

# BMJ Open Incidence and determinants of tuberculosis infection among adult patients with HIV attending HIV care in north-east Ethiopia: a retrospective cohort study

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## ABSTRACT

**Objective** This study assessed the incidence of tuberculosis (TB) and its predictors among adults living with HIV/AIDS in government health facilities in north-east Ethiopia.

**Setting** A 5-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 in north-east Ethiopia.

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

**Primary outcome measure** The primary outcome was the proportion of patients diagnosed with TB or the 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 TB was 8.6 per 100 PY of observation. Previous TB disease (adjusted HR (AHR) 3.65, 95% CI 1.97 to 6.73), being bedridden (AHR 5.45, 95% CI 1.16 to 25.49), being underweight (body mass index (BMI) <18.5 kg/m<sup>2</sup>) (AHR 2.53, 95% CI 1.27 to 5.05), taking isoniazid preventive therapy (IPT) (AHR 0.14, 95% CI 0.05 to 0.39), haemoglobin below 11 g/dL (AHR 2.31, 95% CI 1.35 to 3.93), and being in WHO clinical stages III and IV (AHR 2.84, 95% CI 1.11 to 7.27; AHR 3.07, 95% CI 1.08 to 8.75, respectively) were significant for the incidence of TB.

**Conclusion** The incidence of TB among adults living with HIV/AIDS in the first 3 years of follow-up was higher compared with that of subsequent years. Previous TB disease, no IPT, low BMI and haemoglobin level, advanced WHO clinical stage, and bedridden condition were the determinants of the incidence of TB. Therefore, addressing the significant predictors and improving TB/HIV collaborative activities should be strengthened in the study setting.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* that affects the lungs (pulmonary TB),

## Strengths and limitations of this study

- The study, which involved a 5-year follow-up, covered a longer time than other similar studies and is expected to show the long-term impact of HIV on tuberculosis (TB).
- 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 and the retrospective nature of the method prevented the inclusion of all possible factors that affect the incidence of TB.
- Inability to address TB contacts (other family members/cohabitants) 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 limitations of the study.
- Since the study was conducted in a single region in Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.

but can also affect other sites (extrapulmonary TB), and has remained a major global health problem. In 2015, TB was one of the top 10 causes of death worldwide and the leading killer among HIV-positive people, ranking above HIV/AIDS as one of the leading cause of death from infectious diseases.<sup>1</sup> Out of the 1.4 million TB-caused deaths reported in 2015, 0.4 million occurred in HIV-positive patients. Globally, it was estimated that there were 10.4 million TB cases, including 1.2 million among HIV-positive people.<sup>1</sup>

Since the beginning of the pandemic, nearly 78 million people worldwide have contracted HIV infection, and close to 39 million died of AIDS-related causes, 25%

of which was due to TB.<sup>2</sup> According to the WHO 2014 report, there were an estimated 1.1 million cases of TB coinfecting with HIV,<sup>3</sup> and majority (90%) of the TB-HIV coinfecting people were living in resource-limited settings, such as Ethiopia.<sup>4-6</sup> In the African region, which has the highest TB/HIV burden, three out of four patients with TB knew their HIV status. In fact, 70% of patients with TB known to be living with HIV in 2013 were started on antiretroviral therapy (ART). Sub-Saharan Africa is one of the regions highly hit by the HIV epidemic, covering more than three-quarters (79%) of the burden of TB-HIV coinfections.<sup>7</sup>

In Ethiopia, TB remains one of the leading causes of mortality and the third major cause of hospital admissions. In the last 10 years, the number of new cases has increased from 55 000 to 100 000, and the rise in the number of TB cases has been due to the rapid spread of HIV infection. According to the 2011 Ethiopian Demographic and Health Survey 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,<sup>8</sup> and the global TB report indicated that Ethiopia ranked 10th among the 22 TB high-burden countries, with a TB-HIV coinfection prevalence of 15% in 2012.<sup>6,7</sup> TB-HIV coinfection, 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 workforce.<sup>9</sup> Hence, the Ministry of Health designed a strategy to increase the percentage of patients with TB tested for HIV and vice versa. As a result, the percentage of patients with TB tested for HIV increased from 16% in 2007 to 92% in 2012, and patients with HIV screened for TB from 25% in 2007 to 92% in 2012.<sup>10</sup>

Although HIV increases the risk of developing TB, it is not the only determinant. Various reports indicated that sociodemographic,<sup>11 12</sup> clinical,<sup>13 14</sup> lifestyle<sup>14 15</sup> and environmental<sup>16</sup> 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),<sup>17-21</sup> low haemoglobin (Hgb) level, diabetes and other opportunistic infections, and functional status showed significant associations with the incidence of TB.<sup>20 22-24</sup> However, isoniazid preventive therapy (IPT), ART and co-trimoxazole preventive therapy (CPT) treatments reduce the risk of TB infection among HIV-positive individuals.<sup>23 25 26</sup> In resource-limited countries such as Ethiopia, where there is poor access to healthcare, 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 that are risk factors to better understand the aetiology of HIV/TB coinfection 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 north-east Ethiopia.

