

## HIV-Associated Neurocognitive Disorders—An Issue of Growing Importance

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### Abstract

**Introduction:** HIV-associated neurocognitive disorders (HAND) comprise a wide spectrum of cognitive, motor, and mood abnormalities prevalent in people living with HIV and AIDS (PLWHAs). This field of HIV medicine has gained renewed prominence in recent years with evidence contending that anti-retroviral agents with increased central nervous system (CNS) penetration may improve neurocognitive outcomes in those affected. This review aims at evaluating the available evidence and postulating further study direction in Singapore. **Materials and Methods:** A PubMed search was carried out for original articles and systematic reviews on the subject of HIV-associated neurocognitive disorders, and the results reviewed by the authors. **Results:** There is a growing body of evidence that HAND is not uncommon, and the advent of highly active anti-retroviral therapy has increased its prevalence by improving the prognosis of HIV infection, and hence increasing the likelihood of diagnosing of this neurocognitive condition. Screening and diagnosing HAND is important, and requires clinical suspicion as well as validated test batteries for optimal accuracy. The authors recommend strategies for detection in the local context involving stepwise targeted screening. Anti-retroviral agents with good CNS penetration and activity, as well as adjunctive neuro-rehabilitative interventions, may improve the impairments experienced by affected individuals. **Conclusion:** Increased awareness of HAND, with earlier diagnosis and targeted, multi-disciplinary management of this challenging condition, may lead to better all-round outcomes for people living with HIV and AIDS in Singapore.

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### HAND: A Historical Perspective

The spectrum of neurologic and psychiatric pathology in HIV-infected individuals is wide. AIDS-defining central nervous system (CNS) conditions are perhaps more readily recognised, and include opportunistic infections such as toxoplasma encephalitis, cytomegalovirus (CMV) encephalitis and progressive multifocal leukoencephalopathy (PML), as well as malignancies like primary CNS lymphoma. Psychiatric disorders are also more prevalent in the HIV-positive population, with higher rates seen of depression and anxiety disorders than in the general population, with an American survey finding that the prevalence of major depression and generalised anxiety disorder are nearly 5 and 8 times higher respectively in the HIV-positive population as compared to those without HIV.<sup>1,2</sup>

In the early days of the HIV epidemic, the literature was rich with accounts of patients with advanced AIDS

presenting with accelerated dementia who progressed from apathy, reduced concentration and impaired short-term memory to global dementia, loss of motor function and incontinence in the span of months—especially in the pre-combination anti-retroviral therapy (cART) era.<sup>3</sup>

The hypothesis that HIV-associated dementia was due to the neurotoxic effects of HIV itself, and not due to opportunistic infections, was already established in the mid-1980s.<sup>4</sup> The neuro-imaging features of global atrophy and cerebrospinal fluid (CSF) findings of lymphocytic pleocytosis, elevated protein levels and the presence of oligoclonal immunoglobulin (IgG) bands were also described then.<sup>5</sup> Even prior to the licensing of the first anti-retroviral drug, AZT (zidovudine), Booss and Harris had already postulated that “effective specific antiviral therapy [would have to possess] the capacity to penetrate the blood-brain barrier.”<sup>6</sup>

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## A Spectrum of Disease

In 1991, the Working Group for the American Academy of Neurology AIDS Task Force set out a classification that differentiated Mild Cognitive Motor Disorder (MCMD) from HIV-Associated Dementia (HAD). Both diagnoses were characterised by an acquired abnormality in at least 2 cognitive or behavioural domains that caused impairment in daily life and were not due to other aetiologies (infections, drugs, depression, etc.). The more severe HAD was further defined as causing significant impairment in the activities of daily living (ADLs) and in the workplace.<sup>7</sup> These disorders were found to predict shorter survival, even after statistically controlling for other HIV illness markers.<sup>8</sup>

The applicability of these criteria was restricted by a number of issues. There was significant overlap between mild HAD and MCMD and the number of domains that should be examined for diagnosis was not clearly defined. Milder forms of objective cognitive impairment that had not yet interfered with daily functioning had been convincingly shown in subsequent studies, but were not accounted for in the criteria.<sup>9,10</sup> There was also an increasing recognition of the frequency of confounding conditions that potentially act as compounding factors that were not adequately considered other than the simple exclusionary stipulation.

