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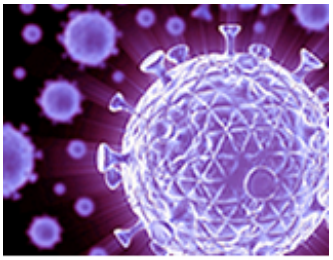

VOLUME 1, NUMBER 7

HIV-Associated Neurocognitive Disorder (HAND)

In this Issue...

HIV-associated neurocognitive disorder (HAND) arises from multifactorial pathologies, including sustained central nervous system (CNS) inflammation, CNS amyloid deposition, and persistent vascular disease. Despite the widespread use of combination antiretroviral therapy (cART) throughout much of the developed world, the prevalence rate for HAND remains high, even among the many who have achieved immune competence and virologic suppression. After more than a decade of research on HAND, no effective pharmacologic treatment has become available other than cART itself, although even this therapy is often inadequate to reverse or even slow disease progression. HAND is associated with broad and severe functional limitations in affected patients, including poor medication management and increased mortality. Thus, a research effort focused not only on therapies, but also on discovering diagnostically accurate bedside screening tests and biomarkers, is paramount.

In this issue, we review reports describing HAND from a variety of perspectives, including prevalence and risk factors, potential predictive biomarkers for cognitive impairment, and the effects of antiviral CNS penetration on development of the disorder.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the meaning of HIV-associated neurocognitive disorder (HAND) and discuss the prevalence of this condition in the current era
- Describe the functional limitations experienced by those affected with HAND
- Evaluate potential strategies for patients with HAND in an outpatient clinical setting

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- Clinicians caring for patients with HIV need current information about: appropriate treatment and maintenance of care…guidance for treating comorbidities…and information about emerging findings for treating HIV-associated neurocognitive disorders (HAND)
- The need for more information on HIV topics including updated guidelines for HIV, treating older patients with HIV, managing patients with comorbidities and coinfections, treatment and sequencing strategies for maximizing future therapeutic options, and new and emerging agents for HIV

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- Treating comorbidities in patients with HIV, especially among people older than age 50

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THIS ISSUE

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COMMENTARY

HIV-associated neurocognitive disorder (HAND) is typically associated with impairments in psychomotor speed (speed of information processing); executive function (planning, multitasking, mental flexibility); and working memory (eg, recalling a progressively longer span of digits). A diagnosis of HAND usually requires exclusion of confounding causes of cognitive impairment, such as a prior central nervous system (CNS) opportunistic infection or a symptomatic traumatic brain injury. Prevalence rates of HAND from well-defined cohort studies are surprisingly high, as seen in the 46.9% rate observed in the 2010 study by Heaton and colleagues (reviewed in this issue). In the era of combination antiretroviral therapy (cART), a large majority of patients are either asymptomatically or mildly affected; however, such impairments still lead to significant functional limitations, as discussed in the 2004 study, also by Heaton and collaborators and also reviewed in this issue.

The most consistent predictor of HAND in the current HIV era is nadir CD4 count, as discussed in the article by Heaton and associates (2010), as well as by Smurzynski and coworkers (2011; also reviewed in this issue). The latter focuses on nadir CD4 count, noting that it is a significant predictor of HAND, even among individuals who achieve viral suppression with cART and when controlling for such variables as ethnicity, gender, and hepatitis C coinfection status. The relative importance of a low nadir CD4 count on the subsequent development of HAND belies the need to treat patients with cART early on — before the potentially permanent CNS injury associated with severe immune suppression. Further, we know from more than a decade of research that cART has the potential to significantly affect the course of HAND (as discussed in the Smurzynski paper). In fact, the widespread use of cART has been associated with a decline in the prevalence of the severest form of HAND — that is, HIV-associated dementia (HAD) — as described in Heaton (2010). Thus, we strongly advocate for the presence of HAND to be included in guidelines for the initiation of cART, even among those with current high CD4 counts.

Again underscoring the need for earlier treatment, infection with HIV leads to early CNS entry. (Antinori et al) The HIV proteins GP120 and TAT frequently have been associated with toxic effects throughout the CNS, including dysregulated cell signaling, increases in

intracellular calcium concentration, neuronal excitability, and ultimately, neuronal cell death. Additionally, GP120 accelerates amyloid deposition in the CNS, and TAT inhibits clearance of this amyloid. (Pulliam) At autopsy, patients with HAND have levels of diffuse amyloid plaques in a pattern similar to, yet still unique from, that of Alzheimer disease pathology. (Green et al) In the article by Clifford and collaborators (reviewed in this issue), a unique cerebrospinal fluid (CSF) pattern for HAND is described that not only confirms this pathologic mechanism for development of the disorder, but also provides a potential biomarker for HAND. Such disease biomarkers are crucial not only for diagnosing HAND without a time-consuming neuropsychological battery of tests, but also because of the desperate need for a marker that could be objectively and quantitatively used as a surrogate for change in disease severity in treatment intervention trials. Although extensive research is still needed to decide whether CSF amyloid could fulfill such a role, this finding marks an important early development.

