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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Rifampin. [Updated 2018 Jun 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Rifampin

Updated: June 10, 2018.

OVERVIEW

Introduction

Rifampin (also referred to as rifampicin) is a macrocyclic antibiotic with major activity against mycobacteria, commonly used in combination with other agents as therapy of tuberculosis. Rifampin is associated with transient and asymptomatic elevations in serum aminotransferase and bilirubin levels and is a well known cause of clinically apparent, acute liver disease that can be severe and even fatal.

Background

Rifampin (rif am' pin) belongs to a class of medications know as rifamycins and is a synthetic derivative of natural products of the bacterium, S. mediterranei. Rifampin is a complex macrocyclic antibiotic that has activity against several bacteria, but most prominently inhibits growth of M. tuberculosis and several atypical mycobacterial species, probably as a result of inhibition of the DNA-dependent RNA polymerase of mycobacteria. Rifampin was approved for use in therapy of tuberculosis in the United States in 1971. Rifampin remains a mainstay of therapy of tuberculosis and atypical mycobacteria infections and is usually used in conjunction with isoniazid and/or pyrazinamide. Other approved uses of rifampin include chemoprophylaxis of meningococcal disease and meningitis due to H. influenza. Rifampin is used off-label as therapy of itching due to liver disease. Rifampin is available in multiple generic forms and under the trade names of Rimactane and Rifadin in capsules of 150 and 300 mg. Pediatric formulations are available as well, as are powdered preparations for parenteral administration. The recommended dose for therapy of tuberculosis in adults is 600 mg (~10 mg/kg) daily and in children 10-20 mg/kg, but no more than 600 mg daily. Fixed combinations of rifampin (300 mg) with isoniazid (150 mg) are available under the brand name Rifamate, and combinations of rifampin (120 mg) with both isoniazid (50 mg) and pyrazinamide (300 mg) under the brand name Rifater. Side effects of rifampin are uncommon, but include rash, fever, flu-like symptoms, gastrointestinal upset and orange discoloration of urine and sweat. Rifampin is a potent inducer of many hepatic enzymes including the drug metabolizing enzymes, CYP 1A2, 2C9, 2C19 and 3A4 for which reason use of concurrent medications (such as oral contraceptives, anticoagulants, some antiretroviral agents, cyclosporine, benzodiazepines, and macrolide antibiotics) should be carefully chosen and monitored. Rifabutin and rifapentine are two other rifamycins that can be used in place of rifampin, rifabutin being useful if drug-interactions are an issue and rifapentine if once weekly dosing is preferred.

Hepatotoxicity

Liver injury from rifampin is uncommon, but well documented. Long term therapy with rifampin is associated with minor, transient elevations in serum aminotransferase levels in 10% to 20% of patients, abnormalities that

usually do not require dose adjustment or discontinuation. Rifampin has unusual and paradoxical effects on serum bilirubin levels. In most patients, serum bilirubin levels (both total and indirect) increase during the first few days of rifampin therapy, whereupon they usually decrease to below baseline. In addition, rifampin therapy can be associated with a prominent increase in both direct and total bilirubin within a few weeks of starting therapy without evidence of liver injury. This effect is seen in patients with significant underlying liver disease such as cirrhosis, as well as in the rare individual with Dubin Johnson syndrome or mutations in the hepatic canicular protein known as ABC C2 or MRP2 which is responsible for transport of conjugated bilirubin from the hepatocyte into the bile canalicus.

Rifampin is also associated with rare instances of clinically apparent liver injury accompanied by symptoms and jaundice, which can be severe and even fatal. Because rifampin is usually given in combination with isoniazid and/or pyrazinamide, two other known hepatotoxic agents, the cause of the acute liver injury in patients on rifampin may be difficult to relate to a single agent and some evidence suggests that these combinations are more likely to cause injury than the individual drugs would suggest. Typically, the onset of injury due to rifampin is within 1 to 6 weeks (which may help separate it from isoniazid injury which is often later), but cases with longer latency have been reported. The serum enzyme pattern is usually hepatocellular at the onset of injury, but can cholestatic and mixed in contrast to isoniazid. Extrahepatic manifestations such as fever, rash, arthralgias, facial edema and eosinophilia are uncommon as is autoantibody formation.

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

Mechanism of Injury

The mechanism of rifampin hepatotoxicity is not well known, but it is extensively metabolized by the liver and induces multiple hepatic enzymes including CYP 3A4 and ABC C2 (MRP2). Thus, the cause of injury is likely to be due to idiosyncratic metabolic products that are either directly toxic or induce an immunologic reaction. The rise in direct and total bilirubin in rare patients receiving rifampin may relate to gene defects in MRP2 (ABC C2), the major bilirubin glucuronide transporter in hepatocytes that is known to be abnormal in the Dubin-Johnson syndrome. Patients with preexisting liver disease and cirrhosis are particularly likely to develop jaundice on rifampin therapy.

Outcome and Management

Severity ranges from asymptomatic elevations in serum aminotransferase levels, jaundice without apparent hepatic injury, symptomatic self-limited hepatitis to severe fulminant liver failure and death. Complete recovery is expected after stopping the drug and is usually rapid and complete. Rifampin has not been associated with vanishing bile duct syndrome or chronic hepatitis. There is likely to be cross sensitivity to liver injury among the rifamycins (rifampin, rifabutin and rifapentine), but not with the other first or second line antituberculosis agents. Routine monitoring for seurm enzyme elevations during rifampin therapy of tuberculosis is not recommended except in high risk individuals. Nevertheless, routine monitoring for symptoms of liver disease is recommended for all regimens, whether for clinically active or latent tuberculosis.

