The utility of a rapid screening tool for depression and HIV dementia amongst patients with low CD4 counts- a preliminary report

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Abstract
Objective: To assess the utility of the International HIV Dementia Scale (IHDS) and Centre for Epidemiological Studies Depression Scale (CESD) as rapid screening tools of depression and HIV dementia amongst patients with low cluster of differentiation 4 (CD4) counts. **Method:** The rapid screening tools were tested on a sample of 20 patients with low CD4 counts who were recruited from the inpatient ward at McCord Hospital from August to October 2007. **Results:** The CESD was found to have 91 % sensitivity and 44 % specificity. Using the recommended cut-off of 10, the sensitivity of the IHDS was 88 %. The specificity was 50 %. The results suggest that CESD and IHDS are sensitive, however their low specificity may limit their clinical utility. **Conclusions:** This is a pilot study and no firm conclusions are drawn. Further research is needed to verify the high burden of depression and neuro-cognitive impairment (NCI) among people with low CD4. A larger study is needed to validate the IHDS in South Africa. Other researchers are encouraged to validate and determine the optimal cut off value for the IHDS in their local population.

Key words: HIV neuro-cognitive deficits; Depression; Dementia; Screening

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Introduction

Mental disorders e.g. depression, anxiety, substance abuse and cognitive impairment are frequently associated with negative physical health outcomes in Human immunodeficiency virus (HIV) positive people, but remain under-recognised. Chronic depressive symptoms are associated with impaired cell-mediated immunity[1] increased Acquired Immune Deficiency Syndrome (AIDS) –related mortality[2,3] and rapid disease progression.[4] Cognitive impairment is associated with increased mortality independent of clinical stage, CD4 count and anti-retroviral (ARV) treatment.[5] Depression and cognitive impairment are associated with poor adherence to ARVs.[6,7]

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Even though 99 % of all deaths from HIV/AIDS are in low and middle-income countries (LAMIC) and 80 % of the world's HIV positive people lives in Sub Saharan Africa[2,3], almost all the research on mental disorders and chronic management of HIV is from the developed countries.[8] Evidence from LAMIC is limited.[8,9] The rapid scale up of access to ARVs in LAMIC has created an urgency to address the mental health needs and implement robust mental health interventions in HIV positive people. Depression and dementia are the commonest mental health problems. There are screening tools available to detect depression and HIV dementia; they have not been tested in clinical practice in a HIV roll out setting in sub Saharan Africa.

HIV dementia is an umbrella term used to describe the cognitive impairment associated with HIV infection and AIDS, plus the behavioural and motor disabilities that interfere with normal daily life and in extreme cases lead to total disability.[10] Recently the research nosology of HIV- associated neuro-cognitive disorders (HAND) has been revised and includes a category of asymptomatic neuro-cognitive impairment for

people with subclinical impairment.[11] HAND is treatable and potentially reversible with the same ARVs that are used to treat the infection. Under the South African ARV roll out guidelines, HIV dementia is a Stage 4 AIDS defining illness and people qualify for ARVs even if their CD4 count is over 200 cells/mm^3.[12] The lack of clear guidelines and screening tools to rapidly diagnose depression and dementia by lay ARV nurses and physicians may unfairly limit a patient's access to ARVs.

In the United States, the diagnosis of HIV dementia requires knowledge of a patient's clinical history and a neurological examination consistent with criteria determined by the American Academy of Neurology (AAN).[13] While neuropsychological testing is an important component of the testing for HIV dementia, it is also time consuming, language and education dependent, and not always available in less well resourced countries.[14]

Other dementia screening tests exist such as the Mini Mental State Examination (MMSE).[15] The MMSE was designed with the aim of diagnosing cortical dementia, whereas HIV dementia is sub cortical.[16] Another screening tool is the HIV Dementia Scale (HDS)[17], which includes subtests that aspects such motor speed and attention. However, its use was limited because of difficulties assessing anti- saccadic eye movement by people without training in neurology.[18] The International HIV Dementia Scale (IHDS) is currently one of the better beside tests.[19] It focuses on tests of motor speed and psychomotor speed, which can more easily be used across different cultures.[19] The IHDS does not require one to be proficient in the English language, can be performed in 2-3 minutes in an outpatient setting and requires no special instrumentation other than a stop watch. However, the scale is far from ideal. The sensitivity was 80 % and specificity was 27 %. There is just a 1.3 point difference between classifying a person as demented or not. When the cut-off was lowered to increase sensitivity, the specificity diminished as more false positives were detected. There is thus a need to establish local cut off values.

