

# HIV-Associated Neurocognitive Disorders (HAND)

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Since the introduction of HAART (highly active antiretroviral therapy), the course of human immunodeficiency virus (HIV) has transformed dramatically from an incurable fatal disease to a chronic treatable disease. Following this change, the focus has turned from treating the acute complications of the disease (usually opportunistic infections)

to managing long-term complications, such as diseases of the cardiovascular, renal, osteological and central nervous systems. These complications are due to numerous factors, including the long-lasting inflammatory response, the HIV infection itself, HAART-related adverse events, host genetics, socioeconomic factors, and the combination of some of the above factors [1].

HIV-associated dementia (HAD), the most severe manifestation of HIV-associated neurocognitive disorders (HAND), occurred at the start of the AIDS epidemic primarily in patients with advanced HIV disease and low CD4 cell counts [2]. The wide use of HAART since the mid-1990s has had a major influence on the treatment of HIV infections, but its impact on HAND is less clear. In the HAART era, a significant decrease in the incidence of HIV-associated dementia has been reported [1]. However, the prevalence of less severe forms of cognitive impairment has increased (ranging from 20% to 50%, depending on the neurocognitive tools and definitions used) and is consistently higher than in the general population [3]. HAND, even in its mild form, is associated with lower medication adherence, a decreased ability to perform the most complex daily tasks, poorer quality of life, and difficulty obtaining employment [4]. Moreover, HIV-infected individuals with mild cognitive impairment may have an increased risk of dementia and death. In addition, as patients treated with HAART survive

into older ages, it is expected that the prevalence of neurocognitive impairment in the aging HIV-infected population will rise due to the increase in concomitant age-related diseases (diabetes mellitus, cardiovascular disease) and age-associated degenerative diseases of the central nervous system (CNS) (Alzheimer's disease, Parkinson's disease) [5].

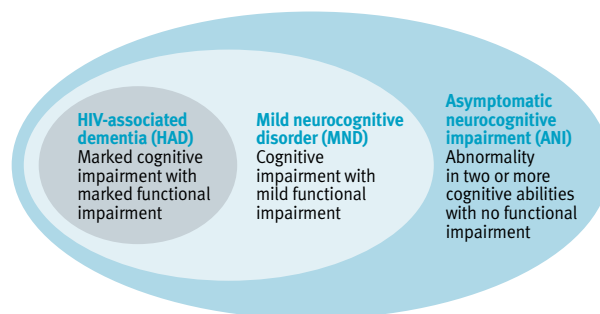
## PREVALENCE AND NOMENCLATURE

In the HIV-infected individual, neurocognitive abnormalities can occur as a result of emotional and behavioral disturbances (e.g., depression, anxiety, sleep disorders, mania, and psychosis), secondary to co-infections, cerebrovascular disease, malnutrition, substance abuse, and treatment-related disorders [6]. In contrast, HIV-associated neurocognitive disorder (HAND) is a primary neurocognitive abnormality in HIV-infected individuals.

HAND is divided into three sub-disorders (also known as the Frascati criteria) [Figure 1] [2]:

- Asymptomatic neurocognitive impairment (ANI): abnormality in two or more cognitive abilities with no functional impairment
- Mild neurocognitive disorder (MND): cognitive impairment with mild functional impairment
- HIV-associated dementia (HAD): marked cognitive impairment with marked functional impairment.

figure 1. HIV-associated neurocognitive disorders (HAND): Frascati criteria



Courtesy of Dr. I. Grant for the HNRP Group, University of California, San Diego, CA, USA

It is difficult to estimate the exact prevalence of this disorder due to the wide range of disorders covered by the definition of HAND. Thus, knowledge of the prevalence and incidence of HAND is based on a few key observational studies. According to one of the estimations [7], the prevalence of HAND in the pre-HAART era (before 1996) was found to be around 35% with 14% suffering from HAD, 5% from MND and 16% from ANI. While the overall prevalence did not change significantly during the HAART era (44%), HAD was found to affect only 2% of the HIV-infected individuals while MND affected 10%, and ANI was found in 32% of the cohort. In the Swiss HIV cohort, in the HAART era, 27% of patients had complaints about cognitive function and 73% did not, with neuropsychological testing showing neurocognitive impairment in 84% of those with complaints and 64% of those without (69% of the total clinic population). Among those with complaints, 24% had ANI, 52% had MND, and 8% had HAD, with only 16% not having measurable impairment [8]. The prevalence of similar cognitive impairments was found to be significantly higher in HIV-infected individuals when compared to HIV-seronegative age-matched subjects during the same periods [4].

