STUDY PROTOCOL COVER PAGE

Official Study title: Observational Study on Isoniazid-Induced Hepatotoxicity: Incidence, Risk Factors and Therapeutic Strategies

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Summary

List of abbreviations

AFB: Acid-Fast Bacilli

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

BMI: Body Mass Index

CXR: Chest X-Ray

CT: Computed Tomography

eCRF: Electronic Case Report Form

DILI: Drug-Induced Liver Injury

DLCO: Diffusing Capacity of the Lung for Carbon Monoxide

FVC: Forced Vital Capacity

FEV1: Forced Expiratory Volume in 1 second

HIV: Human Immunodeficiency Virus

IGRA: Interferon-Gamma Release Assay

INH: Isoniazid

LTBI: Latent Tuberculosis Infection

MTB/RIF: Mycobacterium tuberculosis/Rifampicin resistance test

MTB/XDR: Mycobacterium tuberculosis/Extensively Drug-Resistant test

PCR: Polymerase Chain Reaction

RV: Residual Volume

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TB: Tuberculosis

TDM: Therapeutic Drug Monitoring

TLC: Total Lung Capacity

TST: Tuberculin Skin Test

ULN: Upper Limit of Normal

VA: Alveolar Volume

Abstract

Background:

Isoniazid (INH) is a key component of tuberculosis (TB) and latent TB infection (LTBI) treatment regimens. Despite its efficacy, INH-induced hepatotoxicity remains a major concern, with unpredictable onset and potentially severe outcomes. Real-world data on incidence, risk factors, and management strategies are limited, particularly in European cohorts.

Objectives:

The primary objective is to determine the incidence and clinical course of INH-induced hepatotoxicity in patients treated for TB or LTBI. Secondary objectives include identifying demographic, clinical, microbiological, and genetic risk factors; describing therapeutic regimens and management strategies (including corticosteroid use); and assessing their impact on biochemical recovery and treatment outcomes.

Methods:

This single-centre, non-profit observational study will analyse both retrospective data (2020–2024) and prospective data (2025–2028) from adult patients diagnosed with TB or LTBI and treated with INH as part of their regimen at Luigi Sacco Hospital, Milan. Data are derived from a comprehensive clinical database and include demographic characteristics, comorbidities, TB risk factors, imaging and microbiology results, therapeutic regimens, drug monitoring parameters, and adverse events. Hepatotoxicity will be defined according to international DILI criteria (ALT >5× ULN or ALT >3× ULN with symptoms). Statistical analysis will combine descriptive measures with multivariable logistic regression to explore associations between patient-related and treatment-related factors and the occurrence of hepatotoxicity.

Expected Impact:

This study will provide comprehensive real-world evidence on INH-induced hepatotoxicity, inform clinical decision-making, and support the development of strategies to optimise TB and LTBI treatment while minimising hepatic risk.

Introduction

Isoniazid (INH) continues to represent a key component of first-line therapeutic regimens for both active tuberculosis (TB) and latent tuberculosis infection (LTBI) (1). For many years, it has played a central role in global TB control strategies because of its strong bactericidal activity, low cost and simplicity of administration (1,2). Despite these advantages, INH is widely recognised as one of the principal causes of drug-induced liver injury (DILI), with reported rates of symptomatic hepatitis ranging from 0.1–0.5%, and asymptomatic liver enzyme elevation occurring in up to 20% of treated patients (3,4). The unpredictable nature of hepatotoxicity is of particular concern, as it can occur even in patients without pre-existing liver disease or other apparent vulnerabilities (5). Although several risk factors have been consistently associated with an increased likelihood of adverse hepatic events, including advanced age, regular alcohol consumption, chronic viral hepatitis, and specific genetic predispositions (6,7), these determinants do not fully account for the variability observed in clinical practice, thereby underscoring the need for further investigation into patient-specific susceptibility and the mechanisms underlying this idiosyncratic response.

Management strategies for INH-induced hepatotoxicity primarily depend on discontinuing the causative drug, accompanied by monitoring of liver function and administration of supportive interventions (7,8). However, interruption of INH in patients with active TB may compromise treatment efficacy, necessitate the use of alternative regimens that may be less effective or more toxic, or prolong treatment duration (9). In the context of LTBI, treatment discontinuation substantially reduces completion rates and compromises both individual protection and broader public health benefits (10). Therefore, developing strategies that prevent or mitigate hepatotoxicity without interrupting INH would be of marked clinical and epidemiological value.