As a second outcome, the study considered the incidence of TB in relation to years of follow-up.

## METHODS

### Study design and setting

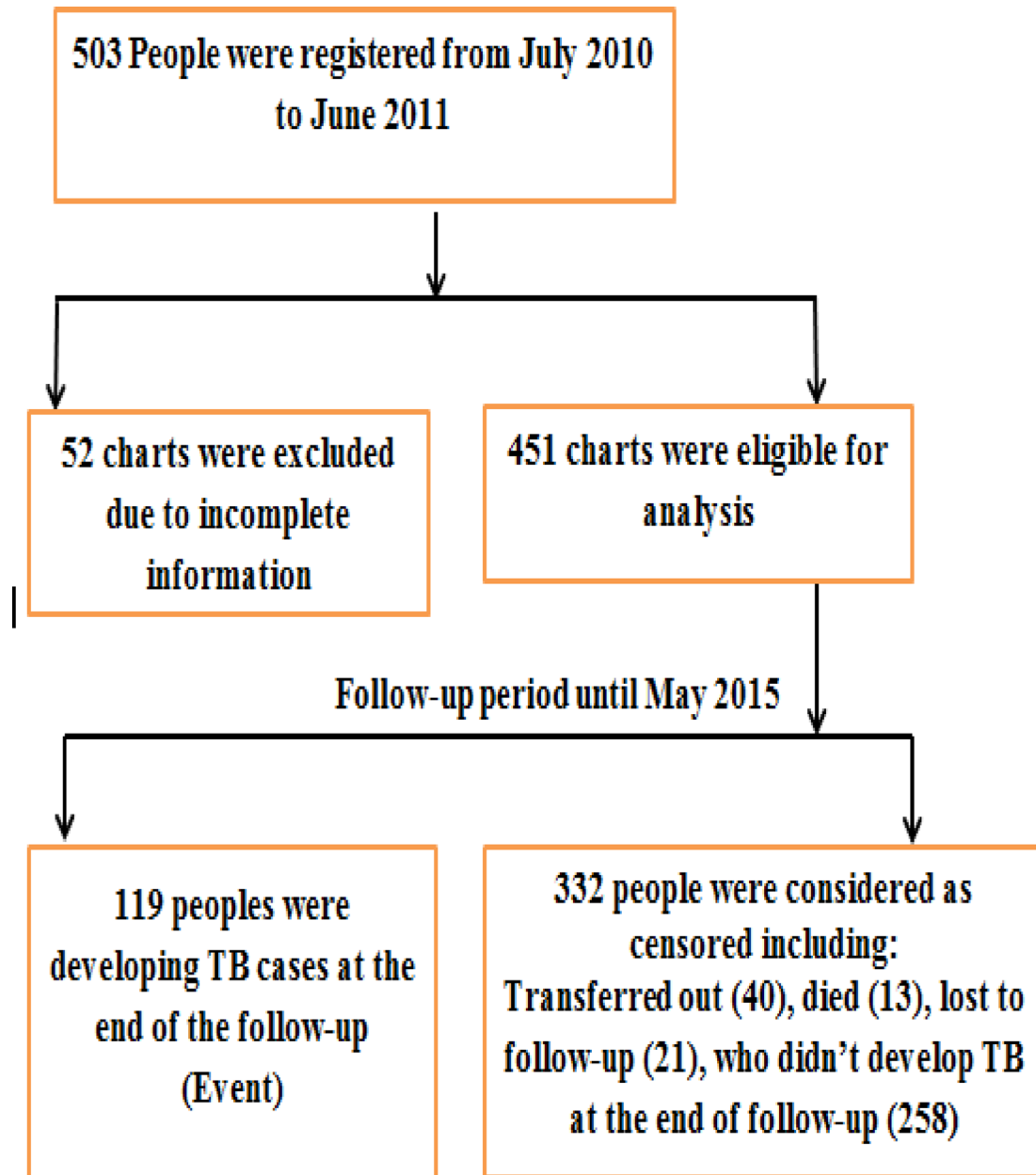
A 5-year retrospective cohort study was conducted on HIV-positive patients attending chronic HIV care clinics in selected government health facilities in Afar Regional State, north-east Ethiopia, from July 2010 to June 2011. The region is located in the north-eastern part of Ethiopia and has a total population of 1 678 000, of whom only 289 000 live in urban and semiurban areas.<sup>27</sup> In the region, there are 4 hospitals, 40 health centres 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 4000 people living with HIV (PLHIV). In this study, two health centres (Awash and Samara) and three hospitals (Asayta, Abala and Dubti General) were selected based on the availability of clients with TB/HIV. 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 patients with HIV/AIDS aged 15 years and above and newly enrolled for HIV care in selected government health facilities in 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 5 years, until May 2015. Out of the total 503 people living with HIV and registered from 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, such as missing the date of enrolment, outcome of interest and follow-up data, were excluded. However, individual charts deleted for analysis were compared with 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 coinfection among HIV-positive patients, and it was calculated using the total duration of follow-up for the whole cohort in person-year (PY) of observation. 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 programme until the development of TB. An event of an incidence of TB in this study was considered as any form of TB that was diagnosed clinically or radiographically and confirmed by laboratory examinations or by patients who have empirically started anti-TB treatment after enrolment.



