Received: 27 January 2020 | Accepted: 24 May 2020
DOI: 10.1002/gps.5357

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Risk factors for symptomatic HIV-associated neurocognitive disorder in adults aged 50 and over attending a HIV clinic in Tanzania

Patrick Eaton[1] | Thomas Lewis[2] | Johanna Kellett-Wright[1] | Aidan Flatt[1] | Sarah Urasa[3] | William Howlett[3] | Marieke Dekker[3] | Aloyce Kisoli[3] | Jane Rogathe[3] | Jessica Thornton[4] | Judith McCartney[4] | Vanessa Yarwood[4] | Charlotte Irwin[4] | Elizabeta B. Mukaetova-Ladinska[5,6] | Rufus Akinyemi[7] | William K. Gray[8] | Richard W. Walker[8,9] | Catherine L. Dotchin[8,9] | Philip C. Makupa[10] | Andrew-Leon S. Quaker[10] | Stella-Maria Paddick[2,11]

[1]The Medical School, Newcastle University, Newcastle upon Tyne, UK

[2]Old Age Psychiatry, Northumberland Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK

[3]Clinical Medicine, Kilimanjaro Christian Medical University College, Moshi, Tanzania

[4]The London School of Hygiene and Tropical Medicine, London, UK

[5]Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK

[6]The Evington Centre, Leicestershire NHS Partnership Trust, Leicester, UK

[7]Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria

[8]Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, UK

[9]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

[10]HIV Care and Treatment Centre (CTC), Mawenzi Regional Referral Hospital, Moshi, Tanzania

[11]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

Correspondence
Stella-Maria Paddick, Campus for Ageing and Vitality, Newcastle University, Newcastle Upon Tyne, NE4 5PL, UK.
Email: Stella-maria.paddick@ncl.ac.uk

Abstract

Objectives: HIV-associated neurocognitive disorder (HAND), although prevalent, remains a poorly researched cause of morbidity particularly in sub-Saharan Africa (SSA). We aimed to explore the risk factors for HAND in people aged 50 and over under regular follow-up at a government HIV clinic in Tanzania.

Methods: HIV-positive adults aged 50 years and over were approached for recruitment at a routine HIV clinic appointment over a 4-month period. A diagnostic assessment for HAND was implemented, including a full medical/neurological assessment and a collateral history from a relative. We investigated potential risk factors using a structured questionnaire and by examination of clinic records.

Results: Of the cohort (n = 253), 183 (72.3%) were female and the median age was 57 years. Fifty-five individuals (21.7%) met the criteria for symptomatic HAND. Participants were at a greater risk of having symptomatic HAND if they lived alone [odds ratio (OR) = 2.566, P = .015], were illiterate (OR 3.171, P = .003) or older at the time of HIV diagnosis (OR = 1.057, P = .015). Age was correlated with symptomatic HAND in univariate, but not multivariate analysis.

Conclusions: In this setting, HIV-specific factors, such as nadir CD4 count, were not related to symptomatic HAND. The "legacy theory" of early central nervous system damage prior to initiation of anti-retroviral therapy initiation may contribute, only in part, to a multifactorial aetiology of HAND in older people. Social isolation and illiteracy were associated with symptomatic HAND, suggesting greater cognitive reserve might be protective.

Funding information
Grand Challenges Canada, Grant/Award Number: 0086-04; Newcastle University Masters by Research Programme; Northumbria Healthcare NHS Foundation Trust

KEYWORDS
cognitive impairment, HIV, older adults, risk factors, sub-Saharan Africa

1 | INTRODUCTION

Combination antiretroviral therapy (cART) has greatly improved the life expectancy for HIV-positive individuals worldwide.[1] Sub-Saharan Africa (SSA) is home to 70% of the world's 36.9 million cases of HIV, where 15 million people living with HIV (PLWH) now have access to cART.[2] Consequently, as in high-income countries (HICs), the SSA population of PLWH is ageing: an estimated 3 million PLWH in SSA are now aged 50 or older, with this number expected to grow to 9 million by 2040.[3]

HIV-associated neurocognitive disorder (HAND) is a neurocognitive impairment occurring in HIV independent of central nervous system opportunistic infection.[4] International diagnostic criteria for HAND recognise a spectrum of three progressively severe conditions[5]: HIV-associated dementia (HAD), mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI) (see Table 1). cART is thought to lower the incidence of the severest forms (HAD/MND) but does not decrease the prevalence of ANI.[7] In SSA, one meta-analysis estimates 8.1 million HIV-positive individuals have neurocognitive impairment.[8] Neurocognitive impairment can severely limit an individual's social, economic and emotional wellbeing and can lead to medication non-adherence.[9]

Key points

HAND in older people; Cognitive impairment in sub-Saharan Africa, Complications of HIV.