Although the exact molecular pathways underlying INH-induced hepatotoxicity remains incompletely understood, an emerging body of evidence supports a significant immuno-allergic or immune-mediated component, as reflected by its delayed onset, reproducible recurrence upon rechallenge, occasional hypersensitivity manifestations, and proved immune reactivity to INH–protein adducts (11,12). These observations provide a biological rationale for considering immunomodulatory strategies to attenuate hepatic inflammation. Corticosteroids, with their powerful anti-inflammatory and immunosuppressive effect, have been proposed as a therapeutic option in this context. A systematic review indicates that corticosteroids have been frequently employed in clinical practice for DILI, particularly in

phenotypes characterised by immuno-allergic or autoimmune features, although robust evidence remains lacking (13). Among 24 studies analysed, six of eight investigating moderate or severe DILI reported beneficial effects of corticosteroids, including accelerated biochemical recovery, while two did not demonstrate improvement (13,14). In the context of drug-induced autoimmune hepatitis (DI-AIH), all five studies documented rapid and sustained responses without relapse following steroid withdrawal (13,14). Conversely, corticosteroids did not improve outcomes in drug-induced fulminant acute liver failure, underscoring the heterogeneity of therapeutic responses and the absence of controlled trials (15,16). Current international guidelines, including those issued from the World Health Organization, do not recommend routine corticosteroid use for INH-induced hepatotoxicity, reflecting the paucity of high-quality evidence and the need for careful patient selection (17,18).

Rationale

INH-induced hepatotoxicity represents a significant challenge in the management of TB and LTBI, while real-world evidence on its incidence, clinical course, and therapeutic strategies remains scarce. Current guidelines recommend discontinuation of INH in the presence of hepatotoxicity (7,17), compromising TB treatment success and reducing LTBI completion rates (10). No validated alternatives or evidence-based adjunctive therapies are available, and management practices widely across clinical settings.

To address this gap, we propose an observational study, retrospective and prospective, aimed to collecting data on patients with TB or LTBI who develop INH-induced hepatotoxicity. The study will include demographic and clinical characteristics, biochemical trends, treatment modifications, and patterns of adjunctive therapy use, including corticosteroids. This structured approach will allow us to:

1. Characterise the real-world manifestations and outcomes of INH-induced hepatotoxicity.
2. Describe current management strategies.
3. Explore associations between therapeutic interventions, biochemical recovery, treatment continuity, and safety.
4. Generate evidence to inform future guidelines and controlled trials.

By integrating retrospective data (from 2020) with prospective follow-up (until 2028), this study will provide a comprehensive understanding of INH-induced hepatotoxicity and support evidence-based optimisation of TB and LTBI care.

Study Objectives

Primary Objective

To assess the incidence and clinical course of INH-induced hepatotoxicity in patients treated for TB or LTBI

Primary Endpoint

Proportion of patients developing hepatotoxicity, defined according to international DILI criteria (ALT >5× ULN and/or bilirubin >3x ULN or ALT >3× ULN and/or bilirubin >2x ULN with symptoms).

Secondary Objectives

1. Identify risk factors (demographic, clinical, microbiological) associated with INH-induced hepatotoxicity, including comorbidities (e.g., HIV, systemic diseases), and lifestyle factors.
    - Endpoint**:** Odds ratios for each risk factor.
2. Describe therapeutic regimens and management strategies, including treatment modifications and corticosteroid use, and assess their impact on biochemical recovery.
    - Endpoint: Time to ALT normalisation; frequency and timing of regimen changes.
3. Analyse the impact on treatment continuity
    - Endpoint: Percentage of TB/LTBI treatment completion.
4. Explore the effectiveness of corticosteroid therapy:
    - Endpoint: Time to biochemical recovery in patients treated with corticosteroids versus those not treated.
5. Evaluate the effect of hepatotoxicity on treatment outcomes, including therapy completion rates, smear and culture conversion, and pulmonary function parameters.
    - Endpoint: Completion rate; time to smear/culture conversion; changes in Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), Total Lung Capacity (TLC).

