

# Risk Factors for Tuberculosis Co-infection in People Living with HIV: A Single-center Retrospective Cross-sectional Study

## HIV'le Yaşayan Bireylerde Tüberküloz Ko-enfeksiyonu için Risk Faktörleri: Tek Merkezli Retrospektif Kesitsel Bir Çalışma

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**Cite as:** Akbulut İ, Ödemiş İ, Öz ED, Demirci F, Atalay S. Risk Factors for Tuberculosis Co-infection in People Living with HIV: A Single-center Retrospective Cross-sectional Study. Anatol J Gen Med Res. 2024;34(2):194-200

### Abstract

**Objective:** Tuberculosis (TB) remains a leading cause of morbidity and mortality among people living with HIV (PWH). The coexistence of HIV and TB mutually enhances their pathogenicity and disrupts immunological functions. This study aims to analyze the biopsychosocial risk factors predicting HIV-TB co-infection in our center.

**Methods:** A retrospective cross-sectional cohort study was conducted using the records of PWH followed between 2019 and 2022 at the Infectious Diseases and Clinical Microbiology Clinic of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. Logistic regression analysis was employed to examine factors influencing the development of TB. Results were considered statistically significant when the p-value was less than 0.05.

**Results:** Among the 73 individuals living with HIV in the study, 22 (30.1%) had TB co-infection, with a median age of 40 years (32-50). Multivariate logistic regression analysis identified baseline BMI and the number of people living in the household as independent risk factors for TB co-infection in PWH. Each increase in baseline BMI was associated with a 0.73-times reduced risk of developing TB (0.57-0.94, p=0.016), while each additional person in the household increased the risk of TB co-infection by 1.16 times (1.00-1.35, p=0.047).

**Conclusion:** TB is influenced by various social factors, and this study demonstrates that PWHs with specific characteristics are at a higher risk of TB co-infection. Therefore, multicenter studies are needed to identify the risk factors predicting HIV-TB co-infection.

**Keywords:** HIV, co-infection, risk factors, tuberculosis

### Öz

**Amaç:** Tüberküloz (TB), HIV ile yaşayan bireyler (PWH) arasında morbidite ve mortalitenin önde gelen nedenlerinden biridir. HIV ve TB birlikteliği birbirlerinin patojenitesini güçlendirir ve immünolojik fonksiyonları bozar. Bu çalışmanın amacı, merkezimizde HIV+TB birlikteliğini öngören biyopsikososyal risk faktörlerini analiz etmektir.

**Yöntem:** Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'nde 2019-2022 arasında takipli PWH'lerin kayıtları kullanılarak kesitsel retrospektif bir kohort çalışması yürüttük. TB gelişmesine etki eden risk faktörlerinin incelenmesinde de lojistik regresyon analizi kullanıldı. Sonuçlar, p-değerinin 0,05'ten küçük olduğunda istatistiksel olarak anlamlı kabul edildi.



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**Received/Geliş tarihi:** 06.02.2024  
**Accepted/Kabul tarihi:** 27.02.2024



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## Öz

**Bulgular:** Çalışmadaki 73 HIV'le yaşayan bireyin 22'sinde (%30,1) TB birlikteliği mevcut olup yaş medyanı 40 (32-50) idi. Çok değişkenli lojistik regresyon analizinde başlangıç vücut kitle indeksi (VKİ) ve evde yaşayan kişi sayısının PWH'de TB ko-enfeksiyonu açısından bağımsız risk faktörleri olduğu belirlenmiştir. Başlangıç VKİ değerindeki her bir artışın 0,73 kat TB gelişmesini azalttığı görüldürken (0,57-0,94, p=0,016), evde yaşayan kişi sayısındaki her bir kişilik artış TB gelişmesini 1,16 kat artırdığı görülmüştür (1,00-1,35, p=0,047).

**Sonuç:** TB çeşitli sosyal faktörlerin belirlendiği bir hastalıktır. Bu çalışma, belirli özelliklere sahip PWH'lerin TB geliştirme riskinin daha yüksek olduğunu göstermektedir. Bu yüzden HIV+TB birlikteliğini öngören risk faktörlerini belirlemek için çok merkezli çalışmalara ihtiyaç duyulmaktadır.

**Anahtar Kelimeler:** HIV, ko-enfeksiyon, risk faktörleri, tüberküloz

## Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality among people living with HIV (PWH). The co-existence of HIV and TB mutually reinforces their pathogenicity and disrupts their immunological functions. *Mycobacterium tuberculosis* accelerates the progression of AIDS in individuals with HIV<sup>(1)</sup>.

