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Incidence of tuberculosis co-infection and its determinants among adult people living with HIV/AIDS at Afar Region government health facilities, northeast Ethiopia: A retrospective cohort study

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Abstract

Background: Globally tuberculosis is the leading cause of death among people living with HIV/AIDS, and most of the deaths occurred in resource limited countries. To be sure, data on the incidence of tuberculosis is limited in Ethiopia.

Objective: This study assessed the incidence of tuberculosis and its predictors among adults living with HIV/AIDS in government health facilities of northeast Ethiopia.

Setting: A five year retrospective cohort study was conducted from May to June, 2015, on 451 adult HIV/AIDS infected individuals who enrolled in the chronic HIV Care Clinic of Government health facilities of northeast Ethiopia.

Participants: A total of 451 HIV infected adults who newly enrolled in the chronic adult HIV care clinic, from July 1, 2010 with complete information were followed until May 2015.

Primary outcome measure: The primary outcome was the proportion of patients diagnosed with TB or TB incidence rate, which was measured using a retrospective cohort study

Results: A total of 451 charts with complete information were followed for a total of 1377.41 Person-Years (PY) of observation. The overall incidence density of tuberculosis was 8.6 per 100 person-year observation. Previous TB disease (AHR=2.32, 95% CI=1.51-3.57), bedridden (AHR=2.42, 95% CI = 1.05-5.59),and ambulatory functional status at the baseline (AHR=2.42, 95% CI=1.56-3.76), BMI<18.5kg/m^2 (AHR=1.62, 95 % CI =1.09-2.39), Not taking IPT (AHR=6.96, 95% CI=2.53-19.08), and hemoglobin level below 10 g/dl (AHR= 2.54, 95% CI=1.57- 4.11) were determinants for the incidence of tuberculosis.

Conclusion: The incidence of TB disease among adults living with HIV/AIDS in the first and second years of follow-up was higher compared with subsequent years. Previous TB disease, not receiving IPT, low BMI, and low hemoglobin level and unable to work were found to be determinants of the incidence of tuberculosis. Therefore, improving TB/HIV collaborative activities should be strengthened in the study setting.

Strengths and limitations of this study

- The study which involved a five year follow up covered longer time than other similar studies and is expected to show the long term impact of HIV on TB.
- The study attempted to show the incidence of TB and its predictors among PLHIV using a five-year retrospective data
- The retrospective nature of the method prevented the inclusion of all possible factors that affect the incidence of tuberculosis.
- Some participants whose data were incomplete were excluded from the study because if such patients had TB they would undermine the findings of the study.
- Variables such as housing condition and household income were some of the plausible factors that were not measured in this study.
- Culture confirmation was not performed during the study period.

Introduction

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB), but it can also affect other sites (extra pulmonary TB). It has remained the major health problem globally. In 2015, TB was one of the top 10 causes of death worldwide and a leading cause of death among HIV positive people, ranking above HIV/AIDS as one of the leading causes of death from infectious diseases[1]. Out of the 1.4 million TB-caused deaths reported in 2015, 0.4 million occurred to HIV positive TB patients. Globally it was estimated that there were 10.4 million TB cases, including 1.2 million among HIV positive people[1].

Globally, nearly 78 million people have contracted HIV infection since the beginning of the HIV pandemic, and close to 39 million have died of AIDS related causes. Among these, TB was responsible for twenty-five percent of the deaths[2]. According to the WHO 2014 report, there were an estimated 1.1 million cases of TB co-infected with HIV[3], where the majority (90%) of the TB-HIV co-infected people were living in resource limited setting; like Ethiopia[4-6]. In the African region that has the highest TB/HIV burden, three-out of four TB patients knew their HIV status, and 70% of the TB patients known to be living with HIV in 2013 were started on antiretroviral therapy (ART). Sub-Saharan Africa is among the regions highly hit by the HIV epidemic and covers more than three-fourths (79%) of the burden of TB-HIV co-infections[7].

In Ethiopia, TB remains one of the leading causes of mortality and the third cause of hospital admission. In the last ten years, the number of new cases has increased from 55,000 to 100,000, and the increase in the number of tuberculosis cases is due to the rapid spread of HIV infection. According to the 2011 Ethiopian Demographic and Health Survey (EDHS) report, the prevalence of HIV in Ethiopia was 1.5%, and in Afar Region, where the study was conducted, it was 1.8%. Similarly, it was reported that the prevalence of TB was 211 per 100,000 of the population[8], and the global TB report indicated that Ethiopia ranked 10th among 22 TB high burden countries. Moreover, Ethiopia is one of the high TB/HIV burden countries, and the prevalence of TB/HIV co-infection was 15% in 2012[6, 7]. TB/HIV co-infection in the country is associated with diagnostic and therapeutic challenges and constitutes an immense burden in the health care system. The dual epidemics have drained resources and overburdened the limited health work-force[9]. Considering this challenge, the Ministry of Health designed a strategy to increase the

percentage of TB patients tested for HIV and vice versa. As a result, the percentage of TB patients tested for HIV increased from 16 percent in 2007 to 92 percent in 2012, and the proportion of HIV patients screened for TB from 25 percent in 2007 to 92 percent in 2012[10]

Though HIV increases the risk of developing TB, it is not the only determinant for developing TB. Various reports indicated that socio-demographic[11, 12], clinical[13, 14], life style[14, 15] and environmental[16] factors were some of the determinants of the incidence of TB infection among HIV positive individuals. Among the clinical factors, low CD4 count [17-21], low hemoglobin level, diabetes and other opportunistic infections, and functional status showed significant associations with the incidence of TB [20, 22-24]. However, IPT, ART, and CPT treatments reduce the risk of TB infection among HIV positive individuals [23, 25, 26]. In resource limited countries, such as Ethiopia, where there is poor access to health care, there are very few studies on the determinants of the incidence of TB among HIV infected people. Therefore, this study assessed the incidence of active TB disease and its determinants among HIV positive people in northeast Ethiopia.

Methods

Study design and setting

A five year retrospective cohort study was conducted on HIV positive patients attending the chronic HIV care clinics from July 2010 to June 2011, in selected government health facilities of the Afar Regional State, northeast Ethiopia. The region is located in the north-eastern part of Ethiopia and has a total population of 1,678,000 , of whom only 289,000 live in urban and semi-urban areas [27]. In the region, there are four hospitals, 40 health centers, and 15 private clinics providing health services. When HIV care service was first introduced to the region in 2006, 15 public health institutions were providing chronic HIV care and support to around more than 4,000 people living with HIV (PLHIV). Two health centers (Awash, and Samara) and three hospitals (Asayta, Abala, and Dubti General) were selected based on the availability of TB/HIV clients. These health institutions were providing chronic HIV care and follow up for TB to about 85% of the patients living with HIV in the region.

Study population and eligibility criteria

All HIV/AIDS patients who were 15 years and above and newly enrolled into HIV care in selected government health facilities of Afar Region from July 2010 to June 2011 were the population under study. These individuals, who enrolled into HIV care from July 2010 to June, 2011 were followed for five years, until May 2015. Consequently, a total of 503 people living with HIV were registered during the period. Individuals with incomplete information, like missing the date of enrollment and follow-up data, were excluded from the study. However, individuals that were deleted for analysis were compared to the study groups and showed no significant baseline demographic characteristics. In addition, those who died or were lost to follow-up were considered as censored

Measurements and study variables

The outcome variable in this study was the incidence rate of TB co-infection among HIV positive patients. An event of an incidence of TB in this study was considered as any form of TB that was not only diagnosed clinically or radio-graphically but also confirmed by laboratory examinations or by patients who have empirically started anti-TB treatment even after enrollment. TB was diagnosed using microscopic examinations of three sputum samples, chest x-ray, and fine needle aspiration of lymphadenopathy. Culture confirmation was not available in the study areas during the study period. When an individual became diagnosed with active TB, treatment was given based on the National TB Program, which WAS 8 months of treatment (currently 6 months). HIV positive individuals who were lost to follow-up, transferred, died, and who were not diagnosed for TB until the end of the follow-up period were considered as censored. Study variables, including socio-demographic and economic characteristics, such as age, sex, educational status, employment status, residence, religion, family size, marital status, and clinical characteristics, such as WHO clinical stage, baseline CD4 count, functional status, and history of TB, BMI, and hemoglobin level were reviewed. Functional status was measured at baseline, and a person was categorized as working if "he/she was able to perform usual work in or out of the house", ambulatory if "he/she was unable to perform work but able to perform activities of daily living" and bedridden if "he/she was not able to perform activities of daily living". CPT prophylaxis in this study was defined as a patient who took co-trimaxazole for longer than one month for a prophylaxis purpose. Substance use in this study was

considered as any substance used by the patient that is recorded on in-take form of the patient chart.

Sample size and sampling procedure

All HIV/AIDS patients who were 15 years and above and enrolled newly into HIV care from July 2010 to June 2011were the population under study. Sample size was calculated using the single proportion formula, considering the following assumptions: 17% prevalence of TB among HIV positive people in Jimma, Ethiopia[28], 95% level of confidence, 3.5 margin of error, and 3.3% expected incomplete record. Finally, the minimum sample size of 458 was obtained. Thus, there were 503 PLHIV registered in the selected health facilities of chronic HIV care clinics, all of the 503 records were included in the study.

In Afar Region, where the study was conducted, there are four hospitals, 40 health centers, and 15 private clinics providing health services to the community. Out of these health facilities, two health centers (Awash and Samara), and three hospitals (Asayta, Abala and Dubti General) were selected based on client flow and availability of TB and HIV follow-up services. In these selected health facilities, 503 HIV positive people were newly registered from July 2010 to June 2011. However, people living with HIV and registered in health facilities from July 2010 to June 2011 and had complete information were followed until May, 2015.

Data collection tool and procedure

Data were collected through chart reviewing, using the patient chart data extraction format by nurses who took training on ART. All records of HIV/AIDS patients between July 2010 and May 2015 were considered. Charts were retrieved by using patient medical record number and ART registration numbers found on the database of the selected health facilities. Forms used for laboratory request, TB records, ART intake, and patient cards were reviewed. Data quality was assured by using a pretested questionnaire and trained data collectors. Data completeness and consistency was checked by supervisors. The data clerk and case managers assisted the data collectors by identifying charts.

Data Processing and Analysis

Extracted data were checked for completeness, coded, and entered into EPI-INFO version 7 and exported to SPSS version 20 for further analysis. Statistical summary measures and incidence density were calculated. Magnitude was calculated and described by frequencies and tables. Incidence density rate was calculated for the study period. Life table and log rank test was used

to estimate TB free survival among study participants and to compare different categories of survival probability respectively. Time-to-event data that the study considered and survival analysis were carried out, the cox proportional hazards model was fitted, and a life table was used to estimate cumulative probabilities. Bi-variable and multivariate cox regression model was used to identify the predictors of the incidence of TB. Variables with p-value less than 0.2 in the bi-variable analysis were considered for the multivariate cox proportional hazard model. A 95% confidence interval of hazard ratio (HR) was computed and variables having p-values less than 0.05 in the multivariate cox proportional hazards model were taken as significant predictors for the outcome variable. Moreover, basic assumptions of cox proportional hazard model were checked using the Schoenfield residuals test.

Ethical consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Public Health, the University of Gondar. A letter of permission was obtained from the Afar Regional Health Bueuro (ARHO), and a written permission letter was sent to each selected health facilities. In addition, confidentiality was maintained by using only unique identification codes rather than patient names and identifications.

Results

Socio-demographic characteristics of PLHIV

A total of 451 records of PLHIV who were enrolled at health facilities from July 1, 2010 to June 30, 2011 were reviewed and followed until 2015. A total of 451 HIV/AIDS patient charts with complete information were analyzed in the study, while 24 charts were not included in the analysis because they did not contain complete information. Out of the 451 patients that remained in the analysis, more than half, 267(59.2%), were females, and more than two-thirds, 297 (65.9%) were below the age of 35 years. The mean age (±SD) of the patients was 32.55(±7.48) years. Most of the respondents, 410 (90.9%), were urban residents, and 275 (61.0%) were Muslims **(Table 1)**.

Almost half, 234(51.9%), of the participants were self-employed. Of the 130 (28.8%) patients recorded as substance users, 14 (5.0%) were tobacco users, 26 (20.0%) alcohol consumers, and 90 (75.0%) were using both of these. Only 76 (16.9%) of the patients had more than 5 family

members. Almost half, 212(47%), of the subjects never went to formal school. More than two-thirds (68.1%) of the patients were currently or formerly married **(Table 1)**.

Table 1: Baseline characteristics of PLHIV who were enrolled for chronic HIV care at selected government health facilities in Afar Regional State, northeast Ethiopia from 2010-2011

Characteristics	Frequency	Percent (%)
Age (years)		
15-25	55	12.2
26-34	242	53.7
35-44	119	26.3
≥45	35	7.8
Sex		
Male	184	40.8
Female	267	59.2
Marital status		
Single	144	31.9
Married	200	44.3
Divorced	77	17.1
Widowed	30	6.7
Residence		
Urban	410	90.9
Rural	41	9.1
Religion		
Muslim	275	61.0
Orthodox	165	36.6
Others	11	2.4
Educational status		
illiterate	212	47.0
Primary school	177	39.2
Above secondary	62	13.8
Family size		
1-3	216	47.9
4-5	159	35.3
>5	76	16.8
Occupation		
Self-employed	234	51.9
Governmental employed	45	10.0
Non-employed	172	38.1
Substance use		
Yes	130	28.8
No	321	71.2
Type of substance used		
Tobacco	14	5.0
Alcohol	26	20.0
Both tobacco and alcohol	90	75.0

Clinical characteristics of PLHIV

Out of the total 451 study participants with complete information for analysis, more than half (53.4%) had a baseline WHO clinical stage III and IV. The majority, 366 (81.2%), of the participants were enrolled with working functional status. The baseline median CD4 cell count was 285cell/µl with IQR of 178-383 ell/µl at the time of enrollment. Almost half, 218 (48.3%), of the participants were enrolled with BMI less than18.5 kg/m2, whereas more than half, 270(59.9%), of the study subjects had a baseline hemoglobin level below 12.5g/dl. During the five year retrospective follow up, most, 413(91.8%), of the participants were provided with CPT treatment, while only 94(20.8%) received IPT**.** Similarly, more than one-third (40.6% and 37%, respectively) of the respondents were initiated into ART therapy based on the patients' WHO clinical stage and CD4 cell count. More than one-third (37.7%) of the HIV/AIDS positive people took a combination of TDF, 3TC and EFV; likewise, one-fifth, 110(24.4%), of the patients took AZT, 3TC, and EFV. Another one-fifth, 96 (21.3%), of the patients changed their initial regimen, 92 due to substitution, 4 due to switching to second line treatment for HIV. Out of the 96 HIV/AIDS patients who changed their initial regimen, side effect and the development of TB were the major reasons for 50(52.08%) and 29(30.2%), respectively.(**Table 2).**

Table 2: Clinical characteristics of PLHIV on chronic HIV care at selected government health facilities of Afar Regional State, July 2010 to May 2015

variables	Frequency	Percent (%)
On ART		
Yes	215	47.7
No	236	52.3
WHO clinical stage		
I	62	14.1
II	138	31.3
III	172	39.0
IV	69	15.6
Functional status at baseline		
Working	366	81.2
Ambulatory	74	16.4
Bedridden	11	2.4
CD4 cell count (cell/ul)		
<100	44	9.8
100-200	124	27.5
201-349	125	27.7
>350	158	35.0
BMI (kg/m2)		
<18.5	218	51.7
≥18.5	203	48.3

Hgb level (g/dl)		
<12.5	270	59.8
≥12.5	181	40.2
CPT use		
Yes	413	91.6
No	38	8.4
IPT use		
Yes	94	20.8
No	357	79.2
Initial regimen		
d4t-3TC-NVP	65	14.4
AZT-3TC-EFV	89	19.7
AZT-3TC-NVP	110	24.4
TDF-3TC-EFV	170	37.7
Others	17	3.8
History of TB		
Yes	74	16.4
No	377	83.6
Opportunistic infection (OI)		
Yes	34	7.5
No	417	92.5
Chronic illness		
Yes	35	7.8
No	416	92.2
Regimen change		
To First line	92	20.4
To Second line	4	0.9
Not changed	355	78.7
Reason for change		
Due to TB development	29	30.2
Due to side effect	50	52.1
Failure of treatment	4	4.2
Others	13	13.5

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation; CPT, Cotrimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efaverenze; Hgb, Hemoglobin; IPT, Izonized preventive therapy; NVP, Neverapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofevir; 3TC, Lamavudine; WHO, World Health Organization

The incidence of TB among PLHIV

Out of the total 451 HIV/AIDS patients, 119 (26.4%) developed active TB infection during the follow-up period, while 332 were censored (40 patients were transferred out; 13 died; 21 dropped out, and 258 remained till the end of follow up.) Therefore, the overall TB incidence rate in the five year retrospective data was 8.64 cases per 100 Person-years of observation. The incidence of patients diagnosed with TB at the end of one year was 4.9 per 100 person-year

observation. The cumulative proportions of patients diagnosed with TB at the end of one year, two, three, and four years was 77%, 68.4%, 34.4% and 10.1%, respectively. The sum of the whole follow-up period for all 451 HIV / AIDS infected individuals was 1377.3 Person-years of observation. The minimum and maximum follow-up observation was 0.03 and 58.8 months, respectively. The median (IQR) follow-up period was 46.74 months of observation [IQR=15.95-52.42 months]. The median survival time was 54 months. Females constituted more than half, 67 (56.3%) of the total TB disease. Three-fourths, 91 (76.47%), of the cases were pulmonary TB. The majority, 114(96%) of the TB incidents occurred in the first one year of follow-up; 46 (38.6%) of the TB incidents within the first month of follow up, and 68 (57.14%) within the first year of follow up. The incidence of TB was 105 and 14 among urban and rural dwellers, respectively. The test of equality for survival distribution for different levels of different categories was performed with Kaplan Meier, using the long rank test. The association of differences was observed among the explanatory variables, like BMI and IPT. Baseline BMI had a significant difference for tuberculosis free survival. BMI <18.5 kg/m^2 had low TB free survival compared to those with BMI >18.5 kg/m^2 with the overall comparison result long rank of p-value $p<0.002$ and for the IPT was $p<0.0001$ which shows a significant difference of TB free survival among patients provided with IPT (Figure 2 & 3). Out of the participants who developed TB, 41(34.5%) had history of TB, and 47(39.5%) were either ambulatory or bedridden at enrollment. One hundred fifteen (96.6%) of TB cases were not provided with INH prophylactic therapy. Ninety-five (79.9%) participants with incident cases of TB were enrolled with Hgb level below12.5g/dl.

Table 3: The incidence of tuberculosis stratified by socio-demographic characteristics of PLHIV on HIV chronic care at selected government health facilities of Afar Regional State, July 2010 to May 2015

Characteristics	Total N (%)	TB incidence N (%)	Person-Years observation (PY)
Years of follow-up			
One year	88(19.5)	68(57.1)	35.07
Two years	41(9.0)	28(23.5)	54.73
Three years	32(7.0)	11(9.3)	76.66
Forth	89(19.8)	9(7.6)	322.67
Fifth	201(44.6)	3(2.5)	888.28
Age (years)			
15-25	55(12.2)	14(11.7)	158.81
26-34	242(53.7)	63(52.9)	739.05
35-44	119(26.3)	30(25.3)	384.1
≥45	35(7.8)	12(10.1)	95.45
Sex			
Male	184(40.8)	52(43.7)	536.9
Female	267(59.2)	67(56.3)	840.51
Residence			
Urban	410(90.9)	105(88.2)	1260.67
Rural	41(9.1)	14(11.8)	116.74
Marital status			
Single	144(31.9)	30(25.2)	435.14
Married	200(44.3)	52(43.7)	616.07
Divorced	77(17.1)	30(25.2)	184.5
Widowed	30(6.7)	7(7.9)	91.61
Educational status			
Illiterate	212(47.0)	55(46.2)	683.8
Primary School	177(39.3)	49 (41.2)	510.54
Secondary and above	62(13.7)	15(12.6)	183.07
Occupation			
Self-employed	234(51.8)	59(49.6)	741.68
Government-employed	45(10.1)	9(7.6)	121.45
Non- employment	172(38.1)	51(42.8)	514.28
Religion			
Muslim	275(61.0)	70(58.8)	826.69
Orthodox	165(36.6)	47(39.5)	520.89
Others	11(2.4)	2(1.7)	29.83
Family size			
1-3	216(47.9)	51(42.9)	668.68
4-5	159(35.3)	43(36.1)	484.74
>5	76(16.8)	25(21.0)	223.99
Substance use			
Yes	130(28.8)	42(35.3)	379.7
No	321(71.2)	77(64.7)	997.71

Table 4: the incidence of tuberculosis stratified by clinical characteristics of PLHIV on chronic HIV care at selected government health facilities of Afar Regional State, July 2010 to May 2015

variables	Total N (%)	TB incidence N (%)	Person –year observation (PY)
History of TB			
Yes	74(16.4)	41(34.5)	164.74
No	377(83.6)	78(65.5)	1212.67
Opportunistic infection (OI)			
Yes	34(7.5)	19(16)	85.28
No	417(92.5)	100(84)	1292.13
Chronic illness			
Yes	35(7.8)	11(9.2)	106.28
No	416(92.2)	108(90.8)	1271.13
Functional status at baseline			
Working	366(81.1)	72(60.5)	1210.84
Ambulatory	74(16.4)	39(32.8)	145.92
Bedridden	11(2.4)	8(6.7)	20.65
BMI (kg/m^2)			
<18.5	218(48.3)	75(64)	626.46
≥18.5	203(45.0)	42(36)	750.95
Hgb level (g/dl)			
<12.5	270(60.0)	95(79.8)	731.63
≥12.5	181(40.0)	24(20.2)	645.78
CD4 cell count (cell/ul)			
<100	44(9.7)	22(18.5)	84.77
100-200	124(27.5)	40(33.6)	343.72
201-349	125(27.7)	29(24.4)	384.29
≥350	158(35.0)	28(23.5)	564.63
On ART			
Yes	215 (47.7)	36 (30.3)	941.7
No	236(52.3)	83(69.7)	435.71
WHO clinical stage			
I	62(13.7)	7(6.0)	216.11
II	138(30.6)	29(24.4)	569.19
III	172(38.1)	59(49.6)	464.98
IV	69(15.3)	24(20.0)	187.13
Initial regimen			
d4t-3TC-NVP	65(14.4)	14(11.7)	223.56
AZT-3TC-EFV	89(19.7)	20(16.8)	296.28
AZT-3TC-NVP	110(24.4)	28(23.5)	349.17
TDF-3TC-EFV	170(37.7)	52(43.7)	461.71
Others	17(3.8)	5(4.3)	46.69
IPT use			
Yes	94(20.8)	4(3.4)	363.60
No	357(79.1)	115(96.6)	1013.81
CPT use			
Yes	413(91.6)	108(90.8)	1259.65
No	38(8.4)	11(9.2)	117.76

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation; CPT, Cotrimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efaverenze; Hgb, Hemoglobin; IPT, Izonized preventive therapy; NVP, Neverapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofevir; 3TC, Lamavudine; WHO, World Health Organization

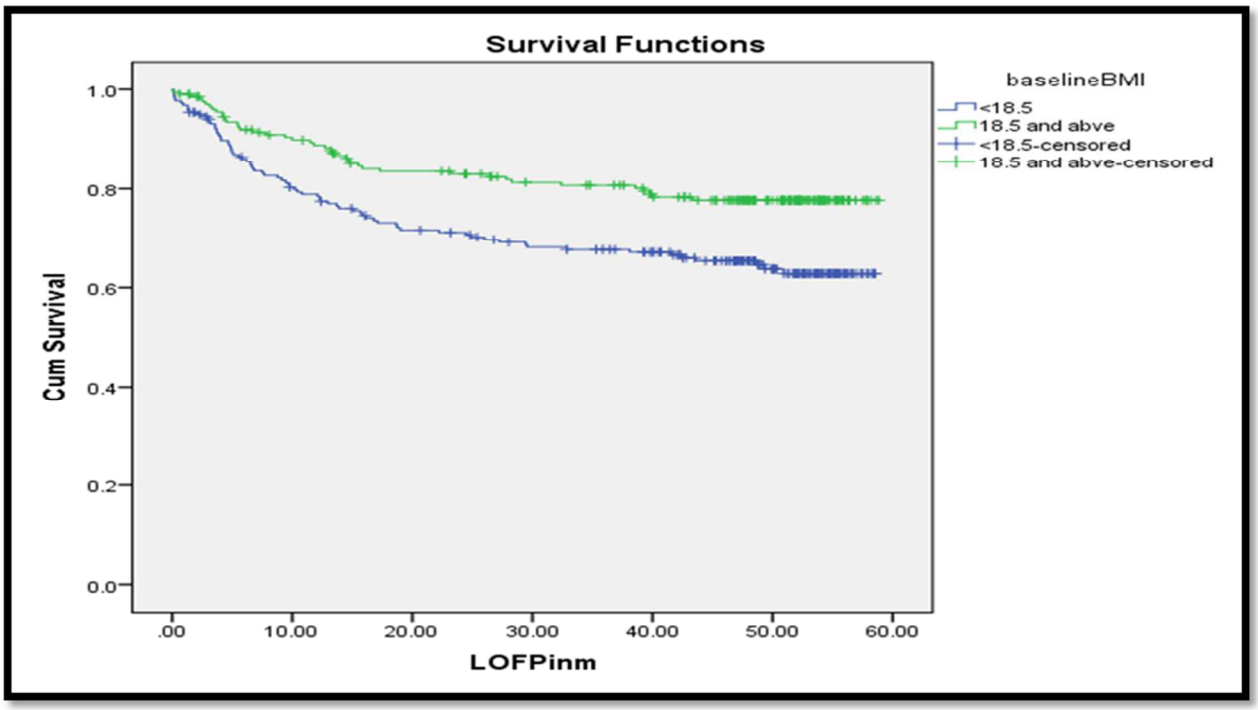

Figure 1: TB free survival probability with BMI among PLHIV in Afar governmental health facilities, Northeast Ethiopia

