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Research Article

Neuropsychological tests associated with symptomatic HIV-associated neurocognitive disorder (HAND) in a cohort of older adults in Tanzania

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Abstract

Objective: Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) prevalence is expected to increase in East Africa as treatment coverage increases, survival improves, and this population ages. This study aimed to better understand the current cognitive phenotype of this newly emergent population of older combination antiretroviral therapy (cART)-treated people living with HIV (PLWH), in which current screening measures lack accuracy. This will facilitate the refinement of HAND cognitive screening tools for this setting. **Method:** This is a secondary analysis of 253 PLWH aged ≥50 years receiving standard government HIV clinic follow-up in Kilimanjaro, Tanzania. They were evaluated with a detailed locally normed low-literacy neuropsychological battery annually on three occasions and a consensus panel diagnosis of HAND by Frascati criteria based on clinical evaluation and collateral history. **Results:** Tests of verbal learning and memory, categorical verbal fluency, visual memory, and visuoconstruction had an area under the receiver operating characteristic curve >0.7 for symptomatic HAND (s-HAND) (0.70–0.72; $p < 0.001$ for all tests). Tests of visual memory, verbal learning with delayed recall and recognition memory, psychomotor speed, language comprehension, and categorical verbal fluency were independently associated with s-HAND in a logistic mixed effects model ($p < 0.01$ for all). Neuropsychological impairments varied by educational background. **Conclusions:** A broad range of cognitive domains are affected in older, well-controlled, East African PLWH, including those not captured in widely used screening measures. It is possible that educational background affects the observed cognitive impairments in this setting. Future screening measures for similar populations should consider assessment of visual memory, verbal learning, language comprehension, and executive and motor function.

Keywords: HIV; neuropsychological tests; mental status and dementia tests; cognitive dysfunction; aging; Africa South of the Sahara

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Introduction

Globally, 38.4 million people are living with human immunodeficiency virus (HIV), the majority of whom live in sub-Saharan Africa (SSA) (UNAIDS, 2021). HIV-associated neurocognitive disorder (HAND) is a common long-term complication of treated HIV, well-recognised in high-income countries (HICs). Older people appear to be at higher risk of HAND, although the mechanism for this is unclear and likely multifaceted (Hardy & Vance, 2009; Nightingale et al., 2023). This poses a new challenge in SSA, as recent substantial progress toward the UNAIDS targets for HIV diagnosis, treatment, and viral suppression (Estill et al., 2018; UNAIDS, 2014) has led to a recent rapid aging of the HIV population.

HAND is currently conceptualized as a spectrum of impairments, hypothesized to result from the direct and indirect effects of the HIV virus, potential neurotoxic effects of combination antiretroviral treatment (cART), comorbid disease, environmental factors, and sociodemographic vulnerabilities (Deeks et al., 2013; Manji et al., 2013). Current operationalized criteria describe asymptomatic neurocognitive impairment (ANI), mild

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neurocognitive disorder (MND), and HIV-associated dementia (HAD) in order of severity (Antinori et al., 2007). We acknowledge the critique particularly of ANI as a diagnostic entity of uncertain clinical significance and the substantial potential for false positives and associated negative consequences, and that revision of the current HAND diagnostic concept is advocated (Nightingale et al., 2023). In seeking to provide clinically relevant findings, we have placed an emphasis here on HAND stages with a functional impairment (MND and HAD). Together, these are termed symptomatic HAND (s-HAND), which require clear evidence of functional impairment in addition to measured cognitive impairment.

Access to effective HIV treatment has a substantial impact on the prevalence of HAND subtypes (Habib et al., 2013). HIV-associated dementia was classically described as a subcortical dementia, characterized by prominent motor slowing and the presence of frontal reflexes (Robinson-Papp et al., 2009). Modern treatment with cART can reduce the more severe stages of HAND, but it does not entirely prevent it (Saylor et al., 2016). Instead a milder and broader spectrum of clinical impairment is observed in an increasingly well-treated population, with both cortical and subcortical domains affected (Sacktor, 2018). A recent global estimate suggests that while 40% of adult PLWH meet HAND criteria, only a minority have symptomatic HAND (MND 13–26% and HAD 5–9%) (Wang et al., 2020; Wei et al., 2020), with substantial differences seen between the pre- and post-cART era (Sacktor, 2018; Wang et al., 2020). Regional differences in previous and current cART provision, and differing hypothesized neurotoxic effects of different HIV clades, may also create important differences between populations (Habib et al., 2013; Hardy & Vance, 2009; Tyor et al., 2013), meriting specific attention to the East African and even Tanzanian context. Pooled prevalence of HAND in SSA was estimated at 53% in a meta-analysis of 2009–2019 studies, but prevalence varied between 14% and 88% and marked heterogeneity was reported (Nweke et al., 2021).

Age can also impact the prevalence and the profile of impairments in older PLWH (Hardy & Vance, 2009). This is hypothesized to result from accelerated amyloid deposition and/or cerebrovascular disease associated with aging (Canet et al., 2018; Deeks et al., 2013; Mackiewicz et al., 2019). Where aging impacts the presentation of HAND due to an altered disease process, there is merit in considering older people separately. Relevant data are limited however and originate almost exclusively from HICs. A 2013 meta-analysis of African HAND studies was unable to identify any studies of individuals aged ≥50 years (Habib et al., 2013), and a 2021 analysis identified only five studies with an identifiable subgroup aged ≥50 years, most of which used a screening tool only (Mwangala et al., 2021). In SSA, the number of PLWH >50 years is expected to triple by 2040 (Hontelez et al., 2012).

Finally, culture and educational background play an important role on individual performance on neuropsychological testing (Ardila, 2007; Rosselli et al., 2022). It is therefore important to study the pattern of cognitive impairment across cultural contexts, potentially highlighting diverse testing needs and even differences in observed cognitive phenotype. The Global NeuroAIDS Roundtable advised that a lack of culturally appropriate study instruments was limiting HAND research in a range of international settings (Joseph et al., 2013). There are similar challenges around literacy, where the impression of cognitive phenotype can be distorted by tasks relying on reading, writing, and arithmetic (Ardila, 2007). This could be particularly important in low- and middle-income countries (LMIC) where low literacy is more common (Roser & Ortiz-Ospina, 2018).

