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Review Article

Hepatic Adverse Effects of Anti-Mycobacterium Tuberculosis Drugs and Their Associations with Various Genetic Variants

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Abstract

Tuberculosis is a significant healthcare burden, especially in the developing world. Current first-line therapies for tuberculosis treatment (isoniazid, pyrazinamide, rifampicin, and ethambutol) have significant efficacy but they all have the potential to cause hepatotoxicity. Effects produced by these drugs may be asymptomatic with increased levels of aminotransferases in some patients or the development of severe hepatotoxicity in others. On the other hand, it can also lead to hepatic failure in some patients. In this review, we evaluated the studies on genetic variants showing associations with drug-induced hepatic injury in tuberculosis patients. Several studies on important genes such as *NAT2, AADAC, CYP2E1, HLA, CYP7A1, ALDH1A1, NFkB, PXR, HMOX1, SLCO1B1, UGT1A1, NRF2 and MAFF* were reviewed and discussed for utilising them as predictors of hepatic injury in tuberculosis patients. Recommendations are made on the potential of some of these genetic variants as a screening tool for determining patients most likely to experience hepatic adverse effects after receiving standard first-line anti-mycobacterial tuberculosis treatment.

Keywords: Mycobacterium tuberculosis, hepatic injury, genetic variants, pharmacogenomics

Introduction

Tuberculosis or TB is one of the leading causes of death across the globe and a growing public health burden. The disease is caused by Mycobacterium tuberculosis. Lungs are the primary organ affected by TB but the infection can spread to the whole body causing extrapulmonary TB (Bloom et al. 2017). New treatment approaches have been introduced into the market to fight against the disease however the side effects, toxicities, and genetic variation among the patients have limited its use. Many xenobiotics enter the lungs for biotransformation but they have the potential to cause drug-induced liver injury (Narasimhan et al. , Ramappa and Aithal 2013)

Current first-line therapies for TB treatment (isoniazid (INH), pyrazinamide, rifampicin, and ethambutol) are being used but they all have the potential to cause hepatotoxicity. Various enzymes have been utilized by these drugs for excretion. Among the anti-TB drugs, hepatotoxicity induced by isoniazid is the most common. The major drug-metabolizing enzyme of isoniazid is N-acetyltransferase (NAT), other enzymes include CYP2E1, glutathione S-transferase (GST), and manganese superoxide dismutase (MnSOD, SOD2) (**Figure 1**)(Huang 2014). Variation in the genes encoding these enzymes, for example, minor alleles R64W and D122N decrease *NAT2* activity with a subsequent increase in the risk for Antituberculosis drug-induced liver injury (ATDILI) due to slow acetylation (Li et al. 2021). Isoniazid is metabolized to many hepatotoxic

intermediates, acetyl isoniazid, and acetyl hydrazine via *N-acetyltransferase (NAT)* and amidase respectively. In this review we discuss the associations of various genetic variants with ATDILI after treatment with first-line TB drugs.

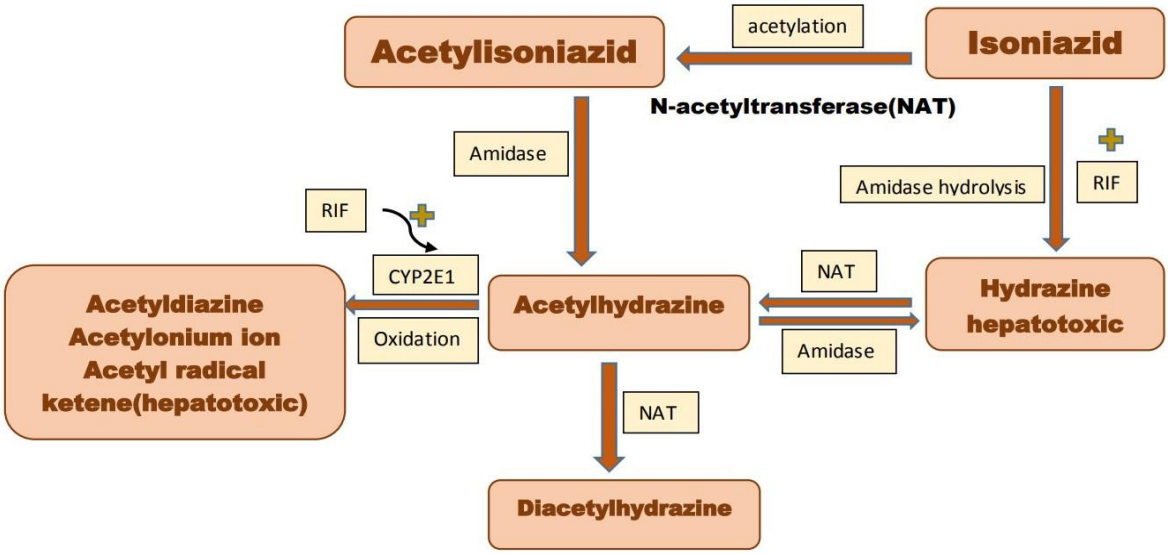

Figure 1 Pathway of major drug-metabolizing enzyme of isoniazid.

Epidemiology

Mostly, the unguarded populations of necessitous countries are affected by TB (Sulis et al. 2014). Geographically, by 2020 the percentage of TB cases observed is displayed in the following pie chart (**Figure 2**). The worldwide report of occurrence of TB cases shows that 30 high-risk countries are responsible for altogether 86% of TB cases (**Figure 3**). Eight of these high-risk countries account for two-thirds of the global total, their names are mentioned in the table below (Table1).