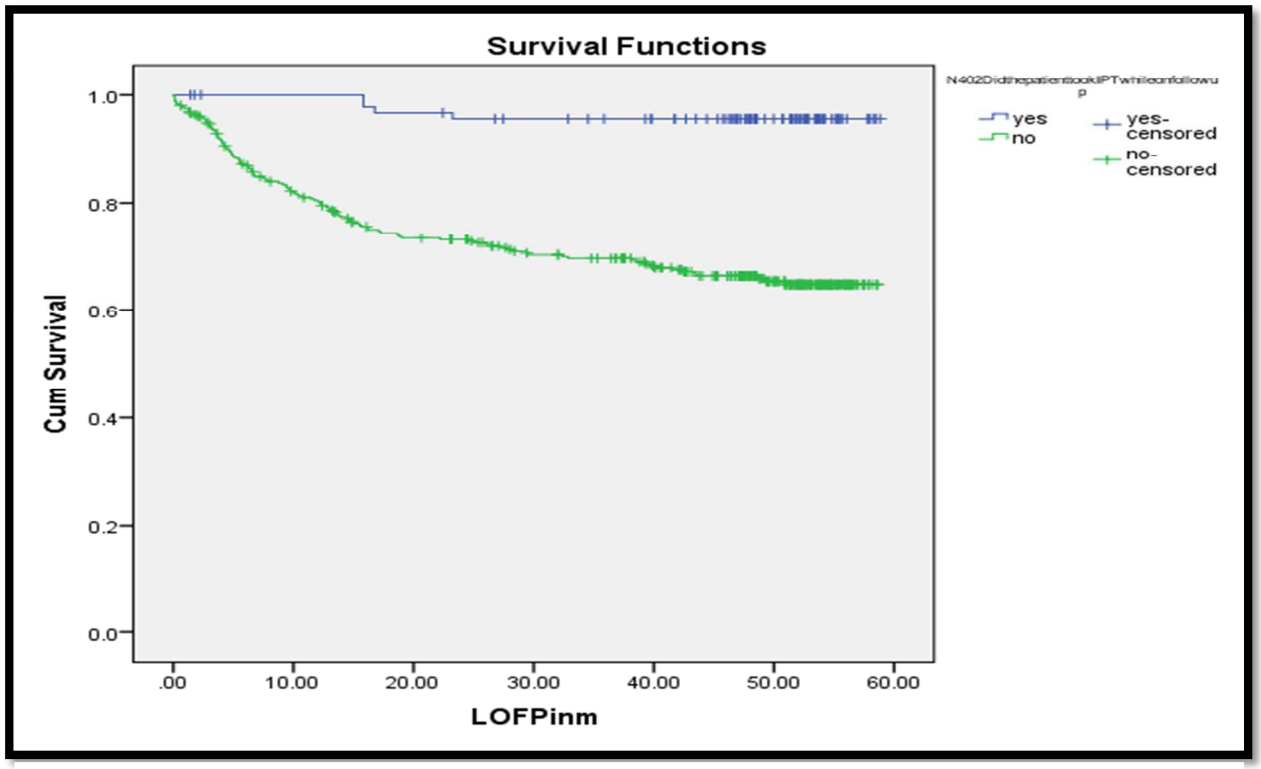

Figure 2: TB free survival probability with IPT among PLHIV in Afar Governmental health facilities, Northeast Ethiopia

Determinants of time to TB incidence

In the bivariable cox regression analysis, baseline CD4 count, WHO clinical stage, substance use, marital status, family size, opportunistic infection, history of TB, BMI, hemoglobin level, and functional status were found to be the predictors for the incidence of tuberculosis at a p-value of less than 0.2. Consequently, these variables were subjected to multivariate cox regression analysis; finally history of TB, baseline functional status, baseline hemoglobin, baseline BMI and IPT were found statistically significant determinants of TB free survival at a p-value of less than 0.05.

Accordingly, the multivariate cox regression analysis indicated that people living with HIV (PLHIV) and had history of TB were 2.32 times at higher risk of developing TB at any time compared to PLHIV who had no history of TB (AHR=2.32, 95% CI: 1.51-3.57). PLHIV who were at bed-ridden and ambulatory functional status at base-line were 2.42 times (each) at higher risk of developing TB compared with PLHIV at working functional status (AHR=2.42, 95% CI: 1.05-5.59), and (AHR=2.42 ,95% CI:1.56-3.75), respectively. Similarly, PLHIV with baseline BMI less than 18.5kg/m^2 were 1.62 times at higher risk of developing TB at any time compared with those with BMI greater than 18.5kg/m^2 (AHR=1.621, 95 % CI: 1.09-2.40). Individuals who did not take Isoniazid prophylaxis therapy (IPT) were almost seven times at higher risk of developing TB at any time compared to those who took IPT (AHR=6.96, 95% CI: 2.53-19.08).In addition, PLHIV who were enrolled with baseline hemoglobin level (Hgb) less than 12.5 g/dl were 2.54 times at higher risk of developing TB compared with those with Hgb level greater than 12.5 g/dl (AHR= 2.54, 95% CI: 1.57- 4.11) (Table-5).

Table 5: Cox regression analysis of the determinants of the incidence of tuberculosis among adult PLHIV on chronic HIV care at selected government health facilities of Afar Regional State from July 2010 to May, 2015

Variables	Survival status		Total	CHR(95%CI)	AHR(95%CI)**
	Event (TB)	Censored			
Marital status					
Single	30	114	144	1.00	1.00
Married	52	148	200	0.94 (0.41-2.15)	1.16(0.69-1.94)
Divorce	30	47	77	1.15 (0.52-2.54)	1.31(0.76-2.28)
Widowed	7	23	30	1.90 (0.83-4.33)	1.55(0.63-3.79)
Family size					
1-3	51	165	216	1.00	1.00
4-5	43	116	159	0.72 (0.83-1.16)	1.33(0.85-2.08)
>5	25	51	76	0.45(0.51-1.36)	1.54(0.90-2.63)
Substance use					
Yes	42	88	130	1.37(0.95-2.01)	1.40(0.92-2.14)
No	77	244	321	1.00	1.00
History of TB					
Yes	41	33	74	3.47(2.38-5.07)	2.32(1.51-3.57)**
No	78	299	377	1.00	1.00
Opportunistic infection (OI)					
Yes	19	15	34	2.62(1.60,4.27)	1.27(0.72-2.23)
No	100	317	417	1.00	1.00
Functional status					
Working	72	294	366	1.00	1.00
Ambulatory	39	35	74	0.20(0.09-0.41)	2.42(1.56-3.76)**
Bedridden	8	3	11	0.74(0.34-1.57)	2.42(1.05-5.59)**
BMI (kg/m2)					
<18.5	75	143	218	1.80(1.24-2.63)	1.62(1.09-2.39)**
≥18.5	42	161	203	1.00	1.00
WHO clinical stage					
I	7	55	62	1.00	1.00
II	29	119	138	0.28(0.12-0.65)	1.32(0.57-3.06)
III	59	113	172	0.49(0.29,0.84)	1.91(0.85-4.29)
IV	24	45	69	1.01(0.63-1.62)	1.91(0.78-4.65)
Hgb level (g/dl)					
<12.5	95	175	270	2.97(1.87-4.72	2.54(1.57-4.11)**
≥12.5	24	157	181	1.00	1.00
CD4 count (cell/ul)					
<100	22	22	44	4.12(2.35-7.22)	1.33(0.68-2.61)
100-200	40	84	124	2.13(1.31-3.46)	1.56(0.89-2.73)
201-349	29	96	125	1.44(0.85-2.42)	0.93(0.53-1.62)
≥350	28	130	158	1.00	1.00
IPT					
Yes	4	90	94	1.00	1.00
No	115	242	357	0.11(0.03-0.28)	6.96(2.53-19.08)**

** Variable significant at p-value less than 0.05

AHR, Adjusted Hazard Ratio; BMI, Body mass index; CD4, Cluster of differentiation; CHR, Crude Hazard Ratio; Hgb, Hemoglobin; IPT, Izonized preventive therapy; OI, Opportunistic Infection; TB, Tuberculosis; WHO, World Health Organization

Discussion

TB and HIV remain the major public health problems in many parts of the world. Ethiopia is among the TB high burden countries with an estimated annual incidence of 211cases per 100,000 people and a prevalence of 224 cases per 100,000 [29].TB is the most common cause of morbidity and mortality among PLHIV. HIV infection increases the risk of TB, and it is estimated that HIV infected individuals are 20-37 times at greater risk to developing TB in their lifetime compared to non-infected individuals [30, 31].

In this study, the overall incidence of TB among PLHIV was 8.64 cases per 100 person-year (PY) observation. This finding is similar to findings reported from Gondar and Assela, Ethiopia, which is 7 cases and 7.9 cases per 100 PY observations [32, 33]. Similarly, the finding is consistent with that of a study in Tanzania and other Sub-Saharan countries which ranged from 7.6-8.2 per 100 PY [34, 35]. However, the incidence density of TB in this study is higher compared with those of studies conducted in Korea, Israel, and Malaysia [36-38]. The lower incidence of TB in the latter studies compared with this one might be due to the availability of better preventive, diagnostic, and treatment setups and strategies for controlling TB in such countries when compared with our study setting. In addition, low health care coverage, a high burden of HIV, and the fact that the study setting is unprivileged might explain the difference. Furthermore, late enrollment at health facilities due to late presentation of HIV infected people at health facilities increases the progression of latent infection to active TB after HIV chronic care. It was noted that individuals with late presentation might get new infections or IRIS after initiation into HAART, and IRIS related TB is commonly seen within the first six months of initiation into HAART[39].

Out of the determinants of the incidence of TB infection in the multivariate cox regression analysis, the study revealed that history of TB, not using IPT, bedridden and ambulatory baseline functional status, low hemoglobin level, and low BMI at baseline were found to be predictors of the incidence of TB. Individuals who had history of TB had greater risk of developing TB

compared with those who had no history of TB treatment. Poor compliance for anti-TB treatment at first episode, reactivation or re-infection of individuals with the existing diminished immunity might be the reasons for higher incidence of TB among individuals with history of TB infection. This finding is consistent with those of studies conducted in Uganda, Malaysia, and Israel [37, 38, 40].

PLHIV who did not take Isoniazid prophylaxis therapy (IPT) were found to be the predictors of TB incidence. Individuals who did not take Isoniazid prophylaxis therapy (IPT) were almost seven times at higher risk of acquiring TB at any time compared to those who took IPT (AHR=6.96, 95% CI: 2.53-19.08). This might be due to the role of IPT in reducing the incidence of TB among people living with HIV. However, this fact, poor uptake, ambiguity, and fear of drug resistance might contribute to no-IPT use. The finding is consistent with those of studies in Ethiopia, South Africa, and Brazil [41-43].

Similarly, in this study, patients' functional status at baseline was found to be the predictor for TB incidence. Patients' ambulatory and bedridden functional status at baseline were 2.42 times at higher risk of developing TB compared with individuals with working functional status at baseline. This might be due to the fact that debilitated patients will be prone to malnutrition and lack of physical activity exposes them to many diseases, including TB. This finding is in line with those of other studies conducted in northwest Ethiopia [32].

Out of the anthropometric variables, HIV patients with Body Mass Index (BMI) <18.5 kg/m^2 at baseline were 1.62 times at higher risk of developing TB compared to individuals with BMI≥18.5 kg/m^2 at base line. This finding was consistent with that of a study done in Tanzania[44], Ethiopia, and South Africa [34, 45]. The possible explanations might be that a low BMI category is a proxy indicator for malnutrition, and malnutrition in HIV patients is associated with increased catabolic activity, infection, loss of appetite, and decreased intake, which further increase the risk of developing opportunistic infections, such as tuberculosis.

Similarly, this study found that patients with Hgb level of <10 and 10-12.5 at base-line were 2.00 and 2.54 times at higher risk of developing TB than those with Hgb level >12.5 at base-line. Hematologic complications were risk factors for the incidence of TB among PLHIV. This finding is in line with those of studies conducted in Ethiopia, Uganda, Tanzania, and South

Africa [44-47]. The Possible explanation might be malnutrition, side effects of medications, opportunistic infections, and advanced stage of the disease. Undiagnosed TB could explain low Hgb level at early enrollment. Variables like CD4 cell count and WHO clinical stage were not independently associated in this study.

Limitation of the study

Though the study did its best to indicate the incidence and predictors of tuberculosis among PLHIV using a five-year retrospective data, it is not free from limitations. The retrospective nature of the study limited the inclusion of all possible factors that could affect the incidence of tuberculosis. Variables such as housing condition and household income were some of the plausible factors that were not measured in this study.

Conclusion

The overall incidence of TB among PLHIV was found to be comparable with similar studies in Ethiopia. However, it was higher in the first year of follow-up. HIV infected individuals with history of TB, not using IPT, base-line BMI<18.5kg/m^2, ambulatory and bedridden functional status, and having baseline Hgb<12.5g/dl were the determinants of the incidence of TB among PLHIV. Therefore, attention to PLHIV and prompt diagnosis and treatment of TB is recommended. Furthermore, prospective studies need to include all factors that influence the risk of TB among PLHIV.

List of abbreviations

AHR, Adjusted hazard ratio; AIDS, Acquired immune deficiency syndrome; ART, Anti-Retroviral Therapy; BMI, Body mass index; CD4, cluster differentiation; CI, Confidence interval; CPT, Cotrimoxazole prophylaxis therapy; EDHS, Ethiopian Demographic health survey; HIV, Human immune deficiency; HAART, Highly active anti retro viral therapy; Hgb, Hemoglobin; INH, Isoniazid; IQR, Inter quartile range; IPT, Isoniazid prophylaxis therapy; IRIS, Immune reconstitution inflammatory syndrome; PLHIV/AIDS, People living with HIV/AIDS; PY, person-year observation; TB, tuberculosis; WHO, World health organization

Competing interests

The authors declare that they have no conflict of interest.

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No specific fund was obtained for this study

Data sharing statement

All data supporting our findings will be shared up on the request.

Authors' contributions

AA, DM and MKY involved in the conception, design, data collection, analysis and report writing. DM, AMS, FB, and MKY assisted with the design, approved the proposal with some revisions, participated in data analysis and manuscript preparation. All authors read and approved the final manuscript.

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The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	The study design in the title is indicated in page-1 and the abstract is found on page-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	The introduction section is found on page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	The objective of the study is stated on page 5 line 13-14		
Methods					
Study Design	4	Present key elements of study design early in the paper	Study design in the method section is found on page 5 line no 17.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure,	Study setting is located on page 5 line 16.		

		follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Study population and eligibility criteria is found on page 6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Study variables and measurement is located on page 6 line 11.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Data collection tool and procedure is located on page7 line 18		

Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at	Sample size calculation and procedure is located on page 7 line 7		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Data processing and analysis is found on page 7 line 27		
Data access and cleaning methods		..	Data processing and analysis is found on page 7 line 27	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Report on the number of participants is located on page 8 line 19	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Descriptive data is located from page 8 to 10		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures	The outcome of the study is located on page 11		

		of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	The main results including 95% confidence limit is reported from page 17 to 18		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	The discussion section is found on page 19		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	The limitation of the study is located on page 21 line 5	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	The conclusion section is found on page 21 line 11		

		analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Regarding the generalizability, since the study was conducted in the setting where more than 75 of HIV/AIDS peoples are enrolled we can generalize the finding to northeast Ethiopia		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding information is located on page 22		
Accessibility of protocol, raw data, and programming code			Regarding data sharing statement, it is located on page 22. And it will be shared up on the request.	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Incidence and determinants of TB infection among adult HIV-infected patients attending HIV care in Northeast Ethiopia: a retrospective cohort study

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Incidence and determinants of TB infection among adult HIV-infected patients attending HIV care in Northeast Ethiopia: a retrospective cohort study

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Abstract

Objective: This study assessed the incidence of tuberculosis and its predictors among adults living with HIV/AIDS in government health facilities of northeast Ethiopia.

Setting: A five year retrospective cohort study was conducted from May to June 2015 on 451 adult HIV/AIDS infected individuals who enrolled in the chronic HIV Care Clinic of government health facilities of northeast Ethiopia.

Participants: A total of 451 HIV infected adults who newly enrolled in the chronic adult HIV Care Clinic from July 1, 2010 with complete information were followed until May 2015.

Primary outcome measure: The primary outcome was the proportion of patients diagnosed with TB or TB incidence rate.

Secondary outcome measure: The incidence of TB was investigated in relation to years of follow-up

Results: A total of 451 charts with complete information were followed for 1377.41 Person-Years (PY) of observation. The overall incidence density of tuberculosis was 8.6 per 100 person-year observation. Previous TB disease (AHR 3.65, 95% CI 1.97-6.73), being bedridden (AHR 5.45, 95% CI 1.16-25.49), being underweight (BMI<18.5kg/m^2) (AHR 2.53, 95 % CI 1.27-5.05), taking isoniazid preventive therapy (IPT) (AHR 0.14, 95% CI 0.05-0.39), hemoglobin below 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93), being in WHO clinical stage III and IV (AHR 2.84, 95% CI 1.11, 7.27), and (AHR 3.07, 95% CI 1.08, 8.75), respectively, were significant for the incidence of tuberculosis.

Conclusion: The incidence of TB among adults living with HIV/AIDS in the first three years of follow-up was higher compared with that of subsequent years. Previous TB disease, not receiving IPT, low BMI, low hemoglobin level, being in advanced WHO clinical stage, and bedridden condition were determinants of the incidence of tuberculosis. Therefore, addressing the significant predictors and improving TB/HIV collaborative activities should be strengthened in the study setting.

Strengths and limitations of this study

- The study which involved a five-year follow up covered longer time than other similar studies and is expected to show the long term impact of HIV on TB.
- The study attempted to show the incidence of TB and its predictors among people living with HIV (PLHIV) using a five-year retrospective data.
- The retrospective nature of the method prevented the inclusion of all possible factors that affect the incidence of tuberculosis.
- Some participants whose data were incomplete were excluded from the study because if such patients had TB they would undermine the findings of the study.
- Variables such as housing condition and household income were some of the plausible factors that were not measured in this study.
- Culture confirmation was not performed during the study period.
- Inability to address TB contacts (other family member/co-inhabitant with TB) is the limitation of the study. The authors didn't address this variable because it was not easy to find it in the study.
- Since the study was conducted in a single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Introduction

TB is an infectious disease caused by bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB), but it can also affect other sites (extra pulmonary TB) and has remained a major global health problem. In 2015, Tuberculosis (TB) was one of the top 10 causes of death worldwide and the leading cause of death among HIV positive people, ranking above HIV/AIDS as one of the leading causes of death from infectious diseases (1). Out of the 1.4 million TB-caused deaths reported in 2015, 0.4 million occurred to HIV positive TB patients. Globally, it was estimated that there were 10.4 million TB cases, including 1.2 million among HIV positive people (1).

Globally, nearly 78 million people have contracted HIV infection since the beginning of the pandemic, and close to 39 million died of AIDS related causes; TB was responsible for twenty-five percent of these deaths (2). According to the World Health Organization (WHO) 2014 report, there were an estimated 1.1 million cases of TB co-infected with HIV (3), where the majority (90%) of the TB-HIV co-infected people were living in resource limited settings like Ethiopia (4-6). In the African region that has the highest TB/HIV burden; three-out of four TB patients knew their HIV status. In fact, 70% of the TB patients known to be living with HIV in 2013 were started on antiretroviral therapy (ART). Sub-Saharan Africa is among the regions highly hit by the HIV epidemic, covering more than three-quarters (79%) of the burden of TB-HIV co-infections (7).

In Ethiopia, TB remains one of the leading causes of mortality and the third major cause of hospital admissions. In the last ten years, the number of new cases has increased from 55,000 to 100,000, and the rise in the number of tuberculosis cases has been due to the rapid spread of HIV infection. According to the 2011 Ethiopian Demographic and Health Survey (EDHS) report, the average prevalence of HIV in Ethiopia was 1.5%, while it was 1.8% in where the study was conducted. Similarly, it was reported that the prevalence of TB was 211 per 100,000 of the population (8), and the global TB report indicated that Ethiopia ranked 10th among 22 TB high burden countries. Moreover, Ethiopia is one of the high TB/HIV burden countries, and the prevalence of TB/HIV co-infection was 15% in 2012 (6, 7). TB/HIV co-infection which constitutes an immense burden in the health system in the country is associated with diagnostic and therapeutic challenges. The dual epidemics have drained resources and overburdened the

limited health work-force (9). Hence, the Ministry of Health designed a strategy to increase the percentage of TB patients tested for HIV and vice versa. As a result, the percentage of TB patients tested for HIV increased from 16 percent in 2007 to 92 percent in 2012, and the proportion of HIV patients screened for TB from 25 percent in 2007 to 92 percent in 2012 (10). Though HIV increases the risk of developing TB, it is not the only determinant for developing it. Various reports indicated that socio-demographic (11, 12), clinical (13, 14), life style (14, 15) and environmental (16) factors were some of the determinants of the incidence of TB infection among HIV positive individuals. Among the clinical factors, low cluster of differentiation 4 (CD4 count) (17-21), low hemoglobin level, diabetes and other opportunistic infections, and functional status showed significant associations with the incidence of TB (20, 22-24). However, Isoniazid Preventive Therapy (IPT), Antiretroviral Therapy (ART), and Co-trimoxazole Preventive Therapy (CPT) treatments reduce the risk of TB infection among HIV positive individuals (23, 25, 26). In resource limited countries such as Ethiopia, where there is poor access to health care, very few studies are conducted on the determinants of the incidence of TB among HIV infected people. As a matter of fact, it is important to know the variables which are the risk factors to better understand the etiology of HIV/TB co-infection in the region. This can contribute to the development of interventions to reduce risks. Therefore, this study assessed the incidence of TB and its determinants among HIV positive people in northeast Ethiopia. As a second outcome, the study considered the incidence of TB in relation to years of follow-up.

Methods

Study design and setting

A five year retrospective cohort study was conducted on HIV positive patients attending the chronic HIV care clinics in selected government health facilities of the Afar Regional State, northwest Ethiopia from July 2010 to June 2011. The region is located in the north-eastern part of Ethiopia and has a total population of 1,678,000 of whom only 289,000 live in urban and semi-urban areas (27). In the region, there are four hospitals, 40 health centers, and 15 private clinics providing health services. When HIV care service was first introduced to the region in 2006, 15 public health institutions provided chronic HIV care and support to around more than 4,000 people living with HIV (PLHIV). Two health centers (Awash, and Samara) and three hospitals (Asayta, Abala, and Dubti General) were selected based on the availability of TB/HIV

clients. These health institutions were providing chronic HIV care and follow up to TB to about 85% of the patients living with HIV in the region.

Study population and eligibility criteria

All HIV/AIDS patients aged 15 years and above and newly enrolled into HIV care in selected government health facilities of Afar Region from July 2010 to June 2011 were the population under study. These individuals, who enrolled into HIV care from July 2010 to June, 2011 were followed for five years, until May 2015. A total of 503 people living with HIV were registered during the period July 2010 to June 2011. Individuals with incomplete information, like missing the date of enrollment, outcome of interest, and follow-up data were excluded from the study. However, individuals' chart deleted for analysis were compared to the study groups and showed no significant baseline demographic characteristics. In addition, those who died or were lost to follow-up were considered as censored.

Measurements and study variables

The outcome variable in this study was the incidence rate of TB co-infection among HIV positive patients. An event of an incidence of TB in this study was considered as any form of TB that was not only diagnosed clinically or radio-graphically but also confirmed by laboratory examinations or by patients who have empirically started anti-TB treatment after enrollment. Patients taking anti-tuberculosis treatment at the time of enrollment were excluded from the study. TB was diagnosed using microscopic examinations of three sputum samples, chest x-ray, and fine needle aspiration of lymphadenopathy. Culture confirmation was not available in the study areas during the study period. When an individual became diagnosed with active TB, treatment was given based on the National TB Program, which was 8 months of treatment (currently 6 months). HIV positive individuals who were lost to follow-up, transferred, died, and not diagnosed for TB until the end of the follow-up period were considered as censored. Study variables, including socio-demographic and economic characteristics, such as age, sex, educational status, employment status, residence, religion, family size, marital status; and clinical characteristics, such as WHO clinical stage, baseline CD4 count, functional status, and history of TB along with body mass index (BMI) and hemoglobin level were reviewed. Functional status was measured at baseline, and a person was categorized as working, if "he/she was able to perform usual work in or out of the house" and bedridden if "he/she was not able to perform activities of daily living". CPT prophylaxis in this study was defined as a patient who took co-

trimaxazole for longer than one month for a prophylaxis purpose. Isoniazid preventive therapy (IPT) use in this study was defined as a patient who took IPT for at least 3 months. Substance use in this study was referred to as use of at least one of the substances (alcohol, khat, cigarettes, and illicit drugs) in an individual's life time to alter the mood or behavior. Illicit drugs were defined as the use of psychoactive substances, like hashish, cannabis, and heroin, for which the production, sale, or use is prohibited.