Depression is common, largely unrecognized in HIV positive people and an independent predictor of disease progression and death.[19] The Centre for Epidemiological Studies Depression Scale (CESD) was developed by the National Institute of Mental Health Centre for Epidemiologic Studies. It is a 20-item inventory that has been widely used in assessing depressive symptoms.[20] The overlap of vegetative symptoms to diagnose depression e.g. loss of weight, energy, poor concentration and insomnia with HIV/AIDS related disorders confounds the diagnosis between a psychiatric and medical disorder. The CESD includes few vegetative symptoms in its assessment, and has been used in other HIV research in cross cultural settings[3], and HIV positive people in South Africa.[22]

To address the problem in diagnosing HIV dementia and depression among HIV positive people within a busy ARV clinic setting we aimed to test the sensitivity and specificity of the two most promising candidate bedside screening tests: viz. IHDS and CESD. The data from the first twenty patients of this study is presented.

Method

This was a cross-sectional study carried out amongst 20 HIV positive, ARV naive patients at McCord Hospital, Durban South Africa. McCord Hospital is partly government funded secondary hospital in an urban suburb in Durban. It has one of the countries largest and oldest ARV programs. It started providing ARVs 6 years before the South African national ARV rollout program. The ARV clinic is accredited with the Department of Health and abides by the national ARV rollout guidelines. To date McCord Hospital has initiated more than 4000 people on ARVs and continues to initiate a further 150 people every month. The hospital initiates patients on ARVS from its out patient clinic and in patient wards.

Patients

To be eligible for the study patients were required to be eligible for ARVs, i.e. CD4 < 200 cells/mm3, older than 18 years and not be delirious. Patients were recruited from the inpatient ward from August to October 2007.

Instruments

The CESD and IHDS were translated and back translated into Zulu. The IHDS has three subsets: timed finger tapping, timed alternating hand sequence tests and 4 item recall two minutes.[13] The screening instruments were administered in either English or isiZulu, depending on the patient's requirements. The principal investigator (DS), a registered psychiatrist, trained a psychology counsellor in the instruments. The counsellor recruited, obtained written informed consent and administered the CESD and IHDS to eligible participants. Within a week and prior to starting ARVs, DS assessed the participants with a diagnostic clinical interview and limited neuropsychiatric battery. DS was blind to the scores from the CESD and IHDS.

Diagnosis was made according to Diagnostic and Statistical Manual IV TR criteria except for criterion E due to general medical condition.[9] The neuropsychiatric battery consisted of Reys Complex Figure (RCF), digit span forward and back ward, trail making A (TMT A) and trail making B (TMT B). These tests are described elsewhere.[23] The norms of the neuropsychiatric battery were extracted from other published research on HIV dementia.[13,21]

RCF was rated as follows:

0 = failure to recall or reproduce design
= recognizable but distorted, rotated, partially omitted or confabulated features of design
2 = easily recognizable with minor errors of integration, omission or addition
3 = perfect or near perfect reproduction.

DS provided the 'gold standard' diagnosis. The diagnosis of depressive disorders were made according to Diagnostic and Statistical Manual IV TR criteria, and collapsed into either depressed or not for data analysis. Participants were rated as 'moderate' neuro-cognitive impairment (NCI) if they were beyond the norms on at least 2 tests and 'severe' NCI if their performance on three or more tests were abnormal. The CESD and IHDS scores were collected by the counsellor and compared with the clinical diagnosis. Sensitivity, specificity, positive and negative predictive values are presented.

