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Incidence and associated risk factors of anti-tuberculosis drug induced liver injury among TB patients

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Abstract

Background Tuberculosis (TB) is a global health challenge. Use of anti-TB drugs to treat TB is associated with high prevalence of side effects that include anti-TB drug induced liver injury (ATDILI). The aim of this study was to determine the incidence and associated clinical risk factors of ATDILI among South African patients on treatment for TB disease.

Methods This was an ambispective case-control study of patients on treatment for TB disease receiving drug sensitive and drug resistant treatment regimens. The retrospective and prospective studies were done from January 2021 to June 2024, involving a total of 610 patients on treatment for TB disease from whom 13 had ATDILI. From the retrospective and prospective cohorts, we extracted 13 ATDILI cases and 276 controls. Additionally, 44 severe ATDILI cases were directly recruited from the hospital to enrich the number of cases in the study. Prospective patients were followed for up to 6 months, while retrospective participants had a single visit with follow-up durations determined by their parent studies. Logistic regression analysis was performed to identify clinical and demographic factors associated with the development of ATDILI).

Results In the studied cohorts, the incidence of ATDILI was 2.1% (13/610). The ATDILI cases and controls consisted of 215 (64.6%) male patients; 57 patients were diagnosed with hepatotoxicity, 44 from the hospitalized cohort,12 from the retrospective cohort and 1 patient from the prospective cohort. The median time from the initiation of treatment to the onset of hepatotoxicity was approximately 30 days. Univariate logistic regression revealed significant differences ($p < 0.05$) in sex ($p = 0.003$), HIV status ($p = 0.002$), BMI ($p = 0.038$), hypertension ($p = 0.047$) smoking ($p = 0.006$), and alcohol consumption ($p = 0.001$) in relation to ATDILI. Multivariate analysis further revealed that female sex ($p = 0.041$), HIV status (0.022) and alcohol consumption (0.048) were independently associated with an increased risk of ATDILI.

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Conclusions The incidence of ATDILI in this study was 2.1%, lower than the previously reported range of 3–36% and highlights the need for standardized definitions of phenotypes across studies. In univariable analysis, female sex, HIV status, BMI, hypertension, smoking, and alcohol consumption were identified as potential risk factors for ATDILI. Among these, multivariable analysis suggested that female sex, HIV status and alcohol consumption were associated with an increased risk of developing ATDILI.

Keywords Tuberculosis, Anti-tuberculosis regimens, Risk factors, Drug induced liver injury

Background

Tuberculosis (TB) is a global health challenge with an estimated 10.8 million people with TB in 2023, a slight increase from 10.7 million in 2022. South Africa, with an estimated annual incidence rate of 468 per 100,000 population accounts for 3% of global patients with TB cases [1]. According to current World Health Organization (WHO) recommendations, first-line treatment of drug-sensitive TB (TB sensitive to all first-line anti-TB drugs) is a combination regimen of four TB drugs with an initial intensive 2-month phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by a 4-month continuation phase of INH and RIF [1]. Current treatment regimens for drug-resistant TB range from 6 to 20 months, with longer durations used selectively but increasingly discouraged [2].

Despite the effectiveness against TB, this polychemotherapy may cause anti-TB drug-induced liver injury (ATDILI), estimated to occur in 3–36% of patients with drug-susceptible tuberculosis [3], often leading to early treatment withdrawal to allow recovery, prolonged treatment duration, treatment failure, and selection of drug resistance [4]. ATDILI may result from direct toxicity of the primary compound, from a metabolite, or from an immunologically mediated response affecting hepatocytes, biliary epithelial cells and/or liver vasculature [4–6]. The incidence of ATDILI when INH is combined with RIF appears higher than for INH alone, with addition of PZA the risk increases further by 3-fold [7]. Because mechanisms of ATDILI are poorly understood, ATDILI is difficult to predict and avoid [8]. Therapeutic responses to ATDILI requires temporary cessation of all TB treatment for days to weeks with re-challenge of TB treatment once liver enzymes have normalized. This may result in re-escalation of liver enzymes warranting change in TB therapy. Changes in therapy are difficult as primary care clinics often do not stock alternative agents to the routine four-drug, fixed dose combination tablet for drug sensitive TB treatment. Should TB treatment be continued in the face of elevated liver enzymes, severe liver necrosis and death may result [5, 9]. Although predicting in whom, and when ATDILI will occur is challenging, some patient characteristics increase risk. These risk factors include co-infection with Human Immunodeficiency Virus (HIV), hepatitis B/C, high alcohol intake, smoking, advanced age, female sex, pre-existing chronic liver disease, malnutrition, and genetic factors [6, 10, 11]. Several studies reported that advanced age as a potential risk factor for ATDILI [6, 10] but, a study in Ethiopia showed that the incidence of ATDILI was higher in younger patients [12]. Chronic alcohol intake is a predisposing factor for ATDILI [13].Some studies suggest that female sex is an independent predictor of ATDILI [14, 15]. However, a recent report suggested that males have a higher risk of developing ATDILI [3, 5, 10]. Pre-existing chronic liver disease and malnourishment have been associated with ATDILI [10, 16]. Differences in study design, study population, ATDLI definitions and monitoring practices restricts understanding of ATDILI.

In South Africa Costiniuk et al. reported ATDILI incidence of 12% in treatment re-challenge in HIV co-infection with TB from 2005 to 2013 at King Edward VIII Hospital in Durban [17]. Although previous studies such as those by Costiniuk et al. have explored aspects of ATDILI in South African TB populations, data is limited on the combined incidence and detailed clinical risk factors using harmonized diagnostic criteria. Our ambispective case-control study aims to address this gap. We therefore aim to determine the incidence and associated clinical risk factors of ATDILI among South African TB patients.

Methods

Study design

This was an exploratory, ambispective case-control study of patients on treatment for TB disease receiving drug-sensitive and drug-resistant treatment regimens. We recruited participants from the following four retrospective studies: the India-South Africa collaboration on pharmacokinetics in drug resistant TB patients (ISA-DRPK) [18], the Adjunctive Aspirin and Ibuprofen for tuberculosis (SMA-TB) [19], the Bedaquiline, Pretomanid and Linezolid Clinical Access Program (BPAL) study [20] and Statin Adjunctive Therapy for TB (STAT-TB) study [21]. Patients with TB who received access to the Bedaquiline–Pretomanid–Linezolid (BPaL) regimen in South Africa were primarily individuals with rifampicin-resistant TB (RR-TB). Controls were defined as patients receiving standard anti-TB therapy who did not develop ATDILI throughout the course of treatment, as evidenced by normal liver function test results on routinely scheduled testing and the absence of clinical signs

