

## NEUROCOGNITIVE IMPAIRMENT IN PLWHA: CLINICAL FEATURES AND ASSESSMENT

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Neurocognitive impairment (NCI) occurs in 10 - 60% of people living with HIV/AIDS (PLWHA), depending on the severity of the NCI and the stage of the disease. The clinical features and definitions have evolved over the past two decades. HIV-associated neurocognitive disorder (HAND) is a new term used to describe the spectrum of neurocognitive impairment seen in HIV/AIDS. The earliest to most advanced stages are asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND) and HIV dementia (HAD), respectively. People with HAND have impairment on multiple cognitive domains, including attention, concentration, memory, executive function, motor functioning and speed of information processing, and sensory perceptual/motor skills deficits. The milder forms of HAND are easily missed. Diagnosis can be made on clinical grounds in the most severe cases; however, milder forms and confirmation of the diagnosis require neuropsychological testing. Screening tests have limited utility, especially in the milder forms of HAND. Individual subtests derived from longer neuropsychological batteries may be complementary in the diagnosis of HAND. Highly active antiretroviral therapy (HAART) has led to a 40% decline in the incidence of HAD. In the post-HAART era, HAD runs a more chronic course, is milder and is reversed in about a third of cases. However, HAART is not universally successful because incident cases occur in people on HAART. Overall HAART has been shown to be of benefit, and screening for HAND should be the standard of care for PLWHA. HAD is an AIDS-defining illness and patients qualify for HAART irrespective of their CD4 count. However, the benefit of starting ARVs for people with ANI and MND is currently inconclusive.

HIV infection of the central nervous system occurs almost simultaneously with systemic infection. Primary neurological disorders can affect the brain (e.g. HIV-associated dementia), spinal cord (e.g. HIV-associated vacuolar myelopathy) and meninges.<sup>1</sup> HIV-associated dementia (HAD) has also been referred to as HIV encephalopathy or AIDS dementia complex. These terms have been used interchangeably and describe a syndrome that includes the symptom triad of psychomotor slowing, memory impairment and behavioural problems. We now understand that neurocognitive impairment (NCI) in HIV is a spectrum of disorders.<sup>2</sup> In addition to HAD, lesser forms of NCI have also been described, namely HIV-associated minor cognitive-motor deficit (now called mild neurocognitive disorder) and asymptomatic neurocognitive impairment (ANI).<sup>3</sup> These disorders now fall under the new term HIV-associated neurocognitive disorder (HAND) (Table I). The diagnosis of HAND requires a history, clinical examination, appropriate investigations and neuropsychological testing. This review presents the clinical features, diagnostic criteria and tools to help diagnose HAND.

people is partly or wholly due to the direct effects of HIV, to secondary effects from the chronic hyperimmune activation, to other immunological factors (e.g. cytokines, chemokines and tumour necrosis factor) in the CNS, or to other factors such as hepatitis co-infection and clade diversity. However, it is understood that:<sup>4</sup>

- HIV does not infect the neurons and oligodendrocytes but the monocytes, microglia, astrocytes and endothelial cells.
- Once in the CNS the virus persists and evolves into different strains independent of the systemic reservoir.
- HIV is not evenly distributed in the CNS, and has a predilection for the basal ganglia.
- HIV RNA levels in the cerebrospinal fluid do not correlate with those in the peripheral circulation, especially in advanced HIV disease.

Involvement of the basal ganglia accounts for the clinical distinction between 'subcortical dementia' seen in HAD and the 'cortical dementia' typically seen in Alzheimer's disease.

