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Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature

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Objective(s): To systematically review literature on brief screening tools used to detect and differentiate between normal cognition and neurocognitive impairment and HIV-associated neurocognitive disorders (HANDs) in adult populations of persons with HIV.

Design: A formal systematic review.

Methods: We searched six electronic databases in 2011 and contacted experts to identify relevant studies published through May 2012. We selected empirical studies that focused on evaluating brief screening tools (<20 min) for neurocognitive impairment in persons with HIV. Two reviewers independently reviewed retrieved literature for potential relevance and methodological quality. Meta-analyses were completed on screening tools that had sufficient data.

Results: Fifty-one studies met inclusion criteria; we focused on 31 studies that compared brief screening tools with reference tests. Within these 31 studies, 39 tools were evaluated and 67% used a comprehensive neuropsychological battery as a reference. The majority of these studies evaluated HIV-associated dementia (HAD). Meta-analyses demonstrated that the HIV Dementia Scale (HDS) has poor pooled sensitivity (0.48) and the International HIV Dementia Scale (IHDS) has moderate pooled sensitivity (0.62) in detecting a range of cognitive impairment. Five newer screening tools had relatively good sensitivities (>0.70); however, none of the tools differentiated HAND conditions well enough to suggest broader use. There were significant methodological shortcomings noted in most studies.

Conclusion: HDS and IHDS perform well to screen for HAD but poorly for milder HAND conditions. Further investigation, with improved methodology, is required to understand the utility of newer screening tools for HAND; further tools may need to be developed for milder HAND conditions.

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Introduction

Since the introduction of combination antiretroviral therapy (cART), the incidence of severe forms of HIV-associated neurocognitive impairment has declined significantly, whereas the prevalence of the milder forms has increased [1,2]. The nomenclature originally developed by the American Academy of Neurology Task Force on AIDS in 1991 was recently updated in 2007 in response to the change in presentation and research available on the natural history of HIV-associated neurocognitive complications [3]. There are now three different HIV-associated neurocognitive disorder (HAND) conditions. In order of increasing severity and related impact on everyday functioning, these are first, asymptomatic neurocognitive disorder (ANI) with a prevalence of 30–35% and characterized by at least mild neurocognitive impairment in two domains (at least 1.0 SD below the mean for age-education-appropriate norms) but with no evidence of difficulty with day-to-day functioning; second, mild neurocognitive disorder (MND) with a prevalence of 20–25% and characterized by at least mild neurocognitive impairment in two domains (at least 1.0 SD below the mean for age–education appropriate norms) and with mild interference with day-to-day functioning; and third, HIV-associated dementia (HAD) with a prevalence of 2–3% with generally moderate to severe impairments in neurocognitive functioning in multiple domains (2 SD or greater than demographically corrected means) and marked difficulties with everyday functioning [3]. Overall, the prevalence of HAND based on the new criteria is approximately 50–60% [1,4].

In the early years of the HIV epidemic, 20–30% of patients presented with severe cognitive impairment that was later classified as HIV-1-associated dementia complex [5]. The HIV Dementia Scale (HDS) was developed to screen for HAD [6] and later the International HDS (IHDS) [7] was developed for use in global settings. These instruments have had varying degrees of success in screening of those with the milder forms of HAND (i.e. ANI and MND). The clinical significance of identifying the milder forms of HAND is important, as they can have a significant impact on the lives of people living with HIV. They have been shown to interfere with medication adherence [8,9], workplace performance [10], driving [11] and ability to carry out tasks independently [12,13]. The consequences of these effects have been seen in decreased health-related quality of life [14] and increased mortality rates [2,15] in people with HAND.

To better assist in prevention, treatment and management of HAND, it is important that screening tools be developed and evaluated. Before widespread use for clinical treatment decision-making, these tools need to be shown to have adequate sensitivity and specificity with HAND; they need to be brief enough to be used in the clinic or health centre, and able to be administered by a trained individual with minimal equipment.

To determine which screening tools for HAND meet these criteria, we have undertaken the first systematic review of the literature with respect to the screening tools for HAND. Our objective is to systematically review the literature on brief screening tools that can detect neurocognitive impairment and are able to differentiate among the various forms of HAND in the adolescent and adult population of persons living with HIV and AIDS.

Materials and methods

We conducted literature searches in MEDLINE, EMBASE, PsycINFO, LILACS and CINAHL in May 2011 for published, full-length research articles. An experienced librarian in systematic review methods assisted us in developing a search strategy (included in Appendix A, http://links.lww.com/QAD/A370). We did not apply date or language restrictions in the search strategy because we did not want to limit the investigation to tools administered only in English. We also contacted key experts in the field for recommendations and received articles for potential inclusion until the start of May 2012.

Inclusion criteria

Participants

Only studies reporting on participants who were adolescent or adult age were included (generally age >16 years). To be included in the review, individual studies needed to include participants who were HIV-positive and with some form of documented HIV-associated neurocognitive impairment, or be characterized/diagnosed with having any HAND [i.e. ANI, MND, minor cognitive motor disorder (MCMD), or HAD] [3,5]. The studies evaluated neurocognitive impairment in different ways, and this is a limitation of the current state of the literature.

Screening tools

We considered studies that focused on screening for 'neurocognitive' or 'neuropsychological' impairments or HAND [3,5]. The ways in which studies addressed screening tools included evaluating the utility of a specific screening tool, comparing different screening tools and validating screening tools. The focus of the review was then restricted to include only those articles that evaluated the utility of screening tool(s) against a separate reference or criterion. We defined screening tools to include pen and paper tests, algorithms and computerized tests and excluded biological tests (i.e. studies looking at biomarkers). In addition, we focused on 'brief' screening tools, and we defined this as those that took approximately 20 min or less to perform. This was done because the focus was screening tests that might be potentially useful in a clinic or healthcare setting to detect HAND.

Study designs
All studies needed to report findings from empirical research. We included primary studies and considered both cross-sectional and longitudinal investigations. We excluded primary studies that used qualitative methods or case study methods. We also considered systematic review articles.

Search and data extraction
Two reviewers independently assessed the titles and abstracts of the citations from the search according to the selection criteria. For the citations that met the criteria, data from full texts were extracted by one reviewer and checked independently for accuracy by a second reviewer. We contacted study authors to obtain any information that was missing. Any disagreements between reviewers on data extracted were resolved by consensus or by a third reviewer.

Methodological quality
Two reviewers independently appraised the quality of the selected articles from the search using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [16]. This 14-item tool was specifically designed to assess the quality of primary studies addressing diagnostic accuracy. Disagreements between the reviewers on the different QUADAS items were resolved by consensus.

Results
There were 2030 citations in the database searches and 334 of these were duplicates between databases. The review of titles and abstracts resulted in the identification of 316 articles for full assessment, with 1380 articles being excluded because they did not meet our inclusion criteria. We completed a full appraisal of 304 articles (we were unable to locate 12 full articles despite contacting the authors), and at this stage found that 253 of the 304 did not meet inclusion criteria resulting in 51 studies for inclusion. Articles that did not meet inclusion criteria were for the following reasons: six did not focus on people living with HIV; 185 did not evaluate screening tools; 28 did not include screening tools that are brief; eight did not report on empirical studies; and 26 articles did not include participants with HAND or impairment. [See Fig. 1 for Search strategy].