**Figure 1** Flow chart showing selection of people with HIV/AIDS at selected government health facilities in north-east Ethiopia, July 2010–May 2015. TB, tuberculosis.

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 programme, which was 8 months of treatment (currently 6 months). Patients taking anti-TB treatment at the time of enrolment were excluded from the study. HIV-positive individuals who were lost to follow-up, transferred, died and not diagnosed with 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 and marital status, plus clinical characteristics such as WHO clinical stage, baseline cluster of differentiation (CD4 count), bedridden functional status, history of

TB, along with body mass index (BMI) and Hgb level, and including sociodemographic 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 or she said 'yes', it was taken as bedridden functional status and coded as '1'; otherwise, he or she was deemed to be not of bedridden functional status. In this study, CPT prophylaxis was defined as a patient who took co-trimoxazole for longer than 1 month for a prophylaxis purpose. 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 lifetime to alter mood or behaviour. Illicit drugs were defined as psychoactive

substances, such as hashish, cannabis and heroin, the production, sale or use of which is prohibited.

### Sample size and sampling procedure

All patients with HIV/AIDS aged 15 years and above and were newly enrolled into HIV care from July 2010 to June 2011 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,<sup>28</sup> 95% level of confidence, 3.5 margin of error and 3.3% expected incomplete record.<sup>29</sup> Finally, the minimum sample size of 458 was obtained. Although 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 4 hospitals, 40 health centres and 15 private clinics providing services to the community. Out of these, two health centres (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 patients with HIV/AIDS between July 2010 and May 2015 were considered. Charts were retrieved 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 using a pretested questionnaire and trained data collectors. Data completeness and consistency were 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 V.7 and exported to SPSS V.20.0 software for further analysis. Statistical summary measures and incidence density were calculated. Descriptive statistics were used to characterise the sociodemographic and clinical variables. The event of interest was TB incidence. The incidence of TB (measured by incidence and incidence density rates) was stratified by sociodemographic 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 bivariable and multivariate Cox regression models were used to identify the predictors of the incidence of TB. Variables with P values of less than 0.2 in the bivariable analysis were considered for the multivariate Cox proportional hazard model. A 95% CI of the 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 Schoenfeld residuals test.

### Ethical considerations

A letter of permission was secured from the Afar Regional Health Bureau, and a written permission letter was sent to each selected health facility. In addition, confidentiality was maintained by using only unique identification codes rather than patient names and identifications.

## RESULTS

### Sociodemographic 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 patients with HIV/AIDS with complete information were analysed, while 52 records were excluded because they did not contain complete information (figure 1). Out of the 451 patients who 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 ( $\pm$ SD) of patients was 32.6 ( $\pm$ 7.5) years. Most of the respondents (410, 90.9%) were urban dwellers and 275 (61.0%) were Muslims (table 1).

Almost half (234, 51.9%) of the participants were self-employed. Only 76 (16.9%) had more than five 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 stages 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<sup>2</sup>), whereas more than three-quarters (344, 76.3%) were anaemic (Hgb <11 g/dL). During the 5-year retrospective follow-up, most (413, 91.6%) of the participants were provided with CPT, while only 94 (20.8%) received 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, lamivudine (3TC) and efavirenz (EFV); likewise, one-fifth (110, 24.4%) of the patients

**Table 1** Sociodemographic and clinical characteristics of people living with HIV who were enrolled for chronic HIV care at selected government health facilities in Afar Regional State, north-east Ethiopia from 2010 to 2011

Characteristics	Frequency	%
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
Government-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

Continued

**Table 1** Continued

Characteristics	Frequency	%
WHO clinical stage		
I and 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/μL)		
<100	44	9.8
100–200	124	27.5
201–349	125	27.7
>350	158	35.0
BMI (kg/m <sup>2</sup> )		
<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		
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

Continued

**Table 1** Continued

Characteristics	Frequency	%
Due to side effect	50	52.1
Failure of treatment	4	4.2
Others	13	13.5
<b>Form of TB</b>		
Pulmonary	91	76.4
Extrapulmonary	28	23.6

