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Time to reoccurrence of tuberculosis and its predictors among adult HIV/AIDS patients on ART at public hospitals in East and Horro Guduru Wollega zones, West Ethiopia: a retrospective cohort study

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Abstract

Background The reoccurrence of Tuberculosis infection is one of the challenging problems in meeting the global Tuberculosis prevention goal. It contributes to morbidity and mortality, economic crisis, spread of infection among the population, and affects health-related quality of life. Despite the public health significance of the problem, there is a paucity of knowledge to well understand the time to reoccurrence of tuberculosis among HIV population and the factors that determine the recurrence of the problem in the context of Ethiopia.

Objective To assess the time to reoccurrence of tuberculosis and its predictors among adult HIV/AIDS patients attending ART clinics at health facilities in East and Horro Guduru wollega zones.

Methods A Hospital-based retrospective follow-up study was conducted among HIV/AIDS patients attending the ART clinic from Jan 1, 2015 to Feb, 30, 2020 by collecting information from the medical records of 442 patients. A sampling frame from the ART log book was prepared. A simple random sampling technique from patient records was employed. The structured checklist was used. Bivariable and multivariable Cox regression with crude hazard ratio and the adjusted hazard ratio, respectively, were used to identify independent predictors for the reoccurrence of Tuberculosis. A P-value of < 0.05 with 95% CI was used to declare significantly associated predictors.

Result The median survival time of TB reoccurrence in this study was 72 months. Sex (AHR = 4.90 (95%CI:1.98, 12.53), widowed marital status (AHR = 4.00; 95%CI:1.13, 14.14), occupational status (AHR = 3.45;95%CI: 1.12, 10.64), advanced WHO clinical stages (AHR = 6.98; 95%CI: 1.71, 28.45), recurrence of opportunistic infections (AHR = 10.49; 95%CI:2.14, 51.54), low adherence to Anti-TB drugs (AHR = 2.38; 95%CI:1.01, 5.64), facing multidrug resistance during the preceding episode of TB (AHR = 25.06; 95%CI:6.49, 96.66), CD4 count < 200 (AHR = 10.09 95%CI: 3.62, 28.17), and viral load (AHR = 1.01 (95%CI:1.00, 1.02) were significant predictors of TB reoccurrence among HIV patients.

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Conclusion The median survival time among adult HIV patients was higher in the first 80 months of ART initiation and it decreased over the time of ART. Sex, occupational status, marital status, low CD4 count, viral load, advanced WHO clinical stage, reoccurrence of other opportunistic infections, poor adherence to TB treatment, and facing multidrug-resistant TB were independent predictors for reoccurrence of TB among HIV-positive adults.

Keywords Tuberculosis reoccurrence, Tuberculosis, Tuberculosis predictors, Ethiopia

Background

Tuberculosis (TB) is a chronic communicable disease that is caused by Mycobacterium Tuberculosis complex and other related species. It affects the lung and other organs thus classified as Pulmonary TB (PTB) and Extrapulmonary TB (EPTB) [1]. Early diagnosis of infectious TB cases and providing effective treatment are the keystones of global TB control programs [2].

Despite the exhaustive strategies of the World Health Organization (WHO) for controlling this disease, millions of people are still being infected annually [3]. The challenging issue regarding these TB controlling strategies is a recurrence of TB infection among previously treated and cured patients as recurrence/reoccurrence of opportunistic infections (OIs), related to human immune deficiency virus (HIV) [4].

Among the common OIs and cancers following HIV/AIDS (tuberculosis, Candidiasis, cryptococcal meningitis, cryptosporidiosis, cytomegalovirus, herpes simplex virus, pneumocystis pneumonia, salmonella septicemia, toxoplasmosis, Kaposi sarcoma, invasive cervical cancer and non-Hodgkin's lymphoma) [4], tuberculosis is the most common reoccurring OI [5]. TB recurrence is resulted from endogenous relapse and/or exogenous reinfection [6, 7].

TB recurrence continues to cause morbidity and mortality in patients with HIV throughout the world [8, 9]. Potent combination antiretroviral therapy (ART) has reduced the incidence of TB and other OIs among patients with access to care. However, common OIs are remaining the major reoccurring cases with patients in the developed and developing world having access to care while other patients do not have a sustained response to antiretroviral agents for multiple reasons [4, 6, 9].

TB disease needs long-term treatment which is the challenging issue of the case both on the patient as well as resource reduction directly and indirectly as well as can be felt to provide positive outcome [10] as a result of HIV contribution to the recurrence of TB infection [11, 12].

Among the OIs, TB is the most challenging problem among HIV-infected patients to meet the global TB prevention goal [13, 14, 15]. As of the 2020 WHO TB case report, Southeast Asia (44%), Africa (25%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%) while Eight countries accounted for two third of the global total: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%) [16]. The other 22 countries in WHO's list of 30 high TB burden countries accounted for 21% of the global total. The TB incidence rate at the national level varies from less than 5 to more than 500 new and relapse cases per 100,000 population per year [16]. In Ethiopia, the reoccurrence of TB ranked first among the reoccurring OIs, accounting for 21% [5].

TB reoccurrence resulted in different negative outcomes. These negative outcomes are death and failed treatment [17], Multidrug resistance TB (MDRTB) [18], default and failure [19] as well as economic crisis and reduced health-related quality of life [20]. AIDS-related illness (including TB) and bacterial infection were the second most common cause of adult HIV admission in all geographic regions and the most common cause of hospital mortality [21]. A study showed that high dropout rates from ART treatment were associated with the reoccurrence of OIs in HIV/AIDS patients which hinders effective treatment of cases and attributed unnecessary cost to the health system [22].

