HIV-Associated Neurocognitive Disorders: The First Longitudinal Follow-Up of a cART-Treated Cohort of Older People in Sub-Saharan Africa

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Background: HIV-associated neurocognitive disorders (HAND) are a highly prevalent chronic complication in older people living with HIV (PLWH) in high-income countries. Although sub-Saharan Africa has a newly emergent population of older combination antiretroviral therapy (cART)-treated PLWH, HAND have not been studied longitudinally. We assessed longitudinal prevalence of HAND and have identified possible modifiable factors in a population of PLWH aged 50 years or older, over 3 years of follow-up.

Methods: Detailed neuropsychological and clinical assessment was completed annually in the period 2016–2019 in a systematic sample of cART-treated PLWH in Kilimanjaro, Tanzania. A consensus panel defined HAND using American Academy of Neurology criteria for asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia. HIV disease severity and other factors associated with HAND progression, improvement, and stability were evaluated in individuals fully assessed at baseline and in 2019.

Results: At baseline, 47% of the cohort (n = 253, 72.3% female individuals) met HAND criteria despite good HIV disease control [Y1 59.5% (n = 185), Y2 61.7% (n = 162), and Y3 57.9% (n = 121)]. Of participants fully assessed at baseline and year 3 (n = 121), HAND remained stable in 54% (n = 57), improved in 15% (n = 16), and declined in 31% (n = 33). Older age and lower education level significantly predicted HAND progression, whereas HIV-specific factors did not. Male sex and shorter cART duration were associated with improvement.

Conclusions: In this first longitudinal study characterizing clinical course of HAND in older cART-treated PLWH in sub-Saharan Africa, HAND was highly prevalent with variable progression and reversibility. Progression may be more related to cognitive reserve than HIV disease in cART-treated PLWH.

Key Words: HIV, Tanzania, dementia, HAND, older adults, sub-Saharan Africa

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INTRODUCTION

HIV infection is a leading cause of morbidity across sub-Saharan Africa (SSA) where more than 25 million people are living with HIV.[1] Progress toward the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 goals of HIV testing, combination antiretroviral therapy (cART) coverage, and viral suppression in SSA has been rapid.[2] As a result, life expectancy seems to be increasing (22–29 years post-HIV diagnosis at age 35 years),[3] and this population of people living with HIV (PLWH) is aging, with the proportion aged 50 years or older predicted to triple by

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R.S. and S.R. contributed equally to this work. S.M.P., W.K.G., R.W.W., C.L.D., E.B.M.-L., M.D., W.H., R.K., and S.U. led on the study conception and design. S.M.P. supervised acquisition of data, led on the clinical protocol, and trained the team. S.K., M.Y., S.R., A.K., P.C.M., T.L., and B.L. developed different aspects of the clinical protocol and collected/supervised clinical data. S.M.P., W.K.G., and R.S. verified the underlying data and performed data analysis and interpretation. Consensus panel diagnoses were completed by S.-M.P., E.B.M.-L., R.A., and T.L. R.S. and S.R. completed the first draft, supervised by S.M.P. All authors were involved in drafting and revising the manuscript and gave their approval of the version submitted for publication.

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2040.[4] Overall HIV prevalence is also increasing because of reduced mortality.[5] In high-income countries (HICs), the chronic complications of aging with HIV are well recognized,[6] but SSA data on this newly emergent aging population of PLWH are lacking.

HIV-associated neurocognitive disorders (HAND) are a well-recognized, increasingly prevalent chronic complication of treated HIV in both HICs and low-income and middle-income countries.[7,8] They incorporate a spectrum of disorders currently categorized [American Academy of Neurology, (AAN) 2007] as HIV-associated dementia (HAD), mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI).[9] An estimated 16 million people are affected worldwide, most (72%, >11.5 million) of whom live in SSA.[10] Older PLWH appear disproportionately affected, although etiology remains poorly understood. Hypothesized causes include direct neurotoxic effect of the HIV virus, impact of long-term central nervous system (CNS) inflammation, neurotoxic properties of cART, opportunistic CNS infection, and effect of frequent comorbidities.[7,11,12] Prevalence estimates between 30.4% and 69.9% are reported in SSA settings of differing geography, demographics, and proportion receiving cART.[8] Current data remain challenging to synthesize due to both methodological and cohort differences.[8]

HAND seem to progress despite cART and a degree of reversibility is reported, unlike neurodegenerative dementias.[13,14] Existing longitudinal studies are few, largely limited to the United States,[13,14] and may lack applicability to SSA where demographics, HIV disease management, virus subtypes, and comorbidity factors are likely to differ for those in HICs. We recently reported what we believe to be the only currently available cross-sectional data on older cART-treated adults in SSA with an estimated HAND prevalence of 47% in 253 PLWH aged 50 years or older (95.5% on cART).[15,16] To the best of our knowledge, there are no longitudinal studies looking at the burden and pattern of change in HAND in an older, cART-treated population in SSA.