Globally, it has been reported that in 2022, there will be 7.5 million newly diagnosed TB cases, leading to an estimated 1.3 million deaths, with 167.000 of them occurring in HIV-positive individuals<sup>(2)</sup>. In our country, TB incidence (12.000 cases) ranks first in Europe in terms of HIV-TB co-infection and mortality<sup>(2,3)</sup>. Although TB incidence in our country has decreased by 25% between 2015 and 2022, the incidence among HIV-positive individuals has increased by 0.22%. Furthermore, while TB mortality has decreased by 37% among HIV-negative individuals from 2015 to 2022, it has increased 2.5 times among HIV-positive individuals<sup>(2,4)</sup>. TB remains a primary cause of mortality among HIV-positive individuals in our country<sup>(3)</sup>.

In Turkey, the rate of people diagnosed with TB who are known to be HIV-positive is 1.6%, and this rate has doubled in the last 5 years. Despite an increase in the rates of requesting HIV tests for known TB patients, it is observed that we lag proportionally behind when considering the estimated co-existence<sup>(5)</sup>. Of the individuals with HIV-TB co-infection in Turkey, 82% are under treatment for TB, and treatment success has been achieved in 62% of them<sup>(2,6)</sup>.

Despite all available data, the rate of individuals living with HIV who underwent latent TB testing is determined to be 45%, and it is estimated that the rates of latent TB are higher in our country; however, there is insufficient data on the actual numbers<sup>(2,7)</sup>.

TB is influenced by various social factors. When examining general risk factors for TB; smoking, alcohol consumption,

diabetes, and HIV incidence are increasing in our country and worldwide. Among the risk factors, poverty has shown the most striking increase, having tripled in the last 5 years<sup>(8)</sup>. Due to the high incidence and mortality in our country, the co-infection of TB in individuals living with HIV is a worthwhile topic to investigate; however, there are relatively few studies available.

The aim of this study was to analyze the biopsychosocial risk factors predicting HIV-TB co-infection in our center.

## Materials and Methods

### Study Setting and Design

We conducted a retrospective cross-sectional cohort study using the electronic medical records of individuals with HIV followed up between 2019 and 2022 at the Infectious Diseases and Clinical Microbiology Clinic of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. The inclusion criteria for the case group were confirmed HIV diagnosis, age 18 years and older, and inclusion of patients with bacteriologically confirmed TB coinfection<sup>(9)</sup>. For the selection of the control group, patients with confirmed HIV diagnosis, aged 18 years, with no known or suspected TB diagnosis, and patients in whom TB was excluded by microscopic/molecular/pathological or bacteriological methods were included. Subsequently, patients with no available data in the control group or those who were lost to follow-up were eliminated through secondary screening.

### Study Definitions and Variables

The diagnosis of TB was based on clinical manifestations (fever, night sweats, weight loss), laboratory findings (acid-fast staining, adenosine deaminase), imaging results, pathological results (necrotic granulomatous reaction), and the positivity of Xpert MTB/RIF TB polymerase chain reaction or culture results (bacteriologically confirmed TB).

Subclassifications of clinical TB diagnoses were made in accordance with national/international guidelines<sup>(9,10)</sup>.

**Pulmonary TB:** Used for TB affecting the lung parenchyma or the tracheobronchial tree.

**Extrapulmonary tuberculosis (EPTB):** Patients showing extrapulmonary organ involvement with demonstrated acid-fast bacilli (AFB) in samples taken from organs outside the lung parenchyma, along with histological and clinical evidence compatible with TB, fall into this category. Miliary TB is considered to be both pulmonary and EPTB. In the case of TB lymphadenitis in the mediastinum or hilum, it is designated as EPTB<sup>(9,10)</sup>.

Variables included demographic data (gender, age, education level, marital status, monthly income level, household crowding, number of cohabitants), baseline weight and body mass index (BMI), smoking, alcohol consumption, drug use status, presence of comorbidities, tuberculin skin test (TST) results, history of latent TB prophylaxis, history of BCG vaccination, nadir and baseline CD4<sup>+</sup> T-lymphocyte count/percentage, and baseline HIV RNA results. The term "nadir CD4<sup>+</sup> T-lymphocyte" refers to the individual's measured lowest CD4<sup>+</sup> T-lymphocyte level. The education level was classified into five categories: Illiterate, primary school, secondary school, high school, and undergraduate and above. TST was performed using purified protein derivative, and the results were categorized as anergic (0 mm), 0-5 mm, 6-14 mm, and 15 mm and above. The monthly income level was categorized as 0-499 US dollars (USD), 500-999-USD, and 1000 USD and above. The term "Household crowding" was used for situations such as prisons, military barracks, refugee camps, and situations where three or more people live in the same room<sup>(11)</sup>.

