Independent Predictors of Tuberculosis Coinfection among People Living with HIV in Medan, Indonesia: A Case-Control Study

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Abstract

Tuberculosis (TB) remains a major cause of morbidity among people living with HIV (PLHIV), particularly in high-burden countries such as Indonesia. This study aimed to identify factors independently associated with TB-HIV coinfection among PLHIV in Medan, Indonesia. An unmatched case-control study with a 1:3 case-to-control ratio was conducted in seven HIV Care, Support, and Treatment facilities in Medan. TB-HIV cases were ascertained from SIHA 2.1 records for January–August 2025, and participant data were collected from September 2025 to January 2026. A total of 144 participants were included, comprising 36 cases and 108 controls. Cases were identified from eligible records, while controls were selected sequentially until three controls were obtained per case. TB-HIV coinfection was confirmed by medical records documenting a positive molecular test (GeneXpert/TCM) and/or chest radiography. Underweight was defined as body mass index (BMI) <18.5 kg/m². Bivariate analyses and multivariable logistic regression were performed. Underweight was strongly associated with TB-HIV coinfection (COR=68.200; 95% CI: 21.268–218.702) and remained independently associated after adjustment (AOR=48.776; 95% CI: 10.394–228.895; p<0.001). Participants who had never received tuberculosis preventive therapy (TPT) had higher odds of coinfection (COR=14.826; 95% CI: 4.282–51.332; AOR=18.895; 95% CI: 3.161–112.965; p=0.001). Non-adherence to antiretroviral therapy (ART) was also associated with coinfection (COR=34.000; 95% CI: 7.731–149.530; AOR=15.820; 95% CI: 2.537–98.637; p=0.003). Large effect estimates and wide confidence intervals warrant cautious interpretation given the small number of cases and sparse data. Underweight, absence of TPT, and non-adherence to ART were independently associated with TB-HIV coinfection. Larger prospective studies are needed to validate these findings and clarify temporality before causal or prospective predictive conclusions are drawn.

Keywords: Tuberculosis Coinfection, HIV, Nutritional Status, Antiretroviral Adherence, Tuberculosis Preventive Therapy

INTRODUCTION

Tuberculosis is the most common secondary infection and leading cause of death among people living with HIV, with the two pathogens reciprocally amplifying each other's pathogenic potential in a synergistic epidemic (Azevedo-Pereira et al., 2023; Bell & Noursadeghi, 2018; Rangaraj et al., 2025). HIV increases susceptibility to primary TB, reactivation of latent TB, and reinfection, while TB in turn accelerates HIV disease progression to AIDS (Bruchfeld et al., 2026; Rangaraj et al., 2025). Globally, people living with HIV (PLHIV) are estimated to have a 12 times higher risk of developing active TB than individuals without HIV (World Health Organization, 2024b). In 2023, approximately 6.1% of incident TB cases occurred among PLHIV, and TB remained the leading cause of death among PLHIV worldwide (World

Health Organization, 2024b). Despite advances in antiretroviral therapy (ART), TB therefore remains an important opportunistic infection and cause of mortality among PLHIV.

Indonesia faces a dual burden of TB and HIV. The country ranks second globally in TB burden, contributing approximately 10% of all TB cases worldwide (World Health Organization, 2024a). At the same time, an estimated 568,401 people were living with HIV in Indonesia in 2024; however, only 61% were estimated to be aware of their HIV status, 64% of diagnosed PLHIV were receiving ART, and 54% of those receiving ART had achieved viral suppression (Kementerian Kesehatan RI, 2025). These gaps in HIV diagnosis, treatment coverage, and viral suppression underscore the continuing vulnerability of PLHIV to opportunistic infections and the importance of integrated TB-HIV prevention and care.

The burden is particularly relevant in North Sumatra, where Medan City represents the main concentration of HIV cases and HIV care services. In 2024, Medan reported 1,579 newly diagnosed HIV cases and a cumulative 17,194 HIV cases, the highest number in North Sumatra (Dinas Kesehatan Provinsi Sumatera Utara, 2025). The local HIV care system also comprises multiple hospitals and primary healthcare facilities providing HIV Care, Support, and Treatment (CST) services, although their distribution across districts is uneven. This combination of a substantial HIV burden, ongoing TB-HIV challenges, and variation in access to HIV care services makes Medan an important setting for examining factors associated with TB-HIV coinfection. However, local evidence on the factors independently associated with TB-HIV coinfection among PLHIV receiving care in Medan remains limited.