Sample size and sampling procedure

All HIV/AIDS patients aged 15 years and above and enrolled newly into HIV care from July 2010 to June 2011 were the population under study. Sample size was calculated using the single proportion formula, considering the following assumptions: 17% prevalence of TB among HIV positive people in Jimma, Ethiopia (28), 95% level of confidence, 3.5 margin of error, and 3.3% expected incomplete record(29). Finally, the minimum sample size of 458 was obtained. Thus, there were 503 PLHIV registered in the selected health facilities of chronic HIV care clinics, all of the 503 records were included in the study.

In Afar Region, where the study was conducted, there were four hospitals, 40 health centers, and 15 private clinics providing health services to the community. Out of these health facilities, two health centers (Awash and Samara), and three hospitals (Asayta, Abala and Dubti General) were selected based on client flow and availability of TB and HIV follow-up services. In these selected health facilities, 503 HIV positive people were newly registered from July 2010 to June 2011. However, people living with HIV and registered in health facilities from July 2010 to June 2011 and had complete information were followed until May 2015.

Data collection tool and procedure

Data were collected through chart reviewing, using patient chart data extraction format by nurses who took training on ART. All records of HIV/AIDS patients between July 2010 and May 2015 were considered. Charts were retrieved by using patient medical record numbers and ART registration numbers found on the database of the selected health facilities. Forms used for laboratory request, TB records, ART intake, and patient cards were reviewed. Data quality was assured by using a pretested questionnaire and trained data collectors. Data completeness and consistency was checked by supervisors. The data clerk and case managers assisted the data collectors by identifying charts.

Data Processing and Analysis

Extracted data were checked for completeness, coded, entered, and cleaned into EPI-INFO version 7 and exported to SPSS version 20.0 software for further analysis. Statistical summary measures and incidence density were calculated. Descriptive statistics were used to characterize the socio-demographic and clinical variables. The event of interest was TB incidence. The incidence of TB (measured by incidence rate and incidence density rate) was stratified by socio-demographic and clinical variables. The Kaplan-Meier estimates were used to describe time to event distributions. Log-rank tests were used to compare time-to-event across the different categories. Time-to-event data that the study considered and survival analysis were carried out, the cox proportional hazards model was fitted, and a life table was used to estimate cumulative probabilities. Bi-variable and multivariate cox regression model was used to identify the predictors of the incidence of TB. Variables with p-value less than 0.2 in the bi-variable analysis were considered for the multivariate cox proportional hazard model. A 95% confidence interval of hazard ratio (HR) was computed and variables with less than 0.05 p-values in the multivariate cox proportional hazards model were taken as significant predictors for the outcome variable. Moreover, basic assumptions of cox proportional hazard model were checked using the Schoenfield residuals test.

Ethical consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Public Health, the University of Gondar. A letter of permission was obtained from the Afar Regional Health Bueuro (ARHO), and a written permission letter was sent to each selected health facilities. In addition, confidentiality was maintained by using only unique identification codes rather than patient names and identifications.

Results

Socio-demographic and clinical characteristics of PLHIV

A total of 451 records of PLHIV enrolled at health facilities from July 1, 2010 to June 30, 2011 were reviewed and followed until May 2015. The charts of 451 HIV/AIDS patients with complete information were analyzed in the study, while 52 charts were excluded from the analysis because they did not contain complete information (**Figure-1**). Out of the 451 patients

that remained in the analysis, more than half, 267(59.2%), were females and more than half, 242 (53.7%) were aged 26-34 years. The mean age (±SD) of the patients was 32.6(±7.5) years. Most of the respondents, 410 (90.9%), were urban residents, and 275 (61.0%) were Muslims **(Table 1)**.

Almost half, 234 (51.9%), of the participants were self-employed. Only 76 (16.9%) of the patients had more than 5 family members. Almost half, 212 (47%), of the subjects never went to formal school. More than two-thirds (68.1%) of the patients were currently or formerly married Of the 130 (28.8%) patients recorded as substance users, 14 (5.0%) were tobacco users, 26 (20.0%) alcohol consumers, and 90 (75.0%) were using both of these **(Table 1)**.

Out of the total 451 study participants with complete information for analysis, more than half (45.4%) had a baseline WHO clinical stage I and II. The majority, 440 (97.6%), of the participants were enrolled with working functional status. Almost half, 218 (51.7%), of the participants were underweight (BMI less than 18.5 kg/m^2), whereas more than three-quarters, 344 (76.3%), of the study subjects were anemic (Hgb<11g/dL). During the five year retrospective follow up, most, 413 (91.6%), of the participants were provided with co-trimoxazole preventive therapy (CPT), while only 94 (20.8%) received isoniazid preventive therapy (IPT). Similarly, nearly half 215 (47.7%) of the respondents were initiated into ART therapy either on WHO clinical stage or CD4 cell count. More than one-third 170 (37.7%) of the HIV/AIDS positive people took a combination of TDF, 3TC and EFV; likewise, one-fifth, 110 (24.4%), of the patients took AZT, 3TC, and EFV. Another one-fifth, 96 (21.3%), of the patients changed their initial regimen, 92 due to substitution, and 4 due to switching to second line treatment for HIV. Out of the 96 HIV/AIDS patients who changed their initial regimen, side effect and development of TB were the major reasons for 50 (52.1%) and 29 (30.2%), respectively (**Table 1).**

Table 1: Socio-demographic and clinical characteristics of PLHIV who were enrolled for chronic HIV care at selected government health facilities in Afar Regional State, northeast Ethiopia from 2010-2011

Characteristics	Frequency	Percent (%)
Age in years (mean=32.6, SD=7.5)		
15-25	55	12.2
26-34	242	53.7
35-44	119	26.3
≥45	35	7.8
Sex		
Male	184	40.8
Female	267	59.2
Marital status		
Single	144	31.9
Married	200	44.3
Divorced	77	17.1
Widowed	30	6.7
Residence		
Urban	410	90.9
Rural	41	9.1
Religion		
Muslim	275	61.0
Orthodox	165	36.6
Others	11	2.4
Educational status		
Illiterate	212	47.0
Primary school	177	39.2
Above secondary	62	13.8
Family size		
1-3	216	47.9
4-5	159	35.3
≥5	76	16.8
Occupation		
Self-employed	234	51.9
Governmental employed	45	10.0
Non-employed	172	38.1
Substance use		
Yes	130	28.8
No	321	71.2
Type of substance used		
Tobacco	14	5.0
Alcohol	26	20.0
Both tobacco and alcohol	90	75.0
On ART		
Yes	215	47.7
No	236	52.3
WHO clinical stage		
I & II	200	45.4
III	172	39.0
IV	69	15.6

Bedridden		
No	440	97.6
Yes	11	2.4
CD4 cell count (cells/uL)		
<100	44	9.8
100-200	124	27.5
201-349	125	27.7
>350	158	35.0
BMI (kg/m^2)		
<18.5	218	51.7
>18.5	203	48.3
Hgb level (g/dL)		
<11	344	76.3
≥11	107	23.7
CPT use		
Yes	413	91.6
No	38	8.4
IPT use		
Yes	94	20.8
No	357	79.2
Initial regimen		
d4t-3TC-NVP	65	14.4
AZT-3TC-EFV	89	19.7
AZT-3TC-NVP	110	24.4
TDF-3TC-EFV	170	37.7
Others	17	3.8
Previous TB disease		
Yes	74	16.4
No	377	83.6
Opportunistic infection (OI)		
Yes	34	7.5
No	417	92.5
Chronic illness		
Yes	35	7.8
No	416	92.2
Regimen change		
To First line	92	20.4
To Second line	4	0.9
Not changed	355	78.7
Reason for change		
Due to TB development	29	30.2
Due to side effect	50	52.1
Failure of treatment	4	4.2
Others	13	13.5

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation; CPT, Cotrimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efaverenze; Hgb, Hemoglobin; IPT, "isoniazid preventive therapy; NVP, Neverapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofevir; 3TC, Lamavudine; WHO, World Health Organization

The incidence of TB stratified with socio-demographic and clinical characteristics

Out of the total 451 HIV/AIDS patients, 119 (26.4%) developed active TB infection during the follow-up period, while 332 were censored (40 patients were transferred out, 13 died, 21 lost to follow-up, and 258 remained TB-negative till the end of follow-up period) **(Figure-1)**. Therefore, the overall TB incidence rate in the five year retrospective data was 8.64 cases per 100 Person-years (PY) of observation. The incidence of patients diagnosed with TB at the end of one year was 4.9 per 100 person-year observation. The sum of the whole follow-up period for all 451 HIV/AIDS infected individuals was 1377.41 Person-years of observation. The minimum and maximum follow-up observation was 0.03 and 58.8 months, respectively. The median (IQR) follow-up period was 46.74 months of observation [IQR=15.95-52.42 months]. Females constituted more than half, 67 (56.3%) of the total TB disease. Three-quarters, 91 (76.47%), of the cases were pulmonary TB. The majority, 114 (96%) of the TB incidents occurred in the first one year of follow-up; 46 (38.6%) of the TB incidents within the first month of follow up, and 68 (57.14%) within the first year of follow up. The incidence of TB was 105 cases and 14 cases among urban and rural dwellers, respectively. The test of equality for survival distribution for different levels of different categories was performed with Kaplan Meier, using the long rank test. The cumulative probability of TB patient's survival at the end of one year, two, three, and four years was 0.77, 0.68, 0.34 and 0.10, respectively. The median survival time was 54 months (**Figure-2**). An association of differences was observed among the explanatory variables, like BMI and IPT. BMI, IPT use, WHO stage, Hgb level and bed-ridden functional status had a significant difference for tuberculosis free survival. To mention some, BMI <18.5 kg/m^2 had low TB free survival compared to those with BMI >18.5 kg/m^2 with the overall comparison result long rank of p-value p<0.002 and for the IPT was p<0.0001 which shows a significant difference of TB free survival among patients provided with IPT (**Figure 3-7**). Out of the participants who developed TB, 41 (34.5%) had previous TB disease, and 8 (6.7%) were bedridden at the time of enrollment. One hundred fifteen (96.6%) of TB cases were not given INH prophylactic therapy. Fifty (42.0%) participants with incident cases of TB were enrolled with Hgb level below11g/dL (**Table-2**).

Table 2: The incidence of tuberculosis stratified by socio-demographic and clinical characteristics of PLHIV on HIV chronic care at selected government health facilities of Afar Regional State, July 2010 to May 2015

Characteristics	Total N (%)	TB incidence N (%)	Person-Years observation (PY)
Years of follow-up (median=46.74, IQR=15.95-52.42, months)			
One year	88(19.5)	68(57.1)	35.07
Two years	41(9.0)	28(23.5)	54.73
Three years	32(7.0)	11(9.3)	76.66
Forth	89(19.8)	9(7.6)	322.67
Fifth	201(44.6)	3(2.5)	888.28
Age (years)			
15-25	55(12.2)	14(11.7)	158.81
26-34	242(53.7)	63(52.9)	739.05
35-44	119(26.3)	30(25.3)	384.1
≥45	35(7.8)	12(10.1)	95.45
Sex			
Male	184(40.8)	52(43.7)	536.9
Female	267(59.2)	67(56.3)	840.51
Residence			
Urban	410(90.9)	105(88.2)	1260.67
Rural	41(9.1)	14(11.8)	116.74
Marital status			
Single	144(31.9)	30(25.2)	435.14
Married	200(44.3)	52(43.7)	616.07
Divorced	77(17.1)	30(25.2)	184.5
Widowed	30(6.7)	7(7.9)	91.61
Educational status			
Illiterate	212(47.0)	55(46.2)	683.8
Primary School	177(39.3)	49 (41.2)	510.54
Secondary and above	62(13.7)	15(12.6)	183.07
Occupation			
Self-employed	234(51.8)	59(49.6)	741.68
Government-employed	45(10.1)	9(7.6)	121.45
Non- employment	172(38.1)	51(42.8)	514.28
Religion			
Muslim	275(61.0)	70(58.8)	826.69
Orthodox	165(36.6)	47(39.5)	520.89
Others	11(2.4)	2(1.7)	29.83
Family size			
1-3	216(47.9)	51(42.9)	668.68
4-5	159(35.3)	43(36.1)	484.74
>5	76(16.8)	25(21.0)	223.99
Substance use			
Yes	130(28.8)	42(35.3)	379.7
No	321(71.2)	77(64.7)	997.71
Previous TB disease			

Yes	74(16.4)	41(34.5)	164.74
No	377(83.6)	78(65.5)	1212.67
Opportunistic infection (OI)			
Yes	34(7.5)	19(16)	85.28
No	417(92.5)	100(84)	1292.13
Chronic illness			
Yes	35(7.8)	11(9.2)	106.28
No	416(92.2)	108(90.8)	1271.13
Bedridden			
Yes	11 (2.4)	8(6.7)	33
No	440(97.6)	111(93.3)	1356.76
BMI (kg/m2)			
<18.5	218(48.3)	75(64)	626.46
>18.5	203(45.0)	42(36)	750.95
Hgb level (g/dL)			
<11	107(23.7)	50(42.0)	233.8
≥11	344(76.3)	69(58.0)	1143.6
CD4 cell count (cells/uL)			
<100	44(9.7)	22(18.5)	84.77
100-200	124(27.5)	40(33.6)	343.72
201-349	125(27.7)	29(24.4)	384.29
>350	158(35.0)	28(23.5)	564.63
On ART			
Yes	215 (47.7)	36 (30.3)	941.7
No	236(52.3)	83(69.7)	435.71
WHO clinical stage			
I & II	210(46.6%)	36(30.3)	785.3
III	172(38.1)	59(49.6)	464.98
IV	69(15.3)	24(20.1)	187.13
Initial regimen			
d4t-3TC-NVP	65(14.4)	14(11.7)	223.56
AZT-3TC-EFV	89(19.7)	20(16.8)	296.28
AZT-3TC-NVP	110(24.4)	28(23.5)	349.17
TDF-3TC-EFV	170(37.7)	52(43.7)	461.71
Others	17(3.8)	5(4.3)	46.69
IPT use			
Yes	94(20.8)	4(3.4)	363.60
No	357(79.1)	115(96.6)	1013.81
CPT use			
Yes	413(91.6)	108(90.8)	1259.65
No	38(8.4)	11(9.2)	117.76

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation; CPT, Cotrimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efaverenze; Hgb, Hemoglobin; IPT, isoniazid preventive therapy; NVP, Neverapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofevir; 3TC, Lamavudine; WHO, World Health Organization

Determinants of TB incidence

In the bivariable cox regression analysis, marital status, family size, substance use, history of TB, baseline CD4 count, WHO clinical stage, opportunistic infection, body mass index (BMI), hemoglobin level, isoniazid preventive therapy (IPT), and functional status were found to be the predictors for the incidence of tuberculosis at a p-value of less than 0.2. Consequently, these variables were subjected to multivariate cox regression analysis; finally, previous TB disease, bed-ridden functional status, hemoglobin, BMI, IPT and advanced WHO clinical stage were found statistically significant determinants of TB free survival at a p-value of less than 0.05.

Accordingly, the multivariate cox regression analysis indicated that people living with HIV (PLHIV) and had history of TB disease were 3.65 times at higher risk of developing TB at any time compared to PLHIV who had no history of TB (AHR 3.65, 95% CI 1.97-6.73). PLHIV who were in bed-ridden functional status at base-line were 5.45 times at more risk of developing TB compared with PLHIV not in bedridden functional status (AHR 5.45, 95% CI 1.16-25.49). Similarly, PLHIV with baseline BMI less than 18.5kg/m^2 were 2.53 times at higher risk of developing TB at any time compared with those with BMI greater than 18.5kg/m^2 (AHR 2.53, 95 % CI 1.27-5.05). Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR 0.14, 95% CI 0.05-0.39). PLHIV in WHO clinical stage III and IV had a greater risk of developing TB compared with WHO stage I and II (AHR 2.84, 95% CI 1.11, 7.27), and (AHR3.07, 95% CI 1.08, 8.75), respectively. The study also revealed that the incidence of TB in the first three years of follow-up was higher when compared with the other subsequent years. In addition, PLHIV who were underweight (Hgb <11g/dL) were 2.31 times at higher risk of developing TB compared with those with Hgb level greater than 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93) (**Table-3**).

Table 3: Cox regression analysis of the determinants of the incidence of tuberculosis among adult PLHIV on chronic HIV care at selected government health facilities of Afar Regional State from July 2010 to May, 2015

Variables	Survival status		Total	CHR(95% CI)	AHR(95% CI)**
	Event (TB)	Censored			
Marital status					
Single	30	114	144	1.00	1.00
Married	52	148	200	1.34 (0.80-2.23)	1.26 (0.65-2.43)
Divorce	30	47	77	2.43 (1.32-4.46)	1.75 (0.83-3.68)
Widowed	7	23	30	1.16 (0.45-2.95)	2.42 (0.79-7.38)
Family size					
1-3	51	165	216	1.00	1.00
4-5	43	116	159	1.19 (0.75-1.92)	0.49 (0.25-1.34)
>5	25	51	76	1.58 (0.89-2.81)	0.71 (0.35-1.76)
Substance use					
Yes	42	88	130	1.51 (0.96-2.37)	1.47 (0.84-2.56)
No	77	244	321	1.00	1.00
Previous TB disease					
Yes	41	33	74	4.76 (2.83-8.03)	3.65 (1.97-6.73)**
No	78	299	377	1.00	1.00
Opportunistic infection (OI)					
Yes	19	15	34	4.02 (1.97,8.19)	2.31 (0.98-5.45)
No	100	317	417	1.00	1.00
Bedridden					
Yes	8	3	11	7.90 (2.06,30.31)	5.45 (1.16, 25.49)**
No	111	329	440	1.00	1.00
BMI (kg/m^2)					
<18.5	75	143	218	2.01(1.29-3.12)	2.53(1.27-5.05)**
≥18.5	42	161	203	1.00	1.00
Length of follow-up					
≤ 1 year	68	20	88	78.76 (36.7, 168.9)	83.76 (33.94, 206.7)**
2-3 years	39	34	73	26.57 (12.7, 55.6)	33.81(14.12, 80.96)**
4-5 years	12	278	290	1.00	1.00
WHO clinical stage					
I &II	36	174	200	1.00	1.00
III	59	113	172	2.52 (1.57-4.07)	2.84(1.11-7.27)**
IV	24	45	69	2.58 (1.40-4.75)	3.07(1.08-8.75)**
Hgb level (g/dL)					
<11	50	57	107	3.49 (2.20-5.55)	2.31(1.35-3.93)**
≥11	69	275	344	1.00	1.00
CD4 count (cells/uL)					
<100	22	22	44	4.64 (2.26-9.52)	1.14(0.46-2.82)
100-200	40	84	124	2.21 (1.27-3.85)	1.29(0.66-2.57)
201-349	29	96	125	1.40 (0.78-2.51)	0.99(0.49-1.99)
≥350	28	130	158	1.00	1.00
IPT					
Yes	4	90	94	0.09 (0.03-0.26)	0.14 (0.05, 0.39)**
No	115	242	357	1.00	1.00

** Variable significant at p-value less than 0.05

Discussion

TB and HIV remain the major public health problems in many parts of the world. Ethiopia is among the TB high burden countries with an estimated annual incidence of 211cases per 100,000 people and a prevalence of 224 cases per 100,000 (30).

In this study, the overall incidence of TB among PLHIV was 8.64 cases per 100 person-year (PY) observation. This finding is similar to those reported from Gondar and Assela, Ethiopia, which are 7 and 7.9 cases per 100 person-year (PY) observations (31, 32). Similarly, the finding is consistent with that of a study in Tanzania and other Sub-Saharan countries ranging from 7.6-8.2 per 100 person-year observation (PY) (33, 34). However, the incidence density of TB in this study is higher compared with those of studies conducted in Korea, Israel, and Malaysia (35-37). The lower incidence of TB in the latter studies compared with this one might be due to the availability of better preventive, diagnostic, and treatment setups and strategies for controlling TB in such countries when compared with our study setting. In addition, low health care coverage, a high burden of HIV, and the fact that the study setting is so unprivileged might explain the difference. Furthermore, late enrollment at health facilities due to late presentation of HIV infected people at health facilities increases the progression of latent infection to active TB after HIV chronic care. It was noted that individuals with late presentation might get new infections or IRIS after initiation into highly active antiretroviral therapy (HAART), and Immune Reconstitution Inflammatory Syndrome (IRIS) related TB is commonly seen within the first six months of initiation into HAART (38). Similarly, it was revealed that the incidence of TB is significantly associated with the length of follow-up year. It was reported that the incidence of TB decreased as the years of follow-up increased, and a higher incidence of TB was reported in the first three of follow-up years compared with the other subsequent years.

Out of the determinants of the incidence of TB infection in the multivariate cox regression analysis, the study revealed that previous TB disease, using IPT, bedridden functional status, low hemoglobin level, advanced WHO staging (III and IV), years of follow-up, and low BMI were found to be significantly associated with the incidence of TB. Individuals who had history of TB disease had greater risk of developing TB compared with those who had no history of TB treatment. Poor compliance for anti-TB treatment at the first episode, reactivation or re-infection

of individuals with the existing diminished immunity might be the reasons for higher incidence of TB among individuals with history of TB infection. This finding is consistent with those of studies conducted in Uganda, Malaysia, and Israel (36, 37, 39).

PLHIV who took Isoniazid preventive therapy (IPT) were found to be protective for the incidence of TB. Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR=0.14, 95% CI: 0.05-0.39). This might be due to the role of IPT in reducing the incidence of TB among people living with HIV. The finding is consistent with those of studies in Ethiopia, South Africa, and Brazil (40-42). In spite of this fact, poor uptake, ambiguity, and fear of drug resistance might contribute to no-IPT use.

Similarly, in this study, patients' functional status at baseline was found to be the predictor for TB incidence. Patients' bedridden functional status at baseline was 5.45 times at higher risk of developing TB compared with individuals with working functional status at baseline. This might be due to the fact that debilitated patients will be prone to malnutrition, and lack of physical activity exposes them to many diseases, including TB. This finding is in line with those of other studies conducted in Ethiopia (16, 31, 43).

Out of the anthropometric variables, HIV patients who were underweight (BMI <18.5 kg/m^2) were 2.53 times at higher risk of developing TB compared to individuals with BMI≥18.5 kg/m^2. This finding was consistent with that of a study done in Tanzania (44), Ethiopia, and South Africa (33, 45). The possible explanations might be that a low BMI category is a proxy indicator for malnutrition, and malnutrition in HIV patients is associated with increased catabolic activity, infection, loss of appetite, and decreased intake, which further increase the risk of developing opportunistic infections such as tuberculosis.

Similarly, this study found that patients with Hgb level of <11 g/dL at base-line were 2.31 times at higher risk of developing TB than those with Hgb level ≥11 at base-line. Hematologic complications were risk factors for the incidence of TB among PLHIV. This finding is similar with those of studies conducted in Ethiopia, Uganda, Tanzania, and South Africa (44-47). The possible explanation might be malnutrition, side effects of medications, opportunistic infections,

and advanced stage of the disease. Undiagnosed TB could explain low Hgb level at early enrollment.

The other important result which was found to have a significant association with the incidence of TB was advanced clinical staging (III & IV). PLHIV with advanced WHO staging (III and IV, respectively) had 2.84 and 3.07 times higher risk of developing TB compared with people with stages(I &II). The finding corresponded to that studies conducted in Nigeria (48), South Africa (49), and Gambia (50). This might be due to the fact that once patients get into late stages; the immunity protective capacity will be minimal, making them predisposed to tuberculosis infection. Something worth to mentioning as well is that TB is one of AIDS' defining factor to categorize patients into late WHO clinical staging which used HIV/AIDS clinics in Ethiopia as criteria.

Limitations of the study

Though the study did its best to indicate the incidence and predictors of tuberculosis among PLHIV using a five-year retrospective data, it is not free from limitations. The retrospective nature of the study limited the inclusion of all possible factors that could affect the incidence of tuberculosis. Variables such as housing condition and household income were some of the plausible factors that were not measured in this study. Unable to conduct *culture confirmation* (the gold standard method) is another limitation of the study. Inability to address TB contacts (other family member/co-inhabitant) is also the limitation of the study. The authors didn't address this variable because it was not easy to get it in the study type. Since the study was conducted in the single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Conclusion

The overall incidence of TB among PLHIV was found to be comparable with those of similar studies in Ethiopia. However, it was higher in the first year of follow-up. HIV infected individuals with history of TB disease, not using IPT, in underweight status (BMI<18.5kg/m^2), bedridden functional status, being anemic (Hgb<11g/dL), advanced WHO stage (III &IV), and shorter duration of follow-up were determinants of the incidence of TB among PLHIV. Therefore, our study suggested early screening and diagnosis among high risk PLHIV such as

those in bed-ridden functional status, underweight (BMI <18.5kg/m$^{2)}$, and anemic (Hgb <11g/dL). In addition, providing IPT to PLHIV without active TB and intensified TB case screening for those with advanced WHO stage is highly recommended. In addition, emphasis should be given to those with shorter follow-up period. Therefore, attention to PLHIV and prompt diagnosis and treatment of TB are recommended. Furthermore, prospective studies need to include all factors that influence the risk of TB among PLHIV. Since our study was conducted in a single region of Ethiopia, collaborative projects that can include several regions of the country is recommended to give a more balanced view of the incidence of TB and potential risk factors in HIV-infected patients.

