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CHAPTER 6

PREDICTIVE VALIDITY OF FOUR COGNITIVE SCREENING INSTRUMENTS FOR DETECTING HIV-1-ASSOCIATED COGNITIVE IMPAIRMENT

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ABSTRACT

We assessed the performance of four cognitive screening instruments (Mini Mental State Examination (MMSE), HIV Dementia Scale (HDS), Montreal Cognitive Assessment (MoCA), and the questionnaire as proposed by Simioni et al. (Simioni questionnaire)) for detecting HIV-associated cognitive impairment (CI) in HIV-positive individuals with suppressed viremia on combination antiretroviral therapy (cART). One-hundred and three HIV-1-positive men with suppressed viremia on cART for ≥12 months, and 74 highly similar HIV-negative men, all aged ≥45, underwent neuropsychological assessment as well as the above four screening instruments. CI was determined using Frascati criteria and multivariate normative comparison (MNC). Scores of each screening instrument were compared between the two study groups. In the HIV-1-positive group, sensitivity and specificity, area under the curve by receiver operator characteristics (ROC) analyses, and the optimal cut-off point of each screening instrument were assessed, using CI by Frascati criteria or by MNC as criterion standard. All cognitive screening tools showed comparable scores and abnormality rates among HIV-1-positive and HIV-negative participants. Each screening instrument showed low sensitivity (35-67% [Frascati]; 24-71% [MNC]) and moderate specificity (54-93% [Frascati]; 69-90% [MNC]), even at their optimal cut-off point. By ROC analyses, MMSE, HDS, and MoCA, irrespective of the criterion standard used, showed at best moderate accuracy for identifying CI. The area under the ROC curve varied between 0.58 and 0.71. All cognitive screening instruments, irrespective of which of both criterion standards was used, showed at best moderate accuracy for identifying CI. Cognitive deficits in the context of HIV are subtle, and no screening instrument so far seems optimal for use in clinical practice.

INTRODUCTION

With the introduction of combination antiretroviral therapy (cART), AIDS-associated mortality and morbidity have markedly diminished. Severe HIV encephalopathy or HIV-associated dementia (HAD), have largely disappeared (1–3). In the past few years however, a high but varying prevalence of milder forms of cognitive impairment, ranging from 15-69%, has been reported among HIV-positive people, including those with systemically well-controlled infection (4–10).

To classify this broadening clinical spectrum of HIV-associated neurocognitive disorders (HAND), a set of research criteria, commonly referred to as Frascati criteria, have been developed (11). These criteria are heavily debated, as they are probably oversensitive, resulting in unlikely high prevalence estimates and high false-positive rates (12,13). In view of these limitations and a lack of clinical application for the Frascati criteria, we have recently shown multivariate normative comparison (MNC) to be an alternative and possibly more accurate method of detecting cognitive impairment (CI) (14).

Irrespective of the method of classification, comprehensive neuropsychological assessment (NPA) is the recommended method for establishing the diagnosis of HIV-associated CI. However, an NPA is time-consuming. The availability of a short and accurate cognitive screening tool to identify those who are most likely to actually have HIV-associated CI and can subsequently be referred for NPA, would therefore be of great importance.

Several cognitive screening instruments have been proposed, including the Mini Mental State Examination (MMSE), HIV Dementia Scale (HDS), Montreal Cognitive Assessment (MoCA), and the 3-item questionnaire as published by Simioni et al. (from now on referred to as Simioni questionnaire) (8). The latter, which assesses cognitive complaints in daily life, is proposed by the European AIDS Clinical Society as one option to guide physicians in identifying those most likely of having HIV-associated CI and who should be referred for NPA (15). To date, the predictive validity of these four screening instruments has not been simultaneously evaluated among HIV-1-positive individuals with suppressed viremia on cART. Hence, the usefulness of each of these screening instruments for detecting especially milder forms of HIV-associated CI remains to be clarified in this specific population.

Therefore, the purpose of this study was to assess the predictive validity of four screening instruments (MMSE, HDS, MoCA, and the Simioni questionnaire). We compared scores and rates with abnormal scores between HIV-1-positive individuals

with suppressed viremia on cART and highly comparable HIV-negative participants, and we assessed sensitivity and specificity, area under the curve by receiver operator characteristics (ROC) analyses, and the optimal cut-off point of each screening instrument, using an abnormal NPA (CI as determined by Frascati criteria (to enable comparison with previous publications) or CI as determined by MNC) as criterion standards.