To our knowledge, this is the only longitudinal cohort of older PLWH with a comprehensive neuropsychological battery and a rigorous consensus diagnostic process in East Africa. The current limited data on older PLWH are focused on South Africa, where cross-sectional screening (Joska et al., 2019) and incidence using a neuropsychological battery have been examined (Asiimwe et al., 2020). These populations differ from East Africa demographically, socioculturally, and in HIV prevalence (Asiimwe et al., 2020; Gómez-Olivé et al., 2018). A better understanding of the cognitive phenotype in this unique and important cohort will greatly aid the development of HAND screening tools for older adults in East Africa and more widely in the region. While understanding HAND across diverse settings in an evolving context is challenging, it is crucial to address.

Eleven million adults are estimated to have HAND in SSA currently (Wang et al., 2020), and as this population ages, HAND may become a leading cause of cognitive impairment in SSA. As treatment provision improves throughout SSA, the aging, stable, longstanding, and well-managed cohort described in this study is likely to be increasingly representative of PLWH throughout the region.

Our primary aim was therefore to identify the neuropsychological tests associated with s-HAND diagnosed according to Frascati criteria (Antinori et al., 2007) in older PLWH in Tanzania assessed using a locally normed low-literacy neuropsychological test battery including subcortical and cortical domains (Flatt et al., 2023). This would inform the development of future screening tools for s-HAND in older people in similar populations.

Methods

Participants and setting

This secondary analysis used longitudinal data from an initial cohort of individuals aged ≥50 years ($n = 253$) systematically sampled from attendees of a government-funded HIV clinic in Northern Tanzania and offered detailed neuropsychological assessment and consensus HAND diagnosis by Frascati criteria at baseline and annually thereafter for 2 years. The recruitment methods and characterization of the baseline study cohort are previously published (Flatt et al., 2023). Recruitment of this cohort took place between March and June 2016. Informed consent was requested following provision of verbal and written information, with assent sought from a close relative where participants lacked capacity to consent due to cognitive impairment. The secondary analysis was approved by Newcastle University's Faculty of Medical Sciences Research Ethics Committee (ref: 2125/12519) in addition to Kilimanjaro Christian Medical University College Research Ethics and Review Committee and the National Institute for Medical Research, Tanzania, including necessary data transfer agreements. The human data included in this manuscript were obtained in compliance with the Helsinki Declaration (World Medical Association, 2001).

HIV disease severity and other clinical measures

HIV disease severity measures were taken from a standardized clinical data sheet maintained by the clinic for each patient from diagnosis. Available data included nadir CD4 (with ≤200 cells/mm^3, categorized as "low"), current CD4, current and previous cART regimen, World Health Organization (WHO) HIV disease

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stage, current and previous tuberculosis (TB), and, from mid-2017, HIV viral load when this became accessible locally. HIV viral load measurements above 10,000 copies/mm^3 were categorized as "high." Non-HIV measures included visual acuity using a Landholt C illiterate logmar chart (categorized as per WHO as mild, moderate, and severe visual impairment) and hearing impairment by self-report and clinician subjective rating. Demographic data included self-reported year of birth (cross-checked with clinic records), biological sex, and highest level of education (in years) attained by self-report. This methodology and measures are described in more detail in previously published work (Flatt et al., 2023), notably finding no association between HAND and HIV disease stage or CD4 nadir.

Neuropsychological testing

Participants underwent a series of neuropsychological tests aimed at assessing a range of cognitive domains at each time point (Table 1). Low-literacy measures were selected from those validated in the original cross-cultural WHO HAD studies (Maj et al., 1993; Maj et al., 1991; Maj et al., 1994) and to cover domains required by Frascati criteria (Alkali et al., 2013). Neuropsychological tests included in the battery aimed to assess the following cognitive domains: working memory, visual memory, visuoconstruction, verbal learning, learning interference, delayed recall, recognition memory, psychomotor speed, executive function, language comprehension, orientation, fine motor/2D spatial awareness, and categorical verbal fluency. These are detailed in Table 1. Additional low-literacy versions of tests examining typically cortical domains were added to account for a potentially evolving picture of HAND in the post-combination-ART era (Cysique & Brew, 2009; Hardy & Vance, 2009). Where possible, these were locally or regionally developed or validated (Table 1). Normative data were derived from local controls who self-identified as HIV negative. These were recruited from another chronic disease clinic at the same government hospital, matched by age band and education. Timed tests where the time recorded was greater than the maximum allowed were assigned the maximum time. Other test scores out of range were voided as the score was felt to be unreliable.

HAND diagnosis

HAND diagnoses were made by consensus panel review in line with the process outlined in Fig. 1. This included detailed case note review and additional confirmatory bedside neurological and mental state examination to consider other sources of cognitive impairment such as Alzheimer's disease type changes and previous stroke based on clinical presentation and collateral history. Further details of this assessment are previously published (Kellett-Wright et al., 2021). For the purposes of the analysis, a distinction was made between those with impaired function in everyday living attributable to HAND, that is, symptomatic HAND (s-HAND), and those without. Individuals meeting criteria for MND and HAD were classified s-HAND and compared to individuals with ANI and no cognitive impairment. Assessment of function to distinguish s-HAND was supported by a locally validated Instrumental Activities of Daily Living scale (Paddick et al., 2015), clinician-rated Karnofsky Performance Status (Karnofsky et al., 1948), observation of clear functional difficulties on assessment (i.e., persistent difficulties following instructions), self-reported impairments using a standardized questionnaire and collateral informant history, available for the majority of participants (Collingwood et al., 2014). Functional impairment was judged by the consensus panel using all the information available.