## PATHOGENESIS

The precise pathogenesis of HAND is still unknown. In recent years our knowledge gaps have narrowed due to extensive research. It is well known that damage and death of neural cells in the brain is associated with the development of neurocognitive impairment. Since the infection of neural cells by HIV itself is limited, it is accepted that most of the damage leading to clinical HAND is the result of secondary events following an HIV infection [9].

HIV enters the brain primarily by migrating monocytes and lymphocytes that cross the blood-brain barrier (BBB), known as the “Trojan horse” mechanism. In the brain, HIV-infected monocytes turn into perivascular macrophages. As a result of HIV replication, activated macrophages and microglia express neurotoxic molecules (soluble immune mediators) that activate astrocytes; these activated astrocytes lead to increased BBB permeability and further monocyte and lymphocyte migration [10].

Two models, direct and indirect, explain the neurodegeneration and development of neurological symptoms in HAND [11]. Both models require that HIV initially infect the perivascular macrophages and microglia in the brain. The direct model proposes that viral proteins released from infected monocyte-derived cells can cause neuronal death through the direct interaction of viral proteins with neurons (gp 120, Tat and Vpr). The indirect model suggests that neuronal

death is mediated by the inflammatory response mounted by inflammatory cells against the HIV infection and against HIV proteins released by directly infected cells [12]. Macrophages and microglia that are activated (because of HIV infection or exposure to viral particles) secrete a wide range of mediators: quinolinic and arachidonic acids, nitric oxide (NO), platelet-activating factor, superoxide anions, matrix metalloproteases, chemokines, growth factors, and pro-inflammatory cytokines including tumor necrosis factor (TNF). Some of these molecules, such as growth factors (i.e., brain-derived neurotrophic factor) and some  $\beta$ -chemokines (RANTES: Regulated upon Activation-Normal T cell Expressed and Secreted), are believed to play a neuroprotective role. Other molecules have proven to be neurotoxic. Additionally, other substances and cytokines that are released during this process, such as NO and TNF, impair the neuroprotective functions of astrocytes (maintenance of the BBB and glutamate reuptake) and increase the rates of astrocytic apoptosis [10,13].

The concomitant release of excessive excitatory amino acids such as glutamate (a neurotransmitter that is an excitatory neurotoxin at high levels), and other N-methyl-D-aspartate glutamate receptor (NMDAR) agonists in association with a reduction in glutamate re-uptake as seen in HIV infection, can create an excitotoxic environment that results in excessive activation of NMDAR. Consequently, intraneuronal  $Ca^{2+}$  concentrations reach toxic levels, which results in the production of free radicals, including reactive oxygen species (ROS) and NO, and in neuronal death [14-16].

Recently, the role of inflammation and monocyte activation in the process of secondary damage to end organs and especially to the CNS focused on the central role of bacterial products such as lipopolysaccharide (LPS) translocating from the gut [17]. Elevated systemic LPS levels and immune activation in chronic HIV infection resulting from microbial translocation are associated not only with HIV-induced depletion of gut-

associated lymphoid tissue but presumably also have effects on HAD. It has been demonstrated that individuals with HAD express higher levels of circulating

activated CD14 and monocytes that co-express CD69 when compared with individuals without HAD. Hence the hypothesis that these activated monocytes (due to microbial translocation) enter the brain and subsequently initiate neurotoxin production [17,18]. Further, an association between plasma soluble CD14 (sCD14) and cognitive dysfunction in HIV infection has also been shown.

The association between the abundance of activated macrophages/microglia in the CNS and neuronal damage and cognitive dysfunction suggests that neuroinflammation resulting from systemic immune activation and/or inflammation triggers the neurodegeneration observed in HAND [10].

### **HAND defines three categories of disorders: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD)**

## HOST VIRAL INTERACTION

As HIV invades and replicates in the brain of most HIV-infected individuals, studies have shown that both host and viral factors may contribute to the development of HAND in some HIV-infected individuals but not in others [9]. Host factors include genetic predisposition (apolipoprotein E e4 alleles, polymorphism in the *MCP-1* gene), metabolic disorders (e.g., insulin resistance), aging, vascular disease, anemia, and malnutrition [19]. Recent data on phosphorylated Tau protein and other age-related markers show that the levels of these markers in the cerebrospinal fluid (CSF) of HIV-infected patients are comparable to those in non-infected subjects who are 15 to 20 years older [20]. Factors that are HIV associated and contribute to the development of HAND include AIDS, immune activation, HIV subtype, neuroadaptation, drug resistance, and CD4+ nadir [21].

