

Low Cholesterol Associated With TB in People Living With HIV in an Asia-Pacific Cohort

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Background: Tuberculosis (TB) remains the leading cause of illness and death among people living with HIV (PLHIV), particularly in high-burden areas. This study examined associations between TB and routine clinical markers: serum cholesterol, platelet count, and CD4 cell count.

Setting: The analysis included data from the TREAT Asia HIV Observational Database, a multicenter cohort of adult PLHIV receiving care across the Asia-Pacific region.

Methods: The authors conducted a cross-sectional matched case-control study of prospective and retrospective patients with TB, comparing clinical and laboratory data within ± 3 months of TB diagnosis. Conditional logistic regression assessed associations between TB and covariates.

Results: The analysis included 4244 PLHIV from 20 sites: 1427 patients with TB and 2817 matched controls. Patients with TB were predominantly male (75.3%) and 45.7% aged 31–40 years. Multivariable analysis showed greater odds of TB diagnosis among males, those with low BMI, prior AIDS diagnosis, high HIV viral load, low CD4⁺ counts, or low total cholesterol. CD4⁺ counts <200 cells/ μ L had higher TB odds (adjusted OR [aOR] 12.90, 95% CI: 8.84–18.82) than CD4⁺ >500 cells/ μ L. Cholesterol <3.9 mmol/L had higher TB odds (aOR 3.11, 95% CI: 1.94 to 4.98) than cholesterol >5.5 mmol/L.

Conclusions: In this Asia-Pacific cohort of adults living with HIV, low CD4⁺ cell count and low total serum cholesterol were associated with increased TB odds. Cholesterol may represent a low-cost adjunct marker to support TB risk stratification in PLHIV in endemic

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settings, but requires validation and evaluation of feasibility and cost-effectiveness.

Key Words: tuberculosis, human immunodeficiency virus, cholesterol, CD4 lymphocyte count, case-control studies, odds ratio

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INTRODUCTION

Tuberculosis (TB), caused by the bacteria *Mycobacterium tuberculosis*, is the most frequent opportunistic infection among people living with HIV (PLHIV) and is responsible for more than a quarter of all HIV-associated deaths.^{1,2} Nearly half of the HIV-associated deaths are estimated to be associated with undiagnosed TB (45.8%).³ This failure to detect TB contributes significantly to mortality in PLHIV. The World Health Organization (WHO) estimates that just 10 countries account for most of undiagnosed patients worldwide: 8 of these are located in the Southeast Asian region.¹ Although CD4⁺ cell depletion is a well-established risk factor for TB in HIV-positive individuals, the identification of additional routine clinical markers associated with TB diagnosis could support more effective clinical screening strategies in high-burden settings.

Previous analysis of clinical trial data from the SECOND-LINE study,⁴ which enrolled participants from sites across Africa, Asia, and South America, identified that the routine laboratory markers, cholesterol and platelets, together with CD4⁺ cell counts, were inversely associated with the risk of incident TB in PLHIV receiving second-line antiretroviral treatment (ART).⁵ Researchers have established the link between low CD4⁺ cell counts and TB, leading to the routine inclusion of CD4 monitoring in clinical care for PLHIV in TB-endemic settings.^{6,7} There is also a growing body of research, principally in the general population, reporting low total cholesterol as a clinical finding at diagnosis of *M. tuberculosis* infection and associated with a greater risk of TB disease, independent of BMI.^{8–12} The evidence for the role of platelets in TB disease is variable. Although elevated platelet counts are often a sign of inflammation associated with TB disease severity,¹³ low platelet counts have been identified as a presenting sign of TB in endemic areas.¹⁴ There are limited data on the relationship of these clinical markers with TB disease in PLHIV in the Asia-Pacific region. This study uses data from a large, multinational cohort in the Asia-Pacific region, to investigate associations between TB diagnoses and serum cholesterol, platelet counts, and CD4⁺ cell counts.

METHODS

Study Design and Population

The authors conducted a cross-sectional study among adults living with HIV enrolled in the TREAT Asia HIV Observational Database (TAHOD), a regional cohort of the International Epidemiology Databases to Evaluate AIDS (IeDEA) Asia-Pacific collaboration. TAHOD is a collaborative observational cohort study of adults living with HIV in the Asia-Pacific region,¹⁵ which collected routine clinical data from PLHIV enrolled at clinical sites between 2003 and 2021.

Observational data evaluated in this study come from 20 TAHOD sites in 12 Asia-Pacific countries: Cambodia (n = 1 site), Hong Kong SAR, China (1), India (3), Indonesia (2), Japan (1), Malaysia (2), Philippines (1), Singapore (1), South Korea (1), Taiwan (1), Thailand (4), and Vietnam (2).