METHODS

Study design and participants
The AGE$_h$IV Cohort Study is a prospective cohort study investigating the prevalence, incidence and risk factors of ageing-associated comorbidities and organ dysfunction among HIV-1-positive individuals and highly comparable HIV-negative controls, aged ≥45, in Amsterdam, The Netherlands (16). At baseline, and every two years thereafter, participants undergo extensive screening for age-associated comorbidity and organ dysfunction.

All eligible participants from the main AGE$_h$IV Cohort were consecutively invited to participate in a nested cognitive sub study, which began enrolment in December 2011 (14). Additional eligibility criteria for the sub study were male sex (as the availability of Dutch-speaking women in the main AGE$_h$IV Cohort was limited), and for the HIV-1-positive group, sustained suppression of HIV-1 viremia on cART (plasma HIV-1-RNA <40 copies/ml) for ≥12 months; the presence of so-called viral 'blips' (transient low-level viremia) was not an exclusion criterion.

Exclusion criteria for the sub study were a history of severe neurological disorder (e.g., stroke, seizure disorders, multiple sclerosis, dementia [including previous or current diagnosis of HAD]), history of traumatic brain injury with loss of consciousness for >30 minutes, current/past (HIV-associated) central nervous system infection or tumour, current severe psychiatric disorder (e.g., psychosis, major depression), current intravenous drug use, daily use of illicit drugs (with the exception of daily cannabis use), current excessive alcohol consumption (>48 units of alcohol/week), insufficient command of the Dutch language and mental retardation. With respect to major depression as one of the exclusion criteria, depressive symptoms were assessed in the main AGE$_h$IV Cohort Study by the nine-item Patient Health Questionnaire (PHQ-9). Participants with a PHQ-9 score of ≥15 (indicative of severe depressive symptoms and potentially of major depression) were excluded from participation in the sub study (17).

Standard protocol approval, registration, and patient consent

The protocol of the AGE_hIV Cohort Study (including the abovementioned sub study) was approved by the local ethics committee and has been registered at www. clinicaltrials.gov (identifier: NCT01466582). Written informed consent was obtained from all participants, both for the main study and sub study.

Neuropsychological assessment (NPA)

As part of the sub study, NPA was performed by trained neuropsychologists and covered six cognitive domains commonly affected by HIV-associated CI, including fluency, attention, information processing speed, executive function, memory, and motor function (Supplementary Table 6.1) (14). Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (18), and subjective cognitive complaints with the Cognitive Failures Questionnaire (CFQ) (19). Everyday functioning was assessed using the Instrumental Activities of Daily Living (IADL) (20) questionnaire and pre-morbid intelligence was estimated by the Dutch Adult Reading Test (DART) (21). Use of psychotropic medication was assessed and included use of antidepressants, benzodiazepines, and methylphenidate.

Determining CI according to Frascati criteria and MNC

As reported in detail in a previous publication, Frascati criteria as well as MNC were applied to determine CI (14).

Frascati criteria were applied as published by Antinori et al. (Supplementary Table 6.2) (14,22).

MNC is a statistical method that may be seen as a multivariate version of Student's t-test for one sample (14,23). MNC is able to control the family-wise error (the probability of falsely determining individuals as cognitively abnormal) by performing a single multivariate comparison of the complete cognitive profile of a particular patient to the distribution of all the cognitive profiles of the control sample, rather than comparing each test result separately to the reference population. MNC thus compares the complete cognitive profile of each HIV-1-positive participant with the cognitive profile of the HIV-negative control group as a whole. The test statistic is Hotelling's T^2. The false positive rate, i.e., erroneously concluding that an individual deviates from the control sample while this is not the case, is limited by the level of significance (alpha). In the present study alpha was set at 5% one-tailed, resulting in a specificity of at least 95%, as previously confirmed (14). In this previous report, the false-positive rate for CI was shown to be high when applying Frascati criteria, and was greatly reduced by applying MNC, indicating MNC to be a very powerful and more accurate tool for detecting CI.

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Cognitive screening instruments

MMSE, HDS, Simioni questionnaire, and MoCA were applied to each sub study participant. The following (classical) cut-offs were used to define abnormal scores: MMSE ≤24/30, MoCA ≤25/30, and HDS ≤10/16. The more recently proposed HDS cut-off of ≤14/16 as proposed by Simioni et al. was used as well (8).

The Simioni questionnaire was considered abnormal when at least one of the following three questions was answered with "yes, definitely": 1)"Do you experience frequent memory loss (e.g., do you forget the occurrence of special events even the more recent ones, appointments, etc.)?", 2)"Do you feel that you are slower when reasoning, planning activities, or solving problems?", 3)"Do you have difficulties paying attention (e.g., to a conversation, a book, or a movie)?", (each question to be answered with "never", "hardly ever", or "yes, definitely") (8).

