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Isoniazid

Updated: April 5, 2018.

OVERVIEW

Introduction

Isoniazid is the most reliable and most commonly used medication for tuberculosis. Isoniazid therapy is often associated with minor, transient and asymptomatic elevations in serum aminotransferase levels but, more importantly, isoniazid is a well known cause of acute clinically apparent liver injury which can be severe and is sometimes fatal.

Background

Isoniazid (eye' soe nye' a zid) or isonicotinic acid hydrazine is a potent antimycobacterial agent which is thought to act by inhibition of lipid and DNA synthesis of Mycobacterium tuberculosis, thus inhibiting its cell wall synthesis. Isoniazid was introduced into clinical practice in 1954 and contributed greatly to the subsequent dramatic decrease in morbidity and mortality of tuberculosis. In early studies, isoniazid was found to have few side effects, excellent complicance and rapid efficacy. Isoniazid rapidly became the mainstay of antituberculosis therapy but, because of the frequency of antibacterial resistance, was always used in combination with other agents. Rare instances of clinically apparent liver injury were reported in patients on antituberculosis therapy, but were usually attributed to the other agents being used (such as paraaminosalyclic acid [PAS]). In 1963, isoniazid was recommended as monotherapy for prevention of active disease in patients with latent tuberculosis, diagnosed on the basis of a positive purified protein derivative (PPD) tuberculin skin test. Cases of severe hepatotoxicity due to isoniazid alone soon appeared and clearly defined its hepatotoxic potential. Recommendations on use of isoniazid were then modified and restricted.

Because of the rapid development of antibacterial resistance, therapy of active tuberculosis usually employs two or more agents. Most modern antituberculosis regimens include the combination of isoniazid with either rifampin or pyrazinamide, or both. In cases of suspected or proven multidrug resistance, ethambutol or streptomycin may be added. Isoniazid is available in generic forms in tablets of 100 and 300 mg and as an oral solution of 50 mg/5 mL. Isoniazid is also available in fixed combinations with rifampin (Rifamate and Isonarif: isoniazid 150 mg with rifampin 300 mg) and pyrazinamide (Rifater: isoniazid 50 mg with rifampin 120 mg and pyrazinamide 300 mg). The recommended dose of isoniazid in adults is 300 mg (~5 mg/kg) daily or up to 900 mg (~15 mg/kg) once or twice weekly, either alone (in prevention) or in combination with other antituberculosis medications such as rifampin, pyrazinamide, streptomycin, and ethambutol. Once and twice weekly regimens are often used, because these regimens allow for directly observed therapy that is highly effective in improving compliance and completion rates. Common side effects include gastrointestinal upset, nausea, fever and rash. High doses of isoniazid can cause peripheral neuropathy which is preventable with concurrent administration of

pyridoxine (vitamin B6). Guidelines and detailed discussion of therapy of tuberculosis is available at the Centers for Disease Control and Prevention website: http://www.cdc.gov/tb/publications/guidelines/Treatment.htm.

Hepatotoxicity

Despite its limited use, isoniazid remains one of the most common causes of serious, idiosyncratic liver injury in the United States. Therapy with isoniazid is associated with transient serum aminotransferase elevations in 10% to 20% of patients, and levels rising above 5 times the upper limit of the normal range (ULN) in 3% to 5%. These enzyme elevations are usually asymptomatic and often resolve even with continuation of therapy without dose adjustment (Case 1 and 2).

In addition, isoniazid can also cause clinically apparent acute liver injury with jaundice, which arises in 0.5% to 1% and is fatal in 0.05 to 0.1% of recipients. Rates of hepatic injury vary greatly in the published literature. A major determinant of the variability is probably age. The rates of clinically apparent hepatitis due to isoniazid are estimated at 0.5% in patients 20 to 35 years of age, 1.5% in those 35 to 50 years of age, and 3% or higher in persons above the age of 50 years. Isoniazid hepatotoxicity is rare in children (but still occurs and can be fatal). Other risk factors are preexisting liver disease (hepatitis B or C), concurrent use of rifampin or pyrazinamide, and possibly alcoholism, black race and genetic factors. The typical time to onset of injury ranges from 2 weeks to 6 months, but can be as long as one year and as short as one week. The onset is usuallly insidious and resembles acute viral hepatitis with a prodromal period of nausea, anorexia, abdominal discomfort and fatigue, which is followed by dark urine and jaundice (Case 3 and 4). The pattern of liver enzyme elevations is typically hepatocellular with marked increases in ALT levels (>10 times ULN) and minimal increases in alkaline phosphatase values (usually <2 times ULN). Most frequently, the injury is self-limited and begins to resolve within a week of stopping isoniazid. However, at least 10% of jaundiced cases are severe and can be fatal or require emergency liver transplantation (Case 4 and 5). Acute liver failure from isoniazid appears to be more common in women than men, and in African Americans more than Caucasians. Severe outcomes are also probably related to delays in stopping therapy in symptomatic cases, pre-existing liver disease and concurrent use of other potentially hepatoxici medications. Features of hypersensitivity such as rash, fever and eosinophilia can occur, but are uncommon and usually mild if present at all. Isoniazid therapy can induce antinuclear antibodies even without hepatotoxicity or hypersensitivity reactions. For this reason, autoantibodies may be present during acute hepatic injury due to isoniazid, but they are generally low in titer and not accompanied by other features of autoimmune liver injury (hyperglobulinemia, arthralgias). Liver histology resembles acute viral hepatitis, but may show increased numbers of eosinophils or prominence of cholestasis.

Likelihood score: A (well established cause of clinically apparent liver injury).

Mechanism of Injury

The cause of liver injury due to isoniazid is believed to be accumulation of a toxic intermediate of its metabolism. Rates of injury may be somewhat higher in patients with a slow acetylation status, marked by genotypic variants in N-acetylation, or with abnormalities in CYP 2E1, the second major enzymatic pathway of its metabolism. Risk factors for developing isoniazid hepatotoxicity are older age and possibly alcohol use, cirrhosis, Asian race, malnutrition, underlying chronic hepatitis B or C, slow acetylator status, and use in combination with other antituberculosis medications. Despite the lack of prominent features of hypersensitivity, rapid recurrence of injury can occur with rechallenge, suggesting that the injury is immune-mediated, at least in part.

Outcome and Management

While isoniazid commonly causes serum ALT elevations, it is unclear at which level of elevation isoniazid should be stopped and whether monitoring of liver tests is effective in avoiding the clinically significant

hepatotoxicity of this agent. Importantly, the appearance of any symptoms of hepatitis (fatigue, nausea, poor appetite or jaundice) accompanied by liver enzyme elevations should lead to the immediate discontinuation of isoniazid. Using the appearance of clinical symptoms to guide decisions on discontinuation appears to be partially effective in preventing serious injury in patients on isoniazid therapy, but patients need to be carefully instructed and regularly reminded to pay attention to new onset of symptoms of fatigue or nausea that persist for more than a day and, if symptoms arise, to have serum enzyme levels tested promptly. If biochemical monitoring is done (generally at monthly intervals initially), isoniazid should be discontinued for any confirmed elevation of ALT above 5 times the ULN (or above 3 times ULN in the presence of symptoms). Biochemical monitoring is usually recommended for patients at high risk of developing hepatotoxicty--those with preexisting liver disease or above the age of 50 years. Even with monitoring, isoniazid remains a major cause of acute liver failure due to idiosyncratic reactions, and is associated with several instances of acute liver failure and death or emergency liver transplanation in the United States each year.

Chronic liver injury from isoniazid is rare and cases of vanishing bile duct syndrome have not been reported. There are no specific therapies for isoniazid induced liver injury. Corticosteroids are often used, but there is scant evidence for their benefit. A recent trial has suggested that N-acetylcysteine administration early in the course of acute severe liver injury due to medications improves spontaneous survival rates. Rechallenge with isoniazid can result in recurrence, but not always. Indeed, in prospective studies, up to 80% of persons with suspected isoniazid induced liver injury have tolerated reintroduction of treatment once the initial injury has resolved. Restarting therapy, however, should be done with caution and limited to mild cases, or those with serum enzyme elevations only and those in whom isoniazid is considered essential.

[First line medications used in the therapy of tuberculosis in the US include ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifapentine. Second line medications include streptomycin, capreomycin, cycloserine, ethionamide, fluoroquinolones such as levofloxacin and moxifloxacin, aminoglycosides such as amikacin, and para-aminosalicylic acid (PAS).]

Drug Class: Antituberculosis Agents

Other Drugs in the Class: Bedaquiline, Capreomycin, Cycloserine, Ethambutol, Ethionamide, Pyrazinamide, Rifabutin, Rifampin, Rifapentine, Streptomycin

CASE REPORTS

Case 1 and 2. Transient and persistent serum aminotransferase elevations during isoniazid therapy for latent tuberculosis.

[Modified from: Mitchell JR, Long MW, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventive therapy. Chest 1975; 68: 181-90. PubMed Citation]

Among 218 patients with latent tuberculosis (positive tuberculin skin test) treated with a one year course of isoniazid, 8 developed elevations in both AST and bilirubin, but none developed clinically apparent hepatitis. The course of AST and bilirubin elevations from two patients (table 4 from the publication: Cases 1 and 2) are shown.

Key Points

Medication:	Isoniazid (300 mg daily for 52 weeks)
Pattern:	Hepatocellular (Alk P values not given)
Severity:	2+ (jaundiced, not hospitalized)
Latency:	4 and 16 weeks to elevations in AST

Table continued from previous page.

Recovery:	20 weeks despite continuation of isoniazid in one patient, and persistent in the second
Other medications:	None mentioned

Laboratory Values

Weeks After Starting	Case #1 AST (U/L)	Case #1 Bilirubin (mg/dL)	Case #2 AST (U/L)	Case #2 Bilirubin (mg/dL)
0	16	0.3	19	0.5
4	135	0.9	35	0.4
8	663	5.2	37	0.4
12	412	3.6	49	0.4
16	78	1.2	92	0.4
20	37	1.4	181	0.6
20	29	1.1	342	0.6
24	29	1.1	342	0.6
28	22	1.2	920	4.9
32	22	1.3	201	1.8
40	20	0.6	77	0.6
48	18	0.9	124	0.7
52	15	0.8	138	0.6
After	17	1.3	62	0.6
Normal	**<30**	**<1.2**	**<30**	**<1.2**

Comment

Despite developing evidence of liver injury with jaundice, these two patients continued therapy with isoniazid and recovered completely (#1) or partially (#2). Serum aminotransferase elevations occur in 10% to 20% of patients treated with isoniazid for 1 year, but levels are usually minimally elevated and transient and are rarely (~1%) associated with symptoms. The aminotransferase elevations generally arise within the first 12 weeks of therapy, but can appear as late as 48 weeks. In up to 5% of patients, aminotransferase levels rise to at least 3 times the upper limit of normal and a proportion of these patients develop jaundice. It is prudent to stop therapy for any elevation of ALT or AST above 5 fold the upper limit of normal or for sustained values above 3 times the upper limit of normal, and certainly for any symptoms or appearance of jaundice. However, as shown in these two cases, "adaptation" and spontaneous recovery can occur even with fairly high aminotransferase elevations. The difficulty is that injury can be sustained and severe and result in acute liver failure. Furthermore, there are no reliable predictive features for recovery versus progressive damage. In this study, the laboratory testing was done in retrospect and results were not available until the study was over. Of course, tests for hepatitis A, B and C were not available at the time and the possible contribution of viral hepatitis to the abnormalities could not be assessed. Because the patients did not have symptoms of liver injury, therapy was continued.

Case 3. Acute hepatitis due to isoniazid.

[Modified from a case in the database of the Drug-Induced Liver Injury Network.]

A 66 year old Hispanic man developed nausea followed by dark urine and jaundice 6 weeks after starting isoniazid for latent tuberculosis. He had been in good health except for hypertension for which he had been taking enalapril for more than a decade. Because of a positive purified protein derivative (PPD) tuberculin skin test, he was started on a 6 month course of isoniazid [300 mg daily with pyridoxine]. Laboratory tests taken before starting therapy were normal except for a slightly raised total serum bilirubin. He remained asymptomatic until onset of nausea and indigestion during week 6 of therapy. He denied fever or rash. He had not taken any over-the-counter medications, herbals or acetaminophen. He had a history of heavy drinking but had stopped 4 years previously. Physical examination showed jaundice but no signs of chronic liver disease. Laboratory tests showed a total bilirubin of 6.3 mg/dL and marked elevations in ALT but minimal increase in alkaline phosphatase levels (Table). Tests for hepatitis A, B and C were negative. Serum ANA was strongly positive (1:20,480), but smooth muscle antibody was negative, and immunoglobulin levels were normal. Liver imaging showed no evidence of biliary obstruction. Liver biopsy was not done. Isoniazid was stopped promptly and he began to improve within days. Enalapril was restarted but therapy for latent tuberculosis was not pursued. One month later, he was asymptomatic and liver tests had returned to baseline.

Key Points

Medication:	Isoniazid (300 mg daily)
Pattern:	Hepatocellular (R=45.9)
Severity:	2+ (jaundice, but not hospitalized)
Latency:	6 weeks
Recovery:	4 weeks
Other medications:	Enalapril (chronically), pyridoxine

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		29	71	1.7	
0		Isoniazid (300 mg daily) started			
6 weeks	0	2326	114	6.3	Isoniazid stopped
	1 day	2486	137	9.0	INR=1.2
	4 days	1836	113	9.5	
7 weeks	1 week	773	104	6.1	
2 months	2 weeks	199	80	2.6	
3 months	5 weeks	32	64	1.3	
Normal Values		**<56**	**<130**	**<1.2**	

Comment

An acute viral hepatitis-like syndrome arising 6 weeks after starting therapy is typical of isoniazid hepatitis. Symptoms and signs may worsen for a few days after stopping but then usually improve rapidly. Immunoallergic features are unusual and, if present, are mild. Isoniazid therapy can induce ANA reactivity, but autoantibodies titers are usually low [making this case somewhat atypical] and not associated with other features that would suggest autoimmune hepatitis. Age above 35 years is the single major risk factor for isoniazid hepatitis. Alcohol use may also be a risk factor, but it is not clear whether the risk is related to concurrent use or with an alcohol history (probably the former). Treatment of latent tuberculosis in persons over the age of 35 should be done with caution. Patients should be informed of the risk of liver injury and warned of the signs and symptoms of liver

injury. Routine biochemical monitoring is prudent if there is pre-existing liver disease or perceived increased risk for liver injury. The mortality rate of isoniazid hepatitis with jaundice is at least 10%.

Case 4. Acute liver failure due to isoniazid.

[Modified from a case in the database of the Drug-Induced Liver Injury Network.]

A 58 year old Korean-American woman was found to have a positive tuberculin test when undergoing a routine physical examination at the time of changing her health plan. A chest X-ray was normal; despite this, she was started on isoniazid (300 mg daily) and pyridoxine (50 mg daily) for latent tuberculosis. Six months after starting isoniazid, she began to feel unwell and subsequently developed nausea, dark urine and jaundice. After being symptomatic for at least a week, she consulted her nephew for advice who told her to stop the isoniazid and seek medical help immediately. On presentation, she complained of fatigue, nausea and dark urine but denied fever, rash or pruritus. She had no previous history of liver disease and did not drink alcohol or take other medications or herbal products. Physical examination showed no evidence of chronic liver disease. Laboratory tests showed a serum bilirubin of 8.6 mg/dL, ALT 781 U/L and alkaline phosphatase of 185 U/L (Table). Isoniazid was discontinued and she was followed carefully as an outpatient. She was reactive for both anti-HBs and anti-HBc but HBsAg and IgM anti-HBc were negative as were tests for hepatitis A and C and serum autoantibodies. Ultrasound of the abdomen showed a mild degree of ascites and the liver appeared small and possibly cirrhotic. There were gallstones but no evidence of biliary obstruction. Serum bilirubin peaked two days later at 13.3 mg/dL and concurrent INR was 1.5. Thereafter, she improved and six weeks later was almost back to normal but refused further follow up.

Key Points

Medication:	Isoniazid (300 mg daily)
Pattern:	Hepatocellular (R=8.1)
Severity:	4+ (jaundice and features of hepatic failure)
Latency:	7 months
Recovery:	Almost complete within 6 weeks
Other medications:	Pyridoxine

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		20			
0		Isoniazid (300 mg daily) for latent tuberculosis			
6 months	0	781	185	8.6	
	3 days	637	189	13.3	INR=1.5
	5 days	609	186	11.8	
	7 days	584	246	15/9	INR=1.5
6.5 months	11 days	302	162	12.9	INR=1.3
8 months	7 weeks	62	206	2.6	
Normal Values		**<40**	**<55**	**<1.2**	

Comment

The frequency of hepatitis due to isoniazid increases with age and rates of hepatitis with jaundice in persons above the age of 55 are as high as 3%. Patients on antituberculosis therapy should be carefully warned of the risk of liver injury and told of the symptoms that should lead them to stop therapy or seek immediate medical advice these being fatigue lasting more than a day, nausea, dark urine and jaundice. This patient delayed stopping isoniazid and the subsequent liver injury was severe with ultrasound evidence of ascites and prolongation of the prothrombin time. She remained jaundiced for over a month and blood tests had not returned to normal levels when she was seen 6 weeks after stopping isoniazid. She refused further follow up.

Case 5. Acute liver failure due to combination antituberculosis therapy.

[Modified from: Farrell FJ, Keeffe EB, Man KM, Imperial JC, Esquivel CO. Treatment of hepatic failure secondary to isoniazid hepatitis with liver transplantation. Dig Dis Sc 1994; 39: 2255-9. PubMed Citation]

A 60 year old woman with pulmonary tuberculosis was treated with isoniazid (300 mg daily), rifampin (600 mg daily) and pyrazinamide (1.5 grams daily) and improved rapidly, but was found to have jaundice with bilirubin 3.5 mg/dL, AST 538 U/L and alkaline phosphatase of 148 U/L six weeks after starting therapy (Table). Her liver tests were reported to be normal before treatment. She had no history of liver disease, alcohol abuse, or risk factors for viral hepatitis. Isoniazid and rifampin were stopped, but pyrazinamide continued. One week later, she was admitted to a local hospital for worsening hepatic function. She was mildly encephalopathic and the prothrombin time was prolonged. She was transferred to a liver transplant center. She was in stage 3 hepatic coma and required artificial ventilation. Pyrazinamide was stopped and ofloxacin, ethambutol and streptomycin started. Blood tests for hepatitis A, B and C were negative. She underwent successful liver transplantation 5 days after transfer and 3 weeks after onset of symptoms. She recovered uneventfully and was discharged 16 days after transplant on cyclosporine and prednisone. She was maintained on ethambutol, streptomycin and ofloxacin for tuberculosis, and sputum cultures remained negative.

Key Points

Medications:	Isoniazid, rifampin, pyrazinamide
Pattern:	Hepatocellular (R=10.1)
Severity:	5+ (acute liver failure requiring liver transplantation)
Latency:	6 weeks
Recovery:	No
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Protime (seconds)	Bilirubin (mg/dL)	Other
Pre	Normal	Normal	Normal		
Isoniazid, rifampin and pyrazinamide started for active tuberculosis					
6 weeks	0	548		3.5	
7 weeks	7 days	1640	22.4	22.4	Admission
	20 days	1100*	34*	32.0*	Transfer
8 weeks	2 weeks	350*	41*	21.0*	
		Liver transplantation			
3 months	5 weeks	30*	11	5.0*	Discharge

Table continued from previous page.

Time After Starting	Time After Stopping	AST (U/L)	Protime (seconds)	Bilirubin (mg/dL)	Other
Normal Values		**<40**	**<14**	**<1.2**	

*Estimated from Figure 2.

Comment

An acute viral-hepatitis like presentation of drug-induced liver disease that was most likely due to isoniazid. While the case represents "definite" drug induced liver disease, it is impossible to be so definitive about which agent was responsible. Isoniazid is most likely, but pyrazinamide and, to a lesser degree, rifampin are also capable of causing acute severe liver injury. Despite stopping therapy promptly, the patient progressed to hepatic failure and required liver transplantation within 3 weeks of initial presentation. Risk factors for isoniazid hepatitis included age and combination therapy. Risk factors for severe outcome were age and sex.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Isoniazid – Generic

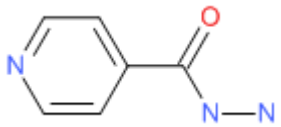
DRUG CLASS

Antituberculosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Isoniazid	54-85-3	C6-H7-N3-O	

ANNOTATED BIBLIOGRAPHY

References updated: 05 April 2018

Zimmerman HJ. Antituberculosis agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 611-21.

(Extensive review of hepatotoxicity of antituberculosis medications including isoniazid published in 1999).

Verma S, Kaplowitz N. Hepatotoxicity of antituberculosis drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 483-504.

(Review of hepatotoxicity of antituberculosis drugs published in 2013 mentions that approximately 1% of pateints on isoniazid develop overt hepatitis).

Gumbo T. Chemotherapy of tuberculosis, mycobacterium avium complex disease and leprosy. In, Brunton LL, Chabner KA, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1549-70.

(Textbook of pharmacology and therapeutics).

Randolph H, Joseph S. Toxic hepatitis with jaundice occurring in a patient treated with isoniazid. JAMA 1953; 152: 38-40. PubMed PMID: 13034525.

(Initial report of isoniazid hepatotoxicity; 46 year old man developed jaundice 6-7 weeks after starting isoniazid [bilirubin 21 mg/dL, Alk P 2 times ULN], with resolution in 2 months).

Gellis SN, Murphy RV. Hepatitis following isoniazid. Dis Chest 1955; 28: 462-4. PubMed PMID: 13261870.

(30 year old man with active tuberculosis developed jaundice and pruritus [bilirubin 5.4 mg/dL] after starting isoniazid, having had an allergic reaction to streptomycin, resolving clinically in 1 month).

Paine D. Fatal hepatic necrosis associated with aminosalicylic acid: review of literature and report of case. JAMA 1958; 167: 285-9. PubMed PMID: 13538701.

(29 year old woman developed fever and headache 3 weeks after starting isoniazid and PAS with subsequent rash, eosinophilia [8%], and jaundice [AST 830 U/L, Alk P 2 times ULN] progressing to coma and death; autopsy showed massive necrosis).

Berte SJ, Dewlett HJ. Isoniazid and para-aminosalicylic acid toxicity in 513 cases: a study including high doses of INH and gastrointestinal intolerance to PAS. Dis Chest 1959; 36: 146-51. PubMed PMID: 13672072.

(Among 513 patients with active tuberculosis treated with isoniazid alone, 5 had toxic reactions, 1 with fever, rash and jaundice, not otherwise described).

Merritt AD, Fetter BF. Toxic hepatic necrosis(hepatitis) due to isoniazid: report of a case with cirrhosis and death due to hemorrhage from esophageal varices. Ann Intern Med 1959; 50: 804-10. PubMed PMID: 13627721.

(Complex history in a 38 year old woman with tuberculosis who developed jaundice while on isoniazid and PAS [bilirubin 13 mg/dL] and had positive rechallenge with both isoniazid and PAS, but was later desensitized to isoniazid and tolerated therapy, only to present suddenly with cirrhosis and variceal hemorrhage; patient had a history of blood transfusions and may have also had hepatitis C).

Haber E, Osorne RK. Icterus and febrile reactions in response to isonicotinic acid hydrazine; report of two cases and review of the literature. N Engl J Med 1959; 260: 417-20. PubMed PMID: 13632903.

(Two cases; 55 and 35 year old men with active tuberculosis developed high fever 15 and 19 days after starting isoniazid and PAS or streptomycin accompanied by mild liver abnormalities [bilirubin 1.8 and 4.0 mg/dL], with rapid resolution and recurrence of fever on subsequent rechallenge).

Gillis S, Texler K. Unusual reactions to antituberculous chemotherapy. Med J Aust 1960; 2: 99-101. PubMed PMID: 13850127.

(36 year old woman treated for tuberculosis with PAS, isoniazid and streptomycin developed rash after 6 days resolving with stopping PAS, but subsequently developed fever and jaundice [bilirubin 5.0 mg/dL], resolving with stopping isoniazid; PAS rechallenge induced rash, but no liver test abnormalities).

Davies D, Glowinski JJ. Jaundice due to isoniazid. Tubercle 1961; 42: 504-6. PubMed PMID: 13883809.

(8 year old girl with active tuberculosis developed fever, nausea and rash 3 weeks after starting isoniazid later developing jaundice [bilirubin 2.0 mg/dL], resolving quickly, and developing fever and jaundice with rechallenge with both isoniazid and PAS).

Cohen R, Kalser MH, Thompson RV. Fatal hepatic necrosis secondary to isoniazid therapy. JAMA 1961; 176: 877-9. PubMed PMID: 13694414.

(50 year old man developed jaundice and pruritus 2 months after starting isoniazid and corticosteroids for sarcoidosis [bilirubin 17.4 mg/dL, AST 1450 U/L, Alk P 28.1 BU, protime 16.5 sec], with resolution over next 2 months, but recurrence after 6 weeks of restarting isoniazid with progressive hepatic failure and death; autopsy showed massive necrosis).

Medical Research Council. Long term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavitation. Tubercle 1962; 43: 265. Not in PubMed

(Among 284 patients with extensive pulmonary tuberculosis treated with isoniazid and PAS for 3-4 years, one developed hypersensitivity reaction and jaundice).

