Screening tools for HIV-associated neurocognitive disorders among adults living with HIV in sub-Saharan Africa: A scoping review [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: People living with HIV are at risk of developing HIV-associated neurocognitive disorders (HAND) which adversely affects their quality of life. Routine screening of HAND in HIV care is recommended to identify subtle changes in cognitive functioning and allow for early interventions. However, HAND detection is rarely done in sub-Saharan Africa (SSA), partly due to a lack of adequately standardized screening tools. This review was conducted to identify the commonly used screening tools for HAND in SSA and document their psychometric properties and diagnostic accuracy.

Methods: We searched Ovid Medline, PsycINFO and Web of Sciences databases for empirical studies published from 1/1/1980 to 31/8/2018 on HAND among adults living with HIV in SSA.

Results: We identified 14 eligible studies, of which 9 were from South Africa. The International HIV Dementia Scale (IHDS) was the most frequently reported tool, being used in more than half of the studies. However most studies only reported the diagnostic accuracy of this and other tools, with specificity ranging from 37% to 81% and sensitivity ranging from 45% to 100%. Appropriate data on construct validity and reliability of tools was rarely documented. Although most tools performed well in screening for severe forms of HAND, they lacked sensitivity and specificity for moderate forms of HAND. NeuroScreen, one of the newer tools, yielded good diagnostic accuracy in its initial evaluation in South Africa (81% to 93% sensitivity and 71% to 81% specificity).

Conclusions: This review identified a lack of adequately standardized and contextually relevant HAND screening tools in SSA. Most screening tools for HAND used in SSA possess inadequate psychometric properties and diagnostic accuracy. There is a need for further validation of existing tools and development of new tools to make them sensitive and specific enough to identify both severe and moderate forms of HAND in SSA.

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Any reports and responses or comments on the article can be found at the end of the article.
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Introduction

With the advent of highly active antiretroviral therapy (HAART), the 25 million people living with HIV/AIDS in sub-Saharan Africa (SSA) now have the potential for a near-normal life expectancy. Nonetheless, their well-being could be hampered by continuing HIV co-morbidities that adversely affect quality of life. HIV-associated neurocognitive disorder (HAND), at least in its mild form, is one of the commonest comorbidities. Briefly, HAND is a spectrum of neurological complications of HIV infection comprising asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV-associated dementia. The diagnosis of HAND is based on the evaluation of key cognitive domains including executive functioning, episodic memory, motor skills, and speed of information processing, language, working memory, and sensory perception according to the Frascati criteria. These criteria also consider the extent to which the cognitive impairment impacts the person’s performance on activities of daily living.

The prevalence of HAND is estimated to be high across regions, occurring in as many as 50% of all adults living with HIV, including those on HAART and with well-controlled viremia. Nonetheless, its pattern has changed in the era of HAART. Notably, the incidence of severe forms of HAND has reduced significantly, while the prevalence of moderate forms has increased. The persistence of milder forms of HAND is hypothesized to be due to poor adherence to treatment, possible neurotoxicity, multiple co-morbidities, resistance to drugs, poor CNS penetration of some of the ARV drugs as well as chronic HIV brain infection.

The magnitude of HAND among adults living with HIV, especially in SSA is largely unrecognized, partly because of the lack of expertise to recognize it and failure to routinely screen for it. Moreover, there is a paucity of well-designed epidemiological studies describing the burden of the condition. Understanding HAND is important because of its clinical and functional impact on the individual including the heightened risk of mortality; poor treatment adherence; poor quality of life; increased risk-taking behaviors and disruptions to everyday functioning.

Identifying adults at risk of developing HAND is an important first step in planning preventive measures and monitoring risk reduction. Consequently, it is critical to screen for such impairment, both for clinical management and for research. Existing guidelines on the management of HAND almost exclusively originate from high-income countries. These guidelines recommend that all people living with HIV be screened for HAND using standardized tools. Thereafter, the frequency is contingent on whether HAND is already present or whether clinical data suggest increased risk for developing HAND. Additionally, worsening cognitive functioning may necessitate HAART modification when other causes have been excluded. Other management approaches suggested in the literature include preventative and treatment strategies supporting the biopsychosocial aspects of cognition, such as reducing alcohol and substance use, improving nutrition, treating comorbidities, promoting social contact, reducing depression and stress levels, taking part in cognitively stimulating activities, applying cognitive remediation therapies, and incorporating psychopharmacological interventions. These approaches to care could be packaged together and be delivered by trained lay health care providers through task shifting in the context of low resource-settings and help alleviate the shortage of expert clinical staff.

Despite the potential benefits of early screening, few clinics in SSA screen for this condition in routine HIV care services. This is partly due to the lack of adequately standardized tools of neurocognitive functions. Another barrier is the prevailing shortage of trained healthcare personnel with expertise to administer these tests.

Information on the most appropriate HAND screening tools in SSA is poorly addressed. In 2013, Zipursky and colleagues conducted the first systematic review of the literature with the aim of evaluating brief screening tools for HAND across the world. Out of the 31 studies included in the past review, only 5 were from SSA. Overall, the review demonstrated that the commonly utilized screening tools (HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS)) had poor (0.48) and moderate (0.62) pooled sensitivities, respectively. The authors further reported that none of the tools differentiated HAND adequately to suggest wider use. Moreover, substantial methodological flaws were reported in most of the studies. This included: the failure for the studies to use the “gold standard” neuropsychological battery as the reference test, failing to utilize more comprehensive reference tests, non-representativeness of the samples and the varied measurement of functional status.