Our aim was to characterize the clinical course of HAND and estimate prevalence over 3 years of follow-up in older PLWH receiving standard government free-of-charge HIV care in Tanzania, where an estimated 1.7 million adults are living with HIV.[17] Recent guidelines[18] (published in 2017) stipulate that cART is prescribed from HIV diagnosis irrespective of CD4 count or other measures. We also evaluated potentially modifiable factors associated with cognitive decline in this setting given the likely current and future substantial morbidity burden of HAND in older PLWH in SSA.

METHODS

Setting

The study took place at Mawenzi Regional Referral Hospital HIV Care and Treatment Center (CTC), in Moshi, Northern Tanzania. The cART has been available locally for ≥15 years. Patients typically attend CTC review 2/3 monthly, and standardized HIV outcome data are recorded. A total of 3169 patients were registered with the CTC on the 1st of March 2016 [820 (25.9%) aged 50 years or older].

Study Design and Procedures

Baseline study design, recruitment, and data collection have previously been detailed[15,16] and are summarized in this study. A systematic sample (every third eligible individual in the order of arrival for routine review) was recruited between March and June 2016. Demographic data collected included the following: age, sex, educational and occupational background, current employment, and living arrangements. Standardized HIV-specific CTC record data included the following: date of diagnosis, nadir and most recent CD4 count, cART regimen (first/second line and use of efavirenz), WHO HIV stage, body mass index, history of tuberculosis or empirically treated CNS infection, and pneumocysitis carinii pneumonia prophylaxis. Time (in months) on cART, time untreated postdiagnosis, and CNS penetration effectiveness (CPE) ranking of cART regime[19] were calculated and self-reported cART adherence recorded. HIV viral load testing was unavailable and not routinely performed until 2017.

Comorbidities recorded by self-report included history of head injury, epilepsy, stroke, diabetes, and smoking. Self-reported alcohol consumption was categorized as current, previous, or no previous consumption. Hypertension was defined as existing antihypertensive medication prescription and/or blood pressure ≥140/90 mm Hg at assessment (the mean value of 3 automated readings after 5 minutes rest). Visual acuity was assessed using a Landolt C broken-ring low-literacy logMAR distance chart and impairment categorized by International Classification of Diseases-11 criteria.[20] Hearing was classified as normal, impaired, or severely impaired based on clinical interview observations. Hepatitis and syphilis serology, cerebrospinal fluid (CSF), and neuroimaging were not available and not routinely performed in the CTC.

Clinical Assessment for HAND

HAND classifications were made by consensus panel based on the AAN 2007 criteria, outlined in Table 1, Supplemental Digital Content 1, http://links.lww.com/QAI/B806, based on all available clinical information and exclusion of non-HAND cognitive impairments. Clinical assessment included a previously locally normed low-literacy neuropsychological test battery including cortical and subcortical domains described in our baseline study[15,21] and outlined in Tables 2 and 3, Supplemental Digital Content 2 and 3, http://links.lww.com/QAI/B807 and http://links.lww.com/QAI/B808. The testing protocol was supervised by experienced specialist nurses after 1 week of training and harmonization supervised by the senior investigators. Additional harmonization training was repeated annually. Cognitive impairment was defined as 1 or 2 SDs below the mean values in ≥2 cognitive domains when compared by age (those aged 60 years or younger vs those aged 50–59 years) and educational status (≤4 years vs >4 years) with an HIV-negative comparison group (n = 85) attending other clinics

within Mawenzi Regional Referral Hospital. This comparison sample provided the normative data used for classification in the 2016 baseline study.[15] Additional structured clinical and neurological assessment, standardized mental state examination, and informant history were conducted by a research doctor and mental health–experienced nurse. Detailed clinical case notes were created in addition to quantitative measures for consensus panel review (S.M.P., E.B.M.-L., R.A., and T.L.). HAND (ANI, MND, and HAD)[9] were classified based on neuropsychological test performance, presence or absence of functional impairment, and consideration of other likely causes and comorbidities identified during clinical assessment. Functional impairment was defined as impaired instrumental activities of daily living on a locally validated scale,[22] reduced performance status (Karnofsky Performance Scale), or clearly documented functional difficulties observed on clinical assessment and/or informant history. The same consensus panel (S.M.P., E.B.M.-L., and T.L.) completed annual follow-up diagnoses for consistency. The confusion assessment method was used to identify delirium,[23] and the Mini International Neuropsychiatric Interview and 15-item Geriatric Depression Scale were used to perform screening for psychiatric disorders. Where feasible, alternate psychiatric diagnoses by Diagnostic and Statistical Manual of Mental Disorders-5[24] better accounting for cognitive impairment were documented. Where a participant met criteria for both HAND and another disorder, primary and secondary diagnoses were specified.

