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Abstract

Introduction: Tuberculosis is an airborne communicable disease by bacilli of the mycobacterium tuberculosis complex. It is caused by bacteria from mycobacterium tuberculosis complex mainly caused by M.tuberculosis and other closely related species like M.bovis and M.africanum. Despite various HIV care intervention, the zone is noted for its border with Sudan, which facilitates migration in and out, the presence of long-distance drivers, internal and external displaced person due to conflict and also high number of female sexual workers this may be high risk for TB/HIV co-infection. Therefore, this study aimed to assess Time to Tuberculosis development and its predictors among Human Immunodeficiency Virus positive patient's attending follow-up care in health facilities of West Gondar Zone, 2025.

Methods

Institution based retrospective follow-up study care at health facilities from January 1, 2020 to December 30, 2024 in West Gondar Zone, Ethiopia. A two-stage cluster sampling technique were be used. 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. Finally, predictors having p-value<0.05 were be considered as significant variables.

Results

A total 467 HIV-positive individual were followed for 1107.43 PYs, gives an overall incidence density rate was 7.49per 100PYs (83, 17.8%). Ambulatory patients (AHR =1.93; 95% CI 1.09-3.44), didn't take IPT prophylaxis (AHR=2.36;95% CI 1.42-3.93), WHO stage two (AHR=3.22;95%CI 1.54-6.74), WHO stage three and four (AHR=2.37;95%CI 1.01-5.59), being underweight (AHR=2.88; 95%CI 1.71-4.84), co-infection(AHR=0.56; 95%CI 0.34-0.93) and high viral load(AHR=2.42 95%CI 1.02-5.74) were found to be significantly associated with the outcome.

Conclusion

The overall Kaplan Meir curve shows that 50% of patients haven't experienced the event (TB) at the cumulative median survival time. Not taking IPT prophylaxis, being underweight, having an ambulatory functional status, baseline WHO stage II–IV, and high viral load were associated with a higher hazard of developing TB. Hence, it is better to improve the package of care services through improve IPT service, staying in regular contact with health care provider to take HIV medication as soon as and exactly as prescribed to achieve undetectable viral load and maintain health in stage one, improve nutritional status to enhance immunity and also ensuring retention on ART for life long.

INTRODUCTION

Tuberculosis is an airborne communicable disease by bacilli of the mycobacterium tuberculosis complex and its closely related species M.bovis and M.africanum. Infection occurs once these particles reach the alveoli in the lungs, where the bacilli are taken up by alveolar macrophages[1].It is the most common opportunistic infection and a serious health threat for people living with HIV and also TB[2]. HIV-associated TB disproportionally affects African countries, particularly vulnerable groups at risk for both TB and HIV[3]. Globally PLHIV face a 20-30 times higher risk of developing TB compared to HIV-negative individual[4][5]. According

to the WHO global TB report, there were a big drops in new TB cases world-wide, It falls from 7.1million to 6.4 million, in 2019 and 2021, respectively. From the total TB incident cases,6.7% were PLHIV and African took the highest proportion of TB cases co-infected with HIV[6].

In 2019, an estimated 10 million people have fallen ill from TB, and it has claimed the lives of 1.2 million people and additional 208,000 deaths among PLHIV[7].

The national response to the TB and HIV epidemics begun in 2004 and have succeeded in saving lives of hundreds of thousands of affected citizens. Despite this, TB remains to be the leading causes of death of people with HIV accounting for around 40% of AIDS-related deaths. The TB/HIV co-infection rate has declined over several years in Ethiopia ranging from 17% in 2011 to 6% in 2020. However, TB and HIV is still among the highest public health problems of the country[8].

According to the study conducted in United States TB was diagnosed during the study period in HIV Seropositive patients 52% had pulmonary involvement, 23% had extra pulmonary diseases and 26% had both pulmonary and extra pulmonary diseases[9].

According to the study conducted in a public ART centre in Pune, India on first and second line anti-retro viral therapy with incidence rate of TB was 4.39 cases per 100 person-years and 1.64 cases per 100 person-years respectively[10]. In similarly study conducted in Denmark with in a total register of 1,700 patients, with in 67 co-infected patients were identified ,among this only 4% of all TB cases representing during the study period[11],and also in Kazakhstan from HIV-positive patients 8% was co-infected with tuberculosis[12]

According to the study conducted at St.peter and Zewditu memorial hospital in Addis Ababa among 529 patients, the incidence rate was found to be 4.84 per 100 person-years[13]. Similarly in Addis selected health facilities with in a period of January 2013 to December 2018,with a total of 566 patients giving a TB incidence rate of 6.82 per 100person-years[14] and also similarly in Arba Miniche in 5.36 per 100 person years over five years of follow-up time[15].

According to the study conducted in Adama with a retrospective study for five years among 428 patient individual were included in the analysis ,among this 67 new TB cases were observed during the follow-up period[16].

Study conducted in Hawassa health facilities ,with a five year follow-up total of 422 individual, the overall incidence rate of TB among HIV-positive patients was 6.26 per 100 person-years[17]. Similarly with a similar follow-up time in North-East Ethiopia a total of 451 individual were followed with the overall incidence of TB was 8.6 per person-years of observation[18]. And also study conducted in Benishangul Gumuz region among children in a total of 421 seropositive children with the overall incidence rate participant was found 5.9 per 100 person-years of risk observation[19].

However, TB incidence is still the highest public health problem for immune-compromised individual, especially people living with HIV for this reason proper intervention, treatment and further investigation of predictors is needed. Even though different studies conducted in Ethiopia, but which is not enough to asses TB/HIV co-infection especially in our district due to its border with Sudan. The zone is also noted for its border with Sudan Ethio-Sudan highway, which facilitates migration in and out, the presence of long distance drivers, internal and external displaced person due to conflict and also high number of female sexual workers this may be high risk for TB/HIV co-infection[20]. Therefore this study tried to assess time to tuberculosis development and its predictors among Human Immunodeficiency Virus (HIV) positive patients receiving follow-up care in health facilities of West Gondar Zone, so the results of this study were be used by health policy and different projects to design appropriate intervention and treatment about the incidence of TB among HIV patients.

Methods

Study design, setting and period

An institution-based retrospective follow-up study was conducted from May 15-June30, 2025, among HIV-positive patients receiving follow-up care at health facilities from January1, 2020 to December 30, 2024 in West Gondar Zone, Ethiopia. West Gondar Zone is located in North West Ethiopia on the border of Sudan, and the centre is Genda Wuha town located in 897 km north of Addis Ababa and 197km from the ancient city of Gondar. According to the report obtained from West Gondar zone HIV program, the total population of the zone is estimated more than 234,453 persons and also there are 12 health facilities providing ART service, among this three of them

are hospital; the other is health centre serving for the major share of HIV-positive patients on follow-up care in our zone.

Population

All HIV-positive patients age above 15 years and who were enrolled in ART follow-up care between January 1, 2020, and December 30, 2024, at ART centres were the source population. Besides Patients who started ART in the selected facilities between January1, 2020 to December 30, 2024 were the study population. Patients those transferred in from other facilities before starting ART be included in the study, and Participants with missing charts, patients diagnosed with TB and/ or initiated anti-TB with clinician decision at enrolment were excluded from the study.

Sample size determination and Sampling technique

The sample size was calculated for the two main objective of the study. The sample size for estimating time to development of TB was calculated by Schoenfeld's formula for the cox proportional hazard's model.