### PATHOGENESIS

HIV neuropathogenesis is not fully understood. It is unclear whether the cognitive decline seen in HIV-infected

### EPIDEMIOLOGY

HAD occurs in approximately 10 - 15% of all individuals with HIV/AIDS and is more common in late stages

TABLE I. CRITERIA FOR HIV-ASSOCIATED NEUROCOGNITIVE IMPAIRMENT\*

	Asymptomatic neurocognitive deficit (ANI)	Minor neurocognitive disorder (MND)	HIV-associated dementia (HAD)
Level of impairment	None	Mild everyday activities: reduced mental acuity, inefficiency in work, homemaking or social activities affected	Marked impairment in day-to-day activities at work, home or social functioning
Number SD below population norm on neuropsychological test	1		2
Number of domains impaired	2 Attention/working memory; verbal/language; abstraction/executive; complex perceptual motor; memory (learning and recall); speed of information processing; sensory perceptual/motor skills		
Exclusion criteria	Absence of criteria for delirium or other causes for dementia. The condition cannot be explained by another co-morbid condition, e.g. substance abuse, infections, pre-existing neurological condition		
*Summarised from Antinori <i>et al.</i> <sup>3</sup>			

of infection.<sup>1</sup> Less severe forms of HAND occur in 30 – 60% of people infected with HIV, depending on the stage of the disease.<sup>1</sup> Approximately 17% of the people attending a highly active antiretroviral therapy (HAART) primary health clinic in Cape Town had some level of NCI, including HAND.<sup>5</sup> The epidemiology of NCI has changed distinctly with the introduction of HAART. In the pre-HAART era HAD was common and more severe, with death likely within 6 months of diagnosis.<sup>6</sup> The introduction of HAART led to a major decline in the incidence of HAD.<sup>1,6,7</sup> However, data from cohorts on long-term HAART in the USA show that incident cases of HAD occur despite HAART, that progression of HAD is variable, and that NCI seems to be milder.<sup>1</sup> The overall prevalence of HAND continues to rise, presumably owing to incomplete reversal or prevention of cognitive impairment, longer survival on HAART and an increasing HIV prevalence.

At present there are no guidelines that recommend specific HAART regimens for the treatment or prevention of HAND. However, epidemiological data suggest at least partial benefit in giving HAART to prevent and reverse HAND.<sup>7-9</sup> HAD is an AIDS-defining illness and people with HAD qualify for HAART irrespective of CD4 counts. There is therefore an urgent need to raise awareness and develop rapid screening tools to detect and monitor HAND.

### CLINICAL FEATURES

Most clinicians can recognise frank HAD, but the more subtle HANDs are easily missed. HAND is: (i) a cognitive disorder, accompanied by (ii) motor dysfunction and/or (iii) behaviour problems.

**Cognitive changes** are problems with memory, decreased attention and concentration. These patients have decreased ability to learn new information and

the speed at which they process information and mental tasks is slower than normal. Executive functioning, which includes planning, impulse control, organisation, abstract thinking and judgement, is also affected.

**Motor changes** are more subtle and are often missed. Patients complain of changes in their handwriting, tremor, and 'clumsiness'. They have gait abnormalities in the late stages.

**Behaviour problems** vary and range from aggression or marked isolation to the vegetative state seen in the late stages when patients are mute, immobile and incontinent. The presentation is similar to that of severe depression, because patients appear very apathetic and amotivated, with lack of initiative and psychomotor slowing.

The new classification requires systematic assessment of the following six domains:<sup>3</sup> (i) attention-information processing; (ii) language; (iii) abstraction/executive; (iv) complex perceptual motor; (v) memory; and (vi) sensory perceptual/motor.

Assessment of these domains requires neuropsychological tests that are often not intuitive to the clinician. Most clinicians can test memory with 'bedside' tests; however, assessment of executive functioning and psychomotor speed is more difficult. The challenge is to translate these research criteria and recommend specific tests that can be widely used by non-neuropsychologists. We can recommend a few tests that can assess these various domains (Table II).

The distinction between ANI, MND and HAD depends on: (i) the severity of impairment (when compared with population age- and education-appropriate norms for the above domains); and (ii) level of functional impairment in everyday activities at work, home or socially.