Of the 51 studies that met criteria [6,7,17–65], we identified two main categories into which these studies

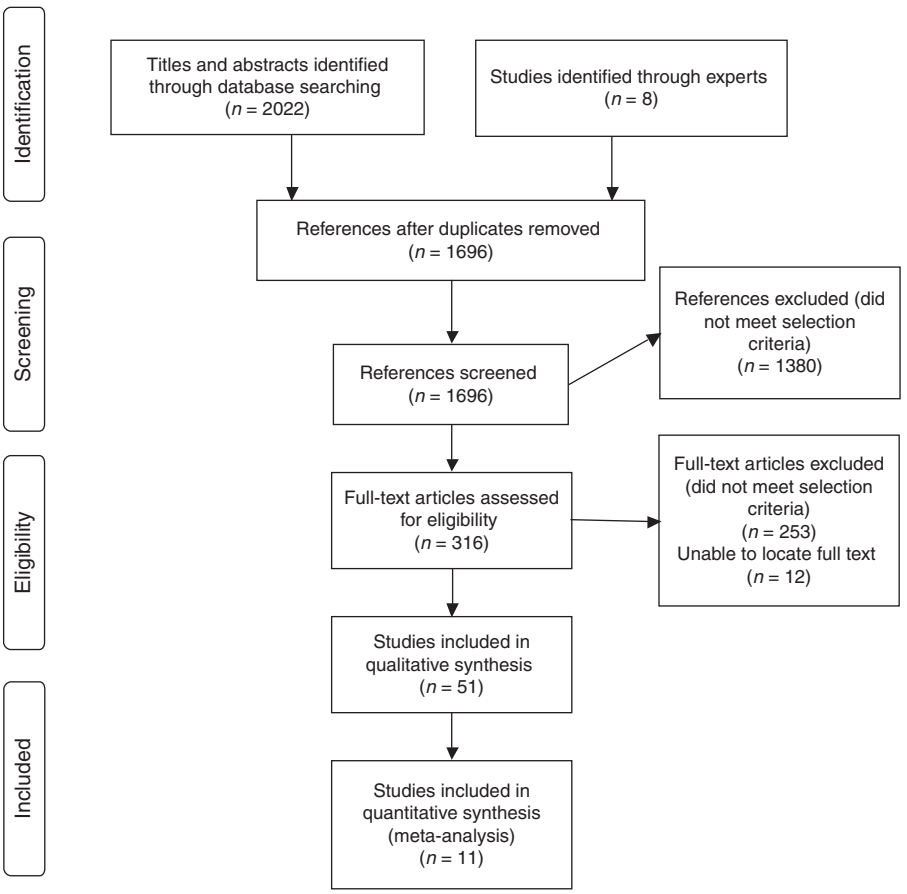

Fig. 1. Search strategy.

could be divided: first, studies that evaluated screening tools by comparing them with a reference standard or criterion ($n = 31$ of 51 or 61% of studies evaluated) [6,7,17–44,64], and second, studies that evaluated screening tools by other methods ($n = 20$ of 51 or 39% of studies) [45–63,65]. For the purposes of the current article, we decided to focus our systematic review analyses on the first category of studies ($n = 31$), [see Table 1 for Characteristics of studies on brief screening tools for HIV-associated neurocognitive disorders] as this is the most accepted method of evaluating a diagnostic tool (Results from the second category of studies can be found in Appendix B).

Study characteristics ($N = 31$ studies)

Thirty-one studies are the focus of this subsequent analysis. Thirty of the 31 used a cross-sectional design [6,7,17–36,38–44,64] and one used a longitudinal design [37]. Eighteen of these studies (60% of all studies examined) were conducted in the USA [6,7,17–19,22, 23,26,27,31,33–38,42,44]; three in Australia [20,21,32]; three in South Africa [24,28,41]; one each in the UK [25]; Germany [43]; Belgium and the Netherlands [29]; Switzerland [40]; Uganda [7]; Kenya [30]; India [64]; and one at sites across the world [39]. The participants in all of the studies combined totalled a sample of 5837 participants, and the individual study samples ranged from 20 [41] to 1549 [39] participants. Twenty-five studies used convenience sampling [6,7,17–19,22,24,25,27–33, 35–41,43,44,64], and two used random sampling [20,34].

Neurocognitive screening tool evaluations

Types of screening tools evaluated

Within these 31 studies, 39 screening tool evaluations were conducted with 21 unique screening tools. Eleven studies evaluated the HDS (35%) [6,18,19,24,31,34, 38,40,42–44]; four the IHDS (13%) [7,28,41,64]; three the CogState Computerized Battery (10%) [20,32,35]; three the Mini-Mental State Examination (MMSE) (10%) [6,31,64]; and other tools were evaluated in the remaining 16 studies [6,17,19,21–23,25–27,29,30,33,36,37,39,64]. Twenty-one (68%) [6,7,17–23,26,27,30,32,33,35–39, 41,42] studies reported evaluating screening tools in English and eight (26% of studies overall) [7,24,28–30, 41,43,44] in another language.

Presence and severity of neurocognitive impairment assessed

Of the 31 studies, 11 (35%) focused on detecting HAD [6,7,18,22,28,30,31,34,40,44,64], four also screened for MND [28,30,40,64] or MCMD [18,22,34,44], and five screened for ANI [28,30,34,40,64]. Seventeen studies (55%) focused on detecting neurocognitive impairments and/or deficits [17,18,20–23,25–27,29,33,35,36,38,41, 42,66]. Eight studies (26%) [6,7,18,19,22,31,34,44] used 1991 criteria [5] and five studies (16%) [21,28,30,40,64] used the revised 2007 criteria [3] for diagnosing HAND. It is important to note that many of the studies were published prior to the establishment of the 2007 HAND criteria.

Assessment of functional status

Functional status was measured objectively in nine studies (29%) [20–22,30,34,38,39,44,64] (29%) and subjectively in seven studies (23%) [23,26,28,29,37, 40,42]. It is worth noting that functional status was assessed differently across studies, and only three of the studies that objectively assessed functional status [20,29,63] used the recent 2007 Frascati criteria to classify participants.

Length of time of reference test/criterion

We were interested in determining whether the quality and rigour of the criterion or reference test used was related to the outcome of the screening tests. We examined and coded the length and comprehensiveness of the neuropsychological test battery into 'short', 'medium' and 'long and comprehensive' battery (See Table 2 for 'short', 'medium' and 'long' battery criteria). Nine studies (29%) used a 'short' [6,23–25,27,33,37, 41,43], 11 (35%) used a 'medium' [7,22,28–30,32,35, 38,40,42,44] and seven (23%) used a 'long' [17–21,26,36] battery. For the HDS and IHDS, there were sufficient data to evaluate the associations between sensitivity and specificity and battery size. There was a significant association for the HDS between sensitivity and size of battery ($P < 0.05$), with sensitivity decreasing with increasing battery size. There was a trend for increasing specificity with increasing battery size, but this association was not significant.

Type of reference test / criterion and sensitivity performance

Twenty-six of the 39 tool evaluations (67%) used a detailed neuropsychological battery as the reference standard [18–22,26,28–30,32,35,36,38,40–44,64]. Fifteen tool evaluations (38%) reported adequate sensitivities (≥ 0.75). Adequate sensitivities (≥ 0.75) were reported for the HDS [6,24,31,40,44], IHDS [7,41], CogState [20], Grooved Pegboard [6], Hopkins Verbal Learning Test-Revised/Grooved Pegboard Test Non-Dominant Hand [19], Hopkins Verbal Learning Test/WAIS-III Digit Symbol [19], Mental Alternation Test [27], Motor Battery [36], the Screening Algorithm [21] and the Timed Gait Test [39].

Meta-analysis findings

The HDS and IHDS have been sufficiently studied to perform a meta-analysis for each tool. For inclusion in the meta-analysis, the articles we reviewed were required to use a neuropsychological battery as the reference test; use the neuropsychological battery to classify the participants as 'impaired'; and report the incidence of impairment, sensitivity and specificity of the tools. Seven studies on the HDS [6,19,34,38,40,42,44] and three studies on the

Table 1. Characteristics of studies on brief screening tools for HIV-associated neurocognitive disorders.