List of abbreviations

AHR, Adjusted hazard ratio; AIDS, Acquired immune deficiency syndrome; ART, Anti-Retroviral Therapy; BMI, Body mass index; CD4, cluster differentiation 4; CI, Confidence interval; CPT, Cotrimoxazole prophylaxis therapy; EDHS, Ethiopian Demographic health survey; HIV, Human immune deficiency; HAART, Highly active anti retro viral therapy; Hgb, Hemoglobin; INH, Isoniazid; IQR, Inter quartile range; IPT, Isoniazid preventive therapy; IRIS, Immune reconstitution inflammatory syndrome; PLHIV/AIDS, People living with HIV/AIDS; PY, person-year observation; TB, tuberculosis; WHO, World health organization

Competing interests

The authors declare that they have no conflict of interest.

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No specific fund was obtained for this study

Data sharing statement

All data supporting our findings will be shared upon the request.

Authors' contributions

AA, DM and MKY involved in the conception, design, data collection, analysis and report writing. DM, AMS, FB, and MKY assisted with the design, approved the proposal with some revisions, participated in data analysis and manuscript preparation. All authors read and approved the final manuscript.

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Figure legends

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 4: Kaplan Meier survival curve of TB patients based on the WHO stage among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 5: Kaplan Meier survival curve of TB patients based on hemoglobin level among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

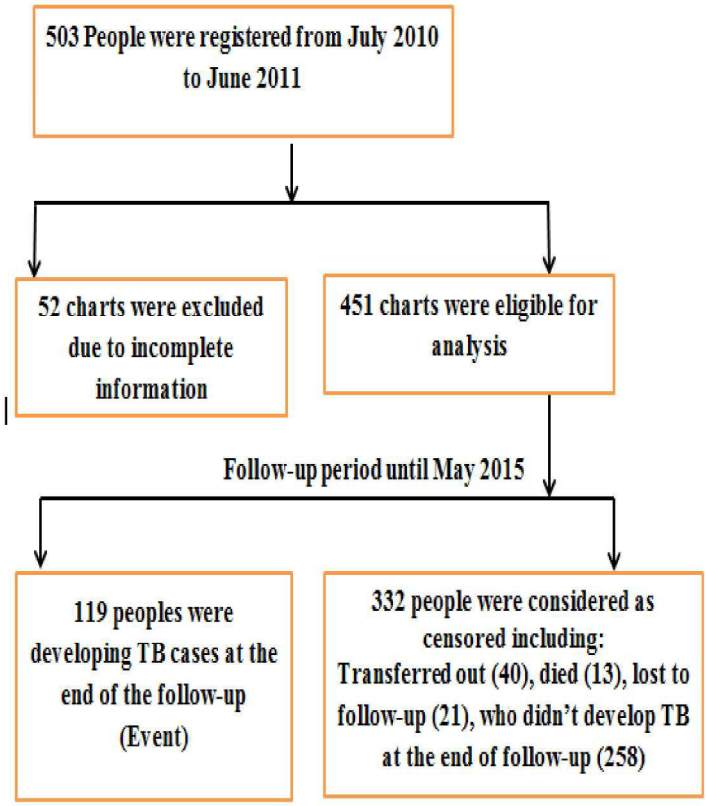

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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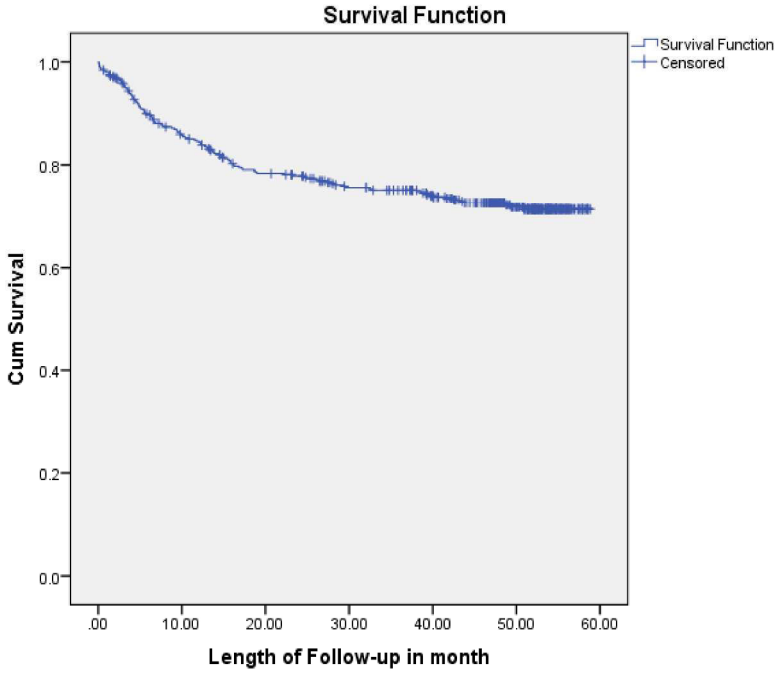

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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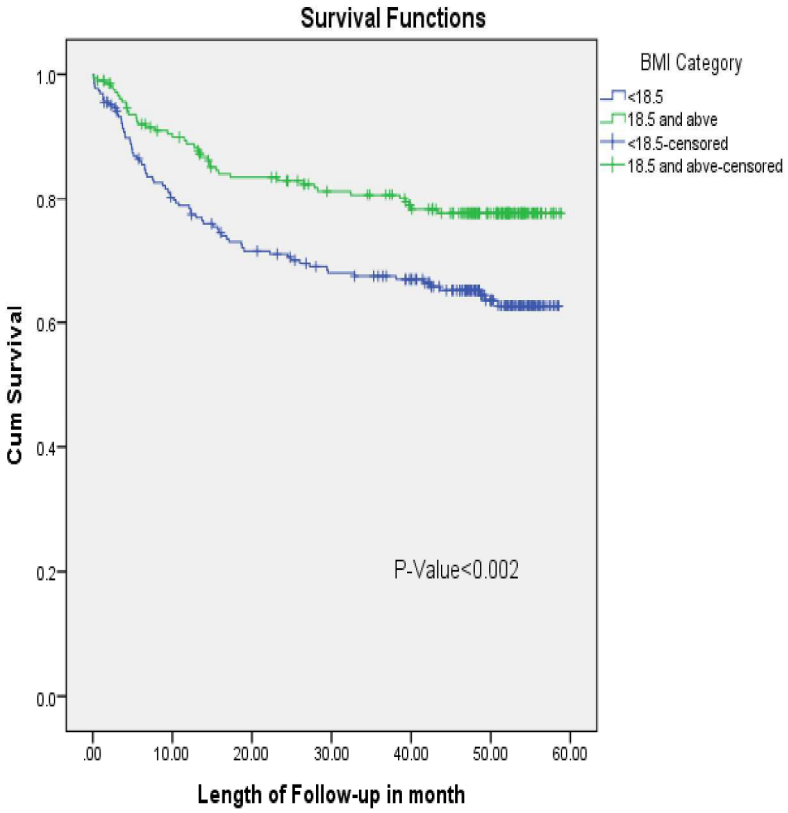

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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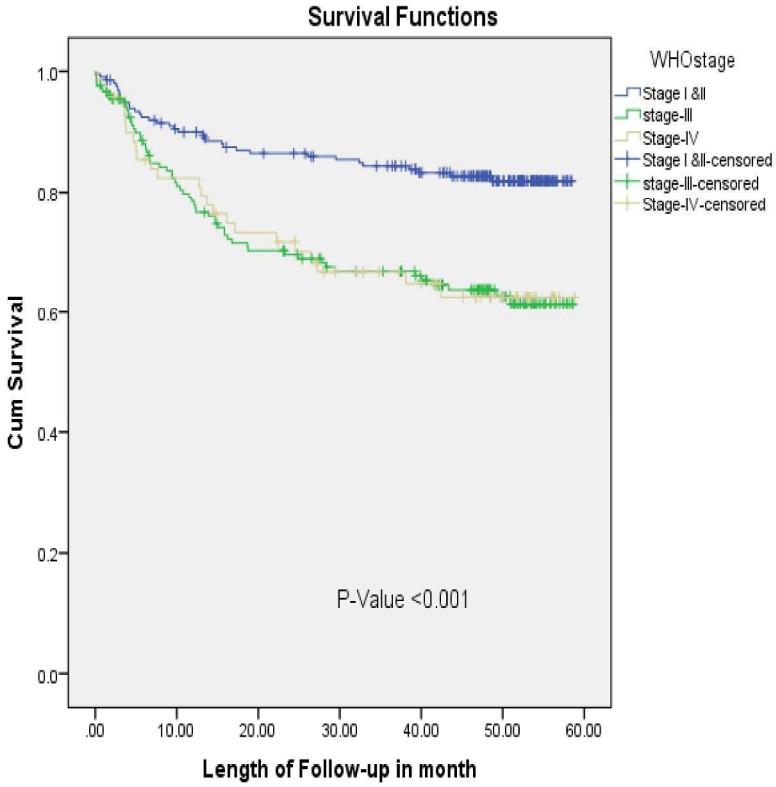

Figure 4: Kaplan Meier survival curve of TB patients based on the WHO stage among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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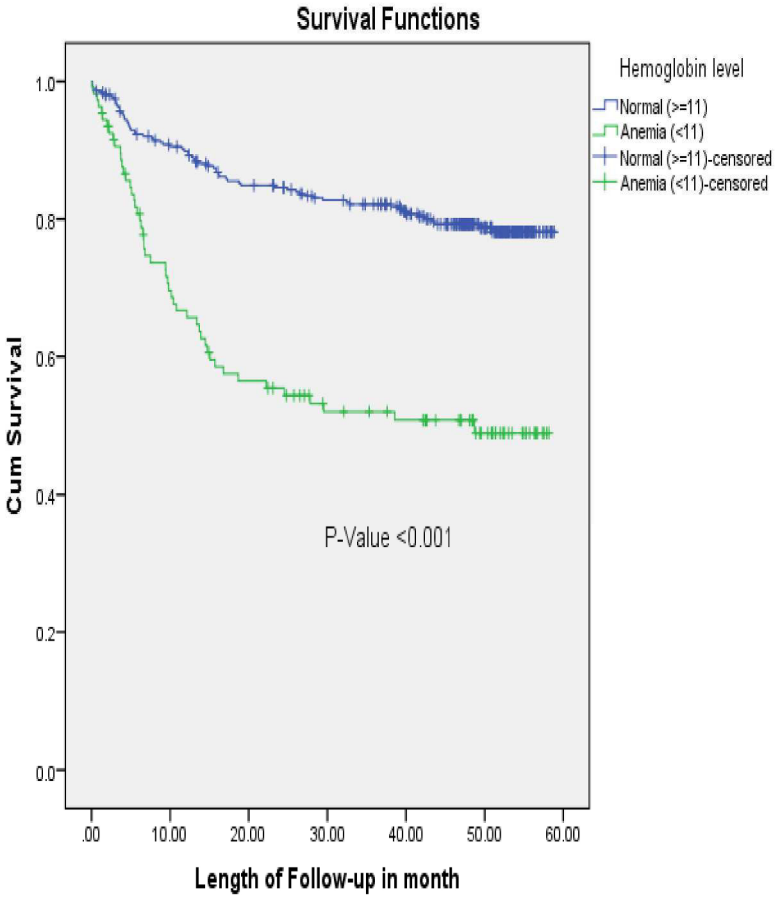

Figure 5: Kaplan Meier survival curve of TB patients based on hemoglobin level among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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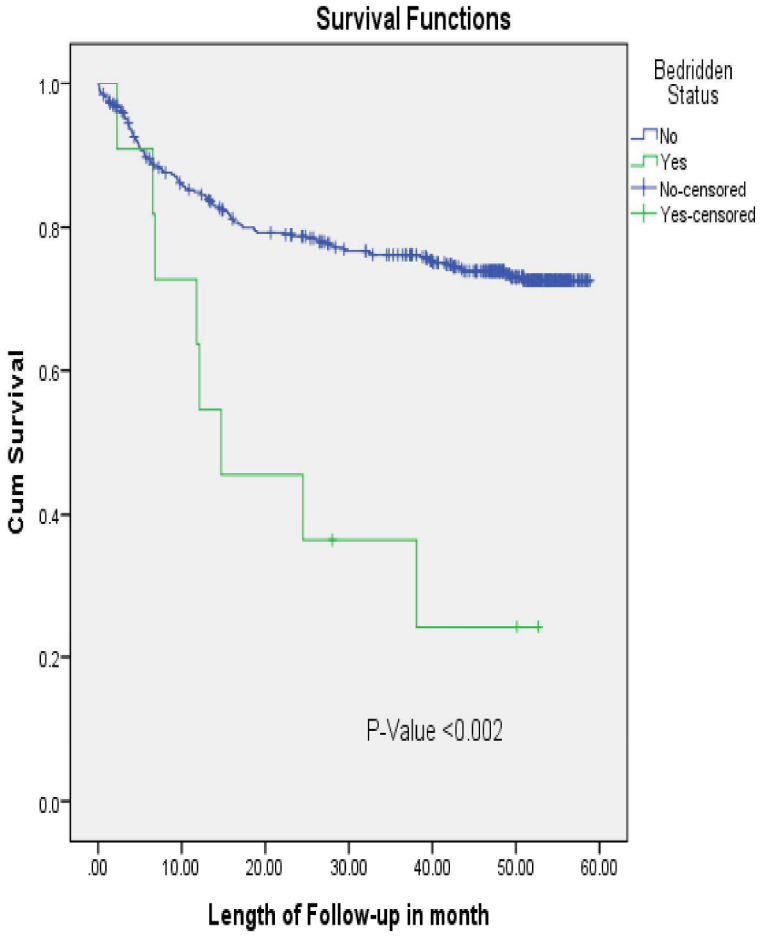

Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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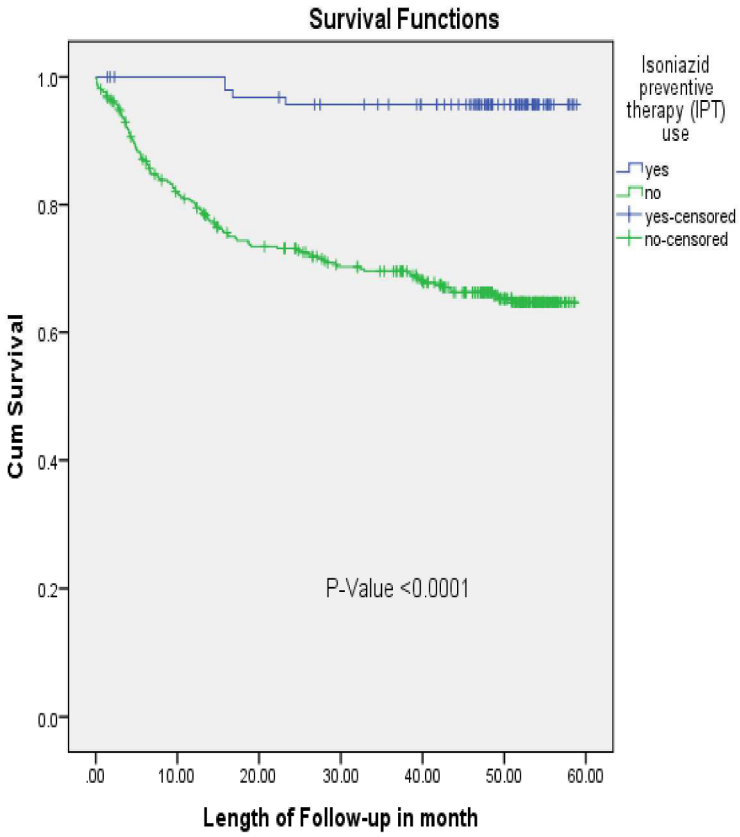

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

279x361mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	• Study design is indicated in the title and abstract sections (page 1 line-2 OR on page-2 line-4) • Abstract section is informative and is indicated in page-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	• The type of data which was retrospective cohort is given in the title and the abstract section (pages 1&2) • The geographical region (northeast Ethiopia) is mentioned in the title and abstract sections (pages 1 & 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	• Background/Introduction section is presented on page-4 • Rationale of the study is mentioned on page-5 lines 13-		

			18		
Objectives	3	State specific objectives, including any prespecified hypotheses	• Objectives of the study are indicated on page-5 lines 17-20. In addition, it is also clearly mentioned in the abstract section on page-2 lines 13-16.		
Methods					
Study Design	4	Present key elements of study design early in the paper	• Study design is found on page 5 lines 23-24.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	• Study setting is stated on page-5 line 21 to page-6 line 2.		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants	• Study population and eligibility criteria are found on page-6 lines 4-13	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a	• The methods of data collection are on page 7 • The flow diagram indicating how the study subjects are selected is presented in figure 1.

		(b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	• Measurement and study variables are presented on page-6, lines 14 to page -7 line-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	• Data collection tool and procedure is located on page-7 lines 22-30		
Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at	• Sample size calculation and procedure is described on page-7 lines 7-14		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to	• Data processing and analysis is found on page-8,		

		examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	lines 1-17		
Data access and cleaning methods		..	• Data access and cleaning is found on page-7 lines 22-27	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	• How the authors accessed data is stated in the data collection procedure (page-7) • Information on data coding, entering and cleaning is given in the data processing and analysis sub-sections (page-8, lines 1-17)
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	• The study

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	setting is on page 5 lines 21 to page 6 lines 1-2
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	• Number of participants included in this study is indicated on page-8 lines 27-28 • Flow diagram representing how study participants are presented on figure-1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	• A flow diagram indicating the eligibility of study participants for the study is presented in a graph 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	• Descriptive data, including the socio-demographic and clinical factors are located from pages 8-11		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report	• The outcome data (incidence of TB) is on pages 12-14		

		numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	• The adjusted estimates with 95% confidence interval are reported on page 16		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	None		
Discussion					
Key results	18	Summarise key results with reference to study objectives	• The discussion section is presented on pages 17-19		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	• The limitation of the study is pointed out on page 19 lines 12-22	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	• The conclusion section is on page 19 line 23 to page		

		analyses, results from similar studies, and other relevant evidence	20 lines 1-9		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Since the study was conducted in a setting where more than 85% of HIV/AIDS patients are enrolled, we can generalize the finding to northeast Ethiopia		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	• Funding information is on page 20 lines 20-21		
Accessibility of protocol, raw data, and programming code			• Data sharing statements are on page 20 lines 22-23	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	• Data collection procedure is on page-7 and data sharing statement is on page 24.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Incidence and determinants of TB infection among adult HIV patients attending HIV care in northeast Ethiopia: A retrospective cohort study

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Abstract

Objective: This study assessed the incidence of tuberculosis and its predictors among adults living with HIV/AIDS in government health facilities of northeast Ethiopia.

Setting: A five year retrospective cohort study was conducted from May to June 2015 on 451 adult HIV/AIDS infected individuals who enrolled in the HIV Care Clinics of government health facilities of northeast Ethiopia.

Participants: A total of 451 HIV infected adults who newly enrolled in the adult HIV Care Clinic from July 1, 2010 with complete information were followed until May 2015.

Primary outcome measure: The primary outcome was the proportion of patients diagnosed with TB or TB incidence rate.

Secondary outcome measure: The incidence of TB was investigated in relation to years of follow-up

Results: A total of 451 charts with complete information were followed for 1377.41 Person-Years (PY) of observation. The overall incidence density of tuberculosis was 8.6 per 100 person-year observation. Previous TB disease [Adjusted Hazard Ratio (AHR) 3.65, 95% CI 1.97-6.73], being bedridden [AHR 5.45, 95% CI 1.16-25.49], being underweight [Body Mass Index (BMI) <18.5kg/m^2) (AHR 2.53, 95 % CI 1.27-5.05)], taking isoniazid preventive therapy (IPT) (AHR 0.14, 95% CI 0.05-0.39), hemoglobin below 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93), being in WHO clinical stage III and IV (AHR 2.84, 95% CI 1.11, 7.27), and (AHR 3.07, 95% CI 1.08, 8.75), respectively, were significant for the incidence of tuberculosis.

Conclusion: The incidence of TB among adults living with HIV/AIDS in the first three years of follow-up was higher compared with that of subsequent years. Previous TB disease, no IPT, low BMI and hemoglobin level, advanced WHO clinical stage and bedridden condition were the determinants of the incidence of tuberculosis. Therefore, addressing the significant predictors and improving TB/HIV collaborative activities should be strengthened in the study setting.

Strengths and limitations of this study

- The study which involved a five-year follow up covered longer time than other similar studies and is expected to show the long term impact of HIV on TB.
- The study attempted to show the incidence of TB and its predictors among people living with HIV (PLHIV) using a five-year retrospective data.
- The retrospective nature of the method prevented the inclusion of all possible factors that affect the incidence of tuberculosis.
- Some participants whose data were incomplete were excluded from the study because if such patients had TB they would undermine the findings of the study.
- The sample size used, due to the overall low incidence rate of TB, had limited power to provide clinically relevant conclusions for some risk factors, such as CD4 counts.
- As there was no culture confirmation of TB infections during the study, the cases in the study might be potential ones.
- Inability to address TB contacts (other family members/co-inhabitants) due to the type of study and the introduction of selection bias due to the exclusion of patients who did not use the hospitals chosen are also the limitation of the study.
- Since the study was conducted in a single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Introduction

TB is an infectious disease caused by bacillus *Mycobacterium tuberculosis* which affects the lungs (pulmonary TB), but it can also affect other sites (extra pulmonary TB) and has remained a major global health problem. In 2015, Tuberculosis (TB) was one of the top 10 causes of death worldwide and the leading killer among HIV positive people, exceeding HIV/AIDS as a killer with infectious diseases (1). Out of the 1.4 million TB-caused deaths reported in 2015, 0.4 million occurred to HIV positive TB patients. Globally, it was estimated that there were 10.4 million TB cases, including 1.2 million among the HIV positive people (1).

Worldwide, nearly 78 million people have contracted HIV infection since the beginning of the pandemic, and close to 39 million died of AIDS-related causes for 25% of which TB was responsible (2). According to the World Health Organization (WHO) 2014 report, there were an estimated 1.1 million cases of TB co-infected with HIV (3), where the majority (90%) of the TB-HIV co-infected people were living in resource limited settings, like Ethiopia (4-6). In the African region, that has the highest TB/HIV burden; three out of four TB patients knew their HIV status. In fact, 70% of the TB patients known to be living with HIV in 2013 were started on antiretroviral therapy (ART). Sub-Saharan Africa is among the regions highly hit by the HIV epidemic, covering more than three-quarters (79%) of the burden of TB-HIV co-infections (7).

In Ethiopia, TB remains one of the leading causes of mortality and the third major cause of hospital admissions. In the last ten years, the number of new cases has increased from 55,000 to 100,000, and the rise in the number of tuberculosis cases has been due to the rapid spread of HIV infection. According to the 2011 Ethiopian Demographic and Health Survey (EDHS) report, the average prevalence of HIV in Ethiopia was 1.5%, while it was 1.8% where the study was conducted. Similarly, it was reported that the prevalence of TB was 211 per 100,000 of the population (8), and the global TB report indicated that Ethiopia ranked 10th among the 22 TB high burden countries with a TB/HIV co-infection prevalence of 15% in 2012 (6, 7). TB/HIV co-infection which constitutes an immense burden in the health system in the country is associated with diagnostic and therapeutic challenges. The dual epidemic has been draining resources and overburdening the limited health work-force (9). Hence, the Ministry of Health designed a strategy to increase the percentage of TB patients tested for HIV and vice versa. As a result, the

percentage of TB patients tested for HIV increased from 16 percent in 2007 to 92 percent in 2012, and HIV patients screened for TB from 25 percent in 2007 to 92 percent in 2012 (10).

Though HIV increases the risk of developing TB, it is not the only determinant for it. Various reports indicated that socio-demographic (11, 12), clinical (13, 14), life style (14, 15) and environmental (16) factors were some of the determinants of the incidence of TB infection among HIV positive individuals. Among the clinical factors, low cluster of differentiation (CD4 count) (17-21), low hemoglobin level, diabetes and other opportunistic infections, and functional status showed significant associations with the incidence of TB (20, 22-24). However, Isoniazid Preventive Therapy (IPT), Antiretroviral Therapy (ART), and Co-trimoxazole Preventive Therapy (CPT) treatments reduce the risk of TB infection among HIV positive individuals (23, 25, 26). In resource limited countries such as Ethiopia, where there is poor access to health care, very few studies are conducted on the determinants of the incidence of TB among HIV infected people. As a matter of fact, it is important to know the variables which are risk factors for better understanding the etiology of HIV/TB co-infection in the region. This can contribute to the development of interventions to reduce risks. Therefore, this study assessed the incidence of TB and its determinants among HIV positive people in northeast Ethiopia. As a second outcome, the study considered the incidence of TB in relation to years of follow-up.

Methods

Study design and setting

A five-year retrospective cohort study was conducted on HIV positive patients attending the chronic HIV care clinics in selected government health facilities of the Afar Regional State, northeast Ethiopia, from July 2010 to June 2011. The region is located in the north-eastern part of Ethiopia and has a total population of 1,678,000 of whom only 289,000 live in urban and semi-urban areas (27). In the region, there are four hospitals, 40 health centers, and 15 private clinics actively providing services. When HIV care service was first introduced to the region in 2006, 15 public health institutions provided chronic HIV care and support to around more than 4,000 people living with HIV (PLHIV). For this study, two health centers (Awash, and Samara) and three hospitals (Asayta, Abala, and Dubti General) were selected based on the availability of TB/HIV clients. These health institutions were providing chronic HIV care and follow up to about 85% of the patients living with HIV in the region.