The authors used a matched case-control design to compare people with and without TB diagnoses under similar clinical conditions. Matching on calendar time and site to control for variation in TB diagnostic and treatment practices across countries and over time.¹⁵

Definition of TB

TB was any *M. tuberculosis* infection, either definitive or presumptive. A definitive diagnosis included a confirmed culture of *M. tuberculosis* complex from a clinical specimen. A presumptive diagnosis included a demonstration of acid-fast bacilli in a clinical specimen, histopathology of a person with clinical signs or symptoms compatible with TB disease, or a successful response to therapy for TB with 2 or more anti-TB medications.

Case and Control Selection

Cases were participants diagnosed with TB at any time, classified as either prospective (diagnosed after TAHOD enrollment) or retrospective (diagnosed before cohort entry). Only the first TB episode was included, and individuals diagnosed before age 18 years were excluded. For each patient, the authors used clinical and laboratory data collected within ± 3 months of the first TB diagnosis date (Fig. 1). Patients were randomized before matching to minimize selection bias.

Each patient was matched to 2 controls by clinical site and calendar time, using a ± 3 -month window around the case TB diagnosis date (Fig. 1). Eligible controls had no recorded TB diagnosis and had data available during the same time window at the same clinic. Prospective controls were required to have available data during the same calendar period as the matched prospective patient's TB diagnosis. Retrospective controls were required to have data within the window period of the matched retrospective patient. When more than 2 controls were available, the authors randomly sampled 2 controls from eligible controls. If 2 or fewer potential controls were available, all were selected. Selected controls were then removed from the pool to prevent resampling.

Covariates

Primary covariates of interest were total serum cholesterol, platelet count, and CD4⁺ cell count. Additional covariates included sex, age, body mass index (BMI), smoking status (never/ever), hepatitis B or C coinfection, HIV exposure category, ART regimen, prior AIDS diagnosis, and HIV viral load. Hepatitis B or C coinfection was established using reported serologic and virologic assay results. People with a positive HBsAg or anti-HBc result were identified as having HBV coinfection, and a positive HCV antibody or detectable RNA result identified HCV

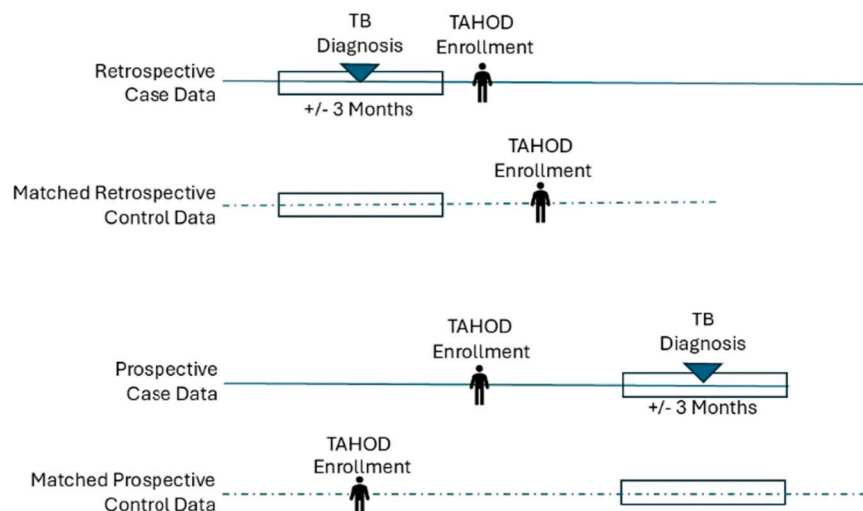


FIGURE 1. Illustration of the ± 3 -month data inclusion window used to define covariate observations for patients with TB and matched controls. For each patient, the window was centered on the TB diagnosis date. Matched control data were selected from the same calendar period, aligned with the patient's window, to ensure comparable timing of clinical and laboratory measurements.

coinfection. BMI was calculated using weight measurements collected within the ± 3 -month window (Fig. 1), assuming stable adult height. Continuous variables were categorized using established clinical thresholds: total serum cholesterol (<3.9 , 3.9 – 5.5 , >5.5 mmol/L),¹⁶ platelet counts (<150 and $\geq 150 \times 10^9/L$),¹⁷ CD4⁺ cell count (<200 , 200 – 500 , >500 cells/ μL),¹⁸ HIV viral load (≤ 1000 copies/mL and >1000 copies/mL),¹⁸ and BMI (<18.5 , ≥ 18.5 – <23 , >23 kg/m²).¹⁹ The clinical site and calendar time were accounted for through matching, and country income level was included for descriptive purposes only.

When multiple clinical or laboratory measurements were available within the defined ± 3 -month time frame (Fig. 1), the authors selected the observation closest to the date of the case TB diagnosis for matched case–controls. Each participant contributed a single observation for each covariate.