The recent studies of varied CNS penetration-effectiveness (CPE) scores for different cART regimens have led many to consider either initiation of or a switch to better CNS-penetrating regimens for appropriate patients. (Letendre et al, Tozzi et al) The higher a patient's CPE score, the better the ability of the regimen to penetrate the CNS. To date, results have not led to recommendations for such regimens, and much research is still warranted. In the large study by Smurzynski and colleagues that enrolled 2636 participants, the authors demonstrated improved neuropsychological performance with higher CPE scores; however, this effect was observed only in those participants receiving more than three antiretrovirals (ARVs). Results from this large study are promising as a potential treatment strategy. Other studies, including several randomized, controlled trials, have failed to find significant benefit from anti-inflammatory, antiexcitatory, or antioxidant therapies. (Sacktor et al, Schifitto et al)

For many HIV patient providers, HAND may be difficult to recognize, given the relative sparing of most memory functions that we typically think of with cognitive impairment. And when it is recognized, few options are available that may modify the disease process, particularly for patients already on a stable, suppressive cART regimen. The association of HAND with Alzheimer-type pathology and with vascular risk factors suggests that the treatment of these contributing disease processes may lead to greater improvements in quality of life. Such interventions as aerobic exercise, a Mediterranean diet, and cognitively stimulating activities do just that for patients with Alzheimer disease, and the treatment of vascular risk factors, including smoking, hypertension, and hyperlipidemia, may lessen the contribution of vascular disease to HAND. These interventions have not been studied formally in patients with HAND and no guidelines currently exist for the treatment of this disorder, although such interventions are generally considered part of routine primary care and should be strongly emphasized to HAND-affected patients at primary care or HIV-specialty clinics.

Complacency in assuming that a cART regimen that achieves viral suppression and good immunologic control will translate into control of CNS complications is a dangerous idea. We know that HAND persists and may progress in such settings, and we must be proactive for affected patients. Even asymptomatic HAND can impair medication management. We need to have in place screening measures that detect HAND early on, biomarkers that can be tracked with intervention trials, and therapies that can either halt or reverse impairments. Although this is an ongoing process and it may take years or perhaps decades to achieve these goals, we advocate for support from providers, friends, and family, with the aim being to modify vascular risk factors and focus on known nonpharmacologic therapies for patients with HIV who have cognitive impairment.

Commentary References

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69(18):1789-1799.
2. Pulliam L. HIV regulation of amyloid beta production. *J Neuroimmune Pharmacol*. 2009;4(2):213-217.
3. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS*. 2005;19(4):407-411.
4. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65(1):65-70.

5. Tozzi V, Balestra P, Salvatori MF, et al. Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders. *J Acquir Immune Defic Syndr*. 2009;52(1):56-63.
6. Sacktor N, Miyahara S, Deng L, et al. Minocycline treatment for HIV-associated cognitive impairment: results from a randomized trial. *Neurology*. 2011;77(12):1135-1142.
7. Schifitto G, Navia BA, Yiannoutsos CT, et al. Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. *AIDS*. 2007;21(14):1877-1886.
8. Schifitto G, Zhang J, Evans SR. A multicenter trial of selegiline transdermal system for HIV-associated cognitive impairment. *Neurology*. 2007;69(13):1314-1321.

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PREVALENCE OF AND RISK FACTORS FOR HAND

Heaton RK, Clifford DB, Franklin DR Jr, et al; **CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study.** *Neurology*. 2010;75(23): 2087-2096.

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Despite the advent and widespread availability of cART throughout much of the developed world, HAND commonly affects the HIV population. Heaton and colleagues at the University of California, San Diego (UCSD) sought to define the prevalence of and risk factors for such impairments in the cART era.

Cross-sectional data from 1555 participants from six sites (Baltimore, Galveston, New York City, San Diego, Seattle, and St. Louis) enrolled in a longitudinal cohort were analyzed for this study. Using a comprehensive neurocognitive test battery and assessments of function in activities of daily living, participants were classified in one of four groups, based on their level of neurocognitive impairment: (1) neurocognitively normal, (2) asymptomatic neurocognitive impairment (ANI), (3) mild neurocognitive disorder (MND), or (4) HIV-associated dementia (HAD). This categorization was developed by a consensus panel of neurologists, neuropsychologists, and infectious disease specialists to define specific HAND diagnoses.[1] ANI represents testing impairment without limitations in daily activities, MND denotes impairment with recognizable limitations, and HAD represents severe impairment in both testing and functional activities. This classification has become a standard for current HAND research.

