

Incidence and Determinants of Active Tuberculosis in HIV-Positive Patients on Second-Line ART in Addis Ababa, Ethiopia: A Five-Year Retrospective Study

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Abstract

Background: Tuberculosis (TB) remains a major cause of morbidity and mortality among people living with HIV (PLHIV), particularly in sub-Saharan Africa like Ethiopia. Although second-line antiretroviral therapy (ART) improves survival among patients with treatment failure, evidence on the incidence and predictors of TB in this population is limited.

Objectives: To assess the incidence and determinants of active TB in HIV-positive patients on second-line ART over a five-year period at Yekatit 12 Hospital Medical College.

Methods: An institution-based retrospective cohort study was conducted among 350 HIV-infected patients receiving second-line ART from January 1, 2021 to December 31, 2025. Data was collected from patients' medical records using Kobo-tool and exported to SPSS Version 25 and Stata 17 for analysis. Patients were followed for a total of 18,162 person-months (approximately 1,513 person-years). Cox proportional hazard regression model used to identify factors associated with active TB, and adjusted hazard ratios (AHR) with 95% confidence intervals (CI) were reported.

Results: During the follow-up period, 17 (4.9%) HIV-positive patients on second-line ART developed active tuberculosis. The overall incidence rate was 0.94 per 1,000 person-months, equivalent to 1.13 per 100 person-years (95% CI: 0.58–1.51). In multivariable Cox regression analysis, advanced WHO clinical stage (III–IV) was significantly associated with increased risk of tuberculosis (AHR = 9.13, 95% CI: 1.78–46.80). ART adherence showed a strong dose–response relationship, with fair adherence (AHR = 7.17, 95% CI: 1.83–28.07) and poor adherence (AHR = 13.06, 95% CI: 3.26–57.29) significantly increasing TB risk compared to good adherence. Additionally, patients with BMI <18.5 kg/m² had higher hazard of developing tuberculosis (AHR = 4.31, 95% CI: 1.14–16.43).

Conclusion: The incidence of tuberculosis among patients on second-line ART was moderate but persistent. Advanced HIV clinical stage, poor ART adherence, and undernutrition were the main predictors. Strengthening early clinical management, adherence support, and nutritional intervention is essential to further reduce tuberculosis burden among second-line ART patients.

Background

Tuberculosis is an infectious disease caused by an organism called Mycobacterium Tuberculosis Complex (MTBC), a rod-shaped bacillus that are known to cause TB disease in humans [1]. It is among the major disease burdens worldwide. According to the world health organization (WHO) report published in 2024, about one fourth of the world's population was estimated to have been infected with the tuberculosis (TB) bacilli, and about 5–10% of those infected develop TB disease in their lifetime, usually within 5 years of the initial infection [1]. 10.6 million People are estimated to have fallen ill with TB in 2022 and 1.3 million deaths due to TB were reported in the same year [2].

Africa is the second TB burden region (25%) next to south-east Asia (44%). However, the incidence of TB among patients living with HIV is highest in Africa region [3]. In sub-Saharan Africa, approximately 10%–15% of the population is affected by the twin epidemic, with a 51% case fatality rate and higher lifetime risk compared to those without TB and HIV [4]. Ethiopia is among the 30 High TB and HIV Burden Countries, with annual

estimated TB incidence of 126/100,000 populations and death rate of 17 per 100,000 populations for 2022 [2]. TB-associated mortality varied by region, with 23.01 cases per 100 person-years in Tigray for adults [5] and 17.15 cases per 100 person-years for children in Southern Nations, Nationalities, and Peoples' Region (SNNPR) [6].

Despite the availability of preventive measures and effective treatment, TB remains a leading cause of death and had likely replaced coronavirus disease (COVID-19) as the leading cause of infectious-disease-related mortality worldwide following the COVID-19 pandemic [7].

Widespread use of anti-retroviral therapy (ART) has significantly reduced the incidence of TB among people living with HIV (PLHIV). However, the burden remains high in this population with prevalence ranging from 3 to 72% in high burden settings [8]. While first-line ART regimens containing a non-nucleotide reverse transcriptase inhibitor (NNRTI) have significantly reduced the burden of AIDS and non-AIDS defining events, treatment failure can occur in nearly 20% of patients, requiring a switch to a second line protease inhibitor (PI)-based regimen [9].

Furthermore, immune recovery achieved through ART alone may not fully eliminate TB risk in the absence of preventive therapy, particularly in regions with high background TB transmission [10]. The coexistence of TB and HIV accelerates disease progression, weakens immunity, and complicates treatment outcomes [11]. Evidence suggests that the incidence of TB is higher among patients transitioning to second-line regimens following first-line ART failure compared to those with sustained viral suppression [12].

Although ART significantly reduced TB risk, this protective effect appeared to diminish among individuals who failed first-line ART and required second-line regimens [13]. The immunological and virologic challenges of managing second-line ART patients increase their susceptibility to opportunistic infections, including TB, mainly due to delayed switching to second-line ART after treatment failure diagnosis [14].

Virologic failure in patients on first-line ART often results in delayed immune recovery and prolonged periods of vulnerability to TB [15]. In many resource-limited settings, the delay in recognizing and addressing first-line treatment failure contributes to the increased TB burden among those on second-line ART [16]. Furthermore, even after switching, viral suppression and immune reconstitution are not always achieved, placing patients at continued risk [17].