The occurrence of TB among PLHIV is influenced by multiple interrelated biological, treatment-related, and social factors. Age and sex have been identified as potential determinants of TB among PLHIV. Individuals in the productive age groups constitute a large proportion of PLHIV and may experience greater social mobility and occupational exposure, while sex-related differences may reflect differences in smoking, occupational exposures, healthcare-seeking behavior, and other social conditions(Iftitah et al., 2020; Ministry of Health of The Republic of Indonesia, 2025; UNAIDS, 2022). Nutritional status is another important factor, as low body mass index has been associated with increased TB incidence among PLHIV. In HIV-infected individuals receiving ART in Tanzania and Zambia, lower BMI was associated with higher TB incidence, while evidence from other settings has also linked low BMI with adverse TB-related outcomes (Ojo et al., 2022; Schwalb et al., 2023). History of contact with an active TB case may additionally increase the likelihood of TB among PLHIV, with Indonesian evidence reporting substantially higher odds among exposed individuals (Arismaya, 2023).

Treatment-related factors may also influence TB occurrence. Tuberculosis preventive therapy (TPT) is an important preventive intervention for PLHIV, and a recent meta-analysis reported a substantial reduction in TB incidence among PLHIV receiving TPT (Júnior et al., 2025). Conversely, inadequate adherence to ART may compromise immune recovery and viral suppression and consequently increase susceptibility to opportunistic infections, including TB (Nursalam et al., 2023). These factors are closely interconnected with social determinants. Low income may contribute to unfavorable living conditions, food insecurity, and barriers to healthcare access, while educational attainment, employment, smoking, and marital status may reflect differences in socioeconomic circumstances, health behavior, or access to care. Previous studies have reported associations between these social characteristics and TB, although findings have varied across populations and settings (Choi et al., 2023; Nkiene et al., 2026; Tang et al., 2025; Tegegne & Minwagaw, 2022).

Conceptually, these determinants can be viewed along a proximal–distal continuum rather than as independent domains. Social and socioeconomic conditions may influence more proximal factors, including nutritional status, access to preventive services such as TPT, and adherence to ART, which may in turn influence susceptibility to TB among PLHIV. Accordingly, the present study considered both distal social characteristics and more proximal biological and treatment-related factors in the same analytical framework. This framework also provides a basis for understanding why associations observed for social factors may be attenuated after adjustment for nutritional status, TPT history, ART adherence, and other covariates, without assuming a formal mediation pathway.

Although previous studies have identified multiple factors associated with TB among PLHIV, important gaps remain in the existing evidence. Much of the available evidence has originated from populations outside Indonesia, while studies conducted in Indonesia have often focused on different settings or used cross-sectional designs. Such evidence provides important information on potential associations but may have limited applicability to PLHIV receiving care in Medan and provides limited insight into the ordering of exposure and TB status. A case-control design allows simultaneous assessment of multiple potential factors and estimation of their associations with TB-HIV coinfection, although it cannot by itself establish temporality or causality. Local evidence examining biological, treatment-related, and social factors together therefore remains needed.

We hypothesized that underweight nutritional status, absence of TPT, and non-adherence to ART would be independently associated with higher odds of TB-HIV coinfection among PLHIV after adjustment for socioeconomic and other potential confounding factors. Therefore,

this study aimed to identify factors independently associated with TB-HIV coinfection among PLHIV in Medan, Indonesia, using an unmatched case-control design.

METHOD

This unmatched case-control study with a 1:3 case-to-control ratio was conducted among people living with HIV (PLHIV) at seven HIV Care, Support, and Treatment (CST) facilities in Medan, Indonesia. The facilities were RSUP H. Adam Malik, RSUD Dr. Pirngadi Medan, Rumkit Bhayangkara Tk. II Medan, and four primary health centers: Helvetia, Martubung, Padang Bulan Selayang II, and Teladan. TB-HIV cases were identified from SIHA 2.1 records for January–August 2025, while participant-level data were collected from September 2025 to January 2026.

The study population comprised PLHIV aged 15–59 years receiving HIV care at the selected facilities. Cases were PLHIV with confirmed TB-HIV coinfection, diagnosed with TB using molecular testing (TCM) and/or chest radiography, who had received ART for more than three months and had initiated anti-TB treatment. Controls were PLHIV who had received ART for at least three months, had no previous TB diagnosis, and had no signs or symptoms suggestive of TB at their most recent screening. Participants with severe medical conditions or hospitalization were excluded, as were cases with pulmonary TB diagnosed before HIV infection.