1.1 | Risk factors for HAND

Current data suggest HAND prevalence increases with age and will be an increasingly pertinent issue as the HIV-positive population ages in SSA, as in the rest of the world.[10,11] In the pre-cART era, HAD was clearly associated with markers of HIV infection severity including low CD4+ T cell count and high plasma and cerebrospinal fluid HIV viral load measurements.[12] In the cART era, this relationship is less clear. Lower nadir CD4 count predicted HAND in several large HIC studies,[13,14] resulting in the "HAND legacy theory" that neurocognitive impairment results from irreparable neurotoxic effects of the HIV virus prior to treatment initiation.[13] Counter-intuitively cART may also increase HAND risk.[15,16] Regimens vary in central nervous system (CNS) penetration effectiveness score (CPE) and low CPE score may increase HAND risk, although evidence is conflicting.[15,17] Some older medications are now seldom used in HIC due to concerns about toxicity.[18] Others, such as Efavirenz, are recognized to cause neuropsychiatric side effects and may affect cognition.[19] Comorbidities currently studied as potential risk factors for HAND include cardiovascular disease (diabetes, body habitus and lipid profile may correlate with HAND),[20] Hepatitis C co-infection[21] and psychiatric comorbidities (including substance abuse and depression).[12,22-24] Table 2 summarises a selection of previous studies of HAND risk factors.

Adults aged 50 and over account for the fastest growing proportion of PLWH.[3] Existing reports of HAND risk factors in SSA are limited to younger populations, sample sizes are often small and methodological inconsistencies limit generalisability. Many rely upon brief screening tools for diagnosis, despite these tools having limited sensitivity and specificity in the cART era where milder forms of HAND predominate.[27] In addition, many reports study risk factors in untreated individuals, and are not generalisable to older populations where PLWH are stable on

TABLE 1 Frascati criteria for classifying HAND[5]

HAND category	Neuropsychological criteria	Functional impairment
ANI	Impairment in at least two cognitive domains[a] (> 1 SD[b])	No impairment
MND	Impairment in at least two cognitive domains (> 1 SD)	Mild impairment of function (Self-report or observation from other of an increase in assistance with at least two IADLs.[c] The individual can maintain employment but may have experienced reduced productivity)
HAD	Severe Impairment in at least two cognitive domains (> 2 SD)	Severe impairment of functioning (an inability to maintain employment and substantial assistance with two or more IADLs)

[a]The test battery must examine at least five domains of cognition, which would ideally include: language, memory, sensory perception, motor skills, executive function, attention and speed of information processing.
[b]Refers to below the mean of demographically adjusted normative scores. It is important to adjust norms for age, sex, education and ethnicity in order to avoid under- or over-diagnosing HAND.
[c]Assessment of functional capacity usually involves an evaluation of instrumental activities of daily living (IADL), which are the tasks that allow an individual to live independently.[6] They are culturally sensitive but can include tasks, such as cooking, cleaning and medication management.

TABLE 2 Sample characteristics and major findings of the current study compared with a selection of studies in different settings

	Current study	CHARTER cohort[13]	Gascón et al[22]	Korean NeuroAIDS Project[16]	Kinai et al[11]	Joska et al[25]	Yakasai et al[26]
Setting	Tanzania	United States	Sao Paulo, Brazil	Korea	Japan	South Africa	Nigeria
Sample size	253	1555	412	194	728	170	80
Mean age (SD)	57.9 (6.198)	43.2	45.30 (10.70)	45.12	45.6 (10.6)	29.5 (3.65)	36.76 (8.97)
Female gender (%)	72.3	23	31.8	6.2	5.2	74	45
Years in education (mean)	(77% <8 years education)	12.3	12.07	13.4	(53.3% <13 years education)	10.06	12
Current CD4 (median [IQR or SD])	500 (316 to 672)	420 (262 to 603)	625.78 (291.09)	481 (236.0)	549.7 (251.7)	169 (115 to 199)	314
Nadir CD4 (median [IQR or SD])	165 (94 to 254)	174 (49 to 300)	-	186.4 (136.0)	163.4 (139.0)	-	-
On cART (%)	94.8	71	-	80	97.0	0	50
Detectable viral load (%)	-	59	16.3	18	15.5	-	63.75
AIDS diagnosis (%)	11.5[a]	63	-	-	-	-	40
WHO stage 1:2:3:4 (%)	73:6:17:4[a]	-	-	-	-	-	-
CDC stage A:B:C (%)	73:24:3[a]	37:26:37	-	27% in stages B and C	-	-	-
HAND prevalence (%)	47	46.9	73.5	26.3	25.3	76	76.25
Symptomatic HAND (%)	21.7	14.1	22.5	12.3	11.8	67	35
Risk Factors	Illiteracy Living alone Age at diagnosis	Lower Nadir CD4 count	Becks Depression Score 13 to 19	Hb ≤13 g/dL PI-based[b] regimen	Age ≥ 50; IVS;[c] Unemployed; not on cART	Fewer years of education; male gender	Fewer years of education

[a]AIDS diagnosis, CDC and WHO stage for the current study based on assessment at the time of data collection.
[b]Incomplete virologic suppression.
[c]Protease inhibitor.

cART. Similarly, HIC studies of older PLWH are unlikely to be generalisable to SSA where transmission routes and demographic composition of the HIV positive population differs to that in HICs.

1.2 | Aims

This study explores risk factors for symptomatic HAND (HAD or MND) in HIV-positive individuals aged 50 years and over under regular follow-up at a government HIV clinic in Tanzania.