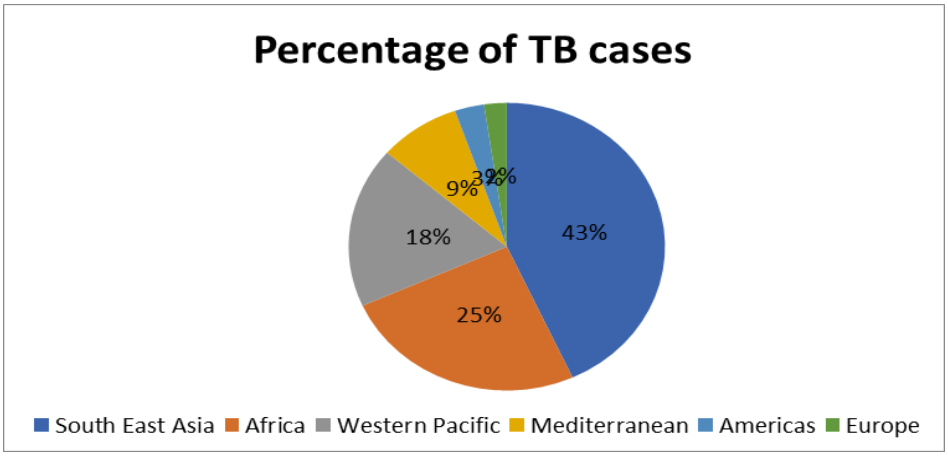

Figure 2 The percentage of TB cases observed in 2020

Table 1 TB incidence in various Asian countries in 2020.

Countries	Percentage
India	26
China	8.5
Indonesia	8.4
Philippines	6
Pakistan	5.8
Nigeria	4.6
Bangladesh	3.6
South Africa	3.3

TB can affect anyone but in the year 2020, 56% of all TB cases were accounted for by male adults. Meanwhile, 33% of the TB cases were in adult women and children made up 11% of all TB cases (Martinson, Hoffmann, and Chaisson 2011). A study suggested that the incidence rate is higher in men because men lack the resources from national TB prevalence surveys steadily shows the high prevalence of TB infection in me required for proper TB care (Horton et al. 2016). Data obtained n suggesting that TB affects men more than women. Out of all TB cases, the percentage of patients HIV-infected are 8%, and the proportion of people with TB co-infection along with HIV is the highest in the WHO (Organization 2020). African Region, exceeding 50% in the southern regions of Africa. HIV is the most dominant risk factor for TB increasing the risk of TB by 20-fold (Martinson, Hoffmann, and Chaisson 2011).

An unpleasant trend of TB deaths and incidence was observed in 2021-2022. **(Figure 4)** The trend predicted that the mortality rate of TB is anticipated to be much higher than it was in 2020 in all 16 countries modelled by WHO, and the incidence of TB in 2022 is expected to be above 2020 levels in most of these countries.

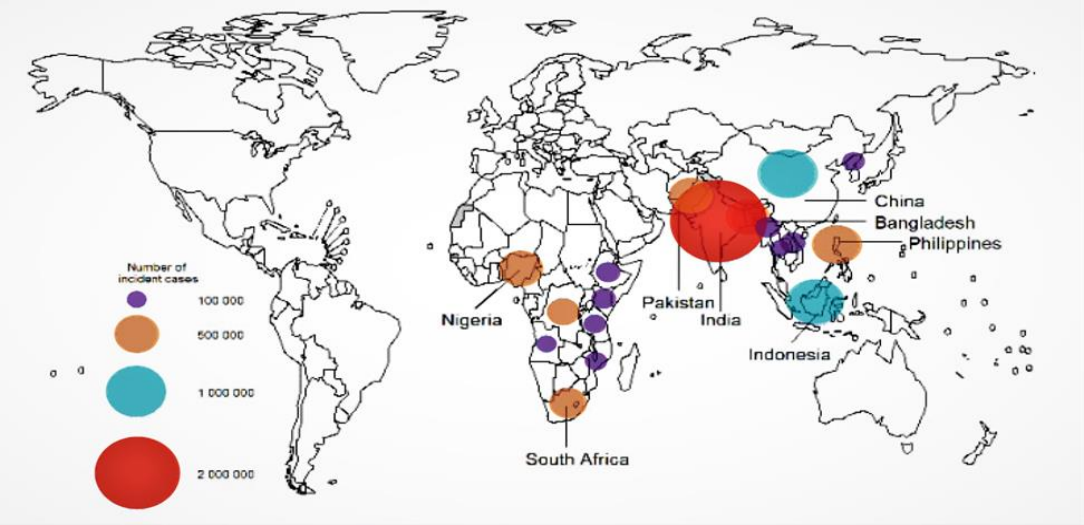

Figure 3 Worldwide report of occurrence of TB cases.