### Statistical Analysis

Patient data collected within the scope of the study were analyzed using IBM Statistical Package for the Social Sciences (SPSS) for MacOS 29.0 (IBM Corp., Armonk, NY). Frequency and percentage were provided as descriptive values for categorical data, whereas median (interquartile range) was used for continuous data. The "Mann-Whitney U test" was employed for intergroup comparisons, and the "chi-square or Fisher's Exact test" was used for comparing categorical variables. Logistic regression analysis was used to examine the risk factors influencing the development of TB. Results were considered statistically significant when the p-value was 0.05.

The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on May 4, 2023, with approval number 2023/03-19.

### Results

Among the 73 individuals living with HIV included in the study, 22 (30.1%) had TB coinfection, with a median age of 40 years (32-50). Of the sample group, 26% were married. The average baseline BMI value for the patients was 22.9. Among the cases, 52.1% smoked and 43.8% consumed alcohol. Substance abuse was observed in 12.3% of cases, with marijuana and methamphetamine being the most commonly used. Comorbidities were present in 30.1% of the cases, with the most common being psychiatric disorders (9.6%), hyperlipidemia (6.8%), diabetes mellitus (5.5%), and hypertension (5.5%). When examining the social variables of our cohort, it was found that 38.4% had completed primary school education, the average number of cohabitants was 3.8 (min-max: 1-24), 12.3% lived in crowded households, and 87.7% had a monthly income below 1.000 USD.

In terms of clinical data, it is noteworthy that 69.9% of the cohort did not undergo the TST, 5.5% had results above 5 mm, and latent TB prophylaxis treatment was given to this group. In addition, 89% of our cohort had a history of BCG vaccination. Descriptive statistics for nadir/basal CD4<sup>+</sup> T-lymphocyte and baseline HIV RNA results and all other variables are detailed in Table 1.

HIV-infected individuals with TB coinfection were clinically subclassified, with pulmonary TB being the most common (77.3%). The frequencies are presented in Table 2 in descending order.

Univariate analysis revealed that low BMI at the time of diagnosis in HIV-infected individuals had a statistically significant effect on the presence of TB coinfection risk (odds ratio: 0.73,  $p < 0.001$ ). Furthermore, as the number of people living in the same household increased, the probability of TB presence increased by 1.08 times (0.97-1.21,  $p = 0.011$ ). When examining the CD4<sup>+</sup> T-lymphocyte levels of the cases, it was statistically significant that the decrease in the number of nadir CD4<sup>+</sup> T-lymphocytes and baseline CD4<sup>+</sup> T-lymphocytes increased the risk of TB/HIV coinfection in the univariate model (Table 3).

