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# The performance of International HIV dementia Scale (IHDS) versus Mini Mental Status Examition Scale (MMSE) in assessment of HIV-associated Neurocognitive Disorders (HAND) among HIV-Infected Tanzanian adults: a Case-Control Study

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**Abstract**

**Introduction**

Availability of HAART has improved the outcome of HIV-associated neurocognitive disorders (HAND) though the prevalence is still high. Routine screening for HAND may offer room for early detection and prompt management that may improve overall outcome.

**Objective**

To compare the performance of International HIV dementia scale (IHDS) and Mini Mental Status Examination (MMSE) Scale in assessing HIV-associated neurocognitive disorders.

**Methods**

This was a case- control study involving 351 HIV-cases and 150 HIV-negative controls. International HIV dementia scale and Mini Mental Status Examination scale were used to screen for neurocognitive deficits.

**Results**

For cases, 91(25.9%) were males and 260(74.1%) were females while for 150 controls, 38(25.3%) were males and 112 (74.7%) were females. Under IHDS score 240(68.4%) of cases had HAND compared to 10(2.8%) when MMSE was used. The mean scores under MMSE for cases was 29±1.7 compared to 29.3± 1.2 for controls ($p = 1.00$). The mean IHDS scores for cases was 9.35 ± 1.89 compared to 10.35±0.89 ($p < 0.0001$) for controls.

**Conclusion**

Our findings suggests that IHDS has better sensitivity in detecting cases of HAND and perform better in identifying HIV/AIDS cases that requires further cognitive evaluation on comprehensive neuropsychological batteries.

**Keywords**: HIV-associated neurocognitive deficits, Mini-Mental Status Examination, International HIV Dementia Scale.

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**Introduction**

The use of highly active antiretroviral treatment (HAART) has significantly improved the quality of life for people living with HIV/AIDS (PLWHA); however, HIV-associated neurocognitive disorders (HAND) continue to be encountered(1). ARVs, in general, have changed the pattern of AIDS dementia complex in a sense that has significantly reduced the incidence of a severe form of HAD though the prevalence of MCI continues to be high(2,3).

The spectrum of HAND may range from asymptomatic cognitive impairment (ANI) which is the least severe form of HAND followed Mild Cognitive Impairment (MCD) and HIV-1 associated dementia (HAD) which is considered the most severe form of HAND(4), see Table 1.

Milder forms of HAND have been shown to interfere with ART adherence(5,6), workplace performance(7), driving and ability to carry out tasks independently(8,9), these in turn negatively affects health-related quality of life(10) and increase mortality rates(2) thus early detection and prompt management of milder forms of HAND are crucial for better clinical outcome among PLWHA.

Historically, Mini-Mental Status Examination (MMSE) which was originally developed to screen delirium and dementia have been used widely used to screen cognitive impairment, however, the validity of MMSE as a screening to for HAND has been criticized(11). In the pre-HAART era, the HIV dementia scale (HDS) was developed(12) which was later modified for use in the International settings as the International HIV Dementia Scale (IHDS)(13).

Our study aimed at comparing IHDS and MMSE in assessing neurocognitive impairment among patients living with HIV. We hypothesized that IHDS will detect more people with HAND compared to MMSE, thus a significant difference in detecting HAND when IHDS is used compared to when MMSE is used. The study also aimed either to support or refutes the common practice of using MMSE as a screening tool for HIV dementia.

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## Methods

### Study design and settings

This was a case- control study which was conducted at Muhimbili National Hospital (MNH), a National Referral and Teaching Hospital with more than 1,500 bed capacity, with 1,000 - 1,200 outpatients per day(14). The hospital is located in Dar es Salaam, a major city in Tanzania with a population of about 4,364,541 as per the 2012 census. MNH also runs a CTC clinic from Monday to Friday with at least, 100 patients attending per day(15).