Specific, regularly updated recommendations on therapy of tuberculosis can be found on the U.S. Centers for Disease Control and Prevention website: https://www.cdc.gov/tb/topic/treatment/

[First line medications used in the therapy of tuberculosis in the United States include isoniazid, pyrazinamide, ethambutol and the rifamycins including 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; Leprosy Agents

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

CASE REPORTS

Case 1. Elevations in serum aminotransferase levels during rifampin therapy.

[Modified from: Corrigan D, Paton J. Hepatic enzyme abnormalities in children on triple therapy for tuberculosis. Ped Pulmonol 1999; 27: 37-42. PubMed Citation]

A child with tuberculosis was treated with isoniazid, rifampin and pyrazinamide for six months. During the first week of therapy, serum ALT and AST were elevated, but bilirubin remained normal and the child did not develop symptoms of rash, fatigue, itching or jaundice. Therapy was continued and the abnormalities resolved.

Key Points

Medication:	Rifampin
Pattern:	Hepatocellular
Severity:	1+ (never jaundiced, no symptoms)
Latency:	2 weeks
Recovery:	Complete within a few months
Other medications:	Isoniazid, pyrazinamide

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	0	40	15	0.6	
2 weeks	0	195	105	0.2	No symptoms
4 weeks	0	65	35	0.8	Therapy continued
8 weeks	0	45	25	0.8	
18 weeks	0	45	20	0.6	
Normal Values		**<45**	**<50**	**<1.2**	

Comment

Transient and asymptomatic elevations of serum aminotransferase levels are common during antituberculosis therapy, particularly when using three agents such as rifampin, isoniazid, and pyrazinamide. The abnormalities usually arise during the first month of therapy and return to normal even with continuation of the medications without dose reduction. The appearance of symptoms or jaundice with ALT elevations should lead to immediate discontinuation of therapy and close observation. This phenomenon of transient enzyme elevations which resolve despite continuing therapy is considered “adaptation”, but its actual cause is unknown, but may relate to induction of enzymes of secondary metabolism which more efficiently clear toxic intermediates. Liver biopsy taken during such episodes generally shows minor, focal hepatocyte injury.

Case 2. Jaundice without evidence of liver injury due to rifampin.

[Modified from: Corpechot C, Ping C, Wendum D, Matsuda F, Barbu V, Poupon R. Identification of a novel 974C-->G nonsense mutation of the MRP2/ABCC2 gene in a patient with Dubin-Johnson syndrome and analysis of the effects of rifampicin and ursodeoxycholic acid on serum bilirubin and bile acids. Am J Gastroenterol 2006; 101: 2427-32. PubMed Citation]

A 24 year old African-born man with pulmonary tuberculosis and mild jaundice was started on antituberculosis therapy and developed worsening jaundice, without elevations in serum aminotransferase or alkaline phosphatase levels.

Key Points

Medication:	Rifampicin
Pattern:	Bilirubin elevations only
Severity:	Mild, asymptomatic
Latency:	Few days
Recovery:	Complete in 4 months
Other medications:	Isoniazid, ethambutol

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	0	Normal	Normal	3.0	
5 days	0	Normal	Normal	6.0	Conjugated bilirubin 5.0 mg/dL
~4 months	0	Normal	Normal		
Normal Values		**<42**	**<115**	**<1.2**	

Comment

Few clinical details are presented by the authors; the point of the case presentation was to attempt to demonstrate a selective interaction of rifampin with the hepatobiliary transport of bilirubin, through competitive inhibition of MRP2 and induction of the MRP3 transporter. The patient likely had Dubin Johnson syndrome, accounting for the benign conjugated hyperbilirubinemia that was exacerbated by rifampin therapy.

Case 3. Acute liver failure complicating two month course of rifampin and pyrazinamide.

[Modified from: Medinger A. Death associated with rifampin and pyrazinamide 2-month treatment of latent Mycobacterium tuberculosis. Chest 2002; 121: 1710-2. PubMed Citation]

A 68 year old man with a history of a positive tuberculin test requested antituberculosis therapy so as to obviate the need for annual chest X-rays required by his employer. He had a history of alcoholic liver disease but had stopped drinking 5 years previously. He also had gout, hypertension and type 2 diabetes for which he took aspirin, colchicine, ibuprofen, lisinopril and metformin on a chronic basis. He was started on rifampin (600 mg daily) and pyrazinamide (2 grams daily) and monitored monthly. He tolerated therapy without symptoms, and liver tests were normal at baseline and one month (Table). Immediately after stopping therapy, however, he began to feel ill and presented to the emergency room shortly after with jaundice, lethargy and confusion. On examination, he was icteric and had asterixis. Laboratory tests showed marked elevations in serum aminotransferase levels and bilirubin of 16.7 mg/dL. The prothrombin time was prolonged [INR 6.0], and there

were elevations in serum creatinine [5.4 mg/dL], ammonia [181 µmol/L: normal <35] and lactate [13.2 mmol/L, normal <2.2]. Abdominal ultrasound showed ascites, but no evidence of biliary obstruction. He was given supportive care but developed worsening coma, respiratory and renal failure and died 3 days after admission.

Key Points

Medication:	Pyrazinamide, rifampin
Pattern:	Hepatocellular (R=10.3)
Severity:	5+ (death)
Latency:	2 months
Recovery:	None
Other medications:	Aspirin, colchicine, ibuprofen, lisinopril, metformin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		48	66	0.5	INR=1.0
0		Pyrazinamide and rifampin started			
2 weeks		31	63	0.5	
8 weeks	0	Pyrazinamide and rifampin stopped: asymptomatic			
	4 days	620	175	6.7	INR=6.0
9 weeks	7 days	1930	207	19.2	INR=10.1
		Death from multiorgan failure			
Normal Values		**<45**	**<130**	**<1.2**	