Statistical analysis

Group comparisons were performed using the non-parametric test for trend, chi-square, Fisher's exact test, or Wilcoxon rank-sum test as appropriate.

Predictive validity of each of the four screening instruments (MMSE, HDS, MoCA, and Simioni questionnaire) was assessed using either of the two different criterion standards, i.e., CI as determined by Frascati criteria or by MNC, respectively. These analyses were restricted to the HIV-1-positive study group. A nonparametric ROC analysis was performed to examine the ability of the MMSE, HDS, and MoCA to detect CI using the presence of CI (as determined by Frascati criteria or by MNC, respectively) as the outcome. Furthermore, Youden index was calculated, to determine an optimal cut-off point for MMSE, HDS, and MoCA, using CI as determined by Frascati criteria and CI by MNC as the criterion standards.

MNC analyses were performed using R statistical software (http://purl.oclc.org/NET/RGRASMAN/MNC); for remaining analyses STATA (version 10.1, StataCorp, Texas, USA) was used.

RESULTS

Participants' characteristics (Table 6.1)

One-hundred and three HIV-1-positive and 74 HIV-negative participants were consecutively enrolled into the sub study between December 2011 and March 2014. Both groups were highly comparable, with a median age of 54 years in both groups, and

the majority being men who have sex with men (MSM). The prevalence of most factors related to cognition and behaviour was similar in both groups, except for a higher prevalence of smoking among HIV-1-positive participants (30% vs. 19% currently smoking, p=0.048) and a higher prevalence of ecstasy use among HIV-negative controls (13% vs. 2%, p=0.008).

HIV-1-positive participants were known to be HIV-seropositive and treated with antiretroviral medication for a prolonged period of time, and 35% had previously been diagnosed with AIDS. The majority had experienced substantial immune recovery on treatment, with a median nadir CD4-count of 170 cells/mm^3, current median CD4-count of 625 cells/mm^3, and undetectable plasma viral load for a median of 8 years.

CI by Frascati criteria and by MNC
Applying Frascati criteria, CI was present in 49 of 103 (48%) HIV-1-positive, but also in 27 of 74 (36%) HIV-negative men (p=0.14).

Using MNC, CI was detected in 17 (17%) HIV-1-positive men. To verify the specificity of the MNC criterion, which was assumed to be at least 95%, we compared the scores of each individual HIV-negative control with the scores of the remaining control group (n=73), using MNC. Four (5%, p=0.02) uninfected controls showed test results significantly below the remainder of the group, supporting the assumption of 95% specificity.

Results of the MMSE, HDS, MoCA, and Simioni questionnaire (Table 6.2)
All 177 sub study participants had an available MMSE, HDS, and MoCA score. Simioni questionnaires were missing from two HIV-negative participants.

None of the screening instruments showed statistically significant differences between the HIV-1-positive and HIV-negative study groups, neither in terms of abnormal scoring nor regarding median scores.

Sensitivity and specificity of the MMSE (Table 6.3)
Using CI by Frascati criteria, or CI by MNC as the criterion standard, an MMSE score ≤24/30 showed a very low sensitivity of 2% and 6%, respectively. Specificity was 100% irrespective of the criterion standard used. The single HIV-1-positive participant with an MMSE score ≤24/30 was determined as being cognitively impaired by Frascati criteria as well as by MNC.

TABLE 6.1. BASELINE DEMOGRAPHIC AND HIV-1-RELATED CHARACTERISTICS, AND FACTORS RELATED TO COGNITION AND BEHAVIOUR.