Author; Location	Design	Recruitment method	Participants (mean age; mean years education; percentage male)	Tools examined
Becker *et al.* [17]; USA	Cross-sectional	Convenience sampling	Age: 51 (HIV+); 51 (HIV−); Education: 15 (HIV+); 15 (HIV−) Male: 96% (HIV+); 78% (HIV−)	The Computer Assessment of Mild Cognitive Impairment (CAMCI)
Bottiggi *et al.* [18]; Kentucky, USA	Cross-sectional	Convenience sampling	Age: 39; Education: 14; Male: 87%	HIV Dementia Scale
Carey *et al.* [19]; San Diego, USA	Cross-sectional	Convenience sampling	Age: 41; Education: 14; Male: 84%	Hopkins Verbal Learning Test Revised and Grooved Pegboard Test nondominant hand (PND) pair; Hopkins Verbal Learning Test Revised and WAIS-III Digit Symbol (DS) subtest pair; HIV Dementia Scale
Cysique *et al.* [20]; Sydney, Australia	Cross-sectional	Random sampling	Age: 47 (Advanced HIV); 48 (ADC); 49 (HIV−); Education: 14 (Advanced HIV); 14 (ADC); 15 (HIV−); Male: 98% (Advanced HIV); 100% (ADC); 100% (HIV−)	CogState
Cysique *et al.* [21]; Sydney, Australia	Cross-sectional	Convenience sampling	Age: 49 (HIV+); 47 (HIV−); Education: 14 (HIV+); 15 (HIV−); Male: 100% (HIV+); 100% (HIV−)	Screening Algorithm
Ellis *et al.* [22]; 15 sites, USA	Cross-sectional	Convenience sampling	Age: 44; Education: 14; Male: 86%	The NeuroScreen – Brief Neurocognitive Screen (BNCS) and Brief Peripheral Neuropathy Screen (BPNS)
Fogel [23]; USA	Cross-sectional	NR	Age: NR; Education: NR; Male: 92%	Brief Cognitive Screen (BCS) – memory subtest, verbal fluency items and conflicting stimulus test of the High Sensitivity Cognitive Screen (HSCS)
Ganasen *et al.* [24]; Western Cape, South Africa	Cross-sectional	Convenience sampling	Age: 34; Education: 10; Male: 26%	HIV Dementia Scale
Garvey *et al.* [25]; London, UK	Cross-sectional	Convenience sampling	Age: 48; Education: NR; Male: 84%	Prospective and Retrospective Memory Questionnaire (PRMQ)
Gonzalez *et al.* [26]; USA	Cross-sectional	Not reported	Age: 40; Education: 14; Male: 100%	California Computerized Assessment Package (CalCAP), mini-version
Jones *et al.* [27]; Baltimore, USA	Cross-sectional	Convenience sampling	Age: NR; Education: 13; Male: 79%	Mental Alternation Test
Joska *et al.* [28]; Cape Town, South Africa	Cross-sectional	Convenience sampling	Age: 30 (HIV+); 25 (HIV−); Education: 10 (HIV+); 11 (HIV−); Male: 21% (HIV+); 38% (HIV−)	International HIV Dementia Scale
Knippels *et al.* [29]; the Netherlands and Flanders, Belgium	Cross-sectional	Convenience sampling	Age: 39; Education: NR; Male: 100%	Medical Outcomes Study HIV (MOS-HIV), four-item version in Dutch
Kwasa *et al.* [30]; Kisumu, Kenya	Cross-sectional	Convenience sampling	Age: 39; Education: NR; Male: 57%	HIV Dementia Diagnostic Tool
Lyon *et al.* [31]; Washington, DC; USA	Cross-sectional	Convenience sampling	Age: 17 (Dementia); 17 (No dementia); Education: NR; Male: 83% (Dementia); 45% (No dementia)	HIV Dementia Scale; Mini Mental State Examination
Maruff *et al.* [32]; Melbourne, Australia	Cross-sectional	Convenience sampling	Age: 46 (ADC); 47 (controls, AIDS but no ADC or MND); Education: 13 (ADC); 12 (controls, AIDS but no ADC or MND); Male: 89% (ADC); 91% (controls, AIDS but no ADC or MND)	CogState (brief battery)
Minor *et al.* [33]; USA	Cross-sectional	Convenience sampling	Age: 38; Education: 12; Male: 52%	Coin Rotation Test
Morgan *et al.* [34]; San Diego, USA	Cross-sectional	Random sampling	Age: 40 (HIV+); 37 (HIV−); Education: 13 (HIV+); 14 (HIV−); Male: 83% (HIV+); 68% (HIV−)	HIV Dementia Scale
Muniyandi *et al.* [64]; Thanjavur, India	Cross-sectional	Convenience sampling	Age: NR; Education: NR; Male: 61%	Mini Mental State Examination (MMSE); Bender Gestalt Test (BGT); Wechsler Memory Scale; International HIV Dementia Scale (IHDS)
Overton *et al.* [35]; St. Louis, USA	Cross-sectional	Convenience sampling	Age: 40 (median); Education: NR; Male: 72%	CogState
Parsons *et al.* [36]; USA	Cross-sectional	Convenience sampling	Age: 24; Education: 13; Male: 66%	Motor battery (timed gait, grooved pegboard, finger-tapping)
Power *et al.* [6]; Baltimore, USA	Cross-sectional	Convenience sampling	Age: 42 (HIV−); 37 (Asymptomatic HIV+); 36 (nondemented AIDS); 39 (mildly demented AIDS); 39 (severely demented AIDS); Education: 15 (HIV−); 14 (Asymptomatic HIV+); 14 (Non-demented AIDS); 14 (mildly demented AIDS); 11 (severely demented AIDS); Male: 89%	HIV Dementia Scale; Mini Mental State Examination; Grooved Pegboard
Revicki *et al.* [37]; Baltimore-Washington, USA	Longitudinal	Convenience sampling	Age: 37; Education: NR; Male: 66%	4-item Cognitive Function Scale (CF4) from HIV Health Survey and Complete 6-item Cognitive Function Scale (CF6) from Medical Outcomes Study (MOS)
Richardson *et al.* [38]; Boston Area, USA	Cross-sectional	Convenience sampling	Age: 41; Education: 12; Male: 65%	HIV Dementia Scale

(*continued overleaf*)

Table 1. (*continued*)

Author; Location	Design	Recruitment method	Participants (mean age; mean years education; percentage male)	Tools examined
Robertson *et al.* [39]; ACTG sites all over the world NYC, Chapel Hill and 42 sites around the world	Cross-sectional	Convenience sampling	Age: 38 (AIDS); 39 (SX); 35 (ASX); 35 (HIV−); Education: 14 (AIDS); 15 (SX); 15 (ASX); 16 (HIV−); Male: 87% (AIDS); 96% (SX); 91% (ASX); 56% (HIV−)	Timed Gait Test
Sacktor *et al.* [7]; Baltimore, USA and Uganda	Cross-sectional	Convenience sampling	Age: US HIV+: 43 (no impairment); 44 (subclinical impairment); 47 (mild dementia); 44 (moderate dementia); 49 (severe dementia); Uganda: 37 (HIV+); 31 (HIV−); Education: US HIV+: 14 (no impairment); 13 (subclinical impairment); 13 (mild dementia); 12 (moderate dementia); 13 (severe dementia); Uganda: 9 (HIV+); 10 (HIV−); Male: NR	International HIV Dementia Scale
Simioni *et al.* [40]; Geneva, Switzerland	Cross-sectional	Convenience sampling	Age: NR; Education: NR; Male: 72%	HIV Dementia Scale
Singh *et al.* [41]; Durban, South Africa	Cross-sectional	Convenience sampling	Age: 34 (median); Education: NR; Male: 40%	International HIV Dementia Scale
Smith *et al.* [42]; USA	Cross-sectional	Not reported	Age: 41 (NP normal); 41 (NP abnormal); Education: 14 (NP normal); 13 (NP abnormal); Male: NR	HIV Dementia Scale
Von Giesen *et al.* [43]; Dusseldorf, Germany	Cross-sectional	Convenience sampling	Age: 45 (mildly demented); 41 (not demented); Education: NR; Male: 100% (mildly demented); 100% (not demented)	HIV Dementia Scale
Wojna *et al.* [44]; Puerto Rico, USA	Cross-sectional	Convenience sampling	Age: 36 (HIV+); 34 (HIV−); Education: 12 (HIV+); 13 (HIV−); Male: 0%	HIV Dementia Scale, Spanish

ADC, AIDS Dementia Complex; ASX, asymptomatic; MND, mild neurocognitive disorder; NR, not reported; SX, symptomatic.

IHDS met these criteria [7,28,41]. One study on the IHDS looked at this tool in two different participant pools [7], and as such, the results from each of the participant pools were included in the meta-analysis.

Meta-analysis and qualitative results with the HIV Dementia Scale

The Forest Plot of the meta-analysis of the HDS (Fig. 2a) shows a large range in the sensitivities for the HDS across studies; four studies [19,34,38,42] reported poor sensitivity (i.e. $\leq$0.55) and three studies [6,40,44] reported good sensitivity (i.e. $>$0.80). Overall, the pooled sensitivity of these studies (i.e. 0.48) would suggest that the HDS (without any corrections for demographics) is not useful for detecting a range of HAND conditions.