The Frascati criteria for the classification of HAND was published in 2007, and was developed primarily as an updated research nosology for the disease entity by the HIV Neurobehavioural Research Centre (HNRC) in response to these issues and rapidly emerging research findings. It defined clearly that HAND would be based on impairments in at least 2 of 7 domains: attention and information processing, language, abstraction and executive function, complex perceptual motor skills, memory (learning and recall), simple motor skills, and sensory perceptual abilities.<sup>9</sup>

Asymptomatic neurocognitive impairment (ANI) was defined as performance of at least 1 standard deviation (SD) below the mean in at least 2 cognitive areas, with no observed and subjective impairment in everyday function, and that was not due to delirium or other organic causes. Mild neurocognitive disorder (MND) is marked by mild to moderate impairment (at least 1 SD below the mean) in at least 2 domains, with observed and reported interference with work or ADLs, while PLWHAs with HAD have moderate to severe impairment (at least 2 SD below the mean), with marked difficulties in ADLs and work (Table 1). The addition of the ANI category gave the criteria improved positive predictive power, sensitivity and specificity, and had some prognostic significance.<sup>10,11</sup>

Table 1. Updated Research Nosology for HIV-Associated Neurocognitive Disorders<sup>9</sup>

	Neuropsychological (NP) Testing is available	NP Testing not available
<b>Asymptomatic Neurocognitive Impairment (ANI)</b>	NP impairment in > 2 cognitive domains that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects. No reported or demonstrated functional decline.	Mental Status Exam (MSE) impairment involving >2 cognitive domains, that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects. No reported or demonstrated functional decline.
<b>Mild Neurocognitive Disorder (MND)</b>	At least mild NP impairment (>1 SD below a demographically appropriate normative mean), involving >2 cognitive domains that cannot be explained by confounding conditions. AND Reported or demonstrated mild functional decline that cannot be explained by confounding conditions.	At least mild MSE impairment (>1SD below a demographically appropriate normative mean), involving >2 cognitive domains, that cannot be explained by confounding conditions. AND Reported or demonstrated mild functional decline that cannot be explained by confounding conditions.
<b>HIV-Associated Dementia (HAD)</b> <b>Note: Severity of NP impairment and functional decline must both meet these standards in order to diagnose the person as having HAD. If either NP impairment or functional decline is mild, the condition should be classified as MND.</b>	> Moderate NP impairment (>2SD below a demographically appropriate normative mean) on > 2 cognitive domains.* Impairment cannot be explained by confounding conditions. AND Reported or demonstrated major functional decline that cannot be explained by confounding conditions. *Alternatively, one domain could be more severely impaired (>2.5 SD below the mean) and another less severely impaired (>1 SD below the mean)	> Moderate MSE impairment (>2SD below a demographically appropriate normative mean), involving >2 cognitive domains, that cannot be explained by confounding conditions. AND Reported or demonstrated major functional decline that cannot be explained by confounding conditions.

- The neuropsychological assessment should at least survey 5 of the following: verbal/language, attention/working memory, abstraction/executive, memory (learning, recall), speed of information processing, sensory-perceptual, motor skills.
- The impairment does not occur solely as part of delirium, and cannot be adequately explained by other comorbidities.
- If HAND is suspected in an individual who also meets criteria for major depressive episode or substance dependence, the diagnosis should be deferred to a subsequent examination at a time of remission from major depression or at least 1 month after cessation of substance use.

This criteria appears to be in line with the proposed revisions regarding the classification of cognitive disorders in DSM-V (Diagnostic and Statistical Manual of Mental Disorders), where the requirement for memory impairment is eliminated and “cortical” abnormalities such as aphasia, apraxia and agnosia are de-emphasised. Also, the 2 criteria are consistent in the requirement that cognitive decline be confirmed by objective patient assessment whether using standardised bedside assessment or formal neuropsychological assessment, as opposed to only by history.<sup>12</sup> However, the DSM revisions categorise cognitive disorders as Major Neurocognitive Disorder and Minor Neurocognitive Disorder based on whether functional independence is affected. Hence, there appears to be difficulty in classifying ANI and MND with the proposed revised DSM criteria.