Reynolds E. Isoniazid jaundice and its relationship to iproniazid jaundice. Tubercle 1962; 43: 375-81. PubMed PMID: 13986418.

(56 year old man developed rash 5 weeks after starting isoniazid and PAS for tuberculosis and noted jaundice ten days after stopping [bilirubin 12 mg/dL, ALT 100 U/L, Alk P 26 KAU], which resolved but recurred twice with restarting isoniazid; author compared clinical features to those of iproniazid jaundice).

Berger HW, Berte SJ. Hypersensitivity to isoniazid. Report of a case with discussion of management and oral desensitization. Am Rev Respir Dis 1962 Jan; 85: 100-4. PubMed PMID: 13867657.

(29 year old man developed fever, malaise and rash followed by lymphadenopathy 22 days after starting isoniazid and PAS which persisted when PAS was stopped and resolved once isoniazid was stopped [bilirubin normal, AST 159 U/L, Alk P 1.5 times ULN], positive rechallenge to isoniazid, but ultimately successfully desensitized and continued both).

Gokecen M Zinneman HH. Liver "autoantibodies" in a case of drug-induced jaundice. Gastroenterology 1963; 44: 69-72. PubMed PMID: 13948619.

(49 year old man developed fever, rash and jaundice 39 days after starting isoniazid and PAS [bilirubin 23 mg/dL, AST 1760 U/L, Alk P 7 times ULN], with leukocytosis and high globulin levels and autoantibodies to normal liver membranes).

Berte SJ, Dimase JD, Christianson CS. Isoniazid, para-aminosalicylic acid, and streptomycin intolerance in 1,744 patients: An analysis of reactions to single drugs and drug groups plus data on multiple reactions, type and time of reactions, and desensitization. Am Rev Respir Dis 1964; 90: 598-606. PubMed PMID: 14221672.

(Among 1724 patients treated with isoniazid for tuberculosis, 22 [1.3%] had drug intolerance including 13 [0.7%] with fever and 6 [0.3%] with hepatitis, of whom 2 had jaundice and 5 were successfully desensitized and resumed therapy).

Smith JM, Springett VH. Serum transaminase levels during treatment with isoniazid. Tubercle 1966; 47: 245-9. PubMed PMID: 5971411.

(Among 15 patients with drug rash attributed to PAS, 40% had ALT elevations compared to only 1 of 10 with rash attributed to streptomycin).

O'Sullivan DC. Isoniazid jaundice during the treatment of genitourinary tuberculosis. Tubercle 1966; 47: 221-4. PubMed PMID: 6007094.

(44 year old man developed fever and body aches 3 weeks after starting PAS, streptomycin and isoniazid followed by rash and jaundice [bilirubin 3.0 mg/dL, AST 120 U/L]; restarting isoniazid led to fever, abdominal pain and rise in ALT, restarting PAS led to fever and rash).

Bruno MS, Ober WB. Acute fulminant hepatic failure with bilateral tuberculous cavitation. N Y State J Med 1968; 68: 2934-40. PubMed PMID: 5247023.

(74 year old man developed jaundice 7 weeks after starting isoniazid and PAS for active tuberculosis [bilirubin 9.5 mg/dL, ALT 460 U/L, Alk P 6 times ULN, protime 23 sec], with subsequent hepatic failure and death; autopsy showed massive necrosis).

Lederman RJ, Davis FB, Davis PJ. Exchange transfusion as treatment of acute hepatic failure due to antituberculosis drugs. Ann Intern Med 1968; 68: 830-8. PubMed PMID: 5642965.

(23 year old woman developed fever, rash and malaise 41 days after starting isoniazid, ethambutol and PAS for tuberculosis [bilirubin 3.0 rising to 15.5 mg/dL, ALT 850, Alk P 2 times ULN] accompanied by confusion and coma; treated with exchange transfusions and recovered; PAS was stopped promptly, but isoniazid continued for a period).

Scharer L, Smith JP. Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 1969; 71: 1113-20. PubMed PMID: 5361410.

(Over a 3 year period, 11% of 77 patients with active tuberculosis and 10% of 90 employees with positive PPD developed serum ALT elevations during isoniazid therapy, 9 patients stopped therapy and ALT fell to normal within 2 weeks in all; 8 continued treatment whereupon ALT levels normalized; several patients were able to restart isoniazid without recurrence).

Assem ES, Ndoping N, Nicholson H, Wade JR. Liver damage and isoniazid allergy. Clin Exp Immunol 1969; 5: 439-42. PubMed PMID: 5359962.

(42 year old man developed rash followed by jaundice 1 month after starting streptomycin, PAS and isoniazid for active tuberculosis; positive lymphocyte stimulation tests to isoniazid only; subsequently desensitized to all three agents).

Grossman LA, Kaplan HJ, Brittingham TE. Jaundice and death from isoniazid. J Tenn Med Assoc 1970; 63: 23-8. PubMed PMID: 5410185.

(Five cases of severe hepatotoxicity attributed to isoniazid [2 also received PAS]; 1 man and 4 women, ages 35-67 years, onset of jaundice in 3-8 weeks; 3 had fever and rash; 2 had positive rechallenges; fatal in two with massive necrosis on autopsy).

Martin CE, Arthaud JB. Hepatitis after isoniazid administration. N Engl J Med 1970; 282: 433-4. PubMed PMID: 5412191.

(40 year old man developed jaundice 4 weeks after starting isoniazid alone for latent tuberculosis [bilirubin 18.4 mg/dL, AST 1885 U/L, Alk P 8.8 Sigma Units], with resolution in 2 months and two positive rechallenges).

Brummer DL. Isoniazid and liver disease. Ann Intern Med 1971; 75: 643-4. PubMed PMID: 5094080.

(Summary of report of Ad Hoc Committee on Isoniazid and Liver Disease recommending monitoring of patients receiving isoniazid and prioritizing indications for prophylaxis).

Noble J. Isoniazid prophylaxis re-examined. N Engl J Med 1971; 285: 687-9. PubMed PMID: 5563483.

(Editorial on issues of safety of isoniazid after two deaths reported in Washington DC among persons receiving therapy for latent tuberculosis, recommending restricting use to children and high risk persons).

Lees AW, Allan GW, Smith J, Tyrrell WF, Fallon RJ. Toxicity from rifampicin plus isoniazid and rifampicin plus ethambutol therapy. Tubercle 1971; 52: 182-90. PubMed PMID: 4255439.

(Among 105 patients with active tuberculosis treated with isoniazid and rifampin, 22% had ALT and 13% bilirubin elevations, 8% skin rash and 3 hypersensitivity reactions, two with jaundice [bilirubin 3.8 and 1.8 mg/dL; ALT 330 and 235 U/L], resolving on stopping).

Kester NM. Isoniazid hepatotoxicity—fact of fantasy. JAMA 1971; 217: 699. PubMed PMID: 5109098.

(Among 84 institutionalized adults treated with isoniazid for 1 year, 2 developed jaundice [bilirubin 7.4 and 12.4 mg/dL] but isoniazid was continued, tests returned to normal, and both patients finished therapy).

Mosley JW, Sencer DJ. Isoniazid toxicity. JAMA 1971; 218: 447. PubMed PMID: 5109874.

(Two letters in response to Kester 1971, stressing serious nature of isoniazid associated jaundice and need for monthly monitoring).

Tizes R, Hayden CH, Perrin P. Screening for prevention of isoniazid-associated liver disease. JAMA 1971; 218: 1703. PubMed PMID: 5171051.

(Developed screening questionnaire given monthly to persons on isoniazid for latent tuberculosis, but one still developed isoniazid associated liver disease).

Moulding T. Chemoprophylaxis of tuberculosis: when is the benefit worth the risk and cost? Ann Intern Med 1971; 74: 761-70. PubMed PMID: 5314806.

(Review of risks of developing active tuberculosis among persons in various categories of risk questioning the need to treat adults with positive PPD reactions who have no risk factors for reactivation of tuberculosis and normal chest X-ray).

Stadler ET, Steiner M. Isoniazid treatment for tuberculosis. N Engl J Med 1971; 284: 730-1. PubMed PMID: 4993672.

(Letter raising issue of safety and need for treatment of latent tuberculosis; reply from author on lack of resistance arising with isoniazid monotherapy and infrequency of clinically significant liver injury).

Lal S, Singhal SN, Burley DM, Crossley G. Effect of rifampicin and isoniazid on liver function. Br Med J 1972; 1: 148-50. PubMed PMID: 5007842.

(63 patients given, isoniazid, streptomycin and rifampin; 29% had AST elevations, but all were self-limited, lasting for only 5-20 days even with continuing drug).

Moss JD, Lewis JE, Knauer CM. Isoniazid-associated hepatitis. A study of five cases. Am Rev Respir Dis 1972; 106: 849-56. PubMed PMID: 4641220.

(Five cases of isoniazid hepatitis in patients treated for latent tuberculosis at single institution over 12 month period, 2 men and 3 women, ages 44-56 years, onset in 6 days-4.5 months, bilirubin 0.8-19 mg/dL, ALT 125-1300 U/L, Alk P 1.5-3 times ULN, resolution in 6-12 weeks).

Dove JT, Chaparas SD, Hedrick SR. Failure to demonstrate transformation of lymphocytes of patients with isoniazid-associated hepatitis. Am Rev Respir Dis 1972; 106: 485-7. PubMed PMID: 5080721.

(Lymphocyte stimulation tests to isoniazid done in 12 patients with isoniazid hepatitis who were off of therapy for 7-241 days failed to show reactivity in any patient).

Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB. Isoniazid-associated hepatitis. Report of an outbreak. Am Rev Respir Dis 1972; 106: 357-65. PubMed PMID: 5080707.

(Among 2321 Capitol Hill employees treated with isoniazid for latent tuberculosis, 19 [0.8%] developed clinically apparent liver injury over a 9 month period, 13 were jaundiced and 2 died; 1 case of hepatitis among 2154 controls).

Meade GM. Isoniazid and the liver. Clin Pediatr(Phila) 1972; 11: 498. PubMed PMID: 5073797.

(Summary of conclusions of CDC's Committee on Isoniazid and Liver Disease; that isoniazid can cause liver disease, similar to viral hepatitis that is unpredictable, rate being 0-10 cases/1000 person-years, and "does not appear to occur in children").

Hyde L, Woolpert SF. Hypersensitivity reactions and liver toxicity attributed to isoniazid. Am Rev Respir Dis 1972; 106: 281-2. PubMed PMID: 5049663.

(Two letters on isoniazid hepatotoxicity; hypersensitivity reactions may be more common with higher doses; no evidence for contamination as an explanation of recent outbreaks of isoniazid hepatitis).

Byrd CB, Nelson R, Elliott RC. Isoniazid toxicity. A prospective study in secondary chemoprophylaxis. JAMA 1972; 220: 1471-3. PubMed PMID: 5067581.

(Prospective study of 160 military personnel given isoniazid for 1 year for treatment of latent tuberculosis, 12 [8%] developed symptoms with ALT elevations in 9 [60-1400 U/L], usually in first 4 weeks; all resolved, no jaundice).

Smith J, Tyrell WF, Gow A, Allan GW, Lees AW. Hepatotoxicity in rifampin-isoniazid treated patients related to their rate of isoniazid inactivation. Chest 1972; 61: 587-8. PubMed PMID: 5032153.

(Among 126 patients on isoniazid and rifampin, 23% developed transient AST elevations with similar rates in slow and rapid acetylators; increases in both AST and bilirubin in 14% of slow, but only 2.7% of rapid acetylators).

Bailey WC, Thompson DH, Carson B, Greenberg HB. Fatal hepatic necrosis in a woman receiving chemoprophylaxis with isoniazid. Am J Gastroenterol 1973; 59: 512-7. PubMed PMID: 4711068.

(38 year old woman developed jaundice 1 month after starting isoniazid for latent tuberculosis but continued taking drug for 3-4 more months when she developed deep jaundice, ascites and hepatic coma [bilirubin 27.7 mg/dL, AST 860 U/L] and died; autopsy showed massive necrosis).

Bailey WC, Taylor SL, Dascomb HE, Greenberg HB, Ziskind MM. Disturbed hepatic function during isoniazid chemoprophylaxis. Monitoring the hepatic function of 427 hospital employees receiving isoniazid chemoprophylaxis for tuberculosis. Am Rev Respir Dis 1973; 107: 523-9. PubMed PMID: 4697661.

(Among 427 hospital employees with latent tuberculosis receiving isoniazid, 37 [9%] developed elevated AST values and 5 [1.2%] had symptomatic hepatitis, arising 4-8 months after starting with jaundice in 3 [bilirubin 3.5-6.2 mg/dL, AST 180-940 U/L], all resolving rapidly with stopping).

Levy SA. Letter: Disturbed hepatic function during isoniazid chemoprophylaxis. Am Rev Respir Dis 1973; 108: 1452-3. PubMed PMID: 4751738.

(Letter in response to Bailey et al. [1973b] suggesting that monitoring of AST values should be done in patients on isoniazid to prevent asymptomatic as well as symptomatic liver injury).

Rudoy R, Stuemky J, Poley JR. Isoniazid administration and liver injury. Am J Dis Child 1973; 125: 733-6. PubMed PMID: 4266968.

(6 year old boy developed fever and rash 4 weeks after starting isoniazid, streptomycin and PAS for active tuberculosis [bilirubin 0.5 mg/dL, AST 156 U/L, Alk P 2.5 times ULN], with rapid resolution on stopping drugs; challenge with isoniazid led to fever, rash and rise in AST; switched to rifampin and ethambutol and later had a febrile response again to isoniazid rechallenge [bilirubin 0.6 mg/dL, AST 204 U/L]).

Bailey WC, Taylor SL, Samuels MS, Dascomb HE, Ziskind M, DeRouen TA. Validity of serum glutamic oxalacetic transaminase determinations in isoniazid recipients. Am Rev Respir Dis 1973; 107: 670-2. PubMed PMID: 4697675.

(Blood samples from 12 patients on isoniazid with elevated AST levels were retested using a different method and all were found to be elevated to a similar extent).

Maddrey WC, Boitnott JK. Isoniazid hepatitis. Ann Intern Med 1973; 79: 1-12. PubMed PMID: 4721174.

(Summary of 14 cases of isoniazid hepatotoxicity seen over 5 year period at Johns Hopkins Hospital; 11 women and 3 men, ages 19 to 65, onset after 2-25 weeks, 3 with eosinophilia, 4 with fever, all with jaundice, usually marked

AST elevations with minimal increase Alk P, 3 fatalities, 3 had positive rechallenge, histology showed viral hepatitis-like changes and more severe cases with multilobular or bridging necrosis).

Stead WW, Texter EC Jr. Isoniazid hepatitis: backlash of progress. Ann Intern Med 1973; 79: 125-7. PubMed PMID: 4721156.

(Editorial in response to Maddrey and Boitnott [1973] summarizing recent reports of hepatotoxicity of isoniazid and recommending monitoring for symptoms rather than routine liver tests).

Gould DB, Falcao H, Galdabini J. Letter: Isoniazid hepatotoxicity. Ann Intern Med 1973; 79: 902-3. PubMed PMID: 4586818.

(In response to article by Maddrey and Boitnott [1973], authors report 29 year old male renal transplant recipient given isoniazid for prophylaxis of latent tuberculosis who developed jaundice 3 months later [bilirubin 5.9 mg/dL, AST 1830 U/L, Alk P 2 times ULN], with rapid recovery upon stopping).

Badger TL, Levy SA, Stead WW, Alonso K, Starke WR. Letter: Isoniazid hepatitis. Ann Intern Med 1973; 79: 751-2. PubMed PMID: 4751753.

(Letters in response to editorial by Stead [1973], raising issues of possible viral causes of hepatitis in patients on isoniazid, the role of AST monitoring, and another case of fatal isoniazid hepatotoxicity [53 year old woman developed jaundice 6 weeks after starting isoniazid with bilirubin rising to 35.4 mg/dL, AST 1000 U/L, and prothrombin time 38.5 seconds, autopsy showing massive hepatic necrosis]).

Badger TL; Boitnott JK, Maddrey WC; Murphy D. Isoniazid hepatitis. Letters. Ann Intern Med 1974; 80: 113-4. PubMed PMID: 4810337.

(Badger raises issue of other causes of hepatitis in cases attributed to isoniazid by Maddrey and Boitnott [1973], who reply by citing overwhelming evidence that isoniazid can cause severe hepatitis; Murphy reports that 3 of 249 [1.2%] United Farm Workers in California treated with isoniazid for latent tuberculosis developed symptomatic hepatitis after 6-8 weeks, 2 with jaundice, all recovering within 1-3 months).

Stein SC. Letter: Isoniazid hepatitis. Ann Intern Med 1974; 80: 423-4. PubMed PMID: 4816197.

(Letter in response to Maddrey and Boitnott [1973] reporting 33 cases of suspected isoniazid hepatotoxicity from Philadelphia, the majority of cases [31 of the total] in patients receiving prophylaxis for latent tuberculosis, frequency being approximately 2.5 per 1000 treated).

Black M. Editorial: Isoniazid and the liver. Am Rev Respir Dis 1974; 110: 1-3. PubMed PMID: 4834614.

(Isoniazid hepatitis arises in ~1% of recipients of prophylaxis with higher rates in older persons and in alcohol users; onset usually in 4-8 weeks with a viral hepatitis-like syndrome; 24 fatalities reported).

Rolla AR. Letter: Isoniazid hepatoxicity. Ann Intern Med 1974; 80: 278-9. PubMed PMID: 4811806.

(Author reports case from Hel Med Acta [1996; 33: 6-21] in which a 53 year man old developed lactic acidosis within days of starting isoniazid, viomycin and thicarlide [ALT 4200 U/L, Alk P 105 U/L, pH 7.15] who subsequently died and had diffuse hepatic necrosis on autopsy).

Swasey LK. Hepatotoxicity to isoniazid. A case report. Ariz Med 1974; 31: 17-9. PubMed PMID: 4812384.

(59 year old man developed fever, jaundice and listlessness 3 weeks after starting isoniazid for active tuberculosis [bilirubin 25 mg/dL, ALT 600 U/L, Alk P 100 U/L], with slow recovery over next 6 weeks after stopping isoniazid; later treated with rifampin and streptomycin).

Beaudry PH, Brickman HF, Wise MB, MacDougall D. Liver enzyme disturbances during isoniazid chemoprophylaxis in children. Am Rev Respir Dis 1974; 110: 581-4. PubMed PMID: 4429254.

(Among 369 children ages 1-18 years treated for latent tuberculosis with isoniazid, 7% had abnormal AST values at 2 months but only 4 stopped therapy, 3 of whom resumed treatment without problems; in other patients, AST fell to normal despite continuing isoniazid; no hepatitis or jaundice).

Craner GE, Cooper EB. Letter: Isoniazid. Ann Intern Med 1974; 81: 273. PubMed PMID: 4843589.

(40 year old woman developed jaundice 8 months after starting isoniazid and taking it intermittently [bilirubin 20.4 mg/dL, AST >2500 U/L, Alk P 201 U/L], with progressive liver failure and death in 10 days of admission; patient had also taken erythromycin).

Salyer IL, Cynamon MH. Letter: Isoniazid. Ann Intern Med 1974; 81: 272. PubMed PMID: 4843588.

(Letter arguing for continuing use of isoniazid to treat latent tuberculosis and attention to surveillance of patients for symptoms of hepatitis).

Bailey WC, Weill H, DeRouen TA, Ziskind MM, Jackson HA, Greenberg HB. The effect of isoniazid on transaminase levels. Ann Intern Med 1974; 81: 200-2. PubMed PMID: 4843577.

(Among 85 employees treated with isoniazid for latent tuberculosis, 12% developed AST levels above 100 U/L compared to none of 90 untreated controls [all resolved after stopping; no mention of symptoms or jaundice]).

Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. Q J Med 1975; 44: 1-16. PubMed PMID: 50605.

(Retrospective review identified 38 cases of hepatitis [~0.32%] due to antituberculosis therapy [Capetown, SA], 16 due to PAS, 12 to PAS with isoniazid, 3 isoniazid alone, 1 each of others including ethambutol; rash and fever typical of PAS reactions, most within 90 days; 33 with jaundice).

Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975; 69: 289-302. PubMed PMID: 1150039.

(Between July 1971 and November 1972, 13,838 patients were enrolled in a nationwide surveillance program while being treated with isoniazid for latent tuberculosis, 114 developed probable isoniazid hepatitis [0.8%]; clinical features were available on 66; similar to viral hepatitis with fever in 6%, rash in 1, mild eosinophilia in 10%, AST often >ALT, onset after 1-12 months, half in first 2 months, 13 deaths [12%] of whom 9 were black females; histology in 33 cases, hepatocellular in all but one, fatal cases had submassive or massive necrosis).

Hanson AS. Letter: Isoniazid and the liver. Am Rev Respir Dis 1974; 110: 817. PubMed PMID: 4429278.

(Letter in response to Black [1975] arguing for routine biochemical monitoring during isoniazid prophylaxis; reply by author citing recommendations from the USPHS).

Israel HL. Editorial: Isoniazid-associated hepatitis. Reconsideration of the indications for administration of isoniazid. Gastroenterology 1975; 69: 539-42. PubMed PMID: 1150056.

(Editorial in response to Black [1975] on the history of isoniazid, its gradual wide scale use and the subsequent finding of hepatotoxicity; hepatitis occurring in 0.6% of recipients and 1.3% of those receiving one year of therapy).

Farer LS. Letter: The isoniazid problem. Gastroenterology 1976; 70: 631. PubMed PMID: 1254145.

(Letter in response to editorial by Israel [1975] arguing for use of isoniazid for latent tuberculosis, questioning the reported mortality rate of isoniazid hepatitis).

Reichman LB. Letter: The isoniazid problem. Gastroenterology 1976; 70: 631-2. PubMed PMID: 1254146.

(Letter in response to editorial by Israel [1975] arguing the need for preventive therapy in PPD responders; reply by author indicating that those who need prophylaxis are limited group who may not respond and often refuse or drop out of therapy).

Mitchell JR, Long MW, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventive therapy. Chest 1975; 68: 181-90. PubMed PMID: 1080096.

(Prospective study of 218 psychiatric inpatients with latent tuberculosis treated with isoniazid for 1 year and 140 controls; AST values above 30 U/L were present in 3% before and 10-12% on therapy [at least 1 abnormal value in 38% of treated vs 15% of controls]; 3 patients became jaundiced [bilirubin 2.5-5.3 mg/dL], but none developed frank hepatitis and many resolved despite continuing isoniazid [adaptation], persistent abnormalities in only 2; no predictive factors: Cases 1 and 2).

Mitchell JR, Thorgeirsson UP, Black M, Timbrell JA, Snodgrass WR, Potter WZ, Jollow HR, et al. Increased incidence of isoniazid hepatitis in rapid acetylators: possible relation to hydrazine metabolites. Clin Pharmacol Ther 1975; 18: 70-9. PubMed PMID: 1149365.

(Rapid acetylator phenotype was found in 18 of 21 patients recovered from isoniazid hepatitis, and 3 of 5 with ALT elevations during therapy compared to expected frequency of 45%).

Moulding TS. The competing risks of tuberculosis and hepatitis for adult tuberculin reactors. Am Rev Respir Dis 1975; 112: 1975. PubMed PMID: 1200492.

(Letter questioning treatment of latent tuberculosis in persons above the age of 35 who are without other risk factors for developing active disease).

Lewis JE, Mello P, Knauer CM. Isoniazid-associated hepatitis—serum enzyme determinations and histologic features. West J Med 1975; 122: 371-6. PubMed PMID: 1130028.

(Among 189 outpatients treated for latent tuberculosis, AST elevations occurred in 21% of adults [1 jaundiced] and 6% of children; 11% were symptomatic, AST elevations persisted after stopping in some patients).

Casteels-Van Daele M, Igodt-Ameye L, Corbeel L, Eeckels R. Hepatotoxicity of rifampicin and isoniazid in children. J Pediatr 1975; 86: 739-41. PubMed PMID: 1079531.

(13 year old boy developed symptoms after 7 days and coma after 11 of isoniazid, rifampin and ethambutol for active tuberculosis [bilirubin 5.2 mg/dL, ALT 1500 U/L, Alk P 302 U/L, prothrombin index <10%]; patient nevertheless recovered and was later treated with isoniazid without recurrence; short latency suggests rifampin as a cause).

Litt IF, Cohen MI, McNamara H. Isoniazid hepatitis in adolescents. J Pediatr. 1976; 89: 133-5. PubMed PMID: 819639.

(Among 178 adolescents in detention facility treated with isoniazid for latent tuberculosis for up to 1 year, ALT elevations occurred in 10% [56-1200 U/L] usually within 10 weeks; therapy stopped in only one for ALT elevations, whereas in the rest the elevations resolved despite continuation).

Vanderhoof JA, Ament ME. Fatal hepatic necrosis due to isoniazid chemoprophylaxis in a 15-year-old girl. J Pediatr 1976; 88: 867-8. PubMed PMID: 1271153.

(15 year old girl with ulcerative colitis developed jaundice 2-3 weeks after starting isoniazid for latent tuberculosis [ALT 1254 U/L, Alk P 45 U/L], developing deep jaundice, liver coma and death despite stopping isoniazid promptly).