The studies that report adequate sensitivities for the HDS fall into three main groups. The first group, the study by Power *et al.* [6] (sensitivity 0.81), utilized the HDS to detect frank dementia. The second group, studies by Simioni *et al.* [40] and Wojna *et al.* [44] (sensitivity 0.82 and 0.87), used a high cut-off score (13 or 14). We meta-analysed these two studies together (Fig. 2b) and determined that the pooled sensitivity increased greatly when only evaluations with higher cut-offs were used (0.84). Finally, Morgan *et al.* [34] used demographic corrections for age and education (*T*-scores) and increased the sensitivity from 0.17 with a cut-off of 10 or less to 0.71. These results suggest that the utility of the HDS can be improved by increasing the cut-off score, or by using demographically adjusted *T*-scores, but only for the detection of dementia.

The two studies with the lowest and comparable sensitivities [i.e. 0.09 and 0.17; Preliminary results from our CIHR Screening study ($n = 20$) also produced similar results with a sensitivity of 0.12 using a 'long and comprehensive' battery (personal communication, S.B.R., 13 March 2013)] both used a 'long and comprehensive' reference battery [19,34], whereas those that used a 'medium' reference battery [38,40,42,44] had not only higher sensitivities but also a larger range of sensitivities (0.39–0.87). These discrepancies in results using 'medium' versus 'long' reference batteries suggest that the rigour and comprehensiveness of the battery may be important determinants to consider when evaluting the overall test performance of screening tests for HAND.

Meta-analysis with the International HIV Dementia Scale

The meta-analysis of the IHDS (Fig. 2c) demonstrated more consistency than the HDS, although these studies employed only 'small' and 'medium' length reference batteries. One [28] study reported a poor sensitivity for the IHDS (0.45) and the other three [7,41] studies reported good sensitivities ($\geq$0.80). Overall, the pooled sensitivity of these studies (0.62)

Table 2. Study outcome in literature on screening tools for HIV-associated neurocognitive disorders.

Study (Author; Location)	Sample size (total; by group)	Impairment evaluated (type(s); classification system)	Tool characteristics (person can administer; time to administer; materials needed)	Reference test	Reference test details (size of battery; objective assessment; domains assessed; language of administration)	Sensitivity; Specificity	Main findings
HIV Dementia Scale (HDS)							
Bottiggi *et al.* [18]; Kentucky, USA	46	Types: MCMD, HAD, Neurocognitive Deficits or Impairment (memory, attention, psychomotor, and construction); Classification: 1991	Person: NR; Time: NR; Materials: NR	NP battery	Size: long; Objective: NR; Domains: Intelligence, attention/concentration, memory, language, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Cut-off ≤10: Sensitivity: 0.36; Specificity: 0.94;	HDS is not efficient in predicting the presence of subtle and mild HIV-dementia.
Carey *et al.* [19]; San Diego, USA	190	Type: NP impaired and unimpaired; Classification: DSM-IV 1994, AAN 1991, Grant and Atkinson 1995	Person: NR; Time: 5 min; Materials: NR	NP battery	Size: long; Objective: NR; Domains: Intelligence, attention/concentration, memory, language, executive functioning. visuo-spatial, speed of processing, motor; Language: English	Cut-off <11: Sensitivity: 0.09; Specificity: 0.98;	HDS is less accurate than paired NP test combinations- Hopkins Verbal Learning Test Revised (HVLTR; Total Recall) and the Grooved Pegboard Test nondominant hand (PND) pair, and the HVLTR and WAIS-III Digit Symbol (DS) subtest pair in classifying HIV-positive participants as NP impaired or not.
Ganasen *et al.* [24], Western Cape, South Africa	474	Type: NP impaired and unimpaired; Classification: MMSE used as the gold standard	Person: NR; Time: NR; Materials: NR	Mini-Mental State Examination (MMSE)	Size: short; Objective: NR; Domains: Attention/ concentration, memory, motor; Language: Xhosa, Afrikaans	Cut-off ≤10: Sensitivity: 0.80; Specificity: 0.80;	HDS and MMSE were significantly correlated and showed significant agreement. Nonetheless, the HDS identified more participants who demonstrated cognitive impairment than the MMSE. HDS cut-off of ≤10 yielded a sensitivity of 80%, specificity of 80% and discriminated between the presence and absence of cognitive impairment 90% of the time.
Lyon *et al.* [31]; Washington, DC, USA	71	Type: HAD, HIV encephalopathy in adolescents; Classification: 1991	Person: NR; Time: 10 min; Materials: NR	ANI 1991 Criteria	Size: NR; Objective: NR; Domains: Intelligence, attention/memory, language. Language: NR	Cut-off of ≤10: Sensitivity: 0.83; Specificity: 0.79; Cut-off of ≤9: Sensitivity: 0.88; Specificity: 0.83;	No statistically significant differences in sensitivity and specificity between the HDS and MMSE. Using standard cut-offs, HDS had 83% sensitivity and 79% specificity, although MMSE had 50% sensitivity and 92% specificity. The optimal cut-off score for the HDS, producing the highest sensitivity and specificity, was ≤9, providing 88% sensitivity and 83% specificity (87% correct classification).
Morgan *et al.* [34]; San Diego, California	317; 135 (HIV+), 182 (HIV-)	Type: ANI, MCMD, HAD; Classification: 1991	Person: NR; Time: 5–10 min; Materials: NR	Modified AAN 1991 Criteria and Grant and Atkinson 1995 Criteria	Size: long; Objective: Yes; Domains: NR; Language: NR	Demographically adjusted *T*-score <40: Sensitivity: 0.71; Specificity: 0.74; Raw cut-off score ≤10: Sensitivity: 0.17; Specificity: 0.94;	In comparison to the traditional HDS cut-off score (raw score total ≤10), use of the demographically adjusted normative standards significantly improved the sensitivity (from 17% to 71%) and overall classification accuracy (increasing the odds ratio from 3 to approximately 6). The application of demographically adjusted normative standards on the HDS improves the clinical applicability and accuracy.
Power *et al.* [6]; Baltimore, USA	130	Type: HAD; Classification: 1991	Person: NR; Time: NR; Materials: NR	Memorial Sloan Kettering Dementia Evaluation; Mini-Mental State Exam (MMSE); Grooved Pegboard (PB)	Size: short; Objective: NR; Domains: Attention/ concentration, memory, executive functioning, motor; Language: English	Cut-off ≤10: Sensitivity: 0.80; Specificity: 0.91;	HDS demonstrated greater efficiency in identifying HIV dementia than Grooved Pegboard and the Mini-Mental State Examination.

(*continued overleaf*)

Table 2. (*continued*)

