

## RESEARCH ARTICLE

# Incidence and predictors of Tuberculosis among patients enrolled in Anti-Retroviral Therapy after universal test and treat program, Addis Ababa, Ethiopia. A retrospective follow-up study

Amare Getu<sup>1</sup>, Haileab Fekadu Wolde<sup>2</sup>, Yaregal Animut<sup>2</sup>, Anteneh Ayelign Kibret<sup>3\*</sup>

**1** Ethiopian Public Health Institute, Addis Ababa, Ethiopia, **2** Department of Epidemiology and Biostatistics, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia, **3** Department of Human Anatomy, School of Medicine, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

\* [antesha04@gmail.com](mailto:antesha04@gmail.com)



## OPEN ACCESS

**Citation:** Getu A, Wolde HF, Animut Y, Kibret AA (2022) Incidence and predictors of Tuberculosis among patients enrolled in Anti-Retroviral Therapy after universal test and treat program, Addis Ababa, Ethiopia. A retrospective follow-up study. PLoS ONE 17(8): e0272358. <https://doi.org/10.1371/journal.pone.0272358>

**Editor:** Frederick Quinn, The University of Georgia, UNITED STATES

**Received:** September 21, 2021

**Accepted:** July 18, 2022

**Published:** August 3, 2022

**Copyright:** © 2022 Getu et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** According to the ethical review committee, the data contains potentially identifying sensitive patient information and cannot be shared publicly. All data requests can be sent to the Director of the School of Medicine (Dr. Mezgebu Silamsew at [msilamsaw@gmail.com](mailto:msilamsaw@gmail.com)), the Director of the Postgraduate Committee (Mr. Getasew Amare at [getasewa23@gmail.com](mailto:getasewa23@gmail.com)), or the Chair, Ethical review board (Dr. Abebe Muche at [abemuche14@gmail.com](mailto:abemuche14@gmail.com)).

## Abstract

### Introduction

Tuberculosis (TB) is the leading killer of people living with HIV (PLHIV) and almost one-third of deaths in the world are attributed to it and many of these deaths occur in developing countries. Despite these evidences, after the implementation of universal test and treat (UTT) strategy, information regarding the incidence and predictors of tuberculosis among PLHIV is limited in Ethiopia. Therefore, this study aimed to assess the incidence and predictors of tuberculosis among patients enrolled in Anti-Retroviral Therapy (ART) after universal test and treat program at St. Peter hospital and Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

### Methods

Institutional-based retrospective cohort study was conducted from November 1 to 30, 2020. Simple random sampling was used to select a total of 539 adults records which was enrolled on ART. Data was collected and entered into EPI DATA 3.1 and analyzed using STATA version 14.1. Time-to-event distributions were estimated using Kaplan–Meier estimates. Hazards across different categories were compared using log-rank tests. Predictors were identified using the Cox proportional hazards model. The hazard ratio (HR) and 95% confidence interval (CI) were computed. Variables having P-value < 0.05 from the multivariable analysis were considered as a statistically significant.

### Result

Among 539 records reviewed, 529 (98%) were included in the final analysis. The total follow-up period was 1529 Person-Year (PY). The incidence rate in this cohort was found to be 4.84 per 100-person year (95%CI, 3.83–6.11). CD4 count < 200 (AHR: 3.14, 95% CI: 1.64–

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

**Abbreviations:** AFB, Acid Fast Bacilli; AHR, Adjusted Hazard Ratio; AIDS, Acquired Immunodeficiency Syndrome; ART, Anti-Retroviral Therapy; CI, Confidence Interval; CPT, Co-trimoxazole Preventive Therapy; EDHS, Ethiopian Demographic Health Survey; HAART, Highly Active Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; INH, Isonicotinic acid Hydrazide; IPT, Isoniazid Preventive Therapy; MTB, Mycobacterium Tuberculosis; OI, Opportunistic infections; PLHIV, People Living with Human Immunodeficiency Virus; PTB, Pulmonary Tuberculosis; PY, Person Year; TB, Tuberculosis; TB/HIV, HIV-related Tuberculosis; UNAIDS, United Nation Program of HIV/AIDS; UTT, Universal Test and Treat.

7.10), poor adherence (AHR:2.16, 95% CI:1.21–3.85), underweight (AHR:2.42, 95% CI: 1.30–4.51), not taking isoniazid prophylaxis therapy (AHR: 2.78,95% CI: 1.06–7.30), being bedridden 3.06; (AHR: 3.06, 95% CI: 1.50–6.24), and baseline WHO stage three or four (AHR:2.33, 95% CI:1.08–5.02) were independent predictors for the incidence of TB among HIV positive patients.

## Conclusion

In this study, the incidence of tuberculosis is relatively low as compared to studies done before the initiation of test and treat program in Ethiopia. low CD4count, poor level of adherence, low BMI, not taking IPT prophylaxis, bedridden functional status, and being on baseline WHO stage III or IV were found to increase the hazard of tuberculosis. Hence, close follow up, reminders, surveillance, and tracing mechanisms targeting this higher risk group would decrease Tuberculosis among PLHIV.

