

An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

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Methods

The Liver: Structure and Function

Hepatic Drug Metabolism: Transporters, Enzymes, and Excretion

Drug-induced Liver Injury: General Concepts

Definition

Dimensions of the Problem

Pathogenesis of DILI

Hepatic Enzyme Measurement

Types of DILI

DILI during Treatment of Latent TB Infection

Isoniazid

Rifampin

Isoniazid and Rifampin

Pyrazinamide

Rifampin and Pyrazinamide

Rifabutin

Ethambutol

Fluoroquinolones

Hepatotoxicity during Treatment of TB Disease

Age over 35

Children

Sex

Cofactors

Abnormal Baseline Transaminases

Acetylator Status

Other Factors

Regimen

HIV-infected Individuals

Hepatitis B

Hepatitis C

DILI with Second-line Anti-TB Agents

Recommendations regarding TB DILI

Program Infrastructure

Provider Education and Resources

Pretreatment Clinical Evaluation

Patient Education

Medication Administration and Pharmacy

Treatment of LTBI

Treatment of TB Disease

Priorities for Research of Hepatotoxicity in Treatment of LTBI and of TB Disease

Conclusions

Drug-induced liver injury (DILI) is a problem of increasing significance, but has been a long-standing concern in the treatment

of tuberculosis (TB) infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury. The pathogenesis and types of DILI are presented, ranging from hepatic adaptation to hepatocellular injury. Knowledge of the metabolism of anti-TB medications and of the mechanisms of TB DILI is incomplete. Understanding of TB DILI has been hampered by differences in study populations, definitions of hepatotoxicity, and monitoring and reporting practices. Available data regarding the incidence and severity of TB DILI overall, in selected demographic groups, and in those coinfecting with HIV or hepatitis B or C virus are presented. Systematic steps for prevention and management of TB DILI are recommended. These include patient and regimen selection to optimize benefits over risks, effective staff and patient education, ready access to care for patients, good communication among providers, and judicious use of clinical and biochemical monitoring. During treatment of latent TB infection (LTBI) alanine aminotransferase (ALT) monitoring is recommended for those who chronically consume alcohol, take concomitant hepatotoxic drugs, have viral hepatitis or other preexisting liver disease or abnormal baseline ALT, have experienced prior isoniazid hepatitis, are pregnant or are within 3 months postpartum. During treatment of TB disease, in addition to these individuals, patients with HIV infection should have ALT monitoring. Some experts recommend biochemical monitoring for those older than 35 years. Treatment should be interrupted and, generally, a modified or alternative regimen used for those with ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. Priorities for future studies to develop safer treatments for LTBI and for TB disease are presented.

Keywords: hepatitis; treatment; latent tuberculosis

METHODS

Material presented here was generated by a multidisciplinary symposium held on November 13–14, 2002, which included presentations and discussion by specialists in tuberculosis (TB), pharmacology, and hepatology. This information was supplemented by material obtained through literature searches performed before and after the symposium during the course of this project. PubMed searches used various combinations of the terms “tuberculosis,” “treatment,” “hepatitis,” “liver injury,” “hepatotoxicity,” “adverse events,” “latent,” “infection,” and/or individual names of the anti-TB medications mentioned here. The bibliographies of publications were also reviewed for additional references. Publications were evaluated for numbers of patients treated, regimens used, incidence and severity of hepatotoxicity, confounding features, and type of publication.

THE LIVER: STRUCTURE AND FUNCTION

The liver is situated between the alimentary tract and the systemic circulation to maximize processing of absorbed nutrients

and to minimize exposure of the body to toxins and foreign chemicals. Consequently, the liver may be exposed to large concentrations of exogenous substances and their metabolites.

Hepatic Drug Metabolism: Transporters, Enzymes, and Excretion

The splanchnic circulation carries ingested drugs directly into the liver, a phenomenon known as the "first pass" through the liver. Metabolic enzymes convert these chemicals through phase 1 pathways of oxidation, reduction, or hydrolysis, which are carried out principally by the cytochrome P450 class of enzymes. Phase 2 pathways include glucuronidation, sulfation, acetylation, and glutathione conjugation to form compounds that are readily excreted from the body. Other subsequent steps include deacetylation and deamination. Many drugs may be metabolized through alternative pathways, and their relative contributions may explain some differences in toxicity between individuals. In phase 3 pathways, cellular transporter proteins facilitate excretion of these compounds into bile or the systemic circulation. Transporters and enzyme activities are influenced by endogenous factors such as circadian rhythms, hormones, cytokines, disease states, genetic factors, sex, ethnicity, age, and nutritional status, as well as by exogenous drugs or chemicals (1). Bile is the major excretory route for hepatic metabolites. Compounds excreted in bile may undergo enterohepatic circulation, being reabsorbed in the small intestine and re-entering the portal circulation (2).

DRUG-INDUCED LIVER INJURY: GENERAL CONCEPTS

Definition

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. Histologic specimens of the liver are often not obtained. Other causes of liver injury, such as acute viral hepatitis, should be methodically sought, and their absence makes the diagnosis plausible. Usually, the time of onset to acute injury is within months of initiating a drug. Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis (3). Rechallenge may, in some instances, endanger the patient and is usually confined to essential drugs or used when multiple potentially hepatotoxic drugs have been administered concomitantly (4).

Dimensions of the Problem

DILI accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure (4, 5). DILI has replaced viral hepatitis as the most apparent cause of acute liver failure (6). A brief search of commercial pharmacopoeia databases suggests there are more than 700 drugs with reported hepatotoxicity and approved for use in the United States (7). With an estimated background rate of idiopathic liver failure of 1 in 1,000,000 (4, 8), the U.S. Food and Drug Administration (FDA) has withdrawn drugs or mandated relabeling for severe or fatal liver injury exceeding 1 in 50,000 individuals (5, 8, 9).

Pathogenesis of DILI

DILI may result from direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature. In many cases, the exact mechanism and factors contributing to liver toxicity remain poorly understood. Predictable DILI is generally characterized by certain dose-related injury in experimental animal models, has a higher attack rate, and tends to occur

rapidly. Injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic arterioles, where metabolism is greatest and antioxidant detoxifying capacity is the least (10, 11).

Unpredictable or idiosyncratic reactions comprise most types of DILI. These hypersensitivity or metabolic reactions occur largely independent of dose and relatively rarely for each drug, and may result in hepatocellular injury and/or cholestasis. Hepatocyte necrosis is often distributed throughout hepatic lobules rather than being zonal, as is often seen with predictable DILI. In hypersensitivity reactions, immunogenic drug or its metabolites may be free or covalently bound to hepatic proteins, forming haptens or "neoantigens." Antibody-dependent cytotoxic, T-cell, and occasionally eosinophilic hypersensitivity responses may be evoked. Released tumor necrosis factor- α , interleukin (IL)-12, and IFN- γ promote hepatocellular programmed cell death (apoptosis), an effect opposed by IL-4, IL-10, IL-13, and monocyte chemoattractant protein-1 (12).

Metabolic idiosyncratic reactions may result from genetic or acquired variations in drug biotransformation pathways, with synthesis or abnormally slow detoxification of a hepatotoxic metabolite. Metabolic idiosyncratic reactions may have a widely variable latent period, but recur within days to weeks after re-exposure (4).

Hepatic Enzyme Measurement

An increase in serum ALT, formerly known as serum glutamate pyruvate transaminase (SGPT), is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST or serum glutamic oxaloacetic transaminase [SGOT]), which can also signify abnormalities in muscle, heart, or kidney (13, 14).

Serum enzyme concentrations are measured by functional catalytic assays with normal values established from "healthy" populations. The normal range lies within 2 standard deviations of the mean of the distribution, with 2.5% of persons who are otherwise healthy having concentrations above and below the limits of normal on a single measurement (15). Populations used to set standard values in the past probably included individuals with occult liver disease, whose exclusion has led to decreases in the upper limit of normal (ULN) (16). Interlaboratory variation in assay results can be substantial. Consequently, comparison of multiples of the ULN has become standard (13, 14).

In an individual, transaminases may vary as much as 45% on a single day, with the highest levels occurring in the afternoon, or 10 to 30% on successive days. ALT and AST elevation may occur after exercise, hemolysis, or muscle injury. A recent retrospective review of healthy volunteers participating in drug trials who received placebo found that 20% had at least one ALT value greater than the ULN, and 7% had one value at least two times the ULN (17). Serum hepatic transaminase concentration tends to be higher in men and in those with greater body mass index. Children and older adults tend to have lower transaminase concentrations. The National Academy of Clinical Biochemistry recommends that laboratories establish reference limits for enzymes adjusted for sex in adults, and for children and adults older than 60 years (13, 14).

Increases in alkaline phosphatase and/or bilirubin with little or no increase in ALT indicate cholestasis. Alkaline phosphatase concentration may also increase because of processes in bone, placenta, or intestine. An increased concentration of serum γ -glutamyl transpeptidase, an inducible enzyme expressed in hepatic cholangioles, is useful in distinguishing liver-related from other organ-related alkaline phosphatase increases (5, 18). Jaundice is usually detectable on the physical examination when serum bilirubin exceeds 3.0 mg/dl.

