

## Liver Dysfunction in Pulmonary Tuberculosis Patients on DOTS: A Study and Review

Abha Pandit, Abhay Kumar Pandey

Abha Pandit, Department of Medicine, Index Medical College, Indore, M.P., India

Abhay Kumar Pandey, Department of Physiology, Government Medical College, Banda, U.P., India

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**Correspondence to:** Abha Pandit, Associate Professor, Department of Medicine, Index Medical College, Indore-452001, M.P., India.

Email: [drabhaypphysiol@gmail.com](mailto:drabhaypphysiol@gmail.com)

Telephone: +91-7607980255

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### ABSTRACT

**CONTEXT:** Phenomenal number of people suffers tuberculosis and is prescribed primary line DOTS antitubercular chemotherapy. Evidence based clinical practice to minimize risk of hepatotoxicity is primary imperative.

**AIM:** Study generates evidence for predicting individual hepatotoxic risk using patient's constitutional and health parameters and disease characteristics and adopting right course of management. It is observational study in patients consecutively selected by defined inclusion and exclusion criteria.

**METHODS:** Newly enrolled pulmonary tuberculosis patients for DOTS were studied to examine host and disease specific predictors of hepatotoxicity risk. Pretreatment baseline liver function tests and

eGFR were done. Development of hepatotoxicity was watched by monthly monitoring of liver enzymes and bilirubin serum profiles.

**RESULT:** The selected 148 patients were older and four fifths were males. 16 patients developed ATT-DIH at first or second month monitoring following DOTS. They were more undernourished, hypoproteinaemic, bore more extensive disease and were sputum AFB positive. Their eGFR profiles were normal but significantly lower and plasma antioxidant capacity significantly reduced. Oxidative stress marker levels also were insignificantly raised. They exhibited subclinical elevation of serum enzymes AST and ALT. No significant influence of age and gender was seen on incidence of ATT-DIH.

**CONCLUSION:** Frailty with extensive disease constituted phenotype vulnerable to ATT-DIH. Hypoalbuminaemia, reduced plasma antioxidant capacity, subclinical elevated profile of transaminases before starting DOTS were forewarning laboratory indices. LFT ought to be monitored at fortnight, a month and at 2 months in such patients as minimum necessity to timely detect and address hepatotoxicity.

**Key words:** DOTS; Primary antitubercular drugs; Hepatotoxicity; transaminases; monitoring in tuberculosis

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### INTRODUCTION

Tuberculosis continues as huge health care problem globally. Currently recommended first line treatment for TB includes regimen of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB) for initial 2 months followed by 4 months of INH and RMP and/or EMB<sup>[1]</sup>. Among the first line quadruple therapy drugs (INH, RMP, PZA, EMB), first three are metabolized mainly by the liver and are potentially hepatotoxic. A fair fraction of TB patients on chemotherapy with isoniazide and rifampicin exhibit elevations in serum levels of liver enzymes, alanine aminotransferase (ALT, earlier called SGPT) and aspartate aminotransferase (AST, earlier SGOT) activities. A small fraction of these can worsen further to compel

chemotherapeutic agent withdrawal that may increase morbidity and substitute drug may have worse profile leading to treatment failure and relapse<sup>[2]</sup>.

#### Liver dysfunction markers

Serum levels of liver enzymes ALT and AST are markers of hepatocyte integrity and ALP (alkaline phosphatase), is shed into circulation in cholestasis. Decreased serum albumin can truly be called indicator of decreased functional liver mass. Both transaminases are concentrated in liver however, AST is present in other tissues as well hence, ALT is more specific indicator of liver damage.

Up to 5 fold rise over upper normal levels (UNL) of the transaminases is taken to indicate mild liver damage; 5 to 10 fold indicates moderate and >10 fold severe damage<sup>[3]</sup>. Conjugated bilirubin is virtually absent in serum due to rapid secretion in bile. Levels increase when liver has lost half its excretory capacity. Raised bilirubin therefore always indicates liver disease. In absence of enzyme elevation raised bilirubin level would indicate drug induced cholestasis. Hypoalbuminaemia without rise in levels of transaminases indicates extrahepatic cause for low albumin level.

#### Hepatic drug metabolism

Drug induced liver injury most often is consequent to unpredictable idiosyncratic reactions that are metabolic reactions or hypersensitivity and do not depend on the drug dose. Metabolic idiosyncratic reactions may result from genetic or acquired variations in drug metabolism pathways effecting synthesis or abnormally slow detoxification of a hepatotoxic metabolite. Such reactions occur at unpredictable latent period after drug administration. A recurrence of such reactions on re-exposure to the drug is more predictable however<sup>[4]</sup>. Asymptomatic transient elevations of ALT may reflect minor, non progressing injury to hepatocyte, mitochondria, cell membrane or other structures. The latter does not lead to inflammation or histopathological damage. Induction of hepatic microsomal P450 enzymes represents another kind of adaptation.

#### Antitubercular drug induced hepatotoxicity (ATT-DIH)

First line anti-TB chemotherapeutic agents have hepatotoxic potential. RMP is found to increase serum level of liver enzymes AST, ALT and ALP<sup>[5]</sup>. INH and RMP increase formation of reactive oxygen species which play role in mediating hepatotoxic effect and elevation of markers of structural and functional impairment. Tuberculosis is prooxidant state as active inflammation involves activated inflammatory cells that secrete cytokines and free radicals. There is progressive decline in plasma antioxidant activity and increasing oxidative stress causing organ damage including liver in TB patients<sup>[6,7]</sup>.