Comment

The patient developed an abrupt onset of acute liver failure a few days after stopping an 8 week course of rifampin and pyrazinamide for latent tuberculosis. This combination is highly effective for latent tuberculosis, but has been associated with an unacceptably high rate of liver injury and cases of acute liver failure, for which reasons it is no longer recommended. Whether the injury was due to pyrazinamide or rifampin was unclear; there is likely an interaction that promotes the risk of injury. The risk of liver injury increases with age not just with isoniazid, but also with other antituberculosis medications and combinations. History of alcohol abuse or alcoholic liver injury is believed to also be a risk factor for antituberculosis medication hepatotoxicity, but it has not been clearly defined. This report does not mention testing for viral hepatitis or autopsy results, but the clinical history and course are entirely compatible with drug induced liver injury from antituberculosis medications.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rifampin – Generic, Rifadin®, Rimactane®

DRUG CLASS

Antituberculosis Agents

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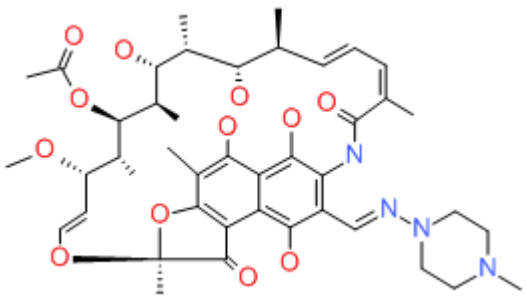
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Rifampin	13292-46-1	C43-H58-N4-O12	

ANNOTATED BIBLIOGRAPHY

References updated: 10 June 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 rifampin 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).

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

(Textbook of pharmacology and therapeutics).

Acocella G, Lamarina F, Tenconi LT, Nicolis FB. Study of the excretion in bile and concentration in the gall bladder wall of rifamide. Gut 1966; 7: 380-6. PubMed PMID: 5917425.

(Rifamide had no effect on bilirubin levels and led to high levels in bile).

Lesorbre R, Ruffino J, Teyssier L, Achard F, Brefort G. [Jaundice occurring during treatment with rifampicin: twelve observations]. Les icteres au cours du traitement par la rifampicine (12 observations). Rev Tuber Pneumonol 1969; 33: 393. PubMed PMID: 5383009.

(Among 50 patients given isoniazid and rifampin, 12 developed jaundice on therapy and one shortly afterwards; another 3 had asymptomatic ALT elevations without jaundice; 4 died most having alcoholic cirrhosis and advanced tuberculosis; latency 6-14 days with jaundice and mild-moderate ALT elevations).

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 and ALT levels normalized; several patients were able to restart isoniazid without recurrence).

Hellström PE, Repo UK. Capreomycin, ethambutol and rifampicin in apparently incurable pulmonary tuberculosis. Scand J Respir Dis Suppl 1969; 69: 69-74. PubMed PMID: 4906377.

(Retrospective analysis of 35 patients with severe, chronic or relapsing tuberculosis who were treated with capreomycin, ethambutol and rifampin; "liver damage" occurred in 49%, but was reversible in all; details not given).

Lesobre R, Ruffino J, Teyssier L, Drutel P, Brefort G. [Jaundice epidemiology in 1,974 hospitalized tubercular patients, treated or untreated by rifampicin]. Rev Tuberc Pneumol (Paris) 1970; 34: 296-304. PubMed PMID: 5510316.

(Statistical analysis of cases of jaundice in tuberculosis treatment clinic showing association with rifampin and with underlying liver disease compared to patients not treated with rifampin).

Lees AW, Asgher B, Hashem MA, Sinha BN. Jaundice after rifampicin. Br J Dis Chest 1970; 64: 90-5. PubMed PMID: 5432630.

(4 of 50 patients developed jaundice on rifampin and isoniazid after 8-30 days [bilirubin 3.1-4.9 mg/dL, ALT 76-600 U/L, Alk P <2 times ULN], with mild symptoms and recurrence upon restarting both drugs, but 3 did not redevelop jaundice and were able to tolerate long term therapy with resolution of abnormalities).

Hollins PJ, Simmons AV. Jaundice associated with rifampicin. Tubercle 1970; 51: 328. PubMed PMID: 5495656.

(Two cases of acute liver injury arising 9 and 30 days after starting INH and rifampin [bilirubin 7.1 and 3.6 mg/dL, AST 1440 and 83 U/L, Alk P 14.6 and 15.4 KA/L], resolving rapidly on stoping rifampin and despite continuing isoniazid).

Sehm G. [Rifampicin and liver damage]. Prax Pneumol 1970; 24: 439-42. PubMed PMID: 5433240.

Verbist L, Rollier F. Pharmacological study of rifampicin after repeated high dosage during intermittent combined therapy. II. Bilirubin levels and other biochemical determinations. Respiration 1971; 28: Suppl: 17-28. PubMed PMID: 5150793.

(Evaluation of 100 patients receiving rifampin found rises in direct [0.3→0.8 mg/dL] and total bilirubin [0.6→1.3 mg/dL] during 1st week, and then declining and not associated with AST or Alk P elevations).

Marche J, Hugues FC, Graisely B, Marche J. [Hepatitis caused by the combination of rifampicin and isoniazid]. Ann Med Interne (Paris) 1971; 122: 1045-54. PubMed PMID: 5146732.

(Three cases of hepatitis [2 men, 1 woman, ages 37-53 years] arising within 13-17 days after starting rifampin [600 mg daily] and isoniazid [600 mg daily] for tuberculosis, with mild jaundice and resolving upon stopping rifampin).

Laroche C, Caquet R, Desche-Labarthe S, Fraisse B, Lemaigre G. [A case of icterus in the course of treatment with rifampicin. Histological records]. Ann Med Interne(Paris). 1971; 122: 1119-22. French. PubMed PMID: 5150312.

(68 year old woman developed jaundice 7 days after starting isoniazid, rifampin and ethionamide without ALT elevations and then developed acute abdomen and died after surgery; autopsy showed bland intrahepatic cholestasis).