### The Pathophysiology of HAND

The defects of HAND are primarily subcortical, involving (but not limited to) psychomotor speed, information processing and executive function, as well as memory. The disease may then progress to deeper grey-matter structures including the caudate nucleus, causing deterioration in cognitive ability; and the nucleus accumbens, resulting in apathy and abulia. If allowed to further worsen, extrapyramidal motor effects may develop, representing basal ganglia disease.<sup>12</sup> The diagnosis of HAND has conventionally required the exclusion of pre-existing neurobehavioural pathologies or strongly confounding conditions which may afflict HIV-infected individuals. These include the spectrum of disturbances resulting from neural damage to cortical structures mediating the emotional and behavioural problems (e.g. depression, anxiety, sleep disorders, psychosis and mania) that are prevalent in the HIV-positive population but which do not fit diagnostic criteria for HAND.<sup>13</sup> This significant overlap underlines the difficulty in arriving at a diagnosis of HAND and efforts at subsequent therapy.

A large body of evidence now exists that demonstrates that HAND is not a result of direct damage to neurons by HIV, but rather by inflammation mediated by HIV-infected macrophages and microglial cells in the CNS.<sup>14</sup> These infected cells pass from the peripheral circulation into the CNS via the blood-brain barrier (BBB); they then effect neurotoxicity through the action of viral proteins (e.g. gp120, tat, etc.), as well as cause dysregulation of cytokine release and increase the oxidative stress within the CNS milieu.<sup>15,16</sup> This barrage of abnormal signals then causes impaired regulation of neuronal genes, especially those maintaining normal neuronal cytoskeleton, leading to neuronal damage and loss. This process persists throughout the entire lifespan of the neuron, affecting immature and

mature neurons alike – and the more prolonged the period of unsuppressed viral replication, the greater the extent of damage.<sup>14,17</sup>

Pathologic examination of affected brains in autopsy reveal characteristic multinucleated giant cells and multifocal dendritic loss, gadolinium-contrasted MRI of the brain shows global cerebral atrophy out of proportion to age, and diffuse white and grey matter changes (differentiating it from PML).<sup>12,18</sup>

### HAND—Incidence and Prevalence

The prevalence of HAND in the HIV-infected population has been extensively studied in recent years in a variety of different settings, with fairly consistent findings. Heaton et al found that in a predominantly Caucasian and well-educated cohort, the prevalence of ANI was 33%, MND was 12% and HAD a minority at 2%.<sup>17</sup> This correlates well with historical findings based on the older 1991 classification—with roughly a quarter of PLWHAs showing neuropsychiatric impairment without subjective complaints, and less than 2% exhibiting symptoms and signs meeting criteria for HAD, with these proportions being similar throughout the CDC classes of immunocompromise.<sup>18</sup>

Local data from Chan et al show that in a cohort of 132 HIV-infected individuals, 22.7% displayed any degree of HAND. Of these, 70% had ANI, less than a quarter had MND, and a small minority (6.7%) had HAD.<sup>19</sup> This was in keeping with other Asia-Pacific studies, including Thailand, Australia and Cambodia.<sup>20</sup>

The incidence of HIV dementia has been shown to have decreased following the introduction of HAART, but with improved survival, the prevalence of all forms of cognitive impairment may have actually increased.<sup>21</sup>

### HAND—Diagnostic Pitfalls and Barriers

The diagnosis of HAND is challenging for several reasons. First and foremost, it remains a diagnosis of exclusion, and is predicated on ruling out the presence of other CNS pathologies like CNS-involving opportunistic infections, pre-existent mood and psychotic disorders and the use of psychotropic substances (whether prescribed or illicit). What's more, it is important to bear in mind that HIV infection does not preclude the development of other, non-AIDS-defining comorbid conditions that may result in neurocognitive insult, such as hypothyroidism, Parkinson's disease and metabolic disorders.

Secondly, the under-diagnosing and under-reporting of HAND are likely due to a low threshold of suspicion for the condition on the parts of both physicians and patients alike. This may be because the majority of those affected

are asymptomatic with no problems coping at work or at home, and hence do not present to their physicians with any cognitive complaints (such as worsening memory and slowing of thoughts). Many patients who do subjectively observe these impairments may not volunteer them to their physicians, whether it is due to fear of the stigma of cognitive impairment or the reluctance to undergo extensive and often expensive, investigation and possible treatment.

Healthcare workers themselves have a low level of awareness of HAND and hence may not suspect that their patients may actually be affected. By being unaware of the significance of HAND and its implications for the management of HIV/AIDS as a whole, there is a consequent lack of widespread training in the diagnostic process and management of HAND. Practical issues may also mar the adoption of universal screening for HAND in HIV-infected patients: the process is time-consuming in its entirety, and places demands on space and manpower, which may be difficult especially in resource-limited populations.

