

ORIGINAL ARTICLE**Prevalence of HIV Associated Neurocognitive Deficit among HIV Positive People in Ethiopia: A Cross Sectional Study at Ayder Referral Hospital****Tilahun Belete^{1*}, Girmaw Medfu², Ephrem Yemiyamrew³****ABSTRACT**

BACKGROUND: HIV associated neurocognitive deficit impairs motor activity, neuropsychiatric functioning, daily activity and work activity usually due to the immune suppression effect of the virus. Sub-Saharan region including Ethiopia is the region with the highest burden of HIV. However, a few studies are found on this aspect nationally. This study was aimed at determining the prevalence and the factors associated with cognitive impairment among HIV positive people in Ethiopia who attended Ayder Comprehensive Specialized Hospital.

METHOD: A hospital based cross sectional study was employed on 234 participants selected using systematic random sampling technique. Data was collected through face-to-face interview, observation and document review. International HIV dementia scale, activity of daily living scale and Hospital Anxiety and Depression scale were used to assess neuro cognitive deficit, activity of daily living, anxiety and depression respectively. The data was analyzed by using SPSS window 20.

RESULT: About 88% of the subjects were receiving highly active antiretroviral therapy. The magnitude of Neuro cognitive deficit was 33.3% (95% CI; 27.7% - 40.6%). Impairment in the activity of daily living was observed on 9.8% of the participants. Besides, 55.6% and 67.1% had anxiety and depressive disorders respectively. Late clinical stage of the illness (AOR= 4.2 (95% CI; 1.19, 14.44)) and impairment in the activity of daily living were significantly associated with neurocognitive deficit (AOR= 7.19 (95% CI; 1.73, 21.83)).

CONCLUSION: A higher prevalence of neurocognitive deficit was observed that was related to impaired activity of daily living and being in late stages of the illness. Hence, this should be a strong alarm for early detection of the problem and consistent review of the treatment regimen.

KEYWORDS: HIV associated Neurocognitive Deficit, Neuro cognitive deficit, HIV Associated Dementia, Cognitive Impairment, International HIV Dementia Scale, Ethiopia

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INTRODUCTION

The area with the highest burden of Human Immune Deficiency Virus (HIV) that accounts for 75% of the case is Sub-Saharan region. This is the region with only 12% of the global population (1). Neurocognitive deficit (NCD) occurs mainly due to HIV among HIV positive people (2,3). The problem in sub-Saharan area is expected to be large as HIV infection and its sequel are prevalent in the region (2,4). Previous studies conclude that neurocognitive deficit has been found at any stage of the illness (5,6,7,8).

Neurocognitive deficit is a deficit in neurological activities, motor activities, psychological functioning, daily activities and activities at work place. The major cause of morbidity and disability among HIV positive people has been accounted to NCD, although the problem is rarely studied in the region. Deficits in different areas of life such as cognitive, motor, emotional and even personality changes can be caused by HIV especially lately as the disease progression fastens. These problems range from the asymptomatic impairments to mild forms and to the more severe HIV dementia (3,4,9,10,11).

A Metaanalysis (systematic review) found out that in sub-Saharan region, a higher prevalence was observed in the pre-highly active antiretroviral therapy (HAART) participants in which neurocognitive impairment (NCI) pre-HAART was 42.37%, and among those on HAART was 30.39% (2). Respective NCI estimates in studies from Uganda were 46.49%. In addition, NCI was more common among patients with a concomitant psychiatric ailment. And, the study concluded that HIV strongly predisposes to NCI leading to a huge burden in Sub-Saharan Africa (4).

The more common impairments are the asymptomatic and mild forms that are more prevalent with advanced age (12). The problem of NCD in sub-Saharan area ranges from 20% - 37% as reported in prior studies (2,11,13). A report in the multi-center international studies that were conducted in Thailand, Zaire, Kenya, Brazil and Germany revealed that the neuropsychological

deficit among HIV-positive people ranged from 13% in Brazil to 19% in Zaire (14,15,16).

