



SYSTEMATIC REVIEW

REVISED Screening tools for HIV-associated neurocognitive disorders among adults living with HIV in sub-Saharan Africa: A scoping review [version 2; peer review: 2 approved]

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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 clinically important changes in cognitive functioning and allow for early interventions. However, HAND detection in routine clinical practice has never been reported 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 mild 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 HAND screening tools in SSA.

Open Peer Review

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

Keywords

Screening tools, HIV, HIV-associated neurocognitive disorders, Adults, sub-Saharan Africa, Scoping review

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REVISED Amendments from Version 1

Aspects of the paper highlighting the clinical utility of HAND screening tools have been reduced and moved to a more discursive section in the discussion. We have also added a column in the main table, highlighting how HAND was assessed across the included studies to aid in the interpretation of the findings from the included studies. The listing of the statistical parameters needed for good quality studies have been moved from the introduction to the Methods section. More information on 'decent' sensitivity, specificity, NPV and PPV has been provided in the discussion. We have also updated some of the references and included some recent papers.

Any further responses from the reviewers can be found at the end of the article

Introduction

With the advent of highly active antiretroviral therapy (HAART), the 25 million people living with HIV-1/AIDS in sub-Saharan Africa (SSA) now have the potential for a near-normal life expectancy¹⁻³. Nonetheless, their wellbeing 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 dementia⁴. 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 criteria⁴. 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 viremia⁵⁻⁷. Nonetheless, its pattern has changed in the era of HAART⁸. Notably, the incidence of severe forms of HAND has reduced significantly, while the prevalence of moderate forms has increased⁵⁻⁷. 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, low educational achievement, irreversible CNS injury before ART initiation (the so-called legacy effect of untreated HIV), poor CNS penetration of some of the ARV drugs as well as chronic HIV brain infection^{9,10}.

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^{10,11}. Understanding HAND is important because of its clinical and functional impact on the individual including the heightened risk of mortality¹²; poor treatment adherence¹³; poor quality of life¹⁴; increased risk-taking behaviors¹⁵ and disruptions to everyday functioning¹⁶.

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 tools¹⁷. 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 excluded¹⁸. 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^{19,20}. Nonetheless, there is limited empirical evidence documenting the appropriateness of the suggested HAND management approaches. There is a need for more research to build such evidence and after that, 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.

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 functions²¹. 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 world²¹. 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. A recently published systematic review provided important information on the comprehensive neuropsychological assessment of NCI in people living with HIV in the SSA²².

Unlike the recently published review which focused on comprehensive neuropsychological assessment in SSA, our scoping review focusses on the HAND screening tools that are being used in the region 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. For validity, criterion-related validity (predictive, concurrence) and construct validity (convergent, discriminant)²³ 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 impairment* OR *neurocognitive impairment* OR *neurological complications* AND *HIV* OR *HIV-1* OR *HIV/AIDS* AND *adults* OR *youth* OR *older people* AND *Africa* OR *sub-Saharan Africa*. Additionally, reference lists of retrieved studies were searched for potentially eligible studies that were not identified from the database search.

Inclusion and exclusion criteria

Studies are eligible if they met the following criteria: i) included participants who were HIV-infected and with documented HAND; ii) focussed on screening HAND; iii) were conducted in SSA; and iv) conducted among adults (mean or median age of at least 18 years). The exclusion criteria are: i) non-empirical studies; ii) studies using other methods for screening HAND apart from brief screening (taking more than 20 minutes); iii) studies published in other languages other than English; iv) studies not conducted among adults, and v) studies carried out outside SSA.

Data extraction

Data extraction was done by two independent reviewers (PNM and AA). The data was extracted to Microsoft Excel spreadsheets with the following details: first author, date of publication, country of origin, study design, patient characteristics, tool administrators, type of screening tool used, reference neuropsychological tool used, and psychometric properties of the tool. For reliability, we extracted measures of internal consistency, test re-test and inter-rater reliability. For validity, we extracted construct, criterion, divergent or convergent validities whenever reported. Generally, a Cronbach alpha correlation close to 1 is considered good while a Pearson correlation ($r \geq 0.70$) is considered good^{24,25}

Data handling and synthesis

Data analysis involved collating and summarizing of 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

IHDS. Of the reviewed studies, eight evaluated the validity and diagnostic accuracy of the International HIV dementia scale^{26–33} 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 countries³⁰. It was initially evaluated in Uganda, where a cut-off of 10 was suggested, yielding a sensitivity of 80% and specificity of 55%³⁰. 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%^{28,29} and specificity ranged from 37% to 79%^{28,29}. Data was unavailable on other key components of validity such as test-retest reliability and construct validity.