### Sample size and sampling procedure

For HIV positive cases, a sample size of 328 was calculated using the Kish Leslie formula. The systematic sampling procedure was observed whereby every fifth participant from the attendance list was directed for an interview once the inclusion and exclusion criteria were applied.

### Inclusion/exclusion criteria

Patients included in the study were 18 years or older, able to give informed consent and fluent in either Swahili or English. Those with significant hearing or visual impairments, impaired articulation or limb disabilities (and unable to perform neurocognitive tasks) were excluded. However, no patient in our sample met the stated exclusion criteria.

**For HIV-negative controls**, arbitrary sample of 150 was randomly selected. This sample came from those patients who underwent voluntary counseling and testing (VCT) or provider initiating counseling and testing (PICT) and found negative afterward. This group was matched against HIV cases for age, sex, level of education and presence or absence of chronic illness.

### Data collection and analysis

It took 45 working days to conduct the interview and assess 351 cases between July - August 2012. A total of 358 cases were recruited but seven of them were lost to follow-up. These patients were not included in the analysis.

A questionnaire was used to determine socio-demographic and clinical profiles of participants. Socio-demographic characteristics included age, gender, years of formal education and duration of illness in years.

As for screening for neurocognitive deficits, this was assessed by using both IHDS and MMSE for all cases and controls which were performed by a resident medical doctor in Psychiatry who is conversant with using both instruments.

**Description of study instruments**

Mini Mental Status examination (MMSE) has been extensively used since its inception. It is the most reliable tool for brief assessment of cognitive function which can give insight to areas to assess further. This tool can be easily communicated among clinicians with minimal variability and assess five domains of cognitive functions such as (orientation, memory registration, attention and calculation, memory recall and language) with the maximum possible score of 30 on which the cutting point for defining cognitive impairment was set at 24.

International HIV Dementia Scale (IHDS) assesses memory recall, motor speed and psychomotor speeds as domains of neurocognitive functions. It consists of 3 subsets: timed finger tapping which measures motor speed; timed alternating hand sequence which assesses the psychomotor speed; recall of 4 items in 2 minutes which assesses memory registration and recall. Each of these subtests is rated on a scale of 0–4. The tests were administered as follows: for assessment of the verbal recall subtest, registration (new learning) was measured by reciting 4 words(in either Swahili or English) to the subject (dog, hat, potato and green) taking 1 second to say each of the words. The subject was asked to repeat the words and recall the 4 words after the timed finger tapping, and alternating hand sequence tests were performed. The cutoff point for defining neurocognitive impairment was set at 10.In some studies this screening tool has demonstrated a good pooled sensitivity of 0.90 [95% confidence interval (CI), 0.88-0.91] and an overall specificity of 0.96 (95% CI, 0.95-0.97) under summary receiver operation(16).

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**Results**

**Demographic profile**.

Of all 351 cases (HIV positive), 91(25.9%) were males and 260(74.1%) were females with the mean age of 42.3 years and standard deviation of 9.7 years. As for 150 controls, 38(25.3%) were males while 112(74.7%) were females, the mean age was 43.3 years with the standard deviation of 9.2 years. The mean neurocognitive scores under MMSE for cases was 29 with the standard deviation of 1.7 ranging from 17 to 30 while the mean neurocognitive score under MMSE for controls was 29.3 with the standard deviation of 1.2 ranging from 22 to 30. Under IHDS, the mean neurocognitive score for cases was 9.35 with the standard deviation of 1.89 ranging from a minimal score of 2 to maximum score of 12 while the non-HIV controls had the mean score of 10.35 with a standard deviation of 0.89 ranging from the minimum score of 6 to maximum score of 12 ( Table 2).