The use of tuberculosis preventive therapy (TPT) has been shown to reduce TB incidence among PLHIV; however, its uptake is suboptimal in many HIV care programs, including those in Ethiopia [18]. A study conducted in Debre Berhan reported that a significant proportion of HIV patients did not complete TB preventive therapy, contributing to the high incidence of TB in this group [19].

Although second-line ART is associated with improved virologic outcomes [17, 21], TB incidence in this subgroup remains unacceptably high. Most national studies in Ethiopia have focused on TB incidence among first-line ART users [12, 22, 24], leaving a critical evidence gap regarding second-line ART users. Only one multicenter study from North Wollo has explored TB incidence in patients with first-line ART failure [25].

National TB/HIV programs do not adequately address the specific needs of second-line ART users, a high-risk group often overlooked in surveillance and intervention strategies [16]. The lack of data on TB burden and its predictors among this population limits the ability to design targeted preventive and clinical responses.

This study addresses a critical gap in the literature by focusing specifically on the incidence and predictors of TB among HIV-positive patients on second-line ART in Ethiopian clinical setting.

Methods and Materials

Study setting, design and Period

A 5-year retrospective cohort study was conducted to assess the incidence and identify determinants of active tuberculosis among HIV-positive patients on second-line antiretroviral therapy (ART) at Yekatit 12 Hospital Medical College.

This study was conducted at Yekatit 12 Hospital Medical College, a teaching hospital located in Addis Ababa, the capital city of Ethiopia, which is one of the biggest public referral hospitals in Addis Ababa with high inpatient and outpatient flow and it is giving both clinical and academic services. The hospital has several departments including the four major departments. Each department has emergency, inpatient and outpatient units. The internal medicine department has a medical emergency department, general medical wards, an isolation ward, medical referral follow up clinics and a medical ICU. The hospital provides a full range of HIV-related services, including HIV testing and counseling, ART, TB screening and treatment and follow-up care for PLHIV. The hospital has a dedicated ART clinic staffed with trained physicians and nurses. Second-line ART services have been implemented at Yekatit 12 Medical College for many years.

The data collection was conducted from December, 2025 to January, 2026 and the medical record review included patient data from a five-year period.

Population, sample size, and study variables

The source population consisted of all adult HIV-positive patients (aged 18 years and above) who have been enrolled on second-line antiretroviral therapy at Yekatit 12 hospital medical college.

The study population included all HIV-positive adult patients (aged ≥ 18 years) who initiated second-line antiretroviral therapy at Yekatit 12 Hospital Medical College from January 1, 2021, to December 31, 2025 and who had at least follow-up visit for 3 months during study period.

Patients receiving anti-TB medication at the start of the follow-up period, transferred-in patients without prior second-line ART initiation documents to Yekatit 12 hospital medical college and patients diagnosed with multidrug-resistant tuberculosis were excluded.

Since the study assessed the incidence and determinants of active tuberculosis (TB) among HIV-positive patients on second-line antiretroviral therapy over a five-year period, the sample size was determined based on the total number of eligible patients available at Yekatit 12 Hospital Medical College during the study period.

A total of 380 patients were on second-line ART during the follow-up period. Given this manageable population size and the retrospective nature of the study, a non-probable convenient sampling method was used, including all 350 patients who fulfilled the eligibility criteria

Dependent Variable

The **outcome of interest** was development of Active Tuberculosis during the follow up period.

Independent Variables

The **potential predictor variables** considered for the development of active tuberculosis (TB) were categorized into five domains: socio-demographic, clinical, treatment-related, laboratory-associated, and behavioral and nutritional factors.

Socio demographic

age, sex, marital status, educational level

Clinical factors

WHO clinical stage at second-line ART initiation, CD4 count, presence of comorbidities, history of previous TB, opportunistic infections (OI) other than TB

Treatment-related factors

adherence level, use of IPT, reason for switching to second-line ART, duration of second-line ART

Laboratory associated factors

hemoglobin, platelet, cholesterol

Behavioral and nutritional factors

smoking, alcohol use, body mass index (BMI).

Data collection procedure and data quality

Structured questionnaire was used to collect the data. The questionnaire was developed based on existing literatures and national HIV/TB monitoring guidelines. Data were retrieved from the patient charts and electronic medical records by two trained general practitioners. The data collectors received two days of training prior to data collection. The principal investigator closely supervised the data collection process and reviewed completed tools daily for completeness and consistency.

To ensure record completeness, each patient chart was reviewed before inclusion. Only records containing essential baseline and follow-up information, including ART initiation date, CD4 count, TB status, and follow-up visits were included in the final dataset. Records missing critical outcome or predictor variables were excluded.

The questionnaire was pretested on 5% of the sample size in a similar follow up clinic. Data quality was ensured through daily supervision and regular meetings between the principal investigator and data collectors to identify and correct inconsistencies.

Data analysis and statistics

Data were collected using KoboToolbox, and the completed datasets were exported to SPSS version 25 and STATA version 17 for data cleaning and analysis. Data cleaning was performed to check for completeness, consistency and missing values before analysis. Descriptive statistics were used to summarize sociodemographic, clinical and laboratory, and treatment-related characteristics of the study participants.