**Table 1. Demographics and clinical findings of the patients**

Variables	Total (n=73)	No tuberculosis (n=51)	Tuberculosis (n=22)	p-value
	n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	
<b>Gender</b>				1.000
Male	66 (90.4)	46 (90.2)	20 (90.9)	
Female	7 (9.6)	5 (9.8)	2 (9.1)	
<b>Age (years)</b>	40 (32-50)	38 (31-50)	43 (32-52)	0.463
<b>Baseline BMI</b>	22.9 (20.7-25.6)	<b>24.1 (21.7-26.6)</b>	<b>19.4 (17.5-22.9)</b>	<b>&lt;0.001</b>
<b>Marital status</b>				0.565
Married	26 (35.6)	18 (35.3)	8 (36.4)	
Single	38 (52.1)	28 (54.9)	10 (45.5)	
Divorced	9 (12.3)	5 (9.8)	4 (18.2)	
<b>Education level</b>				0.944
Primary school	28 (38.4)	19 (37.3)	9 (40.9)	
Secondary school	13 (17.8)	10 (19.6)	3 (13.6)	
High school	13 (17.8)	9 (17.6)	4 (18.2)	
University	19 (26)	13 (25.5)	6 (27.3)	
<b>Number of households</b>	2 (1-4)	<b>2 (1-3)</b>	<b>4 (2-6)</b>	<b>0.011</b>
<b>Household crowding</b>	9 (12.3)	5 (9.8)	4 (18.2)	0.439
<b>Monthly income level (USD)</b>				0.250
0-499	25 (34.2)	15 (29.4)	10 (45.5)	
499-999	39 (53.4)	28 (54.9)	11 (50)	
1000 and above	9 (12.3)	8 (15.7)	1 (4.5)	
<b>Smoking</b>	38 (52.1)	26 (51)	12 (54.5)	0.980
<b>Alcohol consumption</b>	32 (43.8)	23 (45.1)	9 (40.9)	0.941
<b>Drug use</b>	9 (12.3)	6 (11.8)	3 (13.6)	1.000
<b>Comorbidity</b>	22 (30.1)	13 (25.5)	9 (40.9)	0.299
DM	4 (5.5)	3 (5.9)	1 (4.5)	1.000
HT	4 (5.5)	3 (5.9)	1 (4.5)	1.000
<b>Latent TB prophylaxis</b>	4 (5.5)	2 (3.9)	2 (9.1)	0.579
<b>PPD (mm)</b>				0.458
Unknown	51 (69.9)	37 (72.5)	14 (63.6)	
0-5	18 (24.7)	12 (23.5)	6 (27.3)	
6-14	1 (1.4)	1 (2)	0 (0)	
≥15	3 (4.1)	1 (2)	2 (9.1)	
<b>BCG vaccination</b>	65 (89)	47 (92.2)	18 (81.8)	0.232
<b>Nadir CD4<sup>+</sup> T-lymphocyte (cell/mm<sup>3</sup>)</b>	390 (119-602)	<b>448 (219-660)</b>	<b>164.5 (46-427)</b>	<b>0.004</b>
<b>Baseline CD4<sup>+</sup> T- lymphocyte (cell/mm<sup>3</sup>)</b>	408 (168-620)	<b>448 (250-656)</b>	<b>172 (46-436)</b>	<b>0.009</b>
<b>Baseline HIV RNA (x10<sup>3</sup>) (copies/mm<sup>3</sup>)</b>	69.9 (18.3-343)	62.1 (5.21-261)	166.5 (40-545)	0.069

IQR: Interquartile range, BMI: Body mass index, BCG: Bacillus Calmette-Guérin, PPD: Purified protein derivative, USD: United States dollar, DM: Diabetes mellitus, HT: Hypertension, TB: Tuberculosis, \*: p-value ≤0.05 is considered statistically significant

Tuberculosis diagnosis	n (%)
Pulmonary	17 (77.3)
Extra-pulmonary	10 (45.4)
Lymph node	4 (18.2)
Ileum	1 (4.5)
Renal	1 (4.5)
Pleura	2 (9.1)
Miliary	2 (9.1)

In one patient with diagnoses of renal, ileal, and lymph node tuberculosis, there was a co-occurrence of pulmonary tuberculosis

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	p-value*	Odds ratio (95% CI)	p-value*
Baseline BMI	0.73 (0.61-0.88)	<0.001	0.73 (0.57-0.94)	<b>0.016</b>
Number of households	1.08 (0.97-1.21)	0.011	1.16 (1.00-1.35)	<b>0.047</b>
Nadir CD4 <sup>+</sup> T lymphocytes (cell/mm <sup>3</sup> )	0.997 (0.995-0.999)	0.010	0.99 (0.98-1.00)	0.065
Baseline CD4 <sup>+</sup> T lymphocytes (cell/mm <sup>3</sup> )	0.998 (0.996-1.000)	0.038	1.01 (1.00-1.02)	0.070

CI: Confidence interval, BMI: Body mass index, PWH: People living with HIV, \*: p-value ≤0.05 is considered statistically significant

The distribution of risk factors affecting the development of TB in the multivariate logistic regression analysis within the scope of the study is presented in Table 3. Baseline BMI and the number of people living in the same household were independent risk factors for TB coinfection. While each increase in baseline BMI value reduced the development of TB by 0.73 times (0.57-0.94,  $p=0.016$ ), each increase in the number of people living in the same household increased the development of TB by 1.16 times (1.00-1.35,  $p=0.047$ ).

## Discussion

In our study, the predictive variables for the development of TB in individuals living with HIV were identified as low BMI at the time of diagnosis and more people living in the same household.