$n=\frac{(Z\alpha/2+Z\beta)2}{p(\log(HR))2}$,Whereas: n=required sample size, $Z\alpha/2$ =critical level for significance level ,$Z\beta$=critical value for the power, P=proportion of the cohort developing the outcome (0.137 from the previous study)[17], HR=hazard ratio (4.943 from the previous study)[14]

Then by substituting the values

$n=\frac{(1.96+0.84)2}{0.137(\log(4.943))2}\approx 119$ then based on design effect n=179

For the second objective: Sample size was determined by using cox regression analysis model for survival analysis by STATA software version 17 and considering statistically associated variables from the previous studies. Accordingly, BMI, IPT and ART Initiation time less a week and above a week were most frequently associated variables with time to TB development[17][14]. All variables were considered to obtain the adequate sample size and finally, BMI with adjusted hazard ratio (AHR)=1.907, observed probability of TB (25.8%), 95% confidence interval, level of certainty (α=0.05), power (80%) and assuming 10% withdrawal, the

sample size for study was determined to be 325 with estimated number of events (E) 76. Considering design effect of two stage sampling.

Table 1: Sample size and sample size determination parameters

Co-variant	Adjusted HR	probability of TB (event)	Withdrawal	Estimated number of events	Sample size	Design effect	Final sample size (event free)
BMI[14]	1.907	0.258	10%	76	325	1.5	488 (114)
IPT[14]	4.943	0.258	10%	13	53	1.5	80 (20)
ART Initiation time[17]	0.4	0.1374	10%	38	303	1.5	455 (57)

Therefore, our final sample size for this study was 488 (Table 2). A two-stage cluster sampling technique were be used. We were randomly select six based on its cluster out of 12 health facilities in the zone that provide ART service in the first stage by a simple random sampling technique. Finally, the required sample size was obtained using a simple random sampling technique, employing computer generated numbers from each health facility during the second stage of sampling.

Variables

The Dependent variable was time to TB development defined as were be the time from enrollment dates to ART clinic to TB diagnosis and also **TB case** were be an event ascertained when diagnosed with TB by approved diagnostic workups by Acid fast bacilli(AFB) and Gene expert [8]. The first group of predictors was socio-demographic such as age, sex, occupation, family size, marital status, residence, religion, educational status, substance use, address and disclosure status of the patient to others. The second was baseline clinical and laboratory variables including CD4 count, first viral load result, BMI, WHO clinical stage, functional status, haemoglobin, co-infection except TB and previous TB status. Finally ART and other medication related characteristics including ART regimen, time to ART initiation ,duration of ART, time to linkage, adherence level, DSD-category and IPT prophylaxis. These elements were ascertained by reviewing patient records. In this study **Time to linkage** were be between dates of HIV-positive status identification and enrollment to the facility for ART follow-up care. Additionally **Time to ART initiation** were be the time between enrollment dates to the facility for ART follow-up care and ART initiation. And also **Co-infection** were be evidence of diagnosis and/or treatment for any infectious

(except TB) and non-infectious diseases during the follow-up period. Furthermore**, BMI** is a measure of body fat based on height and weight, calculated by dividing weight in kilogram by the square of height in meters, BMI≥18.5 is normal weight and BMI <18.5 is underweight[7]. Finally **Adherence to ART** were be documented adherence level to ART medications at the first visit or at the first month after enrollment, whichever comes early, as Good (95% or < 2 doses missed per month or < 3 dose missed per 2 months), fair (85–94% or 3–5 doses missed per 30 doses or 3–9 doses of 60 doses), and poor (less than 85% or > 6 doses of 30 doses or > 9 dose of 60 doses) [21].

Data Collection tools and procedures

Data were collected retrospectively from the patient charts, smart-care and registration book of HIV-positive individuals newly registered at ART in the selected facilities between January1, 2020 to December 30, 2024. Data were extracted for one month and half from May 15-June30, 2025 with kobo-tool box. A structured English version checklist was developed based on the national ART intake and follow-up forms in ART clinics. Questionnaires developed in English with kobo-tool box for data collector. The data collector was trained for one days on how to interview and how to fill the questioners prior to the onset of the study. The quality of data was assured by proper designing of the questionnaire. The collected data were reviewed each day and checked for completeness and consistency.

Data Analysis

The collected data were exported to STATA-17 for cleaning and analysis. Then we were performing a descriptive statistic to summarize and present the data after that we were calculate the TB incidence in per person years after compute the total duration of the follow up period. The K-M survival curves can give us an insight about the difference of survival functions in two or more groups among our study participants, but whether this observed difference is statistically significant requires a formal statistical test, one commonly used non-parametric tests for comparison of two or more survival distributions is the log-rank test. We have estimated the Median Survival Time among our participants**.** This is the time beyond which 50% of the ART users in the population under study are expected to survive from TB and is given by that value t (50).

The Cox proportional hazards (PH) regression model was conducted and we have checked the assumption of proportional hazards before proceeding further with other inferential activities. Schoenfeld residual based on p-value and cox-snell residuals graph based on line fitness to 45 degree then determinant factors of TB incidence were be identified by competing for bi-variable and multivariable Cox regression with a p-value < 0.2 in the bi-variable analysis were be

included in the multivariable analysis, we were be computed AHR with 95% confidence intervals, and we declared that statistical significance with a P-value of < 0.05.

Results

Socio-demographic characteristics

Data were extracted from the charts and ART-smart care for 488 HIV-positive patients. Among these patients 467(96%) records were included in the final analysis while 21 records were excluded because they didn't contain the required information. The median age of the participants was 34 and 282 (60.39%) were females. Most of the study participants 305 (65.3%) were urban residence and 239(51.18%) were married. Concerning to disclosure status of the patient to others 350(74.95%) of them were disclosed their status. Besides, majority of the participant 459(98.29%) were in west Gondar people and 325(69.59%) were orthodox (Table 3).

Table 4: base line Socio-demographic characteristics for HIV-positive individuals newly registered at ART in the selected facilities between January1, 2020 to December 30, 2024

Variable	Category	Frequency	Percentage
Sex	Male	185	39.61
	Female	282	60.39
Age	16-24	83	17.77
	25-34	165	35.33
	35-44	162	34.69
	45 and above	57	12.21
Marital Status	Single	92	19.7
	Married	239	51.18
	Divorced	94	20.13

	Widowed	15	3.21
	Separated	27	5.78
Residence	Urban	305	65.31
	Rural	162	34.69
Address	West Gondar	459	98.29
	EDP/refuges/	8	1.71
Religion	Orthodox	325	69.59
	Muslim	126	26.98
	Others	16	3.43
Educational status	No formal education	117	25.05
	Formal education	350	74.95
Occupational status	Merchant	119	25.48
	Governmental and non- Governmental employer	56	11.99
	Farmer	48	10.28
	Housewife	163	34.90
	Daily laborer	58	12.42
	Other	23	4.93
Disclosure status	Yes	350	74.95
	No	117	25.05
Family size	1-3	281	60.17
	4-5	147	31.48

	>5	39	8.35
Tobacco smoking	Yes	62	13.28
	No	405	86.72
Alcohol addiction	Yes	164	35.12
	No	303	64.88
Taking Khat	Yes	97	20.77
	No	370	79.23

Baseline clinical and laboratory related characteristics

At baseline, most of the participants (n=392, 83.94%) had a working functional status. Likewise, the majority (n=373, 79.87%) were categorized as WHO stage one/two. Of the participants 328(70.24) had a history of at least one type of infection except TB during their presentation and 304(65.10%) had greater than 200cells/Ui CD4 count. Furthermore, 303 (64.88%) had BMI between18.5-24.9, 372(79.66%) had Hgb 11g/dl and above, and 383(82.01%) had no previous TB history (Table 5).