2 | METHODS

2.1 | Setting

This study took place at Mawenzi Regional Referral Hospital (MRRH) HIV clinic in the town of Moshi, within the Kilimanjaro region of Northern Tanzania. The Kilimanjaro region is relatively prosperous by Tanzanian standards, due in part to the fertility of the soil allowing cash crops to be grown in some areas. Nevertheless, Tanzania remains one of the world's poorest countries, and most of the population is engaged in farming at a subsistence level. The project was a partnership between the UK-based research team, local clinic staff and hospital management. This Government clinic offers free-of-charge HIV treatment and has been a pioneer site for cART, now available locally for over 15 years. Detailed HIV-specific records and outcome data are kept from first diagnosis and updated at each clinic visit. Treatment is based on Tanzanian national guidelines[28] with three-monthly or bimonthly clinic review. First-line cART regimens are generally based on two nucleotide reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). Second-line therapy is also available. Neuroimaging was generally unavailable at the time of the study and CNS infections were treated empirically as per local protocols. CD4 lymphocyte counts were performed at the time of diagnosis and annually. HIV viral load measurement became available in 2017 but was unavailable at the time of this study.

2.2 | Ethics and consent

The Kilimanjaro Christian Medical University College Research Ethics and Review Committee and the Tanzanian National Institute for Medical Research approved the study. Participants were given written and verbal information in English and Swahili about the study and its aims before informed consent was requested. Illiterate participants indicated consent by thumbprint. Where patients lacked the capacity to consent, a close relative was asked to assent on the patient's behalf.

2.3 | Patients and data collection

Baseline data collection took place from March to June 2016. Individuals aged 50 and over were systematically sampled in order of attendance for routine follow-up. Individuals attending for unscheduled, emergency appointments due to physical illness were excluded. Assessments took place in Swahili or English, dependent on preference, using translators where required.

2.4 | Demographic and functional performance data

Baseline demographic data were collected by self-report and included age, sex, occupation, literacy, years of education and household composition. The Karnofsky index, frequently used in HIV studies,[6] was used to measure functional performance status.

2.5 | HIV-specific data

HIV-related data were collected from clinic records and data sheets. Available data included date of diagnosis, most recent and nadir CD4 count, HIV stage by CDC criteria (determined through case note review), history of tuberculosis (TB), empirical treatment for CNS infection, current and previous cART regimen (first- vs second-line therapy), and self-reported medication concordance. The CPE score for each regimen was calculated using previously documented criteria.[29] In addition, medications widely associated with neuropsychiatric effects and possible cognitive effects (Efavirenz) and older medications known to be toxic (stavudine and didanosine) were examined individually.

2.6 | Assessment of comorbidities

The 15-item Geriatric depression scale (GDS) was used for identification of depression at a cut-off of 5/15. The GDS has previously been used in epidemiological research in SSA.[30] Current and previous use of alcohol and cigarettes was determined by self-report and classified as current, previous or never. Previous stroke, diabetes and hypertension diagnoses and previous antihypertensive medication prescription were also assessed by self-report. Body Mass Index (BMI) was measured at clinic attendance, as was resting blood pressure.

2.7 | Assessment for HIV-associated neurocognitive disorders (HAND)

All individuals underwent a comprehensive neurocognitive assessment battery (see Data S1 for details of the specific tests) adapted for low-literacy settings to allow HAND diagnosis and classification based on the Frascati criteria (see Table 1.). Normative values were derived from 85 HIV-negative controls recruited from attendees of MRRH eye clinic and relatives of patients on the medical wards. Norms were stratified by age group and educational background. Neuropsychological testing (in Swahili) was performed by trained researchers (AK, JR)

and observed by a UK-based team member (AF, J K-L, PE). The Mini International Neuropsychiatric Interview (MINI) was used for identification of psychiatric disorders[31] alongside clinical neurological examination, mental state examination and bedside cognitive assessment by a research doctor (CI, JT, VY, JM). A structured collateral history to confirm cognitive and functional impairment was obtained (where necessary by telephone) and included a locally validated instrumental activities of daily living (IADL) scale.[32] Physiological observations were obtained, and a focused systemic examination was conducted where necessary. Visual acuity was measured using a broken-ring logMAR chart designed for illiterate populations to aid interpretation of cognitive test scores. Delirium was excluded using the Confusion Assessment Method (CAM), previously validated in Tanzania.[33] HAND diagnosis was by consensus panel discussion with clinicians and specialists in old age psychiatry and neurology (EBM-L, RA, SMP and TL) considering all available information. Additional psychiatric diagnoses were made by DSM-IV criteria. The Frascati criteria, if strictly applied, indicate that HAND cannot be diagnosed in individuals with depression or other psychiatric disorders. In this setting, where individuals could only be assessed once, we felt it would lack generalizability to exclude any individual with depression, particularly, because depression may form part of the HAND continuum. Therefore, it was attempted to assign a HAND diagnosis wherever possible, excluding only those where depression was severe and likely to account for the cognitive impairment observed. The study focuses on risk factors for symptomatic HAND because prevalence of HAD alone was expected to be low and it has been suggested that ANI category exaggerates the true clinical burden of HAND.[34] Furthermore, this allows for more direct comparison with other contemporary studies.[11,22]

2.8 | Statistical methods

Data analysis was supported by IBM SPSS (version 23; IBM, Armonk, NY, USA). Standard descriptive statistics (eg, mean, median, SD (SD), interquartile range (IQR) and frequency) and inferential tests (eg, chi-squared, Mann-Whitney U and *t*-test) were used as summary measures, depending on the level and distribution of the data. Fisher's correction was applied to the chi-squared test where numbers were small for categorical data. Factors associated with symptomatic HAND were initially investigated using bivariate inferential methods and any variables with a significance value <10% were included in a multivariable regression model to identify factors independently associated with cognitive status. The final model was checked for validity and robustness by investigation of residual values, tolerance, eigenvalues, influential cases and outliers. Statistical significance was set at 5% (except when considering which variables to take forward to multivariable analysis) and two-tailed tests were used throughout.