Table 2. Baseline data and neurocognitive scores for study participants.

| Variable | | HIV positive N (%) | HIV negative N (%) |
|---|---|---|---|
| Gender | Male | 91(25.9) | 38(25.3) |
| | Female | 260(74.1) | 112(74.6) |
| Mean age in years ± 1SD | | 42.9 ± 9.7 | 43.3 ± 9.2 |
| Mean score MMSE ± 1SD | | 29 ± 1.7 | 29.3 ± 1.2 |
| Mean score IHDS ± 1SD | | 9.3 ±1.8 | 10.4 ± 0.8 |

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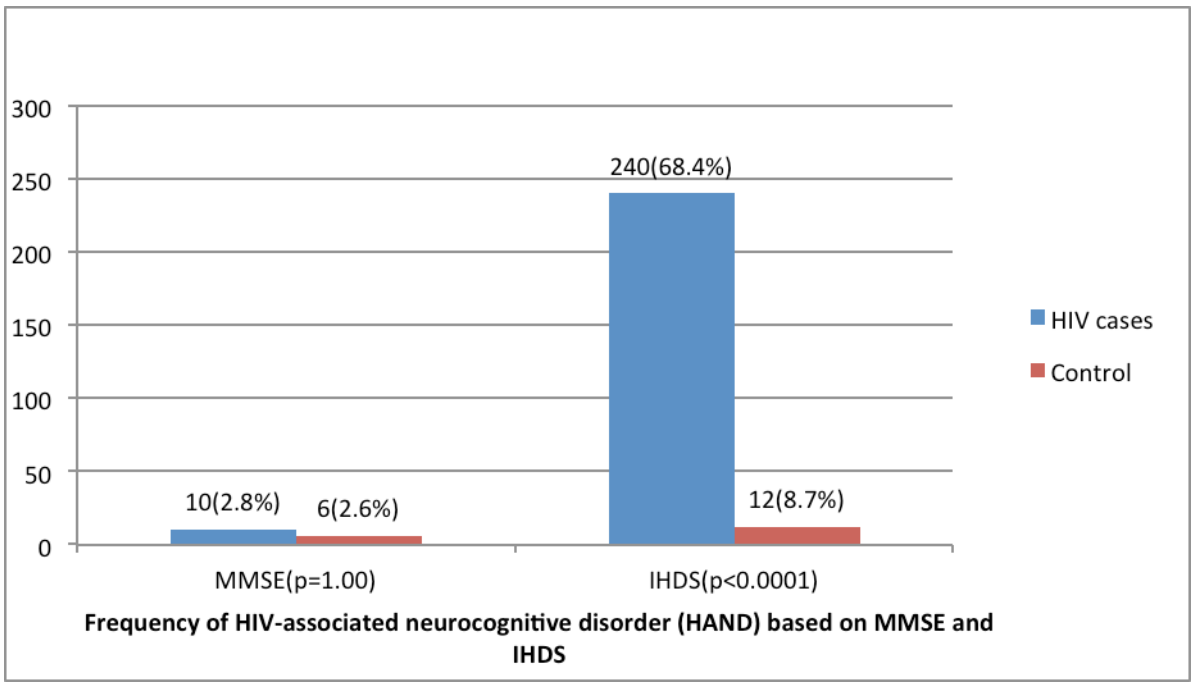
**Comparison of Neurocognitive Performance Using the IHDS and the MMSE Scores**.

Figure 1 display that using IHDS, the rate of detecting HAND was 241(68.4%) for all 351 participants whereas only 10(2.8%) were detected to have HAND when screened by MMSE. Furthermore, we that using the MMSE scale set at the cutoff point of 24, 10 (2.9%) of 351 HIV cases were identified to have HAND compared to 4(2.6%) of the 150 controls (Fisher exact $P$ = 1.00). Using the IHDS scale, set at a cutoff score of 10 to define HAND, 351 HIV-positive cases (68.4%) were found to have HAND compared with 12(8.7%) among the150 controls ($X2$ = 153.24; $P < 0.0001$), whereas the MMSE did not detect any significant difference between HIV cases and controls (P=1.00), the IHDS showed a significantly higher frequency of HAND in cases (P<0.0001).