TABLE II. SELECTED NEUROPSYCHOLOGICAL TESTS AND THE DOMAINS ASSESSED

Neuropsychological test	Description	Domains assessed
Rey Auditory Verbal Learning Test	Recall as many words as possible from a list of 15 words	Memory
Grooved peg-board		Motor
Digit span forward	Patient is given an increasing number of random digits. They must repeat digits in the same order	Attention and concentration
Digit span backward	Patient is given an increasing number of random digits. They must repeat the digits in reverse order	Attention, concentration and working memory
Trail making test A	Join 25 circles with numbers in the correct sequence as quickly as possible. The numbers are distributed across the page and are not in order	Motor and speed of information processing
Trail making test B	Join 25 circles with numbers and letters in alternating sequence, i.e. join 1, A, 2, B, 3, C as quickly as possible	Motor and speed of information processing and executive function

#### ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT

This is the mildest form of HAND. The person has no impairment in everyday activities. They may complain of mild slowing in mental acuity and loss of concentration. Abnormalities can only be detected by testing the six domains and comparing against population norms. Patients must have 1 standard deviation (SD) abnormality on two of the six domains. ANI can progress to the next stage in the spectrum of HAND.

#### MINOR NEUROCOGNITIVE DISORDER

MND was previously called HIV-associated minor motor-cognitive disorder. MND has the same criteria as ANI, i.e. the patient has 1 SD abnormality on two of the six domains. Unlike patients with ANI, they have impairment in their daily activities, at work or in social functioning or homemaking. This can be by self-report or by observation by someone who knows the patient.

#### HIV-ASSOCIATED DEMENTIA

HAD is the most severe form of HAND. By definition patients have at least 2 SD abnormality on two domains, and these deficits cause significant impairment in everyday activities.<sup>3</sup> However, the clinical presentation can vary widely. In early HAD, the patient may appear depressed with apathy, lethargy and social withdrawal. Personality changes are not uncommon, and are often reported more by others than by the patient. In late HAD, psychotic symptoms may be prominent along with severe language dysfunction, verbal memory loss, seizures and mutism. The patient may be incontinent of urine and stool.

Neurological examination may show interruption of smooth ocular pursuit, slowing or inaccuracy of saccades, hyper-reflexia, 'frontal release' signs, slowing of rapid alternating movement of fingers, wrist or feet, and ataxia.

In the post-HAART era the progression of HAD has changed. Based on clinical observation of long-term

treatment cohorts, three sub-types of HAD have been defined:<sup>7</sup>

1. **Sub-acute progressive dementia** occurs in ARV-naïve people and has a course similar to that observed in the pre-HAART era.
2. **Chronic active dementia.** These patients are on treatment but have poor adherence leading to viral resistance. They are at risk of developing other neurological complications.
3. **Chronic inactive dementia** occurs in people who are adherent to HAART and have undetectable viral loads. They have some recovery from neuronal injury and are neurologically stable.

#### CLINICAL WORK-UP FOR HAND

HAND is a diagnosis of exclusion. Other diseases that affect CNS functioning, i.e. opportunistic infections, neoplasms, metabolic disturbances and iatrogenic complications, have to be systematically ruled out. Delirium and substance use are common in HIV-infected patients. Appropriate first-line investigations, e.g. a full blood count, assessment of kidney, liver and thyroid function, measurement of the vitamin B<sub>12</sub> level and serological testing for syphilis, are necessary. Lumbar puncture is also useful to exclude other opportunistic infections. The CSF viral load is not useful in the diagnosis of HAND and does not correlate with the severity of the impairment. Neuro-radiological investigations, e.g. computed tomography and magnetic resonance imaging, are necessary to exclude conditions such as progressive multifocal leuco-encephalopathy and primary CNS lymphomas that can mimic HAND. However, in resource-constrained settings these investigations are not readily available and they are not vital in the absence of focal localising signs.