3 | RESULTS

Of 820 PLWH, aged 50 years and over, registered with the clinic, 530 attended during the study period of whom 310 were approached for

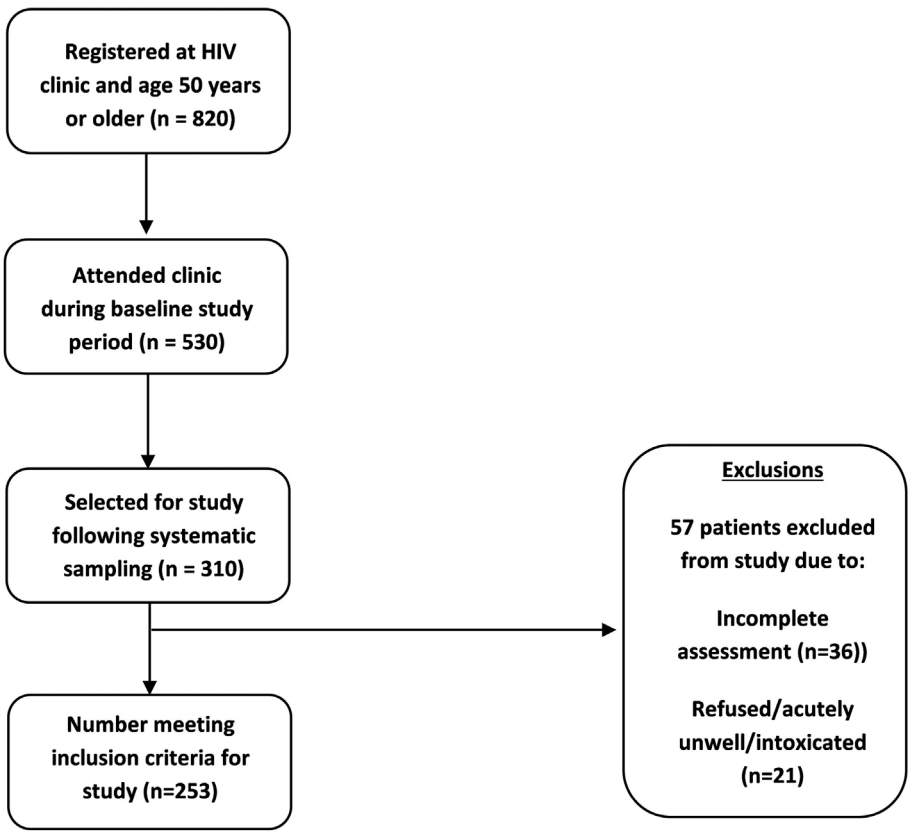

FIGURE 1 Study flow chart

TABLE 3 Demographic, comorbid and HIV-related factors associated with the presence and absence of symptomatic HAND

	Risk Factor	Symptomatic HAND (n = 55)	No symptomatic HAND (n = 198)	Significance
Demographic Variables	Median age (IQR)	58 (54 to 65)	56 (53 to 61)	U = 4734.0, *P* = .134
	Aged 65 years and over	**16 (29.1%)**	**28 (14.1%)**	**X^2 (1) = 6.696, *P* = .010**
	Number of Females	37 (67.3%)	146 (73.7%)	X^2 (1) = 0.899, *P* = .343
	Number unable to read or write	**15 (27.8%), 1 missing value**	**25 (12.8%), 2 missing values**	**X^2 (1) = 7.109, *P* = .008**
	Highest education level	None: 8 (14.5%)	None: 21 (10.8%)	X^2 (3) = 1.578, *P* = .664
		1-4 years of primary school: 12 (21.8%)	1-4 years of primary school: 46 (23.7%)	
		5-7 years of primary school: 20 (36.4%)	5-7 years of primary school: 88 (44.3%)	
		Secondary school or higher: 14 (25.5%)	Secondary school or higher: 41 (21.1%)	
		1 missing value	4 missing value	
	Lives alone	**15 (28.3%), 2 missing values**	**27 (13.8%), 2 missing value**	**X^2 (1) = 6.278, *P* = .012**
	Still working	43 (84.3%), 4 missing values	175 (89.7%), 3 missing values	X^2 (1) = 1.182, *P* = .277
Comorbidities	Mean BMI	22.2 (4.072), 3 missing values	22.7 (4.725), 7 missing values	t (241) = 0.828, *P* = .408
	Smoking status	Current: 2 (3.6%)	Current: 11 (5.6%)	X^2 (2) = 0.608, *P* = .738
		Previous: 13 (23.6%)	Previous: 40 (20.2%)	
		Never: 39 (70.9%), 1 missing value	Never: 147 (74.2%)	
	Alcohol consumption	Current: 18 (32.7%)	Current: 49 (24.7%)	X^2 (2) = 1.905, *P* = .386
		Previous: 29 (52.7%)	Previous: 108 (54.5%)	
		Never: 8 (14.5%)	Never: 41 (20.7%)	
	Mean systolic BP[a] (SD)	133.0 (21.804), 1 missing value	132.7 (27.967), 1 missing value	t (249) = 0.079, *P* = .937
	Mean diastolic BP (SD)	84.0 (12.485), 1 missing value	86.5 (13.484), 1 missing value	t (249) = 1.252, *P* = .212
	Median GDS[b] score (IQR)	3 (1 to 4)	2 (0 to 4)	U = 4605.0, *P* = .080
	GDS >5/15 (evidence of depression)	11 (20.0%)	33 (16.7%)	X^2 (1) = 0.333, *P* = .564
	Previous stroke	1 (1.9%), 1 missing value	11 (5.6%), 1 missing value	X^2 (1) = 1.297, *P* = .255
	Previous or current TB	8 (15.1%), 2 missing values	38 (19.7%), 5 missing values	X^2 (1) = 0.577, *P* = .447
	Previous or current CNS infection	6 (11.3%), 2 missing values	17 (8.8%), 5 missing values	X^2 (1) = 0.310, *P* = .596
HIV specific factors	Mean years since diagnosis	6.5 (3.319), 1 missing value	7.3 (3.312), 4 missing values	t (246) = 1.608, *P* = .109
	Median age at diagnosis (IQR)	**52.9 (48.5 to 57.2), 1 missing value**	**49.4 (45.7 to 54.5), 4 missing values**	**U = 4021.5, *P* = .009**
	Mean nadir CD4 count	212.8 (170.959), 4 missing values	191.7 (157.487), 9 missing values	t (238) = 0.831, *P* = .407
	Mean most recent CD4 count	474.2 (268.664), 3 missing values	528.1 (250.817), 10 missing values	t (238) = 0.828, *P* = .408
	Mean years since starting cART	5.2 (3.067)	5.6 (3.022)	t (242) = 0.743, *P* = .458
	Median CPE score (IQR)	9 (6 to 10), 2 missing values	9 (6 to 10), 15 missing values	U = 4833.5, *P* = .970