## Introduction

Tuberculosis (TB) is one of the public health burdens and the leading cause of morbidity and mortality among HIV positive patients. *Mycobacterium tuberculosis* (MTB) is a causative agent for TB and mainly affects the lungs but also involve almost all body organs [1,2]. World Health Organization (WHO) depict that around 4 billion deaths per year is recorded due to TB and HIV Co-infection [3]. Among all TB cases, 8.6% were people living with HIV and the rate of progression is much higher at about 10–15% per year [1,3,4]. Approximately 1.1 million peoples are living with TB and HIV/AIDS worldwide and from them 80% are living in Sub-Saharan countries [3]. A recent report by UNAIDS revealed that more than 75% of all estimated HIV-TB co-infected individuals live in just 10 countries, and nine of those countries are in SSA [5]. Even though, TB-related deaths among people living with HIV (PLHIV) in the year between 2004 and 2012 dropped by 36% worldwide, TB is still the leading cause of morbidity and mortality [6]. From world's 30 highest TB burden countries, Ethiopia ranked seventh and comprises the highest proportion of TB/HIV among SSA countries [7]. Globally, various studies were conducted to assess the incidence and predictors of tuberculosis among HIV-infected patients. For instance, studies conducted in South Africa and Nigeria reveals that the incidence of Tuberculosis was 2.4 and 7.43 per 100 PY respectively [8,9]. Studies conducted in different part of Ethiopia revealed that the incidence of tuberculosis among HIV-infected patients ranging from 3.3 per to 8.6 per 100 PY of observation [2,10]. Studies conducted in Ethiopia and south Africa indicated that being male [11,12], low level of education [13], low baseline CD4 count [14], bedridden functional status [12], WHO clinical stage III and IV [12,14], smoking and alcohol intake [12], were significant predictors of TB among HIV infected patients. On the other hand, INH therapy and cotrimoxazole prophylaxis has shown a protective effect against TB among PLHIV [12].

Ethiopia started the UTT program in 2016 in order to change the distribution of HIV infection [15]. After initiation of UTT program, different intervention strategies have been implemented among PLHIV to reduce the occurrence of TB/HIV co-infection and overcome TB related morbidity and mortality among PLHIV. However, many of deaths occurs due to TB/HIV co-infection and reports regarding the incidence and predictors of tuberculosis among PLHIV after UTT program is limited in Ethiopia. Therefore, the intent of this study is to assess

the incidence and predictors of tuberculosis among patients enrolled in Anti-Retroviral Therapy (ART) after UTT program at two public hospitals in Addis Ababa, Ethiopia. The finding of this study will help the health care practitioners, program managers and policy makers to advance TB control and prevention among HIV-infected people.

## Methods

### Study design and setting

A retrospective cohort study design was employed among HIV-positive individuals enrolled at two selected hospitals in Addis Ababa between January 1, 2016, and August 25, 2020. Addis Ababa is the capital of Ethiopia with a total population of 4,794,000. There are 12 governmental hospitals in Addis Ababa. Among these, St. Peter specialized hospital and Zewditu memorial hospital are the leading, excellence and provide more ART service. From January 1, 2016 to August 25, 2020 there were 1479 and 1589 PLHIV on ART at St. Peter specialized hospital and Zewditu memorial hospital respectively. The hospitals also provide palliative care, HIV counseling and testing, STI services and post-exposure prophylaxis (PEP) services.

### Population and sample size determination

All HIV-positive adults ( $\geq 15$  years) on ART at Addis Ababa and who had at least 1 month of ART follow-up since the UTT program were the target population. Besides, patients who started ART in the selected facilities between January 1, 2016, to August 25, 2020 were the study population. HIV patients who have already developed TB before ART initiation, transferred in from other institution, with unknown date of initiation of treatment and outcome occurrence date were excluded from the study.

The sample size was determined using power cox command of Stata 14 software. Factors such as CD4 count, functional status, sex, and WHO clinical staging were used to estimate the sample size and final sample size was found to be 539. To select the study participants, medical records of all HIV-positive adults on ART from January 1, 2016, to August 25, 2020, were sorted. Then, records were selected using a simple random sampling technique through computer-generated numbers.

### Variables

The dependent variable of this study was the incidence of TB among HIV positive patients. Incident TB case, which is an event of interest, defined as the occurrence of TB cases after ART initiation which is bacteriologically confirmed (with at least one positive AFB microscopy, Xpert MTB/Rif assay positive, or culture positive) or based on clinical decision of expert clinician by analyzing the supportive evidences (suggestive of TB) during follow up. The first group of predictors assessed was socio-demographic characteristics including age, sex, marital status, residence, level of education, and occupation. The second was baseline clinical and laboratory characteristics including WHO clinical stage, CD4 cell count, hemoglobin level, history of TB, and history of opportunistic infections (OIs) and body mass index (BMI). Lastly ART and other medication-related characteristics such as (type ART regimens, regimen change, ART side effects, ART adherence, IPT, and CPT were collected). Occurrence of TB after initiation of ART was considered as event, while, a patient was classified as censored if he/she lost to follow-up, died or didn't develop TB at the end of the study. These elements were ascertained by reviewing patient records. In this study, lost to follow-up was defined as an HIV-positive patient missing an ART appointment for one to 3 months. Additionally, adherence was classified as good, fair, or poor, according to the percentage of drug dosage calculated from a

monthly total dose of ART drugs; hence, good was reported if equal to or greater than 95% or  $\leq 3$  doses missing per month, fair if 85–94% or 4–8 dose missing per month, or poor if less than 85% or  $\geq 9$  doses missing per month [15]. Furthermore, low hemoglobin level was defined as hemoglobin level less than 10 g/dl. Finally, opportunistic infections were diagnosed if HIV-positive adults developed any morbidities after starting ART, as documented by the health care professionals.