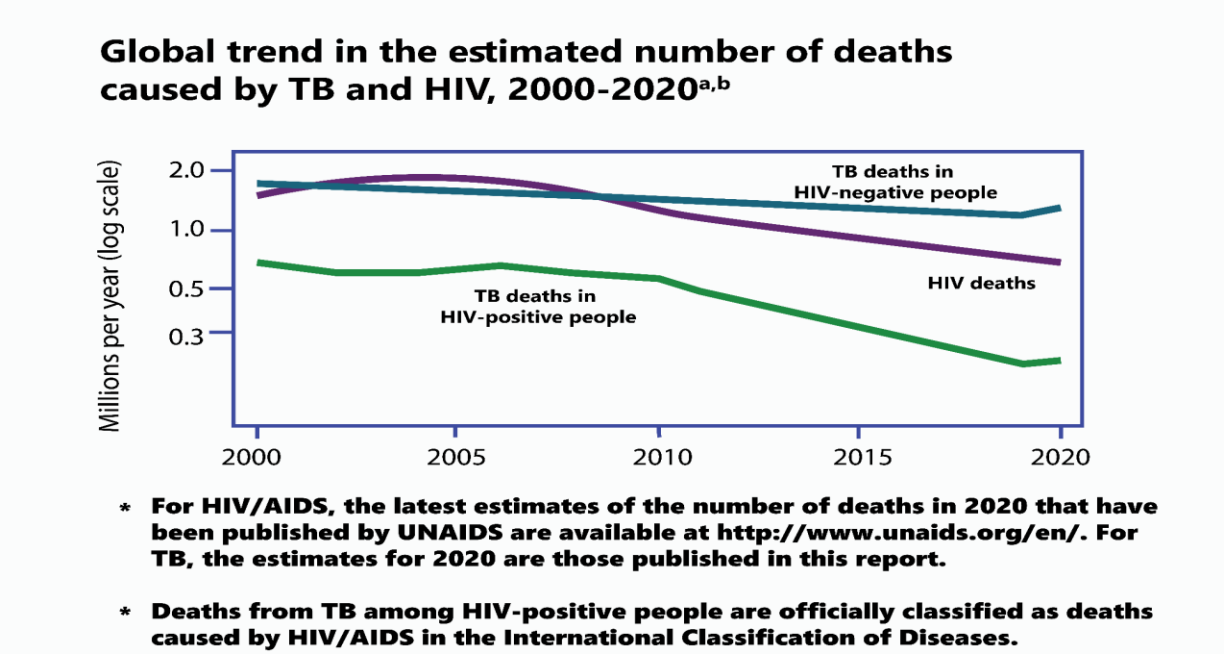

Figure 4 Trend of TB deaths and incidence observed in 2021-2022.

A sharp fall in the number of people newly diagnosed and reported with TB globally was observed from 7.1 million in 2019 to 5.8 million in 2020. It is one of the reasons for the increase in the number of deaths by TB. (Figure 5). Countries accounting for 93% of the decrease in diagnosis and reporting are 16 in number, among which India, Indonesia, and the Philippines were the ones that were the most affected (Organization 1997). Lack of resources and access to diagnosis and treatment of TB due to COVID are primary causes of an increased death count (Pai, Kasaeva, and Swaminathan 2022). The estimate of TB deaths in 2020 is 1.3 million among HIV-negative people (compared to 1.2 million in 2019) and another 214,000 among HIV-positive people (in comparison to 209,000 in 2019), totaling back to data observed in 2017. Whereas in former years, the TB incidence achieved has mostly lowered.

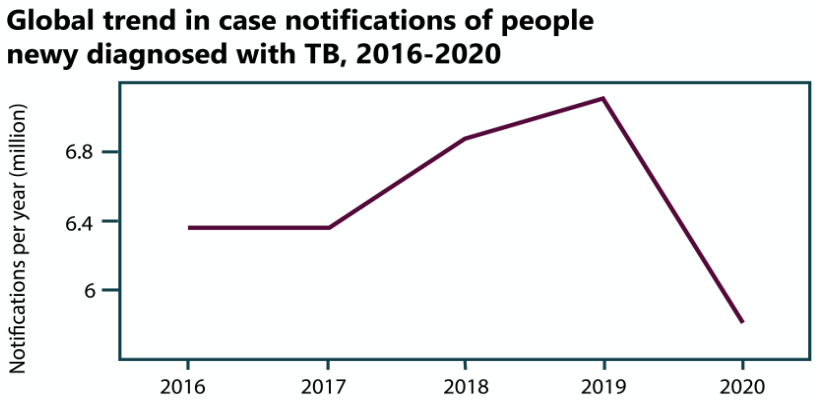

Figure 5 Global trend for newly diagnosed TB cases in 2016-2020

According to the WHO global all-cause mortality estimate in 2019 TB was the 13th major cause of death worldwide and the main cause of death from a single infectious agent. In 2020, TB is predicted to be the second major cause of death from a single infectious agent, after COVID19 (Organization 1997).

Pathogenesis of TB

Transmission

Transmission occurs by inhaling the infectious droplet nuclei containing viable bacilli. The formation of droplet nuclei occurs when an active TB patient coughs, sneezes, or sings, the droplet nuclei can remain in the atmosphere for a considerable amount of time. Chances of the transmission are determined by the bacillary load of the source (smear-positive sputum), proximity, and time duration of exposure.

The person might not get infected with TB after inhalation of M. tuberculosis, or the individual may contain the infection but show no symptoms (latent TB infection). On the other hand, the individual might acquire a progressive TB infection (Caws et al. 2015) Statistically, after transmission, 90 % of individuals do not become infected by TB, and one-third of the world's population has latent TB infection.

Genetic polymorphisms along with other risk factors including poor socioeconomic status, smoking, malnutrition, alcohol consumption, young age, and comorbidities such as diabetes, immunosuppressive conditions, HIV, and pathogen factors make the host more prone to developing TB infection (Narasimhan et al. 2013).

The Innate Immune Response

Alveolar macrophages and dendritic cells including other immune cells provide the innate immune defense by recognizing several components of mycobacterial cell walls and pathogen-associated molecular patterns (PAMPs) with membrane-associated pattern recognition receptors (PRRs) (involving TLR2, TLR4). Toll-like receptors play their role by recognizing PAMPs such as mycobacterial nucleic acids, heat shock proteins, and phosphatidylinositol. After the recognition, the interaction of these PAMPs takes place leading to the activation of signaling pathways producing pro-inflammatory cytokines including nitric oxide, TNF, Interleukin-1B, and Interleukin-12

The pathogen is then phagocytosed with PRRs by macrophages. The pathogen is then destroyed by phagosome-lysosome fusion and acidification by reactive oxygen intermediates, there is also a possibility that it may not be destroyed. This process can cause uncontrolled cell death, programmed cell death, and survival of the infected macrophage. There is a chance of infection of more macrophages as mycobacteria are released by uncontrolled cell death. Bacteria are destroyed with macrophages if programmed cell death occurs and if the infected macrophage survives, the mycobacteria can multiply even before the activation of adaptive immune response by T-cells.

