

## REVIEW

## Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review

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### Key words

adverse effect, antitubercular agents, antituberculous treatment, drug-induced hepatitis, hydrazine, isoniazid, pyrazinamide, rifampicin, rifampin, toxic hepatitis.

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### Abstract

The cornerstone of tuberculosis management is a 6-month course of isoniazid, rifampicin, pyrazinamide and ethambutol. Compliance is crucial for curing tuberculosis. Adverse effects often negatively affect the compliance, because they frequently require a change of treatment, which may have negative consequences for treatment outcome. In this paper we review the incidence, pathology and clinical features of antituberculosis drug-induced hepatotoxicity, discuss the metabolism and mechanisms of toxicity of isoniazid, rifampicin and pyrazinamide, and describe risk factors and management of antituberculosis drug-induced hepatotoxicity. The reported incidence of antituberculosis drug-induced hepatotoxicity, the most serious and potentially fatal adverse reaction, varies between 2% and 28%. Risk factors are advanced age, female sex, slow acetylator status, malnutrition, HIV and pre-existent liver disease. Still, it is difficult to predict what patient will develop hepatotoxicity during tuberculosis treatment. The exact mechanism of antituberculosis drug-induced hepatotoxicity is unknown, but toxic metabolites are suggested to play a crucial role in the development, at least in the case of isoniazid. Priorities for future studies include basic studies to elucidate the mechanism of antituberculosis drug-induced hepatotoxicity, genetic risk factor studies and the development of shorter and safer tuberculosis drug regimens.

### Introduction

Tuberculosis (TB) is one of the major causes of death from a curable infectious disease. About 9 million new TB cases occurred in 2004 and 1.7 million people died from TB that year. Sub-Saharan Africa has the highest incidence and mortality rates, mainly due to HIV/AIDS, whereas the South-East Asian region has the largest number of both new cases and deaths from TB.<sup>1</sup> Recommended standard treatment for adult respiratory TB is a regimen of isoniazid, rifampicin, and pyrazinamide for 2 months, followed by 4 months of isoniazid and rifampicin. Ethambutol is usually added to this regimen and streptomycin is recommended by the World Health Organization (WHO) in retreatment cases in most developing countries.<sup>2</sup>

The most frequent adverse effects of antituberculosis treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders. Hepatotoxicity is the most serious one and is the focus of the present review.<sup>3</sup> Antituberculosis drug-induced hepatotoxicity (ATDH) causes substantial morbidity and mortality and diminishes treatment effectiveness. Asymptomatic transaminase elevations are common during antituberculosis treatment, but

hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time.

Adverse effects diminish treatment effectiveness, because they significantly contribute to nonadherence, eventually contributing to treatment failure, relapse or the emergence of drug-resistance.<sup>4-6</sup> Adherence to the prescribed treatment is crucial for curing patients with active TB. Because of the long treatment period, the patient should keep motivated to continue treatment even when he is feeling better. Additionally, the interruption of TB treatment and the switch to second-line antituberculosis drugs, which is required in patients who do not tolerate standard drugs, results in a sub-optimal treatment response.

Isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic drugs.<sup>7</sup> These drugs are metabolized by the liver. No hepatotoxicity has been described for ethambutol or streptomycin.

Metabolism is crucial in ATDH and toxic metabolites play a central role. This paper presents a concise up-to-date review on the incidence and mechanism of hepatotoxicity caused by first-line standard multidrug TB treatment in adults, a view on clinical management of ATDH and future directions for research.

**Table 1** Definition of hepatotoxicity according to the WHO Adverse Drug Reaction Terminology

WHO definition of hepatotoxicity	
Grade 1 (mild)	<2.5 times ULN (ALT 51–125 U/L)
Grade 2 (mild)	2.5–5 times ULN (ALT 126–250 U/L)
Grade 3 (moderate)	5–10 times ULN (ALT 251–500 U/L)
Grade 4 (severe)	>10 times ULN (ALT > 500 U/L)

ALT, alanine aminotransferase; ULN, upper limit of normal, i.e. 50 U/L.

## Incidence, pathology and clinical features

Many definitions for drug-induced hepatotoxicity have been used in the literature. It is difficult to define and diagnose ATDH, because part of the definition is the exclusion of viral hepatitis or other possible causes of hepatotoxicity. There are numerous methods for assessing causality of adverse drug reactions, such as the chronology of the administration of the drugs, results of laboratory testing or the response to re-administration of the drug. Histological findings (liver biopsy or autopsy) can support the diagnosis of drug-induced hepatotoxicity.<sup>8</sup>

A common definition of ATDH is a treatment-emergent increase in serum alanine aminotransaminase greater than three or five times the upper limit of normal, with or without symptoms of hepatitis, respectively. The severity of hepatotoxicity is classified according to the WHO Toxicity Classification Standards.<sup>9</sup> (See Table 1).

### Incidence

The incidence of ATDH during standard multidrug TB treatment has been variably reported as between 2% and 28%.<sup>10–24</sup> This rate depends on the investigators' definition of hepatotoxicity as well as the population studied. (See Table 2) Most studies on ATDH have been performed in Europe, Asia and the USA and the incidence varies between different world regions. Orientals are reported to have the highest rates, especially Indian patients.<sup>13,19,21,25</sup> Hepatotoxicity in sub-Saharan Africa is mentioned in some papers but incidence rates are not reported. This is probably due to the fact that liver function tests are not carried out routinely in monitoring TB patients on therapy in most African countries.

Active TB is usually treated with multiple drugs. Therefore, there are limited data on toxicity rates of antituberculosis drugs individually, except for isoniazid, which has been widely used as prophylactic monotherapy for latent TB infections. This can complicate the attribution of the reaction to a specific medication. Only temporal relationships can provide evidence that a given drug is responsible for the adverse effect, for example when symptoms appear with the start of a new drug, resolve with withdrawal of a drug and/or reappear with rechallenge of that same drug.

Significant transaminase elevations are reported in about 0.5% of all patients treated with isoniazid monotherapy.<sup>26,27</sup> In general, rifampicin is a well-tolerated drug and hepatotoxicity occurs in about 1–2% of patients treated with prophylactic rifampicin mono-

therapy.<sup>7,28</sup> Hepatotoxicity is a major toxic effect of pyrazinamide. When the drug was introduced in the 1950s, a high incidence of hepatotoxicity was reported and the drug was nearly abandoned. This appeared to be related to the high dosage of 40–70 mg/kg. Toxicity was not a major problem when pyrazinamide was used at a daily dosage of 20–30 mg/kg.<sup>7</sup> Nowadays, pyrazinamide is used in the intensive phase of TB treatment. The rate of hepatotoxicity of pyrazinamide monotherapy in its currently used dosage is unknown. It was recently reported that pyrazinamide causes more hepatotoxicity than isoniazid or rifampicin.<sup>13,18</sup> In a recent study, seven out of 12 patients (58%) treated for latent TB with ethambutol and pyrazinamide developed transaminase elevation of more than four times the upper limit of normal.<sup>29</sup> Because ethambutol alone is not hepatotoxic, pyrazinamide was likely to be the offending agent.