Gabriel R. Rifampicin jaundice. Br Med J 1971; 3: 182. PubMed PMID: 5557874.

(26 year old woman with renal tuberculosis developed jaundice 12 days after starting isoniazid, rifampin and streptomycin [bilirubin 3.5 mg/dL but normal ALT and Alk P], resolving in 10 days without stopping).

Newman R, Doster B, Murray FJ, Ferebee S. Rifampin in initial treatment of pulmonary tuberculosis. A U.S. Public Health Service tuberculosis therapy trial. Am Rev Respir Dis 1971; 103: 461-76. PubMed PMID: 4204541.

(Among the first 234 patients enrolled in a controlled trial of 3 antituberculosis regimens who received rifampin, ALT levels rose above ULN in 24%, >100 U/L in 7% [minimal bilirubin rises in half], resolving in all, some without stopping therapy).

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 treated for 3 months to 2 years with rifampin and isoniazid, 22% had transient ALT rise for 2-15 weeks, with resolution despite continuing therapy; 14 had bilirubin and ALT rise, of whom 4 resolved despite continuing therapy, 4 resolved on stopping and therapy restarted, 6 [5%] abandoned treatment [most of whom had symptoms and positive rechallenge]).

Proust AJ. The Australian rifampicin trial. Med J Aust 1971; 2: 85-94. PubMed PMID: 4999365.

(54 patients enrolled in the Australian trial and 226 treated outside the study given rifampin for 2-18 months in combination with isoniazid and/or another agent; 14% had at least one liver test abnormality and 1.4% jaundice; one case had onset of jaundice after 10 days [bilirubin 7.8 mg/dL, ALT 740 U/L, Alk P ~1.6x ULN] and resolving 1 month after stopping; 4 other patients had jaundice, with short latency and rapid recovery; no fatalities).

Riska N, Mattson K. Adverse reactions during rifampicin treatment. Scand J Respir Dis 1972; 53: 87-96. PubMed PMID: 5052728.

(Among 115 patients treated with daily rifampin, 20% had elevations in AST [also on isoniazid or ethambutol] and bilirubin levels rose during first 6-12 hours, a dose related effect that was worsened by renal disease).

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 [22%] and rapid [25%] acetylators; however, the combination of AST and bilirubin elevations occurred in 14% of slow, but only 2.7% of rapid acetylators).

Capelle P, Dhumeaux D, Mora M, Feldmann G, Berthelot P. Effect of rifampicin on liver function in man. Gut 1972; 13: 366-71. PubMed PMID: 5036092.

(Single doses of rifampin caused rise in BSP retention and indirect bilirubin [total bilirubin rising from 0.9 to 1.5 mg/dL], which resolved within 2-3 weeks).

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.

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

Anah CO. Rifampicin and isoniazid and liver function. Br Med J 1972; 1: 691-2. PubMed PMID: 5015313.

(Letter in response to Lal [1972] giving experience with the combination of rifampin and isoniazid in 26 patients, 1 patient had solitary Alk P elevation, 1 had solitary bilirubin rise, 6 had ALT, Alk P and/or bilirubin rises, many with nonspecific symptoms).

Godeau P, Catz G, Cenac A, De Saint-Maur P, Radvanyi M-F. Ictere d'evolution fatale au cours d'un traitement par la rifampicine. [Fatal icterus during treatment with rifampin]. Ann Med Interne 1972; 123: 119-20. PubMed PMID: 5055067.

(66 year old woman developed jaundice 7 days after starting isoniazid, rifampin and ethambutol [bilirubin 4.7 mg/dL, ALT 180 U/L, AST 1300 U/L, Alk P minimal elevation], followed by anuria and coma and death, autopsy showed severe necrosis).

Mattson K. Side effects of rifampicin. Scand J Respir Dis 1973; Suppl 82: 16-52. PubMed PMID: 4518740.

(Thesis on rifampin side effects with review of literature and prospective study of 515 subjects; 20% had ALT or AST elevations, but only 12% were attributed to rifampin, 4% >100 U/L, none with jaundice; most resolved even with drug continuation).

Zierski M. A trial of intermittent rifampicin and ethambutol in retreatment regimens. Scand J Respir Dis Suppl 1973; 84: 132-5. PubMed PMID: 4522067.

(Among 122 patients with tuberculosis treated with rifampin and ethambutol daily for 2 months and then once or twice weekly for 1-2 years, abnormal liver tests occurred in 10% during daily regimen and in 5% during long term treatment, but all changes were transient and mild not requiring discontinuation and attributed to rifampin).

Scheuer PJ, Summerfield JA, Lal S, Sherlock S. Rifampicin hepatitis. Lancet 1974; i: 421-5. PubMed PMID: 4131429.

(Analysis of 11 patients with hepatitis due to antituberculosis medications, some attributed to rifampin [none received it alone]; in rifampin cases the onset was usually within 3 weeks, several having hepatitis with cholestasis).

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).

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 days and coma 11 days after starting isoniazid, rifampin and ethambutol for active tuberculosis [bilirubin 5.2 mg/dL, ALT 1500, Alk P 302, prothrombin index <10%], nonetheless, recovering spontaneously and later tolerating isoniazid without recurrence).

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 occurred 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 children, 2 boys and 1 girl, ages 8, 9 and 2 years, developed jaundice 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).

Abeledo Mezquita G, Otero Reigada MC. [Toxic hepatitis caused by rifampin and isoniazid in treatment of tuberculosis]. An Esp Pediatr 1977; 10: 167-70. Spanish. PubMed PMID: 869341.

(5 children with rifampin hepatotoxicity arising after 5-27 days with jaundice [bilirubin 1.9-10.6 mg/dL, ALT 110-208 U/L, protime 28-70%], one with eosinophilia, resolving within 1 month of switching to ethambutol).