of liver injury documented in their medical records. Patients with ATDILI and controls were harmonized across studies by applying the same ATDILI definition and the same exclusion criteria, and time points for liver enzyme evaluation relative to TB treatment initiation. Pharmacogenomics of hepatotoxicity in the treatment of drug sensitive and drug-resistant TB in Africans (PGx@DILI) study recruited a prospective cohort of TB patients in Gauteng, and North West, provinces in South Africa. All participants who had laboratory confirmed TB were started on TB treatment; patients with ATDILI developed biochemical evidence of liver injury during their patient follow up attributable to TB drugs after initiating TB therapy. Controls did not develop biochemical liver injury during TB therapy during the patient follow up, despite undergoing repeated screening. The study was conducted in clinics and hospitals at existing research sites where well-established cohorts were already in place, facilitating participant recruitment and data collection (Fig. 1). In prospective studies, ATDILI causality was assessed by study clinicians using Alanine aminotransferase (ALT) measurements. For retrospective cohorts and hospitalized cases, clinical records and laboratory data were reviewed to confirm ATDILI. Prospective patients were followed for up to 6 months, while retrospective participants had a single visit with follow-up durations determined by their parent studies. Two controls were matched to each case of ATDILI based on their TB drug regimen, age, gender, alcohol consumption, and HIV/ART status. Where feasible, we prioritized the selection of controls from the same study or sub-study as the ATDILI cases. The current analysis integrates data across these cohorts to examine the incidence and risk factors associated with ATDILI. By leveraging standardized clinical, demographic, and biochemical data, this approach enables a comprehensive assessment of ATDILI in a real-world, multicenter context.

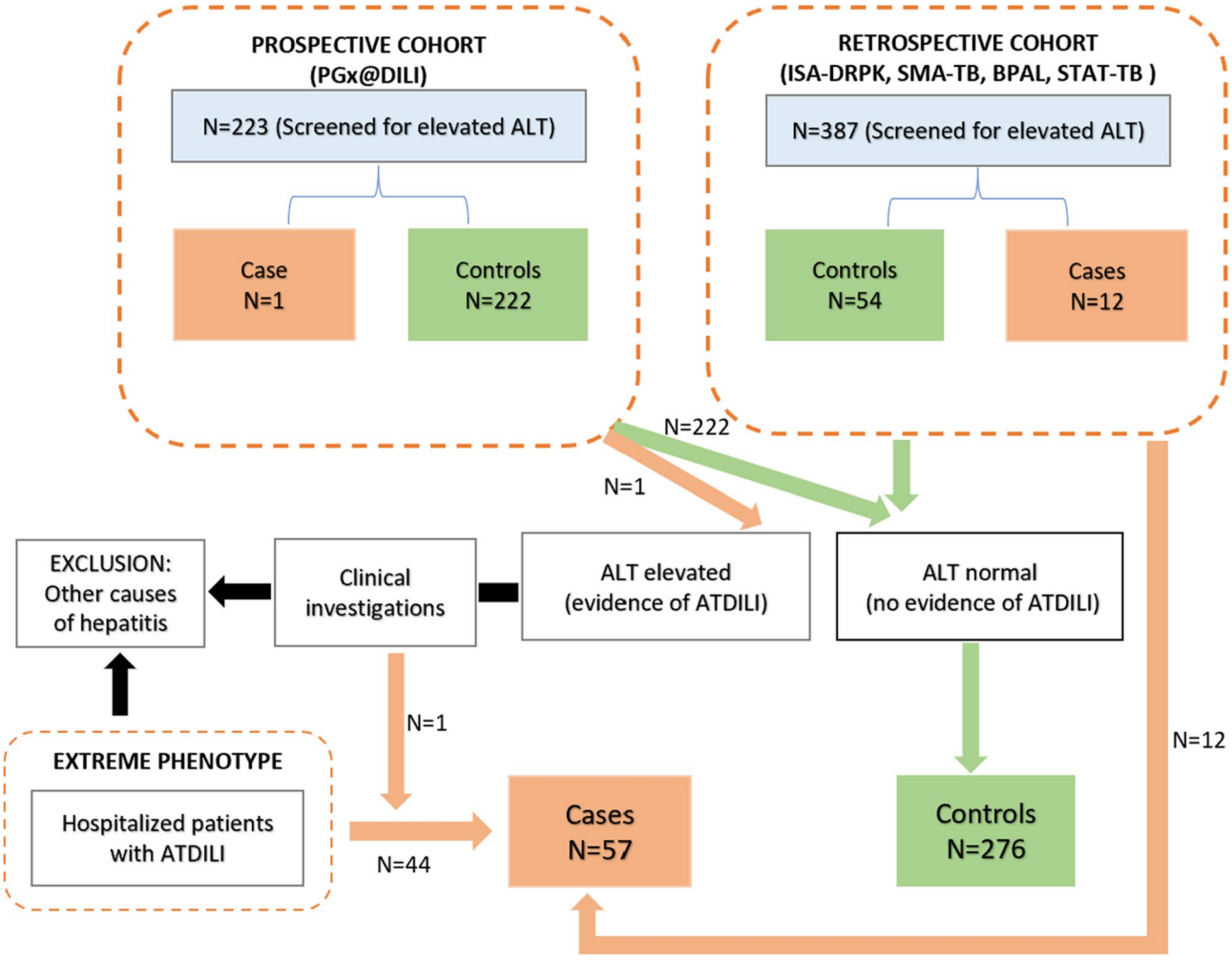


Fig. 1 The study comprised three arms: prospective, retrospective, and extreme phenotype cohorts. Extreme phenotype were patients who reported to the hospital with a suspected ATDILI case

Sample size estimation

Sample size to assess genetic associations for the risk for developing ATDILI was determined using the CaTS power calculator (http://csg.sph.umich.edu/abecasis/gas_power_calculator) developed by Skol et al. 2006 [22]. In the sample size estimation, odds ratios of 2.5 to 3.5 were assessed. A sample size of 160 cases and 320 controls was estimated to have 80% power to detect the effect of SNPs with a MAF of 0.05 for an OR of 3.5. The sample sizes and odd ratios (ORs) for this study were within ranges used and observed in a meta-analysis of risk factors for the association of the NAT-2 slow acetylator status with drug induced liver injury [23]. Moreover, studies have also found association in ATDILI case-control study with fewer samples [24, 25] suggesting that our study is powered enough to found clinical associations.

Patient inclusion/exclusion criteria

Participants were enrolled from clinical trials, observational studies, or directly by study staff. Inclusion criteria were: age > 18 years; self-identified Black South African; laboratory-confirmed Mycobacterium tuberculosis infection (Xpert Ultra or culture); ≤1 week on TB treatment at enrolment; baseline ALT within normal limits; and written informed consent. Additional consent was obtained for HIV testing (unless already documented), sample storage (blood, urine, oral swab, sputum), genomic analysis, and national/international data sharing. Exclusion criteria included: active psychiatric illness or substance abuse affecting consent or adherence; pre-treatment liver injury; hepatitis B/C infection; use of hepatotoxic drugs (other than TB); undocumented concomitant medications; refusal of HIV testing; poor TB treatment adherence; or investigator-assessed unsuitability. Participants not meeting ATDILI criteria post-enrolment were withdrawn and excluded from analysis. Hospitalized ATDILI cases were included if they met the study case definition and had clinical evidence excluding other causes of liver injury. They also consented to HIV testing, biospecimen storage, and hepatic biopsy retention. Exclusion criteria for hospitalized patients included inability to consent, critical illness with poor prognosis (< 48 h), or an alternative diagnosis for liver injury. More information on the study inclusion and exclusion criteria has been extensively addressed on the protocol paper which has been submitted for publication on a separate journal.

