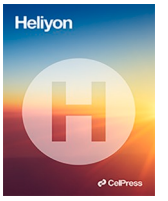
Heliyon 10 (2024) e37420

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Factors associated with time to death among HIV/TB co-infected patients on ART in Dire Dawa, Ethiopia: A retrospective study

Feyisa Shasho, Mengistu Yilma, Zeytu Gashaw Asfaw *

Department of Epidemiology and Biostatistics, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia

ARTICLE INFO

Keywords:
HIV/TB co-infected
Time to death
Survival analysis
Cox-regression

ABSTRACT

Background: Tuberculosis is one of the leading causes of death, especially for people living with HIV. However, little is known about the time to death of HIV/TB co-infected patients and associated factors in the study area. This study focused on identifying factors associated with time to death among HIV/TB co-infected patients under antiretroviral therapy in Ethiopia.

Methods: From January 2008 to January 2023, a hospital-based retrospective study was conducted on 434 HIV/TB co-infected patients attending the ART clinic at Dilchora Referral Hospital in Dire Dawa, Ethiopia. The medical records were reviewed using a structured data extraction tool. Data were entered with Epi Info version 7 and analyzed with Stata version 17. The Kaplan-Meier survival curve was used along with log-rank tests to estimate and compare survival times. Bi-variable and multivariable Cox regression were performed to identify factors associated with time to mortality in HIV/TB co-infected patients. The adjusted hazard ratio with its 95 % confidence interval was used to estimate the strength of the association and a P-value of 0.05 was considered statistically significant.

Results: The study included 434 HIV/TB co-infected patients. The overall median survival time was 144 months (95 % CI: [132, 156]). One hundred thirty-four (30.88 %) deaths were observed during follow-up, resulting in an all-cause mortality rate of 5.1 (95 % CI: [4.29, 6.02]) per 1000 person-months of study follow-up. The independent determinants of mortality were underweight BMI (AHR: 4.52; 95 % CI: [1.30, 15.67]), poor ART adherence (AHR: 1.60; 95 % CI: [1.03, 2.50]), advanced WHO clinical stage (AHR: 1.69; 95 % CI: [1.1, 2.62]), bedridden functional status (AHR: 1.63; 95 % CI: [1.04, 2.57]), initial ART regimen (AHR: 2.68; 95 % CI: [1.74, 4.12]), and smoking status (AHR: 1.48; 95 % CI: [1.01, 2.16]).

Conclusion: The mortality rate of HIV/TB co-infected patients in this study was very high. While implementing target improvements in the National Tuberculosis and HIV Program, healthcare providers and policymakers should give higher priority to these risk factors identified in the present study.

1. Introduction

One of the most common infectious diseases in the world and a key contributor to poor health is tuberculosis (TB). Prior to the COVID-19 pandemic, tuberculosis (TB) was the most common infectious agent-related cause of death, surpassing HIV/AIDS-related deaths [1]. Tuberculosis is the second leading cause of death (after COVID-19 and before HIV and AIDS) and the thirteenth leading

* Corresponding author.
E-mail address: zeytu.gashaw@aau.edu.et (Z.G. Asfaw).

https://doi.org/10.1016/j.heliyon.2024.e37420
Received 13 September 2023; Received in revised form 2 September 2024; Accepted 3 September 2024
Available online 5 September 2024

cause of death worldwide [1]. The risk of developing and dying from tuberculosis was 30–35 times higher in HIV-positive individuals, including those receiving antiretroviral treatment (ART) [2]. Globally, the number of tuberculosis deaths were increased between 2019 and 2021, reversing the annual decline between 2005 and 2019 [1,3]. In 2020, 1.5 million people worldwide died from tuberculosis (TB), with 0.21 million of these deaths attributable to HIV/TB co-infection [4]. A total of 1.6 million deaths were reported in 2021, including an estimated 1.4 million HIV-negative individuals (95 % uncertainty interval [UI]: 1.3–1.5 million) and 187,000 HIV-positive individuals (95 % UI: 158,000–218,000). This brought the total back to what it was in 2017, surpassing the best estimates of 1.5 million for 2020 and 1.4 million for 2019. With a net decrease of 5.9 % between 2015 and 2021, the first milestone of the WHO End TB Strategy was accomplished about one-sixth of the way [1]. In 2022, the total number of deaths caused by tuberculosis (including deaths among HIV-infected people) worldwide was 1.30 million (95 % uncertainty interval [UI]: 1.18–1.43 million), below the best estimates of 1.4 million in 2020 and 2021 and almost back to the 2019 level [3].

HIV-positive individuals who died from tuberculosis accounted for 50 % of men, 40 % of women, and 10 % of infant mortality [5]. The 2021 study found that most of the 30 countries with a high burden of tuberculosis reported an increase in tuberculosis deaths in 2020 [6]. The global frequency of co-infection between tuberculosis and HIV varies greatly. In sub-Saharan Africa, tuberculosis (TB) and HIV co-infection are associated with high rates of morbidity and mortality among people living with HIV/AIDS. According to the World Health Organization (WHO), the African region had the highest proportion of TB/HIV co-infections and 251,000 deaths from HIV-associated tuberculosis in 2019; about 84 % of these occurred in sub-Saharan Africa [7]. The greatest predicted increases in tuberculosis mortality and incidence are expected to occur in 2021 and 2022, respectively [8].

The Ethiopian HIV and AIDS prevention and control offices estimated that the single national adult HIV prevalence was 0.93 % in 2019 and the country is among 30 countries with a high prevalence of tuberculosis, TB/HIV, and MDR-TB. An estimated 165,000 people (151/100,000 population) suffer from all forms of tuberculosis. 1600 cases of MDR-TB incidents and 24,000 (22/100,000 population) deaths from tuberculosis in 2018 [9]. Among people with HIV, tuberculosis remains the leading cause of hospitalization and mortality. HIV prevalence is 7.34 percent of tuberculosis patients, with wide regional heterogeneity ranging from 0.7 percent in Oromia to 14.5 percent in Afar [9].

HIV can establish reservoirs in the body where the virus remains in a latent or inactive state, making it difficult for the immune system to detect and eliminate. These reservoirs can include immune cells such as $CD4^+$ T cells and other tissues where the virus can persist despite treatment. Due to the presence of these stable reservoirs, complete eradication of HIV from the body is currently not achievable with existing treatments. The ability of the virus to hide in these reservoirs poses a challenge to efforts to cure HIV infection. ART is the cornerstone of HIV treatment and management. While ART cannot cure HIV, it is highly effective in suppressing viral replication, reducing the viral load in the blood, and slowing down the progression of the disease [10].

HIV medications prolong and improve the health of those living with the virus. In the ART era, the morbidity and mortality of people living with HIV/TB co-infection have been reduced significantly in both industrialized and less developed regions. ART significantly increased the probability of survival and reduced the risk of death for HIV/TB-infected patients. The Government of Ethiopia (GOE) released the first antiretroviral (ARV) recommendations in 2003 after realizing the need for antiretroviral therapy. These guidelines were later changed in 2005 and 2008 to enable a swift increase in the use of antiretroviral therapy [10]. Ethiopian researchers have conducted some research on the causes and predictors of mortality in HIV/TB co-infections. On the other hand, research was not conducted in the current study area on HIV/TB co-infection patients' survival time to death and its associated factors. Thus, this study is important to show the incidence density of mortality among HIV/TB co-infected individuals and its predictors in the study area. Reducing the death rate of HIV/TB co-infection is currently the most important public health concern worldwide and in Ethiopia. Therefore, this study aimed to identify the factors associated with the mortality of HIV/TB co-infected patients at follow-up after ART in Dilchora Referral Hospital.