In order to reliably define HAND prevalence, demographic and medical history variables were considered as incidental, contributing, or confounding for each patient based on published guidelines.[1] Participants with only incidental or contributing factors were classified into a HAND category, whereas those with confounding factors (15%; n = 239) were excluded from further analysis. Overall, 46.9% of the participants without confounding factors were diagnosed as having HAND; 32.7% had ANI, 11.7% had MND, and 2.4% had HAD. Among cART-treated participants with incidental comorbidities, HAND was associated with a nadir CD4 count < 200 cells/uL, a detectable plasma viral load, and the interaction between them.

The high prevalence rate of 46.9% in this cohort of patients from academic, urban settings may not be generalizable to the entire HIV population, although it does reflect the strong persistence of HIV-related CNS disease in the current era of cART. Approximately 70% of the cohort were currently receiving cART, and only about 60% were virally suppressed. Interestingly, those undergoing treatment with cART actually had a higher rate of HAND, probablyreflecting the fact that these participants also had higher rates of having an AIDS diagnosis. The reason for this is unclear, but perhaps these participants are "survivors" who have overcome advanced immune suppression and now, despite immunologic recovery, the CNS effects of their low nadir CD4 counts are persistent. In fact, the 30% of participants receiving cART who had nadir CD4 counts (>= 200 cells/uL) had much lower rates of HAND compared with those with an AIDS diagnosis.

Although the overall proportion of patients with neurocognitive impairment has not changed significantly compared with the pre-cART era, much less overt dementia is now observed in this population, with a predominance of asymptomatic and mild forms of

HAND being reported. These types of impairment are more difficult to detect in the exam room than HAD, thus emphasizing the need for a valid, reliable screening tool that would enable primary care clinicians to identify more than just HAD.

References

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69(18):1789-1799.

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CSF BIOMARKERS FOR HAND

Clifford DB, Fagan AM, Holtzman DM, . **CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease.** *Neurology*. 2009;73(23):1982-1987.

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For patients with Alzheimer disease, measurements of CSF proteins have become a biomarker of disease. Reduced ?-amyloid$_{1-42}$ (A?42), normal ?-amyloid$_{1-40}$ (A?40), and elevated phosphorylated tau (p-tau181) and total tau (t-tau) represent the characteristic Alzheimer disease pattern. Previous autopsy studies of patients affected by HAND have shown amyloid plaques similar to those seen in Alzheimer disease, although without the neurofibrillary tangles that are also present in those with Alzheimer disease. The aim of this study by Clifford and associates was to determine whether a unique CSF protein pattern also exists for HAND-affected patients by using the same biomarkers that help to define Alzheimer disease.

CSF samples of 198 patients were included in this analysis. Groups included 21 participants infected with HIV who did not have HAND, 49 patients infected with HIV who had HAND of varied severity, and 68 participants who did not have HIV but had mild Alzheimer disease, and 50 controls without HIV infection. Because the participants with Alzheimer disease were significantly older than those in the other groups ($P < .0001$), age was considered a continuous variable throughout the analysis. A?42 levels were lower among those with HAND and those with Alzheimer disease, compared with both participants infected with HIV without HAND and the control group. No significant differences were observed in the lowered A?42 levels between those with HAND and those with Alzheimer disease. A?40 levels remained normal among all groups. In the Alzheimer group only, there were significant elevations in both t-tau ($P = .020$) and p-tau181 ($P = .044$) compared with all other groups including the HAND group.

In summary, study participants with HAND experienced significant reductions in A?42 comparable to those in patients with Alzheimer disease. However, no significant elevation in either form of tau, which characterizes the Alzheimer population, was reported among HAND patients. These results suggest that amyloid is deposited within the brain and thus does not enter the CSF. The investigators posit that there is a unique CSF pattern in

HAND that does not simply reflect aging — a factor that was controlled for in this analysis. Further, the pattern observed in HAND does not just reflect neuronal cell death that would cause a concurrent elevation in A?40 and instead probably represents the diffuse extracellular amyloid deposition seen at autopsy.

This analysis delineates a potentially significant pattern of reduced A?42 with normal levels of A?40, t-tau, and p-tau181. This unique pattern may be a potential biomarker for HAND, and if validated in other studies — particularly longitudinally, in a larger group of participants infected with HIV and without HAND and in patients with a range of defined severities of HAND — it could serve as a research tool for evaluating the effects of intervention trials.

