Neurocognitive deficit in HIV Patient: An Update

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Abstract

The HIV-1 (Human immuno deficiency Virus) epidemic enters its fifth decade. HIV-1 associated neurological disorders (HAND) continue to be a major concern in the infected population, despite the widespread use of anti-retroviral therapy. The introduction of combination antiretroviral treatment (cART) has significantly reduced the mortality secondary to opportunistic infections in HIV patients by restoring the immune system. In the central nervous system (CNS), there has also been benefit with a marked reduction of HIV associated dementia. However, the milder forms of HIV associated neurocognitive disorder (HAND), namely asymptomatic neurocognitive impairment and mild neurocognitive disorder, remain prevalent in the cART era. Currently, in clinical practice, patients with HIV are still visited to the psychiatric clinic for cognitive problem like memory, concentration etc. even when virology is under control. These usually begin with subtle changes but it can lead to more severe forms of neurocognitive impairment. The aim of this review is to describe the different types of neurocognitive disorders, possible mechanisms of development, epidemiology and risk factors in HIV patients, as well as the clinical approach and current treatment of HAND.

Introduction

HIV infection often results in varying degree of dysfunction, ranging from mild impairment to frank dementia[1]. In the latest revision, the Diagnostic and Statistical Manual- (DSM)-5 categories mild and major neurocognitive disorders on the basis or presumed etiology, association with behavioral disturbances and degree of severity[2]. HIV associated neurocognitive disorders (HAND) are a potential consequence of HIV-1 infection, and about half of all adults with AIDS suffer from neurological complications related to HIV-1[3]. HIV-1 infection plays a pivotal role in HAND by generating products that lead to neurological damage in the central nervous system (CNS). HAND includes a spectrum of neurological disorders ranging from asymptomatic neurocognitive impairment (ANI), an intermediate form termed mild neurocognitive disorder (MND) and the severe form, HIV associated dementia (HAD)[4]. HAND is highly prevalent: it is estimated that 30 - 60% of HIV positive individuals are affected[5]. The resulting cognitive impairment can interfere with social and occupational functioning, and affect adherence to antiretroviral therapy (ART)[6]. As the availability of highly active anti-retroviral therapy (HAART) has become more widespread worldwide, HIV-1-infected individuals are living longer. Although the incidence and prevalence of HAD have been reduced in the era of HAART, the prevalence of HAND overall is actually increasing worldwide. The success of HAART in controlling peripheral viral load is not necessarily accompanied by reduction in the immune activation in the brain[7]. The main issues remaining for neuro AIDS include the implications of persistent low levels of HIV, ongoing inflammatory responses, potential therapeutic toxicity, and interactions between ageing and neurodegeneration caused by the virus[8-10]. The introduction of combination antiretroviral treatment (cART) has markedly reduced the prevalence of the more severe form of HIV associated neurocognitive disorder (HAND), namely, HIV associated dementia (HAD) from about 20 %[1] to less than 5%[11]. However, the incidence of less severe forms of HAND, namely asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), remain common among HIV patients in the cART era, ranging from 20-50% in various studies[11,12]. This milder form of HAND not only impacts the quality of life of HIV patients[13-14], it also affects cART adherence[15], with the consequences of increased risk of development of cART resistance[16] and mortality[17,18].

Classification

Before 1991, there was only one kind of neurocognitive disorder defined, the HIV-associated dementia (HAD), which was known as the complex AIDS-Dementia. It affected patients with severe immune-depression causing severe impairment of cognition, frequently accompanied by motor and behavioral alterations.

More recently, the American Academy of Neurology (AAN) proposed a new classification by defining two levels of neurological impairment in patients with HIV: the classical HAD and the minor cognitive motor disorder (MCMD) representing patients that did not meet dementia criteria but complained of slight impairments that interfered with their daily life[19].