Follow-Up Assessment

Annual follow-up with a similar protocol was offered over the same 3-month period (March–June), in 2017, 2018, and 2019 to all individuals recruited at baseline. Where possible, this was scheduled to coincide with existing clinic appointments. All previously recruited individuals were contacted by telephone before follow-up and given the option to return on a convenient alternative day if preferred. Transport costs were refunded if participants attended outside planned routine appointments. Those not traced by the study team for follow-up were cross-checked with clinic records to determine if they continued to attend the clinic, were lost to CTC follow-up, deceased, or transferred to another facility. The demographic and HIV-specific data of those assessed and not assessed in year 3 were compared to assess for significant differences in HIV disease severity or other factors likely to affect cognitive impairment.

HIV-specific, demographic, and risk factor data were checked annually and updated where necessary. From mid-2017, updated national guidelines facilitated HIV viral load testing, and these values were recorded annually where available. Viral suppression was defined as ≤20 copies/mL.

Progression (decline) at year 3 was defined as a progression to a subsequent category (a move to the right) on the ordinal scale normal-ANI-MND-HAD by AAN criteria. Reversibility (improvement) was therefore defined as a move to the left on the same ordinal scale.

Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 25). Key parameters were assessed for normality on visual inspection of histograms. Standard descriptive statistics [mean, median, SD, interquartile range (IQR), and frequency] were used to describe and compare individuals assessed at baseline and follow-up depending on the level and distribution of the data. The follow-up cohort assessed at baseline and year 3 were categorized into stable, improved, or decline in HAND category in 2019 compared with 2016. Standard descriptive statistics were used to describe participants in each of the 3 (stable, declined, and improved) groups: the mean and SD for interval/ratio data, the median and IQR for ordinal data, and frequency for categorical data. Inferential tests were used to identify differences in characteristics between the 3 groups: analysis of variance for interval/ratio data, the Kruskal–Wallis test for ordinal data, and the χ^2 test for categorical data. Risk factors were selected for analysis based on the findings of previous studies.[13,14] Variables with P value < 0.1 from bivariate analysis were taken forward to logistic regression to investigate factors associated with cognitive decline. For this analysis, the improved and stable groups were combined into a single group. Backward elimination determined those retained in the model. The significance level was 5% throughout.

Ethical Considerations

Ethical approval was granted by Kilimanjaro Christian Medical College Research Ethics and Review Committee (N.896) and the Tanzanian National Institute for Medical Research (NIMR/HQ/R.8a/Vol.IX/2136). Participants were given written and verbal study information as appropriate by trained nurses. Where participants lacked capacity to consent due to cognitive impairment, assent was sought from a close relative. Consent was reviewed annually, and additional informed consent was requested to obtain informant history to corroborate cognitive and functional decline. HIV status was not discussed with informants who were told this was an aging study. Participants diagnosed with psychiatric or neurological disorders requiring treatment and those with other novel abnormal clinical findings were referred to CTC clinicians, neurologists, or mental health clinicians according to locally agreed protocols.

RESULTS

At baseline, 253 participants had complete data and were eligible for follow-up. Of them, 185 were assessed in year 1, a total of 162 in year 2, and 121 in year 3 (Fig. 1).

A total of 121 participants were fully assessed at baseline and 2019 and were included in the baseline/year 3 follow-up analysis. Reasons for non follow-up are shown in Figure 1. Individuals followed up and not followed up did not differ in age, sex, or most recent CD4 or viral load measurement. Eight patients (6 male individuals, md baseline age 56 years) were recorded as deceased [3-year mortality rate 3.16% (95% confidence interval: 1.37 to 6.23)].