The Confusion Assessment Method (Inouye et al., 1990; Paddick et al., 2018), the 15-item Geriatric Depression Scale (GDS) (Yesavage & Sheikh, 1986), and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) supported clinical assessment to help screen for delirium, depression, and other psychiatric disorders, respectively. Where any of these was the primary diagnosis, the patient was excluded from the analysis (Supplementary Materials, S1).

Statistical analysis

Analysis was carried out in R software (version 3.6.3; R Foundation for Statistical Computing, Austria (R Core Team, 2020)). Data were examined visually for normality of distribution. Groups were compared using Skillings–Mack and Kruskal–Wallis tests as appropriate. The statistical significance level was set at alpha = 0.05. Benjamini–Hochberg multiple comparison corrections were carried out with a 5% false discovery rate.

The outcome of the analysis was s-HAND. Educational subgroups were created using a median split of 4 years of school education: "low education" ≤4 years and "high education" >4 years. Locally, there is an important transition from elementary education at this age, and local work has highlighted the importance of little to no formal education on cognitive testing (Paddick et al., 2014). It was not feasible to dichotomize at no education due to the small numbers in this category ($n = 30$). Dichotomozing at 4 years was the most statistically significant on exploratory preliminary modeling and resulted in the highest Youden index on receiver operating characteristic (ROC) curve analysis (data not shown). This confounder was prioritized due to the wide range of education in the cohort, from university level to none at all.

Accuracy of neuropsychological test scores to identify s-HAND was determined using area under the ROC curves (AUC). Using *cutpointr* (Thiele & Hirschfeld, 2021), sensitivity and specificity were calculated, and 95% confidence intervals (95% CI) were produced by bootstrapping. Youden's index was used to identify optimal cutoffs. Neuropsychological test scores were dichotomized as normal or impaired using these cutoffs.

Binomial mixed effects modeling to examine the relationship between neuropsychological test performance and s-HAND from baseline to year 2 was performed using *lme4* (Bates et al., 2015), using all available assessments throughout this period. A random intercept model was used, varying at the individual and time level. This was able to account for repeated testing of individuals at more than one time point and does not exclude subjects with missing data from the analysis. A basic model was established, including variables of age, sex, GDS score, CD4 nadir, TB status, education, viral load, hearing and visual impairment, as fixed effects. These were expected to influence cognitive impairment or performance on neuropsychological tests. A backward stepwise approach was taken to exclude coefficients with $p > 0.05$.

To examine each neuropsychological test individually, dichotomized neuropsychological test (impaired *vs.* not impaired) scores and an interaction with time were added to the basic model as fixed effects. A further model was constructed including all neuropsychological tests that were significantly associated with s-HAND individually including the basic model, all as fixed effects. Non-significant neuropsychological tests and interactions were excluded using a backward stepwise approach. Each analysis was repeated with low- and high-education subgroups, with education removed from the basic model.

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Table 1. Descriptions of individual cognitive tests and associated areas of impairment.

Area of impairment	Test name	Description	Units	Reference validation study
Working memory	Digit span forward	The subject recalls progressively longer lists of digits. A subtest of the WAIS-IV (Wechsler, 2008)	Longest list of digits recalled	An educationally diverse elderly population (Carey et al., 2004; Choi et al., 2014; Silverstein et al., 2007) and HIV subjects in Zaire and Kenya (Maj et al., 1993)
	Digit span backward	The list of digits is recited backwards (Wechsler, 2008)	Longest list of digits recalled	
	Digit span total	Digit span forward + digit span backward	Total score	
Visual memory	Matchstick construction 1	Accuracy in reconstructing four designs made out of matchsticks (Baiyewu et al., 2005)	Score out of 12 according to testing manual	Non-HIV subjects in Nigeria (Baiyewu et al., 2005) and Brazil (de Paula et al., 2013) (low-literacy)
Visuoconstruction	Matchstick construction 2	Accuracy in copying four designs made out of matchsticks (Baiyewu et al., 2005)	Score out of 12 according to testing manual	Non-HIV cognitively impaired subjects in Tanzania (Paddick et al., 2015)
Verbal learning	AVLT trial IV	Recall of a 15-item list (list A) after 4 consecutive verbal presentations (Maj et al., 1991)[a]	Number of items/15	HIV subjects in Zaire and Kenya (Maj et al., 1993)
	AVLT trial V	Recall of a list A after five consecutive verbal presentations[a]	Number of items/15	
	AVLT sum of trials I–V	Sum of the first five attempts at recalling list A[a]	Number of items/75	
	AVLT trial V minus I	Difference between the first and fifth attempt at recalling list A[a]	Number of items -15–15	
Learning interference	AVLT trial VI	Recall of a new 15-item list (list B)[a]	Number of items/15	
	AVLT trial VII	Recall of list A without an additional learning opportunity[a]	Number of items/15	
Delayed recall	AVLT trial VIII	Further recall of list A after a delay of 20 min[a]	Number of items/15	
Recognition memory	AVLT trial IX correct	A new list is presented, containing list A mixed with phonetically or semantically related words. The test is scored according to the number of items from list A correctly identified[a]	Number of items/15	
	AVLT trial IX incorrect	Incorrect identifications from this trial[a]	Number of items/15	
	AVLT trial IX difference	The difference between the number of correct and incorrect identifications from this trial[a]	Number of items -15–15	
Psychomotor speed	Color trails 1	The participant connects the numbers 1–25 in sequence (D'Elia et al., 1996)[b]	Time to complete (s). Cutoff at 300s	HIV subjects in Zaire and Kenya (Maj et al., 1993)
Executive function	Color trails 2	The participant again connects numbers in sequence, but alternates between pink and yellow colors (D'Elia et al., 1996)[b]	Time to complete (s). Cutoff at 300s	
Orientation	Orientation	The subject is asked to name the person, day, date, month, year, time of day, and place. Scored according to the number of correct answers (Paddick et al., 2017)[c]	Score/7	Non-HIV subjects in Tanzania (Paddick et al., 2017)
Language comprehension	Commands	The subject is asked to perform commands that involve one to five steps. Scored according to the most steps that could be followed (Paddick et al., 2017)[c]	Score /5	
Fine motor/2D spatial awareness	Peg board – dominant hand	The subject inserts 25 metal pins into differently orientated slots in a board with their preferred hand (Matthews & Klove, 1964)[d]	Time to complete (s). Cutoff at 300s	HIV subjects in Uganda (Sacktor et al., 2005) and Brazil (de Almeida et al., 2017) (low literacy)
	Peg board – non-dominant hand	Pins inserted with the subject's non-preferred hand (Matthews & Klove, 1964)[d]	Time to complete (s). Cutoff at 300s	
Categorical verbal fluency (includes executive function)	Market items verbal fluency	The subject generates as many items as possible in one minute (Lopes et al., 2009)[e]	Valid items named	Not validated