Kwasa and colleagues³¹ 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 colleagues³³ 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).

HDS. HDS was originally developed in 1995 as a brief HAND screening tool³⁴ 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 HDS were deemed difficult for administration by non-neurologists and informally trained individuals, which led to the modified version, the IHDS in 2005³⁰. 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%³⁵. 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

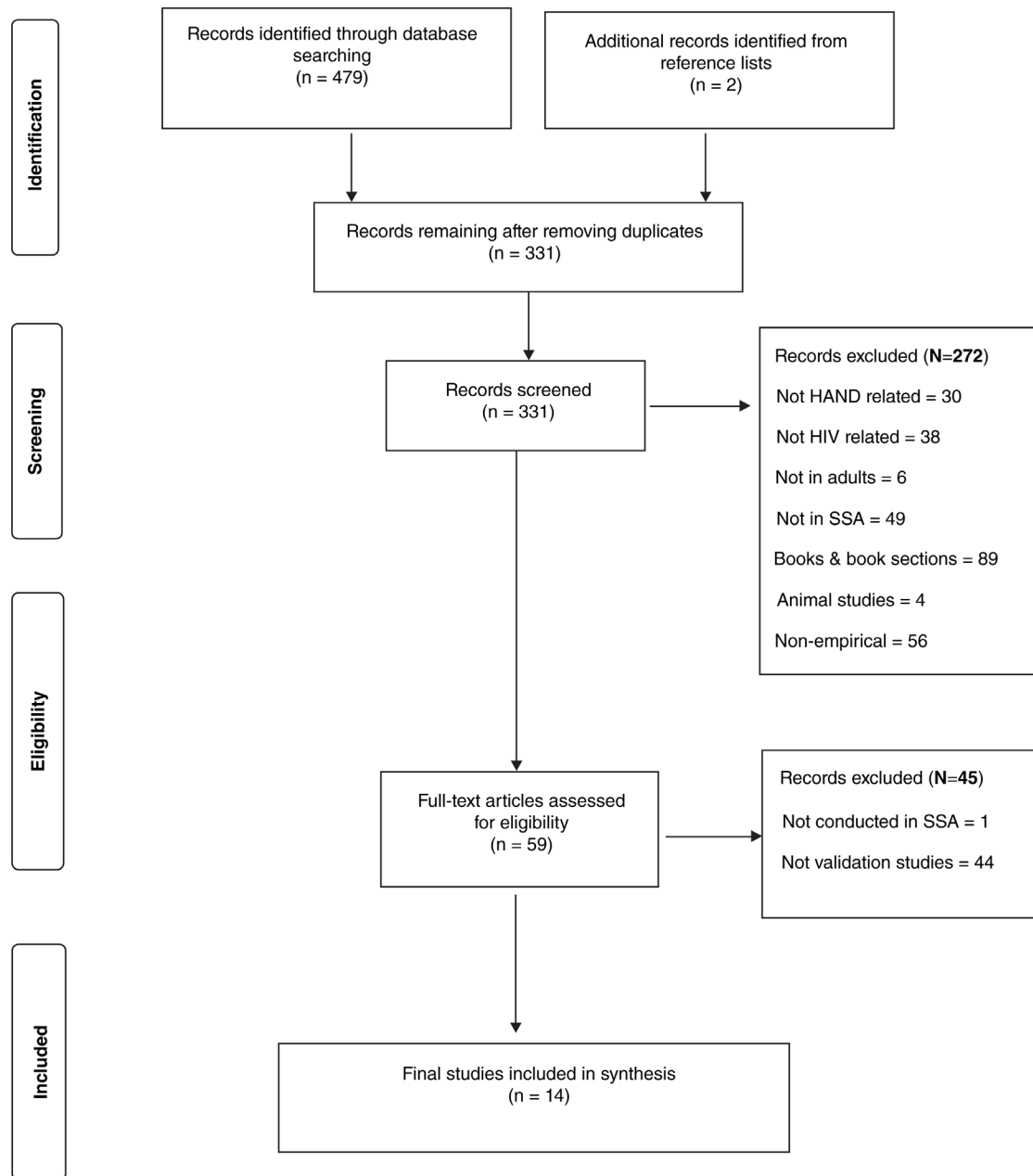


Figure 1. A flow diagram showing the article screening process of this review.