Mitchell JR, Zimmerman HJ, Ishak KG, Thorgeirsson UP, Timbrell JA, Snodgrass WR, Nelson SD. Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. Ann Intern Med 1976; 84: 181-92. PubMed PMID: 766682.

(Review of major epidemiological, clinical, histological and mechanistic studies on isoniazid hepatotoxicity).

Farer LS. Isoniazid and liver injury. Reply by Authors. Ann Intern Med 1976; 84: 753-4. PubMed PMID: 937897.

(Letter raising issue of fatality rate quoted by Zimmerman et al. [1976] as not being representative; reply by authors stresses that drug induced liver disease with hepatocellular injury has a fatality rate of 10 to 50%).

Brown A. Risks of isoniazid therapy. Ann Intern Med 1976; 85: 828-9. PubMed PMID: 999121.

(Letter questioning the association of rapid acetylator status with isoniazid hepatotoxicity reported by Mitchell et al. [1976]).

Brasfield DM, Goodloe TB, Tiller RE. Isoniazid hepatotoxicity in childhood. Pediatrics 1976; 58: 291. PubMed PMID: 951149.

(12 year old girl developed jaundice after 11 weeks of isoniazid, PAS and streptomycin for suspected tuberculosis [bilirubin 17.6 mg/dL, AST 6,880 U/L, normal protime], resolving with prednisone and stopping isoniazid alone; positive rechallenge for 30 days with AST rising to 3,100 U/L and bilirubin to 13.2 mg/dL before resolving).

Levin ML, Moodie AS. Isoniazid prophylaxis and deaths in Baltimore, Maryland 1972. Bull Int Union Tuberc 1976; 51: 213-23. PubMed PMID: 1030285.

(Further analysis of 13 deaths from liver failure in patients on isoniazid from Baltimore between 1966-74 [among ~27,000 treated: 0.04%]; 11 were women and 10 were black, most common group being black women above the age of 45; patients were said to have heavy alcohol intake but without documentation).

Edwards PQ. Isoniazid-associated hepatitis. Bull Int Union Tuberc 1976; 51: 209-12. PubMed PMID: 1030283.

(Summary of results of USPHS study of a 1 year course of isoniazid for latent tuberculosis in 13,838 persons; frequency of hepatitis was 0.8% overall, but age related: no cases below the age of 20 years, 0.3% 20-34 years, 1.2% 35-49, 2.3% 50-64 and 0.8% >64 years, 8 deaths; 7 in Baltimore "The risk of isoniazid-associated hepatitis exists only while a person is taking isoniazid, whereas the risk of developing tuberculosis disease is lifelong").

Riska N. Hepatitis cases in isoniazid treated groups and in a control group. Bull Int Union Tuberc 1976; 51: 203-8. PubMed PMID: 1030282.

(Summary of results of international controlled trial of isoniazid prophylaxis; rates of hepatitis were 0.5% in 20,838 isoniazid treated and 0.1% in 6991 placebo recipients; mostly in first 2 months, indistinguishable from acute viral hepatitis even by biopsy [read by Hans Popper]; no association with acetylator status, but risk increased with increasing age and with preexisting liver disease).

Hong Kong Tuberculosis Treatment services/British Medical Research Council. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. Tubercle 1976; 57: 81-95. PubMed PMID: 134476.

(Summary of 3 clinical trials of antituberculosis therapy [isoniazid, rifampin and pyrazinamide] from Hong Kong; hepatotoxicity in 6-11% of subjects, jaundice in 0.7%, no deaths, pyrazinamide most often implicated).

Allue X, Sanjurjo P, Fidalgo I, Bilbao F. Hepatic toxicity of antituberculous drugs in children. Helv Paediatr Acta 1976; 31: 381-7. PubMed PMID: 1017983.

(3 cases of jaundice in children, 2 boys and 1 girl, ages 8, 9 and 2 years, arising 14, 4 and 25 days after starting antituberculosis therapy with isoniazid and rifampin, two recovering upon withdrawal of rifampin only, one developed jaundice only when rifampin was added and subsequently died).

Moulding R, Iseman M, Sbarbaro J. Letter: Preventing isoniazid hepatotoxicity. Ann Intern Med 1976; 85: 398-9. PubMed PMID: 962233.

(Letter indicating that among 203 patients who received isoniazid twice weekly with ethambutol or streptomycin, none developed hepatotoxicity, suggesting that twice weekly regimen or concurrent less toxic agents may decrease rates of hepatic injury due to isoniazid).

Farer LS, Glassroth JL, Snider DE Jr. Isoniazid-related hepatotoxicity. Ann Intern Med 1977; 86: 114-5. PubMed PMID: 835915.

(Reply to suggestion by Moulding et al. [1976] stating that the quoted rates of hepatotoxicity are high and the safety and efficacy of twice weekly isoniazid with streptomycin or ethambutol needs further study).

Bhandari B, Sharda B. Isoniazid hepatotoxicity: report of two cases. Indian Pediatr 1977; 14: 859-60. PubMed PMID: 612620.

(Two boys, ages 8 and 1 years, developed jaundice 1.5-2 months after starting isoniazid and streptomycin [bilirubin 3.0 and 2.0 mg/dL, ALT 70 and 54 U/L], biopsies showing fatty change only, resolving rapidly on stopping, one redeveloped jaundice on rechallenge).

Byrd RB, Horn BR, Griggs GA, Solomon DA. Isoniazid chemoprophylaxis. Association with detection and incidence of liver toxicity. Arch Intern Med 1977; 137: 1130-3. PubMed PMID: 332099.

(Randomized trial of 3 month course of isoniazid vs placebo in 120 military subjects with latent tuberculosis; 18% of isoniazid vs 7% of placebo recipients had at least one raised AST level [range 32-328 U/L]; none jaundiced; age and alcohol use were weak predictors of abnormalities).

Walker SH, Park-Hah JO. Possible isoniazid-induced hepatotoxicity in a two-year-old child. J Pediatr 1977; 91: 344-5. PubMed PMID: 874702.

(2 year old boy developed fever and vomiting one day after starting isoniazid for latent tuberculosis and 3 days later had abnormal liver tests [bilirubin 1.6 mg/dL, ALT 1448 U/L, AST 2400 U/L], resolving rapidly after switching to rifampin and streptomycin; positive rechallenge [AST 1356 U/L]).

Maddrey WC, Boitnott JK. Drug-induced chronic liver disease. Gastroenterology 1977; 72: 1348-53. PubMed PMID: 323097.

(Review of drugs that can cause chronic liver injury; histologic features of chronic hepatitis have been described in some patients on isoniazid usually when drug is continued despite presence of injury, resolves when isoniazid is stopped).

Atuk NO, Hart AD, Hunt EH. Close monitoring is essential during isoniazid prophylaxis. South Med J 1977; 70: 156-9. PubMed PMID: 841390.

(Abstract: among 100 hospital employees treated with isoniazid for latent tuberculosis, 32% developed AST elevations usually within 12 weeks but throughout the 1 year of therapy; 1 had clinical hepatitis; 4 had symptoms with AST elevations).

Pessayre D, Bentata M, Degott C, Nouel O, Miguet JP, Rueff B, Benhamou JP. Isoniazid-rifampin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. Gastroenterology 1977; 72: 284-9. PubMed PMID: 830577.

(6 cases of fulminant hepatitis, 5 women and 1 man, ages 15 to 67 years, onset 6-10 days after starting isoniazid and rifampin, all had encephalopathy [peak bilirubin 2.4-13.6 mg/dL, ALT 26-80 times ULN, protime 18-36%], without fever, rash, eosinophilia or autoantibodies, rapid onset, recovery in all).

Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978; 117: 991-1001. PubMed PMID: 666111.

(Among 13,838 persons treated for latent tuberculosis with isoniazid at 26 public health departments, 236 [1.7%] developed hepatitis, and on review, 82 [0.6%] were considered possible and 92 [0.7%] probable; 70 [0.5%] were jaundiced and 8 died [0.05%]; hepatitis rates increased with age: <20 year=none; 20-35 years=0.3%; 35-49 years=1.2%; 50-65 years=2.3%; >65 years=0.8%; highest in Asian males; rates higher in drinkers; unexplained variation in rates by location).

Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1978; 59: 13-32. PubMed PMID: 345572.

(History and review of hepatotoxicity of first line antituberculosis medications).

Rapp RS, Campbell RW, Howell JC, Kendig EL Jr. Isoniazid hepatotoxicity in children. Am Rev Respir Dis 1978; 118: 794-6. PubMed PMID: 309296.

(Among 116 children treated with isoniazid for latent tuberculosis, 5 developed abnormal liver tests, but all were asymptomatic, anicteric and able to complete therapy).

Ellard GA, Mitchison DA, Girling DJ, Nunn AJ, Fox W. The hepatic toxicity of isoniazid among rapid and slow acetylators of the drug. Am Rev Respir Dis 1978; 118: 628-9. PubMed PMID: 707886.

(Among 145 patients with active tuberculosis treated with isoniazid, pyrazinamide and streptomycin, no correlation was found between acetylator phenotype and ALT elevations; postulate that rapid acetylators also rapidly metabolize and excrete monoacetylhydrazine the first product of acetylation and purported hepatotoxin).

Grönhagen-Riska C, Hellstrom PE, Fröseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. Am Rev Respir Dis 1978; 118: 461-6. PubMed PMID: 707874.

(Among 319 patients with tuberculosis treated with isoniazid and rifampin, 45 [14%] had minor transient ALT elevations and 13 [4%] had ALT >150 U/L: major risk factor was age, acetylator status not associated with ALT elevations overall, but weakly with early high elevations).

Rothfield NF, Bierer WF, Garfield JW. Isoniazid induction of antinuclear antibodies: a prospective study. Ann Intern Med 1978; 88: 650-2. PubMed PMID: 306216.

(Among 98 patients with tuberculosis treated with isoniazid, 22% developed ANA positivity on therapy, tended to rise with duration and persist, no patient developed autoimmune disease).

Thompson JE. How safe is isoniazid? Med J Aust 1978; 1: 165-9. PubMed PMID: 651734.

Chapoy P, Ferracci JP, Mattei JF, Granjon B, Louchet E. [Severe hepatitis induced by chemotherapy with antitubercular agents in childhood. 2 cases]. Pediatrie 1978; 3: 637-45. French. PubMed PMID: 740454.

(Two children, ages 4 and 12 years with onset of severe hepatitis 3 and 8 months after starting rifampin, isoniazid and PAS/prothionamide; one case was fatal and one resulted in cirrhosis; authors attributed injury to isoniazid).

Burke M, Logan J. Hepatic dysfunction in tuberculous patients treated with rifampicin and isoniazid. Ir Med J 1979; 72: 430-4. PubMed PMID: 500344.

(Retrospective analysis of 370 Irish patients treated for tuberculosis between 1975-77; 33 [9%] developed liver dysfunction, clinically apparent in 15 [4.1%]; onset in 9-77 days, 9 with jaundice, no deaths).

Thomas PA Jr, Mozes MF, Jonasson O. Hepatic dysfunction during isoniazid chemoprophylaxis in renal allograft recipients. Arch Surg 1979; 114: 597-9. PubMed PMID: 375876.

(Among 181 patients undergoing renal transplantation between 1969-75, all received isoniazid prophylaxis and 13 [7%] developed hepatitis, due to isoniazid in 3 [onset after 2-5 months, resolving in 3-8 weeks of stopping], azathioprine in 1, hepatitis viruses in 5 and unknown in 4).

Byrd RB, Horn BR, Solomon DA, Griggs GA. Toxic effects of isoniazid in tuberculosis chemoprophylaxis. Role of biochemical monitoring in 1,000 patients. JAMA 1979; 241: 1239-41. PubMed PMID: 762788.

(Among 1000 military personnel given isoniazid for latent tuberculosis, 22% had AST elevations, 6.4% >5 times ULN, 1.7% symptomatic, no deaths; higher rates in subjects over 40 years).

Poupon RY, Meyniel D, Petit J, Gustot P, Darnis F. [Cholestatic hepatitis during treatment with I.N.H. and rifampicin: arguments in favour of the hepatotoxicity of rifampicin]. Ann Med Interne (Paris) 1979; 130 (6-7): 371-5. French. PubMed PMID: 496138.

(69 year old woman developed jaundice 50 days after starting isoniazid and rifampin for tuberculous peritonitis [bilirubin 7.4 mg/dL, ALT 3 times baseline], with positive rechallenge with rifampin and later tolerating isoniazid).

Spyridis P, Sinaniotis C, Papadea I, Oreopoulos L, Hadjiyiannis S, Papadatos C. Isoniazid liver injury during chemoprophylaxis in children. Arch Dis Child 1979; 54: 65-7. PubMed PMID: 420524.

(Among 239 children [ages 9-14] given isoniazid for latent tuberculosis, 9.6% had at least one ALT elevation, usually in first 2 months, only 2 with ALT >100 U/L; duration of therapy unclear).

Warrington RJ, Olivier SL. Lymphocyte-mediated cytotoxicity in isoniazid-associated hepatitis. Clin Exp Immunol 1979; 38: 561-7. PubMed PMID: 317034.

(Five of six patients with isoniazid hepatotoxicity had lymphocytes that produced lymphotoxin when exposed to isoniazid in vitro; 5 of 6 also had cytotoxicity to isoniazid treated hepatoma cells).

Stein MT, Liang D. Clinical hepatotoxicity of isoniazid in children. Pediatrics 1979; 64: 499-505. PubMed PMID: 492816.

(2 year old boy developed nausea 2 months after starting isoniazid and PAS [bilirubin 1.5 mg/dL, ALT 545 U/L, Alk P 505 U/L], worsening on continuing therapy [ALT 2000 U/L, bilirubin 4.2 mg/dL] and rapid improvement on stopping; rechallenge with isoniazid led to recurrence [ALT rising from 16 to 735 U/L]).

Graham WG, Dundas GR. Isoniazid-related liver disease. Occurrence with portal hypertension, hypoalbuminemia, and hypersplenism. JAMA 1979; 242: 353-4. PubMed PMID: 448941.

(57 year old woman developed abdominal pain and nausea 8 months after starting isoniazid therapy for latent tuberculosis and at 10 months had ascites and jaundice [bilirubin 3.3 mg/dL, Alk P 210 U/L, AST 141 U/L, albumin 2.5 g/dL, ANA 1:160], biopsy showing cirrhosis, but with biochemical and clinical resolution within 9 months of stopping).

Singapore Tuberculosis Service/British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1979; 119: 579-85. PubMed PMID: 375787.

(Among 397 patients with active tuberculosis treated with combination regimens, 11 [3%] developed hepatitis with jaundice, all in first 3 months, all recovered upon withdrawal of drugs [rifampin in 11, pyrazinamide in 10 and isoniazid in 2]).

Long MW, Snider DE Jr, Farer LS. U.S. Public Health Service Cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. Am Rev Respir Dis 1979; 119: 879-94. PubMed PMID: 110184.

(Among 822 patients with active tuberculosis randomized to three different doses of rifampin with fixed dose of isoniazid, 44% had at least one AST elevation during therapy, 8% >2.5 times and 2% >5 times ULN; risk factors included black race, preexisting AST elevations, lesser extent of disease, and alcohol, but none were clinically useful; 4% had symptoms, 2.5% were jaundiced, usually during first month; most AST elevations resolved without dose modification).

Addington WW. The side effects and interactions of antituberculosis drugs. Chest 1979; 76 (6 Suppl): 782-4. PubMed PMID: 510025.

(Review of side effects of antituberculosis medications; isoniazid, rifampin and pyrazinamide are major causes of hepatotoxicity; ethambutol rarely causes liver injury).

Linna O, Uhari M. Hepatotoxicity of rifampicin and isoniazid in children treated for tuberculosis. Eur J Pediatr 1980; 134: 227-9. PubMed PMID: 6968680.

(Among 18 Finnish children treated for active tuberculosis with rifampin and isoniazid, 11 [61%] had a rise in ALT, 8 with values >100 U/L and one >1000 U/L, but abnormalities often resolved spontaneously even while continuing therapy).

Bistritzer T, Barzilay Z, Jonas A. Isoniazid-rifampin--induced fulminant liver disease in an infant. J Pediatr 1980; 97: 480-2. PubMed PMID: 6967966.

(1 year old boy developed fever within 24 hours and jaundice and stupor after 3 days of isoniazid and rifampin [bilirubin 10.5 mg/dL, AST 3600 U/L, prothrombin index 15%], with rapid resolution within 2 weeks of stopping).

Cross FS, Long MW, Banner AS, Snider DE Jr. Rifampin-isoniazid therapy of alcoholic and nonalcoholic tuberculous patients in a U.S. Public Health Service Cooperative Therapy Trial. Am Rev Respir Dis 1980; 122: 349-53. PubMed PMID: 6998337.

(Results of first 531 patients in trial of 6 month course of isoniazid and rifampin for active tuberculosis found rates of AST elevations higher, but values requiring drug discontinuation in similar proportion of alcoholic [2.6%] as nonalcoholic [3.2%] patients; results varied by definition of alcoholism).

Zierski M, Bek E. Side-effects of drug regimens used in short-course chemotherapy for pulmonary tuberculosis. A controlled clinical study. Tubercle 1980; 61: 41-9. PubMed PMID: 6989067.

(Among 530 patients treated with 5 regimens for active tuberculosis and monitored monthly, 9% developed hepatic injury, but usually without symptoms; ALT >250 U/L in 1.1%, bilirubin rise in 7 [1.3%]).

Timbrell JA, Mitchell JR, Snodgrass WR, Nelson SD. Isoniazid hepatoxicity: the relationship between covalent binding and metabolism in vivo. J Pharmacol Exp Ther 1980; 213: 364-9. PubMed PMID: 6767840.

(In vitro study of metabolic pathways of isoniazid and binding of intermediates to macromolecules).

Bobrowitz ID. Ethambutol compared to rifampin in original treatment of pulmonary tuberculosis. Lung 1980; 157: 117-25. PubMed PMID: 7382540.

(218 patients treated with 3 regimens for tuberculosis; isoniazid with rifampin or ethambutol or both for 4 months followed by isoniazid for 20 months; 39 [18%] developed abnormal liver tests; 5 cases of hepatitis attributed to rifampin [2-8 weeks: overall 3.4%] and 3 to isoniazid [1-16 months: 1.3%], none to ethambutol).

British Thoracic Association. A controlled trial of six month chemotherapy in pulmonary tuberculosis. First report: results during chemotherapy. Br J Dis Chest 1981; 75: 141-53. PubMed PMID: 7023526.

(Comparison of 3 regimens of therapy in 611 patients with active tuberculosis; 6 vs 9 months duration, with and without pyrazinamide; hepatitis occurred in 4% of patients with all 3 regimens and 8 patients [1.3%] had jaundice; hepatotoxicity in 3% of men and 6% of women).

Maddrey WC. Isoniazid-induced liver disease. Semin Liver Dis 1981; 1: 129-33. PubMed PMID: 7347016.

(Review of isoniazid hepatotoxicity, mentioning the rarity of reports in the first 20 years of its use and the multitude of cases reported in the late 1960s and early 1970s: clinically apparent isoniazid hepatoxicity estimated to occur in 0.5% of persons 20-35 years old, 1.5% of those 35-50 and 3% of those over 50 years; may be more severe in black females).

Taylor WC, Aronson MD, Delbanco TL. Should young adults with a positive tuberculin test take isoniazid? Ann Intern Med 1981; 94: 808-13. PubMed PMID: 7235424.

(Analysis of risks and benefits of isoniazid prophylaxis of latent tuberculosis in young adults assuming risk of active tuberculosis to be 0.56-1.3%, the reduction in risk to be 30-70% and the risk of hepatitis to be 0.3-1.1% concludes that the benefits do not outweigh the risks in young adults).

Comstock GW. Evaluating isoniazid preventive therapy: the need for more data. Ann Intern Med 1981; 94: 817-9. PubMed PMID: 7235427.

(Editorial in response to Taylor et al. [1981] questioning rates of subsequent active tuberculosis in healthy young adults with a positive PPD and risk of hepatitis and calling for better data on both of these risks).

Dickinson DS, Bailey WC, Hirschowitz BI, Soong SJ, Eidus L, Hodgkin MM. Risk factors for isoniazid(NIH)-induced liver dysfunction. J Clin Gastroenterol 1981; 3: 271-9. PubMed PMID: 7288121.

(Among 113 patients given isoniazid for latent tuberculosis, 17% had liver toxicity, 2 with symptoms [bilirubin 2.4 and 4.1 mg/dL, peak AST 31-201 U/L]; rates were higher in slow [25%] than rapid [13%] acetylators and more frequent in older age groups).

Dutt AK, Stead WW. Short-course chemotherapy. The Arkansas experience. Chest 1981; 80: 724-7. PubMed PMID: 7030655.

(Among 585 patients with active tuberculosis treated with isoniazid and rifampin in public health departments in Arkansas, 8 [1.4%] developed jaundice).

Snider D Jr, Long M, Zierski M, Rogowski J, Bek E. Preliminary results of six-month regimens studied in the United States and in Poland. Chest 1981; 80: 727-9. PubMed PMID: 7307596.

(Comparison of efficacy of 6-month vs 15 month regimens for active tuberculosis in 672 patients, 9 relapses after short, but none after long duration regimen; 21 [3.1%] had hepatotoxicity).

Ellard GA, Girling DJ, Nunn AJ. The hepatotoxicity of isoniazid among the three acetylator phenotypes. Am Rev Respir Dis 1981; 123: 568-70. PubMed PMID: 7235381.

(Letter in response to editorial by Bernstein summarizing their results on lack of association of acetylator status with ALT elevations during isoniazid therapy).

Døssing M, Andreasen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. Scand J Gastroenterol 1982; 17: 205-11. PubMed PMID: 6982502.

(Among 572 reports of drug induced liver injury from Denmark between 1968-78; the most common causes were halothane [25%], chlorpromazine [9%], sulfonamides [9%], antituberculosis agents [7%], oxyphenisatin [4%], and methyldopa [2%]).

Thompson NJ. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull Wld Hlth Org 1982; 60: 555-64. PubMed PMID: 6754120.

(Among 27,830 patients [ages 20-64 years] from Eastern Europe who received prophylaxis for latent tuberculosis [with chest X-ray abnormalities] and were followed for 5 years [97% follow up], rates of active tuberculosis after placebo was 1.43 per 100 person years, compared to 1.13 for 12 weeks, 0.5 for 24, and 0.4 for 52 week regimens of isoniazid, while rates of hepatitis were 0.26-0.52%, suggesting that a 24 week course had optimal benefit-to-risk ratio).

Hong Kong Chest Service/British Medical Research Council. Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Tubercle 1982; 63: 89-98. PubMed PMID: 6758252.

(Among 833 patients with active tuberculosis randomized to one of 5 regimens all of which included isoniazid and rifampin, hepatotoxicity occurred in 2.7%, but only 3 patients [0.4%] were jaundiced; most were able to finish therapy).

Girling DJ. Adverse effects of antituberculosis drugs. Drugs 1982; 23: 56-74. PubMed PMID: 6459920.

(Review of side effects of drugs for tuberculosis; isoniazid alone leads to hepatitis in 0.5% of patients increasing with age from 0.3% <35 to 0.8 % >55 years, higher rates when it is combined with other agents; pyrazinamide found to be hepatotoxic in high doses [40 mg/kg/day], but not with lower doses – "So far there has been no report of a high incidence of hepatotoxicity with the modern pyrazinamide regimens studied").

Comstock GW. New data on preventive treatment with isoniazid. Ann Intern Med 1983; 98: 663-5. PubMed PMID: 6342492.

(Editorial summarizing results of trial of isoniazid prophylaxis in patients with positive PPD and chest x-ray abnormalities by the International Union against Tuberculosis showing 0.46% rate of hepatitis [3 fatalities] in 20840 persons on therapy and 0.1% rate in 6990 controls).

Danielides IC, Constantoulakis M, Daikos GK. Hepatitis on high dose isoniazid: reintroduction of the drug in severe tuberculous meningitis. Am J Gastroenterol 1983; 78: 378-80. PubMed PMID: 6859018.

(Two men, ages 48 and 29 years, with tuberculous meningitis developed liver injury within 8-10 days of starting high dose isoniazid with rifampin and ethambutol [bilirubin 3.8 mg/dL and normal; ALT 380 and 700 U/L], improving rapidly upon stopping and later tolerating all 3 medications with lower doses of isoniazid).

Cohen CD, Sayed AR, Kirsch RE. Hepatic complications of antituberculosis therapy revisited. S Afr Med J 1983; 63: 960-3. PubMed PMID: 6857425.

(Among 5565 patients treated for tuberculosis in Capetown SA, 17 [0.3%] developed hepatitis, rate similar to that when PAS was used. Among 28 cases seen, 13 attributed to isoniazid, 16 pyrazinamide and 8 rifampin, mostly in combination; 2 deaths).

O'Brien RJ, Long MW, Cross FS, Lyle MA, Snider DE Jr. Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. Pediatrics 1983; 72: 491-9. PubMed PMID: 6604257.

(Retrospective questionnaire survey regarding 874 children treated with isoniazid and rifampin for active tuberculosis identified 68 [7.6%] adverse reactions including hepatotoxicity in 16 [1.7%], including 2 attributed to isoniazid, 12 to rifampin and 2 to the combination; hepatitis rates being 0.5% for isoniazid and 3.2% for rifampin; half during first month, 75% within 10 weeks, only risk factor identified was severe disease for rifampin hepatotoxicity; recommended monitoring during therapy).