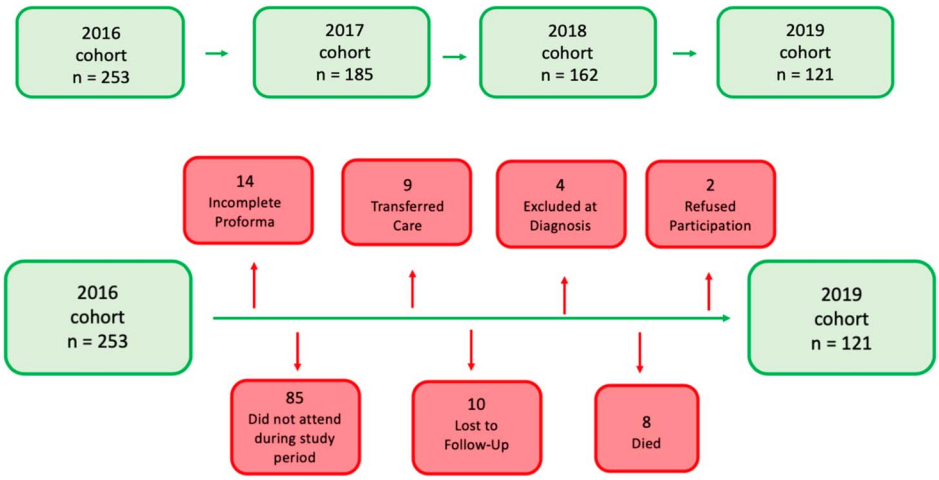


FIGURE 1. Longitudinal cohort and 2016–2019 comparison cohort. full color online

Characteristics of the baseline cohort are summarized and tabulated in Table 4, Supplemental Digital Content 4, http://links.lww.com/QAI/B809, and as previously published.[16] The median age was 57 (IQR 53–61.5) years, and most of them (72.3%) were female individuals. Few (6.7%) completed secondary education (n = 17), although most of them (64.0%) completed primary education (n = 164). Most of them (86.2%) were employed.

At baseline, HIV disease seemed well controlled [95.5% on cART, median CD4 499.5 (IQR 316.25–672)], although a high proportion (82.6%) were WHO stage 3 to 4. Self-reported cART adherence was good (77.8% never forgetting medication). Only 28 individuals (11.5%) were receiving second-line treatment (indicative of initial treatment failure). The mean age at HIV diagnosis was 51.2 years, and the median time from diagnosis to cART commencement was 3 months. Correspondingly, the median nadir CD4 count was low (165), indicating that from diagnosis, a high proportion met the superseded WHO treatment guidelines (where cART treatment was delayed until advanced disease).[25]

HIV disease characteristics of participants seen at each time point are summarized in Table 1. HIV disease control seemed to improve over the study period in those participants followed up, and the median CD4 increased (499.5 in 2016; 551 in 2019). From 2017 (when testing became available), the proportion virally suppressed (HIV viral load ≤20 c/mL) increased and the median HIV viral load decreased.

HAND prevalence and subtypes at each follow-up time point are presented in Figure 2. HAND were highly prevalent and present in 47% at baseline, 60% at year 1, 62% at year 2, and 58% at year 3. Overall prevalence increased by 11% from 2016 to 2019. In 2016, 2017, and 2018 ANI predominated; however, in 2019, MND increased substantially, altering subtype distribution. HAD remained uncommon (minimum 2.47%, 2018, maximum 6.49%, 2017). Non-HAND causes of cognitive impairment are summarized annually in Figure 2.

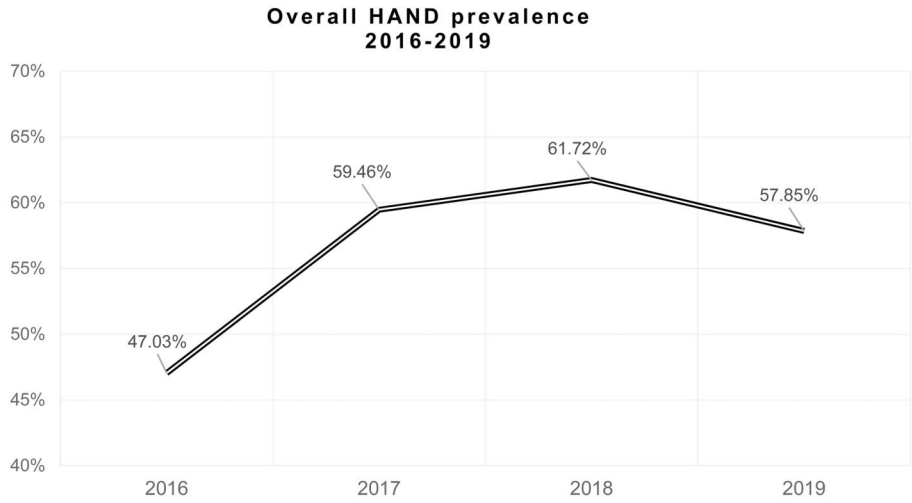
Clinical Course and Progression of HAND

Of those assessed at baseline and year 3 (n = 121), HAND category remained stable/unchanged in 54% (n = 57), improved in 15% (n = 16), and declined in 31% (n = 33) of individuals. Individuals meeting criteria for non-HAND cognitive impairments at baseline or year 3 (n = 15) were excluded from this analysis. HAND category (normal/ANI/MND/HAD) remained unchanged or declined, termed stable

TABLE 1. HIV Disease Management Factors in the Cohort Evaluated During 2016–2019

Variable	2016 n= 253	2017 n = 185	2018 n = 162	2019 n = 121
Most recent CD4 (cells/mm^3)	Missing = 13	Missing = 5	Missing = 35	Missing = 2
md, IQR	499.5 (316.25–672)	486 (295.75–662.25)	523 (372–707)	551 (423–746)
Viral load, copies/mL	Not available	Missing = 66	Missing = 17	Missing = 9
Undetectable (<20)		n = 82 (68.9%)	n = 93 (64.1%)	n = 85 (75.9%)
Detectable, md, IQR		n = 37 (31.1%), 189 (53–591)	n = 52 (35.9%), 120 (44–830.75)	n = 27 (24.1%), 63 (28–127)
Very high (>100,000)		n = 1	n = 1	n = 1
Second-line cART regime*	Missing = 10	Missing = 16	Missing = 31	Missing = 14
	28 (11.5%)	25 (14.8%)	21 (16.0%)	21 (19.6%)