Anti-TB drug induced liver injury diagnosis

For the purposes of this study, patients were screened for elevated ALT using a definition of ATDILI defined as alanine transaminase (ALT) level > 120 IU/L and symptomatic (nausea, vomiting, abdominal pain, jaundice); or ALT level > 200 IU/L and asymptomatic as described by the Drug-Induced Liver Injury Network (DILIN) [26]. In the prospective arm of the study ALT, were assessed at three predefined time points: at baseline, on day 15, and on day 30 of treatment. These time points were selected based on existing evidence indicating that the majority of ATDILI cases manifest within the first months of therapy [3, 4]. For the retrospective arm, LFT data were extracted from routine clinical records and hospital databases. In this study, we categorized ATDILI cases into two subgroups for descriptive purposes: Standard ATDILI were participants who developed liver injury during the course of anti-TB treatment, confirmed through routine monitoring and clinical evaluation while severe ATDILI were participants who presented to the hospital with severe liver injury while on anti-TB therapy, often requiring hospitalization and immediate clinical intervention. Both groups were included in the ATDILI case definition, and all met the biochemical thresholds for ATDILI based on ALT elevation as per the study criteria. All the participants were put on standard four-drug regimen for drug-susceptible TB (isoniazid, rifampicin, pyrazinamide, and ethambutol). Patients later diagnosed with drug-resistant TB were transitioned to the BPaL regimen (bedaquiline, pretomanid, and linezolid). All participants provided written informed consent and the study was approved by the University of the Witwatersrand's Human Research Ethics Committee (Wits HREC: M240904).

Statistical analysis

The data were analyzed using STATA (version 18; Stata Corp, College Station, TX, USA) and R Statistical Software (version 3.4.3, https://www.r-project.org/). The incidence of ATDILI was defined as the number of new ATDILI cases observed during anti-TB treatment divided by the total number of individuals who were followed up in each individual study. In the pooled dataset, cumulative incidence was calculated by dividing the number of participants who developed ATDILI by the total number who met the inclusion criteria and had complete follow-up data. Patients hospitalized with severe ATDILI, were excluded from incidence calculations because we did not have a clearly defined denominator. Comparisons across subgroups such as sex, ALT, HIV status, BMI category, smoking and alcohol use were performed using non-parametric tests i.e. Mann-Whitney U or Kruskal-Wallis test where appropriate. To identify factors associated with ATDILI, we conducted univariable and multivariable logistic regression analyses. The outcome variable was the occurrence of ATDILI. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantify associations between clinical characteristics and ATDILI risk. Variables with a p-value < 0.20 in univariable analysis were considered for inclusion in the multivariable model. Backward elimination, guided by likelihood ratio tests ($p < 0.05$), was applied to derive the final model.

Results

Table1 summarizes the number of participants with ATDILI recruited across the various studies. A total of 57 cases were identified: 4 out of 52 participants from the ISA DRPK study, 5 out of 217 from the SMA TB study, 1 out of 90 from the BPAL study, 2 out of 16 from the STAT-TB study, and 1 from the prospective arm of the PGx@DILI study..

Among 610 participants from the prospective and routine cohorts, 13 developed ATDILI during treatment, yielding a cumulative risk of 2.1% (13/610) in patients who started TB treatment with apparent normal liver function at baseline. The 44 severe ATDILI cases were excluded from this estimate due to lack of a denominator. In our study, the average time from the initiation of anti-TB treatment to the development of ATDILI was 30 days.

Table 2 presents a comparison of the clinical and demographic characteristics among participants without ATDILI, those with standard ATDILI, and hospitalized individuals with severe ATDILI. A total of 333 patients with TB infections were enrolled, of whom 215 (64.6%) were male. The median age was 39 years (IQR: 30.00–46.00); however, patients in the severe ATDILI group were older on average (42 years) than those in the standard ATDILI (41 years) and non-ATDILI (40 years) groups. ALT levels varied significantly across the groups, participants with severe ATDILI exhibited a median ALT of 478.88 U/L (IQR: 265.00–626.00), markedly higher than the standard ATDILI group (389.06 U/L; IQR: 189.00–729.00) and the non-ATDILI group (21.53 U/L; IQR: 12.00–28.00).

HIV infection was a major comorbidity, affecting 59.2% of the entire cohort. The proportion of HIV-positive individuals differed by ATDILI severity—56.5% in non-ATDILI, 69.2% in standard ATDILI, and 84.1% in severe ATDILI. BMI across groups was generally similar, with all means approximately 23 kg/m^2. In terms of sex distribution, the standard ATDILI group had a greater proportion of female participants (61.5%, $n = 8$) than the non-ATDILI group (19.2%), while the severe ATDILI group had a more balanced sex composition (52.3%,). Unemployment was common across all groups ranging from 63.6% – 66.4%.

Although the overall prevalence of diabetes was low (1.8%), it was considerably higher in the severe ATDILI group (9.1%). A similar trend was observed with hypertension, which was more common in the standard (23.1%) and severe (13.6%) ATDILI groups compared to the non-ATDILI group (5.1%). Smoking was also prevalent (71.5% overall), with current smoking common in the standard ATDILI group (53.9%) compared to the non-ATDILI group (42.8%). Alcohol use was widespread (67.6%) but declined with ATDILI severity: 80.8% among

Table 1 Summary of sources of patients included in this study

Short Title	Long Title	Reference Numbers	Number of atdili/total (%)	Number of atdili/control included in the analysis
Group 1: Consent for Genetic Testing while in parent study				
India-SA drpk [18]	India-South Africa collaboration on pharmacokinetics in drug resistant TB patients ($n = 52$)	Wits HREC: 171115B	4/52 (7.7)	4/16
Group 2: No consent for genetic testing in parent study				
Sma-TB [19]	**Adjunctive Aspirin and Ibuprofen for Tuberculosis**: Phase 2b Randomized double-blind, placebo-controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetyl salicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen ($n = 217$)	Wits HREC: 200408B	5/217 (2.3)	5/27
Bpal [20]	Bedaquiline, Pretomanid and Linezolid clinical access program (in South Africa (($n = 90$)	*Wits HREC:201,004*	*1/90 (1.1)*	*1/4*
Stat-TB [21]	Statin Adjunctive Therapy for TB A Phase 2b Dose- finding Study of Pravastatin in Adults with Tuberculosis ($n = 16$)	*Wits HREC: 180,409*	2/16 (12.5)	2/7
Group 3: Prospectively recruited patients admitted to hospital with severe ATDILI				
Pgx@dili ##	Pharmacogenomics of Hepatotoxicity in the treatment of drug sensitive and drug-resistant TB in Africans ($n = 44$)	*Wits HREC: 220612B*	44, no denominator	44, no denominator
Group 4: Prospectively recruited cohort of patients with TB recruited at the start of TB treatment				
Pgx@dili	Pharmacogenomics of Hepatotoxicity in the treatment of drug sensitive and drug-resistant TB in Africans ($n = 223$)	*Wits HREC: 220612B*	1/222 (0.5)	1/222