Comorbidities and behavioral factors can also influence HAND. Consumption of drugs such as methamphetamine and cocaine, common in some HIV-infected populations, can have persistent adverse effects on the CNS. Hepatitis C (HCV) and HIV co-infection was found to be an independent risk factor for developing HAND. HCV can infect glial cells. Although only approximately 10% of HCV-infected patients have detectable HCV RNA in their CSF (and typically at low levels), high levels of HCV core antigen can be found in a much larger percentage of patients. The core antigen is highly immunogenic and may be a stimulus for brain injury [22].

## SCREENING AND DIAGNOSIS

The recognition that HAND is a highly underdiagnosed problem in the HIV-positive population (especially in its milder forms, ANI or MND) should prompt early screening to detect these patients.

A range of tests are available for use in the clinic to assess neurocognitive function, some of which are relatively simple and brief [Table 1] [3]. For example, symptom questionnaires (Medical Outcomes Study–HIV Health Survey MOS-HIV and the Patient's Assessment of Own Functioning Index – PAOFI) are self-administered and can be completed by the patient in the waiting room before meeting with the physician, thus serving as a baseline tool for basic evaluation, subsequent follow-up and further comprehensive evaluation. Longer and more detailed screening tests (which require 5 to 10 minutes to complete) include the HIV Dementia Scale, the International HIV Dementia Scale, and the Montreal Cognitive Assessment [23-30].

The European AIDS Clinical Society recently emphasized the need for identification of those patients at risk for HAND and

suggested that as part of the routine assessment of HIV-infected individuals, three screening questions should be posed [31]:

- Do you experience frequent memory loss (e.g., do you forget the occurrence of special events, even the more recent ones, appointments, etc.)?
- Do you feel that you are slower when reasoning, planning activities, or solving problems?
- Do you have difficulties paying attention (in a conversation, reading a book, or watching a movie)?

Positive screening (a “yes” response to any of these questions) should be followed by a complete neuropsychological (NP) examination (assessment of at least five cognitive abilities – fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning and motor skills – with at least two tests per ability).

## TREATMENT

HAART is currently the only treatment for HIV-infected individuals with neurocognitive complications. While treatment with HAART affects the incidence of HAD, it cannot completely prevent the progression of neurocognitive decline [4]. Not all the drugs used to treat HIV penetrate the brain equally. A number of drug characteristics influence penetration across the BBB: drugs highly bound to plasma proteins are less available to cross the BBB, while fat soluble and low molecular weight drugs favor the crossing of the BBB [32].

The CHARTER (CNS HIV Antiviral Therapy Effects Research) group was one of the first to publish data on CSF pharmacokinetics of antiretroviral drugs. Using CSF viral load data from 615 patients, they constructed a CNS penetration-effectiveness (CPE) ranking system for antiretrovirals [Table 2] [6]. In their work, higher CPE scores were statistically significantly associated with lower CSF viral loads (higher numbers indicate better estimated penetration; for combination regimens, the scores for each drug were added). Further work demonstrated that a cutoff of CPE score > 7 was associated with a statistically significantly smaller proportion of patients having a detectable viral load in the CSF [33]. Other observational and uncontrolled interventional studies support the concept that antiretroviral regimens that penetrate the CNS effectively are more likely to reduce HIV RNA levels in the CSF [34]. However, the evidence that antiretroviral regimens that effectively penetrate the CNS also protect the brain from HIV-related injury and prevent or reverse neurocognitive function is controversial [35]. For example, in one study of 37 patients, higher CPE of an antiretroviral regimen was associated with lower CSF viral load and better performance in neuropsychological studies

### To prevent or reverse HAND, therapy with drugs with high central nervous system penetration effectiveness score (CPE) should be considered