The minimum sample size was initially calculated using the Fleiss formula with continuity correction, a 95% confidence level, and 80% power, resulting in a requirement of 54 cases and 54 controls. However, only 36 eligible cases were identified during the predefined case-ascertainment period. Therefore, all eligible cases were included, and the control-to-case ratio was increased to 3:1 to improve statistical efficiency. A total of 108 eligible controls were recruited sequentially from the participating facilities, resulting in a final sample of 144 participants. No individual matching was performed.

The dependent variable was TB-HIV coinfection. Independent variables included age, sex, nutritional status, contact with an active TB case, history of TB preventive therapy (TPT), ART adherence, income, employment, education, smoking behavior, and marital status. Nutritional status was classified as underweight (BMI <18.5 kg/m^2) or non-underweight (BMI ≥ 18.5 kg/m^2). BMI was based on measurements recorded two months before TB diagnosis for cases and two months before recruitment for controls. TPT history was defined as completion of at least one course of preventive therapy. ART adherence was measured using the validated Indonesian version of the eight-item Morisky Medication Adherence Scale (MMAS-8)

(Cronbach's alpha=0.908) (Rushartini, 2022). Smoking behavior was classified using the Brinkman Index as non-smoker, light (≤200), moderate (201–600), or heavy (>600).

Categorical variables were summarized as frequencies and percentages. Bivariate analysis used the Chi-square test for dichotomous variables and simple logistic regression for smoking categories. Crude odds ratios (CORs), 95% confidence intervals (CIs), and p-values were reported. Variables with p≤0.25 were entered into multiple logistic regression, followed by backward elimination. Adjusted odds ratios (AORs) with 95% CIs were reported, with statistical significance set at p<0.05. Model fit was assessed using the Hosmer–Lemeshow test and area under the receiver operating characteristic curve (AUC-ROC), while variance inflation factors (VIFs) were examined for multicollinearity. Sparse-data patterns and potential separation were also evaluated.

A sensitivity analysis was performed by adding age and sex to the final model containing nutritional status, TPT history, and ART adherence to assess the robustness of the principal associations. CD4 cell count and viral load were not analyzed because these data were inconsistently available across facilities during the transition to SIHA 2.1. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Sumatera Utara (No. 1391/KEPK/USU/2025), and written informed consent was obtained from all participants.

RESULTS

Prior to multivariable modeling, bivariate analyses were performed to identify candidate variables associated with TB coinfection among PLHIV. Pearson's chi-square test was used to compare the distribution of dichotomous independent variables between cases and controls. Because smoking behavior was classified into four categories, its association with TB coinfection was assessed using simple logistic regression, with non-smokers serving as the reference group. Variables meeting the predetermined selection criterion (p <0.25) were included in the initial multivariable logistic regression model.

A total of 144 PLHIV participated in this study, consisting of 36 cases with TB coinfection and 108 controls without TB. Among the cases, 61.1% were aged 31–59 years, compared with 66.7% among controls. Male participants predominated in both groups, accounting for 86.1% of cases and 77.8% of controls. However, neither age nor sex was significantly associated with TB coinfection (p=0.686 and p=0.401, respectively).

Table 1 Bivariate Analysis of Factors Associated with Tuberculosis Coinfection among PLHIV in Medan

Variable	Cases n (%) (n=36)	Controls n (%) (n=108)	Crude OR	95% CI	*p-value*
Age					
31-59 years	22 (61.1)	72 (66.7)	0.786	0.360-1.715	0.686

Variable	Cases n (%) (n=36)	Controls n (%) (n=108)	Crude OR	95% CI	*p-value*
15-30 years	14 (38.9)	36 (33.3)	Ref		
Sex					
Male	31 (86.1)	84 (77.8)	1.771	0.621-5.051	0.401
Female	5 (13.9)	24 (22.2)	Ref		
Nutritional status					
Underweight	31 (86.1)	9 (8.3)	68.200	21.268-218.702	<0.001
Non-underweight	5 (13.9)	99 (91.7)	Ref		
History of contact with an active TB case					
Yes	12 (33.3)	9 (8.3)	5.500	2.080-14.545	0.001
No	24 (66.7)	99 (91.7)	Ref		
History of TPT					
Never received	33 (91.7)	46 (42.6)	14.826	4.282-51.332	<0.001
Received TPT	3 (8.3)	62 (57.4)	Ref		
ART adherence					
Non-adherent	34 (94.4)	36 (33.3)	34.000	7.731-149.530	<0.001
Adherent	2 (5.6)	72 (66.7)	Ref		
Income level					
Low	32 (88.9)	46 (42.6)	10.783	3.563-32.627	<0.001
High	4 (11.1)	63 (57.4)	Ref		
Employment status					
Unemployed	20 (55.6)	12 (11.1)	10.000	4,106-24,354	<0.001
Employed	16 (44.4)	96 (88.9)	Ref		
Educational level					
Low	29 (80.6)	76 (70.4)	1.744	0.693-4.390	0,330
High	7 (19.4)	32 (29.6)	Ref		
Smoking behavior					0.054
Heavy smoker	5 (13.9)	3 (2.8)	7.564	1.602-35.717	0.011
Moderate smoker	9 (25.0)	18 (16.7)	2.269	0.834-6.171	0.108
Light smoker	9 (25.0)	28 (25.9)	1.459	0.558-3.816	0.441
Non-smoker	13 (36.1)	59 (54.6)	Ref		
Marital status					
Unmarried	26 (72.2)	75 (69.4)	1.144	0.496-2.640	0.916
Married	10 (27.8)	33 (30.6)	Ref		