Laboratory monitoring. A benefit of ALT and/or bilirubin monitoring in preventing or alleviating drug-induced liver injury

has not been rigorously tested. A recent small nonrandomized report suggested that monitoring may decrease the severity of pyrazinamide-induced liver injury (19). Disadvantages of laboratory monitoring include questionable cost-efficacy of frequent testing for rare adverse events, development and progression of injury between testing events, unclear enzyme thresholds for medication discontinuation, and confusion of hepatic adaptation with significant liver injury. The cost of obtaining AST with ALT is often marginal and may be useful in identifying alcohol-related transaminase elevation, where the AST is characteristically higher than the ALT.

The diagnosis of a superimposed injury may be difficult with initially abnormal or fluctuating transaminases. Prior laboratory data may be of use in this regard. Monitoring and the use of a potentially less hepatotoxic regimen is generally recommended for those with preexisting liver disease in the hope that superimposed DILI may be detected preclinically and mitigated. Transaminase elevation during the course of anti-TB therapy may in some instances actually represent coincidentally developed hepatitis A, B, or C (20, 21).

Types of DILI

A variety of clinical syndromes may be seen with DILI, even with a single drug.

Hepatic adaptation. Exposure to certain drugs may evoke physiologic adaptive responses (18). The induction of survival genes, including those that regulate antioxidant, antiinflammatory, and antiapoptotic pathways, may attenuate toxin-related injurious responses. Such injury may also stimulate hepatocyte proliferation and protective adaptation. Asymptomatic, transient elevations of ALT may reflect slight, nonprogressive injury to hepatocyte mitochondria, cell membranes, or other structures. Such injury rarely leads to inflammation, cell death, or significant histopathologic changes. Certain toxins, such as ethanol, possibly interfere with these adaptive protective responses. Excessive persistence of an adaptive response may, in some instances, render hepatocytes more vulnerable when they are subjected to additional new insults (22). The induction of hepatic microsomal (cytochrome P450) enzymes, capable of metabolizing the inducing medication (4, 18), is another form of hepatic adaptation.

Drug-induced acute hepatitis or hepatocellular injury. A transaminase threshold for clinicopathologically significant drug-induced hepatitis has not been systematically determined for most medications. Patients who take phenytoin often have transaminase elevation up to three times the ULN, but liver biopsies do not reveal significant pathology (23). However, in patients treated for rheumatoid arthritis with methotrexate, microscopic evidence of liver injury has been found for any transaminase elevation above the ULN (24).

Patients with acute hepatocellular injury may be asymptomatic or may report a prodrome of fever and constitutional symptoms, followed by nausea, vomiting, anorexia, and lethargy. Histopathology may reveal focal hepatic necrosis, with bridging in severe cases (4).

Markedly increased transaminase concentrations followed by jaundice imply severe liver disease with a 10% possibility of fulminant failure, a maxim known as "Hy's Law," after the late hepatologist and DILI expert Hyman Zimmerman. Coagulopathy may develop 24 to 36 hours after onset, although this can subsequently resolve. Coagulopathy persisting beyond 4 days is a poor prognostic sign in acetaminophen-related hepatotoxicity (13, 14).

Nonalcoholic fatty liver disease. Steatosis, or simple fatty liver, is most commonly caused by obesity, insulin resistance, and probably alterations in triglyceride metabolism. Ethanol, steroids, and highly active antiretroviral therapy (HAART) are

associated with the development and exacerbation of non-alcoholic fatty liver disease (25–28). Constitutional symptoms, nausea, vomiting, or abdominal pain are uncommon. Laboratory findings in severe cases include hypoglycemia, increased serum transaminase concentrations, prolonged coagulation times, and metabolic acidosis (4, 27, 29). Most instances of drug-induced steatosis are reversible, if the offending agent is stopped. Persistent steatotic injury may progress to steatohepatitis, characterized histopathologically by hepatic inflammatory and fatty infiltration, and by a subsequently higher risk of cirrhosis (30).

Granulomatous hepatitis. Granulomata are common, nonspecific findings in liver histology and are potentially related to infectious, inflammatory, or neoplastic etiologies. Hypersensitivity reactions to drugs, such as allopurinol, quinidine, sulfonamides, and pyrazinamide, are a common cause of this type of lesion. Patients may have fever, lethargy, myalgias, rash, lymphadenopathy, hepatosplenomegaly with increased serum ALT concentration, and even vasculitis (4, 31).

Cholestasis. Bland cholestasis, typically reported with estrogen treatment, consists of asymptomatic, usually reversible, increases in serum alkaline phosphatase and bilirubin concentration, caused by a failure of bilirubin transport. There is a lack of inflammation in liver tissue (4).

Chemical cofactors for DILI. Ethanol induces cytochrome P450 2E1, which promotes metabolism of ethanol itself, acetaminophen, and others (32). Ethanol metabolism yields acetaldehyde, which contributes to glutathione depletion, protein conjugation, free radical generation, and lipid peroxidation. Chronic ethanol abuse activates hepatic collagen-producing sinusoidal (stellate) cells, potentially contributing to fibrosis (33). Some medications, such as calcium channel blockers, may influence cytochrome P450 metabolism of potentially hepatotoxic drugs, such as simvastatin, which may lead to DILI (34).

Preexisting liver disease. Abnormal baseline transaminases are an independent risk factor for DILI (35–39). Patients with HIV and hepatitis C, however, appear to have increased frequency of antiretroviral medication-related DILI (26, 27). The severity of DILI, when it occurs, may be greater in patients with underlying liver disease (40), likely reflecting a summation of injuries.

DILI DURING TREATMENT OF LATENT TB INFECTION

DILI may occur with all currently recommended regimens for the treatment of latent TB infection (LTBI), including isoniazid for 6 to preferably 9 months, rifampin for 4 months, or isoniazid and rifampin for 4 months (41). This is also true of two-drug regimens of pyrazinamide with either ethambutol or a fluoroquinolone used to treat contacts of multidrug-resistant (MDR) TB cases (42–44). Metabolic idiosyncratic reactions appear to be responsible for most DILI from the first-line anti-TB medications and fluoroquinolones.

Isoniazid

Metabolism. Isoniazid is cleared mostly by the liver, primarily by acetylation by N-acetyl transferase 2 (NAT-2). Acetyl-isoniazid is metabolized mainly to mono-acetyl hydrazine (MAH) and to the nontoxic diacetyl hydrazine, as well as other minor metabolites (45). Interindividual variation in plasma elimination half-life ($t_{1/2}$), independent of drug dose and concentration, is considerable. Individuals with prolonged $t_{1/2}$ have extended exposure to the drug. Genetic polymorphisms of NAT-2 correlate with fast, slow, and intermediate acetylation phenotypes (45–47). Microsomal enzymes (e.g., cytochrome P450 2E1) further metabolize isoniazid intermediates through phase 1 pathways (46).

Acetylator status. In fast acetylators, more than 90% of the drug is excreted as acetyl-isoniazid, whereas in slow acetylators,

67% of the drug is excreted as acetyl-isoniazid and a greater percentage of isoniazid is excreted as unchanged drug into the urine. The influence of acetylation rate on isoniazid hepatotoxicity is controversial. Most studies on this question involved patients on multidrug regimens for TB disease and relied on phenotypic assays of acetylation, which can be imprecise (45). Fast acetylators may be misidentified as slow if they exhibit delayed drug absorption during blood sampling at limited time points (46). Early studies suggested that fast acetylators were at higher risk for hepatic injury because they generated more acetyl-isoniazid, which could be further metabolized to other toxic intermediaries (45, 48, 49). However, fast acetylators clear MAH more rapidly. Slow acetylators may actually have greater cumulative MAH exposure. Increased susceptibility among slow acetylators (31, 50) or a lack of correlation with acetylation rate has been reported (51). NAT-2 genotyping by polymerase chain reaction recently demonstrated that slow acetylators experience transaminase elevations of more than three times the ULN more frequently than rapid acetylators (26 vs. 11%) (45). Slow acetylators also had higher peak ALT than did fast acetylators and, when rechallenged with isoniazid, more frequently developed transaminase elevation of at least three times the ULN. The significance of these findings awaits further studies.

Mechanism of injury. Reactive metabolites of MAH are probably toxic to tissues through free radical generation (48). In rats, the free radical scavenger glutathione-related thiols, and antioxidant glutathione peroxidase and catalase activities, are diminished by isoniazid, although glutathione reductase activity is increased (52, 53). The antioxidant N-acetyl-cysteine, a substrate for glutathione synthesis, inhibits isoniazid-induced liver injury in pretreated rats (52), with unknown relevance in humans.

Additional metabolic idiosyncratic mechanisms appear to be operative. The isoniazid metabolite acetyl-hydrazine covalently binds to liver macromolecules, a process mediated by microsomal enzymes (48). Patients with homozygous cytochrome P450 2E1 c1/c1 host gene polymorphism, who have enhanced cytochrome P450 2E1 activity, in one study had a higher risk of hepatotoxicity, particularly in slow acetylators (46).

Histopathology. Nonspecific changes resemble those of viral hepatitis with nonzonal necrosis, and are massive in up to 10% of severe cases. Subacute hepatic necrosis can be seen in 30% of cases (54).

Drug interactions. Isoniazid inhibits the activity of several cytochrome P450 2E and 2C enzymes, potentially increasing the plasma concentrations of other potentially hepatotoxic drugs, such as phenytoin and carbamazepine (55–57). Rifampin appears to enhance a metabolic hepatocellular idiosyncratic reaction in patients receiving isoniazid, perhaps by promoting the formation of toxic isoniazid metabolites (58, 59).

Hepatic adaptation. Up to 20% of individuals treated with isoniazid alone for LTBI may experience low-grade, transient, asymptomatic transaminase elevation (54, 60), most of which represents hepatic adaptation (18, 60).