**Table 1.** Available tools and tests for HIV-associated neurocognitive disorders (HAND) screening [3]

Tool or test	Description of the test	Advantages	Limitations
<b>HIV Dementia Scale (HDS)</b>	A validated brief screening tool designed primarily for use in outpatient clinics to identify dementia in people with HIV, using NP tests of motor speed, concentration and memory	<ul style="list-style-type: none"> <li>• Very fast to administer (3–5 minutes)</li> <li>• Very fast to score and interpret</li> <li>• Excellent specificity</li> </ul>	<ul style="list-style-type: none"> <li>• Modest sensitivity (80% when the score was ≤ 10 for a maximum of 16 points) leading to high rates of false negatives. High sensitivity for HAD, but HAD is relatively rare in successfully cART-treated patients</li> <li>• Requires a trained examiner to assess anti-saccadic eye movement</li> <li>• Not sufficiently sensitive to detect mild HAND, particularly in highly educated individuals in whom the use of demographically corrected norms or a cutoff of 14 points may be useful</li> <li>• Alphabet writing and cube-copying tests may be difficult for those with a non-Western educational background; the IHDS is more appropriate in these cases</li> </ul>
<b>International HIV Dementia Scale (IHDS)</b>	A sensitive and rapid screening test for HIV dementia, which relies on assessment of motor speed and psychomotor speed. It includes three subtests: timed finger-tapping, timed alternating hand sequence test, and recall of four items at 2 minutes	<ul style="list-style-type: none"> <li>• Very fast to administer and score. Can be conducted in 2–3 minutes and only requires a stopwatch</li> <li>• Demonstrated appropriate sensitivity and specificity for screening for dementia</li> <li>• Does not require a trained examiner</li> <li>• Does not require proficiency in English</li> <li>• Can be easily applied in different settings and cultures</li> </ul>	<ul style="list-style-type: none"> <li>• Limited ability to detect milder forms of HIV-associated neurocognitive impairment and distinguish between different stages of HIV dementia</li> <li>• Additional research is needed to determine appropriate cutoff values in different clinical and geographic settings.</li> <li>• Additional research needed on the role of depression in performance and scoring</li> </ul>
<b>Total Recall measure of the Hopkins Verbal Learning Test-Revised</b>	Originally developed to detect dementia, it has been shown to measure neurocognitive impairment in HIV. In particular, it can be used to detect verbal learning and retrieval deficits	<ul style="list-style-type: none"> <li>• Has six alternate forms, reducing potential practice effects and enabling its use in follow-up and monitoring of neurocognitive changes over time</li> <li>• Easy and fast (4 minutes) to administer</li> <li>• Good test for assessing patients with severe peripheral neuropathy and/or extreme motor limitations</li> </ul>	<ul style="list-style-type: none"> <li>• Must be administered by a trained examiner</li> <li>• Must be scored and interpreted by a trained psychologist or neuropsychologist</li> <li>• Scoring and interpretation must be based on adequate normative data (i.e., data appropriate to the individual being assessed)</li> </ul>
<b>Grooved Pegboard Test</b>	Test of manipulative dexterity requiring complex visual-motor coordination		<ul style="list-style-type: none"> <li>• Difficult to use in patients with severe peripheral neuropathy and/or extreme motor limitations</li> <li>• Requires equipment, although the cost is relatively low (US\$100), and stopwatch</li> <li>• Must be scored and interpreted by a trained psychologist or neuropsychologist</li> <li>• Scoring and interpretation must be based on adequate normative data (i.e., data appropriate to the individual being assessed)</li> </ul>
<b>Executive Interview</b>	Developed and validated in geriatric patients and patients with Alzheimer’s disease as a brief assessment of frontal or executive neurocognitive function. Has been shown to be significant individual predictor of dementia in hospitalized patients with HIV	<ul style="list-style-type: none"> <li>• Has good internal consistency</li> <li>• Correlates with other measures of executive neurocognitive function</li> <li>• Not affected by age or gender</li> </ul>	<ul style="list-style-type: none"> <li>• Less sensitive than HDS</li> <li>• Lower education was associated with an increased risk of incorrect classification of dementia</li> <li>• Accuracy in mild HAND</li> </ul>
<b>Cognitive functional status subscale of the (Medical Outcomes Study HIV Health Survey: MOS-HIV)</b>	MOS-HIV is a widely used instrument to assess QoL in patients with HIV. Best use may be as a screening instrument to select those subjects whose self-reported neurocognitive functional status warrants formal NP test evaluation	<ul style="list-style-type: none"> <li>• Sensitive to changes in NP test performance in early disease</li> <li>• Sensitive to neurocognitive behavior that involves neurocognitive or psychomotor speed</li> </ul>	<ul style="list-style-type: none"> <li>• No sensitivity to attention and only limited sensitivity to memory function</li> <li>• Accuracy in mild HAND has not been reliably shown</li> </ul>

NP = neuropsychological, QoL = quality of life

than patients on regimens with lower CPE scores. On the other hand, other studies failed to show improvement in cognitively impaired patients who received regimens with higher CPE scores [36]. These findings raise the issue of potential antiretroviral therapy-related neurologic toxicity and highlight the need for careful consideration of treatment strategies based on better CNS penetration.