The incidence rate of active tuberculosis was calculated using person-years of observation. Time-to-event data were analyzed using Cox proportional hazards regression

Bivariable cox regression analysis was conducted, and variables with a p-value ≤ 0.25 were entered into the multivariable Cox regression model to identify independent predictors of active tuberculosis. Adjusted hazard ratios (AHRs) with 95% confidence intervals were reported and statistical significance was declared at $p < 0.05$

Records with missing key variables (e.g., TB status, CD4 count, IPT use) were excluded list wise deletion.

Operational Definitions

Active Tuberculosis

A diagnosis of tuberculosis (pulmonary or extra-pulmonary) confirmed by bacteriological evidence (e.g., GeneXpert, AFB smear, or culture) or diagnosed clinically by a physician and initiated on anti-TB treatment during the follow-up period [1, 2].

Adherence to ART

Measured by pill count [39].

Good: $\geq 95\%$

Fair: 85–94%

Poor: $< 85\%$

For a patient on a once-daily regimen (30 doses /month):

Missed ≤ 2 dose = Good

Missed 3–4 doses = Fair

Missed ≥ 5 doses = Poor

For twice-daily regimens (60 doses /month):

≤ 3 missed = Good

4–9 missed = Fair

> 9 missed = Poor

Time to active Tuberculosis

Defined as the time (in months) from start of follow-up (January 1, 2021) until the diagnosis of active tuberculosis, censoring, or end of follow-up (December 31, 2025), whichever occurred first [2].

Treatment failure

Two consecutive viral load measurements within a 3-month interval with adherence support between measurements are greater than 1000 copies/ml [2].

Ethical consideration and dissemination

Ethical clearance and approval were obtained from the Institutional Review Board of Yekatit 12 Hospital Medical College before data collection (Y12HMC/IRB/175/25).

The findings will be presented to Yekatit 12 Hospital Medical College, Addis Ababa Health Bureau and MOH

- National HIV program
- The manuscript will be submitted for publication in a peer-reviewed medical journal.
- Abstracts will be presented at national or international conferences.

Results

Presentation of Sociodemographic characteristics

A total of 350 patients receiving second line ART were included for analysis. The median age of participants was 40 years (SD ±13.2), and 127 (36.3%) participants were younger than 35 years, 195 (55.7%) were between 35 and 54 years, and 28 (8.0%) were 55 years or older. Females constituted the majority of the participants 196(56%). The majority of cases were from Addis Ababa 333(95%). The largest proportion had completed secondary education 120(34.3%). (Table 1).

Table 1: Socio-demographic characteristics of HIV-infected individuals who were on second line ART in Yekatit 12 HMC, Addis Ababa, Ethiopia, 2026.

Variables	Variable category	Frequency	Percentage (%)
Age in years	18- 35	127	36.3
	36-54	195	55.7
	>54	28	8
Sex	Male	154	44
	Female	196	56
Maritalstatus	Single	122	34.9
	Married	112	32
	Divorced	69	19.7
	Widowed	47	13.4
Educational status	No education	54	15.4
	Primary	101	28.9
	Secondary	120	34.3
	Tertiary	64	18.3
	Not documented	11	3.1
Residence	Addis Ababa	333	95.1
	Out of Addis Ababa	17	4.9
BMI	Underweight	34	9.7
	Normal	282	80.6
	Overweight	34	9.7

Baseline clinical and laboratory investigations of the patients

At baseline 52.5% (184/350) of patients were in WHO clinical stage I or II, while 161(46.0%) were in stage III or IV; WHO clinical stage was unknown for 5(1.4%) of participants. Similarly, 160(45.7%) of patients had a CD4 count of <200 cells/mm³, while 54.3% had a CD4 count of ≥200 cells/mm³.

Nearly one-third of the participants **30.3%** (106/350) had a **previous history of tuberculosis** before the study period (before January 2021) either while on first-line or second-line ART.

In terms of comorbid conditions, the majority of patients had **no documented comorbidity** (84.9%). Among those with comorbidities, **hypertension** (8.6%) and **diabetes mellitus** (6.0%) were the most common, while chronic kidney disease (0.9%), mental illness (0.9%), and other comorbid conditions (2.0%) were less frequent (Table 2).

Baseline laboratory investigations showed that **46.0%** of patients had **normal hemoglobin levels**, while **24.9%** had **mild anemia**. Most participants had a **normal platelet count** (61.7%), and only **6.0%** had a low platelet count.

Among patients with documented information, the majority were **non-alcohol users** (86.9%) and **non-smokers** (88.6%). Only **4.9%** reported alcohol use and **1.4%** reported cigarette smoking.

Table 2: Baseline clinical and laboratory investigations of HIV-infected individuals who were on second line ART in Yekatit 12 HMC, Addis Ababa, Ethiopia, 2026.

Variables	Variable category	Frequency	Percentage (%)
WHO clinical stage	T1	130	37.1
	T2	54	15.4
	T3	117	33.4
	T4	44	12.6
	Unknown	5	1.4
Baseline CD4	<200	160	45.7
	200-500	148	42.3
	>500	18	5.1
	Not documented	24	6.9
History of TB before follow-up time	Yes	106	30.3
	No	244	69.7
Comorbidity history	No comorbidity	297	84.9
	Hypertension	30	8.6
	DM	21	6
	CKD	3	0.9
	Mental health	3	0.9
	Other	7	2
Hemoglobin	Normal	161	46
	Mild	87	24.9
	Sever	1	0.3
	Not documented	101	28.9
Platelet	Normal	216	61.7
	Low	21	6
	Not documented	113	32.3
Alcohol	No	304	86.9
	Yes	17	4.9
	Not documented	29	8.3

Smoking			
	No	310	88.6
	Yes	5	1.4
	Not documented	35	10

Treatment and follow-up

Mean follow-up time (censoring time or time to diagnosis of active tuberculosis) was 51.9 months (SD $\pm$ 11.4), with a median of 60 months.