Table 6: baseline clinical and laboratory characteristics for HIV-positive individuals newly registered at ART in the selected facilities between January1, 2020 to December 30, 2024

Variable	Category	Frequency	Percentage
CD4 count (in cells/Ui)	200 and more	163	35.98
	>200	304	65.10
Hgb	<11g/dl	95	20.34
	11g/dl and above	372	79.66
Viral load	High viral load	49	10.49
	Low viral load	229	49.04
	Undetectable viral load	189	40.47

WHO stage	Stage one	191	40.9
	Stage two	182	38.97
	Stage three and four	94	20.13
Functional status	Working	392	83.94
	Ambulatory	66	14.13
	Bedridden	9	1.93
BMI	<18.5	125	26.77
	18.5-24.9	303	64.88
	25 and above	39	8.35
Previous TB	Yes	84	17.99
	No	383	82.01
Co-infection except TB	Yes	328	70.24
	No	139	29.76

ART and other medication related characteristics

Most of the participant, 414(88.65%) had the time to link them to ART cite from the identification of their HIV-positive status was less than one week and almost half of the participant 237(50.75%) had initiated ART within one week of being linked to ART cite. Majority of the participant, 416(89.08%) had DTG based initial ART regimen and also 402(86.08%) had taken ART for one year and above. Of the total participant, 205(43.9%) had good adherence and 311(66.6%) had 3MMD DSD Category. Regarding to IPT prophylaxis more than half 274(58.67%) of the participants took this therapy (Table 7).

Table 8: ART and other medication related characteristics HIV-positive individuals newly registered at ART in the selected facilities between January1, 2020 to December 30, 2024.

Variable	Category	Frequency	Percentage
ART regimen	DTG based	416	89.08
	Non-DTG based	51	10.92
Linkage time in a week	<1 week	414	88.65
	1 week and above	53	11.35

ART initiation time in a week	<1 week	237	50.75
	1 week and above	230	49.25
Duration of ART in months	<6 months	18	3.85
	6-12 months	47	10.06
	12 and above months	402	86.08
ART Adherence	Good adherence	205	43.9
	Fair adherence	151	32.33
	Poor adherence	111	23.77
DSD_ category	3 MMD	311	66.6
	6 MMD	42	8.99
	Other	114	24.41
IPT prophylaxis	Yes	274	58.67
	No	193	41.33

Incidence of TB among HIV-positive patients

During the five-year follow-up period, a total of 467 HIV-positive individual was followed for 1107.43 PYs. Within the follow-up period, 83 patients were found to develop TB which gives an overall incidence density rate was 7.49per 100PYs. Study participants stayed in the follow-up for a minimum of 1.033 months and maximum of 60 months. The highest incidence rate of TB was found among patients who took ART for less than six months (277.19 per 100PYs), followed by those who took ART between six and twelve months (72.21per100PYs), Address of EDP (35.16per100PYs) and also high viral load (31.78per100PYs). In contrast with, the lowest incidence rate was among patients WHO stage one (2.79per100PYs) (Table 9).

Table 10: Incidence of TB among HIV-positive patients

Characteristics(n=467)		Survival status		PYs observation	IDR (per 100PYs)	95% CI
		TB	Censored			
Age in years	16-24	10	73	166.79	6.00	3.23-11.14
	25-34	31	134	346.93	8.94	6.28-12.71
	35-44	30	132	435.14	6.89	4.82-9.86
	45 and above	12	45	158.58	7.57	4.30-13.32
Sex	Female	45	237	681.99	6.6	4.93-8.84
	Male	38	147	425.44	8.93	6.50-12.28
Occupation	Daily laborer	13	45	115.84	11.22	6.52-19.33
	Farmer	9	39	119.66	7.52	3.91-14.46
	Gov and non-gov employer	14	42	128.69	10.88	6.44-18.37
	Housewife	28	135	410.26	6.82	4.71-9.88
	Merchant	17	102	290.83	5.85	3.63-9.40
	Other	2	21	42.16	4.74	1.19-18.97
Residence	Urban	52	253	701.59	7.41	5.65-9.73
	Rural	31	131	405.84	7.64	5.37-10.86
Religion	Orthodox	58	267	774.40	7.49	5.79-9.69
	Muslim	23	103	286.32	8.03	5.34-12.09
	Others	2	14	46.71	4.28	1.07-17.12
Marital status	Married	42	197	584.26	7.19	5.31-9.73
	Divorced	21	73	217.87	9.64	6.28-14.78
	Single	13	79	188.54	6.90	4.00-11.87
	Separated	5	22	70.61	7.08	2.95-17.01
	Windowed	2	13	46.16	4.33	1.08-17.33
Educational status	Primary	24	168	460.84	5.21	3.49-7.77
	Secondary	14	82	225.22	6.22	3.68-10.50
	College and higher	18	44	146.25	12.31	7.75-19.53

	No formal education	27	90	275.12	9.81	6.73-14.31
Address	West Gondar	81	378	1101.74	7.35	5.91-9.14
	EDP/refuges/	2	6	5.69	35.16	8.79-140.57
Family size	1-3	44	237	627.48	7.01	5.22-9.42
	4-5	31	116	360.25	8.61	6.05-12.24
	>5	8	31	119.7	6.68	3.34-13.36
Tobacco	Yes	17	45	122.89	13.83	8.60-22.25
smoking	No	66	339	984.55	6.70	5.27-8.52
Alcohol	Yes	39	125	364.95	10.69	7.81-14.63
addiction	No	44	259	742.48	5.93	4.41-7.96
Taking khat	Yes	24	73	193.56	12.40	8.31-18.50
	No	59	311	913.87	6.46	5.00-8.33
Previous TB	Yes	8	76	224.70	3.56	1.78-7.12
history	No	75	308	882.73	8.50	6.78-10.65
Disclosure	Disclosed	55	295	866.11	6.35	4.88-8.27
status	Not disclosed	28	89	241.32	11.60	8.01-16.80
Co-infection	Yes	46	282	798.77	5.76	4.31-7.69
Except TB	No	37	102	308.67	11.99	8.69-16.54
Baseline	<18.5	42	83	258.26	16.26	12.02-22.01
nutritional	18.5-24.9	34	269	727.81	4.67	3.34-6.54
status (BMI)	25 and above	7	32	121.36	5.77	2.75-12.10
Functional	Working	60	332	930.39	6.45	5.01-8.31
status	Ambulatory	18	48	158.84	11.33	7.14-17.99
	Bedridden	5	4	18.20	27.47	11.43-66.00
Viral load	High viral load	25	24	78.66	31.78	21.48-47.04
result	Low viral load	38	191	532.84	7.13	5.19-9.80
	Undetectable viral load	20	169	495.93	4.03	2.60-6.25
Baseline	<11g/dl	31	64	190.37	16.28	11.45-23.16
Hgb	11g/dl and above	52	320	917.07	5.67	4.32-7.44
Baseline	≤200	44	119	342.04	12.86	9.57-17.29