Evidence showed that different predictors contributed to the recurrence of TB cases among HIV/AIDS patients. These predictors are the CD4 lymphocyte count of the patient [23], weight of the patient [24], smoking, alcohol, and sputum smear test [25, 26, 27].

Despite the intervention to reduce the incidence of TB infection using a directly observed therapy (DOT) strategy, TB reoccurrence after full treatment completion is still high according to recent reports [5, 16]. They have shown a high initial rate of TB associated with HIV (9). Over the past number of years, a large amount of evidence has been gathered about the negative impact of HIV on TB control. The HIV infection has markedly increased morbidity and mortality from.

TB. Furthermore, the tremendously high frequency of undiagnosed disseminated TB in post-mortem studies of HIV/AIDS patients in Sub-Saharan Africa (SSA) indicates that HIV-AIDS-associated TB mortality is considerably underestimated [28].

However, the burden and the factors that contributed to TB occurrence hurt the health system and population, and are the challenging issue to meet the sustainable development goal set for 2030. To the level of our knowledge, there was no prior study in the context of Ethiopia

regarding this issue. Therefore, this study was aimed to assess the time to reoccurrence of TB and its predictors among HIV/AIDS patients in East wollega and Horro Guduru wollega zones in Oromia region of Ethiopia.

Methods and materials

Study area and period

This study was conducted in the hospitals that are found in two Wollega Zones, East Wollega and Horro Guduru Wollega Zones. There are eight hospitals in the Zones; Wallaga University comprehensive especialized Hospital, Nekemte especialized hospital, Shambu general hospital, and other five primary hospitals located in Gida, Sire and Jimma, Abedongoro and Guduru woredas. The hospitals provide services for the people from the Zones and other nearby Zones and regions. Services like referral services, preventive, curative, and rehabilitative care are provided in the form of outpatient department service, delivery services, dental treatment, emergency services, eye treatment, follow-up services for chronic illness including HIV and TB, laboratory, pharmacy, Radiology, & Ward activities are provided in those hospitals.

Study design and period

A health facility-based retrospective follow-up study design was conducted in hospitals in East wollega and Horro Guduru wollega zones from Jan 1, 2015 to Feb 30, 2020.

Source population

All HIV/AIDS patients who were attending the ART clinic and who had one episode of TB that was successfully treated previously in the two Wollega Zones were the source population of this study.

Study population

All HIV/AIDS patients who had one episode of TB, cured from previous TB, and who were attending ART clinic between Jan 1, 2015 to Feb 30, 2020 at public health facilities in the East and Horro Guduru Wollega Zones were the study population.

Inclusion and exclusion criteria

Inclusion criteria

Adult HIV/AIDS patients on ART and who had been treated and cured of TB previously as well as patients who have complete records on ART medical cards for at least a dependent variable were included in the study.

Exclusion criteria

Patients who developed TB infection and do not take ART were excluded.

Sample size determination

The sample size was calculated by using the formula,

$n= (Z\alpha/2)^2 p\ (1\text{-}p)/d^2$.

where n = final sample size, Z = coefficient of reliability, p = incidence of reoccurrence, and d = margin of error.

Considering the maximum incidence rate (50%) due to lack of literature previously published in the country or countries with similar socio-demographic and economic status, $n= (1.96)^2(0.5)\ (0.5)/(0.05)^2 n = 384$. Then, after adding a non-response rate of 20%, the formula gives the sample size $n = 461$. To calculate the sample size for the predictors, the shoenfed formula was used. This sample size was determined with the assumptions: 0.05 significant level, 80% power, and 20% proportion of withdrawal by using STATA version 14.0. The formula was;

Sample size (n) = Number of event /Probability of event.

Number of Event (E) = $4\,(Z\,\alpha\,/2 +\ ZB\,)2\,/\ [\ln(\,AHR\,)]\,2$

Probability of event = p (event) = 1- Probability of survival.

Z α/2 is the significant level at α/2 of 0.05 = 1.96, Power ZB = 0.8 = 0.84

Event (E); the number of events (Recurrence of TB) needed to keep the optimum statistical power. P (E): the probability of observing an event in the study at the end of the study period taken from the same study but all considered variables for calculation yielded a sample size less than the sample size calculated for the first objective. Therefore, the final sample size of the study was 461.

Sampling procedure

The records of study participants who fulfilled the inclusion criteria were identified by the data collectors from the list of PLWHIV, previously treated and cured from TB among patients on ART who were attending the ART clinic of hospitals. The sampling frame was prepared using the ART log book for PLWHIV on ART. Record of patients who had been treated for TB infection between Jan 1, 2015 to Feb 30, 2020 were included in the study. The recruitment was continued until Feb 30, 2020 and the study end was Feb 30, 2021 because the recruited patient should be followed for at least one year to identify between relapse and reinfection. It is said to be a relapse if TB occurs within one year of cure and reinfection when it occurs after one year of cure from the initial TB [29]. The ART patients who fulfilled the inclusion criteria were given a code and then selected by a simple random sampling technique until the desired sample size for the study was achieved. For selecting the study unit by a simple random sampling technique, a computer-generated random number was used [5].

Study variables

The study variables particularly the predictor variables were selected based on the review of different previous literatures that have relevance for our study. In addition, the availability of data for those selected variables was considered before considering as the study variables. To do this, the registers were revised to align the variables and the questions.