In 2007, a further revised classification system of HAND was introduced which is thought to be more precise and sensitive (Fascarti Criteria). It describes, beside HAD, other two neurocognitive disorders: Mild Neurocognitive disorder (MND) and Asymptomatic Neurocognitive impairment (ANI).

MND is defined as mild to moderate impairment within at least two cognitive areas with at least mild impairment of daily function.

ANI is defined as any degree of neuropsychological testing impairment in at least two cognitive domains but without causing an observable functional impairment[20].

Finally, cognitive neuropsychology aims to elucidate the component processes of HAND across the domains of executive functions, motor skills, speeded information processing, episodic memory, attention/ working memory, language, and visuoperception[21].

Proposed research criteria developed by HIV Neurobehavioral Research Center at UCSD

To address some of these concerns, the HIV Neurobehavioral Research Center (HNRC) at UCSD established working research criteria for HIV related neurocognitive complications which were intended to represent a refinement of the AAN criteria. These criteria recognize the following three conditions: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

Classification of HIV-associated neurocognitive disorders[22]

Asymptomatic neurocognitive impairment (ANI):

1. No evidence of preexisting cause. Cognitive impairment must be attributable to HIV and no other etiology (e.g. dementia, delirium).
2. The cognitive impairment does not interfere with activities of daily living.
3. Involves at least two cognitive areas (memory, attention, language, processing speed, sensory-perceptual, motor skills) documented by performance of > 1 standard deviation below the mean of standardized neuropsychological testing.

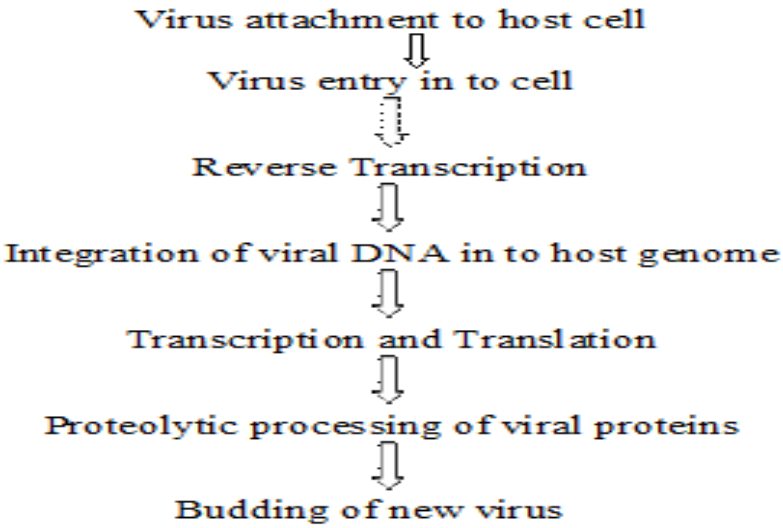
Mild neurocognitive disorder (MND):

1. No evidence of preexisting cause. Cognitive impairment must be attributable to HIV and no other etiology (e.g. dementia, delirium).
2. At least mild interference in > 1 activities of daily living including mental acuity, inefficiency at work, homemaking or social functioning.

HIV-Associated dementia (HAD):

1. No evidence of another preexisting cause for dementia (i.e. CNS infections, CNS neoplasm, cerebrovascular disease).
2. Marked interference in activities of daily living.
3. Marked cognitive impairment involving at least two cognitive domains by performance of > two standard deviation below the mean of standardized neuropsychological tests, especially in learning of new information, slowed information processing and defective attention or concentration.