Clinical presentation of hepatotoxicity. Some individuals may be asymptomatic, whereas others may experience symptomatic hepatotoxicity at varying serum transaminase concentrations. Constitutional symptoms may be seen early in severe hepatotoxicity, and may last from days to weeks. Nausea, vomiting, and abdominal pain are seen in 50 to 75% of patients with severe illness, whereas fever is noted in 10% and rash in 5% of patients. Overt jaundice, dark urine, and clay-colored stools are late signs of clinical worsening. Coagulopathy, hypoalbuminemia, and hypoglycemia signify life-threatening hepatic dysfunction. The regression of isoniazid hepatotoxicity usually takes weeks. Recovery is complete in most after discontinuation of isoniazid (54).

Overall rates of hepatotoxicity. Initial experience with isoniazid up to the 1960s indicated the rates of treatment-limiting adverse events were similar in placebo- and isoniazid-treated groups, except for gastrointestinal complaints (61), with hepatitis occurring relatively rarely. In the late 1960s, isoniazid's ability to cause asymptomatic elevations in hepatic transaminases and clinically significant hepatitis was recognized (54). In 1970, 19 of 2,321 Capitol Hill workers treated with isoniazid developed clinical signs of liver disease and two died of resulting complications (62). The U.S. Public Health Service (USPHS) surveillance study (63) of 14,000 isoniazid-treated individuals found an overall rate of significant, probable isoniazid hepatitis of 1%, with a cluster of seven of eight reported deaths in one city. A subsequent study, using passive detection, by the International Union Against Tuberculosis (IUAT), found the overall rate of hepatitis in patients receiving up to 12 months of isoniazid was 0.5 versus 0.1% receiving placebo (64).

From the 1970s to the 1990s, isoniazid-related hospitalization rates declined from as much as 5.0 per 1,000 treatment initiations to 0.1 to 0.2 (median, 0.15), and mortality rates fell from as high as 1.0 per 1,000 to 0–0.3 per 1,000 (median, 0.04) (40, 41, 62, 63). These declines may have been related to careful patient selection, education, and active monitoring for adverse reactions to isoniazid (65).

A study of isoniazid for treatment of LTBI, involving more than 11,000 patients in Seattle–King County, Washington, reported that symptomatic transaminase elevation of more than five times the ULN occurred in 0.1% of treatment initiations (66). Routine follow-up transaminase monitoring of asymptomatic individuals was not done in this clinic, which the authors estimated could have raised the incidence of significant transaminase elevation into the range of older studies, to approximately 0.6%. Hepatotoxicity rates could also have been higher if based on those patients actually taking medication, rather than on treatment initiations. The study generally demonstrated a relatively low risk of isoniazid hepatotoxicity within the context of a TB program providing patient education, specific instructions about adverse events, and monthly clinical observations.

A subsequent study of 3,788 patients treated for LTBI with isoniazid in San Diego, California, reported that transaminase elevations of three times the ULN in symptomatic individuals and five times the ULN in asymptomatic individuals occurred in 0.3% of cases (67). An observational study from 1996 to 2003 of isoniazid hepatotoxicity during LTBI treatment in 3,377 patients from Memphis, Tennessee, found AST elevations at least five times the ULN in 0.56% of those treated. In this study, AST was measured at baseline and 1, 3, and 6 months after treatment initiation. Only 1 of the 19 patients who developed significant transaminase elevation was symptomatic in this study. Seven of the 19 who experienced significant AST elevations consumed alcohol chronically, warranting biochemical monitoring. Testing for development of viral hepatitis was not reported, nor was use of concomitant potentially hepatotoxic medications (68).

Recent smaller treatment studies have reported significant transaminase elevation in 1 to 4% of those treated with isoniazid for LTBI (19, 69), whereas in recent large reviews, the range has been 0.1 to 0.56% (66–68). Differences among these studies may be due to sample size variations in the definitions of hepatotoxicity, patient selection, and potential confounding causes of hepatotoxicity. Subgroup analyses to assess for those most at risk for isoniazid hepatotoxicity should be interpreted within the limitations and methodology of each study.

Timing. Hepatotoxicity occurs generally within weeks to months rather than the days to weeks of onset seen with hypersensitivity reactions (52, 54). Unlike a classical hypersensitivity

reaction, isoniazid rechallenge does not always elicit rapid recurrence of hepatotoxicity (54). Approximately 60% of the hepatotoxicity incidence in the USPHS study occurred in the first 3 months of treatment, and 80% of the incidence occurred in the first 6 months (63, 64, 68). A retrospective case fatality review found that the median interval from treatment initiation to symptom onset was 16 weeks (69).

Age. Most isoniazid-associated hepatotoxicity is age associated. The Seattle study of symptomatic transaminase elevation showed ranges from 0% in those younger than 14 years to 0.28% in those older than 65 (66). The San Diego study reported a trend toward age-related hepatotoxicity, with only 15% of the study population aged 35 years or older (67). The Tennessee study reported that age-specific AST elevation more than five times the ULN ranged from 0.44% in those younger than 35 years to 2.08% for those older than 49 years (68), a statistically significant difference. In comparing these studies, 20% of the more than 11,000 patients in the Seattle study population were at least 35 years old, compared to 59% in the USPHS and 54.6% in the Tennessee studies. Sample sizes for this age group were comparable in the Seattle ($n = 2,228$) and the Tennessee studies ($n = 1844$). Differences in the findings among these studies may be attributed to differing definitions of hepatotoxicity, patient selection, and in ability to exclude confounding causes of hepatotoxicity. The severity of isoniazid-related hepatitis has been reported to also increase with age, with higher mortality in those older than 50 years (54, 69, 70).

Racial differences. In the USPHS study (63), African-American males appeared to have less risk of DILI than white males, but there was no difference for women of any race. Asian males appeared to have nearly double the rate of probable isoniazid hepatitis than white males and nearly 14 times that of black males. In the Seattle–King County study, there was a nonsignificant trend toward higher hepatotoxicity in white individuals, without other significant racial differences (66). The Memphis, Tennessee, study found no associations among racial groups or demographic subgroups and hepatotoxicity (68). There do not appear to be consistent racially based risks for high-grade hepatotoxicity.

Sex. There is currently no clear evidence to point to an overall sex-related difference in the incidence of hepatotoxicity. Pregnant women in the third trimester and in the first 3 months of the postpartum period may be at higher risk for the development of hepatitis (71). In the USPHS study, there was no overall difference between women and men in rates of probable isoniazid hepatotoxicity (63). The Seattle–King County study (66) found a nonsignificant trend toward higher isoniazid-related hepatotoxicity in women compared with men, although the incidence of severe hepatotoxicity was relatively low in both men and women. The Memphis and San Diego studies found no significant associations between sex and hepatotoxicity (67, 68).

Deaths. Several retrospective studies and reviews with methodologic limitations suggest that the severity of isoniazid-induced hepatotoxicity, when it does occur, may be worse in women. In the USPHS study (63), there were 8 deaths among 13,838 enrolled subjects (0.57 per 1,000 treated), 5 of which were in African-American women, with 7 of 8 deaths occurring in Baltimore, Maryland. Most of those who died had potential cofactors for hepatotoxicity, including severe alcoholism or ingestion of other hepatotoxic drugs. Another cofactor may have been involved in the observed clustering, as a subsequent review of death certificates showed a surge in cirrhosis-related deaths in Baltimore and surrounding counties during the time period of this study (72). In the IUAT study, there were three deaths with a death rate of 0.14 of 1,000 treated (64). A review of probable and possible isoniazid hepatitis cases from 1970 to 1992

suggested a case fatality rate of 0.042 per 1,000 persons beginning therapy and a rate of no greater than 0.07 per 1,000 persons completing therapy (69). This review included some of the previously discussed fatalities. There were 62 probable and possible isoniazid hepatitis deaths, 50 (81%) of the patients were female, and 49 (79%) were non-Hispanic black or Hispanic. Although most individuals who died were older than 35 years, a surprising 31% were younger. Although these are numerator data only, they indicate that no age group is free of risk. Another review of fatal cases also suggested that women may be at higher risk for death from isoniazid-related hepatitis (70).

Cofactors. In the USPHS surveillance study (63), alcohol consumption appeared to more than double the rate of probable isoniazid hepatitis, with daily consumption increasing the rate more than four times. Transaminase elevation may be, in some cases, related to chronic ethanol use. Hepatotoxicity during concomitant administration of other hepatotoxic drugs, such as acetaminophen (73), methotrexate (74), sulfasalazine (74), or carbamazepine (75), as well as others, has been reported.

HIV-infected individuals. HIV-infected individuals appear to experience isoniazid-related hepatotoxicity in the same range as HIV-uninfected individuals (41, 76), although no direct comparisons through clinical trials have been done.

Hepatitis B. Few studies have addressed the issue of isoniazid hepatotoxicity during LTBI in patients infected with hepatitis B. In a small study from Philadelphia, among Southeast-Asian individuals, the incidence of isoniazid hepatotoxicity was indistinguishable between chronic hepatitis B carriers and noncarriers (77). A second study of Vietnamese immigrants treated for LTBI with isoniazid in Iowa and Illinois distinguished between hepatitis B carriers with and without hepatitis B “e” antigen (HBeAg), a marker of active hepatitis B viral replication and related liver inflammation. Three of 21 (14%) individuals with HBeAg experienced symptomatic transaminase elevation of more than five times the ULN while taking isoniazid, whereas none of the 121 without HBeAg did, nearly an eightfold increased risk (78). Although additional data are needed, these studies suggest that active, but not quiescent, hepatitis may be a risk factor for increased incidence of isoniazid hepatotoxicity.