Study (Author; Location)	Sample size (total; by group)	Impairment evaluated (type(s); classification system)	Tool characteristics (person can administer; time to administer; materials needed)	Reference test	Reference test details (size of battery; objective assessment; domains assessed; language of administration)	Sensitivity; Specificity	Main findings
Richardson *et al.* [38]; Boston area, USA	40	Types: Neurocognitive Deficit or Impairment (impairment in attention and concentration, psychomotor functioning, behavioural inhibition, constructional praxis); Classification: Performance at least 2 standard deviation units below established norms on one or more independent NP measures in two or more domains of functioning	Person: NR; Time: 10 min; Materials: NR	NP battery	Size: Medium; Objective: Yes; Domains: Memory, executive functioning, motor; Language: English	Cut-off ≤10: Sensitivity: 0.55; Specificity: 0.75;	HDS prediction resulted in modest sensitivity and moderate specificity. In ROC curve analysis, area under the curve was only modestly better than chance (0.58). Optimal cut-off for the HDS is ≤10.
Simioni *et al.* [40], Geneva, Switzerland	100 (50 with cognitive complaints, 50 without cognitive complaints)	Types: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: Medium; Objective: No; Domains: Intelligence, attention/ concentration, memory, language, executive functioning, speed of processing, motor; Language: NR	Cut-off 10: Sensitivity: 0.54; Specificity: 0.96; Cut-Off 14: Complaining: Sensitivity 0.83; Specificity: 0.63; Noncomplaining: Sensitivity: 0.88; Specificity: 0.67;	Prevalence of HAND is high even in long-standing aviremic HIV-positive patients. HAND without functional repercussion in daily life is most frequent. Cut-off of 14 points or less seemed to provide a useful tool to screen for HANDs.
Smith *et al.* [42]; USA	90	Type: Neurocognitive Deficit or Impairment (subtle HIV-related cognitive dysfunction); Classification: Cognitive 'abnormality' defined as performance that deviated at least 2 SD units below established norms on at least two independent NP measures	Person: NR; Time: NR (noted 'brief'); Materials: NR	NP battery	Size: Medium; Objective: No; Domains: Intelligence, memory, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Cut-off ≤10: Sensitivity: 0.39; Specificity: 0.85;	HDS lacks sufficient sensitivity to screen for NP abnormality beyond frank dementia. Intact performance (i.e. performance above established cut-off levels) contributes to a significant number of false-negative errors, suggesting need for NP battery for subtle neurocognitive deficits.
Von Giesen *et al.* [43]; Dusseldorf, Germany	266; 55 (mildly demented), 211 (not demented)	Types: mild dementia, no dementia; Classification: Mild dementia (HDS score ≤10), No dementia (HDS score >10)	Person: NR; Time: NR (noted 'brief'); Materials: NR	NP battery	Size: short; Objective: NR; Domains: Motor; Language: German	Sensitivity: NR; Specificity: NR;	Patients with mild dementia showed significant slowing of most rapid alternating movement (MRAM) and significantly prolonged contraction time compared to nondemented patients. Motor performance correlated significantly with time-dependent HDS subscores for psychomotor speed and construction.
Wojna *et al.* [44]; Puerto Rico, USA	96; 60 (HIV+), 36 (HIV-)	Types: Asymptomatic cognitive impairment, and symptomatic impairment (MCMD, HAD); Classification: modified 1991	Person: NR; Time: NR (noted 'rapid'); Materials: NR	NP battery	Size: Medium; Objective: Yes; Domains: Intelligence, memory, executive functioning, speed of processing, motor. Language: Spanish	Cut-off ≤12: Sensitivity: 0.63; Specificity: 0.84; Cut-off ≤13: Sensitivity: 0.87; Specificity: 0.46;	HDS-Spanish total score and subscores for psychomotor speed and memory recall showed a significant difference between HIV-negative women and HIV-positive women with dementia and between HIV-positive women with normal cognition and with dementia. Optimal cut-off point was ≤13.

International HIV Dementia Scale							
Joska *et al*. [28]; Cape Town, South Africa	190; 96 (HIV+); 94 (HIV-)	Types: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: Medium; Objective: No; Domains: Attention/ concentration, memory, executive function, visuo-spatial, motor; Language: isiXhosa, Afrikaans	Cut-off of 10: Sensitivity = 0.45; Specificity = 0.79;	In ART-naive sample, HIV-positive individuals displayed greater impairment than HIV-negative individuals on IHDS and range of NP tests. With ROC analysis, the area under curve was 0.64. These data suggest that the IHDS may have limitations as a tool to screen for HAD in South Africa.
Muniyandi *et al*. [64]; Thanjavur, India	33	Type: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: NR; Objective: Yes; Domains: NR; Language: NR	NR	Tests that assess cognitive and motor speed may be more helpful than clinical psychiatric interview to spot the AIDS patients who have cognitive impairment. The International HIV Dementia Scale was the most sensitive instrument.
Sacktor *et al*. [7]; Uganda/ Baltimore, USA	247; 66 (HIV+ USA), 81 (HIV+ Uganda), 100 (HIV- control, Uganda)	Type: HAD; Classification: 1991	Person: Non-Neurologist; Time: 2–3 min; Materials: Watch with a second hand	Memorial Sloan Kettering Dementia Staging; NP battery	Size: Medium; Objective: Yes; Domains: Attention/ concentration, memory, language, executive functioning, speed of processing, motor; Language: English, Luganda	Cut-off ≤10: USA: Sensitivity: 0.80; Specificity: 0.57; Uganda: Sensitivity: 0.80; Specificity: 0.55;	IHDS may be a useful screening test to identify individuals at a risk for HIV dementia in both industrialized and developing world. Full NP testing should be performed to confirm diagnosis of HIV dementia.
Singh *et al*. [41]; Durban, South Africa	20	Type: Neurocognitive Deficit or Impairment (moderate and severe); Classification: Moderate – Beyond the norms on at least 2 tests; Severe – three or more tests abnormal	Person: Nonspecialist; Time: 2–3 min; Materials: None	NP battery	Size: short; Objective: NR; Domains: Attention, memory, executive functioning, motor; Language: English, isiZulu	Cut-off of 10: Specificity = 0.88; Sensitivity = 0.50;	Low specificity may limit clinical utility of IHDS. Research needed to verify the high burden on neurocognitive impairment among people with low $CD4^+$ cell count. Larger study needed to validate IHDS in South Africa.
CogState							
Cysique *et al*. [20]; Sydney, Australia	81	Types: ADC; Neurocognitive Deficits or Impairments (psychomotor speed, working memory, attention, learning); Classification System: ≤−2 SD in 2 of 14 neuropsychological measures (Cysique 2004)	Person: NR; Time: 10–15 min; Materials: Desktop computer	NP battery	Size: long; Objective: Yes; Domains: Intelligence, attention/concentration, memory, language, executive functioning, visuo-spatial, motor; Language: English	Sensitivity: 0.81; Specificity: 0.70;	Study supports utility of brief computerized battery in detection of HIV-associated neurocognitive impairment. Good agreement between standard neuropsychological tests and the CogState indices in identifying neurocognitive impairment.
Maruff, 2009; Melbourne, Australia	293; 20 (ADC), 20 (ADC controls); 253 healthy adults	Type: ADC; Definition: Price and Brew, 1988	Person: NR; Time: 8–10 min; Materials: Personal computer	NP battery	Size: Medium; Objective: NR; Domains: Memory, visuo-spatial processing, motor; Language: English	Sensitivity: NR; Specificity: NR;	Brief CogState battery has adequate construct validity and is sensitive to subtle cognitive impairment in ADC. Recommends that assessment of attention, processing speed, memory and working memory based only on CogState can support solely on broad conclusions.
Overton *et al*. [35]; St. Louis, USA	46	Type: Neurocognitive Deficit or Impairment (mild to moderate impairment); Classification: Carey 2004	Person: NR; Time: 12–15 min: Materials: Computer and computer program	NP battery	Size: Medium; Objective: NR; Domains: Attention/ concentration, memory, language, executive functioning, motor; Language: English	GDS ≥0.5: Sensitivity: NR; Specificity: NR;	Measures of both simple detection tests and identification task correlated with GDS and had the highest level of correlation with tests in CHARTER battery. Other tests correlated poorly with NP testing. Composite score of five tests (significant in ROC analyses) correctly classified 90% of individuals according to impairment.
Mini-Mental State Examination (MMSE)							
Lyon *et al*. [31]; Washington, DC, USA	71	Type: HIV-Encephalopathy in adolescents; Classification: 1991	Person: NR; Time: 10 min; Materials: NR	ANI 1991 Criteria	Size: NR; Objective: NR; Domains: NR; Language: NR	Cut-off <24; Sensitivity: 0.50; Specificity: 0.92;	MMSE identified 3 of 6 cases of encephalopathy. HDS appeared to be more clinically useful.
Muniyandi *et al*. [64]; Thanjavur, India	33	Type: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: NR; Objective: Yes; Domains: NR; Language: NR	NR	Tests that assess cognitive and motor speed may be more helpful than clinical psychiatric interview to spot the AIDS patients who have cognitive impairment. The International HIV Dementia Scale was the most sensitive instrument.