Nearly 314 (90%) of the patients demonstrated good ART adherence. The majority of the study population had been on second-line antiretroviral therapy for 5–10 years 317(90.6%). Most 326(93.1%) patients were receiving a protease inhibitor-based regimen. Regarding virologic status, 312(89.1%) had a non-detectable viral load at their most recent measurement. Tuberculosis preventive therapy (TPT) was administered to 333(95%) of patients and among those who initiated TPT 328(93%) completed the full course (Table 3).

Table 3: Treatment and follow-up of HIV-infected individuals who were on second line ART in Yekatit 12 HMC, Addis Ababa, Ethiopia, 2026.

Variables	Variable category	Frequency	Percentage (%)
Follow-up time	Censoring time or time to diagnosis of active TB, mean +SD	51.90 ± 11.416	
Adherence status	Good	314	89.7
	Fair	20	5.7
	Poor	16	4.6
Duration on second-line ART	<1	1	0.3
	1-5	15	4.3
	5-10	317	90.6
	>10	17	4.9
Regimen type	PI-based	326	93.1
	INST/InSTI based	24	6.9
Last CD4	<200	3	0.9
	>200	13	3.7
	Not done	334	95.4
Last viral load	Low viremia	21	6
	Not detected	312	89.1
	Unsuppressed	17	4.9
TPT received	Yes	333	95.1
	No	9	2.6
	Unknown	8	2.3
TPT completion status	Completed	328	93.7
	Not completed	1	0.3
	Not recorded	4	1.1

TB outcome

Out of 350 HIV-positive patients on second-line ART followed for a total of 18,162 person-months (1,513 person-years). During the observation period, 17(4.9%) patients developed active tuberculosis (Fig 1). Resulting in an incidence density rate of 0.94 per 1,000 person-months with a 95% confidence interval of (0.58 -1.51), equivalent to 1.13 per 100 person-years. Among the 17 patients who developed tuberculosis, the majority 9(52.9%) had pulmonary tuberculosis and TB was diagnosed using molecular methods (Urine LAM and GeneXpert) in 6(35.3%) of patients. At the time of TB diagnosis, viral load was not detected in 12(70.6 %) of patients, while 5(29.4%) had low viremia (Table 4).

Table 4: Tuberculosis-related characteristics among Second-Line ART Patients with TB (n = 17) at Yekatit 12 HMC, Addis Ababa, Ethiopia,2026.

Variables	Variable category	Frequency	Percentage (%)
Active TB	Yes	17	4.9
	No	333	95.1
Type of TB	Pulmonary	9	52.9
	Extra-pulmonary	5	29.4
	Disseminated	1	5.9
	Not documented	2	11.8
Method of diagnosis	Clinical and radiological	5	29.4
	Histopathology	1	5.9
	Molecular	6	35.3
	Not documented	5	29.4
Viral load at the time of TB diagnosis	Not detected	12	70.6
	Low viremia	5	29.4
	Unsuppressed	0	
Final patient outcome	Improved	17	100
	Transferred-out	0	
	Died	0	

Factors associated with TB incidence for second-line treatment cases

In the bivariable Cox regression analysis, several factors were associated with the hazard of developing active tuberculosis among HIV-infected patients on second-line ART. Patients with advanced WHO clinical stage (III–IV) had a significantly higher hazard of developing tuberculosis compared to those in early stage (I–II) (CHR = 8.41, 95% CI: 1.92–36.79, $p = 0.01$).

Body mass index (BMI) was also associated with tuberculosis incidence. Underweight patients had 3.35 times higher hazard of developing active tuberculosis compared to patients with normal BMI (CHR = 3.35, 95% CI: 1.07–10.53, $p = 0.04$). ART adherence demonstrated a strong dose–response relationship. Patients with fair adherence had 8.75 times higher hazard, while those with poor adherence had 13.35 times higher hazard of developing tuberculosis compared to patients with good adherence ($p < 0.001$ for both).

In the multivariable cox regression analysis, advanced WHO clinical stage (III–IV) remained an independent predictor of active tuberculosis with patients in advanced stage having a significantly higher hazard compared to those in early stage (AHR = 9.13, 95% CI: 1.78–46.80, $p = 0.01$). Patients with both fair adherence (AHR = 7.17, 95% CI: 1.83–28.07) and poor adherence (AHR = 13.06, 95% CI: 3.26–57.29) had significantly higher hazards compared to those with good adherence ($p < 0.01$). In addition, patients with BMI $< 18.5 \text{ kg/m}^2$ had a higher hazard of developing tuberculosis compared to those with normal BMI (AHR = 4.31, 95% CI: 1.14–16.43, $p = 0.03$). Other variables included in the model were not significantly associated with tuberculosis incidence after adjustment (Table 5).