2. Methods

2.1. Study setting

Dilchora Referral Hospital is located in Dire Dawa City Administration in the eastern part of Ethiopia, about 515 km from Addis Ababa. Dilchora is the only referral hospital among the six hospitals in Dire Dawa. It serves as a referral hospital, mainly for the people from the Dire Dawa city administration. The neighboring regions of Oromia regional state, Somali regional state and Harari regional state also referring patients to this hospital. Since 2004, the hospital has offered various healthcare services and clinical care for TB-HIV patients. These include ART, voluntary counseling and testing (VCT), ophthalmology, and emergency services. It has a separate ART clinic and ART follow-up units for people living with HIV. All patients who were diagnosed and started TB treatment in the hospital were linked to VCT services. Moreover, those TB patients who were tested positive for HIV were enrolled in co-trimoxazole preventive therapy (CPT) and HIV chronic care. The prevalence of HIV and TB in the study area was 2.67 % and 0.96 % respectively which was the third in HIV prevalence and the leading in the prevalence of TB in the country [11].

2.2. Study design

A hospital-based retrospective study was used to identify factors associated with time to death among HIV/TB co-infected patients on antiretroviral therapy (ART) at Dilchora Referral Hospital, Dire Dawa.

2.3. Study population

All HIV/TB co-infected patients receiving ART at Dilchora Referral Hospital in Dire-Dawa from January 2008 to January 2023 are included in this hospital-based retrospective study. The Dire-Dawa Administration Health Bureau granted data access for research on January 15, 2023, and HIV/TB co-infected patients' files were reviewed between January 15 and March 16, 2023.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

All patients with HIV/TB co-infection who started treatment at Dilchora Referral Hospital and patients who were initiated on ART from January 2008 to January 2023 and all enrolled HIV/TB co-infected patients who had at least two follow up period.

2.4.2. Exclusion criteria

Charts from study participants were excluded if they contained insufficient data for important study variables such as WHO clinical stage, hemoglobin level, and CD4 count. Patients who were transferred in and out, and had fewer than two ART follow-up visits were not included in this study.

2.4.3. Sample size determination and sampling procedure

Since there were few individuals with co-infections of HIV and TB, the study included all medical records of those patients who satisfied the inclusion requirements. Within the ART registries of the selected institution, 753 charts with patients co-infected with HIV and TB were discovered. The study was carried out in a particular Dire Dawa public hospital. The hospital with the largest patient volume was chosen through the use of purposeful sampling. Next, from January 1, 2008, to January 1, 2023, medical record numbers of patients receiving antiretroviral therapy (ART) and co-infected with HIV and tuberculosis were determined. Those having a history of tuberculosis were sought out using the ART logbook. The patient charts of every patient who met the inclusion criteria were then included in the trial because the number of co-infected patients in the chosen hospital was manageable. Finally, 434 of the 753 recognized charts were chosen. Because of the exclusion criteria, the remaining charts were not included. An overview is given in the diagram (Fig. 1). Consequently, 319 people were disqualified according to the previously established exclusion standards. Consequently, 434 people with HIV and TB were chosen for the study. There was no sample size estimation done before the investigation. But

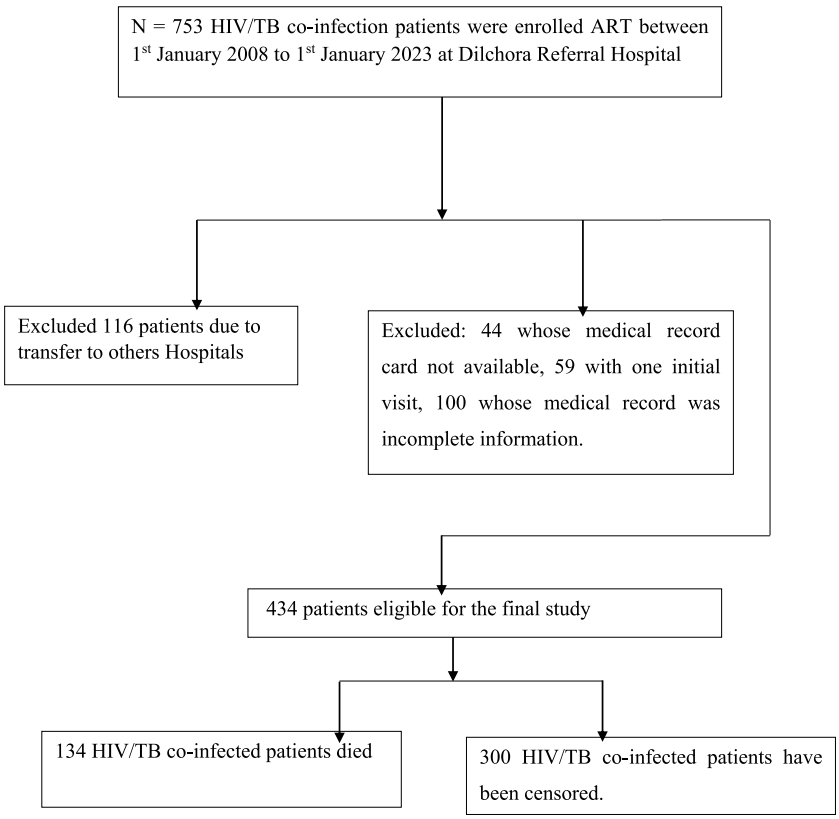


Fig. 1. Overall enrollment of patients with HIV/TB co-infection on ART at Dilchora Referral Hospital, Dire Dawa, Ethiopia, 2008–2023 (n = 434).

utilizing the G-power software, the post-hoc power analysis was carried out after the data was gathered. The power value was determined using a sample size of 434, a medium effect size of 1.3, and a significant threshold of 0.05. The power analysis revealed a value of 1.00, indicating that the sample size was sufficient to identify the intended.

2.5. Variables of the study

2.5.1. Outcome variables

The primary outcome variable for the present study was the patients' time to death among HIV/TB co-infected patients.

2.5.2. Independent variables

Socio-demographic characteristics: Age, Sex, Marital status, Residence, Religion, Educational level, Occupation.

Clinical characteristics: CD4 cell count, Hemoglobin level, WHO clinical stage, Presence of Opportunistic infections, Site of TB, Time of TB diagnosis, Previous history of TB, ART regimen, Adherence, Co-trimoxazole prophylaxis, Viral load change, Functional status, Weight, Height, BMI. **Behavioral factors:** smoking, alcohol and other.

2.5.3. Operational definition

Event: The event was defined as death from any cause during the course of ART and follow up period.

Time to death: The time between the initiations of ART to occurrence of the event (death) during the follow up period.

Censored: If the patients is loss to follow up, transferred out, dropout before developing the event and if the patients is alive at the end of the study period.

Adherence: According to the WHO, patients show good adherence when they follow the recommendations of health professionals such as personal behavior changes, taking medication, following a diet and changing lifestyle. In addition, adherence was rated as good, fair, or poor, based on the percentage of drug dose calculated from the total monthly ART drugs dose. therefore, 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 [12].

Loss to Follow Up: When the patient misses appointment for more than 3 months.

Transferred Out: when the patient transferred to other health facility.

Co-trimoxazole preventive therapy (CPT): should be administered to all PLHIV who have active TB disease regardless of CD4/mm3 counts.