Statistical Analysis

Associations between covariates and TB diagnosis were assessed using conditional logistic regression, accounting for the matched design. Unreported values were coded as a separate indicator category for each covariate.²⁰ Global *P*-values for covariates were generated using Wald tests, with the unreported category excluded, to assess heterogeneity and test for overall association. Multivariable models were analyzed using backward stepwise selection, including covariates with $P < 0.10$ in univariate analysis and retaining those with a global $P < 0.05$ in the final model. Data management, matching, and analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC), R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria), and STATA version 18 (Stata Corp., College Station, TX).

RESULTS

Demographic and Clinical Characteristics of the Cohort

The authors included 4244 PLHIV from 20 sites: 1427 patients with TB and 2817 controls. Where possible, the

authors matched patients with TB with 2 controls; however, the authors did include 37 patients with TB with only 1 eligible control matched. TB diagnoses included in the analysis occurred between 1996 and 2022. Among the 1427 patients with TB, 296 (20.74%) were prospective patients (diagnosed after cohort entry), and 1131 (79.26%) were retrospective patients (diagnosed before cohort enrollment).

Table 1 summarizes the characteristics of patients and controls. At the time of TB diagnosis, the median age of patients was 35 years (interquartile range [IQR] 30–42), and 75.26% were male. Of 1427 patients with TB, 678 (47.51%) were from lower-middle-income countries, 567 (39.73%) from upper-middle-income countries, and 182 (12.75%) from high-income countries. More than half of the cases (962 [67.41%]) occurred in countries with a high TB burden.¹ Of the 1228 (88.57%) patients with TB with available CD4⁺ cell counts, 918 (64.33%) had CD4⁺ cell counts <200 cells/ μL . Among 515 (36.09%) patients with TB with reported cholesterol data, 260 (18.22%) had total cholesterol levels <3.9 mmol/L. Platelet data were scarce; of the 105 (8.46%) patients with TB with platelet measurements available, only 10 (0.70%) had platelet levels $<150 \times 10^9/L$.

Factors Associated With TB Diagnosis

Table 2 presents the factors associated with a diagnosis of TB. Variables with $P < 0.10$ in univariate analysis included sex, age, smoking status, BMI, hepatitis C coinfection, HIV exposure mode, ART regimen, prior AIDS diagnosis, HIV viral load, CD4⁺ cell count, and total cholesterol.

In the multivariable model, female sex was associated with lower odds of TB diagnosis (adjusted OR [aOR] 0.52, 95% CI: 0.44–0.63) compared with male sex. Compared with normal BMI (≥ 18.5 and <23), low BMI (<18.5) had higher odds of TB diagnosis (aOR 2.36, 95% CI: 1.88 to 2.96), while high BMI (>23) had lower odds of TB (aOR 0.44, 95% CI: 0.33–0.58). Prior AIDS diagnosis (aOR 2.14, 95% CI: 1.74 to 2.65) and HIV viral load >1000 copies/mL (aOR 3.15, 95% CI: 2.21 to 4.49) were associated with higher odds of TB