Table 5: Bi-variable and multivariable Cox-regression for determinants of active tuberculosis in those who were on second-line treatment in Yekatit 12 HMC, Addis Ababa, Ethiopia, 2026.

Variables	Variable category	Bi-variable analysis	Multivariable analysis	
		CHR (95% CI)	AHR (95% CI)	P-Value
Age in years()	18- 35			
	35-54	0.92(0.10-8.26)	3.41(0.56-20.68)	0.18
	>54	1.79(0.23 – 13.77)	0.79(0.38-16.54)	0.88
Sex	Male			
	Female	2.3(0.85-6.22)	0.57(0.15-2.19)	0.41
Maritalstatus	Single			
	Married	0.65(0.16-2.71)	1.36(0.23-8.08)	0.73
	Divorced	0.85(0.21-3.39)	0.94(0.10-8.46)	0.95
	Widowed	0.69(0.14-3.43)	2.30(0.29-18.12)	0.43
Educational status	Formal education			
	No formal education	1.75(0.56-5.41)	3.90(0.91-16.75)	0.07
Residency	Addis Ababa			
	Out of Addis Ababa	21.73(0.00-326444)	.000	0.98
BMI	Normal			
	Underweight	3.35(1.07-10.53)	4.33(1.14-16.43)	0.03
	Overweight	1.51(0.34-6.83)	1.18(0.19-7.26)	0.86
Comorbidities	No			
	Yes	2.53(0.89-7.18)	2.73(0.79-9.43)	0.11
WHO Clinical stage	Early (Stage I-II)			
	Advanced (Stage III-IV)	8.41(1.92 – 36.79)	9.13(1.78-46.80)	0.01
Baseline CD4	< 200	2.80(0.88–8.92)		
	>200			
Previous TB hx	Yes	0.67(0.22–2.06)		
	No			
Adherence	Good			
	Fair	8.75(2.64–29.08)	7.17(1.83-28.07)	0.01
	Poor	13.38(4.37–40.94)	13.66(3.26-57.29)	<0.01
Regimen type	PI-based			
	INST/InSTI based (DTG)	3.47(1.00–12.09)	2.73(0.69-10.71)	0.15

TPT(	Yes	
	No	1.7(0.4-8.05)

CHR: Crude hazard ratio **AHR:** Adjusted hazard ratio **CI:** Confidence interval

Discussion

The main objective of this study was to determine the incidence and predictors of active tuberculosis among HIV-positive patients receiving second-line antiretroviral therapy at Yekatit 12 Hospital medical college. In this cohort of 350 patients followed for a total of 18,162 person-months, 17(4.9%) patients developed active tuberculosis, resulting in an incidence density rate of 0.94 per 1,000 person-months, equivalent to 1.13 per 100 person-years. This finding indicates that although the overall tuberculosis incidence among patients on second-line ART is relatively low, tuberculosis remains an important clinical problem in this population.

Comparing our finding from other similar studies on those second-line ART patients, the incidence observed in this study is higher than 0.39 per 100 person-years reported in Ethiopian cohorts but lower than 3.4 per 100 person-years observed in retrospective analysis of second-line clinical trial. A multicenter cohort study from North Wollo Zone reported low (0.39 cases per 100 person-years) but persistent incidence of active tuberculosis among ART-experienced patients, highlighting that second-line ART does not completely eliminate tuberculosis risk [23]. Likewise, a retrospective analysis of second-line clinical trial participants demonstrated that tuberculosis continues to occur despite virologic control and prolonged ART exposure with an incidence rate of 3.4 per 100 person-years [25]. The relatively lower incidence compared to earlier ART-era studies may be explained by improved HIV care, high viral suppression rates, and expanded use of tuberculosis preventive therapy (TPT), as recommended by WHO and national guidelines [1, 2].

Multivariable cox regression analysis identified advanced WHO clinical stage (III–IV), poor ART adherence and low body mass index as independent predictors of tuberculosis. Patients with advanced WHO clinical stage had a significantly (9.13 times) higher risk of developing tuberculosis compared to those in early stages (AHR = 9.13, 95% CI: 1.78–46.80, $p = 0.01$). This finding is consistent with multiple Ethiopian and international studies showing advanced HIV disease is strongly associated with increased tuberculosis risk due to severe immune compromise [22, 23, 25, 26]. Advanced clinical stage likely reflects cumulative immunologic damage that persists even after switching to second-line ART.

ART adherence showed a strong association with tuberculosis incidence among patients starting second-line ART treatment. Patients with fair (AHR = 7.17, 95% CI: 1.83–28.07) and poor (AHR = 13.06, 95% CI: 3.26–57.29) adherence had substantially higher hazards of developing tuberculosis compared to those with good adherence. This finding is in line with studies from Ethiopia and other settings demonstrating that suboptimal adherence leads to impaired immune recovery and increased susceptibility to opportunistic infections, including tuberculosis [25, 27, 28]. Adherence remains a critical and modifiable factor, particularly for patients on second-line regimens, which are often more complex and associated with higher pill burden.

Low BMI was also an independent predictor of tuberculosis in this cohort. Patients in this category had 4.3 times higher risk of developing tuberculosis compared to the reference group (AHR = 4.31, 95% CI: 1.14–16.43,

$p = 0.03$). Undernutrition is a well-established risk factor for tuberculosis and may indicate advanced disease, socioeconomic vulnerability, or chronic inflammation. Similar associations between low BMI and tuberculosis have been reported in several Ethiopian studies [22, 26, 29, 30]. This highlights the importance of integrating nutritional assessment and support into routine HIV care, especially for patients receiving second-line ART.