The distribution of underweight status was highly imbalanced between cases and controls, with 31 of 36 cases (86.1%) classified as underweight compared with 9 of 108 controls (8.3%). Although no empty cell was observed for the primary predictors, this sparse distribution contributed to the large effect estimate and wide confidence interval for underweight. Therefore, the magnitude of the adjusted association should be interpreted cautiously. Underweight PLHIV had significantly higher odds of TB coinfection than those with non-underweight nutritional status (OR=68.20; 95% CI: 21.27–218.70; p<0.001). Similarly, a history of contact with an active TB case was more common among cases (33.3%) than controls (8.3%), and was significantly associated with TB coinfection (OR=5.50; 95% CI: 2.08–14.55; p<0.001).

Regarding preventive and treatment-related factors, 91.7% of cases had never received tuberculosis preventive therapy (TPT), compared with 42.6% of controls. PLHIV who had never received TPT had 14.83 times higher odds of TB-HIV coinfection than those who had received TPT (OR=14.83; 95% CI: 4.28–51.33; p<0.001). Likewise, non-adherence to antiretroviral therapy (ART) was substantially more frequent among cases (94.4%) than controls (33.3%). Non-adherent participants had 34 times higher odds of TB coinfection compared with adherent participants (OR=34.00; 95% CI: 7.73–149.53; p<0.001).

Socioeconomic factors were also associated with TB coinfection. Low income was reported by 88.9% of cases and 42.6% of controls, and was significantly associated with TB coinfection (OR=10.78; 95% CI: 3.56–32.63; p<0.001). Similarly, unemployment was more common among cases (55.6%) than controls (11.1%), with unemployed participants showing tenfold higher odds of TB coinfection (OR=10.00; 95% CI: 4.11–24.35; p<0.001). In contrast, educational level was not significantly associated with TB coinfection (p=0.330).

For smoking behavior, heavy smokers constituted 13.9% of cases and 2.8% of controls. Compared with non-smokers, heavy smokers had significantly higher odds of TB coinfection (OR=7.56; 95% CI: 1.60–35.72; p=0.011). However, moderate smoking (p=0.108) and light smoking (p=0.441) were not significantly associated with TB coinfection. Overall, smoking behavior showed a borderline significant association with TB coinfection (p=0.054). Finally, marital status was comparable between cases and controls and was not significantly associated with TB coinfection (p=0.916).

Variables with p-values <0.25 in the bivariate analysis were entered into the full multivariable logistic regression model. Backward elimination was then applied sequentially, with the final model retaining variables that remained statistically significant at p<0.05. Age and sex, although not meeting the bivariate selection criterion, were subsequently forced into the final model in a sensitivity analysis because of their established epidemiological relevance as potential confounders.

Table 2 Multivariable Logistic Regression Models for Tuberculosis Coinfection among PLHIV in Medan

Variable	COR (95% CI)	Full Model		Final Model		Sensitivity Model (Age- and sex-adjusted)	
		p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)
Underweight nutritional status	68.200 (21.268-218.702)	<0.001	38.223 (6.358–229.792)	<0.001	48.776 (10.394–228.895)	<0.001	57.353 (10.904-301.654)