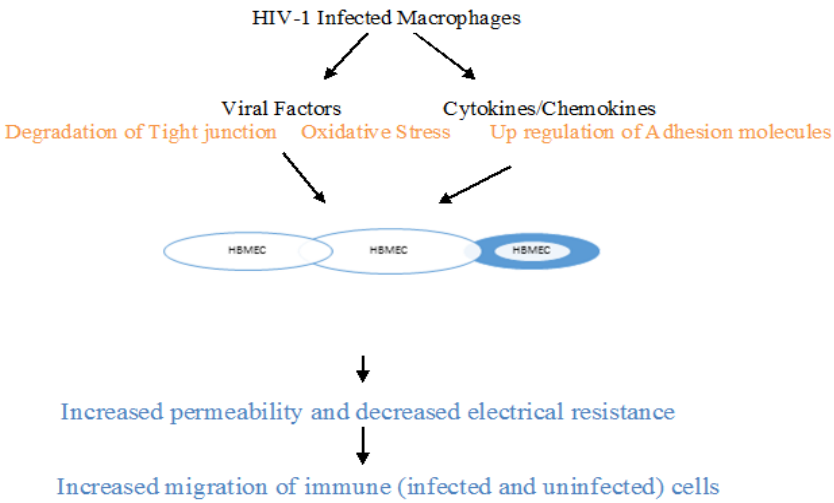
Neuropathogenesis:



The reason for neurocognitive disorders in HIV-patients is still unclear. It is well known that the central nervous system (CNS) is one of the target organs where HIV can be detected soon after primary infection. Infiltration of monocytes into the brain is a hallmark of HAND[23]. Monocyte derived macrophages (MDM) are one of the major types of cell that are infected by HIV-1 (CD4+ T lymphocytes and dendritic cells being the other two cell types). Once the HIV-1-infected macrophages have established residence in the CNS, they secrete chemokines that establish a chemotaxis gradient across the blood–brain barrier (BBB), which recruits more monocytic cells from the peripheral compartment into the CNS[24]. This influx of HIV-1-infected monocytic cells leads to the infection of other CNS resident monocytic cells, namely perivascular macrophages and microglia[25], which in turn results in greater BBB damage and accelerates the rate at which HIV-1-infected and uninfected monocytic cells can enter the brain. The key events that contribute to HAND include direct neuronal apoptosis, dysregulation of key neuronal support cells, and the loss of dendritic arbor. The process of HIV-1 infection begins by HIV-1 binding to CD4 receptor on the target cell surface, through the viral envelope protein gp120[26].

Macrophages are also characterized by the budding of virions into internal multivesicular bodies, which are vacuoles within the cells, rather than budding through the plasma membrane directly to the external medium. This mechanism allows HIV-1 to 'hide' inside the infected macrophages, making macrophages one of the latent reservoirs of HIV-1[27].

The predominant route of CNS exposure to HIV-1 is through peripheral blood monocytic cells/macrophages that have been infected by virus and transmigrate across the blood–brain barrier (BBB)[23].



Development of Screens and Biomarkers for HAND: Early neuroinvasion is characterized by measurable markers of CSF inflammation (e.g. Neopterin level) and by brain parenchymal inflammation detected by Magnetic Resonance Spectroscopy (MRS), although changes in neurocognitive functioning are seen more clearly in an advanced stages[4,28] .

While a simple test like the HIV dementia scale (HDS) provides good sensitivity and specificity for detecting HAD[29-32]. However, one may need a thorough NP battery assessment in order to quantify the effect of treatment. That's why the usage of biomarkers for disease detection and monitoring potentially carries an important role in clinical management. The findings of biomarker research in the last few years will be discussed as follows.

Systemic and Plasma Biomarkers: In the pre-cART era and in those patients naïve to cART, both current plasma viral load and CD4 count are important predictors for developing HAND but this association is no longer true in the cARTera[3,12,33]. Thus far, the nadir CD4 count serves as an important predicting factor for HAND across the treatment era[3,12,33]. In the multisite CHARTER study, both absence of a low nadir CD4 and currently undetectable viral load were associated with lower risk of HAND (ref attached). Importantly, nadir CD4 does not seem to be a threshold effect; that is to say that the evidence so far would suggest that the earlier cART is started the less likely HAND will be.