In the current scoping review, we aim to update the literature, specifically focussing on the HAND screening tools that are being used in SSA and document the extent of their validation. Precisely, we document the psychometric properties of these tools. Key constructs of reliability and validity are reviewed. Internal consistency (using Cronbach alpha correlation), test-retest reliability (often measured as correlation, with Pearson r), and inter-rater reliability (generally estimated by percent agreement, kappa (for binary outcomes), or Kendall tau) will be examined to describe reliability. Generally, a Cronbach alpha correlation close to 1 is considered good while a Pearson correlation (r) ≥ 0.70 is considered good. For validity, criterion-related validity (predictive, concurrence) and construct validity (convergent, discriminant) will be evaluated. The focus on SSA is important to provide context relevant information to guide both clinical and research practice in the region.

Methods

Search strategy

A comprehensive database search in Ovid Medline, PsycINFO and Web of Sciences was conducted for peer-reviewed articles published from January 1980 up to 31st August 2018. The search strategy was formulated by two reviewers (PNM and AA) and comprised of the following terms combined with Boolean operators: HIV-associated neurocognitive disorders OR cognitive
The International HIV dementia scale (IHDS) is a brief HAND screening measure made up of three items assessing motor speed, psychomotor speed and memory specifically developed for use in low- and middle-income countries. It was initially evaluated in Uganda, where a cut-off of 10 was suggested, yielding a sensitivity of 80% and specificity of 55%. Subsequent validation studies of the IHDS (included in this review) have reported varied sensitivity and specificity (Table 1). Overall, sensitivity ranged from 45% to 100% and specificity ranged from 37% to 79%. Data was unavailable on other key components of validity such as test-retest reliability and construct validity.

Kwasa and colleagues evaluated the utility of a modified version of the IHDS in Kenya, the HIV Dementia Diagnostic Test, (by adding neurological and functional status items). The modified tool exhibited moderate sensitivity and specificity of 63% and 67% respectively. Nonetheless, the inter-rater reliability was poor (K = 0.03–0.65), with the authors suggesting further training and formal evaluations for health care workers (HCW) to reliably administer the tool. Elsewhere in South Africa, Gouse and colleagues evaluated a version of the IHDS which had been modified by adding a brief self-report cognitive tool. The modified IHDS tool was reportedly more effective (94% sensitivity, 63% specificity) in screening for severe forms of HAND than the original IHDS tool (74% sensitivity, 70% specificity).

**Data handling and synthesis**

Data analysis involved collating and summarizing results from individual studies. The synthesis of data extracted from the eligible studies is performed narratively. Frequencies and/or percentages are computed in Microsoft Excel program to summarize the findings on the frequency of the various tools reported in studies. Where applicable, ranges are used to compare the diagnostic accuracy and psychometric properties of the identified HAND screening tools in the final synthesis. Being a scoping review, risk of bias of individual studies was not assessed in this review so as to include as many studies as possible.

**Results**

**Study characteristics**

The search strategy yielded 479 studies (flow diagram given in Figure 1). Of the retrieved studies, 14 eligible articles were included in this review, and these were published between 2005 and 2018. All the 14 included studies utilized a cross-sectional design. In total, nine (64.3%) of these studies were conducted in South Africa and the rest were conducted in Nigeria, Uganda and Kenya. The study samples ranged from 16 to 269 participants, as presented in Table 1.

**Screening tools identified and their psychometric properties**

The IHDS was originally developed in 1995 as a brief HAND screening tool with four scales designed to screen for cognitive impairments in attention, motor speed, construction and working memory domains. Some of the subtests in the original version of IHDS were deemed difficult for administration by non-neurologists and informally trained individuals, which led to the modified version, the IHDS in 2005. In the current review, the study by Olubunmi in Nigeria demonstrated good HDS sensitivity (97%) and specificity of 80% with a positive predictive value (PPV) of 91% and a negative predictive value (NPV) of 93%. Nonetheless, the HDS tool was insensitive to memory impairment in asymptomatic HIV-infected patients. Likewise, data was unavailable on other key components of validity, such as test-retest reliability and construct validity.