The Adaptive Immune Response

Generally, 3 weeks after the exposure adaptive immune response is developed. Presentation to naïve T cells of the live mycobacteria by dendritic cells occurs after they have reached the regional lymph nodes. Next, activation of CD4+ T cells occurs as the presentation of antigen in the lymph nodes takes place and they slow down the progression of mycobacteria by migrating into the lungs. T cells play a significant role in building immunity against TB as they produce IFN-γ which guards against TB infection, individuals with missing *IFN-γ* genes are more prone to getting severe TB infection as IFN-γ activates the macrophages. TNF-α is involved in granuloma formation and the induction of macrophages thus individuals

using agents that suppress TNF are more susceptible to infection.

A characteristic feature of TB infection after the adaptive immune response is the formation of granuloma also known as tuberculoma. Based on the appearance of granuloma it can be solid or non-necrotic, caseous or necrotic, or end-stage cavitary. Calcification of granuloma occurs after the deposition of fibrotic components which encloses the bacilli inside and safeguards it against the immune response of the host (Delogu, Sali, and Fadda 2013). According to the extent of liquefaction in a granuloma, the caseum is classified as soft or hard. Typically, granuloma stops the bacilli from spreading but it also releases the live bacteria into the lung causing progressive TB infection (Caws et al. 2015)

Treatment Options for TB

The goal of treatment for TB is to stop the progression of the disease and to reduce transmittance. The award-winning discovery of streptomycin has opened the gate for the cure of several infectious diseases including TB (Dartois and Rubin 2022) but resistance developed very quickly due to chromosomal mutation that is occurring at a speed of 10^6-10^8. Therefore prescribing a multidrug regimen simultaneously reduces the possibility of developing resistance by 10^18-10^20 because the chromosomal loci causing resistance are not linked (Shehzad et al. 2013).

The effectiveness and efficacy of currently used TB drugs vary among different ethnic groups. Failure of drug therapy is due to non-adherence, irrational use, drug tolerance, and genetic variation and these factors lead to problems such as multidrug-resistant TB (MDR-TB) and death of the patients. (Rabahi et al. 2017)

MDR-TB also occur in patients co-infected with HIV infection and incidences are increasing not only in developing countries but also in developed countries throughout the world (Tomioka and Namba 2006).

Therefore pyrazinamide and levofloxacin are being used both in adults and children for prophylaxis in household contacts of patients with MDR-TB (Dartois and Rubin 2022). The global upturn and speedy surfacing of MDR-TB emphasize the development of new first-line anti-TB therapy (ATT) for effectively controlling the TB resurgence. But the new emerging challenges complicate the discovery process as many compounds are either derivatives of previously discovered compounds or show the same cellular activity as those currently in use (Shehzad et al. 2013).

There are various programs run by WHO such as TB DOTS (directly observed treatment short course) to achieve compliance and optimize the effectiveness of therapy (2006). To achieve optimal response to therapy drug must diffuse into necrotized granuloma, large cavities containing liquified content that contains the infectious agent Mycobacterium tuberculosis (Dooley et al. 2019). ATT consisting of ethambutol, pyrazinamide, isoniazid, rifampin, rifabutin and streptomycin prescribes for 6 months with 2 months of intensive therapy with isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE) followed by INH4 months of continuation phase with isoniazid and rifampicin and this regimen is effective for all age groups. Intensive phase therapy is effective even when bacteria are resistant to INH (Bass et al. 1994).

TB management in Special Populations

All first-line ATT drugs can safely be used in pregnancy except streptomycin which has the potential to cause fetal ototoxicity (2006).

INH causes peripheral neuropathy by inhibiting the enzyme pyridoxine phosphokinase, an enzyme essential for the activation of pyridoxine to active pyridoxal 5' phosphate. Therefore, drug

INH is supplemented with 10mg/kg pyridoxine (vitamin B6).

Diabetic patients need to strictly control their blood sugar levels and dosage adjustments are required for oral hypoglycemic agents due to the potential interaction of ATT, especially with rifampicin. Dosage adjustments for streptomycin, INH, and ethambutol are also required in renal failure based on creatinine clearance. For those patients who are on hemodialysis, ethambutol should be administered 8h before the procedure. Many immunosuppressants are prescribed for renal transplant to decrease the chances of graft rejection therefore rifampicin containing regimen should be avoided as it increases the clearance of cyclosporin. Liver enzymes should be monitored carefully for patients with preexisting liver disease.

Multidrug-Resistant TB

Resistance to any one of the first-line agents HRZE are called mono-resistant TB and resistance to more than one anti-TB drug but not from (HR) isoniazid and rifampicin is named poly-resistant TB. Contrary resistance to HR has been named MDR-TB which is a growing health concern for TB control strategies.

TB diagnosis, prevention and treatment are becoming more complex due to emerging resistance to first-line agents. Many advanced molecular tests and regimens have been published by WHO in 2019 for MDR-TB management but still further assessments for novel agents and a shorter course of treatment are needed (Jang and Chung 2020).

The current regimen for MDR-TB is costly, less efficacious and causes more liver injuries compared to first-line agents and therapy continues for 2 years with a success rate of 54%. (Organization 2020). In 2019 WHO updated the guidelines based on clinical trials and individualized patient data meta-analysis (IPD-MA) (Bastos, Lan, and Menzies 2017) and included new drug classification and divided the drugs into three groups (A, B, C) based on their efficacy and toxicity profile and improved the monitoring strategies (Table2).

Table 2 New drug classification based on their efficacy and toxicity profile.

Group	Medicines
A	Levofloxacin or moxifloxacin Bedaquiline Linezolid
B	Clofazimine Cycloserine or terizidone
C	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin or meropenem Amikacin or streptomycin Ethionamide or prothionamide Para-aminosalicylic acid

Mechanism of Drug Resistance

Two types of resistance mechanisms have been observed, namely primary resistance and secondary resistance. They have been classified according to their pattern for causing resistance. Primary resistance occurs when a person is infected with a resistance strain from an active MDR-TB person and secondary resistance occurs due to patient's specific factors like poor patient compliance, non-adherence and de-novo mutation during treatment. Among the two types, the transmission of resistance strain is the most common cause of resistance (Jang and Chung 2020). Resistance occurs due to the generation of several efflux pumps onto the bacterial surface which pushes the drug out leaving a minimum concentration enough for bacterial survival. Furthermore numerous receptor protein and enzymes changes due to mutation leading to resistant strains (Singh et al. 2020).