Study Design

This is a single-centre, non-profit observational study, combining retrospective and prospective data collection, aimed at evaluating the incidence, risk factors, and management strategies of isoniazid-induced hepatotoxicity in patients treated for tuberculosis (TB) or latent tuberculosis infection (LTBI). Retrospective data will be collected from patients enrolled at the Department of Infectious Diseases, Luigi Sacco Hospital (Milan, Italy), between July 2020 and December 2025, while prospective data will be gathered from January 2026 to December 2028. All patients were or will be followed at the Tuberculosis Clinic of Luigi Sacco Hospital, including those previously hospitalised in other centres within the Lombardy Region.

Study Population

Inclusion criteria:

1. Adults aged ≥18 years.
2. Patients diagnosed with TB or LTBI who received INH as part of their treatment regimen (either first-line or second-line therapy), regardless of combination with other anti-TB drugs.
3. Normal baseline liver function tests (ALT, AST and bilirubin within reference range) and absence of clinical symptoms of liver dysfunction prior to initiation of anti-TB therapy.
4. Signed informed consent.

Exclusion criteria:

1. Patients who did not receive isoniazid during their treatment course.
2. Pre-existing liver dysfunction, including biliary origin, before anti-TB therapy.
3. Pregnancy or lactation.
4. Concomitant use of non-TB hepatotoxic drugs.
5. Abnormal hepatic function on baseline laboratory testing.
6. Known INH resistance at treatment initiation.
7. Refusal to provide informed consent.

Patients will receive standard anti-TB treatment according to international guidelines (RMP 10 mg/kg, INH 5 mg/kg), primarily administered orally. Intravenous administration may be used for inpatients, when necessary, with transition to oral therapy as soon as feasible. Additional drugs include pyrazinamide (15–30 mg/kg) and ethambutol (15–20 mg/kg) as per standard regimens.

Data Collection

Clinical, demographic, biochemical, microbiological, imaging, and pharmacological data will be inserted in a database of patients treated at Luigi Sacco Hospital TB Outpatients Clinic. Data collection will include all variables routinely recorded during TB and LTBI management, grouped as follows:

1. Demographics and Anthropometrics

- Age, gender, country of origin, ethnicity, years of stay in Italy, referral source.
- Weight, height, BMI at first visit.

2. Past Medical History and Comorbidities

- Cardiovascular, pulmonary, infective, renal, gastrointestinal, hepatic, haematological, rheumatological, endocrine, metabolic, oncological, neurological, psychiatric, and immunosuppressive conditions.
- HIV infection (CD4 count, antiretroviral therapy).
- Lifestyle factors: smoking, alcohol use, substance abuse, pregnancy status.

3. TB Risk Factors and Clinical Presentation

- Previous TB history (year of diagnosis, duration of therapy).
- TB-related symptoms, chest imaging (CXR, CT), presence of cavitation and other radiological findings.

4. Microbiology and Diagnostic Data

- Tuberculin skin test (TST), interferon-gamma release assay (IGRA).
- Sample types, AFB smear, culture, PCR, molecular resistance testing (MTB/RIF, MTB/XDR), drug resistance profile.

5. Hospitalisation and Clinical Course

- Admission and discharge dates, length of stay, oxygen requirement.

6. Anti-TB Therapy Details

- Regimens (up to eight), start and end dates, duration, reasons for modification.
- Isoniazid dosing (mg/kg), dose changes.
- Concomitant use of rifampicin and other first-line drugs.
- Corticosteroid use (prednisone dose, tapering schedule).

7. Blood tests

- Full blood count
- Liver function tests (including AST, ALT, ALP, GGT, bilirubin)
- Inflammatory markers (VES, CRP)

8. Hepatotoxicity and Adverse Events

- Occurrence of hepatotoxicity (including INH-induced hepatotoxicity), ALT peak values, timing of onset.
- Other adverse events: gastrointestinal, dermatologic, neuropathy, tendinopathy, gout, drug fever, ototoxicity.

8. Treatment Outcomes

- Completion of therapy, interruptions (intensive and continuation phases), smear and culture conversion times, total treatment duration.
- Pulmonary function tests: FVC, FEV1, TLC, RV, DLCO, VA and related percentages.