Study population and eligibility criteria

All HIV/AIDS patients aged 15 years and above and newly enrolled for HIV care in selected government health facilities of Afar Region from July 2010 to June 2011 participated in the study. These individuals, who enrolled for HIV care from July 2010 to June 2011, were followed for five years, until May 2015. Out of the total 503 people living with HIV and registered during July 2010 to June 2011 in the selected hospitals, 451 records with complete information were included in the analysis. Fifty-two records with incomplete information, like missing the date of enrollment, outcome of interest, and follow-up data were excluded. However, individual charts deleted for analysis were compared to the study groups and showed no significant baseline demographic characteristics. In addition, those who died or were lost to follow-up were considered as censored.

Measurements and study variables

The outcome variable in this study was the incidence rate of TB co-infection among HIV positive patients, and it was calculated using the total duration of follow-up for the whole cohort in person-year observation (PY). For individuals who did not develop TB, the duration of follow-up from the time of enrolment for HIV care until the end was considered as TB-free. For those who developed TB, TB-free survival time was measured from the time of enrolment in the HIV Care Program until the development of TB. An event of an incidence of TB in this study was considered as any form of TB that was not only diagnosed clinically or radio-graphically but also confirmed by laboratory examinations or by patients who have empirically started anti-TB treatment after enrollment. However, since there was no culture confirmation of TB infections during the study period, the cases in the study might be potential ones. When an individual became diagnosed with active TB, treatment was given based on the National TB Program, which was 8 months of treatment (currently 6 months). Patients taking anti-tuberculosis treatment at the time of enrollment were excluded from the study. HIV positive individuals who were lost to follow-up, transferred, died, and not diagnosed for TB until the end of the follow-up period were considered as censored. Study variables, such as age, sex, educational status, employment status, residence, religion, family size, marital status, plus clinical characteristics, like WHO clinical stage, baseline cluster of differentiation (CD4 count), bedridden functional status, history of TB along with body mass index (BMI), hemoglobin level including socio-demographic and economic characteristics were reviewed. Bedridden functional status was

measured by asking the patient whether he or she was able to perform activities of daily living or not. If he/she said "yes", it was taken as bedridden functional status and coded '1'; otherwise, he/she was deemed to be not bedridden functional status. In this study, CPT prophylaxis was defined as a patient who took co-trimoxazole for longer than one month for a prophylaxis purpose. Isoniazid preventive therapy (IPT) use was defined as a patient who took IPT for at least 3 months. Substance use was referred to as use of at least one of the substances (alcohol, khat, cigarettes, and illicit drugs) in an individual's life time to alter mood or behavior. Illicit drugs were defined as psychoactive substances, like hashish, cannabis, and heroin, the production, sale, or use of which is prohibited.

Sample size and sampling procedure

All HIV/AIDS patients aged 15 years and above and enrolled newly into HIV care from July 2010 to June 2011 were participated in the study. Sample size was calculated using the single proportion formula, considering the following assumptions: 17% prevalence of TB among HIV positive people in Jimma, Ethiopia (28), 95% level of confidence, 3.5 margin of error, and 3.3% expected incomplete record (29). Finally, the minimum sample size of 458 was obtained. Though, 503 PLHIV were registered in the selected health facilities for chronic HIV care, a total of 451 patients with complete information were included in the analysis, while 52 records were excluded because of incomplete information.

In Afar Region, where the study was conducted, there were four hospitals, 40 health centers, and 15 private clinics providing services to the community. Out of these, two health centers (Awash and Samara), and three hospitals (Asayta, Abala and Dubti General) were selected based on client flow and the availability of TB and HIV follow-up services. In these selected health facilities, 503 HIV positive people were newly registered from July 2010 to June 2011. However, people living with HIV and registered in the facilities from July 2010 to June 2011 and had complete information were followed until May 2015.

Data collection tool and procedure

Nurses trained on ART collected the data by reviewing charts and using the patient chart data extraction format. All records of HIV/AIDS patients between July 2010 and May 2015 were considered. Charts were retrieved by using patient medical record and ART registration numbers found on the database of the selected health facilities. Forms used for laboratory request, TB

records, ART intake, and patient cards were reviewed. Data quality was assured by using a pretested questionnaire and trained data collectors. Data completeness and consistency was checked by supervisors. The data clerk and case managers assisted the data collectors by identifying charts.

Data Processing and Analysis

Extracted data were checked for completeness, coded, entered, and cleaned into EPI-INFO version 7 and exported to SPSS version 20.0 software for further analysis. Statistical summary measures and incidence density were calculated. Descriptive statistics were used to characterize the socio-demographic and clinical variables. The event of interest was TB incidence. The incidence of TB (measured by incidence and incidence density rates) was stratified by socio-demographic and clinical variables. Kaplan-Meier estimates were used to describe time to event distributions. Log-rank tests were used to compare time-to-event across the different categories. Time-to-event data that the study considered and survival analysis were carried out; the cox proportional hazards model was fitted, and a life table was used to estimate cumulative probabilities. The bi-variable and multivariate cox regression model was used to identify the predictors of the incidence of TB. Variables with p-values of less than 0.2 in the bi-variable analysis were considered for the multivariate cox proportional hazard model. A 95% confidence interval of the hazard ratio (HR) was computed, and variables with less than 0.05 p-values in the multivariate cox proportional hazards model were taken as significant predictors for the outcome variable. Moreover, basic assumptions of the cox proportional hazard model were checked using the Schoenfield residuals test.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Public Health, the University of Gondar. A letter of permission was secured from the Afar Regional Health Bueuro (ARHO), and a written permission letter was sent to each selected health facilities. In addition, confidentiality was maintained by using only unique identification codes rather than patient names and identifications.

Results

Socio-demographic and clinical characteristics of PLHIV

Out of the total 503 PLHIV registered at the selected hospitals from July 2010 to June 2011, 451 records with complete information were followed until May 2015. The charts of 451 HIV/AIDS patients with complete information were analyzed, while 52 records were excluded because they did not contain complete information (**Figure-1**). Out of the 451 patients that remained in the analysis, more than half (267/59.2%) were female, and over half of the total (242/53.7%) were 26-34 years of age. The mean age (±SD) of the patients was 32.6 (±7.5) years. Most of the respondents, 410 (90.9%), were urban dwellers and 275 (61.0%) Muslims **(Table 1)**.

Almost half, 234 (51.9%), of the participants were self-employed. Only 76 (16.9%) had more than 5 family members. Almost half, 212 (47%), of the subjects never went to formal school. More than two-thirds (68.1%) of the patients were currently or formerly married. Of the 130 (28.8%) patients recorded as substance users, 14 (5.0%) were tobacco users, 26 (20.0%) alcohol consumers, and 90 (75.0%) used both **(Table 1)**.

Out of the total 451 study participants with complete information for analysis, more than half (45.4%) had a baseline WHO clinical stage I and II. The majority, 440 (97.6%), of the participants were enrolled with working functional status. Almost half, 218 (51.7%), of the participants were underweight (BMI less than 18.5 kg/m^2), whereas more than three-quarters, 344 (76.3%), were anemic (Hgb<11g/dL). During the five year retrospective follow up, most, 413 (91.6%), of the participants were provided with co-trimoxazole preventive therapy (CPT), while only 94 (20.8%) received isoniazid preventive therapy (IPT). Similarly, nearly half, 215 (47.7%), of the respondents were initiated into ART therapy either on WHO clinical stage or CD4 cell count. More than one-third, 170 (37.7%), of the HIV/AIDS positive people took a combination of Tenofovir (TDF), Lamivudine (3TC), and Efavirenz (EFV); likewise, one-fifth, 110 (24.4%), of the patients took Zidovudine (AZT), Lamivudine (3TC), and Efavirenz (EFV). Another one-fifth, 96 (21.3%), of the patients changed their initial regimen, 92 due to substitution and 4 due to switching to second line treatment for HIV. Out of the 96 HIV/AIDS patients who changed their initial regimen, side effect and development of TB were the major reasons for 50 (52.1%) and 29 (30.2%), respectively (**Table 1).**

Table 1: Socio-demographic and clinical characteristics of PLHIV who were enrolled for chronic HIV care at selected government health facilities in Afar Regional State, northeast Ethiopia from 2010-2011

Characteristics	Frequency	Percent (%)
Age in years (mean=32.6, SD=7.5)		
15-25	55	12.2
26-34	242	53.7
35-44	119	26.3
≥45	35	7.8
Sex		
Male	184	40.8
Female	267	59.2
Marital status		
Single	144	31.9
Married	200	44.3
Divorced	77	17.1
Widowed	30	6.7
Residence		
Urban	410	90.9
Rural	41	9.1
Religion		
Muslim	275	61.0
Orthodox	165	36.6
Others	11	2.4
Educational status		
Illiterate	212	47.0
Primary school	177	39.2
Above secondary	62	13.8
Family size		
1-3	216	47.9
4-5	159	35.3
≥5	76	16.8
Occupation		
Self-employed	234	51.9
Governmental employed	45	10.0
Non-employed	172	38.1
Substance use		
Yes	130	28.8
No	321	71.2
Type of substance used		
Tobacco	14	5.0
Alcohol	26	20.0
Both tobacco and alcohol	90	75.0
On ART		
Yes	215	47.7
No	236	52.3
WHO clinical stage		
I & II	200	45.4
III	172	39.0
IV	69	15.6

Bedridden		
No	440	97.6
Yes	11	2.4
CD4 cell count (cells/uL)		
<100	44	9.8
100-200	124	27.5
201-349	125	27.7
>350	158	35.0
BMI (kg/m^2)		
<18.5	218	51.7
>18.5	203	48.3
Hgb level (g/dL)		
<11	344	76.3
≥11	107	23.7
CPT use		
Yes	413	91.6
No	38	8.4
IPT use		
Yes	94	20.8
No	357	79.2
Initial regimen		
d4t-3TC-NVP	65	14.4
AZT-3TC-EFV	89	19.7
AZT-3TC-NVP	110	24.4
TDF-3TC-EFV	170	37.7
Others	17	3.8
Previous TB disease		
Yes	74	16.4
No	377	83.6
Opportunistic infection (OI)		
Yes	34	7.5
No	417	92.5
Chronic illness		
Yes	35	7.8
No	416	92.2
Regimen change		
To First line	92	20.4
To Second line	4	0.9
Not changed	355	78.7
Reason for change		
Due to TB development	29	30.2
Due to side effect	50	52.1
Failure of treatment	4	4.2
Others	13	13.5
Form of TB		
Pulmonary	91	76.4
extra pulmonary	28	23.6

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation 4; CPT, Co-trimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efavirenz; Hgb, Hemoglobin; IPT, isoniazid preventive therapy; NVP, Nevirapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofovir; 3TC, Lamivudine; WHO, World Health Organization

The incidence of TB stratified with socio-demographic and clinical characteristics

Out of the total 451 HIV/AIDS patients, 119 (26.4%) developed active TB infection during the follow-up period, while 332 were censored (40 transferred out, 13 died, 21 lost to follow-up, and 258 remained TB-negative till the end of follow-up period) **(Figure-1)**. Therefore, the overall TB incidence rate in the five year retrospective data was 8.64 cases per 100 Person-years (PY) of observation. The incidence of patients diagnosed with TB at the end of one year was 4.9 per 100 person-year observation. The sum of the whole follow-up period for all 451 HIV/AIDS infected individuals was 1377.41 Person-years of observation. The minimum and maximum follow-up observation was 0.03 and 58.8 months, respectively. The median (IQR) follow-up period was 46.74 months of observation [IQR=15.95-52.42 months]. Females constituted more than half, 67 (56.3%), of the total TB patients. Three-quarters, 91 (76.47%), of the cases were pulmonary TB. About 68 (57.14%) of the TB incidents occurred within the first year of follow up. The incidence of TB was 105 cases and 14 cases among urban and rural dwellers, respectively. The test of equality for survival distribution for different levels of different categories was performed with Kaplan Meier, using the long rank test. The cumulative probability of TB patient survival at the end of one year, two, three, and four years was 0.77, 0.68, 0.34 and 0.10, respectively. The median survival time was 54 months (**Figure-2**). In terms of survival curves, there were significant variations among underweight and normal weight ($p<0.002$) (**Figure-3**); different WHO clinical stage categories ($P<0.001$) (**Figure-4**); anemic and non-anemic ($p<0.001$) (**Figure-5**); bedridden and otherwise ($p<0.002$) (**Figure-6**); and IPT receivers and non-receivers ($P<0.0001$) (**Figure-7**). Out of the participants who developed TB, 41 (34.5%) had previous TB disease, and 8 (6.7%) were bedridden at the time of enrollment. One hundred fifteen (96.6%) of the TB cases were not given INH prophylactic therapy. Fifty (42.0%) with incident cases of TB were enrolled with Hgb level below11g/dL (**Table-2**).

Table 2: The incidence of tuberculosis stratified by socio-demographic and clinical characteristics of PLHIV on HIV chronic care at selected government health facilities of Afar Regional State, July 2010 to May 2015

Characteristics	Total N (%)	TB incidence N (%)	Person-Years observation (PY)
Years of follow-up (median=46.74, IQR=15.95-52.42, months)			
One year	88(19.5)	68(57.1)	35.07
Two years	41(9.0)	28(23.5)	54.73
Three years	32(7.0)	11(9.3)	76.66
Forth	89(19.8)	9(7.6)	322.67
Fifth	201(44.6)	3(2.5)	888.28
Age (years)			
15-25	55(12.2)	14(11.7)	158.81
26-34	242(53.7)	63(52.9)	739.05
35-44	119(26.3)	30(25.3)	384.1
≥45	35(7.8)	12(10.1)	95.45
Sex			
Male	184(40.8)	52(43.7)	536.9
Female	267(59.2)	67(56.3)	840.51
Residence			
Urban	410(90.9)	105(88.2)	1260.67
Rural	41(9.1)	14(11.8)	116.74
Marital status			
Single	144(31.9)	30(25.2)	435.14
Married	200(44.3)	52(43.7)	616.07
Divorced	77(17.1)	30(25.2)	184.5
Widowed	30(6.7)	7(7.9)	91.61
Educational status			
Illiterate	212(47.0)	55(46.2)	683.8
Primary School	177(39.3)	49 (41.2)	510.54
Secondary and above	62(13.7)	15(12.6)	183.07
Occupation			
Self-employed	234(51.8)	59(49.6)	741.68
Government-employed	45(10.1)	9(7.6)	121.45
Non- employment	172(38.1)	51(42.8)	514.28
Religion			
Muslim	275(61.0)	70(58.8)	826.69
Orthodox	165(36.6)	47(39.5)	520.89
Others	11(2.4)	2(1.7)	29.83
Family size			
1-3	216(47.9)	51(42.9)	668.68
4-5	159(35.3)	43(36.1)	484.74
>5	76(16.8)	25(21.0)	223.99
Substance use			
Yes	130(28.8)	42(35.3)	379.7
No	321(71.2)	77(64.7)	997.71

Previous TB disease			
Yes	74(16.4)	41(34.5)	164.74
No	377(83.6)	78(65.5)	1212.67
Opportunistic infection (OI)			
Yes	34(7.5)	19(16)	85.28
No	417(92.5)	100(84)	1292.13
Chronic illness			
Yes	35(7.8)	11(9.2)	106.28
No	416(92.2)	108(90.8)	1271.13
Bedridden			
Yes	11 (2.4)	8(6.7)	33
No	440(97.6)	111(93.3)	1356.76
BMI (kg/m^2)			
<18.5	218(48.3)	75(64)	626.46
>18.5	203(45.0)	42(36)	750.95
Hgb level (g/dL)			
<11	107(23.7)	50(42.0)	233.8
≥11	344(76.3)	69(58.0)	1143.6
CD4 cell count (cells/uL)			
<100	44(9.7)	22(18.5)	84.77
100-200	124(27.5)	40(33.6)	343.72
201-349	125(27.7)	29(24.4)	384.29
>350	158(35.0)	28(23.5)	564.63
On ART			
Yes	215 (47.7)	36 (30.3)	941.70
No	236(52.3)	83(69.7)	435.71
WHO clinical stage			
I & II	210(46.6%)	36(30.3)	785.3
III	172(38.1)	59(49.6)	464.98
IV	69(15.3)	24(20.1)	187.13
Initial regimen			
d4t-3TC-NVP	65(14.4)	14(11.7)	223.56
AZT-3TC-EFV	89(19.7)	20(16.8)	296.28
AZT-3TC-NVP	110(24.4)	28(23.5)	349.17
TDF-3TC-EFV	170(37.7)	52(43.7)	461.71
Others	17(3.8)	5(4.3)	46.69
IPT use			
Yes	94(20.8)	4(3.4)	363.60
No	357(79.1)	115(96.6)	1013.81
CPT use			
Yes	413(91.6)	108(90.8)	1259.65
No	38(8.4)	11(9.2)	117.76

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation 4; CPT, Co-trimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efavirenz; Hgb, Hemoglobin; IPT, isoniazid preventive therapy; NVP, Nevirapine; OI, Opportunistic Infections; TB, Tuberculosis; TDF, Tenofovir; 3TC, Lamivudine; WHO, World Health Organization

Determinants of TB incidence

In the bivariable cox regression analysis, marital status, family size, substance use, history of TB, baseline CD4 count, WHO clinical stage, opportunistic infection, body mass index (BMI), hemoglobin level, isoniazid preventive therapy (IPT), and functional status were found to be predictors of the incidence of tuberculosis at a p-value of less than 0.2. Consequently, these variables were subjected to multivariate cox regression analysis and previous TB disease, bed-ridden functional status, hemoglobin, BMI, IPT and advanced WHO clinical stage were found statistically significant determinants of TB free survival at a p-value of less than 0.05.

Accordingly, the multivariate cox regression analysis indicated that people living with HIV (PLHIV) and had history of TB disease were 3.65 times at higher risk of developing TB at any time than to PLHIV who had no history of TB (AHR 3.65, 95% CI 1.97-6.73). PLHIV who were in bed-ridden functional status at base-line were 5.45 times at more risk of developing TB compared with PLHIV not in bedridden functional status (AHR 5.45, 95% CI 1.16-25.49). Similarly, PLHIV with baseline BMI less than 18.5kg/m^2 were 2.53 times at higher risk of developing TB at any time than those with BMI greater than 18.5kg/m^2 (AHR 2.53, 95 % CI 1.27-5.05). Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR 0.14, 95% CI 0.05-0.39). PLHIV in WHO clinical stage III and IV had a greater risk of developing TB compared with WHO stage I and II (AHR 2.84, 95% CI 1.11, 7.27), and (AHR3.07, 95% CI 1.08, 8.75), respectively. The study also revealed that the incidence of TB in the first three years of follow-up was higher when compared with the other subsequent years. In addition, PLHIV who were anemic (Hgb <11g/dL) were 2.31 times at higher risk of developing TB than those with Hgb level greater than 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93) (**Table-3**).

Table 3: Cox regression analysis of the determinants of the incidence of tuberculosis among adult on chronic HIV care at selected government health facilities of Afar Regional State from July 2010 to May, 2015

Variables	Survival status		Total	CHR (95% CI)	AHR(95% CI)
	Event (TB)	Censored			
Marital status					
Single	30	114	144	1.00	1.00
Married	52	148	200	1.34 (0.80-2.23)	1.26 (0.65-2.43)
Divorce	30	47	77	2.43 (1.32-4.46)	1.75 (0.83-3.68)
Widowed	7	23	30	1.16 (0.45-2.95)	2.42 (0.79-7.38)
Family size					
1-3	51	165	216	1.00	1.00
4-5	43	116	159	1.19 (0.75-1.92)	0.49 (0.25-1.34)
>5	25	51	76	1.58 (0.89-2.81)	0.71 (0.35-1.76)
Substance use					
Yes	42	88	130	1.51 (0.96-2.37)	1.47 (0.84-2.56)
No	77	244	321	1.00	1.00
Previous TB disease					
Yes	41	33	74	4.76 (2.83-8.03)	3.65 (1.97-6.73)**
No	78	299	377	1.00	1.00
Opportunistic infection (OI)					
Yes	19	15	34	4.02 (1.97-8.19)	2.31 (0.98-5.45)
No	100	317	417	1.00	1.00
Bedridden					
Yes	8	3	11	7.90 (2.06-30.31)	5.45 (1.16-25.49)**
No	111	329	440	1.00	1.00
BMI (kg/m^2)					
<18.5	75	143	218	2.01(1.29-3.12)	2.53(1.27-5.05)**
≥18.5	42	161	203	1.00	1.00
Length of follow-up					
≤ 1 year	68	20	88	78.76 (36.7-168.9)	83.76 (33.94-206.7)**
2-3 years	39	34	73	26.57 (12.7-55.6)	33.81(14.12-80.96)**
4-5 years	12	278	290	1.00	1.00
WHO clinical stage					
I &II	36	174	200	1.00	1.00
III	59	113	172	2.52 (1.57-4.07)	2.84(1.11-7.27)**
IV	24	45	69	2.58 (1.40-4.75)	3.07(1.08-8.75)**
Hgb level (g/dL)					
<11	50	57	107	3.49 (2.20-5.55)	2.31(1.35-3.93)**
≥11	69	275	344	1.00	1.00
CD4 count (cells/uL)					
<100	22	22	44	4.64 (2.26-9.52)	1.14(0.46-2.82)
100-200	40	84	124	2.21 (1.27-3.85)	1.29(0.66-2.57)
201-349	29	96	125	1.40 (0.78-2.51)	0.99(0.49-1.99)
≥350	28	130	158	1.00	1.00
IPT					
Yes	4	90	94	0.09 (0.03-0.26)	0.14 (0.05, 0.39)**
No	115	242	357	1.00	1.00

** Variable significant at p-value less than 0.05

BMI, Body mass index; CD4, Cluster of differentiation 4; Cells/ul, cells per microliter (ul); Hgb, Hemoglobin; g/dl, grams (g) per decilitre (dL); OI, Opportunistic Infection; IPT, isoniazid preventive therapy; TB, Tuberculosis; WHO, World Health Organization

Discussion

TB and HIV remain the major public health problems in many parts of the world. Ethiopia is among the TB high burden countries with an estimated annual incidence of 211cases per 100,000 people and a prevalence of 224 cases per 100,000 (30).

In this study, the overall incidence of TB among PLHIV was 8.64 cases per 100 person-year (PY) observation. This finding is similar to those reported from Gondar and Assela, Ethiopia, which are 7 and 7.9 cases, respectively, per 100 person-year (PY) observations (31, 32). The finding is consistent with that of a study in Tanzania and other Sub-Saharan countries with incidence ranging from 7.6-8.2 per 100 person-year observation (PY) (33, 34). However, the incidence density of TB in this study is higher than those of studies conducted in Korea, Israel, and Malaysia (35-37). The lower incidence of TB in the latter studies compared with this one might be due to the availability of better preventive, diagnostic, and treatment setups and strategies for controlling TB in such countries when compared with our study setting. In addition, low health care coverage, high burden of HIV, and the fact that the study setting is so unprivileged might explain the difference. Furthermore, late enrollment at health facilities due to late presentation of HIV infected people at health facilities, increases the progression of latent infection to active TB after HIV chronic care. It was noted that individuals with late presentation might get new infections or IRIS after initiation into highly active antiretroviral therapy (HAART), and Immune Reconstitution Inflammatory Syndrome (IRIS) related TB is commonly seen within the first six months of initiation into HAART (38). Similarly, it was revealed that the incidence of TB is significantly associated with the length of follow-up year. It was reported that the incidence of TB decreased as the years of follow-up increased, and a higher incidence of TB was reported in the first three of follow-up years compared with the other subsequent years.

Out of the determinants of the incidence of TB infection in the multivariate cox regression analysis, the study revealed that previous TB disease, using IPT, bedridden functional status, low hemoglobin level, advanced WHO staging (III and IV), years of follow-up, and low BMI were

found to be significantly associated with the incidence of TB. Individuals who had history of TB disease had greater risk of developing TB compared with those who had no history of TB treatment. Poor compliance with anti-TB treatment at the first episode, reactivation or re-infection of individuals with the existing diminished immunity might be the reasons for higher incidence of TB among individuals with history of TB infection. This finding is consistent with those of studies conducted in Uganda, Malaysia, and Israel (36, 37, 39).

PLHIV who took Isoniazid preventive therapy (IPT) were found to be protective of the incidence of TB. Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR=0.14, 95% CI: 0.05-0.39). This might be due to the role of IPT in reducing the incidence of TB among people living with HIV. The finding is consistent with those of studies in Ethiopia, South Africa, and Brazil (40-42). In spite of this fact, poor uptake, ambiguity, and fear of drug resistance might contribute to no-IPT use.

Similarly, in this study, patients' functional status at baseline was found to be the predictor of TB incidence. Patient bedridden functional status at baseline was 5.45 times at higher risk of developing TB than individuals with working functional status at baseline. This might be due to the fact that debilitated patients will be prone to malnutrition, and lack of physical activity exposes them to many diseases, including TB. This finding is in line with those of other studies conducted in Ethiopia (16, 31, 43).

Out of the anthropometric variables, HIV patients who were underweight (BMI <18.5 kg/m^2) were 2.53 times at higher risk of developing TB compared to individuals with BMI≥18.5 kg/m^2. This finding was consistent with that of a study done in Tanzania (44), Ethiopia, and South Africa (33, 45). The possible explanations might be that a low BMI category is a proxy indicator of malnutrition, and malnutrition in HIV patients is associated with increased catabolic activity, infection, loss of appetite, and decreased intake, which further increase the risk of developing opportunistic infections such as tuberculosis.