Note: WAIS = Wechsler Adult Intelligence Scale, AVLT = auditory verbal learning test, HIV = human immunodeficiency virus, WHO = World Health Organization, UCLA = University of California, Los Angeles, HAND = HIV-associated neurocognitive disorder.

[a]A WHO/UCLA adapted version of the AVLT (Maj et al., 1993; Peaker & Stewart, 1989; Rey, 1958) was used, consistent with initial descriptions of HAND. This draws on a standard lexicon of culturally neutral concepts (Snodgrass & Vanderwart).

[b]Color trails 1 and 2 are intended to be culture neutral versions of Trail Making Tests A and B (Army Individual Test Battery, 1944; Strauss et al., 2006), with good applicability to non-English speaking, low-literacy populations (Llorente et al., 2003).

[c]Orientation and commands tests were taken from a version of the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog), validated in Tanzania and Nigeria for the diagnosis of Alzheimer's disease in rural-dwelling older adults (Paddick et al., 2017). "Season" was removed from the original ADAS-Cog as it was not well understood in the validation pilot.

[d]Presumed to be culture neutral due to lack of culturally contingent concepts (Maj et al., 1991).

[e]A version of the Brazilian "supermarket items" categorical fluency test was used (Lopes et al., 2009), with items substituted for locally relevant ones. This test has not been locally validated.

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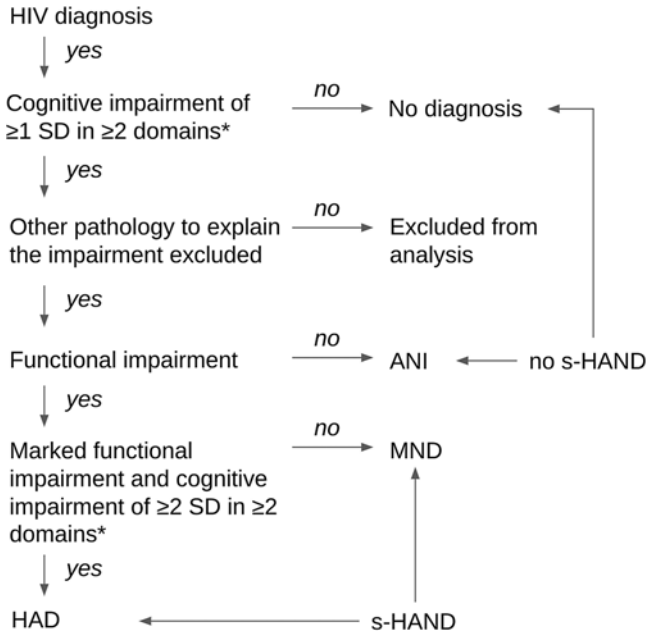

Figure 1. Simplified diagnostic flowchart based on Frascati criteria (Antinori et al., 2007) and demonstrating the relationship between HAND stages and s-HAND. *After an assessment of at least the following domains: verbal/language, attention/working memory, abstraction/executive, memory (learning, recall), speed of information processing, sensory-perceptual, and motor skills. Scores compared to age–education appropriate norms. Standard deviation (SD) in relation to age- and education-matched comparison group; symptomatic HAND (s-HAND).

Results

Of 830 patients ≥50 years of age registered at the clinic, 310 were systematically sampled in accordance with the study protocol. Expected clinic capacity determined whether every 2nd or 3rd patient could be approached each day. Based on acute illness, intoxication, or refusal, 21 patients were excluded; 36 patients could not complete a full assessment and were also excluded, leaving a baseline study sample of 253 participants (Table 2). Further details regarding the study protocol and those excluded are previously published (Flatt et al., 2023). Of the 253 participants, $n = 117$ (46.2%) were assessed at all 3 time points (baseline, year 1 and year 2), 85 were assessed twice, and 51 were assessed on only one occasion. This provided 572 observations over all the time points. A collateral history was possible in 452 of these observations (79%). HIV control was good where measured (median latest CD4 count ≥497, median viral load = 0 where available although this was not done in 2016). At baseline, the mean time since diagnosis was 7.1 years (range = 0.7–23.94; SD = 3.3) (Flatt et al., 2023). Depression scores were significantly higher at baseline ($p < 0.001$); there was a higher proportion of individuals with suppressed HIV viral load (i.e., $<10^5$) at year 2 compared to year 1 (84.2% *vs.* 61.5%, respectively, $p = 0.004$) and poorer visual acuity at year 1 compared to baseline ($p = 0.003$). There were no other significant differences between sessions for expected confounders included in the model.

Neuropsychological test performance in relation to symptomatic HAND at baseline

All cognitive tests could significantly discriminate between groups (with or without s-HAND) at baseline assessment ($p < 0.05$, Table 3, educational subgroups in Supplementary Materials, S2), with the exception of Auditory Verbal Learning Test (AVLT) trial IX,false ($p > 0.05$). Baseline market items (categorical verbal fluency); AVLT trials IV, V, VII and VIII and sum of I–V (verbal learning with delayed recall and recognition memory); and matchstick construction 1 and 2 (visual memory and visuoconstruction, respectively) had the highest area under the receiver operating characteristic (AUROC) (Mandrekar, 2010) of ≥ 0.70 ($p < 0.001$ for all; AUROC = 0.70–0.72; sensitivities = 0.51AVLT 0.73; specificities = 0.60–0.81).