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 with encephalopathy [peak bilirubin 2.4-13.6 mg/dL, ALT 26-80 times ULN, prothrombin index 18-36%], without fever, rash, eosinophilia or autoantibodies, rapid onset, recovery in all).

Di Piazza S, Cottone M, Craxi A, Gatto G, Pinzelle G, Pagliaro L. Severe rifampicin-associated liver failure in patients with compensated cirrhosis. Lancet 1978; 1: 774. PubMed PMID: 76779.

(Five patients with cirrhosis developed jaundice 6-8 [one 150] days after starting rifampin with clinical deterioration, 3 fatalities; no other laboratory results).

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 girls, ages 4 and 12 years, developed severe hepatitis 3 and 8 months after starting rifampin, isoniazid and PAS/prothionamide; one fatal and one resulting in cirrhosis; authors attributed injury to isoniazid).

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).

Gutman L. More adverse reactions to rifampicin. J Antimicrob Chemother 1978; 4: 283. PubMed PMID: 670121.

(Letter in response to Girling [1978] describing 5 month old girl who developed jaundice 7 days after adding rifampin to isoniazid and streptomycin [bilirubin 3.2 rising to 20.1 mg/dL, ALT 661 U/L], dying 21 days later from perforated ulcer possibly due to corticosteroid therapy).

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).

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).

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 risk factors were not clinically useful; 4% had symptoms, 2.5% were jaundiced, usually during first month; most AST elevations resolved without dose modification).

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 to 77 days, 9 with jaundice, no deaths).

Piette F, Peyrard P. [Benign drug jaundice during treatment combining rifampicin and triacetyloleandomycin]. Nouv Presse Med 1979; 8: 368. PubMed PMID: 317969.

(90 year old woman developed jaundice 3 days after starting rifampin [bilirubin 5.3 mg/dL but normal ALT and Alk P], resolving rapidly after stopping).

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: 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]; positive rechallenge with rifampin and later tolerated isoniazid).

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, all on rifampin, 10 on pyrazinamide and 2 on isoniazid).

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).

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

(One 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%], resolving rapidly 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%]).

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).

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 [overall 3.4%: onset in 2-8 weeks] and 3 to isoniazid [1.3%: onset in 1-16 months], no cases attributed 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).

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).

Frontera Izquierdo P, Unceta Aguirre L, Tomás Vila M, Calvo Rigual F, Pérez Tamarit D. [Hepatotoxicity of rifampicin and isoniazid in the treatment of tuberculous meningitis]. An Esp Pediatr 1981; 15: 549-52. PubMed PMID: 7337308.

(Among 34 children given isoniazid and rifampin, 15 [44%] had ALT elevations and 4 [12%] jaundice [peak bilirubin 10.6 mg/dL] 5-35 days after starting; all resolving with stopping rifampin).

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, 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 hepatotoxicty with the modern pyrazinamide regimens studied").

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 and 1980, most common causes were halothane [25%], chlorpromazine [9%], sulfonamides [9%], antituberculosis agents [7%], oxyphenisatin [4%], and methyldopa [2%]).

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, hepatotoxicity occurred in 2.7%, but only 3 patients [0.4%] were jaundiced; most were able to finish therapy).

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).

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 Citation

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

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).

Tsagaropoulou-Stinga H, Mataki-Emmanouilidou T, Karida-Kavalioti S, Manios S. Hepatotoxic reactions in children with severe tuberculosis treated with isoniazid-rifampin. Pediatr Infect Dis 1985; 4: 270-3. PubMed PMID: 4000989.

(Among 44 children given isoniazid and rifampin, 82% had ALT elevation >100 U/L and 34% jaundice and hepatitis; most occurred with 6-30 days of onset, one died; ALT elevations resolved despite continuing therapy).

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).

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.

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

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).

van Aalderen WMC, Knoester H, Knol K. Fulminant hepatitis during treatment with rifampicin, pyrazinamide and ethambutol. Eur J Pediatr 1987; 146: 290-1. PubMed PMID: 3595648.

(10 year old girl developed nausea and ALT elevations 2 weeks after starting isoniazid, rifampin, pyrazinamide and ethambuto,l resolving with stopping all drugs, but severe recurrence with fever, rash and fatal acute liver failure 6 weeks after adding pyrazinamide back to rifampin, ethambutol and kanamycin).

Taillan B, Chichmanian RM, Fuzibet JG, Vinti H, Taillan F, Dellamonica P, Dujardin P. [Jaundice caused by rifampicin: 3 cases] Rev Med Interne 1989; 10: 409-11. PubMed PMID: 2488482.

(3 women, ages 67 yo 79 years, developed jaundice [bilirubin 2-8 times ULN] within 6-7 days of starting rifampin [bilirubin 2-8 times ULN, ALT normal, Alk P 2-3 times ULN], resolving within 14-30 days of stopping; in one patient biopsy showed "centrolobular cholestasis").

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 3 weeks after starting 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).

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).

Chiu J, Nussbaum J, Bozzette S, Tilles JG, Young LS, Leedom J, Heseltine PN, et al. and California Collaborative Treatment Group. Treatment of disseminated Mycobacterium avium complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. Ann Intern Med 1990; 113: 358-61. PubMed PMID: 2382918.

(17 patients with AIDs and MAC infection were treated with amikacin for 4 and then ciprofloxacin, ethambutol and rifampin for 12 weeks; therapy stopped early in 2 patients for hepatitis, but no details given).

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

Roden S, Lagneau M, Homasson JP. [Fulminant hepatitis induced by pyrazinamide]. Rev Pneumol Clin 1990; 46: 43. French. PubMed PMID: 2371480.

(68 year old woman developed jaundice 3.5 months after starting antituberculosis therapy with rifampin, pyrazinamide and ethambutol [bilirubin 9.6 mg/dL, ALT 1100 U/L, Alk P 185 U/L, prothrombin index 45%], with progressive hepatic failure, liver transplantation, death 10 days postoperatively).

