https://dx.doi.org/10.4314/emj.v62i1.4

Ethiopian Medical Journal 2024, 62(1) *ISSN 0014-1755* *eISSN 2415-2420* *Ayele et al.*

Original Article

Factors Associated with Neurocognitive Impairment in Treatment Experienced HIV+ Adults from a Tertiary Care Center in Ethiopia

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Abstract

Background: Given the improvement in life expectancy of people living with HIV (PLWH) in sub-Saharan Africa, the risk of asymptomatic HIV-associated neurocognitive disorder (HAND) has increased. The study objectives were to investigate the prevalence of HAND and associated factors among treatment experienced adults in Ethiopia.

Methods: A single-center observational cross-sectional study was conducted between December 2019 and June 2020 to investigate HAND. International HIV dementia scale (IHDS) was used to screen for the disorder. Both descriptive and analytical statistics were used to analyze the data.

Results: Total of 324 PLWH (63% females) who were on combination antiretroviral therapy for median of 144 months (IQR: 108-168) were investigated. The mean age was 42.5 years (1SD=12.2). The prevalence of HAND was 75.3% and the difference was significantly more in those above 40 years of age (65.8% vs. 80.7%, p=0.003). Age is the only risk factor identified with multivariable logistic regression analysis. A linear decrement in the total score of cognitive performance was observed as the patient's age increase; age was responsible for 9.4% variation observed in IHDS score (r= -0.31, R^2=0.094, p<0.0001). Although statistically not-significant, the trend for cardiometabolic and behavioral risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol and khat use) was higher in the group diagnosed with HAND.

Conclusion: The occurrence of neurocognitive impairment was more pronounced in individuals aged 40 years and above who were HIV positive, compared to those below 40 years. Age was found to be an independent predictor of HAND. Cardiovascular and behavioral risk factors were observed more among patients with HAND compared to no-HAND.

Keywords*: HIV-associated neurocognitive disorder; aging; cardiovascular risk factors; behavioral risk factors; Ethiopia*

Citation : *Ayele BA, Thakur KT, Amogne W et al. Factors associated with neurocognitive impairment in treatment experienced HIV+ adults from a tertiary care center in Ethiopia: A perspective study. Ethiop Med J 62 (1) 25 - 31*

Submission date : *14 March 2023 Accepted: 22 November 2023 Published: 1 January 2024*

Introduction

HIV-associated neurocognitive disorder is an umbrella term, which includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) in individuals suffering from chronic HIV infection (1–3). Post combination antiretroviral therapy (cART) era is characterized by relative decrement in incidence of the severe form of HAND (i.e., HAD) and increment in incidence of ANI and MND (1–3). Likewise, the overall prevalence of HAND has remained similar in the post-cART era with almost affecting half of HIV infected individuals (1–3). Early identification of those at risk, accurate diagnosis, and treatment of HAND is vital especially in low and middle income (LMIC) countries such as Ethiopia, where HAND related health bur- den is highest (3).

Prior studies have identified that decline in cognitive function of HIV + patients were strongly associated with poor cART adherence, engaging in unsafe sex, substance abuse, alcohol addiction, and loss to follow up; ultimately resulting in poor quality of life and increased HIV-associated morbidity and

mortality (1,3–5). Prevalence of HAND in LMICs varies widely ranging from 14% to 64% for adults and 6% for children (3). In Ethiopia, the prevalence of HAND is estimated to be between 33.3% and 67.1% (5–8). In addition, being older age, lack of formal education, low baseline CD4, and un-employment were found to be significantly associated with HAND (5–8).

Unemployment can exacerbate the challenges faced by adults living with HIV, potentially impacting their cognitive health through lack of cognitive stimulation that employment often provides, and higher levels of education are associated with a lifetime of cognitive stimulation and ongoing intellectual challenges, which may contribute to the development and maintenance of cognitive reserve (5–8).

However, little is known about other potential risk factors of HAND such as, peripheral HIV RNA level and presences of cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidemia among HIV + individuals (3,4,9–15). The study objectives of the present study were to investigate association between social determinant of health, behavioral, and cardiovascular risk factors and HIV assocaited cognitive impairments among treatment experienced HIV+ adults at a Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia.