CD4 count	>200	39	265	765.40	5.10	3.72-6.97
WHO stage	Stage one	14	177	502.05	2.79	1.65-4.71
	Stage two	37	145	417.82	8.86	6.42-12.22
	Stage three and four	32	62	187.56	17.06	12.07-24.13
DSD_ category	3MMD	53	258	737.59	7.19	5.49-9.41
	6MMD	4	38	113.18	3.53	1.33-9.42
	Other	26	88	256.66	10.13	6.90-14.88
Initial ART regimen	DTG based	75	341	980.01	7.65	6.10-9.60
	Non-DTG based	8	43	127.43	6.28	3.14-12.55
IPT prophylaxis	Yes	26	248	687.65	3.78	2.57-5.55
	No	57	136	419.78	13.58	10.47-17.60
Adherence of the patient	Good adherence	22	183	530.64	4.15	2.73-6.30
	Fair adherence	22	129	354.69	6.20	4.08-9.42
	Poor adherence	39	72	222.10	17.56	12.83-24.03
Duration of ART	<6 months	16	2	5.77	277.19	169.82-452.46
	6-12 months	27	20	37.39	72.21	49.52-105.29
	12 and above months	40	362	1064.27	3.76	2.76-5.12
Time to linkage	<1 week	78	336	944.96	8.25	6.61-10.31
	1 week and above	5	48	162.48	3.08	1.28-7.39
Time to ART initiation	<1 week	37	200	511.93	7.23	5.24-9.98
	1 week and above	46	184	595.51	7.72	5.79-10.31

Kaplan-Meier Survival Curve

The mean survival time was 4.196(95% CI: 4.040-4.352) years. The cumulative probability of TB-free survival at the end of 1, 2, 3, 4, and 5 years of follow-up was 0. 9125, 0.8461, 0.8049, 0.7741, and 0.7122, respectively(Figure 1). In terms of log-rank test, a significant difference in TB-free survival was observed among participants based on several factors such as; take IPT prophylaxis's ($p<0.001$) (**Error! Reference source not found.**), undetectable viral load result ($p<0.001$) (Figure 2), WHO clinical stage one ($p<0.001$) (**Error! Reference source not found.**), Good adherence ($p<0.001$), working functional status ($p<0.01$), duration of ART for one year and above ($p<0.001$) (Figure 3), Hgb 11g/dl and above ($p<0.001$), normal weight ($p<0.001$)(Figure 4) have better survival for TB.

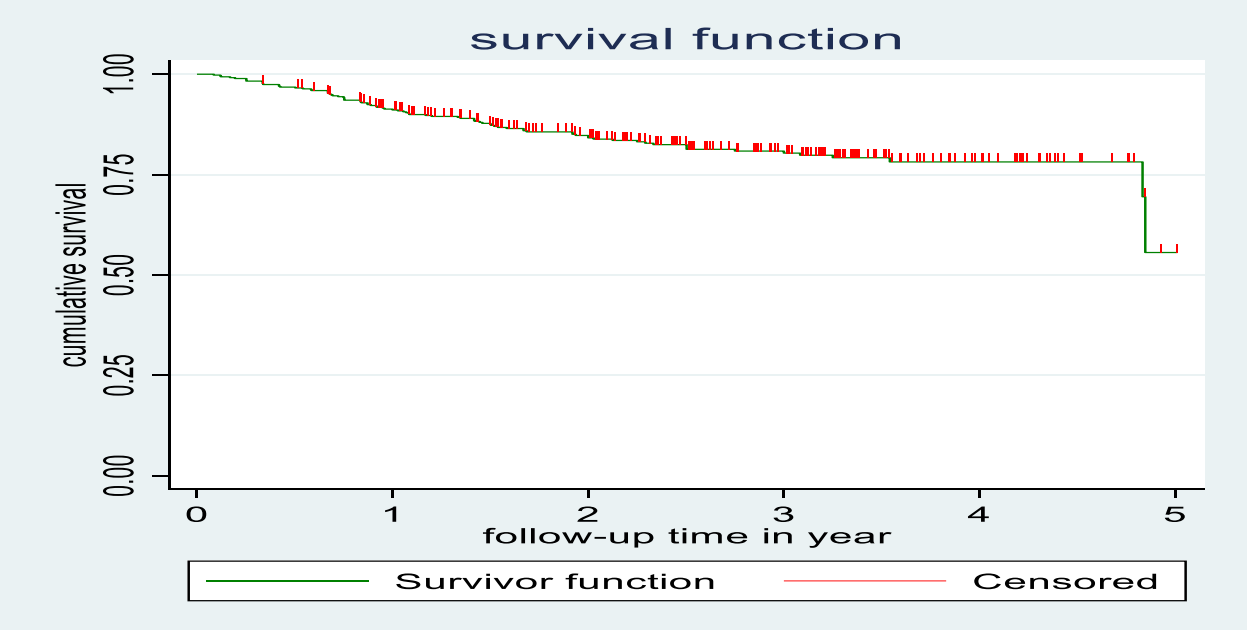

Figure 5: Cumulative survival probability to develop TB among patients on ART in West Gondar zone in the selected facilities between January1, 2020 to December 30, 2024.

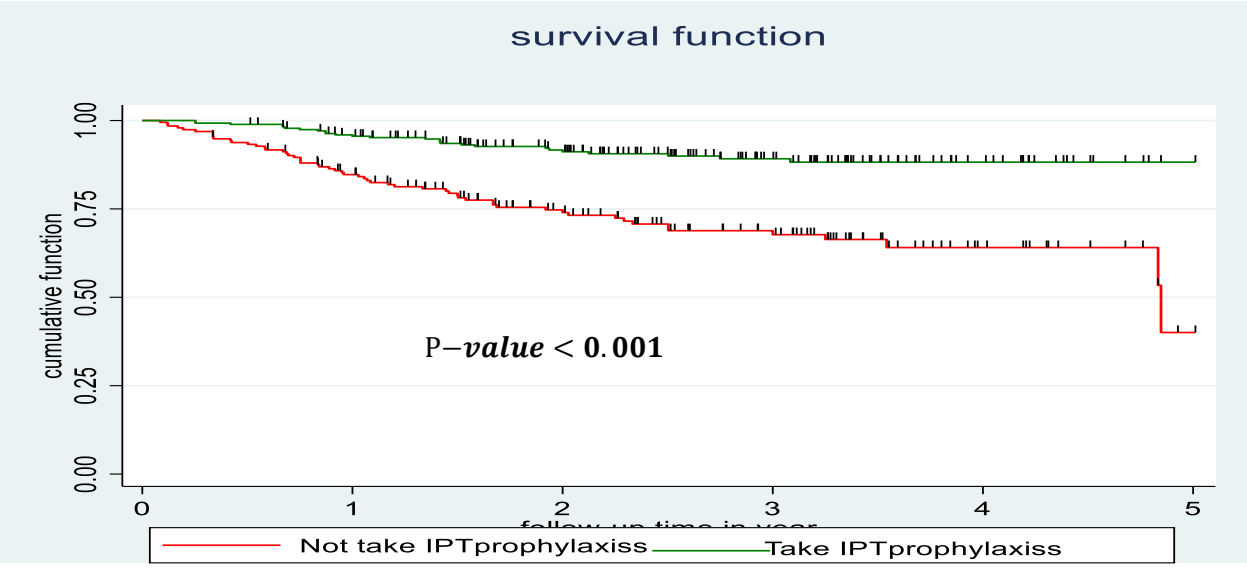

Figure 6: Cumulative survival probability to develop TB among patients on ART by IPT prophylaxis's status in west Gondar in the selected facilities between January1, 2020 to December 30, 2024