TABLE 3 (Continued)

Risk Factor	Symptomatic HAND (n = 55)	No symptomatic HAND (n = 198)	Significance
On second line treatment	7 (13.2%), 2 missing values	18 (9.8%), 15 missing values	X^2 (1) = 0.493, P = .482
Current efavirenz treatment	28 (50.9%)	106 (53.5%)	X^2 (1) = 0.119, P = .730
Current stavudine treatment	0	1 (0.5%)	X^2 (1) = 0.279, P = 1.000
Current didanosine treatment	0	2 (1.0%)	X^2 (1) = 0.560, P = 1.000

Note: n = number of individuals unless average specified. Factors significantly associated with symptomatic HAND denoted in bold.

[a]Blood pressure.

[b]Geriatric depression scale.

inclusion (Figure 1). A final sample of 253 met the inclusion criteria, consented and had a complete dataset available for consensus panel diagnosis. All exclusions are detailed in the study flow diagram (Figure 1). Of the cohort, the majority 183 (72.3%) were female, median age was 57 (range 50-79, [IQR 53-61.5]) and 40 of 250 with data available (16.0%) were illiterate. Symptomatic HAND was present in 55 (21.7%). HAD was present in 9 (3.6%). The characteristics of the cohort categorized by the presence of symptomatic HAND or not are presented in Tables 2 and 3.

Factors associated with symptomatic HAND are shown in Table 3. A diagnosis of symptomatic HAND was significantly associated with being aged over 65 years, being unable to read and write, living alone and greater age at diagnosis. In multivariable analysis, symptomatic HAND was independently associated with age at diagnosis, illiteracy and living alone (Table 4).

4 | DISCUSSION

Our study is the first from SSA to specifically investigate symptomatic HAND risk factors. Our population is older than previous studies. Differences in the number of females and the education level, when comparing SSA and studies from other world regions is notable (see Table 2).

In our study, being aged ≥65 years was associated with symptomatic HAND on univariate analysis but not following adjustment for other variables. Studies from Botswana and Uganda have reported older age as an independent risk factor for HAND.[35,36] These cohorts were small and focused on substantially younger populations (mean ages were 37 for both). The association in the current study may be less marked because we used age-adjusted norms for neuropsychological test scores to account for normal age-related cognitive change. The age structure of our population is also likely to have played a role. Studies using age-adjusted norms have all reported older age as a risk factor for neurocognitive impairment in younger PLWH. Our study suggests this relationship may be less robust within an older cohort. A sub-analysis of those aged 50 and over in the Hawaii Ageing with HIV cohort reported similar findings to our study.[10] Nevertheless, previous data are limited and, although it is possible that increasing age is less significant within populations of older PLWH, our study and the Hawaiian study may also lack power to detect these differences. There were relatively few of the oldest old—individuals over 64 years of age—in the present study (n = 44).

Our study showed no association between symptomatic HAND and lower nadir CD4 count. In the era of cART, and notably in the CHARTER study, lower nadir CD4 count is commonly reported to be associated with cognitive dysfunction.[14,17,37] This finding has resulted in the hypothesis that most cognitive impairment in the cART era occurs through irreversible neuronal loss prior to cART initiation, termed a "legacy event."[13] Our study population appears to be well managed with regard to medication, with generally high recent CD4 counts as with the CHARTER cohort. Similar findings to our study were reported in other well-managed populations in Brazil,[22] Japan[11]

TABLE 4 Independent risk factors for symptomatic HAND

			95% confidence interval for odds ratio	
	Significance	Odds ratio	Lower	Upper
Age at diagnosis	0.015	1.057	1.011	1.105
Lives alone	0.015	2.566	1.202	5.479
Unable to read and write	0.003	3.171	1.469	6.845

and Korea[16] (see Table 2), although the two Asian studies reported significantly lower prevalence of HAND. One possible explanation for the difference in the present study is the age of our population. It is possible that within an older population, older age, or factors closely associated with age, dilute the influence of past immune injury on HAND pathogenesis.