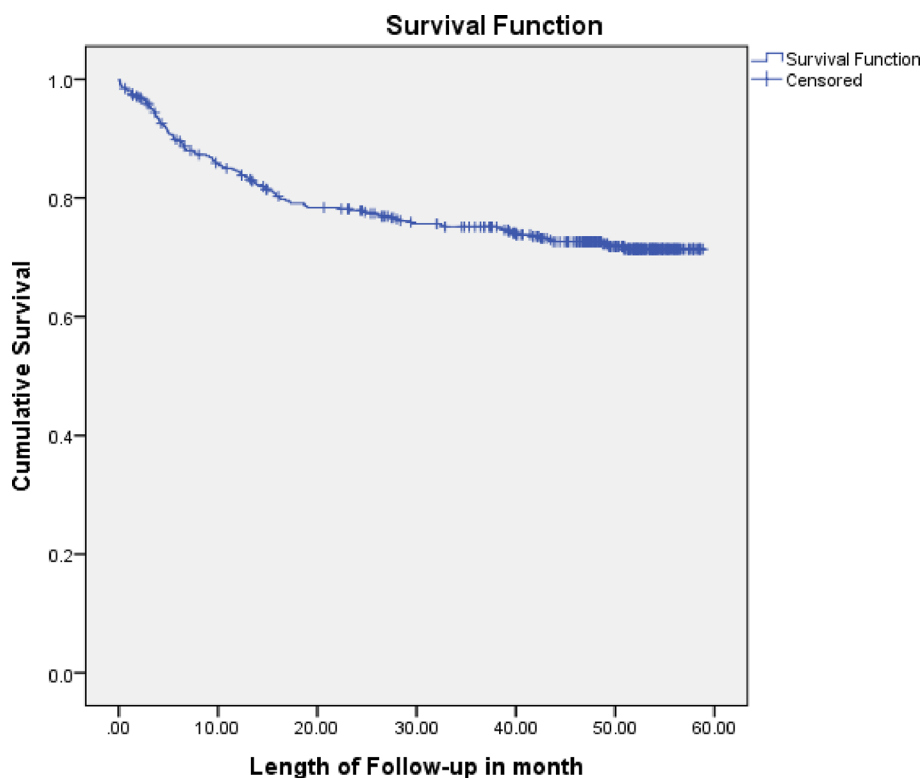
3TC, lamivudine; ART, isoniazid preventive therapy; AZT, zidovudine; BMI, body mass index; CD4, cluster of differentiation 4; CPT, co-trimoxazole preventive therapy; D4T, stavudine; EFV, efavirenz; Hgb, haemoglobin; IPT, isoniazid preventive therapy; NVP, nevirapine; TB, tuberculosis; TDF, tenofovir.

took zidovudine, 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 patients with HIV/AIDS 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).

#### Incidence of TB stratified with sociodemographic and clinical characteristics

Out of the total 451 patients with HIV/AIDS, 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 until the end of follow-up period) (figure 1). Therefore,

the overall TB incidence rate in the 5-year retrospective data was 8.64 cases per 100 PY of observation. The incidence of patients diagnosed with TB at the end of 1 year was 4.9 per 100 PY of observation. The sum of the whole follow-up period for all 451 HIV/AIDS-infected individuals was 1377.41 PY 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). Women constituted more than half (67, 56.3%) of the total patients with TB. 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 log-rank test. The cumulative probability of survival of a patient with TB at the end of 1, 2, 3 and 4 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), anaemic and non-anaemic ( $P<0.001$ ) (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 and 8 (6.7%) were bedridden at the time of enrolment. One hundred and fifteen (96.6%) of the TB cases were not



**Figure 2** Kaplan-Meier curve of tuberculosis survival proportion of people with HIV/AIDS at selected government health facilities in north-east Ethiopia, July 2010–May 2015.

given isoniazid (INH) prophylactic therapy. Fifty (42.0%) with incident cases of TB were enrolled with Hgb level below 11 g/dL (table 2).

### 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, BMI, Hgb level, IPT and functional status were found to be predictors of the incidence of TB at a P value of less than 0.2. Consequently, these variables were subjected to multivariate Cox regression analysis, and previous TB, bedridden functional status, Hgb, BMI, IPT and advanced WHO clinical stage were found to be statistically significant determinants of TB-free survival at a P value of less than 0.05.

Accordingly, the multivariate Cox regression analysis indicated that PLHIV and people who had history of TB were 3.65 times at higher risk of developing TB at any time than PLHIV who had no history of TB (adjusted HR (AHR) 3.65, 95% CI 1.97 to 6.73). PLHIV who were in bedridden functional status at baseline 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 to 25.49). Similarly, PLHIV with baseline BMI less than 18.5 kg/m<sup>2</sup> were 2.53 times at higher risk of developing TB at any time than those with BMI greater than 18.5 kg/m<sup>2</sup> (AHR 2.53, 95% CI 1.27 to 5.05). Individuals who took IPT were 86% less likely to develop TB at any time compared with those who did not take IPT (AHR 0.14, 95% CI 0.05 to 0.39). PLHIV in WHO clinical stages III and IV had a greater risk of developing TB compared with WHO stages I and II (AHR 2.84, 95% CI 1.11 to 7.27; AHR 3.07, 95% CI 1.08 to 8.75, respectively). The study also revealed that the incidence of TB in the first 3 years of follow-up was higher when compared with the other subsequent years. In addition, PLHIV who were anaemic (Hgb <11 g/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 to 3.93) (table 3).