Dependent variable

Time to reoccurrence of Tuberculosis.

Independent variables

- Socio-demographic (age, sex, residence, occupation, educational status, marital status).
- Clinical factors (BMI, CD4 count, WHO clinical stage, prophylaxis exposure, viral load, hemoglobin level, type of ART administered, MDR).
- Functional status (working, ambulatory, bedridden).
- Behavioral factor (ART and anti-TB adherence, and prophylaxis adherence).

Operational definitions

Censored no reoccurrence of TB among study participants during follow-up and at the end of the study period, loss to follow-up, and death among ART patients.

Event diagnosing outcome of interest, which was diagnosing of reoccurrence of TB.

Reoccurrence happening\diagnosis of TB for the second episode and more by health personnel working in the hospitals after successfully completing the preceding treatment of TB [30].

Loss to follow-up is defined as no visit in the past 3 months for ART patients and the status not documented as dead or transferred out to another HIV clinic [31].

Transfer out If PLHIV on HIV care in the zonal hospitals shifts to another health institution.

Good ART adherence If PLHIV adherent (>95%) that is the percentage of missed doses is <2 doses of 30 doses or <3 doses of 60 doses) as documented by ART health personnel [31, 32].

Fair ART adherence If PLHIV adherent (85–94%) that is the percentage of missed doses are 3–5 doses of 30 doses or 3–9 doses of 60 doses) as documented by ART health personnel [31, 32].

Poor ART adherence If PLHIV adherent (<85%) that is the percentage of missed dose is >6 doses of 30 doses or >9 doses of 60 dose) as documented by ART health personnel [31, 32].

Functional status- It was classified as 'working' if able to perform usual work in or out of the house, 'ambulatory' if able to move, and 'bedridden' if either not able to perform activities of daily living or not moving [31].

Data collection procedure and instrument

After taking medical record numbers of patients on ART from chronic care follow-up clinic, the patient folders were drawn from the card room and data about cohorts of ART patients were extracted by using the pre-tested structured checklist. All available information on patient records was checked and questionnaires from other literatures were reviewed. Then an appropriate data extraction tool was adapted in English to extract all the relevant variables to meet the study objectives from the patient card. Sixteen (16) nurses who have been working in ART clinics of East wollega and Horro Guduru wollega zones hospitals extracted the data from patients' cards. The investigators supervised all the data collection processes.

Data quality control

To maintain the data quality, training was given for data collectors and supervisors. Supervisors and principal investigators supervised the data collection procedures. A properly designed data collection checklist was developed from the Ethiopian Federal Ministry of Health HIV care/ ART follow-up form and patients' card. Incompletely recorded follow-up formats that missed the outcome variable were excluded from abstraction. 5% of the sample was randomly selected and the data were re-abstracted by the supervisors to check the reliability and consistency of data then correction was made accordingly. Supervision was carried out daily to check completeness and consistency both by the supervisors and by the principal investigator to keep the quality of data. At the end of the data entry, data cleaning was done using frequencies, cross-tabulations, sorting, and listing to check the missed values and outliers. Errors identified were corrected by revising the original abstracting format. Patient records that missed the data on the dependent variable were excluded. Predictor variables that showed significant missing value or for which the health institutions were not capturing the data as a result of service unavailability were excluded.

Data processing and analysis

The completeness and the consistency of the data were checked, coded and double entered into EPI info version 7 and exported to STATA software version 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College

Station, TX: StataCorp LLC.) for analysis. Descriptive and summary statistics were carried out. Observational independence and other assumptions of proportional hazard were checked. A loglog plot was used to check the parallel appearance of the strata. Also, Shoenfed residual was used to check the time independency of the covariates and the result of the global test was 0.12 which was non-significant being greater than the cutoff value of 0.05. Variables like residence, marital status, educational status, occupational status were non-compliant with the assumptions and excluded. Bi-variable and multivariable Cox regression analyses were used to identify variables associated with the reoccurrence of TB infection. The statistical significance and strength of the association between the independent variable and an outcome variable was measured by the bi-variable Cox regression model. Variables with P-value less than 0.25 were transferred to the multivariable Cox regression model to adjust for confounder's effects, and a p-value less than 0.05 was declared as significant predictors. The association of the outcome and independent variables was explained by hazard ratios together with their 95% confidence intervals. The multicollinearity among the independent variables was checked by using variance inflation factor (VIF) and found no significant multicollinearity problem at cutoff value > 10. All independent variables in multivariable Cox regression model had VIF < 10. The goodness of fit test was employed using cox-Snell residual to check model fitness graphically [33] and it was found to fit the data as the Hazard line follows 45° close to the baseline (Fig. 1). Bootstrap validation was carried out and the optimism-adjusted concordance index was 0.94, indicating good discrimination ability of the model between events and non-events. Finally, the result of the study was presented using tables, figures and texts.