TABLE 1. Study Population Demographics

	Total (%)	Non-TB Controls (%)	Patients with TB (%)
	4244 (100%)	2817 (66.38)	1427 (33.62)
Sex			
Male	2814 (66.31)	1740 (61.77)	1074 (75.26)
Female	1430 (33.69)	1077 (38.23)	353 (24.74)
Age (yr)	<i>median</i> 36.00 [IQR: 30.00–42.00]	<i>median</i> 36.00 [IQR: 30.00–43.00]	<i>median</i> 35.00 [IQR: 30.00–42.00]
≤30	1131 (26.67)	766 (27.23)	365 (25.58)
31–40	1821 (42.95)	1169 (41.56)	652 (45.69)
41–50	889 (20.97)	1169 (41.56)	290 (20.32)
51+	399 (9.41)	279 (9.92)	120 (8.41)
World Bank income classification			
Lower middle	2018 (47.55)	1340 (47.57)	678 (47.51)
Upper middle	1684 (39.68)	1117 (39.65)	567 (39.73)
High	542 (12.77)	360 (12.78)	182 (12.75)
Smoking			
Never smoked	1649 (38.85)	1176 (41.75)	473 (33.15)
Ever smoker	1325 (31.22)	827 (29.36)	498 (34.90)
Not reported	1270 (29.92)	814 (28.90)	456 (31.96)
BMI (kg/m ²)	<i>Median</i> = 20.72 [IQR: 18.61–23.15]	<i>Median</i> = 21.48 [IQR: 19.39–23.90]	<i>Median</i> = 19.23 [IQR: 17.30–21.36]
<18.5	772 (18.19)	344 (12.21)	428 (29.99)
≥18.5 and < 23	1566 (36.90)	1069 (37.95)	497 (34.83)
≥23	851 (20.05)	708 (25.13)	143 (10.02)
Not reported	1055 (24.86)	696 (24.71)	359 (25.16)
Hepatitis B coinfection			
Negative	2502 (58.95)	1660 (58.93)	842 (59.00)
Positive	724 (17.06)	484 (17.18)	240 (16.82)
Not tested	1018 (23.99)	673 (23.89)	345 (24.18)
Hepatitis C coinfection			
Negative	2760 (65.03)	1863 (66.13)	897 (62.86)
Positive	466 (10.98)	281 (9.98)	185 (12.96)
Not tested	1018 (23.99)	673 (23.89)	345 (24.18)
Mode of HIV exposure			
Heterosexual	3111 (73.30)	2096 (74.41)	1015 (71.13)
MSM	519 (12.23)	357 (12.67)	162 (11.35)
IDU	609 (14.35)	360 (12.78)	249 (17.45)
Other/Unknown	5 (0.12)	4 (0.14)	1 (0.07)
ART regimen			
NNRTI+NRTI based	2812 (66.26)	1841 (65.35)	971 (68.04)
PI based	457 (10.77)	330 (11.71)	127 (8.90)
INSTI based	52 (1.23)	28 (0.99)	24 (1.68)
Other	105 (2.47)	75 (2.66)	30 (2.10)
No ART	818 (19.27)	543 (19.28)	275 (19.27)
Previous AIDS diagnosis reported			
Yes	1260 (29.69)	1004 (35.64)	256 (17.94)
No	2984 (70.31)	1813 (64.36)	1171 (82.06)
HIV viral load (copies/mL)	<i>Median</i> = 422.00 [IQR: 49.00, 92200.75]	<i>Median</i> = 76.50 [IQR: 40.00, 14588.50]	<i>Median</i> = 98853.50 [IQR: 1201.00, 334220.50]
≤1000	874 (20.59)	746 (26.48)	128 (8.97)
>1000	764 (18.00)	366 (12.99)	398 (27.89)
Not reported	2606 (61.40)	1705 (60.53)	901 (63.14)
CD4 cell count (cells/mm ³)	<i>Median</i> = 225.00 [IQR: 80.00–408.00]	<i>Median</i> = 304.50 [IQR: 161.00–483.00]	<i>Median</i> = 83.50 [IQR: 33.00–202.25]
<200	1703 (40.13)	785 (27.87)	918 (64.33)

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TABLE 1. (Continued) Study Population Demographics

	Total (%)	Non-TB Controls (%)	Patients with TB (%)
200–500	1369 (32.26)	1109 (39.37)	260 (18.22)
>500	620 (14.61)	570 (20.23)	50 (3.50)
Not reported	552 (13.01)	353 (12.53)	199 (13.95)
Platelets x 10 ⁹ /L	Median = 248.00 [IQR: 207.75–315.75]	Median = 244.00 [IQR: 207.00–288.50]	Median = 280.00 [IQR: 210.00–361.00]
<150	22 (0.52)	12 (0.43)	10 (0.70)
≥150	290 (6.83)	195 (6.92)	95 (6.66)
Not reported	3932 (92.65)	2610 (92.65)	1322 (92.64)
Total cholesterol (mmol/L)	Median = 4.40 [IQR: 3.60–5.30]	Median = 4.70 [IQR: 3.80–5.60]	Median = 3.80 [IQR: 3.15–4.60]
<3.9	581 (13.69)	321 (11.40)	260 (18.22)
3.9–5.5	818 (19.27)	606 (21.51)	212 (14.86)
>5.5	362 (8.53)	319 (11.32)	43 (3.01)
Not reported	2483 (58.51)	1571 (55.77)	912 (63.91)

Primary covariates were total cholesterol, platelets, and CD4 count. Continuous variables were categorized using clinical thresholds. Missing values were included as an indicator category of the variable. Country income group was reported descriptively.

diagnosis. CD4⁺ cell counts showed an inverse association with the diagnosis of TB. Compared with high CD4⁺ cell counts (>500 cells/μL), <200 cells/μL (aOR 12.90, 95% CI: 8.84 to 18.82) and 200–500 cells/μL (aOR 3.08, 95% CI: 2.12 to 4.48) were associated with higher odds of TB diagnosis. Total cholesterol was also inversely associated with TB. Compared with high cholesterol (>5.5 mmol/L), low cholesterol (<3.9 mmol/L) was associated with higher odds of TB (aOR 3.11, 95% CI: 1.94 to 4.98), and cholesterol between 3.9 and 5.5 mmol/L also showed increased odds of TB (aOR 1.99, 95% CI: 1.28 to 3.11). No association was observed between platelet counts and the diagnosis of TB.