With delirium and medical causes excluded, the diagnosis of HAND requires testing of the six domains using neuropsychological tests. However, these are often impractical or not available in busy clinical settings. Two-stage

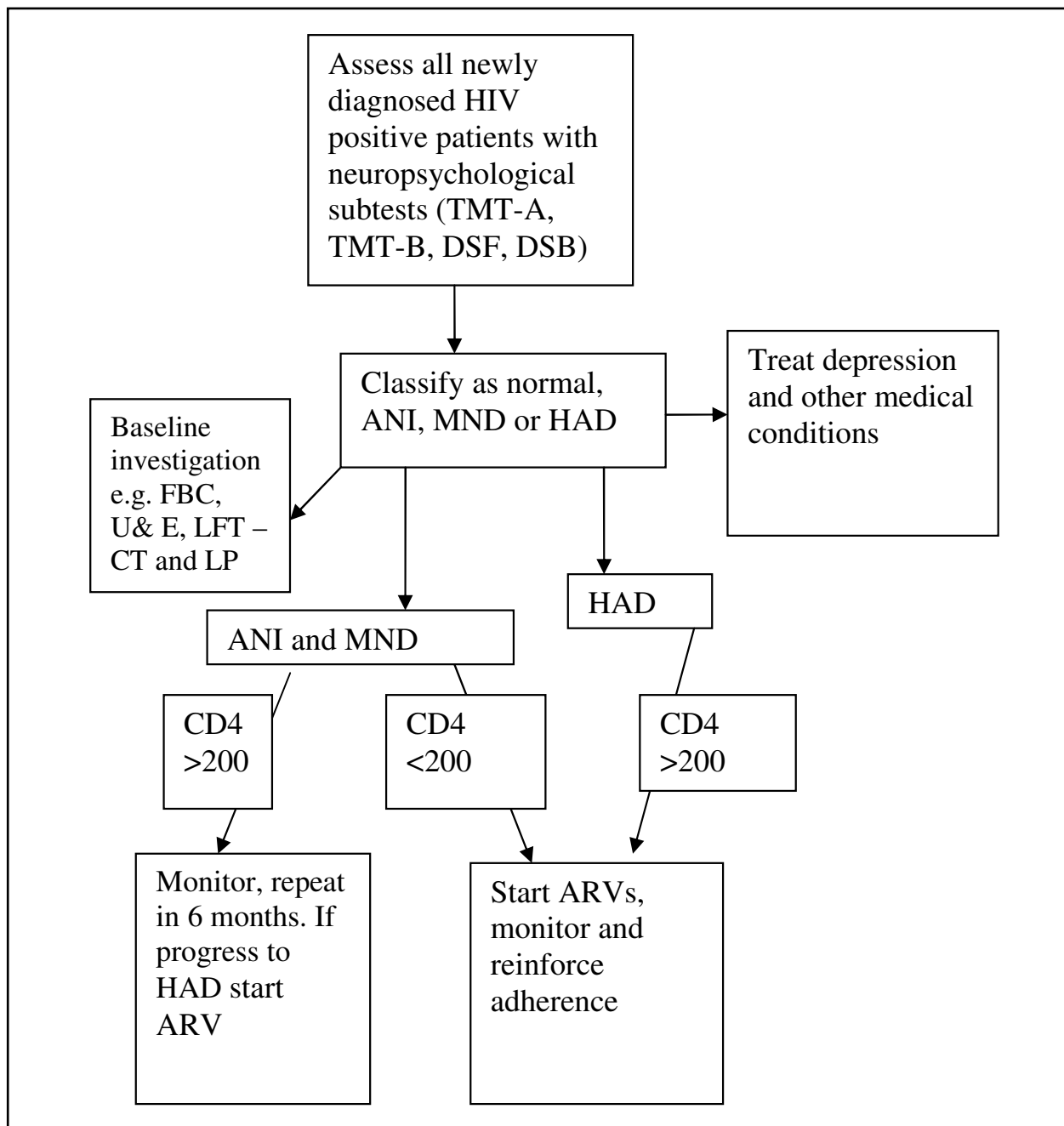


Fig. 1. Summary assessment and management of neurocognitive function in newly diagnosed PLWHA.

testing is commonly used in psychiatry. In the first stage a brief, bedside cognitive screening test is administered and people who screen positive can then be subjected to more detailed testing in the form of a neuropsychological battery. See Fig. 1 for algorithm for assessing and managing newly diagnosed patients with HIV.

