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Central Nervous System Tuberculosis (CNS-TB) in treated HIV-infected adults in Tikur Anbessa Specialized Hospital, Ethiopia: A cross sectional study

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ABSTRACT

Background: Central nervous system (CNS) tuberculosis (TB) is a calamitous infection with high rates of morbidity and mortality. Underlying HIV infection often increases susceptibility for acquiring TB and also complicates TB treatment. The study objectives were to assess the burden of CNS TB and associated factors in treatment experienced HIV infected adults.

Methods: A single-center observational cross-sectional study was conducted between December 2019 and June 2020. Both descriptive and analytical statistics were used to analyze the data.

Results: Ninety-five HIV infected adults with presumptive TB-HIV co-infection on combination antiretroviral therapy for median of 144 months were assessed. The mean age was 40.8 years (1SD = 12.4). Male to female ratio was 1:2. The prevalence of CNS tuberculosis was 56.8% (TB meningitis 53.7%, tuberculoma 2.1%, and spinal TB 1.1%). Patients with CNS TB were younger compared to those with extra CNS TB (38.6 vs. 43.6 years, $p = 0.04$). A higher proportion of patients with CNS TB had undetectable HIV RNA compared to those with extra CNS TB (55.8% vs. 36.8% $p = 0.04$). In multivariate regression analysis, advanced disease stages, deferred cotrimoxazole preventive therapy (CPT), and deferred INH preventive therapy (IPT) were found to be independent predictors of CNS TB. Although not statistically significant, the trend for HIV-associated cognitive decline was higher in the group with CNS TB.

Conclusion: The prevalence of CNS TB was higher among HIV-infected adults with TB-HIV co-infection. TB meningitis was the most common type of CNS TB. Advanced disease stages, deferred CPT, and deferred IPT were predictors of CNS tuberculosis. Although statistically not-significant, the trend for HAND was higher in the group diagnosed with CNS tuberculosis.

1. Introduction

Central nervous system (CNS) tuberculosis (TB) is the most devastating manifestation of tuberculosis carrying high rates of morbidity and mortality worldwide [1]. CNS TB may manifest as TB meningitis, tuberculoma, tuberculous abscess, and TB arachidionitis [2]. Underlying HIV infection often increases susceptibility for acquiring or reactivating TB and may complicates the management. According to a review done by Hawllet et al 2019 [3], a high frequency 72–75% of neurological disorders (NDs) and abnormal neurological findings has been reported in clinical studies in HIV-infected patients in Africa. In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease. HIV

is the strongest risk factor for developing TB, and up to 13% of identified TB cases globally in 2012 occurred in those who were HIV infected. In a recent systematic review, the pooled prevalence of TB and HIV co-infection was 31.3% for African countries, 20.1% in European studies, 17.2% in Asia, 25.1% in Latin America, and 14.8% for the United States [4].

HIV significantly increases the risk of TB coinfection, including CNS TB; early diagnosis and treatment of CNS TB is essential to minimizing morbidity and mortality. However, CNS TB recognition in the HIV + populations is especially challenging because of the increased risk of CNS opportunistic infections and malignancies that may mimic CNS TB [5]. HIV-TB coinfection management is complicated by drug–drug

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interactions; the initiation of ART must be balanced with the risk of TB-immune reconstitution inflammatory syndrome (TB-IRIS) to avoid a paradoxical exacerbation of the immune response against TB [4].

Isoniazid preventive therapy (IPT) and cotrimoxazole prophylaxis (CPT) have been recommended for the benefit of HIV/AIDS-infected individuals to prevent opportunistic infections such as tuberculosis [6]. Recently published studies from Ethiopia have shown that IPT and CPT use were associated with significant reduction in tuberculosis incidence among treatment experienced HIV + adults and children compared to those deferred of IPT and CPT [7–9]. However, little is known about CNS tuberculosis in Ethiopia; the objectives of this study were to assess the burden of CNS TB and associated factors among treatment experienced HIV-infected adults at a tertiary care center in Ethiopia.

2. Methods

2.1. 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 study was conducted between December 2019 and June 2020.

2.2. Clinical and international HIV dementia scale (IHDS) interview

All the 95 patients with HIV + TB co-infection were interviewed and questionnaires were filled by trained seven nurses working in the TASH ID clinics. There was training of the IHDS tool by the primary investigator and this was used to assess cognitive function of the patients. In all 95 patients, the diagnosis of tuberculosis was made based on clinical presentation, laboratory investigations, and imaging findings such as chest X ray, spine and brain magnetic resonance imaging (MRI) and computed tomography (CT) scans.

