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Hepatotoxicity from antituberculous therapy in the elderly: A systematic review

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Summary

Background—Elderly persons have the highest rates of tuberculosis (TB) in the United States compared to all other age groups. A systematic literature review was conducted to determine if older age was a risk factor for hepatotoxicity resulting from treatment with first-line drugs used to treat active (TB) and latent tuberculosis (LTBI).

Methods—A systematic review of MEDLINE, Cochrane Controlled Trial Registry, CINAHL®, and Science Citation Index Expanded (from 1970 to 2011) was performed to determine the risk of hepatotoxicity, comparing those over 60 with those under 60. A meta-analysis was performed using a random effects model along with log odds ratios and the chi-square test.

Findings—Thirty-eight studies (40,034 participants; 1208 cases of hepatotoxicity) met the selection criteria. For active TB, an overall mean effect of 0.277 (p = 0.024, 95% CI: 0.037–0.517) was observed, which is equivalent to an odds ratio of 1.32 (95% CI: 1.04–1.68). For LTBI, an overall mean effect of 1.42 (p < 0.001, 95% CI: 0.794–2.05) was observed, which translates to an odds ratio of 4.14 (95% CI: 2.21 –7.74).

Interpretation—Our analysis revealed that patients older than 60 had significantly more risk of hepatotoxicity. These studies suggest that a gentler regimen of treatment for older individuals

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Appendix A. Supplementary data: Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tube.2014.10.006.

could benefit health outcomes in this population of TB patients and minimize risks to the public's health.

Keywords

Tuberculosis; Latent tuberculosis; Therapy; Treatment; Elderly; Hepatotoxicity; Aging; Systematic review; Toxicity; Antituberculous

1. Introduction

Elderly persons (65 years of age and older) have the highest rates of tuberculosis (TB) in the United States compared to all other age groups [1]. Additionally, anti-tuberculosis treatment regimens are considered the leading cause of drug induced liver injury (DILI) and drug-induced acute liver failure in much of the developing world [2]. Most guidelines have considered hepatotoxicity from TB treatment as a function of age over 35 years old and have not discussed issues related to treating more aged individuals [3]. The current TB treatment guidelines in the United States, only mention dosage adjustments in the elderly for the aminoglycosides. Otherwise the dosing and the frequency of drugs for both active disease and latent infection is the same for elderly as for younger patients [4]. In contrast, special problems of drug tolerance in the elderly are considered in guidelines for the treatment of nontuberculous mycobacterial diseases, including initiation with a single drug and then gradual addition of other drugs [5]. Such an approach is not usually considered in managing tuberculosis due to the perceived urgency to reduce infectiousness to protect the publics' health. However after observing cases of severe drug-induced hepatotoxicity in elderly patients, we questioned whether the approach to initiation of TB treatment in the elderly should be re-evaluated. A systematic literature review was conducted to determine if older age was a risk factor for hepatotoxicity resulting from treatment with first-line drugs used to treat active and latent tuberculosis. We hypothesized that older patients have higher rates of hepatotoxicity.

2. Methods

2.1. Data sources

Studies were identified from an electronic search of MEDLINE (1970–2011), Cochrane Controlled Trial Registry (1970–2011), CINAHL® (1970–2011), and Science Citation Index Expanded (1970–2011). Variants of key words such as “tuberculosis,” “first-line drugs,” “antitubercular agents”, “hepatotoxicity,” “aged,” and “adverse effects” were used. References from articles we identified were also searched for relevant publications. Only manuscripts in English and Spanish were considered. An elderly person was defined as being an individual who was 60 years of age or older.

2.2. Study selection

Two independent reviewers (J.H. and M.V.) screened titles and abstracts for relevant content using broad criteria, yielding 321 full text selections. Information on study characteristics, overall quality, and relevant results were extracted from each article using a well-established form based off of the PRISMA model [6]. Reviewers compared notes and article selection

instruments on the texts and operated by consensus. These full texts were further scrutinized and reduced to 38 eligible publications using the following study selection criteria: 1) infection with active TB or LTBI; 2) treatment with INH, RMP, PZA, streptomycin (STM) or ethambutol (EMB) in combination or given as single drugs; 3) information on age-related rate of hepatotoxicity, defined as clinically confirmed elevation in LFTS >2–5 times the upper reference level reported by the laboratory, equivalent elevated liver enzymes, and/or symptoms of hepatitis; 4) contained participants above the age of 60. Single patient case reports, news articles and editorials were not considered for review. The main outcome of interest was TB or LTBI drug-induced hepatotoxicity leading to: mortality, change in drug/treatment regimen, hospitalization, or liver transplantation. All authors whose articles were published after 1990 were contacted and asked to provide full datasets from their published study of interest.

2.3. Data analysis

A log odds ratio was used as the effect size statistic, with estimates of odds ratios amendedbyadding0.5toeach cell frequency.A positive value of log odds ratio indicates a positive association between age >60 and hepatotoxicity, while a negative value indicates a negative association. Each effect size was weighted by its inverse variance in calculating mean effect sizes. Heterogeneity was examined using an I-square statistic, which represents the approximate proportion of total variability (0%–100%) in the association between age >60 and hepato toxicity that can be attributed to systematic difference across studies (larger percentages reflects greater heterogeneity). Heterogeneity was evaluated by chi-square test. The overall effect sizes reported are based on the random effect model since these estimates are more conservative than a fixed effect model. SAS software (SAS institute, Cary, North Carolina), version 9.2 was used for all analysis.

3. Results

There were a total of 1852 citations obtained through electronic searches and an additional 290 were obtained through reference checking. After duplications were removed, 1567 published abstracts remained, spanning from 1970 until 2011 for review. Three-hundred and twenty-one full text selections were further reviewed. However, many did not meet the study criteria due to the absence of measurable data on hepatotoxicity or failure to specify age-specific groups/events under comparison, leaving 38 studies for which we were able to obtain full datasets from the authors or article [7–44]. These included 40,034 participants with 1208 cases of hepatotoxicity, of which 339 occurred in those over the age of 60. See Figure 1. There was 95.7% agreement between the two independent reviewers based on agreement between study selection instruments. See appendix.

Twelve out of the 38 studies evaluated age-specific risk of hepatotoxicity in persons using a first-line agent for treatment of LTBI. The other 26 studies looked at treatment of active TB infection. Six of these studies focused on treatment in patients who were undergoing organ transplant or dialysis. Selected articles are listed in Table 1. All articles were in English.

3.1. Meta-analysis

The effect sizes (log odds ratios with 95% CI) from all studies (N = 38) included in the meta-analysis are listed in Table 2. Among the 38 studies, 25 (66%) reported a positive association (log odds ratio > 0), and 13 (34%) reported a negative association (log odds ratio < 0). An I-square value of 71% was calculated, indicated that most of the variation in the association between age >60 and hepatotoxicity was due heterogeneity across studies. This was confirmed by the Chi-square test ($p < 0.001$). Therefore, a random effect model was used to estimate the overall effect size. Based on the random effect model, the overall mean effect size was 0.534 (95% CI: 0.215–0.853), which is equivalent to an odds ratio of 1.71 (95% CI: 1.24–2.35). This analysis reveals that patients older than 60 had significantly higher risk of hepatotoxicity than patients 60 years or younger ($p < 0.001$, chi-square test).

Data was analyzed separately analyzed between active TB studies (Table 3) and LTBI studies (Table 4). Among the 26 studies for active TB, 16 (61%) reported a positive association (log odds ratio > 0), and 10 (39%) reported a negative association (log odds ratio <0) between age > 60 and hepatotoxicity. An I-square value of 45% ($p = 0.01$), indicates substantial variation in association due to heterogeneity across studies. Based on a random effect model, an overall mean effect of 0.277 was ($p = 0.024$, 95% CI: 0.037–0.517) is equivalent to an odds ratio of 1.32 (95% CI: 1.04–1.68), as presented in Figure 2. Among the 13 studies for LTBI, 10 (77%) reported a positive association, and 3 (23%) reported a negative association. An I-square value of 40% ($p = 0.09$) was observed. Based on the random effect model, an overall mean effect of 1.42 was observed in the LTBI studies ($p < 0.001$, 95% CI: 0.794–2.05), as seen in Figure 3, which is equivalent to an odds ratio of 4.14 (95% CI: 2.21–7.74). This analysis reveals that patients older than 60 had significantly higher risk of hepatotoxicity than patients 60 years or younger, for both active TB and LTBI treatment groups.

4. Discussion

As the population in industrially developed countries ages and the incidence of TB in these same countries recedes into more well-defined risk groups, TB among the elderly will become an increasingly important problem. Relatively little information exists in the literature that is specific to TB in the elderly and the unique challenges faced by older people with TB. The findings from this study provide evidence of the independent association of older age and the incidence of TB drug associated hepatic events. An odds ratio of 1.71 (95% CI 1.24–2.35), based on a random effects model, suggests a significant increase in hepatotoxic events in those over 60 years of age when compared to those younger than 60. The higher odds ratio observed in LTBI studies, 4.14 (95% CI 2.21–7.74) could be attributed to toxicity associated with standard INH monotherapy, or to less stringent patient monitoring in this group compared to active TB infections. Furthermore, there has never been a study looking at the rate of hepatotoxic events in older LTBI patients and measuring these events against a gain in quality-adjusted life years (QALYs). Should we be treating this older group of patients for LTBI if the risk of developing an active infection is smaller than the risk of developing a life-threatening adverse event? We believe

that further studies are warranted to determine if policy changes are necessary to address how we treat latent infection in older populations.

But is the increased risk of hepatotoxicity in older patients undergoing therapy for either latent infection or active disease really something new? Remarkably the earliest clinical trials of isoniazid did not report on the risk of hepatotoxicity in any age group. It was not until an outbreak of TB at the US Capitol in the early 1970s that the risk of hepatotoxicity from isoniazid became well known and it was from that event that the guidelines regarding age and risk were first established [45]. However, the age cut-off was above 35 years of age and co-morbidities that could contribute to hepatotoxicity were not controlled. Thus in 2003, CDC guidelines for the treatment of TB infection in the United States do not mention age at all and recommend monitoring for toxicity based on risk factors other than age [46]. Treatment guidelines for active TB disease in the US and elsewhere make few if any specific recommendations regarding age and risk of toxicity.

In a landmark observational study published in 1999, it was found that the rate of hepatotoxicity in persons receiving preventive therapy increased with increasing age (X2 for linear trend = 5.22, $p = 0.02$) [24]. More recently, investigators in India explored the risk of hepatotoxicity in all patients undergoing therapy for active TB [47]. In their prospective case-control study they found that age over 35 years was associated with increased risk of hepatotoxicity (Adjusted OR 1.61, $p \leq 0.01$). Furthermore, in another systematic review [48], which evaluated the age-related risk of hepatotoxicity in those undergoing treatment of latent TB infection (this study included 18,610 participants, including 115 cases of hepatotoxicity) it was found that the median rate of hepatotoxicity was 1.8% (range 0.07–11.9). On average, rates were higher among those aged ≥35 years (1.7%, 95%CI 1.4–2.2) than those aged <35 years (0.2%, 95%CI 0.1–0.3).

A study by Borgdorff et al. [49] suggested that transmission of pulmonary tuberculosis is associated with the age and sex of source cases. This study found that the number of secondary cases of tuberculosis generated per source case decreased with increasing age. An analysis of a contact investigation in Rotterdam in similarly found that older individuals were less likely to transmit TB [50]. Implications to be drawn from these findings include the potential mismanagement of tuberculosis and LTBI infections in elderly patients. Further research examining alternative TB treatment dosing schedules and regimens for the 60+ population are necessary to ensure patients receive the proper quality of care. These studies suggest that a gentler regimen of treatment for older individuals, who do not have additional risk factors which could impact transmission of TB infection, could benefit health outcomes in this population of TB patients and minimize risks to the publics' health. Providers and policy makers should have a serious discussion on developing stricter standards for hepatic event monitoring and grounds for treatment discontinuation in the elderly. Current treatment guidelines for those over the age of 60 should be reevaluated, as this age group has been proven to be less likely to spread disease and more likely to need treatment modification due to other underlying conditions.

These findings add to our knowledge in the sense that although numerous studies have used 35 years of age as a cut-off, no studies to our knowledge have looked at older age, 60 and

above, nor have previous studies looked systematically at the risk of older patients undergoing therapy for active or latent TB therapy. Efforts to increase the sensitivity of drug-induced adverse event monitoring, should investigate novel biomarkers, e.g., keratin M65 and micro-RNA expression, as early predictors of liver injury, that could be incorporated into current treatment practices [51,52]. The strengths of the study are the robust methodological standards used for study inclusion, the novelty of examining hepatotoxicity by the age cutoff of 60 opposed to previous standards of 35 and the biological plausibility between treatment tolerance and age. We were able to examine datasets from 38 studies, giving a final sample size of 40,034 participants with 1208 cases of hepatotoxicity, 339 of which occurred in those over the age of 60.

4.1. Limitations

The limitations include those common to most systematic reviews, being variability of subjects within the studies, limited information on other potential risk factors for hepatotoxicity, and variable definitions of hepatotoxicity. However, the purpose of this review was to determine if elderly individuals over the age of 60 on anti-tuberculosis drugs were more likely to experience hepatic events than those 60 years and younger. Only one study focused on a population of HIV infected individuals, making it difficult to extend our conclusions to this population in particular [28]. Future studies are needed to determine the driving factors behind this phenomenon, including gender, concomitant medications, alcohol use, and other co-morbidities.

The evidence provided by this systematic review and the work of others is sufficient to warrant a re-examination of current TB treatment policies in the United States and recommend enhanced monitoring for hepatotoxicity in patients 60 and older who are undergoing treatment for either latent or active TB. Moreover, it is possible we need to re-evaluate treating older LTBI patients with INH monotherapy as the four-fold risk in experiencing a hepatotoxic event might obviate the benefit of treatment. We propose for patients 60 and over, careful review of the medical record to minimize other co-morbidities, choose effective, yet potentially more “liver sparing” drug regimens to reduce toxicity as much as possible, and more frequent symptom and biochemical monitoring (e.g., every two weeks symptom and liver function monitoring) in older patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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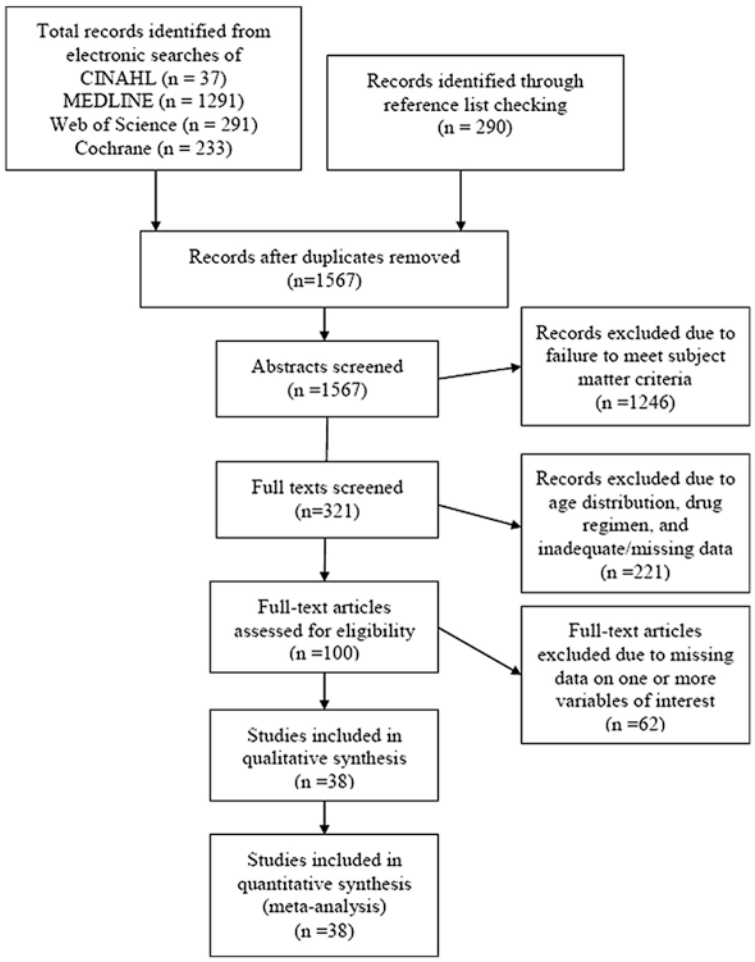

Figure 1.

Study selection process for systematic review of studies comparing age-related rates of hepatotoxicity in treatment for tuberculosis infection.

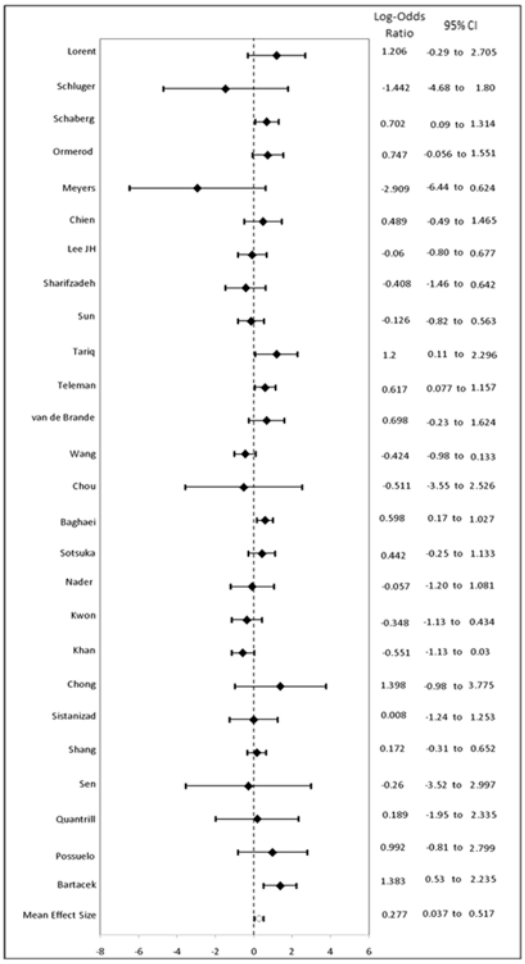

Figure 2.

Log Odds Ratios and Associated 95% Confidence Intervals of studies included in a Meta-Analysis assessing age-related risk of hepatotoxicity in those with Active Tuberculosis.

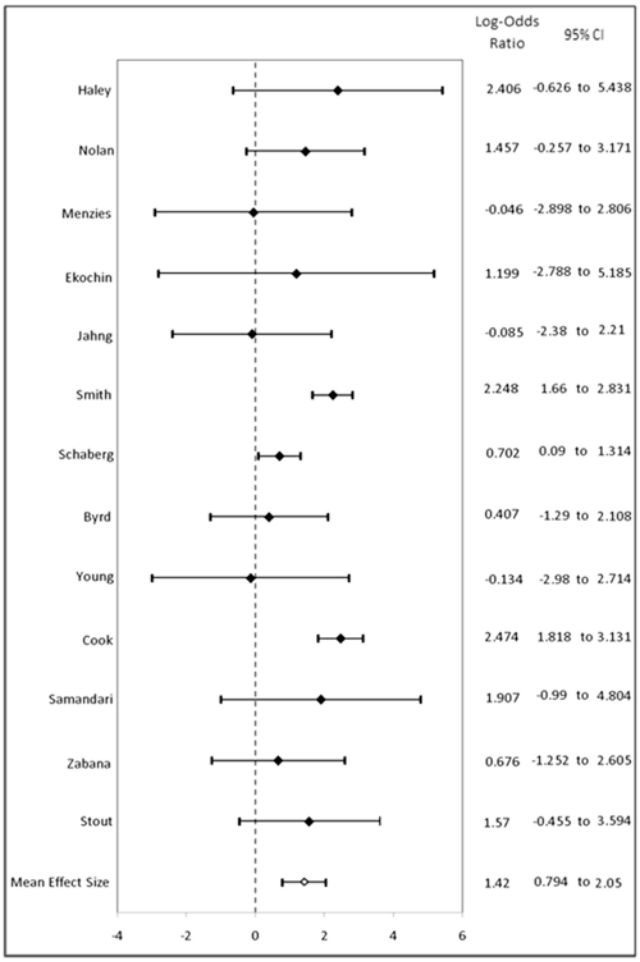

Figure 3.

Log Odds Ratios and Associated 95% Confidence Intervals of studies included in a Meta-Analysis assessing age-related risk of hepatotoxicity in those with LTBI Tuberculosis.

Table 1

Characteristics of studies included in a systematic review of age-related risk of hepatotoxicity in the treatment of LTBI and Active Tuberculosis.

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
Baghaei et al., Iran, 2010	2006–2008	Prospective	Patients treated for pulmonary tuberculosis, regardless of age *N* = 662	Elevated AST/ALT; clinically evident hepatotoxicity	Standard 6 month regimen	Active TB	No
Bartacek et al., Multinational, 2009	2003–2004	Open label RCT	Patients aged >15 years who were AFB positive and no hx of drug-induced hepatitis *N* = 1142	Elevated SGOT, as defined by guidelines; evidence of clinical hepatitis	HRZE 75/150/400/275 mg per tablet daily for 2 months followed by H/R 75/150 mg daily for 4 months	Active TB	No
Byrd et al., US, 1979	Not reported	Prospective	Patients with an intermediate PPD reaction given INH chemoprophylaxis, regardless of age *N* = 1000	SGOT >5× normal level with or without symptoms	Standard INH regimen for 9 months	LTBI	No
Chien et al., Taiwan, 2010	2004–2008	Retrospective	Patients of all ages with active TB disease with normal AST/ ALT levels of <40 IU/I at baseline *N* = 295	Increase in ALT and/or AST >3× ULN with symptoms, or 5× without symptoms	INH (5 mg/kg), RMP (10 mg/kg), EMB (15 mg/kg), PZA (20 mg/kg) for 2 months, followed by 4 months of INH, RMP, EMB	Active TB	No
Chong, Brunei, 2008	1995–2005	Retrospective	Patients with clinically diagnosed hepatobilliary TB, regardless of age *N* = 14	ALT >2–3× ULN	STP (15 mg/kg daily), RIF (10 mg/kg daily), INH (5 mg/kg daily), PZA (30 mg/kg daily) before 1997 and RIF, INH, PZA, and EMB (20 mg/kg day) after 1997, length of treatment-unknown	Active TB	No
Chou et al., Taiwan, 2004	1989–2003	Retrospective	Patients undergoing IST following HTx, with AFB confirmed TB, regardless of age *N*=5	Clinical hepatitis as defined by guidelines	Standard WHO regimen, adjusted for concentration interactions with transplant drugs. Twenty-four months for extrapulmonry, and at least twelve	Active TB	Yes

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
					months for pulmonary TB months for pulmonary TB		
Cook et al., US, 2006	2000–2006	Prospective	Patients, of all ages, treated for LTBI *N* = 291	2–5× normal ALT/AST levels	PZA (15 mg/kg daily), RIF (10 mg/kg daily); PZA (50 mg/kg), RIF (10 mg/kg) two times/ week for 2 months; RIF (10 mg/kg daily) for 4 months (6 months for children <15 years old); INH (5 mg/kg daily) for adults, INH (10 mg/kg daily) for children	LTBI	No
Ekochin et al., US, 2009	2001–2008	Retrospective	Patients, of all ages, treated for LTBI with concommittant MTX treatment *N* = 40	LFT elevation >3× ULN	INH (5 mg/kg per day for adults, and 10 mg/ kg per day for children [maximum, 300 mg per day]) length of treatment-unknown	LTBI	No
Haley et al., US, 2008	2000–2004	Retrospective	Patients >18 years of age treated for LTBI, with no previous treatment history *N* = 749	Serum ALT ≥ 120 U/l with GI symptoms or ≥200 regardless of symptoms	RMP (10 mg/kg daily) for 4 months	LTBI	No
Jahng et al., US, 2007	2003–2006	Prospective	Patients with end-stage liver disease > 18 years of age treated for LTBI *N* = 14	2× baseline LFT; clinical presentation of Hepatoxicity	INH (600 mg daily) for 4 months; RIF (300 mg daily) for 9 months	LTBI	Yes
Khan et al., Malaysia, 2010	2006–2008	Retrospective cohort	Patients of all ages with active TB disease with normal AST/ ALT levels of <40 IU/I at baseline *N* = 1542	Increase to 5× the ULN ALT/ AST; Bilirubin >2 mg/dl; clinical jaundice	INH (5 mg/kg), RMP (10 mg/kg), EMB (15 mg/kg), PZA (25 mg/kg), STP (15 mg/kg) daily until end of treatment	Active TB	No
Kwon et al., South Korea, 2007	1994–2005	Case-control	Patients of all ages with newly diagnosed active TB disease with normal AST/ALT levels of <40 IU/I at baseline, positive for HCV antibody and negative	AST/ALT > 120IU/L AST/ ALT < 200 IU/L, defined as mild AST/ALT ≥ 200–500 IU/L defined as moderate hepatotoxicity AST/ALT levels ≥ 500 IU/L defined as severe hepatotoxicity	RIF (450–600 mgdaily), INH (300 mg daily), PZA (1500 mg daily), EMB(800 to 1200 mg daily) for 2 months followed by 4 months of INH, RIF, EMB	Active TB	No

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
			for hepatitis B surface antigen for hepatitis B surface antigen N = 51				
Lee et al., South Korea, 2005	1994–2000	Prospective	Patients of all ages with active Pulmonary TB disease *N* = 232	AST/ALT increase >3 times ULN; any elevation of transaminase above basal levels in the presence of icteric hepatitis	INH (300–400 mg daily), RIF (450–600 mg daily), EMB (600–800 mg daily), PZA (1000 –1500 mg daily) for at least 6 months	Active TB	No
Lorent et al., Rawanda, 2011	2008–2010	Prospective	Patients aged ≥21 years, both inpatient and outpatient – with newly diagnosed active TB *N* = 245	Elevated liver enzymes and/or serum creatinin per guidelines	RIF (450–600 mg daily), INH (300 mg daily), PZA (1500 mg daily), EMB (800–1200 mg daily) for 6 months followed by 4 months of INH, RMP, EMB	Active TB	No
Menzies et al., Canada, Brazil, and Saudi Arabia, 2008	2004–2007	Open label RCT	Patients >18 years of age treated for LTBI *N* = 847	ALT 3–10 or 5–10× ULN w/ symptoms met criteria for grade 3 hepatotoxicity ALT >10× ULN met criteria for grade 4 toxicity	RIF (600 mg daily for 4 months) INH (300 mg daily for 9 months)	LTBI	No
Meyers et al., US, 2000	1988–1996	Retrospective	Patients undergoing therapy for active TB following OLTx, regardless of age *N* = 8	Elevation in AST/ALT per guidelines; histological features consistent with toxicity	RIF (450–600 mg daily), INH (300 mg daily), PZA (1500 mg daily), EMB (15 mg/kg/day) for 6 months, followed by 6–12 months of INH, RIF or OFL (800 mg daily) and EMB (15 mg/kg/day)	Active TB	Yes
Nader et al., Brazil, 2010	1998–2006	Retrospective	Patients ≥18 years of age treated for active TB infection *N* = 534	Increase in ALT >3× ULN; total bilirubin >2× ULN	Patients 20–40 kg: RMP (300 mg), INH (200 mg), PZA (1000 mg); Patients 40 –60 kg: RMP (450 mg), INH (300), PZA (1500 mg); Patients > 60 kg: RMP (600 mg), INH (400 mg), PZA (2000 mg); Standard RHZ length of treatment	Active TB	No
Nolan et al., US, 1999	1989–1995	Prospective	Patients, of all ages, treated for LTBI *N* = 11,141	AST 5× ULN without symptoms, clinical symptoms of hepatitis; resolution of signs	INH preventative therapy, length of	LTBI	No

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
				and symptoms after withdrawl of INH and symptoms after withdrawl of INH	Nd atment-6–12 Nd months		
Ormerod et al., UK, 1996	1978–1992	Retrospective cohort	Patients, of all ages, treated for active TB disease *N* = 1317	Jaundice and/or elevation of ALT 5× pretreatment level	Adults: INH (300 mg), RMP (450–600 mg), PZA (1500–2000 mg), EMB (15 mg/kg), STM (1.0 gm 6 d/w) Children: INH (10 mg/kg), RMP (10 mg/kg), PZA (30 mg/kg), 2–4 months of RMP, INH, EMB, with continuation of INH/EMB for up to 15 mos/ RMP/INH for up to 12 months	Active TB	No
Possuelo et al., Brazil, 2008	2005–2007	Prospective	Patient ≥ 18 years of age with newly diagnosed active TB disease *N* = 253	AST/ALT > 3× ULN; and/or total bilirubin >2.0 mg/dL	<45 kg: RIF (300 mg), INH (200 mg), PZA (1000 mg); 45–55 kg: RIF (450 mg), INH (300 mg), PZA (1500 mg); >55 kg: RIF (600 mg), INH (400 mg), PZA (2000 mg); 2 months of daily INH, RIF, PZA, EMB followed by 4 months INH, RMP daily	Active TB	No
Quantrill et al., UK, 2003	1986–1999	Retrospective	Patients of all ages with active TB disease and CRF *N* = 24	Clinical Hepatitis as defined by BTS guidelines	Standard combination and doses of RMP, INH and PZA, per the BTS Guidelines for 6–18 months	Active TB	Yes
Samandari et al., Botswana, 2011	2004–2006	RCT	Patient ≥18 years of age or older with HIV infection and no symptoms or previous treatment of active TB *N* = 1995	AST/ALT > 5× ULN, irrespective of symptoms	INH (300 mg per day) for individuals weighing 30–49 kg; INH (400 mg per day) for those weighing ≥50 kg; 6 months vs 36 months INH prophylaxis	LTBI	No
Schaberg et al., Germany, 1996	1990–1994	Retrospective	Patients of all ages with active TB disease *N* = 519	AST/ALT 3× the ULM; SGOT>54 U/L; SGPT>60 U/L	INH (5 m/kg daily), RIF (10 mg/kg daily), and PZA (25–30 mg/kg daily), with	Active TB	No

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
					or without EMB and/or STP; length of treatment not reported		
					or without EMB and/or STP; length of treatment not reported		
					or without EMB and/or STP; length of treatment not reported		
					or without EMB and/or STP; length of treatment not reported		
Schluger et al., US, 1996	1988–1995	Retrospective	Patients undergoing therapy for LTBI or active TB following OLTx, regardless of age *N* = 13	Abnormal LFTs; exclusion of other causes of hepatitis	INH (300 mg daily); INH (300 mg daily), RIF (600 mg daily), EMB (15 mg/kg daily), PZA (20 mg/kg daily) or HRZE + OFL (800 mg daily) for up to 1 year	Both	Yes
Sen et al., Turkey, 2008	2002–2007	Retrospective	Patients of all ages undergoing treatment for active TB with ESRD *N* = 18	Elevated AST/ALT; jaundice	INH (300 mg daily), RMP (600 mg daily), MPZ (35–40 mg/kg 3d/w), EMB (20 mg/kg 3 d/w) for 2 months followed by INH and RMP for 4–6 months	Active TB	Yes
Shang et al., China, 2011	2007–2008	Prospective	Patients of all ages undergoing treatment for active TB *N* = 4304	ALT/AST > three times ULN; >2× ULN, when other causes were excluded	HRZE 75/150/400/275 mg per tablet daily for 2 months followed by H/R 75/150 mg daily for 4 months with or without STP	Active TB	No
Sharifzadeh et al., Iran, 2005	1999–2002	Prospective	Patients of all ages undergoing treatment for active TB *N* = 112	AST/ALT > three times ULN with any clinical signs/ symptoms or AST/ALT > five times ULN with no symptoms	RIF (10 mg/kg daily), INH (5 mg/kg daily), PZA (25 mg/kg daily), EMB (15 mg/kg daily) for standard treatment length	Active TB	No
Sistanizad et al., Iran, 2011	2006–2008	Prospective	Patients of all ages undergoing treatment for newly diagnosed active TB disease *N* = 50	ALT or AST > 2–3× ULN; clinical symptoms of liver disease i.e., jaundice and ascites	INH (5 mg/kg), RIF (10 mg/kg), PZA (25 –30 mg/kg), EMB (15 mg/kg daily) for 2 months, followed by 4 months of INH, RIF	Active TB	No
Smith et al., Canada, 2011	1998–2003	Cross-sectional	Patients of all ages undergoing treatment for LTBI = 9145	Toxic hepatitis as defined by guidelines	INH (5 mg/kg daily) for 6 months; RIF (10 mg/kg daily) for 4 months	LTBI	No

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
Sotsuka et al., Japan, 2011	Not reported	Prospective	Patients of all ages undergoing treatment for active TB = 144	AST/ALT > 5× ULN, irrespective of symptoms; AST/ALT > 3× ULN in the presence of symptoms; Bilirubin >3 mg/dL	INH (5 mg/kg), RIF (10 mg/kg), PZA (25 –30 mg/kg), EMB (15 mg/kg daily) for 2 months, followed by 4 months of INH, RIF; HER or HRZ were alternative regimens	Active TB	No
Stout et al., US, 2003	1999–2002	Retrospective	Patients of all ages undergoing treatment for LTBI *N* = 119	AST/ALT >5× ULN with one or more accompanying clinical symptoms/signs (nausea, vomiting, abdominal pain, or jaundice)	60 doses of daily RIF (10 mg/kg, maximum daily dose of 600 mg) plus PZA (20 mg/kg, maximum daily dose of 2000 mg) or 16 doses of twice-weekly RIF (10 mg/kg, maximum dose of 600 mg) plus PZA (50 mg/kg, maximum dose of 4000 mg) for two months	LTBI	No
Sun et al., Taiwan, 2009	2000–2001	Prospective	Patients of all ages undergoing treatment for active TB *N* = 261	AST/ALT > 5× ULN, irrespective of symptoms; AST/ALT > 3× ULN in the presence of symptoms; Bilirubin >3 mg/dL	HERZ; HRZ; Combinations of: RIF (mg/kg/ day) INH (mg/kg/day) EMB (mg/kg/day) PZA (mg/kg/day)	Active TB	No
Tariq et al., Pakistan, 2009	Not reported	Descriptive	Patients of all ages undergoing treatment for active TB *N* = 500	ALT > 5× ULN; clinically evident hepatitis	Standard first-line regimen of HRZE	Active TB	No
Teleman et al., Singapore, 2002	1998	Retrospective	Patients >16 years of age undergoing treatment for active TB disease *N* = 1036	ALT/AST > 3× ULN; Bilirubin > ULN and ALT and/or AST >2 × ULN	INH, RMP, PZA with or without EMB or STP for 6 months; RMP, EMB, INH for 9 months	Active TB	No
van den Brande et al., Belgium, 1995	1980–1985	Retrospective	Patients of all ages undergoing treatment for active TB *N* = 131	ALT > 5× ULN with or without symptoms	RIF (10 mg/kg daily), INH (5 mg/kg daily), EMB (25 mg/kg for 6 wk and 15 mg/kg thereafter) for 9 months	Active TB	No
Wang et al., Taiwan, 2011	2007–2008	Prospective	Patients >16 years of age undergoing treatment for active TB disease *N* = 360	AST/ALT > 5× ULN, irrespective of symptoms; AST/ALT > 3× ULN in the presence of symptoms	Standard daily INH, RMP, EMB, PZA for 2 months followed	Active TB	No

Studies assessing hepatotoxicity reference, country, year	Study period	Study design	Study population number of subjects	Definition of hepatotoxicity	Drugs administered and length of treatment	LTBI/Active TB disease	Transplant/Dialysis
					by daily INH and RMP by daily INH and RMP		
Young et al., US, 2009	2003–2007	Retrospective	Patients > 18 years of age treated for LTBI $N = 777$	ALT > 2.5–5× ULN with or without symptoms	INH (5 mg/kg daily) for 9 months; RIF (10 mg/kg daily) for 4 months	LTBI	No
Zabana et al., Spain, 2008	2003–2006	Retrospective	Patients of all ages with LTBI and concomitant anti-TNF therapy $N = 83$	AST/ALT elevation by standard definition	INH (5 mg/kg daily) for 6 months; INH (15 mg/kg 2× weekly) for 6 months; INH (5 mg/kg daily) for 9 months; INH (15 mg/kg 2× weekly) for 9 months; INH (5 mg/kg daily) for 12 months; RMP (15 mg/kg daily), INH (10 mg/kg daily) for 6 months	LTBI	No

Table 2

Characteristics and Log Odds Ratios of studies included in a Meta-Analysis.

Study	ID	Study N	# ≥60	#with Event	Event ≥60	LTBI/Active TB	Transplant-dialysis	Log OR	95% CI	
Bartacek	1	1142	89	30	7	Active TB	No	1.383	0.531	2.235
Possuelo	2	253	10	14	1	Active TB	No	0.992	−0.816	2.799
Quantrill	3	24	6	4	1	Active TB	Yes	0.189	−1.957	2.335
Sen	4	18	2	3	0	Active TB	Yes	−0.260	−3.516	2.997
Shang	5	4304	754	106	21	Active TB	No	0.172	−0.307	0.652
Sistanizad	6	50	18	14	5	Active TB	No	0.008	−1.238	1.253
Chong	10	14	5	3	2	Active TB	No	1.398	−0.978	3.775
Khan	12	1548	256	126	13	Active TB	No	−0.551	−1.132	0.030
Kwon	13	151	48	42	11	Active TB	No	−0.348	−1.130	0.434
Nader	14	534	40	47	3	Active TB	No	−0.057	−1.195	1.081
Sotsuka	15	144	54	52	23	Active TB	No	0.442	−0.250	1.133
Baghaei	17	662	246	99	49	Active TB	No	0.598	0.170	1.027
Chou	19	5	2	3	1	Active TB	Yes	−0.511	−3.547	2.526
Wang	20	360	182	60	25	Active TB	No	−0.424	−0.981	0.133
van de Brande	21	131	64	22	14	Active TB	No	0.698	−0.228	1.624
Teleman	22	1036	397	55	29	Active TB	No	0.617	0.077	1.157
Tariq	23	500	20	40	4	Active TB	No	1.200	0.105	2.296
Sun	24	261	94	42	14	Active TB	No	−0.126	−0.815	0.563
Sharifzadeh	26	112	24	31	5	Active TB	No	−0.408	−1.457	0.642
Lee JH	28	232	119	32	16	Active TB	No	−0.060	−0.796	0.677
Chien	29	295	208	25	20	Active TB	No	0.489	−0.487	1.465
Meyers	32	8	2	5	0	Active TB	Yes	−2.909	−6.441	0.624
Ormerod	34	1317	203	30	8	Active TB	No	0.747	−0.056	1.551
Schaberg	36	519	102	55	17	Both	No	0.702	0.090	1.314
Schluger	37	13	2	5	0	Active TB	Yes	−1.442	−4.684	1.799
Lorent	38	245	9	23	2	Active TB	No	1.206	−0.292	2.705
Stout	7	119	10	4	1	LTBI	No	1.570	−0.455	3.594
Zabana	8	83	6	10	1	LTBI	No	0.676	−1.252	2.605