Recommendations for Detection of HAND

The European AIDS Society 2011 guidelines recommend routine screening at diagnosis and every 2 years thereafter, using screening questions to elicit patients’ subjective report of their cognitive functioning.<sup>22</sup> A panel of experts from Asia, Australia and Middle East (AAME HAND Advisory Board) has also come up with recommendations for routine screening of all newly-diagnosed HIV cases.<sup>23</sup> (Table 2, unpublished data)

Table 2. Stepwise routine screening for HAND (AAME Advisory Board)

<ul style="list-style-type: none"><li>• Screen all newly-diagnosed HIV cases for CNS confounding conditions</li><li>• Screen for depression and refer to psychiatrist if positive</li><li>• If negative for depression or depression in remission, screen for cognitive impairment using recommended tools</li><li>• If positive, refer for full neuropsychological testing to confirm presence of HAND; if negative, repeat screening process every 6 months or if symptoms reported</li></ul>
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With an expected local prevalence of 1 in 4 to 5 HIV patients, there does appear to be an indication for routine screening of all HIV-positive patients. However, the same local study by Chan et al also found that the majority (70%) of the HAND cases were asymptomatic, and did not report subjective impairment on a standardised questionnaire.<sup>19</sup> Furthermore, current manpower and logistic resources are inadequate to initiate routine cognitive surveillance for all patients. Hence, we postulate that targeted screening done on the basis of clinical suspicion is likely to be more useful (Table 3).

The local study by Chan, et al also provided useful information to generate a demographic and clinical profile of an HIV-positive patient who is at risk of suffering from HAND.<sup>24</sup> A high-risk patient is usually older (mean of 54 years), has had fewer years of formal education (mean of 8 years), and is more likely to present with very low CD4 (<200) counts at diagnosis. Other risk factors that are probably clinically important but did not reach statistical significance in the study are a history of CNS-involving opportunistic infections and the presence of comorbid vascular risk factors.<sup>19</sup> Other international studies have shown that HAND is also associated with current or previous use of stimulant drugs, HIV Clade-C, evidence of viral resistance as well as co-infection with Hepatitis C, and low nadir CD4 count.<sup>24-26</sup> Risk profiling of HIV patients will identify the ones for whom cognitive testing is indicated and likely to be positive.

Table 3. Suggested Stepwise Targeted Screening for HAND

<ul style="list-style-type: none"><li>• Evaluate individual risk profile for HAND<ul style="list-style-type: none"><li>◦ Higher age (&gt;44 years)</li><li>◦ Lower educational level (&lt;6 years formal education)</li><li>◦ CD4&lt;200 nadir or at diagnosis</li><li>◦ History of CNS opportunistic infections</li><li>◦ Comorbid vascular risk factors</li><li>◦ Past or present substance use</li><li>◦ HIV Clade-C</li><li>◦ Co-infection with Hepatitis C</li><li>◦ Evidence of viral resistance</li></ul></li><li>• Screen cognition using MOCA (cutoff 26/27)<sup>33</sup> and IHDS (cut-off 10)<sup>32</sup> and measure functional impairment</li><li>• Refer to psychiatrist and/or neurologist to exclude other neuropsychiatric causes of cognitive impairment</li><li>• Select appropriate patients for formal neuropsychological testing</li><li>• Make a clinical diagnosis in the absence of formal testing and proceed with treatment</li></ul>
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Even though the Singapore CDC study showed that the majority of the study population were asymptomatic, it should be noted that this may be due to the use of the Lawton’s scale to measure functional impairment, which only measures function in terms of instrumental activities of daily living and not occupational functioning.<sup>26</sup> Cumulative clinical experience shows that complaints of functional decline at work are not only more common than complaints of a decline in ADLs, but also significantly impact daily psychosocial functioning. A detailed history of previous occupational functioning and current problems is also necessary for the next step in the evaluation of a patient for HAND.



When managing a HIV-positive individual with neurologic, cognitive or functional complaints, it is useful to work together with a psychiatrist and/or neurologist whose role would be to exclude neuropsychiatric causes that may mimic HAND, such as depressive pseudodementia and other causes of early-onset dementia. Their input is especially useful in challenging cases where the presentation is atypical, a detailed history is difficult to obtain, the patient is unable to undergo cognitive testing, or there may be multiple contemporaneous diagnoses contributing to cognitive impairment.