Vascular risk factors in our study population, such as smoking status, BMI and blood pressure were not associated with symptomatic HAND. Previous research has identified an association between HAND and vascular pathology. Becker et al (2009) demonstrated carotid intima media thickness (cIMT) and glomerular filtration rate to be linked to poorer cognitive performance.[38] Fabbiani et al (2013) also found cIMT, along with diabetes, to affect cognition in a multicenter Italian study.[39] In addition, the CHARTER study highlighted central obesity and diabetes as risk factors for HAND.[20] Likewise, cerebrovascular disease is linked to HIV, with higher rates of stroke reported in HIV-positive individuals.[40] Stroke was not associated with symptomatic HAND in our population, although stroke was self-reported, and the numbers with stroke were small. A wider exploration of vascular disease and HAND should be considered with the use of neuroimaging and prospective identification of stroke cases.

In contrast to older age at the time of study, older age at HIV diagnosis was significantly associated with the condition. This risk factor has not been extensively explored previously. A recent publication from Japan found that older participants had greater vulnerability to developing HAND in the early stages of infection compared with younger individuals.[11] HIV is known to enter the CNS early in the course of infection via infected perivascular macrophages and microglial cells, leading to neuronal injury via toxic viral proteins and proinflammatory cytokines.[41] It is possible that younger brains have greater resilience to this acute stage of infection. A resilience to neuronal damage could be likened to the cognitive reserve hypothesis, with people with greater reserve being resilient to more damage before a disease presents clinically.[42] Cognitive reserve is thought to be increased by greater educational and occupational attainment. Previous research shows a mixed picture regarding the link between education and risk of HAND. In a pre-cART analysis of the MACS cohort, 38% of PLWH with 12 years or fewer of education were cognitively impaired compared with 17% of those with more than 12 years.[23] Similarly, a Nigerian study reported lower education to be independently associated with HAD, although cART coverage was less comprehensive than in our cohort, and cognitive performance assessments were not standardized to reflect normative data.[25] Conversely, the CHARTER study, where normative data were used to adjust cognitive performance in HAND diagnosis,[12] demonstrated no difference in years in education between impaired and unimpaired individuals. We used similarly demographically appropriate norms—our controls were stratified by educational background as well as age group—and contrastingly we found illiteracy to be an independent predictor. One explanation for this difference is that the less educated in the CHARTER study refers to those who did not progress beyond secondary school, whereas we looked at illiteracy, a far more debilitating educational marker, which is still common throughout SSA. The literacy rate in our study was relatively high at 82.5% compared with the average of 59% across SSA.[43] The largest study of HAND risk factors in low- and middle-income countries, found that education level was not a predictor of HAND in a Brazilian cohort; however, those with less than 4 years of education were excluded.[22] Education, to a point of being literate, seems to have a protective effect against progression to symptomatic HAND in our study. A previous study in the older general population by our team identified never having attended school as significantly associated with cognitive decline over 2 years, with school attendance for as little as 1 year being protective.[44] Greater social interaction is thought to be associated with increased "cognitive reserve"[45] in studies of neurodegenerative dementias.[46] We found that older PLWH living alone were at a greater risk of symptomatic HAND. This finding remained significant following adjustment for possible confounders, such as signs of depression as measured by the GDS. Loneliness and social isolation are recognized as social problems in HIV, which may, in part, be due to stigma.[47] Social isolation has not been found to moderate risk for HAND in previous studies and may be a novel risk factor for HAND specific to older PLWH. Indeed, current employment, a possible marker of social engagement, is reported to be protective against HAND.[11] We did not find such an association, possibly because it is customary to work into old age in Tanzania wherever possible.

Social isolation and illiteracy are both known risk factors for Alzheimer's disease (AD),[45] and in our older cohort, there may be similarities in the pathological profile of AD and symptomatic HAND. Furthermore, the changing clinical phenotype of HAND in the cART era, which describes a shift from subcortical to cortical impairments, is characteristic of AD.[48] There is evidence from postmortem studies and disease markers within cerebrospinal fluid (CSF) that also suggests similarities between HAND and AD. Significantly higher levels of β-amyloid and tau proteins have been found in the brains of PLWH with cognitive impairment.[49,50] However, amyloid deposition in HIV-positive brains appears to be diffuse and intraneuronal, as opposed to extracellular and plaque-forming as typically seen in AD.[50]

5 | LIMITATIONS

We relied on self-report to identify several risk factors and comorbidities including past or current smoking, drug and alcohol use. Although HIV-related clinic records were available, details of past medical history were often incomplete and a reliance on patients with potential cognitive problems to recall past medical history was problematic. To help improve the reliability of recall, we sought to reduce the effects of fatigue through frequent breaks and refreshments for participants. There may also have been an element of selection bias, in that, those attending for regular follow-up may have been less likely to have cognitive impairment than those who did not attend during the study period.