(*continued overleaf*)

Table 2. (*continued*)

Study (Author; Location)	Sample size (total; by group)	Impairment evaluated (type(s); classification system)	Tool characteristics (person can administer; time to administer; materials needed)	Reference test	Reference test details (size of battery; objective assessment; domains assessed; language of administration)	Sensitivity; Specificity	Main findings
Power *et al.* [6]; Baltimore, USA	130	Type: HAD; Classification: 1991	Person: NR; Time: NR; Materials: NR	Memorial Sloan Kettering Dementia Evaluation; HIV Dementia Scale (HDS); Grooved Pegboard (PB)	Size: short; Objective: NR; Domains: Attention/ concentration, memory, executive functioning, motor; Language: English	Cut-off ≤28: Sensitivity: 0.50; Specificity: 0.88;	MMSE was less efficient at identifying HIV Dementia than the HDS and the Grooved Pegboard.
Brief Neurocognitive Screen (Component Neuroscreen)							
Ellis *et al.* [22]; 15 sites, USA	301	Type: MCMD, HAD, Neurocognitive Deficits or Impairment (speed of information processing, mental flexibility, working memory); Classification: 1991 Classification	Person: Non-neurologist; Time: 12–15 min; Materials: NR	NP battery	Size: Medium; Objective: Yes; Domains: Attention/ concentration, memory, language, speed of processing, motor; Language: English	Sensitivity: 0.65; Specificity: 0.72;	Designed to estimate the frequency of HIV-associated neurocognitive disorders. In ROC, when compared with NP battery, the area under the curve was 0.74. Yields (Neuroscreen as a whole) a substantial number of false positives and negatives so more useful for tracking prevalence in large cohorts rather than individual patients.
Bender Gestalt Test (BGT)							
Muniyandi *et al.* [64]; Thanjavur, India	33	Type: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: NR; Objective: Yes; Domains: NR; Language: NR	NR	Tests that assess cognitive and motor speed may be more helpful than clinical psychiatric interview to spot the AIDS patients who have cognitive impairment. The International HIV Dementia Scale was the most sensitive instrument.
California Computerized Assessment Package (CalCAP) Mini Battery							
Gonzalez *et al.* [26]; California, USA	82	Type: Neurocognitive Deficits (normal, mild, mild-moderate, moderate, moderate-severe, severe) or Impairments (attention and speed of information processing, abstraction, learning); Heaton 1995	Person: NR; Time: 10 min; Materials: Computer	NP battery	Size: long; Objective: No; Domains: Attention/ concentration, memory, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Cut-off D-score of ≥0.5: Sensitivity: 0.68; Specificity: 0.77;	Traditional NP batteries and computerized reaction time tests do not measure the same thing. They are not interchangeable in examining HIV-related NP impairment.
Coin Rotation Test							
Minor *et al.* [33]; Louisiana, USA	204	Type: Neurocognitive Deficits or Impairment (psychomotor performance); Classification: NR	Person: not specified; Time: 1 min; Materials: NR (infer coin and timer)	Psychomotor speed subscale of the modified HIV Dementia Scale (MHDS-PS).	Size: short; Objective: NR; Domains: Memory, executive functioning, motor; Language: English	Cut-off of 20 Rotations: Sensitivity: 0.72; Specificity: 0.61;	Good convergent validity between Coin Rotation Test and Modified HDS. Gender did not significantly affect CRT performance but did affect modified HDS performance. CRT performance was less affected by education than MHDS performance.
The Computer Assessment of Mild Cognitive Impairment							
Becker *et al.* [17]; USA	59; 29 (HIV+), 30 (HIV-)	Type: Neurocognitive Deficits or Impairment (normal, borderline, impaired); Classification: Global Impairment Rating (Woods, 2004)	Person: Health Professionals; Time: 20 min; Materials: Tablet with touch screen	NP battery	Size: long; Objective: NR; Domains: Memory, language, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Sensitivity: 0.72; Specificity: 0.97;	Detected mild impairment and median stability over 12 and 24 weeks of follow-up was 0.32 and 0.46 (did not differ as a function of serostatus). Discriminate functional analysis (6 CAMCI scores) correctly classified 90% of subjects.
Four-item scale from Health Survey; Six-item scale from MOS							
Revicki *et al.* [37]; Baltimore, USA	162 (baseline); 131 follow-up	Type: Mild, Severe impairment; Classification: TMT manual (Reitan, 1992)	Person: NR; Time: less than 2 min; Materials: NR	Trail-Making Test (TMT)	Size: short; Objective: No; Domains: Executive functioning, speed of processing, motor; Language: English	Sensitivity: NR; Specificity: NR;	Logistic regression analysis showed both four-item version (CF4) included in the HIV Health Survey and the complete six-item scale (CF6) from the Medical Outcomes Study - MOS predicted mild cognitive impairment based on TMT scores ($P = 0.046–0.008$) and severe cognitive impairment based on TMT scores ($P = 0.0012–0.0003$). Baseline significant differences in mean CF6 and CF4 scores for mildly impaired compared with less than mildly impaired and severely impaired and less than severely impaired.

Grooved Pegboard							
Power *et al*. [6]; Baltimore, USA	130	Type: HAD; Classification: 1991	Person: NR; Time: NR; Materials: NR	Memorial Sloan Kettering Dementia Evaluation; HIV-Dementia Scale (HDS); Mini-Mental State Exam (MMSE);	Size: short; Objective: NR; Domains: Attention/ concentration, memory, executive functioning, motor; Language: English	Cut-off ≥90 s: Sensitivity: 0.91; Specificity: 0.82;	Was efficient in detecting HAD (86%) compared with the HDS (84%) and MMSE (72%).
Brief Cognitive Screen (BCS) – memory subtest, verbal fluency items and conflicting stimulus test of the High Sensitivity Cognitive Screen (HSCS)							
Fogel [23]; 3 locations, USA	156	Type: Neurocognitive Deficits or Impairment (memory, verbal fluency, conflicting stimulus); Classification: Abnormality on the Brief Dementia Screen	Person: NR; Time: NR; Materials: NR	Standardized Dementia Screen (registration and delayed memory for three simple words, months in reverse, five serial sevens, and orientation to month and year)	Size: short; Objective: No; Domains: Memory, language, orientation; Language: English	Sensitivity: NR; Specificity: NR;	Patients with abnormal scores on the Brief Cognitive Screen showed greater symptoms and functional impairment.
HIV Dementia Diagnostic Test							
Kwasa *et al*. [30]; Kisumu, Kenya	26; 14 (ANI, MND), 6 (HAD)	Type: ANI, MDN,HAD; Classification: 2007	Person: Nonphysician health-care worker; Time: NR; Materials: NR	NP battery	Size: Medium; Objective: Yes; Domains: Attention/ concentration, memory, language, executive functioning, speed of processing, motor; Language: English, Dhulou	Cut-off ≤22: Sensitivity: 0.63; Specificity: 0.67;	Moderate sensitivity and specificity for HAD. Reliability was poor, suggesting that substantial training and formal evaluations of training adequacy will be critical.
Hopkins verbal test –revised – and Grooved Pegboard Test Nondominant Hand							
Carey *et al*. [19]; San Diego, USA	190	Type: Neurocognitive Deficits or Impairment (NP impaired or unimpaired) Classification: DSM-IV 1994, AAN 1991, Grant and Atkinson 1995	Person: Trained psychometrist; Time: 5 min; Materials: NR	NP battery	Size: long; Objective: NR; Domains: Intelligence, attention/concentration, memory, language, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Sensitivity: 0.78; Specificity: 0.85;	The combination of Hopkins Verbal Test-Revised and Grooved Pegboard Test Nondominant Hand was more accurate than the HIV Dementia Scale (HDS) in classifying HIV-positive participants as NP impaired or unimpaired.
Hopkins Verbal Learning Test/WAIS-III Digit Symbol							
Carey *et al*. [19]; San Diego, USA	190	Type: Neurocognitive Deficits or Impairment (NP impaired and unimpaired) Classification: DSM-IV 1994, AAN 1991, Grant and Atkinson 1995	Person: Trained Psychometrist; Time: 5 min; Materials: NR	NP battery	Size: long; Objective: NR; Domains: Intelligence, attention/concentration, memory, language, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Sensitivity: 0.75; Specificity: 0.92;	The combination of Hopkins Verbal Test-Revised and WAIS-III Digit Symbol (DS) subtest was more accurate than the HIV Dementia Scale (HDS) in classifying HIV-positive participants as NP impaired or unimpaired.
Medical Outcome Study HIV (MOS-HIV) Health Survey							
Knippels *et al*. [29]; the Netherlands and Flanders, Belgium	82	Type: Neurocognitive Deficits or Impairment (neuropsychological impairment); Classification: NR	Person: Completed at home; Time: NR; Materials: Questionnaire	NP battery	Size: Medium; Objective: No; Domains: Attention/ concentration, memory, language, executive functioning, visuo-spatial, motor; Language: Dutch	Sensitivity: NR; Specificity: NR;	Showed significant associations with NP test performance overall and, specifically, with the domains of abstraction, language, visuo-spatial abilities (controlling for $CD4^+$ cell count and CDC disease stage). Trend towards significance in memory domain. Seems particularly sensitive to changes in NP test performance in early HIV infection.