A study conducted in Northern Nigeria in 2014 in which a total of 418 patients participated showed that a total of 21.5% participants were found to have cognitive impairment. Using a Frascati criterion, 13.3% were found to have HIV associated dementia (HAD), 42.2% had mild neurocognitive deficit, and 44.4% had asymptomatic neurocognitive impairment, within this group. Cognitive impairment was significantly associated with duration of illness, CD4 count, viral load, education, severity of the illness and history of complete stopping of HAART in the past (17).

A similar study from India between October 2011 and September 2012, on 80 HIV-positive individuals randomly selected from the ART Centre, the patients were clinically examined and tested using International HIV dementia scale (IHDS). Accordingly, all HIV-positive participants who were already on HAART were found to have neurocognitive deficit; the overall prevalence was 32.5% (18).

In a similar finding, all participants were either in World Health Organization (WHO) clinical stage I or stage II of HIV illness and 87.1% of them were on HAART. The prevalence of HIV associated neurocognitive deficit (HAND) was 90%. And it was determined by IHDS (19).

In Malawi and Botswana, studies conducted on 106 and 120 patients reported that in the former symptomatic neurocognitive impairment was present in 15%; 55% fulfilled Frascati criteria for asymptomatic neurocognitive impairment (20). As well, 38% had severe form of NCD (HIV associated dementia) in Botswana that was significantly associated with educational level and age. In that study, 24% of the subjects also had co-existing depression (21). However, the level of education significantly affected performance on all three cognitive measures, and age affected processing speed and performance on the IHDS. Depression and current CD4 count did not affect performance on any of the cognitive measures (21).

A study conducted in Ethiopia in 2014 on 423 HIV positive participants by using IHDS, determined that the prevalence of HIV associated

dementia (severe form of neurocognitive impairment) was 24.8%. Also, low levels of education, older age of 50 years or above, co morbid opportunistic infection and substance use were significantly associated with HIV dementia (22).

Neurocognitive impairment is one of the serious problems among HIV-positive people. It can lead to morbidity, treatment non-adherence, faster progression of the illness, disability and bed ridden state if we fail to detect it early. Even it can result in death in severe cases despite easier methods to screen the problem.

It is important to study such problems in order to improve the well being and quality of life of HIV-positive people. Nevertheless, there is scarcity of studies on this research title in Ethiopia. Therefore, the findings of this study might be valuable to different stakeholders, healthcare facilities and clinicians who are working in the scope. Thus, this study aimed at assessing the prevalence and factors associated with cognitive impairment among HIV-positive people attending at Ayder Comprehensive Specialized Hospital (ACSH), Mekelle, Ethiopia.

METHODS AND SUBJECTS

Mekelle is the capital city of Tigray Administrative Regional State located 783 kms North of Addis Ababa. The city is divided into seven sub-administrative units, and it has one comprehensive specialized hospital (Ayder), two other public hospitals and one military hospital. A hospital based cross sectional study was conducted at Ayder Comprehensive Specialized Hospital between February and June 2016 (23).

All HIV positive people who had follow up at the hospital were the source population. And, the study population included those participants who visited the hospital during the data collection period.

The inclusion criteria was age between 18-64 years (because age related neurocognitive deficit i.e. dementia starts from age of 65 years) and having documented HIV-positive status. Those with known cognitive impairment unrelated to HIV (neurological, severe medical illnesses

unrelated to HIV, severe mental illness) were excluded from the study.

Sample size and sampling procedure: The actual sample size was determined by using the single population proportion formula where the following were considered: 95% confidence interval, 24.8% proportion of neurocognitive deficit among HIV positive patients (22) and 5% margin of error. Since the total population was 1184, we employed correction formula, and then added 10% estimated non-response rate that made a final sample size of 254.