Results

Socio-demographic characteristics

The records of 442 patients were reviewed with the response rate of 95.9%. Of these, about two–thirds of the participants (53.4%) were females. Regarding the level of education, 111 (24.34%) had no formal education and

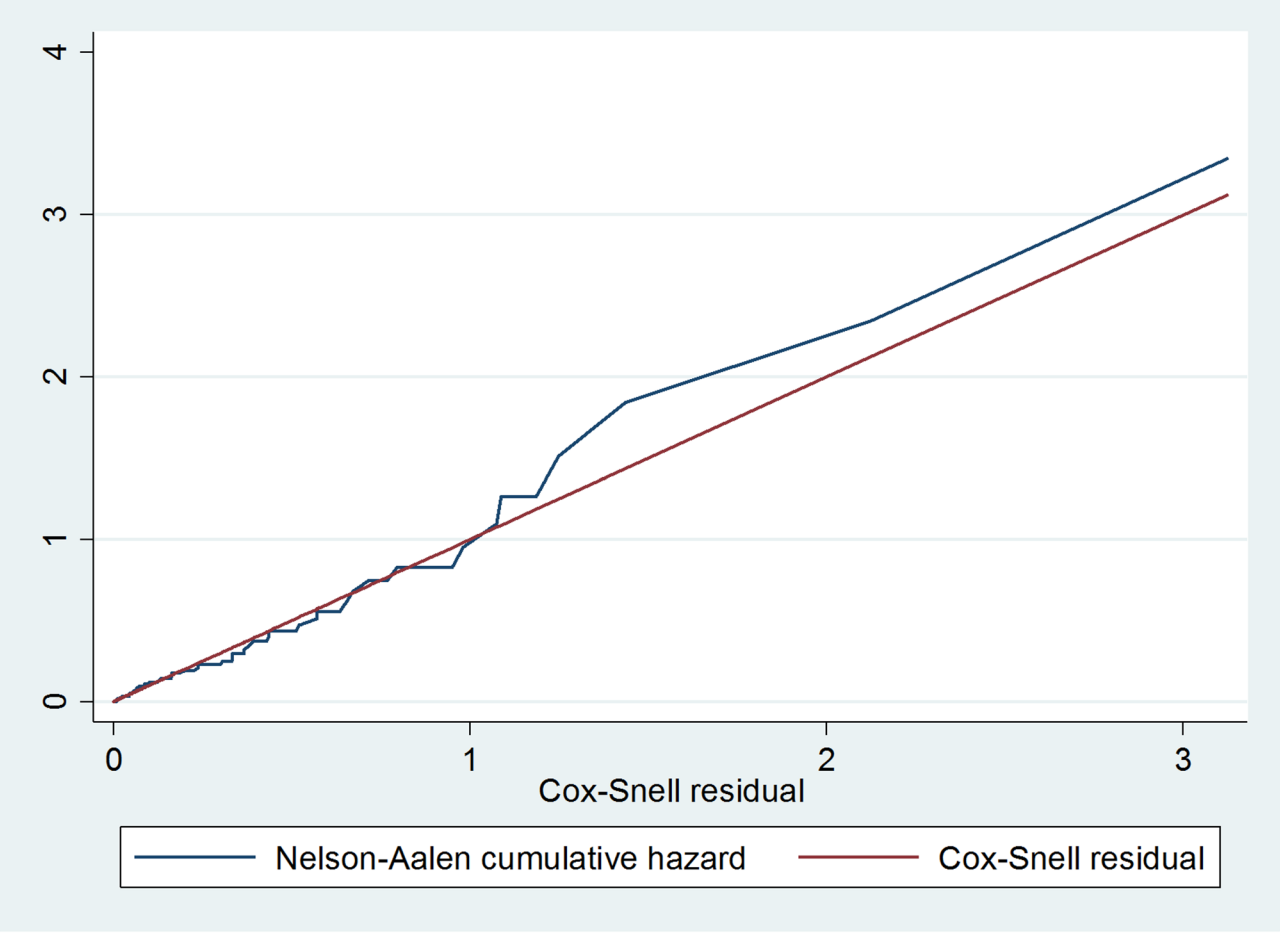

Fig. 1 The fitness of the final model for the analyzed data in the study of TB reoccurrence and its predictors among adult HIV positive patients on ART in the hospitals found in East and Horro Guduru Wollega Zones, 2023 ($n = 442$)

Table 1 Socio-demographic characteristics of HIV positive adults on ART at East and Horro Guduru Wollega hospitals, January 2015 to February 2020 ($n=442$)

Variables	Category	Frequency	Percentage
Sex	Male	206	46.6
	Female	236	53.4
Age at initiation ART	15–24	64	14.5
	25–34	114	25.8
	35–44	156	35.3
	≥45	108	24.4
Marital status	Married	264	59.7
	Divorced	46	10.4
	Single	84	19.0
	Widowed	48	10.9
Educational status	No formal education	112	25.3
	Primary	180	40.7
	Secondary	92	20.8
	Tertiary	58	13.2
Occupation	Farmer	96	21.7
	Merchant	84	19.0
	governmental employee	34	7.7
	day laborer	114	25.8
	Wife and students	114	25.8
Residence	Urban	316	71.5
	Rural	126	28.5

Table 2 Behavioral characteristics of HIV positive adults on ART at East and Horro Guduru Wollega hospitals, January 2015 to February 2020 ($n=442$)

Variables	Categories	Frequency	Percentage
ART adherence	Good	390	88.2
	Fair	22	5.0
	Poor	26	5.9
	Missing	4	0.9
prophylaxes given	Yes	258	58.4
	No	184	41.6
Functional status	Working	336	76.0
	Ambulatory	80	18.1
	bed ridded	26	5.9

among those who had formal education 293 (64.25%) were primary and secondary educated and (40.7%) were tertiary educated. Regarding the residence, 316 (71.5%) were from urban area (Table 1).

Behavioral characteristics

Of the total patients whose medical records were reviewed, 88.2% showed good adherence to ART. Regarding prophylaxes more than half (58.4) of the participants had been given. Regarding the functional status at the base line, 76.0% of them were working (Table 2).