Anemia: anemia is defined as a reduction in hemoglobin level. It was further categorized into mild anemia (hemoglobin 90–109 g/L in females or 90–119 g/L in males), moderate anemia (hemoglobin 60–89 g/L), and severe anemia (hemoglobin <60 g/L).

Clinical stage 1: Asymptomatic**,** persistent generalized lymphadenopathy.

Clinical stage 2: Moderate unexplained weight loss**,** recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and Pharyngitis).

Clinical stage 3: Unexplained severe weight loss (>10 % of presumed or measured body weight)**,** unexplained chronic diarrhea for longer than one month, unexplained persistent fever (above 37.6 °C intermittent or constant for longer than one month), persistent oral candidiasis, oral hairy leukoplakia**,** pulmonary tuberculosis, severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteremia).

Clinical stage 4: HIV wasting syndrome**,** pneumocystis pneumonia**,** recurrent severe bacterial pneumonia**,** Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)**,** esophageal candidiasis (or candidiasis of trachea, bronchi or lungs).

Patient functional status: Working: able to perform usual work in or out of the house.

Being ambulatory patient: able to perform activities of daily living.

Being bedridden patient: not able to perform activities of daily living.

2.6. Data collection tools and procedures

The data extraction tool was developed from the ART national registration and tracking form and is currently used by the ART clinics in the study area, as well as from previous published articles. It includes socio-demographic characteristics, clinical characteristics, and behavioral patterns. The data was collected from patient records (charts) and the database. The health management information system (HMIS) card number was used to identify an individual's patient card. Three BSc nurses working in the ART clinic of the Dilchora Referral Hospital collected the data.

2.7. Quality assurance

Before actual data collection, the preliminary review of 5 % of the sample at Dilchora Referral Hospital was performed. The adequacy of the checklist was then assessed and unclear questions were changed before the actual data collection. A one-day training session was conducted for data collectors on the objectives and variables of the study, as well as data extraction using the tool. The ethical approval was obtained from the Review Ethics Committee (REC) of the School of Public Health, College of Health Sciences, Addis Ababa University with grant number (Ref.No. SPH/154/2023). Confidentiality was maintained at all stages of research activities and data was stored on a secure, password-protected system.

2.8. Data processing and analysis

The data were entered, coded, and cleaned using Epi Info version 7, then exported into Stata version 17 for statistical analysis. Summary statistics such as mean with standard deviation and median with interquartile range of continuous data were used to describe patient follow-up characteristics. The frequency distribution, count and percentage were applied to categorical data. Kaplan Meier survival curves were used to draw time to death and Log-rank tests were performed to compare survival curves between groups. The Schoenfeld and Cox-Snell residual tests were used to verify the Cox proportional hazards model's assumption statistically and graphically. A bivariate Cox proportional hazard regression model was fitted for each explanatory variable to determine the association between the outcome variable and the individual independent variables. A P value of less than 0.25 in the bivariable analysis was a candidate for multivariable analysis. The adjusted hazard ratio with its 95 percent confidence interval was used, and a p value of 0.05 was considered statistically significant in the multivariable analysis.

3. Results

3.1. Socio-demographic information of the study participants

This study included 434 HIV/TB co-infected patients. Among these patients, 30.88 % died, and the remaining 69.12 % were censored. There were 242 (55.76 %) female patients and of them, 66 (27.27 %) died. The mean (standard deviation) age at the start of ART was 35.4 (11.7) years. The proportion of deaths was 32 % among the 386 (88.94 %) patients who lived in urban areas. Of the total number of patients, 140 (32.26 %) and 154 (35.48 %) were never married and married, respectively. Among the study participants, 183 (42.17 %) had completed primary school, while 121 (27.88 %) had no formal education. Regarding the patients' employment status, 128 (29.49 %) were merchant workers. More than half of the total participants, 254 (58.53 %), were Orthodox in religion, Table 1.

3.2. Clinical characteristics of HIV/TB co-infected individuals and behavioral patterns

From the total study participants, the majority of them 297 (68.43 %) had an opportunistic infection at baseline. Recurrent upper respiratory tract infections (URTIs) 96 (22.1 %) were the most common opportunistic infection among all participants. At baseline, 265

Table 1
Baseline socio-demographic information for patients with HIV/TB co-infections receiving ART at Dilchora Referral Hospital in Dire Dawa, Ethiopia from 2008 to 2023.

Variables	Category	Count, n (%)	Patient status	
			Censored, n (%)	Death, n (%)
Sex	Male	192(44.24)	124(64.58)	68(35.42)
	Female	242(55.76)	176(72.72)	66(27.27)
Age	<15	22(5.07)	19(86.33)	3(13.63)
	15–24	45(10.37)	32(71.11)	13(28.89)
	25–34	124(28.57)	82(66.13)	42(33.87)
	35–44	148(34.10)	96(64.86)	52(35.14)
	>44	95(21.89)	71(74.74)	24(25.26)
Residence	Urban	386(88.94)	264(68.39)	122(31.61)
	rural	48(11.06)	36(75)	12(25)
Marital status	Never married	140(32.26)	99(70.71)	41(29.29)
	Married	154(35.48)	106(68.83)	48(31.17)
	Divorced	71(16.36)	55(77.46)	16(22.54)
	Widowed	43(9.91)	26(60.47)	17(39.53)
	separated	26(5.99)	14(53.85)	12(46.15)
Occupation	Government Employed	35(8.06)	25(71.43)	10(28.57)
	Non-Government Employed	14(3.23)	8(57.14)	6(42.86)
	Student	26(5.99)	21(80.77)	5(19.23)
	Housewife	52(11.98)	36(69.23)	16(30.77)
	Merchant	77(17.74)	59(76.62)	18(23.38)
	Others	128(29.49)	86(67.19)	42(32.81)
		102(23.50)	65(63.73)	37(36.27)
Educational status	No formal education	108(24.88)	69(63.89)	39(36.11)
	Primary	183(42.17)	128(69.95)	55(30.05)
	Secondary	121(27.88)	86(71.07)	35(29.93)
	Tertiary	22(5.07)	17(77.27)	5(22.73)
Religion	Muslim	141(32.49)	100(70.92)	41(29.08)
	Orthodox	254(58.53)	173(68.11)	81(31.89)
	Others	39(8.99)	27(69.23)	12(30.77)
HIV Disclosure	Yes	302(69.59)	205(67.88)	97(32.12)
	No	132(30.41)	95(71.97)	37(28.03)

Note: Others[1]: include daily worker, farmer, driver and jobless. Others[2]: include protestant and catholic.

(61.06 %) of patients were classified as WHO stages III and IV. Based on the WHO clinical stage criteria, 128 (29.49 %) of all participants were eligible for ART. In terms of CPT use, the majority 380 (87.56 %) were on co-trimoxazole medication, and 121 (27.88 %) of study participants were smokers. Among total patients, 201 (46.31 %) and 138 (31.8 %) were commonly prescribed the initial ART regimens 1j (TDF+3 TC + DTG) and 1e (TDF-3TC-EFV), respectively, and 106 (24.42 %) had poor ART medication adherence. Of HIV-infected patients, 286 (65.9 %) had pulmonary tuberculosis, and 223 (51.38 %) had a CD4 count less than 200 cells/l (Table 2).