(*continued overleaf*)

Table 2. (*continued*)

Study (Author; Location)	Sample size (total; by group)	Impairment evaluated (type(s); classification system)	Tool characteristics (person can administer; time to administer; materials needed)	Reference test	Reference test details (size of battery; objective assessment; domains assessed; language of administration)	Sensitivity; Specificity	Main findings
Mental Alternation Test							
Jones *et al*. [27]; Baltimore, USA	62	Type: Neurocognitive Deficits or Impairment (orientation, memory, concentration, language, praxis, psycho or speed, sequencing ability); Classification: abnormal performance on MMSE and Trailmaking (Crum 1993, Nornstein, 1985)	Person: NR; Time: 60 s; Materials: NR;	Mini-Mental State Examination; Trailmaking Part A and B	Size: short; Objective: NR; Domains: Intelligence, attention/concentration, memory, language, executive functioning, speed of processing; Language: English	With MMSE: Sensitivity: 0.95; Specificity: 0.79; With Trailmaking: Sensitivity: 0.78; Specificity: 0.93;	Scores correlated significantly with MMSE and Trailmaking Test Part B scores when controlled for confounders. ROC curve showed cut-off of 15 yielded best results for detection of abnormal performance on MMSE and Trailmaking Test Part B.
Motor Battery (Timed Gait, Grooved Pegboard, Finger-tapping)							
Parsons *et al*. [36]; USA	361	Type: Neurocognitive Deficits or Impairment (attention, executive, figural memory, verbal memory, language); Classification: NR	Person: NR; Time: NR (noted 'brief'); Materials: NR	NP battery	Size: long; Objective: NR; Domains: Attention/ concentration, memory, language, executive functioning, visuo-spatial, speed of processing, motor; Language: English	Cut-off of −0.42: Sensitivity: 0.79; Specificity: 0.76;	Significant correlation with comprehensive battery (52% variance). Increased variance to 73% when Digit Symbol and Trailmaking added. Motor battery may have broader utility to diagnose and monitor HIV-related neurocognitive disorder in international settings.
Prospective and Retrospective Memory Questionnaire (PRMQ)							
Garvey *et al*. [25]; London, UK	45	Types: Neurocognitive Deficits or Impairment (asymptomatic neurocognitive impairment aNCI, memory); Classification: aNCI- performance score more than 1 SD below the normative mean in at least 2 domains of CogState.	Person: NR; Time: 10 min; Materials: questionnaire, writing utensil	CogState	Size: short; Objective: NR; Domains: Attention/ concentration, memory, executive functioning, motor, learning; Language: English	Sensitivity: NR; Specificity: NR;	No statistically significant associations between PRMQ and CogState; questionnaire should not be used as a screening tool. Association between PRMQ and set-shifting task of CogState; questionnaire able to capture part of the executive function deterioration in HIV-associated NCI.
Screening Algorithm							
Cysique *et al*. [21]; Sydney, Australia	127; 97 (HIV+), 30 (HIV-)	Types: Neurocognitive Deficits or Impairment (HAND); Classification: 2007	Person: Clinical Individual; Time: 3 min; Materials: patient's clinical characteristics	NP battery	Size: long; Objective: Yes; Domains: Intelligence, attention/concentration, memory, language, speed of processing, motor, reasoning; Language: English	Sensitivity: 0.78; Specificity: 0.70;	Good overall prediction accuracy and specificity. Proved useful to identify HIV-infected patients with advanced disease at a high risk of HAND who require more formal assessment. Recommended for HIV-infected white men with advanced disease.
Timed Gait Test							
Robertson *et al*. [39]; ACTG sites all over the world	1549; 1122 (AIDS), 113 (symptomatic), 165 (asymptomatic), 87 (HIV-)	Type: ADC; Classification: Neurologic History (Robertson, 1997)	Person: NR; Time: NR; Materials: Stopwatch, recording sheet	ADC Staging; NP battery	Size: NR; Objective: Yes; Domains: Memory, language, executive functioning, visuo-spatial processing, motor; Language: English	Sensitivity: 0.83; Specificity: 0.59;	Good sensitivity and moderate specificity for detection of ADC. Abnormal Timed Gait scores were also significantly correlated with abnormal scores on neurological and neuropsychological evaluations. Cutting scores on the Timed Gait procedure resulted in reasonably good classification rates of ADC staging, especially for use as a screening tool.
Wechster Memory Scale							
Muniyandi *et al*. [64]; Thanjavur, India	33	Type: ANI, MND, HAD; Classification: 2007	Person: NR; Time: NR; Materials: NR	NP battery	Size: NR; Objective: Yes; Domains: NR; Language: NR	NR	Tests that assess cognitive and motor speed may be more helpful than clinical psychiatric interview to spot the AIDS patients who have cognitive impairment. The International HIV Dementia Scale was the most sensitive instrument.

Criteria for Battery Size: 'short' battery – criterion was defined by testing that took <30 min to administer; 'medium' battery – criterion was defined by testing that took 30–90 min to administer; and 'long and comprehensive' battery – criterion was defined by testing that took >90 min to administer. ADC, AIDS Dementia Complex; aNCI, asymptomatic neurocognitive impairment; ANI, asymptomatic neurocognitive disorder; HAD, HIV-associated dementia; MCMD, minor cognitive-motor disorder; MND, mild neurocognitive disorder; NP, neuropsychological; NR, not reported.

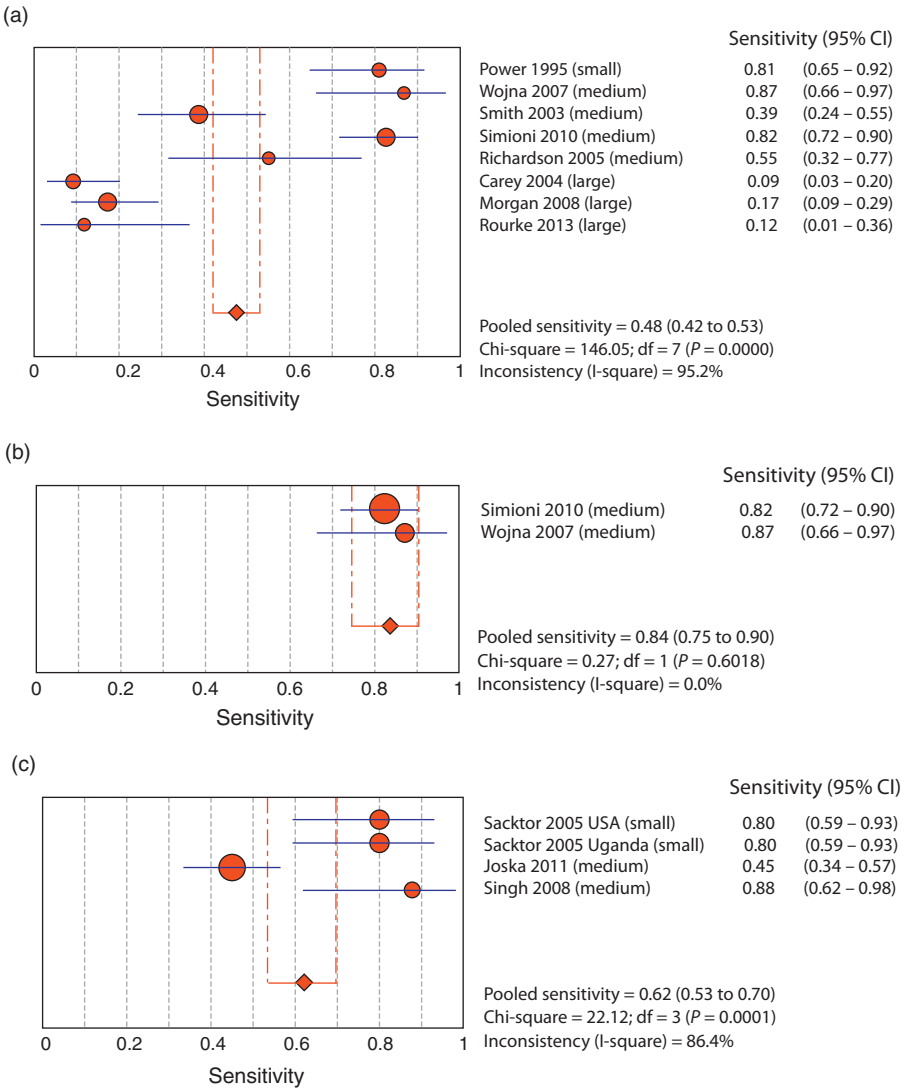

Fig. 2. Forest plots. (a) Utility of the HIV Dementia Scale in detecting HIV-associated neurocognitive disorders. (b) Utility of the HIV Dementia Scale with cut-off of 13 or 14. (c) Utility of the International HIV Dementia Scale in detecting HIV-associated neurocognitive disorders. CI, confidence interval.

demonstrates that the IHDS may be moderately useful in detecting HAND.