In this study, pulmonary tuberculosis was the most common form, accounting for more than half of all cases (52.9%). This pattern is consistent with reports from Ethiopia and other high TB-burden countries, where pulmonary disease remains the predominant presentation among people living with HIV [21, 22, 23, 26]. The use of molecular diagnostic methods in more than one-third of TB cases reflects improved access to modern diagnostic tools, which may contribute to earlier detection and better treatment outcomes [7]. Importantly, the majority of patients had undetectable viral load at the time of tuberculosis diagnosis, supporting evidence that tuberculosis can develop even in virologically suppressed patients, likely due to residual immune dysfunction or prior advanced disease [25, 31].

An additional important observation is that all patients who developed tuberculosis had improved treatment outcomes, with no recorded deaths. This favorable outcome may reflect early diagnosis, effective tuberculosis management, and strong linkage to HIV care services. However, it is important to note that this cohort included patients who were currently active in follow-up. Patients who died, transferred out, or were lost to follow-up may not have been fully represented, potentially underestimating mortality. Therefore, the absence of mortality in this study should be interpreted in the context of cohort selection and follow-up design.

Regarding tuberculosis preventive therapy (TPT) was not statistically significant in the bivariable model (AHR = 1.7, 95% CI: 0.4–8.05). The absence of statistical significance may be explained by the very high TPT coverage (95.1%), the small number of tuberculosis events, and limited statistical power. While previous studies and WHO recommendations demonstrate the protective effect of TPT [1, 2, 4, 18, 23]. This finding should therefore be interpreted cautiously.

Baseline CD4 count and previous history of tuberculosis were not independently associated with tuberculosis in the adjusted model. This may suggest that current clinical status and treatment adherence are more important determinants of tuberculosis risk among patients established on second-line ART than historical immunologic markers.

One of the main strengths of this study is the use of a five-year retrospective cohort design, which allowed calculation of tuberculosis incidence using person-time analysis. This provides a more accurate estimation of risk compared to cross-sectional studies. This makes the findings particularly important for program evaluation and clinical decision-making. Another strength is the use of Cox proportional hazards regression to identify independent predictors of tuberculosis. This method accounts for time-to-event data and controls for potential confounders, increasing the validity of the findings.

The study was conducted in a single tertiary hospital, which may limit the generalizability of the findings to other settings. Due to retrospective design, some important variables were not fully captured. The relatively small number of tuberculosis events (17 cases) may have reduced the statistical power to detect weaker associations.

Conclusion

In The incidence of active tuberculosis among HIV-positive patients on second-line ART in this study was 0.94 per 1,000 person-months (1.13 per 100 person-years), indicating that tuberculosis remains an important clinical problem even among ART-experienced patients. Advanced WHO clinical stage (III–IV), poor ART adherence, and low body mass index (BMI < 18.5 kg/m²) were identified as independent predictors of active tuberculosis. Patients with advanced disease stage had nearly nine times higher risk of developing tuberculosis. Similarly, patients with fair and poor adherence showed a markedly increased hazard, demonstrating a clear dose–response relationship. Undernourished patients were also at significantly higher risk. These findings highlight that advanced immunosuppression, suboptimal treatment adherence, and poor nutritional status are the main determinants of tuberculosis occurrence among patients receiving second-line ART in this setting.

Enhancing strategies focusing on early identification of treatment failure and timely initiation of ART to prevent progression to advanced WHO stages and strengthen adherence support interventions at programmatic level, including community-based follow-up and defaulter tracing systems and integrating nutritional support programs within HIV care services in line with national HIV/TB management guidelines are crucial. In addition, multicenter prospective studies with larger sample sizes are recommended to further assess long-term tuberculosis incidence among second-line ART patients.

Declarations

Ethical considerations and consent participation:

This study was approved by the ethical committee of Yekatit-12 Hospital Medical College and was conducted according to the declaration.

Consent for publication: Not applicable

Consent to participate declaration: Not Applicable

Availability of data and materials: Supporting data is available with the corresponding author and it will be accessible upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contribution:

AW involved in conceptualization, data curation, formal analysis, writing of original manuscript draft, reviewing, editing and validation; AS participated in conceptualization, data curation, methodology, analysis, reviewing and validation; AG: methodology, analysis, writing of original draft and reviewing; AZ: data curation, analysis, writing of original draft, reviewing and validation; SB: data curation, analysis, writing of original draft, reviewing and validation; YA: analysis, writing of original draft and validation; BB: data curation, methodology and analysis; MA: analysis, writing of original draft and validation; GM: data curation, analysis, writing of original draft and validation; KF: data curation, analysis, writing of original draft and validation; KY: analysis, writing of original draft and validation; ST: data curation, analysis, writing of original draft and validation; MM: Analysis and validation;

BA: conceptualization, data curation, formal analysis, writing, reviewing, editing of the manuscript and validation;

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Lists of Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV/r	Atazanavir/Ritonavir
BMI	Body Mass Index
CD4	Cluster of Differentiation 4 (T-helper cell)
CDC	Center for disease control
CPT	Cotrimoxazole Preventive Therapy
DNA	Deoxyribonucleic Acid
ETB	Ethiopian birr
FMOH	Federal Ministry of Health
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IU/MI	International Units per Milliliter
LPV/r	Lopinavir/Ritonavir