The goal of antiretroviral therapy in patients with HAND is to achieve adequate drug levels in the CNS without causing drug-related neurotoxic effects. If drug levels in the CSF are too low, there is greater risk of damage caused by viral replication and ongoing immune activation, as well as the potential risk

of drug resistance. The therapeutic window for antiretroviral therapy in the CNS may thus be defined as the range of CNS drug concentrations that are associated with keeping damage below the clinical cognitive threshold and that do not expose patients to excessive risk of neurotoxicity from the drug.

A unique way to reduce indirect CNS toxicity can be demonstrated with the use of maraviroc. Maraviroc, the first CCR5 inhibitor approved for HIV treatment, itself has limited effect on the CNS (CPE score of 3). Maraviroc is known to accumulate in high concentration in the gut-associated lymphocytic tissue (GALT). Given the previously discussed finding that a compromised bacteria- or endotoxin-leaking gut may promote

**Table 2.** Central nervous system Penetration-Effectiveness score (CPE) [6]

CNS Penetration-Effectiveness Score	4	3	2	1
<b>Nucleoside reverse transcriptase inhibitor (NRTI)</b>	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</b>	Nevirapine	Delavirdine Efavirenz	Etravirine	
<b>Protease inhibitors (PI)</b>	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
<b>Entry/fusion Inhibitors</b>		Maraviroc		Enfuvirtide
<b>Integrase inhibitors</b>		Raltegravir		

CNS = central nervous system, r = boosted with ritonavir

the development of HAND [15], protection of the GALT by maraviroc could potentially indirectly contribute to the treatment or prevention of HAND [37].

Besides the use of HAART, other drugs such as antioxidants, serotonin reuptake inhibitors (SRI: citalopram, paroxetine), lithium, valproic acid and selegiline (monoamine oxidase-B inhibitor) have been tested as adjunct treatments of HAND and were found to have limited beneficial effect [4,9]. Minocycline, a tetracycline-type antibiotic, has been shown to suppress SIV in monkey brains via a mechanism that involves inhibition of apoptosis signal-regulating kinase (ASK)1 and is one of the drugs being tested for clinical use in humans [9]. Lately, HMG-CoA reductase inhibitors (e.g., atorvastatin, simvastatin) have gained interest because of in vitro evidence of modulation of the immune system, of cell activation, and possibly of HIV replication. However, two small studies of HIV-infected individuals did not show any appreciable effect of atorvastatin on levels of HIV RNA or markers of immune and cellular activation in the CSF. A larger cross-sectional study investigating several statins also failed to show an effect on CSF HIV RNA or neurocognitive performance [38].

Additional potential therapeutic options for HAD are being explored, including erythropoietin (EPO), insulin-like growth factor, neurotrophins, antibiotics, inhibitors of p38 MAPK, and blockers of Ca<sup>2+</sup> ion channels, and are awaiting further evaluation [9].

Due to the paucity of evidence, the current recommendations for the treatment of HAND are to consider the use of an antiretroviral combination with higher CPE score for those HIV-infected patients with HAND (HAART-naïve patients or HAART-experienced patients who are currently treated with a low CPE HAART combination), and in HIV-infected individuals treated with HAART and achieving full suppression of the virus in the plasma (viral load < 50 copies/ml) but not in the CSF (“CSF escape”) [26].

## SUMMARY

Neurocognitive impairment still occurs in the era of HAART, though its onset appears to be delayed and its severity reduced, while HIV-infected individuals live longer with the infection. HAND defines three categories of disorders according to standardized measures of dysfunction: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). The pathogenic mechanisms underlying HAND involve host and virus characterizations and interactions and seem to depend heavily on the overall condition of the immune system. Since there are insufficient data at this point to determine the best therapeutic approach, and since HAART apparently is not sufficient to prevent or reverse HAND, therapy with a combination of drugs with high CPE should be considered while adjunctive and alternative therapies are being explored.

## Correspondence

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