3.3. Mortality rate of HIV/TB co-infected patients at ART follow-up

All participants with HIV/TB co-infection and on ART were followed up for different periods, with a total of 26,350 persons per month of observation. They were followed for at least six months up to a maximum of 15 years (180 months). The overall median survival time was 12 years (144 months) (95%CI: 132, 156). One hundred thirty four (30.88 %) deaths were observed during the follow-up period, making the overall mortality rate 5.1 per 1000 person-months of follow-up (95%CI: 4.29, 6.02) for the study. From

Table 2
Clinical and behavioral characteristics of HIV/TB co-infected persons attending the ART clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia from 2008 to 2023.

Variables	Category	Count, n (%)	Patient status	
			Censored, n (%)	Death, n (%)
WHO clinical stages	Stage I &II	169(38.94)	132(78)	37(22)
	Stage III &IV	265(61.06)	168(63.4)	97(36.6)
TB status at start of ART	Positive	255(58.76)	168(65.9)	87(34.1)
	Negative	179(41.24)	132(73.7)	47(26.3)
BMI	Underweight	231(53.23)	148(64.1)	83(35.9)
	Overweight	180(41.47)	132(73.3)	48(26.7)
	Normal	23(5.3)	20(87)	3(13)
Functional status	Ambulatory	144(33.18)	102(83.3)	42(16.7)
	Bedridden	98(22.58)	51(52)	47(48)
	Working	192(44.24)	147(76.6)	45(23.4)
Time of TB diagnosis	Pre- ART	213(49.08)	145(68.1)	68(31.9)
	ART	221(50.92)	155(70.1)	66(29.9)
Types of TB infection	Pulmonary	286(65.90)	202(70.6)	84(29.4)
	Extra pulmonary	102(23.50)	70(68.6)	32(31.4)
	Disseminated TB	46(10.6)	28(60.9)	18(39.1)
Past Opportunistic	Yes	297(68.43)	202(68)	95(32)
Infections	No	137(31.57)	98(71.5)	39(28.5)
Having Diarrhea	Yes	69(15.9)	45(65.2)	24(34.8)
	No	365(84.1)	255(69.9)	110(30.1)
Having Oral Candidiasis	Yes	75(17.28)	48(64)	27(36)
	No	359(82.72)	252(70.2)	107(29.8)
Having Pneumonia and recurrent pneumonia	Yes	29(6.68)	22(75.9)	7(24.1)
	No	405(93.32)	278(68.6)	127(32.4)
Having Severe Anemia	Yes	39(8.99)	25(64.1)	14(35.9)
	No	395(91.01)	275(69.6)	120(30.4)
Recurrent URTIs	Yes	96(22.12)	68(70.8)	28(29.2)
	No	338(77.88)	232(68.6)	106(31.4)
CD4 cell count	<200	223(51.38)	154(69)	69(31)
	≥ 200	211(48.62)	146(69.2)	65(30.8)
Hemoglobin	mean $\pm$ *SD*	11.53 $\pm$2.64	11.82 $\pm$2.55	10.88 $\pm$2.73
Adherence status	Good	244(56.22)	182(74.6)	62(25.4)
	Fair	84(19.35)	54(64.3)	30(35.7)
	Poor	106(24.42)	64(60.4)	42(39.6)
CTP	Yes	380(87.56)	257(67.6)	123(32.4)
	No	54(12.44)	43(79.6)	11(20.4)
Alcohol drinking	Yes	94(21.66)	54(57.4)	40(42.6)
	No	340(78.34)	246(72.4)	94(27.6)
Smoking status	Yes	121(27.88)	68(56.2)	53(43.8)
	No	313(72.12)	232(74.1)	81(25.9)
ART eligibility criteria	WHO Clinical Stage	128(29.49)	83(64.8)	45(35.2)
	CD4 Cell Count	142(32.72)	110(77.5)	32(22.5)
	Not specified	31(7.14)	26(83.9)	5(16.1)
	Pregnancy	9(2.07)	5(55.6)	4(44.4)
	WHO stage and CD4	124(28.57)	76(61.3)	48(38.7)
Viral load test	Detected	86(19.82)	58(67.4)	28(32.6)
	Not Detected	348(80.18)	242(69.5)	106(30.5)
Initial ART Regimen	1c (AZT- 3 TC- NVP)	23(5.3)	18(78.3)	5(21.7)
	1d (AZT- 3 TC- EFV)	72(16.59)	52(72.2)	20(27.8)
	1e (TDF- 3 TC- EFV)	138(31.8)	71(51.4)	67(48.5)
	1j (TDF+3 TC + DTG)	201(46.31)	159(79.1)	42(20.9)

those who died, the mortality rate was higher in males: 5.5 per 1000 person-months (95 % CI: 4.4, 6.9) in HIV/TB co-infected patients, compared to 4.7 per 1000 person-months (95 % CI: 3.7, 5.9) in females. Similarly, the mortality rate from HIV/TB co-infected patients classified with WHO clinical stage was higher in stages III and IV 6.2 per 1000 person-months (95 % CI: 5.1, 7.6) compares to 3.5 per 1000 person-months (95 % CI: 2.5, 4.8) in stages I and II. The mortality rate is higher in those whose body mass index underweight is 6.5 per 100 person-months (95 % CI: 5.2, 8.1) compared to 1.7 person-months (95 % CI: 0.54, 5.2) in normal BMI. In terms of CD4 cell count, the mortality rate for patients with HIV/TB co-infection who had less than 200 cells was 5.8 per 1000 person-months, compared to 4.5 per 1000 person-months for those who had more than 200 cells (Table 3).

According to the above overall Kaplan Meier curve, the patients who were co-infected with TB and HIV had a median survival time of 12 years (144 months) (Fig. 2).

3.4. Kaplan-Meier curve with logarithmic rank test of HIV/TB co-infected patients

In this study some covariates, such as functional status and ART medication regimen, medication adherence and WHO clinical stages, were presented as Kaplan-Meier curves (Figs. 3 and 4). These curves allowed us to determine whether the survival of HIV/TB co-infected individuals varied by subgroup. Accordingly, the survival curve showed that HIV/TB co-infected patients who are able to work have a higher survival rate than bedridden and ambulatory patients (log-rank value = 7.57, p-value = 0.0059). There also appears to be a difference in survival between clinical stage III and IV patients and stage II and I patients ((log-rank value = 8.01, p-value = 0.0046)). In clinical WHO stages II and I, survival was longer than in stages III and IV, indicating that they have a relatively lower mortality risk than stages III and IV. There was also survival time difference among Initial regimen (log-rank value = 41.54, p-value = 0.0000) and good drug adherence had longer survival time compared to poor drug adherence (log-rank value = 16.90, p-value = 0.0000). As we know, the log-rank test is the most frequently used test for an overall comparison of two interesting Kaplan-Meier curves. The test has optimal power in the case of PH, but can lead to poor rejection rates when the survival curves cross. Some Kaplan-Meier curve in this study showed that the curves crossed. Thus, by adding a weighting function, we can obtain a test that is more powerful for crossing Kaplan-Meier curves. However, recent advances solve the above problem by flexibly combining multiple weighted log-rank tests into one test procedure. This method was recently implemented in the R package mdir.logrank. Therefore, the results of the omnibus test (mdir) for crossed curves showed that the curves of all different subgroups of the study did not show strong evidence against PH, means the test was not reject the proportional hazard assumption, indicating good consistency among PH settings (supplements).