Methods

Study area and duration

The study was conducted at Tikur Anbessa Specialized Hospital (TASH), the largest tertiary referral hospital in Ethiopia with close to 1000 inpatient beds and located at the center of the capital, Addis Ababa. The TASH infectious diseases (ID) clinic cares for more than 2547 HIV + active patients. The study was conducted between December 2019 and June 2020.

Study design and sampling:

A cross-sectional observational study was conducted. We enrolled a consecutive adult who visited the ID clinic during the study period and used a convenience sampling technique. The actual sample size was determined using the single population proportion formula, where the following assumptions were considered: 95% confidence interval, 35.7 % proportion of neurocognitive impairment among HIV-positive patients (7), and 5% margin of error. Finite population correction for the given proportion was done considering the total population of 2547 and then 10% non- responder rate was added, which gave rise to a final sample size of 345. We have included all HIV + patients aged ≥ 18 years, on anti-retroviral treatment at least for six months, not critically ill at the time of the interview, and able to give written or verbal consent. Final data analyses of 324 patients were conducted with a response rate of 97% (Fig. Sup. 1).

Clinical and International HIV Dementia Scale (IHDS) interview

All the included patients were interviewed, and questionnaires were filled by seven trained nurses working in the TASH ID clinics. The training was given by the primary investigator on how to administer the cognitive assessment tool. This tool has been validated in South Africa, Uganda, and Ethiopia and found to have coherent psychometric properties in African populations with sensitivity of 88% and 80% and specificity of 50% and 55% respectively at a cut-off 10 or less (5,7,16–18). Therefore, for our study, we used IHDS cut-off point ≤ 10 to diagnose HAND. Additional clinical data were collected from patient's medical records.

Statistical analysis

We used SPSS version 26. Socio-demographic data, anthropometric data, HIV-related clinical data, CD4 cells counts, HIV RNA level, CV and behavioral risk factors, and IHDS score were first described by their means, frequency, percentile, and standard deviation. Association between HAND and age, CV, and behavioral risk factors were done using chi square or Fisher exact test, logistic regression analysis and results were presented using odds ratio (OR), and p value was set at < 0.05 as statistically significant.

Ethical considerations

The study received ethical approval from Addis Ababa University College of Health Sciences Institutional Review Board (IRB) (Protocol number: 102/19/ Neuro). All questionnaires were coded to maintain maximum confidentiality. All patients gave a written or verbal consent before the interview.

Results

Baseline characteristics of the study participants

The mean (1SD) age of the participants was 42.8 (±12.2) years. Females accounted for 68%. Hundred twenty-four (58.8%) participants were married. Twenty four (7.4%) were illiterate. More than half of the participants were employed (55.6%) and lived on a monthly income <50 USD (54.3%). Hypertension, diabetes mellitus, and dyslipidemia were observed in 9.3%, 4%, and 6.5% of the participants respectively. Likewise, alcohol use, smoking, and khat use was reported by 32.4%, 8.3%, and 13.6%, respectively (Table 1).

HIV associated neurocognitive disorder was observed in 75.3% of the patients. The prevalence of HAND for those above and below 40 years of age was 65.8% and 80.7% p=0.003 respectively. More than half (55.2%) of the study participants received INH preventive therapy. The median duration of HIV treatment was 144 (IQR: 108-168) months. HIV treatment was deferred in 23.8% of our patients. The median baseline CD4 cell count was 165 (IQR: 82-270) cells/uL. Likewise, the median last CD4 cell count of the patients was 477 (IQR: 356-633) cells/uL. The majority (79.6%) of the

Table 1: Characteristics of the study participants (N=324)