**Montreal Cognitive Assessment (MoCA) test.** The MoCA test is a brief screening tool originally developed in 1996 to screen for mild cognitive impairment. So far, only two studies in Africa (as identified in this review) have evaluated its utility in screening for HAND, both of which were in South Africa. In the initial evaluation study, the tool was able to discriminate neurocognitive performance between HIV-infected and non-infected individuals. However, it has problematic sections that need to be removed. Additionally, a ceiling effect was observed with some of the items making the authors conclude that the tool needs extensive cultural adaptation to make it suitable for South Africa’s linguistically, culturally, educationally, and economically diverse population. Reliability and construct validity were not explored in this initial evaluation. In the second evaluation study, a moderate correlation (Pearson’s
NeuroScreen. NeuroScreen is a computerized neuropsychological screening test battery designed for a smartphone running on the Android operating system. This measure is mobile-based, takes around 15–20 minutes to administer, and needs limited training. It was originally developed and tested in the United States of America. The measure comprises 10 brief neuropsychological tests assessing verbal learning, memory, processing speed, attention/concentration, executive functioning and motor functioning. In Africa, the NeuroScreen has only been evaluated in South Africa. In this review, the sensitivity of the NeuroScreen ranged between 81% to 93% and its specificity ranged from 71% to 81% when administered by lay health workers. Unfortunately, data was unavailable on other key aspects of validity such as test-retest reliability and construct validity.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country &amp; year of publication</th>
<th>Sample size</th>
<th>ART use</th>
<th>Mean/median age/age range</th>
<th>Tool validated</th>
<th>Reference tool</th>
<th>Test-retest reliability</th>
<th>Inter-Rater reliability</th>
<th>Sensitivity and Specificity</th>
<th>PPV and NPV</th>
<th>Test administrator</th>
<th>Summary of findings</th>
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</thead>
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<tr>
<td>[35] Hakkers</td>
<td>South Africa, 2018</td>
<td>121</td>
<td>All</td>
<td>35</td>
<td>MOCA-B (Montreal cognitive assessment-basic)</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>40% sensitivity, 72% specificity. Diagnostic accuracy of 59%, Pearson’s r of 0.36.</td>
<td>PPV of 43%, NPV of 70%</td>
<td>Trained local counsellor</td>
<td>The validity of MOCA-B was poor in this setting. The tool lacked speed of information processing domain. MoCA-B demonstrated best test characteristics when screening for severe forms of HAND.</td>
</tr>
<tr>
<td>[38] Robbins</td>
<td>South Africa, 2018</td>
<td>102</td>
<td>All</td>
<td>33.31</td>
<td>NeuroScreen</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>81% to 93% sensitivity and 71% to 81% specificity for different combination of test scores.</td>
<td>53% to 61% PPV and 92% to 96% NPV</td>
<td>lay health workers</td>
<td>NeuroScreen is a promising screening tool given the good test characteristics and administration by lay workers. However, the number of false positives is still high (14 to 22 people). More research with larger samples still needed.</td>
</tr>
<tr>
<td>[31] Gouse</td>
<td>South Africa, 2017</td>
<td>94</td>
<td>75%</td>
<td>37.50</td>
<td>IHDS versus IHDS+HCSQ (International HIV Dementia Scale - HIV Cognitive Symptom Questionnaire)</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>94% sensitivity and 63% specificity for IHDS-HCSQ and 74% sensitivity and 70% specificity for IHDS</td>
<td>74% PPV and 70% NPV for IHDS; 75% PPV and 90% NPV for IHDS-HCSQ</td>
<td>Neuropsychology technician supervised by clinical psychologist.</td>
<td>Supplementing the IHDS with the HCSQ improves its ability to detect severe forms of HAND. The study lacked a control group, did not report construct validity and did not assess feasibility in practice. More studies with larger samples needed to evaluate it further.</td>
</tr>
<tr>
<td>[39] Yechoor</td>
<td>Uganda, 2016</td>
<td>181</td>
<td>80%</td>
<td>37</td>
<td>CogState</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>Sensitivity of 57% and specificity of 77% at the optimal cut-off point</td>
<td>60% PPV and 74% NPV at the optimal cut-off</td>
<td>A trained research assistant</td>
<td>CogState may not be a useful tool to screen for HIV-associated NCI in Uganda, as many cases of NCI would be missed.</td>
</tr>
<tr>
<td>[25] Goodkin</td>
<td>South Africa, 2014</td>
<td>70</td>
<td>NR</td>
<td>31.5</td>
<td>International HIV Dementia Scale</td>
<td>Digit span, TMT</td>
<td>Not done</td>
<td>Not done</td>
<td>69% Sensitivity, 74% specificity at cut off of 10.5</td>
<td>PPV of 67.7% and NPV of 76.9%</td>
<td>Not reported</td>
<td>The sensitivity for ANI/MND was less than for HAD. Lacked a measure of functional status.</td>
</tr>
<tr>
<td>[36] Robbins</td>
<td>South Africa, 2013</td>
<td>78</td>
<td>some</td>
<td>29.62</td>
<td>Montreal Cognitive Assessment Test</td>
<td>none</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>trained research staff</td>
<td>Floor effects were observed on some items. More validation needed.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Country &amp; year of publication</td>
<td>Sample size</td>
<td>ART use</td>
<td>Mean/median age/age range</td>
<td>Tool validated</td>
<td>Reference tool</td>
<td>Test-retest reliability</td>
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<td>Summary of findings</td>
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</tr>
<tr>
<td>[27] Royal</td>
<td>Nigeria, 2012</td>
<td>116</td>
<td>some</td>
<td>31.7</td>
<td>International HIV Dementia Scale</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>100% sensitivity; 37% specificity at cut off of 10</td>
<td>Not done</td>
<td>Not reported</td>
<td>The tool had very low specificity at the recommended cut off of 10.</td>
</tr>
<tr>
<td>[29] Kwasa</td>
<td>Kenya, 2012</td>
<td>30</td>
<td>Not reported</td>
<td>39</td>
<td>HIV Dementia Diagnostic Test</td>
<td>NP battery</td>
<td>Not done</td>
<td>K = 0.03 -0.65</td>
<td>63% sensitivity and 67% specificity</td>
<td>Not done</td>
<td>non-physician health workers and experts</td>
<td>Agreement between HCW and expert examiners was poor for many individual items of the tool. The tool had moderate sensitivity and specificity</td>
</tr>
<tr>
<td>[24] Breuer</td>
<td>South Africa, 2012</td>
<td>269</td>
<td>all</td>
<td>20–42</td>
<td>International HIV Dementia Scale</td>
<td>None</td>
<td>Not done</td>
<td>K of 0.11</td>
<td>50% sensitivity; 69% specificity</td>
<td>Not done</td>
<td>Lay counsellors and nurses</td>
<td>There were many HAD false positives and negatives by counsellors.</td>
</tr>
<tr>
<td>[26] Joska</td>
<td>South Africa, 2011</td>
<td>190</td>
<td>none</td>
<td>27.5</td>
<td>International HIV Dementia Scale</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>45% Sensitivity, 79% specificity at cut off of 10</td>
<td>Not done</td>
<td>Trained technicians</td>
<td>Individuals with HAD, who screened negative on the IHDS, performed poorly on some tests of executive function.</td>
</tr>
<tr>
<td>[40] Mupawose</td>
<td>South Africa, 2010</td>
<td>16</td>
<td>none</td>
<td>37.5</td>
<td>Cognitive Linguistic Quick Test</td>
<td>none</td>
<td>k of 0.61-0.90</td>
<td>Not done</td>
<td>Not done</td>
<td>Trained research assistants</td>
<td>Validation was not done</td>
<td></td>
</tr>
<tr>
<td>[33] Ogunrin</td>
<td>Nigeria, 2009</td>
<td>240</td>
<td>none</td>
<td>18-64</td>
<td>Modified HIV Dementia Scale</td>
<td>none</td>
<td>Not done</td>
<td>Not done</td>
<td>PPV of 91.4%, NPV of 93.2%</td>
<td>trained research staff</td>
<td>The tool was insensitive to memory impairment in asymptomatic HIV-infected patients.</td>
<td></td>
</tr>
<tr>
<td>[30] Singh</td>
<td>South Africa, 2008</td>
<td>20</td>
<td>none</td>
<td>34</td>
<td>International HIV Dementia Scale</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>88% Sensitivity; 50% specificity at cut off of 10</td>
<td>Not done</td>
<td>Not reported</td>
<td>IHDS is sensitive, however, its low specificity may limit its clinical utility.</td>
</tr>
<tr>
<td>[28] Sacktor</td>
<td>Uganda, 2005</td>
<td>181</td>
<td>some</td>
<td>34.2</td>
<td>International HIV Dementia Scale</td>
<td>NP battery</td>
<td>Not done</td>
<td>Not done</td>
<td>80% Sensitivity; 55% specificity at cut off of 10</td>
<td>Not done</td>
<td>Trained physicians</td>
<td>IHDS is sensitive, however, its low specificity may limit its clinical utility.</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; NPV, negative predictive value; PPV, positive predictive value; NP, neuropsychological battery; NCI, neurocognitive impairment; TMT, trail making test; ANI, asymptomatic neurocognitive impairment; MND, mild neurocognitive disorder; HAD, HIV-associated dementia; HCW, healthcare worker.
CogState Brief Battery. This is a brief computerized neuropsychological battery (taking around 15 minutes to administer) developed to screen and monitor cognitive impairment in patients including those living with HIV\textsuperscript{41–42}. In SSA, the tool has been evaluated once in Uganda\textsuperscript{20}. In this evaluation, the tool exhibited a sensitivity of 57% and a specificity of 74% at the optimal cut-off point. Data was also unavailable on other key components of validity such as test-retest reliability and construct validity.