Table 3 Clinical and immunological characteristics of HIV positive adults on ART at East and Horro Guduru Wollega hospitals, January 2015 to February 2020 ($n=442$)

Variables	Category	Frequency	Percentage
WHO clinical stage at initiation of ART	Stage 1	122	27.6
	Stage 2	78	17.6
	Stage 3	202	45.7
	Stage 4	40	9.1
CD4 count at initiation of ART	≤200 cells/μl	130	29.4
	>200 cells/μl	312	70.6
BMI	<18.5	222	50.23
	18.5-24.99	178	40.27
	>24.99	42	9.5
Reoccurrence of OIs	Yes	284	64.3
	No	158	35.7
Comorbidities	DM	24	5.43
	Hypertension	20	4.53
	cardiac disease	8	1.81
	other specify	390	88.23

Clinical and immunological characteristics

At the start of highly active HIV drugs, 77.41% of patients were on stages I and II WHO clinical stages. Regarding the CD4 count, the median and IQR of CD4 count for the patients were 347 and 236, respectively while 52 patients lacked at the baseline. The mean and standard deviation of the BMI of the patients was 21.18 ± 2.88. In this regard, 15.13% and 1.54% of participants were moderately and severely malnourished, respectively based on their BMI. On the other hand, 33.33% were also infected with OIs and 3.07% had other non-AIDS related diseases (Table 3).

Time to TB reoccurrence

Among the reviewed records, eighty eight (88) patients were found to have TB reoccurrence. The incidence rate of TB reoccurrence was 6.8 (95%CI: 5.6–8.4) per 100 person-years (PY). The median time to TB reoccurrence was found to be 72 months. The overall Kaplan-Meier survival estimate curve showed that the failure, TB reoccurrence, was highest in the first 80 months of ART initiation and reduced over the time of ART (Fig. 2).

Predictors of time to TB reoccurrence

In the bivariate cox regression, covariates such as sex, age category, occupation, marital status, recent CD4 count category, reoccurrence of OIs, ART adherence, adherence to TB drugs, WHO clinical stages, viral load, and facing MDR for preceding TB were potential confounders selected for multivariable cox regression at p-value 0.25. However, in multi-variable cox-regression, sex, marital status, occupational status, baseline WHO Clinical stages, reoccurrence of OIs, Anti-Tb adherence, facing MDR TB during the preceding episode, low CD4 count (<200) and viral load were found to be