3.5. Cox proportional hazard assumption test

The proportional hazard assumption was checked by using the cumulative hazard plot (cox-Snell residual) and Schoenfeld residual test. As we can see from the figure, the hazard function closely follows the 45-degree line, indicating that the overall model goodness of fitness was met. Therefore, the final model had good data fitting (Fig. 5). The proportional hazard assumption test for individual variables were also tested based on Schoenfeld residuals, the P-value for Global test for this study is 0.7368 which is greater than 0.05 level of significance. It showed that proportional hazard assumption for individual determinant factors is satisfied. It can be demonstrated that the multivariable Cox regression model is fit for the analysis and interpretation of the results of the study.

Table 3
Mortality rate for HIV/TB co-infected persons attending the ART clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia from 2008 to 2023.

Variables	Categories	Times at risks	Incidence rate per 1000 person months	95 % CI per 1000
Sex	Male	12335	5.5	(4.4, 6.9)
	Female	14014	4.7	(3.7, 5.9)
WHO Clinical stages	Stage I &II	10684	3.5	(2.5, 4.8)
	Stage III &IV	15665	6.2	(5.1, 7.6)
BMI	Underweight	12760	6.5	(5.2, 8.1)
	Overweight	11798	4.1	(3.1, 5.4)
	Normal	1791	1.7	(0.54, 5.2)
Drug adherence	Good	14583	4.3	(3.3, 5.4)
	Fair	5330	5.6	(3.9, 8.0)
	Poor	6436	6.5	(4.8, 8.8)
Functional status	Ambulatory	8611	4.9	(3.6, 6.6)
	Bedridden	5549	8.5	(6.4, 11.3)
	Working	12189	3.7	(2.8, 4.9)
CD4 cell count	<200	14387	5.8	(4.5, 7.3)
	≥200	11962	4.5	(3.5, 5.8)
ART regimen	1c (AZT- 3 TC- NVP)	1714	2.9	(1.2, 7.0)
	1d (AZT- 3 TC- EFV)	5115	3.9	(2.5, 6.1)
	1e (TDF- 3 TC- EFV)	6879	9.7	(7.6, 12.3)
	1j (TDF+3 TC + DTG)	12641	3.3	(2.5, 4.5)

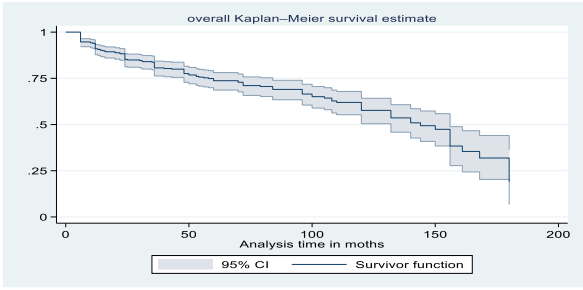


Fig. 2. Overall Kaplan-Meier survival estimated curve of HIV/TB co-infection patients attending ART clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia, from 2008 to 2023 (n = 434).

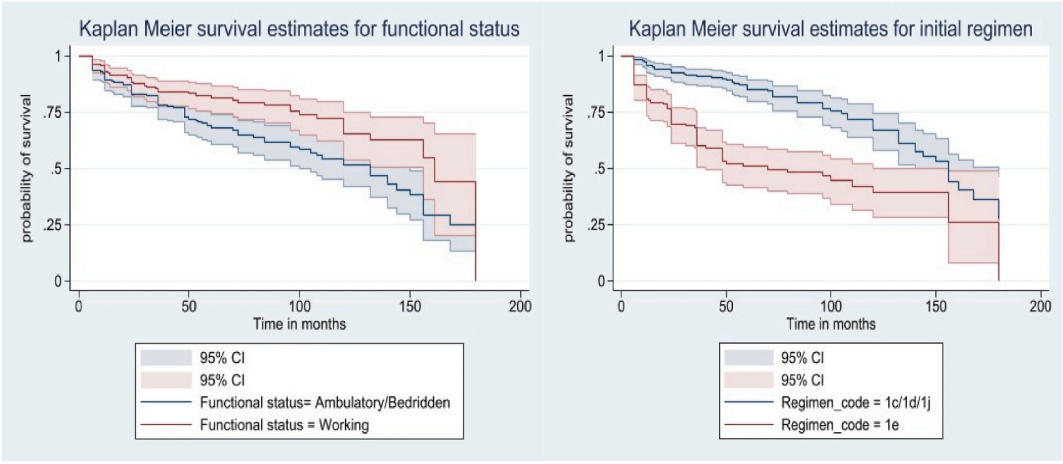


Fig. 3. Kaplan-Meier survival estimated curve by functional status and initial ART regimen of HIV/TB co-infection patients attending ART clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia, from 2008 to 2023 (n = 434).

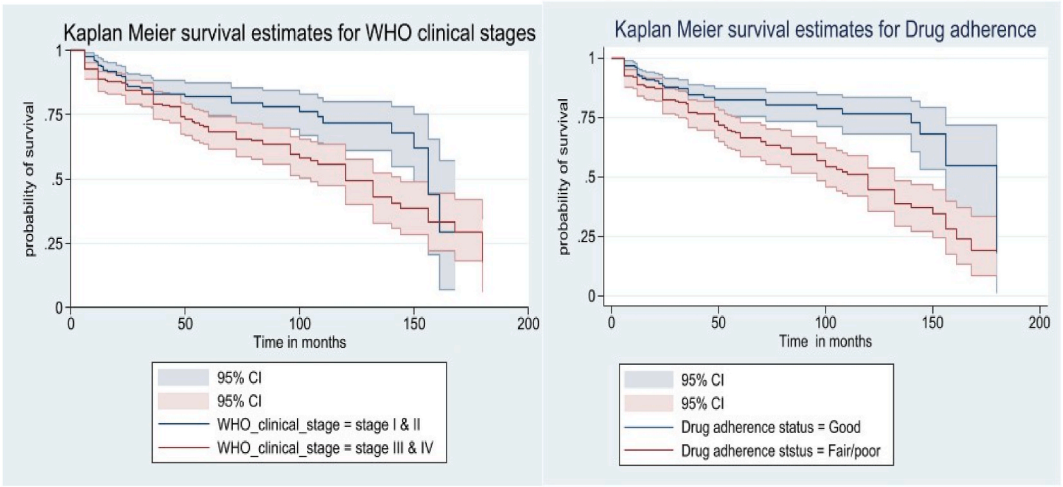


Fig. 4. Kaplan-Meier survival estimated curve by drug adherence and WHO clinical stages of HIV/TB co-infection patients attending ART clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia from 2008 to 2023 (n = 434).

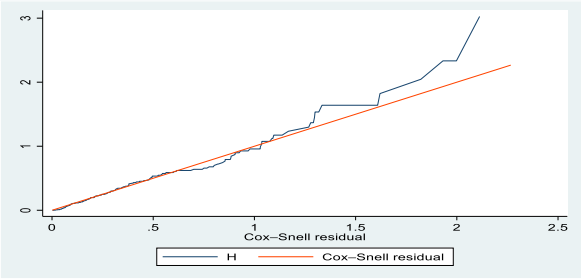


Fig. 5. Cox-Snell Residual plots for HIV/TB co-infected patients at Dilchora Referral Hospital, Dire Dawa, Ethiopia, from 2008 to 2023 (n = 434).