DISCUSSION

In this analysis of patients with TB in a cohort of adults living with HIV in the Asia-Pacific region, the authors found that low CD4⁺ cell counts (<200 cells/μL) and low total serum cholesterol (≤3.9 mmol/L), adjusted for sex, BMI, prior AIDS, and HIV viral load, were associated with greater odds of TB diagnosis. The observed associations of sex and BMI with TB diagnosis in this analysis are consistent with established epidemiologic patterns, with adult males having a higher likelihood of TB,¹ and BMI associated with TB.²¹ By leveraging TAHOD’s nearly 2 decades of routine clinical data from PLHIV in TB-endemic countries, this analysis provides insight into a real-world population beyond controlled trial settings.²²

The results in the population of PLHIV align with the growing evidence that low cholesterol is associated with TB. Similar observations in SECONDLINE participants found an association between low baseline cholesterol and subsequent TB in PLHIV receiving ART.⁵ However, such findings in HIV-positive populations remain limited, because research on dyslipidemia and TB frequently excludes PLHIV, likely to avoid confounding by HIV coinfection, a well-known risk factor for TB.^{1,23} Although the mechanisms underlying low cholesterol and TB are poorly understood, observational studies in the general population have consistently found an

association between low serum cholesterol and TB, independent of BMI.^{10,11} Many studies assess serum cholesterol after diagnosis, comparing patients with TB with healthy controls.^{5,8,9} More recently, longitudinal analyses have strengthened the link between cholesterol and TB by showing that cholesterol levels serve as predictors of future TB risk. A study of the South Korean National Health Database found that low total cholesterol (<4.5 mmol/L) significantly increased the risk of developing TB; notably, in this study, HIV status was not reported.¹² Existing research suggests that the cholesterol–TB association may be even stronger among PLHIV. For example, in an Ethiopian cohort, serum cholesterol levels were significantly lower in patients with TB co-infected with HIV than in HIV-negative counterparts.⁸

Although this study cannot establish causality, potential mechanisms linking cholesterol and TB warrant further exploration. Cholesterol seems to play a complex role in both host immunity and the pathogenesis of *M. tuberculosis*. Experimental evidence suggests that cholesterol levels have a direct influence on immune competence. In vitro studies have demonstrated that when cholesterol availability is restricted, T-cell function is impaired, including reduced T-cell proliferation and impaired antigen presentation in mouse models,²⁴ suggesting that low serum cholesterol may be either a proxy for or a driver of immunocompromise, increasing susceptibility to TB. This relationship is complicated by evidence that *M. tuberculosis* itself requires host cholesterol to establish and maintain infection. Initially, bacteria use host-derived cholesterol to facilitate entry into macrophages.^{25,26} Once established, *M. tuberculosis* manipulates host lipid metabolism by enhancing cholesterol uptake and suppressing efflux, maintaining intracellular cholesterol availability for energy production, and facilitating chronic infection.^{27,28} In this context, TB disease may lower cholesterol levels by directing the host’s lipid resources to infected cells and disrupting normal cholesterol balance. Understanding these competing roles of cholesterol, both as a host defense mechanism and as a resource for pathogens, is

TABLE 2. Conditional Logistic Regression of Covariates Associated With TB Diagnosis

	Non-TB controls (n =)	Patients With TB (n =)	Univariate			Multivariate		
			OR	95% CI	P	OR	95% CI	P
Total	2817	1427						
Sex								
Male	1740	1074	1			1		
Female	1077	353	0.51	0.44 to 0.59	<0.0001	0.52	0.44 to 0.63	<0.0001
Age (yr)					0.0531			
≤30	766	365	1					
31–40	1169	652	1.19	1.01 to 1.40	0.037			
41–50	599	290	1.03	0.85 to 1.26	0.748			
51+	279	120	0.91	0.71 to 1.18	0.487			
Smoking					<0.0001			
Never smoked	1176	473	1					
Ever/current smoker	827	498	1.54	1.31 to 1.81	<0.0001			
Not reported	814	456	1.47	1.23 to 1.75	<0.0001			
BMI					<0.0001			<0.0001
<18.5	344	428	2.77	2.30 to 3.34	<0.0001	2.36	1.88 to 2.96	<0.0001
≥18.5 and <23	1069	497	1			1		
≥23	708	143	0.41	0.33 to 0.51	<0.0001	0.44	0.33 to 0.58	<0.0001
Not reported	696	359	1.05	0.83 to 1.33	0.679	1.03	0.77 to 1.37	0.846
Hepatitis B coinfection					0.8339			
Negative	1660	842	1					
Positive	484	240	0.98	0.81 to 1.19	0.834			
Not tested	673	345	1.01	0.82 to 1.25	0.897			
Hepatitis C coinfection					0.0010			
Negative	1863	897	1					
Positive	281	185	1.46	1.17 to 1.84	0.001			
Not tested	673	345	1.08	0.87 to 1.33	0.501			
Mode of HIV exposure					0.0002			
Heterosexual	2096	1015	1					
MSM	357	162	0.93	0.72 to 1.20	0.557			
IDU	360	249	1.54	1.25 to 1.89	<0.0001			
Other/unknown	4	1	0.52	0.06 to 4.65	0.558			
ARV treatment regimen					0.0009			
NNRTI+NRTI based	1841	971	1					
PI based	330	127	0.65	0.51 to 0.84	0.001			
INSTI based	28	24	2.15	1.05 to 4.44	0.037			
Other	75	30	0.63	0.39 to 1.02	0.060			
No ART	543	275	0.89	0.74 to 1.07	0.221			
Prior AIDS diagnosis								
Yes	1004	256	2.83	2.39 to 3.36	<0.0001	2.14	1.74 to 2.65	<0.0001
No	1813	1171	1			1		
HIV viral load (copies/mL)					<0.0001			<0.0001
≤1000	746	128	1			1		
>1000	366	398	8.94	6.72 to 11.88	<0.0001	3.15	2.21 to 4.49	<0.0001
Not reported	1705	901	4.36	3.31 to 5.75	<0.0001	2.19	1.55 to 3.10	<0.0001
CD4 cell count (cells/mm ³)					<0.0001			<0.0001
<200	785	918	20.11	14.21 to 28.47	<0.0001	12.90	8.84 to 18.82	<0.0001
200–500	1109	260	3.19	2.22 to 4.48	<0.0001	3.08	2.12 to 4.48	<0.0001
>500	570	50	1			1		
Not reported	353	199	9.03	6.13 to 13.31	<0.0001	7.95	5.19 to 12.18	<0.0001
Platelets x 10 ⁹ /L					0.2229			
<150	12	10	1.74	0.71 to 4.27	0.223			
≥150	195	95	1					