Whittington RM. Fatal hepatotoxicity of anti-tubercular chemotherapy. Lancet 1991; 338: 1083-4. PubMed PMID: 1681387.

(Report from Birmingham coroner of 3 cases of fatal hepatotoxicity in patients on isoniazid, rifampin and pyrazinamide; frequently had symptoms for several weeks before stopping antituberculosis therapy).

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).

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 or additive).

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 cases; 69% female [often in young adulthood], 9% in children; high proportion in Hispanics and blacks; 38% of women 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%).

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, 9 were due to antituberculosis medications, usually combinations of isoniazid, rifampin and pyrazinamide; 2 deaths).

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] and the French pharmacovigilance system [n=30] demonstrated an overall mortality rate of 23%; rifampin attributed cases had short latency [average 2 weeks] compared to isoniazid [11 weeks] and pyrazinamide [7 weeks]; no association with alcohol, but some with higher doses of drugs 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; authors suggest that isoniazid or rifampin may potentiate hepatotoxicity of acetaminophen and vice versa).

Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. Clin Infect Dis 1995; 21: 594-8. PubMed PMID: 8527549.

(Open label study of rifabutin in 24 patients with MAC; side effects were common and 3 had liver test abnormalities, one requiring dose modification who had a positive rechallenge).

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%]; elderly also had higher peak ALT levels).

Schwander S, Rüsch-Gerdes S, Mateega A, Lutalo T, Tugume S, Kityo C, Rubaramira R, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. A single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. Tuber Lung Dis 1995; 76: 210-8. PubMed PMID: 7548903.

(Controlled trial comparing rifabutin to rifampin combined with isoniazid and pyrazinamide in 50 patients with HIV and tuberculosis; no clinically apparent liver injury or jaundice; rates of ALT elevations not given).

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; 345: 867. PubMed PMID: 7898259.

(Letter in response to Mitchell et al. [1995] suggesting that patients be warned to stop drugs if they develop symptoms of liver injury).

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

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

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).

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 among 9 patients with acute liver failure on isoniazid, rifampin and pyrazinamide [78%] than in 9 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 BMI 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 of 0.6-2.9 mg/dL).

Dautzenberg B, Olliaro P, Ruf B, Esposito R, Opravil M, Hoy JF, Rozenbaum W, et al. Rifabutin versus placebo in combination with three drugs in the treatment of nontuberculous mycobacterial infection in patients with AIDS. Clin Infect Dis 1996; 22: 705-8. PubMed PMID: 8729209.

(Results of using rifabutin in 102 patients with HIV infection and MAC in European trials; no information on hepatotoxicity).

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 and recommendations on monitoring, with biochemical monitoring recommended only for patients with preexisting liver disease; in the UK since from 1965-86, 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 of 86 patients with hepatitis due to antituberculosis therapy and 406 patients who tolerated therapy; risk factors were older age, 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 for 6-9 months; 16% had AST elevations >2 times ULN usually in first month, but only 2% required modification of regimen; 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 for only 2 months).

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 by Barcelona group, 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).

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).

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

(Among 43 children prospectively monitored on rifampin, isoniazid and pyrazinamide, 30% had abnormal liver tests, usually in first few weeks, 2 with symptoms, 1 with jaundice; all patients continued or were restarted on antituberculosis medications and finished therapy).

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 in 10 days, autopsy showing massive liver necrosis and acute renal tubular necrosis).

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).

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 77 patients with tuberculosis starting isoniazid and rifampin; 28 were rapid, 42 intermediate and 7 slow acetylators based upon genetic testing for NAT-2; 18% developed ALT elevations >1.5 times ULN, in 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 et al.; 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 [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 reported to CDC associated with 2 month regimens of rifampin-pyrazinamide; 5 died of liver failure, ages 32-68 years, onset in 2nd month; as a consequence, CDC recommends use of 9 months of isoniazid as standard regimen for latent tuberculosis and biochemical monitoring if rifampin-pyrazinamide is used).

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; authors advise biochemical monitoring for patients above the age of 35).

Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N, Aksoy E. The management of antituberculosis 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 in patients given gradual reintroduction of regimen without pyrazinamide, compared to 6 cases of recurrence [24%] with abrupt reintroduction).

Medinger A. Death associated with rifampin and pyrazinamide 2-month treatment of latent Mycobacterium tuberculosis. Chest 2002; 121: 1710-2. PubMed PMID: 12006469.

(68 year old woman developed jaundice at end of 2 month course of rifampin and pyrazinamide for latent tuberculosis [bilirubin 19.2 mg/dL, ALT 1930 U/L, Alk P 207 U/L], with liver failure and death within 3 days of presentation: Case 3).

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).

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).

Benator D, Bhattacharya M, Bozeman L, Burman W, Cantazaro A, Chaisson R, Gordin F, et al; Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet 2002 17; 360: 528-34. PubMed PMID: 12241657.

(Among 1004 patients treated with either rifapentine [once weekly] or rifampin [twice weekly] with isoniazid, ALT elevations >5 times ULN occurred in 2.6% on rifapentine and 3.5% on rifampin, but no deaths due to liver injury).

Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. Int J Tuberc Lung Dis 2002; 6: 995-1000. PubMed PMID: 12475146.

(Among 148 patients with latent tuberculosis treated with rifampin/pyrazinamide, 14 [9.4%] had ALT elevations >5 times ULN, 12 symptomatic [8%]; risk factors were female sex and recent infection).

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 after transplant, 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).

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).

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 for patients with no preexisting liver disease or alcohol use, and with regular ALT monitoring and provision of drugs in two week increments).

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 issuance 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.

(Detailed recommendations on therapy of tuberculosis including drug regimens, side effects, monitoring and optimal approaches to follow up; estimated rates of clinical hepatitis from published reports as 0.6% with isoniazid alone, 1.6% with isoniazid and other drugs but not rifampin, 2.7% with isoniazid and rifampin, and 1.1% with rifampin and other drugs but not isoniazid).