Cognitive Linguistic Quick Test (CLQT). The sixth measure evaluated was the CLQT\textsuperscript{39}. The measure was originally normed on 171 non-clinical and 38 clinical cases in the US as a quick screen for people to identify cognitive strengths and weaknesses in different at-risk populations. In the current review, it is difficult to make conclusions on the potential usefulness of this measure as a screening tool given its small sample size of 16 participants and minimal psychometric evaluations\textsuperscript{40}.

Tool administrators
A total of eleven studies described the administrators of the HAND screening tools\textsuperscript{24,26,28–30,33,35,37,38,39,40}. In nine of these studies, the administrators were trained research assistants who were either physicians, neuropsychology technicians, counsellors, nurses or clinical officers. There were two studies that included lay health workers in the screening for neurocognitive impairment\textsuperscript{28,38}. In one of them, the authors reported the effect of having trained research administrators versus lay administrators\textsuperscript{28}. In the study by Kwasa and colleagues\textsuperscript{28}, the agreement between healthcare workers and expert examiners was poor for many individual items of the tool (K = 0.03–0.6). Similarly, in another study by Breuer and colleagues, lay counsellors tended not to miss symptoms, and detected symptoms more often than nurses for the IHDS\textsuperscript{34}.

Methodological shortfalls of reviewed studies
Some of the reviewed studies had small sample sizes such as 16\textsuperscript{28}, 20\textsuperscript{28} and 30\textsuperscript{29}. Additionally, only 9 studies\textsuperscript{26–31,33,35,37,38,39} utilized comprehensive neuropsychological battery to define HAND in the identified studies. Similarly, only seven studies\textsuperscript{26–29,31,33,35} considered the functional status of their participants in categorizing neurocognitive impairment.