Challenges in the Development of Drugs for the Treatment of TB

WHO has divided the TB drugs into two groups group 1 and group 2 consisting of the first-line and second-line anti-TB drugs respectively. First-line agents are the core treatment for patients who are newly diagnosed and have never been exposed to anti - TB drugs. From the first-line agents, isoniazid, rifampicin, and pyrazinamide (HRZ) are bactericidal and Ethambutol is bacteriostatic (Singh et al. 2020).

A recent survey in 2017 has shown an upsurge of new 558,000 cases of TB which are resistant to the most effective first-line anti-TB drug rifampicin, of the 82% of cases are of MDR-TB, therefore it is necessary to continually update knowledge on the evolution of resistance at molecular basis and develop new promising compounds to combat with the emerging resistance patterns. Moreover, non-compliance, non-adherence, poor socioeconomic status, lifestyle such as smoking, alcohol intake and various other co-morbidities like HIV/AIDS, and infections could also lead to Multidrug-Resistant TB therefore prompt diagnosis, lifestyle changes, social awareness and patient counseling to improve adherence should be ensured to control the development of resistance.

In addition, various mutations cause changes in the structure of enzymes and target protein, drug deterioration and modification and drug tolerance due to phenotypic changes are the cause of resistance development (Singh et al. 2020). Recently immune base targeting delivery and host-directed therapies (HDT) is under investigation for shortening the duration of therapy, being used as an adjunct therapy and reducing the hepatotoxicity and liver injuries caused by aggressive TB treatment. (Tiberi et al. 2018) Extensive drug resistance (XDR) TB is becoming another global challenge Because the strain is not only resistant to HR but also showing resistance to quinolones (such as levofloxacin and moxifloxacin) and at least one of the second-line injectables such as (amikacin, capreomycin or kanamycin). Drug-drug interaction reduces the possibility of Co-administration of TB drugs with other drugs used in various cases of chronic disease management. Immune response in LTBI is constantly reacting to TB antigen but the disease remains asymptomatic.

Hepatic Adverse Effects of TB Drugs

One of the prime adverse effects of TB drugs includes Drug-induced liver injury (Narasimhan et al.). Effects of DILI include the patient being asymptomatic with increased levels of aminotransferases or severe hepatotoxicity in a patient. On the other hand, it can also lead to hepatic failure in some patients. Several approaches include consistent monitoring of the liver function, the detection of high-risk genes for drug-metabolizing enzymes, administering hepato-protective agents and the adjustment of

an anti-TB regimen for the prevention of Anti-TB drug-induced liver injury (ATLI) (Chang et al. 2019).

Counselling patients about the possibility of hepatotoxicity while getting treatment and about getting immediate medical advice if they experience any symptoms associated with drug-induced hepatitis, such as feeling unwell, jaundice or GIT upset, is very important (Thompson et al. 1995).

For preventing hepatic adverse effects, an uncomplicated approach exists that is regular monitoring of liver function, although its necessity is still in need of verification. The National Institute for Health and Clinical Excellence (Sebastián et al.) of the UK, the American Thoracic Society (ATS), and the World Health Organization (WHO) have recommended that patients who have liver abnormalities, former liver disease, active cancer, hepatitis B virus, hepatitis C virus, earlier DILI or are persistently consuming alcohol are more prone to developing hepatotoxicity thus the regular monitoring of liver function is only essential for them. Conversely, liver function monitoring in all patients was recommended by the Taiwanese CDC guidelines regardless of the baseline liver function in patients receiving anti-TB drugs.

A retrospective study suggests that the patients receiving regular monitoring of liver function enabled the early detection of ATLI and resulted in decreased liver injury in patients. This study backs up the Taiwanese CDC policy (Chang et al. 2019).

The frequency of liver function tests for the first eight weeks should be after every two weeks and then one month later. LFTs should be performed fortnightly initially if rifampicin and isoniazid are used. Liver injury can occur even after a year and by the time symptoms start to appear the chances of death are high so it's not a good idea to stop doing LFTs at any time while getting treatment (Thompson et al. 1995).

11% of the total patients who are treated with a combination of isoniazid, rifampicin and pyrazinamide discontinue the drug regimen due to hepatotoxicity. A sudden elevation in liver enzymes was found in 20 % of patients receiving isoniazid alone or in combination with other drugs. We are still unable to fully recognize the pathogenesis of hepatotoxicity.

According to investigations, several factors are associated with the processes causing DILI and susceptibility to hepatotoxicity which include factors related to drugs, and gene-related factors of host and environmental factors (Ramappa and Aithal 2013).

Factors Related to the Drug

Identification of hepatotoxicity due to individual drugs used for treating TB is challenging but studies have shown that isoniazid, rifampicin and pyrazinamide are responsible for hepatotoxicity whereas no cases of hepatotoxicity were observed with the use of the drug ethambutol and streptomycin. The most common drug causing toxicity is INH as it is associated with a greater risk of elevation of enzymes (Tweed et al. 2018). Though, A study showed no relation between the basal serum drug concentration and the risk of anti-TB DIH in patients being treated with first-line anti-TB drugs (Jeong et al. 2015).

Biotransformation and Detoxification of Drug

When reactive metabolites aren't detoxified, they react with the nucleophilic groups present on cellular proteins thus impairing them, even if it doesn't happen the drug-metabolite adduct formation damages the functions of cells causing injury to the target organ. High levels of formation of reactive metabolites in a person can be due to the excessive activity of phase I cytochrome P450 enzymes participating in the biotransformation of the drug. Increased reactive metabolites can also be present in

individuals having lower activity of phase II enzymes that detoxify reactive metabolites.