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VASCULAR RISK FACTORS AND HAND

Becker JT, Kingsley L, Mullen J, et al; Multicenter AIDS Cohort Study. **Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men.** *Neurology*. 2009;73(16):1292-1299.

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As cART extends life expectancy and reduces HIV mortality rates, the population infected with HIV is growing older. Subsequently, nearly three-fourths of all individuals infected with HIV > 50 years of age die of non–HIV-related causes. A growing body of literature is now aimed at detecting factors other than HIV itself that contribute to or cause neurocognitive impairment in older patients infected with HIV.

Becker and colleagues used a cross-sectional study design to analyze Multicenter AIDS Cohort Study participants >= 40 years of age with no self-reported history of heart disease or cerebrovascular disease. A multidomain neuropsychological evaluation was administered to 635 participants, with the results compared between the 428 participants who were HIV-positive (mean age 48.4 years) and 207 participants who were HIV-negative (mean age 52 years). Interestingly, HIV infection was not significantly associated with slowed psychomotor speed performance ($P = .26$), although it did portend impaired memory performance ($P = .015$). In all comparisons, African American race, lower education (possibly associated with race), and depression were associated with both reduced speed and memory performance. Additionally, significant predictors of slower psychomotor speed performance among all participants included carotid intima-media thickness (IMT, a surrogate for cerebrovascular disease; P = .023); a higher glomerular filtration rate (representing cumulative hypertension; P = .048); and fasting glucose >= 126 mg/dL ($P = .044$). Among only participants infected with HIV, carotid IMT ($P = .040$) and fasting glucose ($P = .037$) were significant predictors of psychomotor slowing, whereas the significant predictor of impaired memory performance was a detectable viral load (P = .003) and no vascular risk factors.

These findings suggest that vascular risk factors, not HIV infection, are the most important predictors of slowed psychomotor speed. Cerebrovascular disease primarily affects the subcortical white matter that is crucial for psychomotor speed performance, and psychomotor slowing is a characteristic clinical feature of HAND suggesting that such vascular disease may contribute to the development and/or persistence of HAND. Vascular disease is a modifiable risk factor that, if improved, could potentially lead to improvement in HAND-related psychomotor slowing; however, this is an area that needs to be explored with further research.

In this study, poor memory performance among older gay and bisexual men infected with HIV was associated with both HIV serostatus and a detectable viral load rather than the vascular risk factors observed for psychomotor slowing. Poor memory performance is strongly linked to age-related cognitive impairments, and these results are especially important in supporting a notion that age-related complications such as memory-predominant cognitive impairment is a significant concern for older patients infected with HIV. The idea that such complications may affect those with HIV at earlier ages than in those without HIV infection is still controversial, and additional research is ongoing. HIV providers and neurologists must carefully consider both vascular risk factors and age-related cognitive complications when evaluating patients with HIV, as they may be contributing components to an evolving concept of HAND.

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Smurzynski M, Wu K, Letendre S, et al. **Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort.** *AIDS.* 2011;25(3):357-365

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The idea that better cART penetration into the CNS may modify or treat HAND has led to an accumulating body of evidence over the past five years.[1-3] A quantified CPE index developed by Dr. Scott Letendre at UCSD ranks cARTs according to the CNS concentration of each agent. In the current study, Smurzynski and coworkers evaluated whether the CPE scores of participants' cART regimens were associated with neuropsychological test performance.

This cross-sectional study with repeated-measures analysis included data from 2636 HIV-infected participants on stable cART regimens for at least six weeks and a suppressed plasma viral load of < 50 copies/mL. The results of neuropsychological tests of executive function and psychomotor speed were collected, along with demographic and immunologic data longitudinally, over 10,413 patient visits. CPE was classified as low (0.0), medium (0.5), or high (1.0). In the authors' multivariate linear regression analysis, better neuropsychological performance was associated with a higher CPE score in those taking > 3 ARVs (30% of participants; +0.07 per one unit increase in CPE score; P =.004), whereas no such association was observed in those taking <= 3 ARVs (70% of participants; +0.01 per one unit increase in CPE score; P = 0.5). This effect in those taking > 3 ARVs was compared with the effect of nadir CD4 cell count — a consistent predictor of HAND — on neuropsychological performance, and the estimates were similar (+0.07 vs +0.06 for nadir CD4 > 200 cells/uL vs <= 200 cells/uL, respectively).