Abbreviations: *atdili* anti-tuberculosis drug-induced liver injury, *India-SA drpk* India–South Africa collaboration on pharmacokinetics in drug-resistant TB patients, *Sma-TB* Adjunctive Aspirin and Ibuprofen for Tuberculosis study, *Bpal* Bedaquiline, Pretomanid, and Linezolid regimen, *Stat-TB* Statin Adjunctive Therapy for TB, *Pgx@dili* Pharmacogenomics of Hepatotoxicity in the Treatment of Drug-Sensitive and Drug-Resistant TB in Africans, *Wits HREC* University of the Witwatersrand Human Research Ethics Committee

These patients are continuing to be recruited and because we don't have a good sense of the total denominator, they are not included in the incidence calculations

Table 2 Demographic data and clinical characteristics of 333 study participants

Patient characteristics	All participants (*N* = 333)	Without ATDILI (*N* = 276)	Standard ATDILI (*N* = 13)	Severe ATDILI (*N* = 44)
Age (years), Median (IQR)	39.0 (30.0–45.0)	40.0 (30.0–46.0)	41.0 (38.0–45.0)	42.0 (34.0–49.0)
ALT (U/L), Median (IQR)	94.9 (12.0–32.0)	21.5 (12.0–28.0)	389.1 (189.0–729.0)	478.9 (265.0–626.0)
BMI Categories				
Underweight (< 18.5)	104 (31.2%)	94 (34.1%)	4 (30.8%)	15 (34.1%)
Normal (18.5–24.9)	146 (43.8%)	128 (46.4%)	4 (30.8%)	19 (43.2%)
Overweight (≥ 25.0)	83 (24.9%)	54 (19.6%)	5 (38.5%)	10 (22.7%)
Sex				
Male	215 (64.6%)	212 (80.8%)	5 (38.5%)	21 (47.7%)
Female	118 (35.4%)	64 (19.2%)	8 (61.5%)	23 (52.3%)
Employment				
Employed	77 (23.1%)	72 (26.1%)	6 (46.2%)	14 (31.8%)
Unemployed	221 (66.4%)	178 (64.5%)	5 (38.5%)	28 (63.6%)
Unknown	35 (10.5%)	26 (9.4%)	2 (15.4%)	2 (4.5%)
Diabetes				
Yes	6 (1.8%)	2 (0.7%)	0 (0.0%)	4 (9.1%)
No	327 (98.2%)	274 (99.3%)	13 (100.0%)	40 (90.9%)
Hypertension				
Yes	25 (7.5%)	14 (5.1%)	3 (23.1%)	6 (13.6%)
No	308 (92.5%)	262 (94.9%)	10 (76.9%)	38 (86.4%)
HIV Status				
Positive	197 (59.2%)	156 (56.5%)	9 (69.2%)	37 (84.1%)
Negative	136 (40.8%)	120 (43.5%)	4 (30.8%)	7 (15.9%)
Smoking				
Current	118 (35.4%)	118 (42.8%)	7 (53.8%)	12 (27.3%)
Previous	120 (36.0%)	72 (26.1%)	4 (30.8%)	15 (34.1%)
Never	95 (28.5%)	86 (31.2%)	2 (15.4%)	17 (38.6%)
Alcohol Use				
Yes	225 (67.6%)	223 (80.8%)	9 (69.2%)	23 (52.3%)
No	108 (32.4%)	53 (19.2%)	4 (30.8%)	21 (47.7%)
Jaundice				
Yes	115 (34.5%)	21 (6.3%)	1 (7.7%)	16 (36.4%)
No	218 (65.5%)	255 (93.7%)	12 (92.3%)	28 (63.6%)
Abdominal Pain				
Yes	112 (33.6%)	86 (27.6%)	4 (30.8%)	19 (43.2%)
No	221 (66.4%)	247 (72.4%)	9 (69.2%)	25 (56.8%)
Dark Urine				
Yes	94 (28.2%)	58 (17.4%)	4 (30.8%)	23 (52.3%)
No	239 (71.8%)	275 (82.6%)	9 (69.2%)	21 (47.7%)

Alcohol use is defined as any self-reported consumption of alcoholic beverages within the past month

Abbreviations: *ALT* alanine aminotransferase, *BMI* body mass index, *IQR* interquartile range, *HIV* human immunodeficiency virus

non-ATDILI participants, 69.2% in the standard ATDILI group, and 52.3% in the severe ATDILI group.

Clinical symptoms were more pronounced in patients with severe ATDILI. Jaundice was observed in 36.4% ($n = 16$, $N = 44$) of patients in this group, compared to 7.9% ($n = 1$, $N = 13$) in the standard ATDILI group and 7.6% ($n = 21$, $N = 276$) in the non-ATDILI group. Similarly, abdominal pain and dark urine were most frequent in the severe ATDILI group (43.2% and 52.3%, respectively), followed by the standard (30.8% for both symptoms) and non-ATDILI groups (31.2% and 21.0%, respectively).

All TB patients who developed anti ATDILI had documented adherence to their prescribed anti-TB treatment regimens throughout therapy. Adherence was measured using pill counts, clinician assessment, or patient self-report, depending on the study. For hospitalized cases, adherence was inferred from medical records prior to admission. Similarly, all patients living with HIV were initiated on the standard fixed-dose combination therapy comprising Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC), and Dolutegravir (DTG) (TLD regimen), in line with international treatment guidelines.

Table 3 summarizes the univariable and multivariable logistic regression analyses of factors associated with ATDILI. In the univariable analysis, female sex was significantly associated with higher odds of ATDILI (OR = 3.29, SE = 0.37, $p = 0.003$, 95% CI: 1.16–3.69). HIV-positive status was also significantly associated with increased risk (OR = 3.24, SE = 0.44, $p = 0.002$, 95% CI: 1.09–3.55). Higher body mass index (BMI) showed a borderline protective effect (OR = 0.94, SE = 0.04, $p = 0.038$, 95% CI: 0.87–1.01). Hypertension was significantly associated with increased odds of ATDILI (OR = 0.62, SE = 0.69, $p = 0.047$, 95% CI: 1.17–2.88). Smoking (OR = 3.76, SE = 0.47, $p = 0.006$, 95% CI: 1.53–3.87) and alcohol consumption (OR = 3.21, SE = 0.37, $p = 0.001$, 95% CI: 1.57–3.69) were also significantly associated with increased risk. In the multivariable analysis, sex remained a significant independent predictor, with females continuing to show higher odds of ATDILI (OR = 2.31, SE = 0.43, $p = 0.041$, 95% CI: 0.23–1.19). HIV status also remained significant (OR = 0.35, SE = 0.46, $p = 0.022$, 95% CI: 0.13–0.82). Alcohol use was independently associated with increased risk of ATDILI (OR = 2.20, SE = 0.40, $p = 0.048$, 95% CI: 1.00–4.83). However, BMI, hypertension, and smoking were not statistically significant in the multivariable model. Age was not significantly associated with ATDILI in either model and was excluded from the final multivariable analysis.