Characteristic	HIV-1-positive (n=103)	HIV-negative (n=74)	P Value
Demographics			
Age, years	54 (49-62)	54 (49-61)	0.94[a]
MSM[1]	93%	90%	0.48[b]
Dutch as native language (%)	91%	95%	0.56[c]
Education (ISCED level)[2]	6 (5-6)	6 (5-6)	0.50[d]
Cognition and depression			
Premorbid intelligence (IQ)[3]	101 (95-111)	103 (96-112)	0.48[c]
Subjective cognitive complaints (%)[4]	13%	5%	0.13[c]
Mild to moderate depressive symptoms (%)[5]	6%	4%	0.74[c]
Severe depressive symptoms (%)[6]	0	0	. . .
Use of psychotropic medication (%)[7]	16%	14%	0.71[b]
Interference with daily functioning (based on IADL score)[8]	0%	0%	. . .
Smoking and recreational drug use			
Smoking status			0.048[d]
Never smoker	24%	36%	
Ever smoker	46%	44%	
Current smoker	30%	19%	
Pack-years of smoking (pack years)	9.9 (0.2-31.6)	2.3 (0.0-14.0)	0.005[a]
Weekly to monthly use of ecstasy (%)	2%	13%	0.008[c]
Weekly to monthly use of cocaine (%)	4%	4%	1.00[c]
Daily to monthly use of cannabis (%)	16%	15%	0.96[b]
Alcohol intake (units per week)	6 (2-14)	5 (3-12)	0.89[a]
Hepatitis B and C infection			
Hepatitis C RNA positive (%)	1%	0%	1.00[c]
Hepatitis B antigen and/or hepatitis B DNA positive (%)	2%	0%	0.51[c]
HIV-related characteristics			
Time since HIV-1 diagnosis (years)	13.5 (7.4-17.1)	. . .	. . .
Diagnosed with HIV-1 before 1996 (%)	35%	. . .	. . .
CD4-count at enrolment (cells/mm^3)	625 (475-800)	. . .	. . .
Nadir CD4-count (cells/mm^3)	170 (60-250)	. . .	. . .
Known duration of CD4<350 cells/mm^3 (months)	15.4 (4.2-45.2)	. . .	. . .
Duration of plasma viral load ≤200 c/mL (years)[9]	8.3 (3.5-11.2)	. . .	. . .
Time since ART was first initiated (years)	11.6 (4.9-14.9)	. . .	. . .
Naive at start of cART (%)[10]	80%	. . .	. . .
Prior clinical AIDS (%)[11]	35%	. . .	. . .
Use of efavirenz		. . .	. . .
Prior use	47%	. . .	. . .
Current use	21%	. . .	. . .
Central nervous system penetration effectiveness score of current cART regimen[12]	7 (7-8)	. . .	. . .

◀ Data presented as median (IQR) or percentage as appropriate.

Test type used: [a] Wilcoxon rank-sum test, [b] Chi-square test, [c] Fisher's exact test, [d] Nonparametric test for trend

[1] The term "MSM" (Men having Sex with Men) applied to male participants that stated in the questionnaire to feel mostly or exclusively sexually attracted to men.

[2] Educational level was defined using the International Standard Classification of Education (ISCED) 2011: 0, early childhood education; 1, primary education; 2, lower secondary education; 3, upper secondary education; 4, post-secondary non-tertiary education; 5, short-cycle tertiary education; 6, bachelor's or equivalent level; 7, master's or equivalent level; 8, doctoral or equivalent level.

[3] Premorbid intelligence quotient (IQ) was estimated using the Dutch Adult Reading Test (DART). One of in total 74 HIV-negative controls and 6 of in total 103 HIV-1-positive individuals were unable to complete this test due to dyslexia.

[4] Subjective cognitive complaints were assessed using Cognitive Failure Questionnaire (CFQ). A cut-off of ≥42 was used to indicate significant amount of subjective complaints, percentages scoring above this cut-off is shown.

[5] A Beck Depression Inventory score >13 and <29 reflects presence of mild to moderate depressive symptoms, percentages scoring >13 and <29 are shown. One of 103 HIV-1-positive individuals did not complete this test.

[6] A Beck Depression Inventory score ≥29 reflects severe depressive symptoms. None of the participants had a score ≥29. One of 103 HIV-1-positive individuals did not complete this test.

[7] Psychotropic medication included: antidepressants, benzodiazepines, methylphenidate.

[8] Level of day-to-day functioning was defined using the Independent Activities of Daily Living (IADL) questionnaire (20).

[9] Duration of undetectable plasma viral load was defined as: number of years since last plasma viral load >200 c/mL.

[10] The term "cART" was used for a combination of ≥3 antiretroviral drugs, other than ritonavir used as a pharmacologic booster.

[11] The term "prior AIDS" was used in case of a previous AIDS-defining condition according to the United States Centers for Disease Control and Prevention (CDC) classification.

[12] Central nervous system penetration effectiveness (CPE) score of the cART regimen of each HIV-1-positive participant was calculated using the algorithm as proposed by Letendre et al. in 2010 (24).

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TABLE 6.2. RESULTS OF THE MMSE, HDS, MOCA, AND SIMIONI QUESTIONNAIRE.