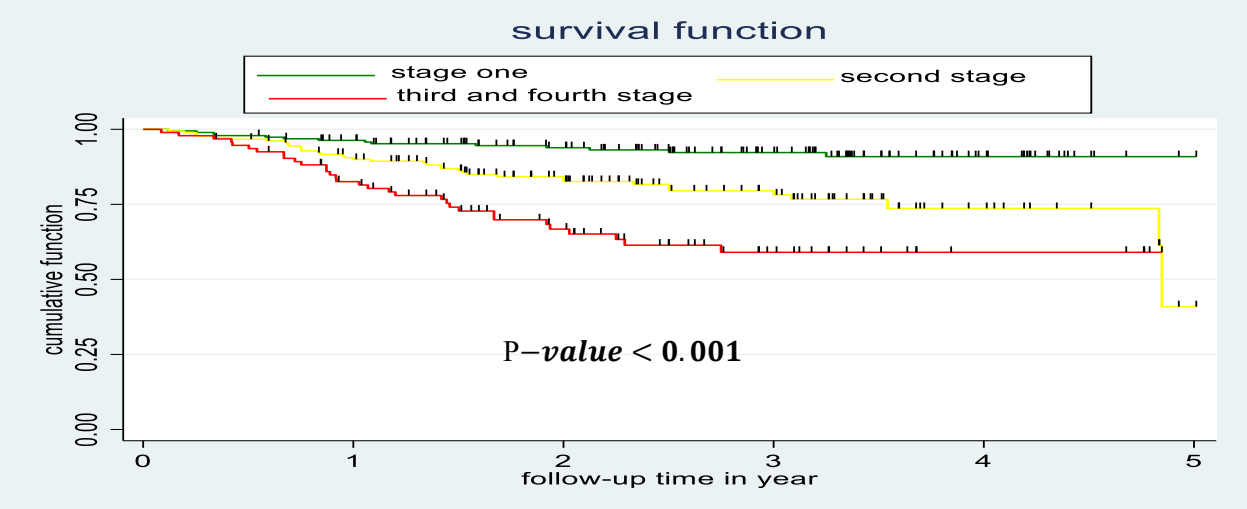

Figure 7:: Cumulative survival probability to develop TB among patients on ART by WHO stages in west Gondar in the selected facilities between January1, 2020 to December 30, 2024

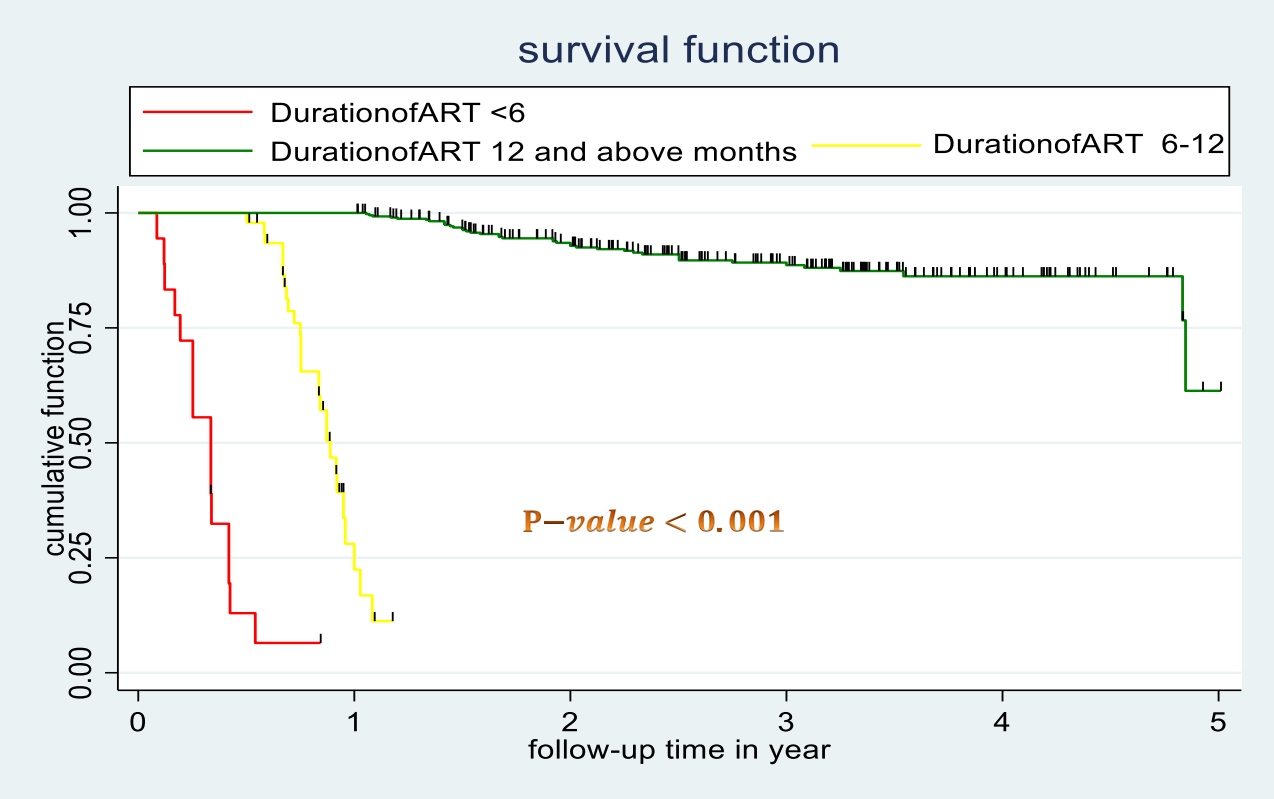

Figure 8: Cumulative survival probability to develop TB among patients on ART by duration of ART in west Gondar in the selected facilities between January1, 2020 to December 30, 2024.

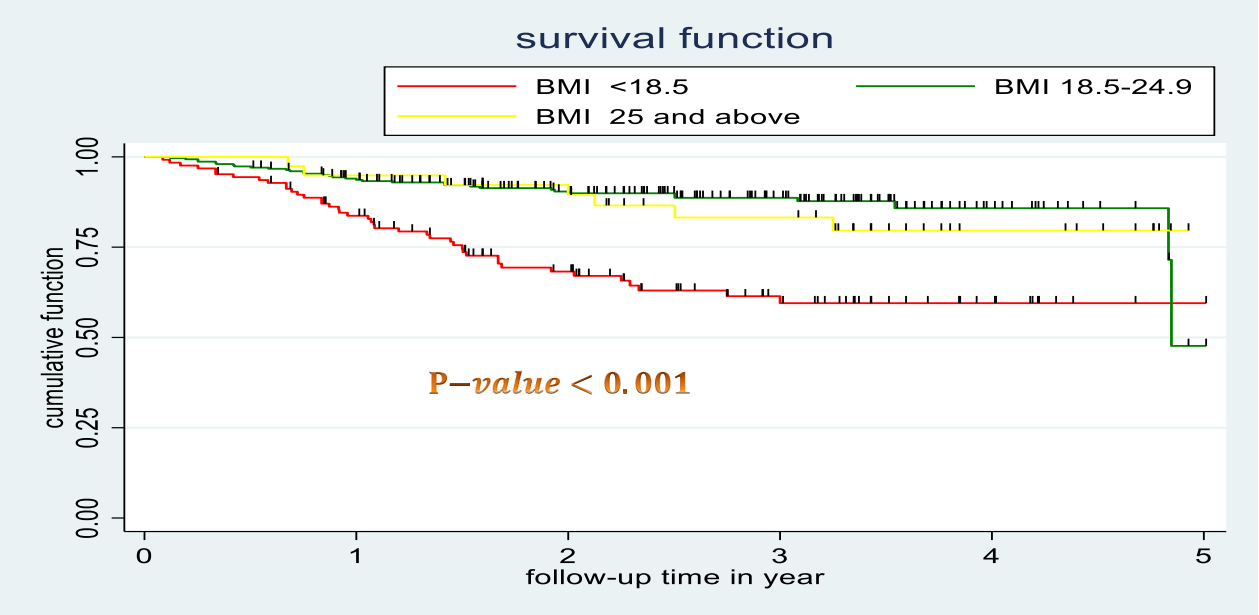

Figure 9: Cumulative survival probability to develop TB among patients on ART by baseline nutritional status in west Gondar in the selected facilities between January1, 2020 to December 30, 2024