The participants were selected through systematic random sampling technique after having the monthly client flow to the hospital. Two psychiatric nurses were employed to collect data. Data were collected through face-to-face interview, observation and document review. Local language versions of International HIV dementia scale, activity of daily living scale and hospital anxiety and depression scale were used to assess neurocognitive deficit, activity of daily living, anxiety and depression respectively. These tools have been validated in sub-Saharan region, and HADS has been validated in Ethiopia, too, (24,25,26,27).

Translation of the tools was carried out from their English version into local language version (Tigrigna) by professional translators, and the local language version was translated back into English by another professional with the help of a mental health specialist. Then, consistency was assured. Also, training was provided to the data collectors for one day on what information to gather and how to approach each client. A pretest was done at another public facility on 5% of the sample to check for necessary modifications. Also, daily supervision was employed during the data collection period. Daily data checkup and entry were also done.

Operational definitions

● **HIV Associated Neurocognitive Deficit:** It is a reduction or impairment of brain function; any patient who score less than or equal to 9.5 from IHD scale (24) has this problem.

● **Activities of daily living:** A score of 4 or less on Ketz Activity of Daily Living scale is considered to be a person impaired in his/her activity of daily living (25,26).

● **Anxiety:** A score of 8 or more on anxiety symptoms on Hospital Anxiety and Depression scale is considered that the person has anxiety (27).

● **Depression:** A score of 8 or more of depression symptoms on Hospital Anxiety and Depression scale is considered that the person has depression (27).

Data checkup, coding, entry and analysis were computed using SPSS window 20. To determine the degree of association between different variables and neurocognitive deficit, logistic regression was employed. Variables with p-value of 0.2 or less in the bivariate analysis were selected for multivariate analysis. The degree of association was determined with adjusted odds ratio (and 95% confidence interval).

Ethical consideration: Ethical was obtained from Health Research Ethics Review Committee of the College of Health Sciences, Mekelle University. Permission was obtained from the hospital, and then consent was collected from the study

participants before filling each questionnaire respecting their rights to withdraw from the study at any time. Confidentiality was assured for all the information provided, and no personal identifiers were used on the questionnaire. Participants who had neurocognitive deficit were resented to the clinicians for further evaluation.

RESULTS

A total of 234 HIV-positive people who had follow-up at Ayder Comprehensive Specialized Hospital participated in the study. Thus, the response rate was 92.1%.

Socio-demographic characteristics: The respondents were predominantly females 151(64.5%). The mean age (standard deviation) of participants was 38.26(±9.94) with a range of 18 to 64 years. The proportions of participants in the age group of 18 to 30 years, 31 to 40 years and above 40 years were 32.1% 34.1% and 33.8% respectively.

Table 1: Socio demographic characteristics of HIV-positive people, Ayder Comprehensive Specialized Hospital, Ethiopia, June 2016 (n=234).

Characteristics		Frequency	Percent
Sex	Female	151	64.5
	Male	83	35.5
Age (years)	18-30	75	32
	31-40	80	34.2
	> 40	79	33.8
Marital status	Single	40	17.1
	Married	135	57.7
	Divorced	33	14.1
	Widowed	26	11.1
Educational status	No education	110	47
	Primary	61	26.1
	Secondary	30	12.8
	Higher education	33	14.1
Occupation	Laborer	48	20.5
	Civil servant	53	22.6
	Merchant	64	27.4
	Housewife	50	21.1
	Farmer	16	6.8
	Others	3	1.3
	Monthly income (Birr)	<500	123
	501-1000	32	13.7
	1001-1500	50	21.1
	>1500	29	12.4

Educational status showed that 69(29.5%) of them were not able to read and write. Additionally, 53(22.6%) and 64(27.4%) were daily laborers and government employee by occupation respectively. Married participants were 135(57.7%). Also, 206(88%) and 169(72.2%) were Tigray by ethnicity and Orthodox Christian by religion respectively; 123(52.6%) of the respondents had a monthly income of 500 Birr or less (Table 1).