To limit interviewer bias only one counsellor was used to collect the screening data and one psychiatrist for the clinical diagnosis. Sampling bias was limited by choosing a random,

albeit convenient sample of in patients. The psychiatrist was blind to the assessments made by the counsellor. Since ARVs improve cognition, the subjects were assessed prior to starting ARVs.

The study was approved by McCord Hospital Ethics committee.

Results

As summarized in Table I, this sample comprised of 95 % Africans with critically low CD4 cell count; the median was 34 cells/mm^3. Sixty percent were females; the median age was 34 years.

The overall prevalence of depressive disorders was 60 %. Using a cut off of 16 for the CESD, the sensitivity (proportion of depressed people according to clinical diagnosis by psychiatrist correctly identified by CESD) was 91 % (CI 100% - 38%) of the specificity (proportion of non depressed cases correctly identified) was 44 % (CI 67-31 %). Given a positive test, the probability of having a depressive disorder was 67 % (the positive predictive value).

The results of the IHDS and the neuropsychiatric battery is summarized in Table II. 80 % of this sample had some degree of NCI. The deficits involved many domains. Almost all had deficits with their working memory (digit span, RCF-copy), and varying degrees of difficulty with Trials A and B (attention, sequencing, mental flexibility and visual search and motor function). The deficits became very pronounced when the subjects were required to alternate between letters and numbers. 7/20 subjects took more than 5 minutes to complete a task that should take a little over one minute. The RCF assessed multiple domains (visuoconstructional, frontal lobes, motor) and was 15/16 sensitive in detecting NCI. 45 % of the sample had depressive symptoms and NCI.

Table I: Socio demographic and clinical characteristics of 20 participants.

Characteristic	*N= 20*
Age in years median (IQR)	34 (30-39)
CD 4 count Median (IQR)	35 (22-91)
Female (%)	60
African (%)	95
Any mood disorder (%)	60
Major depression	40
Substance induced mood disorder	10
dysthymia	10
Any neuro-cognitive impairment (%)	80

Table III: A comparison of the sensitivity and specificity of the IHDS at various cut off values

Cut off	*Sensitivity (%)*	*Specificity (%)*
9.5	38	75
10	88	50
10.5	94	25

Using the recommended cut-off of 10, the sensitivity of the IHDS was 88 % (CI 100 - 45 %). The specificity (correctly identifying the absence of NCI) was 50 %. To determine the optimal cut-off value of the IHDS to maximize sensitivity and specificity in our sample, we compared the sensitivity and specificity at various cut off as shown in Table III. When the cut-off is set at 9.5, the sensitivity drops to 38 % and specificity increases to 75 %. The sensitivity increases to 94 %, but the specificity decreases to 25 % when the cut-off is raised to 10.5.

Table II: Summary of International HIV Dementia scale scores, and neuropsychological testing performance

I.D	*IHDS Score*	*REYS Complex Figure – Memory (0-3)*	*REYS Complex Figure – Copy*	*Trial A (time to complete in sec)*	*Trial B (time to complete in sec)*	*Digit Span Span Backward score*	*Digit Span Span Forward score*	*Diagnosis of NCI 1=severe 2=moderate 3=normal*
1.	7.5	1-	1	80	300	3.1	4.2	1
2.	10	2-	2+	60	100	3.1	4.1	2
3.	9	2+	3	75	125	2.1	3.2	2
4.	10	2+	3	40	120	4.2	5.1	2
5.	10	3-	3	26	70	3.2	4.1	3
6.	10	3-	3	55	240	3.1	5.2	1
7.	10	3-	3	120	240	3.1	4.1	2
8.	6	2	3	80	360	2.2	4.2	1
9.	10	1	3-	60	360	2.1	5.1	1
10.	9.5	1+	3	42	92	4.2	5.1	2
11.	10.5	1+	2+	55	120	2.1	5.1	1
12.	10	1	2-	80	200	3.1	5.1	1
13.	9	1	1	110	360	2.2	3.1	1
14.	9	3	3	30	70	3.2	6.1	3
15.	10.5	2+	3	20	70	3.2	4.1	3
16.	10	1-	2-	90	360	2.2	5.2	1
17.	6	1	1	30	360	1.2	3.2	1
18.	10	1-	1+	70	360	2.2	4.1	1
19.	11	3	3	80	200	4.1	4.2	3
20.	11	1	3	70	240	2.1	5.1	1