When evaluated in terms of gender and age, no significant difference in the risk of TB infection was observed among HIV-positive individuals in our cohort. This finding is consistent with similar studies conducted in different settings worldwide<sup>(12)</sup>. However, there are also studies indicating that male gender and increased age contribute to the incidence of HIV-TB co-infection<sup>(13,14)</sup>. It is worth noting that the incidence of TB in the regions where these studies were conducted is several times higher than that in our country. Social and cultural dynamics may contribute to prolonged exposure

and movement within the community, increasing exposure to the TB bacillus.

A study conducted among prisoners living in crowded conditions revealed that contrary to our study, alcoholism, smoking, and drug addiction are risk factors for TB/HIV coinfection. Our cohort did not include individuals with alcoholism. Moreover, the presence of these risk factors may be associated with increased vulnerability due to factors such as overcrowded prisons, insufficient food, high alcohol and drug consumption, and inadequate access to health services.

Similar to our study, recent findings from a study by Hanifa et al.<sup>(15)</sup> and another study by Suwanpimolkul et al.<sup>(13)</sup> have shown, respectively, that having a BMI below 18 and an initial weight below 50 kg significantly increases the risk of TB coinfection. Additionally, a research study with a methodology similar to ours demonstrated that each increase in BMI by 1 kg/m<sup>2</sup> reduces the development of TB coinfection by 0.9 times<sup>(16)</sup>.

A large-scale meta-analysis suggested that conditions creating social vulnerability, such as low monthly income and many people living in the same household, increase the risk of HIV-TB co-infection<sup>(17)</sup>. In our study, only 12% of the study population had a monthly income above USD 1000, and it is possible that poverty did not create a difference

because this condition, which increases social vulnerability, was present in most of our cohort. However, as expected, many studies, including ours, concluded that an increase in the number of people in the household, which is a social situation that increases bacillus exposure, is a risk factor for HIV-TB co-existence.

Univariate analysis revealed that CD4<sup>+</sup> T lymphocyte levels, which are important for the individual's immune monitoring and immune system, increase the risk of TB coinfection. However, multivariate analysis showed that the immunological and virological status of the individual, including CD4<sup>+</sup> T- lymphocyte and HIV RNA levels, did not alter the risk of TB coinfection. Although this relationship was not significant in the multivariate analysis, studies suggest that individuals with suppressed immune systems are at a higher risk of developing TB<sup>(13,16,18)</sup>. This result could be attributed to the fact that our unit has extensive experience in HIV health services and has been successful in accessing and using the available resources. Furthermore, this discrepancy in the results among studies may be caused by unequal access to healthcare between countries.

Latent TB infection progresses to active TB disease more rapidly with suppressed immunity<sup>(19)</sup>. Despite the proven effectiveness of latent TB prophylaxis in reducing the risk of TB infection among people with HIV and the general population, our study did not observe any impact on the prevention of TB. The limited number of individuals receiving latent TB prophylaxis in our study may account for this result. In contrast to this study, other studies conducted in different geographical settings have indicated a significant impact on preventing TB coinfection<sup>(20,21)</sup>.

The strength of this study lies in its execution within an experienced HIV healthcare clinic, which is co-located on the same campus as an actively managed TB sanatorium. This co-location contributes to high rates of HIV-TB co-infection.

### Study Limitations

The study is cross-sectional and single-centered, potentially limiting the generalizability of the results due to constraints in the case set. Our research design is retrospective and relies on existing clinical records; thus, the results may be influenced by the possibility of undocumented additional clinical factors. In addition, the retrospective nature of the study prevented the screening of patients' family history of TB.

### Conclusion

Given the high incidence and mortality rates of TB in our country, it remains a significant issue. Numerous studies indicate that TB is the leading cause of death among individuals living with HIV in our country. TB is influenced by various social factors. This study demonstrates that PWHs with specific characteristics are at a higher risk of developing TB. Among the individuals living with HIV, access to healthcare and individual's social opportunities influence the outcomes of our study. Considering all these data, multicenter studies from different regions predicting HIV-TB co-infection and interventions addressing it is needed.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee on May 4, 2023, with approval number 2023/03-19.

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: İ.A., İ.Ö., E.D.Ö., S.A., Concept: İ.A., F.D., S.A., Design: İ.A., İ.Ö., E.D.Ö., F.D., S.A., Data Collection or Processing: İ.A., E.D.Ö., Analysis or Interpretation: İ.A., İ.Ö., F.D., Literature Search: İ.A., İ.Ö., E.D.Ö., Writing: İ.A., İ.Ö., F.D., S.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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