3.6. Factors associated with time to death in HIV/TB co-infected patients on ART

In this study, the multivariable analysis discovered that baseline WHO clinical stage, baseline BMI, baseline functional status, baseline hemoglobin level, adherence status, initial ART therapy, and smoking were selected risk factors for time to death. The risk of death was approximately 1.7 times higher in patients with WHO clinical stages III and IV than in patients with clinical Stage I and II (AHR: 1.69 (95 % CI: 1.09, 2.62)). Patients with an underweight baseline BMI had 4.52 times higher risk of death as compared with patients with normal BMI (AHR: 4.52 (95 % CI: 1.30, 15.67)). The risk of death in bedridden patients was 1.63 times higher than in ambulatory patients (AHR: 1.63 (95 % CI: 1.04, 2.57)). As increasing hemoglobin levels by one unit reduces the risk of death by 13 % (AHR: 0.87; 95 % CI: 0.82, 0.93). Smoking HIV/TB co-infected patients had a 1.48-fold higher risk of death than nonsmokers did in HIV/TB co-infected patients (AHR: 1.48 (95 % CI: 1.01, 2.16)). Patients with poor ART medication adherence were about 1.6 times more likely to die than patients with good ART medication adherence (AHR: 1.60 (95 % CI: 1.03, 2.50)). The risk of death was 2.68 times higher in patients receiving initial ART regimen type 1e (TDF-3TC-EFV) compared to patients receiving initial ART regimen type 1j (TDF+3 TC + DTG) (AHR: 2.68 (95 % CI: 2.68(1.74, 4.12)), at P-value = 0.0001) (Table 4).

4. Discussion

The purpose of this study was assessed the factors associated with the mortality from HIV/TB co-infected patients under ART in Dire Dawa, Ethiopia. The death rate in this study was notably high, with 30.88 % of patients who were co-infected with HIV and TB dying during the follow-up period. This did not align with findings from other research projects in related fields. The results were significantly higher than those of studies carried out in Ethiopia at Mettu Karl Hospital, 20.9 % [13], in selected public hospitals in SNNPR, Ethiopia 12.3 % [14], at Mizan Tepi University Teaching Hospital, Southwest, Ethiopia 22.8 % [15], in Dubti General Hospital, Afar, Ethiopia 11.7 % [16], and studies conducted in Malaysia, 23.3 % [17], Brazil, 14.1 % [18] and Tanzania, 3.6 % [19]. These differences might be caused by differences in the follow-up time, the number of participants, the research location, and the accessibility of services.

For this study, the overall death rate was 5.1 per 1000 person-months. The total death rate was 6.31 per 1000 persons per month of observation in a retrospective study carried out in Tanzania, which is higher than the findings of this investigation [19]. There exist multiple factors that may lead to variations in the mortality incidence rate among patients co-infected with HIV and tuberculosis. These variables may change depending on the population under study, the healthcare environment, the standard of care given, and the existence of particular risk factors. The incidence rate of death can be impacted by differences in access to healthcare services, age, gender, and socioeconomic position. For instance, underlying medical issues and restricted access to care may contribute to increased death rates in the elderly or those from poorer socioeconomic backgrounds. The incidence rate of death can be influenced by variables such the body mass index, immunological status (measured by CD4 cell count), comorbidities, TB disease severity, HIV infection stage, and nutritional condition. People who have weak immune function or advanced illness stages may be at a higher risk of dying. In order to manage HIV/TB co-infection, adherence to antiretroviral therapy (ART) and TB treatment is essential. Medication noncompliance can result in treatment failure, the advancement of the illness, and higher death rates. Mortality rates can be impacted by differences in healthcare infrastructure, practitioner expertise, resource availability, and quality of care. The mortality rate of people with co-infections of HIV and TB is significantly lower when they have access to prompt and efficient care.

Furthermore, the study's overall incidence rate was lower than the Sichuan, China, all-cause death rate of 7.76 per 1000 person-months [20]. However, compared to a cohort research carried out at the Mettu Karl Referral Hospital in Ethiopia, our result is lower, 12.1 incident cases per 1000 person-months was the overall rate (95 % CI: 9.77, 14.98) [13]. The fact that only children under the age of two were included in the Mettu Karl Referral Hospital study helps to explain this. Children under the age of two are at high risk of death due to immature immune systems, leading to serious illness and death. The probability of dying from HIV/TB co-infection was statistically associated with WHO clinical stages, according to the current study. Compared to patients with WHO clinical stages I & II, the risk of death was 1.69 times higher in co-infected individuals with WHO clinical stages IV and II. This is in line with earlier research that discovered the clinical WHO stages raise mortality in HIV-positive TB patients [21]. Research at the Dubti General Hospital in Afar, Ethiopia, found that TB-positive persons with HIV who had WHO clinical stages III and IV had a 4.36-fold higher mortality rate than those who had stages I and II [16]. According to a comparable study done in Addis Ababa, Ethiopia, patients with stage I and stage

Table 4
Results of the bivariate and multivariable Cox-PH regression model for HIV/TB co-infected patients attending the ART Clinic at Dilchora Referral Hospital, Dire Dawa, Ethiopia from 2008 to 2023 (n = 434).

Variables	Patients Status		CHR (95%CI)	AHR (95%CI)	P-value
	Death	Censored			
Educational status					
No formal education	39	69	**1**	**1**	
Primary	55	128	0.74(0.49, 1.12)	0.76(0.48, 1.20)	0.242
Secondary	35	86	0.63(0.40, 1.00)	0.78(0.47, 1.28)	0.319
Tertiary	5	17	0.59(0.23, 1.52)	0.56(0.20, 1.54)	0.263
Marital status			**1**	**1**	
Never married	41	99	1.01(0.67, 1.54)	0.90(0.56, 1.43)	0.663
Married	48	106	0.79(0.45, 1.42)	0.69(0.37, 1.29)	0.249
Divorced	16	55	1.28(0.73, 2.26)	1.05(0.56, 1.96)	0.876
Widowed	17	26	1.23(0.64, 2.35)	1.93(0.95, 3.90)	0.068
Separated	12	14			
WHO clinical stage			**1**	**1**	
Stage I & II	37	132	1.71(1.17, 2.49)	**1.69(1.09, 2.62)**	**0.018** *
Stage III & IV	97	168			
TB at start ART					
Positive	87	168	1.30(0.91, 1.86)	0.79(0.53, 1.21)	0.290
Negative	47	132	**1**	**1**	
BMI					
Underweight	71	133	4.32(1.35, 13.78)	**4.52(1.30, 15.67)**	**0.017** *
Overweight	26	147	2.83(0.87, 9.17)	3.27(0.95, 11.32)	0.061
Normal	37	20	**1**	**1**	
Functional status					
Ambulatory	42	102	**1**	**1**	
Bedridden	47	51	1.65(1.08, 2.5)	**1.63(1.04, 2.57)**	**0.034** *
Working	45	147	0.77(0.506, 1.17)	0.99(0.62, 1.56)	0.953
Site of TB infection					
Pulmonary	84	202	**1**	**1**	
Extra pulmonary	32	70	1.1(0.74, 1.66)	0.96(0.61, 1.5)	0.87
Disseminated TB	18	28	1.6(0.96, 2.66)	1.41(0.8, 2.48)	0.233
Having Anemia			1.58(0.91, 2.75)	1.06(0.59, 1.91)	0.835
Yes	14	25	**1**	**1**	
No	120	275			
CD4 cell count			**1**	**1**	
>200	76	169	1.3(0.94, 1.88)	1.07(0.74, 1.56)	0.729
< =200	58	131			
Hemoglobin			0.85(0.79, 0.90)	**0.87(0.82, 0 0.93)**	**0.0001** *
Adherence status				**1**	
Good	43	182	**1**		
Fair	27	54	1.32(0.86, 2.04)	1.37(0.85, 2.20)	0.196
Poor	64	64	1.52(1.03, 2.26)	**1.60(1.03, 2.50)**	**0.038** *
CTP					
Yes	123	257	**1**	**1**	
No	11	43	2.1(1.11, 3.86)	1.59(0.83, 3.04)	0.161
Alcohol drinking					
Yes	55	54	1.28(0.88, 1.85)	1.08(0.72, 1.64)	0.702
No	79	246	**1**	**1**	
Smoking status					
Yes	81	68	1.28(0.90, 1.82)	**1.48(1.01, 2.16)**	**0.045** *
No	53	232	**1**	**1**	
Initial ART Regimen					
1c (AZT- 3 TC- NVP)	5	18	0.89(0.35, 2.25)	0.89(0.34, 2.35)	0.827
1d (AZT- 3 TC- EFV)	20	52	1.19(0.69, 2.02)	0.77(0.43, 1.37)	0.379
1e (TDF- 3 TC- EFV)	67	71	2.99(2.03, 4.42)	**2.68(1.74, 4.12)**	**0.0001** *
1j (TDF+3 TC + DTG)	42	159	**1**	**1**	