Hepatitis C. Two studies showed no independent isoniazid hepatotoxicity risk associated with hepatitis C infection. In Baltimore, Maryland, a cohort of 146 tuberculin skin test–positive injection-drug users, 95% of whom were infected with hepatitis C, with baseline serum transaminase concentrations less than three times the ULN, and 25% of whom were HIV infected, received isoniazid for LTBI (79). Observed with monthly blood tests, 32 patients (22%) had increased transaminase concentrations to more than five times the ULN. Abnormal results were associated with alcohol use, but not with race, age, chronic hepatitis B infection, or HIV infection. Both the rate of hepatitis and the rate of isoniazid discontinuation were within the historical range for populations with a low prevalence of hepatitis C infection (10 to 22% and 0.1 to 10%, respectively). A second study in Spain (36) found that only excessive alcohol consumption and a high baseline ALT concentration were independently associated with isoniazid hepatotoxicity. The presence of hepatitis C virus (HCV) antibody was associated with hepatotoxicity only on univariate analysis in this study.

Elevated baseline transaminases. The Tennessee retrospective study found that a baseline AST greater than the ULN was a risk factor for developing transaminase elevation greater than five times the ULN (68), as did another study among intravenous drug users (36).

Other factors increasing frequency or severity of hepatotoxicity. Concomitant treatment with rifampin, malnutrition, prior isoniazid-related hepatotoxicity, and continued use of isoniazid while

symptomatic have been described to contribute to higher-grade isoniazid hepatotoxicity (54).

Rifampin

Rifampin, and similarly rifapentine, may occasionally cause dose-dependent interference with bilirubin uptake, resulting in subclinical, unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. This may be transient and occur early in treatment or in some individuals with preexisting liver disease (80–83). Rifampin occasionally can cause hepatocellular injury and potentiate hepatotoxicities of other anti-TB medications (84, 85). In a study of patients with brucellosis treated with the combination of rifampin and minocycline, rifampin-attributed ALT increases of at least 250 IU/L were seen in approximately 5% of patients (86). In two small series of patients with primary biliary cirrhosis, in whom baseline transaminases were significantly elevated, clinically significant hepatitis was attributed to rifampin in 7.3 and 12.5% of patients (87, 88).

Mechanisms of hepatotoxicity. Conjugated hyperbilirubinemia probably is caused by rifampin inhibiting the major bile salt exporter pump (89). Asymptomatic elevated bilirubin may also result from dose-dependent competition with bilirubin for clearance at the sinusoidal membrane or from impeded secretion at the canalicular level (4, 80, 81).

Rare hepatocellular injury appears to be a hypersensitivity reaction, and it may be more common with large, intermittent doses (80). Hypersensitivity reactions have been reported in combination with renal dysfunction, hemolytic anemia, or “flu-like syndrome” (90, 91).

Drug interactions. Rifampin activates hepatocyte pregnane X receptors, leading to induction of cytochromes. Rifampin also induces uridine diphosphate-glucuronosyl-transferases and P-glycoprotein transport, which are involved in the metabolism of other drugs (92–94). Rifampin interacts with numerous drugs metabolized by these and other hepatic enzymes, including warfarin, prednisone, digitoxin, quinidine, ketoconazole, itraconazole, propranolol, clofibrate, sulfonyleureas, phenytoin, HIV protease inhibitors, and HIV nonnucleoside reverse transcriptase inhibitors (95).

Clinical characteristics of hepatotoxicity. Cholestasis may be insidious. Idiosyncratic hypersensitivity reaction to rifampin, manifested as anorexia, nausea, vomiting, malaise, fever, mildly elevated ALT, and elevated bilirubin, usually occurs in the first month of treatment initiation (24, 80, 91, 96).

Overall hepatotoxicity. Four published TB-related studies have assessed rifampin alone for treatment of LTBI. In a study by the Hong Kong Chest Service, transaminase elevations above the ULN were more common among patients receiving isoniazid-containing regimens than they were among the 77 of 172 patients treated with rifampin alone who had follow-up liver enzyme analyses (85). There was no significant difference between the geometric means of serum ALT for the placebo and rifampin groups. In the second study (97), none of the 49 individuals, 20% of whom used alcohol and 8% of whom used injection drugs, treated with rifampin for 6 months had symptomatic liver injury. There was no assessment for asymptomatic transaminase elevations. Among 157 adolescents treated with rifampin, 4 (2.5%) developed ALT elevations at least two times the ULN, for which treatment was permanently discontinued in one (98). A randomized study of isoniazid versus rifampin for treatment of LTBI in Montreal, Canada (84), found that, among 53 patients who completed 80% of a 4-month course of rifampin for LTBI, none experienced significant transaminase elevation. The apparent low rate of hepatotoxicity observed in these limited studies awaits confirmation in larger prospective studies.

Isoniazid and Rifampin

A Canadian study found that rates of hepatitis were similar for patients treated with intermittent isoniazid and rifampin compared with historical control subjects receiving daily isoniazid for 12 months (99). The rate of symptomatic hepatitis with the combination of isoniazid and rifampin has been estimated at 2.55% in a meta-analysis that included patients with TB disease, a higher incidence than in regimens containing one or the other drug (100).

Pyrazinamide

Pyrazinamide has been used with rifampin, ethambutol, or a fluoroquinolone for treatment of LTBI. Transaminase elevation more than four times the ULN was seen in 7 of 12 (58%) LTBI cases treated with pyrazinamide and ethambutol (42). Three of 17 (18%) patients prescribed levofloxacin and pyrazinamide for treatment of LTBI after exposure to MDR TB developed transaminase elevation more than four times the ULN (43). Nine of 22 (41%) patients treated with ofloxacin and pyrazinamide developed transaminase elevation of at least five times the ULN (44). Because these fluoroquinolones and ethambutol alone rarely cause hepatotoxicity, pyrazinamide is believed to be the offending agent in most cases of hepatotoxicity associated with these regimens.

Metabolism. The half-life ($t_{1/2}$) of pyrazinamide is notably longer than that of either isoniazid or rifampin, approximately 10 hours (46). In patients with preexisting hepatic disease, $t_{1/2}$ is increased to 15 hours (101). Pyrazinamide, a nicotinic acid derivative, is de-amidated to pyrazinoic acid in the liver and subsequently metabolized to 5-hydroxy-pyrazinoic acid by xanthine oxidase (101), aldehyde oxidase (102), and xanthine dehydrogenase (103, 104). In addition, 5-hydroxy-pyrazinamide may be generated during metabolism (105). The kidneys clear metabolites of pyrazinamide, requiring intermittent dosing in patients with renal insufficiency (106).

Mechanism of injury. Pyrazinamide may exhibit both dose-dependent and idiosyncratic hepatotoxicity. Several decades ago, daily doses of pyrazinamide at 40 to 50 mg/kg commonly caused hepatotoxicity, and a relationship to dose was noted (11). Pyrazinamide alters nicotinamide acetyl dehydrogenase levels in rat liver (107), which might result in generation of free radical species. There may be shared mechanisms of injury for isoniazid and pyrazinamide, because there is some similarity in molecular structure. Patients who previously had hepatotoxic reactions with isoniazid have had more severe reactions with rifampin and pyrazinamide given for LTBI (108). Pyrazinamide may induce hypersensitivity reactions with eosinophilia and liver injury (108) or granulomatous hepatitis (109).

Drug interactions. Allopurinol alone or with pyrazinamide can be hepatotoxic (4, 110). Allopurinol inhibits xanthine oxidase, which metabolizes pyrazinamide, decreasing its clearance (111).

Rifampin and Pyrazinamide

The 2-month regimen of rifampin and pyrazinamide (RZ) is no longer recommended due to its hepatotoxicity (65, 108, 112).

HIV population. Several studies in HIV-infected patients suggested RZ had either less or equal hepatotoxicity to isoniazid. A multicenter international trial reported less life-threatening and treatment-limiting hepatotoxicity among the study subjects taking RZ in comparison to subjects taking 12 months of isoniazid (113), and there were no differences in the incidence of significant AST elevations (114). Twice-weekly RZ was as well tolerated as isoniazid in two studies in Haiti and Zambia (115, 116). Two RZ-related deaths were reported among HIV-infected individuals in Centers for Disease Control and Prevention (CDC)

retrospective surveillance. The regimen is no longer recommended in this population (65).

Non-HIV population. Pilot studies showed higher transaminase elevations among individuals treated with RZ (117–119), but a small pediatric study in Germany did not (120). In a study of 168 largely male jail inmates treated with RZ (121), most tolerated the regimen well, but two (1.2%) had increases of serum liver enzymes at least five times the ULN. Among 589 patients treated with either RZ or isoniazid, 7.8% of RZ patients had high-grade transaminase elevation versus 1% of those treated with 6 months of isoniazid (122). In North Carolina, 7.3% of 110 adults treated with RZ developed significant transaminase elevation, whereas none of the 114 treated with isoniazid did (19). In an observational study (123) of 1,210 jail inmates and homeless persons, all treated with RZ, 5.8% experienced significant transaminase elevation, and 2.5% had treatment discontinued because of liver injury. In contrast, in a retrospective study of 589 inmates in Maryland who received RZ twice weekly and had serum transaminases measured periodically, only one patient (0.17%) developed significant transaminase elevation (124). Two additional retrospective reviews (125, 126) found that RZ caused severe hepatotoxicity more often than did isoniazid.