AIDS	Acquired Immune Deficiency Syndrome
LMIC	Low- and Middle-Income Countries
NNRTI	Non-nucleotide reverse transcriptase inhibitors
OI	Opportunistic Infection
PI	Protease inhibitors
PLHIV	People Living with HIV
RNA	Ribonucleic acid
SNNPR	South nation nationalities people region
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TPT	Tuberculosis Preventive Therapy
VL	Viral load
WHO	World Health Organization

References

1. WHO DR TB GUIDLINE. 2025. *Consolidated Guidelines on Tuberculosis Treatment*. 2025.
2. M. of Health. Training on Clinical and Programmatic Management of TB, TB / HIV, DR-TB, Leprosy and other Lung Diseases in Ethiopia Participants ' Manual. September. 2024: 1–313.
3. WHO. *Are Updated Every Year. for the Tuberculosis*. 2019.
4. Kebede F, Kebede B, Kebede T, Agmasu M. Effect of Isoniazid Preventive Therapy on the Incidence of Tuberculosis among Seropositive Children Attending HIV/AIDS Care in Two General Hospitals, Northwest Ethiopia. *J Trop Med*. 2021. 10.1155/2021/9996953.
5. Gezae KE, Abebe HT, Gebretsadik LG-E, Gebremeskel AK. Predictors of Accelerated Mortality of Tb/Hiv Co-Infected Patients on Art in Mekelle, Ethiopia: an 8 Years Retrospective Follow- Up Study. *Ann Biostat Biometric Appl*. 2019;3(5):2–6. 10.33552/abba.2019.03.000572.

6. Dawit Z, Abebe S, Dessu S, Mesele M, Sahile S, Ajema D. Incidence and predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus at public hospitals in Southern Ethiopia. *PLoS ONE*. 2021;16(6):1–14. 10.1371/journal.pone.0253449.
7. Tuberculosis G. Public announcement to TB in vitro diagnostics manufacturers, procurement agencies and national TB programmes on inclusion of WHO Prequalification for TB in vitro diagnostics. no. February. 2021.
8. Gao J, Zheng P, Fu H. Prevalence of TB/HIV Co-Infection in Countries Except China: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2013;8(5). 10.1371/journal.pone.0064915.
9. Campbell TB, Smeaton LM, Kumarasamy N, et al. Efficacy and Safety of Three Antiretroviral Regimens for Initial Treatment of HIV-1: A Randomized Clinical Trial in Diverse Multinational Settings. *PLoS Med*. 2012;9(8). 10.1371/journal.pmed.1001290.
10. Trajman A, Campbell JR, Kunor T, et al. Tuberculosis. *Tuberculosis. Lancet*. 2015;342(8872):677. 10.1383/medc.33.5.112.64954.
11. Tesfaye B, Alebel A, Gebrie A, Zegeye A, Tesema C, Kassie B. The twin epidemics: Prevalence of TB/HIV coinfection and its associated factors in Ethiopia; A systematic review and meta-analysis. *PLoS ONE*. 2018;13(10):1–18. 10.1371/journal.pone.0203986.
12. Kufa T, Mabuto T, Muchiri E, Charalambous S, Rosillon D, Churchyard G, Harris RC. Incidence of HIV-associated tuberculosis among individuals taking combination antiretroviral therapy: A systematic review and meta-analysis. *PLoS ONE*. 2014;9(11). 10.1371/journal.pone.0111209.
13. Pujades-Rodriguez M, Balkan S, Arnould L et al. Receiving Second-Line HIV Therapy in Resource-Limited Countries. 2016; 304(3): 303–12.
14. Ramadhani HO, et al. The effect of switching to second-line antiretroviral therapy on the risk of opportunistic infections among patients infected with human immunodeficiency virus in Northern Tanzania. *Open Forum Infect Dis*. 2016;3(1):1–7. 10.1093/ofid/ofw018.
15. Salvi S, et al. Virological failure among people living with HIV receiving second-line antiretroviral therapy in Pune, India. *BMC Infect Dis*. 2022;22(1):1–8. 10.1186/s12879-022-07894-2.
16. Kassie GA, Wolda GD, Woldegeorgis BZ, Gebrekidan AY, Haile KE, Meskele M, Asgedom YS. Second-line antiretroviral treatment failure and its predictors among patients with HIV in Ethiopia: A systematic review and metaanalysis. *PLOS Glob Public Heal*. 2024;4(4):1–18. 10.1371/journal.pgph.0003138.
17. Win MM, Maek-A-Nantawat W, Phonrat B, et al. Virologic and immunologic outcomes of the second-line regimens of antiretroviral therapy among HIV-infected patients in Thailand. *J Int Assoc Physicians AIDS Care*. 2011;10(1):57–63. 10.1177/1545109710387301.
18. Geremew D, Endalamaw A, Negash M, Eshetie S, Tessema B. The protective effect of isoniazid preventive therapy on tuberculosis incidence among HIV positive patients receiving ART in Ethiopian settings: A meta-analysis. *BMC Infect Dis*. 2019;19(1):1–9. 10.1186/s12879-019-4031-2.
19. Tegegnetwork AZ, Aemiro MT, Bilchut AH, et al. Completion of tuberculosis preventive therapy and associated factors among clients on antiretroviral therapy at Debre Berhan town health facilities, North Shoa Zone, Ethiopia. *AIDS Res Ther*. 2024;21(1):1–5. 10.1186/s12981-024-00629-0.
20. Fox MP, Ive P, Long L, et al. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. *J Acquir Immune Defic Syndr*. 2010;53(4):500–6. 10.1097/QAI.0b013e3181bcdac1.