### Pathological features

Both animal and human case studies show that isoniazid-induced hepatotoxicity manifests mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic isoniazid metabolites bind covalently to cell macromolecules.<sup>30–32</sup> Hydrazine is the proposed toxic metabolite of isoniazid and animal studies have shown that hydrazine causes steatosis, hepatocyte vacuolation and glutathione depletion. Lipid vacuoles and mitochondrial swelling is found in periportal and midzonal hepatocytes.<sup>33–35</sup>

Rifampicin may cause transient hyperbilirubinemia, which is not a toxic effect but is due to interference with bilirubin excretion.<sup>36</sup> Rifampicin can cause hepatic lesions characterized by hepatocellular changes, with centrilobular necrosis, possibly associated with cholestasis. Histopathological findings range from spotty to diffuse necrosis with more or less complete cholestasis.<sup>37</sup> Bridging necrosis, lymphocytic infiltration, focal cholestasis, increased fibrosis, and micronodular cirrhosis were observed in the liver of a patient who died of rifampicin- and pyrazinamide-induced hepatotoxicity.<sup>38</sup>

### Clinical features

Hepatic drug reactions usually occur in the first 2 months of treatment but may happen at any moment during the treatment period. Clinical, biochemical and histological features of ATDH are hard to distinguish from viral hepatitis.<sup>31,32</sup> The signs and symptoms of liver injury are jaundice, abdominal pain, nausea, vomiting and asthenia. They are not specific enough to ascertain a liver disorder. Therefore, confirmation by laboratory liver testing is required.<sup>8</sup> Complaints of ATDH are mostly relieved when treatment is interrupted. When treatment is not interrupted in time, ATDH can be fatal.<sup>12,23</sup>

### Metabolism and mechanisms of toxicity

The exact mechanism of ATDH is unknown. Isoniazid-induced hepatotoxicity is considered idiosyncratic.<sup>39</sup> Unpredictable or idiosyncratic reactions are adverse drug reactions that are not related to the pharmacological properties of the drug. Although they are dose dependent in susceptible individuals, they do not occur at any dose in most patients. Idiosyncratic reactions can affect any organ system, and include IgE-mediated reactions as well as reactive

**Table 2** Incidence and risk factors for antituberculosis drug-induced hepatotoxicity (ATDH) with regimens containing isoniazid, rifampicin and pyrazinamide

Proportion ATDH (%)	Definition of hepatotoxicity	Risk factors	Population <sup>†</sup>
2.0 <sup>10</sup>	AST > 6× ULN and confirmation by re-challenge	Female sex, advanced age	E 78%, As 17%, Af 4%, NA + SA 1%
2.3 <sup>11</sup>	ALT > 5× pretreatment level	Advanced age	As (India, Pakistan) 70%, E 30%
2.6 <sup>12</sup>	ALT/AST > 10× ULN	Alcoholism, hepatitis B carriage, other hepatotoxic drugs	E (Spain) 86%, C/SA 14%
3.0 <sup>13</sup>	ALT > 3× ULN	Advanced age, female sex, HIV-status, Asian	As 42%, E +C/SA 29%, Af 16%, NA 12%
3.4 <sup>14</sup>	ALT > 5× ULN	Female sex	Dutch (94%), non-Dutch (6%)
5.3 <sup>15‡</sup>	ALT/AST > 3× ULN	Abnormal baseline values, female sex, advanced age	As (Singapore)
8.1 <sup>16</sup>	ALT/AST > 5× ULN	Abnormal baseline liver function, low BMI, hepatitis B/C, other drugs	Not mentioned
10.7 <sup>17§</sup>	ALT > 5× ULN	Fluconazole exposure, baseline CD4 < 100 cells/mL, bilirubin > 13 mmol/L or ALT > 51 U/L	E 60%, Af 34%, other 5%
11.0 <sup>18</sup>	ALT/AST > 3× ULN	Advanced age, history of hepatitis, female sex	E 90%, As 6%, Af 3%, SA 1%
13.0 <sup>19</sup>	ALT/AST > 5× ULN	HIV infection, Asian	Af 60%, As 15%, E 24%, other 3%
15.0 <sup>20,55¶</sup>	ALT > 3× ULN	Advanced age, low BMI, slow acetylator status, CYP2E1 c1/c1 genotype	As (Taiwan)
16.1 <sup>21</sup>	ALT/AST > 5× ULN, or any increase + symptoms	Advanced age	As (India)
19.0 <sup>22</sup>	ALT/AST > 3× ULN	HIV or hepatitis C infection	Not mentioned
27.7 <sup>23</sup>	ALT > 3× ULN with or > 5× ULN without symptoms	No significant risk factors	Iran
ND <sup>24††</sup>	AST > 3× ULN	Advanced age, high alcohol intake, slow acetylators	As (India)

<sup>†</sup>Regions of origin: Af, Africa; As, Asia; C/SA, Central and South America; E, Europe; NA, North America, SA, South America.

<sup>‡</sup>Patients at risk did not receive pyrazinamide.

<sup>§</sup>Study performed in HIV patients only.

<sup>¶</sup>Same study population.

<sup>††</sup>No incidence: case-control study.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATDH, antituberculosis drug-induced hepatotoxicity; BMI, body-mass index; ND, not done; ULN, upper limit of normal (based on WHO criteria: ULN = 50 IU/L).

metabolite syndromes. It is suggested that reactive metabolites, rather than the parent drug, are responsible for most idiosyncratic drug reactions.<sup>40</sup> Isoniazid-induced hepatotoxicity is not the result of a hypersensitivity or allergic reaction<sup>31,32</sup> and is most probably caused by toxic metabolites.

Most antituberculosis drugs are liposoluble and their elimination requires biotransformation into more water-soluble compounds. This is mostly performed by hepatic phase I and phase II biotransformation enzymes. In the phase I reaction, oxidation or demethylation occurs, usually performed by cytochrome P450 (CYP450) enzymes. The compound is usually still not very water soluble, and requires further metabolism. Phase I reactions often produce toxic intermediates. In a typical phase II reaction, a large water-soluble compound is attached by glucuronidation or sulfation, resulting in non-toxic metabolites which can easily be eliminated. A third metabolic step for detoxification involved glutathione, which can covalently bind to toxic compounds by the enzyme glutathione S-transferase.<sup>41</sup>