1. **CSF markers:** The clinical importance of viral load determination in the CSF is to monitor the therapeutic effect of HAART, to identify patients with CNS escape, distinguishing diagnosis with psychiatric symptoms[34].

In the pre-cART era and in those patients naïve to cART, both current plasma viral load and CD4 count are important predictors for developing HAND but this association is no longer true in the cART era[3,12,33].

The linkage between CSF viral escape and cognitive impairment is still not fully understood. It can occur in both neurocognitive unimpaired and HAND patients. Moreover, other neurological presentations including headache, altered sensation and encephalopathy were reported with CSF viral escape in various case series[35,36]. The nadir CD4 count serves as an important predicting factor for HAND across the treatment era[12,33].

2. **Chemokines:** Chemokines and their receptors have a central role in the interactions between HIV and the host. Chemokines, including MCP-1, also known as CCL2, are low molecular weight cytokines expressed by a wide variety of cell types including immune, endothelial and neural cells[37]. MCP-1 accumulates in the CSF of HAD (HIV associated dementia) patients and its level correlates with the degree of dementia. MCP-1 probably regulates CSF viral load because changes in MCP-1 levels occurred before or concomitantly to changes in CSF viral load[38].

3. **Beta2-microglobulin and neopterin:** Immunological activation markers, such as neopterin, Beta2 microglobulin, quinolonic acid, PGE2, and PAF, studied in CSF, could help in the diagnosis, mainly neopterin and Beta-2 microglobulin, although they are not used routinely[39]. CSF levels of neopterin are higher in the groups who have undergone successful ARV therapy and in the group on HAART, than the control group without HIV, indicating chronic macrophage activation[39]. Patients on long-term suppressive Cart have mildly raised CSF neopterin and IgG index[40].

Radiological Tools for HAND: HAND demonstrates no specific pattern on conventional magnetic resonance imaging (MRI) besides showing diffuse white matter (WM) hyper intensities on T2-weighted sequences and cerebral atrophy particularly in advanced disease, there is a reasonable body of evidence supporting a consistent and specific pattern on MRS[41].

In contrast to conventional MRI and DTI which provide structural information, fMRI makes use of the blood oxygenation level dependent (BOLD) contrast to provide dynamic information during resting state or performing cognitive tasks. Abnormal activation and connectivity were detected by fMRI among HIV patients with mild cognitive impairment[42]. In a recently published resting state fMRI study, it was found that functional connection within and between particular networks may be compromised in HAND, in a similar fashion as aging but they are independent of each other[43].

Screening, detection, and long-term follow-up: With the prevalence of milder forms of HAND increasing, and limited resources available for

formal neuropsychological examinations, there is a critical need to be able to screen and identity people with HAND. The early detection of HAND is becoming an important public health issue, especially as patients are aging and living with an increasing burden of comorbid conditions that are themselves risk factors for brain damage. Standard neuropsychological assessment has become a key evaluation in HAND diagnosis. It's difficult to assess the entire patient in detail as it would be too costly from a public health perspective. So, Cysique et al have suggested a staged approach, whereby individuals who are most at risk for HAND are assessed by a very brief screen, lasting only a few minutes. If deemed necessary, this can then be followed by a longer cognitive screen (approximately 15 minutes) as well as an assessment of mood and IADL (approximately 10 minutes). If the more formal cognitive screen is also positive then the patient should be referred for clinical assessment, neurological workup, and more extensive neuropsychological assessment where possible.