2.3. Statistical analysis

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, independent *t*-test, bivariate and multivariable analysis and results were presented using odds ratio (OR), and *p* value was set at <0.05 as statistically significant.

2.4. 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.

3. Results

3.1. Baseline characteristics of the study participants

Ninety-five treatment experienced HIV-infected adults were included in the current study. The mean age (1SD) age of the participants was 40.8 (±12.4) years. Male to female (M:F) ratio was 1:2. The median duration of cART was 144 (120–168) months. Antiretroviral treatment initiation was deferred in 9.6 (0–12) months. The median baseline and recent CD4 count was 173 (69–259.5) and 473 (356–648) respectively. The majority (82.1%) of the study participants were on

Tenofovir/Lamivudine/Efavirenz or Dolutegravir. The majority (92.6%) of the patients had undetectable HIV RNA (Table 1).

3.2. Clinical characteristics of the study participants

HIV associated neurocognitive disorder (HAND) was observed in 69.5% (n = 66) of study participants. Forgetfulness and apathy were reported by 23.1% and 20% respectively. Behavioral risk factors such as smoking and alcohol use were reported by 8.4% and 32.6% respectively. All ninety-five patients had some sort of TB-co infection. The prevalence of tuberculosis affecting the Central Nervous System (CNS) was 56.8% (TB meningitis 53.7%, tuberculoma 2.1%, and spinal TB 1.1%). Pulmonary TB and disseminated TB were seen in 31.6% and 11.6% of the study participants respectively. Cotrimoxazole preventive therapy (CPT) and INH prophylaxis therapy (IPT) were deferred in 34.7% and 52.6% of the participants respectively (Table 1).

3.3. Risk factors of central nervous system TB in study participants

Patients with CNS TB were younger compared to those with extra CNS TB (38.6 vs. 43.6 years, *p* = 0.04); no gender difference was observed between the two groups (*p* = 0.9). No difference was observed between CNS TB and extra CNS TB regarding monthly income, duration of cART, recent CD4 counts, baseline CD4, and cART regimen of study participants. Higher proportion of patients with CNS TB had undetectable HIV RNA compared to those with extra CNS TB (55.8% vs. 36.8% *p* = 0.04). No difference was observed between the two groups regarding HIV associated neurocognitive disorder (HAND), current smoking, alcohol use, forgetfulness, and apathy. Tuberculous infection may occur in any HIV treatment stage; however, increased frequency of CNS tuberculosis was observed in patients with advanced HIV stages (*p* = 0.005) (Table 2 & Fig. 1). Higher proportions of HIV infected patients who were deferred of CPT and IPT developed CNS TB compared to those with extra CNS TB (Table 2).

Table 1

Baseline characteristics of study participants (n = 95).

Characteristics	Value
Sex (M: F)	1:2
Age in years (mean, 1SD)	40.8 (12.4)
Estimated monthly income <50 USD (n, %)	42 (54.7)
Months on cART (median, IQR)	144 (120–168)
cART initiation was deferred in months (n, %)	9.6 (0–12)
Baseline CD4 count (median, IQR)	173 (69–259.5)
Recent CD4 count (median, IQR)	473 (356–648)
Antiretroviral treatment regimen (n, %)	
Tenofovir/Lamivudine/Efavirenz or Dolutegravir	78 (82.1)
Zidovudine/Lamivudine + Atazanavir/ritonavir	17 (17.9)
HIV treatment (T) stages (n, %)	
Stage T1	78 (82.1)
Stage T2 and above	17 (17.9)
Undetectable HIV RNA	88 (92.6)
Current smoking	8 (8.4)
Any alcohol use	31 (32.6)
HAND diagnosed (n, %)	66 (69.5)
Forgetfulness (n, %)	22 (23.2)
Apathy (n, %)	19 (20)
Deferred CPT* (n, %)	33 (34.7)
Deferred IPT* (n, %)	50 (52.6)
Classifications of TB infection	
Pulmonary TB	30 (31.6)
TB meningitis	51 (53.7)
Tuberculoma	2 (2.1)
Spinal TB	1 (1.1)
Disseminated TB	11 (11.6)

Table 2
Risk factors for CNS tuberculosis of study participants (n = 95).