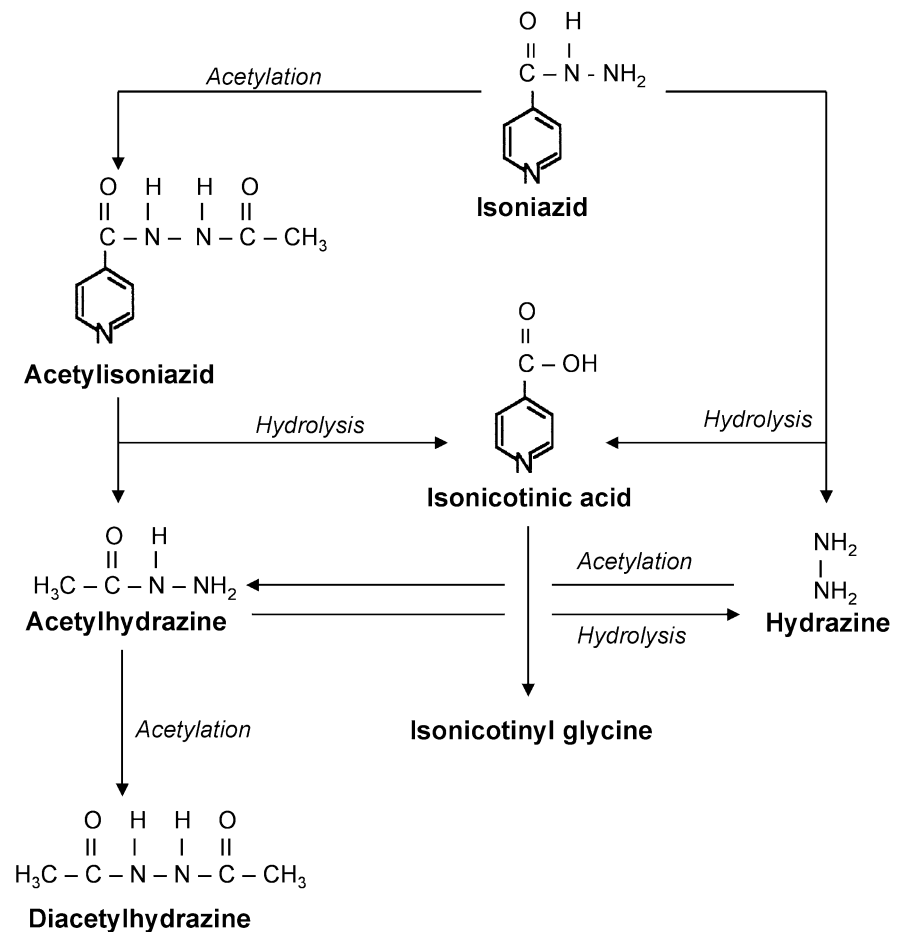
Transporters (e.g. P-glycoprotein) and nuclear receptors (e.g. pregnane X-receptor) also play a critical role in the orderly

elimination of drugs and their metabolites, and these processes are sometimes called phase III metabolism.<sup>42</sup>

## Isoniazid

The predominant metabolic pathway of isoniazid metabolism is acetylation by the hepatic enzyme N-acetyltransferase 2 (NAT2). Isoniazid (INH; isonicotinic acid hydrazide) is acetylated into acetylisoniazid and then hydrolyzed into acetylhydrazine and isonicotinic acid. Acetylhydrazine is either hydrolyzed in hydrazine, or acetylated into diacetylhydrazine.<sup>32,43</sup> (See Fig. 1). A small part of isoniazid is directly hydrolyzed into isonicotinic acid and hydrazine and this pathway is of greater quantitative significance in slow than in rapid acetylators.<sup>43</sup>

Most previous research has focused on the hypothesis that acetylhydrazine is the toxic metabolite of isoniazid.<sup>32,44</sup> More recent studies, however, suggest that hydrazine, and not isoniazid or acetylhydrazine, is most likely to be the cause of isoniazid-induced hepatotoxicity.<sup>30,45–47</sup> Hydrazine toxicity has been described as early as 1908 and is known to cause irreversible



**Figure 1** Isoniazid metabolism.

cellular damage.<sup>48</sup> Several hydrazine metabolites have been identified (e.g. acetylated hydrazine, hydrazones and nitrogen gas). Oxidation is the major route of hydrazine metabolism. Nitrogen and diimide, a powerful diazene reducing agent, are the probable intermediates in hydrazine reactions.<sup>49</sup> A study in rat liver microsomes showed that nitrogen-centered radicals are formed during oxidative hydrazine metabolism, which probably participate in the hepatotoxic process.<sup>50</sup> *In vitro* studies show that free oxygen radicals are not involved in isoniazid toxicity.<sup>51</sup>

Human acetylation rate is genetically determined and humans can be divided into slow and rapid acetylators.<sup>52</sup> Acetylator status can be assessed by using phenotypic or genotypic methods. Early studies suggested that fast acetylators are more susceptible to developing ATDH.<sup>32,53,54</sup> More recent studies show that slow acetylators develop ATDH more often and also more severely as compared with fast acetylators.<sup>24,55,56</sup> In slow acetylators, more isoniazid is left for direct hydrolysis into hydrazine and also the 'accumulated' acetylhydrazine can be converted into hydrazine. Huang *et al.* demonstrated that slow acetylators have a more than two-fold risk of developing ATDH compared with fast acetylators.<sup>55</sup> These studies are the first in which acetylator genotype was determined; earlier studies determined acetylator phenotype using biochemical methods.

Although limited information exists regarding isoniazid concentrations that cause toxic reactions, it can be proposed to adjust

isoniazid dosage on acetylator status: a lower dosage in slow acetylators to reduce the risk of ATDH and a higher isoniazid dosage in fast acetylators to increase the early bactericidal activity and thereby lower the probability of treatment failure.<sup>57</sup>

Human genetic studies have shown that cytochrome P450 2E1 (CYP2E1) is involved in ATDH.<sup>20,58</sup> The CYP2E1 c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins. Rat studies showed that isoniazid and hydrazine induce CYP2E1 activity.<sup>59–61</sup> Isoniazid has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity.<sup>57,62</sup> CYP1A2 is suggested to be involved in hydrazine detoxification.<sup>59,60</sup> Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes.

Whether oxidative stress is involved in ATDH is still a matter of debate. Oxidative stress results from an imbalance between oxidants and antioxidants in favor of the oxidants. Non-enzymatic scavengers (antioxidants) as well as enzymatic systems (e.g. glutathione conjugation) are involved in the detoxification of reactive oxygen species.<sup>63</sup> Reduced glutathione levels and reduced activity of glutathione-S transferase, catalase and superoxide dismutase after isoniazid or hydrazine administration to rats indicates that oxidative stress is involved in isoniazid-induced hepatotoxicity.<sup>34,60,64–66</sup> The observed hepatoprotective effect of *N*-acetylcysteine (a sulfhydryl-containing compound that can reduce oxidated glutathione into reduced glutathione) in rats

treated with isoniazid and rifampicin further supports this involvement.<sup>67,68</sup> Furthermore, TB patients with ATDH have been shown to have lower reduced plasma levels of glutathione and higher malondialdehyde, which is an oxidative stress parameter, maybe as a result of oxidative stress from the antituberculosis therapy.<sup>66</sup> The cause of the observed glutathione depletion is not apparent, however, and could reflect a general disturbance of intermediate metabolism, and be as well a consequence instead of a cause of toxicity. The observation that an induced glutathione depletion does not affect *in vitro* isoniazid-induced toxicity, suggests that glutathione is not directly involved in isoniazid-induced toxicity.<sup>69</sup>

### Rifampicin

The major pathway is desacetylation into desacetyl-rifampicin and separately hydrolysis produces a 3-formyl rifampicin.<sup>70,71</sup> Rifampicin may induce hepatocellular dysfunction early in the treatment, which resolves without discontinuing the drug.<sup>72</sup> The mechanism of rifampicin-induced hepatotoxicity is unknown and also unpredictable. There is no evidence for the presence of a toxic metabolite.<sup>37</sup>