Gurumurthy P, Krishnamurthy MS, Nazareth O, Parthasarathy R, Sarma GR, Somasundaram PR, Tripathy SP, et al. Lack of relationship between hepatic toxicity and acetylator phenotype in three thousand South Indian patients during treatment with isoniazid for tuberculosis. Am Rev Respir Dis 1984; 129: 58-61. PubMed PMID: 6367570.

(In six controlled trials of antituberculosis therapy from India, rates of clinical hepatitis with jaundice was 1.9% in slow and 1.2% in rapid acetylators; similar rates of ALT elevations with both phenotypes).

Rugmini PS, Mehta S. Hepatotoxicity of isoniazid and rifampin in children. Indian Pediatr 1984; 21: 119-26. PubMed PMID: 6469294.

(Among 130 children treated with antituberculosis medications, 17 [13%] developed jaundice and another 15 had ALT elevations; higher rates with higher doses of isoniazid; many children able to restart and complete therapy).

Valerdiz Casasola S, Linares Rodríguez A, Zaballa Martín P, Rodrigo Saez L. [Hepatitis caused by isoniazid: study of 9 cases]. Rev Esp Enferm Apar Dig 1984; 65: 157-61. Spanish. PubMed PMID: 6739935.

(Retrospective analysis of 9 cases of isoniazid hepatotoxicity seen between 1975-81 among total of 22 cases of drug induced liver disease undergoing liver biopsy; 6 men, 3 women; ages 7-69 years [2 children], 1 with cirrhosis; 5 also on rifampin, 4 ethambutol; onset after 8-180 days, 2 had rash and fever, mean peak bilirubin 5.4 mg/dL, ALT 1026 U/L, Alk P 272 U/L, all recovered, symptoms resolving in 5-60 days).

Dutt AK, Moers D, Stead WW. Short-course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampin. Community physicians' seven-year experience with mainly outpatients. Am J Med 1984; 77: 233-42. PubMed PMID: 6431810.

(Experience in treating 1028 patients in Arkansas with active tuberculosis with isoniazid and rifampin for 9 months; 27 [2.6%] developed liver toxicity, 8 from rifampin, 14 isoniazid and 5 uncertain; jaundice in 14).

Bailey WC, Byrd RB, Glassroth JL, Hopewell PC, Reichman LB. Preventive treatment of tuberculosis. Chest 1985; 87(2 Suppl): 128S-32S. PubMed PMID: 3967548.

(Recommended indications for therapy of latent tuberculosis from a "National Consensus Conference on Tuberculosis" concluded that subjects above 35 years in age may benefit from biochemical monitoring).

Lauterburg BH, Smith CV, Todd EL, Mitchell JR. Pharmacokinetics of the toxic hydrazine metabolites formed from isoniazid in humans. J Pharmacol Exp Ther 1985; 235: 566-70. PubMed PMID: 4078724.

(Analysis of acetylhydrazine levels in 3 fast and 3 slow acetylators; higher levels achieved in slow acetylators because of rapid production of diacetylhydralazine [which is quickly metabolized] in rapid acetylators).

Homberg JC, Abuaf N, Helmy-Khalil S, Biour M, Poupon R, Islam S, Darnis F, et al. Drug-induced hepatitis associated with anticytoplasmic organelle autoantibodies. Hepatology 1985; 5: 722-7. PubMed PMID: 4029887.

(Analysis of autoantibodies in 157 cases of drug induced liver injury; 3 categories – drugs that are associated with and without antibodies to cytoplasmic organelles and those with specific antibodies; 4 cases of isoniazid hepatitis had no antibodies to nuclei, mitochondria, liver microsomes or smooth muscle).

Snider DE Jr, Caras GJ, Koplan JP. Preventive therapy with isoniazid. Cost-effectiveness of different durations of therapy. JAMA 1986; 255: 1579-83. PubMed PMID: 3081740.

(Cost effectiveness analysis of 12 vs 24 vs 52 weeks of isoniazid for latent tuberculosis; assumptions being that 3.6, 12.4 and 14.3 case per 1000 persons would be prevented and frequency of hepatitis would be 0.3 vs 0.5 vs 0.6%; 12 month course was most cost effective).

Gangadharam PR. Isoniazid, rifampin, and hepatotoxicity. Am Rev Respir Dis 1986; 133: 963-5. PubMed PMID: 3013057.

(Editorial on the effects of rifampin on isoniazid metabolism and potential for greater hepatotoxicity of the combination).

Martinez-Roíg A, Camí J, Llorens-Terol J, de la Torre R, Perich F. Acetylation phenotype and hepatotoxicity in the treatment of tuberculosis in children. Pediatrics 1986; 77: 912-5. PubMed PMID: 3487069.

(73 children with tuberculosis treated with isoniazid and rifampin; 27 [37%] had ALT or AST elevations, but mostly minor, 5 [7%] symptomatic; not associated with acetylator status).

Yamamoto T, Suou T, Hirayama C. Elevated serum aminotransferase induced by isoniazid in relation to isoniazid acetylator phenotype. Hepatology 1986; 6: 295-8. PubMed PMID: 3957235.

(Among 36 patients on isoniazid for tuberculosis, 78% of those with ALT elevations vs 39% of those without were rapid acetylators by pharmacokinetic analysis).

Parthasarathy R, Sarma GR, Janardhanam B, Ramachandran P, Santha T, Sivasubramanian S, Somasundaram PR, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1986; 67: 99-108. PubMed PMID: 3775870.

(Hepatic injury occurred in 10% of patients with spinal tuberculosis, 16-39% of children with meningitis and 2-8% with pulmonary disease treated with rifampin and isoniazid, arising 1-6 months after starting therapy, more commonly in slow than fast acetylators).

Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum- positive pulmonary tuberculosis in South India. Am Rev Respir Dis 1986; 134: 27-33. PubMed PMID: 3524334.

(Analysis of 3 regimens for therapy of active tuberculosis in 908 patients; jaundice occurred in 6-8% of subjects on rifampin, but only 1% of subjects on nonrifampin regimens [isoniazid, pyrazinamide and streptomycin], but no mention of rates of death or clinically apparent hepatitis).

Gal AA, Klatt EC. Fatal isoniazid hepatitis in a child. Pediatr Infect Dis 1986; 5: 490-1. PubMed PMID: 3725664.

(5 year old boy developed jaundice 10 weeks after starting isoniazid for recent exposure [bilirubin 17.1 mg/dL, ALT 2580 U/L], developing worsening hepatic failure and death 22 days after presentation).

Rose DN, Schechter CB, Silver AL. The age threshold for isoniazid hemoprophylaxis. A decision analysis for low-risk tuberculin reactors. JAMA 1986; 256: 2709-13. PubMed PMID: 3773178.

(Decision analysis for isoniazid therapy of latent tuberculosis using varying estimates for rates of risk of reactivation and case fatality rates; using 70% rate of efficacy and 0.1% risk of fatal hepatitis found no age threshold for excess of risks over benefits).

McGlynn KA, Lustbader ED, Sharrar RG, Murphy EC, London WT. Isoniazid prophylaxis in hepatitis B carriers. Am Rev Respir Dis 1986; 134: 666-8. PubMed PMID: 3767121.

(Among 2282 Southeast Asians immigrants undergoing testing in Philadelphia, 12% were HBsAg-positive and 60% had a positive PPD; ALT levels were higher in HBsAg carriers and in those on isoniazid, but no interaction was found statistically).

Guilliford M, MacKay AD, Prawse K. Cholestatic jaundice caused by ethambutol. Br Med J 1986; 292: 866. PubMed PMID: 3083914.

(78 year old woman developed jaundice 2 months after starting isoniazid, streptomycin and ethambutol [bilirubin 11.8 mg/dL, AST 264 U/L, Alk P 976 U/L], with negative rechallenge to isoniazid and positive rechallenge twice to ethambutol [Alk P rising from 767 to 1225 U/L and AST from 144 to 356 U/L], later tolerating isoniazid and streptomycin long term).

Donald PR, Schoeman JF, O'Kennedy A. Hepatic toxicity during chemotherapy for severe tuberculosis meningitis. Am J Dis Child 1987; 141: 741-3. PubMed PMID: 2884866.

(Among 33 children with tuberculous meningitis treated with 3-4 agents, liver test abnormalities were common [85%] but usually mild and transient, only one child developing jaundice who was also IgM anti-HAV positive and who later tolerated therapy without recurrence).

Swamy R, Acharyulu GS, Duraipandian M, Jawahar MS, Ramachandran R, Sarma GR. Liver function tests during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin & pyrazinamide. Indian J Med Res 1987; 86: 549-57. PubMed PMID: 345189.

(Average ALT and AST levels increased slightly in patients on antituberculosis therapy, generally after 1-2 months).

Stead WW, To T, Harrison RW, Abraham JH 3rd. Benefit-risk considerations in preventive treatment for tuberculosis in elderly persons. Ann Intern Med 1987; 107: 843-5. PubMed PMID: 3688677.

(Among 1935 residents of nursing homes undergoing isoniazid prophylaxis for latent tuberculosis [PPD conversion], 84 [4.4%] developed symptomatic hepatotoxicity, but no fatalities occurred).

Rose DN, Silver AL, Schechter CB. Preventive treatment for tuberculosis in elderly persons. Ann Intern Med 1988; 108: 908-9. PubMed PMID: 3369787.

(Letter in response to Stead et al. [1987] raising issue that benefits of prophylaxis are long term, while risk from isoniazid hepatitis is limited to the period of therapy which should be included in the analyses).

Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989; 104: 151-5. PubMed PMID: 2495549.

(Among 3681 women beginning isoniazid during prenatal care, 5 developed clinically apparent hepatitis and 2 died; onset after 2 weeks to 7 months of starting; most during the 6 months postpartum).

Kasantikul V. Isoniazid-rifampicin-induced submassive hepatic necrosis. J Med Assoc Thai 1989; 72: 56-8. PubMed PMID: 2723568.

(58 year old woman developed nausea after 3 weeks of isoniazid, rifampin and ethambutol and jaundice at 6 weeks [bilirubin 3.7 mg/dL, ALT 1590 U/L, Alk P 54 U/L, protime 72 sec], dying 5 days later).

Moulding TS, Redeker AG, Kanel GC. Twenty isoniazid-associated deaths in one state. Am Rev Respir Dis 1989; 140: 700-5. PubMed PMID: 2782741.

(20 cases of death from suspected isoniazid hepatitis identified between 1973 and 1986 in California, 19 given isoniazid for latent and 1 for active tuberculosis, ages 5-73 years, 16 [80%] in women, no other clear risk factors, most not regularly monitored, 4 had delay in stopping isoniazid; peak ALT 469-2580 U/L, bilirubin 6.4-47 mg/dL).

Iseman MD, Miller B. If a tree falls in the middle of the forest. Isoniazid and hepatitis. Am Rev Respir Dis 1989; 140: 575-6. PubMed PMID: 2782732.

(Editorial on article by Moulding et al. stating that "...flaws in this report are profound" and places "...future patients at risk of tuberculosis" and "We believe in the efficacy, safety, and favorable risk-benefit profile of INH preventive therapy...").

Hansen JE. Twenty isoniazid-associated deaths in one state. Am Rev Respir Dis 1990; 141(4 Pt 1): 1081-2. PubMed PMID: 2327643.

(Letter in response to Moulding et al. [1989] supporting the need to publish cases of suspected hepatotoxicity).

Wu JC, Lee SD, Yeh PF, Chan CY, Wang YJ, Huang YS, Tsai YT, et al. Isoniazid-rifampin-induced hepatitis in hepatitis B carriers. Gastroenterology 1990; 98: 502-4. PubMed PMID: 2295408.

(Among 1783 patients with active tuberculosis treated with combination therapy [isoniazid, rifampin and ethambutol], 42 [2.3%] developed clinical hepatitis of whom 15 were HBsAg positive; fatality rate being 47% vs 4%, but no information on background features in the treated cohort or exclusion of reactivation of hepatitis B).

Murphy R, Swartz R, Watkins PB. Severe acetaminophen toxicity in a patient receiving isoniazid. Ann Intern Med 1990; 113:799-800. PubMed PMID: 2240884.

(19 year old woman on isoniazid prophylaxis took an overdose of acetaminophen [~11.5 g] and developed marked ALT elevations [7923 U/L] and acute renal failure despite administration of N-acetylcysteine and modest acetaminophen levels 13 hours after ingestion, suggesting drug-interaction predisposing to more severe injury perhaps by induction of CYP 2E1).

Moulding TS, Redeker AG, Kanel GC. Acetaminophen, isoniazid, and hepatic toxicity. Ann Intern Med 1991; 114: 431. PubMed PMID: 1992890.

(Authors mention 3 cases of possible isoniazid-acetaminophen interactions causing more severe outcomes of isoniazid hepatotoxicity and acetaminophen overdose).

Combs DL, O'Brien RJ, Geiter LJ. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability. Ann Int Med 1990; 112: 397-406. PubMed PMID: 2155569.

(Controlled trial of isoniazid and rifampin given either for 6 months [with 2 months of pyrazinamide] or alone for 9 months in 1451 patients with active tuberculosis; side effects were more common in first 24 weeks with triple therapy, but rates were similar for hepatotoxicity [2.4% vs 3.6%: 75% symptomatic] and AST or bilirubin elevations [23% vs 27%]).

Aziz S, Agha F, Hassan R, Fairoz SA, Hassan K. Hepatotoxicity to different antituberculosis drug combinations. J Pak Med Assoc 1990; 40: 290-4. PubMed PMID: 2126569.

Kumar A, Misra PK, Mehotra R, Govil YC, Rana GS. Hepatotoxicity of rifampin and isoniazid. Is it all drug-induced hepatitis? Am Rev Respir Dis 1991; 143: 1350-2. PubMed PMID: 1904700.

(Serologic testing on 40 children with acute hepatitis during therapy [9 with acute liver failure] with isoniazid and rifampin found 3 [8%] with hepatitis A and 14 [35%] with acute hepatitis B; non-A, non-B hepatitis suspected in several others).

O'Brien RJ. Hepatoxic reaction to antituberculous drugs: Adjustments to therapeutic regimen. JAMA 1991; 265: 3323. PubMed PMID: 2046117.

(Recommends temporarily stopping isoniazid if ALT levels rise above 3 times ULN with later careful reintroduction).

Yew WW, Lau KS, Ling MH. Phenytoin toxicity in a patient with isoniazid-induced hepatitis. Tubercle 1991; 72: 309-10. PubMed PMID: 1811369.

(28 year old woman developed phenytoin toxicity [truncal ataxia and high blood levels] during isoniazid induced hepatitis).

Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest 1991; 99: 465-71. PubMed PMID: 1824929.

(Metaanalysis reporting higher rate of hepatotoxicity with combination of rifampin and isoniazid [2.6%] than isoniazid alone [1.6%] and rifampin alone [1.1%], with relative risk of 1.6 in adults; in children rates were higher with the combination [6.9%] than isoniazid alone [1.0%], but unclear whether interactions were synergistic vs additive).

Veale KS, Huff ES, Nelson BK, Coffman DS. Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. J Pediatr 1992; 120: 146-8. PubMed PMID: 1731013.

(7 year old boy developed jaundice 9 months after starting isoniazid for latent tuberculosis [bilirubin 4.5 mg/dL, ALT 1030 U/L], later developing red cell aplasia during recovery [hemoglobin 3.6 g/dL with bilirubin 1.8 mg/dL], with ultimate recovery).

Kshirsagar NA, Karande SC, Potkar CN. A prospective survey of drug induced hepatotoxicity in a large hospital. Indian J Gastroenterol 1992; 11: 13-5. PubMed PMID: 1551705.

(Among 11 cases of drug induced liver disease seen at one hospital in India, 9 were due to antituberculosis medications, usually combinations of isoniazid, rifampin and pyrazinamide, 2 deaths).

Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992; 145: 494-7. PubMed PMID: 1736764.

(Combined literature search, review of adverse event reports to FDA, death records and public health department reports of deaths due to isoniazid given as monotherapy for latent tuberculosis identified 177 US cases; 69% female [often in young adulthood], 9% in children; high proportion in Hispanics and blacks; 38% of women affected were within a year postpartum; an estimated 1.1 million persons received isoniazid prophylaxis during this time, for death rate of 14 per 100,000 starting and 23.2 finishing therapy; ~0.02%).

Israel HL, Gottlieb JE. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992; 146: 1643. PubMed PMID: 1456590.

(Letter in response to Snider et al. [1992] questioning the accuracy of estimates of reactivation and case fatality rates for tuberculosis as being based upon outdated studies).

Moulding T. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992; 146: 1643-4; author reply: 1644. PubMed PMID: 1456591.

(Letter in response to Snider et al. [1992] questioning the rates of reactivation and death used to calculate risk-benefit ratio of isoniazid chemoprophylaxis for tuberculosis; author's reply stresses the need for better prospective information).

Israel HL, Gottlieb JE, Maddrey WC. Perspective: preventive isoniazid therapy and the liver. Chest 1992; 101: 1298-301. PubMed PMID: 1582287.

(3 cases: ages 17, 66, and 77 years with onset of jaundice 2-6 months after starting isoniazid for latent tuberculosis, with rapid progression to hepatic failure and death; review of each case found weak support for prophylaxis and lack of prompt discontinuation of therapy; review of cost effectiveness analyses raises issues of modification of guidelines for use).

Centers for Disease Control and Prevention (CDC). Severe isoniazid-associated hepatitis—New York, 1991-1993. MMWR Morb Mortal Wkly Rep 1993; 42: 545-7. PubMed PMID: 8326947.

(Survey of New York liver transplant centers identified 8 cases of acute liver failure associated with prophylactic isoniazid use over a two year period, ages 5-68 years, 75% female, all denied daily alcohol use, onset after 21-142 days, 7 continued therapy >10 days after symptom onset, all presented with jaundice, 5 underwent transplant and 3 died).

Salpeter SR. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. West J Med 1993; 159: 560-4. PubMed PMID: 8279152.

(Review of published reports on isoniazid use; among 20,212 persons started on preventive therapy, hepatitis occurred in 1% but no fatalities; among unpublished results on 182,285 patients started since 1983, hepatitis occurred in 1.2%, but only two deaths [0.001%]; lower rates than previously reported).

Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. Am J Gastroenterol 1993; 88: 590-2. PubMed PMID: 8470644.

(21 year old woman on isoniazid took 3.2 g of acetaminophen and presented with nausea followed by rise in ALT from 118 to 13,860 U/L, bilirubin peak at 9.3 mg/dL; suggesting potentiation of acetaminophen toxicity by isoniazid).

Altman C, Biour M, Grangé JD. [Hepatic toxicity of antitubercular agents. Role of different drugs. 199 cases]. Presse Med 1993; 22: 1212-6. French. PubMed PMID: 8248040.

(Analysis of 199 cases of hepatotoxicity from antituberculosis medications from literature [n=169] or French pharmacovigilance system [n=30]; mortality rate was 23%, rifampin cases had short latency [average 2 weeks] compared to isoniazid [11 weeks] and pyrazinamide [7 weeks]; no association with alcohol, but some association with higher doses, particularly isoniazid).

Padmini R, Srinivasan S, Nalini P, Mahadevan S. Short course chemotherapy for tuberculosis in children. J Trop Pediatr 1993; 39: 361-4. PubMed PMID: 8133559.

(Among 83 children [<12 years] treated for tuberculosis in India between 1988-91, 4 developed hepatitis with jaundice [bilirubin 2.0-4.5 mg/dL, ALT >4 times ULN], but all resolved with decrease in dose of isoniazid and rifampin).

Türktaş H, Unsal M, Tülek N, Orüç O. Hepatotoxicity of antituberculosis therapy(rifampicin, isoniazid and pyrazinamide) or viral hepatitis. Tuber Lung Dis 1993; 75: 58-60. PubMed PMID: 8161767.

(Among 705 Turkish adults with tuberculosis, 57 [8%] developed hepatitis with jaundice during therapy with isoniazid and rifampin; serologic testing showed hepatitis A in none, B in 6, and C in 4).

Farrell FJ, Keeffe EB, Man KM, Imperial JC, Esquivel CO. Treatment of hepatic failure secondary to isoniazid hepatitis with liver transplantation. Dig Dis Sc 1994; 39: 2255-9. PubMed PMID: 7924752.

(Two cases of acute liver failure attributed to isoniazid; 49 year old man on isoniazid for latent tuberculosis for 4 months developed jaundice [bilirubin 16.1 mg/dL, AST 2882 U/L], and 60 year old woman with onset of jaundice 6 weeks after starting isoniazid, rifampin, and pyrazinamide for active tuberculosis [bilirubin 3.5 mg/dL, AST 548 U/L]; both progressing to hepatic failure and undergoing successful transplant).

Nolan MC, Sandblom RE, Thummel KE, Slattery JT, Nelson SD. Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. Chest 1994; 105: 408-11. PubMed PMID: 7508362.

(Three patients on isoniazid, rifampin and pyrazinamide developed marked ALT or AST elevations [490, 517 and 920 U/L; bilirubin 1.1, 0.3 and 1.3 mg/dL] in association with taking 2.4-6 g of acetaminophen for 1-4 days either as suicide [n=1] or symptomatic relief of fever and pain [n=2], all resolved and tolerated restarting isoniazid; suggesting that isoniazid or rifampin may potentiate hepatotoxicity of acetaminophen and vice versa).

van der Kooi K, Mottet JJ, Regamey C. Isoniazid is not always the cause of hepatitis during treatment of tuberculosis. Clin Infect Dis 1994; 19: 987-8. PubMed PMID: 7893906.

(46 year old man developed hepatitis [ALT 900 U/L] 2 weeks after starting isoniazid, rifampin, pyrazinamide and ethambutol with positive challenge to pyrazinamide and not isoniazid; no mention of fever, rash or bilirubin levels).

Askgaard DS, Wilcke T, Døssing M. Hepatotoxicity caused by the combined action of isoniazid and rifampicin. Thorax 1995; 50: 213-4. PubMed PMID: 7701468.

(35 year old woman with tuberculosis developed symptomatic hepatotoxicity [bilirubin 1.8 mg/dL, AST ~1000 U/L, Alk P 1.5 times ULN] within a week of starting isoniazid, rifampin, ethambutol and pyrazinamide, resolving rapidly with stopping and recurring when given the combination of isoniazid and rifampin but not with either alone, eventually also tolerating pyrazinamide and ethambutol).

Palusci VJ, O'Hare D, Lawrence RM. Hepatotoxicity and transaminase measurement during isoniazid chemoprophylaxis in children. Pediatr Infect Dis J 1995; 14: 144-8. PubMed PMID: 7746698.

(16 year old woman developed jaundice 4 months after starting isoniazid for latent tuberculosis [bilirubin 10.4 mg/dL, ALT 313 U/L, Alk P 380 U/L, protime 20.9 seconds], with progressive hepatic failure requiring liver transplantation).

Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. Lancet 1995; 345: 555-6. PubMed PMID: 7786350.

(Four cases of acute liver failure in patients on isoniazid, rifampin and pyrazinamide; 3 women and 1 man, ages 31-61 years, jaundice after 1-6 weeks, two requiring liver transplantation, one recovered, one died; unclear which agent was responsible).

Noble A. Antituberculous therapy and acute liver failure. Lancet 1995 Apr 1; 345: 867. PubMed PMID: 7898259.

(Letter in response to Mitchell [1995] suggesting that patients be warned to stop medication if they develop symptoms).

Janes SL, Behrens J. Antituberculous therapy and acute liver failure. Lancet 1995; 345: 867. PubMed PMID: 7898259.

(Letter in response to Mitchell [1995] reporting 45 year old man who developed hepatitis 5 weeks after starting isoniazid and rifampin [bilirubin 3.3 mg/dL, ALT 1884 U/L], who recovered rapidly with prompt stopping of both).

Durand F, Bernuau J, Pessayre D, Samuel D, Belaiche J, Degott C, Bismuth H, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology 1995; 21: 929-32. PubMed PMID: 7705802.

(Mortality rate was higher in 9 patients with acute liver failure on isoniazid, rifampin and pyrazinamide [78%] than in 9 with acute liver failure on isoniazid and rifampin alone [11%]).

Singh J, Arora A, Garg PK, Thakur VS, Pande JN, Tandon RK. Antituberculosis treatment-induced hepatotoxicity: role of predictive factors. Postgrad Med J 1995; 71: 359-62. PubMed PMID: 7644398.

(Case control study of 60 patients with liver injury due to antituberculosis medications and 60 controls from India identified lower body mass index and pyrazinamide, but not age, sex, or acetylator status as risk factors).

Ozick LA, Jacob L, Comer GM, Lee TP, Ben-Zvi J, Donelson SS, Felton CP. Hepatotoxicity from isoniazid and rifampin in inner-city AIDS patients. Am J Gastroenterol 1995; 90: 1978-80. PubMed PMID: 7485004.

(Among 70 AIDS patients with active tuberculosis receiving isoniazid, rifampin and pyrazinamide for 2 months, ALT or AST levels >200 U/L occurred in 8 [11%] with peak bilirubin values 0.6-2.9 mg/dL).

van den Brande P, van Steenbergen W, Vervoort G, Demedts M. Aging and hepatotoxicity of isoniazid and rifampin in pulmonary tuberculosis. Am J Respir Crit Care Med 1995; 152: 1705-8. PubMed PMID: 7582317.