Discussion
We conducted the scoping review to identify the commonly used HAND screening tools in SSA and document their psychometric properties and diagnostic accuracy. The most frequently utilized HAND screening tool identified was the IHDS, observed in more than half of the included studies. The other tools reported were: MoCA, HDS, NeuroScreen, CogState cognitive battery, and the CLQT. Overall, our results show that most of the commonly utilized HAND screening tools in SSA are suboptimal as evidenced by their varied sensitivity and specificity. Additionally, the extent of validation is inadequate as most of the studies only report specificity and sensitivity, and are missing important validation constructs notably construct validity and reliability. Besides, close to two-thirds of the included studies originated from a single country (South Africa). This potentially limits the generalizability of the current evidence on screening tools for HAND to other settings in SSA. These results are similar to earlier reviews on HAND screening tools\textsuperscript{20,41}.

Among the identified tools, IHDS had the most data on validation. However, its validation is suboptimal. Most studies reported only diagnostic accuracy\textsuperscript{24–30,33}. There is hardly any data on its construct validity and reliability over time. Besides, the diagnostic accuracy reported is generally not within the expected range (sensitivity of ≥80% and specificity of ≥55%) with some studies having very low specificity (37%)\textsuperscript{37} and very low sensitivity (45%)\textsuperscript{28} for the IHDS. The huge variation in the diagnostic accuracy could partly be due to the non-standard definition of HAND in the different studies and possible sociodemographic and clinical heterogeneity of the included samples.

The question as to whether all people living with HIV should be screened for HAND is an ongoing debate\textsuperscript{44}. An expert committee drawn from 30 countries, the Mind Exchange Working Group, recommends the screening of HIV-infected people early in the disease and then every 6–24 months, regardless of symptoms or risk factors\textsuperscript{15}. Another body, the British HIV Association, shares these sentiments by advocating for annual screening without giving details of the methods to be used or which populations to target\textsuperscript{45}. Likewise, the European AIDS Clinical Society recommends that screening should be limited to patients showing symptoms of cognitive impairment\textsuperscript{46}. Generally, universal screening interventions are rarely advocated, except when the screening strategy is very cheap, the screening measure has high accuracy, the consequences for being a false positive (such as distress, anxiety and healthcare costs) are minimal and the consequences of failing to diagnose are grave (that is, there is a highly effective and cost-effective intervention and a very poor outcome without the treatment). One important screening strategy could be to identify known risk factors of HAND (from well-designed epidemiological studies and clinical practice) and use these to develop a risk score and only screen those with a higher risk score (this will increase the diagnostic accuracy of the screening tool). Another strategy could be to train health care workers to be more aware of the signs and cues of HAND and then conduct indicated screening only on patients with suggestive signs and symptoms. Currently, the existing literature lacks evidence on the clinical utility of these tools (cost-effectiveness). More studies evaluating the utility of these tools are needed, especially in resource-limited settings. Before a screening test can be rolled out for use in the clinical setting, it should be subject to interventional research and the evidence should address the next steps in the clinical pathway. Unfortunately, this data is not available among the tools reviewed. There is an urgent need to extend the research in SSA to look at the clinical utility of screening tools to allow for adequate planning on how to incorporate HAND screening and monitoring into the health systems in areas having high HIV burden.

Among the newer HAND screening tools, the NeuroScreen is promising. Its initial evaluation in South Africa yielded good diagnostic accuracy when administered by lay healthcare workers. The tool has the potential to address some of the unique challenges and gaps facing resource-limited settings in screening for HAND including difficulty in performing long test
batteries, limited screening tools and a shortage of clinical staff. Nonetheless, more research with larger samples should be undertaken to validate the tool in several cultural settings in SSA to clarify its internal and external validity. Some of the issues raised during the initial evaluation need clarification in further studies including the possibility of floor effects and practice effects. The MoCA, the other new screening test, is gaining momentum in SSA. So far, its validation in SSA has yielded poor criterion validity, showing best test characteristics when screening for severe forms of HAND, before it can be widely used, more studies are needed to validate it.

It is worth noting that several methodological shortfalls were identified in the design and conduct of reviewed studies, which need to be considered by researchers in further validation studies. Some of the studies had small sample sizes and might have lacked the power to detect differences. There was also a huge variation in the definition of HAND in the studies. Only nine out of the 14 studies reviewed utilized a reference neuropsychological battery to define HAND and few considered the functional consequences brought about by HAND. Additionally, hardly any study reported construct validity and reliability of the screening measure. It is imperative that these aspects of validation are conducted and reported to comprehensively assess the utility of the given tools. Assessment of the feasibility of the screening measure in practice is another important aspect that was hardly reported by the reviewed studies. Feasibility data would be critical in guiding policymakers make informed decisions in primary health care as regard to screening for HAND. This includes the training of test administrators and the cost-effectiveness of the screening programme. These issues are particularly relevant in SSA where there is a scarcity of human, financial and technical resources and where the only option is task sharing/task-shifting.

The introduction of HAART altered the course of the HIV from a fatal disease to a chronic illness. A consequence of improved survival rates is the increasing number of people aging with HIV, shown to have heightened their risk of developing HAND. There is an important need to understand how the current HAND screening tools perform amongst those aging with HIV. So far, none of the studies reviewed has explored this important gap in research.