Figure 2 presents the distribution of natural log-transformed alanine aminotransferase (ln[ALT]) levels stratified by age, sex, smoking status, and alcohol use among participants with and without ATDILI. Unless otherwise specified, observations of differences across stratified

Table 3 Univariable and multivariable logistic regression analysis

Parameter	Univariable logistic regression analysis			Multivariable logistic regression analysis		
	Odd ratio (SE)	*p*-value	95% CI	Odd Ratio (SE)	*p*-value	95% CI
Age	0.99 (0.01)	0.147	0.95, 1.01	-	-	-
Sex	3.29 (0.37)	0.003	1.16, 3.69	2.31 (0.43)	0.041	0.23, 1.19
HIV	3.24 (0.44)	0.002	1.09, 3.55	0.35 (0.46)	0.022	0.13, 0.82
BMI	0.94 (0.04)	0.038	0.87, 1.01	0.98 (0.05)	0.590	0.89,1.07
Hypertension	0.62 (0.69)	0.047	1.17, 2.88	1.51 (0.82)	0.618	0.32, 8.68
Smoker	3.76 (0.47)	0.006	1.53, 3.87	1.88 (0.54)	0.244	0.66, 5.76
Alcohol	3.21 (0.37)	0.001	1.57, 3.69	2.20 (0.40)	0.048	1.00, 4.83

Standard error (*SE*), Confidence Interval (*CI*), Body mass index (*BMI*)

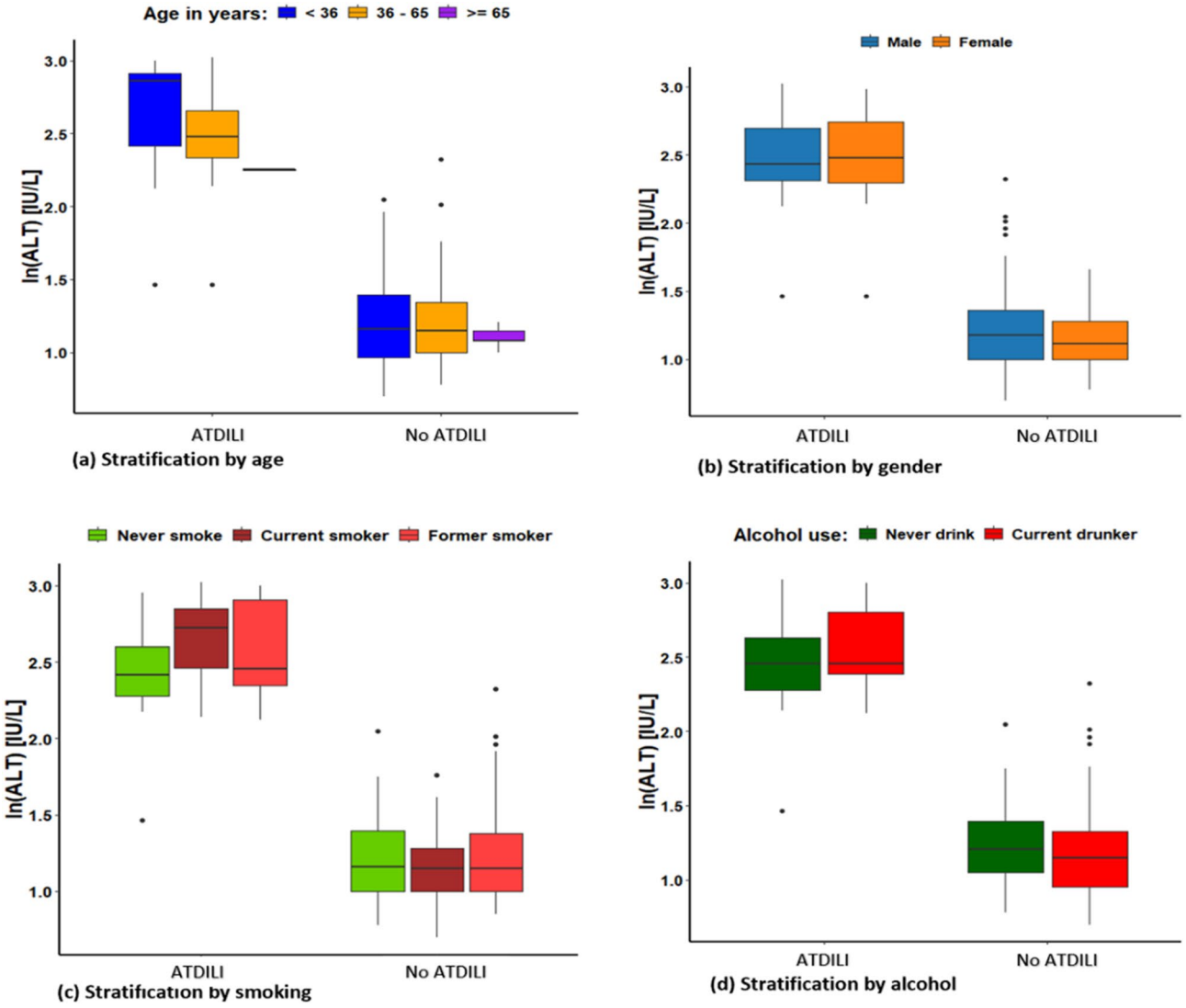


Fig. 2 Stratified box plots showing the distribution of ln(ALT) values across demographic and behavioral factors (age, gender, smoking, and alcohol use) among participants with and without ATDILI. Each box represents the interquartile range (IQR) from the 25th to the 75th percentile, with the horizontal line inside the box indicating the median. Whiskers extend to the smallest and largest values within 1.5 × IQR from the lower and upper quartiles, respectively. *P*-values for group comparisons are shown above the plots

groups are descriptive and based on visual comparison of the median and IQR values shown in Fig. 2. Figure 2. (a) illustrates the relationship between age and ln(ALT) levels. Among individuals who developed ATDILI, those aged below 36 years exhibited the highest ALT levels, followed by participants in the 36–65 years group. The oldest age group (≥ 65 years) showed the lowest ALT elevation among those with ATDILI. Specifically, these age brackets reflect young adults, middle-aged adults, and older adults, which are commonly used groupings in hepatotoxicity and pharmacogenetic studies to capture potential differences in liver function, and risk profiles across the lifespan [27].In contrast, among participants without ATDILI, ALT levels remained uniformly low across all age categories, with minimal variability. In Fig. 2. (b), ALT levels are compared between male and female participants. Both sexes showed elevated enzyme levels in the ATDILI group, with slightly higher median values in females. In the ATDILI group, the median ln(ALT) was approximately 2.47 in males and 2.53 in females, corresponding to back-transformed ALT values of approximately 11.8 U/L and 12.6 U/L, respectively.