The bolded figures above revealed statistically associated risk factors for mortality.
CHR = Crude Hazard Ratio; AHR = Adjusted Hazard Ratio; CI = Confidence Interval.
P-value = level of significance at <0.05; **1** = Reference group.

II TB had a 2.33 % higher risk of dying from HIV/TB co-infection [22]. This may indicate an increased risk of opportunistic infections in individuals who are believed to have progressed beyond the WHO clinical stage.

Individuals who were bedridden and co-infected with HIV/TB were significantly more likely to pass away than those who were working [13]. Similar findings from previous studies were made in Addis Ababa, Ethiopia, where it was shown that bedridden patients had a three times higher risk of passing away than those who were functioning [22]. The results of this analysis were in agreement with those of a previous study carried out in Ethiopia [23]. Research revealed that the risk of death for bedridden patients was almost twice

that of well-functioning people. These results are not surprising given that immobile individuals experience worse health outcomes due to a vicious cycle that lowers immunity and increases the risk of opportunistic infections and deadly diseases. In order to implement prompt and efficient management techniques, support for regular and necessary screening for opportunistic infections and other disorders makes sense. In the context of controlling infectious diseases like co-infection between HIV and TB, reducing preventable deaths is an essential public health goal. Appropriate antiretroviral medication (ART) and TB treatment can be started promptly after HIV and TB diagnosis, which can greatly lower death rates and minimize preventable deaths among people with HIV/TB co-infection. Prompt intervention can halt the advancement of the illness and enhance results. Optimizing treatment outcomes and lowering mortality require ensuring integrated care for people with co-infections of HIV and TB, which includes coordinated management of both illnesses, routine monitoring, and adherence support. In order to lower the risk of preventable fatalities, people can be empowered to take charge of their health and make educated decisions by receiving education on HIV, TB, treatment adherence, healthy habits, and prevention initiatives.

Adherence to antiretroviral therapy was another predictor of death in patients co-infected with HIV and tuberculosis. AHR: 1.60: 95%CI: 1.03, 2.50) revealed that the risk of death was 1.6 times higher for those with poor drug compliance than for those with strong ART compliance. This result was consistent with research done in Ethiopia [22,23]. This may be due to the function of antiretroviral drugs (ART) in reducing viral load and promoting immune system recuperation via viral inhibition. As a result, patients who strictly follow the regimen have a higher chance of overcoming the co-infection. On the other hand, patients who do not take their medications as prescribed run the danger of treatment failure, which would accelerate the spread of viruses, lower immunity, and increase mortality. A patient's increased hemoglobin level lowers their chance of dying from co-infection with HIV and tuberculosis.

A meta-analysis and comprehensive evaluation of the literature indicate that this result is similar to research conducted in Ethiopia [24]. This could be as a result of HIV's direct impact on the bone marrow; as the virus spreads, anemia may become more common, which would have increased the chance of death. In addition, impaired physical function, mental distress, a worse quality of life, a quicker progression of the illness, and a shortened life span are all possible outcomes of anemia in HIV patients. Patients in this study who were overweight (BMI >25 kg/m2) had a 4.52-fold increased risk of death compared to those whose BMI was normal (AHR: 4.52; 95%CI: 1.30, 15.67). This research was done in two parts, one in Metema [25], and the other in Addis Ababa [12,22]. Patients with low body mass index are undernourished, ill-equipped to handle their condition, and particularly vulnerable to lethal opportunistic infections. Patients on the 1e (TDF- 3 TC- EFV) regimen had a higher death risk than those on the 1j (TDF+3 TC + DTG) regimen, according to a research conducted at Dubti General Hospital in Afar, Ethiopia [16]. This shows that the initial ART regimen selected may have a major impact on how well HIV/TB co-infected people survive. In order to maximize survival and lower death rates in this population, healthcare practitioners should take into account the possible effects of various ART regimens on patient outcomes and modify treatment strategies accordingly. The statement further implies that drug-resistant tuberculosis, which is known to be related with greater mortality in HIV patients, may be connected to the higher mortality rates found in HIV/TB co-infected patients on the initial ART regimen 1e (TDF-3TC-EFV). This emphasizes how crucial it is to combine drug-resistant tuberculosis and HIV services in order to enhance patient outcomes.

Promptly initiating suitable second-line anti-tuberculosis therapy and antiretroviral therapy (ART) in conjunction with early identification of drug-resistant tuberculosis and HIV is imperative in addressing this issue. Handling drug-resistant tuberculosis in HIV-positive individuals also requires a robust patient support system and application of strict infection control protocols. A major determining factor among the individuals with co-infection of HIV and TB in this study was their history of cigarette smoking. This result was in conflict with research conducted at Dubti General Hospital in Afar, Ethiopia [16], but it was in agreement with other studies conducted in Addis Ababa, Ethiopia [12,26]. This might be because people don't smoke as much perhaps only once a week as opposed to every day.

4.1. Limitation, and strengthens of the study

The current study concentrated on the regions of the country where HIV/TB is particularly prevalent, an area that has received less attention from researchers. This suggests that the study may serve as a useful introduction to the field. Nevertheless, the current analysis was based on secondary data from medical records, which meant that important clinical factors that affected mortality in HIV/TB co-infections in earlier studies such as changes in viral load, treatment toxicity, and drug resistance were not adequately documented. Since this was a single hospital research of individuals with HIV and tuberculosis co-infection, results may not generalize to the general population or populations with co-infection at the national level. Hence, larger sample sizes and multi-center studies should be used in research if superior results are desired. During the data collection period, patient charts that were absent or lacking information were not included. Selection bias may emerge from this, which could cause study outcomes to be overstated or underestimated. An overestimation of mortality may result from assuming that all fatalities are attributable to HIV/AIDS because the actual cause of death may not always be known. Working with secondary data, where a number of opportunistic diseases were taken to be the reason and several important factors were not sufficiently disclosed.

5. Conclusion

The present study found that HIV/TB co-infections significantly increase mortality rates, with a mortality rate of 5.1 per 1000 person-months. Factors such as underweight body mass index, advanced WHO stages, bedridden functioning, initial ART regimen 1e, poor ART drug adherence, and smoking status were associated with higher mortality rates. Health professionals should prioritize these risk factors and conduct prospective retrospective studies to improve the National Tuberculosis and HIV Program.

5.1. What is already know on this topic

1 There is no cure for HIV, but we can control it with HIV treatment.
2 ART is recommended for everyone who has HIV. ART cannot cure HIV, but HIV medicines help people with HIV live longer, healthier lives.