Variable	COR (95% CI)	Full Model		Final Model		Sensitivity Model (Age- and sex-adjusted)	
		p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)
History of active TB contact	5.500 (2.080-14.545)	0.972	0.965 (0.127–7.318)	–	–	-	-
Never received TPT	14.826 (4.282-51.332)	0.003	30.766 (3.102–305.169)	0.001	18.895 (3.161–112.965)	0.002	18.465 (3.023-112.794)
Non-adherence to ART	34.000 (7.731-149.530)	0.005	19.372 (2.504–149.864)	0.003	15.820 (2.537–98.637)	0.004	15.657 (2.353-104.191)
Low income	10.783 (3.563-32.627)	0.248	3.232 (0.441–23.673)	–	–	-	-
Unemployed	10.000 (4.106-24.354)	0.623	1.636 (0.230–11.662)	–	–	-	-
Heavy smoker	7.564 (1.602-35.717)	0.458	3.233 (0.146–71.733)	–	–	-	-
Moderate smoker	2.269 (0.834-6.171)	0.878	0.832 (0.080–8.663)	–	–	-	-
Light smoker	1.459 (0.558-3.816)	0.097	5.345 (0.738–38.713)	–	–	-	-
Age 31–59 years	0.786 (0.360-1.715)	-	-	-	-	0.717	1.371 (0.249-7.540)
Male	1.771 (0.621-5.051)	-	-	-	-	0.402	2.789 (0.253-30.681)

In the full model (initial model), nutritional status, history of TPT, and ART adherence had a significant effect on TB coinfection, while history of contact with active TB cases, income level, employment status, and smoking behavior were not statistically significant. History of contact with active TB cases showed the highest p-value and was removed first from the model. Subsequent stages of model reduction demonstrated that employment status, smoking behavior, and income level did not retain independent associations after adjustment for other covariates and were sequentially excluded. Throughout the model-building process, nutritional status, history of TPT, and ART adherence consistently remained statistically significant predictors.

The final model identified three factors independently associated with TB coinfection among PLHIV. Underweight participants had substantially higher adjusted odds of TB-HIV coinfection (AOR=48.776; 95% CI: 10.394–228.895; p<0.001). However, the wide confidence

interval indicates substantial imprecision in the estimate. The large effect estimate should therefore be interpreted cautiously in view of the small number of cases and the marked imbalance in nutritional status between cases and controls. Participants who had never received TPT had higher odds of coinfection (AOR=18.895; 95% CI=3.161–112.965; p=0.001), as did those who were non-adherent to ART (AOR=15.820; 95% CI=2.537–98.637; p=0.003). In the age- and sex-adjusted sensitivity analysis, the associations remained in the same direction and were not materially altered. The AORs for underweight, never having received TPT, and non-adherence to ART were 57.353; 18.465; and 15.657, respectively. The consistency of these associations with the primary model supports the robustness of the main findings to adjustment for age and sex.

The final multivariable logistic regression model was further assessed for model fit, discrimination, and potential multicollinearity using the Hosmer–Lemeshow test, area under the receiver operating characteristic curve (AUC), and variance inflation factor (VIF), respectively. The results are presented in the table below.

Table 2 Diagnostic Assessment of the Final Multivariable Logistic Regression Model

Diagnostic	Result
Hosmer–Lemeshow χ^2	2.485
df	4
p-value	0.647
AUC	0.971
95% CI for AUC	0.948–0.995
VIF range	1.088–1.333

The final multivariable logistic regression model showed no evidence of poor model fit according to the Hosmer–Lemeshow test (χ^2=2.485, df=4, p=0.647). The model showed high apparent discriminatory performance, with an AUC of 0.971 (95% CI: 0.948–0.995). VIF values ranged from 1.088 to 1.333, indicating no evidence of problematic multicollinearity among the predictors. Although the final model showed no evidence of poor fit, high apparent discriminatory performance, and no problematic multicollinearity, the very large effect estimates and wide confidence intervals indicate that the findings should still be interpreted cautiously given the small number of cases and potential sparse-data instability.

DISCUSSION

This study found that underweight nutritional status, absence of TPT, and non-adherence to ART were independently associated with TB-HIV coinfection among PLHIV in Medan. Although history of TB contact, low income, unemployment, and smoking behavior were associated with TB-HIV coinfection in bivariate analyses, these associations did not remain statistically significant after multivariable adjustment. These findings suggest that the observed

associations of social and behavioral characteristics may overlap with more proximal nutritional and treatment-related factors, although the present study did not formally assess mediation.

The strong association observed for underweight should be interpreted cautiously because temporality cannot be established in this case-control study. In particular, low BMI may increase susceptibility to TB, but TB disease itself can also cause weight loss and wasting. Therefore, the observed association may be bidirectional, and the present findings should not be interpreted as evidence that underweight causes TB-HIV coinfection. Prospective studies with repeated measurements of nutritional status before TB diagnosis are needed to clarify the temporal relationship.