Among 234 participants, 206(88%) were receiving HAART; about 54.3% were on follow-

up for 6 or more years. Also, 139(59.4%) patients were at stage 1 while 64(27.4%) were at stage 2 according to WHO clinical staging. In addition, the recent CD4 count (within 3 months of the data collection period) was 351-500 cells/dl and 201-350 cells/dl for about 32.9% and 31.2% of the subjects respectively. Opportunistic infections were observed in 14.5% of the participants. Besides, current use of psycho-active substances was reported in 13.7% of them (Table 2).

Table 2: Clinical factors of HIV Positive People, Ayder Comprehensive Specialized Hospital, Ethiopia, June 2016 (n=234).

Clinical factors		Number	%
CD4 count (cells/dl)	<201	25	10.7
	201-350	73	31.2
	351-500	77	32.9
	>500	59	25.2
Duration of illness (Years)	1 or less	29	12.4
	2- 4	78	33.3
	5 or more	127	54.3
Clinical stage (WHO)	Stage I	139	59.4
	Stage II	64	27.4
	Stage III	25	10.7
	Stage IV	6	2.6
Status of HAART	On HAART	206	88
	Pre-HAART	28	12
Current OIs	No	200	85.5
	Tuberculosis	17	7.4
	Pneumonia	3	1.3
	Others	14	6

Magnitude of NCD: Of the study participants, 78 scored 9.5 or less on IHDS. Thus, the magnitude of HIV associated neurocognitive deficit was 33.3% (95% CI; 27.7% - 40.6%). The score on international HIV/AIDS dementia scale (IHDS) is as follows:

The first part on IHDS is timed finger tapping. On this part, motor speed is assessed, and 107(45.7%) did well, scoring 4 out of 4. However, 34(14.5%), 17(7.3%) and 9(3.8%) did worse, scoring 2/4, 1/4 and 0/4 respectively. On the next part, which assessed psychomotor speed, 125(53.4%) worked well without any impairment, scoring 4 out of 4, also 19 (8.1%), and 8(3.4%) scored one and zero out of 4 respectively. Memory recall was assessed in the third part, and it was

found that 119(50.9%) recalled all the four things without any clue, scoring 4 out of 4, but about 7(3%) could not recall all the things even with a clue, and they score zero out of 4.

The magnitude across sex reveals that 34.4% of women and 31.3% of men developed NCD. Similarly, the problem increased with increment in age. Thus, it was 25%, 25.3% and 49.4% for the age groups of 18 - 30 years, 31 - 40 years and above 40 years respectively. Besides, it was 36.4% for unmarried participants. Concerning occupation, higher magnitude was observed for farmers and merchants with a proportion of 50% and 48.4% respectively. In the level of income, 58.6% of participants who earned above 1500 Birr and 37.5% of those who earned 500 -100 Birr per

month had NCD while 36.4% of the participants who were on HAART had NCD, 39.4% of those on follow-up for 5 years or more had NCD. From the sub-group of clinical stages, 74.2% of the participants in clinical stages of stage 3 and stage 4 developed NCD. Based on the CD4 count, it was found that 64% of them with 200 cells/dl or less had NCD; and 39.7% of the participants with a count of 201 - 350 cells/dl had NCD. Similarly, the magnitude of NCD among participants who had impairment in their activity of daily living, among those who developed anxiety and among those who had depression was 82.6%, 38.5% and 37.6% respectively.

Other independent factors: Activity of daily living was assessed using *Katz Index of Independence in Activity of Daily Living*, and we found that about 23(9.8%) of the participants had impairment in the function of activity of daily living. The levels of anxiety and depression as measured by *Hospital Anxiety and Depression scale* showed that 55.6% and 67.1% of HIV positive people had anxiety and depression respectively.

Substance use assessment: Of the total participants, 32(13.7%) had used substance in the last three months. Alcohol was the commonest substance used by 14(6%) of them. Both Tobacco and Khat use was also reported by 6(2.6%). Of substance users, about 11(34.3%) had HAND as determined by IHDS.