(Among 131 patients with active tuberculosis treated with isoniazid and rifampin, ALT elevations were more common in patients >60 years of age [38%] than younger [18%] patients; elderly also had higher peak levels).

Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy. Clinical profile and reintroduction of therapy. J Clin Gastroenterol 1996; 22: 211-4. PubMed PMID: 8724260.

(Among 72 patients with symptomatic liver injury due to antituberculosis medications, 12 had acute or subacute liver failure; among those who recovered, reinstitution of therapy was possible in 93%).

Schluger LK, Sheiner PA, Jonas M, Guarrera JV, Fiel IM, Meyers B, Berk PD. Isoniazid hepatotoxicity after orthotopic liver transplantation. Mt Sinai J Med 1996; 63: 364-9. PubMed PMID: 8898542.

(Among 14 liver transplant recipients treated with isoniazid, all five given combination therapy developed hepatitis after 1-4 months, 4 were jaundiced, and all recovered [bilirubin 0.5-16.0 mg/dL], later tolerating ethambutol and ofloxacin; in contrast, isoniazid monotherapy was tolerated with only mild ALT elevations).

de Souza AF, de Oliveira e Silva A, Baldi J, de Souza TN, Rizzo PM. [Hepatic functional changes induced by the combined use of isoniazid, pyrazinamide and rifampicin in the treatment of pulmonary tuberculosis]. Arq Gastroenterol 1996; 33: 194-200. Portuguese. PubMed PMID: 9302332.

Millard PS, Wilcosky TC, Reade-Christopher SJ, Weber DJ. Isoniazid-related fatal hepatitis. West J Med 1996; 164: 486-91. PubMed PMID: 8764622.

(Analysis of 108 deaths from acute liver failure due to isoniazid reported to state health departments and published reports: 81% in women, 79% Hispanic or black, 31% younger than 35 years, 42% were undergoing monthly monitoring).

Salpeter SR. Isoniazid-related fatal hepatitis. West J Med 1996; 165: 323. PubMed PMID: 8993215.

(Letter in response to Millard et al. [1996] suggesting that the fatality rate is 4.2 per 100,000 persons starting therapy).

Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis 1996; 77: 37-42. PubMed PMID: 8733412.

(Among 1317 patients treated for active tuberculosis, hepatitis was attributed to rifampin in 1.4%, pyrazinamide in 1.2%, and isoniazid in 0.3%, but none to ethambutol or streptomycin).

Ormerod LP, Skinner C, Wales J. Hepatotoxicity of antituberculosis drugs. Thorax 1996; 51: 111-3. PubMed PMID: 8711637.

(Review of the problem of hepatotoxicity of antituberculosis medications, with biochemical monitoring recommended only for patients with preexisting liver disease; in the UK from 1965-86, there were 243 reports of liver injury due to antituberculosis therapy and 45 fatalities).

Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandom RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax 1996; 51: 1304-11. PubMed PMID: 8711642.

(Comparison 86 patients with hepatitis due to antituberculosis therapy and 406 patients who tolerated therapy; risk factors were older age, history of high alcohol intake [20% vs 5%], more extensive disease [14% vs 3.5%], slow acetylator status [83% vs 64%], and use of pyrazinamide [63% vs 25%]).

Døssing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis 1996; 77: 335-40. PubMed PMID: 8796249.

(Retrospective chart review on 765 Danish patients treated for tuberculosis with 3 or 4 drugs [isoniazid, rifampin, pyrazinamide and ethambutol] for 6-9 months; 16% had AST elevations >2 times ULN usually in first month, but only 2% required dose modification; 7 with jaundice, no fatalities: risk factors for hepatotoxicity were female sex, age and severe tuberculosis).

Durand F, Jebrak G, Pessayre D, Fournier M, Bernuau J. Hepatotoxicity of antitubercular treatments. Rationale for monitoring liver status. Drug Saf 1996; 15: 394-405. PubMed PMID: 8968694.

(Review and recommendations from France regarding monitoring of serum enzymes during therapy of tuberculosis; isoniazid may have direct hepatotoxicity because of dose-relatedness and usual absence of recurrence on rechallenge; rifampin is rare cause of liver injury, usually with short latency period; pyrazinamide is clearly hepatotoxic at higher doses, which should be kept to a minimum and given for 2 months only).

Moitinho E, Salmerón JM, Mas A, Bruguera M, Rodés J. [Severe hepatotoxicity of tuberculostatic agents. Increase in the incidence]. Gastroenterol Hepatol 1996; 19: 448-51. Spanish. PubMed PMID: 8998667.

(Among 27 cases of severe acute hepatitis seen in 1994 in Barcelona, 5 cases were due to antituberculosis medications; 1 woman and 4 men, ages 25-62 years, 2 with HBsAg, 1 with anti-HCV, arising after 11-62 days [peak bilirubin 8-41 mg/dL; ALT 450-2320 U/L, Alk P 1.5-2 times ULN], 3 died, one required liver transplant, one recovered spontaneously).

Hwang SJ, Wu JC, Lee CN, Yen FS, Lu CL, Lin TP, Lee SD. A prospective clinical study of isoniazid-rifampicin-pyrazinamide-induced liver injury in an area endemic for hepatitis B. J Gastroenterol Hepatol 1997; 12: 87-91. PubMed PMID: 9076631.

(Prospective study of 240 patients treated for active tuberculosis with 3 drug regimens, found ALT elevations in 45% of 31 HBsAg carriers vs 26% of 209 controls; 1 death in a carrier, none in controls, but nevertheless concluded that HBsAg was not a risk factor for antituberculosis therapy associated liver injury).

García Rodríguez LA, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. Pharmacotherapy 1997; 17: 721-8. PubMed PMID: 9250549.

(In epidemiological studies, antituberculosis medications have the highest relative risk for liver injury, hepatitis occurring in 0.4% of recipients).

Vasudeva R, Woods B. Isoniazid-related hepatitis. Dig Dis 1997; 15: 357-67. PubMed PMID: 9439900.

(Review of isoniazid hepatitis without new information).

Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, Pitchenik AE. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med 1998; 157: 1871-6. PubMed PMID: 9620920.

(Among 134 patients with tuberculosis, 22 developed hepatotoxicity during therapy; risk factors were HCV infection [30% vs 11%] and HIV infection [27% vs 12%]; alpha interferon therapy of hepatitis C allowed for antituberculosis therapy without ALT elevations in some patients).

Guo Y, Cui D. [Antitubercular drug-induced liver injuries]. Zhonghua Jie He He Hu Xi Za Zhi 1998; 21: 308-9. Chinese. PubMed PMID: 132696.

Rose DN. Short-course prophylaxis against tuberculosis in HIV-infected persons. A decision and cost-effectiveness analysis. Ann Intern Med 1998; 129: 779-86. PubMed PMID: 9841583.

(Cost effectiveness analysis of various regimens for treating latent tuberculosis in HIV-infected persons using Markov model and various predictions of efficacy, safety, tuberculosis development and survival [used estimates of fatal hepatitis of 0.002%] found prophylaxis to be "greatly" beneficial, including 2 month regimens using pyrazinamide and rifampin).

Corrigan D, Paton J. Hepatic enzyme abnormalities in children on triple therapy for tuberculosis. Pediatr Pulmonol 1999; 27: 37-42. PubMed PMID: 10023790.

(43 children prospectively monitored on rifampin, isoniazid and pyrazinamide therapy of tuberulosis; 30% had abnormal tests, usually in first few weeks, 2 had symptoms, 1 had jaundice; all patients continued therapy or restarted and were able to finish).

Wada M, Yoshiyama T, Ogata H, Ito K, Mizutani S, Sugita H. [Six-months chemotherapy (2HRZS or E/4HRE) of new cases of pulmonary tuberculosis—six year experiences on its effectiveness, toxicity, and acceptability]. Kekkaku 1999; 74: 353-60. Japanese. PubMed PMID: 10355221.

Bucher HC, Griffith L, Guyatt G, Sudre P, Naef M, Sendi P, Battegay M. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. AIDS 1999; 13: 501-7. PubMed PMID: 10197379.

(Metaanalysis of controlled trials of isoniazid prophylaxis in HIV-positive patients with positive tuberculin skin tests; 7 trials identified in total of 2367 persons treated and 2162 controls; tuberculosis developed in 3-10 per 100 patient-years and relative risk with prophylaxis was 0.4, but prophylaxis had no effect on survival).

Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA 1999; 281: 1014-8. PubMed PMID: 10086436.

(Prospective analysis of 11,141 patients starting isoniazid preventive therapy; 11 [0.1%] developed symptomatic liver injury, onset in 3 weeks to 5 months [10 within 3 months], 9 were jaundiced, 1 hospitalized, all recovered; among 1427 treated with multiple agents for tuberculosis, 15 [1%] developed acute liver injury, all on isoniazid, one died; risk factors were increasing age and possibly female sex).

Moulding T. Toxicity associated with isoniazid preventive therapy. JAMA 1999; 282: 2207-8. PubMed PMID: 10605965.

(Letter in response to Nolan [1999] suggesting that absence of deaths was due to careful monitoring and stopping isoniazid early).

Stuart RL, Grayson ML. A review of isoniazid-related hepatotoxicity during chemoprophylaxis. Aust N Z J Med 1999; 29: 362-7. PubMed PMID: 10868500.

(Systematic review of hepatotoxicity of isoniazid in treatment of latent tuberculosis commenting on the highly variable reported rates of hepatitis of 0.8% to 23% and mortality from none to 0.09%).

Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, Valdespino JL, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. JAMA 2000; 283: 1445-50. PubMed PMID: 10732934.

(Controlled trial in 1583 patients with HIV infection and latent tuberculosis comparing rifampin/pyrazinamide [R/P] for 2 months to isoniazid [INH] for 12 months: active tuberculosis arose in 0.8% per year of R/P vs 1.1% of INH treated; ALT elevations >10 times ULN occurred in 1.3% of R/P vs 3.3% of INH treated; one "grade 4 hepatitis" in R/P versus 2 in INH treated).

Centers for Disease Control and Prevention(CDC). Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 2000; 49(RR-6): 1-51. PubMed PMID: 10881762.

(Recommendations regarding treatment of latent tuberculosis; daily isoniazid for 9 months is preferred, other options being twice weekly regimens, or regimens for 6 or 9 months, or 4 months of rifampin daily; treatment of patients over the age of 35 should be limited to those in a high risk group for developing tuberculosis).

Pereira RM, Tresoldi AT, Hessel G. [Isoniazid-induced hepatic failure. Report of a case]. Arq Gastroenterol 2000; 37: 72-5. Portuguese. PubMed PMID: 10962632.

(5 month old developed vomiting and prostration 4 days after starting isoniazid, rifampin and pyrazinamide for active tuberculosis [bilirubin 5.3 mg/dL, ALT 363 U/L], resolving within 3 weeks of stopping).

Girotto L, Gjonovich A, Preciso G. [Fulminant liver failure caused by antitubercular drugs. Report of a clinical case]. Minerva Anestesiol 2000; 66: 249-51. Italian. PubMed PMID: 10832275.

(26 year old man with pulmonary tuberculosis treated with isoniazid, rifampin, ethambutol and pyrazinamide, presented after 1 month with fever, rash and jaundice [bilirubin 8.5 mg/dL, ALT 2757 U/L], renal insufficiency and hepatic and multiorgan failure; died after 10 days, and autopsy showed massive liver necrosis and acute renal tubular necrosis).

Meyers BR, Papanicolaou GA, Sheiner P, Emre S, Miller C. Tuberculosis in orthotopic liver transplant patients: increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. Transplantation 2000; 69: 64-9. PubMed PMID: 10653382.

(Toxicity was common in liver transplant patients treated for active tuberculosis using first line agents, but switching to second line agents was successful in treating the tuberculosis and was well tolerated).

Ohno M, Yamaguchi I, Yamamoto I, Fukuda T, Yokota S, Maekura R, Ito M, et al. Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. Int J Tuberc Lung Dis 2000; 4: 256-61. PubMed PMID: 10751073.

(Prospective study of isoniazid and rifampin therapy and acetylator status in 77 patients with tuberculosis; 28 were rapid, 42 intermediate and 7 slow acetylators based upon genetic testing for NAT-2; 18% developed ALT elevations >1.5 times ULN including 100% of slow, 17% of intermediate and 4% of rapid acetylators: odds ratio 4.0).

Yew WW. Risk factors for hepatotoxicity during anti-tuberculosis chemotherapy in Asian populations. Int J Tuberc Lung Dis 2001; 5: 99-100. PubMed PMID: 11263525.

(Letter in response to Ohno [2000]; their previous studies using pharmacokinetic analyses also supported the correlation between slow acetylator status and hepatotoxicity of isoniazid; hepatitis B also appears to carry a risk, these two factors perhaps explaining the increased risk among Asians).

Centers for Disease Control and Prevention (CDC). Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection—New York and Georgia, 2000. MMWR Morb Mortal Wkly Rep 2001; 50: 289-91. PubMed PMID: 11330495.

(First alert: Initial report of 2 cases of severe hepatitis during 2 month regimen of rifampin and pyrazinamide for latent tuberculosis; 53 year old man developed ALT elevation [1734 U/L] 33 days after starting regimen followed by jaundice [bilirubin 17.8 mg/dL] and fatal hepatic failure; 59 year old woman developed symptoms at end of therapy with bilirubin 11.4 mg/dL, ALT 1735 U/L, ANA 1:640, treated with prednisone and recovered; in both cases ALT monitoring did not prevent severe hepatitis).

Centers for Disease Control and Prevention (CDC). Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. MMWR Morb Mortal Wkly Rep 2001; 50: 733-5. PubMed PMID: 11787580.

(Second alert: during 6 month period, 21 cases of liver injury were reported to CDC associated with 2 month regimens of rifampin-pyrazinamide; 5 died of liver failure, ages 32-68 years, onset in 2nd month; recommended use of 9 months of isoniazid as standard regimen and need for close monitoring if rifampin-pyrazinamide is used).

Sadaphal P, Astemborski J, Graham NM, Sheely L, Bonds M, Madison A, Vlahov D, et al. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with Mycobacterium tuberculosis. Clin Infect Dis 2001; 33: 1687-91. PubMed PMID: 11641824.

(Among 146 injection drug users treated for tuberculosis, 32 [22%] developed ALT elevations >3 times ULN and 8 were symptomatic; risk factors were concurrent alcohol use but not age, HBsAg, anti-HCV or HIV status; no deaths from hepatoxicity).

Vu D, Macdonald L. Antitubercular drugs (isoniazid, rifampin and pyrazinamide): hepatobiliary reactions. CMAJ 2001; 165: 942-3, 946-7. PubMed PMID: 11599338.

(Review of 420 reports to the Canadian Monitoring Program of hepatotoxicity of antituberculosis drugs identified 258 due to isoniazid alone with 7 deaths; 27 to rifampin alone with 1 death; 110 to isoniazid and rifampin with 6 deaths; 25 related to pyrazinamide alone or in combination with 3 cases of death or hepatic failure; advises biochemical monitoring for patients above the age of 35).

Kiyota K, Hamabe Y. [Acute isoniazid poisoning presenting convulsion and liver dysfunction]. Chudoku Kenkyu 2001; 14: 57-60. Japanese. PubMed PMID: 11381464.

Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001; 5: 65-9. PubMed PMID: 11263519.

(Description of 45 patients with hepatotoxicity from antituberculosis therapy, ages 15-76 years, ALT 42-897 U/L, bilirubin 0.2-7.0 mg/dL, arising in 6-102 days, with resolution in 4-58 days. No recurrence after gradual reintroduction of regimen without pyrazinamide vs 6 cases of recurrence [24%] with abrupt reintroduction).

Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, et al.; Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002; 137: 640-7. PubMed PMID: 12379063.

(Controlled trial of isoniazid [INH: 6 months] vs rifampin and pyrazinamide [RP: 2 months] in 589 patients with latent tuberculosis, similar completion rates [57% vs 61%]; ALT rose >5 times ULN in 1% on INH vs 7.7% on RP; none resulted in hospitalization or death; no mention of jaundice).

Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, Echizen H, et al. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. Clin Pharmacol Ther 2002; 72: 220-6. PubMed PMID: 12189369.

(Retrospective analysis of 99 children who received therapy for tuberculosis, 8 developed hepatotoxicity; risk factors identified were young age and pyrazinamide exposure).

Jin CF, Sable R. Isoniazid-induced acute hepatitis and acute pancreatitis in a patient during chemoprophylaxis. J Clin Gastroenterol 2002; 35: 100-1. PubMed PMID: 12080238.

(28 year old woman developed pancreatitis 3 weeks after starting isoniazid prophylaxis [bilirubin 6.3 mg/dL, ALT 24,040 U/L, Alk P 136 U/L, protime 23.9 sec, amylase 292 U/L]; resolving rapidly on stopping; also on high doses of acetaminophen).

Patel PA, Voigt MD. Prevalence and interaction of hepatitis B and latent tuberculosis in Vietnamese immigrants to the United States. Am J Gastroenterol 2002; 97: 1198-203. PubMed PMID: 12014728.

(Positive tuberculin skin test found in 48% and HBsAg in 14% of 743 Vietnamese immigrants; during isoniazid prophylaxis, ALT elevations occurred in 7% of HBsAg-negative but 48% of HBsAg-positive, 3 of whom developed symptomatic hepatitis).

Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002; 6: 699-705. PubMed PMID: 12150482.

(Retrospective analysis of 1036 patients treated for active tuberculosis in Singapore during 1998 found 55 cases of liver injury [5.3%], 37 symptomatic [3.6%], 18 jaundiced [1.8%], 3 died [0.3%: all on pyrazinamide]; 48 able to restart therapy; risk factors were age >60 years and baseline liver test abnormalities).

Centers for Disease Control and Prevention (CDC). Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. MMWR Morb Mortal Wkly Rep 2002; 51: 998-9. PubMed PMID: 12455909.

(Third alert: 40 cases of severe hepatotoxicity [8 fatal] associated with rifampin/pyrazinamide therapy of latent tuberculosis reported to CDC; issued revised guidelines cautioning against use of this regimen and only with no pre-existing liver disease or alcohol use, with ALT monitoring and provision of drugs in two week increments).

Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Ann Rheum Dis 2003; 62: 1241-2. PubMed PMID: 14644871.

(Among 88 patients with rheumatoid arthritis receiving anti-tumor necrosis factor therapies, 8 were treated with isoniazid to prevent reactivation of tuberculosis and 4 [50%] developed hepatotoxicity [ALT 82-330 U/L] arising 7-16 weeks after starting and resolving 4-11 weeks after stopping; none were clinically apparent).

Nagayama N, Masuda K, Baba M, Tamura A, Nagai H, Akagawa S, Kawabe Y, et al. [Secular increase in the incidence rate of drug-induced hepatitis due to anti-tuberculosis chemotherapy including isoniazid and rifampicin]. Kekkaku 2003; 78: 339-46. Japanese. PubMed PMID: 12739393.

(Apparent increase in rate of ALT elevations during isoniazid and rifampin therapy between 1980-83 [9%] and 1998-2000 [27%]).

el-Agroudy AE, Refaie AF, Moussa OM, Ghoneim MA. Tuberculosis in Egyptian kidney transplant recipients: study of clinical course and outcome. J Nephrol 2003; 16: 404-11. PubMed PMID: 12832742.

(Among 1200 kidney transplants, 45 [4%] developed tuberculosis afterwards, usually after several years, all treated with isoniazid, rifampin and ethambutol; hepatotoxicity in 11 [25%] but severe in only 3 and all responded to withdrawal of isoniazid or rifampin or both).

Kürşad H, Kizilkaya M, Sahin M, Dogan N, Ilgaz A. Treatment of acute isoniazid toxicity of unknown dose. South Med J 2003; 96: 101. PubMed PMID: 12602731.

(20 year old woman took overdose of isoniazid and presented with coma, seizures and respiratory failure; responded to intravenous pyridoxine).

Hussain Z, Kar P, Husain SA. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. Indian J Exp Biol 2003; 41: 1226-32. PubMed PMID: 15332488.

(Review article on role of genetic polymorphisms of NAT2, CYP 2E1 and glutathione-S-transferase in hepatotoxicity of antituberculosis therapies).

Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003; 167: 1472-7. PubMed PMID: 12569078.

(Among 408 adult patients treated for tuberculosis, 37 [9%] had 46 serious adverse events including 12 instances of hepatitis [3%: 11 symptomatic, ALT >5 times ULN]; risk factors were age [hazard ratio 4.8-7.7], female sex [2.2] and Asian birthplace [2.2]; hepatitis arose in 2% on pyrazinamide and 1% on isoniazid).

Mohan A, Sharma SK. Side effects of antituberculosis drugs. Am J Respir Crit Care Med 2004; 169: 882-3. PubMed PMID: 15044223.

(Letter in response to Yee et al. [2003] requesting further information on doses and clinical features; reply by authors stating that high rate of hepatotoxicity in comparison to reports from India was not due to higher doses of pyrazinamide, but may have been partially due to patient age and diverse ethnic background of patients).

McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. Chest 2003; 123: 102-6. PubMed PMID: 12527609.

(Between 1999-2002, 110 patients were treated with pyrazinamide/rifampin [P/R] for 2 months and 114 with isoniazid [INH] alone for 6 months for latent tuberculosis; completion rates were higher [71% vs 59%] as was hepatotoxicity [13% vs 4%] with P/R than INH and 2 patients had clinically apparent hepatitis [ALT 45-67 times ULN at 4 weeks] but both survived; after intensive monitoring no further severe cases occurred on P/R).

Stout JE, Engemann JJ, Cheng AC, Fortenberry ER, Hamilton CD. Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. Am J Respir Crit Care Med 2003; 167: 824-7. PubMed Citation

(Among 114 patients receiving 2-month course of rifampin and pyrazinamide, 67% completed therapy and 6 had hepatitis [5.3%] but all resolved; no hospitalizations or deaths).

Centers for Disease Control and Prevention (CDC); American Thoracic Society. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. MMWR Morb Mortal Wkly Rep 2003; 52: 735-9. PubMed PMID: 12904741.

(Fourth alert and issuing of recommendations against use of rifampin/pyrazinamide for latent tuberculosis; with this regimen, estimated rate of ALT elevations >5 times ULN was 2.6%, hospitalization for hepatitis 0.3% and death 0.09%).

American Thoracic Society; Centers for Disease Control and Prevention (CDC); Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003; 52(RR-11): 1-77. PubMed PMID: 12836625.

(Recommendations for therapy of tuberculosis including details of drug regimens, side effects, monitoring and optimal approaches to follow up).

Fernández-Villar A, Sopeña B, Fernández-Villar J, Vázquez-Gallardo R, Ulloa F, Leiro V, Mosteiro M, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8: 1499-505. PubMed PMID: 15636498.

(Among 471 patients receiving antituberculosis therapy, 56 [12%] developed ALT elevations >3 times ULN, 16 [3.4%] had symptoms and 5 [1%] were jaundiced; no deaths. Rates of hepatotoxicity higher in patients with risk factors than without [18.2% vs 5.6%]).

Marra F, Cox VC, FitzGerald JM, Moadebi S, Elwood RK. Successful treatment of multidrug-resistant tuberculosis following drug-induced hepatic necrosis requiring liver transplant. Int J Tuberc Lung Dis 2004; 8: 905-9. PubMed PMID: 15260286.

(28 year old woman with tuberculous lymphadenitis treated with isoniazid, rifampin, ethambutol and pyrazinamide was switched to ciprofloxacin with pyrazinamide and ethambutol when resistance testing was done; four days later she developed fever, rash and fatigue [bilirubin normal, ALT 285 U/L, Alk P normal], but then worsened [bilirubin 15.2 mg/dL, ALT 1165 U/L, Alk P 141 U/L], requiring liver transplant; later treated successfully with levofloxacin, amikacin and streptomycin).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were for drug-induced acute liver failure, 124 for acetaminophen and 137 for other agents, the most common being isoniazid [24], propylthiouracil [13], phenytoin [10], valproate [10], amanita [9], nitrofurantoin [7], herbals [7], ketoconazole [6], disulfiram [6], troglitazone [4] and 28 others).

Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ; Terry Beirn Community Programs for Clinical Research on AIDS; Adult AIDS Clinical Trials Group; Centers for Disease Control and Prevention. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? Clin Infect Dis 2004; 39: 561-5. PubMed PMID: 15356822.

(Detailed re-analysis of results of randomized controlled trial comparing 12 months of isoniazid [INH] to 2 months of rifampin/pyrazinamide [RP] for latent tuberculosis in HIV infected patients: comparing INH to RP recipients, bilirubin >2.5 mg/dL occurred in 0.6% vs 1.8% and AST >250 U/L in 1.6% vs 2.1% and no hospitalizations or deaths due to hepatotoxicity; older age only risk factor identified).

Kandula NR, Dworkin MS, Carroll MR, Lauderdale DS. Tuberculosis prevention in Mexican immigrants: limitations of short-course therapy. Am J Prev Med 2004; 26: 163-6. PubMed PMID: 14751331.

(Among 34 immigrants and contacts of a patient with multidrug-resistant tuberculosis treated with rifampin/ pyrazinamide, 1 of 11 children [9%] and 4 of 23 adults [17%] developed hepatotoxicity [ALT 165-547 U/L] after 10-53 days; all recovered and were able to finish 4 months of rifampin; points out impracticality of biochemical monitoring in immigrant population).

van Hest R, Baars H, Kik S, van Gerven P, Trompenaars MC, Kalisvaart N, Keizer S, et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. Clin Infect Dis 2004; 39: 488-96. PubMed PMID: 15356811.