The adjusted association between underweight status and TB-HIV coinfection was very large (AOR=48.776), but the estimate was imprecise, as reflected by the wide 95% CI (10.394–228.895). This magnitude should not be interpreted as the true biological effect size. The extreme imbalance in underweight status between cases and controls, together with the relatively small number of cases, may have inflated the point estimate and contributed to estimation instability. Therefore, the magnitude of this association requires validation in larger studies. This estimate is substantially larger than the magnitude generally reported in longitudinal studies, where associations between low BMI and incident TB among PLHIV have typically been more modest. Cohort studies of people living with HIV (PLHIV) consistently report that underweight status (BMI < 18.5 kg/m²) is associated with a 2- to 5-fold increased hazard of incident tuberculosis compared to normal-weight counterparts (Ganesan et al., 2023; Getu et al., 2022; Nguenha et al., 2025). A dose-response meta-analysis of 18 HIV cohorts estimated a relative risk of 5.0 (95% CI 4.2–5.9) for TB associated with undernutrition (Saunders et al., 2025), while a separate meta-analysis of ten sub-Saharan African cohorts pooled the adjusted hazard at 2.1 (95% CI 1.6–2.7) (Alebel et al., 2021).

This finding is biologically plausible because adequate nutrition is essential for maintaining both innate and adaptive immune responses. Undernutrition impairs macrophage function, cytokine production, and T-cell-mediated immunity, all of which are critical for controlling *Mycobacterium tuberculosis* infection (Ozer & Gündoğan, 2024; Vanvalkenburg et al., 2022). In PLHIV, HIV-related immunosuppression combined with poor nutritional status may substantially increase susceptibility to TB infection and accelerate progression from latent infection to active disease. Recent evidence has highlighted the importance of nutrition in TB prevention, with malnutrition now recognized as one of the largest contributors to the global TB burden. A 2024 review estimated that malnutrition contributes to a greater proportion of

incident TB cases worldwide than HIV itself, emphasizing the importance of addressing nutritional deficiencies as part of TB control strategies (Dauphinais et al., 2024).

The findings are also consistent with recent studies showing that weight loss and undernutrition are strongly associated with poor clinical outcomes among PLHIV. A systematic review and meta-analysis published in 2024 reported that weight loss was significantly associated with increased mortality among PLHIV, reflecting the critical role of nutritional status in maintaining immune competence and preventing opportunistic infections (Cordeiro et al., 2024). Furthermore, a recent systematic review from China identified low body mass index as one of the most consistent predictors of TB among PLHIV (Qi et al., 2023).

The high prevalence of underweight among cases suggests that nutritional vulnerability may be an important clinical concern among PLHIV with TB-HIV coinfection in the participating facilities. These findings support the importance of monitoring nutritional status in HIV care and warrant prospective evaluation of whether nutritional interventions can reduce subsequent TB incidence.

The study further demonstrated that participants who had never received TPT had higher odds of TB-HIV coinfection than those who had received TPT (AOR=18.895; 95% CI: 3.161–112.965). This finding is consistent with evidence that TPT is associated with lower incidence of TB among PLHIV. However, because this study was case-control in design, the observed association should not be interpreted as a direct estimate of the preventive effect of TPT in this population. A narrative review states TPT “has been shown to reduce the progression to active TB and mortality among PLHIV, regardless of the concurrent receipt of ART (Vasiliu et al., 2022). Additionally, the trial protocol notes that WHO has declared TPT an essential intervention for all PLHIV without active TB, citing 30–60% reduction in TB risk and up to 40% mortality reduction when combined with ART (Semitala et al., 2022).

Tuberculosis preventive therapy reduces the risk of progression from latent TB infection to active disease by eliminating dormant *M. tuberculosis* bacilli before clinical disease develops. Because PLHIV are substantially more likely to progress from latent infection to active TB than HIV-negative individuals, TPT has become a core component of HIV-TB collaborative activities recommended by the World Health Organization. The present findings are supported by recent high-quality evidence. A systematic review and meta-analysis published in 2025 found that TPT reduced TB incidence among PLHIV by 63%, confirming its substantial effectiveness under routine programmatic conditions (Júnior et al., 2025). Similarly, a network meta-analysis comparing different TPT regimens concluded that TPT

consistently reduces TB morbidity among PLHIV regardless of the specific regimen used (Yanes-Lane et al., 2021).

Despite these benefits, TPT implementation remains suboptimal in many high-burden countries, including Indonesia. Missed opportunities for TPT initiation may leave PLHIV vulnerable to TB infection even when they are already engaged in HIV care. These findings underscore the importance of maintaining high TPT coverage and warrant prospective evaluation of its effect on subsequent TB incidence in this setting. Strengthening screening procedures, improving provider awareness, ensuring drug availability, and monitoring treatment completion should therefore become priorities within HIV care programs.