Factors associated with neurocognitive deficit: Variables with p-value of 0.2 or less in the bivariate logistic regression were selected for multivariate analysis. The final degree of association as determined by adjusted odds ratio revealed that HIV-positive people who had impairment in their activity of daily living were 7 times more prone to develop NCD (AOR= 7.19 (95% CI;1.73, 21.83)).

In a similar pattern, being in the 3rd stage of HIV/AIDS was a risk for NCD compared to stage 1. Thus, participants who were in the 3rd stage were 4 times at risk of developing NCD compared to subjects in stage 1 (AOR= 4.2 (95% CI; 1.19, 14.44)). Nonetheless, other socio-demographic characteristics, clinical factors, depression and anxiety were not significantly associated with NCD (Table 3).

Table 3: Multivariate association between neuro cognitive deficit and other factors, ACSH, Mekelle, Ethiopia, June 2016.

Variables		Neurocognitive deficit		COR (95% CI)	AOR (95% CI)
		Yes	No		
Depression	Yes	59	98	1.84 (.99, 3.38)	1.15 (.49, 2.69)
	No	19	58		
Anxiety	Yes	50	80	1.69 (.97, 2.97)	1.04 (.48, 2.24)
	No	28	76		
Duration of Illness (in year)	1 or less	8	21	1	1
	2-4	20	58	.9 (.35, 2.36)	.84 (.29, 2.46)
	5 or more	50	77	1.7 (.70, 4.14)	.79 (.38, 1.65)
Clinical stage	Stage I	33	106	1	1
	Stage II	22	42	1.68 (.88, 3.21)	1.0 (.45, 2.24)
	Stage III	19	6	10.17 (3.75, 21.58)	4.2 (1.19, 14.44)*
	Stage IV	4	2	6.42 (1.13, 16.67)	.61 (.04, 8.83)
CD4 Count (Cells/dl)	200 or less	16	9	6.29 (2.26, 17.49)	2.39 (.69, 8.29)
	201-350	29	44	2.33 (1.08, 5.06)	1.19 (.47, 3.04)
	351-500	20	57	1.24 (.56, 2.76)	.93 (.39, 2.24)
	> 500	13	46	1	1
Impairment in activity of daily living	Yes	19	4	12.24 (3.99, 21.48)	7.19 (1.73, 21.83)*
	No	59	152	1	1

Where COR=Crude odds ratio, CI=Confidence interval, CI=Confidence interval, *significantly associated

DISCUSSION

This study was undertaken to evaluate neurocognitive dysfunction in HIV patients using IHDS. In another study, among 234 patients, 78(33.3%) had HAND. The prevalence of neurocognitive deficit in our study was higher than expected. Since most of our subjects were receiving treatment with HAART, higher prevalence might be observed. Yet, it is important to note that the high prevalence of neurocognitive deficit in this study may reflect the need for further refinement of the tool, IHDS, at national level. As compared to prior studies, the current finding is similar with the result of a study conducted in India (32.5%) (18), a study done in Nigeria (34.4%) [28] and an earlier Metaanalysis (systemic review) in Sub-Saharan area (30.9%) (2). However, it is less than the findings of previous studies undertaken in Botswana (38%) (21), a study in the international community (37%) (15), a study done in Cameroon (85%) [29], a study conducted in Asia (90%) (19) and a Ugandan study (46.49%) (30,31,32).

Most of the participants among whom higher prevalence was reported might be in late stages of the illness by which neurocognitive impairment is more likely. Additionally, the other reason might be accounted to the difference in rating scales along with the variance in socio-demographic characteristics. However, the current finding is high compared to studies from Ethiopia (24.8%) and another study from Nigeria (21.5%) (17, 22). An earlier study from Ethiopia that employed IHDS determined the more severe form of neurocognitive deficit (HIV associated dementia). That could be the reason for the discrepancy. Other socio-demographic variations might also play a role for the inconsistency.

