What’s in a Name? AIDS Dementia Complex, HIV-associated Dementia, HIV-associated neurocognitive disorder or HIV Encephalopathy

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Abstract
The current paper reviews currently used and proposed nomenclature for neurocognitive disorders associated with HIV, and proposes a unitary system as well as recommends an operational approach to screening/diagnosing severe forms of HIV associated neurocognitive disorder (HAND) in order to identify individuals who might benefit from antiretrovirals (ARVs). The terms HIV dementia complex, HIV-associated dementia (HAD) and HIV encephalopathy (HIE) are being replaced by more refined definitions for the spectrum HIV associated neurocognitive disorder (HANDs). The Diagnostic and Statistical Manual (DSM) will introduce a further term - major neurocognitive disorder. The nosology can become very confusing as the terms are not exactly equivalent. Clinicians need guidance on how to interpret new terms to implement current legislation and treatment guidelines that use the old term HIE. As a WHO stage 4 disease, patients with HIE are eligible for ARVs irrespective of their CD4 count. However, there are no locally available operational criteria how to diagnose HIV encephalopathy (HIE). The updated terminology is preferred because it requires assessing cognition objectively with neuropsychological tests. It is recommended that the International HIV Dementia Scale be used to screen patients and to thereafter confirm diagnosis with further neuropsychological tests e.g. the trail making and digit span tests.

Key words: HIV; AIDS; HIV-associated dementia (HAD); HIV-associated neurocognitive disorder (HAND)

Introduction
The terms HIV dementia complex, HIV-associated dementia (HAD) and HIV encephalopathy (HIE) have been used interchangeably from the late 1980s to describe a clinical triad of cognitive, motor and behavioural changes typically seen in the advanced stages of HIV infection. The terms describing the spectrum of cognitive disorders in HIV positive patients have been revised from this clinical definition to more refined staging that require assessing specific neuropsychological domains. Further changes in nosology are proposed by the Diagnostic and Statistical Manual (DSM) working group for DSM-5.

Antiretroviral treatment
In 1987, the Center for Disease Control and Prevention included HIV dementia as an AIDS-defining illness. The World Health Organization (WHO) included HIV encephalopathy in its case definition of stage four clinical disease. The WHO and the South African government’s clinical guidelines for management of HIV recommend initiating ARVs in people with stage four disease irrespective of CD4 count. As a WHO clinical stage four disease, patients with HIE are eligible for antiretrovirals (ARV) irrespective of their CD4 count in the private and public health sector. The Medical Schemes Act uses the term Prescribed Minimum benefit (PMB) to describe the set of benefits all members have access to certain minimum services irrespective of the benefit option they have selected. HIE is one of 270 PMB conditions. As a PMB condition, patients are eligible for ARVs (and all relevant care). The South African HIV Clinician Society recommends starting ARVs when the CD4 is < 350mmol/l and government has also revised their current
recommendations to start ARVs when CD4 <350mmol/l. Medical aids have no obligation to provide ARVs if the CD4 is >350mmol/l. Clinicians must use the definition of PMB conditions to make medical aids comply with the law. Failure to diagnose HIE, disadvantages patients who may otherwise benefit from ARVs. However, there are no guidelines how to diagnose HIE in the national ARV program. Clinicians need diagnostic tools and clarification how the new terminology relates to current legislation and treatment guidelines.

HIV-associated neurocognitive disorders
The spectrum of HIV-associated neurocognitive disorders were revised twice by the American Academy of Neurology. Since 1987, two further categories were added; in 1991 the American Academy of Neurology introduced the category of HIV-associated minor cognitive-motor deficit and in 2007, the National Institute of Mental Health (NIMH) and the National Institute of Neurological Diseases and Stroke revised the classification and added asymptomatic neurocognitive impairment (ANI). The new term HIV associated neurocognitive disorder (HAND) describes the full spectrum of neurological disease starting from ANI, minor neurocognitive disorder (MND) and HAD. The new classification requires one to systematically assess the following domains (attention-information processing; language; abstraction-executive; complex motor; memory and sensory perceptual/motor skills). The assessment of these domains requires neuropsychological (NP) tests and thereafter to compare their performance in these NP tests against population based norms. There are additional requirements, such as the measurement of functional performance.

DSM-5
In South Africa we use both the American Psychiatric Association’s classification of mental disorders as defined in The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the WHO International Classification of Diseases (ICD). The current proposal for the criteria to be used for neurocognitive disorders in DSM-5 has been published in a draft form. Just as the DSM-IV contained no specific criteria for HAND, the same is proposed for HAND in the DSM-5. There is no reference to the criteria that have been designated for HAND in neurology. If the currently proposed criteria for neurocognitive disorder are successfully promulgated, not only will the criteria for HAND be improperly depicted in an over-generalized fashion but also it will remain the case that there will be no specific criteria for HAND at all. The DSM-5 working group is recommending that HAD be subsumed under a new disorder to be termed “Major Neurocognitive Disorder”. The term dementia has been dropped completely because it has stigmatizing connotations. Further, AAN criteria set requires that at least two neuropsychological domains be impaired, whereas the DSM-5 require that one NP domain be impaired. There are other subtle differences in definitions and one has to be an expert in the field to keep pace with changes (Table I). If the DSM-5 proposal is accepted, we shall minimize the importance of HAND and further add to the ever expanding nosology. We need to demystify these terms and give clear guidance to the clinician to practically implement current legislation and treatment guidelines.