Characteristic	HIV-1-positive (n=103)	HIV-negative (n=74)	P Value
Mini Mental State Examination (MMSE)			
MMSE score	29 (28-30)	29 (28-30)	0.37[a]
MMSE score ≤24/30	1 (1%)	0 (0%)	1.00[b]
HIV Dementia Scale (HDS)			
HDS score	15.0 (13.5-16.0)	14.3 (13.5-16.0)	0.30[a]
HDS score ≤10/16	4 (4%)	6 (8%)	0.32[b]
HDS score ≤14/16	39 (38%)	37 (50%)	0.11[c]
Montreal Cognitive Assessment (MoCA)			
MoCA score	28 (27-29)	29 (27-29)	0.10[a]
MoCA score ≤25/30	13 (13%)	8 (11%)	0.71[c]
Simioni questionnaire			
Simioni questionnaire abnormal	31 (30%)	22 (31%)	0.95[c]

Data presented as median (interquartile range) or No. (%) as appropriate.

Test type used: [a] Wilcoxon rank-sum test, [b] Fisher's exact test, [c] Chi-square test.

Sensitivity and specificity of the HDS (Table 6.3)

An HDS score ≤10/16 showed a low sensitivity of 6%, using either CI by Frascati criteria, or CI by MNC as the criterion standard. Specificity was 97-98%. Raising the cut-off to ≤14/16 showed a sensitivity of 45% using CI by Frascati criteria as the criterion standard, and a higher sensitivity of 71% using CI by MNC as the criterion standard. Irrespective of the criterion standard used, specificity was low (69%).

Sensitivity and specificity of the MoCA (Table 6.3)

A MoCA score ≤25/30 showed a low sensitivity of around 20% and a reasonable specificity of around 90%, by both criterion standards.

Sensitivity and specificity of the Simioni questionnaire (Table 6.3)

An abnormal Simioni questionnaire showed a low sensitivity of around 40% and low specificity of around 70%, by both criterion standards.

Sensitivity and specificity of an HDS cut-off ≤14/16 among those with cognitive complaints (as defined by an abnormal Simioni questionnaire) (Table 6.3)

Applying an HDS cut-off ≤14/16 to HIV-1-positive participants with cognitive complaints, specificity was increased by 10% to 79% (using both criterion standards); sensitivity remained virtually unchanged when compared to the HDS using a cut-off of ≤14/16 irrespective of cognitive complaints.

TABLE 6.3. SENSITIVITY AND SPECIFICITY OF THE MMSE, HDS, MOCA AND SIMIONI QUESTIONNAIRE.

	Criterion standard= CI as determined by Frascati criteria		Criterion standard= CI as determined by MNC	
	Sensitivity	Specificity	Sensitivity	Specificity
Mini Mental State Examination (MMSE) ≤24/30	2%	100%	6%	100%
HIV Dementia Scale (HDS) ≤10/16	6%	98%	6%	97%
HIV Dementia Scale (HDS) ≤14/16	45%	69%	71%	69%
Montreal Cognitive Assessment (MoCA) ≤25/30	20%	94%	24%	90%
Simioni questionnaire abnormal	35%	74%	41%	72%
HIV Dementia Scale (HDS) ≤14/16 among participants with cognitive complaints[1]	41%	79%	71%	79%
HIV Dementia Scale (HDS) ≤14/16 among participants without cognitive complaints[1]	47%	65%	70%	65%

Abbreviations: CI, cognitive impairment; MNC, multivariate normative comparison.
Analyses were restricted to the HIV-1-positive study group.
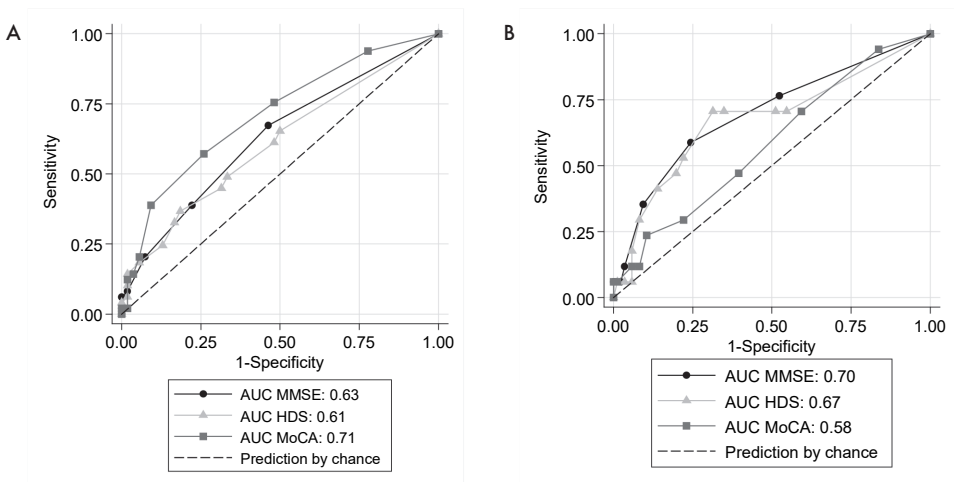[1] Cognitive complaints were defined by an abnormal Simioni questionnaire.