### DISCUSSION

TB and HIV remain the major public health problems in many parts of the world. Ethiopia is one of the TB high-burden countries with an estimated annual incidence of 211 cases per 100 000 people and a prevalence of 224 cases per 100 000.<sup>30</sup>

In this study, the overall incidence of TB among PLHIV was 8.64 cases per 100 PY of observation. This finding is similar to those reported from Gondar and Asella, Ethiopia, which are 7 and 7.9 cases, respectively, per 100 PY of observation.<sup>31 32</sup> The finding is consistent with that of a study in Tanzania and other Sub-Saharan countries, with incidence ranging from 7.6 to 8.2 per 100 PY of observation.<sup>33 34</sup> However, the incidence density of TB in this study is higher than those of studies conducted in Korea, Israel and Malaysia.<sup>19 35 36</sup> The lower incidence of TB in the

**Table 2** Incidence of TB stratified by sociodemographic and clinical characteristics of people living with HIV on HIV chronic care at selected government health facilities in Afar Regional State, July 2010–May 2015

Characteristics	Total n (%)	TB incidence n (%)	Person-years of observation
Years of follow-up (median=46.74, IQR=15.95–52.42, months)			
1 year	88 (19.5)	68 (57.1)	35.07
2 years	41 (9.0)	28 (23.5)	54.73
3 years	32 (7.0)	11 (9.3)	76.66
4 years	89 (19.8)	9 (7.6)	322.67
5 years	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
Not employed	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

Continued

Table 2 Continued

Characteristics	Total n (%)	TB incidence n (%)	Person-years of observation
<b>Substance use</b>			
Yes	130 (28.8)	42 (35.3)	379.7
No	321 (71.2)	77 (64.7)	997.71
<b>Previous TB</b>			
Yes	74 (16.4)	41 (34.5)	164.74
No	377 (83.6)	78 (65.5)	1212.67
<b>Opportunistic infection</b>			
Yes	34 (7.5)	19 (16)	85.28
No	417 (92.5)	100 (84)	1292.13
<b>Chronic illness</b>			
Yes	35 (7.8)	11 (9.2)	106.28
No	416 (92.2)	108 (90.8)	1271.13
<b>Bedridden</b>			
Yes	11 (2.4)	8 (6.7)	33
No	440 (97.6)	111 (93.3)	1356.76
<b>BMI (kg/m<sup>2</sup>)</b>			
<18.5	218 (48.3)	75 (64)	626.46
>18.5	203 (45.0)	42 (35)	750.95
<b>Hgb level (g/dL)</b>			
<11	107 (23.7)	50 (42.0)	233.8
≥11	344 (76.3)	69 (58.0)	1143.6
<b>CD4 cell count (cells/μL)</b>			
<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
<b>On ART</b>			
Yes	215 (47.7)	36 (30.3)	941.70
No	236 (52.3)	83 (69.7)	435.71
<b>WHO clinical stage</b>			
I and 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
<b>Initial regimen</b>			
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
<b>IPT use</b>			
Yes	94 (20.8)	4 (3.4)	363.60
No	357 (79.1)	115 (96.6)	1013.81

Continued

Table 2 Continued

Characteristics	Total n (%)	TB incidence n (%)	Person-years of observation
<b>CPT use</b>			
Yes	413 (91.6)	108 (90.8)	1259.65
No	38 (8.4)	11 (9.2)	117.76

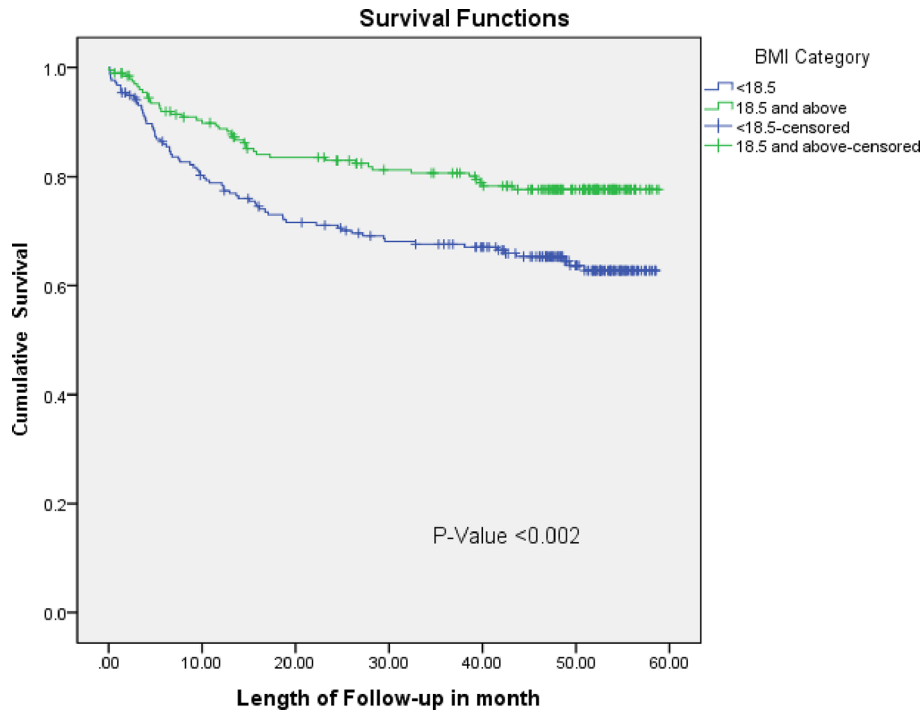
3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; CD4, cluster of differentiation 4; CPT, co-trimoxazole preventive therapy; D4T, stavudine; EFV, efavirenz; Hgb, haemoglobin; IPT, isoniazid preventive therapy; NVP, nevirapine; TB, tuberculosis; TDF, tenofovir.