#### COGNITIVE SCREENING WORK-UP

**The Mini-Mental State Examination (MMSE)** was validated for distinguishing Alzheimer's dementia from other dementing disorders.<sup>10</sup> It is loaded with items that are representative of 'cortical' functions. Since HAND is primarily affects sub-cortical processes, the MMSE is not ideal. It is not useful in detecting the milder forms of HAND, and it is affected by age, education and cultural background.<sup>11</sup>

**The HIV Dementia Scale** comprises four items – an anti-saccadic eye movement error task, timed alphabet, verbal memory and copying a cube.<sup>12</sup> Two of these items are timed and therefore more sensitive to sub-cortical functions. This scale has been used in the USA<sup>13</sup> and validated in South Africa.<sup>5</sup> However, observing the anti-saccadic eye movement requires training and is difficult for non-neurologists to administer.<sup>14</sup>

**Mental alternation test.** Patients are asked to count to 20, say the alphabet, and then alternate between the numbers and letters in the following fashion: '1-A, 2-B, 3-C ...!' Progressing from the most recent number or letter to the next letter or number in the sequence is one alternation. The number of correct alternations in 30 seconds, discounting any errors, determines the

score. The maximum score is 52 points, and a score of  $\leq 15$  indicates the need for more extensive cognitive testing. This tests a limited number of cognitive domains and is dependent on level of education.<sup>15</sup>

**International HIV Dementia Scale (IHDS).** The IHDS was tested in the USA and Uganda and developed specifically for resource-constrained settings.<sup>14</sup> It has three subtests: timed alternating hand sequence, timed finger tapping, and recall of four items after two minutes. This test has many advantages over its predecessors: it is brief, it can be completed in 2 – 3 minutes, and the patient does not need knowledge of English. It can be performed by non-neurologists and does not require any special equipment other than a stop-watch. The recommended cut-off score of 10 had 80% sensitivity and 55% specificity in the Ugandan study.<sup>14</sup> The specificity declines rapidly with small increment changes in the score, and this may limit its utility. While it has many advantages, validation studies are needed for our local population.

**Neuropsychological battery.** Various neuropsychological test batteries have been proposed. Longer batteries may take as long as 9 hours and brief batteries as little as 1 – 2 hours. Further, the absence of local population norms may limit their utility.<sup>16</sup> Work to develop brief, normed bedside tests is underway (Singh *et al.* – unpublished data) focusing on the separate domains of memory and recall, attention and working memory, speed of information processing, executive functioning, and motor abnormalities. We have collected population norms for the following bedside tests: digit span forward, digit span backwards, trail making test A and trail making test B. While these tests require training to conduct and are likely to be beyond the reach of a busy primary care HIV clinical service, they have an important role to play as part of specialist referral to diagnose HAND.

## TREATMENT

### ANTIRETROVIRAL THERAPY

HAART has lowered the incidence of HAND and improved patient outcomes, but HAART is not universally successful in reversing or preventing HAND.<sup>1</sup> While HAART can effectively suppress viral replication in the systemic circulation, its pharmacodynamics and effects on the virus in the CNS are less clear. ARVs, especially protease inhibitors, do not cross the blood-brain bar-

rier easily and do not achieve significant levels in the CSF. There is some evidence that CNS-penetrating HAART (e.g. abacavir and zidovudine) may be effective in improving neuropsychological functioning.<sup>8,17</sup> Growing evidence suggests that for milder neurocognitive disorders the use of antiretrovirals may slow progression or at least prevent severe forms of HAND.

However, owing to the lack of conclusive evidence that HAART can prevent or reverse neurological damage caused by HIV, the role of initiating HAART in asymptomatic individuals is undefined.

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