Figure 1




**Frequency of HIV-associated neurocognitive disorder (HAND) based on MMSE and IHDS**

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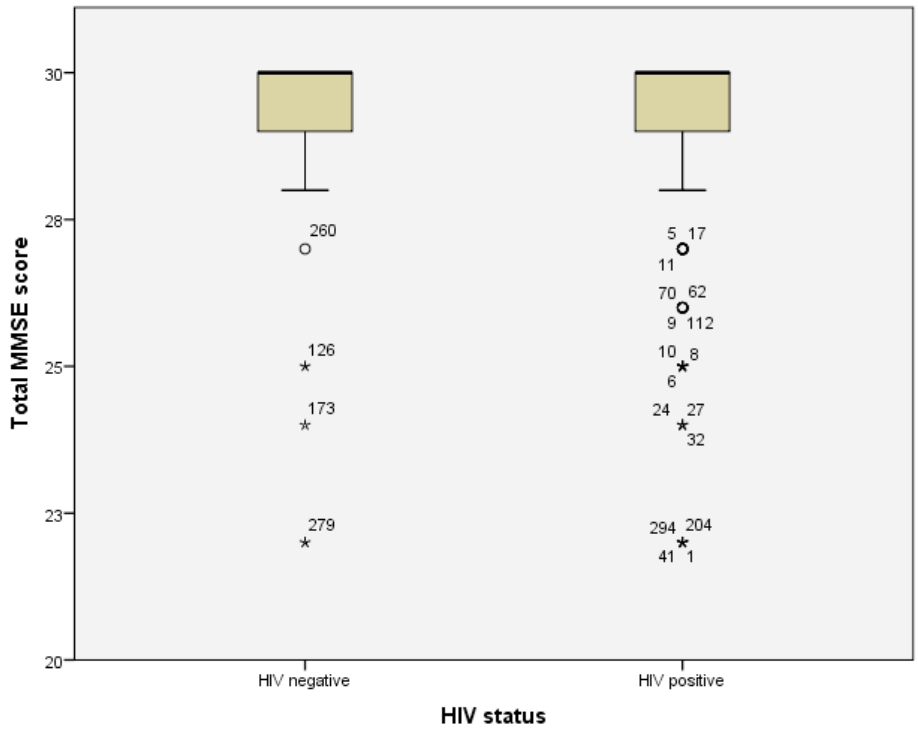
**Comparison of distribution of MMSE scores in HIV- positive cases and HIV- negative controls**.

Box plot below (figure 2) illustrating the distribution of MMSE in cases and controls. The (mean ±SD) MMSE score of the HIV positive cases (29 ± 1.7)and MMSE score of the controls (29.3 ± 1.2) did not differ significantly (ANOVA; P=0.16). Asterisked cases represent outliers within the HIV-positive cases and negative controls with MMSE below the group minimum.

Figure 2




**Comparison of IHDS scores in HIV-positive cases and HIV-negative controls**.

Box plot below (Figure 3) illustrating of IHDS scores in cases and controls. The mean score 9.3 and SD of 1.8 for HIV positive cases and HIV-negative controls with a mean score of 10.4 and SD of 0.8 differed significantly (ANOVA; $P < 0.0001$). Asterisked cases represent outliers within the HIV-positive group with scores below the group minimum.