5.2. What this study adds

1. Risk factors for HIV/AIDS co-infected patients were identified.
2. The current study area has a high prevalence of both HIV and TB. Thus, the present study could be supportive literatures for designing practical intervention.

Funding

The authors received no specific funding for this work.

Data availability statement

All relevant data are within the manuscript and its supporting information.

CRediT authorship contribution statement

Feyisa Shasho: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Mengistu Yilma:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Zeytu Gashaw Asfaw:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviation and acronyms

AIDS	Acquired Immune Deficiency Syndrome
AHR	Adjusted Hazard ratio
ART	Anti-Retroviral Therapy
BMI	Body Mass Index
CD4	Cluster of differentiation4
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
KM	Kaplan Meier
PLHIV	People living with HIV
SNNPRS	South Nation Nationalities People Regional States
TB	Tuberculosis
WHO	World Health Organization

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37420.

References

[1] World Health Organization, Annual report of tuberculosis, Annual Global TB Report of WHO. 8 (2022) 1–68.
[2] E. Letang, J. Ellis, K. Naidoo, E.C. Casas, P. Sánchez, R. Hassan-Moosa, et al., Tuberculosis-HIV Co-infection: progress and challenges after two decades of global antiretroviral treatment roll-out, Arch. Bronconeumol. 56 (7) (2020) 446–454.
[3] World Health Organization, Global Tuberculosis Report, Blood, Geneva, 2023.
[4] D. Maji, U. Agarwal, L. Kumar, V Vinay ShA, Clinicodemographic Profile and Outcome of Tuberculosis Treatment in TB-HIV Coinfected Patients Receiving Daily ATT under a Singlewindow TB/HIV Services Delivery Initiative, 2022.

[5] Joint United Nations Programme on HIV/AIDS (UNAIDS), IN danger: UNAIDS global AIDS update 2022, DANGER UNAIDS Glob AIDS Updat 2022 2022 (2022) 1–22, 2022.
[6] WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and Multidrug/rifampicin-Resistant TB (MDR/RR-TB), 2021–2025: Background Document, 2021. Licence: CC BY-NC-SA 3.0 IGO. ISBN 978-92-4-002943-9 (electronic version) and ISBN 978-92-4-002944-6 (print version). Geneva.
[7] G.H. Shah, R. Ewetola, G. Etheredge, L. Maluantesa, K. Waterfield, E. Engetele, et al., Risk factors for tb/hiv coinfection and consequences for patient outcomes: evidence from 241 clinics in the Democratic republic of Congo, Int. J. Environ. Res. Publ. Health 18 (10) (2021).
[8] World Health Organization, ONU, World Health Organization, Global tuberculosis report 2021, in: Syria Studies, vol. 7, World Health Organization, Geneva, 2021.
[9] FMoH, HIV/AIDS national strategic plan for Ethiopia 2021-2025, Fed Minist Heal Ethiop (2021) 71472 c.
[10] Ministry of Health FDR of E, National Guidelines for Comprehensive HIV Prevention , Care and Treatment, 2017.
[11] K.A. Alene, A. Elagali, D.D. Barth, S.F. Rumisha, P. Amratia, D.J. Weiss, et al., Spatial codistribution of HIV, tuberculosis and malaria in Ethiopia, BMJ Glob. Health 7 (2) (2022).
[12] Mamo Ayana Galana, Yihunie Akalu Temesgen, T.A. Ayele, Joint modeling of incidence of tuberculosis andChange in viral load over time among adult HIV/AIDS patients on anti-retroviral therapy at zewditu memorial hospital in Addis Ababa, Ethiopia, HIV AIDS Res. Palliat. Care 13 (2021) 239–249.
[13] M.E. Lelisho, T.W. Wotale, S.A. Tareke, B.D. Alemu, S.S. Hassen, D.M. Yemane, et al., Survival rate and predictors of mortality among TB/HIV co-infected adult patients: retrospective cohort study, Sci. Rep. 12 (1) (2022) 18360, 20221101st ed.
[14] J. Gemechu, B. Gebremichael, T. Tesfaye, A. Seyum, D. Erkalo, Predictors of mortality among TB-HIV co-infected children attending anti-retroviral therapy clinics of selected public hospitals in southern, Ethiopia: retrospective cohort study, Arch. Publ. Health 80 (1) (2022).
[15] W. Wondimu, L. Dube, T. Kabeta, Factors affecting survival rates among adult TB/HIV Co-infected patients in mizan Tepi university teaching hospital, south west Ethiopia, HIV AIDS 12 (2020) 157–164, 20200423rd ed.
[16] A. Mohammedseid, T. Simeneh, T. Molla, Survival analysis and predictors of mortality among adult HIV/AIDS patients initiated antiretroviral therapy from 2010 to 2015 in Dubti General Hospital , Afar , Ethiopia : a retrospective cohort study, Heliyon 9 (1) (2023) e12840.
[17] I. Ismail, A. Bulgiba, Predictors of death during tuberculosis treatment in TB/HIV Co-infected patients in Malaysia 8 (8) (2013) 1–7.
[18] PV. de S. Viana, N.S. Paiva, D.A.M. Villela, L.S. Bastos, AL. de S. Bierrenbach, P.C. Basta, Factors associated with death in patients with tuberculosis in Brazil: competing risks analysis, PLoS One 15 (10 October) (2020) 1–16.
[19] E.M. Bukundi, F. Mhimbira, R. Kishimba, Z. Kondo, C. Moshiro, Mortality and associated factors among adult patients on tuberculosis treatment in Tanzania: a retrospective cohort study, J Clin Tuberc Other Mycobact Dis 24 (2021) 100263.
[20] N. Yang, J. He, J. Li, Y. Zhong, Y. Song, C. Chen, Predictors of death among TB/HIV co-infected patients on tuberculosis treatment in Sichuan, China: a retrospective cohort study, Méd. 102 (5) (2023) E32811.
[21] A.S. Tegegne, M.T. Minwagaw, M.T.M. Awoke Seyoum Tegegne, Risk factors for the development of tuberculosis among HIV-positive adults under highly active antiretroviral therapy at government hospitals in amhara region, Ethiopia, Int. J. Gen. Med. 15 (2022) 3031.
[22] A. Getu, H.F. Wolde, Y. Animut, A.A. Kibret, 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 17 (8 August) (2022) 1–13.
[23] Y. Getaneh, F. Ning, Q. He, A. Rashid, D. Kassa, Y. Assefa, et al., Survival and predictors of mortality among adults initiating highly active antiretroviral therapy in Ethiopia: a retrospective cohort study (2007-2019), BioMed Res. Int. 2022 (2022).
[24] M.A. Assemie, M. Alene, D.B. Ketema, S. Mulatu, Treatment failure and associated factors among first line patients on highly active antiretroviral therapy in Ethiopia: a systematic review and meta-analysis 4 (1) (2019) 1–10.
[25] K.L. Workie, T.Y. Birhan, D.A. Angaw, Predictors of mortality rate among adult HIV - positive patients on antiretroviral therapy in Metema Hospital , Northwest Ethiopia : a retrospective follow - up study, AIDS Res. Ther. (2021) 1–11.
[26] T. Tewabe, G. Zeleke, A. Mohammed, Journal of Infectious Diseases & Determinants for Tuberculosis in HIV Infected Patients in Debre Birhan Town, vol. 10, 2022, pp. 1–10. Amhara National Regional State , Ethiopia.