Quality appraisal

The quality assessment demonstrated that there are specific areas in which the studies tend to have methodological shortcomings (Fig. 3). Very few studies fulfilled criteria 10 and 11: 10, 'Were the index test results interpreted without knowledge of the results of the reference standard?' (6/31, 19%) [19,22,30,31,41,44] and 11, 'Were the reference standard results interpreted without knowledge of the results of the index test?' (7/31, 23%) [19,22,30,31,39,41,44]. This low level suggests that there may be some introduction of bias in the data interpretation, which may result in an overestimation of sensitivity.

Only about half the studies fulfilled criterion 1, 'Was the spectrum of patients representative of the patients who will receive the test in practice?' (17/31, 54%) [6,7,17,19,21,22,24,25,27,28,31,32,34,36,37,39,41]. This suggests that there are a good number of studies that may have limited applicability to real-life clinical settings.

The quality assessment did highlight some successful methodologies that should be continued in further evaluations. First, the majority of studies administered the same reference test and screening test to all study participants [criterion 5, 'Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?' (30/31, 97%) [6,7, 17–28,30–44,64] and criterion 6, 'Did patients receive the same reference standard regardless of the index test result?' (30/31, 97%) [6,7,17–33,35–44,64]]. This allowed for proper and comprehensive calculation of sensitivity and specificity. Second, the majority of studies described their procedures with sufficient detail for

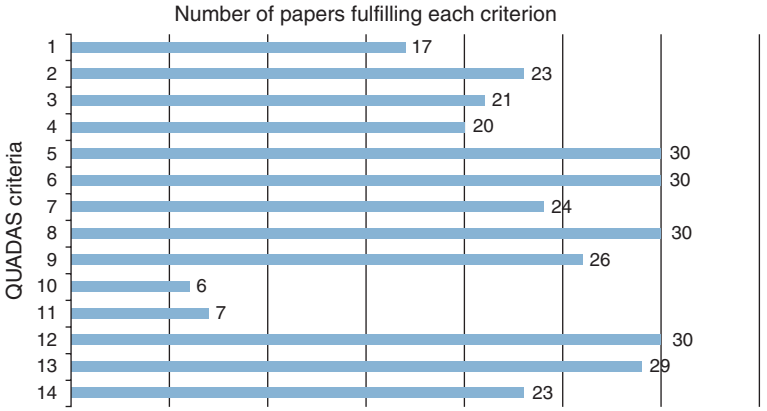

Fig. 3. Number of papers fulfilling the QUADAS criteria (1–14).

replication of criterion 8 - 'Was the executive of the index test described in sufficient detail to permit replication of the test?' (30/31, 97%) [6,7,17–22, 24–44,64], enabling future comparison of newer screening tools to already evaluated tools.

Discussion

With the prevalence of milder forms of HAND increasing, and limited resources available for formal neuropsychological examinations, there is a critical need to be able to screen and identity people with HAND. Our current systematic review identified 51 peer-reviewed articles that focused on screening for neurocognitive impairments associated with HIV/AIDS. Of these, about two-thirds (31/51) used a criterion or reference to characterize the performance of 21 unique screening instruments. About half of the 31 studies examined the performance of the HDS or the IHDS as screening tests. Fifty-five percent of studies focused on detecting neurocognitive impairments, 35% on HAD and 15% in identifying MND or ANI. Only 16% of studies employed the latest 2007 HAND criteria [3].

The results of this systematic review suggest that the HDS and IHDS are not ideal tools for identifying a range of neurocognitive impairment. From the meta-analysis on the HDS and IHDS, we were able to determine that these tools have generally poor (0.48) and moderate (0.62) pooled sensitivities, respectively, in identifying a range of neurocognitive impairment. We also identified a potential relationship between the reference test and criterion with the range of sensitivities on the HDS and the IHDS, that is those studies using the most comprehensive neuropsychological test battery as the 'gold standard' criterion had the lowest (and similar) sensitivity values, whereas those that were considered 'short' or 'medium' in time (and comprehensiveness) resulted in much larger ranges of sensitivities. The association between lower sensitivity (ability to identify true positives) and large reference battery was significant for the HDS ($P < 0.05$). These findings suggest that a longer, more comprehensive neuropsychological battery may be a more stringent and appropriate reference test. Future studies evaluating sensitivity may want to consider using a large neuropsychological battery as a reference test to classify participants in a more discerning way. Studies using the HDS to identify a range of neurocognitive impairment reported higher sensitivities when higher cut-offs were used [40,44] or demographically adjusted *T*-scores were used [34].

The review identified 10 other screening tools with adequate sensitivities (≥ 0.75). Of these, four tools or combinations of tests were used to detect HAND conditions and overall neurocognitive impairment (as opposed to impairment in specific domains) and they used a 'gold-standard' neuropsychological battery as the reference test or criterion. These four tools include the CogState [20], the Screening Algorithm [21], the paired Hopkins Verbal Learning Test and WAIS-III Digit Symbol combination and the paired Hopkins Verbal Learning Test and Grooved Pegboard Non-Dominant Hand combination [19]. It is important to note that the other studies defined neurocognitive impairment in different ways and evaluated these conditions using different criteria; thus, the comparison of efficacy across all studies needs to be carried out with caution given these limitations. In addition to these four tests, Becker *et al.* [17] reported a slightly lower sensitivity (0.72) for the Computer Assessment of Mild Cognitive Impairment (CAMCI) against a comprehensive neuropsychological battery. These are the five tools identified by our review that show some promise to be used to identify HAND in a clinical setting, although they warrant further study and validation.

In the 20 studies that met review criteria and are reported in Appendix B, http://links.lww.com/QAD/A370, one other potentially useful tool, The Montreal Cognitive Assessment (MoCA) [48], was highlighted. This tool is

worth note because of its rising popularity in clinical settings, although the reliability and validity to detect HAND remains to be determined.

The review also highlighted key methodological issues in this body of literature. First, in order to properly determine whether a screening tool can detect the target condition, it is imperative that the reference test properly classifies the condition [16]. Only 19 studies of the 31 (61%) [18–22,26,28–30,32,35,36,38,40–44,64] used the 'gold-standard' neuropsychological battery as the reference test. Furthermore, only seven (23%) studies [17–21,26,36] used more comprehensive reference tests (>90 min) and functional status was measured objectively in only nine studies [20–22,30,34,38,39,44,64] (29%). In addition, only five studies [21,28,30,40,64] used the most recent 2007 criteria to classify HAND [3]. The QUADAS assessment reported that only 17 of the 31 (54%) [6,7,17,21,22,24,25,27,28,31,32,34,36,37,39,41] were using representative samples, noting a severe limitation in the applicability of the studies. For cognitive screening tools to be properly evaluated, and for these evaluations to inform clinical practice, more stringent methodological procedures are needed.

The results of this systematic review provide insights into the performance of the current screening instruments available for HAND and identify key methodological issues that need to be addressed in future studies. In this current context of mild cognitive impairment associated with HIV, it is clear that improved screening tools could go a long way in improving the care, quality of life and study of treatment interventions for individuals living with HIV and AIDS.

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A.R.Z. contributed to development of systematic review project; reviewed articles for inclusion; extracted data; appraised quality of articles; created figures/tables; analysed data; and wrote the manuscript.

D.G. reviewed articles for inclusion; extracted data; appraised quality of articles; and edited the manuscript.

S.R. contributed to development of systematic review project; edited manuscript; and reviewed articles that were in Spanish.

J.B. contributed to development of systematic review project; and edited the manuscript. A.C. edited the manuscript. J.A.M. contributed to development of systematic review project; and edited the manuscript. M.J.G. contributed to development of systematic review project; and edited the manuscript. A.R. edited the manuscript. R.R. edited the manuscript. G.A. edited the manuscript. T.M. contributed to development of systematic review project; and edited the manuscript. S.B.R. developed systematic review project; organized systematic review team; lead systematic review project; and edited the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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