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TABLE 2. (Continued) Conditional Logistic Regression of Covariates Associated With TB Diagnosis

	Non-TB controls (n =)	Patients With TB (n =)	Univariate			Multivariate		
			OR	95% CI	P	OR	95% CI	P
Not reported	2610	1322	1.03	0.71 to 1.49	0.876			
Total cholesterol (mmol/L)					<0.0001			<0.0001
<3.9	321	260	7.74	5.23 to 11.44	<0.0001	3.11	1.94 to 4.98	<0.0001
3.9–5.5	606	212	2.95	2.04 to 4.28	<0.0001	1.99	1.28 to 3.11	0.002
>5.5	319	43	1			1		
Not reported	1571	912	1.94	1.59 to 2.37	<0.0001	3.52	2.29 to 5.43	<0.0001

Models were stratified by matched sets. Global *P*-values were derived from postestimation Wald tests. Multivariable models used backward stepwise selection (*P* < 0.10 entry; *P* < 0.05 retention).

important for interpreting cholesterol’s clinical significance in assessing TB risk. Future well-designed prospective cohort studies are warranted to establish the causal relationship between cholesterol levels and the risk of TB.

HIV coinfection is a known risk factor for TB disease.²⁹ The association of low CD4⁺ cell counts, high viral load, and increased odds of TB diagnosis in this analysis is consistent with the established evidence of HIV-associated TB.³⁰ The authors examined whether cholesterol remained associated with TB in the group of individuals with well-controlled HIV. Among individuals with suppressed HIV viral loads (≤ 1000 copies/mL), there were higher proportions of TB diagnosis among those with low cholesterol than those with high cholesterol (34.6% vs. 8.9%, *P* = 0.011). This finding suggests that the association between cholesterol and TB remains relevant even in patients with effective HIV treatment. These findings are particularly relevant given the evolving lipid landscape in HIV care. Before ART availability, HIV infection commonly caused low cholesterol levels.³¹ After ART initiation, total cholesterol levels are observed to return to preinfection serum levels in PLHIV over time.³² However, with the introduction of newer antiretroviral agents, cholesterol levels are increasing, and PLHIV are now at greater risk of metabolic syndrome.^{33,34} Consequently, current research on lipids in PLHIV has primarily focused on the link with noncommunicable diseases.^{35,36} Given the increased cardiovascular risk in PLHIV, lipid management has become standard clinical practice, primarily through statin therapy.^{37,38} This distinction between pathologic and therapeutic cholesterol reduction is supported by the previously mentioned Korean study.¹² Although low cholesterol levels were associated with increased TB risk, statin use seemed to modify this relationship, with the association losing statistical significance among statin users. Because the evidence indicates that therapeutic lowering of cholesterol does not increase TB susceptibility, standard lipid management practices for PLHIV with elevated cholesterol need not be altered because of TB concerns.

The observed association between low cholesterol and TB in PLHIV raises the possibility that cholesterol monitoring may serve as a potential TB screening tool. In resource-limited settings where CD4⁺ testing is no longer routine,³⁹ cholesterol testing might offer an alternative approach to TB risk stratification, particularly if it proves more accessible

than immunologic monitoring. However, implementation needs to consider the specific resource constraints of each setting. Health economic evaluations would be essential to determine cost-effectiveness and clinical utility compared with existing screening approaches. The optimal target population and integration with existing clinical workflows would require careful evaluation before any implementation.