Discussion

In our sample, 60 % and 80 % had a depressive disorder and NCI respectively. The CESD and IHDS had over 80 % sensitivity in correctly identifying the true cases. This high burden of disease and lack of skilled mental health specialists in LAMIC urges us to find screening tests that are culturally sensitive, rapid, require no instrumentation and can be administered by non specialists. An ideal screening should consequently be highly sensitive and specific. For clinical purposes, a screening test should have at least 80 % sensitivity and low false negatives. Our results suggest that CESD and IHDS are sensitive; however their low specificity may limit their clinical utility.

The high sensitivity of the CESD is desirable, however less than one in two people without the disease were correctly identified with a negative test. Given a positive test, three out of fours cases will have a confirmed depressive disorder. Therefore the CESD is more useful in identifying people with the disease rather than excluding a depressive disorder. The type of depressive disorder cannot be discriminated from this screen. The high proportion of false positives and low specificity implies that a second diagnostic assessment is necessary. This finding is consistent with a recent Cochrane review which concluded that depression screens used alone were not useful for diagnosing depression.[24] Our findings are similar to recent validation study in South Africa.[22]

The IHDS performs within the range predicted by Sacktor.[13] In this sample it had more than 80 % sensitivity and 50 % specificity at a cut-off is 10. However, when the cut-off was raised to 10.5 the specificity dropped to 25 %. The sensitivity also changes dramatically from 94 % to 38 % with a one point change. Further research in different settings is needed to evaluate this characteristic of the IHDS. The choice of an appropriate cut-off in our population has to be determined. This dramatic change in the sensitivity and specificity of the IHDS may limit its utility. Given the change in specificity over a few points, the margin for incorrectly diagnosing dementia is high. This may be exaggerated in a busy ARV setting with differing degrees of competence and individual variation amongst health care workers.

Even though 45 % of the sample had both depressive symptoms and NCI, this may over represent the burden of co-morbid disorders. Depression can cause poor performance on NCI and the burden of NCI may be lower than estimated in this study. Irrespective of the precise estimate, there are a high proportion of co-morbid disorders.

This study has many limitations. It should first be emphasised these are only interim results of a broader study. Data from just 20 patients has been reported and no adjustment was done for confounding variables e.g depression and low CD 4 counts.. The patients recruited into this study have critically low CD4 counts and were physically ill. Our larger study will include a more representative sample of people attending an ARV clinic. Depression and NCI occur more commonly in advanced stages of AIDS. This high prevalence of disease in a population has a profound effect on the predictive power of a test. Since NCI and depression were very common, the positive predictive value and sensitivity of the test will be high. In a population where the prevalence of the disorder declines the positive predictive value will decrease. Thus in our study, the screening tests would have a higher sensitivity and PPV than if it had been conducted in a general population. Firm conclusions cannot be drawn and precise recommendations cannot be made at this early stage. However, we feel there is urgency for other researchers in Africa to explore the issues raised in our pilot study. The findings of our pilot study raise more questions on the utility of the IHDS. We used published data to determine the 'controls' for the neuropsychiatry battery. Age appropriate HIV negative controls from the same population would be preferable. This is planned as part of the larger study.

Conclusion

We emphasize these are preliminary results and we make no firm conclusion. However the findings suggest there is a high burden of NCI and depression amongst people with critically low CD4 counts. The CESD and IHDS maybe useful screening tool for depression and NCI in a busy ARV clinic but local cut offs have to be determined to get the optimal sensitivity and specificity. Further research with a larger sample size and more generalizable population is needed to evaluate the utility of the IHDS in a busy ARV clinic. We would recommend other researchers undertake similar studies to evaluate the IHDS in their local settings and evaluate the problems raised by this pilot study.

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