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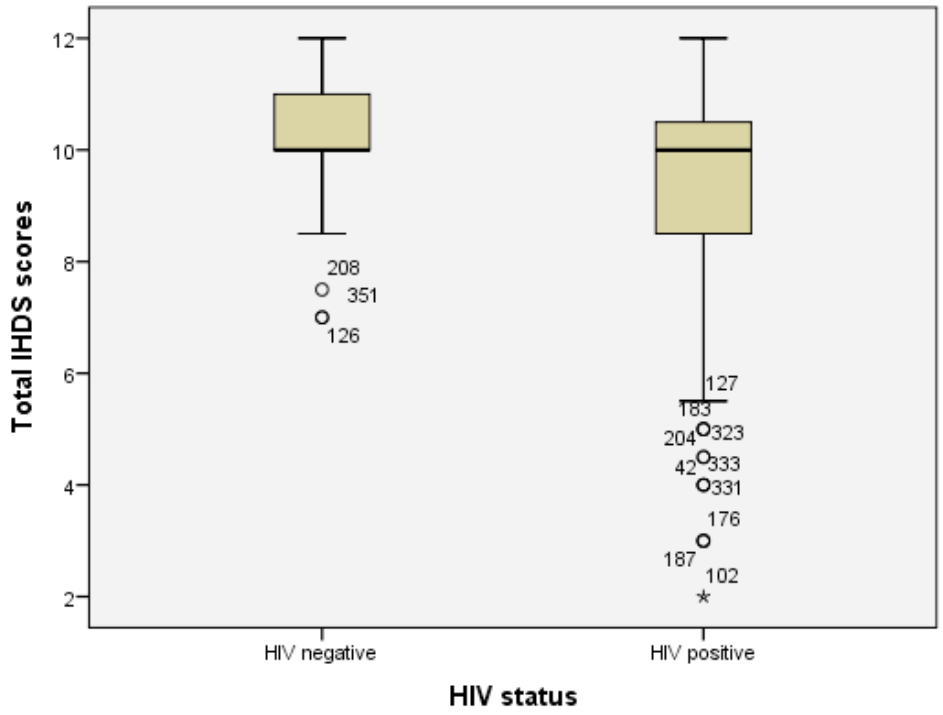
Figure 3




**Disease severity and neurocognitive impairment**

Table 3 shows higher proportions of neurocognitive impairment as the HIV/AIDS gets more severe. Fifty-nine percent of all 54 patient who were in clinical stage I screened positive for neurocognitive impairment compared to 67.6% of all 241 patients in clinical Stage II, or 80% of the 45 patients in clinical stage III and 81% of 11 clinical stage IV patients.

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Table 3. Relationship between disease severity and neurocognitive impairment

| Clinical Staging | | Neurocognitive Impairment (IHDS) | | |
|---|---|---|---|---|
| | | Neurocognitive Impairment | No neurocognitive Impairment | |
| Clinical Stage I | Count | 32 | 22 | 54 |
| | % within Clinical staging | 59.3% | 40.7% | 100.0% |
| Clinical Stage II | Count | 163 | 78 | 241 |
| | % within Clinical staging | 67.6% | 32.4% | 100.0% |
| Clinical Stage III | Count | 36 | 9 | 45 |
| | % within Clinical staging | 80.0% | 20.0% | 100.0% |
| Clinical Stage IV | Count | 9 | 2 | 11 |
| | % within Clinical staging | 81.8% | 18.2% | 100.0% |
| Total | Count | 240 | 110 | 350 |
| | % within Clinical staging | 68.6% | 31.4% | 100.0% |