### Data collection tool and procedures

Data were collected retrospectively from the patient charts and registration book of HIV-positive individuals newly registered at ART clinics during the period January 1, 2016, to August 25, 2020. Data was extracted over 1 month from November 1 to 30, 2020. The data extraction check list was prepared from the ART entry and follow-up forms and the study objectives. Three BSc nurses who have been working in the ART clinics of the selected hospitals collected the data. To ensure data quality, two days of training was given to the data collectors and supervisors about the ways of data extraction. The checklist was pretested before the data collection and amendments were made accordingly. Furthermore, the supervisor and principal investigators performed a strict follow-up and supervision throughout the entire data collection period.

### Data processing and analysis

Data was entered using EPI-DATA Version 3.1 and analyzed using STATA version 14 statistical software. The patient's follow-up characteristics were described for median, interquartile range and frequency distribution table. Separate graph of Kaplan Meier survival functions and log-rank test was estimated for each categorical variable to compare the survival between different exposure groups. The proportional hazard assumption was checked using Schoenfeld residual test and log [- log] (survival probability) versus log of survival time plot. Bivariable Cox-proportional hazard regression model was used to screen variables for the final model. Variables having a p-value of  $\leq 0.20$  in the bi-variable analysis were fitted into the multivariable Cox-proportional hazard regression model. Finally, an adjusted hazard ratio with its corresponding 95% confidence interval was reported to declare the presence of a significant association between the explanatory and outcome variables. The model goodness of fit was assessed using Cox-Snell residual plot. This plot calculates an empirical estimate of the cumulative hazard function-based on the Kaplan–Meier survival estimates taking the Cox–Snell residuals as the time variable. If the model fits the data, the plot should be a straight line with a slope of 1.

### Ethical issues

Ethical approval was obtained from ethical review committee of University of Gondar College of Medicine and Health Sciences. Besides, a permission letter was also obtained from the respective hospitals. As the study was conducted through a review of records, the ethics committee waived the need for informed consent. The patient records were accessed from November 1 to 30, 2020 and all the data were fully anonymized before data collection and confidentiality was maintained in all phases of research activities.

## Results

### Socio-demographic characteristics

Among 539 HIV-positive adults' records reviewed, 529 (98%) records were included in the final analysis while 10 records were excluded because they didn't contain the required

**Table 1. Base line socio-demographic characteristics for adult HIV patients on ART in St. peter specialized hospital and Zewditu memorial hospital between January 1,2016 and August 25,2020.**

Variables	Category	Frequency	Percentage
Sex	Male	226	42.7
	Female	303	57.3
Age	15–24	60	11.3
	25–34	142	26.8
	35–44	182	34.4
	≥45	145	27.5
Marital status	Single	115	21.7
	Married	243	45.9
	Divorced	131	24.8
	Widowed	24	4.5
	Separate	16	3.0
Residence	Urban	519	98.1
	Rural	10	1.9
Educational status	No education	33	6.2
	Primary	173	32.3
	Secondary	267	50.5
	Tertiary and above	56	11
Occupation	Unemployment	81	16.5
	Daily labor	13	2.7
	Governmental -employee	144	29.4
	Private	237	48.5
	House wife	14	2.9
Religion	Orthodox	370	69.9
	Muslim	91	17.2
	Protestant	58	11.0
	others*	10	1.9

others\*: Catholic and Judaism.

<https://doi.org/10.1371/journal.pone.0272358.t001>

information. Of the total study participants more than half were females 303 (57%). The median age of the participants was 37 (IQR = 29–45) years. Of the total sample 243(46%) were married and the majority 370 (70%) of study participants were orthodox. Concerning educational status almost half of participants have a secondary level of education 267(50.47%). Besides, majority of the participants were from urban areas 519(98%) and 237(45%) were engaged in private works (Table 1).

### Clinical and treatment related characteristics

Of the total participants, 170 (32.14%) had a CD4 count of less than 200cells/ml at baseline and the median CD4 count was 289 and IQR (200-438cells/ml). More than half 298(56.33%) of the participants were WHO stage I at the baseline. Almost half of participants 266(50.28%) were started Cotrimoxazole prophylaxis therapy (CPT). Of the participants 205 (38.75%) had a history of at least one type of opportunistic infections during their presentation. Around two-thirds of the participants were working functional status and had normal weight 333 (62.95%) and 337(63.71%) respectively. Regarding their initial ART regimen, more than three quarter 402 (75.99%) of study participants took the TDF-3TC-EFV-based regimen (Table 2).