Furthermore, this study found that patients with Hgb level of <11 g/dL at base-line were 2.31 times at higher risk of developing TB than those with Hgb level ≥11 at base-line. Hematologic complications were risk factors for the incidence of TB among PLHIV. This finding is concordant with those of studies conducted in Ethiopia, Uganda, Tanzania, and South Africa (44-

47). The possible explanation might be malnutrition, side effects of medications, opportunistic infections, and advanced stage of the disease. Undiagnosed TB could explain low Hgb level at early enrollment.

The other important result which was found to have a significant association with the incidence of TB was advanced clinical staging (III & IV). PLHIV with advanced WHO staging (III and IV), respectively had 2.84 and 3.07 times higher risk of developing TB compared with people in stages I & II. The finding corresponded to those of studies conducted in Nigeria (48), South Africa (49), and Gambia (50). This might be due to the fact that once patients get into late stages; the immunity protective capacity will be minimal, making them predisposed to tuberculosis infection. Something worth mentioning as well is that TB is one of the defining factors of AIDS that categorizes patients who use HIV/AIDS clinics in Ethiopia into late WHO clinical staging.

Limitations of the study

Though the study did its best to indicate the incidence and predictors of tuberculosis among PLHIV using a five-year retrospective data, it was not free from limitations. The retrospective nature of the study limited the inclusion of all possible factors that could affect the incidence of tuberculosis. Variables such as housing condition and household income were some of the plausible factors that were not measured in this study. For some risk factors, such as CD4 count, the sample size limited the power to provide clinically relevant conclusions because of the overall low incidence rate of TB. Inability to conduct culture confirmation (the gold standard method) is another limitation of the study. Inability to address TB contacts (other family member/co-inhabitant) and introduction of selection bias due to the exclusion of patients who did not use the selected hospitals is the other drawback. Since the study was conducted in a single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Conclusion

The overall incidence of TB among PLHIV was found to be comparable with those of similar studies in Ethiopia. However, it was higher in the first year of follow-up than it was in the subsequent years. HIV infected individuals with history of TB disease, not using IPT, underweight status (BMI<18.5kg/m^2), bedridden functional status, being anemic (Hgb<11g/dL), advanced WHO stage (III &IV), and short duration of follow-up were determinants of the

incidence of TB among PLHIV. Therefore, our study suggested early screening and diagnosis among high risk PLHIV such as those in bed-ridden functional status, underweight (BMI<18.5kg/$m^{2)}$, and anemic (Hgb <11g/dL). In addition, providing IPT to PLHIV without active TB and intensified TB case screening for those with advanced WHO stage is highly recommended. In addition, emphasis should be given to those with shorter follow-ups. Therefore, attention to PLHIV and prompt diagnosis and treatment of TB are recommended. Furthermore, prospective studies need to include all factors that influence the risk of TB among PLHIV. Since our study was conducted in a single region of Ethiopia, collaborative projects that can include several regions of the country are recommended to give a more balanced view of the incidence of TB and potential risk factors in HIV-infected patients.

List of abbreviations

AHR, Adjusted hazard ratio; AIDS, Acquired immune deficiency syndrome; ART, Anti-Retroviral Therapy; BMI, Body mass index; CD4, cluster of differentiation 4; CI, Confidence interval; CPT, Cotrimoxazole prophylaxis therapy; EDHS, Ethiopian Demographic health survey; HIV, Human immune deficiency; HAART, Highly active anti retro viral therapy; Hgb, Hemoglobin; INH, Isoniazid; IQR, Inter quartile range; IPT, Isoniazid preventive therapy; IRIS, Immune reconstitution inflammatory syndrome; PLHIV/AIDS, People living with HIV/AIDS; PY, person-year observation; TB, tuberculosis; WHO, World health organization

Competing interests

The authors declare that they have no conflict of interest.

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Data sharing statement

All data supporting our findings will be shared upon request.

Authors' contributions

AA, DM and MKY involved in the conception, design, data collection, analysis and report writing. DM, AMS, FB, and MKY assisted with the design, approved the proposal with some revisions, participated in data analysis and manuscript preparation. All authors read and approved the final manuscript.

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Figure legends

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

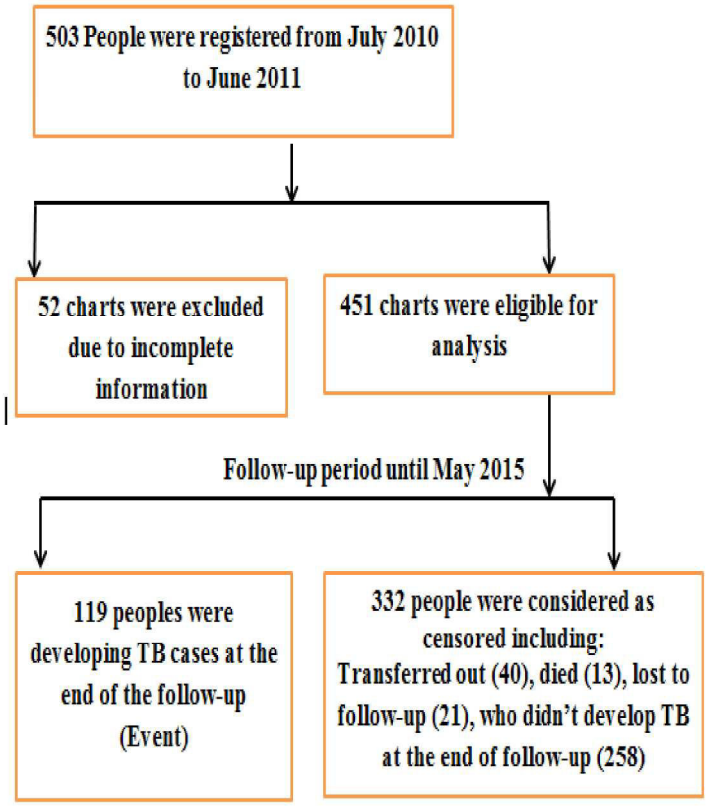

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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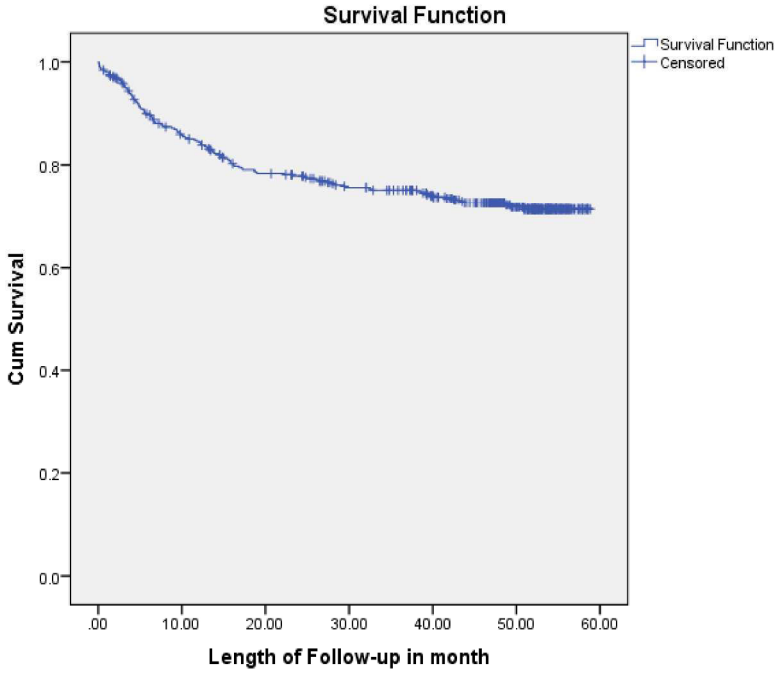

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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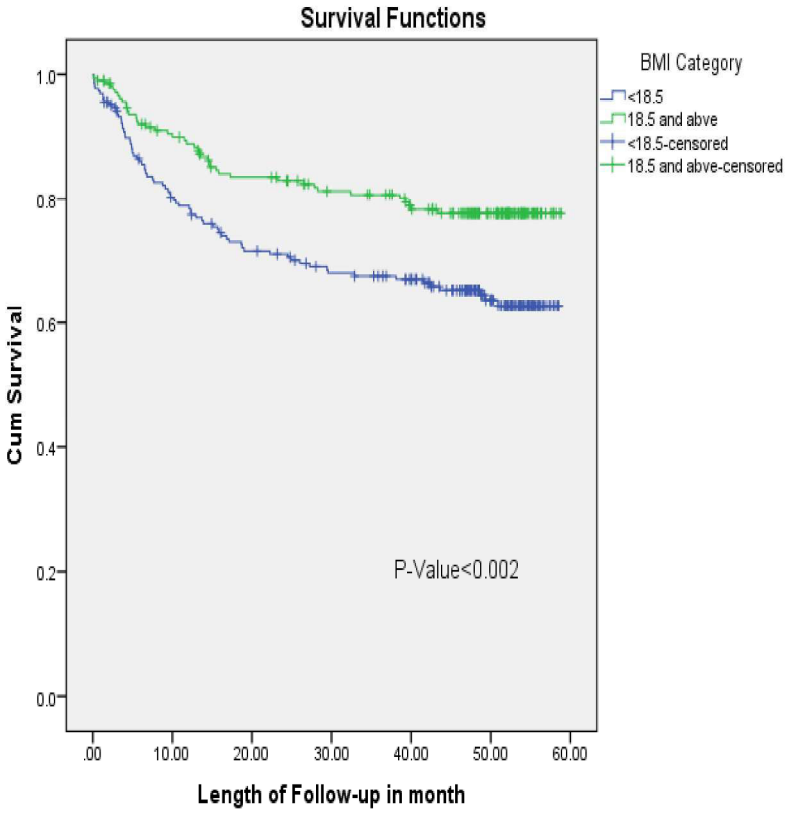

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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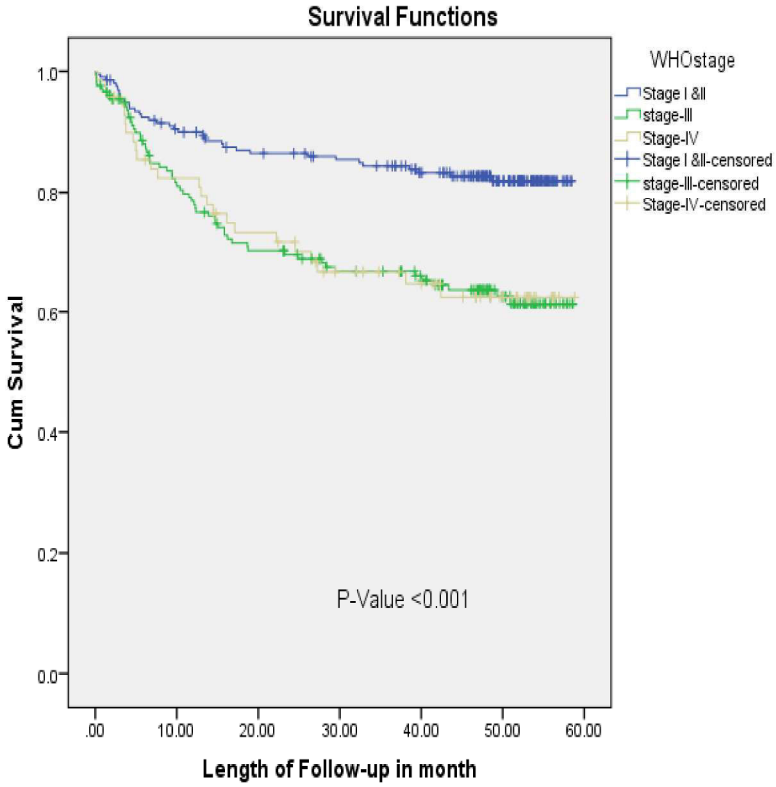

Figure 4: Kaplan Meier survival curve of TB patients based on the WHO stage among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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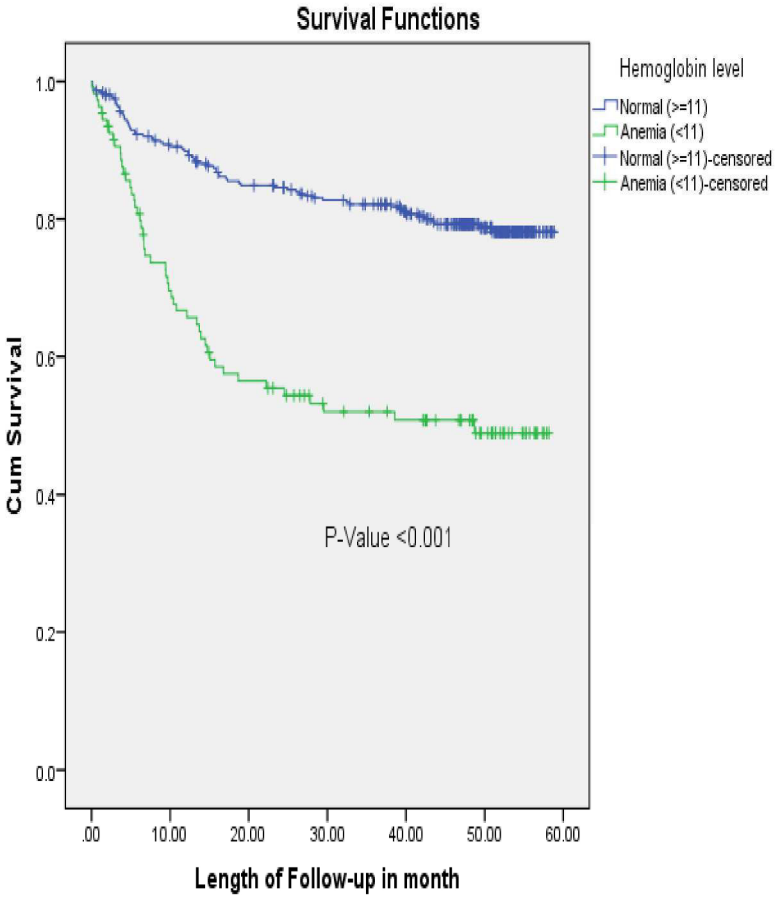

Figure 5: Kaplan Meier survival curve of TB patients based on hemoglobin level among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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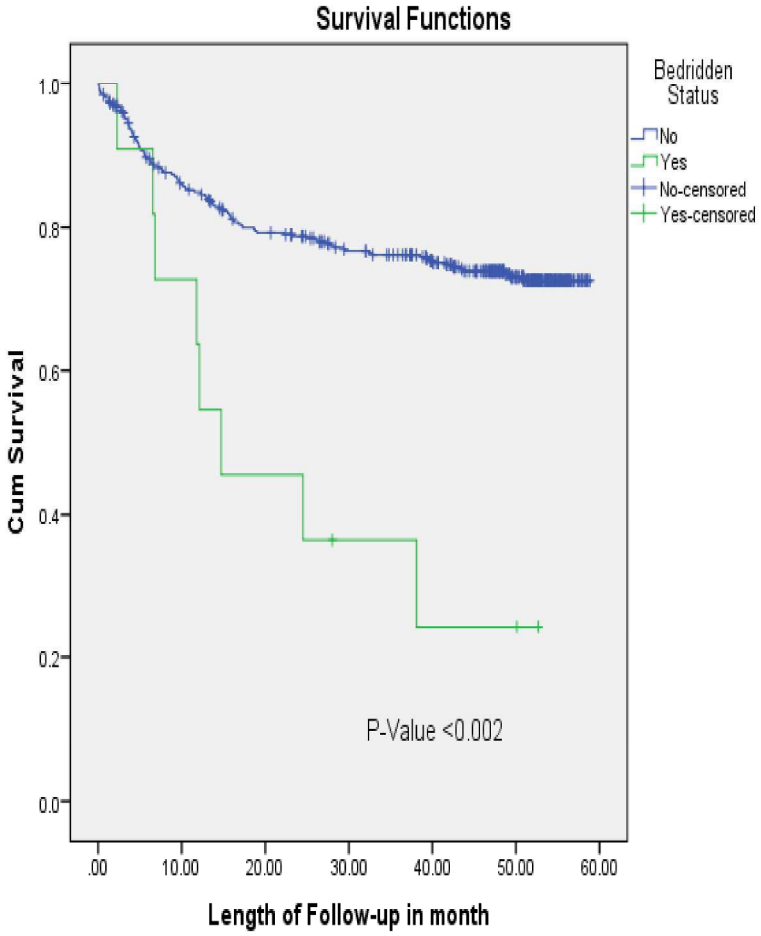

Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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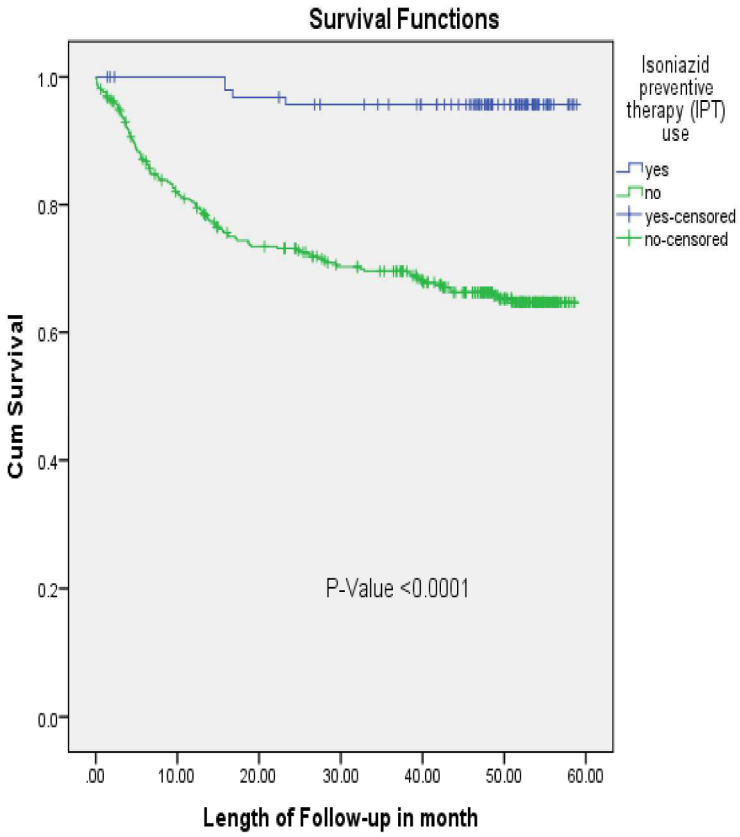

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

279x361mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	• Study design is indicated in the title and abstract sections (page 1 line-2 OR on page-2 line-4) • Abstract section is informative and is indicated in page-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	• The type of data which was retrospective cohort is given in the title and the abstract section (pages 1&2) • The geographical region (northeast Ethiopia) is mentioned in the title and abstract sections (pages 1 & 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	• Background/Introduction section is presented on page-4 • Rationale of the study is mentioned on page-5 lines 13-		

			18		
Objectives	3	State specific objectives, including any prespecified hypotheses	• Objectives of the study are indicated on page-5 lines 17-20. In addition, it is also clearly mentioned in the abstract section on page-2 lines 13-16.		
Methods					
Study Design	4	Present key elements of study design early in the paper	• Study design is found on page 5 lines 23-24.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	• Study setting is stated on page-5 line 21 to page-6 line 2.		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants	• Study population and eligibility criteria are found on page-6 lines 4-13	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a	• The methods of data collection are on page 7 • The flow diagram indicating how the study subjects are selected is presented in figure 1.

		(b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	• Measurement and study variables are presented on page-6, lines 14 to page -7 line-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	• Data collection tool and procedure is located on page-7 lines 22-30		
Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at	• Sample size calculation and procedure is described on page-7 lines 7-14		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to	• Data processing and analysis is found on page-8,		

		examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	lines 1-17		
Data access and cleaning methods		..	• Data access and cleaning is found on page-7 lines 22-27	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	• How the authors accessed data is stated in the data collection procedure (page-7) • Information on data coding, entering and cleaning is given in the data processing and analysis sub-sections (page-8, lines 1-17)
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	• The study

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	setting is on page 5 lines 21 to page 6 lines 1-2
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	• Number of participants included in this study is indicated on page-8 lines 27-28 • Flow diagram representing how study participants are presented on figure-1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	• A flow diagram indicating the eligibility of study participants for the study is presented in a graph 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	• Descriptive data, including the socio-demographic and clinical factors are located from pages 8-11		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report	• The outcome data (incidence of TB) is on pages 12-14		

		numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	• The adjusted estimates with 95% confidence interval are reported on page 16		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	None		
Discussion					
Key results	18	Summarise key results with reference to study objectives	• The discussion section is presented on pages 17-19		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	• The limitation of the study is pointed out on page 19 lines 12-22	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	• The conclusion section is on page 19 line 23 to page		

		analyses, results from similar studies, and other relevant evidence	20 lines 1-9		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Since the study was conducted in a setting where more than 85% of HIV/AIDS patients are enrolled, we can generalize the finding to northeast Ethiopia		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	• Funding information is on page 20 lines 20-21		
Accessibility of protocol, raw data, and programming code			• Data sharing statements are on page 20 lines 22-23	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	• Data collection procedure is on page-7 and data sharing statement is on page 24.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Incidence and determinants of tuberculosis infection among adult HIV patients attending HIV care in Northeast Ethiopia: a retrospective cohort study

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Incidence and determinants of tuberculosis infection among adult HIV patients attending HIV care in northeast Ethiopia: A retrospective cohort study

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Abstract

Objective: This study assessed the incidence of tuberculosis and its predictors among adults living with HIV/AIDS in government health facilities of northeast Ethiopia.

Setting: A five year retrospective cohort study was conducted from May to June 2015 on 451 adult HIV/AIDS infected individuals who enrolled in the HIV Care Clinics of government health facilities of northeast Ethiopia.

Participants: A total of 451 HIV infected adults who newly enrolled in the adult HIV Care Clinic from July 1, 2010 with complete information were followed until May 2015.

Primary outcome measure: The primary outcome was the proportion of patients diagnosed with TB or TB incidence rate.

Secondary outcome measure: The incidence of TB was investigated in relation to years of follow-up

Results: A total of 451 charts with complete information were followed for 1377.41 Person-Years (PY) of observation. The overall incidence density of tuberculosis was 8.6 per 100 person-year observation. Previous TB disease [Adjusted Hazard Ratio (AHR) 3.65, 95% CI 1.97-6.73], being bedridden [AHR 5.45, 95% CI 1.16-25.49], being underweight [Body Mass Index (BMI) <18.5kg/m^2) (AHR 2.53, 95 % CI 1.27-5.05)], taking isoniazid preventive therapy (IPT) (AHR 0.14, 95% CI 0.05-0.39), hemoglobin below 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93), being in WHO clinical stage III and IV (AHR 2.84, 95% CI 1.11, 7.27), and (AHR 3.07, 95% CI 1.08, 8.75), respectively, were significant for the incidence of tuberculosis.

Conclusion: The incidence of TB among adults living with HIV/AIDS in the first three years of follow-up was higher compared with that of subsequent years. Previous TB disease, no IPT, low BMI and hemoglobin level, advanced WHO clinical stage and bedridden condition were the determinants of the incidence of tuberculosis. Therefore, addressing the significant predictors and improving TB/HIV collaborative activities should be strengthened in the study setting.

Strengths and limitations of this study

- The study which involved a five-year follow up covered longer time than other similar studies and is expected to show the long term impact of HIV on TB.
- The study attempted to show the incidence of TB and its predictors among people living with HIV (PLHIV) using a five-year retrospective data.
- The retrospective nature of the method prevented the inclusion of all possible factors that affect the incidence of tuberculosis.
- Some participants whose data were incomplete were excluded from the study because if such patients had TB they would undermine the findings of the study.
- The sample size used, due to the overall low incidence rate of TB, had limited power to provide clinically relevant conclusions for some risk factors, such as CD4 counts.
- As there was no culture confirmation of TB infections during the study, the cases in the study might be potential ones.
- Inability to address TB contacts (other family members/co-inhabitants) due to the type of study and the introduction of selection bias due to the exclusion of patients who did not use the hospitals chosen are also the limitation of the study.
- Since the study was conducted in a single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Introduction

TB is an infectious disease caused by bacillus *Mycobacterium tuberculosis* which affects the lungs (pulmonary TB), but it can also affect other sites (extra pulmonary TB) and has remained a major global health problem. In 2015, Tuberculosis (TB) was one of the top 10 causes of death worldwide and the leading killer among HIV positive people, exceeding HIV/AIDS as a killer with infectious diseases (1). Out of the 1.4 million TB-caused deaths reported in 2015, 0.4 million occurred to HIV positive TB patients. Globally, it was estimated that there were 10.4 million TB cases, including 1.2 million among the HIV positive people (1).

Worldwide, nearly 78 million people have contracted HIV infection since the beginning of the pandemic, and close to 39 million died of AIDS-related causes for 25% of which TB was responsible (2). According to the World Health Organization (WHO) 2014 report, there were an estimated 1.1 million cases of TB co-infected with HIV (3), where the majority (90%) of the TB-HIV co-infected people were living in resource limited settings, like Ethiopia (4-6). In the African region, that has the highest TB/HIV burden; three out of four TB patients knew their HIV status. In fact, 70% of the TB patients known to be living with HIV in 2013 were started on antiretroviral therapy (ART). Sub-Saharan Africa is among the regions highly hit by the HIV epidemic, covering more than three-quarters (79%) of the burden of TB-HIV co-infections (7).