FIGURE 6.1. RECEIVER OPERATOR CHARACTERISTICS (ROC) CURVES OF THE MINI MENTAL STATE EXAMINATION (MMSE), HIV DEMENTIA SCALE (HDS), AND MONTREAL COGNITIVE ASSESSMENT (MOCA) USING HAND AS DETERMINED BY (A) FRASCATI CRITERIA OR (B) MNC AS THE CRITERION STANDARD.

Analyses were restricted to the HIV-1-positive study group. Abbreviation: AUC, area under the curve.

Performance of all the above screening cognitive tools when only including diagnoses of MND, but not ANI, as the criterion standard for CI according to Frascati criteria

When using this approach, in which participants with ANI were considered to be cognitively unimpaired, performance of all the above screening cognitive instruments remained virtually unchanged (data not shown).

ROC analyses of the MMSE, HDS, and MoCA

Figure 6.1A depicts the ROC curve for MMSE, HDS, and MoCA using CI as determined by Frascati criteria as the criterion standard. The area under the curve (AUC) for the MMSE, HDS, and MoCA was 0.63 (95% confidence interval (95%-CI) 0.53-0.73), 0.61 (95%-CI 0.50-0.71), and 0.71 (95%-CI 0.61-0.81), respectively.

Figure 6.1B depicts the ROC curve for MMSE, HDS, and MoCA when using CI as determined by MNC as the criterion standard. The AUC for the MMSE, HDS, and MoCA was 0.70 (95%-CI 0.55-0.84), 0.67 (95%-CI 0.52-0.83), and 0.58 (95%-CI 0.44-0.73), respectively.

Optimal cut-off points (including corresponding sensitivity and specificity) of each screening instrument were calculated by Youden index, and are listed in Table 6.4. Even when using the optimal cut-off scores, no large improvements in sensitivity or

specificity were observed. Applying the HDS with a cut-off of ≤13.5 (using CI by MNC as the criterion standard) among participants with cognitive complaints as defined by an abnormal Simioni questionnaire showed the best, albeit still moderate performance, with a sensitivity of 71% and a specificity of 83%.

TABLE 6.4. OPTIMAL CUT-OFF POINTS (INCLUDING CORRESPONDING SENSITIVITY AND SPECIFICITY) OF THE MMSE, HDS, AND MOCA.

	Criterion standard= CI as determined by Frascati criteria			Criterion standard= CI as determined by MNC		
	Optimal cut-off	Sensitivity	Specificity	Optimal cut-off	Sensitivity	Specificity
Mini Mental State Examination (MMSE)	≤29	67%	54%	≤28	59%	76%
Montreal Cognitive Assessment (MoCA)	≤27	57%	74%	≤25	24%	90%
HIV Dementia Scale (HDS)	≤13.5	37%	81%	≤14	71%	69%
HIV Dementia Scale (HDS) among participants with cognitive complaints[1]	≤13	35%	93%	≤13.5	71%	83%

Abbreviations: CI, cognitive impairment; MNC, multivariate normative comparison.

Analyses were restricted to the HIV-1-positive study group. Optimal cut-off points were calculated using Youden index.

[1] Cognitive complaints were defined by an abnormal Simioni questionnaire.

DISCUSSION

Key results

All four cognitive screening tools showed comparable scores and abnormality rates among HIV-1-positive and HIV-negative study participants.

Having an abnormal Simioni questionnaire, or an abnormal MMSE, HDS, or MoCA score (using the classical cut-offs), each showed low sensitivity and moderate specificity, irrespective of which of both criterion standards was used. The more recently proposed HDS cut-off of ≤14/16 showed the highest, but still moderate, sensitivity, especially when using CI by MNC as the criterion standard (71%). Specificity for this cut-off was 69%. The specificity was increased further to 79% when applying this cut-off to HIV-1-positive participants with cognitive complaints as defined by an abnormal Simioni questionnaire. Sensitivity remained virtually unchanged.

When using CI by Frascati criteria as the criterion standard, ROC analyses showed MoCA to perform slightly better compared to HDS and MMSE. When using CI as determined by MNC, ROC analyses showed MMSE and HDS to perform slightly better than MoCA. However, all screening instruments, irrespective of which of both criterion standards was used, showed at best moderate accuracy for identifying cognitive impairment.

Exploring different cut-offs for MMSE, HDS, and MoCA, in search of an optimal cut-off to detect HIV-associated CI, no large improvements in sensitivity or specificity were observed.