latter studies compared with this one might be due to the availability of better preventive, diagnostic and treatment set-ups and strategies for controlling TB in such countries when compared with our study setting. In addition, low healthcare coverage, high burden of HIV and the fact that the study setting is so unprivileged might explain the difference. Furthermore, late enrolment at health facilities due to late presentation of HIV-infected people 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 immune reconstitution inflammatory syndrome (IRIS) after initiation into highly active antiretroviral therapy (HAART), and IRIS-related TB is commonly seen within the first 6 months of initiation into HAART.<sup>37</sup> 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 Hgb level, advanced WHO staging (III and IV), years of follow-up and low BMI were found to be significantly associated with TB incidence. Individuals who had history of TB 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 reinfection 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.<sup>35 36 38</sup>

PLHIV who took IPT were found to be protective of TB incidence. Individuals who took IPT were 86% less likely to develop TB at any time compared with those who did not take IPT (AHR=0.14, 95% CI 0.05 to 0.39). This might be due to the role of IPT in reducing the incidence of TB among PLHIV. The finding is consistent with those of studies in Ethiopia, South Africa and Brazil.<sup>39–41</sup> In



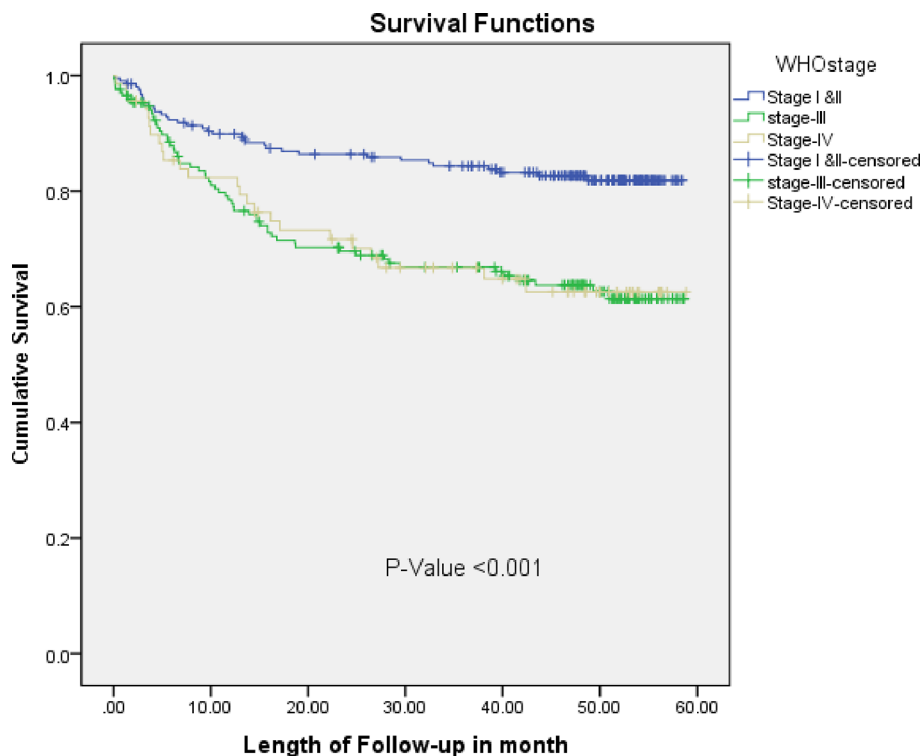


**Figure 3** Kaplan-Meier survival curve of patients with tuberculosis based on body mass index (BMI) category among people living with HIV at selected government health facilities in north-east Ethiopia, July 2010–May 2015.