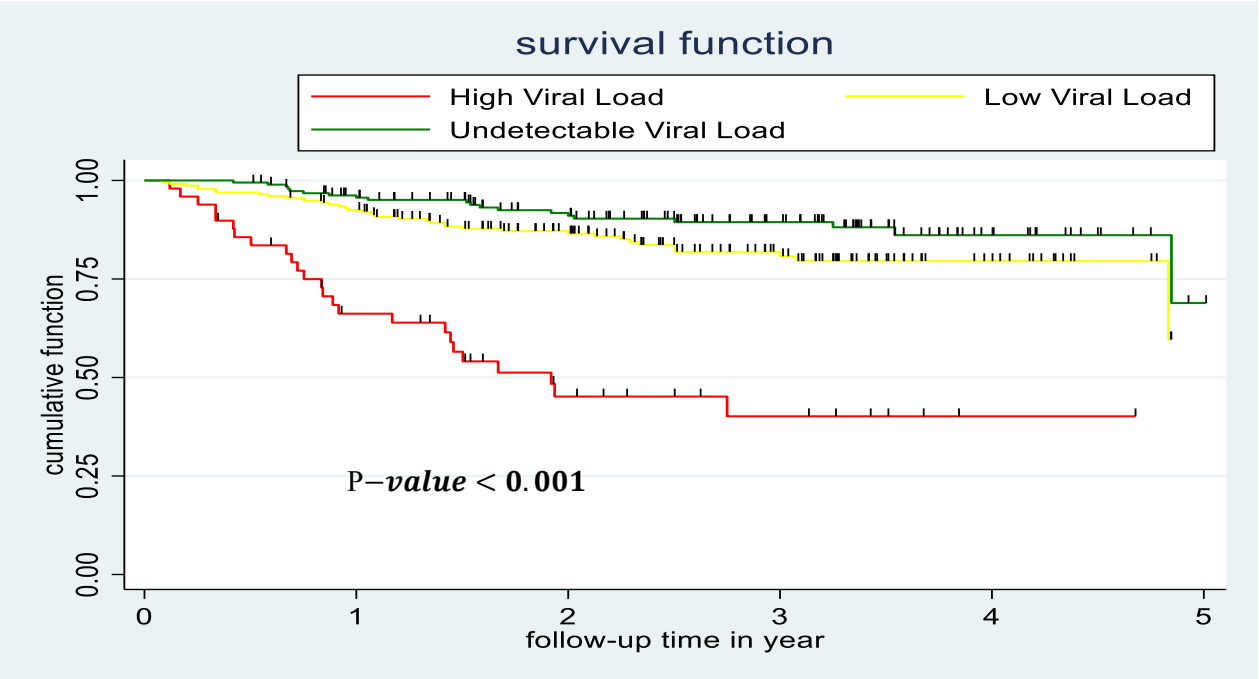

Figure 10: Cumulative survival probability to develop TB among patients on ART by viral load result in west Gondar in the selected facilities between January1, 2020 to December 30, 2024

Median survival time mean is the point in time when 50% of patients have experienced the event (TB) and 50% are still surviving from TB. The overall KMC shows that 50% of patients haven't experienced the event (TB) at the cumulative median survival time. The median

survival time for doesn't take IPT prophylaxis's is 58 months but for taking IPT prophylaxis's is survived longer than 50%. The median survival time in duration of ART for less than six months and between six and twelve months is 4 and 11 months respectively but patients who have duration of ART twelve and above have survived longer than 50%. In terms of viral load result high viral load have 23 months but others have been survived beyond the median survival time. Based on their hemoglobin who have less than 11 g/dl have 58 months of median survival time, and 11 g/dl and above have survived longer than 50%.

Predictors of tuberculosis

Non-parametric comparison of survival: -based on Kaplan-Meir survival curve and its Log-rank test, patients who took IPT prophylaxis's, undetectable viral load result, WHO clinical stage one, duration of ART for one year and above, good adherence, working functional status, high Hgb, normal weight were found to have better survival than their counter parts.

Cox-proportional hazard model: -Among all variables assessed in this study, 15 variables gave a p-value <0.2 in the bi-variable Cox regression analysis. These variables were occupation, addiction to taking khat, disclosure status, service by DSD, baseline functional status, baseline viral load result, previous TB history, IPT prophylaxis's, adherence of the patient, confection except TB, baseline CD4 count, baseline WHO stage, Hgb, baseline BMI and linkage time in week. All of these variables were included in the multivariable Cox regression analysis to identify the independent determinants of TB incidence among PLHIV during the follow up period. In the multivariable Cox regression analysis after controlling for confounding Variables such as baseline functional status, co-infection except TB, IPT prophylaxis's, baseline WHO stage, baseline BMI and viral load result were found to be significantly associated with the outcome.

Participants who didn't take IPT prophylaxis had 2.36 times increased hazard of having TB as compared to those who are taking IPT prophylaxis (AHR=2.36;95% CI 1.42-3.93).

The hazard of TB was 2.88 times higher among participants who are underweight as compared to those with a normal weight (AHR=2.88; 95%CI 1.71-4.84). The hazard of tuberculosis among ambulatory patients was 1.93 times higher than working (AHR =1.93; 95% CI 1.09-3.44). Participants who had co-infection reduced the risk of TB by 44% as compared who had no co-infection (AHR=0.56; 95%CI 0.34-0.93). Participants who were in stage two at baseline had 3.22

times increased hazard of TB as compared to those in stage one (AHR=3.22;95%CI 1.54-6.74) and also Participants who were in stage three and four at baseline had 2.37 times increased hazard of TB as compared to those in stage one (AHR=2.37;95%CI 1.01-5.59). Finally, those patients who were in high viral load had 2.42 times increased hazard of TB as compared to those in undetectable viral load (AHR=2.42 95%CI 1.02-5.74) (Table 11).