Risk Factors Related to the Host

Women are reported to be at a four-fold risk of DILI from anti-TB therapy. A higher incidence of anti-TB drug-induced hepatotoxicity is attributed to malnutrition. Moreover, older age individuals and Asian ethnicity were observed with elevated liver enzymes with anti-TB drugs (Tweed et al. 2018). Also, alcohol's prolongation of anti-TB drug-induced hepatotoxicity has been shown by a vast number of studies (Ramappa and Aithal 2013). Comorbidities including HBV and diabetes make the patients more prone to Anti-TB DILI (Zhong et al. 2021).

Genetic Susceptibility

Polymorphism in genes responsible for coding *NAT2* and *CYP2E1* (drug-metabolizing enzymes) and genes including *MAFK, GST1, BACH1* and *MnSOD* that control the cellular response to oxidative stress are linked with determining the risk of anti-TB DILI (Ramappa and Aithal 2013). Individuals with *CYP2E1* genetic variation or null *GSTT1* are four times more at risk of having DILI (Santos et al. 2020).

Changes in the Drug Therapy

The therapy can be continued if it causes an increase in bilirubin with the same levels of transaminases but it should be discontinued if there is a presence of clinical hepatitis or a decrease in serum albumin in prothrombin time (Thompson et al. 1995). If ALT elevation is three times greater than the upper limit of normal (ULN) and the patient is showing symptoms or the alanine transaminase (ALT) levels are five times greater than the ULN with the patient being asymptomatic the treatment should be altered (Saukkonen et al. 2006). After discontinuation of isoniazid, liver function tests (LFTs) should be done weekly, if LFTs are normal isoniazid can be re-introduced but if not then it is replaced with ethambutol, and streptomycin or a 4-quinolone. The risk of morbidity is present with the reintroduction of isoniazid, rifampicin, and pyrazinamide therapy. There are no specific clinical guidelines available for the schedule of reintroduction of anti-TB drugs (Sharma et al. 2010).

Genetic Polymorphisms and Hepatic Adverse Effects of TB Drugs

NAT2

There is a lot of effort being done to develop the right drugs for TB treatment, the available options have played a vital role in eradicating TB worldwide but antituberculosis drug-induced hepatotoxicity (ADIH) is a serious adverse effect of the available drugs that interfere with the treatment (Headriawan et al. 2021). NAT2 enzyme is involved in the metabolism of isoniazid, which is a very well-tolerated and easily available treatment option for TB. The process of metabolism includes acetylation of isoniazid to acetyl isoniazid and it is then hydrolysed to acetyl hydrazine. At the same doses of the drug, humans showed different acetylation rates of the drug leading to variation in the efficacy of the drug (Hemanth Kumar et al. 2017). So, according to a varying rate of acetylation in humans, they are classified phenotypically into three categories namely slow, intermediate and fast acetylators (Zabost et al. 2013).

Variation of 254 to 332 amino acids is found in the *NAT2* gene creating variation in the metabolizing rate of isoniazid. A relation between polymorphism of *NAT2* gene and ADIH was found (Santos et al. 2020); therefore, *NAT2* genotyping before starting the therapy can be used to predict the phenotype with 95% accuracy and it can assist in predicting the adverse effects of the drug before starting treatment (Zabost et al. 2013). N-acetylation and O- acetylation of many drugs are carried out by *NAT2*, a study showed that the slow acetylation

phenotype is coded by allele NAT2*19 having single nucleotide polymorphisms C190T (R64W) (Zhu, Doll, and Hein 2002).

In the *NAT2* gene, allelic and genotypic frequencies at three SNP loci (rs1799929, rs1799930 and rs1799931) were studied in 33 patients and 173 controls of the Indian population. It was found that all 33 patients and 151 out of 173 control processed mutant alleles at one or more than one of the total three *NAT2* SNP loci. An increase in the presence of two or more mutant alleles was found in patients than the controls, representing slow acetylation rates (table 3). It was concluded that the population with the 'A' allele at SNP rs1799930 in the *NAT2* gene is at greater risk of developing antituberculosis drug hepatotoxicity (ATDH)(Mishra et al. 2013). A cohort study in Indonesia was carried out that included 207 patients recently diagnosed with TB. The study focused on single-nucleotide polymorphisms rs1799929, rs1799930, rs1799931, rs1801280, and rs1041983 of *NAT2*. The study found the association of DILI with *NAT2* genotype. 69.5% of the patients were slow acetylators of *NAT2* (Perwitasari et al. 2018) A case-control study on the pediatric TB population of Indonesia aimed at investigating rs1041983, rs1799929, rs1799930 and rs1799931 *NAT2* gene polymorphisms. 31 pediatric TB patients each with and without ADIH were included and it was found that polymorphism SNP rs1041983 is associated with ADIH occurrence (Headriawan et al. 2021). A group of 163 people belonging to the Moroccan population was studied and the purpose of this study was to determine the frequency of slow acetylators by genotyping *NAT2* gene variants, to predict the adverse effects of TB treatment thus reducing the chances of hepatotoxicity. The study concluded that 72.39 % of the studied group were slow acetylators who are more prone to developing ATDH. It was suggested that genotyping should be done for the prevention of adverse effects and the calculation of the minimum dose of INH (Guaoua et al. 2014). A study on 99 patients with pulmonary tuberculosis (PTB), among which seven had developed hepatotoxicity was performed in the Northeastern Mexican population. Genotyping of *NAT2* SNPs (rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931) was done. The study found that 58 % of the haplotype was associated with the slow acetylation status of PTB and 42.6% with hepatotoxicity (PTB-H). In seven PTB-H patients, three haplotypes were present including NAT2*5Q, NAT2*5U, and NAT2*5. The haplotypes consist of a combination of two SNPs (I114T + R197Q or I114T + G286E). These SNPs disrupt the CoA binding site affecting acetylation (Herrera-Rodulfo et al. 2021).