In Ethiopia, TB remains one of the leading causes of mortality and the third major cause of hospital admissions. In the last ten years, the number of new cases has increased from 55,000 to 100,000, and the rise in the number of tuberculosis cases has been due to the rapid spread of HIV infection. According to the 2011 Ethiopian Demographic and Health Survey (EDHS) report, the average prevalence of HIV in Ethiopia was 1.5%, while it was 1.8% where the study was conducted. Similarly, it was reported that the prevalence of TB was 211 per 100,000 of the population (8), and the global TB report indicated that Ethiopia ranked 10th among the 22 TB high burden countries with a TB/HIV co-infection prevalence of 15% in 2012 (6, 7). TB/HIV co-infection which constitutes an immense burden in the health system in the country is associated with diagnostic and therapeutic challenges. The dual epidemic has been draining resources and overburdening the limited health work-force (9). Hence, the Ministry of Health designed a strategy to increase the percentage of TB patients tested for HIV and vice versa. As a result, the

percentage of TB patients tested for HIV increased from 16 percent in 2007 to 92 percent in 2012, and HIV patients screened for TB from 25 percent in 2007 to 92 percent in 2012 (10).

Though HIV increases the risk of developing TB, it is not the only determinant for it. Various reports indicated that socio-demographic (11, 12), clinical (13, 14), life style (14, 15) and environmental (16) factors were some of the determinants of the incidence of TB infection among HIV positive individuals. Among the clinical factors, low cluster of differentiation (CD4 count) (17-21), low hemoglobin level, diabetes and other opportunistic infections, and functional status showed significant associations with the incidence of TB (20, 22-24). However, Isoniazid Preventive Therapy (IPT), Antiretroviral Therapy (ART), and Co-trimoxazole Preventive Therapy (CPT) treatments reduce the risk of TB infection among HIV positive individuals (23, 25, 26). In resource limited countries such as Ethiopia, where there is poor access to health care, very few studies are conducted on the determinants of the incidence of TB among HIV infected people. As a matter of fact, it is important to know the variables which are risk factors for better understanding the etiology of HIV/TB co-infection in the region. This can contribute to the development of interventions to reduce risks. Therefore, this study assessed the incidence of TB and its determinants among HIV positive people in northeast Ethiopia. As a second outcome, the study considered the incidence of TB in relation to years of follow-up.

Methods

Study design and setting

A five-year retrospective cohort study was conducted on HIV positive patients attending the chronic HIV care clinics in selected government health facilities of the Afar Regional State, northeast Ethiopia, from July 2010 to June 2011. The region is located in the north-eastern part of Ethiopia and has a total population of 1,678,000 of whom only 289,000 live in urban and semi-urban areas (27). In the region, there are four hospitals, 40 health centers, and 15 private clinics actively providing services. When HIV care service was first introduced to the region in 2006, 15 public health institutions provided chronic HIV care and support to around more than 4,000 people living with HIV (PLHIV). For this study, two health centers (Awash, and Samara) and three hospitals (Asayta, Abala, and Dubti General) were selected based on the availability of TB/HIV clients. These health institutions were providing chronic HIV care and follow up to about 85% of the patients living with HIV in the region.

Study population and eligibility criteria

All HIV/AIDS patients aged 15 years and above and newly enrolled for HIV care in selected government health facilities of Afar Region from July 2010 to June 2011 participated in the study. These individuals, who enrolled for HIV care from July 2010 to June 2011, were followed for five years, until May 2015. Out of the total 503 people living with HIV and registered during July 2010 to June 2011 in the selected hospitals, 451 records with complete information were included in the analysis. Fifty-two records with incomplete information, like missing the date of enrollment, outcome of interest, and follow-up data were excluded. However, individual charts deleted for analysis were compared to the study groups and showed no significant baseline demographic characteristics. In addition, those who died or were lost to follow-up were considered as censored.

Measurements and study variables

The outcome variable in this study was the incidence rate of TB co-infection among HIV positive patients, and it was calculated using the total duration of follow-up for the whole cohort in person-year observation (PY). For individuals who did not develop TB, the duration of follow-up from the time of enrolment for HIV care until the end was considered as TB-free. For those who developed TB, TB-free survival time was measured from the time of enrolment in the HIV Care Program until the development of TB. An event of an incidence of TB in this study was considered as any form of TB that was not only diagnosed clinically or radio-graphically but also confirmed by laboratory examinations or by patients who have empirically started anti-TB treatment after enrollment. However, since there was no culture confirmation of TB infections during the study period, the cases in the study might be potential ones. When an individual became diagnosed with active TB, treatment was given based on the National TB Program, which was 8 months of treatment (currently 6 months). Patients taking anti-tuberculosis treatment at the time of enrollment were excluded from the study. HIV positive individuals who were lost to follow-up, transferred, died, and not diagnosed for TB until the end of the follow-up period were considered as censored. Study variables, such as age, sex, educational status, employment status, residence, religion, family size, marital status, plus clinical characteristics, like WHO clinical stage, baseline cluster of differentiation (CD4 count), bedridden functional status, history of TB along with body mass index (BMI), hemoglobin level including socio-demographic and economic characteristics were reviewed. Bedridden functional status was

measured by asking the patient whether he or she was able to perform activities of daily living or not. If he/she said "yes", it was taken as bedridden functional status and coded '1'; otherwise, he/she was deemed to be not bedridden functional status. In this study, CPT prophylaxis was defined as a patient who took co-trimoxazole for longer than one month for a prophylaxis purpose. Isoniazid preventive therapy (IPT) use was defined as a patient who took IPT for at least 3 months. Substance use was referred to as use of at least one of the substances (alcohol, khat, cigarettes, and illicit drugs) in an individual's life time to alter mood or behavior. Illicit drugs were defined as psychoactive substances, like hashish, cannabis, and heroin, the production, sale, or use of which is prohibited.

Sample size and sampling procedure

All HIV/AIDS patients aged 15 years and above and enrolled newly into HIV care from July 2010 to June 2011 were participated in the study. Sample size was calculated using the single proportion formula, considering the following assumptions: 17% prevalence of TB among HIV positive people in Jimma, Ethiopia (28), 95% level of confidence, 3.5 margin of error, and 3.3% expected incomplete record (29). Finally, the minimum sample size of 458 was obtained. Though, 503 PLHIV were registered in the selected health facilities for chronic HIV care, a total of 451 patients with complete information were included in the analysis, while 52 records were excluded because of incomplete information.

In Afar Region, where the study was conducted, there were four hospitals, 40 health centers, and 15 private clinics providing services to the community. Out of these, two health centers (Awash and Samara), and three hospitals (Asayta, Abala and Dubti General) were selected based on client flow and the availability of TB and HIV follow-up services. In these selected health facilities, 503 HIV positive people were newly registered from July 2010 to June 2011. However, people living with HIV and registered in the facilities from July 2010 to June 2011 and had complete information were followed until May 2015.

Data collection tool and procedure

Nurses trained on ART collected the data by reviewing charts and using the patient chart data extraction format. All records of HIV/AIDS patients between July 2010 and May 2015 were considered. Charts were retrieved by using patient medical record and ART registration numbers found on the database of the selected health facilities. Forms used for laboratory request, TB

records, ART intake, and patient cards were reviewed. Data quality was assured by using a pretested questionnaire and trained data collectors. Data completeness and consistency was checked by supervisors. The data clerk and case managers assisted the data collectors by identifying charts.

Data Processing and Analysis

Extracted data were checked for completeness, coded, entered, and cleaned into EPI-INFO version 7 and exported to SPSS version 20.0 software for further analysis. Statistical summary measures and incidence density were calculated. Descriptive statistics were used to characterize the socio-demographic and clinical variables. The event of interest was TB incidence. The incidence of TB (measured by incidence and incidence density rates) was stratified by socio-demographic and clinical variables. Kaplan-Meier estimates were used to describe time to event distributions. Log-rank tests were used to compare time-to-event across the different categories. Time-to-event data that the study considered and survival analysis were carried out; the cox proportional hazards model was fitted, and a life table was used to estimate cumulative probabilities. The bi-variable and multivariate cox regression model was used to identify the predictors of the incidence of TB. Variables with p-values of less than 0.2 in the bi-variable analysis were considered for the multivariate cox proportional hazard model. A 95% confidence interval of the hazard ratio (HR) was computed, and variables with less than 0.05 p-values in the multivariate cox proportional hazards model were taken as significant predictors for the outcome variable. Moreover, basic assumptions of the cox proportional hazard model were checked using the Schoenfield residuals test.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Public Health, the University of Gondar. A letter of permission was secured from the Afar Regional Health Bueuro (ARHO), and a written permission letter was sent to each selected health facilities. In addition, confidentiality was maintained by using only unique identification codes rather than patient names and identifications.

Results

Socio-demographic and clinical characteristics of PLHIV

Out of the total 503 PLHIV registered at the selected hospitals from July 2010 to June 2011, 451 records with complete information were followed until May 2015. The charts of 451 HIV/AIDS patients with complete information were analyzed, while 52 records were excluded because they did not contain complete information (**Figure-1**). Out of the 451 patients that remained in the analysis, more than half (267/59.2%) were female, and over half of the total (242/53.7%) were 26-34 years of age. The mean age (±SD) of the patients was 32.6 (±7.5) years. Most of the respondents, 410 (90.9%), were urban dwellers and 275 (61.0%) Muslims **(Table 1)**.

Almost half, 234 (51.9%), of the participants were self-employed. Only 76 (16.9%) had more than 5 family members. Almost half, 212 (47%), of the subjects never went to formal school. More than two-thirds (68.1%) of the patients were currently or formerly married. Of the 130 (28.8%) patients recorded as substance users, 14 (5.0%) were tobacco users, 26 (20.0%) alcohol consumers, and 90 (75.0%) used both **(Table 1)**.

Out of the total 451 study participants with complete information for analysis, more than half (45.4%) had a baseline WHO clinical stage I and II. The majority, 440 (97.6%), of the participants were enrolled with working functional status. Almost half, 218 (51.7%), of the participants were underweight (BMI less than 18.5 kg/m^2), whereas more than three-quarters, 344 (76.3%), were anemic (Hgb<11g/dL). During the five year retrospective follow up, most, 413 (91.6%), of the participants were provided with co-trimoxazole preventive therapy (CPT), while only 94 (20.8%) received isoniazid preventive therapy (IPT). Similarly, nearly half, 215 (47.7%), of the respondents were initiated into ART therapy either on WHO clinical stage or CD4 cell count. More than one-third, 170 (37.7%), of the HIV/AIDS positive people took a combination of Tenofovir (TDF), Lamivudine (3TC), and Efavirenz (EFV); likewise, one-fifth, 110 (24.4%), of the patients took Zidovudine (AZT), Lamivudine (3TC), and Efavirenz (EFV). Another one-fifth, 96 (21.3%), of the patients changed their initial regimen, 92 due to substitution and 4 due to switching to second line treatment for HIV. Out of the 96 HIV/AIDS patients who changed their initial regimen, side effect and development of TB were the major reasons for 50 (52.1%) and 29 (30.2%), respectively (**Table 1).**

Table 1: Socio-demographic and clinical characteristics of PLHIV who were enrolled for chronic HIV care at selected government health facilities in Afar Regional State, northeast Ethiopia from 2010-2011

Characteristics	Frequency	Percent (%)
Age in years (mean=32.6, SD=7.5)		
15-25	55	12.2
26-34	242	53.7
35-44	119	26.3
≥45	35	7.8
Sex		
Male	184	40.8
Female	267	59.2
Marital status		
Single	144	31.9
Married	200	44.3
Divorced	77	17.1
Widowed	30	6.7
Residence		
Urban	410	90.9
Rural	41	9.1
Religion		
Muslim	275	61.0
Orthodox	165	36.6
Others	11	2.4
Educational status		
Illiterate	212	47.0
Primary school	177	39.2
Above secondary	62	13.8
Family size		
1-3	216	47.9
4-5	159	35.3
≥5	76	16.8
Occupation		
Self-employed	234	51.9
Governmental employed	45	10.0
Non-employed	172	38.1
Substance use		
Yes	130	28.8
No	321	71.2
Type of substance used		
Tobacco	14	5.0
Alcohol	26	20.0
Both tobacco and alcohol	90	75.0
On ART		
Yes	215	47.7
No	236	52.3
WHO clinical stage		
I & II	200	45.4
III	172	39.0
IV	69	15.6

Bedridden		
No	440	97.6
Yes	11	2.4
CD4 cell count (cells/uL)		
<100	44	9.8
100-200	124	27.5
201-349	125	27.7
>350	158	35.0
BMI (kg/m^2)		
<18.5	218	51.7
>18.5	203	48.3
Hgb level (g/dL)		
<11	344	76.3
≥11	107	23.7
CPT use		
Yes	413	91.6
No	38	8.4
IPT use		
Yes	94	20.8
No	357	79.2
Initial regimen		
d4t-3TC-NVP	65	14.4
AZT-3TC-EFV	89	19.7
AZT-3TC-NVP	110	24.4
TDF-3TC-EFV	170	37.7
Others	17	3.8
Previous TB disease		
Yes	74	16.4
No	377	83.6
Opportunistic infection (OI)		
Yes	34	7.5
No	417	92.5
Chronic illness		
Yes	35	7.8
No	416	92.2
Regimen change		
To First line	92	20.4
To Second line	4	0.9
Not changed	355	78.7
Reason for change		
Due to TB development	29	30.2
Due to side effect	50	52.1
Failure of treatment	4	4.2
Others	13	13.5
Form of TB		
Pulmonary	91	76.4
extra pulmonary	28	23.6

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation 4; CPT, Co-trimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efavirenz; Hgb, Hemoglobin; IPT, isoniazid preventive therapy; NVP, Nevirapine; OI, Opportunistic Infection; TB, Tuberculosis; TDF, Tenofovir; 3TC, Lamivudine; WHO, World Health Organization

The incidence of TB stratified with socio-demographic and clinical characteristics

Out of the total 451 HIV/AIDS patients, 119 (26.4%) developed active TB infection during the follow-up period, while 332 were censored (40 transferred out, 13 died, 21 lost to follow-up, and 258 remained TB-negative till the end of follow-up period) **(Figure-1)**. Therefore, the overall TB incidence rate in the five year retrospective data was 8.64 cases per 100 Person-years (PY) of observation. The incidence of patients diagnosed with TB at the end of one year was 4.9 per 100 person-year observation. The sum of the whole follow-up period for all 451 HIV/AIDS infected individuals was 1377.41 Person-years of observation. The minimum and maximum follow-up observation was 0.03 and 58.8 months, respectively. The median (IQR) follow-up period was 46.74 months of observation [IQR=15.95-52.42 months]. Females constituted more than half, 67 (56.3%), of the total TB patients. Three-quarters, 91 (76.47%), of the cases were pulmonary TB. About 68 (57.14%) of the TB incidents occurred within the first year of follow up. The incidence of TB was 105 cases and 14 cases among urban and rural dwellers, respectively. The test of equality for survival distribution for different levels of different categories was performed with Kaplan Meier, using the long rank test. The cumulative probability of TB patient survival at the end of one year, two, three, and four years was 0.77, 0.68, 0.34 and 0.10, respectively. The median survival time was 54 months (**Figure-2**). In terms of survival curves, there were significant variations among underweight and normal weight ($p<0.002$) (**Figure-3**); different WHO clinical stage categories ($P<0.001$) (**Figure-4**); anemic and non-anemic ($p<0.001$) (**Figure-5**); bedridden and otherwise ($p<0.002$) (**Figure-6**); and IPT receivers and non-receivers ($P<0.0001$) (**Figure-7**). Out of the participants who developed TB, 41 (34.5%) had previous TB disease, and 8 (6.7%) were bedridden at the time of enrollment. One hundred fifteen (96.6%) of the TB cases were not given INH prophylactic therapy. Fifty (42.0%) with incident cases of TB were enrolled with Hgb level below11g/dL (**Table-2**).

Table 2: The incidence of tuberculosis stratified by socio-demographic and clinical characteristics of PLHIV on HIV chronic care at selected government health facilities of Afar Regional State, July 2010 to May 2015

Characteristics	Total N (%)	TB incidence N (%)	Person-Years observation (PY)
Years of follow-up (median=46.74, IQR=15.95-52.42, months)			
One year	88(19.5)	68(57.1)	35.07
Two years	41(9.0)	28(23.5)	54.73
Three years	32(7.0)	11(9.3)	76.66
Forth	89(19.8)	9(7.6)	322.67
Fifth	201(44.6)	3(2.5)	888.28
Age (years)			
15-25	55(12.2)	14(11.7)	158.81
26-34	242(53.7)	63(52.9)	739.05
35-44	119(26.3)	30(25.3)	384.1
≥45	35(7.8)	12(10.1)	95.45
Sex			
Male	184(40.8)	52(43.7)	536.9
Female	267(59.2)	67(56.3)	840.51
Residence			
Urban	410(90.9)	105(88.2)	1260.67
Rural	41(9.1)	14(11.8)	116.74
Marital status			
Single	144(31.9)	30(25.2)	435.14
Married	200(44.3)	52(43.7)	616.07
Divorced	77(17.1)	30(25.2)	184.5
Widowed	30(6.7)	7(7.9)	91.61
Educational status			
Illiterate	212(47.0)	55(46.2)	683.8
Primary School	177(39.3)	49 (41.2)	510.54
Secondary and above	62(13.7)	15(12.6)	183.07
Occupation			
Self-employed	234(51.8)	59(49.6)	741.68
Government-employed	45(10.1)	9(7.6)	121.45
Non- employment	172(38.1)	51(42.8)	514.28
Religion			
Muslim	275(61.0)	70(58.8)	826.69
Orthodox	165(36.6)	47(39.5)	520.89
Others	11(2.4)	2(1.7)	29.83
Family size			
1-3	216(47.9)	51(42.9)	668.68
4-5	159(35.3)	43(36.1)	484.74
>5	76(16.8)	25(21.0)	223.99
Substance use			
Yes	130(28.8)	42(35.3)	379.7
No	321(71.2)	77(64.7)	997.71

Previous TB disease			
Yes	74(16.4)	41(34.5)	164.74
No	377(83.6)	78(65.5)	1212.67
Opportunistic infection (OI)			
Yes	34(7.5)	19(16)	85.28
No	417(92.5)	100(84)	1292.13
Chronic illness			
Yes	35(7.8)	11(9.2)	106.28
No	416(92.2)	108(90.8)	1271.13
Bedridden			
Yes	11 (2.4)	8(6.7)	33
No	440(97.6)	111(93.3)	1356.76
BMI (kg/m^2)			
<18.5	218(48.3)	75(64)	626.46
>18.5	203(45.0)	42(36)	750.95
Hgb level (g/dL)			
<11	107(23.7)	50(42.0)	233.8
≥11	344(76.3)	69(58.0)	1143.6
CD4 cell count (cells/uL)			
<100	44(9.7)	22(18.5)	84.77
100-200	124(27.5)	40(33.6)	343.72
201-349	125(27.7)	29(24.4)	384.29
>350	158(35.0)	28(23.5)	564.63
On ART			
Yes	215 (47.7)	36 (30.3)	941.70
No	236(52.3)	83(69.7)	435.71
WHO clinical stage			
I & II	210(46.6%)	36(30.3)	785.3
III	172(38.1)	59(49.6)	464.98
IV	69(15.3)	24(20.1)	187.13
Initial regimen			
d4t-3TC-NVP	65(14.4)	14(11.7)	223.56
AZT-3TC-EFV	89(19.7)	20(16.8)	296.28
AZT-3TC-NVP	110(24.4)	28(23.5)	349.17
TDF-3TC-EFV	170(37.7)	52(43.7)	461.71
Others	17(3.8)	5(4.3)	46.69
IPT use			
Yes	94(20.8)	4(3.4)	363.60
No	357(79.1)	115(96.6)	1013.81
CPT use			
Yes	413(91.6)	108(90.8)	1259.65
No	38(8.4)	11(9.2)	117.76

AZT, Zidovudine; BMI, Body mass index; CD4, Cluster of differentiation 4; CPT, Co-trimoxazole Preventive Therapy; D4T, Stavudine; EFV, Efavirenz; Hgb, Hemoglobin; IPT, isoniazid preventive therapy; NVP, Nevirapine; OI, Opportunistic Infections; TB, Tuberculosis; TDF, Tenofovir; 3TC, Lamivudine; WHO, World Health Organization

Determinants of TB incidence

In the bivariable cox regression analysis, marital status, family size, substance use, history of TB, baseline CD4 count, WHO clinical stage, opportunistic infection, body mass index (BMI), hemoglobin level, isoniazid preventive therapy (IPT), and functional status were found to be predictors of the incidence of tuberculosis at a p-value of less than 0.2. Consequently, these variables were subjected to multivariate cox regression analysis and previous TB disease, bed-ridden functional status, hemoglobin, BMI, IPT and advanced WHO clinical stage were found statistically significant determinants of TB free survival at a p-value of less than 0.05.

Accordingly, the multivariate cox regression analysis indicated that people living with HIV (PLHIV) and had history of TB disease were 3.65 times at higher risk of developing TB at any time than to PLHIV who had no history of TB (AHR 3.65, 95% CI 1.97-6.73). PLHIV who were in bed-ridden functional status at base-line were 5.45 times at more risk of developing TB compared with PLHIV not in bedridden functional status (AHR 5.45, 95% CI 1.16-25.49). Similarly, PLHIV with baseline BMI less than 18.5kg/m^2 were 2.53 times at higher risk of developing TB at any time than those with BMI greater than 18.5kg/m^2 (AHR 2.53, 95 % CI 1.27-5.05). Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR 0.14, 95% CI 0.05-0.39). PLHIV in WHO clinical stage III and IV had a greater risk of developing TB compared with WHO stage I and II (AHR 2.84, 95% CI 1.11, 7.27), and (AHR3.07, 95% CI 1.08, 8.75), respectively. The study also revealed that the incidence of TB in the first three years of follow-up was higher when compared with the other subsequent years. In addition, PLHIV who were anemic (Hgb <11g/dL) were 2.31 times at higher risk of developing TB than those with Hgb level greater than 11 g/dL (AHR 2.31, 95% CI 1.35- 3.93) (**Table-3**).

Table 3: Cox regression analysis of the determinants of the incidence of tuberculosis among adult on chronic HIV care at selected government health facilities of Afar Regional State from July 2010 to May, 2015

Variables	Survival status		Total	CHR (95% CI)	AHR(95% CI)
	Event (TB)	Censored			
Marital status					
Single	30	114	144	1.00	1.00
Married	52	148	200	1.34 (0.80-2.23)	1.26 (0.65-2.43)
Divorce	30	47	77	2.43 (1.32-4.46)	1.75 (0.83-3.68)
Widowed	7	23	30	1.16 (0.45-2.95)	2.42 (0.79-7.38)
Family size					
1-3	51	165	216	1.00	1.00
4-5	43	116	159	1.19 (0.75-1.92)	0.49 (0.25-1.34)
>5	25	51	76	1.58 (0.89-2.81)	0.71 (0.35-1.76)
Substance use					
Yes	42	88	130	1.51 (0.96-2.37)	1.47 (0.84-2.56)
No	77	244	321	1.00	1.00
Previous TB disease					
Yes	41	33	74	4.76 (2.83-8.03)	3.65 (1.97-6.73)**
No	78	299	377	1.00	1.00
Opportunistic infection (OI)					
Yes	19	15	34	4.02 (1.97-8.19)	2.31 (0.98-5.45)
No	100	317	417	1.00	1.00
Bedridden					
Yes	8	3	11	7.90 (2.06-30.31)	5.45 (1.16-25.49)**
No	111	329	440	1.00	1.00
BMI (kg/m^2)					
<18.5	75	143	218	2.01(1.29-3.12)	2.53(1.27-5.05)**
≥18.5	42	161	203	1.00	1.00
Length of follow-up					
≤ 1 year	68	20	88	78.76 (36.7-168.9)	83.76 (33.94-206.7)**
2-3 years	39	34	73	26.57 (12.7-55.6)	33.81(14.12-80.96)**
4-5 years	12	278	290	1.00	1.00
WHO clinical stage					
I &II	36	174	200	1.00	1.00
III	59	113	172	2.52 (1.57-4.07)	2.84(1.11-7.27)**
IV	24	45	69	2.58 (1.40-4.75)	3.07(1.08-8.75)**
Hgb level (g/dL)					
<11	50	57	107	3.49 (2.20-5.55)	2.31(1.35-3.93)**
≥11	69	275	344	1.00	1.00
CD4 count (cells/uL)					
<100	22	22	44	4.64 (2.26-9.52)	1.14(0.46-2.82)
100-200	40	84	124	2.21 (1.27-3.85)	1.29(0.66-2.57)
201-349	29	96	125	1.40 (0.78-2.51)	0.99(0.49-1.99)
≥350	28	130	158	1.00	1.00
IPT					
Yes	4	90	94	0.09 (0.03-0.26)	0.14 (0.05, 0.39)**
No	115	242	357	1.00	1.00

** Variable significant at p-value less than 0.05

BMI, Body mass index; CD4, Cluster of differentiation 4; Cells/ul, cells per microliter (ul); Hgb, Hemoglobin; g/dl, grams (g) per decilitre (dL); OI, Opportunistic Infection; IPT, isoniazid preventive therapy; TB, Tuberculosis; WHO, World Health Organization

Discussion

TB and HIV remain the major public health problems in many parts of the world. Ethiopia is among the TB high burden countries with an estimated annual incidence of 211cases per 100,000 people and a prevalence of 224 cases per 100,000 (30).