Non-adherence to ART was independently associated with higher odds of TB-HIV coinfection (AOR=15.820; 95% CI: 2.537–98.637). These findings support continued attention to ART adherence within HIV care and warrant longitudinal evaluation of whether improved adherence is associated with lower subsequent TB incidence. This association is biologically plausible because inadequate ART exposure may compromise immune recovery. However, the present study cannot establish whether non-adherence preceded TB development or was influenced by illness related to TB, and residual confounding by HIV disease severity cannot be excluded. In line with the findings in this research, a five-year retrospective study from Saint Peter's TB Specialized Hospital reported that non-adherence to ART was a very strong predictor of TB/HIV coinfection: non-adherent PLHIV had an adjusted odds ratio of 51.6 for TB compared with adherent patients, in multivariate logistic regression (Getaw & Tigu, 2024).

The protective effect of ART against TB has been consistently documented. ART suppresses HIV replication, promotes CD4 cell recovery, restores immune function, and reduces vulnerability to opportunistic infections. Conversely, poor adherence can result in virological failure, persistent immunosuppression, and increased susceptibility to TB infection and disease progression. Several studies have shown that ART substantially decreases TB incidence among PLHIV. Recent evidence suggests that the combined implementation of ART and TPT provides greater protection against TB than either intervention alone (Júnior et al., 2025). In addition, a 2023 systematic review identified inadequate HIV treatment and advanced immunosuppression as major factors associated with TB occurrence among PLHIV (Qi et al., 2023; Wondmeneh & Mekonnen, 2023).

The findings highlight the importance of strengthening adherence-support interventions within HIV services. Strategies such as peer support programs, adherence counseling, digital medication reminders, routine adherence monitoring, and community-based follow-up may help improve ART adherence and consequently reduce TB risk among PLHIV. A study by

(Ebrahim et al., 2025) showed that community-based enhanced adherence counseling (CEAC) in Ethiopia achieved viral suppression in 83% of PLHIV with prior unsuppressed viral load, suggesting strong effectiveness of community counseling.

Several social and behavioral factors, including low income, unemployment, and smoking behavior, were associated with TB-HIV coinfection in bivariate analyses but were no longer statistically significant after adjustment. One possible explanation is that their observed associations may overlap with, or be attenuated after adjustment for, more proximal factors included in the model, such as nutritional status and treatment-related characteristics. For example, socioeconomic disadvantage may be associated with food insecurity, access to preventive services, and treatment adherence. However, the present study did not formally test mediation pathways, and the attenuation of these associations should therefore not be interpreted as evidence of mediation. Likewise, smoking behavior may influence TB risk indirectly through impaired pulmonary function and overall health status but may become less important after accounting for major biological determinants. A meta-analysis of TB and lung cancer found that smoking did not confound the TB–lung cancer association, indicating that once TB and other factors are accounted for, smoking may be less central for some downstream risks than TB-related biology itself (Hwang et al., 2022).

History of contact with an active TB case was significantly associated with TB-HIV coinfection in the bivariate analysis; however, this association was attenuated and no longer statistically significant after adjustment for other covariates in the multivariable model. This finding does not necessarily indicate that previous TB contact is unimportant in the development of TB among PLHIV. Rather, the attenuation of the association may suggest that the effect of TB contact on progression to active disease is influenced by, or overlaps with, other determinants of TB disease progression. Although exposure to an infectious TB case increases the likelihood of acquiring Mycobacterium tuberculosis infection, progression from infection to active TB among PLHIV is strongly influenced by host-related and clinical factors, including immune status, nutritional condition, and the use of preventive interventions such as TB preventive treatment (Adhikari et al., 2022; Bizuneh et al., 2024). Thus, once these interrelated factors are accounted for, the independent contribution of contact history may become less apparent.

Preventive therapy directly reduces the bacillary burden that would otherwise drive progression from latent infection to active disease. Modeling studies show a median 28% reduction in active TB incidence with TPT versus no TPT, with all 61 reviewed studies confirming TPT effectiveness regardless of whether TB transmission was modeled (Uppal et

al., 2021). Isoniazid specifically reduces TST and IGRA reactivity, reflecting decreases in TB-specific memory immune responses that would otherwise signal prior exposure (Yengkhom et al., 2026).

ART-mediated immune reconstitution independently suppresses TB progression by restoring CD4+ T-cell function and controlling viral replication. The Swiss HIV Cohort Study demonstrated that CD4 recovery and viral load reduction were the dominant population-level drivers of TB decline over 30 years, with LTBI test positivity capturing only 10.5% of incident TB cases (Zeeb et al., 2023). This means that in well-treated cohorts, the signal from TB exposure is diluted by the overwhelming protective effect of immune restoration.