Objective	**Endpoint**	**Variables**
Primary Objective		
Assess the incidence and clinical course of INH-induced hepatotoxicity in TB or LTBI patients.	Proportion of patients developing hepatotoxicity (ALT >5× ULN and/or bilirubin >3x ULN or ALT >3× ULN and/or bilirubin >2x ULN with symptoms).	ALT, AST, bilirubin, timing of onset, hepatotoxicity classification.
Secondary Objective		
1. Identify risk factors (demographic, clinical, microbiological) associated with INH-induced hepatotoxicity, including comorbidities and lifestyle factors.	Odds ratios for each risk factor.	Age, gender, BMI, HIV status, systemic diseases, smoking, alcohol use, TB risk factors, imaging findings, microbiology results.
2. Describe therapeutic regimens and management strategies, including treatment modifications and corticosteroid use, and assess their impact on biochemical recovery.	Time to ALT normalisation; frequency and timing of regimen changes.	Regimen details (start/end dates, drugs, doses), corticosteroid use (dose, tapering schedule)
3. Analyse the impact on treatment continuity.	Percentage of TB/LTBI treatment completion.	Completion status, interruptions (intensive and continuation phases), total duration of therapy.

4. Explore the effectiveness of corticosteroid therapy.	Time to biochemical recovery in patients treated with corticosteroids versus those not treated.	ALT trend, steroid dose, tapering duration, timing of initiation.
5. Evaluate the effect of hepatotoxicity on treatment outcomes, including therapy completion rates, smear and culture conversion, and pulmonary function parameters.	Completion rate; time to smear/culture conversion; changes in pulmonary function tests.	Smear and culture conversion dates, pulmonary function tests: FVC, FEV1, TLC.

Statistical Methods

The analysis will begin with a comprehensive descriptive evaluation of the study population. Continuous variables will be summarised using measures of central tendency and dispersion (mean, standard deviation, median, interquartile range, and range). Categorical variables will be presented as absolute frequencies and percentages. The incidence of hepatotoxicity will be expressed as the proportion of affected patients within the total cohort, accompanied by 95% confidence intervals.

Inferential analyses will then be conducted to explore associations between patient characteristics and the occurrence of hepatotoxicity. Comparisons between groups will employ Student's t-test or the Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. To identify independent risk factors, multivariable logistic regression models will be fitted, estimating odds ratios and 95% confidence intervals for variables such as age, sex, BMI, HIV infection, alcohol use, and comorbidities. Variable selection will be guided by clinical relevance and statistical criteria.

Secondary endpoints will be analysed using appropriate methods. Time to ALT normalisation will be assessed through survival analysis, with Kaplan–Meier curves and log-rank tests comparing patients treated with corticosteroids versus those who were not. Treatment continuity will be evaluated by calculating completion rates and applying logistic regression to identify predictors of treatment interruption. Changes in pulmonary function will be examined using paired tests (paired t-test or Wilcoxon signed-rank test) to compare pre- and post-treatment measurements.

Missing data will be addressed through sensitivity analyses, including multiple imputation when more than 10% of key variables are incomplete. All statistical tests will be two-sided, with a significance level set at $p < 0.05$. Analyses will be performed using R (version ≥4.3).

Sample Size Calculation

The sample size for this study was determined to ensure adequate precision in estimating the proportion of patients who develop hepatotoxicity during treatment with isoniazid-containing regimens. Previous studies have reported that hepatotoxicity associated with anti-TB drugs occurs in approximately 5% to 28% of treated patients (19). For the purposes of this protocol, we adopted an expected incidence of 15%, which represents the midpoint of this range and is considered clinically plausible for our target population.

To achieve a 95% confidence level with a margin of error of ±5%, the sample size was calculated using the standard formula for estimating a proportion:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

where $Z = 1.96$ (corresponding to a 95% confidence interval), $p = 0.15$ (expected proportion), and $d = 0.05$ (desired precision). Applying these parameters yields an estimated sample size of approximately 196 patients.

This calculation provides the minimum number of participants required to reliably estimate the incidence of hepatotoxicity in the study population. To account for potential loss to follow-up and incomplete data, we plan to oversample by 10-15%, resulting in a target enrolment of 220-230 patients. This approach will ensure sufficient statistical power for the primary endpoint and allow exploratory analyses of secondary outcomes, including risk factor assessment and treatment-related variables.

Data Collection and Management

All data will be retrieved from patients' medical records and entered into the electronic Case Report Form (eCRF) by trained site personnel. The eCRF serves as an electronic data capture tool and does not constitute the original source document. Data recorded in the eCRF must be consistent with source documents; any discrepancies will be documented and explained in the source records. The Principal Investigator will ensure that the eCRF for each participant is completed accurately and signed to attest to its completeness.