Neuropsychological test performance in relation to symptomatic HAND at any time point

Controlling for confounders, impairment in all neuropsychological tests apart from AVLT trial IX – false and digit span – forwards was significantly associated with s-HAND at any time point but not with change over time (i.e., impairment at a given time point was associated with s-HAND regardless of time point, but not developing s-HAND over time, Table 4). The strongest associations were between s-HAND and impaired Matchstick construction 1 (visual memory, odds ratio (OR) = 7.8, 95% CI = 3.0–20.4, $p < 0.001$), AVLT trial V (verbal learning, OR = 7.3, 95% CI = 3.3–16.0, $p < 0.001$), AVLT trial VIII (delayed recall, OR = 5.8, 95% CI = 2.5–13.1, $p < 0.001$), and color trails 1 (psychomotor speed, OR = 5.4, CI = 2.5–12.1, $p < 0.001$) performance at any time point.

Distinct results were seen for educational subgroups (Supplementary Materials S3). For the low-education group (≤ 4 years), after correcting for multiple comparisons, the largest ORs for s-HAND were for impaired AVLT trial V (verbal learning (OR = 11.7, CI = 2.7–49.9, $p < 0.001$), AVLT trial VII (learning interference, OR = 11.5, CI = 2.5–52.1, $p = 0.001$), and AVLT trial VIII (delayed recall, OR = 10.9, 95% CI = 2.4–50.9, $p = 0.002$) test performance at any time point.

For the high-education group (>4 years), the highest ORs for s-HAND were for Matchstick construction 1 (visual memory, OR = 20.2, CI = 3.3–122.7, $p = 0.001$), color trails 1 (psychomotor speed, OR = 10.4, CI = 2.9–37.8, $p < 0.001$), Matchstick construction 2 (visuoconstruction, OR = 7.9, CI = 2.5–24.6, $p < 0.001$), and Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) Commands (language comprehension, OR = 7.6, CI = 2.1 = 27.9, $p = 0.002$) test performance at any time point.

To determine which tests might be useful as part of a more limited testing battery or screening tool identifying those at risk of s-HAND at any time point, all neuropsychological test performances were individually included in a backward mixed effects model, with interactions with time and covariates (Table 5). Impaired performance on Matchstick construction 1 (OR = 3.3, CI = 1.7–6.6, $p < 0.001$), AVLT trial IV (OR = 2.1, CI = 1.2–3.9, $p = 0.014$), AVLT trial VIII (OR = 2.8, CI = 1.4–5.5, $p = 0.003$), AVLT trial IX – difference (OR = 2.6, CI = 1.3–5.1, $p = 0.007$), color trails 1 (OR = 2.7, CI = 1.4–5.4, $p = 0.004$), commands (OR = 2.8, CI = 1.4–5.7, $p = 0.004$), and market items (OR = 3.2, CI = 1.7–6, $p < 0.001$) were significantly associated with s-HAND. Impaired Pegboard with the dominant hand was associated with s-HAND over time (OR = 2.8, CI = 1.3–6.3, $p = 0.011$). For the low-education group, the strongest associations with s-HAND were for impaired AVLT trial VII (learning interference) and matchstick construction 2 (visuoconstruction, Table 5, $p < 0.01$ for all), whereas in the high-education group, the strongest associations were for impaired AVLT Trial IX – difference (recognition memory), color trails 1 (psychomotor speed), and ADAS-Cog Commands (language comprehension) test performance ($p < 0.01$ for all).

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Table 2. Participant characteristics and other relevant measures for each time point.

Participant characteristics	Baseline, 2016 ($n = 252$)[d]	Year 1, 2017 ($n = 174$)	Year 2, 2018 ($n = 146$)	*p*-value
Age	57 (53–61)	57 (54–62)	58 (55–64)	**<0.001**[a]
Sex: female *n* (%)	182 (72.2)	125 (71.8)	103 (71.2)	0.98[b]
Highest level of education: >4 (years)[c] *n* (%)	161 (63.9)	113 (64.9)	99 (67.8)	0.83[b]
CD4+ count current	499 (316.5–672)	497 (301–670)	525.5 (336.2–701.8)	0.56[a]
CD4+ count nadir	165 (95–254)	163.5 (98.5–236.2)	168 (99–253)	0.91[a]
CD4+ count nadir <200, *n* (%)	149 (59.1)	105 (60.3)	86 (58.9)	0.92[b]
Viral load, median (IQR; max)	Not available	0 (0–45.5; 7707)	0 (0–45.5; 169698)	0.46[a]
Viral load $<10^5$, *n* (%)	Not available	107 (61.5)	123 (84.2)	**0.04**[b]
TB status				
Current, *n* (% of total for time point)	5 (2)	3 (1.7)	3 (2.1)	0.98[a]
Previous, *n* (%)	42 (16.7)	30 (17.2)	29 (19.9)	
No history of TB, *n* (%)	196 (77.8)	141 (81)	114 (78.1)	
Not known, *n* (%)	9 (3.6)	0 (0)	0 (0)	
GDS -15	2 (1–4)	1 (0–2)	1 (0–2)	**<0.001**[a]
Visual acuity, logmar right eye median; not available	0.32 (0.25–0.63); 53	0.40 (0.32–0.63); 29	Not available	**0.003**[a]
Diagnosis				
None, *n* (% of total for time point)	133 (52.8)	64 (36.8)	46 (31.5)	0.74[a]
ANI, *n* (%)	64 (25.4)	60 (34.5)	68 (46.6)	
MND, *n* (%)	46 (18.3)	38 (21.8)	28 (19.2)	
HAD, *n* (%)	9 (3.6)	12 (6.9)	4 (2.7)	
Diagnosis – dichotomized				
s-HAND, *n* (%)	55 (21.8)	50 (28.7)	32 (21.9)	0.21[b]

Note: TB = tuberculosis, GDS = Geriatric Depression Scale, ANI = asymptomatic neurocognitive impairment, MND = mild neurocognitive disorder, HAD = HIV-associated dementia, HAND = HIV-associated neurocognitive disorder.
Data presented are median (interquartile range, IQR), unless otherwise stated.
[a]Skillings–Mack test.
[b]Kruskal–Wallis test.
[c]Prior to dichotomizing at baseline, educational groups consisted of none, $n = 30$ (11.9%); 1–4 years, $n = 58$ (22.9%); 5–7, $n = 107$ (42.3%); completed primary (7+), $n = 38$ (15.0%); completed secondary, $n = 13$ (5.1%); higher education, $n = 4$ (1.6%); not known, $n = 3$ (1.2%).
[d]One patient was excluded from the analysis for the baseline assessment as they were diagnosed with pseudo-dementia. They were subsequently diagnosed with HAD at a follow-up assessment and so were included as part of the year 1 (2017) assessments. The total number of patients included is therefore 253, rather than 252 as would be expected from the number included at baseline.