A retrospective CDC surveillance study of patients treated with RZ found ALT elevations of at least five times the ULN in 26.4 of 1,000 treatment initiations. Hospitalization and death rates for these patients were 3 and 0.9 per 1,000 treatment initiations, respectively, substantially higher than the analogous rates estimated for isoniazid-treated patients: 0.1 to 0.2 and 0 to 0.3 per 1,000 treated, respectively (65).

In summary, most of these studies demonstrated an unacceptable rate of moderate or severe hepatotoxicity with daily RZ. The overall rate of liver injury associated with RZ was 7.2% and the rate of grade 3 or 4 liver injury was 5.6%. The RZ hepatotoxicity rates for HIV-uninfected patients may be greater than those for HIV-infected patients (125), but the reasons for this disparity are undetermined. The CDC and American Thoracic Society (ATS) have recommended that RZ should not be offered in general for treatment of LTBI (65).

Rifabutin

At the usual doses (150–300 mg/day), hepatotoxicity is uncommon. There is less induction of hepatic microsomal enzymes than with rifampin (127). Elevated transaminases have been reported with high-dose (600 mg/day) rifabutin treatment in combination with macrolides (128). In two studies of rifabutin for primary prophylaxis of *Mycobacterium avium* complex (MAC) in patients with AIDS, approximately 3 to 6.4% experienced grade 3 or higher AST elevations (129, 130). In patients with AIDS with disseminated MAC treated with rifabutin and a macrolide-containing regimen, hepatotoxicity occurred in approximately 8% (129).

Ethambutol

There has been one report of ethambutol-related liver cholestatic jaundice, with unclear circumstances (131).

Fluoroquinolones

Some fluoroquinolones (ciprofloxacin and moxifloxacin) are metabolized, in part, by the liver, whereas others (gatifloxacin, levofloxacin, ofloxacin) are largely excreted unchanged by the kidneys. Reversible transaminase elevation among the fluoroquinolones may occur in up to 2 to 3% of cases (132, 133). Severe hepatocellular injury and cholestasis have been reported to occur in less than 1% of all fluoroquinolone recipients, excluding trovafloxacin, which was withdrawn due to its hepatotoxicity (4, 134–137).

Clinically significant hepatotoxicity has been reported with ciprofloxacin, trovafloxacin, norfloxacin, ofloxacin, enoxacin, levofloxacin, and gatifloxacin, with large population denominators (138, 139). Direct comparisons of rates of clinically significant hepatotoxicity are not available. Among the newer fluoroquinolones, moxifloxacin-related transaminase elevation of at least 1.5 times the ULN has been reported in 0.9% of cases (140). For levofloxacin, the rate of severe hepatotoxicity was reported to be less than 1 per 1,000,000 (139). The mechanism of fluoroquinolone hepatotoxicity is believed to be a hypersensitivity reaction, often manifested by eosinophilia (138). Regarding hepatotoxicity among contacts of MDR-TB cases treated with a fluoroquinolone and pyrazinamide, the causative agent has generally been assumed to be the latter (42–44, 141).

HEPATOTOXICITY DURING TREATMENT OF TB DISEASE

The use of multiple regimens, vastly different study populations, varying definitions of hepatotoxicity, and different monitoring and reporting practices make it difficult to reach definitive conclusions regarding risks of individual regimens. Overall, the risk of TB DILI in these diverse studies ranges from 5 to as high as 33%.

Age over 35

Several studies suggest that increasing age is a risk factor for TB DILI, but often statistical significance was not achieved or hepatotoxicity was not treatment limiting (45, 142–147). One study reported a TB DILI rate ranging from 2 to 8% as age increased, with an average of 5% (147). Other studies have reported that hepatotoxicity ranges from 22 to 33% in those older than 35 years, compared with 8 to 17% in those younger than 35 years (13, 45).

Children

In a retrospective study, severe TB DILI was diagnosed in 8% of pediatric patients, and was associated with age younger than 5 years, extrapulmonary TB, and use of pyrazinamide (148). In another study of children with a mean age of 4.5 years treated with isoniazid and rifampin, 82% experienced an ALT elevation greater than 100 IU/L, and more than 40% had symptomatic hepatitis with jaundice (149). In a study of South Indian patients with TB of all ages, 16 to 39% of children with tuberculous meningitis developed hepatitis “nearly always with jaundice.” These rates were substantially more than the 2 to 8% seen in the multiage cohorts with pulmonary or spinal TB (150). There are some data suggesting that doses of isoniazid greater than 15 to 20 mg/kg may be associated with a greater risk of hepatotoxicity (149, 151).

Sex

For women, several studies report increased risk of hepatotoxicity (142, 144, 145, 152, 153), but this was not always treatment limiting (146), or did not achieve statistical significance (152, 153). One study did show a four times higher risk of treatment-limiting hepatotoxicity in women, but with an overall incidence of only 2% (144). Two other studies showed no increased risk in women (63, 146).

Cofactors

Several studies have indicated that alcohol use was a significant predictor of TB DILI (31, 63, 147, 154, 155), whereas two studies found no association (144, 146).

Abnormal Baseline Transaminases

One study found an increased risk of hepatotoxicity during treatment of TB disease in individuals with abnormal baseline transaminases (35).

Acetylator Status

When acetylation rate has been determined by phenotypic assays, slow acetylators have experienced more hepatotoxicity in some studies (31, 58, 147, 150), but not in others (156–158). Genotypic assays for acetylation class might improve the precision of future studies. One such study found that slow acetylators experienced more hepatotoxicity (26 vs. 11%) and more severe TB DILI than did fast acetylators (45).

Other Factors

Malnutrition or hypoalbuminemia was associated with TB DILI in several studies from India (147, 159–161). The presence of HLA-DQB1*0201 is an independent risk factor for the development of TB DILI (161). Gene polymorphisms at loci of genes coding for cytochrome P450 2E1 and for glutathione S-transferase have also been associated with hepatotoxicity (45, 162). Extensive TB disease itself may be a risk factor for TB DILI, although confounding factors are impossible to exclude (142, 147). Liver transplant patients with TB appear to have a high rate of hepatotoxicity, with five of six treated patients developing this complication, confirmed by liver biopsy, and three of six suffering graft rejection (163).

Regimen

In a meta-analysis, the presence of rifampin in a multidrug treatment regimen increased the incidence of significant hepatotoxicity for adults from 1.6 to 2.55% and in children from 1.0 to 6.9% (100). The influence of pyrazinamide on TB DILI is ambiguous; some studies indicate little to no increased rate of hepatotoxicity (150, 164–166), whereas others point to it as a contributor to increased incidence or severity of hepatotoxicity (143, 145, 146, 167), although dosing variations and patient selection biases may have contributed to these results.

HIV-infected Individuals

Limited data about TB DILI in HIV-infected patients come from observational studies or treatment trials, generally before the advent of HAART. A retrospective review of TB-AIDS cases in San Francisco from 1991 to 1998 showed a 4.8% rate of treatment alteration because of hepatitis (168). In a Western European clinical trial enrolling patients with TB-AIDS from 1989 to 1994, many who used intravenous drugs, 13 to 15% of patients had transaminase increases of at least three times the ULN in the first 2 months (169). Hepatotoxicity was attributed to isoniazid in 55% of those with hepatitis.

In a U.S. multicenter trial from 1993 through 1997, patients with TB-AIDS treated with regimens containing isoniazid, rifampin, and pyrazinamide had an overall 4.4% rate of clinically significant or treatment-limiting hepatotoxicity (170). Injected drugs were used by 36% of these patients, and the median CD4⁺ T-cell count was 70/ μ l. In a retrospective review of TB disease treatment for HIV-infected patients in six U.S. cities from 1989 to 2000, increases of transaminases to 5 or 10 times the ULN were recorded for 13 and 5% of patients, respectively. Jaundice attributed to TB treatment was reported in 2% of patients (171).

During a prospective study in Haiti from 1990 to 1994 (172), increases in ALT of at least three times the ULN at 8 weeks were found in 12% of HIV-positive and in 9% of HIV-negative patients, and elevated bilirubin in 7 and 5% of patients, but there were no related interruptions in therapy.

In contrast, from a study of HIV, hepatitis C, and TB treatment (173), HIV infection independently increased the risk fourfold of serum transaminase increase to 120 IU/L or of total bilirubin to at least 1.5 mg/dl. Approximately 27% of HIV-infected individuals developed hepatotoxicity, compared with 12% among HIV-uninfected individuals. Nearly 80% of the patients in this study had a history of alcohol abuse, although random testing did not reveal active drinking, patients had not consumed alcohol in the 10 days before study entry, and all had normal baseline hepatic transaminases. The hepatotoxicity of antiretroviral drugs was not factored into the analysis (173).

In summary, definitions of hepatotoxicity and methodology varied among the studies, and most studies lacked HIV-negative control groups. Increases in serum transaminases or hepatitis were reported for 4 to 27% of patients, and increased bilirubin or jaundice in 0 to 7%. More data are needed in patients treated with HAART. The overall influence of HIV infection alone on DILI during treatment of TB disease is difficult to assess, but appears to be slight, with the exception of one study, where other confounding causes of hepatotoxicity, such as injection drug use, alcoholism, HAART, and viral hepatitis, were present.