for mild cognitive impairment³⁶. 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^{37,38}. In the initial evaluation study³⁸, 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 study³⁷, a moderate correlation (Pearson’s $r = 0.36$) was found between the tool and reference neuropsychological battery. The tool demonstrated a sensitivity of 40%, a specificity of 72% and a diagnostic accuracy of 59%. With these results, the authors concluded that the MoCA test is not a reliable screening tool for cognitive impairment in HIV-infected patients in rural South Africa.

NeuroScreen. NeuroScreen is a computerized neuropsychological screening test battery designed for a smartphone running on

Table 1. A summary of the extracted data from eligible studies.

Author	Country & year of publication	Sample size	ART use	Mean/median age/age range	Tool validated	Reference tool	Issues on HAND diagnosis	Test-retest reliability	Inter-Rater reliability	Sensitivity and Specificity	PPV and NPV	Test administrator	Summary of findings
[37] Hakkers	South Africa, 2018	121	All	35	MOCA-B (Montreal cognitive assessment-basic)	NP battery	Used the most recent Frascati criteria to classify HAND). Reference tests were comprehensive (took >90 minutes). However, HAND category was dichotomised into 2 categories only (mild and severe) instead of the 3 standard categories (ANI, MND, HAD). Functional status was not reported.	Not done	Not done	40% sensitivity, 72% specificity. Diagnostic accuracy of 59%. Pearson's r of 0.36.	PPV of 43%, NPV of 70%.	Trained local counsellor	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.
[39] Robbins	South Africa, 2018	102	All	33.31	NeuroScreen	NP battery	Utilized Global Deficit Scores classification to categorize neurocognitive impairment. Reference tests were comprehensive (took >90 minutes). However, functional status was not reported.	Not done	Not done	81% to 93% sensitivity and 71% to 81% specificity for different combination of test scores.	53% to 61% PPV and 92% to 96% NPV.	lay health workers	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.
[33] Gouse	South Africa, 2017	94	75%	37.50	IHDS versus IHDS+HCSQ (International HIV Dementia Scale - HIV Cognitive Symptom Questionnaire)	NP battery	Used the most recent Frascati criteria to categorise HAND into 3 groups - ANI, MND and HAD. Reference tests were comprehensive (took >90 minutes). Functional status was not objectively measured.	Not done	Not done	94% sensitivity and 63% specificity for IHDS-HCSQ and 74% sensitivity and 70% specificity for IHDS	74% PPV and 70% NPV for IHDS; 75% PPV and 90% NPV for IHDS-HCSQ	Neuropsychology technician supervised by clinical psychologist.	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 large samples needed to evaluate it further.

Author	Country & year of publication	Sample size	ART use	Mean/median age/age range	Tool validated	Reference tool	Issues on HAND diagnosis	Test-retest reliability	Inter-Rater reliability	Sensitivity and Specificity	PPV and NPV	Test administrator	Summary of findings
[40] Yechoor	Uganda, 2016	181	80%	37	CogState	NP battery	Utilized Global Deficit Scores classification to categorize neurocognitive impairment. Reference tests were comprehensive (took >90 minutes). However, functional status was not reported.	Not done	Not done	Sensitivity of 57% and specificity of 77% at the optimal cut-off point	60% PPV and 74% NPV at the optimal cut-off	A trained research assistant	CogState may not be a useful tool to screen for HIV-associated NCI in Uganda, as many cases of NCI would be missed.
[27] Goodkin	South Africa, 2014	70	NR	31.5	International HIV Dementia Scale	Digit span, TMT	Used the most recent Frascati criteria to categorise HAND into ANI/MND and HAD. Utilized brief reference tests (took <90 minutes). Functional status was not measured hence the merging of ANI/MND.	Not done	Not done	69% Sensitivity, 74% specificity at cut off of 10.5	PPV of 67.7% and NPV of 76.9%	Not reported	The sensitivity for ANI/MND was less than for HAD. Lacked a measure of functional status.
[38] Robbins	South Africa, 2013	78	some	29.62	Montreal Cognitive Assessment Test	none	The Study explored the utility of MoCA tool by comparing performance between control and HIV-infected participants. Neurocognitive impairment was not categorized, and neither was functional status measured. No reference tests were used.	Not done	Not done	Not done	Not done	trained research staff	Floor effects were observed on some items. More validation needed.