### Incidence of tuberculosis

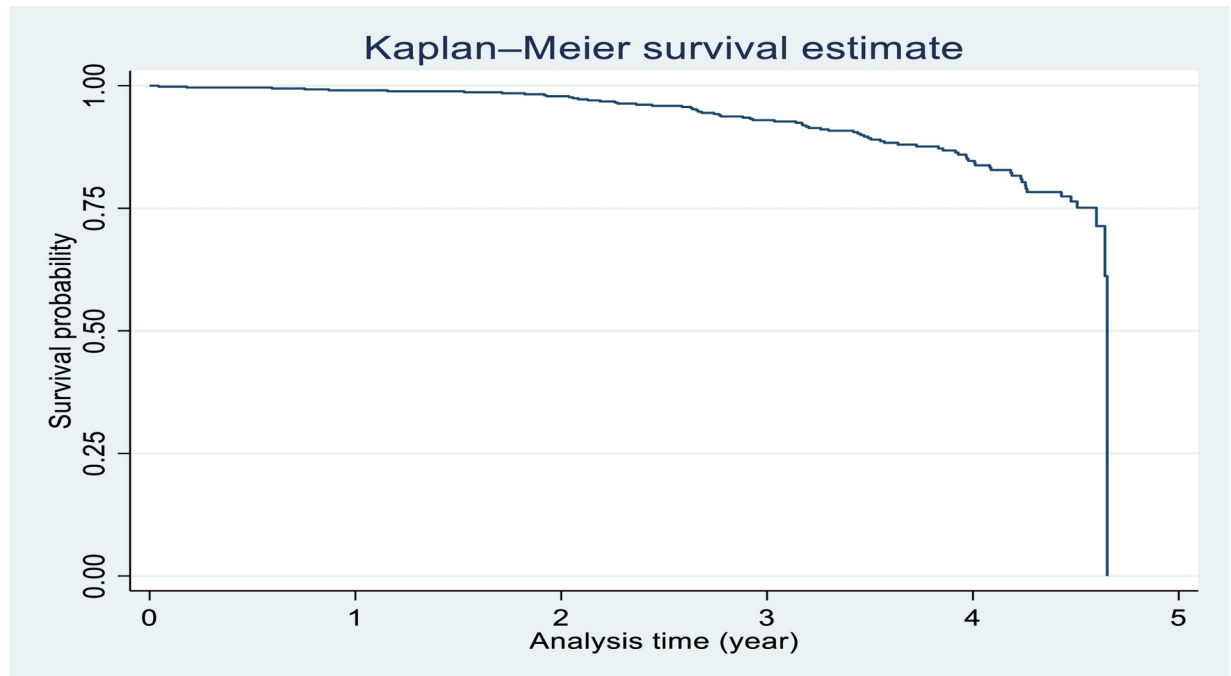
Five hundred twenty-nine study participants were followed for different periods in four years and six months which produced 1529 PY of observation. Within the follow-up period, 74 patients were found to develop TB which gives an overall incidence density of 4.84 cases (95%

**Table 2. Clinical and treatment related characteristics of adult HIV patients on ART in St. peter specialized hospital and Zewditu memorial Hospital between January 1, 2016 and August 25, 2020.**

Variables	Categories	Frequency	Percentage (%)
Baseline CD4 count (In cells/ul)	≤200	170	32.1
	>200	359	67.9
Baseline WHO stage	Stage I	298	56.3
	Stage II	114	21.6
	Stage III/ IV	117	22.1
Last known WHO stage	Stage I	417	78.8
	Stage II	76	14.4
	Stage III/ IV	36	6.8
CPT prophylaxis	Yes	266	50.3
	No	263	49.7
IPT prophylaxis	Yes	208	39.3
	No	321	60.7
Types of OI at enrollment (n = 205)	Zoster	38	18.5
	Toxoplasmosis	25	12.2
	Bacterial pneumonia	100	48.8
	Cryptococcus meningitis	14	6.8
	PCP	26	12.7
	Others*	2	1.0
TB status	Positive	74	14.0
	Negative	455	86.0
Functional status	Working	333	62.9
	Ambulatory	147	27.8
	Bedridden	49	9.3
BMI	<18.5	174	32.9
	18.5–24.9	337	63.7
	≥25	18	3.4
Adherence	Good	388	73.3
	Fair	74	14.0
	Poor	67	12.7
Hgb/Baseline/	<10g/dl	68	12.9
	>10g/dl	461	87.1
Comorbidities at enrollment	Yes	100	18.9
	No	429	81.1
Types of regimens at start	1c (AZT-3TC-NVP)	80	15.2
	1d (AZT-3TC-EFV)	26	4.9
	1e (TDF-3TC-EFV)	402	76.1
	1j (TDF-3TC-DTG)	20	3.8
Regime change during follow up	To first line	355	67.1
	To second line	50	9.5
	Unchanged	124	23.4
Reason for switch first regimen (n = 405)	Toxicity/side effect	16	4.0
	New drug available	351	86.6
	Pregnancy	1	0.2
	immunological failure	10	2.5
	virological failure	27	6.7
Type of TB	PTB	66	89.0
	EPTB	8	11.0
TB case definition	New	69	93.0
	Re-treatment	5	7.0
Viral load	<150(undetectable)	345	66.0
	>150	184	36.0

Others\*: Diarrhea and oral trash.

<https://doi.org/10.1371/journal.pone.0272358.t002>



**Fig 1. Cumulative survival probability to develop TB with time among patients on ART in St. peter specialized hospital and Zewditu memorial Hospital between January 1, 2016 and August 25, 2020.**

<https://doi.org/10.1371/journal.pone.0272358.g001>

CI:3.83–6.11) per 100 PY. Study participants stayed in the follow-up for a minimum of 0.53 months and a maximum of 56.6 months. The cumulative probability of survival of a patient at the end of 1, 2, 3, and 4 years was 0.97,0.93, 0.89, and 0.85, respectively (Fig 1).