Aims of Neuropsychological Assessments: Some of the major goals of neuropsychological evaluations in HIV-infected populations include:

1. Finding neurocognitive impairment directly attributable to HIV
2. Determining if neurocognitive impairment is associated with co-morbid factors such as psychiatric illness, nutritional deficiencies, or co-infections
3. Exploring relationships between neurocognitive impairment and HIV disease variables such as history of immunodeficiency (current and nadir CD4 count), viral load, biomarkers of HIV neuropathogenesis, neuroimaging, and brain pathology
4. Exploring the relationship between HIV-associated neurocognitive impairment and everyday functioning within different populations around the world
5. Determining implications for treatment including adherence and use of CNS penetrating antiretroviral regimens
6. Determining when to start treatment to protect the CNS from damage and promote continued quality of life/productivity over the lifespan.
7. Providing feedback to patients and clinicians on progress of disease and treatment effects

Neurocognitive screening tools that are too brief will miss mild forms of HAND, especially in patients with high premorbid functioning. Indeed, The HIV Dementia Scale[44] may provide some information in moderate to severe cases but it lacks sensitivity to milder forms of HAND[45]. In general, for cognitive screens to be sensitive to mild HAND, they should at least assess psychomotor speed, verbal learning, and memory[33,46]. Additionally, such screens must have corrections for demographic factors, and at least for age, education, and sex. The results of a systematic review suggest that the HDS and IHDS are not ideal tools for identifying a range of neurocognitive impairment[47]. The review identified 10 other screening tools with adequate sensitivities (0.75). Of these, four tools or combinations of tests were used to detect HAND conditions and overall neurocognitive impairment (as opposed to impairment in specific domains) and they used a 'gold-standard' neuropsychological battery as the reference test or criterion. These four tools include the Cog State[48], the Screening Algorithm[49], the paired Hopkins Verbal Learning Test and WAIS-III Digit Symbol combination and the paired Hopkins Verbal Learning Test and Grooved Pegboard Non-Dominant Hand combination[50]. Becker et al[51] reported a slightly lower sensitivity (0.72) for the Computer Assessment of Mild Cognitive Impairment (CAMCI) against a comprehensive neuropsychological battery. Another study found the highest accuracy for detecting NCI in the combination of 3 measures provided by the tests, TMT-A, TMT-B, and COWAT and they called this combination the NEU Screen[52]. The 3 measures assess attention/working memory, executive functioning, and verbal fluency, which were among the most frequently impaired neurocognitive functions in HIV-infected patients[20,53,54]. NCI can also be rapidly detected in the HIV-infected population using the Montreal Cognitive Assessment (MoCA)[55] and the Brief Neurocognitive Screen (BNCS)[56]. Koski et al[57] compared MoCA with computerized tools and found that MoCA was less accurate when used alone; therefore, they recommended using it in combination with other sensitive screening tools (computerized or non-computerized).

Table 1: Available tools and tests for HIV-associated neurocognitive disorders (HAND) screening[54]

Tool or test	Description of the test	Advantages	Limitations
HIV Dementia Scale (HDS)	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	• Very fast to administer (3–5 minutes) • Very fast to score and interpret • Excellent specificity	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 • Requires a trained examiner to assess anti-saccadic eye movement • 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 • 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
International HIV Dementia Scale (IHDS)	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	Very fast to administer and score. Can be conducted in 2–3 minutes and only requires a stopwatch • Demonstrated appropriate sensitivity and specificity for screening for dementia • Does not require a trained examiner • Does not require proficiency in English • Can be easily applied in different settings and cultures	Limited ability to detect milder forms of HIV-associated neurocognitive impairment and distinguish between different stages of HIV dementia • Additional research is needed to determine appropriate cutoff values in different clinical and geographic settings. • Additional research needed on the role of depression in performance and scoring
Total Recall measure of the Hopkins Verbal Learning Test-Revised	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	Has six alternate forms, reducing potential practice effects and enabling its use in follow-up and monitoring of neurocognitive changes over time • Easy and fast (4 minutes) to administer • Good test for assessing patients with severe peripheral neuropathy and/or extreme motor limitations	Must be administered by a trained examiner • Must be scored and interpreted by a trained psychologist or Neuropsychologist • Scoring and interpretation must be based on adequate normative data (i.e., data appropriate to the individual being assessed)