*Second-line regimens nucleotide reverse transcriptase inhibitor × 2 + protease inhibitor 2f-A (TDF, FTC, LPV/r), 2h-A (TDF, FTC, ATV/r), 2s-A (AZT, 3TC, ATC/r), 2g-A (ABC, 3TC, LPV/r), 2e-A (TDF, 3TC, LPV/r), 2k-A (ABC/3TC, ATV/r), 2m-A (TDF, 3TC, ATV/r), 2n-A (AZT, 3TC, LPV/r/AZT, 3TC, EFV), 2x-A (other second line unspecified).



Cognitive impairment (% of total cohort seen)	2016	2017	2018	2019
HAND	119 (47·0%)	110 (59·5%)	100 (61·7%)	70 (57·9%)
ANI	64 (25·3%)	60 (32·4%)	68 (42·0%)	32 (26·5%)
MND	46 (18·2%)	38 (20·5%)	28 (17·3%)	33 (27·3%)
HAD	9 (3·6%)	12 (6·5%)	4 (2·5%)	5 (4·1%)
Major depressive disorder (MDD)	2 (0·8%)	3 (1·6%)	7 (4·3%)	2 (1·7%)
Adjustment disorder	2 (0·8%)	1 (0·5%)	5 (3·1%)	0
Alcohol-related cognitive impairment	3 (1·2%)	2(1·1%)	1 (0·6%)	0
Mild cognitive impairment (MCI)	0	4 (2·2%)	2 (1·2%)	5 (4·1%)
Schizophrenia	0	1 (0·5%)	1 (0·6%)	0
Vascular cognitive impairment (VCI)	6 (2·4%)	5 (2·7%)	0	1 (0·8%)
Delirium/ postdelirium cognitive impairment	5 (2·0%)	0	0	0

FIGURE 2. HAND prevalence, subtypes, and other non-HAND diagnoses over 3 years of follow-up. full color online

or steady progression, in 60 (56.6%) individuals, but fluctuation and reversibility (improvement) were observed, termed fluctuation, in 46 (43.4%) individuals. The degree of yearly fluctuation, indicating the level of heterogeneity in the cohort, is listed descriptively in Table 2.

Factors Associated With Decline or Improvement of HAND Categorization

Of 26 sociodemographic, HIV-specific, and comorbidity characteristics evaluated as possible associations of decline in HAND categorization on bivariate analysis, only female sex and lower educational level (incomplete primary education) were significantly associated with HAND progression/decline (Table 3). Conversely, completed primary education and male sex seem to be associated with HAND improvement/reversibility, although numbers were small. Surprisingly, current HIV disease severity factors (detectable HIV viral load, CD4, and cART regimen) and nadir CD4 (a marker of "legacy effect"[26]) were not associated with either progression (decline) or improvement (Table 3).

At the threshold of $P < 0.1$, the 5 variables, such as age, sex, education, age at HIV diagnosis, and months of cART, were taken forward for multivariable logistic regression modeling to determine independent predictors of decline. The stable and improved categories were combined to create 2 groups: HAND declined (n = 33) and HAND did not decline (n = 73). Only age (OR 1.08, 95% CI: 1.005 to 1.160 $P = 0.036$) and noncompletion of primary education (OR 2.558, 95% CI: 1.044 to 6.268 $P = 0.040$) were independently associated with HAND decline on logistic regression.

DISCUSSION

This is the first longitudinal study of HAND, using standard clinical criteria in an older cART-treated population in SSA. We have previously reported HAND to be highly prevalent in PLWH older than 50 years in SSA, with almost half (47%) meeting criteria for HAND at baseline.[16] Over 3 years of follow-up, the prevalence increased from baseline despite evident improvement in HIV disease parameters (CD4, viral suppression, and cART adherence).