Age (mean, 1SD)	**42.8(12.2)**
Comorbidity	
No-comorbidity	259 (79.9%)
1 Comorbidity	44 (13.6%)
2 Comorbidities*	18 (5.6%)
3 comorbidities*	3 (0.9%)
Hypertension	30 (9.3%)
Diabetes mellitus	13 (4%)
Dyslipidemia	21 (6.5%)
Alcohol use, any	105 (32.4%)
Smoking, any	27 (8.3%)
Khat use, any	44 (13.6%)
HIV RNA level not suppressed	22 (6.8%)
HAND diagnosed (n,%)	244 (75.3%)
Age < 40 years	77 (65.8)
Age ≥ 40 years	167 (80.7)

Risk factors of HIV associated neurocognitive disorder (HAND)

Patients with HAND were older compared to those with no-HAND, mean age 44.6 years vs. 37.1 years p=0.001. In the present study, a linear decrement in the total score of cognitive ability (IHDS score) was observed as the patient's age increase; age was responsible for 9.4% variation observed in IHDS score (r= -0.31, R^2=0.094, p<0.0001) (Figure 1).

No difference was observed between HAND and no-HAND based on gender, BMI, and monthly income. Study participants with HAND were more likely married than no-HAND patients, 48.3% vs.10.4%, p<0.001. All illiterate study participants had HAND (p=0.004)(Table 2).No difference was observed between HAND and no-Hand based on the duration of HIV treatment and deferred HIV treatment. Lower median baseline CD4 count was observed among individuals with HAND compared to no-HAND, 157 cells/uL vs. 187 cells/uL, p=0.1 respectively. Similar findings were observed regarding the last CD4 count of our patients, 466 cell/ uL vs. 539 cells/uL, p=0.07, respectively. Detectable HIV RNA level was observed more among patients with HAND compared to no-HAND patients, 4.6% vs. 2.2%, p=0.4 respectively (Table 2).

Cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia were observed more among patients with HAND compared to no-HAND. Alcohol use was more observed among participants with HAND compared to no-HAND, 27.2% vs. 5.2%, p=0.01. However, no difference was observed between the two groups based on smoking history and khat use. Hundred twenty-seven (39.2%) of the patients with HAND received six months of IPT compared to no-HAND group where only 165 received IPT (p=0.04) (Table 2).

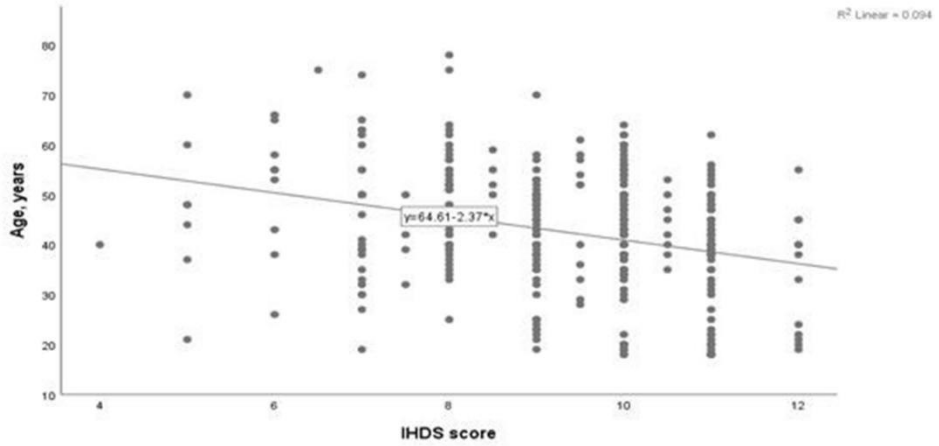

Figure 1: Scatter plot showing a linear decrement in the total score of cognitive ability (IHDS score) was observed as the patient's age increase

Table 2: Risk factors for HIV associated neurocognitive disorder (N=324)