A cohort study including 395 Peruvian patients who completed their antituberculosis treatment was done. Genotyping of SNPs rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931 for *NAT2* was performed. The percentage of participants carrying slow metabolizing genotypes (NAT2*5, NAT2*6, and NAT2*7) was 74%. At low doses, slow metabolizing genotypes increase the risk of DILI. The percentage of fast metabolizing phenotype is 16% and it increases the risk of developing resistance to INH or it can lead to treatment failure. The study suggested that individualized drug regimens should be given to patients because of the great genetic diversity in Peru (Levano et al. 2021). In the Chinese population, a total of 341 people were sampled to understand the genotype and phenotype polymorphisms of *NAT2*. Wild genotype was found as major genotype in seven SNPs of *NAT2*, rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208 and rs1799931. 61.3% of participants were fast metabolizers and 34.1% were from middle to slow. It was concluded that important SNPs of *NAT2* are majorly wild genotypes and a fast metabolic

phenotype is found predominantly in the Chinese population (Liu et al. 2012).

CYP2E1

Approximately 32,970 TB cases has been observed in the Peruvian population in 2019 (Harding 2020), among them a huge population are those who have developed resistance to first-line TB treatment. Therefore, research conducted in the Peruvian population has studied the genetic variability of *CYP2E1*, a major enzyme necessary for the hydrolysis of acetyl isoniazid to acetyl hydrazine (Guaoua et al. 2014). Variation in *CYP2E1* has shown variable responses and hepatotoxicity profiles. The study included 395 participants who were diagnosed with TB in 2014-2015. Most commonly reported SNPs for *CYP2E1* (rs3813867 and rs2031920) were selected for analysis. Results indicated that 64% of the population have wild-type homozygous allele CYP2E1*1A (c1/c1genotype) And have higher *CYP2E1* activity than those with the CYP2E1*5B allele (c1/c2 or c2/c2 genotype) and hence more ATDILI were observed. (Levano et al. 2021) Another prospective cohort study for 207 newly diagnosed TB patients was conducted in the Indonesian population and genetic polymorphism and association of *CYP2E1* (rs2031920, rs8192775 and rs2515641) with INH concentration and DILI were observed. CC of rs2031920, GG of rs8192775 and CC of rs2515641 has the highest genotype and 66.4% of G-carrier of rs8192775 and slow acetylators of T carrier of *CYP2E1* rs 2516451 were related to a higher number of DILI cases (Perwitasari et al. 2018). rs2031920 of *CYP2E1* has no association with DILI in the Indian population (Hemanth Kumar et al. 2017).

Another study in Morocco's population for *CYP2E1* RsaI/PstI (rs2031920) containing 130 controls has studied the prevalence of slow acetylators in a population. From the analysis, it was observed that the c1/c1 genotype has a high frequency in the population leading to more hepatotoxic effects (Guaoua et al. 2014). Chinese and Korean populations have also shown increased susceptibility to ATDILI with *CYP2E1* RsaI/PstI polymorphism (Deng et al. 2012).

AADAC

AADAC enzyme (arylacetamide deacetylase) is involved in the hydrolysis of many drugs and is present in the human liver and intestine. Rifampin is deacetylated to 25-deacetylarifampin by the enzyme AADAC (Thomas et al. 2020). Polymorphism of the *AADAC* gene can affect the efficacy of the drug by causing an accumulation of toxic substances and causing variation in the plasma concentration of RIF (Levano et al. 2021). According to some preclinical studies, there was a reduction in rifampin clearance due to an expression of the AADAC*3 (rs1803155/rs61733692) allele (Sloan et al. 2017). Variants rs1803155 and rs61733693 of *AADAC* are missense mutations that do not affect any change in rifampin concentration in plasma (Thomas et al. 2020).

A cohort study was conducted within the Peruvian population of 395 TB patients who had just completed their TB treatment. Genotyping of rs1803155 for *AADAC* was done and it was found that in 99.9% of the Peruvian population rs1803155 (AADAC*2 allele) was present. AADAC*2 allele is responsible for a change in the coding region due to a change in amino acid (V281I). Reduction in the metabolism of RIF was shown by allele AADAC*3 (g.13651G>A/g.14008T>C) (Levano et al. 2021).

HLA

One of the major histocompatibility complexes (MHC) in humans includes the human leukocyte antigen (HLA). It is involved in immune modulation and initiates an effective cell-mediated immune response. Several polymorphisms exist in the *HLA* gene and it

modifies peptide-binding motifs affecting the specificity of antigen presentation. Several studies concluded conflicting results on the susceptibility and resistance towards TB of HLA II alleles (Wamala et al. 2016). A prospective cohort study was conducted in Indonesia to find the relation between genetic polymorphism of *HLA* genes and DILI. The study included 207 patients out of which 1.9% had experienced DILI. SNPs rs1041981, rs1063355, and rs6906021 of *HLA* were studied and it was found that there is a chance of protection of patients against DILI if they possessed the G carrier ship of *HLA* rs1063355. Furthermore, patients can also be protected from DILI if they have the C carrier ship of HLA rs1041981. There was a notable effect observed on the isoniazid concentration due to the genotype of HLA-DQB*0302. The study also concluded that patients with absent G carrier ship of HLA-DQA*0102 could be protected from DILI (Perwitasari et al. 2018).

CYP7A1

Cholesterol 7-alpha-hydroxylase (CYP7A1) is encoded by the *CYP7A1* gene and this gene is located on chromosome 8q12.1. It regulates the balance of cholesterol and bile acids. The risk of developing several diseases is associated with genetic variations in *CYP7A1*. A study on the Moroccan population identified that there is a risk of developing TB because of the A-204C polymorphism of the *CYP7A1* gene (Qrafli et al. 2014).