The lack of statistical significance in the final model should therefore be interpreted cautiously rather than as evidence that TB contact history is irrelevant to TB-HIV coinfection. Its influence may operate through more complex pathways involving both the acquisition of infection and subsequent progression to active disease. In particular, the degree of immunosuppression may modify the extent to which a prior TB exposure translates into active disease. However, because CD4 cell count and viral load were not systematically available across participants and were therefore not included in the analytical dataset, the extent to which differences in immune status contributed to the observed attenuation cannot be directly assessed in the present study. Consequently, the findings should be interpreted as indicating that the association between TB contact history and TB-HIV coinfection may be partly explained or overshadowed by other clinical and host-related determinants, rather than demonstrating an absence of effect of TB exposure itself. Therefore, future prospective studies should incorporate serial CD4 and viral load measurements to improve control of confounding.

Model diagnostics provided supportive evidence regarding the statistical performance of the final model. The Hosmer–Lemeshow test showed no evidence of poor fit ($p=0.647$), while the AUC of 0.971 indicated high apparent discriminatory performance. VIF values were low (1.088–1.333), suggesting no problematic multicollinearity among the three predictors. Nevertheless, these diagnostics do not eliminate concerns regarding estimation instability arising from the small number of cases and sparse data. The sensitivity analysis additionally adjusted the final model for age and sex, two established epidemiological confounders. The persistence of the principal associations after this adjustment would support the robustness of the findings, although the estimates should still be interpreted cautiously because the number of cases remained limited.

Overall, from a public health perspective, the observed associations point to nutritional status, TPT, and ART adherence as areas warranting further investigation in TB-HIV

prevention and care. However, the case-control design does not permit causal inference, and the findings should therefore not be interpreted as evidence that modifying these factors would reduce TB incidence. Prospective studies with serial monitoring of BMI and CD4 cell counts, together with longitudinal assessment of ART adherence and TPT exposure, are needed to clarify temporal relationships and evaluate these factors as potential targets for future intervention studies.

While these considerations warrant cautious interpretation of the findings, the study has several strengths that enhance its relevance and contribution to the existing evidence. First, the study was conducted across seven HIV care facilities representing different levels of healthcare services in Medan, allowing inclusion of PLHIV receiving care across multiple facility types. However, because facilities were purposively selected and controls were recruited sequentially from participating facilities, generalizability beyond these services may be limited. Second, the study simultaneously evaluated multiple biological and social determinants of TB coinfection using multivariable analysis, allowing identification of independent predictors while controlling for potential confounding factors.

These strengths should, however, be considered in light of several limitations that should be acknowledged. First, the number of cases was relatively small (n=36), which limited statistical precision and increased the potential for sparse-data bias and overfitting. Although no empty cells were observed for the principal predictors, the marked imbalance in some exposure categories may have resulted in sparse-data bias and unstable maximum-likelihood estimates. This is reflected in the large effect estimates and wide confidence intervals, particularly for underweight status. Second, although BMI was measured two months before the index date to reduce potential reverse causality from TB-related weight loss, the retrospective case-control design cannot completely exclude residual uncertainty in temporal ordering. Early, undiagnosed TB may have affected nutritional status before diagnosis; therefore, the direction of the observed association should be interpreted cautiously. Third, the absence of systematically available CD4 cell count and viral load data precluded direct statistical adjustment for HIV disease severity, and residual confounding by underlying immune status cannot be excluded. The robustness of the primary model was assessed through adjustment for age and sex in a sensitivity analysis; however, this analysis does not substitute for direct adjustment for CD4 count and viral load. Fourth, controls were selected sequentially from eligible PLHIV at the selected CST facilities rather than through population-based sampling. Together with purposive selection of facilities, this may limit generalizability beyond the participating services. Finally, some exposures, particularly ART adherence and smoking

behavior, relied on self-reported information and may therefore be subject to recall or social desirability bias.

CONCLUSION

In this case-control study, underweight nutritional status, absence of tuberculosis preventive therapy (TPT), and non-adherence to antiretroviral therapy (ART) were independently associated with TB-HIV coinfection among PLHIV in Medan. The magnitude of the observed associations, particularly for underweight nutritional status, should be interpreted cautiously because of the small number of cases, sparse data, and wide confidence intervals. The findings should not be interpreted as causal or prospective predictive effects because temporal relationships cannot be established in this study design. Future prospective cohort studies among PLHIV receiving HIV care should periodically assess nutritional status, CD4 cell count, viral load, ART adherence, and TPT exposure before and during follow-up, with incident TB as the outcome, to clarify temporality and validate these associations and clarify their temporal relationships before informing policy or intervention strategies.

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