Our review has the following limitations. Firstly, we did not appraise the quality of the reviewed articles. Nonetheless, this is a primary limitation of scoping reviews; by not considering this, our study considered several articles that would have been excluded in a systematic review. Secondly, it is possible that we could have missed some articles not cited in the target databases during our literature search. Thirdly, the variation in the definition of HAND in some of the included studies may limit the comparison of the screening accuracy of identified tools across studies.

In conclusion, our review shows that the commonly utilized HAND screening tools in SSA are inadequately validated and standardized. A clear majority of existing studies only report diagnostic accuracy and fail to report their construct validity and reliability. A few promising tools are available, but they lack normative data to suggest clinical usefulness. As such, it is imperative for researchers to culturally adapt and adequately validate the existing tools in their settings before evaluating their clinical utility. There may be an important need to understand how the current HAND screening tools perform amongst those aging with HIV. So far, none of the studies reviewed has explored this important gap in research.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Grant information
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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments
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Anand A. Moodley
1 Department of Neurology, University of the Free State, Bloemfontein, South Africa
2 Universitas Hospital, Bloemfontein, South Africa

This is a well written and well-presented scoping review on the different screening tools of HAND in SSA. The authors have done an adequate literature search despite their reservations and have presented the currently available data on this very sensitive topic.

Sadly, there is still no consensus on the definition of HAND which makes comparisons of the different screening tools somewhat superfluous. However, any attempt at formalising the process is a step in the right direction. A useful starting point is a clear definition and rigorously tested diagnostic criteria for HAND. A gold standard using a reference neuropsychological battery is paramount in the definition of HAND. There is a visible void in published studies of a gold standard which thereby diminishes the validity of screening tests.

As the authors rightfully assert, screening tools for HAND are hardly ever performed due to a lack of standardisation. An essential point that is missing in this review is the difficulty encountered in using the IHDS for patients with hemiparesis of the non-dominant side, quadiparesis and ataxia which are often encountered in HIV infected patients presenting to neurology. Such patients require a test that focuses more on executive functioning rather than motor skills.

This scoping review sufficiently presents gaps in the knowledge of HAND and its screening. Current screening tests, apart from poor validity also suffer from not being culture-free. In the endeavour to devise a valid and reliable screening test for HAND, clinicians and investigators need to take these various issues into consideration. The test must be valid, reproducible and culture-free to be relevant for use in all SSA countries. The test must be able to differentiate between cortical and subcortical dementia and be relevant in an ageing HIV population.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** General Neurology, Neuroscience, Neuroradiology, Neuro-ophthalmology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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Author Response 23 Oct 2019

**patrick Mwangala**, KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya

We acknowledge the feedback given. Indeed, screening tools e.g. IHDS focusing more on motor skills disadvantage patients presenting with motor difficulties of the limbs. Hence there is a need for tool developers to keep this in mind when developing and refining tools to enhance their utility for such group of patients. Hence, we have noted this in the write-up and inserted the following statement in the conclusion.

“......tool developers also need to bear in mind the unique presentation of certain clients such as those with motor problems who may be naturally biased when taking HAND screening tests with greater emphasis on motor functions. The NeuroScreen presents good progress in this direction by assessing multiple domains of executive functioning such as working memory and attention.

**Competing Interests:** None

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Reviewer Report 18 February 2019

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**John A Joska**
Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

The authors have admirably tackled the thorny issue of screening for HIV-associated neurocognitive disorders (HAND) in Sub-Saharan Africa (SSA). The issue is thorny because the problems of screening span firstly the properties of the tools themselves, and secondly whether or not such tools can be feasibly applied in busy clinical settings. While to some extent, the two problems are linked, the data do not speak
directly to the second, and this is where the authors might consider moving these aspects down to a more "discursive" section of the paper, rather than weaving it into the main text.

The authors are broadly critical of the work done in SSA to date on these measures, primarily on the basis of a lack of evidence of construct validity, and also reliability. They also claim that variability in how HAND was classified across sites, as well as the range of sensitivity and specificity, limit how robust and generalisable the measures are. In lesser part, they are critical of the possibility that studies are limited in power, and by the application of gold standard test batteries.

In my view, not all of these criticisms are correct or fair. It is true that #construct_validity has not been properly addressed by researchers. It must be borne in mind that this requires an ongoing effort to correlate tool factors to theorised constructs of the underlying disease/disorder. In the case of a tool such as the IHDS, each of the 3 sub-items is based on existing neuropsychological sub-tests, so possibly at least some elements of #construct_validity are dealt with. It might be possible to have conducted some type of factor analysis or matrix analysis on data from authors.

The problem of how HAND is assessed across sites was not presented in the main Table, so it is not possible to evaluate whether this was in fact the case or not. The authors also state that "only" 9/14 papers utilised detailed neuropsychological batteries. I venture that 65% is not a minority but a reasonable proportion.