Rifampicin is a potent inducer of the hepatic CYP450 system in the liver and intestine, thereby increasing metabolism of many other compounds.<sup>73,74</sup> The combined use of rifampicin and isoniazid has been associated with an increased risk of hepatotoxicity. Rifampicin induces isoniazid hydrolase, increasing hydrazine production when rifampicin is combined with isoniazid (especially in slow acetylators), which may explain the higher toxicity of the combination.<sup>75,76</sup>

Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity.<sup>77</sup>

### Pyrazinamide

Pyrazinamide (PZA; pyrazoic acid amide) is converted to pyrazinoic acid and further oxidized to 5-hydroxypyrazinoic acid by xanthine oxidase.<sup>78</sup> The serum half-life of pyrazinamide is not related to the length of treatment, indicating that pyrazinamide does not induce the enzymes responsible for its metabolism.<sup>79</sup> The mechanism of pyrazinamide-induced toxicity is unknown; it is unknown what enzymes are involved in pyrazinamide-toxicity and whether toxicity is caused by pyrazinamide or its metabolites. In a rat study, pyrazinamide inhibited the activity of several CYP450 isoenzymes (2B, 2C, 2E1, 3A);<sup>80</sup> but a study in human liver microsomes showed that pyrazinamide has no inhibitory effect on the CYP450 isoenzymes.<sup>81</sup>

### Prophylactic treatment with rifampicin and pyrazinamide

Latent *Mycobacterium tuberculosis* infections are usually treated with 6 months of isoniazid monotherapy. The investigation of a 2-month prophylactic regimen with rifampicin and pyrazinamide led to serious and also fatal cases of hepatotoxicity.<sup>82</sup> It caused more frequent and more serious hepatotoxicity compared with 6 months isoniazid (8–13% compared with 1–4%)<sup>83–85</sup> and even caused more hepatotoxicity compared with standard treatment of active TB.<sup>14</sup>

It is yet unknown why rifampicin and pyrazinamide combined are more toxic than isoniazid only or a 6-month regimen with isoniazid, rifampicin and pyrazinamide. Some authors suggest that pyrazinamide may be the primary cause. Patients treated for latent TB may have a higher alcohol intake during treatment as compared with TB patients on multiple drug-treatment, which increases their risk of ATDH. A drug interaction, whereby isoniazid decreases the hepatotoxic potential of rifampicin and pyrazinamide can also be considered, but mechanisms for this are unclear.<sup>86</sup>

Strikingly, HIV-infected individuals have similar hepatotoxicity rates during prophylactic rifampicin and pyrazinamide treatment and treatment of active TB (between 1% and 5%).<sup>87</sup> This cannot be readily explained. Again the question is raised whether isoniazid provides a protective effect to patients receiving rifampicin and pyrazinamide. An explanation could be that malabsorption of antituberculosis drugs results in lower plasma levels in HIV-infected individuals;<sup>88,89</sup> but only if a dose-toxicity relation is assumed will these lower plasma levels affect the risk of hepatotoxicity.

### Risk factors

Many risk factors for ATDH have been reported. The identification of high-risk patients would be useful to allow early detection of hepatotoxicity and reduce the morbidity and mortality of this condition. Variation in risk factor prevalence among different world regions may explain the observed differences in ATDH incidence.

### Demographic factors

Among the most widely accepted risk factors for ATDH are advanced age (above 60 years), female sex and low body mass index or malnutrition.<sup>11,13–16,18,20,32,90</sup> Older patients may be more vulnerable to hepatotoxic reactions due to a decreased clearance of drugs metabolized by CYP450 enzymes, and changes in liver blood flow, liver size, drug binding or distribution with aging. CYP3A activity was higher in females compared with males, which may explain females being more susceptible to ATDH.<sup>91</sup> Malnutrition results in decreased xenobiotic clearance and higher plasma levels.<sup>92</sup>

### HIV/AIDS

HIV-infection increases the risk of hepatotoxicity during standard multidrug treatment of active TB.<sup>13,19,22,93,94</sup> Why HIV-infected TB patients have an increased risk of ATDH is still a matter of debate. HIV/AIDS patients with acute illnesses have altered activities of oxidative pathways, which may partly explain their increased risk of ATDH.<sup>95</sup>

Concurrent therapy of TB/HIV coinfections requires concomitant use of two to four different antituberculosis drugs and at least three antiretroviral drugs. Unfortunately, combined TB/HIV treatment is often complicated by overlapping toxicities and drug–drug interactions.<sup>77</sup> Nevirapine is the most hepatotoxic non-nucleoside reverse transcriptase inhibitor (NNRTI).<sup>96</sup> The majority of the nucleoside reverse transcriptase inhibitors (NRTI) are potentially hepatotoxic (e.g. didanosine and stavudine) and hepatotoxicity has

been described for some protease inhibitors (e.g. ritonavir, indinavir and saquinavir). The incidence of hepatotoxicity during highly active antiretroviral therapy (HAART) ranges from 2% to 18%.<sup>97</sup> Drug toxicity, including hepatotoxicity, has been implicated as a major cause of TB or HIV treatment interruption during treatment of TB/HIV coinfection. Therefore, HAART is often delayed in HIV-infected TB patients.<sup>98</sup> The concomitant use of antifungals (e.g. fluconazole) which is often seen in HIV-infected patients, is also a risk factor for ATDH.<sup>17</sup>

Strikingly, HIV-positive patients developed less hepatotoxicity compared with HIV-negative patients during 2-month prophylactic treatment of latent *Mycobacterium tuberculosis* infection with rifampicin and pyrazinamide.<sup>87</sup> This cannot be readily explained. Although the hepatic damage from rifampicin and pyrazinamide may be immunologically mediated and may therefore be lower in the HIV-infected persons, there is no clear support for this hypothesis and in this trial patients were not severely immunocompromised.

### Pre-existent liver disease

Hepatitis B and/or C infections are common causes of the chronic liver disease that is frequently seen in populations at risk for TB infection. Several studies show that hepatitis B and C coinfection increase the risk of ATDH.<sup>12,16,22,90,99,100</sup> This has also been described for HIV-positive patients who are being treated with HAART.<sup>101</sup> More in general, patients with prior liver disease are at higher risk of hepatotoxicity.<sup>72</sup>

### Genetic risk factors

There is considerable interindividual variability in metabolism, some of which is caused by human genetic differences. Genetic polymorphisms in drug-metabolizing enzymes can affect enzyme activity. This may cause differences in treatment response or drug toxicity, for example, due to an increased formation of reactive metabolites.<sup>102</sup> Data on genetic risk factors for ATDH are still limited.

As mentioned in the Metabolism section earlier, the proposed risk genotypes for ATDH are the *N*-acetyltransferase slow acetylator (without the NAT2\*4 allele),<sup>55,56</sup> the cytochrome P450 2E1 homozygous wild type<sup>20,58</sup> and the glutathione *S*-transferase homozygous null genotype.<sup>103</sup>

These polymorphisms may explain differences in incidence of ATDH between different populations. The interplay between these genetic risk factors has not been studied.

The pregnane X-receptor (PXR) is involved in CYP3A4 expression and the extent to which inductors such as rifampicin can induce this enzyme.<sup>42</sup> Genetic polymorphisms in PXR play a role in the variability of CYP3A4 expression<sup>104</sup> and could therefore in theory be involved in the susceptibility for ATDH.