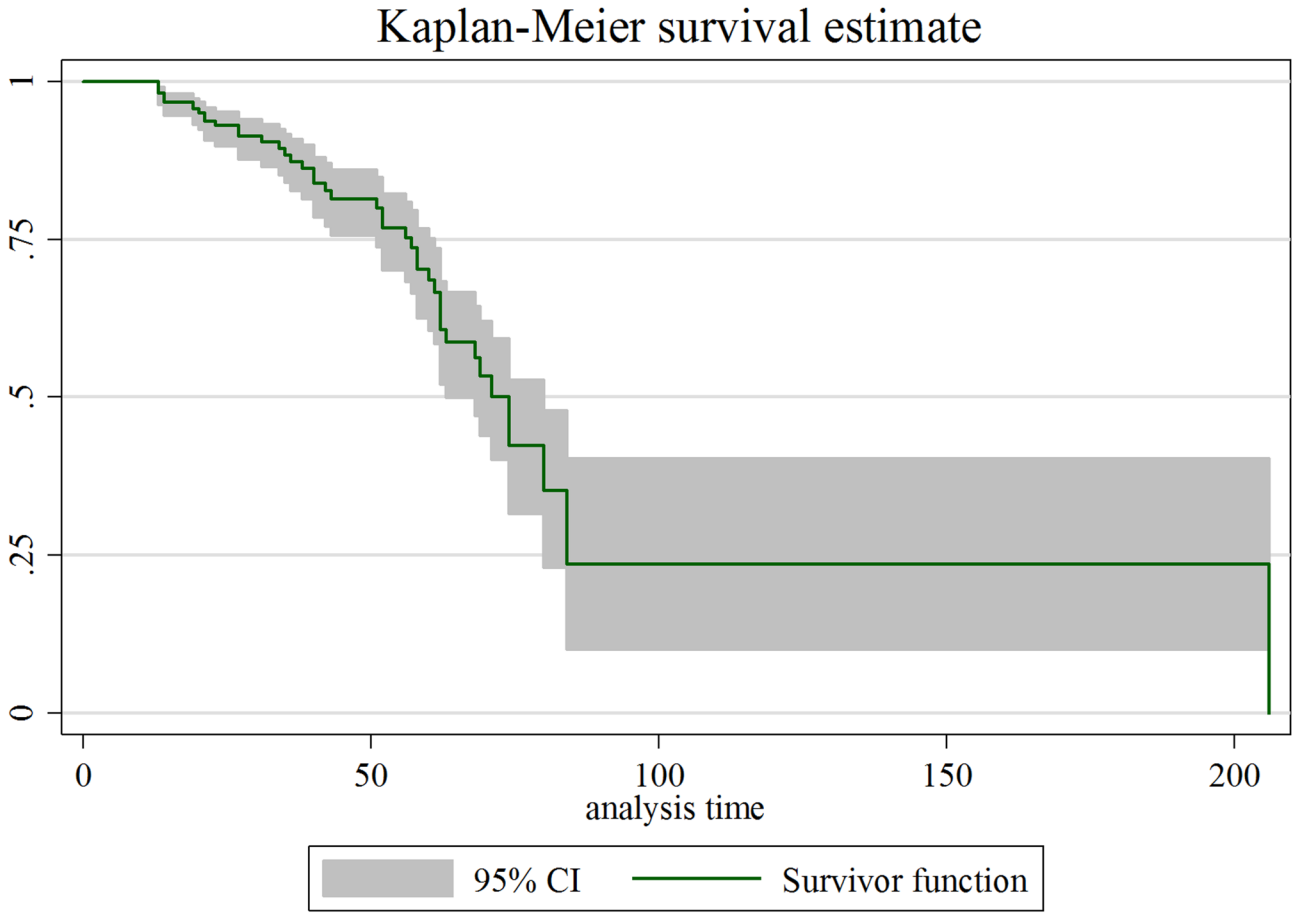

Fig. 2 The overall Kaplan-Meier survival estimate curve of adult HIV positive patients on ART at East and Horro Guduru Wollega zones hospitals (*n* = 442)

statistically significant predictors TB reoccurrence among HIV/AIDS on ART. Accordingly, the hazard of TB reoccurrence was 4.9 times more likely among males as compared to females. Single and widowed were found to have an increased risk of TB reoccurrence (AHR = 16.70;95%CI:3.80, 73.36 and AHR = 4.00; 95%CI:1.13, 14.14), respectively whereas divorce was found to be marginally protective for reoccurrence of TB AHR = 0.01 (95%CI:0.00, 0.18). When compared to farmers, day laborers (AHR = 3.45;95%CI: 1.12, 10.64) and merchants (AHR = 3.77; 95%CI: 1.41, 10.08) had increased hazard of TB reoccurrence. Those HIV patients on ART who were having advanced WHO clinical stages (II and III) were found to have a higher hazard of TB reoccurrence than clinical stage I (AHR = 8.10; 95%CI: 1.80, 36.15 and AHR = 6.98; 95%CI: 1.71, 28.45), respectively. Those HIV patients on ART who faced recurrence of OIs had 10 times (AHR = 10.49; 95%CI:2.14, 51.54) more hazard of TB reoccurrence than their counterparts. Those patients who had a history of low adherence to Anti-TB drugs have 2 times more hazard of TB reoccurrence than their counterparts (AHR = 2.38; 95%CI:1.01, 5.64). HIV patients on ART who faced MDR TB during the preceding episode of TB were found to have 25 times more hazard of TB reoccurrence than their counterparts (AHR = 25.06; 95%CI:6.49, 96.66). The hazard of TB reoccurrence in HIV patients with CD4 count < 200 was 10 times (AHR = 10.09 95%CI: 3.62, 28.17) higher than their counterparts. In another way, when the viral load increases by one unit, the hazard of TB reoccurrence also shows some marginal increment (Table 4).

Discussion

This study was aimed to assess the Time to TB reoccurrence and its predictors with a response rate of 95%. The median survival time of TB reoccurrence in this study was 72 months whereas the incidence rate of TB reoccurrence was found to be 6.9/100 person years.

This figure is high when compared to many other studies in other parts of the world including Southern Ethiopia [30]. In Southern Spain, the median time and incidence rate of reoccurrence of TB infection were 24 months and 1.9/100 person-year, respectively [34]. In Catalonia, the incidence of TB reoccurrence was 0.49 per 100 person-years [29]. A case-control study conducted in Singapore indicated that the median time to the

Table 4 Bi-variable and multivariable Cox regression for predictors of time to TB reoccurrence among HIV positive adults on ART at East and H/G/ Wollega hospitals, January 2015 to February 2020 ($n=442$)