We chose to use the 2007 Frascati criteria for HAND to allow comparability with other international studies, and due to the lack of appropriate locally validated brief screening tools. The Frascati criteria have been criticised as exaggerating the true burden of disease, being culturally biased and too reliant on functional assessment. We excluded ANI from our analyses; however, acknowledge that the MND category may also overestimate the true prevalence of HAND[32]. We attempted to reduce cultural bias by using locally normed and, where possible, locally validated cognitive tests, specifically designed for low literacy settings. We also conducted careful clinical assessment to exclude other causes of cognitive impairment, but these were limited due to lack of neuroimaging locally. The criteria are heavily reliant on confirmation of functional impairment by an informant. Although we were able to obtain structured collateral histories for almost all participants, these may have been limited by local stigma surrounding both HIV and mental health problems. The control population was comparatively more educated than the study sample (84.7% with 5 years of more education compared with 64.4%) leading to small numbers in the less educated stratified control group and consequently less reliable normative values.

Due to resource limitations, it was not possible to obtain useful objective measures of vascular disease such as blood samples, ECGs, cIMT, retinal photography or neuroimaging. Viral load measurements were only commenced routinely during 2017.

6 | CONCLUSIONS

This is the first study of potential risk factors for symptomatic HAND in older PLWH in SSA. In this well-managed clinic population, other than age at diagnosis, we found no association with HIV-specific factors, including nadir CD4 count. The "legacy theory" of early neurotoxicity and CNS damage prior to initiation of cART may contribute only, in part, to a multifactorial aetiology of HAND in older PLWH. Illiteracy and social isolation were associated with symptomatic HAND, suggesting that higher "cognitive reserve" might be protective (as in neurodegenerative dementias). Further studies should examine this relationship and the potential role for cognitive stimulation or interventions to reduce social isolation and stigma in older PLWH. The role of vascular pathology in the development of symptomatic HAND in PLWH also merits further study, including the use of neuroimaging.

ACKNOWLEDGEMENTS

We would like to thank the patients and family members who took part in this study and all staff of the Mawenzi Care and Treatment Centre (CTC) without whom this study could not have taken place.

This study was funded by Grand Challenges Canada (grant number 0086-04), Northumbria Healthcare NHS Foundation Trust and Newcastle University Master's by Research programme.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Stella-Maria Paddick, William K. Gray, Richard W. Walker, Catherine L. Dotchin, Elizabeta B. Mukaetova-Ladinska and Sarah Urasa designed the study. SMP supervised data collection. Consensus panel diagnoses were completed by Elizabeta B. Mukaetova-Ladinska, Rufus Akinyemi, Thomas Lewis and Stella-Maria Paddick. Stella-Maria Paddick, William K. Gray, Patrick Eaton and Thomas Lewis performed data analysis and interpretation. All authors were involved in drafting and revising the manuscript and gave their approval of the version submitted for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Patrick Eaton https://orcid.org/0000-0002-4178-1312
Stella-Maria Paddick https://orcid.org/0000-0002-5409-0879

REFERENCES

1. Teeraananchai S, Kerr S, Amin J, Ruxrungtham K, Law M. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Med*. 2017;18(4):256-266.
2. UNAIDS. 2017 Global HIV statistics [internet]. Fact Sheet 2018 Retrieved on 18 November, 2018 from http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
3. Hontelez JAC, de Vlas SJ, Baltussen R, et al. The impact of antiretroviral treatment on the age composition of the HIV epidemic in sub-Saharan Africa. *AIDS*. 2012;26:S19-30.
4. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. *Lancet Infect Dis*. 2013;13(11):976-986.
5. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69(18):1789-1799.
6. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. *Cancer*. 1984;53(9):2002-2007.
7. Simioni S, Cavassini M, Annoni J-M, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010;24(9):1243-1250.