## Predictors of tuberculosis

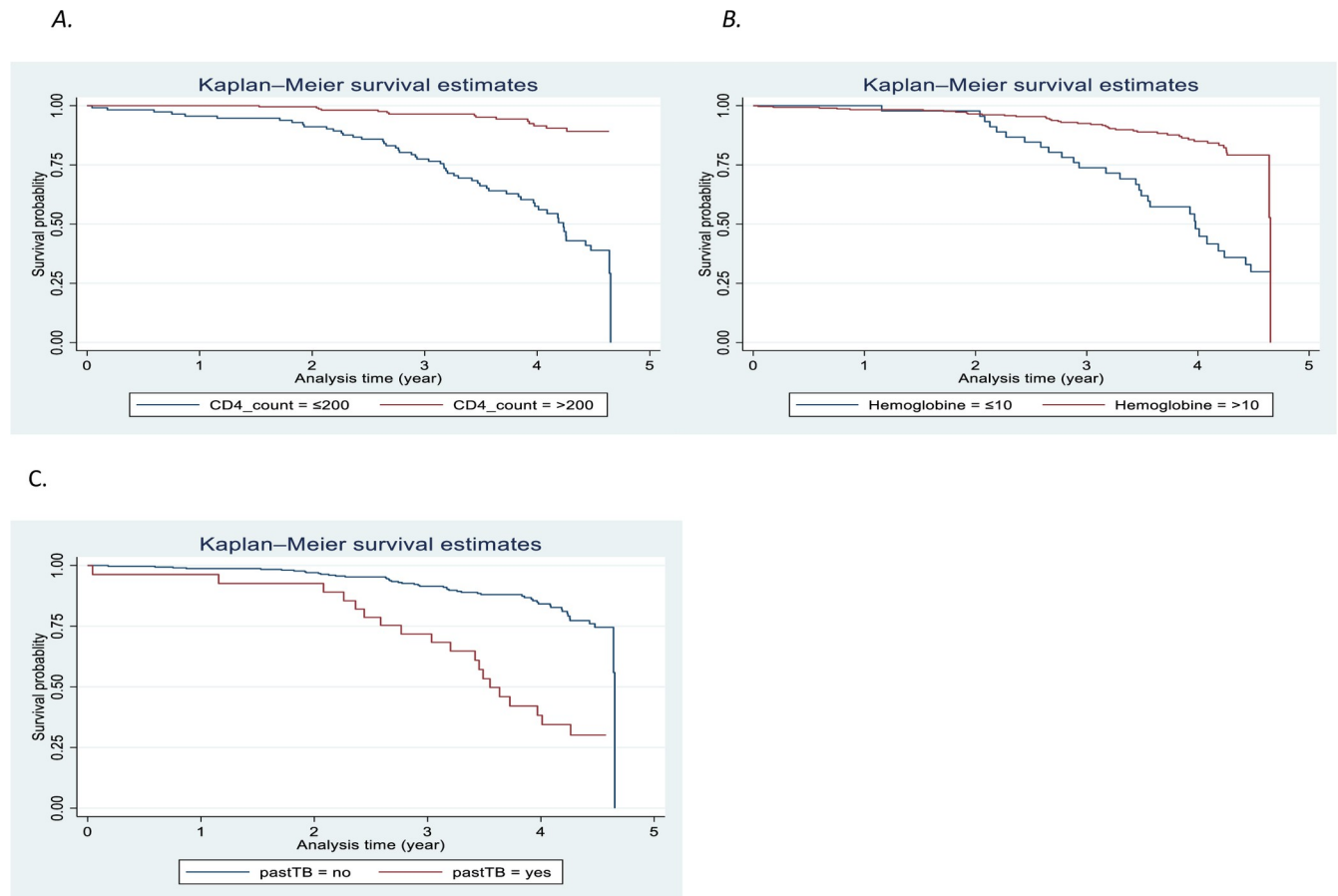
**Non-parametric comparison of survival.** Based on the Kaplan-Meier survival curve, patients with high CD4, no past history of TB, and high hemoglobin were found to have better survival than their counter parts (Fig 2).

**Cox-proportional hazard model.** In multivariable Cox regression analysis, CD4 count, adherence level, BMI, IPT prophylaxis, functional status, and baseline WHO stage were found to be significantly associated with the outcome. The hazard of tuberculosis was 3.14 times higher among participants with CD4 count <200 compared to their counterparts. (AHR = 3.14; 95%CI: 1.64–7.10). The hazard of TB was 2.16 times higher among participants who had poor adherence to treatment compared to their counterparts (AHR = 2.16; 95%CI:1.21–3.85). The hazard of tuberculosis was 2.42 times higher among participants who are underweight as compared to those with a normal weight (AHR = 2.42; 95%CI: 1.30–4.52). Participants who didn't take IPT prophylaxis had 2.78 times increased hazard of having TB as compared to those who are taking IPT prophylaxis (AHR = 2.78, 95% CI: 1.06–7.30). The hazard of tuberculosis among bedridden patients was three times higher than working (AHR = 3.06; 95%CI:1.50–6.24). Participants who were in WHO stage three or four at baseline had 2.33 times increased hazard of TB compared to those in stage one (AHR = 2.33; 95%CI:1.08,5.02) (Table 3).

## Discussion

This retrospective cohort study assessed the incidence and predictors of TB among HIV-positive adults at St. Peter specialized and Zewditu memorial hospitals. The incidence of TB was





**Fig 2.** Non-parametric estimates of cumulative survival curves across categories of CD4 count (A), Hemoglobin (B) and Past history of TB (C).

<https://doi.org/10.1371/journal.pone.0272358.g002>

found to be 4.84 per 100 PY of observation. This finding is in line with studies conducted in the Gurage zone, Ethiopia (4.79 cases per 100 PY), Arba Minch, Ethiopia (5.36 cases per 100 PY), and Tanzania (4.4 cases per 100 PY) [16–18]. However, it is higher than the studies from Brazil and the USA which reported the incidence of TB to be (2.28 cases per 100 PY), and (0.7 cases per 100 PY), respectively [19,20]. This might be due to the differences in sociodemographic characteristics of study participants, low healthcare coverage, and high burden of HIV in the study setting. Besides, our study was conducted at specialized hospitals providing tertiary level services for patients referred from health centers or general hospitals. Hence, patients in these hospitals might have advanced disease stage which would increase the risk of developing TB [21]. On the other hand, the incidence was lower than the studies conducted in Afar, Ethiopia (8.6 cases per 100 PY) and Gondar, Ethiopia (7.896 cases per 100 PY) [2,5]. This variation could be explained by the difference in the study period. This means our study was done after the universal test and treat program and this might decrease the incidence [16] as a result of early initiation, strong follow up, and proper implementation in TB/HIV care service. Moreover, creation of better awareness regarding the prevention of TB/HIV co-infection might also contribute to the low incidence [22,23].