Characteristics	CNS TB (n = 54)	Extra CNS TB (n = 41)	p value
Male (n, %)	19 (20)	15 (15.8)	0.9
Age (mean, 1SD)	38.6 (12.4)	43.6 (11.8)	0.04
Estimated monthly income <50 USD (n, %)	30 (31.6)	22 (23.2)	0.9
Months on cART (mean, 1SD)	11.1 (3.4)	11.5 (3.5)	0.6
cART initiation was deferred (mean, 1SD)	0.7 (2.1)	0.9 (1.9)	0.7
Baseline CD4 count (mean, 1SD)	243.1 (245.3)	169.3 (137.1)	0.08
Recent CD4 count (mean, 1SD)	503.9 (297.7)	510.4 (184.7)	0.9
Antiretroviral treatment regimen (n, %)			
Tenofovir/Lamivudine/ Efavirenz or Dolutegravir	44 (46.3)	34 (34.8)	0.8
Zidovudine/Lamivudine + Atazanavir/ritonavir	10 (10.5)	7 (7.4)	
Undetectable HIV RNA	53 (55.8)	35 (36.8)	0.04
Current smoking	4 (4.2)	4 (4.2)	0.7
Any alcohol use	17 (17.9)	14 (14.7)	0.8
HAND diagnosed (n, %)	39 (41.1)	27 (28.4)	0.6
Forgetfulness (n, %)	14 (14.7)	8 (8.4)	0.6
Apathy (n, %)	12 (12.6)	7 (7.4)	0.6
Deferred CPT* (n, %)	29 (30.5)	4 (4.2)	<0.0001
Deferred IPT* (n, %)	42 (44.2)	8 (8.4)	<0.0001
Treatment stages			
Stage T1	38 (40)	40 (42.1)	<0.0001
Stage T2 and above	16 (16.8)	1 (1.1)	

3.4. Multivariable logistic regression modeling to assess the risk of CNS tuberculosis

In this study, univariate and multivariate logistic regression analysis was done to identify predictors of CNS tuberculosis among 95 HIV infected adults co-infected with TB. Both univariate analysis and multivariate logistic regression showed significant association between: advanced HIV disease stages (treatment stage T2 and above), deferred cotrimoxazole preventive therapy (CPT), and deferred INH preventive therapy (IPT) with CNS tuberculosis, when adjusted for age, baseline CD4 counts, and HIV RNA level (Table 3). In univariate analysis, patients with CNS tuberculosis showed near-significant association with younger age, but not when adjusted for the above covariates (COR 1.04,

95% CI 1.00–1.07, p = 0.05). Similarly, patients with CNS tuberculosis had a higher tendency to have undetectable HIV RNA level compared to those with extra CNS TB (COR 0.11, 95% CI 0.01–0.95, p = 0.04); however, this results were not reproducible when adjusted for the above covariates (Table 3).

4. Discussion and conclusion

To our best knowledge, this is the first study in Ethiopia aimed to investigate CNS TB among patients with TB-HIV co-infection. The prevalence of CNS tuberculosis was high; TB meningitis was the most common sub-type. A higher proportion of patients with CNS TB had undetectable HIV RNA compared to those with extra CNS TB. Advanced disease stages, deferred CPT and IPT were found to be independent predictors of CNS TB. Even though statistically not significant, HIV associated neurocognitive disorder was observed more frequently among patients with CNS TB compared to those with extra-CNS TB.

The present study shows adults with TB-HIV co-infection had average age in the fourth decades, female predominance, and lower baseline CD4 cells. These findings indicate increasing proportion of aging PLWH and disproportionate burden of HIV on female population in Ethiopia. This findings were in agreement with report from Zambia [10]. More-than half of the study participants were diagnosed with presumptive CNS TB based on clinical and radiological evidences. Among patients with CNS TB, more-than half of them were diagnosed with TB meningitis, followed by tuberculoma, and spinal TB arachidionitis. These findings were the result of advanced level of immunosuppression observed in our patients; for granulomatous lesions such as tuberculoma to occur the host need to mount profound immune response, which lacks in those with lower CD4 cells. These results were comparable to previous reports [1,10–13].