### Intoxications

Alcoholism is associated with a higher risk of ATDH because of enzyme induction.<sup>12,24</sup> Patients with alcohol abuse and concomitant use of other hepatotoxic drugs also increases the risk of ATDH.<sup>12,16</sup>

### Dosing schedules

Several studies have shown that daily TB treatment in comparison with thrice-weekly treatment increases the risk of ATDH,<sup>105,106</sup> although a recent study suggested that dosing schedules in the intensive phase have only little impact on the development of ATDH.<sup>107</sup>

### Management

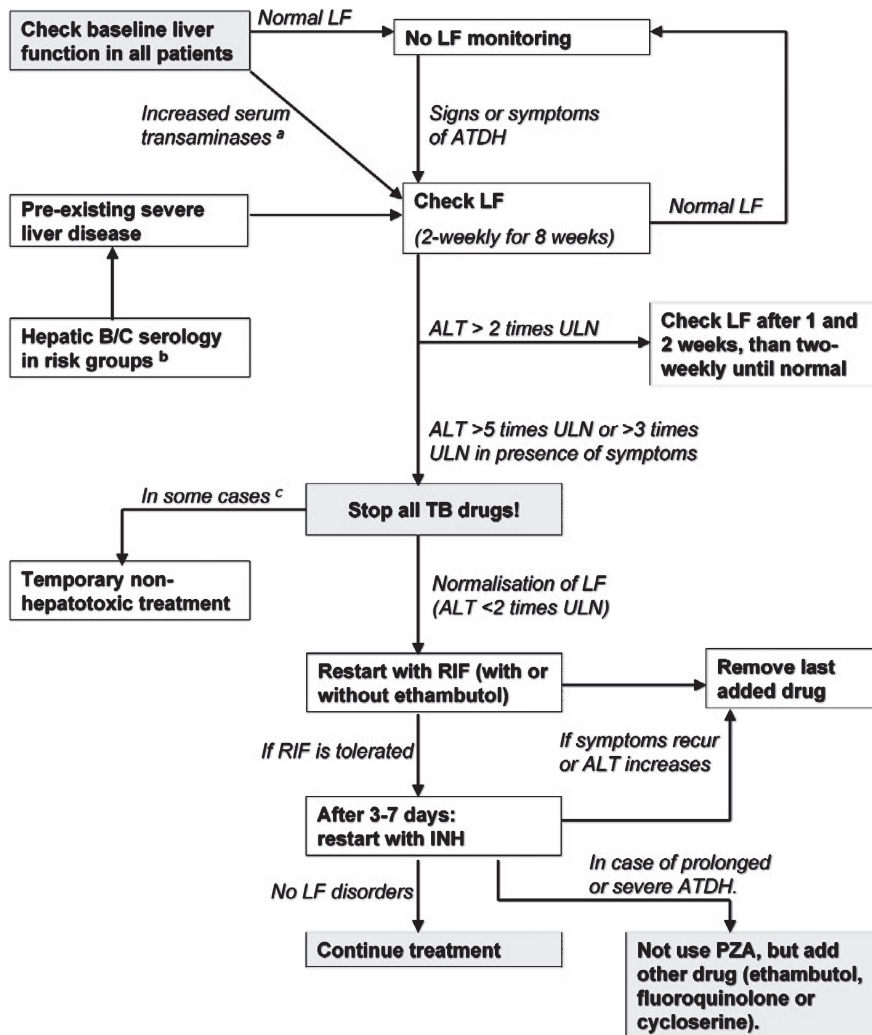
Guidelines for management of ATDH have been published by the American Thoracic Society (ATS), the British Thoracic Society (BTS) and the Task Force of the European Respiratory Society, the WHO and the International Union Against Tuberculosis and Lung Disease.<sup>108–110</sup> The management of ATDH depends on the supposed cause, therefore no unambiguous advice can be given. The hepatocellular pattern of liver injury, which is seen in isoniazid, rifampicin and pyrazinamide toxicity, has a predominant initial elevation of alanine aminotransferase.<sup>111</sup> Therefore, this biochemical parameter is most often used to monitor the liver function during antituberculosis treatment.

In summary, TB should be treated under supervision of a qualified physician. Patients should be advised to seek medical care if they experience any signs or symptoms of hepatotoxicity (i.e. jaundice, malaise, nausea and vomiting). They should be advised not to drink alcohol during TB treatment. During treatment, the liver function only has to be monitored on a regular basis on indication (e.g. in patients with chronic liver disease or increased serum transaminases prior to treatment). In the case of signs or symptoms of hepatotoxicity, the liver function should be examined. In the case of confirmed moderate or severe drug-induced hepatotoxicity, treatment should be interrupted and reintroduced after the hepatotoxicity has resolved. The American Thoracic Society guidelines on management of ATDH are summarized as a flow-chart in Figure 2.<sup>108,112</sup>

It is important to note that asymptomatic transaminase elevations occur in 20% of patients treated with standard antituberculosis regimens; prior to treatment or immediately after the start of treatment. Usually these elevations resolve spontaneously.<sup>7,11,23</sup>

Although the guidelines from the ATS, BTS and the Task Force are more or less the same, there are some differences. The ATS does not recommend baseline liver function testing for healthy patients, but only advises it in patients with possible risk for ATDH (e.g. patients with liver disorders), whereas the Task Force and BTS advise performing baseline liver function testing in all patients. After TB treatment has been stopped because of hepatotoxicity, both the BTS and ATS advise restarting the antituberculosis drugs one at a time. The Task Force advises restarting all the drugs simultaneously; after a second episode of hepatotoxicity the drugs need to be reintroduced consecutively.

In many low-income countries, where the burden of TB is often high, liver function tests cannot be performed. In those situations one has to rely on clinical symptoms of hepatotoxicity, such as jaundice, abdominal pain, nausea and vomiting. The cause of hepatitis during TB treatment can either be the antituberculosis drugs or something else, so the other possibilities have to be excluded before deciding that the hepatitis is drug-induced. If moderate or severe ATDH is diagnosed (i.e. serum aminotransferase level >5 times the upper limit of normal [ULN] or >3 times



**Figure 2** Flow chart monitoring the liver function prior to and during tuberculosis (TB) treatment, and the management of antituberculosis drug-induced hepatotoxicity (ATDH), based on the American Thoracic Society guidelines. ALT, alanine aminotransferase; INH, isoniazid; LF, liver function; PZA, pyrazinamide; RIF, rifampicin; ULN, upper limit of normal. <sup>a</sup>In patients with baseline serum ALT of more than three times ULN, several regimens without PZA and, if necessary, with a fluoroquinolone or cycloserine are recommended. <sup>b</sup>Risk groups in which screening for viral hepatitis is recommended include intravenous drug users, patients from endemic areas (Asia, Africa, the Pacific Islands, Eastern Europe or the Amazon region), sexual or household contacts of infected individuals, HIV infected patients. <sup>c</sup>If the patient is very sick or still sputum smear positive, some form of TB treatment should be given until liver function is normal.

the ULN with symptoms of hepatotoxicity), guidelines recommend to discontinue all drugs until liver function tests have become normal. When it is not possible to perform liver function tests, it is advisable to wait for an extra 2 weeks after the jaundice has disappeared before recommencing TB treatment. Once the ATDH has resolved, the same drugs are reintroduced consecutively. A very ill TB patient may die without antituberculosis drugs. To prevent this, these patients should be temporarily treated with a non-hepatotoxic regimen. After the hepatotoxicity has resolved, the usual TB treatment should be restarted.<sup>2,113</sup>