(Retrospective analysis of patients starting preventive antituberculosis therapy; ALT elevations above 5 times ULN occurred in 8.4% of those receiving 2 months of rifampin/ pyrazinamide vs 3.4% of those receiving 6 months of isoniazid).

Campos-Franco J, González-Quintela A, Alende-Sixto MR. Isoniazid-induced hyperacute liver failure in a young patient receiving carbamazepine. Eur J Intern Med 2004; 15: 396-7. PubMed PMID: 15522577.

(16 year old girl on long-term carbamazepine and clobazam with ileocecal tuberculosis developed hepatitis and drowsiness with tremor, 5 days after starting isoniazid, rifampin and pyrazinamide [bilirubin 3.2 mg/dL, ALT 658 U/L, prothrombin index 12%], resolving spontaneously despite continuing anticonvulsants and later tolerating reintroduction of rifampin and pyrazinamide).

Jasmer RM, Snyder DC, Saukkonen JJ, Hopewell PC, Bernardo J, King MD, Kawamura LM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a cost-effective analysis based on a multicenter clinical trial. Clin Infect Dis 2004; 38: 363-9. PubMed PMID: 14727206.

(Cost effectiveness analysis of two regimens of therapy for latent tuberculosis, suggesting that isoniazid alone for 9 months is less expensive and has similar long-term efficacy [both regimens increased life expectancy by 1.2 years]).

Ijaz K, McElroy PD, Navin TR. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a cost-effectiveness analysis based on a multicenter clinical trial. Clin Infect Dis 2004; 39: 289. PubMed PMID: 15307044.

(Letter from CDC in response to Jasmer et al. [2004], reinforcing the recommendations that rifamin/pyrazinamide not be used to treat latent tuberculosis; a 9 month course of isoniazid being safer and more cost effective).

Reichman LB, Lardizabal A, Hayden CH. Considering the role of four months of rifampin in the treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2004; 170: 832-5. PubMed PMID: 15297274.

(Review of the safety and efficacy of a 4 month course of rifampin monotherapy for treatment of latent tuberculosis).

Sharma SK. Antituberculosis drugs and hepatotoxicity. Infect Genet Evol 2004; 4: 167-70. PubMed PMID: 15157635.

(Review of hepatotoxicity of isoniazid, rifampin and pyrazinamide, with focus on role of acetylator status).

McElroy PD, Ijaz K, Lambert LA, Jereb JA, Iademarco MF, Castro KG, Navin TR. National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis 2005; 41: 1125-33. PubMed PMID: 16163632.

(Survey of 110 health care programs using the 2 month rifampin/pyrazinamide regimen for latent tuberculosis in 8087 patients between 2000-2002; ALT elevations >5 times ULN occurred in 2.4% and hepatitis in 1.9%, with 23 hospitalizations and 7 deaths [0.1%] due to acute liver injury; higher than historical rates with isoniazid).

Cook PP. Rifampin and pyrazinamide for treatment of latent tuberculosis infection. Clin Infect Dis 2006; 42: 892; author reply 892-3. PubMed PMID: 16477576.

(Letter in response to McElroy [2005] questioning use of ALT for AST values used to define hepatotoxicity rates; reply by authors suggesting use of "AT" to indicate both enzymes).

Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology 2005; 129: 512-21. PubMed PMID: 16083708.

(Among 446 cases of drug induced liver injury collected in Spain between 1984-2004, isoniazid [with or without rifampin and pyrazinamide] was implicated in 22 cases [5%: ranking 3rd] and was fatal or required liver transplant in 5 [ranking first]).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(Survey of all cases of DILI with fatal outcome from Swedish Adverse Drug Reporting system from 1966-2002; 103 cases identified as highly probable, probable or possible, isoniazid accounting for 2 cases).

Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest 2005; 128: 116-23. PubMed PMID: 16002924.

(Retrospective analysis of 3377 patients treated with 6-9 months of isoniazid for latent tuberculosis in a public health clinic from 1996-2003, 0.6% developed ALT >5 times ULN, risk factors being older age and baseline AST values).

Lee BH, Koh WJ, Choi MS, Suh GY, Chung MP, Kim H, Kwon OJ. Inactive hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy. Chest 2005; 127: 1304-11. PubMed PMID: 15821209.

(Retrospective case control study of 110 HBsAg carriers and 97 controls from Korea who received 3-4 drug antituberculosis therapy; any ALT elevations occurred in 34% of carriers vs 20% of controls and were >3 times ULN in 8% vs 4%; no risk factors identified, most tolerated reintroduction of therapy without pyrazinamide).

Lobato MN, Reves RR, Jasmer RM, Grabau JC, Bock NN, Shang N; 2RZ Study Group. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. Chest 2005; 127: 1296-303. PubMed PMID: 15821208.

(Analysis of 2 month course of rifampin and pyrazinamide in jail and homeless populations found ALT elevations >5 times ULN in 6% of patients, one of whom died of acute liver failure; risk factors were older age and baseline ALT levels).

Ito K, Hoshino H, Nakazono T, Masuyama H, Sugita H, Yoshiyama T, Kato S. [Liver damage in treatment of latent tuberculous infection by isoniazid]. Kekkaku 2006; 81: 651-60. Japanese. PubMed PMID: 17154043.

(Retrospective analysis of 805 patients treated with prophylactic isoniazid; ALT elevations occurred in 15% and were higher than 400 U/L in 1.5%; 0.4% had clinical symptoms, no deaths).

Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology 2006: 11: 699-707. PubMed PMID: 17052297.

(Review of incidence, causes, risk factors and management of hepatotoxicity of antituberculosis medications).

Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, Moore RD, et al. Weekly rifapentine/ isoniazid or daily rifampin/ pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006; 173: 922-6. PubMed PMID: 16474028.

(In trial comparing rifapentine with isoniazid for 3 months [n=206] vs rifampin and pyrazinamide for 2 months [n=193], hepatotoxicity arose in 10% on pyrazinamide vs 1% on isoniazid combination, all resolved within two months, no hospitalizations or deaths).

Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, et al.; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-52. PubMed PMID: 17021358.

(American Thoracic Society recommendations regarding hepatotoxicity of antituberculosis therapy; for latent infection, 9 months of isoniazid is first choice and 4 months of rifampin second; clinical monitoring is recommend for all patients and biochemical monitoring for those at high risk and possibly the elderly [ALT values at 1, 3 and 6 months or every 1-2 months]; hold therapy if ALT >5 times ULN or if symptoms are present and ALT >3 times ULN).

Senaratne WV, Pinidiyapathirage MJ, Perera GA, Wickremasinghe AR. Anti-tuberculosis drug induced hepatitis – a Sri Lankan experience. Ceylon Med J 2006; 51: 9-14. PubMed PMID: 16898030.

(Among 783 patients treated for active tuberculosis, 9.5% developed hepatitis; major risk factor being older age).

Cook PP, Maldonado RA, Yarnell CT, Holbert D. Safety and completion rate of short-course therapy for treatment of latent tuberculosis infection. Clin Infect Dis 2006; 43: 271-5. PubMed PMID: 16804838.

(Retrospective analysis of 459 patients treated in public health departments for latent tuberculosis; completion rates were 78% for 2 months of rifampin/pyrazinamide vs 66% for 9 months of isoniazid; any ALT elevations in 18% vs 11%; ALT >5 times ULN in 6% vs 2%; no deaths).

Ijaz K, Jereb JA, Lambert LA, Bower WA, Spradling PR, McElroy PD, Iademarco MF, et al. Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis 2006; 42: 346-55. PubMed PMID: 16392079.

(Analysis of 50 cases of severe hepatotoxicity from rifampin/pyrazinamide therapy of latent tuberculosis occurring in US between 1998-2004 and arising during or within 1 month of stopping therapy; fatality rate higher in older patients and with later onset; patients frequently on other potentially hepatotoxic medications).

Vuilleumier N, Rossier MF, Chiappe A, Degoumois F, Dayer P, Mermillod B, Nicod L, et al. CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. Eur J Clin Pharmacol 2006; 62: 423-9. PubMed PMID: 16770646.

(Prospective analysis of genotyping for N-acetyltransferase-2 [NAT2] in 89 patients treated with isoniazid for latent tuberculosis; 26 [29%] had ALT elevations, 8 [9%] had hepatitis and 6 were symptomatic, no association with rapid [33% and 11%], intermediate [33% and 9%] or slow [23% and 9%] acetylators; slight association with CYP 2E1).

Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf 2006; 5: 231-49. PubMed PMID: 16503745.

(Review of side effects including hepatotoxicity of isoniazid, asymptomatic elevations in ALT levels occur in 10-22% of patients, but 80% of these resolve even with continuing therapy; overall rate of hepatotoxicity is 0.9%, mortality 0.04%).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis 2006; 38: 33-8. PubMed PMID: 16054882.

(Survey of drug induced liver fatalities reported to WHO database between 1968-2003 revealed 4690 reports – 89% from the US; 21 drugs were associated with >50 cases included [in order] acetaminophen, troglitazone, valproate, stavudine, halothane, lamivudine, didanosine, amiodarone, nevirapine, SMZ-TMP, flutamide, phenytoin, isoniazid, trovafloxacin, diclofenac, oxycodone, cyclophosphamide, zidovudine, methotrexate, cytarabine, and clarithromycin).

Idilman R, Ersoz S, Coban S, Kumbasar O, Bozkaya H. Antituberculous therapy-induced fulminant hepatic failure: successful treatment with liver transplantation and nonstandard antituberculous therapy. Liver Transpl 2006; 12: 1427-30. PubMed PMID: 16933231.

(19 year old woman with peritoneal tuberculosis developed jaundice 4 days after starting isoniazid, rifampin, ethambutol and pyrazinamide [bilirubin 10.5 mg/dL, ALT 1332 U/L, protime 71 sec], undergoing living donor liver transplantation within 2 days and afterwards treated with streptomycin, ethambutol and cycloserine, with no recurrence).

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther 2007; 25: 1401-9. PubMed PMID: 17539979.

(Population based survey of 126 cases of acute liver injury [24 with acute liver failure] due to drugs between 1993-1999 in Spain calculated relative risk [RR] of injury compared to the general population; highest risk was with antituberculosis triple therapy [RR=1300], chlorpromazine [RR=614], and isoniazid [RR=154]).

Aziz H, Shubair M, Debari VA, Ismail M, Khan MA. Assessment of age-related isoniazid hepatotoxicity during treatment of latent tuberculosis infection. Curr Med Res Opin 2006; 22: 217-21. PubMed PMID: 16393447.

(Retrospective analysis of 300 patients undergoing isoniazid treatment of latent tuberculosis found rates of symptomatic hepatitis similar in patients who were < vs >35 years old [2% vs 3%]).

Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, Fitzgerald JM. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. Int J Tuberc Lung Dis 2007; 11: 868-75. PubMed PMID: 17705952.

(Among 1061 patients treated for active tuberculosis in British Columbia between 2000-2005 [usually with 3-4 drugs for ~8 months], 148 [14%: 2% per month] developed hepatitis defined by ALT >5 times ULN or symptoms and ALT >3 times ULN]; independent risk factors were pyrazinamide, female sex, older age and baseline ALT levels but not HBV, HCV or race).

Cho HJ, Koh WJ, Ryu YJ, Ki CS, Nam MH, Kim JW, Lee SY. Genetic polymorphisms of NAT2 and CYP2E1 associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. Tuberculosis (Edinb) 2007; 87: 551-6. PubMed PMID: 17950035.

(Genotyping for NAT2 and CYP 2E1 in 132 patients with tuberculosis who were followed during therapy; 14% developed ALT elevations >2 times ULN, with higher rates in slow vs rapid acetylators [37% vs 9.7%], but no association with CYP 2E1 genotypes).

Wu SS, Chao CS, Vargas JH, Sharp HL, Martin MG, McDiarmid SV, Sinatra FR, et al. Isoniazid-related hepatic failure in children: a survey of liver transplantation centers. Transplantation 2007; 84: 173-9. PubMed PMID: 17667808.

(Survey of 84 US centers doing pediatric liver transplants between 1987-9 found 20 cases of isoniazid related acute liver failure [0.2% of transplants, 14% of those for drug-toxicity], ages 1.3-17 years, 11 boys, 13 Hispanic, 15 treated for latent disease, 4 recovered, 6 died waiting and 10 were transplanted; estimated 3.2 deaths per 100,000 children treated).

Markov M, Patel K, Raeesy A, Bant A, Van Thiel DH, Nadir A. Liver and pancreatic injury induced by antituberculous therapy. Dig Dis Sci 2007; 52: 3275-81. PubMed PMID: 17909976.

(26 year old woman developed jaundice and nausea 7 days after starting isoniazid, rifampin and pyrazinamide for tuberculous adenitis [bilirubin 3.9 mg/dL, ALT 152 U/L, Alk P 745 U/L], recovering on stopping with positive rechallenge to rifampin and later tolerating pyrazinamide and streptomycin).

Xia YY, Zhan SY. [Systematic review of anti-tuberculosis drug induced adverse reactions in China]. Zhonghua Jie He He Hu Xi Za Zhi 2007; 30: 419-23. Chinese. PubMed PMID: 17673012.

(Abstract: Review of 117 studies published in China on hepatotoxicity of antituberculosis therapy, overall incidence was 12%).

Fernández-Villar A, Sopeña B, García J, Gimena B, Ulloa F, Botana M, Martínez-Vázquez C. Hepatitis C virus RNA in serum as a risk factor for isoniazid hepatotoxicity. Infection 2007; 35: 295-7. PubMed PMID: 17646919.

(Prospective analysis of 293 patients with latent tuberculosis undergoing 6 months of isoniazid therapy; 17 [5.8%] developed ALT elevations 3 >times ULN and 4 had symptoms; risk factors for ALT elevations were alcohol [14.6% v 4.2%], HCV RNA positivity [15.5% vs 3.4%] and baseline ALT elevations).

Chang KC, Leung CC, Yew WW, Tam CM. Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? Eur Respir J 2007: 29: 347-51. PubMed PMID: 17005575.

(Nested case control study among 3007 patients starting treatment during 2001 at government clinics in Hong Kong with analysis of risk factors in 96 patients with hepatotoxicity vs 192 controls; HBsAg carriers [odds ratio 1.8], but not dosing schedules had higher risk; comparing cases to entire cohort showed increased risk with age >49 years [4.1% vs 2.6%]).

Shigeto E; Committee for Treatment Japanese Society for Tuberculosis. [Survey of anti-tuberculosis drug-induced severe liver injury in Japan]. Kekkaku 2007; 82: 467-73. Japanese. PubMed PMID: 17564126.

(Abstract: Survey questionnaire to 114 Japanese hospitals identified 70 cases of severe liver injury and 8 deaths due to antituberculosis therapy between 1994-2003).

Kwon YS, Koh WJ, Suh GY, Chung MP, Kim H, Kwon OJ. Hepatitis C virus infection and hepatotoxicity during antituberculosis chemotherapy. Chest 2007; 131: 803-8. PubMed PMID: 17356096.

(Retrospective analysis of 54 patients with HCV infection and 97 controls receiving therapy for active tuberculosis; ALT >3 times ULN occurred in 13% of HCV infected vs 4% of controls; none died or required hospitalization).

Huang YS. Genetic polymorphisms of drug-metabolizing enzymes and the susceptibility to antituberculosis drug-induced liver injury. Expert Opin Drug Metab Toxicol 2007; 3: 1-8. PubMed PMID: 17269890.

(Two gene variants have been linked to an increased risk of hepatotoxicity of antituberculosis medications; NAT2 and CYP 2E1, but the associations require further confirmation).

Jahng AW, Tran T, Bui L, Joyner JL. Safety of treatment of latent tuberculosis infection in compensated cirrhotic patients during transplant candidacy period. Transplantation 2007; 83: 1557-62. PubMed PMID: 17589337.

(14 patients with latent tuberculous and end-stage liver disease awaiting transplantation were treated with either isoniazid or rifampin; 2 on isoniazid had mild, asymptomatic and self-limited ALT elevations, otherwise therapy was tolerated and finished by all).

Björnsson E, Kalaitzakis E, Olsson R. The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. Aliment Pharmacol Ther 2007; 25: 1411-21. PubMed PMID: 17539980.

(Review of 570 case reports of drug induced liver injury suggested that eosinophilia was associated with a favorable prognosis, lower peak bilirubin and lower fatality rate).

Aouam K, Chaabane A, Loussaïef C, Ben Romdhane F, Boughattas NA, Chakroun M. [Adverse effects of antitubercular drugs: epidemiology, mechanisms, and patient management]. Med Mal Infect 2007; 37: 253-61. French. PubMed PMID: 17336011.

(Review of toxicities of antitubercular agents; isoniazid can cause an acute hepatocellular injury usually during first 3 months of treatment, as well as transient serum enzyme elevations which occur in 10-20% of cases).

Marzuki OA, Fauzi AR, Ayoub S, Kamarul Imran M. Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. Singapore Med J 2008; 49: 688-93. PubMed PMID: 18830542.

(Among 473 patients treated for tuberculosis over a 2 year period in Singapore, 46 [9.7%] developed ALT elevations >3 times ULN; in a case control analysis, concurrent HIV infection was a risk factor).

Lobato MN, Jereb JA, Starke JR. Unintended consequences: mandatory tuberculin skin testing and severe isoniazid hepatotoxicity. Pediatrics 2008; 121: e1732-3. PubMed PMID: 18474531.

(After mandatory school tuberculin skin testing, a 4 year old girl was treated with isoniazid and developed jaundice 11 weeks later [bilirubin 9.0 mg/dL, ALT 3580 U/L], ultimately requiring liver transplantation).

Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. Am J Respir Crit Care Med 2008; 177: 1391-6. PubMed PMID: 18388355.

(Among 3007 patients starting antituberculosis therapy over a six month period, 150 [5.0%] developed ALT elevations >3 times ULN, including 48 that arose after 3 months; in a case control analysis, risk factors were hepatitis B and C and regimens with pyrazinamide).

Vieira DE, Gomes M. Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. J Bras Pneumol 2008; 34: 1049-55. PubMed PMID: 19180340.

(Among 297 patients treated for tuberculosis in Sao Paulo, Brazil between 2000 and 2006, 24 [10.6%] had hepatotoxicity, 7 [2.4%] symptomatic, no deaths).

Makhlouf HA, Helmy A, Fawzy E, El-Attar M, Rashed HA. A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases. Hepatol International 2008; 2: 353-60. PubMed PMID: 19669265.

(Among 100 Middle Eastern patients treated for active tuberculosis with combination therapy, 15% had liver toxicity arising in 15-60 days, resolving in 15-45 days of stopping; bilirubin >2 in 5%, 1 death; able to restart therapy in all).

Yimer G, Aderaye G, Amogne W, Makonnen E, Aklillu E, Lindquist L, Yamuah L, et al. Anti-tuberculosis therapy-induced hepatotoxicity among Ethiopian HIV-positive and negative patients. PLoS One 2008; 3: e1809. PubMed PMID: 18350147.

(Between 2004-5, 103 HIV-positive and 94 HIV-negative Ethiopian patients were treated for tuberculosis; subclinical hepatotoxicity occurred in 17% and clinical apparent liver injury with jaundice in 4.1%; risk factors were HIV positivity and other drug intake, but not age, sex, hepatitis or body mass index).

Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. Int J Tuberc Lung Dis 2008; 12: 994-1002. PubMed PMID: 18713495.

(Prospective study in 261 patients treated for tuberculosis; 16% developed hepatitis [ALT or AST >5 times ULN or >3 times with symptoms/jaundice], predictive factors were preexisting elevations or low albumin; 49% had at least one ALT or AST elevation, 25% >2 times, 17% >3 times and 10% >5 times ULN).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, isoniazid was implicated as a single agent in 13 cases [4%: ranking 2nd] and in combination with other agents in two other cases).

Centers for Disease Control and Prevention (CDC). Trends in tuberculosis—United States, 2008. MMWR Morb Mortal Wkly Rep 2009; 58: 249-53. PubMed PMID: 19300406.

(In 2008, 12,898 cases of active tuberculosis in US, lowest rate since reporting began in 1953; incidence rate=3/100,000; 1.2% with multidrug resistant strains).

Kaneko Y, Nagayama N, Kawabe Y, Shimada M, Suzuki J, Kunogi M, Matsui Y, et al. [Drug-induced hepatotoxicity caused by anti-tuberculosis drugs in tuberculosis patients complicated with chronic hepatitis]. Kekkaku 2008; 83: 13-9. Japanese. PubMed PMID: 18283910.

(Abstract: there is a substantial increase in frequency of ALT elevations in patients with chronic hepatitis C associated with pyrazinamide therapy).

Roy PD, Majumder M, Roy B. Pharmacogenomics of anti-TB drugs-related hepatotoxicity. Pharmacogenomics 2008; 9: 311-21. PubMed PMID: 18303967.

(Review of genetics of isoniazid metabolic pathways: NAT2, CYP 2E1 and glutathione-S-transferase [GSTM1] as relates to hepatotoxicity).

Leiro V, Fernández-Villar A, Valverde D, Constenla L, Vázquez R, Piñeiro L, González-Quintela A. Influence of glutathione S-transferase M1 and T1 homozygous null mutations on the risk of antituberculosis drug-induced hepatotoxicity in a Caucasian population. Liver International 2008; 28: 835-9. PubMed PMID: 18397238.

(Case control study of 35 cases of antituberculosis hepatotoxicity and 60 controls; found higher rate of T1 GST variants in cases [49%] than controls [27%]; no difference for M1 variants [34% vs 42%]).

Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 2008; 23: 192-202. PubMed PMID: 17995946.

(Review of incidence, pathogenesis, clinical course, risk factors and management of drug induced liver disease due to antituberculosis medications).

Palaian PVK, Ojha S. Pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in Western Nepal. Pak J Pharm Sci 2008; 21: 51-6. PubMed PMID: 18166520.

(Abstract: Retrospective analysis of 326 Nepalese patients treated for tuberculosis identified 24 [7.4%] with AST elevations; no fatalities from liver disease).

Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, Memish Z, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008; 149: 689-97. PubMed PMID: 19017587.

(Prospective comparison of 9 months of isoniazid vs 4 months of rifampin as therapy of latent tuberculosis in 847 patients in 3 countries; symptoms and ALT elevations >3 times ULN or ALT elevations >5 times ULN occurred in 3.7% of isoniazid vs 0.7% of rifampin treated patients, but none died of liver disease; completion rates were 60% vs 78%).

Possuelo LG, Castelan JA, de Brito TC, Ribeiro AW, Cafrune PI, Picon PD, Santos AR, et al. Association of slow N-acetyltransferase 2 profile and anti-TB drug-induced hepatotoxicity in patients from Southern Brazil. Eur J Clin Pharmacol 2008; 64: 673-81. PubMed PMID: 18421452.

(Among 17 persons given pyrazinamide and levofloxacin for latent tuberculosis after contact with multidrug resistant tuberculosis, adverse reactions were common, 5 [29%] had ALT elevations [peak 80-504 U/L]; all recovered).

Yamada S, Tang M, Richardson K, Halaschek-Wiener J, Chan M, Cook VJ, Fitzgerald JM, et al. Genetic variations of NAT2 and CYP2E1 and isoniazid hepatotoxicity in a diverse population. Pharmacogenomics 2009; 10:1433-45. PubMed PMID: 19761367.

(In an analysis of 170 patients treated with isoniazid for latent tuberculosis, 23 [13.5%] developed AST elevations >2 times ULN; hepatotoxicity did not correlate with genotypes of NAT2 or CYP 2E1]).

Bliven EE, Podewils LJ. The role of chronic hepatitis in isoniazid hepatotoxicity during treatment for latent tuberculosis infection. Int J Tuberc Lung Dis 2009; 13: 1054-60. PubMed PMID: 19723392.

(Metaanalysis of studies on association of underlying chronic hepatitis C and B with risk of developing hepatotoxicity from antituberculosis medications; because of heterogeneity of studies and weak association, further studies are needed).

Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. Am J Respir Crit Care Med 2009; 179: 1055-60. PubMed PMID: 19299495.

(Analysis of efficacy, completion rates, toxicity and costs of 4 regimens of therapy of latent tuberculosis found 4 months of unobserved daily therapy with rifampin more effective and less expensive than 9 months of isoniazid with or without observation).

Semfke A, Wackernagel C, Vier H, Schütz A, Wiechmann V, Gillissen A. Histologically proven isoniazid hepatoxicity in complicated tuberculous salpingitis. Ther Adv Respir Dis 2009; 3: 159-62. PubMed PMID: 19723821.

(49 year old woman with suspected tuberculous salpingitis developed fever and ALT elevations 1 month after starting isoniazid, rifampin and pyrazinamide, resolved only when she stopped isoniazid, later tolerating rifampin).

Ho CC, Chen YC, Hu FC, Yu CJ, Yang PC, Luh KT. Safety of fluoroquinolone use in patients with hepatotoxicity induced by anti-tuberculosis regimens. Clin Infect Dis 2009; 48: 1526-33. PubMed PMID: 19400686.