Interpretation

Given that all four cognitive screening tools show comparable scores and abnormality rates among HIV-1-positive and uninfected study participants, concerns arise about the ability of these instruments to actually detect HIV-associated CI.

The MMSE is the most widely used cognitive screening tool for Alzheimer's disease (25,26). Cortical dysfunction is a hallmark of Alzheimer's disease, whereas subcortical dysfunction is a more common feature of HIV-associated CI (27). MMSE, not capturing executive function or motor skill, is therefore less sensitive to subcortical dysfunction (28). Another limitation of the MMSE is the ceiling effect, especially among people with high premorbid intelligence or educational level (26). In the context of HIV, three studies have investigated the usefulness of the MMSE in detecting HIV-associated CI using full NPA as criterion standard (29–31). These studies showed low sensitivity (24%-46%), which is in line with other publications (although these did not use full NPA as criterion standard) (28,29,32,33). In our study MMSE showed a very low sensitivity (2-6%), confirming these earlier reports, and we therefore consider the usefulness of the MMSE as a screening instrument for HIV-associated CI to be poor.

The HDS was developed specifically for the detection of HAD, using a cut-off of ≤10 (34). The usefulness of the HDS in detecting the milder forms of HIV-associate CI is being debated, with earlier studies reporting sensitivities of 26%-68% and specificities of 66%-96% (8,28,29,33,35–40). One study, additionally adjusting for age and education, managed to increase sensitivity to 71% (41). In an attempt to increase sensitivity further, a cut-off of ≤14 was proposed by Simioni et al., showing a sensitivity of 83-88% and specificity of 63-67% (8). Additionally, when they distinguished between participants with and without cognitive complaints, as determined by a short questionnaire they developed (the Simioni questionnaire), the positive predictive value of an HDS score of ≤14 among participants with cognitive complaints was 92% versus 82% among those without cognitive complaints.

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In our study, the HDS cut-off of ≤10 showed a low sensitivity of 6% and a high specificity of 97-98%. HAD being an exclusion criterion, this possibly accounts for the lower sensitivity in our analyses compared to previous studies. The higher HDS cut-off of ≤14 showed a sensitivity of 45% and specificity of 69% when using CI as determined by Frascati criteria as the criterion standard, which is lower than the sensitivity as published by Simioni et al. (8). Prevalence of CI was also lower in our cohort compared to their cohort. This might be explained by absence of HAD cases in our cohort, a higher hepatitis C co-infection rate in the Simioni cohort, as well as inclusion of participants with past cerebral toxoplasmosis in their cohort. Using CI as determined by MNC as the criterion standard, an HDS cut-off of ≤14 showed a somewhat higher sensitivity (compared to CI by Frascati criteria as the criterion standard) of 71% and a comparable specificity of 69%. Analogous to the publication by Simioni et al. (8) we also explored the performance of this higher HDS cut-off of ≤14 among participants with and without cognitive complaints as defined by an abnormal Simioni questionnaire. Among those with cognitive complaints, sensitivity remained virtually unchanged, whereas specificity increased by 10%, irrespective of which of both criterion standards was used.

The Simioni questionnaire itself as a cognitive screening instrument in our analyses showed a low sensitivity (35-41%) and moderate specificity (72-74%) for detecting CI. The sensitivity of the Simioni questionnaire in our cohort was lower than the sensitivity as published by Simioni et al. (57%) (2010). Recent studies reported a sensitivity and specificity of the Simioni questionnaire of 78-82% and 24-32%, respectively (30,42). The characteristics of these cohorts however differed from ours, with a higher prevalence and more severe cases of CI (30), partial verification of the screening test by NPA (42), and different demographic and HIV-related characteristics (e.g., median age was lower, not all individuals had a plasma HIV-1-RNA <40 copies/mL) (30,42).

Altogether we consider the usefulness of the Simioni questionnaire to detect HIV-associated CI therefore to be poor. Notably, and as described above, the Simioni questionnaire was developed solely as a scientific tool to distinguish those individuals with and without cognitive complaints, and as a complementary tool to the HDS, and not as a cognitive screening tool by itself. This is in line with a recently published paper describing its limited utility in clinical practice (43) and the most recent European AIDS Clinical Society guidelines which suggest clinicians to focus on patients reporting complaints of CI rather than rely too much on the Simioni questionnaire as a screening tool (15). The HDS (using the higher cut-off of ≤14) in combination with the Simioni questionnaire to determine subjective cognitive complaints in our hands performed modestly better and seemed to be the most appropriate cognitive screening tool.