TABLE 2. Summary of Fluctuation in HAND Classification From 2016 to 2019

Fluctuation from Baseline to Year 3	N = 106
Stable at all visits	33 (31.1%)
Stable with fluctuation eg, normal, ANI, normal, normal	24 (22.6%)
Steady progression eg, ANI, ANI, ANI, MND	27 (25.5%)
Progression with fluctuation eg, ANI, MND, ANI, HAD	22 (20.8%)

Comparisons with other studies are challenging. Demographic and HIV severity factors vary widely in previously reported SSA and HIC studies. In SSA, HAND studies often include a high proportion of cART-untreated PLWH or took place in the pre-cART era[8] and would be expected to show progression given that HIV dementia occurred frequently in the pre-cART era, whereas in treated HIV, a milder HAND spectrum is observed.[7,9]

Longitudinal studies in older PLWH seem few. We compare our cohort with existing longitudinal studies, with similar HAND criteria and follow-up duration in Table 5, Supplemental Digital Content 5, http://links.lww.com/QAI/B810. Direct comparisons are challenging. All are HIC studies with a lower mean age than in our study and, generally, a lower baseline HAND prevalence.[13,14,27,28] Some, such as the Multicenter Aids Cohort Study (MACS), exclude individuals with comorbidities.[14] Only one study comprises mostly female individuals,[28] and generalizability to most female PLWH in SSA may be limited. Similarly, educational level is generally substantially higher.[13,14,28] However, proportion on cART, nadir CD4, current CD4, and years since diagnosis are comparable between this Tanzanian cohort and the presented HIC studies,[13,14,27,28] which is perhaps surprising.

Before the widespread use of cART, HAND (HIV dementia) was considered progressive and irreversible. In this study, 54% of our cohort remained stable, without HAND category decline, lower than that observed in the MACS (77%), CHARTER study (61%), and Nice, France, study presented (68%).[13,14,27] Conversely, over 3 years of follow-up, 30% of PLWH improved in HAND category, indicating potential reversibility. This improvement seems higher than that observed in the HIC studies presented (MACS, 13% CHARTER study 16.5%, Nice study 20%).[8,13,14,27]

The mildest form of HAND, ANI, was the most prevalent at baseline, mirroring the disease spectrum observed in HIC studies reporting by AAN criteria. Of those with[13,14,28] ANI at baseline, approximately a third declined by year 3. A similar finding was reported in the CHARTER study where PLWH with ANI at baseline were 2 to 6 times more likely to decline over a 3-year follow-up.[13] This is an important finding because debate continues as to whether the identification of ANI is clinically relevant.[12] Our findings suggest that early identification of the ANI subgroup could allow for closer monitoring and early intervention, given the risk of progression.

We also found older age to be a significant predictor for HAND decline, as in the CHARTER study and in contrast to the MACS. Older age at HIV diagnosis has been associated with worse outcome[11] potentially due to longer duration of untreated disease. However, we found no association with progression of HAND and older age at diagnosis. We postulate the age-related increased risk of decline we observed could partly be due to age-related cognitive decline and/or neurodegenerative processes such as Alzheimer disease or vascular cognitive impairment. Because neuroimaging was not available, it is possible that these conditions may have been, instead, reported as HAD, although diagnoses were established by senior clinicians with experience in dementia diagnosis.

Noncompletion of primary education was a predictor of decline. The MACS did not show this association (comparison—eighth grade education),[14] and CHARTER study found higher education to be associated with HAND improvement.[13] These studies are difficult to compare given the much higher mean education in HIC cohorts.[13,14] Lower education may represent lower cognitive reserve, a well-evidenced risk factor of cognitive decline and dementia,[29] but in SSA may be confounded by other factors such as childhood disadvantage and lower socioeconomic status. It is therefore difficult to comment on whether education is in fact protective in this setting.

Male sex significantly predicted improvement at year 3, although our numbers are far too small to draw any firm conclusions. Sex differences are often reported in studies of Alzheimer disease (female individuals at greater risk), although other demographic factors may be confounding. We considered whether higher education in male individuals (due to historical differences in access to postelementary education) might be a confounder in this setting, and note that lower education remained significant when controlling for age and sex on multivariable analysis.

Fewer months on cART at baseline predicted improvement. This finding could be explained by the neurotoxic side effects of cART, but notably, we found no association with baseline use of efavirenz, well recognized to exhibit neuropsychiatric side effects.[30] It seems more likely that individuals recently diagnosed with HIV may have greater potential for improvement on starting medication, as noted in other studies.[12] Again, these are tentative conclusions based on small numbers.

Of interest, we found no association with nadir CD4 (often termed legacy effect)[26] and HAND decline despite legacy effect being associated with HAND cross-sectional prevalence in a recent meta-analysis of global data of PLWH of all ages.[10] Generally, we found little association between HIV disease severity factors and decline, a finding also seen in HIC settings, for example, CHARTER study and MACS, although one study found cART CPE score to predict decline. This suggests that other factors, such as comorbidities and socioenvironmental factors, may be relevant.