Variable	HAND (n=244)	No-HAND (n=80)	p-value
Mean Age in years (1SD)	44.6 (11.9)	37.1(11.6)	0.001
Female sex (n, %)	156(63.9%)	50(62.5)	0.8
Married (n,%)	102(48.3%)	22(10.4%)	<0.001
Illiterate (n,%)	24(7.4%)	0	0.004
Monthly income < 50 USD (n,%)	126(38.9%)	50(15.4%)	0.09
Months on cART (mean, 1SD)	132(46.8)	126(49.2%)	0.4
cART was deferred (n,%)	55(22.5%)	22(27.5%)	0.4
BMI, Kgs/m2(mean, 1SD)	24.4(4.5)	24.4(4.6)	0.9
Baseline CD4 count, median (IQR)	157(80-265)	187(84-390)	0.1
Last CD4 count, median (IQR)	466(353-618)	539(363-705)	0.07
HIV RNA level not suppressed (n, %)	15(4.6%)	7(2.2%)	0.4
Hypertension (n,%)	24(7.4%)	6(1.9%)	0.53
Diabetes mellitus (n,%)	11(3.4%)	2(0.6%)	0.53
Dyslipidemia (n,%)	15(4.6%)	6(1.9%)	0.67
Alcohol use, any (n,%)	88(27.2%)	17(5.2%)	0.01
Smoking, any (n,%)	21(6.5%)	6(1.9%)	0.76
Khat use, any (n,%)	33(10.2%)	11(3.4%)	0.9
Received IPT for 6 months(n,%)	127(39.2%)	52(16%)	0.04

Multivariable logistic regression modeling to assess the risk of HAND

Age was an independent predictor of HAND in 324 HIV-infected cohort of patients in Ethiopia (AOR 1.04, 95% CI 1.00-1.07, p=0.04). In univariate analysis currently married individuals were associated with HAND (OR 3.12, 95% CI 1.66-5.86, p<0.001) but not when adjusted for the following variables: demographic, baseline and last CD4 cell counts, alcohol use, and IPT usage. Similarly, in univariate analysis illiterate patents were associated with HAND (AOR 11.1, 95% CI 1.4-87.7, p=0.02) but not when adjusted for covariates. Those patients who were grade 1-12 had near-significant association with HAND (AOR 4.0, 95% CI 1.01-16.5, p=0.05). In univariate analysis, alcohol use and those who did not receive six months of IPT were associated with HAND but not when adjusted for covariates. Monthly income $\leq$ 50 USD, baseline CD4+ T-cell count, and last CD4+ T- cell count was not associated with HAND (Table 3).

Discussion and conclusion

To our knowledge, this is the first study reported from Ethiopia opted to assess the impact of increasing age, CV, and behavioral risk factors on HIV- associated neurocognitive impairment. In the present study, the overall prevalence of HAND was high, especially among older HIV-infected patients aged 40 years and above. Age was the only independent predictor of HAND in the current cohort of HIV+ patients. These findings were consistent with previously reported studies (3,19,20). Furthermore, the findings indicate the increasing number of HIV-infected aging population in Ethiopia; and the need to develop a proper national policy which can address this issue. Females accounted for most of the participants. This is because, females are more vulnerable to acquiring HIV infection due to factors such as biological, environmental, and cultural (21). Thus, special emphasis needs to be given to vulnerable groups such as females and elderly people living with HIV (PLHIV) in Ethiopia. Cardiovascular and behavioral risk factors were frequently observed among patients with HAND compared to those with no-HAND.

Contrary to the ever-increasing number of aging HIV + population in sub-Saharan Africa (SSA), the num-

Table 3: Multivariable logistic regression modeling to assess the risk of HAND

	Crude Odds Ratio			Adjusted Odds Ratio		
	COR	95% CI	p value	AOR	95% CI	p value
Age	1.06	1.03 – 1.08	<0.001	1.04	1.00-1.07	0.04
Married currently	3.12	1.66-5.86	<0.001	1.6	0.73-3.49	0.2
Educational status						
Illiterate	11.1	1.4-87.7	0.02	4	0.4-36.7	0.2
Grade 1-12	1.06	0.57-1.96	0.09	4	1.01-16.5	0.05
Diploma +	1			1		
Monthly income < 50 USD	1.6	0.9-2.6	0.09	1.5	0.68-3.15	0.3
Baseline CD4+ T-cell count	0.9	0.9-1.0	0.08			
Last CD4 count	0.9	0.9-1.0	0.09			
Alcohol use (any)	2.1	1.2-3.8	0.02	1.69	0.79-3.61	0.18
Received six months of IPT	1.7	1.01-2.9	0.04	1.45	0.74-2.85	0.28