Discussion

This study describes the cross-sectional association of s-HAND with cognitive impairments as measured by a battery of neuropsychological tests in cART treated older adults in SSA. The analysis used data from all time points, accounting for this using mixed effects models; however, very few tests were associated with s-HAND over time. A broad range of cortical and subcortical impairments were seen. Broadly, tests with real-life applicability, such as recalling items from the market, tended to be most strongly associated with s-HAND. There were prominent differences in the pattern of association seen in different educational groups. These points will be discussed further in turn.

It is widely acknowledged that increasingly available cART has changed the clinical presentation of HAND (Clifford & Ances, 2013; Sacktor, 2018). These results provide further evidence that impairments typically associated with cortical pathology play an important role in the pathophysiology of HAND in older adults, as well as traditionally subcortical impairments. In fact, almost every test was significantly associated with s-HAND when considered individually, and when combined into a single model with all participants, matchstick construction 1 (visual memory), market items (categorical verbal fluency), commands (language comprehension), color trails 1 (psychomotor speed), and AVLT trials IV, VIII, and IX – difference (verbal learning, delayed recall, and recognition memory respectively) were independently associated with s-HAND. Categorical verbal fluency had the highest AUC at 0.72 (sensitivity 55%, specificity 81%) supporting the established importance of executive function in HAND, although the low sensitivity here suggests that this may be insufficient to provide clinical utility as a stand-alone test.

The cognitive impairments assessed in this study are broadly similar to those used in other longitudinal cohort studies of HIV in working age adults and children in the USA (Elicer et al., 2018; Heaton et al., 2015; Sacktor et al., 2016), France (Vassallo et al., 2017), Uganda (Nakasujja et al., 2010; Sacktor et al., 2009; Sacktor et al., 2006), and Zambia (Adams et al., 2019), however, with the addition of language comprehension and orientation. These data indicate that such cortical processes might be important to assess as part of a comprehensive battery in future research. Without supporting biomarker and neuroimaging data, it is difficult to relate this impression to the underlying pathology with any more certainty.

These findings are relevant to the current difficulties in finding culturally relevant tools to screen for HAND. Existing tools are insufficiently sensitive or specific to provide clinical utility, including the widely used International HIV Dementia Scale (IHDS) (Haddow et al., 2013; Kellett-Wright et al., 2021; Milanini et al., 2018). This may be because the IHDS relies heavily on motor speed, whereas in this and many other settings, a broad range of cognitive processes are impacted. Furthermore, tools developed in HICs for working age adults may have limited utility for older adults in SSA. These data suggest some tests which might have broad applicability to the future development of screening tools. Categorical verbal fluency, assessed by asking participants to name market items, not only had the highest AUC in all participants but also performed well in both high-education (AUC 0.77, sensitivity 0.70, specificity 0.66) and low-education subgroups (AUC 0.70, sensitivity 0.63, specificity 0.74. It is well established that executive dysfunction is often a feature of HAND (Sacktor, 2018) though language ability will of course potentially impact on a task such as

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Table 3. Accuracy and optimal cutoffs of baseline cognitive tests identifying s-HAND.

Area of impairment	Neuropsychological test	AUC (95% CI)	*p*-value	Optimal cut point	Sensitivity	Specificity
Working memory	Digit span – forward	0.629 (0.562–0.703)	**0.003**	≤4	0.56	0.63
	Digit span – backward	0.621 (0.545–0.697)	**0.005**	≤1	0.33	0.89
	Digit span – total	0.64 (0.563–0.714)	**0.002**	≤5	0.38	0.83
Visual memory	Matchstick construction 1	0.715 (0.647–0.776)	**<0.001**	≤5	0.51	0.84
Visuoconstruction	Matchstick construction 2	0.702 (0.638–0.765)	**<0.001**	≤11	0.73	0.60
Verbal learning	AVLT trial IV	0.705 (0.638–0.767)	**<0.001**	≤7	0.71	0.66
	AVLT trial V	0.721 (0.652–0.785)	**<0.001**	≤7	0.64	0.78
	AVLT sum 1–V	0.717 (0.645–0.784)	**<0.001**	≤33	0.69	0.69
	AVLT V minus I	0.64 (0.569–0.711)	**0.001**	≤3	0.69	0.52
Learning interference	AVLT trial VI	0.622 (0.553–0.687)	**0.005**	≤4	0.69	0.51
	AVLT trial VII	0.723 (0.664–0.78)	**<0.001**	≤4	0.65	0.73
Delayed recall	AVLT trial VIII	0.721 (0.655–0.784)	**<0.001**	≤4	0.60	0.78
Recognition memory	AVLT trial IX – correct	0.622 (0.552–0.695)	**0.006**	≤12	0.62	0.57
	AVLT trial IX – false	0.566 (0.495–0.639)	0.120	≥1	0.66	0.47
	AVLT trial IX – difference	0.686 (0.619–0.754)	**<0.001**	≤8	0.44	0.83
Psychomotor speed	Color trails 1	0.677 (0.602–0.746)	**<0.001**	≥196	0.56	0.80
Executive function	Color trails 2	0.665 (0.599–0.728)	**<0.001**	≥259	0.71	0.59
Language comprehension	Commands	0.603 (0.535–0.68)	**0.012**	≤3	0.35	0.85
Orientation	Orientation	0.662 (0.598–0.725)	**<0.001**	≤6	0.56	0.74
Fine motor/2D spatial awareness	Peg board dominant hand	0.623 (0.551–0.694)	**0.006**	≥151	0.58	0.64
	Peg board non-dominant hand	0.621 (0.549–0.687)	**0.008**	≥125	0.80	0.43
Categorical verbal fluency	Verbal fluency – market items	0.724 (0.657–0.789)	**<0.001**	≤12	0.55	0.81

Note: s-HAND = symptomatic HIV-associated neurocognitive disorder, AUC = area under the curve, AVLT = auditory verbal learning test.
Significant results after applying the Benjamini–Hochberg correction are highlighted in bold ($p \leq 0.05$).