Other specific comments to consider:
- In the Abstract, the word "subtle" is used to describe the type of changes intended for HAND screening. I don't believe that this is the intention of any tool. Rather, most clinicians would be keen to identify severe, or clinically symptomatic disease.
- It is also noted in the Abstract that HAND screening is rarely done in SSA- but I suspect it is almost never done in ANY routine clinical practice. At least there are NO publications that I know of that report this.
- In the Introduction, the words "moderate" and "milder" are used interchangeably. While the context is mainly clear to an informed reader, it can be confusing. I suggest that the authors stick to one use of the construct of "less severe".
- Later in para 2 of the Introduction, possible causes of cognitive impairment in HIV are mentioned. But two of the most prevalent possibilities are not: namely low education, and the legacy effect of untreated HIV.
- In the 4th para, a reference is made to “adults at risk” of HAND but is only dealt with in passing. This is a hugely contentious topic. There are some data to suggest that low CD4 nadir, low education and some other factors are risk factors, but it is unclear whether this is of any help in SSA, when low CD4 nadir and low levels of education have historically been the norm. Perhaps either remove this reference, or use a separate paragraph to describe what it might be used for, then move on.
- The authors mention that a “package” of interventions for patients with HAND might be transferable by task-sharing to lay health workers. I would strongly suggest that many of these listed skills and interventions would not be. And that only a small number would be implementable by a LHW.
- Would the listing of the statistical parameters needed for good quality studies not be better mentioned in the Methods section?
- The issue of feasibility is not really addressed in the Introduction, and as there are no data in the Results that speak to it, makes my point above. This issue is perhaps beyond the "scope" of this review, and could be included as a small discursive paragraph.
• In the Discussion, the "variable" sensitivity and specificity are cited as a reason that the tools are sub-optimal. If the psychometric properties of the tools are at stake, then more detailed discussion of "decent" sensitivity/specificity needs to be included, with a discussion of NPV and PPV. Variability on its own is not an issue?
• Para 4 of the Discussion goes into some length about the feasibility of screening. As this review does not obtain data on any of these parameters, it is probably advisable to drop this to a lower discursive commentary. In the same para, the authors refer to the idea that the screening tools should be subject to "interventional research"- can this be clarified, as it could mean different things eg. interventions for HAND, or interventions to ascertain construct validity. Also, the term "clinical utility" is mentioned, followed by "cost-effectiveness" in parentheses. This needs to be clarified. This is again referred to in related to cost-effectiveness. If cost-effectiveness is a major need, then perhaps some detail on how this might be done should be supplied.

References

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mental health services in HIV

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Oct 2019

patrick Mwangala, KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya
The authors have admirably tackled the thorny issue of screening for HIV-associated neurocognitive disorders (HAND) in Sub-Saharan Africa (SSA). The issue is thorny because the problems of screening span firstly the properties of the tools themselves, and secondly whether or not such tools can be feasibly applied in busy clinical settings. While to some extent, the two problems are linked, the data do not speak directly to the second, and this is where the authors might consider moving these aspects down to a more “discursive” section of the paper, rather than weaving it into the main text.

Response:
As suggested by the reviewer, the paragraph highlighting the clinical utility of HAND screening tools has been moved down, towards the end of the discussion.

The authors are broadly critical of the work done in SSA to date on these measures, primarily on the basis of a lack of evidence of construct validity, and also reliability. They also claim that variability in how HAND was classified across sites, as well as the range of sensitivity and specificity, limit how robust and generalizable the measures are. In lesser part, they are critical of the possibility that studies are limited in power, and by the application of gold standard test batteries.

In my view, not all of these criticisms are correct or fair. It is true that construct validity has not been properly addressed by researchers. It must be borne in mind that this requires an ongoing effort to correlate tool factors to theorized constructs of the underlying disease/disorder. In the case of a tool such as the IHDS, each of the 3 sub-items is based on existing neuropsychological sub-tests, so possibly at least some elements of construct validity are dealt with. It might be possible to have conducted some type of factor analysis or matrix analysis on data from authors.

Response
We share the reviewer’s sentiments regarding the validity of the commonly used screening tools in the region up to date. Our arguments don’t in any way disregard the utility of the tools in question especially in the context of research. Our findings majorly emphasize the need for more focussed studies evaluating the construct validity and reliability of these tools (which is inadequately addressed at the moment) while at the same time appreciating the progress made so far. We have exercised due diligence in highlighting this observation in the revised document.

The suggested analyses (factor analysis or matrix analysis) would be difficult to do in the given set of results. This partly because of the heterogeneity of the included studies. Besides, we would require the original datasets of the studies which is beyond the scope of this review.

The problem of how HAND is assessed across sites was not presented in the main Table, so it is not possible to evaluate whether this was, in fact, the case or not. The authors also state that “only” 9/14 papers utilized detailed neuropsychological batteries. I venture that 65% is not a minority but a reasonable proportion.

Response
A column has been added in the main Table highlighting how HAND was assessed across the included studies. Indeed, 65% (proportion of the studies which used neuropsychological batteries in assessing HAND) is a reasonable figure. However, this figure should not be viewed in isolation when evaluating how HAND was assessed. Some of the studies (in the 65% figure) did not assess the functional status of the individuals.
while some did not categorize HAND into the 3 categories recommended by the Frascati criteria. Such methodological differences make it difficult to accurately compare such studies.

Other specific comments to consider:

In the Abstract, the word "subtle" is used to describe the type of changes intended for HAND screening. I don't believe that this is the intention of any tool. Rather, most clinicians would be keen to identify, or clinically symptomatic disease.

