other large-scale studies, the most commonly administered performance-based measures to date assess cognitive function, and these are known (Table 2). These neuropsychological assessments fall within the cognitive system of the RDoC framework. To move forward, the neuroHIV field should consider a broader battery of assessments that also integrates measures of social processing, motor coordination/initiation, negative valence systems (eg, fear/anxiety, sadness/depression), and reward processing (eg, apathy), as PWH also demonstrate deficits in these areas compared to HIV-seronegative controls [54, 55]. Thus, prospectively, studies could consider integrating performance-based metrics that align with other RDoC systems including negative and positive valence, social processing, sensorimotor processing, and arousal and regulatory. One challenge with expanding our performance-based batteries comes the need for consensus on the constructs to be measured in prospective studies that are cross-culturally valid. Some RDoC domains may be less relevant to CNS complications among PWH and henceforth medical management and possible treatment for HAND. In addition to the aforementioned concern regarding participant burden, expansion into other RDoC domains needs to be carefully considered in relation to our current understanding of the clinical relevance and frequency with which other psychosocial, demographic, medical, and other comorbidities occur in PWH, a topic discussed in depth by the Comorbidities Working Group in this supplement.

A second and important challenge is considering the space in which assessors and patients interact during cognitive assessment. One potential solution is again adaptive computerized testing, but also combined with assessments at home to reduce travel burden—an approach that is already being used internationally [56, 57]. Furthermore, we must underscore the importance of removing barriers to participation in treatment and research. Even if the discrepancy between the number of PWH seeking clinical neuropsychological services in comparison to those presumably affected by cognitive impairment is a function of an overestimation of the affected population, increasing cultural competency in diverse settings for currently underserved PWH is important for enhancing competent research and neuropsychological services [58]. Additional challenges with new assessments and expanded batteries entail normative standards as well as data analytic challenges. With respect to norming, novel measures require the development of normative data that cover broad demographic ranges (eg, age, education, biological sex, race, ethnicity, culture, language). Here again the use of an informed cross-cultural framework can assist in selecting relevant factors in a particular context.

With respect to data analysis, multivariate growth curve modeling, for example, is capable of classifying and predicting patterns of cognitive change. Such methods may help to reveal cognitive biotypes among PWH, building upon prior studies that have used cluster analysis and other statistical approaches to delineate patterns of cognitive impairment [59] and change among PWH [60]. Although our group supports the use of machine learning analyses for assessing biotypes of CNS complications in PWH, these techniques are also susceptible to replicability. Nonetheless, the field is moving closer to addressing these shortcomings by ensuring the code, software, and all other relevant parts of the prediction modeling pipeline are publicly available [61]. Additional data analytic methods were discussed as part of the Machine Learning Working Group and broadly support the use of machine learning to determine the prevalence of cognitive impairment in PWH and interactions among the biopsychosocial predictors of impairment over time as well as its associated subtypes in PWH [62, 63].

CONCLUSIONS

The 2021 meeting for Biotypes of CNS Complications in PWH was but a first step in examining the current approaches to CNS complications in PWH in domestic and international settings. Although the goal of our session was to elucidate challenges inherent to determining CNS complications, as well as their heterogeneity and problems and solutions for examining integrated biotypes, the broader aim of these efforts should be the prevention and effective treatment of those medical and mental health complications in PWH. Despite the challenges, there is evidence that approaches such as RDoC may allow for an integration of cognitive performance–based metrics with self-report and biological measures to provide a deeper understanding of mechanisms and treatment targets. To move the field forward, thought leaders from the Neurobehavior Working Group must continue to forge collaborations with PWH; the NeuroImaging, Pathogenesis, Comorbidities, and Machine Learning Groups; the broader neuroHIV research community; and experts from fields outside of neuroHIV, such as computer science and geroscience, to determine the biotypes of CNS complications in PWH and to work toward improving the well-being and quality of life of PWH.

Notes

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