Data collected from each participant will be pseudo-anonymised. Each subject will be assigned a unique alphanumeric code, ensuring that only the Investigator can link the code to the participant's identity. The file associating the participant's code with identifying information will be stored separately on a password-protected computer. The study

database will also be password-protected and accessible exclusively to authorised study personnel designated by the Principal Investigator. Data identification will be managed in such a way that individuals accessing the database cannot trace the identity of participants.

As per routine clinical practice at Luigi Sacco Hospital, all patients will provide written informed consent for participation in this study.

Informed Consent

For the retrospective component of the study, informed consent will be obtained at the first available follow-up visit. For patients for whom no follow-up visit is scheduled, the Investigator will make every reasonable effort to re-contact them, in compliance with the Italian Data Protection Authority's Decision of 9 May 2024 (Ethical Rules for Processing for Statistical or Scientific Research Purposes) and Article 110 of Legislative Decree 196/2003.

The procedure includes:

- verification of the patient's vital status;
- review of clinical documentation to retrieve contact details;
- at least three telephone contact attempts for each subject;
- sending the informed consent form by e-mail, requesting signature and return in digital or, alternatively, paper format;
- documentation of every attempt made.

There is a high likelihood that a significant proportion of patients will be deceased or untraceable due to the time elapsed (up to more than three years) since the clinical service was provided. In such cases, and where subjects remain uncontactable despite documented attempts, data processing will proceed without consent, as permitted under Article 110 of the Privacy Code, because:

- excluding these subjects would significantly compromise the quality of results, affecting statistical validity and sample representativeness;
- the minimum required sample size could not be achieved without including uncontactable subjects;
- the inclusion criteria and retrospective nature of the study, based on past clinical services, further reduce the pool of eligible patients.

The entire procedure of obtaining consent for participants in the retrospective phase of the study presents a considerable workload for the Principal Investigator. As the only person responsible for the conduct of this non-profit, non-sponsored study, the Investigator must manage all related activities without administrative or operational support, while continuing to perform routine clinical activities regulated by hospital assignments and non-delegable workloads. Furthermore, there are no dedicated funds or personnel available to support with these activities. Under these circumstances, the effort required to trace, contact, and obtain consent from over one hundred patients would be disproportionate in terms of time and resources, practically incompatible with the provision of regular clinical care, and poses a concrete risk to the feasibility of the study.

Despite these challenges, the Investigator undertakes to document all attempts to contact patients and maintain full traceability of the process, ensuring compliance with applicable data protection regulations. Data will be processed exclusively in anonymous or pseudonymised form, in accordance with the GDPR, Legislative Decree 196/2003, and the Italian Data Protection Authority's provisions. Should it become necessary to rely on derogations for organisational reasons, the Investigator, in agreement with the Data Controller, will prepare and publish a Data Protection Impact Assessment (DPIA) on the institution's website. This measure will allow the study to proceed even where explicit consent cannot be obtained, while safeguarding the rights, fundamental freedoms, and dignity of all data subjects.

For the prospective cohort, informed consent will be obtained during the initial visit prior to data collection. The Principal Investigator, supported by the multidisciplinary study team, will oversee the coordination and proper conduct of the study in accordance with this protocol. The Principal Investigator will also be responsible for archiving all study-related documentation (protocol, amendments, CRFs, interim and final reports), which will be stored electronically.

Data Retention

Investigators will retain clinical data, including the identity of all participants and original signed informed consent forms. In compliance with international standards, personal data will be stored only for the duration necessary to conduct the study, whereas study results will be retained for 25 years.

Interim Analysis

To ensure data quality, continuous and remote monitoring will be implemented throughout the study without altering the original design. For the prospective component, periodic interim analyses will be conducted to monitor data integrity and generate clinically and scientifically relevant insights.

Study Timeline

The study will commence following approval by the Ethics Committee. After obtaining this approval, an administrative start-up period of approximately six months will be required to complete all institutional procedures and authorisations.

Data collection will cover a retrospective period from July 2020 to December 2025 and a prospective period from January 2026 to December 2028, ensuring a comprehensive dataset that reflects both historical and real-time clinical practice.

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