21. Kassa A, Teka A, Shewaamare A, Jerene D. Incidence of tuberculosis and early mortality in a large cohort of HIV infected patients receiving antiretroviral therapy in a tertiary hospital in Addis Ababa, Ethiopia. *Trans R Soc Trop Med Hyg.* 2012;106(6):363–70. 10.1016/j.trstmh.2012.03.002.
22. Alemu A, Yesuf A, Zerihun B, et al. Incidence and determinants of tuberculosis among HIV-positive individuals in Addis Ababa, Ethiopia: A retrospective cohort study. *Int J Infect Dis.* 2020;95:59–66. 10.1016/j.ijid.2020.02.053.
23. Bizuneh FK, Masresha SA, Yayeh BM, Bizuneh TK. Active tuberculosis incidence among treatment failure experienced patients in North Wollo Zone: A multicenter historical cohort. *Heal Sci Rep.* 2024;7(4). 10.1002/hsr2.
24. FMOH. National consolidated guidelines for comprehensive HIV prevention, care and treatment. Addis Ababa: Federal Ministry of Health; 2018. p. 231.
25. Henry RT et al. Factors Associated With and Characteristic of HIV/Tuberculosis Co-Infection: A Retrospective Analysis of SECOND-LINE Clinical Trial Participants. *JAIDS J. Acquir. Immune Defic. Syndr.* 2021; vol. 87, no. 1, [Online]. Available: https://journals.lww.com/jaids/fulltext/2021/05010/factors_associated_with_and_characteristic_of.13.aspx
26. Alene KA, Nega A, Taye BW. Incidence and predictors of tuberculosis among adult people living with human immunodeficiency virus at the University of Gondar Referral Hospital, Northwest Ethiopia. *BMC Infect Dis.* 2013;13(1). 10.1186/1471-2334-13-292.
27. Angelo AT, Alemayehu DS. Adherence and its associated factors among adult hiv-infected patients on antiretroviral therapy in South Western Ethiopia, 2020. *Patient Prefer Adherence.* 2021;15:299–308. 10.2147/PPA.S298594.
28. Tekle A, Tsegaye A, Ketema T. Adherence to Anti-Retroviral Therapy (ART) and Its Determinants Among People Living with HIV/ AIDS at Bonga, Kaffa, South-West Ethiopia. *Patient Prefer Adherence.* 2024;18:543–54. 10.2147/PPA.S445164.
29. Kiros T, et al. Magnitude and associated factors of pulmonary tuberculosis among hiv/aids patients attending antiretroviral therapy clinic at debre tabor specialized hospital, northwest ethiopia, 2019. *HIV/AIDS - Res Palliat Care.* 2020;12:849–58. 10.2147/HIV.S282616.
30. Asefa A, Bolka H, Woldesemayat EM. Determinants of tuberculosis among adult people living with HIV on antiretroviral therapy at public hospitals in Hawassa City, South Ethiopia. *Front Epidemiol.* 2024;4:1–7. 10.3389/fepid.2024.1353760.
31. Dravid A, et al. Incidence of tuberculosis among HIV infected individuals on long term antiretroviral therapy in private healthcare sector in Pune, Western India. *BMC Infect Dis.* 2019;19(1):1–12. 10.1186/s12879-019-4361-0.

Figures

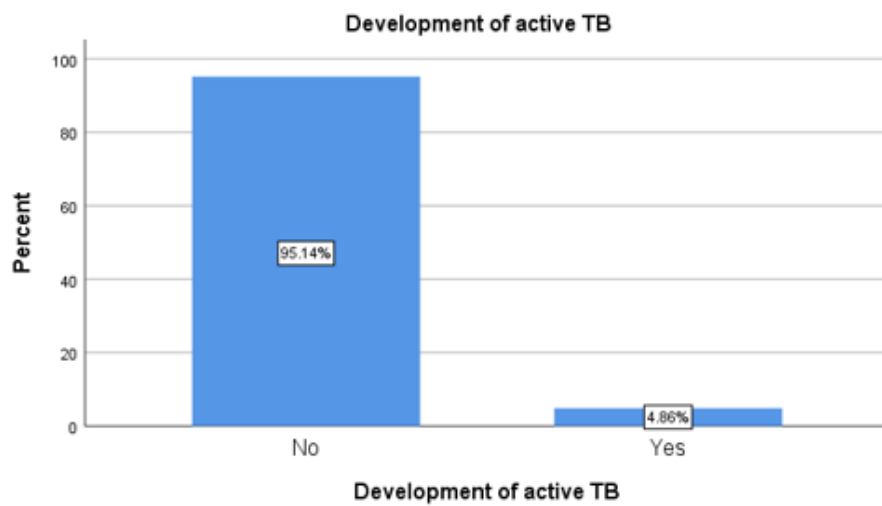


Figure 1

Patients who developed active TB during follow-up period