Hepatitis B

Several studies from Asia have addressed DILI during treatment of TB disease in patients with hepatitis B infection. In Taiwan, 42 (2.4%) of 1,783 patients with TB treated with isoniazid, rifampin, and ethambutol had symptomatic hepatitis. Fifteen were hepatitis B carriers (had hepatitis B surface antigen), and 7 of 15 died of hepatic failure. Of the other 27 patients with symptomatic hepatitis who were not hepatitis B carriers, one died of hepatic failure (174). The severity of hepatotoxicity appears to have been increased in the hepatitis B carrier population.

Also in Taiwan, hepatitis B carriers with TB who received isoniazid, rifampin, pyrazinamide, and ethambutol had a hepatotoxicity rate of 29%, similar to the 26% experienced by hepatitis B-seronegative individuals (157). Patients were excluded if alcohol ingestion exceeded 60 g/day or if baseline serum transaminase concentrations were greater than the ULN.

In a study from Hong Kong (175), which excluded alcoholic and nonviral liver diseases, 16% of patients with TB with hepatitis B surface antigen developed symptomatic hepatitis compared with 4.7% in those without hepatitis B infection. Patients who had hepatitis B surface antigen also had more severe liver injury and were more likely to have a permanent treatment discontinuation, 4.7 compared with 2.5%.

A retrospective case-control study from Seoul, Korea, of 110 patients with hepatitis B surface antigen and normal pretreatment transaminases found a trend toward transaminase elevations of at least five times the ULN more frequently in the hepatitis B carrier group than in the control subjects (8 vs. 2%, $p = 0.05$). However, isoniazid and rifampin were successfully reintroduced in five of the nine carriers (176).

In summary, notable variations in study designs and the potential for confounding reasons preclude firm conclusions about the contribution of hepatitis B carriage alone to the incidence of liver injury for patients being treated for TB disease. Two of these four studies (175, 176) indicate that there may be increased incidence of TB DILI in hepatitis B carriers, whereas one does not (157). Two studies (174, 175) suggest that hepatitis B carriers may incur more severe hepatic disease from treatment-associated liver injury, and the extent of underlying liver disease could be a determinant. These studies did not stratify patients according to evidence of active hepatitis B viral replication, such as HBeAg or hepatitis B viral DNA. Additional studies are needed, but the limited data leave sufficient concern that hepatitis B may

be a risk factor for more frequent or severe hepatotoxicity during treatment of TB disease.

Hepatitis C

One study (173) has evaluated the impact of HCV infection on DILI during treatment for TB disease among 128 inpatients in Florida. All received at least 5 days of isoniazid, rifampin or rifabutin, or pyrazinamide, and had not received alcohol or drugs of abuse for at least 10 days before starting anti-TB therapy. Approximately 30% of hepatitis C–infected individuals developed hepatotoxicity compared with 11% among hepatitis C–uninfected individuals. Hepatitis C was an independent risk factor for the development of hepatotoxicity, elevating the risk fivefold of transaminase elevation of at least 120 U/L, or of serum bilirubin of at least 1.5 mg/dl. Coinfection with both hepatitis C and HIV elevated the risk of hepatotoxicity more than 14-fold.

DILI with Second-line Anti-TB Agents

Hepatotoxicity has been recognized to occur in about 2% of patients treated with ethionomide (177, 178) or prothionamide (179, 180), and in 0.3% of patients treated with para-aminosalicylic acid (181). Cycloserine does not appear to be associated with hepatotoxicity, but should be used with caution in patients at risk for alcohol withdrawal seizures (106).

RECOMMENDATIONS REGARDING TB DILI

Program Infrastructure

Standardized approaches to developing safe treatment of LTBI and TB disease should be implemented in an effort to prevent TB DILI. Optimal care requires the following:

1. Clear and recurring communications with patients in the preferred language
2. Accurate medical evaluation, treatment, and monitoring
3. Convenient access to care and rapid responses to suspected drug adverse events

Provider Education and Resources

1. TB DILI policies and procedures should be included in clinic manuals and in staff training.
2. Other health providers should be made aware of TB diagnosis and treatment, as allowed.
3. Providers without TB treatment experience or infrastructure should consider referral to a specialized clinic.

Pretreatment Clinical Evaluation

1. A standardized history form is recommended, which includes risk factors for hepatotoxicity.
2. The physical examination should include evaluation for signs of liver disease, such as liver tenderness, hepatosplenomegaly, jaundice, caput medusa, spider angiomas, ascites, and edema.
3. Previous laboratory values should be reviewed when available.
4. Screening for viral hepatitis should be considered for individuals who inject drugs; were born in endemic areas of Asia, Africa, the Pacific Islands, Eastern Europe, or the Amazon Basin; are HIV infected; may have had sexual or household contact with chronically infected individuals; may have had occupational exposure to infected blood; are chronic hemodialysis patients; are recipients of clotting factors before 1987; have undiagnosed liver disease; or are

recipients of blood or solid organ transplants before 1992. Infants born to infected mothers should also be considered for screening.

5. Voluntary HIV counseling and testing are recommended for all patients with TB disease.

Patient Education

1. Printed instructions should include clinic telephone numbers, include explicit instructions for after-hours care, and utilize patient's preferred language at a readable level.
2. Patients should be categorically told to immediately stop medications for nausea, vomiting, abdominal discomfort, or unexplained fatigue and to contact the clinic for further evaluation.
3. Patients should attend clinic follow-up visits for monitoring and reinforcement of education.
4. Patients should be warned about concomitant alcohol and hepatotoxic over-the-counter, and alternative and prescription medication use.
5. Patients should inform their health care providers of anti-TB medications prescribed.

Medication Administration and Pharmacy

1. Limiting dispensed doses to 1-month supplies constitutes a partial safeguard against continued drug ingestion when adverse effects are experienced.
2. The pharmacist should reinforce relevant patient education.
3. Medication package labels, in the patient's preferred language, warning against ingestion if specific hepatitis symptoms are present may be useful.

Treatment of LTBI

Patient and regimen selection. The clinician and patient decide on treatment of LTBI based on the benefits of treatment relative to its risks (Figure 1) (41).

1. Isoniazid taken for 9 months remains the preferred regimen.
2. Rifampin is an option for patients who may not tolerate isoniazid, but potential drug interactions should be considered.
3. Because isoniazid with rifampin is more hepatotoxic than either alone (100), this combination should be used with caution in patients at risk for hepatotoxicity.
4. For those with ALT elevation more than 2.5 to 3 times the ULN, chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits. If LTBI treatment is undertaken, close monitoring is indicated.
5. RZ is no longer generally recommended for treatment of LTBI (65).

Clinical monitoring (Figure 2).

1. Face-to-face clinical assessments are the cornerstone of clinical monitoring for treatment adherence and adverse effects.
2. Provider checklists for questioning patients should include adverse effects of anti-TB drugs and use of alcohol and other potentially hepatotoxic drugs.
3. The plan for clinical and/or biochemical monitoring should be explicit in clinic records.