Even though statistically not significant HIV-infected adults with HIV co-infection had a higher prevalence of HIV-associated neurocognitive disorder compared to those without CNS TB. These results may suggest that adult Ethiopian with the dual infection of CNS TB/HIV are most likely going to have slowing in their psychomotor function, registration of new information, and memory retrieving. This finding is compatible with regional study [10]. A plethora of scientific reports have shown, IPT and CPT preventive strategies were associated with significant reduction in incidence and mortality related to TB infection [6–9,11,14]. In the present observation, those HIV + adults with

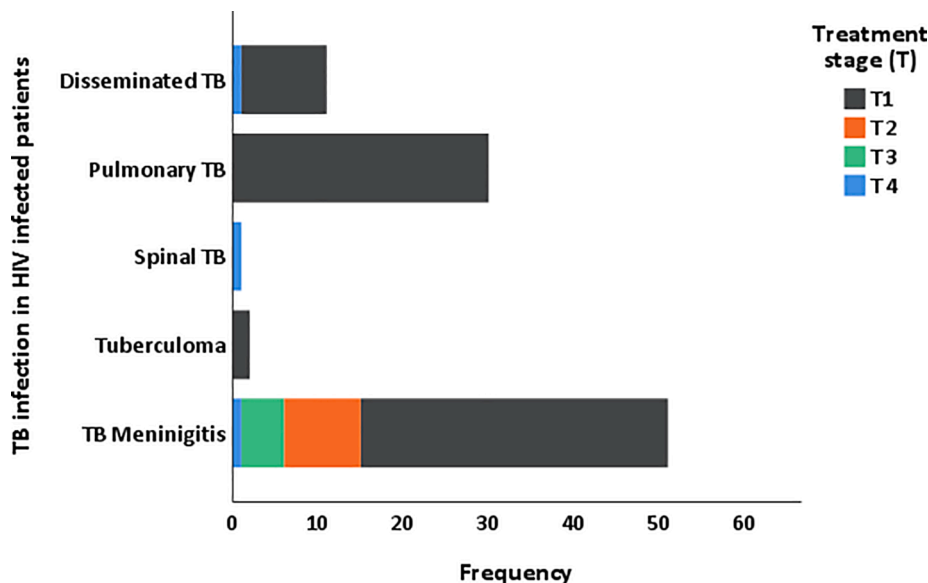


Fig. 1. Stacked Bar graph showing TB infection may occur in any HIV treatment stage; and also showing increased frequency of CNS tuberculosis in patients with advanced HIV stages.

Table 3
Multivariable logistic regression modeling to assess the risk of CNS TB.

Characteristics	COR	95% CI	p value	AOR	95% CI	p value
Age	1.04	1.00–1.07	0.05	1.05	0.98–1.11	0.14
Baseline CD4 count	0.99	0.99–1.00	0.1	1.00	0.99–1.01	0.4
HIV RNA level in serum						
Detectable	1					
Undetectable	0.11	0.01–0.95	0.04	0.11	0.01–1.66	0.1
CPT* treatment						
Received	1					
Deferred	10.73	3.36–34.2	0.0001	6.40	1.29–31.89	0.02
IPT* treatment						
Received	1					
Deferred	14.44	5.29–39.4	0.0001	10.32	2.81–37.98	<0.0001
Treatment stages						
Stage T1	1					
Stage T2 and above	12.84	2.13–133.27	0.007	31.40	2.29–430.59	0.01

advanced HIV stages, those patients deferred of IPT and CPT were found to independent predictors of CNS tuberculosis. These findings further consolidate the importance of IPT and CPT in TB infection prevention strategy among HIV + adults. These results were consistent with reports [6–9,11,14,15]. One of the limitation of our study was the lack/ or incomplete confirmatory CNS TB tests. This includes the lack of positive cerebro-spinal fluid (CSF) AFB and culture results, pathological, and incomplete neuroimaging results for all of CNS TB patients enrolled in the study. This precluded us from evaluating whether certain radiological or bacteriological characteristics were associated with the types and identified predictors of CNS TB. In addition, small sample size and lack of control group may also expose our study to bias.

The present study shows, high prevalence of CNS TB among treatment experienced HIV-infected adults with dual TB-HIV infection. TB meningitis was the commonest type of CNS TB. Advanced HIV disease stages, deferred CPT, and IPT were independent predictors of CNS tuberculosis. Although statistically not-significant, the trend for HAND was higher in the group diagnosed with CNS tuberculosis. We recommend conducting future controlled study in order to consolidate our findings.

Consent to publish: All authors have agreed on the decision to publish this manuscript on EMJ as an MEPI cohort special issue.

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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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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