Author	Country & year of publication	Sample size	ART use	Mean/median age/age range	Tool validated	Reference tool	Issues on HAND diagnosis	Test-retest reliability	Inter-Rater reliability	Sensitivity and Specificity	PPV and NPV	Test administrator	Summary of findings
[29] Royal	Nigeria, 2012	116	some	31.7	International HIV Dementia Scale	NP battery	Details on how neurocognitive impairment was classified are not clearly indicated. Reference tests were comprehensive (took >90 minutes). Functional status was measured using the Karnofsky Performance Status.	Not done	Not done	100% sensitivity; 37% specificity at cut off of 10	Not done	Not reported	The tool had very low specificity at the recommended cut off of 10.
[31] Kwasa	Kenya, 2012	30	Not reported	39	HIV Dementia Test	NP battery	The study used a slightly modified form of the Frascati criteria to categorize HAND into 3 categories – ANI, MND and HAD. Reference tests were comprehensive (took >90 minutes). Functional status was measured using the Karnofsky Performance Status.	Not done	K = 0.03 -0.65	63% sensitivity and 67% specificity	Not done	non-physician health workers and experts	Agreement between HCW and expert examiners was poor for many individual items of the tool. The tool had moderate sensitivity and specificity
[26] Breuer	South Africa, 2012	269	all	20–42	International HIV Dementia Scale	None	Diagnosis of HAND was made using the IHDS with a score 10,5 considered abnormal (positive for dementia). No reference tests were utilized, and neither was functional status measured.	Not done	K of 0.11	50% sensitivity; 69% specificity	Not done	Lay counsellors and nurses	There were many HAD false positives and negatives by counsellors.

Author	Country & year of publication	Sample size	ART use	Mean/median age/age range	Tool validated	Reference tool	Issues on HAND diagnosis	Test-retest reliability	Inter-Rater reliability	Sensitivity and Specificity	PPV and NPV	Test administrator	Summary of findings
[28] Joska	South Africa, 2011	190	none	27.5	International HIV Dementia Scale	NP battery	Used the most recent Frascati criteria to categorise HAND into 3 groups – ANI, MND and HAD. Reference tests were comprehensive (took >90 minutes). Functional status was measured using the Patients' Assessment of Own Function measure.	Not done	Not done	45% Sensitivity, 79% specificity at cut off of 10	Not done	Trained technicians	Individuals with HAD, who screened negative on the IHDS, performed poorly on some tests of executive function.
[41] Mupawose	South Africa, 2010	16	none	37.5	Cognitive Linguistic Quick Test	none	Details of how neurocognitive impairment was measured is not included and neither was functional status measured. No reference tests were used.	k of 0.61-0.90	Not done	Not done	Not done	Trained research assistants	Validation was not done
[35] Ogunrin	Nigeria, 2009	240	none	18-64	Modified HIV Dementia Scale	none	Details of how neurocognitive impairment was classified was not reported. The DSM-IV-TR was used as a gold standard. Functional status was assessed using self-report measures.	Not done	Not done	97.3% sensitivity, 80.4% specificity	PPV of 91.4% NPV of 93.2%	trained research staff	The tool was insensitive to memory impairment in asymptomatic HIV-infected patients.

Author	Country & year of publication	Sample size	ART use	Mean/median age/age range	Tool validated	Reference tool	Issues on HAND diagnosis	Test-retest reliability	Inter-Rater reliability	Sensitivity and Specificity	PPV and NPV	Test administrator	Summary of findings
[32] Singh	South Africa, 2008	20	none	34	International HIV Dementia Scale	NP battery	Used the most recent Frascati criteria to categorise HAND. Functional status was not measured.	Not done	Not done	88% Sensitivity; 50% specificity at cut off of 10	Not done	Not reported	IHDS is sensitive, however, its low specificity may limit its clinical utility.
[30] Sacktor	Uganda, 2005	181	some	34.2	International HIV Dementia Scale	NP battery	Details of how neurocognitive impairment was classified not reported.	Not done	Not done	80% Sensitivity; 55% specificity at cut off of 10	Not done	Trained physicians	IHDS is sensitive, however, its low specificity may limit its clinical utility

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.