The MoCA has been designed as a screening instrument for mild cognitive impairment, using a cut-off of ≤25 (44). Several studies have examined its usefulness for detecting HIV-associated CI, reporting a sensitivity of 53-65% and specificity of 63-75% (28,29,31,33,38,45–49). A recent publication by Milanini et al., investigating HIV-positive individuals aged above 60, reported a higher sensitivity of 72% (50). In addition, two studies investigated the usefulness of the MoCA in detecting HIV-associated CI but using different cut-offs of <22 (31) and ≤26 (30). They reported a sensitivity of 62% and 89%, and a specificity of 76% and 22%, respectively. In our study, MoCA showed a low sensitivity of 20-24% and a specificity of 90-94%, the sensitivity being substantially lower in our analyses compared to those previously published. Some of these studies (31,46,48,49) however concern HIV-positive populations with higher hepatitis C co-infection rates of 3.7%-22%, compared to 1% in our HIV-1-positive cohort. Furthermore, substance abuse and depressive symptoms, both factors known to be associated with cognitive impairment, were not reported in all studies (48–50), and major depressive disorder rates were much higher than in our cohort (46). In addition, CI was more often symptomatic or more severe in some studies (30,45–47,49). This may have influenced rates of CI and performance of MoCA.

Strengths

Major strengths of this study are the inclusion of HIV-1-positive individuals on suppressive cART (representing the vast majority of HIV-positive individuals in countries with unrestricted access to cART), the use of an extensive NPA battery, exclusion of individuals with severe neurological/psychiatric conditions that could potentially affect the prevalence of HIV-associated CI, the comparison of four different screening instruments, and the inclusion of a highly comparable HIV-negative control group.

Limitations

Our participants were all male and predominantly of Caucasian descent, and future studies will be needed to determine whether our findings apply equally to women and populations with other ethnic backgrounds.

Conclusion

All investigated cognitive screening instruments performed poorly for detecting HIV-associated CI. Cognitive deficits in the context of treated HIV infection are subtle, and none of the currently available screening instruments seem sufficiently adequate for use in clinical practice.

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AUTHORS' CONTRIBUTIONS

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SUPPLEMENT

SUPPLEMENTARY TABLE 6.1. OVERVIEW OF ADMINISTERED NEUROPSYCHOLOGICAL ASSESSMENT BATTERY.

Domain	Test administered	Test scores
Verbal fluency	Category Fluency (1)	Total number of animals in 1 minute
		Total number of occupations in 1 minute
	Letter Fluency (2)	Total number of words, 1 minute for each of 3 letters
Executive function	Trail Making Test-B (3)	Total time to complete
	Wisconsin Card Sorting Test (4)	Percentage of perseverative errors
	Stroop color-word test (5)	Interference condition: Time to complete
Information processing speed	Trail Making Test-A (3)	Time to complete
	Digit Symbol (6)	Total correct symbols
	Symbol Search (6)	Total correct symbols
Attention	Paced Auditory Serial Addition Task (PASAT) 3.2 (7)	Total correct summations
	PASAT 2.8 (7)	Total correct summations
	Letter-number sequencing (6)	Total correct sequences
Memory	Rey Adult Verbal Learning Test (AVLT)-learning (8)	Total recalled words trails 1-5
	Rey AVLT-recall (8)	Total words recalled
	Visual Reproduction (VR) learning (9)	Total score
	VR recall (9)	Total score
Motor function	Grooved pegboard (10)	Dominant hand: Time to complete
		Non-dominant hand: Time to complete
	Finger tapping (10)	Dominant hand: Median number of taps
		Non-dominant hand: Median number of taps

SUPPLEMENTARY TABLE 6.2. CLASSIFICATION OF HIV-ASSOCIATED COGNITIVE IMPAIRMENT USING FRASCATI CRITERIA (11).

HAND subcategory	Definition of abnormal test result	Definition of abnormal cognitive domain	Number of affected cognitive domains	Interference with daily functioning
Asymptomatic neurocognitive impairment (ANI)	1 SD	≥1 test result abnormal	≥2	No interference (CFQ-score <42†)
Mild neurocognitive disorder (MND)	1 SD	≥1 test result abnormal	≥2	Mild interference (CFQ-score ≥42†)
HIV-associated dementia (HAD)	2 SD	≥1 test result abnormal	≥2	Marked interference

HAND, HIV-associated neurocognitive disorder; SD, standard deviation.
† The CFQ-score (12) was used as a surrogate for interference with everyday functioning to distinguish between ANI and MND. A score of ≥42 (reflecting the 5% highest scores of the controls) was used to indicate a significant degree of subjective cognitive complaints.

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