According to current diagnostic criteria, HAND is diagnosed, and subtypes differentiated, by formal neuropsychological testing of specified domains. However, the working group from which the criteria originated also allow for the use of short, standardised cognitive tests in resource-limited settings. These abbreviated batteries are useful so long as locally validated cutoff scores are available for meaningful interpretation, and there was evidence of impairment in at least 2 cognitive domains in keeping with the full diagnostic criteria.<sup>9</sup> Singapore presents a unique quandary in the field of HAND management because while formal neuropsychological testing is easily available (albeit in non-integrated settings), it is common clinical experience that many patients are unwilling to return and pay for separate visits for such assessments. In addition, undergoing the full battery of tests, which may last up to 3 hours, is either unsuitable or intolerable for many individuals. Hence, there is a need to balance the need for diagnostic precision with clinical practicalities.

In the selection of the appropriate method of cognitive testing, one needs to consider specific test factors, individual patient factors and rater qualifications. (Table 4)

Table 4. Selection of appropriate cognitive test

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- Patient factors
    - Language, educational level
  - Test factors
    - Domains tested, domains not tested, validity in local population
  - Rater expertise
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The Abbreviated Mental Test (AMT),<sup>27</sup> Mini Mental State Examination (MMSE),<sup>28</sup> Montreal Cognitive Assessment (MOCA)<sup>29</sup> and Frontal Assessment Battery (FAB)<sup>30</sup> are currently in common clinical use in our local setting as they have been validated locally.<sup>31,32</sup> It has previously been shown that for local Chinese elderly persons with less than 6 years of formal education, the AMT is useful to screen for dementia, whereas the MMSE is more useful for those with more than 6 years of formal education. However, the

AMT has so far not been used for evaluation of HAND and the MMSE has been shown to have low sensitivity and specificity for HAND.<sup>33</sup> The utility of the FAB in HAND has also not been investigated so far.

The MOCA appears to be the most useful in elucidating type and more subtle degrees of dysfunction as it was designed to screen for Mild Cognitive Impairment and has been validated locally for MCI of the amnesic type.<sup>34</sup> It has also been validated in other languages.<sup>35</sup> Its other strength is that it is likely to be useful for more highly-educated individuals, while at the same time allowing for score adjustment for those with less than 12 years of formal education. Recent studies have attempted to validate its use in the HIV population, but have shown unsatisfactory sensitivity and specificity.<sup>36</sup> However, there seems to be a suggestion that the sensitivity of the MOCA for HAND can be improved by using it in combination with other cognitive tests.<sup>37</sup>

The local CDC study assigned cases of HAND using scores below the cutoff on either the MOCA or International HIV Dementia Scale (IHDS) in addition to evidence of impairment in at least 2 cognitive domains. The IHDS is still in the process of being validated in Singapore but its combination with MOCA proved to be useful as it ensured that sufficient cognitive domains were tested in accordance with HAND criteria without significantly increasing the test duration. They were also acceptable and well-tolerated by patients in terms of the language used and test duration. The combination of MOCA and IHDS is also useful because they are easy to administer without the need for lengthy training in its administration and the scores (both total and domain-specific) are easy to interpret. These qualities are very likely to be important to the clinicians as well. The AAME HAND Advisory Board has also recommended the use of these 2 tests for the screening and evaluation of HAND.<sup>22</sup>

There still remains a role for formal neuropsychological testing to confirm the diagnosis and severity of HAND in those that have been screened positive. However, mood, mental state and motivational factors may affect test performance and individual tests making up the full battery also depends on the training of the neuropsychologist and the patient's demographic profile, thus affecting comparisons between patients. Neuropsychological testing is more likely to be useful for diagnosing previously high-functioning and highly-educated individuals for whom the short standardised tests may not be sensitive enough to detect impairment. It is also more useful in detecting longitudinal change in individuals, as significant practice effect needs to be considered in the repetitive use of the standardised tests.

## HAND – Treatment Strategies

With the current understanding that the pathophysiology behind the development of HAND is primarily that of the deleterious effects of HIV within the CNS compartment, the prevailing hypothesis is that increased penetration of cART into the CNS would lead to an improvement in cognitive function. This increased drug penetration through the blood-brain barrier is reflected in a higher measured CSF level of the drug in question. This concept of the compartmentalisation of HIV in the CSF as a driver of HAND is further supported by the demonstration that cognitive dysfunction persists despite longstanding peripheral viral suppression.<sup>38</sup>