(Among 1191 patients treated for active tuberculosis, 134 [11%] developed liver injury [risk factors were baseline ALT levels and pyrazinamide use], who were then treated with ethambutol with or without streptomycin and randomized to also receive levofloxacin or moxifloxacin, only 1 in each group continued to have ALT elevations and most were then able to restart isoniazid and rifampin).

Young H, Wessolossky M, Ellis J, Kaminski M, Daly JS. A retrospective evaluation of completion rates, total cost, and adverse effects for treatment of latent tuberculosis infection in a public health clinic in central Massachusetts. Clin Infect Dis 2009; 49: 424-7. PubMed PMID: 19548835.

(Among 767 patients treated for latent tuberculosis between 2003-2007, symptomatic ALT elevations occurred in 14 of 639 [2%] patients receiving 9 months of isoniazid and 1 of 138 [0.7%] receiving 4 months of rifampin, which was also associated with better completion rates).

Sarda P, Sharma SK, Mohan A, Makharia G, Jayaswal A, Pandey RM, Singh S. Role of acute viral hepatitis as a confounding factor in antituberculosis treatment induced hepatotoxicity. Indian J Med Res 2009; 129: 64-7. PubMed PMID: 19287059.

(Among 2906 patients from India treated for tuberculosis over a 2 year period, 102 [3%] developed liver injury [90% symptomatic, 30% jaundiced], 15 had serologic evidence of viral hepatitis; hepatitis A in 1, B in 2, C in 3, E in 8, and both C and E in one; viral cases had longer latency and recovery time and higher ALT levels).

Walker NF, Kliner M, Turner D, Bhagani S, Cropley I, Hopkins S, Lipman M. Hepatotoxicity and antituberculosis therapy: time to revise UK guidance? Thorax 2009; 64: 918. PubMed PMID: 19786720.

(During a one year period, 14 of 94 patients [15%] with active tuberculosis developed ALT elevations >3 times ULN during therapy, more common in HIV-positive [35%] than -negative [7%]; recommended routine HIV screening and biochemical monitoring in high risk groups).

Tostmann A, van den Boogaard J, Semvua H, Kisonga R, Kibiki GS, Aarnoutse RE, Boeree MJ. Antituberculosis drug-induced hepatotoxicity is uncommon in Tanzanian hospitalized pulmonary TB patients. Trop Med Int Health 2010; 15: 268-72. PubMed PMID: 20409289.

(Among 112 Tanzanian patients with tuberculosis monitored during first 2 months of therapy with isoniazid, rifampin, pyrazinamide and ethambutol, only 7 [6.3%] had ALT elevations [peak level 87 U/L], but none required dose modification).

Centers for Disease Control and Prevention(CDC). Severe isoniazid-associated liver injuries among persons being treated for latent tuberculsosis infection – United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2010; 59: 224-7. PubMed PMID: 20203555.

(Between 2004-8, CDC received 17 reports of serious liver injury in persons on isoniazid for prophylaxis of latent tuberculosis; 2 were <15, 5 were 16-35 and 10 were >35 years old; latency to onset ranged from 56-502 days, 5 patients required liver transplant and 5 died, many had other risk factors for hepatotoxicity, but all were being monitored).

Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis 2010; 50: 833-9. PubMed PMID: 20156055.

(175 patients with hepatic injury [ALT or AST >5 times ULN or symptoms with ALT elevations] attributed to antituberculosis medications were randomized to 3 different approaches to restarting therapy after initial episode resolved; 11% had recurrence with rates similar for all three regimens [starting agents at full doses or gradual escalation], onset in 5-35 days, none fatal and few with jaundice).

Saukkonen J. Challenges in reintroducing tuberculosis medications after hepatotoxicity. Clin Infect Dis 2010; 50: 840-2. PubMed PMID: 20156056.

(Editorial in response to Sharma [2010], discussing the paradox of why the injury does not recur more often, whether rechallenge should be with one agent at a time, and whether such rechallenge is warranted in patients with severe hepatotoxicity).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(World wide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children; 2 antituberculosis agents were among the top 41 causes, including isoniazid [24th, 47 cases], and rifampin [35th, 37 cases]).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury and 25 to antituberculosis agents, including 15 to isoniazid alone [ranking first], 6 to isoniazid combined with other agents, 3 to rifampin and pyrazinamide, and 1 to dapsone).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, 181 [58%] were attributed to antituberculosis agents, which accounted for 39 of 54 [72%] fatal cases).

Bray MG, Poulain C, Dougados M, Gossec L. Frequency and tolerance of antituberculosis treatment according to national guidelines for prevention of risk of tuberculosis due to tumor necrosis factor blocker treatment. Joint Bone Spine 2010; 77: 135-41. PubMed PMID: 20097592.

(Among 1028 patients treated with tumor necrosis factor [TNF] antagonists over a 5 year period at a single referral center in France, 216 received isoniazid and rifampin prophylaxis against tuberculosis and 17 of 93 [18%] adequately followed patients developed ALT elevations [1.25 to 17 times ULN], 7 required discontinuation, 1 was jaundiced, none fatal).

Coca NS, Oliveira MS, Voieta I, Antunes CM, Lambertucci JR. Antituberculosis drug-induced hepatotoxicity: a comparison between patients with and without human immunodeficiency virus seropositivity. Rev Soc Bras Med Trop 2010; 43: 624-8. PubMed PMID: 21181011.

(Using different definitions, rates of hepatotoxicity during antituberculosis therapy were either the same or higher among HIV infected than noninfected subjects).

Grant AD, Mngadi KT, van Halsema CL, Luttig MM, Fielding KL, Churchyard GJ. Adverse events with isoniazid preventive therapy: experience from a large trial. AIDS 2010; 24 Suppl 5: S29-36. PubMed PMID: 21079425.

(Among 24,221 miners in South Africa given isoniazid preventive therapy, side effects were uncommon [0.5%] and only 2 persons [0.01%] developed clinically apparent hepatotoxicity, 1 of whom died).

Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. Int J Tuberc Lung Dis 2010; 14: 1374-81. PubMed PMID: 20937175.

(Systematic review of the literature on the age related risk of hepatototoxicity [ALT >3-5 times ULN] caused by therapy of latent tuberculosis found rates were 0.2% in subjects <35 and 1.7% in those >35 years of age).

Ichai P, Saliba F, Antoun F, Azoulay D, Sebagh M, Antonini TM, Escaut L, et al. Acute liver failure due to antitubercular therapy: Strategy for antitubercular treatment before and after liver transplantation. Liver Transpl 2010; 16: 1136-46. PubMed PMID: 20879012.

(Description of 14 patients with acute liver failure due to antituberculosis therapy presenting between 1986 and 2008, including 4 men and 10 women, ages 17 to 64 years, on therapy for 1 week to 9 months, one with isoniazid alone and the remaining with isoniazid in combination with rifampin, pyrazinamide, and/or ethambutol [bilirubin 1.8 to 39 mg/dL, ALT 214-2020], 7 recovering spontaneously, 6 undergoing liver transplantation, and 1 dying without transplant).

Leiro-Fernandez V, Valverde D, Vázquez-Gallardo R, Constenla L, Fernández-Villar A. Genetic variations of NAT2 and CYP2E1 and isoniazid hepatotoxicity in a diverse population. Pharmacogenomics 2010; 11: 1205-6; author reply 1207-8. PubMed PMID: 20860460.

(Letter in response to Yamada [2009] discussing the association of CYP 2E1 polymorphisms with isoniazid induced hepatotoxicity).

Chatterjee S, Lyle N, Mandal A, Kundu S. GSTT1 and GSTM1 gene deletions are not associated with hepatotoxicity caused by antitubercular drugs. J Clin Pharm Ther 2010; 35: 465-70. PubMed PMID: 20853551.

(Case control study of 51 subjects with hepatotoxicity due to antituberculosis therapy and 100 controls found no association of liver injury with glutathione S-transferase [GST] M1 and T1 polymorphisms).

Wang T, Yu HT, Wang W, Pan YY, He LX, Wang ZY. Genetic polymorphisms of cytochrome P450 and glutathione S-transferase associated with antituberculosis drug-induced hepatotoxicity in Chinese tuberculosis patients. J Int Med Res 2010; 38: 977-86. PubMed PMID: 20819434.

(Case control study of 104 patients with hepatotoxicity due to antituberculosis therapy and 111 controls found a weak association of liver injury with the CYP 2E1 c1/c1 genotype, but not with polymorphisms of GSTM1).

Salinas C, Pascual Erquicia S, Diez R, Aguirre U, Egurrola M, Altube L, Capelastegui A. [Three-month course of rifampicin and isoniazid for the treatment of latent tuberculous infection]. Med Clin (Barc) 2010; 135: 293-9. PubMed PMID: 20800162.

(Among 547 subjects given preventive therapy for latent tuberculosis, withdrawals because of hepatotoxicity occurred in 4 of 169 [2.4%] given isoniazid alone for 6 months compared to 5 of 313 [1.6%] given the combination of isoniazid and rifampin for 3 months).

Vilariça AS, Diogo N, André M, Pina J. Adverse reactions to antituberculosis drugs in in-hospital patients: Severity and risk factors. Rev Port Pneumol 2010; 16: 431-51. English, Portuguese. PubMed PMID: 20635058.

(Retrospective analysis of 1400 patients treated for active tuberculosis between 1999 and 2007 identified 175 [12.5%] with an adverse event requiring dose modification or discontinuation, including 83 cases [6%] of hepatotoxicity).

Chang KC, Leung CC. The best approach to reintroducing tuberculosis treatment after hepatotoxicity is still open to debate. Clin Infect Dis 2010; 51: 366-7; author reply 367-8. PubMed PMID: 20597681.

(Letter in response to Sharma [2009] arguing that the sample size of their study was not adequate to demonstrate a clinically important noninferiority of simultaneous vs sequential reintroduction of antituberculosis medications after hepatotoxicity).

Baniasadi S, Eftekhari P, Tabarsi P, Fahimi F, Raoufy MR, Masjedi MR, Velayati AA. Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity. Eur J Gastroenterol Hepatol 2010; 22: 1235-8. PubMed PMID: 20461008.

(Among 60 patients started on antituberculosis therapy using 4 drugs with or without concurrent N-acetylcysteine [NAC: 600 mg twice daily], hepatototoxicity arose in 37% of controls vs 0% of NAC treated subjects, the injury usually arising within the first week and resolving within 8 days of stopping).

Lobue P, Menzies D. Treatment of latent tuberculosis infection: An update. Respirology 2010; 15: 603-22. PubMed PMID: 20409026.

(Extensive review of the efficacy and safety of various regimens used in the treatment of latent tuberculosis).

Lee SW, Chung LS, Huang HH, Chuang TY, Liou YH, Wu LS. NAT2 and CYP2E1 polymorphisms and susceptibility to first-line anti-tuberculosis drug-induced hepatitis. Int J Tuberc Lung Dis 2010; 14: 622-6. PubMed PMID: 20392357.

(Analysis of genetic polymorphisms in 140 patients with tuberculosis undergoing therapy found rates of hepatotoxicity to be higher in slow [51%] vs fast [25%] acetylators [defined by NAT2 genotypes] and the injury to be more severe in those with CYP2E1 c1/c1 genotype).

Nader LA, de Mattos AA, Picon PD, Bassanesi SL, De Mattos AZ, Pineiro Rodriguez M. Hepatotoxicity due to rifampicin, isoniazid and pyrazinamide in patients with tuberculosis: is anti-HCV a risk factor? Ann Hepatol 2010; 9: 70-4. PubMed PMID: 20308724.

(Retrospective analysis of 534 patients treated for tuberculosis between 1998 and 2006 found that HIV positivity and high doses of isoniazid were independently associated with a higher risk of hepatotoxicity).

Devrim I, Olukman O, Can D, Dizdarer C. Risk factors for isoniazid hepatotoxicity in children with latent TB and TB: difference from adults. Chest 2010; 137: 737-8. PubMed PMID: 20202962.

(Retrospective analysis of children treated for active [n=78] or latent [n=617] tuberculosis between 2002 and 2009 found a low overall rate of hepatotoxicity [1.7%], which did not vary by type of infection [active vs latent] or age of the child).

Yamada S, Richardson K, Tang M, Halaschek-Wiener J, Cook VJ, Fitzgerald JM, Elwood K, et al. Genetic variation in carboxylesterase genes and susceptibility to isoniazid-induced hepatotoxicity. Pharmacogenomics J 2010; 10: 524-36. PubMed PMID: 20195289.

(170 patients with latent tuberculosis treated with isoniazid were assessed for polymorphisms and genetic sequences of three carboxylesterase [CES] genes; 23 [13%] developed AST elevations during therapy, but no association was found between AST elevations and CES genetic variations).

Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis 2009; 49: 1883-9. PubMed PMID: 19911936.

(Analysis of pooled data from 3586 patients in published reports on efficacy and safety of 4 months of rifampin and 9 months of isoniazid as therapy of latent tuberculosis indicated that hepatotoxicity was less common with rifampin [0% to 0.7%] than isoniazid [1.4%-5.2%]).

Cagatay T, Aydin M, Sunmez S, Cagatay P, Gulbaran Z, Gul A, Artim B, Kilicaslan Z. Follow-up results of 702 patients receiving tumor necrosis factor-α antagonists and evaluation of risk of tuberculosis. Rheumatol Int 2010; 30: 1459-63. PubMed PMID: 19844718.

(Among 702 Turkish patients treated with tumor necrosis factor antagonists, 481 [69%] had a positive tuberculin test, and 583 received isoniazid prophylaxis of whom 6 developed active tuberculosis [~1%] and 31 hepatotoxicity [5%]).

Naqvi R, Naqvi A, Akhtar S, Ahmed E, Noor H, Saeed T, Akhtar F, Rizvi A. Use of isoniazid chemoprophylaxis in renal transplant recipients. Nephrol Dial Transplant 2010; 25: 634-7. PubMed PMID: 19783599.

(Among 400 Pakistani living donor renal transplant recipients, 181 received prophylaxis with isoniazid for one year and 207 did not; discontinuation for hepatotoxicity was not required in any patient).

Frésard I, Bridevaux PP, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicine 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. Swiss Med Wkly 2011; 141: w13240. PubMed PMID: 21842452.

(Retrospective analysis of patients with latent tuberculosis treated with either 6 months of isoniazid [1993-2002: n=426] or 4 months of rifampin [2004-2007: n=198] found that hepatotoxicity requiring dose interruption and clinical hepatitis were more frequent with isoniazid [6.1% and 1.4%] than rifampin [2.0% and 0%]).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J Pediatr Gastroenterol Nutr 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 cases of suspected drug induced liver injury in children in the US, 3 were attributed to isoniazid).

Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatr Rep 2011; 3: e16. PubMed PMID: 21772953.

(Extensive review of the literature on hepatotoxicity of antituberculosis medications in children concluded that liver injury occurs in children with isoniazid, pyrazinamide and rifampin therapy, but at a lower rate than in adults).

Sotsuka T, Sasaki Y, Hirai S, Yamagishi F, Ueno K. Association of isoniazid-metabolizing enzyme genotypes and isoniazid-induced hepatotoxicity in tuberculosis patients. In Vivo 2011; 25: 803-12. PubMed PMID: 21753138.

(Among 144 patients with tuberculosis undergoing treatment, hepatotoxicity was more frequent in slow acetylators, although the severity of the injury did not correlate with any genetic polymorphism tested).

Perriot J, Chambonnet E, Eschalier A. [Managing the adverse events of antitubercular agents]. Rev Mal Respir 2011; 28: 542-55. French. PubMed PMID: 21549908.

(Review of the side effects of antituberculosis medications).

Metushi IG, Cai P, Zhu X, Nakagawa T, Uetrecht JP. A fresh look at the mechanism of isoniazid-induced hepatotoxicity. Clin Pharmacol Ther 2011; 89: 911-4. PubMed PMID: 21412230.

(Editorial discussing the mechanism of isoniazid hepatotoxicity which has been thought to be due to aberrances of its metabolism [acetylation] to acetylhydrazine, but may relate to oxidative metabolism of isoniazid and to immune mediated responses to these metabolites).

Bose PD, Sarma MP, Medhi S, Das BC, Husain SA, Kar P. Role of polymorphic N-acetyl transferase2 and cytochrome P4502E1 gene in antituberculosis treatment-induced hepatitis. J Gastroenterol Hepatol 2011; 26: 312-8. PubMed PMID: 21261721.

(Among 218 patients with tuberculosis started on therapy who underwent genetic testing, hepatotoxicity was more frequent among slow acetylators [NAT2] and with certain polymorphisms of CYP 2E1).

Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. CMAJ 2011; 183: E173-9. PubMed PMID: 21220436.

(Among 9145 persons with latent tuberculosis treated with isoniazid [95%] or rifampin [5%] registered in a healthcare database in Quebec, 45 [0.5%] were subsequently admitted to hospital for liver injury compared to 0.1% of matched controls, rates being particularly high among those 65 years of age or older [2.6%: odds ratio=6.4]).

Leung CC, Rieder HL, Lange C, Yew WW. Treatment of latent infection with Mycobacterium tuberculosis: update 2010. Eur Respir J 2011; 37: 690-711. PubMed PMID: 20693257.

(Review of the efficacy, adherence rates, cost effectiveness and safety of various regimens for the therapy of latent tuberculosis).

Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, McIntyre JA, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011; 365: 11-20. PubMed PMID: 21732833.

(Among 1148 South African adults with HIV infection and a positive tuberculin skin test who were treated with 4 different antituberculosis regimens, subsequent rates of active tuberculosis were the same in all groups, but adverse events were greatest with long term daily isoniazid, ALT or AST elevations above 5 times ULN occurring in 28%, compared to 1.5% and 2.4% with the two 12-week regimens, and 5.5% for 9 months of daily isoniazid, but none of the 66 deaths were considered drug related).

Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, et al.; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365: 2155-66. PubMed PMID: 22150035.

(7731 subjects with latent tuberculosis at high risk for active disease were treated with either a 3 month course of directly observed once weekly isoniazid and rifapentine [3 mo INH/R] or standard therapy with 9 months of daily isoniazid [9 mo INH]; after 3 years, rates of active tuberculosis were similar [0.19% after 3 mo INH/R and 0.43% after 9 mo INH], whereas hepatotoxicity was less with 3 mo INH/R [0.4%] than 9 mo INH [2.7%]).

Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci 2011; 56: 958-76. PubMed PMID: 21327704.

(Review of drug induced autoimmune hepatitis, the principal causes being minocycline and nitrofurantoin; other caues being methyldopa, hydralazine, statins, fibrates, diclofenac, anti-TNF agents, interferons, propylthiouracil and isoniazid).

Leiro-Fernandez V, Valverde D, Vázquez-Gallardo R, Botana-Rial M, Constenla L, Agúndez JA, Fernández-Villar A. N-acetyltransferase 2 polymorphisms and risk of anti-tuberculosis drug-induced hepatotoxicity in Caucasians. Int J Tuberc Lung Dis 2011; 15: 1403-8. PubMed PMID: 22283902.

(Genetic testing in 50 Spanish patients with and 67 without liver injury during isoniazid based antituberculosis therapy found no association of liver injury with any of the NAT2 alleles, slow acetylation genotypes being present in 72% of cases and 66% of controls).

Teixeira RL, Morato RG, Cabello PH, Muniz LM, Moreira Ada S, Kritski AL, Mello FC, et al. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. Mem Inst Oswaldo Cruz. 2011; 106: 716-24. PubMed PMID: 22012226.

(Genetic testing of 26 patients with and 140 without liver injury during antituberculosis therapy found no variation in genotypes of CYP2E1, GSTT1, GSTM1 or NAT2 between the two groups, but NAT2 alleles with low activity were more frequent in cases than controls).

Cai Y, Yi J, Zhou C, Shen X. Pharmacogenetic study of drug-metabolising enzyme polymorphisms on the risk of anti-tuberculosis drug-induced liver injury: a meta-analysis. PLoS One 2012; 7: e47769. PubMed PMID: 23082213.

(Metaanalysis of studies of genetic polymorphisms and hepatotoxicity of drugs for tuberculosis identified 38 publications including 2225 patients and 4906 controls; modest association was found between slow NAT2

acetylation genotypes and glutathione-S-transferase genotypes and hepatotoxicity, but largely in Asian populations).

An HR, Wu XQ, Wang ZY, Zhang JX, Liang Y. NAT2 and CYP2E1 polymorphisms associated with antituberculosis drug-induced hepatotoxicity in Chinese patients. Clin Exp Pharmacol Physiol 2012; 39: 535-43. PubMed PMID: 22506592.

(Analysis of genetic polymorphisms in NAT2 and CYP2E1 genes in 101 Chinese patients with and 107 without liver injury during antituberculosis therapy; slow acetylators had a higher rate of ALT elevations that rapid acetylators, whereas CYP2E1 variants were similar in the two groups).

Lee CH, Wang JD, Chen PC; Health Data Analysis in Taiwan (hDATa) Research Group. Case-crossover design: an alternative strategy for detecting drug-induced liver injury. J Clin Epidemiol 2012; 65: 560-7. PubMed PMID: 22445086.

(Using the Taiwan National Health Insurance database and a case crossover design, the adjusted odds ratio for hospitalization for liver injury within 90 days of receiving a medication was 24.4 for isoniazid, 30.8 for rifampin, 2.1 for erythromycin and 2.9 for diclofenac).

Nanashima K, Mawatari T, Tahara N, Higuchi N, Nakaura A, Inamine T, Kondo S, et al. Genetic variants in antioxidant pathway: risk factors for hepatotoxicity in tuberculosis patients. Tuberculosis (Edinb) 2012; 92: 253-9. PubMed PMID: 22341855.

(Analysis of single nucleotide polymorphisms in 18 Japanese patients with and 82 without liver injury during combination therapy with isoniazid and rifampin found weak associations with 3 polymorphisms of genes involved in antioxidant pathways: NOS2A, BACH1 and MAFK).

Kim SH, Kim SH, Yoon HJ, Shin DH, Park SS, Kim YS, Park JS, Jee YK. TNF-α genetic polymorphism -308G/A and antituberculosis drug-induced hepatitis. Liver Int 2012; 32: 809-14. PubMed PMID: 22151084.

(The frequency of variant allele of tumor necrosis factor polymorphism -308g/A was higher in 77 Korean patients with liver injury due to antituberculosis therapy [26%] than in 229 drug tolerant controls [15%]).

Thongraung W, Sittidach M, Khwansuwan P, Sariyasuntorn K, Wongsampan S. Evaluation of the physicians' approach to the diagnosis and treatment of patients with antituberculosis drug-induced hepatotoxicity. J Eval Clin Pract 2012; 18: 1119-25. PubMed PMID: 21696520.

(Survey of physician practices in Southern Thailand found variability in diagnosis and management of tuberculosis which were not always in compliance with published guidelines).

Daly AK, Day CP. Genetic association studies in drug-induced liver injury. Drug Metab Rev 2012; 44: 116-26. PubMed PMID: 21913872.

(Review of studies of genetic susceptibility to drug induced liver injury focusing upon HLA associations [ticlopidine, flucloxacillin, amoxicllin-clavulanate, nevirapine, lapatinib, lumiracoxib, ximelagatran] and NAT2 [isonaizid]).

Ben Mahmoud L, Ghozzi H, Kamoun A, Hakim A, Hachicha H, Hammami S, Sahnoun Z, Zalila N, Makni H, Zeghal K. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis. Pathol Biol (Paris) 2012; 60: 324-30. PubMed PMID: 21856096.

(Analysis of NAT2 polymorphisms in 14 Tunisian patients with and 52 without liver injury during antituberculosis therapy found higher rate of hepatotoxicity in those with slow acetylator genotypes).

Stine JG, Sateesh P, Lewis JH. Drug-induced liver injury in the elderly. Curr Gastroenterol Rep 2013; 15: 299. PubMed PMID: 23250699.

(Review of the problems of drug induced liver injury in the elderly, who take a greater number of medications and may be at higher risk of medication error, inappropriate dosing, and drug-drug interactions).

Azuma J, Ohno M, Kubota R, Yokota S, Nagai T, Tsuyuguchi K, Okuda Y, Takashima T, Kamimura S, Fujio Y, Kawase I; Pharmacogenetics-based tuberculosis therapy research group. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A randomized controlled trial for pharmacogenetics-based therapy. Eur J Clin Pharmacol 2013; 69: 1091-101. PubMed PMID: 23150149.

(Among 155 Japanese patients with tuberculosis treated with standard vs NAT2 genotype guided dosing found lower rates of ALT elevations >2 times ULN with the guided dosing regimen).

le Roux SM, Cotton MF, Myer L, le Roux DM, Schaaf HS, Lombard CJ, Zar HJ. Safety of long-term isoniazid preventive therapy in children with HIV: a comparison of two dosing schedules. Int J Tuberc Lung Dis 2013; 17: 26-31. PubMed PMID: 23146410.

(Among 297 South African children with HIV infection and latent tuberculosis who received long term isoniazid preventive therapy, 1.7% developed "severe" liver injury [ALT >10 times ULN], but all recovered).

Loddenkemper R, Diel R. Prolonged isoniazid prevention in HIV-positive children: hepatotoxicity is not a major problem. Int J Tuberc Lung Dis 2013; 17: 1. PubMed PMID: 23231996.

(Editorial accompanying Le Roux [2013]).

Zhou Y, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21 789 patients. Eur J Gastroenterol Hepatol 2013 Mar 18. [Epub ahead of print] PubMed PMID: 23510965.