Variables	Censured	Event	CHR (95% CI)	AHR (95% CI)	P-value
Sex					
Male	160(45.45%)	46(51.1%)	1.47(.96, 2.25)	4.98 (1.98, 12.53)	0.001*
Female	192(54.5%)	44(48.9%)	1	1	
Age categories					
15–24	52 (14.8%)	12(13.3%)	1.24(.62, 2.50)	2.11 (0.11, 41.53)	0.624
25–34	90 (25.6%)	24(26.7%)	1.27(.71, 2.27)	1.29 (0.49, 3.39)	0.6
35–44	126(35.8%)	30(33.3%)	1.10(.64, 1.90)	2.38 (0.88, 6.43)	0.085
>44	84 (23.9%)	24(26.7%)	1	1	
Recent CD4 count category					
<=200	48 (13.6%)	12(13.3%)	1.92(1.02, 3.62)	10.09 (3.62, 28.17)	0.0001*
>200 ml/dl	304(86.4%)	78(86.7%)	1		
Marital status					
Married	200 (56.8%)	64(71.11%)	1	1	
Divorced	42 (11.9%)	4 (4.4%)	0.28(0.10, 0.76)	0.01 (.00, 0.18)	0.002*
Single	70 (19.9%)	14 (15.6%)	0.99(0.55, 1.78)	16.7 (3.8, 73.36)	0.0001*
widowed	40 (11.4%)	8 (8.9%)	0.68 (0.32, 1.45)	4.0 (1.13, 14.14)	0.031*
Occupational status					
Merchant	68 (19.3%)	16 (17.8%)	0.74(0.39, 1.40)	3.77 (1.41, 10.08)	0.008*
Governmental employee	24 (6.8%)	10 (11.1%)	0.89(.42, 1.90)	3.19 (0.89, 11.37)	0.074
Day laborer	90 (25.7%)	24 (26.7%)	1.34(0.75, 2.41)	3.45 (1.12, 10.64)	0.031*
Other	96 (27.3%)	18 (20%)	0.55(.29, 1.05)	0.33 (0.03, 3.43)	0.355
Farmer	74 (21%)	22 (24.4%)	1	1	
Previous Anti-TB adherence					
Fair	10 (2.9%)	8 (8.9%)	2.20(1.06, 4.59)	2.38 (1.01, 5.64)	0.048*
Poor	10 (2.9%)	4 (4.4%)	2.53(0.92, 6.97)	0.47 (0.09, 2.32)	0.355
Good	326 (94%)	78 (86.7%)	1	1	
Art adherence level					
Fair	12 (3.5%)	10 (11.1%)	2.83(1.45, 5.51)	1.09 (0.26, 4.67)	0.9
Poor	16 (4.6%)	10 (11.1%)	1.30(.62, 2.75)	1.33 (0.22,7.93)	0.753
Good	320 (91.9%)	70 (77.8%)	1	1	
Prophylaxis adherence level					
Poor	16 (7.6%)	6 (12.5%)	2.13 (1.18, 3.84)	1.96 (0.55, 6.95)	0.295
Fair	8 (3.8%)	8 (16.7%)	1.32 (0.77, 2.26)	0.63 (0.17, 2.30)	0.49
Good	186 (88.6%)	34 (70.8%)	1	1	1
OI reoccurrence					
Yes	206 (58.5%)	78 (86.7%)	2.09(1.14, 3.87)	10.49 (2.14, 51.54)	0.004*
No	146 (41.5%)	12 (13.3%)	1	1	
Faced MDR for preceding TB					
Yes	6 (1.7%)	12 (13.6%)	3.10(1.63, 5.60)	25.06 (6.49, 96.66)	0.0001*
No	338 (98.3%)	76(86.4%))	1	1	
WHO clinical stages					
I	106 (30.1%)	16 (17.8%)	1	1	1
II	58 (16.5%)	20 (22.2%)	2.35 (1.18, 4.69)	8.10 (1.80, 36.15)	0.006*
III	160 (45.5%)	42 (46.7%)	2.4 (1.27, 4.53)	6.98 (1.71, 28.45)	0.007*
IV	28 (7.9%)	12 (13.3%)	4.22(1.92, 9.29)	4.92 (0.82, 29.48)	0.081
Viral load			1.000004(0.99, 1.000009)	1.01 (1.00, 1.02)	0.002*

AHR: Adjusted Hazard Ratio, CHR: Crude Hazard Ratio, CI: Confidence interval, *p-value < 0.05

recurrence of TB was 24 months [35]. In Eastern China, the median time for the recurrence of TB was 24.04 months [36]. A study conducted in Shanghai revealed that the incidence rate and median time to recurrence of TB was 7.55 per 1000 PYs and 1.3 years, respectively [37]. According to the study conducted in Taiwan, the incidence of TB reoccurrence was 4.9/100 PY [25]. A follow–up study conducted in Durban, South Africa reflected

median time to the recurrence of TB was 3.2 years [38]. The high incidence rate in our study could be attributed to the quality of TB treatment during the preceding episode and also the poor adherence to the treatment. It is also due to the difference in populations studied as our study focused on HIV patients. Because previous studies show that TB reoccurrence varies from population to population while it increases in HIV patients [39, 40]. Regarding the median time, the possible reason for the long median time and high reoccurrence of TB could be that the long time interval between episodes of TB increases the probability of re-infection. This was indicated in the study of Italy which revealed that a time interval of >24 months between the first episode of the disease and recurrence of TB is a risk factor for reinfection or relapse of TB [41].

Being male was essentially related to the reoccurrence of TB. This finding is in line with the studies conducted in Singapore, Beijing Chest Hospital, Durban, South Africa, and South Korea [35, 38, 42, 43]. The possible reason could be that the presence of differences in occupation, smoking, health behavior and biological differences between males and females that will make males to have more risk of TB reoccurrence than females. Males might have a low immunological response to mycobacterium tuberculosis [44, 45] and have a higher incidence and prevalence of TB than females [46]. Also, males might have poorer TB treatment outcomes than females [47]. Although not controlled in this study, the confounding effect of smoking could be there as males are more likely to be smokers than females which might expose them to more chance of TB reoccurrence [48].

Regarding marital status, when compared to married, those single and widowed were found to have an increased risk of TB reoccurrence. This finding is consistent with the previous study [39]. The possible reason could be that those individuals who were widowed and single could have more chance of having final difficulties and these affect their access to balanced food, and health care including transportation costs.

Occupational status was found to be among the predictors of TB recurrence. Occupations like day laborers and merchants were found to be the risk factors for TB reoccurrence. The previous literature supports this result [39, 49, 50]. This might be explained by the fact that day laborers and unemployed individuals might have no sufficient income to fulfill the necessary materials like food and standard housing and they could be exposed to nutrient imbalance from deficiency that will make them to have depressed immunity than others. They might have overcrowded conditions that will expose them to reinfection. When it comes to merchants, they may lack time to care for themselves due to activity overload and this will increase their chance of TB reoccurrence. Those individuals who are in the merchant category might also have more chance of exposure to substance use which will affect having of good TB treatment outcome [51].

The reoccurrence of OIs was the predictor of TB reoccurrence. Similar with this, it was found in the study of Arbaminch that the presence of chronic disease was found to be the significant factor for the reoccurrence of OIs predominantly of TB recurrence [5]. This might be due to the fact that TB by itself is among the opportunistic infection that uses the gap created by depressed immunity and it will follow and occur along with other comorbidities.