Letendre et al developed a system for evaluating the CNS Penetration-Effective (CPE) rank of the available agents in the cART armamentarium.<sup>39</sup> This was recently updated in 2010, with 4 scores now used (1 to 4, in increasing order of CNS penetration (Table 5).<sup>40</sup> The overall CPE rank of the cART regimen is then derived by the summation of the individual drug scores. CSF drug levels were found to be correlated to the degree of viral suppression in the CNS, with the use of high CPE rank agents like AZT and nevirapine associated with a lower detectable CSF HIV viral load.<sup>41</sup>

However, it should be noted that the pharmacokinetics of drugs in the CNS is complex and CSF drug levels do not equate to, and in fact overestimate, levels in brain targets.<sup>42</sup> This has been demonstrated with AZT (zidovudine).<sup>43</sup> There is also conflicting evidence regarding the therapeutic value of “neuroactive” cART: CNS viral suppression does not correlate with cognitive improvement and cognitive improvements do not translate to improved overall survival.<sup>44–49</sup>

Hence, there is still a lack of consensus on the optimal pharmacologic treatment for HAND. Current guidelines for the treatment of HIV (World Health Organisation,

European AIDS Clinical Society 2011, and United States Department of Health and Human Services 2012) do not take into account CPE rank in their recommendations for first-line treatment regimens, nor do they unequivocally suggest specific drugs or combinations for use in the context of HAND. However, there is much ongoing research in the US and Europe investigating the use of high CPE rank regimens (usually taken to be 7 or above) and their effect on neuropsychiatric function. Initiating, or switching to more neuro-active regimens in patients with or at risk of HAND may well be routinely recommended in the future.

Beyond the practice of optimisation of regimes, interim data from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study by the HIV Neurobehavioral Research Centre also presented evidence that the early initiation of cART in all patients led to a lower overall risk for the development of HAND. Virologic suppression and immune reconstitution with high CD4 counts were independent protective factors for HAND, while the risk of HAND was highest in those subjects whose CD4 nadir was the lowest, corresponding to a deferment of treatment initiation.<sup>25</sup> Timely treatment holds promise for the primary prevention of HAND, and hence the reduction of the all-cause morbidity associated with HIV/AIDS.

Management of the functional deterioration due to HAND should be multi-disciplinary. Pharmacologic strategies are targeted at the pathophysiologic basis of disease, but rehabilitation should be instituted to improve function. This comprises direct neuro-rehabilitation, aimed at improving cognition and memory, as well as occupational and physical therapy to ameliorate the gross psychomotor and fine, complex motor deficiencies that may arise due to HAND.<sup>50</sup>

Psychosocial interventions should also be given priority. Becker et al have found that neurocognitive impairment

Table 5. Central Nervous System Penetration Effectiveness Scoring for Antiretroviral Drugs<sup>39</sup>

Agent Type	4 (very good)	3 (good)	2 (fair)	1 (poor)
Nucleoside Reverse Transcriptase Inhibitor	Zidovudine	Abacavir	Didanosine Lamivudine Stavudine	Tenofovir
Non Nucleoside Reverse Transcriptase Inhibitor	Nevirapine	Efavirenz	Etravirine	
Protease Inhibitor	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitor		Maraviroc		Enfuvirtide
Integrase Inhibitor		Raltegravir		

is associated with reduced adherence to treatment, with subsequent increased risk of treatment failure and the development of AIDS-associated morbidity.<sup>51</sup> This may be mediated by worsening memory, apathy, or a general reduced ability to organise tasks and manage the demands of HIV treatment. This impairment in higher functioning and information processing also leads to difficulties in managing finances, ensuring regular meals and the acquisition and maintenance of stable housing—all of which have direct, significant impact on the capacity of the patient to stay healthy.<sup>52</sup>

Heaton et al found that neuropsychological impairment due to HIV rendered sufferers twice as likely to be unemployed.<sup>53</sup> This risk was highest when the domains affected were short-term or episodic memory, and psychomotor impairments, and was compounded by the fact that unemployment led to a resultant increased risk of depression.

## Conclusion

There is a growing importance for the detection and management of HAND in the holistic management of HIV/AIDS. The shift towards earlier initiation of ART at higher CD4 levels is based on a growing body of evidence that this strategy may reduce morbidity and mortality, and may have repercussions for the prevention of HAND as well. Early treatment with greater CNS activity, and ensuring adherence, appear to confer benefits in neuropsychiatric performance, improve function and quality of life, and improve all-round morbidity in HIV-infected individuals. Incorporating these principles into established treatment guidelines should increase awareness of the condition, and empower patients and physicians alike to diagnose and manage this aspect of HIV/AIDS.

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