These results have some important limitations. First, the observational design of the cohort data may limit the generalizability. TAHOD participants were selected based on their likelihood of remaining in care, which may bias toward those already engaged with health care. Owing to the relatively small number of prospective patients with TB, the authors included retrospective patients to increase statistical power. However, as preenrollment data were submitted voluntarily, historical patients with TB may be underreported. Although including retrospectively identified patients may introduce bias, the authors matched the retrospective patients with retrospective controls during the same calendar time, ensuring comparisons were made within the same snapshot period. Given the relatively low incidence of TB in the cohort, including retrospective patients allowed us to maximize the sample size. Data completeness represents another limitation. Cholesterol measurements were available for 1761 participants (41.49% of the study population), while platelet counts were available for only 312 participants (7.35%). The authors used the missing indicator method to retain matched pairs with incomplete covariate data, preserve the matching structure, and maximize the sample size. Although this method reduces standard error, residual bias because of missingness cannot be ruled out.²⁰ Besides the limitations of quantitative data, inconsistencies in clinical classification also restricted this analysis. TAHOD sites inconsistently reported the anatomical site and severity of TB disease, particularly pulmonary versus extrapulmonary TB classification. As a result, the authors were unable to assess risk factors according to anatomical site of TB. In addition, the absence of data on TB prophylaxis, treatment regimens, and clinical outcomes prevented evaluation of interventions or treatment outcomes. Despite these limitations, this analysis provides crucial preliminary evidence that should be examined through well-designed prospective studies.

Several future research directions emerge from these findings. To better understand the underlying mechanisms,

laboratory and longitudinal clinical studies are needed to clarify the biologic pathways linking cholesterol and TB. Future research should assess whether cholesterol monitoring can improve TB risk assessment in routine HIV care in TB-endemic settings and evaluate the feasibility and clinical utility of such monitoring. In parallel, further investigation into the impact of statin therapy on TB risk among PLHIV is needed, given its potential dual role in lipid management and immune modulation. Finally, given the inconsistent findings in the literature, additional research is needed to clarify the role of platelet levels in TB development and whether platelet counts should be considered alongside cholesterol in risk assessment strategies.

CONCLUSIONS

Low CD4⁺ cell count and low total serum cholesterol were associated with increased odds of TB diagnosis in this Asia-Pacific cohort of PLHIV. This analysis provides real-world evidence supporting the growing body of literature linking low cholesterol to TB across diverse populations. Further prospective research is needed to clarify underlying mechanisms direction of this association, and the potential clinical utility of cholesterol measurement in high-burden settings.