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**Discussion**

The main finding of our study is that IHDS significantly detects a higher proportion of HAND among PLWHA compared to MMSE, thus, IHDS offers an advantage as a screening tool for further comprehensive neuropsychological assessment and further interventions to improve clinical outcome and quality of life as a whole. Furthermore, IHDS is easy to administer and requires about five minutes to administer, this is an advantage in real-world clinical practice as opposed to the use of extensive neuropsychological tools which are considered "gold standard" for diagnosing HAND. The observed poor performance of MMSE to distinguish cognitive between cases and control alludes to the previous observations that MMSE has poor sensitivity for detection of subcortical cognitive dysfunctions which primarily affects HIV individuals(11), this has been supported by neuropathological studies that have identified HIV staining in sub-cortical and deep gray matter structure particularly caudate nucleus and nucleus accumbens which are areas that provide clinical-anatomical correlates for HAND features(17). MMSE was primarily developed to assess cortical dysfunctions that occur in conditions like Alzheimer's dementia, this tool does not address items such as psychomotor speed and motor speed which are the distinctive features of IHDS tool. When compared to both HDS and IHDS, MMSE has been observed to perform poorly in the detection of HAND(18). Furthermore MMSE appears to be affected by age, sex, lower education level, language comprehension and social-cultural background thus limiting its utility even more. The seemingly observed advantage of IHDS over MMSE for screening of HAND is more pronounced in severe cases which are thought to account for less than 5% cases of HAND as both IHDS and MMSE performs unsatisfactorily when it comes to screening for asymptomatic neurocognitive disorders(19,20). Our study also highlighted higher proportions of HAND with the severity of HIV/AIDS based on WHO clinical staging criteria, this is supported by few other studies that demonstrate severity HIV/AIDS correlates with neurocognitive impairment and supported by evidence by neuropathological findings (17,21). Lack of information on CD4 count and viral load leaves only WHO clinical staging thus the validity in a description for severity of illness including neurocognitive impairment; many have used CD4 count or viral load to correlate with neurocognitive impairment in HIV patients.

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CD4 related inflammatory changes may be related to neuronal damage while evidence of viral replication predicts more impairment in neurocognitive function(22).

This study alludes to the previous observations that MMSE has poorly detects HAND (19) compared to IHDS which has been shown to have better sensitivity(11,16).

**Conclusion**

Our study supports the hypothesis that IHDS significantly outperform MMSE in detecting HAND among PLWHA and encourages the utility of IHDS in a pragmatic clinical world of HIV care in general. The lower specificity of IHDS calls for more research to improve the instrument by possibly incorporating variables that may improve IHDS performance for detection of early stages of HAND about which current screening tools perform unsatisfactorily.

**Limitations**

Lack of robust comprehensive "gold standard" tools such as neuropsychological battery to compare with our screening tools limits the study from determining sensitivity and specificity of our screening tools. Furthermore since no information about biological markers such as viral load and CD4 count which if combined with clinical criteria would have more accurately predict severity of HIV/AIDS and hence better correlated with neurocognitive performance from the used screening tools.

**Competing interest**

The authors declare no competing interest

**Authors' contribution**

AAN is the main author, he conceived and designed the study and wrote the proposal for the study. DMN, CJO, and AMM all supervised the study from the very beginning of the process; they all reviewed the manuscript and provided intellectual inputs. DMN ensured that AAN gets permission to use standardized tools for this research.

**Acknowledgement**

Special thanks go to Professor Silvia Kaaya of Muhimbili University of health and Allied Science for her intellectual input and advice, Dr Praxeda Swai, Dr Mwajuma Mustapha, Dr Charles Obeid and the late Dr Sheka Joseph Sheka for all their help.

My wife and other family members for their endless support.

Lastly but not least I send my sincere gratitude to the patients who made this work worth doing.

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**Table 1.** Revised research criteria for HIV-associated neurocognitive disorders (HAND) (modified from HIV Neurobehavioral Research Center criteria24)

| **HIV-associated asymptomatic neurocognitive impairment (ANI)*** |
|---|
| 1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.<br>2. The cognitive impairment does not interfere with everyday functioning.<br>3. The cognitive impairment does not meet criteria for delirium or dementia.<br>4. There is no evidence of another preexisting cause for the ANI.†<br>*If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission can be made.<br>†If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use. |
| **HIV-1-associated mild neurocognitive disorder (MND)*** |
| 1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.<br>Typically, this would correspond to an MSK scale stage of 0.5 to 1.0.<br>2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):<br>a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning. |

b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another preexisting cause for the MND.†
*If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.
†If the individual with suspected MND also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

**HIV-1-associated dementia (HAD)***

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below).
Typically, this would correspond to an MSK scale stage of 2.0 or greater.
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
4. There is no evidence of another, preexisting cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder).†
*If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.
†If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression