DOES DIABETES MELLITUS COMORBIDITY INCREASE THE RISK OF DRUG-INDUCED LIVER INJURY DURING TUBERCULOSIS TREATMENT?

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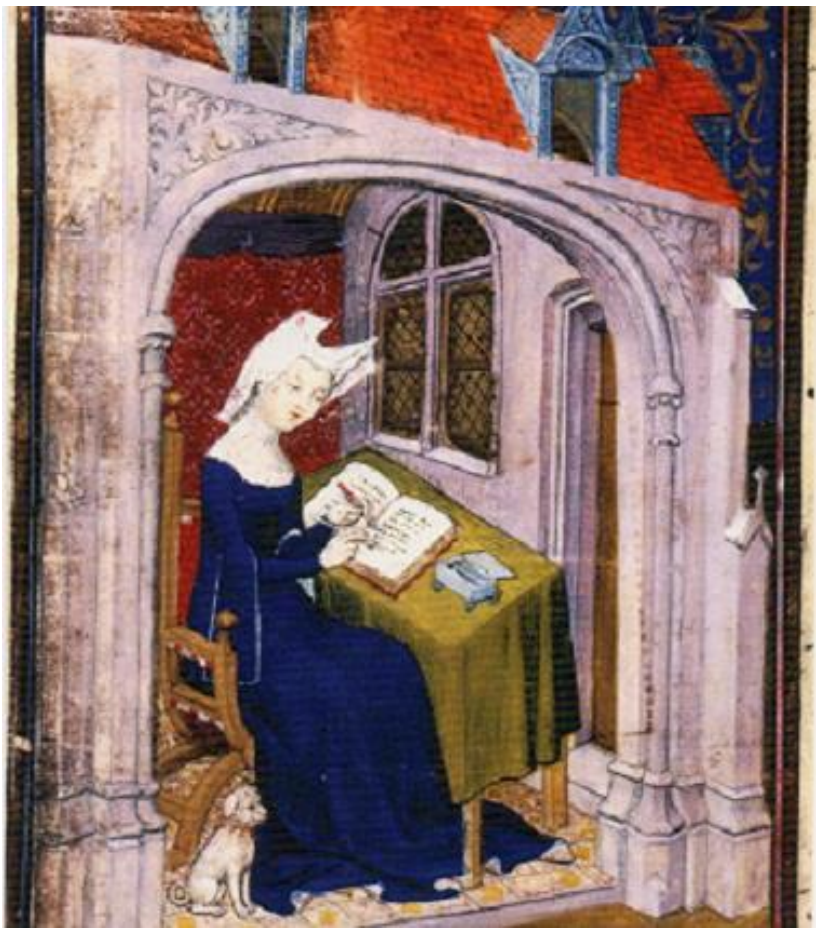

I, Ivanice Duarte Freire, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Background

The growing burden of diabetes (DM) in many countries is contributing to sustain high incidence rates of tuberculosis (TB). The association between DM and TB results in poor treatment outcomes, posing a threat to TB control. Drug-induced liver injury (DILI) due to TB drugs is a major concern. There is currently limited evidence on the effect of DM on TB DILI.

Aim and Objectives

The aim was to determine whether DILI is more frequent amongst TB patients with DM than without it; and to identify co-factors predictive of an increased risk of DM-associated DILI. The objectives were to undertake a case-control study of TB patients with and without DILI to determine the effect of DM as a risk factor for DILI; and to further investigate predictors of DILI in patients with DM and any co-factors associated with increased risk.

Methods

A case control study. The *cases* were all TB patients with DILI due to the use of rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE) who were registered on the *Information System for Special Tuberculosis Treatments* (SITETB) from January 2013 until July 2017 in Porto Alegre, Brazil. The *controls* were TB patients on RHZE who did not develop DILI during the same period. The exposure variables of interest were DM, age, sex, alcohol misuse, HIV, HCV, HBV, concomitant hepatotoxic drugs, other liver diseases, TB site and time to DILI.

Results

The analysis showed that DM, sex, taking other hepatotoxic drugs and having only extrapulmonary TB (EPTB) were not associated with increased odds of DILI. Age over 50 years old, HIV infection, HCV infection and having both pulmonary TB (PTB) and EPTB were shown to increase the odds of having TB DILI. Hepatitis C infection acted as effect modifier on the effect of DM on DILI, although those results should be interpreted with caution.

Conclusions

This study confirms evidence from the literature on the association between DILI and well-known risk factors, but was not able to demonstrate any increased odds of DILI in patients with DM.

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ACRONYMS AND ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATS	American Thoracic Society
BTS	British Thoracic Society
CDC	Centre for Disease Control
CGAE	*Coordenadoria Geral de Atenção Especializada* – General Coordination of Specialized Care
CGVS	*Coordenadoria Geral de Vigilância em Saúde* – General Coordination of Health Surveillance
CI	confidence interval
Cp	capreomycin
CRTB	*Centro de Referência em Tuberculose* - Tuberculosis Referral Centre – the Tuberculosis Clinic
CSV	comma separated value
CT	computerized tomography
DILI	drug induced liver injury
DILIN	Drug Induced Liver Injury Network
DM	diabetes mellitus
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
DRTB	drug resistant tuberculosis
GGT	gamma-glutamyl transferase
HBeAg	hepatitis B E-antigen

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	histocompatibility leukocyte A antigen
HR	hazard ratio
ID	identification
IU	international unit
IUATLD	International Union Against Tuberculosis and Lung Disease
L	litre
LATINDILIN	Latin America DILI Network Registry
LTBI	latent tuberculosis infection
Lx	levofloxacin
MDG	Millennium Development Goals
MDR-TB	multidrug-resistant TB
M-H	Mantel Haenszel
Mtb	*Mycobacterium tuberculosis*
NAFLD	non-alcoholic fatty liver disease
NTCP	national TB control programme
NTM	non-tuberculous mycobacteria
ODK	open data kit
OR	odds ratio
PCR	polymerase chain reaction
qPCR	quantitative polymerase chain reaction
RIF	rifampicin

RHZE	rifampicin, isoniazid, pyrazinamide, ethambutol
RR	relative risk
SDG	Sustainable Development Goals
SINAN	*Sistema de Informação de Agravos de Notificação* – Information System of Notifiable Diseases
SITETB	Sistema de Informação de Tratamentos Especiais de Tuberculose - Information System on Special Tuberculosis Treatments
SSL	Secure Sockets Layer
TB	tuberculosis
TNF	tumour necrosis factor
ULN	upper limit of normal
VS	*versus*
WHO	World Health Organization
XLS	Excel Spreadsheet

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DOES DIABETES MELLITUS COMORBIDITY INCREASE THE RISK OF DRUG-INDUCED LIVER INJURY DURING TUBERCULOSIS TREATMENT?

CHAPTER 1 - INTRODUCTION

1.1 Global epidemiology of tuberculosis

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global health emergency (1). Almost thirty years later, it remains a significant public health problem as a major cause of morbidity and mortality worldwide despite efforts at its control. Worldwide, tuberculosis is one of the top 10 causes of death (2). Ending the global TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals (SDG) (3). In 2017, 10 million people fell ill with TB and 1.6 million died from the disease, including 0.3 million among Human Immunodeficiency Virus (HIV) patients (2). Over 95% of the cases and deaths occur in low-and middle-income countries (3). In 2017, the largest number (62%) of incident TB cases occurred in the South-East Asia and Western Pacific regions, followed by the African region, with 25% of incident cases. In that same year, two thirds of incident TB cases occurred in India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa, all of which are among the 30 high TB burden countries (2). Globally, TB incidence has fallen by an average of 1.5% per year since 2000, remained 1.5% from 2014 to 2015 (3) and is now declining at about 2% per year (2).

One of the targets of the Millenium Development Goals was to stop and begin to reverse TB incidence by 2015. However, this rate of decline of 2% per year needs to accelerate in order for the needed milestones to be reached. The WHO End TB Strategy, adopted by the World Health Assembly in 2014, aims to end the global TB epidemic by decreasing the number of TB deaths by 90%, by reducing new TB cases by 80% between 2015 and 2030, and by eliminating the TB-related financial burden to families (2). Ending the TB epidemic by 2030 is one of the health targets of the most recently adopted by the SDG. Additionally, WHO has set up a new target for 2035: a 95% reduction in deaths and a 90% decline in TB incidence (2).

In Brazil, TB remains a major public health concern, with an incidence rate of 34/100.000 population in 2017 (3). According to data from the Ministry of Health, from 2001 to 2017 its

incidence rate decreased from 42.8 to 35/100.000 population and its mortality rate decreased from 3.1 to 2.2/100.000 population from 2001 to 2016 (4). In 2017, the state of Rio Grande do Sul presented an incidence rate of 41/100.000 population and in its capital, Porto Alegre, the incidence rate was a little over 80/100.000 population (4).

It has been estimated that approximately 1.7 billion persons were infected with *Mycobacterium tuberculosis* (Mtb) globally in 2014, nearly 25% of the world population (5). From this reservoir of 1.7 billion people with latent TB infection (LTBI), approximately 170 million will develop active TB during their lifetime, more than 80% of whom will be in the pulmonary form and, therefore, infectious to others (6). Individuals with active TB can infect 10 – 15 other people per year. Without treatment, 45% of HIV negative patients and nearly all HIV positive patients will be dead in 2 years (2).

1.2 Risk factors for tuberculosis

An impaired immunological status has been acknowledged as an important factor determining TB control. The co-infection with HIV and Mtb is the strongest risk factor for both immediate and delayed progression from latent infection to active TB (7, 8), but there are other clinical conditions also associated with that, such as malnutrition, drug and alcohol abuse, aging, immunosuppressive therapy, and coexistent medical conditions such as diabetes mellitus (DM), chronic renal disease, silicosis, jejuno-ileal bypass, subtotal gastrectomy, cancer (7, 8) and, more recently identified, smoking (7, 9-11).

1.3 Global epidemiology of DM

The prevalence of DM is rapidly increasing and that is a global epidemic (12). Aging, changes in life style, socio-economic factors and population growth have led to an increasing DM prevalence, particularly type 2 DM (13). According to the International Diabetes Federation Atlas (14), one in 11 adults have DM, and 46.5% of adults with DM are undiagnosed. Three quarters of people with DM live in low and middle income countries (14). By 2040, one adult in 10 will have DM. In South and Central America, 9.4% (8.0% – 11.3%) of the adult population have DM. Of these, 39% are undiagnosed and 81% are living in middle income countries (14). Asia is the most affected region in

the globe. According to estimates, India and China are and will continue to be the two countries with the greatest burden of the disease. Up to 80% of patients with DM live in low income countries (15) and 70% of patients with DM live in countries where TB is endemic. Indonesia, with the third highest burden of TB in the world, has the fourth highest number of individuals with DM (16). Other countries in similar situation are Peru and Russia (17). In Central and South Americas, Brazil has the highest number of people with DM: 14.3 million. In 2015, 247.500 adults died as a result of DM in Central and South Americas and over half of the deaths occurred in Brazil (14).

It has been estimated by WHO that the global prevalence of DM among adults has risen from 4.7% in 1980 to 8.5% in 2014. The number of individuals with DM has risen from 108 million in 1980 to 422 million. According to the Global Report on DM, in 2016, an estimated 1.6 million deaths were directly caused by DM, rendering it to be the 7th leading cause of death in that year (18). Likewise, it has been projected by WHO that DM will be the 7th leading cause of death in 2030. In Brazil, 6% of total deaths in 2016 were caused by DM. In the same year, the total prevalence of DM was 8.1%, being 7.4% in males and 8.8% in females (18). It has been estimated that 50% of the population with DM are undiagnosed (10) and low and middle-income countries account for 88% of all the premature mortality due to DM (10). According to the Brazilian Diabetes Association, there are currently over 13 million people with DM, 6.9% of the Brazilian population (19).

1.4 DM and TB

1.4.1 DM and active TB

Diabetes increases the risk of infection in general. The killing of Mtb by drugs requires a properly functioning immune system and although all the precise mechanisms are still not entirely known (12, 20), DM is known to cause immune dysfunction and suppression of the cellular immunity (21, 22). Studies on the effect of DM on both the innate and adaptive immune response to Mtb have shown that the most consistent (although not universal) factor is chronic hyperglycaemia (23).

The current literature suggests that DM has an impact in every stage of the natural history of TB; however, it has also been suggested that TB may increase the risk of developing type 2 DM (20, 24-26). It has been shown that TB patients develop changes in carbohydrate metabolism such as hyperglycaemia and insulin deficiency (27). Glucose intolerance has been reported in 16.5% to 49% of TB patients. Data from one study has shown that 56% of cases with glucose intolerance had

normal glucose levels when TB treatment was finished (28, 29). Other studies have presented this same normalization of glycaemic levels after completion of treatment in patients who had presented hyperglycaemia (30). Tuberculosis can temporarily impair glucose tolerance. In addition to that, some TB drugs including isoniazid and rifampicin have hyperglycaemic effects; and pyrazinamide may cause difficulties in DM control (31-35). The co-presentation DM-TB has also been associated with increased DM-related complications and poorer glucose control (36, 37). According to WHO (2, 18), a large proportion of people with DM as well as TB are not diagnosed or are belatedly diagnosed, which reinforces the great dimension of the problem which remains yet unknown.

Recent systematic reviews and meta-analyses have shown that DM increases the risk of developing TB two to three times higher than in persons without DM, regardless of different study designs, background TB incidence, geographic region, and control of confounders (20, 22). The recognition of this important finding was consolidated by a meta-analysis of 13 observational studies which concluded that individuals with DM have a three-fold higher risk of developing TB (RR 3.1; 95% CI 2.22 - 4.6) (20). A systematic review of nine studies on the subject reported that DM increased the risk of active TB, ranging from 1.5 to 7.8 times (38). It has been estimated that 15% of global active TB cases are attributable to DM (20, 39, 40). This increased risk is even greater during the first two years after DM diagnosis has been made and has a tendency to decrease thereafter (41).

The WHO has declared that DM is an important, re-emerging and neglected risk factor for TB (42-44). The bidirectional association between DM and TB has been known as the next great challenge for global TB control (12). There is a prediction that the burden of DM will increase to close to 552 million people by the year 2030 (45). This important interaction is more prominent in developing countries where TB is endemic and DM is rising. In India, it accounts for approximately 14.8% of incident pulmonary TB cases and 20% of smear-positive pulmonary TB cases (26). In Mumbai, TB was the most frequent concomitant illness in patients with DM, with 5.9% being co-morbidly infected in a cohort of 8,793 patients (46). The increase in the prevalence of DM has been a major impediment to reducing TB incident cases in the country (47). In sub-Saharan Africa, another high TB burden region, the number of patients with DM is predicted to double from 12 million in 2010 to 24 million by 2030 with most cases still undiagnosed (48). In countries where both conditions are

endemic, the population attributable risk can be as high as 20% (26, 49). Data from the Texas-Mexico border reports that DM is the underlying attributable risk for 25% of the TB cases (50).

The lung is a target organ in patients with DM (51). Both acute and chronic pulmonary infections, such as TB, are frequently seen in patients with DM. Diabetes leads to thickness in the basal membrane, decreases lung elasticity and causes neuropathy, which may affect basic lung functions (52, 53). However, there are scarce data in the literature concerning the relationship between DM and extrapulmonary TB (EPTB). Magee *et al.* (54) conducted a study to evaluate whether DM is associated with TB site and the risk of all-cause mortality in those patients being treated for EPTB. In the multivariate analysis, the authors found no increased odds of EPTB in patients with DM when compared to those without DM. This finding aligns with those from other studies on risk factors for EPTB and disseminated TB (55-57), which did not find an association between DM and EPTB. Indeed, there is a dearth of studies concerned with this subject and the majority of existing data suggest that DM does not increase the risk of EPTB (54). Nonetheless, patients with poor glycaemic control may have substantial immune impairment and so still more likely to present extensive disease, similarly to what occurs with patients with both innate and acquired immunodeficiencies (7, 8). In this regard, as a metabolic disorder that weakens the immune system, there is need for further studies specially designed to examine the relationship between DM and EPTB.

According to the Porto Alegre TB Control Programme, the prevalence of DM among the incident TB cases from 2010 until 2016 ranged from 5.4% to 7.3%. Of a total of 8,827 incident TB cases, 548 (6.2 %) patients were notified as having a previous DM diagnosis at the start of TB treatment.

In many parts of the globe, particularly in low to middle income countries including South America, DM accounts for a higher population attributable risk fraction of TB than does HIV. That is why global agencies such as WHO, the International Union Against Tuberculosis and Lung Diseases (IUATLD) and the World Diabetes Foundation have developed a collaborative framework (45) to provide guidance for national programmes, physicians, and other health care professionals engaged in all aspects of prevention and care of DM and TB on how to establish a coordinated response to both diseases, at both organizational and clinical levels. This initiative is a response to a growing concern on this important association between DM and TB and which collaborative measures should be put into action as a complement to and in synergy with the core activities already implemented in both programmes. There are three areas for collaborative actions, listed below.

1. Establish mechanisms for collaboration through TB disease surveillance in patients with DM and DM surveillance in patients with TB; and conduct monitoring and evaluation of these collaborative TB and DM activities.

2. Detect and manage TB and LTBI in patients with DM.

3. Detect and manage DM in patients with TB.

In 2014, the World Health Assembly endorsed WHO's new End TB Strategy which encompasses all fundamental aspects of the TB and DM collaborative activities. Amongst the actions already set in motion by the Collaborative Framework for Care and Control of TB and DM (45), there is the promotion of national policies discussions and research. Ending TB will require a joint plan to ensure that patients with DM and active TB have access to a much-needed tailored approach.

In short, the clear public health message is that TB and DM are both high burden diseases in their own rights which, once affecting concomitantly an individual, exacerbate one another resulting in poorer outcomes to both and thus challenging their respective global control efforts.

1.4.2 DM and LTBI

Diabetes is a disease with an impaired host immunity, leading to increased susceptibility to infections. In a pilot study conducted by Restrepo (23), 79 adult contacts indicated a two-fold higher prevalence of DM or chronic hyperglycaemia among contacts with LTBI versus no LTBI (OR 2.39). The association between DM and LTBI has been very appropriately hypothesized before, but epidemiologic studies have been limited. The few existing studies have not shown consistent findings (58-64), with possible reasons being the absence of control groups (59-61) and of adjustment for confounders (45, 65). A recent systematic review and meta-analysis conducted by Lee *et al*. involving 38,263 individuals from one cohort study and 12 cross-sectional studies (65) showed that patients with DM had increased odds of LTBI (adjusted pooled OR 1.18; 95% CI 1.06 – 1.30). One conclusion from this systematic review was that due to this small prevalence OR found, there was a limited incremental gain if patients with DM should be targeted for LTBI screening. In the case of a LTBI prevalence of 20% in individuals without DM, the expected prevalence of LTBI in the population with DM would be 22.8%. Interestingly, when Hensel *et al*. studied LTBI prevalence

and DM status, they reported a dose-response pattern, with the prevalence of LTBI increasing from 25.9% in individuals without DM, to 39.1% in those with pre-DM and 43.4% in those with DM (66). These results would increase the incremental gain of screening DM for LTBI.

Potential insights into why individuals with DM might be at increased risk of LTBI might be found in mouse studies. Mice with DM were found to present impaired first defence mechanisms of clearance of the Mtb bacilli in their lungs (65). Alveolar macrophages are the first defence and it has been proved that both mice and human beings with DM have a defective innate immune response to the infection of Mtb bacilli (67-69). A contributing factor believed to be of a higher risk for LTBI is that patients with DM in high TB burden places frequently circulate through health care facilities and, thus, are in constant contact with potentially TB-infecting patients. A cross sectional study conducted in the United Kingdom found a 15% higher prevalence of LTBI in patients with DM (prevalence ratio 1.15; 95% CI 1.02-1.30), after adjusting for age, sex, ethnicity, body mass index and other immunocompromising conditions (70).

To conclude, there is some evidence suggesting that DM increases the risk of LTBI although this association still remains unclear. Likewise, the impact of routine LTBI screening in patients with DM and its cost-effectiveness are yet to be ascertained. There has been an increasing trend of recommendations for treating LTBI in low-burden countries, particularly in high risk groups, such as patients with HIV, household contacts of sputum smear-positive cases, patients on immunosuppressant drugs, patients with chronic renal disease on dialysis and patients with silicosis (71). In the WHO guidelines on the management of LTBI in low burden countries, there was no recommendation on the routine screening of LTBI in patients with DM. However, that was a conditional recommendation based on very low quality of evidence (71).

1.4.3 TB-DM treatment outcomes

Evidence from observational studies has shown that, when concomitant, DM and TB lead to delays in sputum smear conversion, prolonged culture positivity at two to three months of treatment, higher failure rates, death, relapse (endogenous reactivation) and re-infection with a new strain (13, 39, 72-75). There is evidence that DM increases the risk of death during TB treatment (pooled RR 1.89; 95% CI 1.52 – 2.36) (75). It also increases the risk of TB relapse, with five studies presenting a pooled RR 3.89 (95% CI 2.43 – 6.23) (75).

Two underlying factors potentially affecting outcomes become evident: poor glycaemic control (45) and possible suboptimal plasma levels of antimycobacterial drugs (76-78). Nevertheless, results have been conflicting and further research is much needed, particularly because of emergent multidrug-resistant TB (MDR-TB). In a meta-analysis conducted in 2011, MDR-TB was not found to be significantly higher in these patients (75). About 15% of TB cases worldwide may be linked to DM, and the likelihood that a TB patient will die or relapse after having successfully treated is significantly higher if they have DM concomitantly (18). It has been suggested that the poor outcomes experienced by TB patients with DM may be due to the immune impairment caused by DM (79).

1.5 Drug Induced Liver Injury

1.5.1 Introduction to DILI

Drug induced liver injury (DILI) is a broad term meaning any injury to the liver by a medication, herb or any dietary supplement. The incidence of DILI is less than 1/10,000 persons for most drugs used in clinical practice (80). It is characterized by biochemical liver abnormalities, but there are pitfalls in the definition. Liver enzyme elevations of 1.25-2.5, 2.6-5.0, 5.1-10, or 10 times the upper limit of normal (ULN) value or their increase to 1.25-2.5, 2.6-3.5, 3.6-5, or 15-fold the baseline value usually define hepatotoxicity of grades 1, 2, 3, and 4, respectively (81). Therefore, the lack of homogenous definition for hepatotoxicity poses difficulties when comparing studies about a drug-related toxicity.

The diagnosis of DILI is mainly based on chronological and semiological criteria (82, 83). Chronological criteria include the recent introduction of a potential hepatotoxic drug, biochemical improvement after its discontinuation and a relapse of liver abnormalities after rechallenge (81). The semiological factors are all the other causes which might be causing or contributing to the liver damage such as acute or chronic viral hepatitis or congestive heart failure, for instance.

Any drug or association between drugs is potentially hepatotoxic. Since numerous medications and diseases can cause abnormalities in liver enzymes, it is important for physicians to be able to distinguish the cause and take appropriate action (84). While the global incidence of DILI is small, its impact is significant (85). DILI is the most frequent cause for acute liver failure in most Western countries, being responsible for more than half of the cases (86, 87)

Risk for DILI is multifactorial, as it involves inter-related risk factors. Predisposing factors have been identified as contributors for the emergence of DILI such as age, female sex, concomitant use of hepatotoxic drugs, chronic liver diseases (including chronic viral hepatitis) (88-93); and alcohol abuse (94) or its daily consumption (95). With some risk factors such as age and female sex, injury may be drug specific. For example, females have been shown to have a higher risk of DILI from nitrofurantoin, erythromycin, flucloxacillin and isoniazid (94, 96-100). Older age is a risk factor for DILI from isoniazid, whereas youth is a risk factor for DILI due to valproate and aspirin (101, 102). It can occur in all age groups, including children. African ancestry has been reported to be associated with DILI due to phenytoin, allopurinol and trimethoprim-sulfamethoxazole (103, 104). The clinical spectrum ranges from asymptomatic elevation of liver tests to acute hepatitis and liver failure.

DILI is ultimately a diagnosis of exclusion. In most cases, there are no specific diagnostic markers for DILI and blood liver tests, biopsy and imaging are routinely performed in the process of excluding differential diagnosis (105). Alternative causes of liver injury, such as acute viral hepatitis, should be sought and their absence makes the diagnosis more plausible. In many cases, the exact mechanism and factors contributing to liver toxicity remain poorly understood (95, 106, 107).

The first distinction to be made is about its predictability. Predictable DILI is generally characterized by a direct, dose-related injury and typically tends to have a short latency period (108), usually with an onset within one to five days after high doses (105). It is reproducible in animal models and its pathogenesis is reasonably well understood (105, 108). The most common drug causing predictable DILI is acetaminophen (108).

Most cases of DILI are unpredictable or idiosyncratic in nature, meaning that it is the characteristics of the host and not the drug that are responsible for the injury. The drug has little or no intrinsic toxicity to the liver, so not dose dependent and not reproducible in animal models. The pathogenesis of idiosyncratic hepatotoxicity is not fully understood yet (105). Genome studies with large numbers of idiosyncratic DILI cases have identified various genetic associations, such as within the histocompatibility complex region and linked to the histocompatibility leukocyte A antigen (HLA) classes I and II, suggesting an immunologic pathogenesis. In general, the HLA associations were drug-specific, for instance, HLA-B*5701 for flucloxacillin, but not reliable enough to warrant screening for alleles pre-treatment. Idiosyncratic DILI are hypersensitivity or metabolic reactions and have longer or variable latency. More frequently, hepatotoxicity due to TB drugs is caused by metabolic idiosyncrasy due to metabolites released or accumulated during the metabolic process

(109). A few other examples of idiosyncratic DILI agents are amoxicillin-clavulanate, non-steroidal anti-inflammatory drugs and isoniazid (108). Without adaptation, these immune and metabolic reactions are likely to ensue further T cell activation, cytokine release and hepatocyte injury (105). All forms of idiosyncratic DILI may present immunoallergic signs and symptoms, such as skin rash, fever and eosinophilia (110-112). The DRESS syndrome and the Stevens-Johnson syndrome are two such examples of a more severe drug hypersensitivity reaction with accompanying systemic involvement. Drugs such as macrolides, allopurinol, carbamazepine and phenytoin are among those that cause idiosyncratic DILI associated with immunoallergic features (103, 112-114).

The most frequent causes of clinically apparent DILI due to prescribed drugs, according to data from medical centres in the United States, between 2004 and 2013, were amoxicillin-clavulanate, isoniazid, nitrofurantoin, trimethoprim-sulfamethoxazole and minocycline (110). It is difficult to precisely estimate the real incidence of idiosyncratic DILI by specific drugs, but it is believed that, for isoniazid, it is one individual per 1,000 exposures; for amoxicillin-clavulanate, 1/2,500; for diclofenac, 1/10,000; for atorvastatin, 1/20,000; and for most drugs, 1/50,000 or more (99, 115). Nine out of the 10 most hepatotoxic drugs are antimicrobials, mostly antibiotics (110).

The second distinction to be made on DILI regards the pattern of drug injury. It may be hepatocellular injury, cholestasis or mixed, based on biochemical test results. An increase in serum alanine aminotransaminase (ALT) is more specific for hepatocellular injury than an increase in serum aspartate aminotransaminase (AST), which can also signify abnormalities in muscle, heart and kidney (95). Increases in gamma-glutamyl transpeptidase (GGT) and/or bilirubin, with little or no increase in AST, indicate cholestasis (95).

The most frequent clinical manifestation of drug-induced idiosyncratic liver injury is acute hepatocellular hepatitis (99, 110, 111). It may occur from five to 90 days after the start of the offending medication. It is also an important cause of acute liver failure, responsible for 11 to 15% of cases in Europe and the United States (86, 87). Isoniazid, diclofenac, nitrofurantoin, azithromycin, ciprofloxacin and phenytoin are widely prescribed drugs which may cause the acute hepatocellular injury phenotype of DILI (110, 111, 116).

Cholestatic DILI is caused by bile duct injury and cholestasis in the small bile canaliculi. According to data from Chalasani *et al.* (110), common causes are amoxicillin-clavulanate, azithromycin, ciprofloxacin, levofloxacin and azathioprine. Lastly, the mixed pattern of DILI is caused by those drugs that can cause both type of injury, hepatocellular and cholestatic hepatitis. Rarely do they

progress to liver failure. Sulfamethoxazole-trimethoprim, azithromycin, ciprofloxacin, levofloxacin and phenytoin are commonly prescribed drugs that may cause DILI through a mixed liver injury pattern (110, 113, 117).

Besides being either *direct* or *idiosyncratic*, there is a third type of DILI emerging, *indirect hepatotoxicity*. This type of DILI is caused by the action of the agent in the liver, rather than by its toxic or idiosyncratic properties. For instance, the drug may exacerbate a pre-existing liver condition such as non-alcoholic fatty liver disease (NAFLD) or chronic hepatitis C virus (HCV) infection, or even induce an immune-mediated hepatitis (105). Some chemotherapy agents can cause hepatitis B virus (HBV) reactivation (118) and antiretroviral agents are known to cause immune reconstitution as well as an exacerbation of hepatitis C (119). Another example of this type of liver injury would be the immune-mediated liver injury caused by immunomodulatory agents, such as monoclonal antibodies. The *indirect* category of liver injury is not a completely acknowledged category of DILI. It takes further the concept of DILI and contributes to its knowledge by bringing to light new possible ways of causing liver damage particularly in those patients with a chronic liver disease (105).

In the United States, the Drug Induced Liver Injury Network (DILIN) (120) reported 300 cases of idiosyncratic DILI cases. The mean age was 48 years, 60% were women and the largest two categories were antimicrobial and central nervous system agents (121). The most frequent agent in an acute liver failure United States registry was isoniazid, followed by sulfamethoxazole-trimethoprim and anti-epilepsy medications (86).

With the intention of overcoming limitations on DILI research, country-based registries and international collaboration have been created in Europe and North America. In 2011, a Latin America DILI Network Registry (LATINDILIN) (122) was set up to prospectively identify and to study genetic biomarkers of genuine DILI cases. Several Latin American countries have joined this network and are involved in this project, such as Brazil, Argentina, Uruguay, Chile, Mexico, Paraguay, Ecuador, Peru, Venezuela and Colombia (122). There are common roots, but also differences in ethnicities, prescription patterns and drug policies and regulations. These differences pose several challenges but also promote development and knowledge transfer between countries.

In order to minimize the risk of severe liver injury, patients should be thoroughly educated about the symptoms of hepatitis: anorexia, nausea, vomiting, right-upper abdominal discomfort, jaundice and instructed to report them promptly to the TB clinic.

1.5.2 DILI and TB treatment

DILI has been a long-standing concern in the treatment of active TB. The first-line TB drug regimen is a combination of four drugs: rifampicin, isoniazid, pyrazinamide and ethambutol (the RHZE regimen), the former three being associated with liver toxicity (106). In this case, the risk is believed to be even greater, because the three drugs are used simultaneously. There is actually little evidence that specific drug combinations will increase the risk for idiosyncratic DILI (105). Nonetheless, combinations of hepatotoxins most likely increase the risk of direct (not idiosyncratic) DILI.

The introduction of rifampicin in the first-line treatment of TB in Rio Grande do Sul, Brazil, (rifampicin, isoniazid and ethambutol, RHE) in 1977 and rifampicin, isoniazid and pyrazinamide (RHZ) in 1982, has led to an increase in the rates of hepatotoxicity (123). DILI in hospitalized patients due to regimens such as STH (streptomycin, thioacetazone and isoniazid) ranged from 0.4% to 2.2%; RHE from 0.8% to 7.3%; and RHZ from 2.5 to 11.1%. (123). That increase is probably explained by the use of two (RHE) and three (RHZ) potentially hepatotoxic TB drugs being taken concomitantly. The current pharmacological presentation of the RHZE tablet in combined doses currently prescribed in Brazil as standardized by the Ministry for Health is: rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275mg.

Hepatotoxicity with the RHZ regimen has been reported with a prevalence ranging from 3 to 28% for idiosyncratic and intrinsic toxic reactions (124-128), and miliary TB has been a well-recognized risk factor for TB DILI (129). In one study, DILI due to RHZ has been found to lead to discontinuation of therapy in 11% of patients (130). In most clinical cases, drug-shared toxicity is a potential confounder in the interpretations of events but there is often no way to discern the contribution of each drug. There is a general consensus around the criteria used for diagnosing TB DILI. In the absence of symptoms, elevation of transaminases ≥ 5 times the ULN; and in the presence of symptoms, ≥ 3 times the ULN or twice the bilirubin ULN constitutes DILI (95, 131).

Definitive conclusions regarding DILI during TB treatment are difficult to achieve because studies vary as to study designs and methodologies, populations, use of multiple drug regimens, definitions of DILI and different blood tests monitoring practices. All in all, the risk of DILI reported in various studies ranges from 0.6% to as high as 33% (95). However, the international literature reports a small and acceptable risk of DILI caused by a combination of isoniazid, rifampicin and pyrazinamide (132-135). Data reported on the proportion of severe hepatotoxicity due to RHZ from the United Kingdom, Canada and Singapore has been 2.3%, 2.8% and 5.3%, respectively (136-138).

A meta-analysis of studies involving the use of a multiplicity of TB drug regimens predominantly in adults has shown an incidence rate of liver toxicity of 1.6% with isoniazid alone; 1.1% with rifampicin alone; and 2.6% with isoniazid and rifampicin co-administration (139). Subsequent studies with patients treated with isoniazid alone have reported that transaminases elevations of three times the ULN in symptomatic individuals and five times the ULN in asymptomatic individuals occurred in 0.3% of cases (140). Nevertheless, in larger reviews, the range has been as low as 0.1% to 0.56% (140-142).

The risk of developing isoniazid related hepatitis is age related and approximate case rates by age are: 0 per 1,000 for persons under 20 years of age; 3 per 1,000 for persons in the 20 - 34-year age group; 12 per 1,000 for persons in the 35 - 49-year age group; and 23 per 1,000 for persons in the 50 - 64-year age group (141). Patients from 36 to 50 years have a 1.2% risk of isoniazid-induced hepatitis (143), but more recent studies have found much lower overall rates of isoniazid hepatotoxicity: 0.1% to 0.3% (141, 144).

It is important to note that studies differ in terms of their definitions of hepatitis and many authors use the terms *hepatotoxicity* and *hepatitis* interchangeably. Drug-induced hepatocellular jaundice is a serious lesion, with mortality from 10% to 50% (145). The reason for that is that considering the liver's great capacity for bilirubin excretion, it must be extensively damaged before jaundice is perceptible. So much liver damage is too extensive to recover from. In 1999, Robert Temple articulated a modified version of this observation for use in controlled clinical trials and as a screening threshold. He called it *Hy's Law*, after the late Dr Hyman Zimmermann, who repeatedly made the clinical observation that drug-induced hepatocellular jaundice is a very serious lesion. Patients with all of the following criteria are defined as Hy's Law cases:

1. ALT or AST >3 times the ULN;
2. Total bilirubin >2 times the ULN;
3. It should not be primarily cholestatic;
4. It should not be caused by any disease, but by a drug (145).

Clinical hepatitis is seen in 1-6% of patients on isoniazid only (139). The mortality range lies between 0.0 - 0.3 per 1,000 persons (median 0.04) (146), but the precise data to provide a fatality rate for isoniazid-related hepatitis is not available. In an United States Public Health Service

Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis (107). Usually enzyme levels return to normal, despite continuation of the drug, but in some cases progressive liver dysfunction occurs. If any symptoms of hepatitis appear, or if signs suggestive of hepatic damage are detected, the drug should be promptly discontinued.

Interactions between genetic, host and environmental factors contributes to drug induced hepatotoxicity due to TB drugs. Risk factors for isoniazid toxicity include chronic viral hepatitis B and C (a 5-fold increase) (92, 147), HIV infection (3 to 5- fold) (92, 147), alcohol abuse, old age, female sex (OR 10.59 and RR 4.0) (109, 148-155), and concurrent use of rifampicin or pyrazinamide (107) or other hepatotoxic drugs. One study has shown that co-infection with both HCV and HIV has elevated the risk of DILI due to TB drugs more than 14-fold (92). Other clinical factors that increase the risk of drug-induced hepatotoxicity during TB treatment include extensive TB disease and malnutrition (92, 95, 107, 156). Abnormal baseline transaminases are an independent risk factor for DILI (95) so that the severity of DILI seems to be greater when an underlying liver disease is present, suggesting a summation of injuries (157).

In an analysis undertaken in Canada (137) the incidence of all major adverse events was 1.48 per 100 person-months of exposure for pyrazinamide as compared with 0.49 for isoniazid, and 0.43 for rifampicin. The incidence of pyrazinamide-induced hepatotoxicity during treatment for active TB was thus substantially higher than those attributable to the other first-line TB drugs and higher than previously recognized. Pyrazinamide seems to be the most hepatotoxic drug of the first-line regimen (137, 158-160). On the other hand, rifampicin alone is possibly associated with a lower potential for hepatotoxicity than isoniazid and pyrazinamide (34, 106, 159, 161). So much so, that the American Thoracic Society (ATS), the Centre for Disease Control (CDC) and the Prevention/Infectious Disease Society of America currently recommend that rifampicin be the first drug to be re-started after recovery from an episode of TB therapy-induced hepatitis (159).

One prospective cohort study from Spain has shown the incidence of TB drug-induced DILI (reflected by serum transaminases more than three times the ULN) to be higher in the group with risk factors (18.2 %) than in the group without them (5.8 %; OR 3.5). Severe DILI (considered as to be serum transaminases above ten times the ULN) occurred in 6.9 % of the risk factor group and in 0.4 % of the group without risk factors (OR 17.7) (154).

1.5.3 Adaptation

DILI encompasses a variety of clinical entities, and their discussion is beyond the scope of this study, but one of them has important clinical relevance to TB management and that is *hepatic adaptation*. Exposure to certain drugs may result in physiologic adaptive responses. Once injury starts, an upregulation of hepatoprotective mechanisms respond, such as hepatocyte proliferation and drug-metabolizing enzyme activities, attenuating toxin-related injuries (105). It may also be through down-regulating hypersensitivity reactions to drugs and its metabolites (105). Rarely does this kind of drug-induced injury lead to inflammation, cell death or histopathologic alterations. This is reflected in mild and transient elevations of transaminases. However, certain toxins such as alcohol interfere with the effectiveness of these adaptive and protective responses. Up to 20% of individuals on isoniazid preventive therapy have experienced slight, asymptomatic and transient transaminases elevation (95, 150, 162-165). In the cases when adaptation does not occur, enzyme elevations and cholestasis continue to rise and symptoms appear.

1.5.4 Advice on monitoring

In order to assist physicians to decide whether elevated transaminases reflect adaptation or initial liver injury, DILIN and other groups currently recommend that TB drugs should be discontinued if ALT and AST are ≥ 5 times the ULN in the absence of hyperbilirubinemia or symptoms; or ≥ 3 times the ULN in the presence of symptoms or hyperbilirubinemia (bilirubin ≥ 2 times the ULN) (120). Various guidelines for the management of DILI have been issued by the ATS (95), British Thoracic Society (BTS) (166), WHO (167) and IUATLD (168). Several national and international TB control guidelines (95, 166-172) address the issue of DILI; however, not all of them establish recommendations on routine monitoring of liver tests and detailed advice on management. Some of those that give more detailed advice on monitoring and management strategies are the guidelines from DILIN (120), the Department of Health and Community Services of the Northern Territory of Australia (171), the ATS official statement on hepatotoxicity of antituberculosis therapy (95), the BTS guidelines on chemotherapy and management of TB (166, 173) and the Brazilian National TB Control Programme (PNCT) (172). The ATS document (95) is the most comprehensive and stipulates that all patients should have baseline liver tests with subsequent monitoring being subject to the presence of risk factors. It suggests monitoring at a variable time between two and four weeks after the start of treatment. The BTS guidelines (166) recommend baseline and

subsequent monitoring in patients with previous chronic liver disease, with weekly tests for the first two weeks and then at two weekly intervals for the first two months. Regular biochemical monitoring is not advised for those without chronic liver disease and normal baseline liver tests, which should be ordered only for those presenting symptoms of liver disease. According to the Australian guidelines (171), monthly tests are not routinely required unless certain circumstances are present, such as abnormal baseline transaminases, underlying chronic liver disease, HIV infection and significant alcohol consumption. The Brazilian PNCT (172) recommends that biochemical monitoring be performed monthly in case of symptomatic patients or in those presenting risk factors for DILI. In Hong Kong, TB specialists deem a stepwise increase in transaminases levels and a persistent rise in bilirubin levels to be more significant as an indicative of DILI than those more frequently used threshold values (106).

The main risk factors for TB DILI are well known and have been extensively discussed in the literature; less well-established, however, are the different weights with which they contribute to increase the risk of DILI. There has not been found any studies specifically on risk stratification of patients before the start of treatment based on biochemical tests.

There seems to be a consensus across national guidelines about the discontinuation of therapy when the transaminases levels reach the already mentioned thresholds of ≥ 3 times the ULN in the presence of symptoms and ≥ 5 times the ULN without them.

1.6 Diabetes, the liver and comorbidities

The collision of the growing DM problem and its concomitance with TB and, additionally, the existing TB-DILI problem, has potential to become a significant public health problem if DM enhances the risk of TB DILI. One important clinical implication of the association between DM and chronic liver disease is the impact it has on drug management. This section presents background information on the possible associations between DM and NAFLD, chronic viral hepatitis, alcohol consumption and HIV infection.

Globally, type 2 DM accounts for most of DM cases (18) and is associated with metabolic syndrome (obesity, insulin resistance and dyslipidaemia). It has been observed that fatty liver, obesity and insulin resistance act as co-factors for liver injury (174-176). Diabetes itself has been reported as a risk factor for severe DILI (97) and obesity is an independent risk factor for severe liver

disease (177). Patients with type 2 DM usually are older and frequently have comorbidities with the need for additional medication, or have harmful drinking patterns, which are associated with DILI.

Other conditions also associated with DM include alcohol intake, chronic HCV infection and hemochromatosis (174, 175, 178-180). Also, polypharmacy is very common in the elderly DM population. Relevant to the present study is the frequent use of DILI-causing drugs, such as statins, by these patients. Few studies have assessed the long-term safety of antidiabetic drugs in patients with chronic liver disease and this could be extrapolated to other potentially hepatotoxic drugs (181). In addition, one chronic complication of DM that may contribute to an increased risk of liver toxicity is chronic renal disease, which is also a potent risk factor for TB.

1.6.1 Non-alcoholic fatty liver disease

Normally, the liver is devoid of fat and fatty changes often coexist with necro-inflammatory and fibrotic changes in the setting of both metabolic and viral injuries such as chronic HCV and HIV infection (182). NAFLD is considered a hepatic manifestation of metabolic syndrome (183). The definition of NAFLD requires that there is evidence of steatosis either by imaging or histology; and absence of any alternative causes for secondary liver fat deposition such as substantial alcohol consumption, steatogenic drugs, or hereditary disorders (184). It is a chronic condition increasing in prevalence with the rise of obesity and type 2 DM rates (48). Data from various studies indicate that the prevalence of NAFLD in the general population ranges from 6.3% to 33% (183). In Europe and in the United States, its prevalence based on imaging studies, ranges from 25% to 30% in the adult population (185). The highest prevalence of NAFLD is seen in South America and in the Middle East, while Africa presents the lowest prevalence (185). There seems to be an “inverted” U-shaped distribution of its prevalence across ages. Younger and older individuals are relatively spared from presenting NAFLD (186). Also, men are at a higher risk of presenting NAFLD, when compared to women (187, 188). In a study with nearly 400 individuals, the NAFLD prevalence defined by ultrasound was 46%, and the histologically confirmed prevalence was 12.2% (189). Clinical disease ranges from mild elevation of liver enzymes to severe disease with fibrosis (183). NAFLD has not been proven to be a risk factor for DILI in general (108).

Convincing evidence shows an association between NAFLD and type 2 DM (190, 191). NAFLD is a precursor and nearly doubles the risk of type 2 DM and metabolic syndrome over a median follow-

up period of 5 years (192, 193). In an ultrasonography study, 69% of patients with type 2 DM presented NAFLD (194). Its prevalence in patients with DM ranges from 30% to 75% varying according to age, ethnicity and diagnostic methods applied (195). Besides, it has been noted that fatty liver may be a shared condition playing a key role in the development of type 2 DM in patients with chronic HCV or HIV infections (182).

1.6.2 DM and alcohol consumption

Alcohol consumption can have an impact not only on the incidence of a range of diseases, but also on their courses and outcomes. The incidence rate of DM is significantly greater among those with alcohol drinking disorders compared to matched controls (196). Patients with alcoholic liver disease have a high relative risk of developing DM, and this risk is directly related to the amount of ingested alcohol (197). There is epidemiological evidence from a number of recent prospective studies indicating a close relationship between alcohol consumption and the risk of development of type 2 DM (198-201).

While heavy alcohol consumption is a risk factor for DM, regular light-to-moderate quantities of alcohol may decrease this risk (202, 203). Moreover, chronic alcohol intake has been associated with poor glycaemic control in individuals with DM and has a negative effect on DM outcomes (202, 203).

Diabetes frequently co-occurs with alcohol abuse or dependence (204). The development of both insulin resistance and impaired glucose tolerance, conditions that precede the onset of type 2 DM, are closely linked to alcohol dependence (205). A study by Engler *et al*. (206) documented that 13.4% of DM patients in an outpatient clinic were at-risk drinkers, of which 11.1% met criteria for alcohol dependence. At-risk drinkers are those considered likely to experience negative health consequences as a result of this drinking behaviour and are at an increased risk for future alcohol-related adverse health events. In 2011, Cullman *et al.* (198) conducted a prospective study to investigate the influence of alcohol consumption and specific alcoholic beverages on the risk of developing pre-DM and type 2 DM in a Swedish population after a follow-up of 8-10 years. A high alcohol intake was found to increase the risk of pre-DM and type 2 DM in men, including binge drinking. In women, the associations with glucose metabolism were more complex. There was a decreased risk with low or moderate alcohol intake and an increased risk with high alcohol intake, in accordance to other studies (202, 203, 207, 208). There was no association between binge

drinking and pre-DM and type 2 DM in women. This is in contrast with a Finnish cohort study (209), that found no association between binge drinking and type 2 DM in men, but a doubled risk in women.

1.6.3 DM and Hepatitis B infection

Globally, HBV infects 350 million people (210). The WHO informs that the areas of high prevalence of HBV infection are similar to the global TB epidemiological high burden regions, such as sub-Saharan Africa and South Asia, where the prevalence is estimated to be between 8% and 20% (128). A Brazilian study conducted in Rio de Janeiro has reported a prevalence of 3.2% of hepatitis B surface antigen (HBsAg) positive patients with active TB (211). Another one, conducted in Goiânia, in 2011, has found a prevalence of 2.8% (212) in TB patients with or without HIV. In 2011, the incidence rate of confirmed cases of HBV (either by HBsAg, anti HBc IGM or HBeAg) in Goiânia was 9.3 per 100,000 population (213) .

HBV is known to lead to liver cirrhosis and hepatocellular carcinoma (210), but its association to DM has been controversial and studied less extensively than the HCV association to DM. A few longitudinal (214) and cross-sectional studies (214) have found no significant association between a positive serology for HBsAg and DM. However, some studies showed an increased prevalence of DM in HBsAg positive patients when compared to HBsAg negative patients (215-217). Papatheodoridis *et al.* studied 434 patients with histologically documented hepatitis B or C and found that DM was present in 13% (58/434) (215). There was no difference between chronic HBV (14%) and HCV (13%). Lao *et al.* found an independent association between HBsAg carrier status with gestational DM (RR 3.51; 95% CI 1.83 – 6.73) (216). Lastly, Li-Ng *et al*. (217) investigated the association between HBV infection and DM among Asian Americans and Pacific Islanders. Overall, DM prevalence was higher in patients with HBV than in those without HBV (58.9% *vs.* 33.3%, $P < 0.001$), and this remained so after adjustment for confounders (OR 3.17; 95% CI 1.58 - 6.35).

A cohort study conducted by Hong *et al*. in 2017, with a large sample of individuals with a low risk of DM and adjustment for multiple covariates, found a clear association between HBsAg and both DM incidence (HR 1.23; 95% CI 1.08-1.41; $P = 0.007$) and prevalence (OR 1.17; 95% CI 1.06 - 1.31; $P = 0.003$) (214). This study adds evidence on a prospective association of HBV infection and DM incidence and shows that HBV infection is related to glucose metabolism abnormalities. There is a

growing body of research suggesting that DM is a metabolic complication of HBV, but evidence is still inconsistent. There is need for further longitudinal studies with longer periods of follow up to better characterize the effect of HBV on the risk of DM.

1.6.4 DM and Hepatitis C infection

The association between HCV and type 2 DM has been known for over 20 years (218). DM and HCV infection are prevalent diseases worldwide and epidemiological studies have shown that they are associated (219-221), regardless of differences in ethnicities and geographical regions (222). It is estimated that 24% to 64% of chronic HCV patients have type 2 DM (223, 224), and it has been shown that HCV infection can precede type 2 DM diagnosis in as many as 73% of cases (223, 225, 226), although that could be related to age of acquisition rather than cause and effect. A large number of studies have revealed an increased risk for type 2 DM in patients with chronic HCV infection (227-230) and the overall prevalence of DM among chronic HCV patients in North America, Europe, Middle East and Asia ranges from 13% to 33% (231-233). These are demonstrably higher than age-matched prevalence in the general population, from which these samples are drawn. Indeed, HCV has been described as an independent predictor for DM (234).

Hepatitis C virus infection is a significant global health burden. According to WHO, it is estimated that HCV infects 170 million people globally, around 3% of the world population (1, 4). The outcome of chronic HCV is variable and over a period of approximately 25 to 30 years, around 20% to 30% of patients develop cirrhosis, which increases the risk of hepatocellular carcinoma (1% - 4% per year) and liver-related death. Besides causing cirrhosis and hepatocellular carcinoma, HCV is thought to be the cause of a number of metabolic disorders (235). In addition, there is evidence that insulin resistance and type 2 DM are strongly related to worse outcomes in HCV patients and are independent predictors of liver-related mortality. They are associated with increased fibrosis progression, cirrhosis decompensation and an increased risk of hepatocellular carcinoma in a variety of studies (236-241). In fact, insulin resistance has been demonstrated to be an independent predictor of fibrosis in chronic HCV individuals (242, 243). A review conducted by Desbois and Cacoub (235) searched for a relation between liver fibrosis and DM, insulin resistance and impaired fasting plasma glucose. Twenty-six out of 30 studies reported a significant association between glucose abnormalities and liver fibrosis severity (OR ranging from 1.28 to 13.72) (235). The association between HCV cirrhosis and DM has long been known (244).

The clinical interactions between HCV and insulin resistance are multi-layered and result in the progression of HCV infection. The prevalence of insulin resistance or type 2 DM in patients infected with HCV has been shown to be high. A study conducted at an outpatient clinic found a 30% prevalence of glucose abnormalities in HCV patients (180). A systematic review of 35 observational studies found a pooled OR 1.7 for type 2 DM in HCV positive patients compared to HCV negative controls and a pooled OR 1.9 when comparing to HBV infected controls (245). A community-based prospective study showed an increased risk of developing DM in HCV positive patients when compared to HCV negative patients (HR 1.53; 95% CI 1.29 – 1.81), after adjustment for age and body mass index (246).

A review conducted by Desbois and Cacoub, in 2017, reported that 16 out of 20 studies found a significant association between glucose abnormalities (insulin resistance and DM) and HCV infection (235). Seven studies with multivariate or adjusted analyses showed an OR between 1.2 and 3.77 (235). When compared to HBV-infected patients, seven out of 11 studies found a significant association between DM and HCV (235).

Diabetes has been clearly shown to increase the risk of hepatocellular carcinoma among patients with HCV. Several studies have found a substantial association between DM and insulin resistance and the development of hepatocellular carcinoma in the follow-up of HCV infected patients, with HR ranging from 1.10 to 6.9 (247-250).

Although there is a substantial body of evidence in favour of a link between DM and HCV infection, some studies have found diverging results (215, 251, 252). Therefore, there is still need for further research to better understands the metabolic pathways connecting insulin resistance, metabolic syndrome, DM and HCV. Regardless, a vast majority of studies have shown a two to tenfold increase of type 2 DM in chronic HCV-infected patients, compared to other liver diseases (228, 253-255) and DM has been recognized as part of the spectrum of HCV-associated diseases by a large body of research (256, 257).

To conclude, HCV infection and DM are both highly prevalent chronic diseases of epidemic proportions and a large body of evidence has attested to this two-way association: HCV infection leads to DM, and DM worsens HCV outcomes (222).

1.6.5 DM and HIV infection

Recent studies have suggested that, currently, the life expectancy of HIV-infected patients may approach that of the general population (258). Consequently, the increasing number of older HIV positive patients results in an increased burden of age-related comorbidities to be managed both by physicians and policy makers. Patients with HIV have been found to be at a higher risk of incident cases of type 2 DM compared to the general adult population (259), although the mechanisms involved are yet to be better understood. The use of some antiretroviral drugs, the co-infection with HCV and the HIV-induced systemic chronic inflammation are amongst the conditions involved (260-263). Therefore, further research is needed to further elucidate possible contributing factors for the development of type 2 DM in patients with HIV infection.

CHAPTER 2 - JUSTIFICATION, AIMS, OBJECTIVES AND HYPOTHESES

2.1 Justification

National TB control programmes have a responsibility for devising, implementing, monitoring and evaluating public policies to reduce the health and social burden of TB, and then further disseminate scientific information and provide guidance. In 2012, the United Nations Conference on SDG held in Brazil established the SDG for the global health agenda as a substitution for the eight Millennium Development Goals, which ended in 2015 (264). The third target of the third SDG's health goal (ensure healthy lives and promote well-being for all at all ages), is focused on ending the TB, AIDS and malaria epidemics, among others, by 2030. The fourth target is about reducing by one third, through prevention and treatment, the premature mortality from non-communicable diseases (264).

Approximately 439 million people worldwide are estimated to develop DM by the year 2030 (265). Type 2 DM, which accounts for approximately 90% of DM cases, has become a global public health concern. In many countries, the current epidemic proportions of DM are increasingly becoming a key determinant of TB. Diabetes prevalence has been rising more rapidly in middle and low-income countries, which are the ones where the burden of TB is greatest (18). Of all the countries with this increasing trend of DM cases, it has been reported that 70% occur in developing countries and 47% in developed ones (266). Several aspects of this subject still need robust evidence to inform global health policies both on TB and DM programmes. Indeed, DM is now prominent on the global health agenda and is recognized as a challenge to national TB control efforts. Consequently, TB control programmes should target patients with DM for any intervention that may have an impact on TB outcomes.

In 2014, WHO's new End TB Strategy established the following global milestones for 2025, relative to 2015 data: a 50% reduction in TB incidence and a 75% reduction in TB mortality; and for 2035, a 90% reduction in TB incidence (<10 cases/100.000 population globally) and a 95% reduction in TB mortality (267). Within the scope of the End TB Strategy and the new SDG, actions focused on a better control of DM will have a positive impact on the global burden of TB.

One important question to TB control programmes worldwide is about the impact that DILI caused by TB drugs has on TB outcomes in patients with DM. Studies have shown that DM patients have

worse TB treatment outcomes. If, in addition to that, they present an increased risk of DILI due to particularities related to DM, then it would be of paramount importance to identify risk co-factors in this population early on. DILI poses an additional threat to a treatment which is already long by nature and frequently fraught with difficulties. The End TB Strategy states that comorbidities should be identified and managed accordingly, and this could be extrapolated to identifying and managing whatever conditions might hinder a successful TB treatment in the DM population. If TB policy makers and implementers succeed in mitigating the serious consequences of DILI, then these patients will stand a better chance of completing a successful treatment. DM is common amongst TB patients and, as well as being a direct cause of hepatic dysfunction (for instance, through fatty liver), DM is associated with a number of comorbidities that can cause hepatic damage. Thus, it is important for TB programmes to understand whether DM is an important independent risk factor for DILI or an important co-factor for DILI due to other hepatotoxic comorbidities; or indeed not actually a condition for which heightened vigilance for DILI is necessary. Those are the questions that this study sets out to address. There is a dearth of evidence on this issue presently available to inform policy makers on this particular matter.

2.2 Aims and objectives

The aim of this study is to determine whether DILI is more frequent amongst TB patients with DM than without it; and to identify co-factors predictive of an increased risk of DM-associated DILI. The objectives are twofold:

1. To undertake a case-control study of TB patients with and without DILI to determine the effect of DM as a risk factor for DILI;

2. To further investigate predictors of DILI in patients with DM and any co-factors associated with this increased risk, if identified.

2.3 Hypotheses

1. DM patients taking the RHZE regimen for active TB will be more likely to develop DILI than those without DM.

2. Any increased risk for DILI in those with DM will be associated with important co-factors that further amplify any DM-associated risk.

CHAPTER 3 - METHODS

3.1 Study design

This is a case-control study. The case-control design was chosen over a cohort study. The large number of TB patients who were followed up during the 4.5-year period of the study precluded the decision to conduct a cohort study. A retrospective cohort would have entailed data extraction from a much larger number of sets of case notes, which would have been unfeasible. A prospective cohort study would take too long to follow up and recruit participants (the DILI outcome is sufficiently uncommon that it would take several years to recruit a few hundred cases). Amongst the advantages of a case-control study design, it should be mentioned that it is suited for studying rare conditions; is relatively quicker to conduct than a prospective design, as the outcome and the exposures of interest have already occurred in the past; it is less expensive; and it allows for studying associations without the need for lengthy follow-up periods. As to its disadvantages, selection bias among controls and information bias were considered as possible issues, as these are the main types of bias that case-control studies are susceptible to. The temporal sequence between the exposures and the outcome was not an issue in this study and this is because the outcome, DILI, always post-dated the main exposure, DM.

3.2 Matching

Matching is a method for reducing the effects of confounding variables. Both the controls and the cases are selected with no differences with respect to certain characteristics. It can be done either by individually pairing a case to one or more controls or by frequency matching, which means that the groups of cases and controls will have the same overall distribution of the matching variable. Frequency matching does not control confounding to a great degree, and further statistical methods are needed; however, it does improve comparability between cases and controls, illustrated, for example, by the way age-matching would avert comparison of cases of neonatal jaundice with an inappropriate control group of people without jaundice, of all ages.

There are methodological issues raised by matching in case-control studies. For instance, by completely precluding detection of any association between the exposure that cases and controls are matched on, because it is designed to be present to the same degree in both groups. This leads

to over-matching, and once overmatching occurs, it cannot be corrected later in the analysis. Other disadvantages would include adding complexity (in terms of time spent and costs) to the recruitment phase; and the exclusion of cases, if matching controls cannot be found. Those issues are beyond the scope of this thesis, but the decision to conduct an unmatched case-control study was based mostly on the reasoning that once patients have been matched in the recruitment phase of the study, there is little flexibility in the analysis phase. The effect of the matching variable on the outcome variable can no longer be studied. It was deemed to be more meaningful to the study if all the pertinent exposures were included in the statistical analysis phase and the confounding variables controlled during the analysis by use of adequate statistical methods.

3.3 Description of the study sites and setting

3.3.1 TB Clinic referral network

The TB referral clinics are TB clinics in the secondary level of health care in the Brazilian public health service. Apart from their attending to patients, these TB clinics also provide training for medical residents and assistance to general practitioners on any TB-related issues, whenever necessary. At the outset of this study, there were five such clinics in Porto Alegre, all of which were data sources for the present study. A small number of TB patients is treated in primary care, by general practitioners or family physicians, but only uncomplicated pulmonary TB (PTB) cases which are eligible for treatment with the first-line drugs, RHZE, and in the absence of adverse effects. DILI is not a condition managed in the primary care setting. According to the PNCT guidelines and recommendations in Brazil, patients should be referred from their general practitioners to a TB referral clinic if they meet the following criteria:

1. The TB diagnosis process is facing difficulties;
2. Major adverse effects, such as allergy, DILI, neurotoxicity, nephrotoxicity;
3. Serious comorbidities such as transplanted patients, immunosuppression, chronic liver diseases and chronic renal disease;
4. Cases of failure to the first line regimen.

The municipal TB Control Programme of Porto Alegre had the following additional criteria included: TB in children under 12 years of age, pregnancy and EPTB. All cases of PTB in adults without the comorbidities mentioned above and eligible for the first-line regimen, are treated by some family doctors and general clinicians. A new public policy on the decentralization of TB treatment has been implemented for the last four years, approximately. It has been a process fraught with difficulties and one which has evolved heterogeneously across the city. It was not possible to gather accurate data on the proportion of patients followed up in the primary care clinics *vs.* TB clinics, but patients are still largely managed in the latter. All suspected DILI cases are routinely transferred to the TB clinics and then managed by the TB physicians, even those cases who are successfully re-challenged and do not need a change of treatment. Primary care clinics are not allowed to decide on any change of TB treatment.

Once a patient is started on TB treatment, there are standard procedures conducted, preferably in the first appointment at the TB clinic. In order to promptly diagnose infectious comorbidities, rapid tests for HIV (HIV Test Bioeasy, by Standards Diagnostic Inc, Republic of Korea); HBsAg (VIKIA HBsAg by bioMérieux SA, France); HCV (ALERE HCV, by Standard Diagnostic Inc, Republic of Korea) and syphilis (ALERE Syphilis, by Standard Diagnostic Inc, Republic of Korea) are performed by the TB nurses. Not all patients are tested by rapid tests, as these may be ordered together with a more comprehensive biochemistry panel, according to the physician's discretion. Another possible scenario is that the patient has been previously tested, either at the hospital or by their attending physician. In such case, the TB physician may not be aware of those tests results. Consequently, a certain heterogeneous pattern of biochemical analyses across all the TB clinics was anticipated, and that might happen either at the outset or during follow-up at the TB clinic. Tests for DM screening during TB treatment are subject to the physician's discretion.

Although there are national guidelines on the monitoring of DILI, those routines were also expected to be heterogeneous. Some patients are monitored regularly in the absence of risk factors or symptoms, while others are tested only if risk factors are present or symptoms occur.

The incident TB case is notified on the first medical appointment, through a hand-written Information System of Notifiable Diseases (SINAN) Form. It is then captured by the TB Epidemiological Surveillance Team (General Coordination of Health Surveillance (CGVS)), where it is recorded on a database, while a paper copy of the form is kept together with the patient records at the TB clinic.

If a patient should present alterations on liver function tests, the physician orders a viral hepatitis panel comprised of anti-HAV IgG/IgM, total anti-HBc/anti-HBc IgM, HBsAg and anti-HCV. Once the physician diagnoses a case of DILI and decides that a change of drug regimen is needed, the patient is then registered on a nationwide electronic system of notification of cases needing special treatments, the Information System of Special Tuberculosis Treatments, SITETB.

3.3.2 Tuberculosis Notification Database

The TB control programme requires that all incident TB cases are notified when the patient is put into treatment, during their first medical consultation. The notifications are done by filling out a TB Notification Form, SINAN, which is subsequently sent to the TB Epidemiological Surveillance Team at the Health Surveillance Department and kept at the electronic Tuberculosis SINAN Database. Appendix A shows the tables with the number of notified incident cases in all the five referral TB clinics in Porto Alegre per year, from 2013 to 2017. Between 453 and 802 patients were notified as incident TB cases between 2013 and 2017 (Appendix A, Table A1), with a median of 635 patients and interquartile range (IQR) 529 – 667. Notification numbers from the referral clinics decreased throughout the years due to the decentralization project that had been under implementation. Treatment outcomes during the same period were as follows (Appendix A, Tables A2 - A6): cure was achieved in a median of 384 patients (IQR 317 – 406); default from treatment occurred in a median of 129 patients (IQR 84 – 158); death occurred in a median of 20 patients (IQR 19 – 21); and discharge by transfer, in a median of 20 patients (IQR 17 – 21).

3.4 Study population

The study population were patients of all ages who were treated for TB with the first-line regimen who either did or did not develop DILI during their treatment. The results from the study are expected to be generalizable to all other TB patients taking the same drug combination.

3.4.1 Cases definition, selection criteria and collection

3.4.1.1 Cases definition

Cases were TB patients who presented with DILI during treatment with RHZE, either in fixed dose combination or in individualized tablets. DILI is defined as drug induced liver injury, as diagnosed by the attending physician with a resulting change in the TB treatment prescribed. For the purposes of this study, DILI was not defined by a threshold increase in transaminases or bilirubin but rather by this operational definition. The DILI episode must have been severe enough for the physician to decide in favour of a change of treatment, including patients who went through an unsuccessful re-challenge.

Patients who presented DILI and were successfully rechallenged with RHZE did not need a change of treatment and, therefore, were neither reported onto SITETB, nor in any registry, so could not be captured. The rationale for the definition of DILI cases as "cases who needed a change of treatment" was that they reflect the most severe DILI cases, which were the focus of the investigation. That was the best quality data.

3.4.1.2 Selection of cases

3.4.1.2.1 Inclusion criteria

Patients were selected as cases if they presented the following criteria:

1. Presentation of DILI diagnosis from 01 January 2013 to 31 July 2017.

2. Patient originated from a general practitioner's clinic, TB clinic or discharged from a hospital.

3. Registration on the Information System for Special Tuberculosis Treatments electronic platform from 01 January 2013 until 31 August 2017 – in so far as the DILI episode happened no later than 31 July 2017 - due to a need of change of treatment prescribed.

4. Follow-up in one of the five TB clinics in Porto Alegre, Rio Grande do Sul, Brazil, either before the DILI episode or since that.

3.4.1.2.2 Exclusion criteria

Patients were excluded based on the following criteria:

1. Patients who were given rifabutin instead of rifampicin, as the former is not considered as potentially hepatotoxic as the latter.

2. Patients missing any one of the three hepatotoxic drugs, namely rifampicin, isoniazid or pyrazinamide. TB DILI is caused by the synergistic hepatotoxic effect of the three drugs taken concomitantly and patient groups (cases and controls) must only be compared if they are taking the same drug combination.

Patients were not excluded if they were not treated with ethambutol, as this drug is not associated with hepatotoxicity. Similarly, patients who died were not excluded.

3.4.1.3 Cases collection

The cases were obtained by reviewing all the patients registered on the Information System of Special Tuberculosis Treatments, the SITETB database, requiring a change of treatment due to hepatotoxicity whilst being treated with RHZE. Besides those patients who had DILI, there were also those presenting with a previous chronic liver condition, to whom RHZE would be best avoided. As a result, they were given a different drug regimen from the start. They were not DILI cases. Although that represented a different category in the SITETB, those two groups were classified together under the term “hepatotoxicity”, so needed be reviewed as well. Conversely, as a way of capturing any hepatotoxicity case that might have been misclassified as “allergy” as the reason for being on SITETB, all the patients registered as having had any allergic reaction were considered as potential DILI cases and reviewed. Patients registered as “intolerance to drugs” were also reviewed, for the sake of thoroughness.

3.4.1.3.1 SITETB Database

SITETB is an electronic information system for notification, management and closure of TB and non-tuberculous mycobacteria (NTM) infection cases. It was implemented in 2013 and first created to standardize the management of multidrug resistance regimens. However, its use has been further

developed into managing cases of mono- and poly-resistance as well as major adverse reactions. The reasons for a special treatment, that is, any drug regimen different from the RHZE tablet in fixed dose combination, may be numerous: mono-resistance, poly-resistance, multidrug- resistance, NTM infection, significant side effects, incompatibility with concomitant drugs, chronic liver disease; and a need for reduced dosages, such as in patients with low body weight, chronic renal disease or a rechallenge with RHZE. Once onto SITETB, the case will be subject to an assessment by a validator from another Brazilian state who, in case of agreement, will grant authorization for the delivery of the new drugs to the TB clinic. All cases are monitored electronically monthly until their final outcome and closure. It provides data on demographics, TB diagnosis, comorbidities, previous TB episodes and outcomes, and pharmacological surveillance. It is a valuable monitoring tool that provides useful and real-time data nationwide for both clinical and research purposes, as well as feedback to the PNCT.

3.4.2 Controls definition, selection criteria and collection

3.4.2.1 Controls definition

The *control* subjects were TB patients who were treated with RHZE, either in combined or individual tablets, and who did not develop DILI during the same time frame, from 01 January 2013 until 31 July 2017.

3.4.2.2 Selection of controls

3.4.2.2.1 Inclusion criteria

Controls were chosen if they had been treated regularly for TB in the same five referral TB clinics during the same period, for a minimum time on treatment of four months.

In the unlikely event of a control being registered on SITETB for any other reasons than DILI, he/she was still considered eligible in so far as they remained on the first-line regimen throughout treatment, even if in the following circumstances: if ethambutol was not prescribed (pediatric patients under ten years of age) or if they were discontinued for any reason; if tablets were prescribed individually due to low weight, chronic renal failure or chronic liver disease. Patients on

individualized tablets of RHZE due to a previously identified risk factor for DILI, were also eligible as controls.

3.4.2.2.2 Exclusion criteria

Patients with the following indications for registration on SITETB were ineligible as a control: mono-resistance to isoniazid or to rifampicin, or any non-DILI side effects leading to a disruption in the RHZ combination, such as untreatable gastro-intestinal intolerance to any of them; patients who had their treatment discontinued before completing 120 days, who were lost to follow-up for whatever reason or died before the 120th day of treatment; and patients with treatment irregularity, defined as taking treatment on less than 15 days in any 30 days period. All reasons for the exclusion of eligible controls were recorded.

3.4.2.3 Controls collection

Candidates for the control group were obtained through the following process: by running a database search on the TB notifications in Porto Alegre from 2013 to 2017, classified by TB clinic and by year. In total they were 4,535 patients, on five separate Excel spreadsheets, extracted from the SINAN database of the General Coordination of Health Surveillance, CGVS. After scanning for duplicates, all potential controls were identified. Each one of the TB clinics had its own list, from which the control patients were selected by systematic sampling. Initially the following approach was used: after ordering the lists by year of notification, every third patient was selected and the corresponding medical record was then examined to ascertain if that patient fulfilled the criteria for being a control. If it was decided that the patient did not fulfil the criteria, the next patient was selected, and their medical records examined. In each clinic, the total number of controls produced was roughly four times the number of cases, by year. In the eventuality that any problems had happened in a certain year and clinic, for instance, a viral hepatitis outbreak in that clinic area, this measure would have made sure that cases and controls had been affected likewise.

At a certain point through data collection, during the first half of it, it was decided not to use the patients lists because they were incomplete, with missing patients and identification numbers, which prevented the investigator from having information on the year of treatment. Moreover, the list for Clinic 5 had no information on the year of notification. Therefore, in all clinics except Clinic

3, the controls were selected directly from the medical records files, according to the same sampling system of every third patient. The TB clinics were dissimilar in their filing system. Table 1 shows their differences.

Table 1. Filing and storage systems in the TB clinics

	Classification system of medical records	Storage order	Deaths
Clinic 1	Year of start of treatment	File ID number	Included
Clinic 2	Year of start of treatment	File ID number	Included
Clinic 3	Year of start of treatment	Patient's first name in alphabetical order	Excluded and stored separately
Clinic 4	Year of start of treatment	File ID number	Included
Clinic 5	Type of treatment (special treatments)	Patient's first name in alphabetical order	Included

ID: identification

3.5 Sample size and statistical power

From preliminary data, it was found that amongst patients on TB treatment, the prevalence of DM was 6.8% and among the cases (TB patients with DILI), it was 12.5%. The DM prevalence among cases of 12.5% was obtained from a pilot assessment of DILI cases in diabetic patients from the five main TB clinics in Porto Alegre.

The sample size needed to detect an odds ratio (OR) of 1.96, assuming a 1:3 ratio of cases: controls, a type I error of 5% and power of 80%, was approximately 244 cases and 730 controls. Nevertheless, the number of 244 cases was not reached during the pre-established study recruitment period from 1st January 2013 to 31st July 2017. In an attempt to maintain the same power to detect the same measure of effect, the number of controls was increased to four to one case. As a result, the sample size needed for an OR of 1.96 was 221 cases and 883 controls. A sample

size calculation for 90% power and a ratio of 1:4 for cases to controls, which would have required 75 additional DILI cases, was also considered. Appendix K shows a table with the relationship between power and sample size for a range of effect sizes.

3.6 Data collection methods

3.6.1 Subjects

All data on subjects were collected from the patients' medical records at the TB clinics and from electronic databases from the Brazilian PNCT. The PNCT notifies and monitors TB cases by way of two complementary information systems, the SINAN and the SITETB databases.

3.6.2 Explanatory variables

The explanatory variables were collected from the SITETB electronic database, the SINAN form and from medical documentation. They are listed below. The main explanatory variable of interest was DM. The potential risk factors for DILI that were considered and recorded were age, sex, chronic hepatitis B and C infection; HIV infection, hazardous drinking, use of hepatotoxic drugs, other concomitant liver diseases and conditions; and site of TB. Other variables studied were method of TB diagnosis, method of DM diagnosis and, for cases, time to DILI. A literature search was performed in order to identify potential confounders. The covariates age, hazardous drinking, HCV and hepatotoxic drugs were previously identified as associated with both the exposure and the outcome.

3.6.2.1 Age

The cases had their age calculated by subtracting the date of birth from the date of DILI diagnosis. In the eventuality of missing dates for DILI diagnosis, the date of start of RHZE was used for the age calculations. For the controls, age was derived by subtracting the date of birth from the date of start of RHZE. The calculations were done in the Excel database and presented in number of years; for children younger than 12 months old, they were recorded as being one year old. Subjects had their ages categorized into five groups: from a minimum age to 39 years; 40 to 50; 51 to 60; 61 to 70; and

71 to maximum age. The reason for that was the large size of the sample and the fact that the literature concerned with risk factors for drug hepatotoxicity reports age in stratified age groups.

3.6.2.2 Date of DILI

The date of DILI was defined as the earliest date of available liver tests showing abnormal results according to the standard definition of TB DILI (95): in the absence of symptoms, elevation of transaminases ≥ 5 times the ULN value; and in the presence of symptoms, ≥ 3 times the ULN value or twice the bilirubin ULN value. The variable was time to DILI and was calculated as the number of days from the start of treatment to the date of DILI, as defined here. In the eventuality of an unknown date, the closest probable date was used, taking into consideration any recorded date of symptoms together with liver tests.

3.6.2.3 Date of SITETB

As a rule, the date of the notification onto SITETB is a few days after the patient has been on the new drug regimen, so that tolerance has been established. For the purposes of the present study, the final date for the DILI episode was 31 July 2017. It was noted by the researchers that patients may have been registered onto SITETB some days later than that. So, because of that time gap, 31 August was the limit for capturing DILI cases on SITETB.

3.6.2.4 TB Clinics

The five TB clinics participating in the study were given a number from one to five (Table 1): *CRTB Centro*, Clinic 1; *CRTB Navegantes*, Clinic 2; *CRTB Vila dos Comerciários*, Clinic 3; *CRTB Bom Jesus*, Clinic 4; and *CRTB Hospital Sanatório Partenon*, Clinic 5.

3.6.2.5 TB diagnosis

Patients initiated on TB treatment included those with either a confirmatory microbiological diagnostic test or those who, despite lacking microbiological confirmation, had been commenced on treatment on strong clinical grounds. There were four categories (Appendix B): *smear positive*,

culture positive, a *positive molecular biology method*; and *not confirmed*, meaning a clinically diagnosed TB case. That would be a case which was not bacteriologically confirmed, but which was believed to be TB because of symptoms, imaging abnormalities and tests suggestive of Mtb infection taken all together into consideration. Culture was either in liquid or solid medium and molecular biology methods were Real Time quantitative PCR (qPCR) or GeneXpert® MTB/RIF assay. In case there were positive results in more than one method (and only one possible record for the data capture sheet), a hierarchy of diagnostics was adopted. The gold standard was the culture, immediately followed by the molecular biology method and, lastly, the smear.

3.6.2.6 Site of TB

This variable had three categories: *only PTB*, *only EPTB* and *both PTB and EPTB*. The latter was an attempt to reflect those with more extensive disease, and therefore, more severely ill patients. All TB sites were reported, and their frequencies analysed.

3.6.2.7 Date of RHZE

The date of RHZE was the date of the start of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol.

3.6.2.8 DM

A patient was recorded as having DM if the diagnosis was reported according to the six categories provided for the DM diagnosis in this study. A patient was recorded as not having DM if a blood test confirmed its absence. In the case of an unconfirmed information of absence of DM, then it was recorded as *unknown*. In order to deal with missing data on DM, patients were classified either as *known to have DM* (with a confirmed DM diagnosis, according to the definitions below) or *not known to have DM* (DM status unknown or negative).

DM diagnosis was defined as:

- ***Definite* DM diagnosis:**

  Established by the TB physician (or any other attending physician) at the outset of or during TB treatment according to the following criteria from the Report of the Expert

Committee on the Diagnosis and Classification of Diabetes Mellitus (268) and from the International Expert Committee report on HbA1c (269):

1. HbA1c ≥ 6.5%; *

or

2. a fasting plasma glucose ≥ 126 mg/dl. Fasting is defined as no caloric intake for at least eight hours*;

or

3. a 2-hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (performed using a glucose load of 75g anhydrous glucose); *

or

4. a random plasma glucose >200 mg/dl + classical symptoms (polyuria, polydipsia and polyphagia).

In the absence of unequivocal hyperglycaemia, the first three criteria (*) should be confirmed by a second test.

- ***Probable*** **DM diagnosis:**

5. The patient informed a DM diagnosis prior to the TB episode associated with classical symptoms at the time of diagnosis, concomitant use of appropriate DM therapy (diet with or without pharmacological therapy) and follow-up;

or

6. The physician indicated in the paperwork that the patient had DM without evidence of the test criteria above.

3.6.2.9 Hazardous alcohol use

Defined as a quantity or pattern of alcohol consumption that places patients at risk for adverse health events, as self-reported by the patient, their family or by the TB clinic team. Any reported use considered as hazardous was captured. There is a tendency for categorizing drinking habits subjectively, as either one of a dependent or abusive pattern or as simply occasional. According to

the United States National Institute on Alcohol Abuse or Alcoholism (270), a hazardous habit is characterized as more than four drinks per day or 14 drinks per week for men; or more than three drinks per day or seven drinks per week for women. What was classified as abusive consumption encompassed hazardous drinking.

To deal with missing data on this variable, patients were classified either as *known to be hazardous drinkers* (a hazardous drinking pattern being reported by the patient or family) or *not known to be hazardous drinkers* (unknown status or a negative response).

3.6.2.10 HIV, HCV and HBV

Patients with HIV, HCV and HBV positive status were captured from blood tests results, ordered by a physician, or from the rapid tests offered to all incident TB patients, as recommended by the PNCT protocol at the TB clinics. In order to deal with missing data on the tests results, patients were classified either as *known to be HIV-*, *HCV-* or *HBV-positive* (a positive test result) or *not known to be HIV-*, *HCV-* or *HBV- positive* (unknown test result or a negative result).

3.6.2.11 Concomitant hepatotoxic drugs

All drugs were considered as taken, once prescribed by a physician, unless medical notes informed otherwise. All drugs prescribed concomitantly to RHZE were initially recorded on the data capture sheet, regardless of their potential for hepatotoxicity. After that, they were searched for in the A and B lists published by Björnsson and Hoofnagle (271), as can be seen in Appendix C (tables C1 and C2) and only those were kept and used for statistical analyses. In case the records would not disclosure the exact period of the drug-taking, or if there was just a mention of the class name, for instance, *nonsteroidal anti-inflammatory drugs or painkillers*, then they were recorded as "unknown" and the drug class was noted, for completeness.

To deal with missing data on this variable, patients were classified either as *known to have taken any concomitant hepatotoxic drugs* if drugs were identified and the concomitance established; or *not known to have taken hepatotoxic drugs* if there was absence of drugs prescribed (interpreted as not prescribed) or lack of data on that.

3.6.2.11.1 Reference for the classification of hepatotoxicity potential

Documentation of hepatotoxicity in the medical literature is variable and many published cases lack critical review. A standardized system for categorizing drugs implicated in causing liver injury was conducted by Einar S. Björnsson and Jay H. Hoofnagle (271), in which drugs were classified into categories of hepatotoxic potential according to a critical assessment based on the number of published reports of convincingly documented liver injury. Drugs described in the LiverTox® database (115) were classified into five categories based on the number of published cases (Category A, ≥ 50 cases; Category B, 12 - 49 cases; Category C, 4 - 11 cases; Category D, 1 - 3 cases; and Category E, none).

LiverTox® is a website on hepatotoxicity designed and supported by the National Institutes of Health of the United States Government. LiverTox® is a joint effort of the Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases and the Division of Specialized Information Services of the National Library of Medicine, National Institutes of Health. It provides updated, comprehensive and unbiased information about DILI caused by prescription and non-prescription drugs, herbal products, dietary supplements, and environmental toxins in general. It represents a collaborative effort by medical and scientific specialists to provide a collection of clinical information on the prevention and control of DILI. By 2017, the LiverTox® website had more than 23,000 annotated references.

For the purposes of this study, drugs from categories A (≥ 50 cases) and B (12 - 49 cases) were reported as hepatotoxic (271). Their individual frequencies were reported and are shown in Appendix J.

3.6.2.12 Other liver diseases

A patient was considered as having another liver disease or condition (apart from having chronic HCV or HBV) if that was made evident by an abdominal ultrasound or computerized tomography (CT) scan, liver biopsy or blood tests; or if there was any report from a physician to that effect. Patients were considered as not having another liver disease or condition if the above-mentioned tests proved its absence. Even in the absence of a conclusive diagnosis of a previous liver disease, the patient's blood tests and imaging abnormalities were noted and it was reported as positive for

a liver disease. All liver conditions were reported and their frequencies presented. Liver TB was included in this category.

To deal with missing data on this variable, patients were classified either as *known to have another liver disease,* if there was a definite diagnosis or strong suggestion of another liver disease; or *not known to have another liver disease*, if there was unconfirmed data on its absence or lack of any mention about it.

3.6.2.13 Time elapsed before DILI

This variable was obtained by subtracting the date of start of RHZE from the date of DILI on the Excel database and reported in number of days.

3.6.2.14 Other aspects

Data were also noted on TB clinic, pregnancy (being associated with liver tests abnormalities) and whether there had been any hospitalizations, in which case there could have been difficulties in data capturing, particularly if for long periods.

3.6.3 Quality control of data collection

Quality control procedures were performed. In order to assess consistency, duplicate data extraction was performed on five records randomly selected, in the last week of data collection of each TB clinic. A 100% agreement was found between data extracted on two separate occasions, which were at least three weeks apart. All data extraction was undertaken by a single investigator (the candidate). Data were extracted from various sources: SINAN, SITETB (the only electronic one), medical records and TB clinic records (used mainly to check inconsistencies whenever necessary) and that made possible frequent quality checks. Not only did the diverse sources give information on the same variables (thus allowing to check data consistency) but provided complementary information as well. Consequently, dependable and valid data were captured by the researcher.

3.6.4 Data sources

3.6.4.1 Outcome sources

The source for the outcome variable, DILI, was the SITETB database. Complementary information came from medical records in the TB clinics.

3.6.4.1.1 SITETB Database

SITETB was the only data source for capturing the cases but, additionally, it provided clinical information on the explanatory variables. Each TB clinic was scrutinized for DILI cases in the following way: all patients registered as of 1st January 2013 until the 31st August 2017 were examined as to their reason for having had a change of treatment. If it was due to *hepatotoxicity* or a *previous liver disease*, then all the data available on SITETB was reviewed. Cases registered as *allergy* or *major intolerance* were also examined, so as to capture any misclassified subjects. After all past cases had been examined, the TB clinics were assessed through SITETB for future incident cases every two weeks until 31st August 2017.

3.6.4.1.2 Tuberculosis Notification Database

The Tuberculosis Notification Database, with information compiled from the TB Notification Form, the SINAN form, was initially chosen as the first source for the extraction of controls. Five lists were generated, one for each TB clinic, and stored as encrypted Excel spreadsheets. The filters for capturing the lists of patients from the Epidemiological Surveillance SINAN database are presented below. The filters included:

1. Date of TB diagnosis: from 01/01/2013 to 31/07/2017;
2. Follow-up clinics: all five CRTB – the TB referral clinics in Porto Alegre;
3. Complete patient's name;
4. SINAN identification (ID) number;
5. Medical record ID number;
6. Date of birth;
7. Complete patient's mother's name.

The filters excluded:

1. Patients with primary default;

2. Patients who had a change of diagnosis any time after TB treatment was instituted.

Table 2. Different sources of variables

Variables					
	Dates of birth, RHZE and DILI	**DM**	**Age**	**Sex**	**Hazardous drinking**
Cases	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN
Controls	-MR -SINAN	-MR -SINAN	-MR -SINAN	-MR -SINAN	-MR -SINAN

Variables						
	HIV	**HCV**	**HBV**	**Hepatotoxic drugs**	**Other liver diseases**	**Site of TB**
Cases	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN	-SITETB -MR -SINAN
Controls	-MR -SINAN	-MR -SINAN	-MR -SINAN	-MR -SINAN	-MR -SINAN	-MR -SINAN

DILI: drug induced liver injury; DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MR: medical records; RHZE: rifampicin, isoniazid, pyrazinamide and ethambutol; SINAN: Information System on Notifiable Diseases; SITETB: System of Information on Special Tuberculosis Treatments; TB: tuberculosis

3.6.4.2 Exposure sources

Data on the main exposure, DM, was extracted from SITETB, the SINAN form and medical records, if it was a case; and from the SINAN form and medical records, if it was a control. Afterwards, all DM patients had their diagnoses confirmed by review of their medical documentation in the TB clinics.

If a patient with DM was not reported as such on SITETB or SINAN, then the medical records review was able to clarify that. All the other variables were extracted from SITETB, SINAN, and medical documentation. In the eventuality that inconsistencies were found, the data from the physician's notes on the medical records were always given preference and more credibility than the data from the SINAN form, SITETB or any other clinic report.

3.6.5 Data Management

Firstly, a survey was created in an Excel file, shown in Appendix D. The project was named *TBDM Project*. It was then converted into an XML Open Data Kit (ODK) Form by using XLS Form Offline. This electronic data capture form was uploaded and stored in ODK@LSHTM, which is a fully encrypted Secure Sockets Layer (SSL) server. The SSL technology aims to securely establish an encrypted link between a server and a client. The electronic form was then transferred to a mobile phone where the data was collected and their records daily submitted to a database in the ODK server. The database was stored in ODK@LSHTM in a comma-separated values (CSV) text file. In order to be managed and analyzed, the database was exported from the server, downloaded and stored safely in a password protected Excel file. It was subsequently cleaned, its variables coded, and fully prepared for the statistical analysis. Its security was assured as individual access to the database was granted solely to the study investigators. Personal identifiers were stripped and records were coded by record numbers. The file linking names with record numbers was securely stored separately in another encrypted Excel file. The subsequent statistical analysis required no personal identification details and was undertaken outside the study database.

3.7 Statistical analysis

The categorical explanatory variables were cross-tabulated against case/control status. Crude (unadjusted) ORs for being a case and their associated 95% confidence intervals (CI) were calculated by logistic regression. Amongst controls, categorical explanatory variables were cross-tabulated with DM to help with the identification of confounders. Confounding and effect modification was initially explored using the Mantel-Haenszel (M-H) analysis, and subsequently using multivariable logistic regression analysis.

In the M-H analysis confounders were identified if the adjusted OR for DM, after stratification, changed by at least 10% compared with the crude OR. Interactions were assessed with the Test of Homogeneity of ORs. The confounders identified were considered for the multivariable logistic regression. *A priori*, age group and sex were always adjusted for. Care was taken not to over-parameterize the model: the maximum number of parameters (ORs) in the adjusted model was restricted to the total number of cases (157) divided by 10.

Initially a fully adjusted model was constructed without any interactions, giving a fully adjusted OR for the effect of known DM on being a case. Finally, interaction between variables and DM, adjusting for all variables currently in the model, was considered using logistic regression, based on effect modification observed in the M-H analysis. All the statistical analysis was undertaken in Stata® V.14 (StataCorp).

The time to DILI was defined as time from the TB treatment start to the date of DILI diagnosis, summarized as median and IQR, and displayed graphically using Kaplan-Meier curves stratified by DM status.

3.8 Ethical considerations

Ethical approval was needed because this study is an analysis of routine human subject data obtained as part of clinical services which are not anonymized. Permissions were sought from the London School of Hygiene and Tropical Medicine Research Ethics Committee (Appendix E) and from three Brazilian ethics committees, namely the Porto Alegre Municipal Health Department Research Ethics Committee, the Research Ethics Committee of the School of Public Health of the State of Rio Grande do Sul Health Department, and the National Commission for Research Ethics, a commission of the National Health Council, so that unrestricted access to medical records and databases may be granted. First, it was necessary to obtain the local approval from two coordinators of the Municipal Department of Health of Porto Alegre, namely from the General Coordination of Specialized Care (CGAE), for permission to have access to medical records at the four municipal TB clinics; and from the General Coordination of Health Surveillance (CGVS), in order to have access to the TB Notifications Database. A third permission was granted by the *Hospital Sanatório Partenon*, for access to the medical records at the fifth TB clinic, the hospital clinic. Once these three local permissions were granted, the project was registered on *Plataforma Brasil*, a nationwide electronic

platform in which all research ethics committees have access to research projects in order to analyze them and report their decisions. Through *Plataforma Brasil*, the Porto Alegre Municipal Health Department Research Ethics Committee; the Research Ethics Committee of the School of Public Health of the State of Rio Grande do Sul Health Department; and the National Commission for Research Ethics, granted their final approvals for the study. All the Brazilian ethics approval documentation may be seen in Appendices F to I, beginning with the final approval from the National Commission for Research Ethics and ending with the local approvals.

The investigators were allowed access to patient identified data without seeking patients' permission. According to the Normative Resolution nº 466/2012 from the National Health Council, the use of the Informed Consent Form was waivered because this was an observational study that analyzed data from medical records, institutional databases and additional data sources available in those institutions without biological material involvement; because all data was to be managed and studied anonymously; the results were to be presented anonymously in an aggregated way; and because it was a retrospective and non-interventional design with no interference on the routine care of the study subjects and, consequently, without any harm to their welfare.

All data were stored safely in a password-protected Excel file and also in the ODK server. Their security was assured as individual access to the database was granted solely to the study investigators. Personal identifiers were deleted and records were coded by record numbers; the file linking names with record numbers was securely stored separately. The subsequent statistical analyses required no personal identification and were undertaken outside the study database.

CHAPTER 4 - RESULTS

4.1 Patients characteristics and univariate analysis

4.1.1 Patients characteristics

A total of 791 subjects with active TB and treated with RHZE between 1st January 2013 and 31st July were included in the study, 157 DILI cases and 634 controls.

4.1.1.1 Cases

4.1.1.1.1 Exclusions of cases

All DILI cases satisfying the inclusion criteria for this study were eligible and captured from the SITETB database. There were five patients with DILI who were started on treatment and registered on SITETB while in hospital, but who defaulted immediately after being discharged, never registering in any TB clinic. As a result, they were excluded due to loss to follow-up up in a TB clinic, which rendered them ineligible because of lack of medical documentation. One patient was excluded due to his TB regimen including rifabutin instead of rifampicin. He was an HIV and HCV positive individual who was also a hazardous drinker taking concomitant hepatotoxic drugs. No patients with DM were excluded among the DILI cases.

4.1.1.1.2 Cases characteristics

Amongst the DILI cases, the prevalence of known DM was 10.8%. The DILI patients' age ranged from 1 year to 93 years old, with a median of 46 years (IQR 37 - 60). The majority of patients (32.5%) were in the youngest age group, being patients under 40 years old. Most patients were males (61.2%). One third (33.1%) of the cases were hazardous drinkers, and nearly half (49.7%) were HIV-positive; 22.9% were HCV infected and 3.2% were HBV infected. (Table 5).

As can be seen in Appendix J, Table J1, hepatotoxic drugs were taken concomitantly by more than half of the cases (59.9%). All drugs known to be potentially hepatotoxic, according to the literature (271), are presented in Appendix C, Tables C1 and C2. The most prevalent hepatotoxic drugs among

the cases were efavirenz and sulfamethoxazole associated with trimethoprim, both with a 29.8% (28/94) prevalence, followed by omeprazole (19.1%; 18/94) and fluconazole (10.6%; 10/94).

Other concomitant liver diseases and any liver-affecting conditions were found in as few as 14% of cases and are displayed in Table 3. Cirrhosis was the most prevalent liver disease, half of the patients were cirrhotic (50%); the second most prevalent disease was liver TB (13.6%).

Table 3. Other liver diseases in cases and controls

Liver disease	Cases (n=22)		Controls (n=16)	
	Frequency	%	Frequency	%
Cirrhosis	11	50	0	0
Liver TB	3	13.6	6	37.5
Congestive heart failure	1	4.5	3	18.8
Others*	6	27.3	6	37.5
Unknown	2	9.1	1	6.3

TB: tuberculosis

***** Cases: Alcoholic liver disease but not cirrhotic (1), steatosis (1), lithiasis (1), granulomatous hepatitis (1), Systemic Lupus Erythematosus (1) and choledocoli-thiasis (1). One patient had cirrhosis and congestive heart failure concomitantly.

* Controls: Alcoholic liver disease but not cirrhotic (2), steatosis (1), autoimmune hepatitis (1), liver metastasis (1), non-alcoholic steatohepatitis (1).

Extrapulmonary TB sites were found in 45.9% of the DILI cases (n=72) (Tables 4 and 5). A little over half of the cases had only PTB (54.1%), and nearly one third (31.2%) had both PTB and EPTB. As detailed in Table 4, both the pleura and lymph nodes were the most prevalent sites (41.7%; 30/72), followed by central nervous system (CNS) (12.5%; 9/72) and liver (8.3%; 6/72).

Table 4. Extrapulmonary TB sites (not mutually exclusive) in cases and controls

Extrapulmonary site	Cases (n=72)		Controls (n=214)	
	Frequency	%	Frequency	%
Pleura	30	41.7	112	52.3
Lymph nodes	30	41.7	65	30.4
CNS	9	12.5	17	7.9
Liver	6	8.3	8	3.7
Intestine	5	6.9	3	1.4
Spleen	2	2.8	8	3.7
Others**	13	18.1	36	16.8
Unknown	0	0	1	0.5

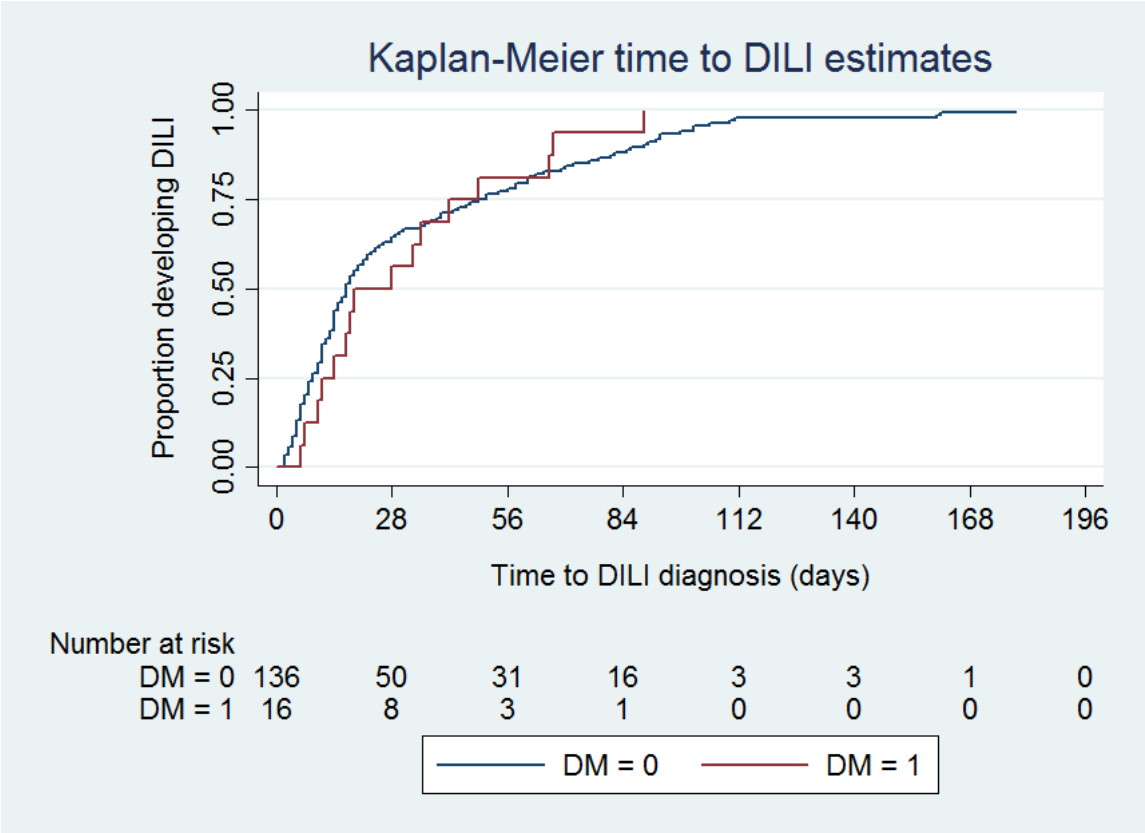
CNS: central nervous system

** Cases: peritoneum (4), bone marrow (3), testicle (2), pericardium (1), bone (1), kidney (1) and psoas (1).

** Controls: eye (7), pericardium (6), peritoneum (5), testicle (3), bone (2), skin (2), joint (1), kidney (1), bladder (1), ureter (1), oesophagus (1), larynx (1), pharynx (1), vertebrae (1), intervertebral disc (1), thoracic wall (1) and bone marrow (1).

Of the 157 cases, the time to DILI diagnosis was observed in 152 patients; five cases could not have their DILI dates identified. The median time to DILI was 17.5 days (IQR 9.5 – 49). In the group with known DM, it was 23.5 days (IQR 12.5 – 45.5) and among those without DM, it was 17 days (IQR 9 – 50). There was no difference in the time to DILI between patients with and without known DM (P = 0.9).

Figure 1. Kaplan-Meier curves for time to DILI, stratified by DM status



DILI: drug induced liver injury; DM: diabetes mellitus

There were no deaths over the course of TB treatment amongst the DILI cases, nor patients who were lost to follow-up at any point in their treatment. None of the DILI cases were pregnant over the course of TB treatment.

4.1.1.2 Controls

4.1.1.2.1 Exclusions of controls

Of the 749 medical records reviewed, 634 patients satisfied the screening criteria for being a control. Of the 115 patients who did not meet the screening criteria, 54 (46.9%) were due to loss to follow-up (defined as missing > 30 days of treatment) before completing at least four months of treatment; 15 (13%) were transferred before the 4th month of treatment; ten (8.7%) died before the 4th month of treatment; five (4.3%) were defined as DILI cases; eight (6.9%) had their treatment

changed (reasons including skin allergy and gastrointestinal intolerance); three (2.6%) were excluded because of their extremely prolonged time in hospital, precluding access to reliable data on drugs; 13 (11.3%) patients experienced irregularity of treatment (taking treatment on ≤ 15 days in any 30 days period); four (3.5%) and three (2.6%) had missing or illegible medical records, respectively. One male patient was excluded because he was taking rifabutin instead of rifampicin. He was HIV positive and was also taking concomitant hepatotoxic drugs. No controls with DM were excluded.

4.1.1.2.2 Controls characteristics

Amongst the 634 controls, 9.9% had known DM. The patients' age ranged from three months to 93 years old, with a median of 37 years (IQR 25 - 50). The majority of patients (55.8%) were in the youngest age group of less than 40 years old. Most patients were males (55.4%). As much as 17% were hazardous drinkers; HIV prevalence was 21.8%, while 5.7% and 0.3% had HCV and HBV infection, respectively.

Hepatotoxic drugs were taken concomitantly by nearly half of the controls (48.6%). The most prevalent hepatotoxic drugs among the controls were omeprazole (32.5%), efavirenz (19.5%) and sulfamethoxazole associated with trimethoprim, (16.9%), as shown in Appendix J, Table J1. Other concomitant liver diseases or conditions were found in 16 (2.5%) controls (Table 5). Liver TB (37.5%) was the most prevalent liver disease among controls, followed by congestive heart failure (18.8%) (Table 3).

Two thirds (66.3%) of the controls had only PTB, while EPTB sites were found in one third (33.8%; n=214), either associated or not to PTB (Table 5). The most common EPTB sites were pleura (52.3%) and lymph nodes (30.4%), followed by CNS (7.9%) (Table 4).

There were 8 pregnant control patients during the course of their TB treatment, of whom one was diagnosed with intra-hepatic cholestasis of pregnancy.

Cross tabulations are shown in Table 5, which includes and additional column indicating separately the characteristics of the subgroup of controls with known DM. The DM prevalence was similar by sex (10.3%; 36/351 *vs.* 9.5%; 27/283), hazardous drinking and HCV. Diabetes prevalence increased with increasing age. Those patients between 61 and 70 years of age had the highest prevalence (29.5%; 18/61). Diabetes prevalence was lower among HIV-positives *versus* HIV-

negatives (3.6% vs 11.7%) and none of those who were HBV-positive had DM. Diabetes prevalence was higher among those taking other hepatotoxic drugs *versus* not (15.9% *vs.* 4.3%), and slightly higher among those with other liver diseases *versus* without other liver diseases (12.5% vs 9.9%). Diabetes prevalence was highest among those with PTB only (13.1%; 55/420).

Table 5. Patients characteristics and univariate analysis.

Patient characteristics	Cases (DILI) (n= 157)		Controls (not DILI) (n= 634)		Controls with known DM		Univariate analysis comparing cases with controls		
	Nº	col %	Nº	col %	Nº	row %	Unadjusted OR	95% CI	*P* - value
Known DM									
No	140	89.2	571	90.1					
Yes	17	10.8	63	9.9			1.10	0.62 - 1.94	0.7
Age group (in years)							1.51**	1.30 - 1.74	< 0.001
1* - 39	51	32.5	354	55.8	9	2.5	1		
40 – 50	43	27.4	127	20.0	19	15.0	2.35	1.49 - 3.70	
51 – 60	24	15.3	74	11.7	12	16.2	2.25	1.30 - 3.89	< 0.001
61 – 70	22	14.0	61	9.6	18	29.5	2.50	1.42 - 4.42	
71 – 93	17	10.8	18	2.8	5	27.8	6.56	3.18- 13.53	
Sex									
Male	96	61.2	351	55.4	36	10.3	1		
Female	61	38.9	283	44.6	27	9.5	0.79	0.55 - 1.13	0.2
Hazardous drinking									
No	105	66.9	526	83.0	51	9.7	1		
Yes	52	33.1	108	17.0	12	11.1	2.41	1.62 - 3.59	< 0.001
Known HIV infection									
No	79	50.3	496	78.2	58	11.7	1		
Yes	78	49.7	138	21.8	5	3.6	3.55	2.43 - 5.18	< 0.001
Known HCV infection									
No	121	77.1	598	94.3	59	9.9	1		
Yes	36	22.9	36	5.7	4	11.1	4.94	2.95 - 8.29	< 0.001
Known HBV infection									
No	152	96.8	632	99.7	63	10.0	1		
Yes	5	3.2	2	0.3	0	0	10.39	1.97 - 54.83	0.003
Known hepatotoxic drugs									

No	63	40.1	326	51.4	14	4.3	1		
Yes	94	59.9	308	48.6	49	15.9	1.58	1.11 - 2.26	0.01
Known other liver diseases									
No	135	86.0	618	97.5	61	9.9	1		
Yes	22	14.0	16	2.5	2	12.5	6.29	3.17 - 12.51	< 0.001
TB site									
Only PTB	85	54.1	420	66.3	55	13.1	1		
Only EPTB	23	14.7	145	22.9	6	4.1	0.78	0.48 - 1.29	< 0.001
PTB and EPTB	49	31.2	69	10.9	2	2.9	3.51	2.27 - 5.42	

* The youngest patient was 3 months old; median age among cases was 46 years old (IQR 37 – 60); median age among controls was 37 years old (IQR 25 – 50)

** OR based on assumed linear trend; *P*-value based on Score test for trend. No evidence for departure from linearity (*P* = 0.3)

P-values for the Likelihood Ratio test

Col: column; CI: Confidence Interval; DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: immunodeficiency virus; IQR interquartile range; OR: odds ratio; PTB: pulmonary tuberculosis; TB: tuberculosis

4.1.2 Univariate analysis

Diabetes prevalence was similar in cases and controls (10.8% vs. 9.9%, respectively), giving an unadjusted OR of 1.10 (95% CI 0.62 - 1.94; *P* = 0.7) (Table 5). DILI cases tended to be older than controls, as a group (median 46 years; IQR 37 – 60 *vs.* median 37 years IQR 25 – 50). There was strong evidence that increasing age was associated with increased odds of DILI (*P* for trend <0.001), suggesting a 1.5-fold increase in odds of DILI for a unit increase in age-band (OR 1.51; 95% CI 1.30 - 1.74). There was no evidence of differences in sex distribution; 38.9% females in cases *versus* 44.6% females in controls (unadjusted OR 0.79; 95% CI 0.55 - 1.13; *P* = 0.2).

Compared to TB patients not experiencing DILI (controls), TB patients experiencing DILI (cases) had two and a half times the odds of being hazardous drinkers (unadjusted OR 2.41; 95% CI 1.62 - 3.59; *P* < 0.001). Compared to TB patients not experiencing DILI, TB patients experiencing DILI had nearly four times the odds of being HIV co-infected (OR 3.55; 95% CI 2.43 - 5.18; *P* < 0.001); five times the odds of having HCV infection (OR 4.94; 95% CI 2.95 - 8.29; *P* < 0.001); and 10 times the

odds of having HBV infection (OR 10.39; 95% CI 1.97 - 54.83; *P* = 0.003). Compared to TB patients without DILI, those who had DILI had one and a half times the odds of having taken hepatotoxic drugs concomitantly with RHZE (OR 1.58; 95% CI 1.11 - 2.26; *P* = 0.01). DILI cases were found to present a substantially higher prevalence of concomitant other liver diseases or transaminases-altering conditions (14% *vs.* 2.5%; *P* < 0.001). The univariate analysis showed that DILI patients were six times as likely to have another liver disease or condition as those without DILI (OR 6.29; 95% CI 3.17 - 12.51; *P* < 0.001). It was demonstrated that DILI patients, were compared to controls, were three and a half times more likely to have both PTB and EPTB than only PTB (OR 3.51; 95% CI 2.27 - 5.42; *P* < 0.001); and there was no evidence that DILI patients, when compared to controls, had increased odds of having only EPTB (OR 0.78; 95% CI 0.48 - 1.29; *P* = 0.34) when compared to only PTB.

4.2 Bivariate analysis

4.2.1 Confounding

Table 6 displays the adjusted Mantel-Haenszel OR for DM after stratifying by the other covariates.

Table 6. Odds Ratios for the effect of DM on DILI, after adjustment for potential confounding variables, individually

Stratified by:	Adjusted OR for known DM (95% CI)		*P* - value for the Test of Homogeneity of ORs
Age	0.72	(0.40 - 1.31)	0.9
Sex	1.09	(0.62 - 1.93)	0.9
Hazardous drinking	1.02	(0.57 - 1.81)	0.09
HIV	1.44	(0.80 - 2.60)	0.7
HCV	0.93	(0.51 - 1.69)	0.06

HBV *		-	-
Hepatotoxic drugs	0.98	(0.55 - 1.75)	0.01
Other liver diseases	1.14	(0.64 - 2.03)	0.3
TB site	1.29	(0.72 - 2.32)	0.5

CI: confidence interval; DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; OR: odds ratio; PTB: pulmonary tuberculosis; TB: tuberculosis

* Adjusted analysis could not be undertaken due to sparsity of data.

Individually, sex, hazardous drinking, HBV and other liver diseases, did not appear to confound any effect of DM on the odds of DILI. The following covariates: age (DM M-H OR 0.72; 95% CI 0.40 - 1.31), HIV (DM M-H OR 1.44; 95% CI 0.80 - 2.60), and TB site (DM M-H OR 1.29; 95% CI 0.72 - 2.32), presented as confounders on the effect of DM on DILI.

Bivariate analysis to explore the effect of HBV on the DM OR for DILI was not conducted due to sparse data (7 patients in total). Similarly, there were no patients with DM in the *only EPTB* stratum among the DILI cases.

4.2.2 Effect modification

After controlling for HCV infection, the effect of DM on DILI became slightly smaller (OR 0.93; 95% CI 0.49 - 1.75), showing a possible confounding effect of HCV. There was, however, weak evidence for HCV modifying the effect of DM on DILI (P = 0.06). Likewise, there was evidence that concomitant use of hepatotoxic drugs modified the effect of DM on DILI (P = 0.01). These two interactions will be considered in more detail in the multivariable regression model.

4.3 Multivariate analysis

4.3.1 Adjusted model without interaction

A multivariate logistic regression analysis was performed to obtain a fully adjusted OR for the effect of DM on DILI (Table 7). The fully adjusted model controlled for age, HIV and TB site as all were identified as important confounders in the Mantel-Haenszel analysis. The sex variable was included in the model, *a priori*. In addition, HCV and hepatotoxic drugs were included in the model for completeness as they will be assessed as effect modifiers in section 4.3.2 and 4.3.3.

The adjusted OR for DM was 0.88 (95% CI 0.45-1.71; $P = 0.7$). Even though the modelling strategy was not based on assessing the causal effect of other variables on DILI, it was noted that the following variables were strongly associated with DILI: increasing age ($P < 0.001$); being HIV-positive ($P < 0.001$); having HCV infection ($P < 0.001$); and having more extensive disease, defined as both PTB and EPTB (*vs.* only PTB; $P< 0.001$).

Table 7. Multivariate logistic regression. Fully adjusted analysis of the model without interactions between the exposure variables (n=791)

Risk factors for DILI	Adjusted OR	95% CI	*P* - value
Known DM			
No	1		
Yes	0.88	0.45 - 1.71	0.7
Age group (in years)			
1 - 39*	1		< 0.001
40 - 50	1.69	1.00 - 2.86	
51 - 60	2.39	1.30 - 4.38	
61 - 70	4.37	2.28 - 8.35	
71 - 93	12.91	5.81 - 28.66	
Sex			
Male	1		
Female	1.09	0.72 - 1.63	0.7
Known HIV infection			
No	1		

Yes	3.59	2.25 - 5.73	< 0.001
Known HCV infection			
No	1		
Yes	3.49	1.96 - 6.21	< 0.001
Known Hepatotoxic drugs			
No	1		
Yes	0.84	0.54 - 1.29	0.4
TB site			
Only PTB	1		< 0.001
Only EPTB	0.75	0.43 - 1.30	
PTB and EPTB	3.16	1.93 - 5.19	

* The youngest patient was 3 months old

P-value for the Likelihood Ratio test

CI: confidence interval; DILI: drug induced liver injury; DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; OR: odds ratio; PTB: pulmonary tuberculosis; TB: tuberculosis

4.3.2 Interaction between DM and hepatotoxic drugs

After adjusting for age, sex, HIV, HCV and TB site, there was not strong evidence for an interaction between hepatotoxic drugs and DM on DILI (*P* value for the interaction = 0.1). The stratum specific ORs for DM were 1.78 (95% CI 0.62 - 5.12) among those taking no hepatotoxic drugs, and 0.61 (95% CI 0.26 – 1.40) among those taking hepatotoxic drugs (Table 8). Note that in the *no hepatotoxic drugs* stratum there were only 7 cases with DM.

Table 8. Interaction between DM and hepatotoxic drugs, adjusted for age, sex, HIV, HCV and TB site. *P*-value for the interaction = 0.1

Odds of DILI by known DM stratified by hepatotoxic drugs	Cases (DILI) (col %)	Controls (not DILI) (col %)	Adjusted OR*	95% CI	*P*-value

No Hepatotoxic drugs	**No DM**	56 (88.9%)	312 (95.7%)	1		
	DM	7 (11.1%)	14 (4.3%)	1.78	0.62 – 5.12	0.3
Hepatotoxic drugs	**No DM**	84 (89.4%)	259 (84.1%)	1		
	DM	10 (10.6%)	49 (15.9%)	0.61	0.26 – 1.40	0.2

* adjusting for age, sex, HIV, HCV and TB site

CI: confidence interval; col: column; DILI: drug induced liver injury; DM: diabetes mellitus; OR: odds ratio

4.3.3 Interaction between DM and HCV

After adjusting for age, sex, HIV, use of hepatotoxic drugs and TB site, there was some evidence that HCV modified the effect of DM on DILI (*P* value for the interaction = 0.02; Table 9). There was no definite evidence of an association between having DM and increase in odds of DILI among those with HCV (OR 3.37; 95% CI 0.86 - 13.16; *P* = 0.08). Likewise, there was no definite evidence of an association between having DM and a 46% reduction in odds of DILI among those without HCV (OR 0.54; 95% CI 0.23 - 1.26; *P* = 0.2). It is also noted in both strata that there are three DM cells with less than ten individuals, so analyses should be treated with caution.

Table 9. Adjusted effect of DM stratified by HCV status, adjusted for age, sex, HIV, hepatotoxic drugs and TB site. *P*-value for the interaction = 0.02

Odds of DILI by known DM stratified by HCV		**Cases (DILI) (col %)**	**Controls (not DILI) (col %)**	**Adjusted OR***	**95% CI**	***P*- value**
No HCV	**No DM**	113 (93.4%)	539 (90.1%)	1		

	DM	8 (6.6%)	59 (9.9%)	0.54	0.23 - 1.26	0.2
HCV	**No DM**	27 (75%)	32 (88.9%)	1		
	DM	9 (25%)	4 (11.1%)	3.37	0.86 - 13.16	0.08

* adjusting for sex, age, hepatotoxic drugs, HIV, and TB site

CI: confidence interval; col: column; DILI: drug induced liver injury; DM: diabetes mellitus; HCV: hepatitis C virus; OR: odds ratio

To conclude, from the present fully adjusted analysis for presenting an OR for DM on DILI (Table 7), it was shown that DM did not increase the odds of having TB DILI. Similarly, other variables such as sex, taking other hepatotoxic drugs and having only EPTB (when compared to only PTB) were not associated with increased odds of DILI. Age over 50 years old, HIV infection, HCV infection and having both PTB and EPTB (when compared to only PTB) were shown to independently increase the odds of having TB DILI. There was some evidence that HCV infection acted as effect modifier on the effect of DM on DILI, although that finding should be interpreted with caution. Having DM was associated with not statistically significant increased odds of DILI among those with HCV infection, and not statistically significant reduction in odds of DILI among those without HCV infection.

4.4 Missing data

Missing data was tabulated and presented as follows. It can be surmised from Table 10 that for a number of the variables the missingness is significantly different between cases and controls, and usually greater in controls. The main exposure (DM) had 10.3% missing data among controls and only 2.6% amongst cases. The percentage with missing data for hazardous drinking and HIV was extremely low (<1.5%). Missing data for HCV, HBV and other liver diseases was high, with the percentage missing data amongst controls much higher than amongst cases. With hepatotoxic drugs, unlike the other exposures, missing data was higher amongst the cases (18.5%) than controls (6.0%). There were no missing data for age group, sex and TB site.

Table 10. Variables with missing data (n=791)

	Cases N (%)	Controls N (%)	*P* value*
DM			
No	136 (86.6%)	506 (79.1%)	0.002
Yes	17 (10.8%)	63 (9.9%)	
Missing	4 (2.6%)	65 (10.3%)	
Hazardous drinking			
No	103 (65.6%)	526 (83.0%)	0.004
Yes	52 (33.1%)	108 (17.0%)	
Missing	2 (1.3%)	0 (0%)	
HIV			
No	78 (49.7%)	492 (77.6%)	> 0.99
Yes	78 (49.7%)	138 (21.8%)	
Missing	1 (0.6%)	4 (0.6%)	
HCV			
No	93 (59.2%)	387 (61.0%)	< 0.001
Yes	36 (22.9%)	36 (5.7%)	
Missing	28 (17.8%)	211 (33.3%)	
HBV			
No	108 (68.8%)	342 (53.9%)	< 0.001
Yes	5 (2.2%)	2 (0.3%)	
Missing	44 (28.0%)	290 (45.7%)	
Hepatotoxic drugs			
No	34 (21.7%)	288 (45.4%)	< 0.001
Yes	94 (59.9%)	308 (48.6%)	
Missing	29 (18.5%)	38 (6.0%)	

Other liver diseases			
No	105 (66.9%)	325 (51.3%)	< 0.001
Yes	22 (14.0%)	16 (2.5%)	
Missing	30 (19.1%)	293 (46.2%)	

**P* value for the association between whether the variable has missing data and the outcome (case/control status)

DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: Human immunodeficiency virus

Comparing the original univariate analysis and the one conducted excluding records with missing data (Table 11), the measures of effect showed slightly decreased (closer to 1), albeit very similar effect sizes, except for hepatotoxic drugs, which presented with an increase in OR.

Table 11. Complete case analysis (varying sample sizes) compared with original analysis (n= 791) - Univariate analysis

Variables with missing data excluded		Cases	Controls	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI) from original analysis*	*P* value
DM	**Yes**	17 (10.8%)	63 (9.9%)	1.0 (0.57 - 1.77)	>0.99	1.10 (0.62 - 1.94)	0.7
	No	136 (86.6%)	506 (79.1%)	1		1	
Hazardous drinking	**Yes**	52 (33.1%)	108 (17.0%)	2.46 (1.66 - 3.64)	<0.001	2.41 (1.62 - 3.59)	<0.001
	No	103 (65.6%)	526 (83.0%)	1			
HIV	**Yes**	78 (49.7%)	138 (21.8%)	3.57 (2.47 - 5.14)	<0.001	3.55 (2.43 - 5.18)	<0.001
	No	78 (49.7%)	492 (77.6%)	1			
HCV	**Yes**	36 (22.9%)	36 (5.7%)	4.16 (2.49 - 6.96)	<0.001	4.94 (2.95 - 8.29)	<0.001
	No	93 (59.2%)	387 (61.0%)	1			

HBV	**Yes**	5 (2.2%)	2 (0.3%)	7.92 (1.51- 41.39)	0.01	10.39 (1.97 - 54.83)	0.003
	No	108 (68.8)	342 (53.9%)	1			
Hepatotoxic drugs	**Yes**	94 (59.9%)	308 (48.6%)	2.59 (1.69-3.95)	<0.001	1.58 (1.11 - 2.26)	0.01
	No	34 (21.7%)	288 (45.4%)	1			
Other liver diseases	**Yes**	22 (14.0%)	16 (2.5%)	4.26 (2.16 -8.41)	<0.001	6.29 (3.17 – 12.51)	<0.001
	No	105 (66.9%)	325 (51.3%)	1			

* where missing data were grouped with the "no" category

CI: confidence interval; DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; OR: odds ratio

The fully adjusted analysis excluding the missing data presented measures of effect sizes very similar to the original multivariate analysis (Table 12). In the 51 – 60 age group, HCV and having both PTB and EPTB, the ORs are a little smaller (2.39 *vs.* 1.56; 3.49 *vs.* 2.81 and 3.16 *vs.* 2.54, respectively), but CIs overlap so results are broadly similar. The *P* values that achieved significance levels in the original analysis remained as such, as were the ones that did not (0.2 for DM, 0.4 for sex and 0.9 for hepatotoxic drugs).

Table 12. Fully adjusted complete case analysis (n =482; 104 cases and 378 controls) and from original analysis (n=791; 157 cases and 634 controls)

Risk factors for DILI	Adjusted OR - complete case	95% CI	*P* - value	Adjusted OR - original analysis	95% CI	*P* – value*
DM						
No	1					
Yes	0.57	0.23 – 1.41	0.2	0.88	0.45 – 1.71	0.7
Age group (in years)						

1 - 39*	1					
40 - 50	1.66	0.89 – 3.09		1.69	1.00 – 2.86	
51 - 60	1.56	0.70 – 3.48	<0.001*	2.39	1.30 – 4.38	<0.001
61 - 70	4.86	2.16 – 10.95		4.37	2.28 – 8.35	
71 - 93	11.53	3.82 – 34.79		12.91	5.81 – 28.66	
Sex						
Male	1					
Female	1.24	0.76 – 2.05	0.4	1.09	0.72 – 1.63	0.7
HIV						
No	1					
Yes	3.42	1.87 – 6.26	<0.001	3.59	2.25 – 5.73	<0.001
HCV						
No	1					
Yes	2.81	1.43 – 5.50	0.003	3.49	1.96 – 6.21	<0.001
Hepatotoxic drugs						
No	1					
Yes	0.95	0.50 – 1.80	0.9	0.84	0.54 – 1.29	0.4
TB site						
Only PTB	1					
Only EPTB	0.66	0.33 – 1.30	<0.001*	0.75	0.43 – 1.30	<0.001
PTB and EPTB	2.54	1.40 – 4.62		3.16	1.93 – 5.19	

**P* value for the likelihood ratio test

CI: confidence interval; DILI: drug induced liver injury; DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HCV: hepatitis C virus; HIV: human immunodeficiency virus; OR: odds ratio; PTB: pulmonary tuberculosis; TB: tuberculosis

Due to the case-control study design, further exploration of missingness was performed separately amongst cases and controls. Amongst the controls (Table 13): in relation to age, the missingness of data for HCV, HBV, hepatotoxic drugs and other liver diseases was similar across age groups, whereas for DM, missingness was more common for those aged <50 year. For those >50 years of age, the proportion of missing data decreased. The proportion of missing data for DM, HCV, HBV, hepatotoxic drugs and other liver diseases was similar for males and females. In the TB site variable, the missingness for DM, HCV, hepatotoxic drugs and other liver diseases was more

pronounced in the *only PTB* category than in the other two categories (*only EPTB* and *both PTB and EPTB*).

Table 13. Cross tabulations between variables with and without missing data amongst the control group

			Missing data for DM	Missing data for HCV	Missing data for HBV	Missing data for hepatotoxic drugs	Missing data for other liver diseases
Total number of controls N = 634			**N = 65 (10.2%)**	**N = 211 (33.3%)**	**N = 290 (45.7%)**	**N = 38 (6.0%)**	**N = 293 (46.2%)**
Explanatory variables		**N**	**N (%) missing**	**N (%) missing**	**N (%) missing**	**N (%) missing**	**N (%) missing**
Age group (in years)	**1 - 39**	354	42 (11.9%)	128 (36.2%)	167 (47.2%)	15 (4.2%)	163 (46.0%)
	40 - 50	127	15 (11.8%)	33 (26.0%)	51 (40.2%)	12 (9.5%)	61 (48.0%)
	51 - 60	74	6 (8.1%)	21 (28.4%)	31 (41.9%)	5 (6.8%)	36 (48.6%)
	61 - 70	61	2 (3.3%)	22 (36.1%)	33 (54.1%)	3 (4.9%)	24 (39.3%)
	71 - 93	18	0 (0%)	7 (38.9%)	8 (44.4%)	3 (16.7%)	9 (50.0)
Sex	**Male**	351	32 (9.1%)	118 (33.6%)	164 (46.7%)	19 (5.4%)	165 (47.0%)
	Female	283	33 (11.7%)	93 (32.9%)	126 (44.5%)	19 (6.7%)	128 (45.2%)
TB site	**Only PTB**	420	56 (13.3%)	151 (36.0%)	206 (49.0%)	29 (6.9%)	215 (51.2%)
	Only EPTB	145	6 (4.1%)	43 (29.7%)	53 (36.5%)	7 (4.8%)	56 (38.6%)
	PTB and EPTB	69	3 (4.3%)	17 (24.6%)	31 (44.9%)	2 (2.9%)	22 (31.9%)

DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus; PTB: pulmonary tuberculosis; TB: tuberculosis

Amongst the cases (Table 14), missing data differs between sexes, with males showing more missing data than women. Missing data for HCV, HBV, hepatotoxic drugs and other liver diseases increased with age,

although not for DM. In terms of the three categories for TB site, it can be observed that missing data for HCV, HBV was higher in *only PTB*; for DM it was higher in *only EPTB*; and for hepatotoxic drugs and other liver diseases, it was higher in the *both PTB and EPTB* category.

Table 14. Cross tabulations between variables with and without missing data amongst cases

			Missing data for DM	Missing data for HCV	Missing data for HBV	Missing data for hepatotoxic drugs	Missing data for other liver diseases
Total number of cases N = 157			**N = 4 (2.5%)**	**N = 28 (17.8%)**	**N = 44 (28%)**	**N = 29 (18.5%)**	**N = 30 (19.1%)**
Explanatory variables		**N**	**N (%) missing**	**N (%) missing**	**N (%) missing**	**N (%) missing**	**N (%) missing**
Age group (in years)	**1 - 39**	51	0 (0%)	7 (13.7%)	9 (17.6%)	8 (15.7%)	12 (23.5%)
	40 - 50	43	0 (0%)	4 (9.3%)	12 (27.9%)	7 (16.3%)	4 (9.3%)
	51 - 60	24	3 (12.5%)	5 (20.8%)	9 (37.5%)	6 (25.0%)	4 (16.7%)
	61 - 70	22	1 (4.5%)	6 (27.3%)	7 (31.8%)	4 (18.2%)	6 (27.3%)
	71 - 93	17	0 (0%)	6 (35.3%)	7 (41.2%)	4 (23.5%)	4 (23.5%)
Sex	**Male**	96	4 (4.2%)	19 (19.8%)	31 (32.3%)	20 (20.8%)	20 (20.8%)
	Female	61	0 (0%)	9 (14.8%)	13 (21.3%)	9 (14.7%)	10 (16.4%)
TB site	**Only PTB**	85	2 (2.4%)	19 (22.4%)	30 (35.3%)	14 (16.5%)	15 (17.6%)
	Only EPTB	23	1 (4.4%)	2 (8.7%)	5 (21.7%)	4 (17.4%)	3 (12.0%)
	PTB and EPTB	49	1 (2.5%)	7 (14.3%)	9 (18.4%)	11 (22.5%)	12 (24.5%)

DM: diabetes mellitus; EPTB: extrapulmonary tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus; PTB: pulmonary tuberculosis; TB: tuberculosis

CHAPTER 5 - DISCUSSION

Tuberculosis remains to be a major health problem globally. Short-course therapy with RHZE has proven to be highly effective but it is not without difficulties. DILI is its most serious adverse effect, leading to considerable morbidity and mortality through non-adherence and eventual default from treatment. It may also lead to failure, relapse and the most dreaded consequence, drug resistance (272). It can also cause acute liver failure, resulting either in liver transplant or death. These negative outcomes result in significant impairment on the effectiveness of any TB control programme. The need for a change of treatment means less efficacious and longer-lasting drug regimens, thus maintaining a favourable scenario for default from treatment and perpetuating the cycle of TB transmission. In the end, the most serious risk factor for a negative outcome of a DILI case is inadvertent continuation of therapy (148). Hepatotoxicity due to TB DILI can be fatal and mortality can reach up to 27% (273, 274). Identifying such episodes early on plays a major role in mitigating the extent of liver injury by allowing for discontinuation of the drugs.

Previous studies have analysed monitoring strategies and shown that they can be beneficial in terms of improving outcomes (95, 173, 275-279). DILI may remain hidden during preclinical and clinical phases of drug development. Besides, post-marketing studies frequently enrol insufficient numbers of individuals to be able to detect hepatotoxicity, before launching drugs in the market to be prescribed to thousands of patients. Epidemiological data from DILI in the literature comes from reports of either isolated cases or small series of cases. Therefore, the creation of an information archive system for DILI cases is vital for quantifying the degree of association and rigorous assessment of causality.

Monitoring is effective but costly, and the literature reports many risks factors for DILI. It should be noted that the risk of development of DILI has been shown to increase in the presence of one or more of specific risk factors (280). Some well-known risk factors include old age (124, 130, 136, 138, 148, 152, 153, 281-283), female sex (95, 106, 137, 138, 150, 153-155, 164, 275, 283-306), HIV infection (88, 90, 92, 156, 164, 307-311), HCV infection (88, 90, 92, 154, 301, 307-310, 312, 313), HBV infection (88, 90, 92, 147, 154, 300, 307-310), pre-existent liver disease (95), alcohol consumption (81, 92, 124, 127, 130, 137, 143, 147, 148, 152-154, 164, 280, 282, 299, 306, 307, 312, 314-320), concomitant use of other hepatotoxic drugs (321-326), malnutrition (124, 153-155, 164, 280, 282, 295, 297, 327-329), extensive tuberculosis disease (148, 150, 153, 155, 297, 309, 330, 331),

and genetic factors (284, 332). However, these well-established and other potential risk factors, such as tobacco smoking (333), are still being explored by researchers worldwide.

As far as could be ascertained, no study has hypothesized an association between DM and DILI and studied it as an independent risk factor for DILI. Thus, a retrospective case-control study of TB patients who developed DILI severe enough to need a change of regimen during treatment with RHZE was conducted in Porto Alegre, Brazil, between January 2013 and July 2017. Patients with DILI were identified from the national electronic database SITETB and controls were captured from the municipal notification database and clinic records. For each case, 4 patients treated with the same drug regimen during the same period (2013 to 2017) and who did not develop DILI, were selected as controls.

It was sought to determine whether DM is associated with an increased risk of TB DILI and to further study any risk factors associated with the DM effect on DILI. From the present fully adjusted analysis, it was seen that DM was not associated with increased odds of DILI. Likewise, female sex and taking other hepatotoxic drugs were not associated with increased odds of DILI. Age over 50 years old, HIV infection, HCV infection, and having both PTB and EPTB (when compared to PTB only) were shown to independently increase the odds of having TB DILI. After adjusting for age, sex, HIV, use of hepatotoxic drugs and TB site, there was some evidence that HCV modified the effect of DM on DILI, although this interaction analysis should be treated with caution. Considering the study objectives, the research questions have been answered.

5.1 Exposure variables

5.1.1 DM

From the vast body of studies on risk factors for TB DILI, only a few studies have included DM as a comorbidity, having found no association with DILI (130, 275, 280), a finding in agreement with the present study. Those studies were not designed to study DM as the main exposure variable of interest, such as the present one.

In the present study, the multivariate analysis has not found any evidence that DM is associated with increased odds of DILI. However, it was found some evidence of an interaction between HCV infection and DM (*P* value for the interaction = 0.02; Table 9). Analyses suggested an interaction

between HCV and DM on the odds of development of DILI, though this did not achieve statistical significance. The biological plausibility for this may lie, amongst other reasons, with the potential for HCV to exacerbate the hepatotoxicity of DM-associated NAFLD and augment susceptibility to DILI. This is consistent with evidence found in the literature on how DM and HCV infection are related (218-222). Individuals with DM and HCV concomitantly have worse outcomes (222, 334), which might explain an increase in the magnitude of liver damage reflected by an association with DILI. No patients with DM were defaulters from treatment, neither cases nor controls.

5.1.2 Age

The risk of DILI induced by TB treatment increases with age and the highest incidence occurs in individuals above 50 year (153). Other studies are in line with these findings, indicating a possible role played by increasing age (130, 136-138, 148, 153, 154, 164, 284, 285, 298, 306, 333, 335-340). Bright-Thomas *et al.* (290) identified a significant trend in increasing age as a risk factor for DILI, with risk increasing 16% for every ten-year increase in age (adjusted OR 1.16; 95% CI 1.02 – 1.32; *P* = 0.02). The morbidity and mortality of DILI have also been reported to be higher in those patients above 50 years of age (341). Gaude e*t al.* (280) have demonstrated that patients over 60 years old were independently associated with increased odds of DILI (OR 3.1; 95% CI 1.6 – 7.6; *P* = 0.002). Likewise, Shaberg *et al.* (130) have found that age 60 years and above was an independent risk factor for TB DILI (OR 3.5; 95% CI 1.3 – 10.1; *P* = 0.02). Warmelink *et al.* (301) also reported that age over 60 years was an independent risk factor for TB DILI (OR 18.5; 95% CI 2.3 – 151).

Across the literature, however, increasing age has not been reported consistently as a risk factor for DILI. In several studies, this association has not been demonstrated (297, 342-344) , while others have suggested otherwise and that increasing age is associated with DILI (124, 130, 136, 138, 148, 152, 153, 281-283, 339, 345, 346). One study reported a TB DILI rate range from 2% to 8% as patients grew older (282). Other studies have reported a range from 22% to 33% in patients older than 35 years of age, compared to a smaller prevalence range of 8% to 17% in those younger than 35 years old (152, 281).

Not all evidence is supportive of an association with increasing age. One explanation for that could be that age was not adjusted for all potential confounders. The higher prevalence of DILI in older age may have been due to an increased prevalence of concomitant chronic diseases and their

respective treatments with hepatotoxic agents and these confounders should be considered in the analysis. Frequently prescribed drugs in the elderly population include captopril, enalapril, clopidogrel, simvastatin, allopurinol, metformin and glibenclamide, all present in category A (50 published hepatotoxicity cases and above) and category B (between 49 and 12 hepatotoxic cases) lists, in a critical assessment by Björnsson and Hoofnagle (271). Additionally, increased susceptibility for hepatotoxicity with old age could be partly due to physiological changes. Intravascular, organ, muscle and distribution volumes are smaller in the elderly (347), which might result in impaired hepatic drug metabolism and elimination, particularly of drugs metabolized by the cytochrome enzyme system (348, 349). Besides, reduced food intake by elderly individuals may cause lower availability of nutrients for liver detoxification of TB drugs (350). Due to the global aging trend (351), hepatotoxicity may become an even more serious problem in the near future.

Further evidence for the association between older age and DILI comes from the Spanish DILI Registry and Latin DILI Registry, which have reported a mean age of 51 and 54 years, respectively, in 1,067 well-vetted DILI cases (122). In another study on the outcome and prognostic markers of severe DILI (352), non-survivors with DILI were significantly older than those who were able to recover and age was found to be an independent predictor of death or transplantation.

This study has been able to show that as patients grew older, the odds of DILI increased and were the greatest in the older age group, with patients ranging from 71 to 93 years old (OR 12.91; 95% CI 5.81 – 28.66). However, TB DILI is known to occur also in early childhood. In a retrospective study conducted in Japan (353), severe TB DILI was diagnosed in 8% paediatric patients and it was associated with being under 5 years old. Other studies have found a similar association between TB DILI and children (354, 355).

5.1.3 Sex

The female sex was not associated with increased odds of DILI in the present study. This finding contrasts with data from other studies reporting an increased risk of DILI in women (136, 138, 148, 283). Ambreen *et al.* (311) have observed that the female sex was at a higher risk for DILI. A study conducted in India by Gaude *et al.* (280) has found that female sex was an independent risk factor for the development of DILI. Likewise, other studies have shown similar findings (95, 106, 137, 138, 148, 150, 153-155, 164, 275, 283-306). Dossing *et al.* (148) found a four times higher risk for women

than for men for DILI requiring a change of TB regimen.

Nonetheless, such results have been inconsistent. In accordance with the present study, others have shown no increased risk in women (124, 130, 143). One possible reason for that could be insufficient numbers leading to unstable estimates. A study conducted in Canada by Yee *et al.* (137) has shown that the female sex was associated with any major side effects from first-line drugs (adjusted HR 2.5; 95% CI 1.3 – 4.7), but not with DILI. A study conducted by Shu *et al.* (284) reported that the risk of DILI was highest in females aged above 67.5 years, followed by males aged above 67.5 years and females aged 67.5 years and under; the lowest risk was in males aged 67.5 years and under. That finding might explain why some studies have not been able to show an association between sex and DILI, as the association in some studies, such as that one, was most evident in older patients.

Studies conducted on patients who had DILI while treating LTBI with isoniazid monotherapy, have found no clear evidence of a sex-related difference, either (140, 142, 143). Nonetheless, some studies on DILI caused by isoniazid have reported that females are more at risk of developing isoniazid-induced DILI than males (276, 294, 295). The underlying mechanisms are unclear and have yet to be unravelled, but the female vulnerability might be due to pharmacokinetics and slow acetylation enzymatic pattern (356). Specific incidence rates across the literature, which were similar in both sexes until age 49, became more than twice as high in women as in men after this age (356). Other factors that might explain a role of female sex in DILI, apart from differences in pharmacokinetics, are hormones. It has been suggested that they might change drug metabolism in the liver and explain the difference in reporting rates between men and women (357). Pyrazinamide is regarded as the most hepatotoxic agent in RHZE and there are three DILI-causing drugs in this regimen, so perhaps the apparent discordance between TB treatment DILI and isoniazid-related DILI is to be expected. Even so, some TB DILI studies were not able to find any association with sex.

There is not a universally consistent finding and therefore no consensus view on the impact of sex for DILI risk. The contradictory findings in the literature may be due to the diversity of study populations and, most importantly, to the impossibility of studies to adjust for all the biological covariates acting as confounders.

5.1.4 Hazardous drinking

Several studies, in agreement to this one, have indicated that alcohol drinking is a significant risk factor for TB DILI (81, 92, 124, 127, 130, 137, 143, 147, 148, 152-154, 164, 280, 282, 299, 306, 307, 312, 314-316, 318-320). A surveillance study conducted in the United States in 1979 reported that alcohol use has more than doubled the rate of isoniazid-related DILI, with daily intake increasing it more than four times (143). A retrospective study conducted in the United Kingdom (342) reported any amount of alcohol intake to be an independently important risk factor for DILI (OR 5.94; 95% CI 2.34 – 15.1). There was a low occurrence of alcohol abuse in that study. Pande *et al.* (153) also found high alcohol consumption to be a significant risk factor for DILI (OR 4.76; 95% CI 2.25 – 10.05).

These results have been disputed by other studies (130, 148, 296, 301, 330, 358), possibly depending on differences in drinking patterns and study methodologies. The degree of underlying alcoholic liver disease has not always been clearly defined in several studies, as was the case in the present study, in which alcohol consumption was self-reported, adding to the uncertainty of classification of the severity of alcoholic liver damage. Physicians tended to classify drinking patterns into three main categories, namely non-drinkers, social drinkers and alcohol abusers, so that there was a lack of objectivity and refinement on these data. It was expected that both abusers and social drinkers might be misclassified as hazardous drinkers. However, non-drinkers were most likely not misclassified as hazardous drinkers and nor were hazardous drinkers misclassified as non-drinkers. This covariate was not included in the final model because, in this study, it was not a confounder for the effect of DM on DILI (DM M-H OR 1.02; 95% CI 0.57 – 1.81) (Table 6).

5.1.5 HIV infection

The present finding of HIV infection as being independently associated with DILI (OR 3.59; 95% CI 2.25 – 5.73) is in agreement with the literature (88, 90, 92, 156, 164, 306-311). A five-year retrospective study in Taiwan (284) reported HIV infection as an independent risk factor for DILI during treatment with RHZE (HR 3.08; 95% CI 1.4 – 6.78), but not HCV and HBV. It has been suggested that the concomitant use of certain antiretroviral therapy (ART) such as protease inhibitors might, at least partially, explain this tendency (359) in the absence of controlling for ART. A retrospective study from a large TB centre in the United Kingdom reported an increased risk of

DILI in HIV infected patients (OR 4.4; 95% CI 1.06 – 18.3) (342).

According to the ATS Statement (95), HIV positive patients do not seem to present a stronger association to isoniazid-related DILI when compared to HIV negative patients (360), although no studies showing direct comparisons have been found. Ungo *et al.* (92) reported that 27% of the HIV positive patients developed DILI with TB treatment, compared to 12% of those who were HIV negative. All patients had normal baseline liver transaminases, and the HIV positive group independently increased 4-fold the risk of having a transaminase level to 120 IU/L. However, the potential for hepatotoxicity of ART drugs was not taken into consideration in the analysis. The effect of HIV on DILI is considered to be a matter of utmost importance and the widespread use of ART should always be taken into consideration in order to correctly assess the mechanisms behind this increased risk.

The introduction of ART has reduced significantly opportunistic infections among the HIV population by between 60% and 90% (361); nonetheless, these drugs may play a role in the increased risk of DILI. Efavirenz is on the category A list (above 50 published cases) by Björnsson and Hoofnagle (271). A comparison between a group taking ART and/or trimethoprim- sulfamethoxazole against a second group taking other classes of hepatotoxic drugs and a third one taking no drugs at all, was not performed. Nevertheless, it is noteworthy that most of the HIV positive patients among the controls (67.4%; 93/138) and cases (64.1%; 50/78) were taking regularly ART and/or trimethoprim-sulfamethoxazole concomitantly with RHZE. When comparing those HIV positive patients to those who were taking other hepatotoxic drugs or none, there was no difference between the cases and control groups ($P = 0.6$).

An association between low T CD4 lymphocyte counts and DILI has been reported by some studies which, having found no evidence of an association between DILI and opportunistic infections and their medications, suggested that there might be an unknown immunological factor accountable for that (81, 343, 362). A Brazilian study (343) on the relationship between DILI and HIV positive patients showed that a T CD4 lymphocyte count < 200 cells/mm^3 increased the risk of DILI when compared to those with ≥ 200 cells/ mm^3 (OR 1.2; $P < 0.001$). Some studies, however, have found no association between HIV and DILI (275, 280, 301).

5.1.6 HCV infection

The reported HCV prevalence in European countries lies between 0.5% and 2% and high burden areas include Africa (particularly Egypt) and Asia (128). In Latin America, specifically in Argentina, Brazil, Mexico, Puerto Rico, Peru and Venezuela, the HCV prevalence ranges from 1.4% to 2.5% (363). In Brazil alone, there are different estimates of prevalence across its five political regions. The Southeast and South regions, being the most densely populated and urbanized in the country, present the highest incident rates. In 2016, the prevalence of hepatitis C in Brazil was estimated to be 0.7% among those between 15 and 69 years of age and the co-infection HIV-HCV was believed to be 9.8% (364). In Porto Alegre, from 2013 to 2017, the incidence of hepatitis C ranged from 43 to 102 per 100,000 population (213). Among all Brazilian regions, the South is the one with the highest co-infection prevalence, 13.2% of HCV patients are HIV-infected (364).

Although results are not universal, a number of studies suggest that co-existing viral hepatitis may be an important risk factor for DILI (88-93). The literature suggests that the relative risk of developing DILI is fivefold for HCV positive patients; fourfold for HIV positive individuals and 14-fold for those co-infected (92). A study by Warmelink *et al.* (301) reported that chronic HCV infection was a significant risk factor for DILI leading to interruption of TB treatment (OR 19.6; 95% CI 2.4 – 164). In a Brazilian study (343) with HIV-TB co-infected patients, with chronic hepatitis B or C, the risk of DILI was significantly increased (OR 18.19; $P = 0.03$). Ungo *et al.* (92) has assessed the effect of HCV infected patients on DILI and found that approximately 30% of HCV-infected patients presented DILI in contrast to 11% among those not HCV-infected. Other studies have suggested that HCV is associated with an increased risk of DILI (88, 90, 92, 154, 301, 307-310, 312, 313). Contrary to that, other researchers found no evidence of such association (284, 342) and two studies on risk factors for isoniazid-related DILI have not shown any increased risk associated with HCV infected individuals (312, 365). A possible reason for that could be that by excluding patients with abnormal baseline liver transaminases, patients with chronic viral hepatitis were excluded as well, as a result.

The prevalence of HCV infection in individuals with DM in a general practice clinic in Brazil has been reported as being 3.3% (366), while the national prevalence has been reported by another study as being 1.4% (367). Since the 1990's, studies have demonstrated a higher prevalence of hepatitis C in patients with DM when compared to those without DM (368-371). A study in France found a prevalence of HCV in patients with DM, when compared to those without DM, of 3.1% *vs.* 0.04% ($P < 0.001$) (372).

The effect of HCV on DILI as well as on DM, in the present study, may have been underestimated, given that HCV status was unknown in 30.2% of cases.

5.1.7 HBV infection

In this study, there was an unavoidable sparsity of data on HBV infection, as became evident from Table 5. On univariate analysis, there was an extremely higher odds of DILI in the HBV infected patients. When compared to controls, HBV infected patients were found to be 10 times (OR 10.39; 95% CI 1.97 - 54.83) as likely to develop DILI than those not HBV infected. However, it must be noted that the very small number of individuals with HBV caused the 95% CI to be extremely wide. HBV infection was not analysed in terms of a confounding effect for DM on DILI, so it was kept out of the multivariate analysis.

Several studies have found HBV infection to be a risk factor for DILI (88, 90, 92, 147, 154, 285, 300, 307-310, 340). In a study by Wong *et al.* (147), it has been reported that 16% of HBV infected patients had symptomatic DILI when compared to 4.7% in those not HBV infected. Also, those individuals who were HBV infected developed more severe DILI than those not infected (4.7% *vs.* 2.5%). A retrospective case-control study from Korea (90) found a trend towards transaminases increase of at least five times the ULN more frequently in the HBV chronically infected patients than among those not infected (8% *vs*. 2%; $P = 0.05$). However, other studies have found no evidence of an association between DILI and HBV (284, 301, 342). At a central London teaching hospital, 2.6% of patients with active TB were HBsAg positive but there was no association between DILI and HBV (128). Similarly, in a study by Hwang *et al.* (282), 29% of HBV infected patients treated with RHZE had DILI, similar to the 26% found in HBV not infected patients ($P > 0.05$).

Additional investigation is needed, but the severity of liver injury appeared to have been increased in those HBV infected patients in a few studies (90, 147, 300). Although there are studies which have not stratified patients according to the evidence of a possible acute virus B hepatitis, still the current evidence is in favour of HBV chronic infection being associated with DILI. As concerns isoniazid-related DILI among those HBV infected, few studies have addressed this issue. In a small study by McGlynn *et al.* (373), no association was found between DILI and HBV. Another study (88) stratified HBV infected patients into HBeAg positive and negative patients. Three of 21 patients with HBeAg presented DILI, whereas none of the 121 of the HBeAg negative group did, nearly an 8-fold increased

risk. Acute viral hepatitis should always be considered as a differential diagnosis for TB DILI in studies conducted in countries where the carrier state of hepatitis B prevalence is high (300, 374). In a study conducted in Spain (154), of the patients without risk factors for chronic infection with such viruses, only 1% had HCV antibodies and 0.3% had chronic HBV.

In a study conducted in Brazil, the prevalence of previous HBV infection with spontaneous cure in patients with DM was 16.8% (366). No case of HBsAg positive was found. The study concluded that the prevalence of exposure to HBV (16.8%) was greater than the national prevalence of 11.6% in the general population aged 20 to 69 years old (366). In Porto Alegre, from 2013 to 2017, the incident cases of hepatitis B ranged from 16.3 to 19.2 per 100,000 population (213).

5.1.8 Concomitant hepatotoxic drugs

A Brazilian study (343) with TB-HIV co-infected patients has reported an absence of effect of hepatotoxic drugs on DILI due to the fact that 100% of cases and 94% of controls were taking concomitant hepatotoxic drugs. This finding was in accord with other studies (137, 310, 375), including the present one. Additionally, other studies have found no association between hepatotoxic drugs and TB DILI (125, 164, 275, 280, 306, 320, 322, 376, 377).

Nonetheless, other studies have found alternative results. There have been reports of isoniazid-related hepatotoxicity during concomitant use of other hepatotoxic drugs such as acetaminophen (321-323, 378), methotrexate (324), sulfasalazine (324) and carbamazepine (325, 326). It is important to make a clear distinction between idiosyncratic DILI (caused by the administration of a drug) and that caused by overdose, such as it happens with acetaminophen. It is a dose-dependent acetaminophen-induced toxicity termed intrinsic DILI, and it is predictable, reproducible and much insight has been gained into the underlying mechanisms (379-381). Acetaminophen has also been reported to be an agent that potentiates alcohol-induced hepatotoxicity (382).

A French population-based study conducted by Sgro *et al.* (96) found the main drugs implicated in DILI cases to be antimicrobials, psychotropic, hypolipidemic and non-steroidal anti-inflammatory drugs. Another study conducted with 1,038 adult TB patients in a TB clinic in Porto Alegre, between 1989 and 1994 (383), found that anticonvulsants were independently associated with DILI, with an OR 13.9; P = 0.0002. They also reported this increased risk to be higher in women taking

phenobarbital, hydantoin or carbamazepine (OR 25.2; $P < 0.0001$).

Acetaminophen was excluded from the present study analysis because it causes a predictable and dose-dependent type of liver injury. Additionally, it is not present in the drugs lists by Björnsson and Hoofnagle (271), used by the researchers as a validated source of drug reports. In this study, only 15 patients, all controls, took acetaminophen as a single drug, and there was no evidence that it had been taken in an overdose. Besides, it is a drug that can be bought without a medical prescription so the fact that it was not prescribed does not mean that it could not have been taken by patients, as opposed to other groups of DILI-causing drugs such as anti-epileptics and antimicrobials, for which a medical prescription is required. Considering the retrospective nature of the present study, it is fair to assume that any drugs could have been taken without the patient informing them or the TB physician registering them on the medical files. With regard to the use of illegal drugs, the present study did not collect data on them. Although marijuana, crack, cocaine and solvents are risk factors for DILI, a study conducted in Brazil has found no evidence of that (343).

5.1.9 Other liver diseases

Concomitant other liver diseases are shown in Table 3 and included mostly cirrhosis and liver TB, or its presumptive diagnosis. Cirrhotic patients were not analysed in terms of their different aetiologies, but were most probably either of an alcoholic nature or HCV related, among others. This variable was not included in the multivariate analysis for two reasons: first, because it was not a confounder for the effect of the main exposure, DM, on DILI (Table 6); and second, it was much associated with other variables: hazardous drinking, HCV, HBV and TB site, in so far as liver TB was a frequent finding among EPTB sites (Table 4).

Of the 22 cases who presented a chronic liver disease, 50% (11/22) were cirrhotic, while there were no cirrhotic individuals among the controls. Only one cirrhotic patient was known to be HBV positive, but he was a hazardous drinker as well. Of the seven patients with hepatitis C infection, four (57.1%) were hazardous drinkers. Finally, among the eight patients who were cirrhotic and known to be hazardous drinkers, (who were very likely also alcohol abusers), four (50%) had hepatitis C chronic infection as well. These data on the group of cirrhotic patients with DILI help make clear the difficulties regarding the *other liver diseases* variable, which was devised originally as a way of capturing chronic liver diseases other than chronic viral hepatitis C and B. Liver TB was

anticipated to be fairly prevalent, as well as other granulomatous hepatitis and steatosis. As diagnostics methods for steatosis were not expected to be routinely performed in TB clinics, for instance, the covariate *other liver diseases* most probably underestimated the effect of chronic liver diseases on DILI. Because of the intimate association with alcohol drinking, HCV and HBV, the multicollinearity between these exposure variables precluded its being added to the multivariate analysis.

5.1.10 TB site

The extent of TB disease has been studied and reported as a risk factor for the development of DILI, but mostly in terms of the radiological aspect and extent of pulmonary disease (153, 280). For instance, in one study, the disease was considered to be extensive if it involved the equivalent of more than one lung radiologically and presented multiple cavities (153). In this study, extensive pulmonary disease was found to be a risk factor for DILI (OR 4.5; 95% CI 1.88 – 10.93). However, in the same study, the presence of miliary shadows on chest radiographs were not associated with any increased risk for DILI. Gaude *et al.* (280) reported extensive pulmonary disease as an independent risk factor for the development of TB DILI (OR 2.3; 95% CI 2.1 – 4.9). Another study (284) used radiological scores to examine TB extent on chest radiographs (384), thus considering radiological lesions only, but did not find TB extent to be associated with an increased risk of DILI.

Several other studies have shown an increased risk of DILI associated with more extensive TB disease (148, 150, 153, 155, 297, 309, 330, 331). One study conducted by Warmelink *et al.* (301) classified TB morbidity according to WHO criteria (385), which differentiates between pulmonary and extrapulmonary TB and further stratifies the latter category into least and most severe. They found no association between TB morbidity and hepatotoxicity ($P = 0.3$), in contrast to other studies (124, 148, 153, 155). A study on DILI among patients co-infected with HIV classified the disease into pulmonary and extra-pulmonary forms but also considered disseminated disease through bloodstream involving sites such as the bone marrow, liver or at least two or more noncontiguous sites (343). They found no evidence of increased odds of DILI associated with TB morbidity in that population ($P = 0.4$). Another study (316) found some evidence of an association between EPTB (abdominal TB) and DILI ($P = 0.05$) when compared to pulmonary TB and other forms of EPTB. A study by Ambreen *et al.* (311) has reported that patients with EPTB are at a 32% higher risk of DILI

than PTB patients. Contrary to that, other studies could not find any association between DILI and extensive pulmonary disease (313, 335). A prospective cohort study conducted in Ethiopia (386) reported no association between DILI and EPTB.

As can be surmised, studies differ in terms of their definitions for the extent and severity of TB disease, but there seems to be a trend for finding more advanced disease as a predictor for DILI. A study conducted at the Hospital Sanatório Partenon in Porto Alegre, where 676 TB patients were followed between 1990-99, has found that miliary TB was a risk factor for DILI (OR 2.3; $P = 0.03$) (129).

The concept of extensive disease was sought to be taken further and it was hypothesized that having TB disease limited to the lungs could be considered, in general terms, less extensive than having both PTB and EPTB. This covariate, *TB site*, is a categorical non-ordered variable. An EPTB site, such as pleura or lymph node alone would present a much less extensive and milder disease than a bilateral and cavitary PTB, for instance. It was beyond the scope of this study the exact classification and characterization of the level of TB extent and miliary dissemination, however interesting it would have been to examine the relation between DILI and increasing degrees of TB disease severity extent.

As for EPTB, it is worth noting that granulomata are nonspecific findings. Granulomatous hepatitis may indicate an infectious, inflammatory or neoplastic aetiology (95) and it is one of the conditions causing DILI. Granulomatous hepatitis with increased transaminases presents itself in the case of hepatic TB and may present with abnormal baseline transaminases which improve with adequate TB treatment. In this study, there were not known baseline transaminases for most of the patients, except for those that came to the TB clinics after being discharged from hospital. It is reasonable to assume that patients with elevated transaminases and TB disease in other extrapulmonary sites would have been believed to present with subclinical liver TB, presumably, if abdominal scans showed a certain degree of liver abnormalities. Having both PTB and EPTB acted as a surrogate for more extensive TB.

5.2 Time to DILI

It is well known that hepatotoxicity occurs, as a rule, within weeks to months (387), so that DILI can be detected prematurely and mitigated. In the literature, it has been found that in most patients, TB DILI has started within 15 days after the start of treatment (275, 316, 343, 345, 388). Several other studies have reported similar findings (155, 272, 301, 331, 389). Median time to onset of DILI has been reported as 12.5 days (IQR 7 - 30); more than half of DILI cases (53%) occurred within the first 14 days, 72% within the first 28 days and 87.6% occurred by 56 days (342). These findings have been comparable to others (34, 91, 124, 126, 138, 155, 275, 345). There have been reports with slightly longer onset times (138, 284, 390). For instance, Sharma *et al.* (391) found a median time to DILI of 23 days (IQR 14 – 44 days) and Nader *et al.* reported that 89.4% of patients developed DILI within the first 30 days of RHZ (91). Tuberculosis drug-related DILI often developed one to three months after DILI in a study by Chen *et al.* (340) and also by Kim *et al.* (289). The present results mirror those found by other researchers. It was found that the time elapsed to DILI in 152 cases had a median of 17 days (IQR 9 – 49 days).

The accurate assessment of the time to DILI is more complex and beyond the possibilities of this study. The onset of injury may be defined as either the date of the onset of symptoms, or signs such as jaundice or bilirubinuria; or the first abnormal laboratory tests results. As for symptoms and clinical signs, in many instances the exact date was not available on the hospital medical discharge notes, as opposed to clinic records, which frequently have these data more accurately registered. It is worth of note that hospitalized patients are more likely to have their DILI diagnoses earlier than ambulatory patients because, in hospital, laboratory tests are routinely done daily, regardless of symptoms. Also, the first date of abnormal transaminases does not necessarily reflect the first day of injury. Based on these reflections, there may have occurred some misclassification concerning the exact date of DILI, which was deemed to be later than it really was, in some instances, although the proportion of patients whose DILI was diagnosed in hospital and therefore having a more accurate DILI date, was 7.6% (12/157). In the present study, time to DILI was not affected by DM status (Figure 1).

According to Picon *et al.* (383), after the discontinuation of TB treatment, the liver injury decreases in an average of 18 days (8 - 39 days). It has been suggested that regular monitoring of liver tests in the first 60 days of treatment would capture most of the patients developing DILI (95)

and this monitoring has been recommended for other DILI-causing drugs, apart from rifampicin, isoniazid and pyrazinamide, like disease-modifying anti-rheumatic drugs, for instance (392).

5.3 Confounding

Being the main exposure of interest, DM had its effect on DILI stratified by the other covariates (Table 6). The crude OR 1.10 (95% CI 0.62 – 1.94) was compared to the adjusted Mantel-Haenszel DM OR. The covariates age, HIV infection, hepatotoxic drugs and TB site acted as confounders in the effect of DM on DILI. Hepatitis C infection acted as effect modifier.

5.3.1 Age

Older age is a well-known risk factor for DILI. In the present study, age proved to be a strong confounder, as the effect of DM on DILI diminished from OR 1.10 (0.62 – 1.94) to OR 0.72 (95% CI 0.40 – 1.31) (Table 6). Older age is associated both with DILI and with DM, so was expected to be a strong confounder.

5.3.2 HIV

Among both cases and controls, most of the patients with DM were not HIV positive. The HIV infection was confounding the effect of DM on DILI, which became higher once DM was adjusted for HIV (M-H OR 1.44; 95% CI 0.80 – 2.60) (Table 6). In the multivariate analysis (Table 7), HIV had a strong effect on DILI (OR 3.59; 95% CI 2.25 – 5.73), while DM had no evidence of having any effect (OR 0.88; 95% CI 0.45 – 1.71). HIV was not initially expected to be a confounder, as it is not associated with DM.

5.3.3 Hazardous drinking

Among the controls, hazardous and not hazardous drinkers had nearly the same DM prevalence (Table 5). However, among the cases, the prevalence of DM was approximately three times higher

in the hazardous drinking group, so that patients with DM were more hazardous drinkers than not. A little of the effect on DILI caused by DM may have been attributable to alcohol drinking, although it did not act as a confounder for the effect of DM on DILI. The DM OR decreased from OR 1.10 (95% CI 0.62 – 1.94) to OR 1.02 (95% CI 0.57 – 1.81). Nevertheless, the literature presents some evidence that DM is associated with alcohol drinking (196, 198, 204).

5.3.4 Hepatotoxic drugs

Among the controls, most patients with DM were taking hepatotoxic drugs, whereas among the cases, the prevalence of patients with DM taking hepatotoxic drugs was the same as those not taking them, so that for those with DM and DILI, it made no difference whether they were taking additional hepatotoxic drugs or not. There was a suggestion that hepatotoxic drugs might be acting as effect modifier on the effect of DM on DILI (*P*-value for the Test of Homogeneity of ORs = 0.01) (Table 6), but the interaction was not confirmed by the multivariate analysis (*P*-value for the interaction = 0.1) (Tables 7 and 8).

5.3.5 TB site

Among the controls, patients with DM had a higher prevalence of only PTB, followed by only EPTB and, least of them, both PTB and EPTB. Patients with DM are often immunosuppressed, so it would be reasonable to hypothesize a higher prevalence of more extensive TB disease in this group. However, this was not so. Among the cases, most of individuals with DM had only PTB (88.2%), and none had only EPTB. This may have contributed to the impossibility to find an association between DM and DILI, even though it was possible to find increased odds of DILI in patients with more extensive disease (PTB and EPTB). Patients with DM presented the same tendency for having a higher prevalence of PTB than EPTB, as is the case in the general population. The confounding effect of TB site on the effect of DM on the odds of having DILI should be interpreted with caution.

5.4 Effect modification

There was weak evidence for HCV being a modifier for the effect of DM on DILI (*P* = 0.06) (Table

6). Among the controls, patients with and without DM had similar HCV prevalence, but among the cases, the HCV prevalence in the DM group was nearly four times higher than in those without HCV (25% *vs.* 6.61%). When patients with DM were stratified by HCV status, the OR for the effect of DM on DILI increased from OR 1.10 (95% CI 0.62 – 1.94) to an OR 2.67 (95% CI 0.72 – 9.93; *P* = 0.1) in the HCV stratum and decreased to an OR 0.65 (95% CI 0.30 – 1.39; *P* = 0.3) in the non-HCV stratum (data not shown). The Test of Homogeneity of ORs *P*-value (*P* = 0.06) suggested that there might be an interaction between HCV and DM (Table 6). In the multivariate analysis (Table 9), after adjusting for age, sex, HIV, hepatotoxic drugs and TB site, there was some evidence that having HCV would affect the effect of DM on DILI, when compared to those without DM (*P*-value for the interaction = 0.02). Having DM was associated with a more than three-fold increase in odds of DILI among those with HCV (OR 3.37; 95% CI 0.86 - 13.16; *P* = 0.08), whereas DM was associated with a 46% reduction in odds of DILI among those without HCV (OR 0.54; 95% CI 0.23 - 1.26; *P* = 0.2). The large *P*-values for the strata reflect the stratification and small number of individuals. It is worth noting that there is evidence in the literature that not only DM worsens HCV outcomes but that this association leads to worse outcomes for DM as well (222, 334). Although those results should be treated with caution, there is a body of evidence that agrees with the finding of an effect modification in those patients with DM and concomitant HCV, as opposed to those with DM without it, regarding their odds of presenting with TB DILI. The double burden of these two diseases is likely to increase the odds of DILI in a group of patients with the additional burden of a chronic consumptive infection and a prolonged intake of three hepatotoxic drugs.

5.5 Limitations of this study inherent to case control studies

5.5.1 Information bias

Being a retrospective study, data reported on certain covariates such as hazardous drinking, use of concomitant hepatotoxic drugs and concomitant liver diseases were subject to inaccuracies and subjectivity. Data on blood tests were subject to physicians' discretion and individual working routines, so not consistently available on medical documentation. The literature has reported a few risk factors for TB DILI which have not been analysed in the present study and which might have, possibly, played a role as confounders. It was not feasible to comment on data that were not a part of clinical routine, such as on acetylator status, nutritional status, or concomitant NAFLD.

Genetic factors have been found to have an effect on DILI (124, 152, 153, 393) and were not analysed in this study. Several genetic polymorphisms in drug metabolizing enzymes have been associated with DILI (164, 294, 316, 390) such as slow acetylator status (N-acetyl-transferase 2) (153). However, it has been observed that both fast and slow acetylators are prone to develop DILI with RHZE (138, 149). When acetylation has been studied by phenotypic assays, slow acetylators have presented more DILI in some studies (282, 299, 355, 394), although not in others (395, 396). A slow acetylator phenotype has been associated with an increased risk of isoniazid-related DILI (OR 4.25; 95% CI 1.36 – 13.22; *P* = 0.01) (332) and another study has found that slow acetylators developed more TB DILI (26% *vs.* 11%), and more severe, than fast acetylators (152).

Malnutrition, ascertained either by body mass index or serum albumin, is another widely accepted risk factor for TB DILI (124, 153-155, 164, 280, 282, 295, 297, 327-329) that was not captured by this study. One mechanism for the effect of undernutrition on DILI is the depletion of glutathione stores that renders individuals vulnerable to oxidative injuries (316). A study in India (397) has found a 3-fold higher incidence of TB DILI in undernourished patients. Although weighing patients monthly during medical appointments is a routine procedure at the TB clinics, height measurements are not, and nor are serum albumin tests.

The present study has not addressed the issue of recreational drug use because this type of data, when asked retrospectively, is likely to be quite unreliable, considering the substantial number of socially vulnerable individuals with TB. Drug misuse has been studied as a risk factor for DILI, but is not a well-established one (301).

Data on drugs were captured based on prescriptions registered on medical records from the clinics and hospital discharge documentation. As such, they may have been both overestimated, because the patient might not have taken the medication prescribed; as well as underestimated, because the patient might have taken other hepatotoxic drugs without the physician's awareness or consent. Hospital discharge documentation, however thoroughly informative, might not have all the drugs prescribed in them, nor did all patients bring their hospital notes to TB clinic appointments.

Alcohol consumption was self-informed by patients and any daily alcohol intake was likely to be either underestimated or under-reported by them. Likewise, data on alcohol intake was not reported by physicians in a standardized way; for instance, as in the number of alcohol units taken daily or over the weekend. Rather, the physicians reported that a patient was either "alcoholic", "eventual drinker", or "no drinker at all". As there was no objective way of differentiating *alcohol*

dependence from *hazardous drinking*, some hazardous drinkers must have been misclassified as alcoholics by their physicians and *vice versa*. In practical terms, they were at least hazardous drinkers, so this limitation was of no importance to the final analysis. Still, there is a possibility that the prevalence of hazardous drinkers may have been rather underestimated than overestimated. Alcohol consumption was self-reported and under-reporting alcohol misuse is a reality.

Other important cause of liver injury are herbal products and dietary supplements, which were not captured by this study. They are frequently overlooked during anamnesis, and these questions may have been neither asked by physicians nor spontaneously informed by patients.

A certain degree of misclassification bias is to be expected in retrospective studies. For instance, missing results on tests for HCV, HBV or DM. The reason for the DM variable being classified in "known DM" and "not known to have DM" has been described previously. There was no demonstrable association between known DM and DILI but one cannot exclude the possibility that some undiagnosed DM subjects were included in the "not known to have DM" category and, but for the lack of a blood test, may have been differently classified.

5.5.2 Selection bias

Another type of bias inherent to case control studies is the selection bias (398). The present study sought to prevent it by selecting the controls from the same population as the DILI case population. They were TB patients of all ages and backgrounds being treated with the same hepatotoxic drug combination (RHZE) and consequently as likely to have the same clinical and epidemiological characteristics as the cases. It is important to note that although DILI patients were followed-up at the CRTB clinics, there was no bias towards TB-HIV co-infected patients, because the DILI diagnoses were made also in primary health care clinics, where co-infected patients are not routinely treated, and several hospitals.

5.6 Study strengths and weaknesses

5.6.1 Study strengths

As far as it could be identified, this was the first study to hypothesize that DM might be a risk

factor for DILI and to seek to investigate its possible associations with other well-known risk factors. Considering the triple burden of DM, TB and DILI, the study hypotheses were fully justified and warranted further investigation.

The main strengths of this study include the SITETB electronic platform, which enabled us to capture the totality of the DILI cases severe enough to have needed a change of drug regimen. Another strength of this study was the inclusion of a heterogeneous study population with a wide spectrum of risk factors for DILI. This study was not restricted to adults. Serious side effects can occur in young children, also, and it has been shown that pyrazinamide is the most common offender (353).

The small group of TB physicians provided a reasonably standard approach to identification and management of a more serious DILI episode requiring a change of treatment and then reporting and registering it onto SITETB, which was the source database for DILI cases. Regardless of where the patient was being treated when DILI was diagnosed, were it in a hospital or in an outpatient Family Medicine clinic, the decision of a change of treatment was endorsed by the same TB physicians in the five TB clinics. This aspect should allow for comparability of results and internal validity. The primary outcome measure (DILI needing a change of treatment) was based on current guidelines for TB DILI management, but as there is not a unique procedure to DILI management, it is actually possible that some DILI patients who had their treatment changed, could have been successfully re-challenged with RHZE.

5.6.2 Study weaknesses

There were several important limitations to the study. First, the sample size needed was not obtained, which led to a decrease in the study power; second, routine rapid tests for HCV and HBsAg were not offered during the whole period of the cases diagnosis; they became systematically implemented in the referral TB clinics as of 2015. As a result, data on HBV and HCV status were missing for a number of patients; they were not offered by the TB Programme at the clinics and, additionally, blood tests are subject to physician discretion. The same was not the case with HIV screening tests. The coverage of HIV status in TB patients was nearly total. The prevalence of co-infection with HBV and HCV among HIV positive patients have been reported in the international literature to be between 10% - 15% and 15% - 30% (399, 400), respectively. However, in 2016, the

prevalence of hepatitis C in Brazil was estimated to be 0.7% among those between 15 and 69 years of age and the co-infection HIV-HCV was estimated to be 9.8% (364). There might have been a number of patients co-infected that was not identified, albeit a small number. Consequently, multicollinearity between these three variables could not be excluded.

Tuberculosis DILI diagnosis is often based on circumstantial evidence. It includes the temporal relationship between the start of RHZE and the onset of liver injury, as well as its resolution after drug withdrawal. However, it certainly requires the exclusion of acute viral hepatitis and other possible causes. It has been shown that patients with acute viral hepatitis take a longer time for normalization of increased liver transaminases. Because the DILI diagnosis is usually prompt and the TB patient has easy access to medical consultations, there is frequently an absence of fever and the improvement of symptoms follow shortly, those are probably the reasons why some patients did not have a viral hepatitis serology panel performed. As far as it could be ascertained, among the 157 DILI cases in the study, there were no misdiagnoses as to the hepatitis aetiology.

Possible confounding and bias could not have been completely excluded. Different backgrounds and life styles among patients can create confounding factors impossible to assess. For instance, it was not possible to include diverse ethnic groups in the study, although Porto Alegre is a multi-ethnical capital. The incidence of Muslim population is minimal, so that a bias towards drinking habits would have been very unlikely. A few other risk factors for DILI were also not controlled for, such as a previous DILI episode and increased pre-treatment transaminases. Baseline altered liver tests may signal a liver comorbidity. Nevertheless, no substantial underestimation of the actual effect of these risk factors for DILI due to the failure to identify these high-risk individuals occurred, because chronic liver diseases were captured and analysed.

Baseline transaminase tests were not always available. Patients with altered baseline transaminases are not treated with RHZE, they are instead put on one of the hepatotoxicity regimens such as capreomycin, levofloxacin and ethambutol (CpLxE) or rifampicin, levofloxacin and ethambutol (RLxE) and thus very unlikely to present DILI. Ascertainment bias could have occurred as some alcohol abusers could have actually a mild cirrhosis or NAFLD without the physician being aware. Ultrasound or CT scans are not routinely ordered. Besides, patients who were previously known to have a history of hazardous drinking, NAFLD or of a previous DILI episode could have been more frequently tested for HCV, HBV or transaminases than those who had no such histories.

Patients who were reported as not having DM in the TB notification database and were not

screened for DM for confirmation tests were considered as “not known to have” DM. There was no demonstrable association between known DM and DILI but there cannot be excluded the possibility that some undiagnosed DM subjects were included in the “not known to have DM” classification and, but for the lack of a test, may have been differently classified.

Likewise, patients who were not tested for HIV, HCV and HBV were considered to be “not known to have” HIV, HCV and HBV. Therefore, results could present an underestimation of these exposures, with the exception of HIV status, as the TB Programme in Porto Alegre has a systematic HIV screening coverage. Rapid tests for HIV were implemented back in 2014, before screening for HCV and HBV tests ever started. It is also worth noting that the lack of reporting of critical data such as HCV and HBV tests may have been because the laboratory results were normal and, therefore, not deemed relevant to be registered.

For a number of the variables, the missingness is significantly different between cases and controls and usually greater in controls. This is not unexpected because patients with DILI are more likely to have more complete questioning and investigations for liver disease. It is likely that missingness was smaller amongst cases in relation to DM, HCV, HBV and other liver diseases because they were more likely to be tested and screened for risk factors for DILI than the controls. This same pattern of missing data could be explained by the fact that patients with EPTB are likely to be more extensively ill than those having only PTB, in general, and therefore were probably more thoroughly investigated for risk factors for DILI. However, with hepatotoxic drugs, missing data was higher amongst the cases and one explanation for that could be that of all DILI risk factors, drug history was the least considered by physicians and inquired during anamnesis, even after DILI had occurred.

Multiple imputation could be an alternative approach to account for missing data in the exposure and confounders. This approach is usually performed under the assumption that the mechanism causing the missing data is “Missing at Random”. Even though this assumption may be plausible, it cannot be verified by the data.

Lastly, with the sample size achieved, the study had a 70% power to detect a measure of effect (OR) of 2.01, which allowed to answer the study questions. Considering a study sample size of 157 cases and 634 controls and a DM prevalence among the controls of 10%, the study has an 80% power to exclude an OR 1.98 or greater.

5.7 Conclusions

The association between TB and DM and their synergistic action in causing morbidity and mortality has been long recognised. The full extent of this double burden, in particular its consequences regarding the care and control of these two diseases, has yet to be fully explored.

While the global incidence of DILI is small, its impact in health outcomes is substantial. TB DILI will remain a problem that carries both clinical and regulatory significance for as long as new drugs continue to enter the market. Physicians must always weigh potential risks *vs*. benefits. Continual efforts in studying determinants of drug induced hepatotoxicity may eventually result in mitigation of detrimental factors for TB outcomes.

The present study supports the concept that specific groups of patients are at a higher risk for developing DILI. A major goal of this study was to determine if DM increases the odds of DILI in patients taking RHZE. As far as it has been possible to ascertain, no studies designed to investigate the role of DM being a major risk factor for DILI have been conducted in Brazil or elsewhere.

This study is limited by its retrospective nature. It was sought to determine whether DM is associated with an increased risk of TB DILI and to further investigate any risk factors associated with the effect of DM on DILI. No association between DM and increased odds of DILI was found. Sex and concomitant hepatotoxic drugs were not associated with increased odds of DILI, either. Nevertheless, age over 50 years old, HIV infection, HCV infection, and having both PTB and EPTB (when compared to PTB only) were shown to independently increase the odds of having TB DILI and these findings corroborate evidence from the literature. Considering the study objectives, the research questions have been answered.

It was deemed important to investigate the issue of TB DILI in a group of patients characterized by an impaired immune system and complex metabolic disorders including hepatic involvement. As far as it could be ascertained, this investigation with a focus on DM is pioneer among research on TB DILI and offers data for comparisons with future studies and improvement in the knowledge of the subject.

5.8 Recommendations

Based on the present study findings, TB patients with DM being treated with the first-line regimen, RHZE, are not at increased odds of presenting DILI and, therefore, are not in need of routine liver

test monitoring. This study recommends that those patients who are older than 50 years of age, HIV positive, HCV positive or presenting both PTB and EPTB, be instructed by the TB team about DILI symptoms awareness. Indeed, those patients should have their liver tests monitored, as they are at increased odds of developing DILI and monitoring has been widely advised in the literature.

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APPENDIX A

Tables of notified incident cases and treatment outcomes from 2013 to 2017 in the five TB referral clinics of Porto Alegre, Brazil.

Table A1. Number of notified incident TB cases per referral TB clinic per year in Porto Alegre, Brazil

Number of notified incident TB cases						
TB Clinic	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Clinic 1	93	84	142	123	97	539
Clinic 2	156	153	136	142	113	700
Clinic 3	164	127	108	81	82	562
Clinic 4	127	102	104	67	69	469
Clinic 5	262	201	145	116	92	816
Total	802	667	635	529	453	3086

TB: tuberculosis

Table A2. Frequencies of outcome events per referral TB Clinic in Porto Alegre - 2013

Frequencies of outcome events									
TB Clinic	**Cure**	**Default**	**Death (TB)**	**Death (not TB)**	**Transfer**	**Change of diagnosis**	**DRTB**	**Change of regimen**	**Total**
Clinic 1	69	17	0	4	0	1	1	1	93
Clinic 2	112	30	1	3	5	3	2	0	156
Clinic 3	126	26	2	2	4	1	3	0	164
Clinic 4	61	57	1	4	2	1	0	1	127
Clinic 5	125	96	4	7	5	4	18	3	262
Total	493	226	8	20	16	10	24	5	802

DRTB: drug resistant tuberculosis; TB: tuberculosis

Table A3. Frequencies of outcome events per referral TB Clinic in Porto Alegre – 2014

Frequencies of outcome events									
TB Clinic	**Cure**	**Default**	**Death (TB)**	**Death (not TB)**	**Transfer**	**Change of diagnosis**	**DRTB**	**Change of regimen**	**Total**
Clinic 1	61	12	2	3	3	3	0	0	84
Clinic 2	107	29	3	3	4	6	1	0	153
Clinic 3	91	22	1	4	2	2	5	0	127
Clinic 4	49	44	2	1	1	2	2	1	102
Clinic 5	98	51	1	0	7	4	37	2	200
Total	406	158	9	11	17	17	45	3	666

DRTB: drug resistant tuberculosis; TB: tuberculosis

Table A4. Frequencies of outcome events per referral TB Clinic in Porto Alegre - 2015

Frequencies of outcome events									
TB Clinic	**Cure**	**Default**	**Death (TB)**	**Death (not TB)**	**Transfer**	**Change of diagnosis**	**DRTB**	**Change of regimen**	**Total**
Clinic 1	97	23	0	3	4	6	0	9	142
Clinic 2	100	24	0	3	3	1	1	4	136
Clinic 3	75	22	1	3	2	1	2	2	108
Clinic 4	56	36	0	5	3	2	1	1	104
Clinic 5	56	24	1	3	10	1	41	9	145
Total	384	129	2	17	22	11	45	25	635

DRTB: drug resistant tuberculosis; TB: tuberculosis

Table A5. Frequencies of outcome events per referral TB Clinic in Porto Alegre - 2016

Frequencies of outcome events									
TB Clinic	**Cure**	**Default**	**Death (TB)**	**Death (not TB)**	**Transfer**	**Change of diagnosis**	**DRTB**	**Change of regimen**	**Total**
Clinic 1	82	22	1	1	9	3	1	4	123
Clinic 2	103	18	3	3	3	2	2	8	142
Clinic 3	54	15	1	3	1	1	3	3	81
Clinic 4	43	14	1	2	3	1	3	0	67
Clinic 5	35	15	1	5	4	4	39	12	116
Total	317	84	7	14	20	11	48	27	529

DRTB: drug resistant tuberculosis; TB: tuberculosis

Table A6. Frequencies of outcome events per referral TB Clinic in Porto Alegre - 2017

Frequencies of outcome events										
TB Clinic	**Cure**	**Default**	**Death (TB)**	**Death (not TB)**	**Transfer**	**Change of diagnosis**	**DRTB**	**Change of regimen**	**Unknown**	**Total**
Clinic 1	63	12	1	1	8	4	1	6	1	97
Clinic 2	92	12	2	1	2	1	1	1	1	113
Clinic 3	57	11	1	2	4	2	2	1	2	82
Clinic 4	45	16	2	2	2	0	2	0	0	69
Clinic 5	27	8	0	2	5	1	34	3	12	92
Total	284	59	6	8	21	8	40	11	16	453

DRTB: drug resistant tuberculosis; TB: tuberculosis

APPENDIX B

TB diagnosis methods

Table B1. TB diagnosis methods in 791 active TB cases

Diagnosis methods	Cases (n = 157)		Controls (n = 634)	
	Frequency	%	Frequency	%
Smear	48	30.6	200	31.6
Culture	53	33.8	162	25.6
Molecular Biology*	26	16.6	70	11.0
Not confirmed	30	19.1	202	31.9

*Methods were qPCR or GeneXpert® MTB/RIF assay

APPENDIX C

Tables from the paper "Categorization of drugs implicated in causing liver injury: Critical assessment based on published case reports" by E. S. Björnsson and J. H. Hoofnagle

Table C1. Category A (≥50 Published Cases)

Drug №	Ingredient	Number of Cases	Fatalities	Rechallenge	Year	Classification
1	Allopurinol	>100	1	1	1965	Rheumato-logic
2	Amiodarone	>100	1	1	1985	Cardiovas-cular
3	Androgenic steroids *	>100	1	1	1981	Endocrine
4	Atorvastatin	65	1	1	1996	Cardiovas-cular
5	Auranofin/Gold products *	>100	1	1	1985	Rheumato-logic
6	Azathioprine/ Mercaptopuri-ne	>100	1	1	1968	Immuno-modulatory
7	Busulfan	>100	1	0	1954	Antineo-plastic
8	Carbamazepine	>100	1	1	1968	CNS
9	Chlorpromazine	>100	1	1	1957	CNS
10	Clavulanate with Amoxicillin	>100	1	1	1984	Antimicro-bial

Drug Nº	Ingredient	Number of Cases	Fatalities	Rechallenge	Year	Classification
11	Dantrolene	51	1	1	1974	CNS
12	Diclofenac	>100	1	1	1988	Analgesic
13	Didanosine	>100	1	1	1991	Antimicro-bial
14	Disulfiram	>100	1	1	1951	Substance abuse agent
15	Efavirenz	>100	1	0	1998	Antimicro-bial
16	Erythromycin	>100	1	1	1967	Antimicro-bial
17	Estrogens / Progestins *	>100	0	1	Pre-1980	Endocrine
18	Floxuridine	>100	1	0	1970	Antineo-plastic
19	Flucloxacillin	>100	1	1	N	Antimicro-bial
20	Flutamide	>100	1	1	1989	Antineo-plastic
21	Halothane	>100	1	1	1956	CNS
22	Hydralazine	>100	1	1	1984	Cardiovas-cular
23	Ibuprofen	52	1	1	1974	Analgesic

Drug №	Ingredient	Number of Cases	Fatalities	Rechallenge	Year	Classification
24	Infliximab	>100	1	1	1998	Immuno-modulatory
25	Interferon-α/Peginter-feron	56	1	1	1986	Antimicro-bial
26	Interferon-β	>100	1	1	1993	Immuno-modulatory
27	Isoniazid	>100	1	1	1974	Antimicro-bial
28	Ketoconazole	>100	1	1	1981	Antimicro-bial
29	Methotrexate	>100	1	0	1971	Antineo-plastic
30	Methyldopa	>100	1	1	1962	Cardiovas-cular
31	Minocycline	>100	1	1	1971	Antimicro-bial
32	Nevirapine	>100	1	1	1996	Antimicro-bial
33	Nimesulide	>100	1	1	N	Analgesic
34	Nitrofurantoin	>100	1	1	1953	Antimicro-bial
35	Phenytoin/Fos-phenytoin	>100	1	1	1946	CNS

Drug Nº	Ingredient	Number of Cases	Fatalities	Rechallenge	Year	Classification
36	Propylthiouracil	>100	1	1	1948	Endocrine
37	Pyrazinamide	>100	1	1	1971	Antimicro-bial
38	Quinidine	53	1	1	1950	Cardiovas-cular
39	Rifampin	>100	1	1	1971	Antimicro-bial
40	Simvastatin	68	1	1	1991	Cardiovas-cular
41	Sulfamethoxa-zole with TMP	>100	1	1	1980	Antimicro-bial
42	Sulfasalazine	>100	1	1	1950	Rheumato-logic
43	Sulfonamides *	>100	1	1	1973	Antimicro-bial
44	Sulindac	>100	1	1	1978	Analgesic
45	Telithromycin	79	1	0	2004	Antimicro-bial
46	Thioguanine	56	1	0	1966	Antineo-plastic
47	Ticlopidine	>100	1	1	1985	Hematolo-gic
48	Valproate	>100	1	1	1978	CNS

* Groups of agents

CNS: central nervous system; N: never approved in the United States; TMP: trimethoprim

Table C2. Category B (12–49 Cases)

Drug №	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
1	Acarbose	13	1	0	1995	Endocrine
2	Amitriptyline	18	1	1	1961	CNS
3	Amodiaquine	37	1	1	1977	Antimicro-bial
4	Amoxicillin	17	1	0	1980	Antimicro-bial
5	Asparaginase/ Pegaspargase	12	1	0	1972	Antineo-plastic
6	Azithromycin	30	1	0	1991	Antimicro-bial
7	Captopril	16	1	0	1981	Cardiovas-cular
8	Cefazolin	25	0	0	1973	Antimicro-bial
9	Ceftriaxone	15	1	0	1984	Antimicro-bial
10	Celecoxib	14	0	1	1998	Analgesic
11	Chlorpropa-mide	13	0	0	1958	Endocrine
12	Chlorzoxazone	41	1	0	1958	CNS
13	Cimetidine	22	0	1	1977	Gastroin-testinal

Drug Nº	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
14	Ciprofloxacin	28	1	0	1987	Antimicro-bial
15	Clarithromycin	14	0	1	1991	Antimicro-bial
16	Clindamycin	12	1	0	1970	Antimicro-bial
17	Clopidogrel	14	1	1	1997	Hematolo-gic
18	Cloxacillin	16	0	1	1974	Antimicro-bial
19	Clozapine	27	1	0	1989	CNS
20	Cyclophos-phamide/ Ifosphamide	25	1	1	1959	Antineo-plastic
21	Cyproterone	49	1	1	N	Antineo-plastic
22	Dacarbazine	24	1	0	1975	Antineo-plastic
23	Dicloxacillin	20	0	1	1968	Antimicro-bial
24	Doxorubicin	16	1	0	1974	Antineo-plastic
25	Duloxetine	13	0	0	2004	CNS

Drug Nº	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
26	Enalapril	25	1	0	1985	Cardiovas-cular
27	Enflurane	29	0	0	1972	CNS
28	Etanercept	16	1	1	1998	Immuno-modulatory
29	Ethionamide	12	1	1	1965	Antimicro-bial
30	Felbamate	15	1	0	1993	CNS
31	Fenofibrate	24	0	1	1993	Cardiovas-cular
32	Fluconazole	25	0	0	1990	Antimicro-bial
33	Fluvastatin	28	0	1	1993	Cardiova-scular
34	Glyburide (Glibenclamide)	13	1	0	1964	Endocrine
35	Haloperidol	25	0	0	1967	CNS
36	Heparin	42	0	0	Pre-1980	Hematolo-gic
37	Imatinib	39	1	1	2001	Antineo-plastic
38	Imipramine	15	1	0	1959	CNS

Drug Nº	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
39	Irinotecan	31	0	0	1996	Antineo-plastic
40	Isoflurane	25	1	1	1979	CNS
41	Itraconazole	18	1	1	1992	Antimicro-bial
42	Ketamine	15	0	1	1970	CNS
43	Lamotrigine	33	1	0	2007	CNS
44	Leflunomide	12	1	0	1998	Rheumato-logic
45	Levofloxacin/ Ofloxacin	40	1	0	1996	Antimicro-bial
46	Lisinopril	14	1	0	1987	Cardiovas-cular
47	Lovastatin	12	0	0	1987	Cardiovas-cular
48	Melphalan	21	1	0	1964	Antineo-plastic
49	Metformin	18	0	0	1995	Endocrine
50	Methimazole (Thiamazole)	27	0	0	1959	Endocrine
51	Moxifloxacin	13	1	0	1999	Antimicro-bial
52	Naproxen	16	1	0	1976	Analgesic

Drug Nº	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
53	Nifedipine	12	0	1	1981	Cardiovas-cular
54	Olanzapine	28	0	1	1996	CNS
55	Omeprazole/ Esomeprazole	16	1	1	1989	Gastroin-testinal
56	Oxacillin	36	0	0	1989	Antimicro-bial
57	Oxaliplatin	12	0	0	2002	Antineo-plastic
58	Paroxetine	23	0	0	1992	CNS
59	Penicillamine	22	1	1	1970	Toxicology
60	Phenobarbital	30	0	0	1911	CNS
61	Piroxicam	12	0	0	1982	Analgesic
62	Propafenone	13	0	1	1989	Cardiovas-cular
63	Quinine	12	0	1	2005	Antimicro-bial
64	Ranitidine	14	1	1	1983	Gastroin-testinal
65	Rivaroxaban	17	0	0	2011	Hematolo-gic
66	Rosuvastatin	13	0	0	2003	Cardiovas-cular

Drug Nº	Ingredient *	Number of Cases	Fatalities	Rechallenge	Year	Classification
67	Sertraline	17	1	1	2005	CNS
68	Sevoflurane	21	0	1	1995	CNS
69	Stavudine	47	1	0	1994	Antimicro-bial
70	Tamoxifen	30	1	0	1997	Antineo-plastic
71	Terbinafine	30	0	0	1998	Antimicro-bial
72	Thiabendazole	13	1	0	1967	Antimicro-bial
73	Thioridazine	12	0	1	1978	CNS
74	Venlafaxine/ Dexvenlafaxine	12	0	1	1965	CNS
75	Voriconazole	23	0	0	2002	Antimicro-bial
76	Zidovudine	13	1	1	1987	Antimicro-bial

* Alternative names are given in parentheses.

CNS: central nervous system; N: never approved in the United States.

APPENDIX D

Open Data Kit Form for the electronic data capture form – survey

TBDM Project ODK Form - survey				
type	**name**	**label**	**relevant**	**constraint**
start	start			
select_one yes_no	case	Is it a case?		
text	name	Name of patient		
date	d_birth	Date of birth		
select_one male_female	sex	Sex		
integer	med_rec	Medical record number		
integer	sinan	SINAN number		
date	d_dili	Date of DILI dx	${case} = 'yes'	
date	d_sitetb	SITETB notification date	${case} = 'yes'	
select_multiple tb_clinic	tb_clin	Name of TB clinic		
select_one yes_no	ptb	Pulmonary TB?		
select_one yes_no	eptb	Extra pulmonary?		
text	tb_site	TB site	${eptb} = 'yes'	
select_one yes_no	ext_tb	Extensive TB?		
select_multiple tb_dx	tb_dx	Type of TB dx		
date	d_rhze	Date of start of RHZE		
select_multiple dm	dm	Has DM?		
select_multiple dm_dx	dm_dx	Type of DM dx	${dm} = 'yes'	
select_multiple hz_drk	hz_drk	Hazardous drinking?		
select_multiple hiv	hiv	HIV infection?		
select_multiple hcv	hcv	Chronic hep C infection?		
select_multiple hbv	hbv	Chronic hep B infection?		
select_multiple hpx_dr	hpx_dr	Concomitants hepatotoxic drugs?		
text	drugs	Which drugs?	${hpx_dr} = 'yes'	
select_multiple oliv_dis	oliv_dis	Other liver diseases?		
text	dis_name	Which diseases?	${oliv_dis} = 'yes'	
text	comm	Any comments?		

Open Data Kit Form for the electronic data capture form – choices

TBDM Project ODK Form - choices		
list name	**name**	**label**
male_female	1	Male
male_female	2	Female
tb_clinic	1	CRTB Centro
tb_clinic	2	CRTB Navegantes
tb_clinic	3	CRTB Vila Comerciários
tb_clinic	4	CRTB Bom Jesus
tb_clinic	5	Hospital Sanatório Partenon
yes_no	yes	Yes
yes_no	no	No
tb_dx	1	Smear positive
tb_dx	2	Culture positive
tb_dx	3	PCR/GeneXpert
tb_dx	4	Not confirmed
dm	yes	Yes
dm	no	No
dm	9	unknown
dm_dx	1	1.a.
dm_dx	2	1.b.
dm_dx	3	1.c.
dm_dx	4	1.d.
dm_dx	5	2.a.
dm_dx	6	2.b.
hz_drk	yes	Yes
hz_drk	no	No
hz_drk	9	unknown
hiv	yes	Yes
hiv	no	No
hiv	9	unknown
hcv	yes	Yes
hcv	no	No
hcv	9	unknown
hbv	yes	Yes
hbv	no	No
hbv	9	unknown
hpx_dr	yes	Yes
hpx_dr	no	No
hpx_dr	9	unknown
oliv_dis	yes	Yes
oliv_dis	no	No
oliv_dis	9	unknown

APPENDIX E

Ethics approval from the London School of Hygiene and Tropical Medicine

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Ivanice Freire
LSHTM

3 August 2017

Dear Ivanice Freire

Study Title: Does diabetes mellitus comorbidity increase the risk of drug-induced liver injury during tuberculosis treatment?

LSHTM Ethics Ref: 11939

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Data capture sheet LEO	07/05/2017	1
Protocol / Proposal	RESEARCH PROTOCOL for LEO 090517	09/05/2017	1
Investigator CV	MOORE brief CV 2016 INS	09/05/2017	1
Investigator CV	CV Ivanice Freire	10/05/2017	1
Covering Letter	Cover Letter for LEO	27/07/2017	2
Information Sheet	Term_of_Awareness_CGVS	27/07/2017	2
Information Sheet	Term_of_Awareness_CGVS_English	27/07/2017	2
Information Sheet	Term_of_Awareness_CGAE	27/07/2017	2
Information Sheet	Term_of_Awareness_CGAE_English	27/07/2017	2
Information Sheet	Scientific_Commission_HSP	27/07/2017	2
Information Sheet	Scientific_Commission_HSP_English	27/07/2017	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

APPENDIX F

Ethics approval from the Brazilian National Committee on Research Ethics

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Plataforma Brasil

Continuação do Parecer: 2.426.619

O investigador principal e demais colaboradores envolvidos no estudo acima se comprometem a utilizar os dados provenientes deste apenas para os fins descritos e a cumprir todas as diretrizes e normas regulamentadoras descritas na Res. CNS Nº 466/12, e suas complementares, no que diz respeito ao sigilo e confidencialidade dos dados coletados.

ANÁLISE: PENDÊNCIA ATENDIDA.

Considerações Finais a critério da CONEP:

Diante do exposto, a Comissão Nacional de Ética em Pesquisa - Conep, de acordo com as atribuições definidas na Resolução CNS nº 466 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação do projeto de pesquisa proposto.

Situação: Protocolo aprovado.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_930453.pdf	22/09/2017 06:58:00		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_justificativa_de_ausencia.docx	22/09/2017 06:56:06	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_CGVS.docx	18/08/2017 06:01:51	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_HSP.docx	18/08/2017 05:59:52	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_CGAE.docx	18/08/2017 05:58:36	IVANICE DUARTE FREIRE	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_detalhado_IF.pdf	02/08/2017 20:27:54	IVANICE DUARTE FREIRE	Aceito
Folha de Rosto	Folha_de_Rosto_3.pdf	02/08/2017 20:13:08	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_CGAE.pdf	02/08/2017 20:03:29	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_CGVS.pdf	02/08/2017 20:02:48	IVANICE DUARTE FREIRE	Aceito
Outros	Termo_de_ciencia_HSP.pdf	02/08/2017 20:01:55	IVANICE DUARTE FREIRE	Aceito

Endereço: SEPN 510 NORTE, BLOCO A 3º ANDAR, Edifício Ex-INAN - Unidade II - Ministério da Saúde
Bairro: Asa Norte **CEP:** 70.750-521
UF: DF **Município:** BRASILIA
Telefone: (61)3315-5878 **E-mail:** conep@saude.gov.br

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Situação do Parecer:
Aprovado

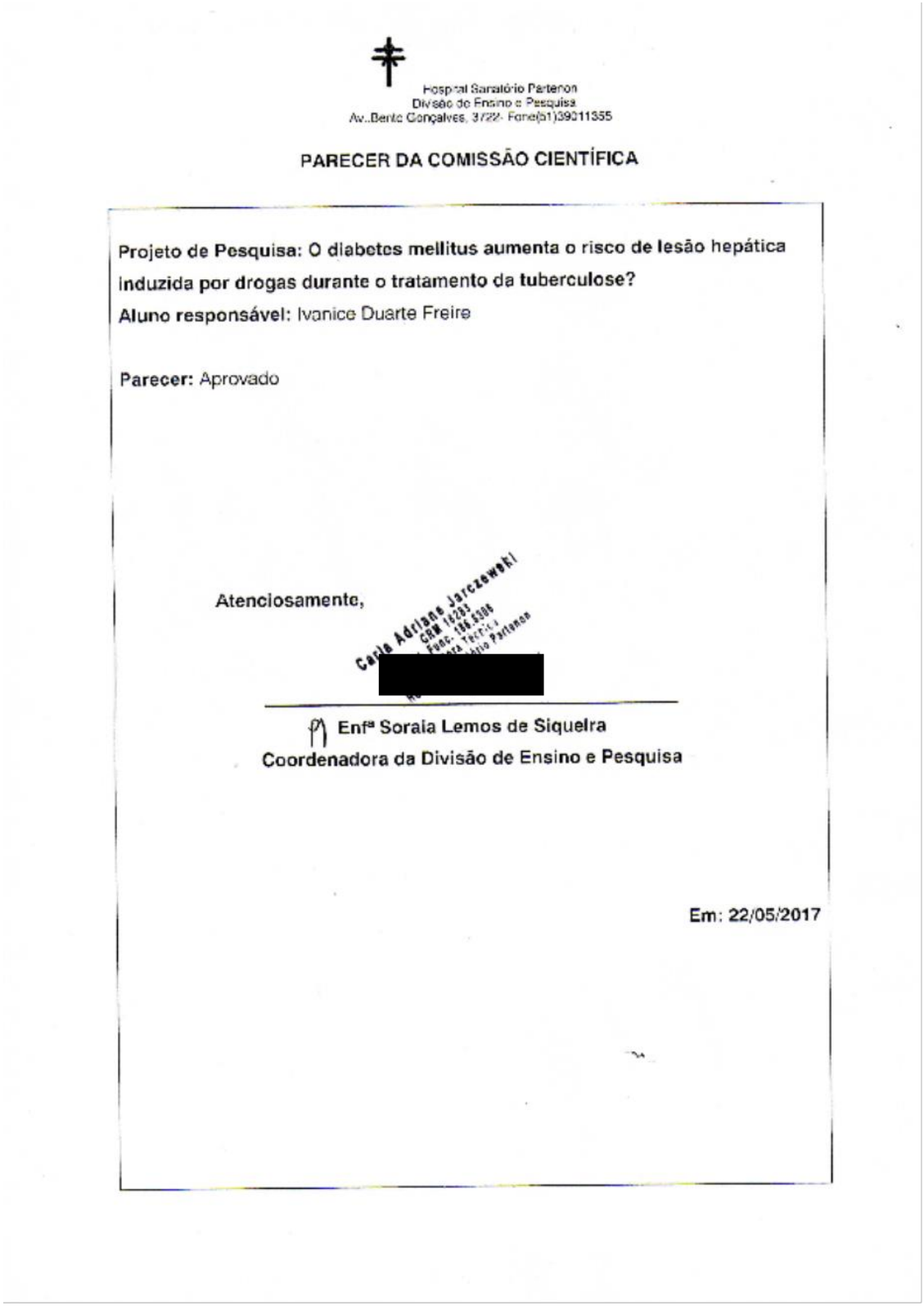
BRASILIA, 10 de Dezembro de 2017

Assinado por:
Jorge Alves de Almeida Venancio
(Coordenador)

Endereço: SEPN 510 NORTE, BLOCO A 3º ANDAR, Edifício Ex-INAN - Unidade II - Ministério da Saúde
Bairro: Asa Norte **CEP:** 70.750-521
UF: DF **Município:** BRASILIA
Telefone: (61)3315-5878 **E-mail:** conep@saude.gov.br

APPENDIX G

Ethics approval from the Hospital Sanatório Partenon Scientific Committee



Hospital Sanatório Partenon
Divisão de Ensino e Pesquisa
Av. Bento Gonçalves, 3722 - Fone(51)39011355

PARECER DA COMISSÃO CIENTÍFICA

Projeto de Pesquisa: O diabetes mellitus aumenta o risco de lesão hepática induzida por drogas durante o tratamento da tuberculose?
Aluno responsável: Ivanice Duarte Freire

Parecer: Aprovado

Atenciosamente,

Carla Adriana Jarczewski
CRM 16283
Resp. Téc. [redacted]
Hospital Partenon

Enfª Soraia Lemos de Siqueira
Coordenadora da Divisão de Ensino e Pesquisa

Em: 22/05/2017

APPENDIX H

Local Authorization Term from the General Coordination of Health Surveillance – Porto Alegre Municipal Department of Health

Prefeitura Municipal de Porto Alegre
Secretaria Municipal de Saúde
Comitê de Ética em Pesquisa

TERMO DE CIÊNCIA E AUTORIZAÇÃO DA COORDENAÇÃO ONDE SERÁ REALIZADA A PESQUISA

Eu ANDERSON ARAÚJO DE LIMA, matrícula 481972

Coordenador do/a Serviços
( ) Coordenadoria da Rede de Atenção Primária em Saúde e Especializados Ambulatoriais e Substitutivos (CGAPSES)
( ) Coordenadoria da Rede de Urgências e Emergências
(X) Coordenadoria Geral de Vigilância em Saúde (CGVS)
( ) Coordenadoria de Regulação de Serviços em Saúde (GRSS)
( ) Comissão Multiprofissional de Ensino-Serviço e Pesquisa (COMESP) do Hospital de Pronto Socorro
( ) Assessoria de Planejamento (ASSEPLA)
( ) Outra área/secretaria: __ .

conheço o Protocolo de Pesquisa intitulado " O diabetes mellitus aumenta o risco de lesão hepática induzida por drogas durante o tratamento da tuberculose?"

tendo como Pesquisador Responsável o Professor David A.J. Moore.

Declaro estar ciente do projeto e autorizo, após o parecer de aprovação do Comitê de Ética em Pesquisa da Secretaria Municipal de Saúde de Porto Alegre, a realização desta pesquisa.

Porto Alegre, 26/04/17.

[redacted]

Assinatura

Obs.: Este documento não autoriza o início da pesquisa, sendo apenas um requisito exigido pelo Comitê de Ética da SMSPA para análise do projeto de pesquisa. Sua finalidade é atestar que a Coordenação da área tem ciência e autoriza a realiza do projeto de pesquisa, quando forem cumpridas as instâncias de avaliação ética.

APPENDIX I

Local Authorization Term from the General Coordination of Specialized Care - Porto Alegre Municipal Department of Health

Prefeitura Municipal de Porto Alegre
Secretaria Municipal de Saúde
Comitê de Ética em Pesquisa

TERMO DE CIÊNCIA E AUTORIZAÇÃO DA COORDENAÇÃO ONDE SERÁ REALIZADA A PESQUISA

Eu Christiane Nunes de Freitas, matrícula 42183502

Coordenador do/a ( ) Coordenadoria da Rede de Atenção Primária em Saúde e Serviços Especializados Ambulatoriais e Substitutivos (CGAPSES)

( ) Coordenadoria da Rede de Urgências e Emergências

( ) Coordenadoria Geral de Vigilância em Saúde (CGVS)

( ) Coordenadoria de Regulação de Serviços em Saúde (GRSS)

( ) Comissão Multiprofissional de Ensino-Serviço e Pesquisa (COMESP) do Hospital de Pronto Socorro

( ) Assessoria de Planejamento (ASSEPLA)

(x) Outra área/secretaria: CGAE

conheço o Protocolo de Pesquisa intitulado " O diabetes mellitus aumenta o risco de lesão hepática induzida por drogas durante o tratamento da tuberculose?"

tendo como Pesquisador Responsável o Professor David A.J. Moore.

Declaro estar ciente do projeto e autorizo, após o parecer de aprovação do Comitê de Ética em Pesquisa da Secretaria Municipal de Saúde de Porto Alegre, a realização desta pesquisa.

Porto Alegre, 18 / 05 / 1[redacted]

Freitas

Assinatura e carimbo

Obs.: Este documento não autoriza o início da pesquisa, sendo apenas um requisito exigido pelo Comitê de Ética da SMSPA para análise do projeto de pesquisa. Sua finalidade é atestar que a Coordenação da área tem ciência e autoriza a realiza do projeto do pesquisa, quando forem cumpridas as instâncias de avaliação ética.

Comitê de Ética em Pesquisa da Secretaria Municipal de Saúde de Porto Alegre – CEP SMSPA
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TERMO DE CIÊNCIA E AUTORIZAÇÃO – CEP SMSPA

APPENDIX J

Table J1. Hepatotoxic drugs taken concomitantly by 402 (50.8%) patients

Drug name	Frequency	%
Omeprazole	118	29.4
Efavirenz	88	21.9
Sulfamethoxazole with Trimethoprim	80	19.9
Amoxicillin with or without clavulanate	49	12.2
Metformin	33	8.2
Azithromycin	28	7.0
Zidovudine	28	7.0
Enalapril	24	6.0
Ibuprofen	24	6.0
Valproic acid	24	6.0
Fluconazole	22	5.5
Simvastatin	18	4.5
Captopril	18	4.5
Amitriptyline	17	4.2
Chlorpromazine	13	3.2
Phenobarbital	12	3.0
Carbamazepine	10	2.5
Contraceptives	10	2.5
Clindamycin	9	2.2
Haloperidol	9	2.2
Glibenclamide	8	2.0
Allopurinol	7	1.7
Ciprofloxacin	7	1.7
Imipramine	7	1.7
Phenytoin	7	1.7
Methotrexate	5	1.2
Sertraline	5	1.2
Azathioprine	4	1.0
Ranitidine	4	1.0
Sulfadiazine	4	1.0
Ceftriaxone	3	0.7
Clopidogrel	3	0.7
Levofloxacin	3	0.7
Nitrofurantoin	3	0.7
Paroxetine	3	0.7
Atorvastatin	2	0.5
Diclofenac	2	0.5
Hydralazine	2	0.5
Infliximab	2	0.5
Itraconazole	2	0.5

Naproxen	2	0.5
Rosuvastatin	2	0.5
Sulfasalazine	2	0.5
Ceftazidime	1	0.2
Clozapine	1	0.2
Duloxetine	1	0.2
Ganciclovir	1	0.2
Interferon	1	0.2
Itolizumab	1	0.2
Ketoconazole	1	0.2
Lamotrigine	1	0.2
Leflunomide	1	0.2
Methimazole	1	0.2
Olanzapine	1	0.2
Progestogens	1	0.2
Estrogens	1	0.2
Venlafaxine	1	0.2

APPENDIX K

Table K1. Relationship between power and sample size for a range of effect sizes

Case:control ratio	Power	Effect size	DM prevalence among controls	DM prevalence among cases	Nº cases	Nº controls
1:1	80	1.96	6.8	12.5	420	420
1:1	90	1.96	6.8	12.5	563	563
1:1	80	1.97	6.8	12.6	413	413
1:1	90	1.97	6.8	12.6	553	553
1:1	80	1.98	6.8	12.6	406	406
1:1	90	1.98	6.8	12.6	544	544
1:2	80	1.96	6.8	12.5	287	574
1:2	90	1.96	6.8	12.5	384	768
1:2	80	1.97	6.8	12.6	282	564
1:2	90	1.97	6.8	12.6	378	755
1:2	80	1.98	6.8	12.6	277	554
1:2	90	1.98	6.8	12.6	371	742
1:3	80	1.96	6.8	12.5	243	727
1:3	90	1.96	6.8	12.5	325	973
1:3	80	1.97	6.8	12.6	238	714
1:3	90	1.97	6.8	12.6	319	956
1:3	80	1.98	6.8	12.6	234	702
1:3	90	1.98	6.8	12.6	313	939
1:4	80	1.96	6.8	12.5	220	880
1:4	90	1.96	6.8	12.5	295	1,178
1:4	80	1.97	6.8	12.6	216	864
1:4	90	1.97	6.8	12.6	290	1,157
1:4	80	1.98	6.8	12.6	213	849
1:4	90	1.98	6.8	12.6	284	1,136
1:1	80	1.96	10	17.9	304	304
1:1	90	1.96	10	17.9	406	406
1:1	80	1.97	10	18.0	299	299
1:1	90	1.97	10	18.8	400	400
1:1	80	1.98	10	18.0	294	294
1:1	90	1.98	10	18.0	393	393
1:2	80	1.96	10	17.9	210	419
1:2	90	1.96	10	17.9	280	560
1:2	80	1.97	10	18.0	206	411
1:2	90	1.97	10	18.0	276	551
1:2	80	1.98	10	18.0	202	404
1:2	90	1.98	10	18.0	271	541
1:3	80	1.96	10	17.9	178	533
1:3	90	1.96	10	17.9	238	713
1:3	80	1.97	10	18.0	175	524

1:3	90	1.97	10	18.0	234	701
1:3	80	1.98	10	18.0	172	515
1:3	90	1.98	10	18.0	230	689
1:4	80	1.96	10	17.9	162	647
1:4	90	1.96	10	17.9	217	866
1:4	80	1.97	10	18.0	159	636
1:4	90	1.97	10	18.0	213	851
1:4	80	1.98	10	18.0	156	624
1:4	90	1.98	10	18.0	209	836

DM: diabetes mellitus

Integrating Statement for the DrPH Course 2011

The Doctor of Public Health (DrPH) programme of the London School of Hygiene and Tropical Medicine aims to provide doctoral level training for future leaders in public health practice in high level skills through a combination of two taught courses - **"**Evidence Based Public Health Policy and Practice" (EBPHP) and "Leadership, Management and Professional Development" (LMPD); an Organizational and Policy Analysis (OPA) project; and a research thesis. The purpose of these three components is to provide the necessary knowledge and experience, as well as hone technical skills for an effective public health leadership.

The "Leadership, Management and Professional Development" module, as it was called back in 2011, explores management and organizational theories and how this could be applied in the student's own professional practice as a health manager. The course aimed at the students considering the application of these theories in public health organizations and their own management practice in a critical way, while developing a deeper understanding of themselves as managers and leaders in public health. There were also discussions on power and politics within and between those organizations and its reflections on decision-making. Not being a health manager myself, some aspects of it were quite challenging to me, such as the professional jargon and my lack of experience in the field, but eventually I learned a whole new set of practical skills and knowledge, particularly in terms of professional relationships, the way people work in organizations and behave as individuals and as teams. Skilful, open minded and inspiring leadership and management are essential for the delivery of good quality health services, whether they belong to a governmental public health service, an NGO or the private sector.

There was a three-day retreat focusing on personal professional development in which we were able to enhance awareness about ourselves as managers and leaders. It was a more personal element of the module, providing the opportunity for the students to interact with each other. The LMPD module focus on a critical approach to management theories and concepts while stimulating the student to measure them against their own experience and perceptions of the public health environment.

There was one assignment for this module, a strategic analysis of a public health organization while trying to undertake a specific challenge. For that assignment, I analysed the context and

assessed the ability of our busiest public trauma hospital in Porto Alegre to prepare to provide emergency care for the participants of the 2014 World Cup.

The other taught module was then called “Evidence Based Public Health Policy and Practice”. Leadership in public health requires skills concerned with, on the one side, health management and leadership and on the other, the devising and shaping of public health policies and their implementation. It is necessary to locate, assess, synthesize and present the evidence, in order to use evidence-based information to influence public health policy and thus improve public health outcomes in a diverse range of settings. The dynamics of the relationship between the academic world, where evidence is generated, and that of policy and practice, is crucial. There is a wide range of stakeholders in the health care environment. Many actors such as scientists and academics, interest groups, policy makers and politicians are all involved in the policy process, participating in the way evidence is used in government health decision making.

There were two assignments for this module: an influencing and knowledge transfer strategy, to be submitted to the Brazilian Thoracic Association TB Committee, aiming to place the issue of homeless TB in the Ministry of Health agenda; and a systematic review on the influence of marketing of alcohol on alcohol use.

The OPA Project

Successful public health management and leadership requires a thorough understanding of the organization and management of institutions. It is essential to understand the ways it can promote and support or hinder the development of effective policy and practice. The OPA project involves the observation of the daily work of a public health organization (which can be a public, non-profit or private institution) engaged in public health practice, focusing on how it works and endeavours to achieve its goals in the relevant policy environment. The student is also expected to reveal not only positive but negative aspects about the chosen organization and present a constructive critique of the way the organization functions and relates with other policy actors. They should also provide advice to the organization in the form of a management consultant’s report. It should be evidence based and the student should use knowledge acquired from the taught courses: management theories and analytical frameworks (organizational behavioural theories, for instance) and/or policy science (analysing a public health process being undertaken by the organization).

The purpose of the OPA project is to understand how public health organizations function to influence public health policy and/or deliver public health goals, drawing knowledge from the module sessions. As it is a qualitative research, the student needs to observe, interview staff and analyse qualitative data.

While considering my OPA, I came across a poem by a favourite poet of mine, Robert Frost, called "The road not taken", which is about what may lie ahead of us when we choose the least trodden path. It occurred to me that the implementation process of any public health policy is never complete, never ceases to improve, and change is a vital aspect of problem solving, because that's the way with health and social environments. As a TB physician working for a TB control programme all my professional life, I had hoped to find a TB organization for my OPA. My supervisor introduced me to the "Find and Treat Project", which is a project for diagnosing and managing TB cases in the London homeless population. I stayed with them for 4 months and then was able to collect all the necessary data for what was to be my first qualitative research. In order to do that, I took a MSc module, "Qualitative Methodologies", where I acquired skills in collecting qualitative data, transcribing interview recordings, coding transcripts and analysing the findings. Most of DrPH students choose the management and leadership approach for their OPA research but, being a clinician, I chose to approach my analysis through a policy process angle. It was a quite new and challenging experience for me, which turned out to be very fruitful both professionally and personally.

Introducing Find &Treat: its history, mission and structure

There is every need for TB control programmes to strengthen their case finding strategies by raising awareness, promoting access to TB services, screening activities and supporting compliance to treatment. In 2005, the Department of Health provided funding for a mobile radiography unit (MXU) to screen for active TB among vulnerable populations across London, due to their extremely low rates of attendance to medical appointments. In a study conducted by Story *et al.* (1), the estimated prevalence of the disease was 788 per 100,000 in homeless individuals; 354 per 100,000 in drug addicts; 208 per 100,000 in prisoners and 147.5 per 100, 000 in recent immigrants. The MXU would visit hostels, drug treatment services and day centres. After a 2-year pilot phase, an evaluation was performed which drew attention to the fact that most of the cases that had been detected and referred to a TB clinic for further diagnostic investigation and treatment had failed to

do it. Consequently, since 2007, the MXU has been greatly improved by the addition of a new set of professionals to address the problems of non-attendance and non-compliance to treatment. They are currently known as “Find and Treat”, an outreach service that aims not only at screening active TB among the homeless, substance abusers and prisoners, but also at supporting them throughout diagnostic procedures and treatment on a patient-centred case management basis. Both the screening unit and the case management support component are cost effective.

My study project aimed to explore policy implementation as a learning and evolutionary process. The first objective was to identify the differences between the project initially put into practice and the one that was currently known as “Find and Treat” when the study was conducted, back in 2012. The second objective was to identify and analyse the lessons learned throughout the years which had influenced its implementation process and modified the intended policy and study them in the light of policy implementation theories. The methods used for my OPA study were mixed qualitative methods and involved participant observation, fieldwork notes, and semi-structured individual interviews with members of staff. The interviews were recorded, transcribed and later coded for analysis according to the policy implementation theoretical approaches concerned with learning and evolution. Although management and leadership theories were not the approach chosen for the study, the findings were also discussed in the light of the organizational context.

In closing, the OPA project concluded that “Find and Treat” is flexible and innovative, with a progressive model of collaborative working which is the best way to achieve its outcomes. Implementation is a dynamic and evolutionary process; learning is better experienced as a continuous process and experimentation is a risk worth taking. Like the poem.

The DrPH Thesis

Public health leaders are involved in commissioning research and they should develop skills in applying research that is relevant to the needs of policy and practice, while providing reliable and robust findings. Both modules contribute to those skills in conducting research with rigorous scientific methods. First, by appraising adequately the quality of existing research so that students could choose their study designs for their future projects and better develop their research questions; second, by learning literature search skills and conducting systematic reviews.

It is not required that the subject for the DrPH thesis be on the public health policy process. My

first research project was a retrospective cohort study on the incident risk of progression to TB in immigrants to the United Kingdom with fibrotic lesions on their chest X-rays. Due to unsurmountable difficulties concerning access to the image database from Public Health England, the project had to be cancelled. My present research has questions that are concerned with practical aspects relevant to any TB control programme in practice. It is foremost an epidemiological (but also clinical) study on risk factors for drug induced liver injury due to TB drugs among patients with diabetes and, as such, relevant to TB practitioners and policy makers in the field.

References

1. Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax.2007;62(8):667-71.

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