(Systematic review of the Chinese literature on drug induced liver injury from 1994 to 2011 identified 1119 reports on 21,789 patients; antituberculosis agents were the most commonly implicated drugs [31%]).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 1 attributed to isoniazid among only 71 persons exposed to the agent).

Thongraung W, Lertphongpiroon W, Pungrassami P, Ratanajamit C. Physicians' practices regarding management of antituberculosis drug-induced hepatotoxicity. Southeast Asian J Trop Med Public Health 2012; 43: 724-34. PubMed PMID: 23077853.

(Survey of physician practices in Southern Thailand found variability in diagnosis and management of tuberculosis which were not always in compliance with published guidelines).

Shu CC, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosis drugs: a five-year experience in a Taiwan medical centre. Int J Tuberc Lung Dis 2013; 17: 934-9. PubMed PMID: 23743313.

(Retrospective analysis of 926 adults who were treated for tuberculosis at the National Taiwan University Hospital between 2005 and 2009 found that 111 [12%] developed a serum ALT elevation above 3 times, 71 [7.7%] 5 times and 32 [3.5%] 10 times ULN; median onset after 38 days, 87% with symptoms, bilirubin not mentioned; pyrizinamide most frequently implicated; factors associated with injury were age, female sex, autoimmune disease and HIV infection).

Jiménez-Fuentes MA, de Souza-Galvao ML, Mila Augé C, Solsona Peiró J, Altet-Gómez MN. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. Int J Tuberc Lung Dis 2013; 17: 326-32. PubMed PMID: 23407221.

(Among 590 immigrants with latent tuberculosis treated with either isoniazid alone for 6 months [6H] or isoniazid and rifampin for 3 months [3HR]), serum enzyme elevations occurred in 9.1% [6H] vs 6.7% [3RH], but were usually mild and above 10 times ULN in only one patient).

Gupta VH, Singh M, Amarapurkar DN, Sasi P, Joshi JM, Baijal R, H R PK, et al. Association of GST null genotypes with anti-tuberculosis drug induced hepatotoxicity in Western Indian population. Ann Hepatol 2013; 12: 959-65. PubMed PMID: 24114827.

(Among 296 patients being treated for tuberculosis, 17% developed ALT elevations during therapy and evidence of liver injury was associated with homozygous null mutations at both glutathione S transferase M1 and T1 gene loci).

Ho HT, Wang TH, Hsiong CH, Perng WC, Wang NC, Huang TY, Jong YJ, et al. The NAT2 tag SNP rs1495741 correlates with the susceptibility of antituberculosis drug-induced hepatotoxicity. Pharmacogenet Genomics 2013; 23: 200-7. PubMed PMID: 23407048.

(Among 348 adults treated for tuberculosis in Taiwan, the rate of serum aminotransferase elevations above 3 times ULN or more occurred in 8.1% with rs1495741 allele AA, vs 3.8% in those with AG or GG, this SNP being linked to NAT2 alleles and slow acetylator activity).

Santos NP, Callegari-Jacques SM, Ribeiro Dos Santos AK, Silva CA, Vallinoto AC, Fernandes DC, de Carvalho DC, et al. N-acetyl transferase 2 and cytochrome P450 2E1 genes and isoniazid-induced hepatotoxicity in Brazilian patients. Int J Tuberc Lung Dis 2013; 17: 499-504. PubMed PMID: 23394127.

(Among 270 pateints being treated for tuberculosis, 18 [7%] developed ALT elevations above 3 times ULN, including 7.3% of those with rapid acetylator and 5.8% with slow acetylator associated genotypes).

Li C, Long J, Hu X, Zhou Y. GSTM1 and GSTT1 genetic polymorphisms and risk of anti-tuberculosis drug-induced hepatotoxicity: an updated meta-analysis. Eur J Clin Microbiol Infect Dis 2013; 32: 859-68. PubMed PMID: 23377313.

(Metaanalysis of studies on the association of tuberculosis drug associated liver injury and polymorphisms of the glutathione S-transferase genes found weak associations only).

Chamorro JG, Castagnino JP, Musella RM, Nogueras M, Aranda FM, Frías A, Visca M, et al. Sex, ethnicity, and slow acetylator profile are the major causes of hepatotoxicity induced by antituberculosis drugs. J Gastroenterol Hepatol 2013; 28: 323-8. PubMed PMID: 23190413.

(Among 175 South American adults treated for tuberculosis, serum aminotransferase elevations above 3 times ULN occurred in 47 [27%] of subjects, including 37% of slow and 17% of rapid acetylators).

Xiang Y, Ma L, Wu W, Liu W, Li Y, Zhu X, Wang Q, et al. The Incidence of Liver Injury in Uyghur Patients Treated for TB in Xinjiang Uyghur Autonomous Region, China, and Its Association with Hepatic Enzyme Polymorphisms NAT2, CYP2E1, GSTM1 and GSTT1. PLoS One 2014; 9: e85905. PubMed PMID: 24465778.

*(Among 2244 patients treated for tuberculosis, 89 [4%] had aminotransferase elevations above 2 times and 0.4% above 5 times ULN after 2 months of treatment; evidence of liver injury was more common in persons with NAT2*5*CT genotype, slow acetylator phenotype, but not with CYP 2E1 polymorphisms).*

Satyaraddi A, Velpandian T, Sharma SK, Vishnubhatla S, Sharma A, Sirohiwal A, Makharia GK, et al. Correlation of plasma anti-tuberculosis drug levels with subsequent development of hepatotoxicity. Int J Tuberc Lung Dis 2014; 18: 188-95, i-iii. PubMed PMID: 24429311.

(Among 110 patients being treated for tuberculosis, 15 developed evidence of liver injury [enzyme or bilirubin elevations or symptoms]; plasma free rifampin, but not isoniazid or pyrazinamide, levels were higher in patients who developed liver injury than in those who did not).

de Castilla DL, Rakita RM, Spitters CE, Narita M, Jain R, Limaye AP. Short-course isoniazid plus rifapentine directly observed therapy for latent tuberculosis in solid-organ transplant candidates. Transplantation 2014; 97: 206-11. PubMed PMID: 24142036.

(Among 17 solid organ transplant candidates treated with 3 months of isoniazid and rifampin, none developed ALT elevations above two times ULN and 13 [76%] successfully finished therapy).

Metushi IG, Sanders C; Acute Liver Study Group, Lee WM, Uetrecht J. Detection of anti-isoniazid and anti-cytochrome P450 antibodies in patients with isoniazid-induced liver failure. Hepatology 2014; 59: 1084-93. PubMed PMID: 23775837.

(Among 19 patients with isoniazid associated acute liver failure, 8 had antibodies to isoniazid and 10 to 14 had antibodies to cytochrome P450 enzymes, including CYP 3A4, 2C9 and 2E1; the antibodies were not found in patients with isoniazid liver injury marked by enzyme elevations only).

James L, Roberts D. Isoniazid hepatotoxicity: Progress in understanding the immunologic component. Hepatology 2014; 59: 746-8. PubMed PMID: 24037911.

(Editorial and comment on Metushi [2014]).

Huang YS. Recent progress in genetic variation and risk of antituberculosis drug-induced liver injury. J Chin Med Assoc 2014; 77: 169-73. PubMed PMID: 24593909.

(Critical review of studies on genetic variations associated with antituberculosis drug induced liver injury focusing on N-acetyltransferase (NAT), CYP 2E1, glutathione S transferase and manganese superoxide dismutase, the strongest association being with NAT and slow acetylator status).

Sheen E, Huang RJ, Uribe LA, Nguyen MH. Isoniazid Hepatotoxicity Requiring Liver Transplantation. Dig Dis Sci 2014; 59: 1370-4. PubMed PMID: 24573717.

(65 year old woman developed jaundice 1 month after starting isoniazid for latent tuberculosis [bilirubin 11.3 mg/dL, ALT 1576 U/L, Alk P 246 U/L, INR 1.2], with subsequent worsening, ascites, encephalopathy and sucessful emergency liver transplantation).

Bourré-Tessier J, Arino-Torregrosa M, Choquette D. Increased incidence of liver enzymes abnormalities in patients treated with isoniazid in combination with disease modifying and/or biologic agents. Clin Rheumatol 2014; 33: 1049-53. PubMed PMID: 24554383.

(Among 87 patients receiving immunomodulatory biologics or disease modifying agents for rheumatic diseases who were also treated with isoniazid for latent tuberculosis, 21 [24%] developed ALT elevations, 14 were mild and transient, but 7 led to discontinuation of isoniazid although all were asymptomatic).

Chang SH, Nahid P, Eitzman SR. Hepatotoxicity in children receiving isoniazid therapy for latent tuberculosis infection. J Pediatric Infect Dis Soc 2014; 3: 221-7. PubMed PMID: 26625385.

(Among 1582 children with "latent tuberculosis" treated with isoniazid for up to 9 months at public health clinics in California, 13 developed hepatotoxicity [0.8%], 11 with symptoms and 3 with jaundice, but all recovered and none died).

Dağ MS, Aydınlı M, Oztürk ZA, Türkbeyler IH, Koruk I, Savaş MC, Koruk M, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014; 25: 41-5. PubMed PMID: 24918129.

(Among 82 patients with drug induced liver injury seen over a 4 year perod at a single referral center in Turkey, one fatal case was attributed to the combination of isoniazid and rifampin).

Devarbhavi H, Andrade RJ. Drug-induced liver injury due to antimicrobials, central nervous system agents, and nonsteroidal anti-inflammatory drugs. Semin Liver Dis 2014; 34: 145-61. PubMed PMID: 24879980.

(Review of hepatoxicity of antimicrobials including INH which is associated with ALT elevations in up to 20% of patients, symptomatic hepatitis in 1% and acute liver failure in 0.1%, risk factors being older age, female sex and slow acetylated status).

Gourishankar A, Navarro F, Debroy AN, Smith KC. Isoniazid hepatotoxicity with clinical and histopathology correlate. Ann Clin Lab Sci 2014; 44: 87-90. PubMed PMID: 24695480.

(15 year old Vietnamese girl developed jaundice 3 months after starting isoniazid for latent tuberculosis [bilirubin 19.3 mg/dL, ALT 1638 U/L, Alk P 277 U/L, INR 1.8], was treated with corticosteroids and N-acetylcysteine and subsequently recovered and was later treated with rifampin, a follow-up liver biopsy showing mild inflammation and fibrosis).

Shin HJ, Lee HS, Kim YI, Lim SC, Jung JP, Ko YC, Kwon YS. Hepatotoxicity of anti-tuberculosis chemotherapy in patients with liver cirrhosis. Int J Tuberc Lung Dis 2014; 18: 347-51. PubMed PMID: 24670574.

(Among 50 patients with cirrhosis and 147 controls without cirrhosis who had active tuberculosis and were treated with isoniazid, rifampin ethambutol and pyrazinamide, abnormal liver tests arose in 72% of cirrhotics vs 46% of controls, and predefined "hepatotoxicity" arose in 8% vs 3%, but no patient required hospitalization or died).

Singla N, Gupta D, Birbian N, Singh J. Association of NAT2, GST and CYP2E1 polymorphisms and anti-tuberculosis drug-induced hepatotoxicity. Tuberculosis (Edinb) 2014; 94 (3): 293-8. PubMed PMID: 24637014.

(Among 408 patients with tuberculosis treated with isoniazid, 17 developed ALT or AST levels, 15 of whom were slow acetylators of N-acetyltransferase 2).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 13 of which [7%] were due to isoniazid, making it rank as the 4th most common cause).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5%] were attributed to isoniazid, making it rank as the 2nd most common cause).

Mengual-Moreno E, Lizarzábal-García M, Ruiz-Soler M, Silva-Suarez N, Andrade-Bellido R, Lucena-González M, Bessone F, et al. [Case reports of drug-induced liver injury in a reference hospital of Zulia state, Venezuela]. Invest Clin. 2015; 56: 3-12. Spanish. PubMed PMID: 25920181.

(Among 13 cases of drug induced liver injury seen during 2013 at a single referral center in Venezuela, 2 were attributed to isoniazid).

Miyazawa S, Matsuoka S, Hamana S, Nagai S, Nakamura H, Nirei K, Moriyama M. Isoniazid-induced acute liver failure during preventive therapy for latent tuberculosis infection. Intern Med 2015; 54: 591-5. PubMed PMID: 25786447.

(53 year old Japanese man developed jaundice 70 days after starting isoniazid for latent tuberculosis [bilirubin 7.8 mg/dL, ALT 2540 U/L, Alk P 724 U/L, INR 1.2], with subsequent progressive liver injury and death from multiorgan failure 4 months later).

Hayashi PH, Fontana RJ, Chalasani NP, Stolz AA, Talwalkar JA, Navarro VJ, Lee WM, et al.; US Drug-Induced Liver Injury Network Investigators. Under-reporting and poor adherence to monitoring guidelines for severe

cases of isoniazid hepatotoxicity. Clin Gastroenterol Hepatol 2015; 13: 1676-82.e1. PubMed PMID: 25724701.

(Among 1091 patients enrolled in a US prospective study of drug induced liver injury, 60 [6%] were attributed to isoniazid with a mean age of 49 years [range 4 to 68], 97% were being treated for "latent tuberculosis", 92% were hepatocellular and none cholestatic, 77% had jaundice and 22% were fatal [death or liver transplantation], and those with severe outcomes were more likely to delay in stopping isoniazid after onset of symptoms).

Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT, Lee JH. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci 2015; 30: 167-72. PubMed PMID: 25653488.

(Among 195 patients treated with isoniazid, rifampin, ethambutol and pyrazinamide, 17 developed ALT or AST abnormalities, but elevations did not correlate with peak plasma levels of the 4 agents taken 2 hours after dosing during the first 5 days of treatment).

Tedla Z, Nguyen ML, Sibanda T, Nyirenda S, Agizew TB, Girde S, Rose CE, et al. Isoniazid-associated hepatitis in adults infected with HIV receiving 36 months of isoniazid prophylaxis in Botswana. Chest 2015; 147: 1376-84. PubMed PMID: 25340318.

(Among 1006 adults with HIV infection treated with isoniazid for 36 months, 129 [13%] developed mild, 31 [3%] moderate and 19 [2%] "severe hepatitis" including 2 [0.2%] who died from acute liver failure).

Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, Drobeniuc J, Bock N, Villarino ME; TB Trials Consortium. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. Int J Tuberc Lung Dis 2015; 19: 1039-44, i-v. PubMed PMID: 26260821.

(Among 6862 patients with latent tuberculosis treated with either 9 months of daily oral isoniazid or 3 months of once weekly rifapentine and isoniazid, liver injury requiring discontinuation was more frequent with the 9 month regimen 1.9% vs 0.4%, as was symptomatic hepatotoxicity [1.3% vs 0.3%], but there were no hospitalizations or deaths from liver injury).

Li X, Liu Y, Zhang E, He Q, Tang YB. Liver transplantation in antituberculosis drugs-induced fulminant hepatic failure: a case report and review of the literature. Medicine (Baltimore) 2015; 94: e1665. PubMed PMID: 26656321.

(Have).

Lin HS, Cheng CW, Lin MS, Chou YL, Chang PJ, Lin JC, Ye JJ. The clinical outcomes of oldest old patients with tuberculosis treated by regimens containing rifampicin, isoniazid, and pyrazinamide. Clin Interv Aging 2016; 11: 299-306. PubMed PMID: 27042029.

(Among 700 Taiwanese patients with active tuberculosis treated with isoniazid, rifampin and pyrazinamide, hepatitis arose in 83 [12%] and was more frequent in those above the age of 80 years [17.4%] compared to younger [10.2%], but details on severity and clinical features were not provided).

Gogtay NJ, Kapileshwar SR, Shah SU, Bendkhale SR, Ramakrishna S, Sridharan K, Thelma BK, et al. Evaluation of cytochrome P4502E1 polymorphisms in healthy adult Western Indians and patients with antituberculous drug-induced hepatotoxicity. Indian J Pharmacol 2016; 48: 42-6. PubMed PMID: 26997721.

(Among 22 patients who developed serum enzyme elevations during antituberculosis treatment, all had the c1/c1 genotype of CYP2E1, compared to 42 of 49 [86%] of controls who did not).

Gray EL, Goldberg HF. Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatoxicity for patients receiving preventive therapy for latent tuberculosis infection. Intern Med J 2016; 46: 281-7. PubMed PMID: 26648478.

(Among 72 patients with "latent tuberculosis" treated with isoniazid, 33% developed some degree of ALT or AST elevation [7 above 3 times ULN], two of whom discontinued therapy for this reason, but none died).

Bright-Thomas RJ, Gondker AR, Morris J, Ormerod LP. Drug-related hepatitis in patients treated with standard anti-tuberculosis chemotherapy over a 30-year period. Int J Tuberc Lung Dis 2016; 20: 1621-4. PubMed PMID: 27931337.

(Among 2070 patients with tuberculosis treated over a 30 year period at a single UK referral center, 63 [3%] developed hepatitis requiring discontinuation of therapy of whom two died; the hepatitis rate was higher in whites than Asians and in females than males, and occurred more commonly with older age; 57% of cases were attributed to pyrazinamide, 32% to rifampin and 11% to isoniazid).

Aït Moussa L, El Bouazzi O, Serragui S, Soussi Tanani D, Soulaymani A, Soulaymani R. Rifampicin and isoniazid plasma concentrations in relation to adverse reactions in tuberculosis patients: a retrospective analysis. Ther Adv Drug Saf 2016; 7: 239-47. PubMed PMID: 27904742.

(Among 120 Moroccan patients treated for active tuberculosis, adverse events during therapy were found to correlated with higher plasma levels of isoniazid, but not rifampin or pyrazinamide).

Wattanapokayakit S, Mushiroda T, Yanai H, Wichukchinda N, Chuchottawon C, Nedsuwan S, Rojanawiwat A, et al. NAT2 slow acetylator associated with anti-tuberculosis drug-induced liver injury in Thai patients. Int J Tuberc Lung Dis 2016; 20: 1364-9. PubMed PMID: 27725049.

(Among 54 adult Thais who developed liver injury during antituberculosis therapy, slow acetylator status for NAT2 was more frequent than in 85 controls [72% vs 22%]).

Ji GY, Wang Y, Wu SQ, Liu QQ, Wu JC, Zhang MM, Sandford AJ, et al. Association between TXNRD1 polymorphisms and anti-tuberculosis drug-induced hepatotoxicity in a prospective study. Genet Mol Res 2016; 15. PubMed PMID: 27706680.

(Among 247 Chinese patients treated for tuberculosis, 24 developed liver test abnormalities, a haplotype of thioredoxin reductase 1 was more frequent than in controls, the susceptibility being stronger in women and in nonsmokers).

Guaoua S, Ratbi I, El Bouazzi O, Hammi S, Tebaa A, Bourkadi JE, Bencheikh RS, Sefiani A. NAT2 genotypes in Moroccan patients with hepatotoxicity due to antituberculosis drugs. Genet Test Mol Biomarkers 2016; 20: 680-4. PubMed PMID: 27541622.

(Among 42 Moroccan adults who developed liver test abnormalities on antituberculosis therapy, 78% had NAT2 alleles associated with rapid acetylator status compared to 72% of 163 controls).

Bouazzi OE, Hammi S, Bourkadi JE, Tebaa A, Tanani DS, Soulaymani-Bencheikh R, Badrane N, et al. First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. Pan Afr Med J 2016; 25: 167. PubMed PMID: 28292129.

(Among 142 Moroccan adults treated for active tuberculosis, liver test abnormalities arose in 35 [25%], and more commonly in those with higher plasma levels of isoniazid, but not rifampin or pyrazinamide to which they were also exposed).

Usui T, Meng X, Saide K, Farrell J, Thomson P, Whitaker P, Watson J, et al. From the cover: characterization of isoniazid-specific T-cell clones in patients with anti-tuberculosis drug-related liver and skin injury. Toxicol Sci 2017; 155: 420-31. PubMed PMID: 27803386.

(Among 6 patients with liver injury arising during antituberculosis therapy, isoniazid-, but not pyrazinamide- or rifampin-activated CD4+ T lymphocyte clones were identified in 3 subjects).

Whritenour J, Ko M, Zong Q, Wang J, Tartaro K, Schneider P, Olson E, et al. Development of a modified lymphocyte transformation test for diagnosing drug-induced liver injury associated with an adaptive immune response. J Immunotoxicol 2017; 14: 31-8. PubMed PMID: 28121193.

(A modified lymphocyte transformation test carried out on peripheral blood mononuclear cells from 24 patients with drug induced liver injury was unsuccessful in all but 2 of 4 samples from patients with liver injury attributed to isoniazid).

Sekaggya-Wiltshire C, von Braun A, Scherrer AU, Manabe YC, Buzibye A, Muller D, Ledergerber B, et al. Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients. J Antimicrob Chemother 2017; 72: 1172-7. PubMed PMID: 28108678.

(Among 268 patients with HIV infection treated for tuberculosis, 67% developed at least transient elevations in liver tests during therapy, but there was no association of peak plasma levels of rifampin and occurrence of hepatotoxicity).

Simkins J, Abbo LM, Camargo JF, Rosa R, Morris MI. Twelve-week rifapentine plus isoniazid versus 9-month isoniazid for the treatment of latent tuberculosis in renal transplant candidates. Transplantation 2017; 101: 1468-72. PubMed PMID: 27548035.

(Among 153 renal transplant candidates with latent tuberculosis treated with 9 months of isoniazid daily or 12 weeks of weekly rifapentine and isoniazid, the 12 week regimen had a higher rate of compliance and lower rate of ALT and AST elevations [0% vs 5%]; subsequent activation of tuberculosis did not occur with either regimen).

Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ, Park HS, Kim SH. Drug-specific CD4(+) T-cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. Br J Dermatol 2017; 176: 378-86. PubMed PMID: 27373553.

(Drug-specific CD4+ T cell reponses were found in most subjects with rash and systemic manifestations attributable to antituderculosis therapy).

Ben Fredj N, Gam R, Kerkni E, Chaabane A, Chadly Z, Boughattas N, Aouam K. Risk factors of isoniazid-induced hepatotoxicity in Tunisian tuberculosis patients. Pharmacogenomics J 2017; 17: 372-7. PubMed PMID: 27089936.

(Among 71 Tunisian patients treated for active tuberculosis with an isoniazid based regimen, 11 [15%] developed liver enzyme elevations, the occurrence of which correlated with high peak isoniazid concentrations as well as slow acetylation status [NAT2: 91% vs 53%] and the combination of this status with specific CYP2E1 Dral alleles).

Shamaei M, Mirsaeidi M, Baghaei P, Mosaei H, Marjani M, Tabarsi P. Recurrent drug-induced hepatitis in tuberculosis-comparison of two drug regimens. Am J Ther 2017; 24: e144-e149. PubMed PMID: 26057141.

(Among 135 Iranian patients who developed hepatitis while on antituberculosis therapy requiring discontinuation and who were subsequently restarted on treatmnet, 23 [17%] had recurrence).

Chan SL, Chua APG, Aminkeng F, Chee CBE, Jin S, Loh M, Gan SH, et al. Association and clinical utility of NAT2 in the prediction of isoniazid-induced liver injury in Singaporean patients. PLoS One 2017; 12: e0186200. PubMed PMID: 29036176.

(Analysis of use of NAT2 genetic testing to predict isoniazid associated liver test abnormalities).

Chalasani N, Reddy KRK, Fontana RJ, Barnhart H, Gu J, Hayashi PH, Ahmad J, et al. Idiosyncratic drug induced liver injury in African-Americans is associated with greater morbidity and mortality compared to caucasians. Am J Gastroenterol 2017; 112: 1382-8. PubMed PMID: 28762375.

(Among 841 Caucasians and 144 African Americans with drug induced liver injury enrolled in a prospective US registry, the most frequent cause in whites was amoxicillin/clavulanate [13.4% vs 4.1%] and in blacks was trimethoprim-sulfamethoxazole [7.6% vs 3.6%], whereas isoniazid represented 4% of cases in both racial groups).

Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. Ann Intern Med 2017; 167: 248-55. PubMed PMID: 28761946.

(A metaanalysis of 61 studies on regimens for therapy of "latent tuberculosis" found evidence of lower rates of hepatotoxicity with rifampin only or with short courses of isoniazid and rifampin in combination compared to longer isoniazid only regimens).

Wang Y, Xiang X, Wu SQ, Chen G, Zhang MM, Wang MG, Wang FJ, et al. Association of CYP2B6 gene polymorphisms and anti-tuberculosis drug-induced hepatotoxicity in a Chinese population. Infect Genet Evol 2017; 51: 198-202. PubMed PMID: 28389387.

(Among 343 Chinese patients treated for tuberculosis, several CYP2B6 gene polymorphisms were found to be associated with a reduced risk for hepatotoxicity).

Tweed CD, Wills GH, Crook AM, Dawson R, Diacon AH, Louw CE, McHugh TD, et al. Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. BMC Med 2018; 16: 46. PubMed PMID: 29592805.

(Among 1928 patients with pulmonary tuberculosis treated with standard therapy [ethambutol, isoniazid, rifampin and pyrazinamide] or regimens in which moxifloxacin was substituted for either ethambutol or isoniazid, liver injury arose in 58 patients [3%] overall, and was less with regimen in which moxifloxacillin replaced isoniazid [2.2%], but there was nevertheless a liver related death on this regimen).