8. Habib AG, Yakasai AM, Owolabi LF, et al. Neurocognitive impairment in HIV-1-infected adults in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Infect Dis*. 2013;17(10):e820–31.
9. Gorman AA, Foley JM, Ettenhofer ML, Hinkin CH, van Gorp WG. Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychol Rev*. 2009;19(2):186-203.
10. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals the Hawaii aging with HIV-1 cohort. *Neurology*. 2004;63(5):822-827.
11. Kinai E, Komatsu K, Sakamoto M, et al. Association of age and time of disease with HIV-associated neurocognitive disorders: a Japanese nationwide multicenter study. *J Neurovirol*. 2017;23(6):864-874.
12. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011;17(1):3-16.
13. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS*. 2011;25(14):1747-1751.
14. McCombe J, Vivithanaporn P, Gill M, Power C. Predictors of symptomatic HIV-associated neurocognitive disorders in universal health care. *HIV Med*. 2013;14(2):99-107.
15. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS*. 2009;23(11):1359-1366.
16. Ku N, Lee Y, Ahn J, et al. HIV-associated neurocognitive disorder in HIV-infected Koreans: the Korean NeuroAIDS project. *HIV Med*. 2014;15(8):470-477.
17. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS*. 2011;25(3):357-365.
18. Schweinsburg BC, Taylor MJ, Alhassoon OM, et al. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. *J Neurovirol*. 2005;11(4):356-364.
19. Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology*. 2011;76(16):1403-1409.
20. McCutchan JA, Marquie-Beck JA, FitzSimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology*. 2012;78(7):485-492.
21. Vivithanaporn P, Nelles K, Deblock L, Newman SC, Gill MJ, Power C. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci*. 2012;312(1-2):45-51.
22. Gascón MRP, Vidal JE, Mazzaro YM, et al. Neuropsychological assessment of 412 HIV-infected individuals in Saõ Paulo. *Brazil AIDS Patient Care STDS*. 2018;32(1):1-8.
23. Satz P, Morgenstern H, Miller EN, et al. Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS cohort study (MACS). *J Acquir Immune Defic Syndr*. 1993;6(5):503-511.
24. Weber E, Morgan EE, Iudicello JE, et al. Substance use is a risk factor for neurocognitive deficits and neuropsychiatric distress in acute and early HIV infection. *J Neurovirol*. 2013;19(1):65-74.
25. Joska JA, Westgarth-Taylor J, Myer L, et al. Characterization of HIV-associated neurocognitive disorders among individuals starting antiretroviral therapy in South Africa. *AIDS Behav*. 2011;15(6):1197-1203.
26. Yakasai AM, Gudaji MI, Muhammad H, et al. Prevalence and correlates of HIV-associated neurocognitive disorders (HAND) in northwestern Nigeria. *Neurol Res Int*. 2015;2015:486960.
27. Milanini B, Paul R, Bahemana E, et al. Limitations of the international HIV dementia scale in the current era. *AIDS*. 2018;32(17):2477-2483.
28. National Guidelines for the Management of HIV and AIDS [Internet]. 2015. Retrieved from https://aidsfree.usaid.gov/sites/default/files/04_11_2016.tanzania_national_guideline_for_management_hiv_and_aids_may_2015._tagged.pdf
29. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. *Top HIV Med*. 2010;18(2):45-55.
30. Baiyewu O, Smith-Gamble V, Lane KA, et al. Prevalence estimates of depression in elderly community-dwelling African Americans in Indianapolis and Yoruba in Ibadan, Nigeria. *Int Psychogeriatrics*. 2007;19(4):679-689.
31. Hergueta T, Baker R, Dunbar GC. The MINI-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IVand ICD-10. *J Clin Psychiatry*. 1998;59(Suppl 20):2233.
32. Collingwood C, Paddick S-M, Kisoli A, et al. Development and community-based validation of the IDEA study instrumental activities of daily living (IDEA-IADL) questionnaire. *Glob Health Action*. 2014;7(1):25988.
33. Paddick S-M, Lewis EG, Duinmaijer AT, et al. Evaluation of the IDEA (identification and interventions for dementia in elderly AFRICANS) brief cognitive screening tool for identification of DELIRIUM in older hospitalised adults in Tanzania. *Alzheimers Dement*. 2016;12(7):P364–5.
34. Gisslén M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infect Dis*. 2011;11(1):356.
35. Wong MH, Robertson K, Nakasujja N, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology*. 2007;68(5):350-355.
36. Lawler K, Jeremiah K, Mosepele M, et al. Neurobehavioral effects in HIV-positive individuals receiving highly active antiretroviral therapy (HAART) in Gaborone. *Botswana PLoS One*. 2011;6(2):e17233.
37. Valcour V, Yee P, Williams AE, et al. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection—the Hawaii aging with HIV cohort. *J Neurovirol*. 2006;12(5):387-391.
38. Becker JT, Kingsley L, Mullen J, et al. Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men. *Neurology*. 2009;73(16):1292-1299.
39. Fabbiani M, Ciccarelli N, Tana M, et al. Cardiovascular risk factors and carotid intima-media thickness are associated with lower cognitive performance in HIV-infected patients. *HIV Med*. 2013 Mar;14(3):136-144.
40. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr*. 2012;60(4):351-358.
41. Manji H, Jäger HR, Winston A. HIV, dementia and antiretroviral drugs: 30 years of an epidemic. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1126-1137.
42. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8(3):448-460.
43. UNESCO Institute for Statistics. Adult and Youth Literacy. National, Regional and Global Trends, 1985-2015. 2015. p. 132
44. Heward J, Stone L, Paddick S-M, et al. A longitudinal study of cognitive decline in rural Tanzania: rates and potentially modifiable risk factors. *Int Psychogeriatrics*. 2018;30(9):1333-1343.
45. Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. Vol 10, 2014. The Netherlands: Elsevier; 2014:e47–92.
46. Tang Y, Arnold SE, Barnes LL, et al. Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry*. 2007;64(2):234.
47. Nachega JB, Morroni C, Zuniga JM, et al. HIV-related stigma, isolation, discrimination, and serostatus disclosure: a global survey of 2035 HIV-infected adults. *J Int Assoc Physicians AIDS Care*. 2012;11(3):172-178.
48. Sacktor N. Changing clinical phenotypes of HIV-associated neurocognitive disorders. *J Neurovirol*. 2018;24:141-145.

49. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS*. 2005;19(4):407-411.
50. Saylor D, Sacktor N. Cognitive impairment among older individuals with HIV infection. *Curr Geriatr Rep*. 2016;5(2):63-70.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Eaton P, Lewis T, Kellett-Wright J, et al. Risk factors for symptomatic HIV-associated neurocognitive disorder in adults aged 50 and over attending a HIV clinic in Tanzania. *Int J Geriatr Psychiatry*. 2020;1–11. https://doi.org/10.1002/gps.5357