Kunimoto D, Warman A, Beckon A, Doering D, Melenka L. Severe hepatotoxicity associated with rifampin-pyrazinamide preventative therapy requiring transplantation in an individual at low risk for hepatotoxicity. Clin Infect Dis 2003; 36: e158-61. PubMed PMID: 12802781.

(37 year old man had AST elevations at end of 2 month course of rifampin/pyrazinamide, with levels rising thereafter [bilirubin 7.8 mg/dL, AST 2409 U/L] and need for liver transplant 2 months later).

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%]).

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 [PR] for 2 months, and 114 with isoniazid [INH] for 6 months for latent tuberculosis; completion rates were higher [71% vs 59%] as was hepatotoxicity [13% vs 4%] with PR than INH, and 2 patients had clinically apparent hepatitis [ALT 45-67 times ULN at 4 weeks], but both survived; after intensive monitoring was introduced, there were no further severe cases on PR).

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/pyrazinamide, 67% completed therapy and 6 had hepatitis [5.3%] but all resolved; no hospitalizations or deaths).

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 [2003] requesting further information on dosages and clinical features of hepatotoxicity; reply by authors stating that high rate of hepatotoxicity in comparison to reports from India was not due to use

of higher doses of pyrazinamide, but may have been partially due to patient age and diverse ethnic background of patients).

Campos-Franco J, GonzÃ¡lez-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).

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 was treated with isoniazid, rifampin, ethambutol and pyrazinamide and switched to ciprofloxacin, pyrazinamide and ethambutol when resistance testing was done; 4 days later she developed fever, rash and fatigue [bilirubin normal, ALT 285 U/L, Alk P normal], but later worsened [bilirubin 15.2 mg/dL, ALT 1165 U/L, Alk P 141 U/L], requiring liver transplantation; posttransplalnt, she was treated successfully with levofloxacin, amikacin and streptomycin).

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 reanalysis 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).

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%] and symptoms and 5 [1%] were jaundiced; no deaths. Rates of hepatotoxicity were higher in patients with risk factors than in those without [18.2% vs 5.6%]).

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).

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 in response to Jasmer [2004], stressing recommendations that rifampin/pyrazinamide not be used to treat latent tuberculosis; a 9 month course of isoniazid being safer and more cost effective).

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).

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).

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 done in the United States between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, 24 cases were linked to isoniazid (ranking 2nd after acetaminophen), but no case was attributed specifically to other antituberculosis medications).

Marschall HU, Wagner M, Zollner G, Fickert P, Diczfalusy U, Gumhold J, Silbert D, et al. Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. Gastroenterology 2005; 129: 476-85. PubMed PMID: 16083704.

(Gene expression changes were found in liver after 1 week of rifampin, ursodiol or placebo in 30 patients undergoing elective cholecystectomy: increase in UGT1A1, CYP 3A4 and ABCC2 [MRP2], which accompanied significant decrease in serum bilirubin levels in all patients receiving rifampin).

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 2000-2; 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 et al. 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]).

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).

Potolidis E, Mantadakis E, Zeniodi MH, Samonis G. Rifampin plus pyrazinamide-induced hepatitis requiring hospitalization in a 30-y-old male with latent tuberculosis. Scand J Infect Dis 2005; 37: 155-7. PubMed PMID: 15773037.

(30 year old man developed nausea and dehydration 6 weeks after starting rifampin and pyrazinamide for latent tuberculosis [bilirubin normal, ALT "in the range of 600 to 2000" U/L], resolving within 3 weeks after stopping).

Corpechot C, Ping C, Wendum D, Matsuda F, Barbu V, Poupon R. Identification of a novel 974C-->G nonsense mutation of the MRP2/ABCC2 gene in a patient with Dubin-Johnson syndrome and analysis of the effects of rifampicin and ursodeoxycholic acid on serum bilirubin and bile acids. Am J Gastroenterol 2006; 101: 2427-32. PubMed PMID: 16952291.

(24 year old African man with Dubin Johnson syndrome and tuberculosis developed jaundice [bilirubin rising to 6 mg/dL, direct 4.2 mg/dL] within a few days of starting rifampin with no change in ALT or Alk P; mutation identified in ABCC2 [MRP2]).

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).

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).

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).

Munsiff SS, Kambili C, Ahuja SD. Rifapentine for the treatment of pulmonary tuberculosis. Clin Infect Dis 2006; 43: 1468-75. PubMed PMID: 17083024.

(Review of role of rifapentin, a cyclopentyl substituted semisynthetic rifamycin with similar activity and resistance pattern to rifampin, but longer half-life allowing for once weekly therapy; efficacy may be slightly less than rifampin and it is recommended only in selected patients; side effects are similar to rifampin).

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).

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%).

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 with 1 month of stopping therapy; fatality rate higher in older patients and with later onset; patients frequently on other potentially hepatotoxic medications).

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).

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).

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 due to drugs between 1993-1999 in Spain calculated relative risk of injury compared to the general population to be 1300 with use of triple antituberculosis therapy [isoniazid, rifampin and pyrazinamide] and 154 for isoniazid alone, ranking first and third).

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).

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 antituberculosis agents; rifampin can cause cholestatic hepatitis and is associated with serum ALT elevations as well as hypersensitivity reactions with fever, rash, urticaria, and anaphylaxis).

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 were linked to an increased risk of hepatotoxicity of antituberculosis medications; NAT2 and CYP 2E1; the authors concluded that the associations require further confirmation).

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 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 therapy).

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 tuberculosis and end stage liver disease were given preventive therapy before transplant; both isoniazid [n=9] and rifampin [n=5] were well tolerated and therapy completed, 2 on isoniazid had transient, minimal ALT elevations).

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).

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).

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

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 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).