Study	ID	Study N	# ≥60	#with Event	Event ≥60	LTBI/Active TB	Transplant-dialysis	Log OR	95% CI	
Samandari	9	1995	7	19	0	LTBI	No	1.907	−0.990	4.804
Cook	11	291	71	57	38	LTBI	No	2.474	1.818	3.131
Young	16	777	33	12	0	LTBI	No	−0.134	−2.982	2.714
Byrd	18	1000	15	64	1	LTBI	No	0.407	−1.293	2.108
Smith	25	9145	857	45	22	LTBI	No	2.248	1.666	2.831
Jahng	27	14	4	4	1	LTBI	Yes	−0.085	−2.380	2.210
Ekochin	30	40	9	0	0	LTBI	No	1.199	−2.788	5.185
Menzies	31	802	34	11	0	LTBI	No	−0.046	−2.898	2.806
Nolan	33	11,141	359	11	1	LTBI	No	1.457	−0.257	3.171
Haley	35	749	9	3	0	LTBI	No	2.406	−0.626	5.438
Mean effect								**0.534**	**0.215**	**0.853**

Table 3

Characteristics and Log Odds Ratios of studies included in a Meta-Analysis assessing age-related risk of hepatotoxicity in those with Active Tuberculosis only.

Study	ID	Study N	# ≥60	# with Event	Event & ≥ 60	Transplant-dialysis (Yes/No)	Log OR	95% CI	
Bartacek	1	1142	89	30	7	No	1.383	0.531	2.235
Possuelo	2	253	10	14	1	No	0.992	−0.816	2.799
Quantrill	3	24	6	4	1	Yes	0.189	−1.957	2.335
Sen	4	18	2	3	0	Yes	−0.260	−3.516	2.997
Shang	5	4304	754	106	21	No	0.172	−0.307	0.652
Sistanizad	6	50	18	14	5	No	0.008	−1.238	1.253
Chong	10	14	5	3	2	No	1.398	−0.978	3.775
Khan	12	1548	256	126	13	No	−0.551	−1.132	0.030
Kwon	13	151	48	42	11	No	−0.348	−1.130	0.434
Nader	14	534	40	47	3	No	−0.057	−1.195	1.081
Sotsuka	15	144	54	52	23	No	0.442	−0.250	1.133
Baghaei	17	662	246	99	49	No	0.598	0.170	1.027
Chou	19	5	2	3	1	Yes	−0.511	−3.547	2.526
Wang	20	360	182	60	25	No	−0.424	−0.981	0.133
van de Brande	21	131	64	22	14	No	0.698	−0.228	1.624
Teleman	22	1036	397	55	29	No	0.617	0.077	1.157
Tariq	23	500	20	40	4	No	1.200	0.105	2.296
Sun	24	261	94	42	14	No	−0.126	−0.815	0.563
Sharifzadeh	26	112	24	31	5	No	−0.408	−1.457	0.642
Lee JH	28	232	119	32	16	No	−0.060	−0.796	0.677
Chien	29	295	208	25	20	No	0.489	−0.487	1.465
Meyers	32	8	2	5	0	Yes	−2.909	−6.441	0.624
Ormerod	34	1317	203	30	8	No	0.747	−0.056	1.551
Schaberg	36	519	102	55	17	No	0.702	0.090	1.314
Schluger	37	13	2	5	0	Yes	−1.442	−4.684	1.799
Lorent	38	245	9	23	2	No	1.206	−0.292	2.705
Mean effect							**0.277**	**0.037**	**0.517**

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Table 4

Characteristics and Log Odds Ratios of studies included in a Meta-Analysis assessing age-related risk of hepatotoxicity in those with LTBI only.

Study	ID	Study N	# ≥60	# with Event	Event & ≥60	Transplant-dialysis (Yes/No)	Log OR	95% CI	
Stout	7	119	10	4	1	No	1.570	−0.455	3.594
Zabana	8	83	6	10	1	No	0.676	−1.252	2.605
Samandari	9	1995	7	19	0	No	1.907	−0.990	4.804
Cook	11	291	71	57	38	No	2.474	1.818	3.131
Young	16	777	33	12	0	No	−0.134	−2.982	2.714
Byrd	18	1000	15	64	1	No	0.407	−1.293	2.108
Schaberg	36	519	102	55	17	No	0.702	0.090	1.314
Smith	25	9145	857	45	22	No	2.248	1.666	2.831
Jahng	27	14	4	4	1	Yes	−0.085	−2.380	2.210
Ekochin	30	40	9	0	0	No	1.199	−2.788	5.185
Menzies	31	802	34	11	0	No	−0.046	−2.898	2.806
Nolan	33	11,141	359	11	1	No	1.457	−0.257	3.171
Haley	35	749	9	3	0	No	2.406	−0.626	5.438
Mean effect							**1.420**	**0.794**	**2.050**