Grooved Pegboard Test (GPT)	Test of manipulative dexterity requiring complex visual-motor coordination		• Difficult to use in patients with severe peripheral neuropathy and/or extreme motor limitations • Requires equipment, although the cost is relatively low (US$100), and stopwatch • Must be scored and interpreted by a trained psychologist or neuropsychologist • Scoring and interpretation must be based on adequate normative data (i.e., data appropriate to the individual being assessed)
Executive Interview	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	Has good internal consistency • Correlates with other measures of executive neurocognitive function • Not affected by age or gender	Less sensitive than HDS • Lower education was associated with an increased risk of incorrect classification of dementia • Accuracy in mild HAND
Cognitive functional status subscale of the (Medical Outcomes Study HIV Health Survey: MOS-HIV)	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	Sensitive to changes in NP test performance in early disease • Sensitive to neurocognitive behavior that involves neurocognitive or psychomotor speed	No sensitivity to attention and only limited sensitivity to memory function • Accuracy in mild HAND has not been reliably shown

Current therapeutic options: As yet, no adjunctive or neuroprotective therapies have effectively produced a clinically relevant level of benefit for patients with HAND. The search for novel pathogenic mechanisms and therapeutic approaches is under way.

Neuro cART: Since the main cause of cognitive impairment in HIV infected patients is the virus infection itself, the treatment of choice (accepted treatment strategy) remains the use of cART defined as a combination of three or more drugs. Some antiretrovirals are known to have better CNS penetration. A cART regimen with good CNS penetration has also been termed neurocART[58]. Conclusive evidence of the superiority of neurocART at this point is lacking. In patients with HAND, or at risk for HAND, a neurocART regimen is recommended where possible (taking into consideration issues such as resistance, adherence, and adverse effects). Lastly, whether early versus delayed initiation of cART is beneficial on neurocognitive functions over-time is currently under investigation in a large-scale international study (Strategic Timing of Anti-Retroviral Treatment [START] Neurology sub study), which will also assess the potential neurocART benefit.

Despite the introduction of cART, the persistence of HAND has led to development of new strategy adjuvants to HAART. Multiple drugs with neuroprotective properties have been evaluated. Minocycline, a tetracyclin with neuroprotective properties and good penetration through the BBB is being evaluated as a possible adjunct to HAART[22].

Memantine, a non-competitive antagonist of N-methyl-D-aspartate, approved for treatment of Alzheimer's disease leads no significant improvement in patients with mild to severe cognitive impairment[59].

Natalizumab, a monoclonal antibody against alpha-4-integrin known to block trafficking of leukocytes across the blood–brain barrier, has been shown to be effective in preventing HIV-1 infected cells from breaching the BBB in a SIV model by Campbell and colleagues[60].

Non pharmacologic interventions: There is a little information regarding pharmacological interventions in HIV populations which can be extrapolated to the general population. It is essential to modify lifestyle (diet, physical activity, stress) and to give up tobacco and alcohol.

Currently, we can prevent cardiovascular risk factors (e.g. HTN, DM, DLP). Adherence to treatment remains the central issue in HIV patients in order to keep control of VL. Neurocognitive impairment is strongly related to poor adherence[61]. The later can lead to drug resistance, increase morbidity/mortality and development of cognitive impairment, especially in the elderly[62]. Neuropsychological intervention programs proved to be useful in multiple pathologies like schizophrenia, acquired brain injury or Alzheimer's disease. However, few studies had been performed in the HIV field. Some of the programs showed some positive effects[63] although proper studies with new strategies presently do not exist.

Conclusions

Neurological involvement in HIV infection remains an important aspect of the infection that needs further research. Objective tests of neurological function confirm that cART, although improving outcomes immensely, has not accomplished full functional protection of the nervous system. Because changes are now subtle, and generally occur slowly, HIV-associated neurocognitive disorder remains challenging to study, but the importance of brain function to independence and quality of life demand that ongoing efforts are directed to optimize this aspect of care for HIV patients.

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