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 America⁴². 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 Africa³⁹. 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.

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^{43,44}. In SSA, the tool has been evaluated once in Uganda⁴⁰. 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 CLQT⁴¹. 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,⁴¹.

Tool administrators

A total of eleven studies described the administrators of the HAND screening tools^{26,28,30–32,35,39–42}. 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^{26,39}. In one of them, the authors compared the effect of having trained research administrators versus lay administrators²⁶. In the study by Kwasa and colleagues³¹, 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 IHDS²⁶.

Methodological shortfalls of reviewed studies

Some of the reviewed studies had small sample sizes such as 16⁴¹, 20³² and 30³¹. Additionally, only 9 studies^{28–33,37,39,40} utilized comprehensive neuropsychological battery to define HAND in the identified studies. Similarly, only seven studies^{28–31,33,35,37} 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 inadequately validated, with most of the studies only reporting specificity and sensitivity while failing to document 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^{21,45}.

Among the identified tools, IHDS had the most data on validation. However, its validation is suboptimal. Most studies reported only diagnostic accuracy^{26–32,35}. 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 $\geq 80\%$ and specificity of $\geq 55\%$) with some studies having very low specificity (37%)²⁹ and very low sensitivity (45%)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.

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 generalizable. 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. Typically, 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 ($\leq 50\%$) are avoided. In principle, high NPV's are regarded as important. Going by this guidance, many of the reported indexes of sensitivity, specificity, PPV and NPV would be inadequate.

NeuroScreen, one of the most recent HAND screening tools 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 recent 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^{31,32,44}. 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.

There is no doubt that the research on HAND screening is gaining momentum in the SSA region, as evidenced by an increasing number of studies on the subject. Nonetheless, there is still a dearth of research on the clinical utility of HAND screening tools. Feasibility data would be critical in guiding the relevant stakeholders make informed decisions regarding the screening of HAND. At the moment, the question as to whether all people living with HIV should be screened for HAND is an ongoing debate⁹. 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 factors¹⁷. 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 target⁴⁶. Likewise, the European AIDS Clinical Society recommends that screening should be limited to patients showing symptoms of cognitive impairment⁴⁷. 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.

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 there is limited evidence on the reliability and validity of commonly utilized HAND screening tools in SSA. A clear majority of the tools are inadequately validated and standardized with most of the reviewed studies only reporting diagnostic accuracy. Among the studies reporting diagnostic accuracy, there is substantial variability in sensitivity, specificity, PPV, and NPV. However, a few promising tools are available such as the NeuroScreen, but they lack normative data to suggest clinical usefulness. These findings emphasize the need for well-designed studies to culturally adapt and validate HAND screening tools within the region. As this work continues, the next step would be to evaluate the clinical utility of these tools. We acknowledge that this work would require an ongoing effort to correlate tool factors to theorized constructs of HIV disease. In addition to this, tool developers 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. There is also 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 gap in research.

Data availability

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

Acknowledgments

The authors would like to thank the Director of Kenya Medical Research Institute for granting permission to publish this work.

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John A Joska 

Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

I am satisfied that the authors have been responsive to the review.

Competing Interests: No competing interests were disclosed.

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.

Version 1

Reviewer Report 24 April 2019

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Anand A. Moodley 

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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, quadriparesis 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.

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 focussing 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

Reviewer Report 18 February 2019

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John A Joska 

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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.
- This paper did not seem to make it in for some reason: [Comparison of Five Brief Screening Tools for HIV-Associated Neurocognitive Disorders in the USA and South Africa](#). Joska JA, Witten J, Thomas KG, Robertson C, Casson-Crook M, Roosa H, Creighton J, Lyons J, McArthur J, Sacktor NC. *AIDS Behav.* 2016 Aug;20(8):1621-31¹.
- 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.

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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.

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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.

This paper did not seem to make it in for some reason: Comparison of Five Brief Screening Tools Joska JA, Witten J HIV-Associated Neurocognitive Disorders in the USA and South Africa KG, Robertson C, Casson-Crook M, Roosa H, Creighton J, Lyons J, McArthur J, Sacktor NC. AIDS Behav. 2016 Aug;20(8):1621-31.

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 ($\leq 50\%$) 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