Table 12: Predictors of TB who started ART in the selected facilities between January1, 2020 to December 30, 2024

Characteristics(n=467)		Survival status		CHR (95%CI)	AHR (95%CI)	p-value
		TB	Censored			
Occupation	Merchant	17	102	1.00		
	Farmer	9	39	1.27(0.56-2.85)	1.35(0.54-3.38)	0.514
	Gov and non-gov employer	14	42	1.89(0.93-3.86)	1.44(0.68-3.03)	0.329
	Housewife	28	135	1.22(0.67-2.24)	1.25(0.65-2.38)	0.493
	Daily laborer	13	45	1.95(0.94-4.04)	0.73(0.31-1.71)	0.471
	Other	2	21	0.74(0.17-3.24)	1.21(0.26-5.71)	0.803
Taking khat	Yes	24	73	1.83(1.14-2.95)	1.5(0.86-2.60)	0.150
	No	59	311	1.00	1.00	
Previous TB history	Yes	8	76	1.00	1	
	No	75	308	2.32(1.11-4.81)	2.10(0.96-4.57)	0.060
Disclosure status	Disclosed	55	295	1	1	
	Not disclosed	28	89	1.81(1.14-2.86)	1.28(0.72-2.26)	0.393
Co-infection except TB	Yes	46	282	0.47(0.30-0.73)	0.56(0.34-0.93) *	0.025
	No	37	102	1.00	1	
Baseline nutritional status (BMI)	<18.5	42	83	3.47(2.21-5.46)	2.88(1.71-4.84) **	0.000
	18.5-24.9	34	269	1.00	1	
	25 and above	7	32	1.32(0.58-2.99)	0.99(0.41-2.41)	0.999
Functional status	Working	60	332	1.00	1	
	Ambulatory	18	48	1.67(0.98-2.84)	1.93(1.09-3.44) *	0.024
	Bedridden	5	4	4.18(1.67-10.41)	1.17(0.40-3.38)	0.764

Viral load result	High viral load	25	24	7.92(4.34-14.45)	2.42(1.02-5.74) *	0.044
	Low viral load	38	191	1.78(1.03-3.10)	1.24(0.66-2.31)	0.487
	Undetectable viral load	20	169	1.00	1	
Baseline CD4 count	≤200	44	119	2.41(1.56-3.71)	1.43(0.88-2.32)	0.141
	>200	39	265	1.00	1	
WHO stage	Stage one	14	177	1	1	
	Stage two	37	145	2.98(1.61-5.53)	3.22(1.54-6.74) **	0.002
	Stage three and four	32	62	5.89(3.13-11.06)	2.37(1.01-5.59) *	0.048
DSD_ category	3MMD	53	258	1		
	6MMD	4	38	0.49(0.17-1.37)	0.66(0.23-1.91)	0.450
	Other	26	88	1.38(0.86-2.21)	1.42(0.82-2.44)	0.207
IPT prophylaxis	Yes	26	248	1	1	
	No	57	136	3.49(2.19-5.56)	2.36(1.42-3.93) **	0.001
Adherence of the patient	Good adherence	22	183	1	1	
	Fair adherence	22	129	1.39(0.76-2.51)	0.95(0.49-1.82)	0.886
	Poor adherence	39	72	3.9(2.30-6.59)	1.42(0.75-2.67)	0.275
Time to linkage	<1 week	78	336	1	1	1
	1 week and above	5	48	0.41(0.16-1.03)	0.42(0.16-1.06)	0.068

** = p value ≤ 0.01

*** = p value<**0.05

By using Schoenfeld residual test, the proportional hazard assumption was found to hold, as indicated by a non-significant result (p=0.7057) (Table 13). In addition, the Cox-Snell residual graph shows that the model fits the data, with the cumulative hazard of the residual closely following the reference line. A slight deviation in the upper tail may indicate a minor lack of fit, may be due to censoring effect or sparse data in that region (Figure 11).

Table 14: Global Schoenfeld residual test

	Chi^2	df (degrees of freedom)	p-value
Global test	19.84	24	0.7057

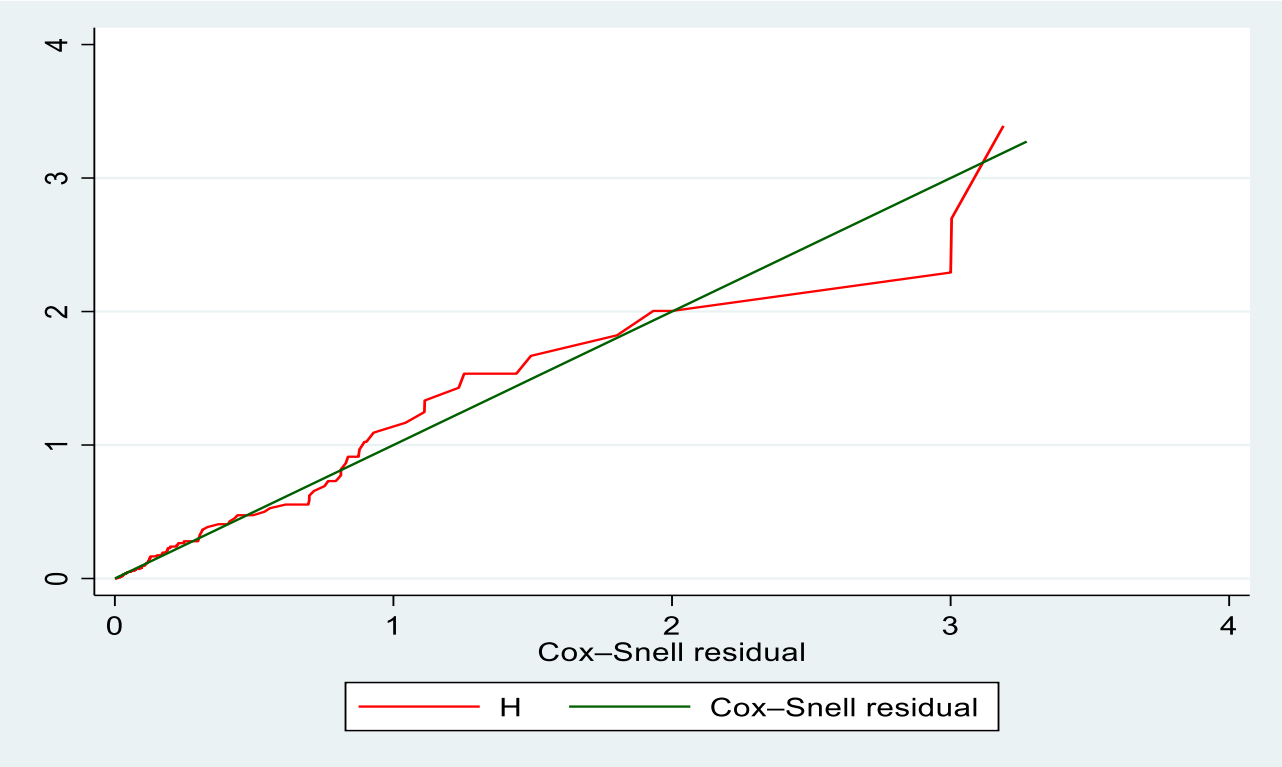

Figure 12: Cox-Snell residual graph for cox proportional hazard model fitness

Discussion

In this retrospective follow-up study, 467 HIV-positive patients were followed for 1107.43 PYs and 83 patients of them developed TB at different times during the 5-year follow-up period, with an overall TB incidence density rate of 7.49 per 100PYs. This findings is in line with studies conducted in North-East, Ethiopia (8.64 cases per 100PYs), Hawassa-city, Ethiopia (6.26 cases per 100PYs), Addis Abeba, Ethiopia (6.82 cases per 100PYs)[18][17][14]. However, it is higher than studies from Arba-Minch, Ethiopia (5.36 cases per 100PYs), Addis Abeba in specialized hospital, Ethiopia (4.84 cases per 100PYs), Northern-Tanzania (2.08 cases per 1000PYs), India (3.94 cases per 100PYs), USA (0.7 cases per 100PYs)[9, 10, 15, 22, 23]. This might be due to difference in sociodemographic characteristics of study participants, high burden of HIV and low healthcare coverage in our study setting, similarly due to the difference in follow-up time

showed that the incidence of TB is significantly associated with the duration of ART or it's follow-up time it was reported that the incidence of TB decreased as the years of follow-up increased[17]. On the contrary 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 modalities in such countries when compared with our study setting.