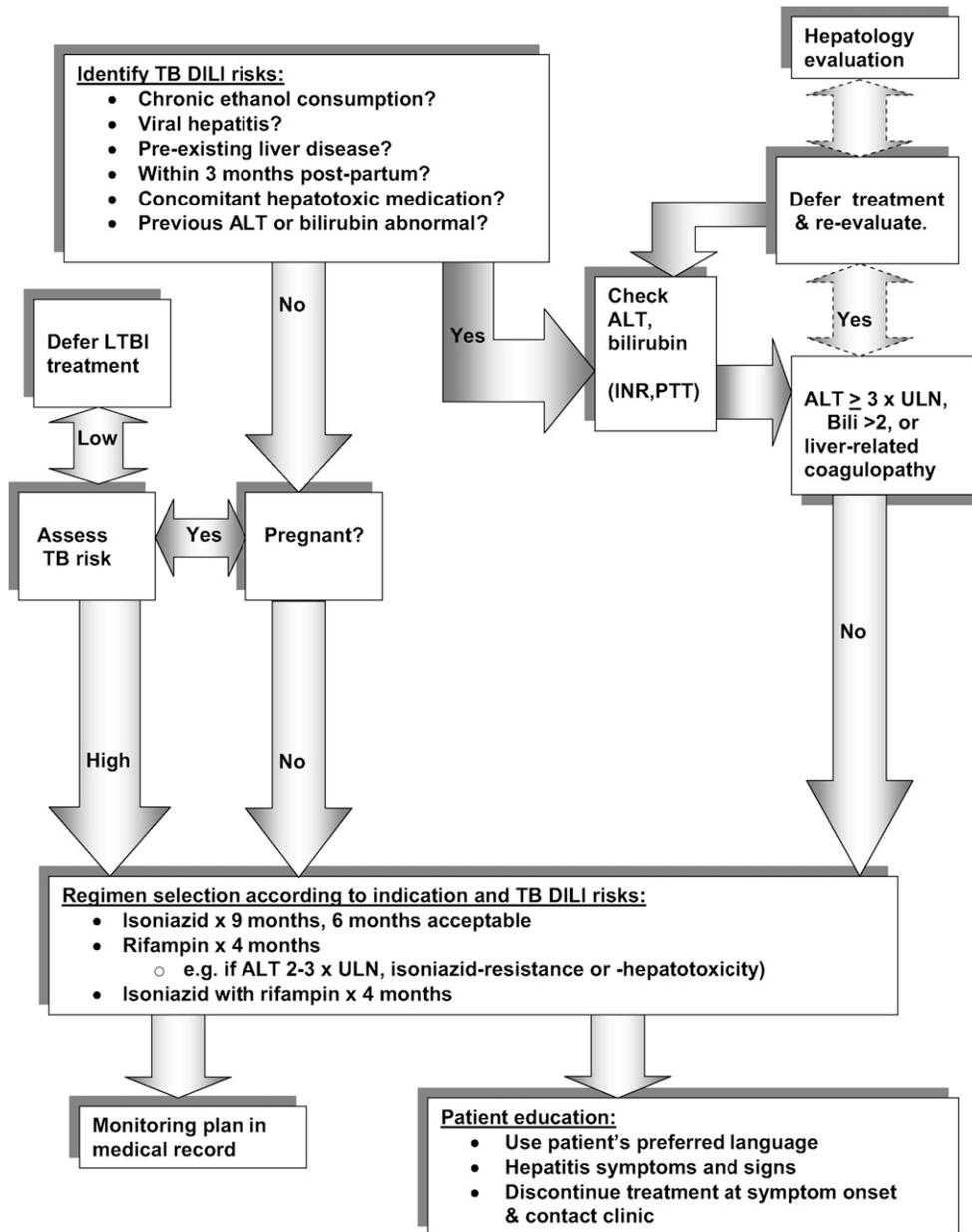


Figure 1. Latent tuberculosis infection (LTBI) pretreatment clinical evaluation and counseling. Dotted lines signify management according to physician's discretion. ALT = alanine aminotransferase; DILI = drug-induced liver injury; INR = international normalized ratio; PTT = partial thromboplastin time; ULN = upper limit of normal.

Baseline laboratory testing and monitoring (Figure 2).

1. Baseline blood tests are generally not recommended for healthy patients treated with isoniazid or rifampin.
2. Baseline and follow-up serum ALT and bilirubin are recommended for patients with a possible liver disorder; those with a history of chronic liver disease (e.g., chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis), patients with chronic use of alcohol, those with HIV infection treated with HAART, pregnant women, and those who are up to 3 months postpartum.
3. Baseline laboratory testing should be considered individually for patients receiving other medications and for those with chronic medical conditions (41).
4. Some experts recommend that healthy individuals older than 35 years treated with isoniazid or isoniazid with rifampin have baseline and scheduled monitoring of ALT. Monitoring schedules in such cases may be monthly; every other month; or at 1, 3, and 6 months in those taking a 9-month regimen (68), depending on the perceived hepatotoxicity risk, effectiveness of patient education, and the stability of ALT.
5. ALT is preferred for detecting and tracking hepatocellular injury in those who develop symptoms of hepatotoxicity.
6. Measurements of AST, bilirubin, and alkaline phosphatase are adjunctive for monitoring chronic liver disease, cholestasis, or severe hepatocellular injury.
7. The ULN used should be that of the laboratory performing the assay.
8. Optimally, reference limits for enzymes should be adjusted for age in children and in adults older than 60, and for sex in adults, if available (13, 14).
9. Hepatitis B surface antigen-seropositive individuals with elevated ALT should have HBeAg testing. If positive,

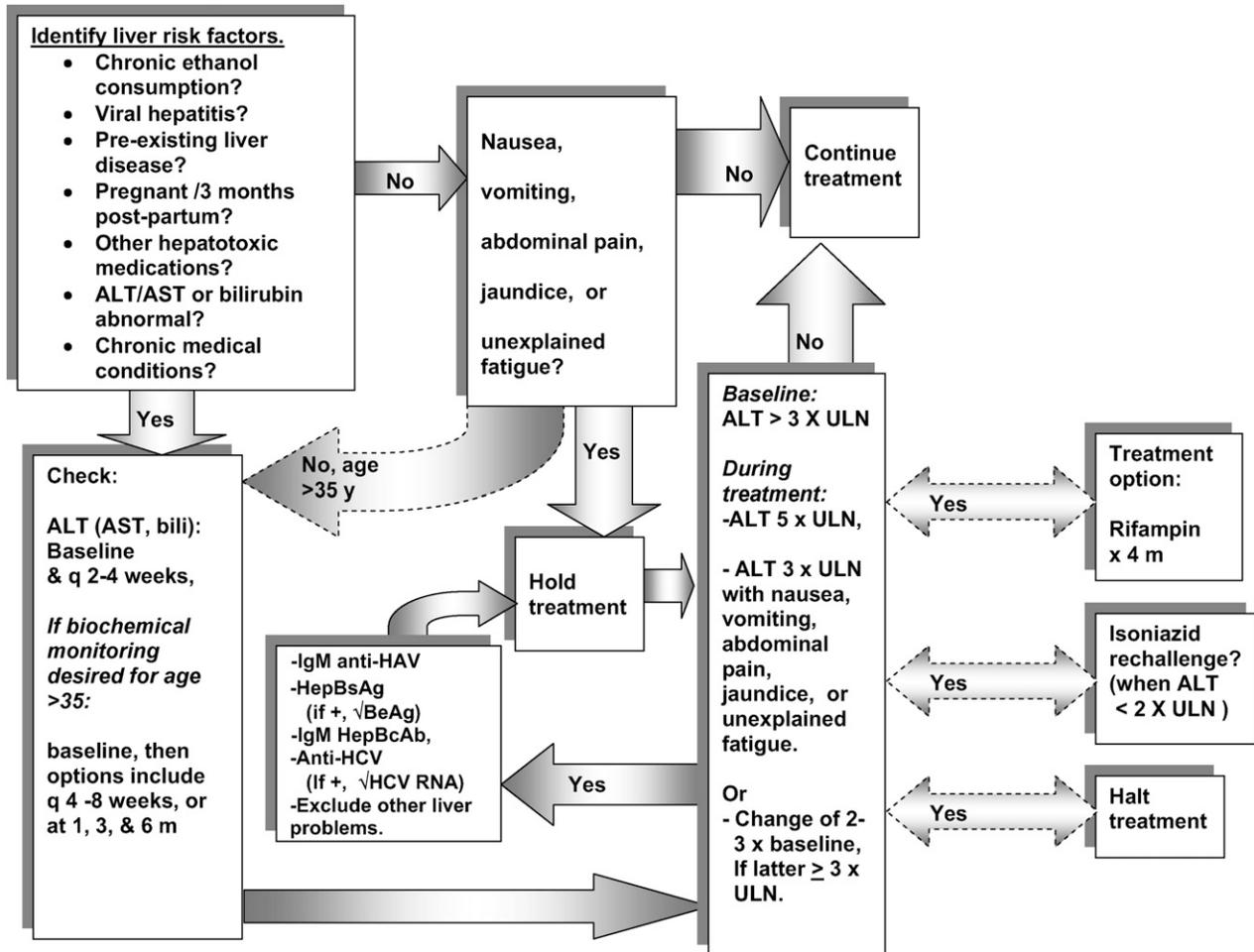


Figure 2. Monitoring for hepatotoxicity during LTBI treatment. Dotted lines signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAV = hepatitis B virus; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen; ULN = upper limit of normal.

rifampin may be preferred over isoniazid. A hepatologist should be consulted regarding further testing and possible pretreatment in individuals with an ALT at least two times the ULN, and who are HBeAg seropositive (182). In HBeAg-seropositive individuals, clinical and ALT monitoring should occur every 2 to 4 weeks.

10. Patients with baseline transaminases more than three times the ULN should have ALT retested along with bilirubin, as well as screening for viral or other causes of hepatitis, including alcohol and hepatotoxic drugs. The decision to treat LTBI, or more likely to defer, should be carefully made on a case-by-case basis, weighing the risk of progression to TB disease against the risk of isoniazid- or rifampin-related DILI. Factors influencing the latter include degree of baseline ALT elevation, alcohol consumption, age, and evidence of active replication of hepatitis virus. If treatment is started, some experts recommend measuring serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months, and as necessary. The international normalized ratio (INR) may be followed periodically as well in patients with severe hepatic impairment.
11. Some experts recommend monitoring transaminases in individuals treated with a combination of pyrazinamide

and a fluoroquinolone or ethambutol for contact with a patient with MDR TB.

Interventions for hepatotoxicity (Figure 2).

1. Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms (41).
2. A rapid increase in ALT may be an indication for more frequent monitoring, every 2 weeks instead of monthly, particularly if one of these treatment-limiting ALT thresholds is being approached, or if the patient has previously identified risk factors for hepatotoxicity.
3. For the few patients who may begin isoniazid LTBI treatment with a baseline ALT more than three times the ULN, some experts recommend, in the absence of adequate clinical data, that treatment should be discontinued if there is more than a two- to threefold increase above baseline or if there is a mental status change, jaundice, or significant increase in bilirubin or INR.

Screening for other causes of hepatitis.