Figure 2. (c) explores the effect of smoking on ALT levels. Current and former smokers with ATDILI exhibited higher ALT concentrations compared to never-smokers. Among participants without ATDILI, the differences were negligible, as ALT levels remained consistently low regardless of smoking history. Figure 2. (d) evaluates ALT levels in relation to alcohol use. Both current drinkers and non-drinkers who developed ATDILI had similarly elevated ALT values, indicating that alcohol use alone may not fully account for enzyme elevation in this group.

Discussion

In this ambispective case-control study, we found ATDILI incidence of 2.1% among patients on treatment for TB disease in South Africa. Female sex, HIV status and alcohol use were independent clinical risk factors significantly associated with ATDILI in multivariable analysis, while in univariable analysis, HIV status, BMI, alcohol use, hypertension, and smoking were associated. Our cohort included a subset of drug-resistant TB patients who were transitioned to the BPaL regimen, none of them developed ATDILI. This supports emerging evidence that newer regimens such as BPaL reduces hepatotoxicity risk in DR-TB patients [28]. We retained these individuals in the analysis for completeness and transparency, while noting this distinction in treatment exposures.

The incidence of ATDILI shows wide variation across ethnic and geographic populations, ranging from around 3% to 36% [29, 30]. The variation in reported incidence of ATDILI globally may be attributed to differences in underlying comorbidities, variations in the definitions used for diagnosing ATDILI, and differences in treatment practices, including different regimens [7, 31, 32]. We defined ATDILI based primarily on elevations in alanine aminotransferase (ALT). While the DILIN criteria recommend evaluating multiple liver enzymes, including AST and ALP [26], in this study ALT was selected as the primary marker due to its higher specificity for hepatocellular injury and because it was used for all the included studies. As such, ALT elevations are more reliably attributed to liver injury, particularly in the context of drug-induced hepatotoxicity [4].

A global meta-analysis by Wang et al. (2022) reported a pooled ATDILI incidence rate of 11.5% across 160 studies, while a recent Indian meta-analysis (2024) found an incidence of 12.6%, and a multi-center cohort study in Korea (2023) reported an incidence of 7.6% [29–34]. In our current study, a higher cutoff for alanine aminotransferase (ALT) values was used for case definition than those used in the Indian and Korean studies, which could partly explain the lower ATDILI incidence observed. Our adherence to the DILIN [26] definition is an important contribution towards a well-defined case-control cohort that can be used to investigate the clinical risk factors for ATDILI although direct comparisons with previous ATDILI studies should be interpreted cautiously due to differences in population characteristics and definitions of ATDILI.

The clinical presentation of ATDILI is varied and nonspecific, ranging from asymptomatic liver dysfunction to severe acute hepatitis or even acute liver failure [3, 35]. The mechanism of ATDILI primarily involves hypersensitivity reactions, which can present with symptoms such as dark urine, jaundice, fever, fatigue, and abdominal pain. In our study, the most commonly reported symptoms among participants who developed ATDILI were dark urine, jaundice, and abdominal pain, observed in approximately 65% of symptomatic cases. ATDILI can sometimes be fatal if not diagnosed and managed promptly [2]. Therefore, it is advisable to routinely monitor liver function in patients receiving anti-TB drugs.

In our study, the mean time from the initiation of anti-TB treatment to the development of ATDILI was approximately 30 days, similar to previous reports of 24–30 days reported by [29, 34, 36]. Several factors have been shown to influence the severity of ATDILI, including advanced age, sex, smoking, alcohol consumption, HIV/AIDS, and body mass index [16, 34, 36]. We found significant association between sex of patients and ATDILI. Studies have reported that women are at increased risk of developing hepatotoxicity when receiving anti-tuberculosis treatment [6].

In our study, the proportion of women with ATDILI was higher than that of men, suggesting that women receiving anti-tuberculosis drugs may be more prone

to liver damage or even liver failure. Kumar et al. [34]. conducted a study in India, reporting that approximately 70% of anti-TB drug-associated liver failure cases occurred in female patients. In contrast, among hospitalized patients with severe ATDILI, the proportion of females was almost the same as that of males but, in the standard ATDILI group, females were also more prevalent accounting for 61.54% of cases. We found no significant difference in age of patients and risk for ATDILI. There are few studies that have reported an association between age and ATDILI [36], although some studies have reported an association between advanced age and ATDILI [6, 37].

Hypertension, alcohol consumption, and smoking were also identified as risk factors for ATDILI in the univariable analysis. These findings suggest that female sex, higher BMI, HIV infection, hypertension, smoking, and alcohol use could contribute to elevated liver enzyme levels and may be considered potential risk factors for ATDILI. Given that tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and dolutegravir (DTG) (TLD) is typically well tolerated and associated with a low incidence of hepatotoxicity, it is likely that the observed risk of ATDILI in this cohort was primarily driven by the anti-TB drug regimens rather than the TLD therapy [29]. Additionally, we consistently observed that all patients appeared to have good adherence to their anti-TB therapy, which could have contributed to an increased risk of ATDILI due to higher cumulative drug exposure. Good adherence was defined as completion of ≥ 90% of prescribed doses during the treatment period under review. Our study found no significant association between the presence of diabetes and the occurrence of ATDILI. Several studies have similarly reported no significant association between diabetes and ATDILI risk [6, 38].

In this study, stratification of ln(ALT) levels by participants demographic and behavioral variables revealed notable trends. Participants younger than 65 years, particularly those less than 36 years of age, exhibited higher ln(ALT) values compared to those aged ≥ 65 years. This may reflect age-related differences in hepatic enzyme activity or susceptibility to hepatocellular injury. Female participants had marginally higher ln(ALT) levels than males among those who developed ATDILI, possibly reinforcing that female sex confers increased ATDILI risk [9]. Additionally, higher ln(ALT) levels were noted among current smokers and alcohol users, indicating possible additive hepatic stress [5, 39]. These findings underscore the need for liver function monitoring in high-risk groups during anti-TB therapy.

Even though this study focused on non-genetic risk factors for ATDILI, DNA samples from cases and controls have been collected and are currently undergoing genomic analysis to investigate genetic biomarkers associated with ATDILI. This future work aims to complement our current findings and contribute to the development of precision risk prediction tools.