This result is very high compared to multi-centered international studies (that were conducted at Thailand, Zaire, Kenya, Brazil and Germany). the problem was in a range of 13% to 19%. Also, this result is higher than the study in Malawi where prevalence of NCD was 15% (14, 15, 16, 20).

Different viral clades and screening tools (or the questionnaire) used may account for the variation in the NCD as certain clades may be

more or less neuropathogenic (33,34). Relatively, neurocognitive deficit is more prevalent in regions where subtype C HIV predominates. As one study reported, 60% of subjects with subtype C-HIV were found to have NCD although they have no functional impairment clinically (35, 36).

The predominance of female participants in this study indicates that HIV/AIDS infection is more common in women than in men in Ethiopia. There are many reasons for this finding. These include cultural and economic factors that make women have little control over sexual and reproductive health issues. Another reason is that men do not come to the hospital either because of stigma or because they do not know their HIV status. Moreover, women are usually screened during antenatal visits as part of prevention of mother to child transmission of HIV. When found to be positive they are referred for treatment. Lastly, the finding of this study indicating that HIV infection is more common in women is similar with the observation made in Ethiopia. The result of this study showed that around 20.5% of the participants were unemployed, one-third of them had no education, and half of them had low level of monthly income which is similar with the country's profile (37).

Among those who had HIV associated neurocognitive deficit, one-fourth had depression as reported in a study done in Botswana (21). In our current study, as measured by HADS, more than half of the participants had depressive symptoms although it was not significantly associated with HAND.

Furthermore, participants classified with neurocognitive impairment using the IHDS were basically asymptomatic in our study, since 62(79.5%) out of 78 of those who had HAND did not report problems with daily activities or complain of cognitive problems. This might be alarming for clinicians and service providers to adopt and routinely screen HIV-positive people for possible NCD.

Late clinical stage was a predictor for the onset of NCD in this study. This is supported by prior studies from Ethiopia in which all of the subjects in late stages were found to have HIV associated dementia (more severe form of HAND). Also, in a Nigerian study, it was

deducted that as the disease progresses more and viral load is increased, the probability of HAND is likely (17). In Uganda where 31% of the subjects had HIV associated dementia, lower CD4 count and advanced HIV disease were risk factors for cognitive decline (30,31,32). The study in Yaounde, Cameroon, which investigated risk factors for HIV associated neurocognitive deficit found that clinical factors of advanced clinical stage and lower CD4 count were predictors for HAND (38).

We found that NCD was significantly associated with impairment in the activity of daily living. Previous studies in India, Nigeria and Malawi found that symptomatic neurocognitive deficits were found in 2.5%, 9% and 12% of the participants respectively (17,18,20). The more likely reason behind impaired daily functioning among HIV-positive people is NCD since it can impair motor activity besides memory and cognitive function (4,11).

Different factors like older age, low level of education, lower level of hemoglobin, psychoactive substance use and opportunistic infections were mentioned as independent factors related to HIV associated NCD or HIV associated dementia in previous studies (17,18,19,20, 21,22). However, any of these factors did not show a significant association with NCD in our study.

In spite of the finding showing that 38.5% and 37.6% of the participants who had anxiety and depression had already developed NCD respectively, neither anxiety nor depression was significantly associated with NCD in this study.

We employed different standardized tools that help to determine the degree of association with the dependent variable. As a limitation, cause and effect relationship was not established between dependent and independent variables because of the cross sectional nature of the study.

The finding reveals that regardless of the use of HAART, HIV associated neurocognitive deficits were common problems especially among participants in late stages of the illness. In addition, it was significantly related with functional disability. Thus, it is highly crucial to prepare neurocognitive deficit screening tools at all clinical setups in order to recognize the problem early. Besides, it is vital for clinicians to

routinely review the treatment regimen of patients and to monitor their clinical progress with special focus on those in late stages of the illness and those who are functionally disabled.

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