From multivariable Cox regression analysis, variables low CD4 count, poor adherence level, low BMI, not taking IPT prophylaxis, bedridden functional status, and being on baseline WHO stage III or IV were found to be significantly associated with the outcome variable.



**Table 3. Predictors of Tuberculosis among Adult HIV patients on ART at St. Peter specialized hospital and Zewditu Memorial Hospital between January 1, 2016 and August 25, 2020.**

Independent variables		Survival status		Tuberculosis	
		Event	Censored	CHR (95% CI)	AHR (95%CI)
Variable	Category				
Hemoglobin level	>10 g/dl	42	419	1.00	1.00
	<10 g/dl	28	40	4.32(2.67–6.99)	1.55(0.91–2.63)
Baseline CD4 count (In cells/ul)	≤200	57	113	1.00	1.00
	>200	17	342	7.66(4.31–13.60)	3.14(1.64–7.10) **
Adherence (last known)	Good	39	349	1.00	1.00
	Fair	5	69	0.66(0.26–1.70)	0.45(0.16–1.24)
	Poor	30	37	5.14(3.14–8.41)	2.16(1.21–3.85)*
TB contact	No	64	423	1.00	1.00
	Yes	10	32	2.03(1.00–4.10)	1.60(0.74–3.44)
TB treatment history	No	52	436	1.00	1.00
	Yes	22	22	4.56(2.68–7.76)	0.75(0.40–1.43)
Body mass index (BMI) in kg/m <sup>2</sup>	18.5–24.9	47	127	1.00	1.00
	>25	25	312	1.63(0.38–700)	1.97(0.43–8.94)
	<18.5	2	16	4.63(2.75–7.75)	2.42(1.30–4.52)*
IPT prophylaxis	Yes	6	204	1.00	1.00
	No	68	251	7.41(2.98–18.43)	2.78(1.06–7.30)*
Functional status (Baseline)	Working	24	309	1.00	1.00
	Ambulatory	17	130	1.64(0.86–3.13)	0.67(0.30–1.49)
	Bedridden	33	16	12(6.94–21.09)	3.06(1.50–6.24)*
WHO Stage(baseline)	Stage I	20	278	1.00	1.00
	Stage II	5	109	0.77(0.22–1.95)	0.77(0.23–2.52)
	Stage III/ IV	49	68	7.56(4.33–13.23)	2.33(1.08–5.02) *
Co morbidity status	No	43	386	1.00	1.00
	Yes	31	69	3.40(2.10–5.51)	1.09(0.63–1.89)
OI(at enrollment)	No	26	286	1.00	1.00
	Yes	48	169	2.93(1.77–4.86)	1.55(0.92–2.63)

\*\* = p value ≤ 0.01

\* = p value &lt; 0.05.

<https://doi.org/10.1371/journal.pone.0272358.t003>

In the present study, a patient with a base line CD4 count of less than 200 cells/ul is 3.41 times more likely to have TB than their counterparts. This is supported by studies done elsewhere in the world [5,17,24]. This could be attributed to HIV often causes immunosuppression directly by reduction of CD4 count, because of progressive impairment of cellular immunity. This leads to decrement of the body's defense ability and enable the disease (HIV) progresses to an advanced stage. Lastly, the patient might develop more serious diseases including TB [25,26].

According to this study, participants with poor adherence to the treatment had an increased hazard of having TB compared to their counterparts. This is in agreement with another study done in Ethiopia [27]. This can be explained by patients with poor adherence to ART are prone to rapid viral replication which worsen immunological and clinical outcomes. This leads to declining of CD4 cell count which will end up with high risk of developing opportunistic infections including TB [28,29].

This study identified that being underweight was found to increase the hazard of TB compared to their counterparts. This finding is consistent with that of different studies done in Ethiopia, Tanzania, and South Africa [5,30,31]. This might be due to the fact that HIV patients frequently encountered symptoms like loss of appetite and decreased intake of food, this leads

to undernutrition which further weakens the immunity level. As a result, these patients will be more at risk to develop both primary and secondary TB [5,32].

In the present study, participants who didn't take IPT prophylaxis had 2.78 times increased hazard of having TB. This result is in line with studies conducted in Brazil and Ethiopia [20,21]. IPT has a significant role in eradicating latent tuberculosis and prevention of new infections which might decrease the incidence of active TB cases [20].

Being bedridden was also found to increase the hazard of tuberculosis among HIV-positive adults compared to their counterpart. This finding corresponds with different studies conducted in Ethiopia [32–34]. This could be attributed to the fact that being bedridden is an indicator of advanced disease. Hence, these patients are prone to malnutrition, inability to perform daily tasks and lack of physical activity, that will eventually lead them to have weak immunity and tuberculosis infection [33].

According to this study, advanced WHO clinical disease stage (III and IV) was found to increase the hazard of TB among HIV-positive patients. This result is similar to studies done in Ethiopia, Tanzania, and South Africa [18,33,35]. This could be explained by patients in advanced WHO stage are at increased risk of having primary or secondary TB infection due to their compromised immunity [5].