Strengths and limitations

A key strength of this study is the ambispective design, including both retrospective and prospective data of patients from several studies ensuring a diverse and representative sample of ATDILI cases that enhances external validity and generalizability across patient subgroups. Additionally, by leveraging existing data and biological samples from participants who have already consented, the study maximizes efficiency and avoids unnecessary duplication of effort. The deliberate focus on patients with severe ATDILI phenotypes, especially from major hospitals, enriches the dataset with cases likely to provide deep insights into risk factors and mechanisms underlying severe liver injury. However, several limitations should be noted. First, the relatively low number of ATDILI cases may have limited the statistical power to detect significant associations in multivariable analysis. Second, the use of ALT alone to define hepatotoxicity, without incorporating other LFT parameters such as AST and ALP, may have underestimated the true incidence of ATDILI. Another limitation of the study is data heterogeneity and selection bias, as it combines data from diverse study designs and clinical settings, which may result in inconsistencies in data quality, laboratory testing, and diagnostic criteria. The other limitation of our study is the lack of comprehensive data on concomitant medications that may influence liver function. In particular, in the SMA-TB study, aspirin was administered as part of the intervention and may have contributed to hepatotoxicity in some patients. We did not adjust for the use of such non-TB medications in our regression models, which could have introduced confounding.

Conclusion

This ambispective case-control study found an incidence of ATDILI at 2.1%. While several factors such as HIV status, BMI, hypertension, smoking, and alcohol consumption were associated with ATDILI in univariable analysis, only female sex, HIV status and alcohol consumption remained significantly associated after multivariable adjustment. These findings suggest that female patients, individuals living with HIV, and those who consume alcohol may be at increased risk of developing ATDILI and could benefit from closer monitoring during tuberculosis treatment. Future studies incorporating genetic and pharmacokinetic data are recommended to improve risk prediction and prevention strategies.

Abbreviations

SMA TB	Adjunctive Aspirin and Ibuprofen for Tuberculosis
ALT	Alanine aminotransferase

ATDILI	Anti-tuberculosis drug induced liver injury
BPAL	Bedaquiline, Pretomanid and Linezolid
BMI	Body Mass Index
CI	Confidence Interval
DTG	Dolutegravir
DILIN	rug Induced Liver Injury Network
DTG	Dolutegravir
EMB	Ethambutol
HR	Hazard Ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ISA DRPK	India-South Africa collaboration on pharmacokinetics in drug resistant TB patients
IQR	Interquartile Range
INH	Isoniazid
3TC	Lamivudine
ln[ALT]	Natural log-transformed ALT
PGx@DILI	Pharmacogenomics of drug induced liver injury
PZA	Pyrazinamide
RIF	Rifampicin
SE	Standard Error
STAT-TB	Statin Adjunctive Therapy for TB
TDF	Tenofovir disoproxil fumarate
TDF	Tenofovir disoproxil fumarate
UK	United Kingdom
USA	United States of America
Wits HREC	University of Witwatersrand Human Research Ethics Committee
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11796-4.

Supplementary Material 1.

Acknowledgements

Thank you to patients who agreed to be part of this study. Enormous gratitude to Mr. Blessing Sitabule and Jocelyn Gayenga for their assistance during the study. World Health Organization. Global tuberculosis report 2024. Geneva: WHO; 2024. ISBN 978-92-4-010153-1.

Clinical trial number

NCT03882177, registered on March 18, 2019.

Authors' contributions

CM, NM, AC, RT, TB, and VN were involved in the conceptualization of the study.VN, ZW, CM, and NM contributed to the methodology.Formal analysis was conducted by VN, ZW, RO, ZP, KM, and BN.VN and ZW prepared the original draft of the manuscript.Writing – review and editing were performed by VN, ZW, CM, and NM.All authors read and approved the final manuscript.

Funding

Research reported in this publication was supported by the South African Medical Research Council (SAMRC) with funds received from Novartis and GSK R&D for Project Africa GRADIENT Grant number (SAMRC-RFA-GSK/NVS 01-2021). The study was also supported by the GATES Foundation (INV-036801) Calestous Juma Fellowship to C.M.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (Wits HREC: M240904). All study procedures were conducted in accordance with the Declaration of Helsinki and adhered to applicable national regulations and ethical guidelines governing research in South Africa. Written informed consent was obtained from all participants prior to their enrolment in the study or prior to collection of specimens that were used in this study.

Consent for publication

Written informed consent for publication of anonymized data was obtained from all participants, including those enrolled in the cohort studies.

Competing interests

The authors declare no competing interests.

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Received: 5 May 2025 / Accepted: 22 September 2025
Published online: 24 October 2025

References

1. World Health Organization. Global tuberculosis report 2024. Geneva: WHO. 2024.ISBN 978-92-4-010153-1.
2. Jain N, Sharma D, Jain NK. Newer research transforming 24-month treatment of MDR/ XDR-TB TO 6 months. Lung India. Wolters Kluwer Medknow Publications. 2025;42:140–6.
3. Zhao H, Wang Y, Zhang T, Wang Q, Xie W. Drug-induced liver injury from antituberculosis treatment: a retrospective cohort study. Med Sci Monit: Int Med J Exp Clin Res. 2020;26:e920350–1.
4. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, Kon OM, Dzvova J, Davidson H, Edwards TE, Hateley C. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. BMC Infect Dis. 2017;17(1):231.
5. Zhong T, Fan Y, Dong XL, Guo X, Wong KH, Wong WT, He D, Liu S. An investigation of the risk factors associated with anti-tuberculosis drug-induced liver injury or abnormal liver functioning in 757 patients with pulmonary tuberculosis. Front Pharmacol. 2021;12:708522.
6. Cavaco MJ, Alcobia C, Oliveiros B, Mesquita LA, Carvalho A, Matos F, Carvalho JM, Villar M, Duarte R, Mendes J, Ribeiro C. Clinical and genetic risk factors for drug-induced liver injury associated with anti-tuberculosis treatment—a study from patients of Portuguese health centers. J Pers Med. 2022;12(5):790.
7. Wang YC, Chen KH, Chen YL, Lin SW, Liu W, Da, Wang JT, et al. Pyrazinamide related prolonged drug-induced liver injury: A case report. Med (United States). 2022;101(39):E30955.
8. Xiao Y, Chen Y, Huang R, Jiang F, Zhou J, Yang T. Interpretable machine learning in predicting drug-induced liver injury among tuberculosis patients: model development and validation study. BMC Med Res Methodol. 2024;24(1):92.
9. Mao Y, Ma S, Liu C, Liu X, Su M, Li D, et al. Chinese guideline for the diagnosis and treatment of drug-induced liver injury: an update. Hepatol Int. 2024;18(2):384–419.
10. Liu Q, Guo D, Yu M, Tang D, Zhang Y, Luo M, He J. Clinical characteristics and risk factors for antituberculosis drug-induced hypersensitivity. Br J Clin Pharmacol. 2025;91(1):134–42.
11. Qi CC, Xu LR, Zhao CJ, Zhang HY, Li QY, Liu MJ, Zhang YX, Tang Z, Ma XX. Prevalence and risk factors of tuberculosis among people living with HIV/AIDS in China: a systematic review and meta-analysis. BMC Infect Dis. 2023;23(1):584.
12. Molla Y, Wubetu M, Dessie B. Anti-tuberculosis drug induced hepatotoxicity and associated factors among tuberculosis patients at selected hospitals, Ethiopia. Hepat Med. 2021;13:1–8.
13. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American thoracic society/Centers for disease control and