Table 4. Summary of the association between impairment on each neuropsychological test and s-HAND diagnosis using logistic mixed effects modeling.

		Neuropsychological test		
Area of impairment	Neuropsychological test	β	OR (95% CI)	*p*-value
Working memory	Digit span – forward	0.277	1.3 (0.6–3.1)	0.52
	Digit span – backward	1.470	4.3 (1.6–12.2)	**0.005**
	Digit span – total	0.929	2.5 (1–6.3)	0.044
Visual memory	Matchstick construction 1	2.054	7.8 (3–20.4)	**<0.001**
Visuoconstruction	Matchstick construction 2	1.467	4.3 (2–9.2)	**<0.001**
Verbal learning	AVLT trial IV	1.622	5.1 (2.3–11.2)	**<0.001**
	AVLT trial V	1.982	7.3 (3.3–16)	**<0.001**
	AVLT sum 1–V	1.556	4.7 (2.2–10.2)	**<0.001**
	AVLT V minus I	0.919	2.5 (1.1–5.7)	0.027
Learning interference	AVLT trial VI	0.642	1.9 (0.8–4.3)	0.122
	AVLT trial VII	1.580	4.9 (2.2–10.6)	**<0.001**
Delayed recall	AVLT trial VIII	1.751	5.8 (2.5–13.1)	**<0.001**
Recognition memory	AVLT trial IX – correct	0.960	2.6 (1.1–6.1)	0.026
	AVLT trial IX – false	0.706	2 (0.9–4.7)	0.102
	AVLT trial IX – difference	1.529	4.6 (1.9–11.3)	**<0.001**
Psychomotor speed	Color trails 1	1.696	5.4 (2.5–12.1)	**<0.001**
Executive function	Color trails 2	1.122	3.1 (1.4–6.8)	**0.006**
Language comprehension	Commands	1.127	3.1 (1.3–7.4)	**0.011**
Orientation	Orientation	1.292	3.6 (1.7–7.9)	**0.001**
Fine motor/2D spatial awareness	Peg board dominant hand	1.090	3 (1.3–6.7)	**0.009**
	Peg board non-dominant hand	0.853	2.3 (1–5.6)	0.056
Categorical verbal fluency	Verbal fluency – market items	1.622	5.1 (2.2–11.4)	**<0.001**

Note: s-HAND = symptomatic HIV-associated neurocognitive disorder, OR = odds radio, CI = confidence interval, AVLT = auditory verbal learning test.
Significant results after Benjamini–Hochberg procedure are highlighted in bold $p \leq 0.013$.
Covariates included in each model: the dichotomized neuropsychological test specified, neuropsychological test × time, current age, and Geriatric Depression Scale. Participant ID and time as random effects throughout to account for repeated measures at baseline, year 1 and year 2.
Interactions with time (test * time) were included for each model; however, none were significant.

category fluency. Less expected was the finding that matchstick construction 1 was the single test most strongly associated with s-HAND in all participants (OR = 7.8, 95% CI = 3.0–20.4, $p < 0.001$). This was thought to assess visual memory primarily, alongside visuoconstruction. This is not generally thought of as a priority cognitive domain to assess in HAND (Antinori et al., 2007). While these tests were intended to reflect specific cognitive domains, they may simply reflect abilities which are more relevant to people's day-to-day lives, more closely resembling tasks that participants have to perform day to day to maintain their function. This may explain the stronger association between these tests and s-HAND, which necessarily involves a degree of functional impairment, rather than specifically representing impaired executive function/language or visuoconstruction/visual memory. A further consideration is the limitations of trying to directly relate these neuropsychological tests with specific cognitive domains,

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Table 5. Summary of the association between impairment on neuropsychological test combinations and s-HAND diagnosis using logistic mixed effects modeling.

Education group	Area of impairment	Test	β	OR (95% CI)	p-value
All	Visual memory	Matchstick construction 1	1.207	3.3 (1.7–6.6)	**<0.001**
	Verbal learning	AVLT trial IV	0.762	2.1 (1.2–3.9)	0.014
	Delayed recall	AVLT trial VIII	1.038	2.8 (1.4–5.5)	**0.003**
	Recognition memory	AVLT trial IX – difference	0.937	2.6 (1.3–5.1)	**0.007**
	Psychomotor speed	Color trails 1	1.006	2.7 (1.4–5.4)	**0.004**
	Language comprehension	Commands	1.033	2.8 (1.4–5.7)	**0.004**
	Categorical verbal fluency	Verbal fluency – market items	1.171	3.2 (1.7–6)	**<0.001**
	Fine motor/2D spatial awareness	Peg board dominant hand	−0.090	0.9 (0.4–2.2)	0.837
		Peg board dominant hand × time	1.042	2.8 (1.3–6.3)	**0.011**
Low ≤4 years	Learning interference	AVLT trial VII	1.751	5.8 (2.2–15.1)	**<0.001**
	Fine motor/2D spatial awareness	Peg board dominant hand	1.483	4.4 (1.7–11.1)	**0.002**
	Categorical verbal fluency	Verbal fluency – market items	1.158	3.2 (1.2–8.4)	0.02
	Visuoconstruction	Matchstick construction 2	1.713	5.5 (1.8–16.7)	**0.002**
High >4 years	Visual memory	Matchstick construction 1	1.331	3.8 (1.5–9.5)	**0.005**
	Verbal learning	AVLT trial V	1.072	2.9 (1.4–6.2)	**0.005**
	Delayed recall	AVLT trial VIII	1.319	3.7 (1.6–8.5)	**0.002**
	Recognition memory	AVLT trial IX – difference	1.744	5.7 (2.4–13.5)	**<0.001**
	Psychomotor speed	Color trails 1	2.000	7.4 (3–17.9)	**<0.001**
	Language comprehension	Commands	2.048	7.8 (2.8–21.3)	**<0.001**