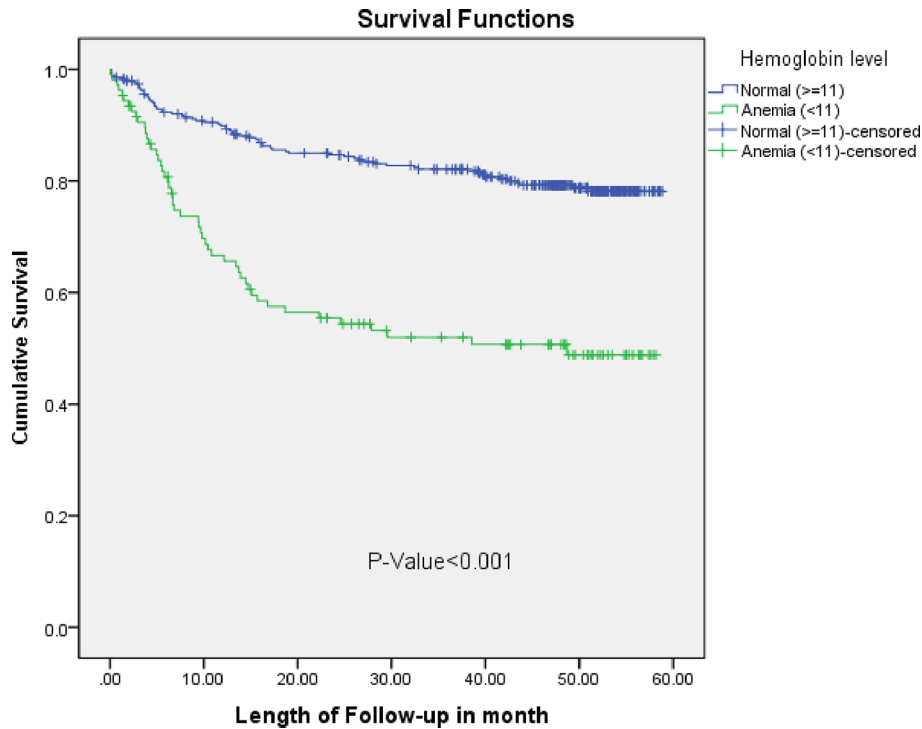
spite of this fact, poor uptake, ambiguity and fear of drug resistance might contribute to no-IPT use.

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.<sup>16 31 42</sup>



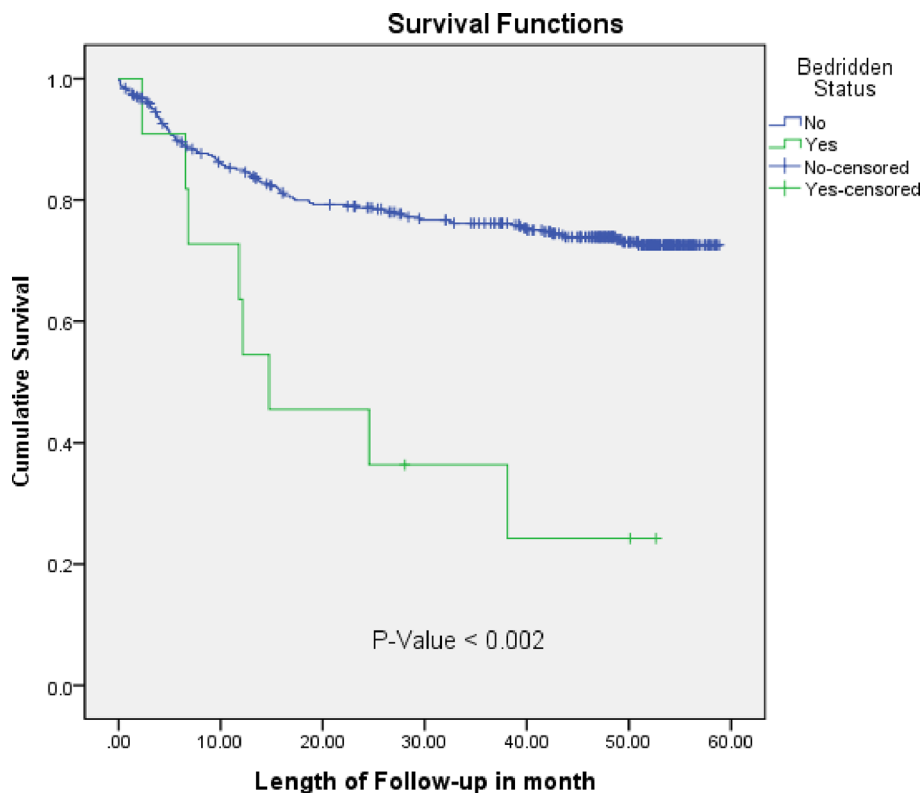
**Figure 4** Kaplan-Meier survival curve of patients with tuberculosis based on the WHO stage among people living with HIV at selected government health facilities in north-east Ethiopia, July 2010–May 2015.