STRENGTHS AND LIMITATIONS

The strengths of the study include the longitudinal design, enabling assessment of change in prevalence of

TABLE 3. Prevalence of Demographic and HIV-Specific Characteristics in Groups With Stable, Improved or Declined HAND Status From 2016 to 2019 Follow-Up and Significance of Bivariate Analysis

	Stable n = 57	Improved n = 16	Declined n = 33	Significance Test Performed	*P*
Demographics					
Median age (IQR)	57 (53–61)	57 (53–59)	61 (55–65.5)	Kruskal–Wallis	0.083
Sex (female)	46 (80.7%)	7 (43.8%)	24 (72.7%)	χ^2	**0.014**
Highest educational level (baseline)				χ^2	**0.012**
Incomplete primary	19 (33.3%)	2 (12.5%)	18 (54.5%)		
Complete primary education	38 (66.7%)	14 (87.6%)	15 (45.4%)		
Living alone (baseline)	Missing = 1 8 (14.0%)	Missing = 0 3 (18.8%)	Missing = 0 3 (9.1%)	χ^2	0.62
Employed (baseline)	Missing = 1 52 (91.2%)	Missing = 1 13 (81.3%)	Missing = 0 29 (87.9%)	χ^2	0.65
HIV disease factors					
Age at HIV diagnosis (mn, SD)	50.6 (6.1)	51.3 (7.0)	53.9 (7.9)	Analysis of variance	0.097
Time untreated, mo (md, IQR)	Missing = 7 3 (1–18.5)	Missing = 1 3 (0–18)	Missing = 0 7 (2–26.5)	Kruskal–Wallis	0.36
Baseline time on cART, mo (md, IQR)	Missing = 6 83 (45–106)	Missing = 1 45 (24–95)	Missing = 0 68 (44.5–91)	Kruskal–Wallis	0.097
Baseline cART regimen	Missing = 2	Missing = 3	Missing = 0	χ^2	0.57
First line*	45 (81.8%)	12 (92.3%)	27 (81.8%)		
Second line*	6 (10.5%)	1 (7.7%)	6 (18.2%)		
Baseline use efavirenz	28 (49.0%)	11 (68.8%)	20 (60.6%)	χ^2	0.14
Baseline CPE score, md, IQR	Missing = 5 9 (7–10)	Missing = 1 9 (6–9)	Missing = 0 9 (6–9.5)	No group difference	
Nadir CD4, md, IQR	Missing = 3 153 (102.5–225.75)	Missing = 1 182 (51–225)	Missing = 0 188 (114–258.5)	Kruskal–Wallis	0.57
Baseline CD4, md, IQR	Missing = 2 531 (306–660)	Missing = 1 484 (333–719)	Missing = 1 470.5 (306.25–656.5)	Kruskal–Wallis	0.92
Viral load 2019, copies/mL	Missing = 7	Missing = 1	Missing = 1	χ^2	0.74
Undetectable (<20)	36 (72.0%)	12 (80.0%)	25 (78.1%)	Counts too small for analysis	
Detectable	14 (28.0%)	3 (20.0%)	7 (21.9%)		
Very high (>100,000)	0	0	1		
Current/previous likely CNS infection	9 (15.8%)	2 (12.5%)	1 (6.1%)	Counts too small for analysis	
Baseline PCP prophylaxis	Missing = 3 22 (40.0%)	Missing = 1 5 (33.3%)	Missing = 0 8 (24.2%)	χ^2	0.29
Current/previous TB treatment	11 (19.3%)	1 (6.3%)	10 (30.3%)	χ^2 (improved category excluded)	0.27
Baseline body mass index, md, IQR	Missing = 2 21.9 (19.6–26.3)	Missing = 1 21.5 (20–26.7)	Missing = 0 23.6 (18.7–26.1)	Kruskal–Wallis	0.98
Baseline WHO stage	Missing = 17	Missing = 10	Missing = 5	χ^2	0.41
1 or 2	5 (12.5%)	1 (16.7%)	7 (25.0%)		
3 or 4	35 (61.4%)	5 (83.3%)	21 (75.0%)		
Baseline Karnofsky performance status, md, IQR	Missing =25 100 (90–100)	Missing = 8 100 (90–100)	Missing = 15 100 (90–100)	No group difference	
Comorbidities					
Baseline hypertension	25 (43.9%)	7 (43.8%)	17 (51.5%)	χ^2	0.76
BP >140/90 mm Hg					
Previous stroke (self-report)	0	0	2 (6.1%)	Counts too small for analysis	
Baseline alcohol intake (self-report)					
Current	16 (28.1%)	5 (31.3%)	4 (12.1%)	χ^2	0.17
Previously/never	41 (70.9%)	11 (68.8%)	29 (87.8%)		
Daily	6 (12.0%)	1 (6.7%)	4 (13.8%)	χ^2	0.781
Baseline Geriatric Depression Scale score >4	10 (17.5%)	1 (6.3%)	10 (30.3%)	χ^2 (improved category excluded)	0.16
Baseline hearing impairment	Missing = 3 2 (3.7%)	Missing = 1 0	Missing = 2 3 (9.7%)	χ^2	0.30

TABLE 3. (*Continued*) Prevalence of Demographic and HIV-Specific Characteristics in Groups With Stable, Improved or Declined HAND Status From 2016 to 2019 Follow-Up and Significance of Bivariate Analysis

	Stable n = 57	Improved n = 16	Declined n = 33	Significance Test Performed	*P*
Baseline visual impairment (in better eye)	Missing = 11	Missing = 4	Missing = 6	χ^2	0.30
None/mild	35 (76.1%)	7 (58.3%)	22 (81.5%)		
Moderate/worse	11 (23.9%)	5 (41.7%)	5 (18.5%)		

Bold indicate statistically significant result.