Note: s-HAND = symptomatic HIV-associated neurocognitive disorder, AVLT = auditory verbal learning test, GDS = Geriatric Depression Scale, TB = tuberculosis.
All participants, $n = 498$; ≤4 years of education only (low), $n = 168$; >4 years of education only (high), $n = 327$.
Significant results after Benjamini–Hochberg procedure are highlighted in bold (all participants, $p \leq 0.013$; low education, $p \leq 0.002$; high education, $p \leq 0.024$). Covariates included in each model: the neuropsychological test specified, neuropsychological test × time, and the basic model. Basic model for each educational group: all participants, age + GDS; low education, age only; and high education, GDS + history of TB. Participant ID and time as random effects throughout to account for repeated measures at baseline, year 1, and year 2.

when in reality they do not each map directly onto isolated cognitive processes (Howieson, 2019). The neuropsychological testing protocol used here does not allow us to make any conclusions as to whether executive function or visual memory, for example, was particularly impaired or whether, instead, the strong association in these data simply reflects a global impairment seen most prominently in the most culturally relevant tests.

These results support the importance of education in the diagnosis of s-HAND. Previous work on this and other cohorts has suggested that education is an important risk factor for developing HAND (Cross et al., 2013; Eaton et al., 2020). These results add to this and suggest that the experience of HAND, or at least the clinical presentation, may be influenced by education too. In the group with ≤4 years of education, the strongest associations were seen with verbal learning, learning interference, delayed recall, and categorical verbal fluency. In the group with >4 years education, visual memory, psychomotor speed, visuoconstruction, language comprehension, and delayed recall were most strongly associated. As a possible explanation, the experience of even a few years of school education and the problem-solving abilities developed may be affecting neuropsychological test performance (Stern, 2009). Alternatively, those with less education, and therefore lower cognitive reserve, may simply be vulnerable to small insults to their brain in a different way, leading to the cognitive and functional impairments seen. While the neuropsychological tests chosen for this battery were designed for low-literacy settings, the heterogeneity within the population poses challenges, with 30 participants having never been to school and some with a university education. Taking account of such difference is likely to be an important factor in any successful HAND screening program, which may require separate screening tests for those with little or no formal education.

Strengths and limitations

These data are derived from a routine clinic population with relatively good HIV control, and thus, they reflect well the types of patients likely to characterize the East African HIV pandemic of the future (Deeks et al., 2013; Estill et al., 2018; Ortblad et al., 2019; Sacktor, 2018; UNAIDS, 2014). The neuropsychological tests were designed to minimize floor and ceiling effects and to be culturally appropriate.

Viral load only became available locally in 2017, limiting analysis of this variable due to missing data. This may have been an important correlate to take account of given the association that has been described between viral suppression and motor speed (Sacktor et al., 2003). Similarly, the data on visual and hearing impairment were insufficiently complete to control for sensory impairments. Many participants did not attend follow-up visits as seen in Table 2, leading to possible spectrum bias.

The consensus diagnostic process, while rigorous, lacked neuroimaging data which might have identified relevant changes such as hippocampal atrophy, previous stroke, and substantial small vessel disease. This limited the ability of this protocol to more confidently exclude other sources of cognitive impairment such as Alzheimer's and vascular dementia. On the other hand, neuroimaging is not routinely available at this outpatient clinic primarily due to affordability. When unavailable, presumed central nervous system (CNS) infections are treated empirically. A diagnostic process more faithful to routine practice might be more generalizable to other clinics in LMICs. While the study protocol was able to exclude a wide range of potential comorbidities, there was no screening for hepatitis B or post-traumatic stress disorder (PTSD), which may have been present in a subset. The consensus panel also lacked a collateral history in 79% of encounters included in this analysis. This may have underestimated the proportion of those with s-HAND, in whom a history of functional impairment might only have been clear from speaking to an informant.

The mixed effects modeling analysis did not identify interactions with time, which may be partly due to the relatively short follow-up period of 3 years. Additionally, a fifth of participants had s-HAND at baseline and at each time point, and this proportion did not significantly change over time,

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therefore limiting the ability of the model to detect changes in those who subsequently developed s-HAND. A future study could include an analysis of those without HAND at baseline to better determine tests predictive of this. A longer period of follow-up might have been more able to detect any changes over time.

Conclusions

Functional impairment secondary to HAND experienced by older PLWH in this cohort was associated with a broad range of cortical and subcortical cognitive impairments. These pilot findings suggest that screening measures for HAND in similar populations should include measures of verbal learning and motor function, as the IHDS does presently, but that also assessing executive function, visual memory, and language comprehension may offer increased accuracy. Cultural adaptation or use of tests designed specifically for a population may offer further benefits. For older adults in SSA, a combination of a matchsticks construction task, verbal fluency with locally relevant items, a measure of language comprehension, and verbal learning with delayed recall may be an effective combination. Assessing the impact or practicalities of this in a potential screening tool was beyond the scope of this study.

The specifics of the clinical setting are likely to determine the balance between sensitivity and specificity that is considered optimal in a screening tool; however, education, culture, and age are likely to influence accuracy and should be considered in design, testing, and implementation. Future research should aim to establish which tests are most associated with HAND-attributable functional impairment over time, in order to identify and target interventions for individuals at greatest risk of future cognitive and functional decline.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617724000201.

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