## Future directions

The mechanism of ATDH is still largely unknown, so further understanding is needed regarding genetic polymorphisms in enzymes involved in TB drug metabolism, potential hepatoprotective agents and the mechanism of ATDH. The development of strong pharmacological bases for a more rational use of existing drugs can be very helpful in lowering the risk of adverse effects of TB treatment. There are still only a few studies on the effect of genetic polymorphisms in drug-metabolizing enzymes on the risk

of ATDH. The relative role of these polymorphisms in relation to other risk factors should be studied in risk factor assessment studies using large sample sizes and different populations. Although the available data in the field are still limited, pharmacogenetic approaches may prevent ATDH in the future. In patients with high-risk genotypes, adjusting treatment dosages should be considered to prevent ATDH while maintaining the therapeutic effect. The association between risk genotype, drug concentrations and the risk of hepatotoxicity should be studied. For example, the NAT2 genotype could be used to divide patients into 'low isoniazid dose' and 'high isoniazid dose' groups.<sup>114</sup>

A hepatoprotective effect of *N*-acetylcysteine<sup>67</sup> and silymarin<sup>115</sup> on ATDH has been shown in rats. More studies are needed on the protective effect of such compounds in humans and possible interactions with antituberculosis drugs.

The long duration of TB treatment is one of the main problems to be overcome. Improvement of the bactericidal effect of the antituberculosis drugs will reduce treatment length and consequently increase treatment adherence and efficacy. New and less hepatotoxic regimens will need safety and tolerability studies. New regimens are in development, with emphasis on fluoroquinolone

lones such as moxifloxacin and levofloxacin,<sup>116,117</sup> and will probably have lower toxicity rates.<sup>118</sup> Although these drugs have been known for their potential activity for several years, they are yet not widely used probably because of microbiological (resistance), toxicological or economic reasons.

Hepatotoxicity can be an indication for therapeutic drug monitoring (TDM) in TB hospitals in the developed world. In TDM, plasma levels of the antituberculosis drugs are monitored during treatment. Although for most antituberculosis drugs, relationships between the serum concentrations and toxicity are not present, pyrazinamide dose is related to hepatotoxicity (more common with daily dosages above 40 mg/kg). The rationale of TDM is to observe high or low plasma levels of the antituberculosis drugs to be able to take appropriate action. Especially in AIDS patients treated for TB/HIV, TDM can resolve issues of drug–drug interactions before the patient develops treatment failure, relapse or toxicity.<sup>119</sup>

Studies are needed to demonstrate whether routine transaminase monitoring during TB treatment reduces the incidence or severity of ATDH.

One of the main future challenges is to design and implement effective and safe treatment regimens for TB/HIV coinfecting patients. Attempts should be made to develop regimens with minimal toxicity to achieve better cure of TB in HIV-infected patients. Hepatotoxicity is a serious adverse effect and is frequently seen in combined TB/HIV treatment, but also other adverse effects such as skin reactions or gastrointestinal disorders should be taken into account.

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## References

- World Health Organization. *Tuberculosis*. WHO Fact Sheet No. 104. Revised. March 2006, 2006.
- World Health Organization Global Tuberculosis Programme. *Treatment of Tuberculosis: Guidelines for National Programmes*, 3rd edn. (WHO/CDS/TB/2003.13). Geneva: World Health Organization, 2003.
- Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet* 2003; **362**: 887–99.
- Kaona FA, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health* 2004; **4**: 68.
- Wares DF, Singh S, Acharya AK, Dangi R. Non-adherence to tuberculosis treatment in the eastern Tarai of Nepal. *Int. J. Tuberc. Lung Dis.* 2003; **7**: 327–35.
- World Health Organization/IUATLD Global project on anti-tuberculous drug Resistance Surveillance. *Anti-tuberculous Drug Resistance in the World*. Third global report. WHO/HTM/TB/2004.343. Geneva: World Health Organization, 2004.
- Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1978; **59**: 13–32.
- Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J. Hepatol.* 1990; **11**: 272–6.
- WHO. *International Monitoring of Adverse Reactions to Drugs: Adverse Reaction Terminology*. Uppsala: WHO Collaborating Center for International Drug Monitoring, 1992.
- Dossing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. *Tuber. Lung Dis.* 1996; **77**: 335–40.
- Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuber. Lung Dis.* 1996; **77**: 37–42.
- Tost JR, Vidal R, Cayla J, Diaz-Cabanela D, Jimenez A, Broquetas JM. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. *Int. J. Tuberc. Lung Dis.* 2005; **9**: 534–40.
- 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.
- van Hest R, Baars H, Kik S *et al.* Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. *Clin. Infect. Dis.* 2004; **39**: 488–96.
- 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.
- Fernandez-Villar A, Sopena B, Fernandez-Villar J *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.
- Pukenyte E, Lescure FX, Rey D *et al.* Incidence of and risk factors for severe liver toxicity in HIV-infected patients on anti-tuberculosis treatment. *Int. J. Tuberc. Lung Dis.* 2007; **11**: 78–84.
- Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur. Respir. J.* 1996; **9**: 2026–30.
- Breen RA, Miller RF, Gorsuch T *et al.* Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax* 2006; **61**: 791–4.
- Huang YS, Chern HD, Su WJ *et al.* Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology* 2003; **37**: 924–30.
- Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *Am. J. Respir. Crit Care Med.* 2002; **166**: 916–19.
- Ungo JR, Jones D, Ashkin D *et al.* Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am. J. Respir. Crit Care Med.* 1998; **157** (6 Pt 1): 1871–6.
- Sharifzadeh M, Rasoulinejad M, Valipour F, Nouraei M, Vaziri S. Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during antituberculosis [correction of antituberculosis] treatment. *Pharmacol. Res.* 2005; **51**: 353–8.
- Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; **51**: 132–6.
- Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991; **99**: 465–71.
- Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; **281**: 1014–18.
- Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis

- infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005; **128**: 116–23.
- 28 Villarino ME, Ridzon R, Weismuller PC *et al.* Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. *Am. J. Respir. Crit. Care Med.* 1997; **155**: 1735–8.
  - 29 Younossian AB, Rochat T, Ketterer JP, Wacker J, Janssens JP. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis. *Eur. Respir. J.* 2005; **26**: 462–4.
  - 30 Sarich TC, Youssefi M, Zhou T, Adams SP, Wall RA, Wright JM. Role of hydrazine in the mechanism of isoniazid hepatotoxicity in rabbits. *Arch. Toxicol.* 1996; **70**: 835–40.
  - 31 Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975; **69**: 289–302.
  - 32 Mitchell JR, Zimmerman HJ, Ishak KG *et al.* Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. *Ann. Intern. Med.* 1976; **84**: 181–92.
  - 33 Scales MD, Timbrell JA. Studies on hydrazine hepatotoxicity. 1. Pathological findings. *J. Toxicol. Environ. Health.* 1982; **10**: 941–53.
  - 34 Timbrell JA, Scales MD, Streeter AJ. Studies on hydrazine hepatotoxicity. 2. Biochemical findings. *J. Toxicol. Environ. Health.* 1982; **10**: 955–68.
  - 35 Sarich TC, Zhou T, Adams SP, Bain AI, Wall RA, Wright JM. A model of isoniazid-induced hepatotoxicity in rabbits. *J. Pharmacol. Toxicol. Methods* 1995; **34**: 109–16.
  - 36 Capelle P, Dhumeaux D, Mora M, Feldmann G, Berthelot P. Effect of rifampicin on liver function in man. *Gut* 1972; **13**: 366–71.
  - 37 Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. *J. Antimicrob. Chemother.* 1994; **33**: 387–401.
  - 38 From the Centers for Disease Control and Prevention. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection – New York and Georgia, 2000. *JAMA* 2001; **285**: 2572–3.
  - 39 Lee WM. Drug-induced hepatotoxicity. *N. Engl. J. Med.* 2003; **349**: 474–85.
  - 40 Knowles SR, Utrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 2000; **356**: 1587–91.
  - 41 Lee WM. Drug-induced hepatotoxicity. *N. Engl. J. Med.* 1995; **333**: 1118–27.
  - 42 Kliewer SA, Goodwin B, Willson TM. The nuclear pregnane X receptor: a key regulator of xenobiotic metabolism. *Endocr. Rev.* 2002; **23**: 687–702.
  - 43 Ellard GA, Gammon PT. Pharmacokinetics of isoniazid metabolism in man. *J. Pharmacokin. Biopharm.* 1976; **4**: 83–113.
  - 44 Nelson SD, Mitchell JR, Timbrell JA, Snodgrass WR, Corcoran GB III. Isoniazid and iproniazid: activation of metabolites to toxic intermediates in man and rat. *Science* 1976; **193**: 901–3.
  - 45 Beaver IW, Blair IA. BMJ. Circulating hydrazine during treatment with isoniazid rifampicin in man. *Br. J. Clin. Pharmacol.* 1982; **13**: 599.
  - 46 Noda A, Hsu KY, Noda H, Yamamoto Y, Kurozumi T. Is isoniazid-hepatotoxicity induced by the metabolite, hydrazine? *J. UOEH* 1983; **5**: 183–90.
  - 47 Gent WL, Seifart HI, Parkin DP, Donald PR, Lamprecht JH. Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients. *Eur. J. Clin. Pharmacol.* 1992; **43**: 131–6.
  - 48 Wells HG. The pathological anatomy of hydrazine poisoning. *J. Exp. Med.* 1908; **10**: 457–64.
  - 49 Nelson SD, Gordon WP. Metabolic activation of hydrazines. *Adv. Exp. Med. Biol.* 1981; **136** (Pt B): 971–81.
  - 50 Noda A, Noda H, Ohno K *et al.* Spin trapping of a free radical intermediate formed during microsomal metabolism of hydrazine. *Biochem. Biophys. Res. Commun.* 1985; **133**: 1086–91.
  - 51 Walubo A, Smith P, Folb PI. The role of oxygen free radicals in isoniazid-induced hepatotoxicity. *Methods Find. Exp. Clin. Pharmacol.* 1998; **20**: 649–55.
  - 52 Parkin DP, Vandenplas S, Botha FJ *et al.* Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. *Am. J. Respir. Crit. Care Med.* 1997; **155**: 1717–22.
  - 53 Yamamoto T, Suou T, Hirayama C. Elevated serum aminotransferase induced by isoniazid in relation to isoniazid acetyltransferase phenotype. *Hepatology* 1986; **6**: 295–8.
  - 54 Mitchell JR, Thorgeirsson UP, Black M *et al.* Increased incidence of isoniazid hepatitis in rapid acetylators: possible relation to hydrazine metabolites. *Clin. Pharmacol. Ther.* 1975; **18**: 70–9.
  - 55 Huang YS, Chern HD, Su WJ *et al.* Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology* 2002; **35**: 883–9.
  - 56 Ohno M, Yamaguchi I, Yamamoto I *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.
  - 57 Wen X, Wang JS, Neuvonen PJ, Backman JT. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes. *Eur. J. Clin. Pharmacol.* 2002; **57**: 799–804.
  - 58 Vuilleumier N, Rossier MF, Chiappe A *et al.* CYP2E1 genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. *Eur. J. Clin. Pharmacol.* 2006; **62**: 423–9.
  - 59 Jenner AM, Timbrell JA. In vitro microsomal metabolism of hydrazine. *Xenobiotica* 1995; **25**: 599–609.
  - 60 Jenner AM, Timbrell JA. Influence of inducers and inhibitors of cytochrome P450 on the hepatotoxicity of hydrazine in vivo. *Arch. Toxicol.* 1994; **68**: 349–57.
  - 61 Jenner AM, Timbrell JA. Effect of acute and repeated exposure to low doses of hydrazine on hepatic microsomal enzymes and biochemical parameters in vivo. *Arch. Toxicol.* 1994; **68**: 240–5.
  - 62 Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A. *Antimicrob. Agents Chemother.* 2001; **45**: 382–92.
  - 63 Sies H. Oxidative stress: from basic research to clinical application. *Am. J. Med.* 1991; **91**: 31S–38S.
  - 64 Sodhi CP, Rana SV, Mehta SK, Vaiphei K, Attari S, Mehta S. Study of oxidative-stress in isoniazid-rifampicin induced hepatic injury in young rats. *Drug Chem. Toxicol.* 1997; **20**: 255–69.
  - 65 Sodhi CP, Rana SV, Mehta SK *et al.* Study of oxidative stress in isoniazid-induced hepatic injury in young rats with and without protein-energy malnutrition. *J. Biochem. Toxicol.* 1996; **11**: 139–46.
  - 66 Chowdhury A, Santra A, Kundu S *et al.* Induction of oxidative stress in antitubercular drug-induced hepatotoxicity. *Indian J. Gastroenterol.* 2001; **20**: 97–100.
  - 67 Attri S, Rana SV, Vaiphei K *et al.* Isoniazid- and rifampicin-induced oxidative hepatic injury – protection by N-acetylcysteine. *Hum. Exp. Toxicol.* 2000; **19**: 517–22.
  - 68 Attri S, Rana SV, Vaiphei K *et al.* Protective effect of N-acetylcysteine in isoniazid induced hepatic injury in growing rats. *Indian J. Exp. Biol.* 2001; **39**: 436–40.
  - 69 Nicod L, Viollon C, Regnier A, Jacqueson A, Richert L. Rifampicin and isoniazid increase acetaminophen and isoniazid cytotoxicity in human HepG2 hepatoma cells. *Hum. Exp. Toxicol.* 1997; **16**: 28–34.
  - 70 Acocella G, Conti R. Interaction of rifampicin with other drugs. *Tubercle* 1980; **61**: 171–7.