This study has lent support to the idea that improved cART CPE scores are associated with less neurocognitive impairment without affecting such immunologic and virologic parameters as viral load or CD4 count. The authors speculate that the better neuropsychological performance reported in those taking < 3 ARVs may be more readily apparent when compared with the performance in those on <= 3 ARVs and that some participants needed > 3 ARVs to achieve a sufficiently high CPE score. This pattern was maintained even when dichotomizing CPE scores at a threshold of 2.0, with those on > 3 ARVs demonstrating better neuropsychological test performance when the CPE was > 2.0. A reasonable explanation for this remains elusive.

This large study does show significant benefit for the higher CNS-penetrating cART regimens with > 3 ARVs. Hopefully, a longitudinal study that measures changes in neuropsychological performance over time with an otherwise similar study design will help determine whether the higher CPE regimens actually have a modifying effect on neurocognitive impairment.

As previously mentioned in the commentary, a much smaller study of the association between CPE and neurocognitive impairment demonstrated an opposite effect, with higher CPE score associated with greater neurocognitive impairment.[4] The absence of consistent findings to date warrants further longitudinal study of CPE to determine which patients may benefit from a change in cART regimen to help improve CNS penetration.

Reference

1. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol.* 2008;65(1):65-70.

2. Tozzi V, Balestra P, Salvatori MF, et al. Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders. *J Acquir Immune Defic Syndr.* 2009;52(1):56-63.

3. Wright E. Neurocognitive impairment and neuroCART. *Curr Opin HIV AIDS.* 2011;6(4):303-308.

4. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid RNA and neurocognitive performance. *AIDS*. 2009;23(11):1359-1366.

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FUNCTIONAL IMPACTS OF HAND

Heaton RK, Marcotte TD, Mindt MR, et al; HNRC Group. **The impact of HIV-associated neuropsychological impairment on everyday functioning.** *J Int Neuropsychol Soc*. 2004;10(3):317-331.

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Similar to other forms of neurocognitive impairment in populations without HIV infection, including Alzheimer disease and dementia with Lewy bodies, HAND has deleterious effects on patients' daily functioning. Such effects from HAND are particularly important, considering the fact that adherence to cART regimens remains a persistent problem, even in cognitively unimpaired patients with HIV infection. In this study, also by Heaton and colleagues at UCSD, participants were evaluated on measures of both instrumental activities of daily living and vocational abilities. Because this study was published before the 2007 consensus guidelines that defined HAND, the authors described it as neuropsychological (NP) impairment.

Data from 267 persons with HIV infection were included in this analysis. Exclusion criteria for this early study included the presence of any comorbidity thought to significantly contribute to cognitive impairment, which is now standard practice for defining HAND. Ninety-nine participants had evidence of varied degrees of NP impairment (mild in 60 participants, mild to moderate in 34, and moderate in 5). NP impairment was associated with poorer functional performance on all measures tested (shopping, financial skills, advanced finances, medication management test-revised, cooking, and vocational assessment), as well as on the functional deficit score — a composite measure of global functioning across all such tested measures. NP impairment was, by far, the largest contributor to poor functional testing; however, nonwhite, NP-impaired, participants experienced greater impairment on the vocational assessment than did white NP-impaired participants. This one demographic influence probably reflected only the lower premorbid vocational functioning among nonwhite participants, because when premorbid functioning was controlled, race no longer showed a significant association with the vocational assessment.

Although the study authors recognize that this cross-sectional analysis limits the results by suggesting that NP impairment is the cause of such functional impairments, the consistent findings among each functional measure provide a strong correlation between NP performance and everyday functioning. This study highlights the broad functional limitations of those with HAND. Additional studies that have assessed functional abilities and have also subcategorized participants according to degree of NP impairment are somewhat limited, although two such studies have shown similar functional difficulties in patients with asymptomatic or mild NP impairment in driving and vocational abilities,[1] as well as in medication management and finances.[2]

Because functional limitations are part of the definition of HAND, at least for MND and HAD, observing such difficulties with everyday tasks in these patients should not be surprising. Yet, the vast majority of patients with a diagnosis of HAND typically have NP impairment in only two of seven cognitive domains, with otherwise normal or near-normal performance in the other domains. Despite normal performance elsewhere, the affected domains lead to multiple and comprehensive impairments throughout the affected patients' lives.

Reference

1. Gorman AA, Foley JM, Ettenhofer ML, Hinkin CH, van Gorp WG. Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychol Rev*. 2009;19(2):186-203.

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2. Gandhi NS, Skolasky RL, Peters KB, et al. A comparison of performance-based measures of function in HIV-associated neurocognitive disorders. *J Neurovirol*. 2011;17(2):159-165

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