A case-control study of 356 TB patients and 89 TB patients who had ATDH was conducted in the Chinese population. Genetic polymorphism of *CYP7A1* was studied to find out the relation of *CYP7A1* with the risk of developing TB. It was found that patients having GG genotype and A-C haplotype are at a lower risk of developing ADTH whereas the people carrying AG genotype of rs1457043 and G-C or G-A haplotypes of rs1457043-rs8192870 in *CYP7A1* are at a higher risk of developing ADTH (Chen et al. 2016)

ALDH1A1

ALDH1A1 aldehyde dehydrogenase 1 family member A1 encodes a protein belonging to the family of aldehyde dehydrogenase. It is involved in the metabolism of alcohol. Cytosolic isozyme is encoded by this gene and also plays role in retinol metabolism (Tunçer, Çamlica, and Yilmaz 2020). In the western Chinese Han population, a prospective study including 747 TB patients was conducted who were treated with first-line TB drugs. Seven SNPs (rs7852860 rs3764435, rs348471, rs63319, rs610529, rs7027604, rs8187876) of *ALDH1A1* were genotyped to find out if the patients carrying genetic variants of *ALDH1A1* are more prone to developing ATDILI (anti-tuberculosis drug-induced liver injury) or not. SNPs (rs3764435, rs348471, rs63319, rs610529, rs7027604, rs8187876) were found to have no association with being susceptible to *ATDILI*. CA genotype and C allele of rs7852860 were found notably associated with the risk of developing ATDILI (Peng et al. 2021).

HMOX1

Oxidative degradation of the heme group is catalyzed by the heme oxygenase 1 (*HMOX1*) enzyme. Carbon monoxide (*CO*), free iron, and biliverdin are produced as by-products in this process. *HMOX1* consists of 288 amino acid residues (Sebastián et al. 2018). In the Chinese population, a case-control study consisting of 314 ATLI patients and 628 controls was conducted to detect the interrelation between ATLI and genetic polymorphisms of *HMOX1*. Results of the study concluded that the patients with AA genotype were not at a greater risk of ATILI than those patients having GG genotype at rs2071748 and it confirmed the relation between *HMOX1* genetic polymorphism and susceptibility to ATLI (Yang et al. 2019).

A dynamic TB treatment cohort was conducted and an analysis of a 1:4 matched nested case-control study was done in the Chinese population. 8 SNPs were genotyped of *HMOX1* and *HPX* genes. Out of the total cases, 7.8% developed ATDH (drug-induced hepatotoxicity). The study concluded that SNP rs1807714 of the *HMOX1* gene has a low impact on the risk of developing ATDH. Results stated that the *HMOX1* gene might not be related to the risk of developing ATDH (Liu et al. 2022).

SLCO1B1 AND *UGT1A1*

Hepatocellular uptake of many compounds and drugs by organic anion transporter *OATP1B* is encoded by Solute carrier organic anion transporter family member 1B1(*SCOL1B1)* (Voora et al. 2009). Vulnerability to ATDH has also been observed in the Chinese population when the prospective study was performed by using 34 tag SNPs in *SLCO1B1* and UDP glucuronosyltransferase family 1 member A1 (s*UGT1A1)* on 466 patients. Increased susceptibility to ATDH was observed in those carrying rs2417957 T/T and rs4149063 T/T genotype of *SLCO1B1*, and reduced risk of ATDH was found in rs4148323 A/A genotype of *UGT1A1* (Sun et al. 2017).

PXR and *NF-kB1*

Drug metabolizing and transport enzyme expression is regulated by pregnane X receptor (PXR) also named nuclear receptor 1I2 (*NR1I2*), therefore variation in the gene expression of *PXR* can cause adverse effects and hepatotoxicity. Regulation of inflammatory processes, liver homeostasis and *PXR* transcription is regulated by (*NF-kB1)* nuclear factor-kappa-B.

In December 2014, 746 patients were enrolled to study nine SNPs. The result has shown that patients were more susceptible to ATDILI after first-line Anti-TB therapy who has rs3814055 variant in *PXR* and rs78872571 and rs4647992 variants in *NF-kB1* (Zhang et al. 2019). Decreased risk of ATDH is observed with rs7643645 and haplotype H0010001 in *PXR* (Wang et al. 2019).

Liver injury due to the accumulation of protoporphyrin IX occurs because of co-administration of isoniazid and rifampicin that increase porphyrin biosynthesis via *PXR*. In the Chinese Han population, seven SNPs were analysed in 584 control and 146 ATDH cases. Observation has shown that those carrying GG genotype for rs7643645 and rs2276707 in NR1I2 are more prone to ATDH but further studies are needed for the validation of the findings (Yang et al. 2020).

NRF2 and *MAFF*

Nrf2-ARE pathway protects the liver from reactive oxygen species. A Chinese cohort study in 314 cases and 628 controls were performed to study 13 tagSNPs in *MAFF* and *NRF2*. Patients carrying the TC genotype (rs4243387) and C-C haplotype (rs2001350-rs6726395) in *NRF2* were at higher risk for ATDH. Decrease susceptibility to ATLI with *MAFF* (rs2267373) and increase hepatotoxicity with *MAFK* (rs4720833) in the Japanese population but still, further analysis is required (Chen et al. 2019).

Conclusions

Data has shown a significant number of Asian populations showing variations in their genes, therefore strict monitoring is essential during the course of treatment for finding the potential candidate who can develop hepatotoxicity with the first line TB therapies. Regardless of the increasing progress in the diagnosis, pathophysiology and treatment of TB, variation in response to TB treatment is observed accompanied by various undesirable side effects as discussed. Therefore, same doses for every patient are not appropriate. Need of individualize therapies for preventing the hepatic and other side effects are required and identifying the gene variants in this regard is the

primary step for the betterment of the patients and for more refined, individualize therapies. Involvement of the principles of pharmacogenomics in clinical practices and research can help not only in the optimization of therapies but can also lead to decrease in cost due less hospitalizations.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

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NA

Authors Contribution

SJ conceptualized the study, SJ and ZA carried out the literature search and analysis and wrote the first draft, SJ supervised the whole project and wrote the final manuscript.

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