Median survival time mean is the point in time when 50% of patients have experienced the event (TB) and 50% are still surviving from TB. Based on this the median survival time for didn't take IPT prophylaxis's, duration of ART for less than six months and between six and twelve months, high viral load result and Hgb who have less than 11 g/dl have 58,4,11,23 and 58 months respectively median survival time but its counter parts have survived longer than 50%. There is no further study which is consistent with our findings.

From multivariable cox regression analysis Variables such as Ambulatory functional status, not taking IPT prophylaxis's, being on baseline WHO stage two and stage three with four, underweight, had co-infection except TB and high viral load were found to be significantly associated with the outcome.

This study identified that being underweight was found to increase the hazard of TB by 2.88 times as compared to normal weight. This finding was consistent with that of different studies done Ethiopia, Uganda, Tanzania and Sub-Saharan Africa [18, 23-25]. This might be due to the fact that a low-BMI category is a proxy indicator of malnutrition with frequently encountered symptoms like decreased intake of food, this leads to significant weight loss; severe malnutrition, infection and other immunosuppressive conditions which further weakness the immunity level and then increase the risk of developing opportunistic infections such as TB[8].

Participants who didn't take IPT prophylaxis had 2.36 times increased hazard of having TB. This might be due to the role of IPT in reducing the incidence of TB among PLHIV. This result is in line with studies conducted in Ethiopia and USA [9, 14, 18, 23]. IPT prophylaxis is recommended by the WHO, has a significant role in eradicating latent tuberculosis and prevention of new infections which might decrease the incidence of active TB cases[8].

Being ambulatory functional status was also found to increase the hazard of TB by 1.93 times among HIV-positive patients as compared to working functional status. This might be due to the fact that being ambulatory is an indicator complication of the disease and these patients are prone to malnutrition, lack of physical activity and inability to perform daily tasks then this expose to

many diseases by reducing their immunity, including TB. This finding is in line with those of other studies conducted in Ethiopia [8, 18, 23].

According to this study baseline WHO clinical stage two and advanced clinical stage (III and IV) was found to increase the hazard of TB as compared to stage one among HIV-positive patients. Our study showed that being stage two had increased the hazard of TB by 3.22 times as compared to stage one. Participants on stage (III and IV) had 2.37 times increased hazard of TB as compared to stage one corresponding with those of studies conducted Ethiopia, Tanzania and systematic review and Meta in Sub-Saharan Africa [14, 15, 22, 23, 25]. This might be due to the fact that patients get into late stages, then the immunity protective capacity will be minimal then it predisposes to different opportunistic infection such as TB. It also suggests that HIV who had from stage two up to four might be decreased their immunity and gets immune-compromised and predisposed to TB. Other findings regarding the viral load result those patients who had high viral load were found to increase the hazard of TB by 2.42 times as compared to undetectable viral load. This might be due to the fact that a high viral load indicates ongoing and actively HIV replication, which weakens and damages the immune system, then resulting immune suppression, makes individuals more vulnerable to developing active TB from a latent infection. This finding is in line with those of other studies conducted in South Africa [26, 27].

Finally, a contradictory finding regarding participants who had co-infection except TB, had reduced the risk of TB among participants who hadn't co-infection with HIV. In other studies conducted in Kenya had co-infection with HIV had increased the risk of TB[28]. Our studies might be participants by take all prescribed medications of ART with combined therapies for other different infection and also patients will get awareness about prevention methods at the time of treatment for different Co-infection such as Hepatitis B (HBV), Hepatitis C (HCV) infections and cytomegalovirus(CMV) infection and also other bacterial infections by continue retention of antiretroviral medicines for your HIV and other co-infection, get vaccinated such as antimicrobial prophylaxis, hand hygiene, personal protective equipment, cleaning, and appropriate handling and disposal of sharps [8]. Based on this medical practices and prevention methods our participants will have awareness about different disease with HIV, through how to prevent and treat by ART medication for HIV for several other infection /will have good adherence for ART/ then their immune system will be strengthened to protect different disease including TB.

Conclusion

The overall KMC shows that 50% of patients haven't experienced the event (TB) at the cumulative median survival time. The median survival time for doesn't take IPT prophylaxis's, high viral load, less than 11 g/dl hemoglobin, duration of ART for less than six months and take between six and twelve months have its own median survival time but its counterparts have been survived beyond the median survival time. Not taking IPT prophylaxis, being underweight, having an ambulatory functional status, baseline WHO stage II–IV, and high viral load were associated with a higher hazard of developing TB. Conversely, participants with co-infections other than TB had a lower risk compared to those without co-infections. The health care providers and TB/HIV program should better to strengthen the package of care services through improve IPT service by integrating into existing care like ART refills, staying in regular contact with health care provider to take HIV medication as soon as and exactly as prescribed to achieve undetectable viral load result and to maintain health in stage one, improve nutritional status focus on balanced diet and supplementation with macro and micronutrients and also manage symptoms like diarrhea, loss of appetite to enhance immunity and improve nutritional status through regular contact, and also ensuring retention on ART for life long, managing opportunistic infection and maintain viral suppression leads to improve the overall quality of life leading to better physical and mental functioning. And also, we recommend to do community and facility based active TB case detection and also educate about how to prevent TB on this high-risk group to decrease the incidence of TB among HIV-positive individuals with community involvement. Furthermore, it is better to conduct prospective study to alleviate the problem of incomplete records and incorporate social, economic and behavioral factors.

Ethical considerations

Ethical clearance was obtained from the University of Gondar, college of medicine and health sciences, institute of public health, institutional review board and permission were be granted from the concerned bodies and also Ethical consent to keep confidentiality of information were be obtained from west Gondar zone, zone health office to each ART cites, according with Declaration of Helsinki, but there were not informed consent to each participant. The study was approved by [University of Gondar] Ethics committee (Approval No.2054/17).

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Abbreviation

AIDS; Acquired Immune- Deficiency Syndrome, AHR; Adjusted Hazard Ratio, AFB; Acid fast bacillus, BMI; Body mass index, CHR; Crude Hazard Ratio, CI; Confidence Interval, DSD; Differentiated service delivery, DTG; Dolutegravir, EDP; External displaced people, FTAR; Fast tract ART refill, FMOH; federal ministry of health, HC; Health centre, Hgb; Hemoglobin, HIV; Human Immunodeficiency Virus, IPT; Isonized preventive therapy, KMC; Kaplan Meir curve, NGO; Non-governmental organization, MMD; Multi-month dispensing, OI; opportunistic infection, PCAD ; Peer-led community ART distribution, PH; Proportional hazard, PLHIV; People living with human immunodeficiency virus, TB; Tuberculosis, VIF; Variance inflation factor, WHO; World Health Organization

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Consent for publication

Written informed consent for publication was obtained from study participants. Personal identifiers were removed to ensure confidentiality.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Authors' contributions

DA and TK conceived the study, carried out most of the begging up to thesis development specially study design, sample size and the analysis part. **WS** specially in literature review.

Competing interests

The authors declare that they have no competing interests.

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