1. Viral hepatitis and concomitant use of hepatotoxic drugs of any type should be excluded.

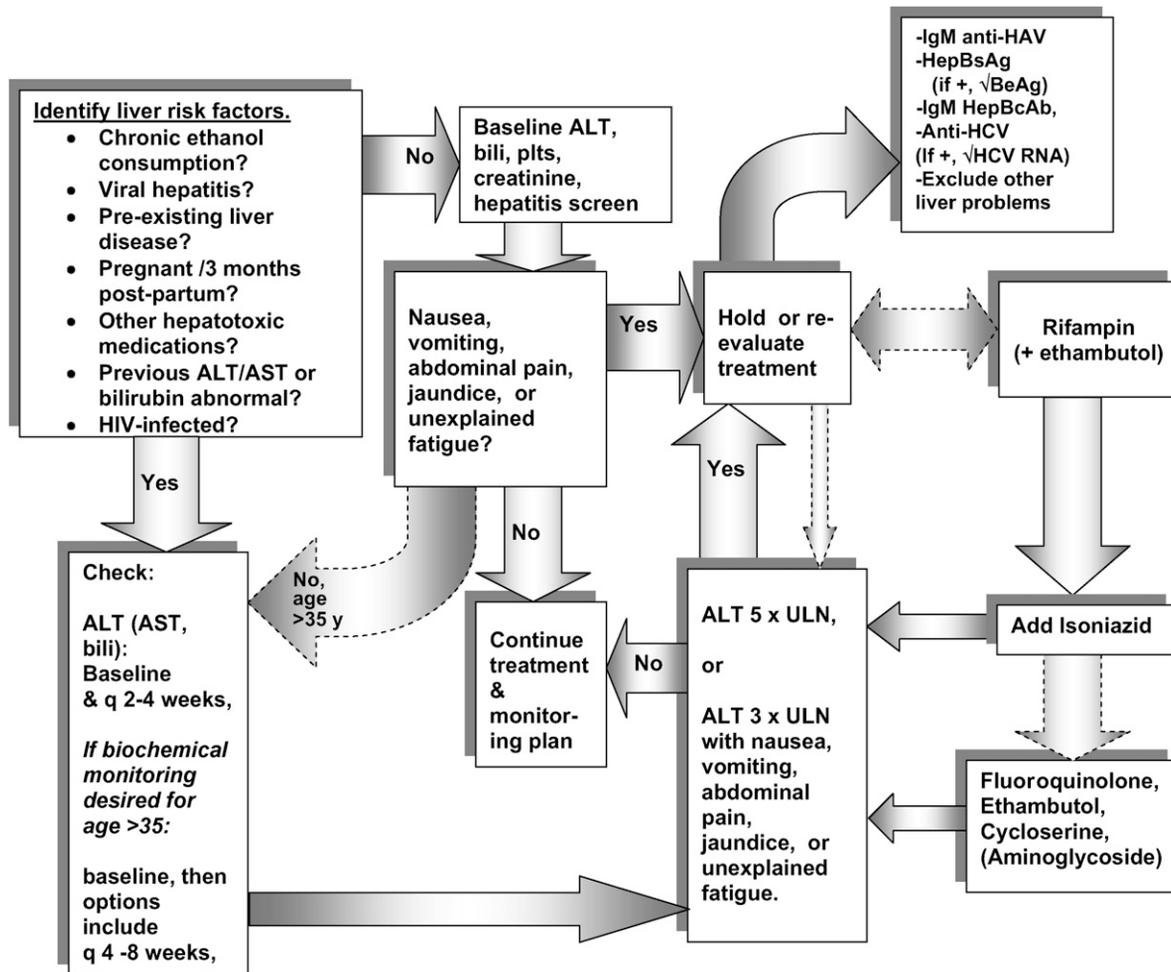


Figure 3. Monitoring for hepatotoxicity during treatment of TB disease. *Dotted lines* signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen.

- Screening tests for viral hepatitis should include IgM anti-hepatitis A virus, hepatitis B surface Ag, IgM anti-hepatitis B core, and anti-HCV antibody.
- In unusual or suggestive cases, the following tests may be considered: (1) anti-hepatitis E for recent residents of or travelers to endemic areas in developing countries, such as in Asia, North Africa, and Mexico; (2) anti-HDV antibodies (IgG and IgM) for injection drug users with evidence of hepatitis B (HBsAg); (3) HCV RNA to assess replication status in HCV antibody-positive cases or to exclude HCV antibody-negative cases (e.g., those with marked immune suppression or early infection); (4) heterophile Epstein-Barr virus antibody; and (5) antibodies to cytomegalovirus and herpes simplex in immunosuppressed patients.
- In severe cases or in those in whom ALT did not recover with drug withdrawal, additional testing for autoimmune disease may also be considered: anti-nuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody, and immunoglobulin profile (IgG, IgM, and IgA).
- Hepatology consultation is recommended for unusual or severe cases of hepatitis, particularly those who become sufficiently ill to require hospital admission or who may require liver transplantation.

Rechallenge.

- The risk of reintroducing of a TB medication could be hazardous and should be considered relative to its potential benefit.
- Rechallenge is considered when it is unclear which medication was the cause of symptoms or of transaminase increases.
- Rechallenge also may be considered if an increase in transaminase concentration did not reach the usual treatment-limiting threshold.
- Rechallenged patients who had reached a treatment-limiting threshold should have clinical and biochemical monitoring at 2- to 4-week intervals.
- Rechallenged patients should be told to stop medication in case of hepatitis symptoms.

Reporting of serious adverse events.

- Health care providers should report serious adverse effects, including hepatotoxicity, to the U.S. FDA's MedWatch program. Reporting may be by mail, telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or at the Internet website (www.fda.gov/medwatch).
- Adverse effects of treating LTBI serious enough to entail hospital admission or death also should be reported to the

CDC through local public health authorities or by calling 404-639-8401.

3. These surveillance systems capture different data, and reporting to both is necessary.

Treatment of TB Disease

Regimen selection. The crucial efficacy of isoniazid, and particularly rifampin, warrants their use and retention, if at all possible, even in the face of preexisting liver disease (106). Several regimens are recommended if baseline serum ALT is more than three times the ULN, and TB is not believed to be the cause (106):

1. Treatment without pyrazinamide might utilize isoniazid and rifampin for 9 months with ethambutol until drug susceptibility testing of the *M. tuberculosis* isolate is completed.
2. In patients with cirrhosis, rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered.
3. For patients with encephalopathic liver disease, ethambutol combined with a fluoroquinolone, cycloserine, and capreomycin or aminoglycoside for 18 to 24 months may be an option. However, these regimens have not been tested systematically (106).
4. Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected medication in patients with thrombocytopenia and/or coagulopathy.

Clinical monitoring.

1. Face-to-face monthly assessments and patient education for adverse drug events are essential.
2. Directly observed treatment (DOT) enhances treatment adherence and monitoring (106).
3. The World Health Organization and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend only clinical monitoring in patients with TB in low-income countries (41, 183, 184).

Baseline testing and monitoring (Figure 3).

1. Baseline measurements of serum transaminases, bilirubin, alkaline phosphatase, and creatinine, and a blood platelet count are recommended for all adults beginning treatment for TB disease.
2. For patients with preexisting severe liver disease, some clinicians also recommend periodic measurement of prothrombin time and INR to assess hepatic synthetic function.
3. Routine measurements during treatment are recommended when baseline abnormalities are present and for patients who chronically consume alcohol, take other potentially hepatotoxic medications, or who have viral hepatitis or history of liver disease, HIV infection, or prior TB DILI.
4. In patients with abnormal baseline transaminases, the range of their prior fluctuations may be of assistance in interpreting results of biochemical monitoring of treatment.
5. Some providers prefer to monitor ALT in women or older adults being treated for TB disease.

Interventions for hepatotoxicity.

1. The first-line anti-TB drugs, especially rifampin, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-TB treatment.

2. If serum transaminase concentrations are more than five times the ULN (with or without symptoms) or more than three times the ULN with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly.
3. Serologic tests for hepatitis A, B, and C viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol, and other hepatotoxic drugs.
4. Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy.
5. If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity.

Rechallenge.

1. After ALT returns to less than two times the ULN, rifampin may be restarted with or without ethambutol.
2. After 3 to 7 days, isoniazid may be reintroduced, subsequently rechecking ALT.
3. If symptoms recur or ALT increases, the last drug added should be stopped.
4. For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity (144), the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.

PRIORITIES FOR RESEARCH OF HEPATOTOXICITY IN TREATMENT OF LTBI AND OF TB DISEASE

1. *Basic mechanisms of TB DILI.* Further understanding is needed regarding mechanisms of drug injury, genetic variation of enzymes involved in TB drug metabolism and transport, potential hepatoprotective agents, and the influence of concomitant viral hepatitis.
2. *Program infrastructure and education modifications.* Education and intervention studies to minimize the impact of TB DILI are needed.
3. *Regimen selection and other hepatotoxic medications.* New, and less hepatotoxic, regimens will need safety and tolerability studies. Studies assessing the effect of hepatoprotective agents and of coadministered potentially hepatotoxic medications on the incidence and severity of TB DILI are needed.
4. *Monitoring.* Studies are needed to demonstrate that ALT monitoring reduces the incidence or severity of TB DILI.
5. *Hepatotoxicity risk assessments.* Additional studies are needed to assess hepatotoxicity in women and in those with viral hepatitis, including whether to treat chronic active hepatitis in selected patients before LTBI treatment.
6. *Medication administration and pharmacy.* Routes of administration that could reduce hepatotoxicity should be developed for clinical trials.

CONCLUSIONS

Many unanswered questions remain regarding TB DILI in an aging population, in an increasingly complex medical environment, with evolving demographics for TB infection and where

new treatments for TB are being developed. Understanding of the basic mechanisms and genetic factors associated with TB DILI is nascent. Such information should eventually allow identification of those most likely to suffer increased incidence and/or severity of DILI. The existing data are, in some instances, insufficient to come to strong conclusions regarding hepatotoxicity risks and monitoring. In the future, issues related to TB DILI will need to be reexamined as new data become available. Safe systems for treating patients, patient and staff education, appropriate selection of patients for treatment, careful regimen selection, and monitoring help minimize risks. The ability to adapt to a changing medical landscape will be crucial to continued safe and effective treatment for TB.

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