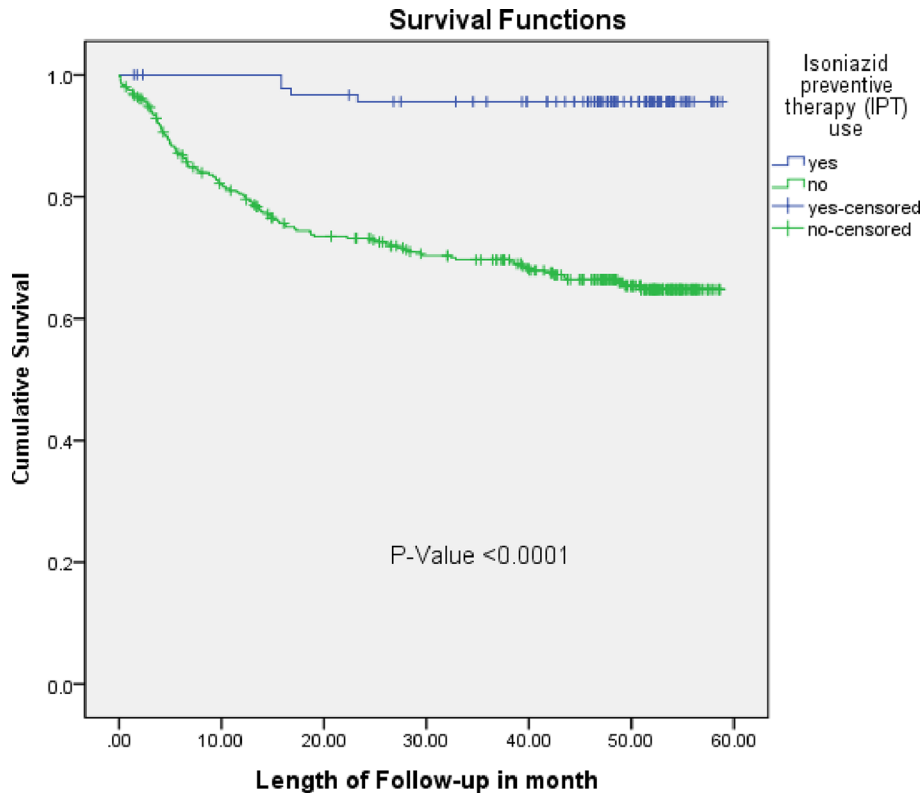
**Figure 5** Kaplan-Meier survival curve of patients with tuberculosis based on haemoglobin level among people living with HIV at selected government health facilities in north-east Ethiopia, July 2010–May 2015.

Out of the anthropometric variables, patients with HIV who were underweight (BMI <18.5 kg/m<sup>2</sup>) were 2.53 times at higher risk of developing TB compared with individuals with BMI ≥18.5 kg/m<sup>2</sup>. This finding was

consistent with that of a study done in Tanzania,<sup>43</sup> Ethiopia and South Africa.<sup>33 44</sup> The possible explanations might be that a low BMI category is a proxy indicator of malnutrition, and malnutrition in patients with HIV is



**Figure 6** Kaplan-Meier survival curve of patients with tuberculosis based on the bedridden function among people living with HIV at selected government health facilities in north-east Ethiopia, July 2010–May 2015.



**Figure 7** Kaplan-Meier survival curve of patients with tuberculosis based on isoniazid preventive therapy use among people living with HIV at selected government health facilities in north-east Ethiopia, July 2010–May 2015.

associated with increased catabolic activity, infection, loss of appetite and decreased intake, which further increase the risk of developing opportunistic infections such as TB.

Furthermore, this study found that patients with Hgb level of  $<11$  g/dL at baseline were 2.31 times at higher risk of developing TB than those with Hgb level  $\geq 11$  at baseline. Haematological 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.<sup>43–46</sup> 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 enrolment.

Another important result that was found to have a significant association with the incidence of TB was advanced clinical staging (III and IV). PLHIV with advanced WHO staging (III and IV) had, respectively, 2.84 and 3.07 times higher risk of developing TB compared with people in stages I and II. This finding corresponded with those of studies conducted in Nigeria,<sup>47</sup> South Africa<sup>48</sup> and Gambia.<sup>49</sup> 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 TB infection. Something worth mentioning as well is that TB is one of the defining factors of AIDS that categorise patients who use HIV/AIDS clinics in Ethiopia into late WHO clinical staging.

#### Limitations of the study

Although the study did its best to indicate the incidence and predictors of TB among PLHIV using a 5-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 TB. 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/coinhabitant) and introduction of selection bias due to the exclusion of patients who did not use the selected hospitals are other drawbacks. Since the study was conducted in a single region in 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, not using IPT, underweight status (BMI  $<18.5$  kg/m<sup>2</sup>), bedridden functional status, being

**Table 3** Cox regression analysis of the determinants of the incidence of TB among adults on chronic HIV care at selected government health facilities in Afar Regional State, July 2010–May 2015

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

\*Variable significant at P value less than 0.05.

AHR, adjusted HR; BMI, body mass index; CD4, cluster of differentiation 4; CHR, crude hazard ratio; Hgb, haemoglobin; IPT, isoniazid preventive therapy; TB, tuberculosis.

anaemic (Hgb <11g/dL), advanced WHO stage (III and 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 bedridden functional status, underweight (BMI <18.5kg/m<sup>2</sup>) and anaemic (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 in 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.

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**Competing interests** None declared.

**Patient consent** Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

**Ethics approval** Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Public Health, the University of Gondar.

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**Data sharing statement** The data will be available upon request.

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