Response
This has been revised to reflect ‘clinically important changes’ and has been updated accordingly in the abstract.

It is also noted in the Abstract that HAND screening is rarely done in SSA- but I suspect it is almost never done in ANY routine clinical practice. At least there are NO publications that I know of that report this.

Response
We agree with the reviewer. To our knowledge, the screening of HAND in routine clinical practice has never been reported in any setting in the SSA region. This has been adjusted accordingly.

In the Introduction, the words "moderate" and "milder" are used interchangeably. While the context is mainly clear to an informed reader, it can be confusing. I suggest that the authors stick to one use of the construct of "less severe".

Response
We agree with the reviewer. For clarity and consistency purposes, we have maintained the term 'mild' and dropped 'moderate' whenever we have used the term to imply 'less severe' in to HAND.

Later in para 2 of the Introduction, possible causes of cognitive impairment in HIV are mentioned. But two of the most prevalent possibilities are not: namely low and the legacy effect of untreated HIV.

Response
This has been noted. We have included these factors as some of the possible causes of HIV-associated neurocognitive impairment in the second paragraph of the introduction.

In the 4th para, a reference is made to "adults at risk" of HAND but is only dealt with in passing. This is a hugely contentious topic. There are some data to suggest that low CD4 nadir, low education some other factors are risk factors, but it is unclear whether this is of any help in when low CD4 nadir and low levels of education have historically been the norm. Perhaps either remove this reference or use a separate paragraph to describe what it might be used for, then move on.

Response
We agree with the reviewer that this is a contentious issue. While there is some data suggesting that certain factors e.g. low CD4 nadir, could be risk factors generally, there is limited evidence from well-designed epidemiological studies within the region documenting such factors. We have deleted this reference in the revised version of the writeup.
The authors mention that a "package" of interventions for patients with HAND might be transferable by task-sharing to lay health workers. I would strongly suggest that many of these listed skills and interventions would not be. And that only a small number would be implementable by .

Response
We agree with the reviewer, and this has been revised accordingly. We have inserted the following statement.

“……there is limited empirical evidence documenting the appropriateness of the suggested HAND management approaches. There is a for more research to build such evidence and thereafter determine which packages of care could potentially be delivered by lay health care workers through task shifting in low-resource settings. Such an approach could prove effective in addressing some of the unique challenges facing the SSA region including inadequate staff with specialized skills, and the many competing healthcare needs.”

Would the listing of the statistical parameters needed for good quality studies not be better mentioned in the Methods section?

Response
We agree with the reviewer’s suggestion. We have moved the portion describing statistical parameters needed for good quality studies to the methods section of the paper under ‘Data extraction.’

The issue of feasibility is not really addressed in the Introduction, and as there are no data in the Results that speak to it, makes my point above. This issue is perhaps beyond the "scope" of this and could be included as a small discursive paragraph.

Response
We agree with the reviewer’s observation and as earlier stated, we have moved this portion to a smaller discursive part towards the end of the paper.


Response
The cited paper was excluded from the analysis because it did not aggregate the relevant results (psychometric properties of the different tools) by geographic location; USA versus South Africa. All the relevant results presented were combined results of the two settings.

In the Discussion, the "variable" sensitivity and specificity are cited as a reason that the tools are sub-optimal. If the psychometric properties of the tools are at stake, then detailed discussion of “decent” sensitivity/specificity needs to be included, with a discussion of NPV and PPV. Variability on its own is not an issue?

Response
From the results of this paper, we cannot make the conclusion the tools observed are ‘suboptimal’, hence not fit for use. Our key observation and finding that virtually all studies reviewed hardly reported construct validity and reliability of the tools they used. Besides, we also note that there is variability in the reported indexes of sensitivity, specificity, PPV, NPV. We have included the following statement (third paragraph of the discussion).
“Generally, the limited data on construct validity and reliability as well as the variability of diagnostic accuracy of the reviewed studies do not imply that these measures are less robust and . This observation calls for more studies to culturally adapt and validate these measures using well-designed studies to better understand their performance in the different settings within the region. With more data, we would be able to accurately determine the psychometric properties of these tools and determine which ones are consistently performing poorly and well. Normally, a cut-off value of 70% is recommended when selecting an optimal screening tool to yield a demanding threshold for type I and II errors. Besides, screening tools with sensitivity close to a chance level (≤50%) are avoided. In principle, high NPV’s are regarded as important. Going by , many of the reported indexes of sensitivity, specificity, PPV NPV would be inadequate.”

Para 4 of the Discussion goes into some length about the feasibility of screening. As this review does not obtain data on any of these parameters, it is probably advisable to drop this to a lower discursive commentary. In the same para, the authors refer to the idea that the screening tools should be subject to “interventional research”- can this be clarified, as it could mean different things e.g interventions for HAND, or interventions to ascertain construct validity. Also, the term “clinical utility” is mentioned, followed by “cost-effectiveness” in parentheses. This needs to be clarified. This is again referred to in related to cost-effectiveness. If cost-effectiveness is a major need, then perhaps some detail on how this might be done should be supplied.

Response
This has been noted, and in response, we have reduced and shifted this portion to a less discursive portion towards the end of the discussion. The small section on interventional research when evaluating the clinical utility of HAND screening tools has been dropped as the data do not directly speak to this.

Competing Interests: None