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 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, 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).

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).

Sathia L, Obiorah I, Taylor G, Kon O, O'Donoghue M, Gibbins S, Walsh J, et al. Concomitant use of nonnucleoside analogue reverse transcriptase inhibitors and rifampicin in TB/HIV type 1-coinfected patients. AIDS Res Hum Retroviruses 2008; 24: 897-901. PubMed PMID: 18671475.

(Among 103 patients with HIV infection and tuberculosis receiving rifampin, 17 were taking nevirapine and 26 efavirenz, yet had a low rate of hepatotoxicity; transient elevations in ALT in 17% and 2 patients stopped therapy for ALT elevations >5x ULN, yet safely restarted antituberculosis therapy after ALT abnormalities resolved).

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; hepatotoxicity [ie, 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%).

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 glutathione S-transferase variants in cases [49%] than controls [27%]; no difference for M1 variants [34% vs 42%]).

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).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, et al.; 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, but not with rifampin which was not listed as a cause of any case).

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]; 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).

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 HIV-negative [7%]; authors recommend routine HIV screening and biochemical monitoring in high risk groups).

Gao XF, Li J, Yang ZW, Li YP. Rifapentine vs. rifampicin for the treatment of pulmonary tuberculosis: a systematic review. Int J Tuberc Lung Dis 2009; 13: 810-9. PubMed PMID: 19555529.

(Systematic review of randomized controlled trials comparing rifapentine to rifampin in combination regimens for tuberculosis found no differences in rates of side effects including hepatotoxicity; no deaths or even hospitalization for liver disease reported in 3 trials involving 644 patients).

Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with treatment of latent tuberculosis infection. Am J Med Sci 2009; 337: 317-20. PubMed PMID: 19295414.

(Among 205 patients treated for latent tuberculosis with rifampin [4 month regimen], 4 [2%] developed ALT or AST elevations above 5 times ULN [AST: 235-528 U/L], of whom 3 had elevations before therapy, only 1 was symptomatic; no mention of jaundice).

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).

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).

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 40 cases, 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).

Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. ClinInfect 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).

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).

Moses M, Zachariah R, Tayler-Smith K, Misinde D, Foncha C, Manzi M, Bauerfeind A, Mwagomba B, Kwanjana J, Harries AD. Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi. Int J Tuberc Lung Dis 2010; 14: 197-202. PubMed PMID: 20074411.

(Among 156 African patients with HIV infection and tuberculosis starting treatment with stavudine, lamivudine and nevirapine and given isoniazid, rifampin and pyrazinamide for tuberculosis, ALT elevations >5 times ULN developed in only one patient and none had clinically apparent liver injury).

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).

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, Delvart V, Castaing D, Samuel D. 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 with isoniazid alone [n=1] or in combination with rifampin, pyrazinamide and ethambutol [bilirubin 1.8 to 39 mg/dL, ALT 214-2020], 7 recovering spontaneously, 6 undergoing liver transplantation, and one dying without transplant).

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 GSTm1 and GSTT1 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).

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 [0-0.7%] than isoniazid [1.4-5.2%]).

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%]).

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, 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).

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).

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).

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).

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 children with suspected drug induced liver injury, 3 were attributed to isoniazid, but none to rifampin).

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%]; hepatotoxicity defined as ALT >3 times ULN with symptoms or any ALT >5 times ULN).

Mankhatitham W, Lueangniyomkul A, Manosuthi W. Hepatotoxicity in patients co-infected with tuberculosis and HIV-1 while receiving non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy and rifampicin-containing anti-tuberculosis regimen. Southeast Asian J Trop Med Public Health 2011; 42: 651-8. PubMed PMID: 21706943.

(Among 134 patients with HIV infection and tuberculosis treated with rifampin, ALT elevations >5 times ULN occurred in 3 patients on nevirapine [4.6%] and 1 [1.4%] on efavirenz).

Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. CMAJ 2011; 183 (3): E173-9. PubMed PMID: 21220436.

(Among 9145 persons with latent tuberculosis treated with isoniazid [95%] or rifampin [5%] registered in a health care database in Quebec, 45 [0.5%] were subsequently admitted to hospital for liver injury within the 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).

Dorman SE, Goldberg S, Stout JE, Muzanyi G, Johnson JL, Weiner M, Bozeman L, et al; Tuberculosis Trials Consortium. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium. J Infect Dis 2012; 206: 1030-40. PubMed PMID: 22850121.

(Among 531 adults with active tuberculosis treated with isoniazid, pyrazinamide, ethambutol and either rifampin or rifapentine [5 days/week] for the first 8 weeks of intensive therapy, hepatitis was reported in 2.8% of rifampin and 4% of rifapentine treated subjects, the later group including 3 serious adverse events due to hepatitis).

Chan PC, Yang CH, Chang LY, Wang KF, Lu BY, Lu CY, Shao PL, Hsueh PR, Fang CT, Huang LM. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial. Int J Tuberc Lung Dis 2012; 16: 633-8. PubMed PMID: 22410137.

(Among 373 Taiwanese prison inmates with latent tuberculosis, ALT elevations >5 times ULN developed in none of 190 patients given 4 months of rifampin compared to 11 of 183 [6%] of those given 6 months of isoniazid, but none developed symptoms or jaundice and abnormalities, most ALT elevations occurred in patients with coexisting hepatitis B or C).

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; 25: 825-9. 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).

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).

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).

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).

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).

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 antituberculosis therapy including 3 cases in which rifampin was combined with other agents).

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, 54 [6%] were attributed to drugs for tuberculosis, most commonly isoniazid [n=48], and occasionally pyrazinamide [n=2], rifampin [n=2], ethambutol [n=1] or the combination of isoniazid and rifampin [n=1].

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).

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).

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).

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).

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).

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 antituberculosis therapy).

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 treatment, 23 [17%] had recurrence).

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).

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).