- 71 Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin. Pharmacokinet.* 1984; **9**: 511–44.
- 72 Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J. Antimicrob. Chemother.* 1977; **3**: 115–32.
- 73 Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, Watkins PB. Identification of rifampin-inducible P450III<sub>A4</sub> (CYP3A4) in human small bowel enterocytes. *J. Clin. Invest.* 1992; **90**: 1871–8.
- 74 Combalbert J, Fabre I, Fabre G *et al.* Metabolism of cyclosporin A. IV. Purification and identification of the rifampicin-inducible human liver cytochrome P-450 (cyclosporin A oxidase) as a product of P450III<sub>A4</sub> gene subfamily. *Drug Metab. Dispos.* 1989; **17**: 197–207.
- 75 Blair IA, Mansilla TR, Brodie MJ *et al.* Plasma hydrazine concentrations in man after isoniazid and hydralazine administration. *Hum. Toxicol.* 1985; **4**: 195–202.
- 76 Sarma GR, Immanuel C, Kailasam S, Narayana AS, Venkatesan P. Rifampin-induced release of hydrazine from isoniazid. A possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. *Am. Rev. Respir. Dis.* 1986; **133**: 1072–5.
- 77 Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. *Int. J. Tuberc. Lung Dis.* 2005; **9**: 248–57.
- 78 Ellard GA, Haslam RM. Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. *Tubercle* 1976; **57**: 97–103.
- 79 Ellard GA. Absorption, metabolism and excretion of pyrazinamide in man. *Tubercle* 1969; **50**: 144–58.
- 80 Maffei FR, Carini M. The inhibitory effect of pyrazinamide on microsomal monooxygenase activities is related to the binding to reduced cytochrome P-450. *Pharmacol. Res. Commun.* 1980; **12**: 523–37.
- 81 Nishimura Y, Kurata N, Sakurai E, Yasuhara H. Inhibitory effect of antituberculosis drugs on human cytochrome P450-mediated activities. *J. Pharmacol. Sci.* 2004; **96**: 293–300.
- 82 American Thoracic Society (ATS) and the Centers for Disease Control (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. This official ATS/CDC update was approved by the ATS Executive Committee, August 2001. *Am. J. Respir. Crit Care Med.* 2001; **164**: 1319–20.
- 83 Jasmer RM, Saukkonen JJ, Blumberg HM *et al.* Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann. Intern. Med.* 2002; **137**: 640–7.
- 84 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.
- 85 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.
- 86 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.
- 87 Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ. 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.
- 88 Gurumurthy P, Ramachandran G, Hemanth Kumar AK *et al.* Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob. Agents Chemother.* 2004; **48**: 4473–5.
- 89 Peloquin CA, Nitta AT, Burman WJ *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann. Pharmacother.* 1996; **30**: 919–25.
- 90 Wong WM, Wu PC, Yuen MF *et al.* Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000; **31**: 201–6.
- 91 Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. *Biochem. Pharmacol.* 1992; **44**: 275–83.
- 92 Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. *Clin. Pharmacokinet.* 1996; **31**: 47–64.
- 93 Small PM, Schechter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *N. Engl. J. Med.* 1991; **324**: 289–94.
- 94 Kucers A. *Rifampicin. The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs*, 5th edn. Oxford: Butterworth-Heinemann, 1997; 676–708.
- 95 Lee BL, Wong D, Benowitz NL, Sullam PM. Altered patterns of drug metabolism in patients with acquired immunodeficiency syndrome. *Clin. Pharmacol. Ther.* 1993; **53**: 529–35.
- 96 Sanne I, Mommeja-Marin H, Hinkle J *et al.* Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J. Infect. Dis.* 2005; **191**: 825–9.
- 97 Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J. Hepatol.* 2006; **44** (Suppl. 1): S132–9.
- 98 Dean GL, Edwards SG, Ives NJ *et al.* Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002; **16**: 75–83.
- 99 Gizińska J, Szymański R, Latarska D, Podlasin RB. Evaluation of risk factors for hepatotoxicity in HIV-infected patients treated for tuberculosis [Abstract]. 10th European AIDS Conference, November 2005, 2005. Available from URL: <http://www.multiwebcast.com/eacs/2005/10th/253/d.latarska.evaluation.of.risk.factors.for.hepatotoxicity.in.hiv.infected.html>
- 100 Turktas H, Unsal M, Tulek N, Oruc O. Hepatotoxicity of antituberculosis therapy (rifampicin, isoniazid and pyrazinamide) or viral hepatitis. *Tuber. Lung Dis.* 1994; **75**: 58–60.
- 101 Pol S, Vallet-Pichard A, Fontaine H. Hepatitis C and human immune deficiency coinfection at the era of highly active antiretroviral therapy. *J. Viral Hepat.* 2002; **9**: 1–8.
- 102 Wilkinson GR. Drug metabolism and variability among patients in drug response. *N. Engl. J. Med.* 2005; **352**: 2211–21.
- 103 Roy B, Chowdhury A, Kundu S *et al.* Increased risk of antituberculosis drug-induced hepatotoxicity in individuals with glutathione S-transferase M1 'null' mutation. *J. Gastroenterol. Hepatol.* 2001; **16**: 1033–7.
- 104 Hustert E, Zibat A, Presecan-Siedel E *et al.* Natural protein variants of pregnane X receptor with altered transactivation activity toward CYP3A4. *Drug Metab. Dispos.* 2001; **29**: 1454–9.
- 105 Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. *Lancet* 1981; **1**: 171–4.
- 106 Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet* 2004; **364**: 1244–51.
- 107 Chang KC, Leung CC, Yew WW, Tam CM. Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter? *Eur. Respir. J.* 2007; **29**: 347–51.
- 108 Blumberg HM, Burman WJ, Chaisson RE *et al.* American Thoracic Society/Centers for Disease Control and Prevention/Infectious

- Diseases Society of America: treatment of tuberculosis. *Am. J. Respir. Crit Care Med.* 2003; **167**: 603–62.
- 109 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.
- 110 Migliori GB, Raviglione MC, Schaberg T *et al.* Tuberculosis management in Europe. Task Force of the European Respiratory Society (ERS), the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region. *Eur. Respir. J.* 1999; **14**: 978–92.
- 111 Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N. Engl. J. Med.* 2006; **354**: 731–9.
- 112 Saukkonen JJ, Cohn DL, Jasmer RM *et al.* An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am. J. Respir. Crit Care Med.* 2006; **174**: 935–52.
- 113 Enarson DA, Rieder H, Arnadottir T, Trébuq A. *Management of Tuberculosis: A Guide for Low Income Countries*, 5th edn. Paris: International Union Against Tuberculosis and Lung Disease, 2000.
- 114 Kinzig-Schippers M, Tomalik-Scharte D, Jetter A *et al.* Should we use N-acetyltransferase type 2 genotyping to personalize isoniazid doses? *Antimicrob. Agents Chemother.* 2005; **49**: 1733–8.
- 115 Tasduq SA, Peerzada K, Koul S, Bhat R, Johri RK. Biochemical manifestations of anti-tuberculosis drugs induced hepatotoxicity and the effect of silymarin. *Hepatol. Res.* 2005; **31**: 132–5.
- 116 Spigelman M, Gillespie S. Tuberculosis drug development pipeline: progress and hope. *Lancet* 2006; **367**: 945–7.
- 117 Johnson JL, Hadad DJ, Boom WH *et al.* Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis.* 2006; **10**: 605–12.
- 118 Marra F, Marra CA, Moadebi S *et al.* Levofloxacin treatment of active tuberculosis and the risk of adverse events. *Chest* 2005; **128**: 1406–13.
- 119 Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs* 2002; **62**: 2169–83.