The increment in viral load increases the hazard of TB reoccurrence. This is in line with the previous study in which high viral loads were found to increase significantly the risk of TB reoccurrence [39]. In relation to this, a low CD4 count (<=200) was increasing the hazard of TB reoccurrence. This is also supported by studies. This is explained by the fact that the presence of high viral load and low CD4 count are indications of affected immunity that will be an opportunity for the reoccurrence of TB.

This study found that low adherence to Anti-TB is among the significant predictors of TB reoccurrence which is similar to other studies [52]. The study conducted on the high incidence of TB among HIV/AIDS showed that treatment noncompliance was a risk factor for TB recurrence than adhered to treatment [52]. A study conducted in Victoria, Australia reflected that nonadherence to treatment resulted in an increased risk of recurrent TB [53]. In the follow-up study conducted in Taiwan, prolonging anti-TB treatment was found to reduce the recurrence of TB [54]. This might be because non-adherence to drugs will not lead to a radical cure and even may contribute to the recurrence of drug-resistant TB. In relation to this, MDR TB is also a significant predictor for the reoccurrence of TB according to this study. There are contradicting findings in this regard. Although in contrast to the study conducted in Italy [41], this current finding is consistent with the studies conducted in Catalonia, Vietnam, and China which revealed that MDR TB patients were at risk of developing recurrence of TB [17, 29, 37, 55]. It might be due to the fact that the presence of drug resistance could affect the curative process and the disease will reappear after the treatment completion. Others also found that recurrence of TB by itself is a risk factor for the development of drug resistance particularly to Rifampicin [56].

WHO clinical stage of HIV at the initiation of ART was also one of the independent predictors of TB reoccurrence among adult HIV patients on ART. In this study, those patients who were at the advanced clinical stage at the time of ART initiation had a significant risk of developing TB recurrence. This finding was in line with a

study conducted in low-income countries, where the risk of developing TB recurrence was higher among advanced WHO clinical stages compared to stage I (36). The possible reason is that the advanced clinical stage by itself could be due to depressed immunity and this contributes to repeated infection and initiation of the latent TB. The possible reason might be that patients with advanced clinical disease might be due to an increased risk of opportunistic infections and associated with this there would be also the use of multiple drugs. Studies suggest that patients with multiple morbidities may have altered immunity which leads to an increment in the rate of TB occurrence.

The strength of this study is that it has used the advanced statistical method to see the relationship between TB reoccurrence and its predictors. One of the limitations of this study was that it was difficult to get all the pre-planned variables required to assess the predictive abilities of some variables. For example, it was difficult to get some behavioral characteristics like substance use as primary data. The other problem was that some variables like hemoglobin level, status of viral hepatitis infection, and organ functional status were excluded due to high missing values as a result of limitations on the investigative capacity of the health facilities and unavailability of the services in the health institutions. We acknowledge that the problem of misclassification and error in data capturing could be there during the data abstraction from the original records given that the use of secondary data was made. Lastly, the wide confidence interval reported in the study could be due to sample size inadequacy and future research can address them by using larger sample size.

Conclusion

Like other previous studies, this study found that median survival time among adult HIV patients was higher in the first 80 months of ART initiation and it decreased over the time of ART. Being male, occupational status, marital status, low CD4 count, viral load, advanced WHO clinical stage, reoccurrence of other OIs, lack of good adherence to TB treatment, and MDRTB were independent predictors for reoccurrence of TB among HIV-positive adults on ART.

Early identification of patients by screening of risk groups and early initiation of ART should be done to reduce the risk as the reoccurrence of TB is higher among patients with advanced clinical stages. The health care provider working at ART clinics should give special emphasis to the patients in the first ART initiation since this is the time of highest risk for TB reoccurrence. The good adherence of TB patients to anti-Tb drugs is highly important to alleviate the recurrence of TB problems and also may help to fight drug-resistant TB. In this regard, good adherence to other prophylactic and ART drugs is also very important to prevent the recurrence of OIs and TB as well. Lastly, nutritional support should be in place to help those individuals with financial difficulties including daily laborers and widowed individuals to avert the TB recurrence that would be due to the nutritional deficiency.

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CD4	Cell Differentiation four (4)
HIV	Human Immune Deficiency Virus
IRR	Incidence Rate Ratio
MDR	Multi drug resistance
OIs	Opportunistic Infections
PLHIV	People Living with HIV
TB	Tuberculosis
WHO	World Health Organization

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Author contributions

JWF conceptualized the study, designed the methods, supervised the data collection, and wrote the first draft of the result. MD contributed in the writeup of the proposal, supported the data collection processes and revised the first draft of the result. BRF contributed in designing the methods and revised the whole proposal. SD and JD prepared the proposal and revised the manuscript. ATS revised the proposal, analyzed the data, wrote the result, prepared the manuscript, and identified the journal for publication. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are not publicly due to the sensitive nature of the topic but are available on reasonable request.

Declarations

Ethics approval and consent to participate

This study was done in accordance with the Declaration of Helsinki. A letter of ethical clearance was obtained from the institutional research ethics review committee of Wollega University with reference number (IHSRPTTAD/147/2023). The ethics committee provided the approval for the waiver of informed consent from the participants as the secondary data were used. Data were collected after explaining to the institutional research ethics review committee that the confidentiality of record review was kept, and no exposition of data at individual level. Permission letter was taken from the East and Horro Guduru Wollega zonal health departments and hospital administrations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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