Table I: Differences between American Academy of Neurologist criteria for HAD and Diagnostic and Statistical Manual – 5 criteria for major neurocognitive disorder

<table>
<thead>
<tr>
<th>Criteria</th>
<th>American Academy of Neurologist criteria for HAD</th>
<th>Diagnostic and Statistical Manual – 5 criteria for major neurocognitive disorder</th>
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</thead>
<tbody>
<tr>
<td>Aetiology</td>
<td>Specific aetiology viz. HIV is identified</td>
<td>No specific aetiology is identified</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Diagnosis must be based upon report by the patient or a knowledgeable informant or by observation by a clinician together with deficits on standardized NP testing</td>
<td>Diagnosis is made wholly by standardized NP testing. Further collateral from informant, self report or clinical observation are not necessary.</td>
</tr>
<tr>
<td>Number of NP domains abnormal</td>
<td>Two NP domains be impaired</td>
<td>One NP domain must be impaired</td>
</tr>
<tr>
<td>Number and type of domain of domains to be tested</td>
<td>Seven domains - Verbal/language; attention/working memory; abstraction/executive functioning; memory; speed of information processing; sensory-perceptual, and motor skills</td>
<td>Six domains - Attention, executive ability, memory, language, visuconstructional-perceptual ability, and social cognition</td>
</tr>
<tr>
<td>Differences in domain</td>
<td>Does not include social cognition (recognition of emotions, theory of mind, behavioural regulation). Information processing speed and motor skills are separate domains</td>
<td>Social cognition has to be affected. Information processing speed and motor skills separate domains Not included</td>
</tr>
<tr>
<td>Functional status</td>
<td>Marked interference with any activities of daily living (e.g., work, home life, or social activities – regardless of whether they interfere with independence),</td>
<td>Interference in activities of daily living must affect independence.</td>
</tr>
<tr>
<td>Exclusionary criteria</td>
<td>No evidence of another, pre-existing cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, and pre-existing neurologic disease).</td>
<td>Deficits must not be attributable to another Axis I psychiatric disorder (e.g., major depressive disorder or schizophrenia).</td>
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HIV-associated dementia (HAD)

HAD occurs in approximately 10-15% of all individuals with HIV/AIDS and is more common in late stages of infection. Less severe forms of HAND occur in 30-60% of people infected with HIV depending on disease stage. In South Africa, 23.5% of the people attending an ARV clinic in Cape Town had HAND. In the pre-HAART era, HAD was common and more severe. People with HAD died within 6 months. The introduction of HAART, led to a greater than 40% improvement in cognition. Whilst we await completion of the NP tests, results are compared against standardized population means to classify if a patient has normal, ANI, MND or HAD. A NP battery can take many hours to complete, require special equipment and specially trained professionals. Population norms for many NP tests cannot be generalized in our population because they are usually derived from educated, Western Caucasian populations. Singh et al recently published local population norms for two NP tests commonly used to assess NP functioning in HIV positive patients. The digit span (A and B) and trail making (A and B) tests assess four of the six cognitive domains impaired in HANDS. These subtests take around 10-15 minutes to complete, require no special material other than a stop watch, paper and pencil. They can be administered by a lay counsellor or other staff after training and certification from a person experienced in its use. The concept of task shifting in mental health is being advocated as one solution to address the resource constraints in developing countries. The tests are culture neutral, however, patients must have some formal education to understand alphabets and numbers and have no visual or hearing impairment. These four subtests can be administered and compared against local population norms to more accurately classify HANDs. Patients can be classified into normal, asymptomatic neurocognitive impairment, minor neurocognitive disorder (MND) or HAD. The skills of neuropsychologists or psychiatrists can never be replaced by task shifting. Where these skills are available, referral must be made to confirm the diagnosis.

When to start ARVs

Patients with HIE and functional impairment can be started on ARVs irrespective of CD4 count according to the current South African government’s treatment guidelines. For patients in the private sector, all benefits are protected as PMB condition as defined in the Medical Schemes Act. Patients with MND and HAD will benefit from ARVs and should be started on ARVs. MND is a more subtle diagnosis and wholly dependent on NP testing. Hence the diagnosis must be clearly documented or confirmed by person familiar with the NP tests. Clinicians must take precautions to reduce false positives in performing these NP tests to limit undue exposure to ARVs.
Future research
We need fewer terms and simplification of criteria. The simplicity of the CD4 count as a proxy measure of one's immunity is well understood by the lay public. The current criteria need to be translated into a group of tests that give a single summary measure of cognitive function. The WHO definition of HIE needs to be revised to incorporate advances in the field. The emphasis on NP testing creates urgency for researchers to gather local population norms for the various subtests.

Conclusion
Whist we await harmonization of terms in HIV cognitive disorders, there is a need to educate all practitioners on implementation of currently available legislation and treatment guidelines for HIE. The term HIE, is not entirely equivalent to the new definition of HAD by the AAN or major neuro-cognitive disorder in DSM-5. However, we should use the updated definitions and diagnostic criteria for HAD and MND to implement the current, terminology, in our national ARV roll out program. All HIV positive patients with CD4 > 350mm/l should be screened with the IHDS and those who are positive should have confirmatory NP testing e.g. trails (A and B) and digit span (forward and backward). More detailed testing and referral to psychiatrists should be done where resources are available. In keeping with legislation patients with HAD must be started on ARVs irrespective of CD4 count. Patients with MND will benefit from ARVs, however, diagnosis and functional impairment must be clearly documented with confirmatory NP tests.

References