This research was conducted after the universal test and treat (UTT) program was established in Ethiopia. Thus, the finding of this study will bring new pieces of evidence on the effect of UTT in a clinical setting. However, there are some limitations of this study such as due to the secondary nature of the data some important variables like housing conditions, family size, household incomes, and substance use were not included. In addition, since this study was facility-based it does not capture HIV-positive individuals who are out of care (at the community level).

## Conclusion

In this study, the incidence of tuberculosis is slightly low comparing to the previous studies done before the universal test and treat program. Patients who had low CD4 (<200 cell/ul), with a poor level of adherence, BMI<18.5kg/m<sup>2</sup>, did not take IPT prophylaxis, bedridden functional status, and baseline WHO stage III or IV are associated with TB co-infection among adult HIV positives. Hence, it is better to improve the package of care services, early screening and diagnosis for patients who have the risks at enrollment. We recommend to do community and facility based active TB case detection on this high-risk groups using health extension workers and health professionals in the facilities. Furthermore, it is better to conduct prospective study to alleviate the problem of incomplete records and incorporate social, economic, and behavioral factors.

## Acknowledgments

We would like to acknowledge St.Peter specialized Hospital, Addis Ababa City Administration Health Bureau, Zewditu memorial Hospital, the administrators and staff of each participating health facility, and the data collectors.

## Author Contributions

**Conceptualization:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

**Data curation:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut.

**Formal analysis:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

**Investigation:** Amare Getu, Haileab Fekadu Wolde, Anteneh Ayelign Kibret.

**Methodology:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

**Project administration:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

**Resources:** Amare Getu.

**Software:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut.

**Supervision:** Haileab Fekadu Wolde, Anteneh Ayelign Kibret.

**Validation:** Yaregal Animut.

**Visualization:** Haileab Fekadu Wolde.

**Writing – original draft:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

**Writing – review & editing:** Amare Getu, Haileab Fekadu Wolde, Yaregal Animut, Anteneh Ayelign Kibret.

## References

1. Kevin Fenton, Kenneth CG: Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis; Recommendations from the National Tuberculosis Controllers Association and CDC. In., vol. 54: CDC; 2005: 1–37.
2. Ahmed A, Mekonnen D, Kindie M. Incidence and predictors of tuberculosis among adult people living with HIV/AIDS in Afar public health facilities, Northeast Ethiopia. *AIDS*. 2015; 1:3–10.
3. Tesfaye B, Alebel A, Gebrie A, Zegeye A, Tesema C, Kassie BJPo. The twin epidemics: prevalence of TB/HIV co-infection and its associated factors in Ethiopia; a systematic review and meta-analysis. 2018; 13(10):e0203986. <https://doi.org/10.1371/journal.pone.0203986> PMID: 30281631
4. World Health Organisation (2019) Global Tuberculosis Report 2019. Geneva, Switzerland.
5. Melkamu H, Seyoum B, Dessie Y. Determinants of tuberculosis infection among adult HIV positives attending clinical care in western Ethiopia: a case-control study. *AIDS Res Treat*. 2013;2013.
6. World Health Organization %M WR J Barnard, Van Pittius NG, van Helden P, Bosman M, Streicher E, Coetzee G, O'Brien R GenoType MTBDRsl line probe assay shortens time to diagnosis of extensively drug resistant tuberculosis in a high throughput diagnostic laboratory *Am J Respir Crit Care Med*. Global Tuberculosis Report. Geneva, Switzerland. 2014; 186.
7. Centers for Diseases control and prevention (CDC): Global HIV & Tuberculosis Ethiopia Country Profile available at <https://www.cdc.gov/globalhivtb/where-we-work/ethiopia/ethiopia.html>. In.; last reviewed: August 29, 2019. Accessed 06 Aug 2019.
8. Badri M, Wilson D, Wood RJTL. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. 2002; 359(9323):2059–64. [https://doi.org/10.1016/S0140-6736\(02\)08904-3](https://doi.org/10.1016/S0140-6736(02)08904-3) PMID: 12086758
9. Musa BM, Musa B, Muhammed H, Ibrahim N, Musa AGJAotm. Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria. 2015; 10(3):185. <https://doi.org/10.4103/1817-1737.160838> PMID: 26229561
10. Kassa A, Teka A, Shewaamare A, Jerene D. Incidence of tuberculosis and early mortality in a large cohort of HIV infected patients receiving antiretroviral therapy in a tertiary hospital in Addis Ababa, Ethiopia. *Trans R Soc Trop Med Hyg*. 2012; 106(6):363–7. <https://doi.org/10.1016/j.trstmh.2012.03.002> PMID: 22521216
11. Jonathan E, Paul P, Lerato M, Nkeko T, Mosa M, et.al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009 March 13; 23(5).
12. Kibret KT, Yalew AW, Belaineh BG, Asres MM (2013) Determinant Factors Associated with Occurrence of Tuberculosis among Adult People Living with HIV after Antiretroviral Treatment Initiation in Addis