In this study, the overall incidence of TB among PLHIV was 8.64 cases per 100 person-year (PY) observation. This finding is similar to those reported from Gondar and Assela, Ethiopia, which are 7 and 7.9 cases, respectively, per 100 person-year (PY) observations (31, 32). The finding is consistent with that of a study in Tanzania and other Sub-Saharan countries with incidence ranging from 7.6-8.2 per 100 person-year observation (PY) (33, 34). However, the incidence density of TB in this study is higher than those of studies conducted in Korea, Israel, and Malaysia (35-37). The lower incidence of TB in the latter studies compared with this one might be due to the availability of better preventive, diagnostic, and treatment setups and strategies for controlling TB in such countries when compared with our study setting. In addition, low health care coverage, high burden of HIV, and the fact that the study setting is so unprivileged might explain the difference. Furthermore, late enrollment at health facilities due to late presentation of HIV infected people at health facilities, increases the progression of latent infection to active TB after HIV chronic care. It was noted that individuals with late presentation might get new infections or IRIS after initiation into highly active antiretroviral therapy (HAART), and Immune Reconstitution Inflammatory Syndrome (IRIS) related TB is commonly seen within the first six months of initiation into HAART (38). Similarly, it was revealed that the incidence of TB is significantly associated with the length of follow-up year. It was reported that the incidence of TB decreased as the years of follow-up increased, and a higher incidence of TB was reported in the first three of follow-up years compared with the other subsequent years.

Out of the determinants of the incidence of TB infection in the multivariate cox regression analysis, the study revealed that previous TB disease, using IPT, bedridden functional status, low hemoglobin level, advanced WHO staging (III and IV), years of follow-up, and low BMI were

found to be significantly associated with the incidence of TB. Individuals who had history of TB disease had greater risk of developing TB compared with those who had no history of TB treatment. Poor compliance with anti-TB treatment at the first episode, reactivation or re-infection of individuals with the existing diminished immunity might be the reasons for higher incidence of TB among individuals with history of TB infection. This finding is consistent with those of studies conducted in Uganda, Malaysia, and Israel (36, 37, 39).

PLHIV who took Isoniazid preventive therapy (IPT) were found to be protective of the incidence of TB. Individuals who took Isoniazid preventive therapy (IPT) were 86% less likely to develop TB at any time compared to those who didn't take IPT (AHR=0.14, 95% CI: 0.05-0.39). This might be due to the role of IPT in reducing the incidence of TB among people living with HIV. The finding is consistent with those of studies in Ethiopia, South Africa, and Brazil (40-42). In spite of this fact, poor uptake, ambiguity, and fear of drug resistance might contribute to no-IPT use.

Similarly, in this study, patients' functional status at baseline was found to be the predictor of TB incidence. Patient bedridden functional status at baseline was 5.45 times at higher risk of developing TB than individuals with working functional status at baseline. This might be due to the fact that debilitated patients will be prone to malnutrition, and lack of physical activity exposes them to many diseases, including TB. This finding is in line with those of other studies conducted in Ethiopia (16, 31, 43).

Out of the anthropometric variables, HIV patients who were underweight (BMI <18.5 kg/m^2) were 2.53 times at higher risk of developing TB compared to individuals with BMI≥18.5 kg/m^2. This finding was consistent with that of a study done in Tanzania (44), Ethiopia, and South Africa (33, 45). The possible explanations might be that a low BMI category is a proxy indicator of malnutrition, and malnutrition in HIV patients is associated with increased catabolic activity, infection, loss of appetite, and decreased intake, which further increase the risk of developing opportunistic infections such as tuberculosis.

Furthermore, this study found that patients with Hgb level of <11 g/dL at base-line were 2.31 times at higher risk of developing TB than those with Hgb level ≥11 at base-line. Hematologic complications were risk factors for the incidence of TB among PLHIV. This finding is concordant with those of studies conducted in Ethiopia, Uganda, Tanzania, and South Africa (44-

47). The possible explanation might be malnutrition, side effects of medications, opportunistic infections, and advanced stage of the disease. Undiagnosed TB could explain low Hgb level at early enrollment.

The other important result which was found to have a significant association with the incidence of TB was advanced clinical staging (III & IV). PLHIV with advanced WHO staging (III and IV), respectively had 2.84 and 3.07 times higher risk of developing TB compared with people in stages I & II. The finding corresponded to those of studies conducted in Nigeria (48), South Africa (49), and Gambia (50). This might be due to the fact that once patients get into late stages; the immunity protective capacity will be minimal, making them predisposed to tuberculosis infection. Something worth mentioning as well is that TB is one of the defining factors of AIDS that categorizes patients who use HIV/AIDS clinics in Ethiopia into late WHO clinical staging.

Limitations of the study

Though the study did its best to indicate the incidence and predictors of tuberculosis among PLHIV using a five-year retrospective data, it was not free from limitations. The retrospective nature of the study limited the inclusion of all possible factors that could affect the incidence of tuberculosis. Variables such as housing condition and household income were some of the plausible factors that were not measured in this study. For some risk factors, such as CD4 count, the sample size limited the power to provide clinically relevant conclusions because of the overall low incidence rate of TB. Inability to conduct culture confirmation (the gold standard method) is another limitation of the study. Inability to address TB contacts (other family member/co-inhabitant) and introduction of selection bias due to the exclusion of patients who did not use the selected hospitals is the other drawback. Since the study was conducted in a single region of Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

Conclusion

The overall incidence of TB among PLHIV was found to be comparable with those of similar studies in Ethiopia. However, it was higher in the first year of follow-up than it was in the subsequent years. HIV infected individuals with history of TB disease, not using IPT, underweight status (BMI<18.5kg/m^2), bedridden functional status, being anemic (Hgb<11g/dL), advanced WHO stage (III &IV), and short duration of follow-up were determinants of the

incidence of TB among PLHIV. Therefore, our study suggested early screening and diagnosis among high risk PLHIV such as those in bed-ridden functional status, underweight (BMI<18.5kg/$m^{2)}$, and anemic (Hgb <11g/dL). In addition, providing IPT to PLHIV without active TB and intensified TB case screening for those with advanced WHO stage is highly recommended. In addition, emphasis should be given to those with shorter follow-ups. Therefore, attention to PLHIV and prompt diagnosis and treatment of TB are recommended. Furthermore, prospective studies need to include all factors that influence the risk of TB among PLHIV. Since our study was conducted in a single region of Ethiopia, collaborative projects that can include several regions of the country are recommended to give a more balanced view of the incidence of TB and potential risk factors in HIV-infected patients.

List of abbreviations

AHR, Adjusted hazard ratio; AIDS, Acquired immune deficiency syndrome; ART, Anti-Retroviral Therapy; BMI, Body mass index; CD4, cluster of differentiation 4; CI, Confidence interval; CPT, Cotrimoxazole prophylaxis therapy; EDHS, Ethiopian Demographic health survey; HIV, Human immune deficiency; HAART, Highly active anti retro viral therapy; Hgb, Hemoglobin; INH, Isoniazid; IQR, Inter quartile range; IPT, Isoniazid preventive therapy; IRIS, Immune reconstitution inflammatory syndrome; PLHIV/AIDS, People living with HIV/AIDS; PY, person-year observation; TB, tuberculosis; WHO, World health organization

Competing interests

The authors declare that they have no conflict of interest.

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Data sharing statement

All data supporting our findings will be shared upon request.

Authors' contributions

AA, DM and MKY involved in the conception, design, data collection, analysis and report writing. DM, AMS, FB, and MKY assisted with the design, approved the proposal with some revisions, participated in data analysis and manuscript preparation. All authors read and approved the final manuscript.

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Figure legends

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 4: Kaplan Meier survival curve of TB patients based on the WHO stage among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 5: Kaplan Meier survival curve of TB patients based on hemoglobin level among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

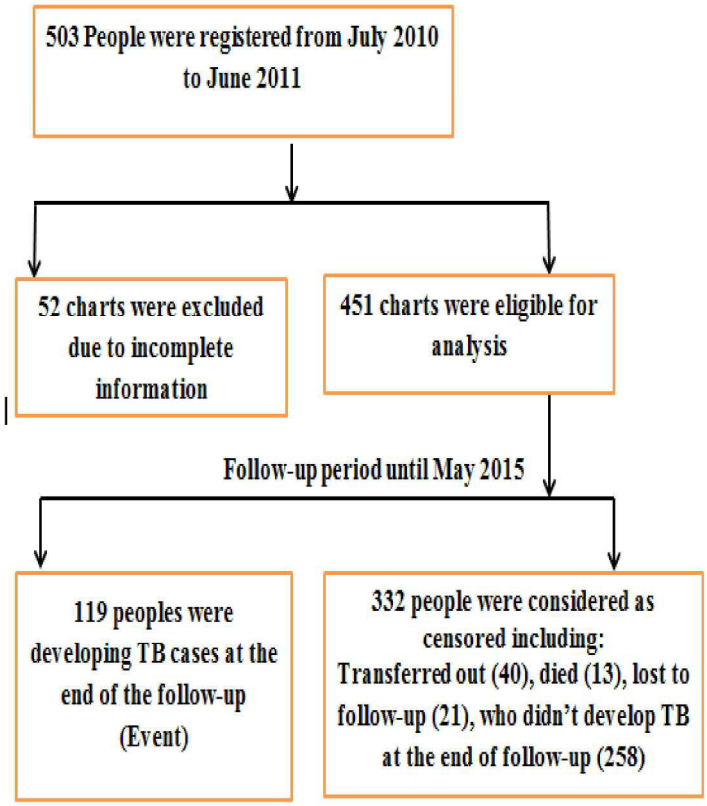

Figure 1: Flow chart showing selection of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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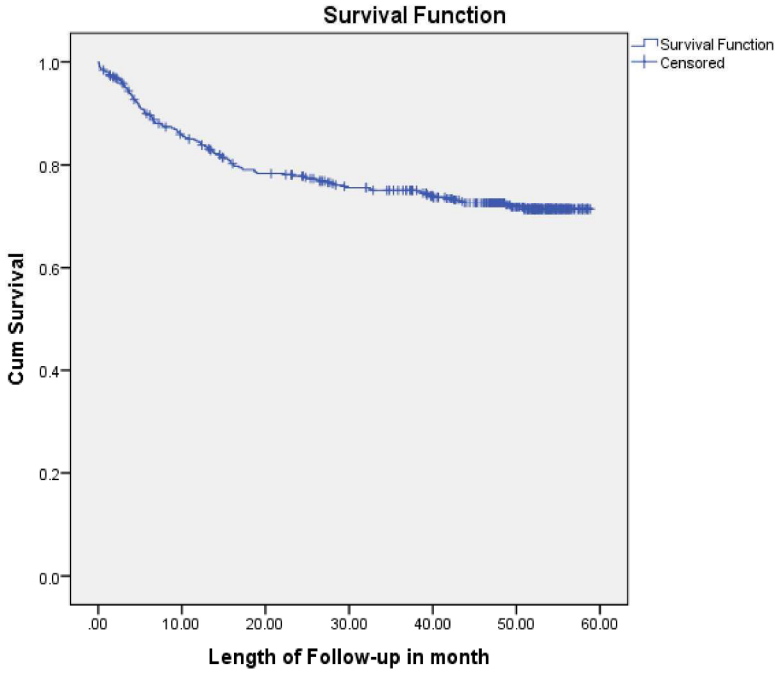

Figure 2: Kaplan Meier curve of TB survival proportion of HIV/AIDS people at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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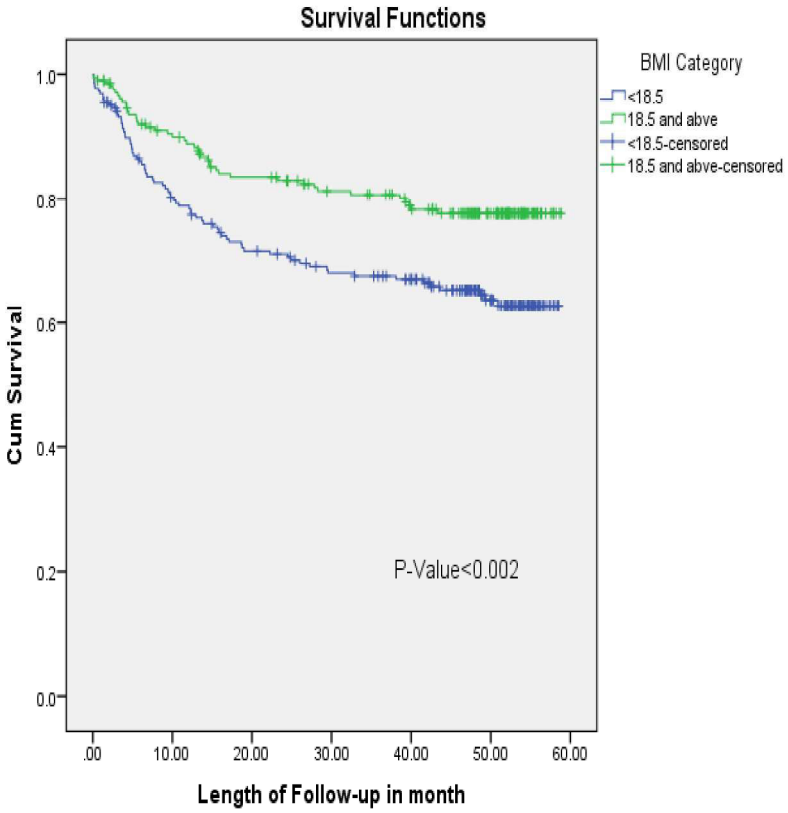

Figure 3: Kaplan Meier survival curve of TB patients based on the BMI category among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

325x420mm (300 x 300 DPI)

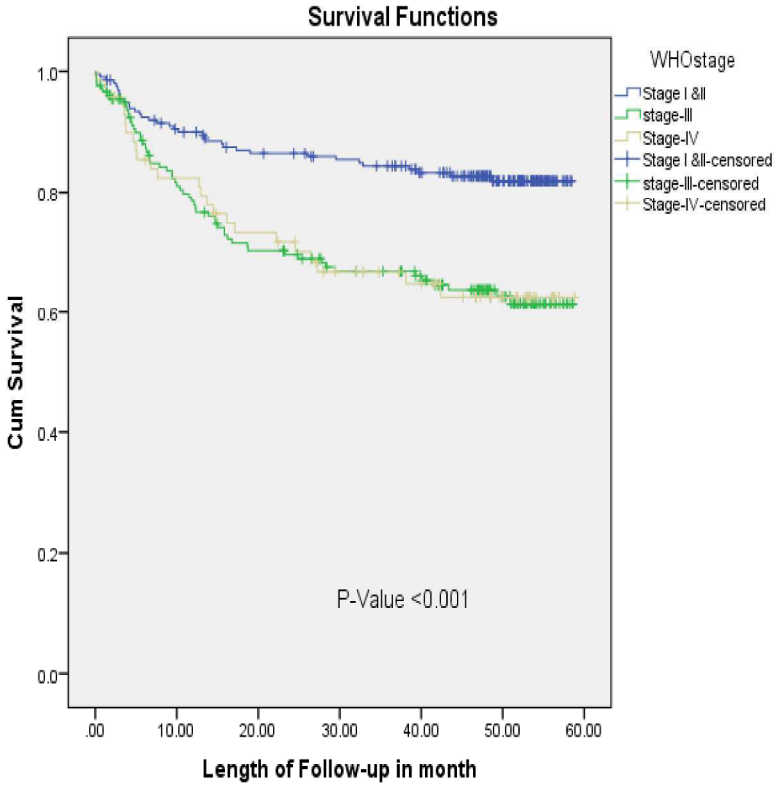

Figure 4: Kaplan Meier survival curve of TB patients based on the WHO stage among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

325x420mm (300 x 300 DPI)

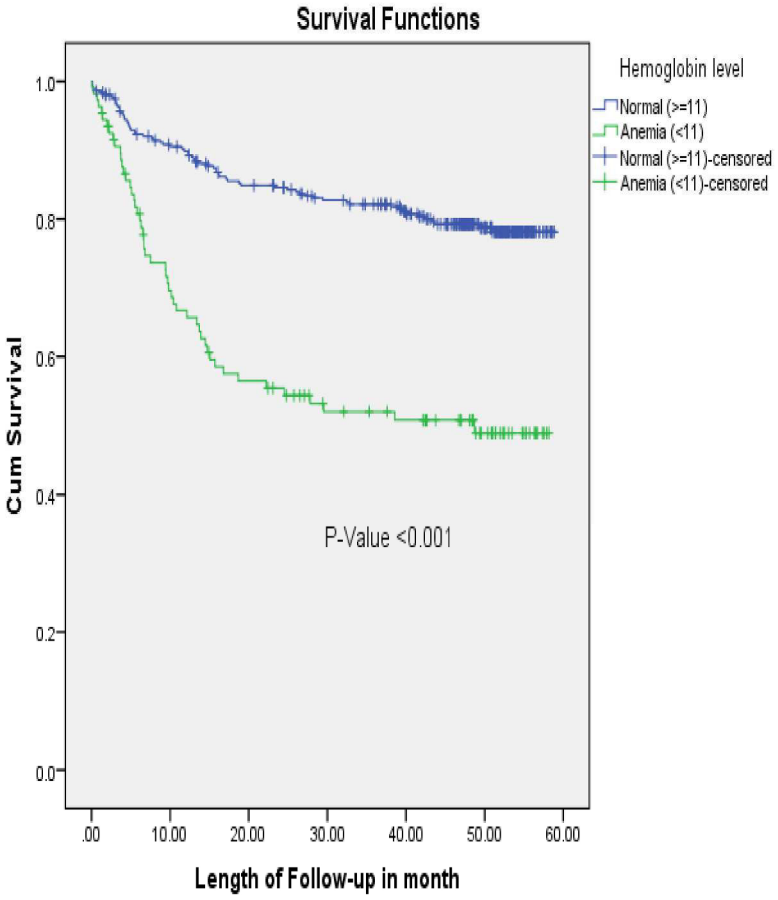

Figure 5: Kaplan Meier survival curve of TB patients based on hemoglobin level among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

279x361mm (300 x 300 DPI)

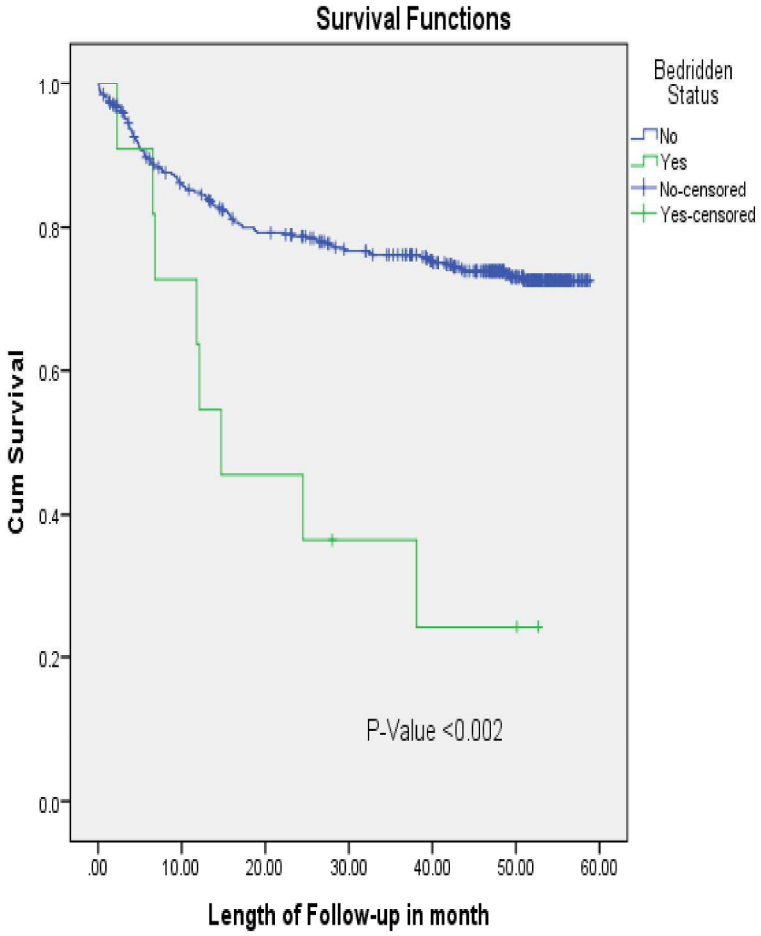

Figure 6: Kaplan Meier survival curve of TB patients based on the bed-ridden functional among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

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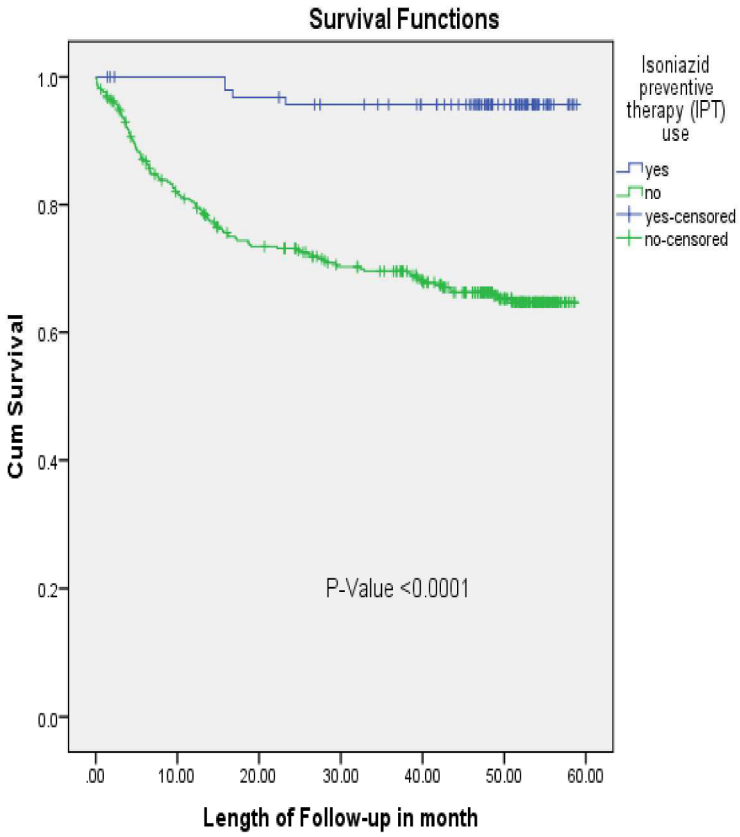

Figure 7: Kaplan Meier survival curve of TB patients based on IPT use among PLHIV at selected Governmental health facilities in Northeast Ethiopia, July 2010 to May, 2015

279x361mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	• Study design is indicated in the title and abstract sections (page 1 line-2 OR on page-2 line-4) • Abstract section is informative and is indicated in page-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	• The type of data which was retrospective cohort is given in the title and the abstract section (pages 1&2) • The geographical region (northeast Ethiopia) is mentioned in the title and abstract sections (pages 1 & 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	• Background/Introduction section is presented on page-4 • Rationale of the study is mentioned on page-5 lines 13-		

			18		
Objectives	3	State specific objectives, including any prespecified hypotheses	• Objectives of the study are indicated on page-5 lines 17-20. In addition, it is also clearly mentioned in the abstract section on page-2 lines 13-16.		
Methods					
Study Design	4	Present key elements of study design early in the paper	• Study design is found on page 5 lines 23-24.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	• Study setting is stated on page-5 line 21 to page-6 line 2.		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants	• Study population and eligibility criteria are found on page-6 lines 4-13	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a	• The methods of data collection are on page 7 • The flow diagram indicating how the study subjects are selected is presented in figure 1.

		(b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	• Measurement and study variables are presented on page-6, lines 14 to page -7 line-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	• Data collection tool and procedure is located on page-7 lines 22-30		
Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at	• Sample size calculation and procedure is described on page-7 lines 7-14		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to	• Data processing and analysis is found on page-8,		

		examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	lines 1-17		
Data access and cleaning methods		..	• Data access and cleaning is found on page-7 lines 22-27	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	• How the authors accessed data is stated in the data collection procedure (page-7) • Information on data coding, entering and cleaning is given in the data processing and analysis sub-sections (page-8, lines 1-17)
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	• The study

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	setting is on page 5 lines 21 to page 6 lines 1-2
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	• Number of participants included in this study is indicated on page-8 lines 27-28 • Flow diagram representing how study participants are presented on figure-1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	• A flow diagram indicating the eligibility of study participants for the study is presented in a graph 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	• Descriptive data, including the socio-demographic and clinical factors are located from pages 8-11		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report	• The outcome data (incidence of TB) is on pages 12-14		

		numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	• The adjusted estimates with 95% confidence interval are reported on page 16		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	None		
Discussion					
Key results	18	Summarise key results with reference to study objectives	• The discussion section is presented on pages 17-19		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	• The limitation of the study is pointed out on page 19 lines 12-22	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	• The conclusion section is on page 19 line 23 to page		

		analyses, results from similar studies, and other relevant evidence	20 lines 1-9		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Since the study was conducted in a setting where more than 85% of HIV/AIDS patients are enrolled, we can generalize the finding to northeast Ethiopia		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	• Funding information is on page 20 lines 20-21		
Accessibility of protocol, raw data, and programming code			• Data sharing statements are on page 20 lines 22-23	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	• Data collection procedure is on page-7 and data sharing statement is on page 24.

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.