BP, blood pressure; PCP, pneumocysitis carinii pneumonia

*=*First-line regimens (NRTI x2 + NNRTI efavirenz/nevirapine) 1g-A (TDF, 3TC, EFV) 1b-A (AZT, 3TC, NVP/ABC,3TC, LPV/r), 1c-A(AZT, 3TC, EFV), 1e-A (TDF,FTC, EFV) 1f-A (TDF,FTC,NVP), 1h-A (TDF, 3TC, NVP), 1k-A (ABC, 3TC, EFV), 1m-A (ABC, 3TC, NVP), 1a-A (d4T, 3TC, NVP/d4T, 3TC, EFV), 1x-A, 1uA (TDF, 3TC,DTG), 1vE (TDF,FTC, DTG) (other 1st line unspecified) Second-line regimens (NRTI x2 + Protease Inhibitor (PI) 2f-A (TDF, FTC, LPV/r), 2h-A (TDF,FTC,ATV/r), 2s-A (AZT,3TC,ATC/r), 2g-A (ABC,3TC,LPV/r), 2e-A (TDF, 3TC, LPV/r), 2k-A (ABC/3TC, ATV/r), 2m-A (TDF, 3TC, ATV/r), 2n-A (AZT, 3TC, LPV/r/AZT, 3TC, EFV), 2x-A (other 2nd line unspecified).

HAND using a standardized detailed assessment. Recruitment from a free-of-charge clinic increased likelihood of generalizability to the local population. Notably, male/female proportions corresponded with Tanzanian national HIV[17] and education[31] data. We chose to report risk factors for decline at year 3 because fluctuations are well recognized, but note the heterogeneity in the cohort evaluated annually, as summarized in Table 2.

Of the 253 baseline participants, we were able to follow-up only 121 in 2019 (48%). This introduced the potential for survivorship bias. However, the primary reason for non–follow–up was non attendance within the annual data collection window. Those seen in 2019 were not significantly different in age, sex, CD4 count, or HIV viral load, to those not followed up according to clinic records reviewed in 2019. Those seen are therefore likely to be representative of the baseline cohort. Nevertheless, because the study coincided annually with the rainy, crop planting season, there may have been bias toward physically fitter individuals prioritizing agricultural work over clinic attendance or those living more rurally and challenged by weather-related transport issues. Anecdotally, where patients could not attend, relatives collected cART prescriptions without clinic review.

Other limitations included restricted availability of tests for comorbidity screening (hepatitis B and C, syphilis, and CSF), and HIV viral load (not available routinely until mid-2017). This limited our comparisons with HIC data and meant we could not assess these as confounders. In addition, neuroimaging was not available, meaning that diagnosis of vascular cognitive impairment relied on clinical assessment, medical notes, and/or examination findings. Clinic protocols included empirical treatment of presumed CNS infection where CSF was unavailable and was coded as such. Neuroimaging would have assisted with differentiation of HAND from other cognitive impairments.

Comorbid neurological conditions may complicate HAND and result in diagnostic challenges.[7] At baseline, 18 participants exhibited non-HAND cognitive impairments and 18 exhibited additional/secondary neurological diagnoses. We did not exclude these participants from follow-up to present the spectrum of cognitive impairment in this cohort and for data to be generalizable to other settings.

Comorbidities were self-reported and as such, prone to recall bias and/or inaccuracy in settings of limited health care availability.[31] We felt unable to inquire about sexual orientation because same sex relationships are illegal in Tanzania. Conversely, detailed HIV-specific outcome data were coded on standard outcome sheets from diagnosis by CTC clinicians allowing detailed characterization of HIV disease severity from diagnosis.

CONCLUSIONS

This investigation represents the first longitudinal study of HAND in older people in SSA. HAND were highly prevalent, despite apparently well-controlled HIV, and increased over follow-up despite improved HIV management.

Our findings suggest that cART and regular follow-up may not prevent HAND progression in this setting, although the potential for reversibility observed is reassuring. Further work is needed to identify those most at risk of progression to symptomatic disease and potentially modifiable risk factors.

Older PLWH on treatment are a rapidly increasing demographic group in SSA. Identification of complications such as HAND may be crucial given the likely increasing impact on individuals, families, and health services. Monitoring and control of risk and protective factors for HAND with the aim of reducing progression may become increasingly clinically important in this group.

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