- Ababa, Ethiopia: A Case Control Study. *PLoS ONE* 8(5): e64488. <https://doi.org/10.1371/journal.pone.0064488> PMID: 23762214
13. Taha M, Robert C, et al. Risk factors of active tuberculosis in people living with HIV/AIDS in southwest Ethiopia: a case control study. *Ethiop J Health Sci.* 2011; 21(2):131–139. <https://doi.org/10.4314/ejhs.v21i2.69053> PMID: 22434992
  14. Abebe A, Etana B, Tsadik M, Terefe W (2014) Assessing the Effect of Highly Active AntiRetroviral Treatment and Associated Factors on Incidence of Tuberculosis among Adult HIV Positive Individuals in Assela, Ethiopia. *J Health Med Informat* 5: 156. <https://doi.org/10.4172/2157-7420.1000156>
  15. Girum T, Yasin F, Dessu S, Zeleke B, Geremew M. "Universal test and treat" program reduced TB incidence by 75% among a cohort of adults taking antiretroviral therapy (ART) in Gurage zone, South Ethiopia. *Trop Dis Travel Med Vaccines.* 2020; 6:12. <https://doi.org/10.1186/s40794-020-00113-3> PMID: 32864154
  16. Girum T, Yasin F, Dessu S, Zeleke B, Geremew M. "Universal test and treat" program reduced TB incidence by 75% among a cohort of adults taking antiretroviral therapy (ART) in Gurage zone, South Ethiopia. 2020. <https://doi.org/10.1186/s40794-020-00113-3> PMID: 32864154
  17. Dalbo M, Tamiso A. Incidence and predictors of tuberculosis among HIV/AIDS infected patients: a five-year retrospective follow-up study. *Adv Infect Dis.* 2016; 6(02):70.
  18. Enju L, Makubi A, Drain P, Spiegelman D, Sando D, Nan L, et al. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy in Tanzania. *AIDS (London, England).* 2015; 29(11):1391.
  19. Markowitz N, Hansen NI, Hopewell PC, Glassroth J, Kvale PA, Mangura BT, et al. Incidence of tuberculosis in the United States among HIV-infected persons. *Annals of Internal Medicine.* 1997; 126(2):123–32. <https://doi.org/10.7326/0003-4819-126-2-199701150-00005> PMID: 9005746
  20. Geremew D, Endalamaw A, Negash M, Eshetie S, Tessema B. The protective effect of isoniazid preventive therapy on tuberculosis incidence among HIV positive patients receiving ART in Ethiopian settings: a meta-analysis. *BMC infectious diseases.* 2019; 19(1):1–9.
  21. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS (London, England).* 2007; 21(11):1441.
  22. CDC. Ethiopia—CDC Division of Global HIV & TB—Country Profile. 2019.
  23. Lawn SD, Kranzer K., Wood R. Antiretroviral therapy in the control of HIV associated tuberculosis in resource-limited settings. *Clinics in Chest Medicine.* 2009.
  24. Inzaule S, Otieno J, Kalyango J, et al. Incidence and predictors of first line antiretroviral regimen modification in western Kenya. *PLoS One.* 2014; 9(4):e93106. <https://doi.org/10.1371/journal.pone.0093106> PMID: 24695108
  25. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tubercle and lung disease.* 1992; 73(6):311–21. [https://doi.org/10.1016/0962-8479\(92\)90033-G](https://doi.org/10.1016/0962-8479(92)90033-G) PMID: 1292709
  26. Okoye AA, Picker LJ. CD 4+ T-cell depletion in HIV infection: mechanisms of immunological failure. *Immunological reviews.* 2013; 254(1):54–64. <https://doi.org/10.1111/immr.12066> PMID: 23772614
  27. Geleto A, Abate D, Egata G. Intensified tuberculosis case finding, implementation of isoniazid preventive therapy and associated factors among people living with human immunodeficiency virus at public health facilities of Harari region, eastern Ethiopia: a cross-sectional study. *Int J Health Sci* 2017; 11(1):1. PMID: 28293159
  28. Kenneth L. Schaecher MFC. The Importance of Treatment Adherence in HIV. *Supplements and Featured Publications.* 2013; 19(12 Suppl).
  29. Abdu M, Ali Y, Anteneh S, Yesuf M, Birhanu A, Mohamed S, et al. Determinant factors for the occurrence of tuberculosis after initiation of antiretroviral treatment among adult patients living with HIV at Dessie Referral Hospital, South Wollo, Northeast Ethiopia, 2020. A case-control study. *PLoS one.* 2021; 16(3):e0248490. <https://doi.org/10.1371/journal.pone.0248490> PMID: 33724992
  30. Maro I, Lahey T, MacKenzie T, et al. Low BMI and falling BMI predict HIV-associated tuberculosis: a prospective study in Tanzania. *Int J Tuberc Lung Dis* 2010; 14:1447–53. PMID: 20937186
  31. Liu E, Makubi A, Drain P, et al. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy. *AIDS* 2015; 29:1391–9. <https://doi.org/10.1097/QAD.0000000000000705> PMID: 26091295
  32. Ahmed A, Mekonnen D, Shiferaw AM, Belayneh F, Yenit MK. Incidence and determinants of tuberculosis infection among adult patients with HIV attending HIV care in north-east Ethiopia: a retrospective cohort study. *BMJ open.* 2018; 8(2):e016961. <https://doi.org/10.1136/bmjopen-2017-016961> PMID: 29437750

33. Alene A, Nega A, Taye W(2013) Incidence and predictors of tuberculosis among adult people living with human immunodeficiency virus at the University of Gondar Referral Hospital, Northwest Ethiopia. *BMC Infectious Diseases* 2013, 13:292. <https://doi.org/10.1186/1471-2334-13-292> PMID: 23806088
34. Habtamu Oljira MI. Determinants of Active Tuberculosis among HIV-Positive Adults Attending Clinical Care in Ambo general hospital and Gedo hospital, West Shoa Zone, Oromia, Ethiopia (unmatched case-control study). *J Med Physiol Biophys*. 2015; 33(ISSN):2422–8427.
35. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a south African cohort. *Aids*. 2005; 19(18):2109–16. <https://doi.org/10.1097/01.aids.0000194808.20035.c1> PMID: 16284460