Prevention/Infectious diseases society of America clinical practice guidelines: treatment of Drug-Susceptible tuberculosis. Clinical Infectious Diseases. Oxford University Press. 2016;63:e147–95.
14. Floreani A, Bizzaro D, Shalaby S, Taliani G, Burra P. Sex disparity and drug-induced liver injury. Digestive and Liver Disease. Elsevier B.V. 2023;55;21–8.
15. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. Therapeutic Advances in Gastroenterology. SAGE Publications Ltd. 2023;16.
16. Liu Q, Huang L, Yan H, Zong Z, Chen Z, Wu X et al. Clinical risk factors for moderate and severe antituberculosis drug-induced liver injury. Front Pharmacol. 2024;15.
17. Costiniuk CT, Gosnell BI, Manzini TC, Du Plessis CN, Moosa MYS. Tuberculous drug-induced liver injury and treatment re-challenge in human immunodeficiency virus co-infection. J Glob Infect Dis. 2015;7(4):151–6.
18. Kengo A, Nabeemeeah F, Denti P, Sabet R, Okyere-Manu G, Abraham P, Weisner L, Mosala MH, Tshabalala S, Scholefield J, Resendiz-Galvan JE. Assessing potential drug-drug interactions between clofazimine and other frequently used agents to treat drug-resistant tuberculosis. Antimicrob Agents Chemother. 2024;68(5):e01583-23.
19. Arias L, Otwombe K, Waja Z, Tukvadze N, Korinteli T, Moloantoa T, Fonseca KL, Pillay N, Seiphetlo T, Ouchi-Vernet D, Siles A. SMA-TB: study protocol for the phase 2b randomized double-blind, placebo-controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen. Trials. 2023;24(1):435.
20. Evans D, Hirasen K, Ramushu C, Long L, Sinanovic E, Conradie F, et al. Patient and provider costs of the new BPaL regimen for drug-resistant tuberculosis treatment in South africa: A cost-effectiveness analysis. PLoS ONE. 2024;19(10):e0309034.
21. Hopkins University J. StAT-TB (Statin adjunctive therapy for TB): A phase 2b Dose-finding study of Pravastatin in adults with tuberculosis. 2019.
22. Skol AD, Scott LJ, Abecasis GR, Boehnke M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet. 2006;38(2):209–13.
23. Zhang M, Wang S, Wilffert B, Tong R, van Soolingen D, van den Hof S, et al. The association between the NAT2 genetic polymorphisms and risk of DILI during anti-TB treatment: a systematic review and meta-analysis. British Journal of Clinical Pharmacology. Blackwell Publishing Ltd. 2018;84:2747–60.
24. Chan SL, Chua AP, Aminkeng F, Chee CB, Jin S, Loh M, Gan SH, Wang YT, Brunham LR. Association and clinical utility of NAT2 in the prediction of isoniazid-induced liver injury in Singaporean patients. PLoS One. 2017;12(10):e0186200.
25. Yuliwulandari R, Susilowati RW, Wicaksono BD, Viyati K, Prayuni K, Razari I, et al. NAT2 variants are associated with drug-induced liver injury caused by antituberculosis drugs in Indonesian patients with tuberculosis. J Hum Genet. 2016;61(6):533–7.
26. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J, DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug safety. 2009;32(1):55-68.
27. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. American Journal of Gastroenterology. Nature Publishing Group; 2014;109:950–66.
28. WHO consolidated guidelines on. tuberculosis Module 4: Treatment Drug-resistant tuberculosis treatment 2022 update.
29. Wang N, Chen X, Hao Z, Guo J, Wang X, Zhu X, Yi H, Wang Q, Tang S. Incidence and temporal trend of antituberculosis drug-induced liver injury: a systematic review and meta-analysis. J Trop Med. 2022;2022(1):8266878.
30. Akkahadsee P, Jantharaksa S, Sawangjit R, Phumart P. Incidence, outcomes, and risk factors of antituberculosis drugs induced liver injury in Thailand: A retrospective cohort study. Pharma Practice. 2024;22(2):1-7.
31. Duarte R, Munsiff SS, Nahid P, Saukkonen JJ, Winston CA, Abubakar I, et al. Updates on the treatment of Drug-Susceptible and Drug-Resistant tuberculosis an official ATS/CDC/ERS/IDSA clinical practice guideline. American Journal of Respiratory and Critical Care Medicine. American Thoracic Society; 2025;211:15–33.
32. Sun Q, Zhang Q, Gu J, Sun WW, Wang P, Bai C, et al. Prevalence, risk factors, management, and treatment outcomes of first-line antituberculous drug-induced liver injury: a prospective cohort study. Pharmacoepidemiol Drug Saf. 2016;25(8):908–17.
33. Lim J, Kim JS, Kim HW, Kim YH, Jung SS, Kim JW, Oh JY, Lee H, Kim SK, Kim SH, Lyu J. Metabolic disorders are associated with drug-induced liver injury during antituberculosis treatment: a multicenter prospective observational cohort study in Korea. InOpen Forum Infectious Diseases. US: Oxford University Press; 2023;10(8):ofad422.
34. Kumar R, Kumar A, Patel R, Prakash SS, Kumar S, Surya H et al. Incidence and risk factors of antituberculosis drug-induced liver injury in India: A systematic review and meta-analysis. Indian Journal of Gastroenterology. Springer. 2024.
35. Wang Y, Xie W. Drug-induced liver injury: an overview and update. Gastroenterology and Endoscopy. KeAi Communications Co. 2023;1:102–9.
36. Jiang F, Yan H, Liang L, Du J, Jin S, Yang S, et al. Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): large cohort study involving 4652 Chinese adult tuberculosis patients. Liver Int. 2021;41(7):1565–75.
37. Hosford JD, Von Fricken ME, Lauzardo M, Chang M, Dai Y, Lyon JA et al. Hepatotoxicity from antituberculous therapy in the elderly: A systematic review HHS Public Access. Tuberculosis (Edinb). 2015;95(2):112–22. Available from: https://doi.org/10.1016/j.tube
38. D. Freire I, L. Fielding K, AJ Moore D. Does diabetes mellitus comorbidity increase the risk of drug-induced liver injury during tuberculosis treatment?. PLoS One. 2023;18(5):e0286306.
39. Zhang F, Zhang F, Qin M, Li L. Alcohol consumption as a risk factor for antituberculosis drug induced liver injury: A systematic review and meta-analysis. Microb Pathog. 2024;196:107003. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0882401024004704

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