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REFERENCES

- World Health Organization. *Global Tuberculosis Report 2024*. Geneva; World Health Organization: 2024.
- AIDSinfo. 2024. Available at: <http://aidsinfo.unaids.org/>. Accessed December 5, 2024.
- Gupta RK, Lucas SB, Fielding KL, et al. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS*. 2015;29:1987–2002.
- SECOND-LINE Study Group, Boyd MA, Kumarasamy N, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet*. 2013;381:2091–2099.
- Henry RT, Jiamsakul A, Law M, et al. Factors associated with and characteristic of HIV/tuberculosis Co-infection: a retrospective analysis of SECOND-LINE clinical trial participants. *J Acquir Immune Defic Syndr*. 2021;87:720–729.
- Antiretroviral Therapy Cohort Collaboration ART-CC, Shepherd BE, Jenkins CA, et al. Higher rates of AIDS during the first year of antiretroviral therapy among migrants: the importance of tuberculosis. *AIDS*. 2013;27:1321–1329.
- Chaisson LH, Saraceni V, Cohn S, et al. CD4+ cell count stratification to guide tuberculosis preventive therapy for people living with HIV. *Aids*. 2020;34:139–147.
- Gebremicael G, Amare Y, Challa F, et al. Lipid profile in tuberculosis patients with and without human Immunodeficiency virus infection. *Int J Chronic Dis*. 2017;2017:3843291.
- Deniz O, Gumus S, Yaman H, et al. Serum total cholesterol, HDL-C and LDL-C concentrations significantly correlate with the radiological extent of disease and the degree of smear positivity in patients with pulmonary tuberculosis. *Clin Biochem*. 2007;40:162–166.
- Parivakkam Mani A, K S, K DK, et al. Assessment of lipid Profile in patients with pulmonary tuberculosis: an observational study. *Cureus*. 2023;15:e39244.
- Chidambaram V, Zhou L, Ruelas Castillo J, et al. Higher serum cholesterol levels are associated with reduced Systemic inflammation and mortality during tuberculosis treatment independent of body mass index. *Front Cardiovasc Med*. 2021;8:696517.
- Jo YS, Han K, Kim D, et al. Relationship between total cholesterol level and tuberculosis risk in a nationwide longitudinal cohort. *Scientific Rep*. 2021;11:16254.
- Rathod S, Samel DR, Kshirsagar P, et al. Thrombocytosis: can it be used as a marker for tuberculosis? *Int J Res Med Sci*. 2017;5:3082–3086.
- Dhibar DP, Sahu KK, Dhir V, et al. Immune thrombocytopenia as a presenting manifestation of tuberculosis- challenge in resource constraint settings. *J Clin Diagn Res*. 2016;10:Od01–od02.
- Jiamsakul A, Kerr SJ, Chandrasekaran E, et al. The occurrence of Simpson's paradox if site-level effect was ignored in the TREAT Asia HIV Observational Database. *J Clin Epidemiol*. 2016;76:183–192.
- Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32:563–572.
- Gauer RL, Braun MM. Thrombocytopenia. *Am Fam Physician*. 2012;85:612–622.
- World Health Organization. *Guidelines: Updated Recommendations on HIV Prevention, Infant Diagnosis, Antiretroviral Initiation and Monitoring*. Geneva: World Health Organization; 2021.
- WHO I. IOTF. The Asia-Pacific Perspective. *Redefining Obesity and its Treatment. Obesity: Preventing and Managing the Global Epidemic*. Geneva: WHO; 2000.
- Huberman M, Langholz B. Application of the missing-indicator method in matched case-control studies with incomplete data. *Am J Epidemiol*. 1999;150:1340–1345.
- Cho SH, Lee H, Kwon H, et al. Association of underweight status with the risk of tuberculosis: a nationwide population-based cohort study. *Scientific Rep*. 2022;12:16207.
- Zhou J, Kumarasamy N, Ditango R, et al. The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr*. 2005;38:174–179.
- Su VY, Pan SW, Yen YF, et al. Statin use and impact on tuberculosis risk. *Expert Rev Anti Infect Ther*. 2021;19:1093–1098.
- Chyu K-Y, Lio WM, Dimayuga PC, et al. Cholesterol lowering modulates T cell function in vivo and in vitro. *PLOS ONE*. 2014;9:e92095.
- Chen Z, Kong X, Ma Q, et al. The impact of Mycobacterium tuberculosis on the macrophage cholesterol metabolism pathway. *Front Immunol*. 2024;15:1402024.
- Gatfield J, Pieters J. Essential Role for Cholesterol in Entry of Mycobacteria into Macrophages. Vol 2882000.
- Pandey AK, Sasseti CM. Mycobacterial persistence requires the utilization of host cholesterol. *Proc Natl Acad Sci USA*. 2008;105:4376–4380.
- Brzostek A, Pawelczyk J, Rumijowska-Galewicz A, et al. *Mycobacterium tuberculosis* is able to accumulate and utilize cholesterol. *J Bacteriol*. 2009;191:6584–6591.
- Aliyu MH, Salihu HM. Tuberculosis and HIV disease: two decades of a dual epidemic. *Wien Klin Wochenschr*. 2003;115:685–697.
- Wolday D, Hailu B, Girma M, et al. Low CD4+ T-cell count and high HIV viral load precede the development of tuberculosis disease in a cohort of HIV-positive Ethiopians. *Ethiop Med J*. 2003;41suppl 1:67–73.
- Neaton JD, Wentworth DN. Low serum cholesterol and risk of death from AIDS. *AIDS*. 1997;11:929–930.
- Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *Jama*. 2003;289:2978–2982.
- Sarkar S, Brown TT. Lipid disorders in people with HIV. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.
- Alvarez C, Salazar R, Galindez J, et al. Metabolic syndrome in HIV-infected patients receiving antiretroviral therapy in Latin America. *Braz J Infect Dis*. 2010;14:256–263.
- Bijker R, Jiamsakul A, Uy E, et al. Cardiovascular disease-related mortality and factors associated with cardiovascular events in the TREAT Asia HIV Observational Database (TAHOD). *Hiv Med*. 2019;20:183–191.
- Uysal S, Basoglu MT, Boydak B, et al. Dyslipidemia and cardiovascular risk assessment in HIV-positive patients. *Turk Kardiyol Dern A*. 2017;45:145–152.
- Strategies for Management of Antiretroviral Therapy SMART Study Group, El-Sadr WM, Lundgren JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med*. 2006;355:2283–2296.
- Lo J. Dyslipidemia and lipid management in HIV-infected patients. *Curr Opin Endocrinol Diabetes Obes*. 2011;18:144–147.
- Syarif O, Oladele R, Gils T, et al. Resolving the CD4-testing crisis to help end AIDS-related deaths. *Lancet Glob Health*. 2025;13:e16–e18.