ber of studies from the region addressing HIV and aging were very few (22). According to the 2007 WHO estimation, approximately 3 million people aged ≥ 50 years were living with HIV in SSA; this represents 14.3% of PLHIV aged ≥ 15 years in the region (22). The present study included patient's age between 18 to 78 years; where close to one-third of them are aged ≥ 50 years and age was an independent predictor of HAND. The figure is higher than the previous report from Ethiopia and Uganda (8,23–26) comparable to report from Lesotho where the estimated prevalence of HIV was 27.8% among those aged ≥ 50 years (22). Such discrepancy could be explained by methodological differences. Moreover, our study findings could contribute to the global effort to fill the knowledge gap regarding HIV and aging in SSA.

Higher proportions of cardiovascular risk factors such as, hypertension, diabetes, and dyslipidemia were observed more among patients with HAND. This is indicator of potential contribution of CV risk factors to development of neurocognitive decline among treated HIV-infected patients. This is consistent with study from Kenya by *Achwoka et al* 2019 (26) where the overall NCD incidence rates for men and women were 42.3 and 31.6 per 1000 person years respectively, indicating higher prevalence of NCD among HIV- infected individuals in Kenya. These findings should alert policy makers in sub–Saharan African countries to consider integrating NCD screening and management strategies in the existing routine HIV chronic care.

The present observation showed higher prevalence of substance (alcohol, smoking, and khat) use among patients having HAND. These is likely due to poor cART adherence associated with substance use of, which subsequently predispose the patient to advanced HIV complications such as HAND (3). Our findings were congruent to recent study from Ethiopia (27). These findings should guide both the clinicians and policy makers to address the issue of substance use among PLHIV in Ethiopia. In the present study, no difference was observed regarding HIV RNA level among HAND and no-HAND group. This finding supports the recent agreement regarding the poor predictive ability of peripheral HIV viral load in predicting HAND (12). Thus, it's imperative to look for more reliable biological biomarkers to identify those at risk, diagnosis, and manage HIV associated neurocognitive impairment. Limitations of this study includes lack of control group for com- parison, failure to screen our patients for neuropsychiatric disorders which could overlap with symptoms of HAND, and failure to have brain imaging of our patients, which could further support our diagnosis.

The prevalence of neurocognitive impartment was

higher among HIV+ patients older than 40 years compared with below. Age was found to be an independent predictor of HAND. Cardiovascular and behavioral risk factors were observed more among patients with HAND compared to no-HAND. These findings highlight on the need to have a comprehensive national policy to address the issue of aging, CV, and behavioral risk factors among HIV-infected adults in Ethiopia. Thus, we recommend future con- trolled studies to consolidate these findings.

Acknowledgements: We thank all the patients who participated in this study and all the nurses working at TASH infectious disease clinic. Finally, we are thankful to the Medical Education Partnership Initiative (MEPI) program, Addis Ababa University for the financial support to cover the cost of data collection and stationary costs related to this study.

Declaration:

Ethical considerations

The study received ethical approval from Addis Ababa University College of Health Sciences Institutional Review Board (IRB) (Protocol number: 102/19/ Neuro). All questionnaires were coded to maintain maximum confidentiality. All patients gave a written or verbal consent before the interview.

Consent to publish: Participants consent for publication is not applicable.

Availability of data and materials:

All data sets on which the conclusions of the manuscript rely are available as spread excel sheets documents and available from the corresponding author on reasonable request from the journal.

Supplementary files

Competing interests:

The authors declare they have no actual or potential competing financial interests.

Funding: No funding was received.

Author's contributions:

BA participated in the design of the study concept, analytical data analysis, interpretation, and wrote the manuscript. WA and TK participated in the design of study concept, data interpretation, and critical revision of the manuscript for important intellectual contents.

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