Elevation of trasaminases is seen more frequently and more markedly in slow acetylators. The monoacetyl hydrazine metabolite is toxic to liver by way of free radical generation<sup>[8]</sup>. RMP, which is inducer of microsomal enzymes, causes faster production of the metabolite and thus increased idiosyncratic toxicity of INH<sup>[9]</sup>.

60% instances of ATT hepatotoxicity were reported to have occurred in first 3 months and around 80% in 6 months<sup>[10]</sup>. INH toxicity is mostly age related. Severity of the same also reportedly increased with age with higher mortality in patients older than 50 years. Women may not suffer more frequently but exhibit more severe INH hepatotoxicity<sup>[11]</sup>. Alcohol consumption doubles the toxicity rate of INH. Active viral hepatitis also increases the risk of hepatotoxicity.

Conjugated hyperbilirubinaemia is caused by RMP inhibiting bile salt exporter pump<sup>[12]</sup>. Intermittent large dose regimen is found associated with hypersensitive cholestatic reaction with symptoms

and moderate elevations of ALT and bilirubin levels<sup>[13]</sup>. The drug increases metabolism of many other drugs due to induction of microsomal enzymes<sup>[14]</sup>. PZA exhibits both dose related and the idiosyncratic toxicities including hypersensitivity. It alters nicotinamide adenyl dehydrogenase activity in hepatocytes resulting in increased generation of free radical species. RMP-PZA combination is far more hepatotoxic<sup>[15]</sup>. Drugs may inhibit mitochondrial function through effect on oxidative and respiratory chain enzymes, impairing cellular aerobic respiration and metabolism of free fatty acids. Accumulation of lactate and reactive oxygen species occurs. Final toxic metabolites getting into bile would damage biliary epithelium<sup>[16,17]</sup>. INH and RMP induced hepatotoxicity also apparently involves oxidative stress. There are multiple factors believed to increase risk of ATT-DIH namely, older age, female sex, alcoholism, underlying liver disease, acetylation phenotype, N-acetyl transferase-2 activity, glutathione transferase activity, hepatitis B and C virus infection, HIV infection, extensive disease and malnutrition<sup>[18]</sup>. Asymptomatic increase in AST has been observed in 20% of patients receiving standard four drug ATT regimen<sup>[19]</sup>.

There is no easy means to predict individuals destined to develop liver damage, however. Drug monitoring is too costly to be practical. Awareness of risk groups therefore is crucial to detect and address ATT-DIH. Findings from evaluation of hepatic dysfunction among pulmonary tuberculosis patients newly put on primary line anti TB treatment (ATT), under the DOTS unit in the medical college over period of June 2012 to December 2013 are presented. The findings contribute local clinical evidence base facilitating appraisal of hepatotoxicity risk in TB patient, and evidence based preventive approaches.

## PATIENTS AND METHOD

Consecutive patients with diagnosed pulmonary tuberculosis aged between 20 to 65 years, of either sex, newly enrolled for DOTS regimen were chosen for the observational study. Those consuming alcohol, any other prescribed or over the counter medications, suffering co-morbidity besides TB or giving history of liver disease and current symptoms were excluded. Extrapulmonary TB cases were excluded for reason of uniform application of chest X-ray and sputum tests as measures of disease severity. Patients were to be further assessed over course of study and excluded whenever any alcohol consumption or viral hepatitis came to detection.

The protocol was approved by college ethics committee and involved monthly checkup including liver function tests. Patients were explained of the protocol and were assured of no revelation of personal identity without concurrence. Their informed consent was so obtained before inclusion in study. Patients were educated about signs and symptoms of hepatotoxicity. They were instructed to report upon experiencing any adverse event to the unit and comply with necessary instructions. Every month they were enquired for any experience of adverse events or taking any other medications or alcohol, and if so found, were removed from the study. Liver function tests were performed at each monthly follow up, and at instance of symptoms suggestive of hepatotoxicity. 219 cases of pulmonary TB of chosen age range were included in study. 23 of these were excluded for alcohol consumption; 43 for significant co-morbidities, past history of hepatitis and exhibiting aberrant liver function profile at the outset and 5 patients for acquiring viral hepatitis. Total 148 cases of pulmonary tuberculosis were retained and the count includes those suffering hepatotoxicity with consequent treatment withdrawals.

Detailed clinical history, demographic details age, gender, body

weight and height record was made. Symptoms of hepatitis, i.e. nausea, anorexia, malaise, vomiting, abdominal pain, fever and jaundice were keenly enquired for. Body mass index (BMI) was calculated as body weight in kg/height in m<sup>2</sup>. Sputum smear was examined for acid fast bacilli. Chest X-rays were sought and patients showing infiltration under 30% of lung field were rated as mild; those between 30 to 50% as moderated and those > 50% as having severe disease.

All patients underwent liver function test before starting antitubercular therapy. Patients were instructed to come overnight fasting for blood collection. 10 mL blood samples were collected in anticoagulant (EDTA) vials. Plasma was separated by centrifugation at 2,500 g for 10 minutes. After taking third of aliquot for assay of malonaldehyde and plasma total antioxidant capacity, rest was sent to central laboratory facility for serum creatinine determination and tests for liver function. The latter included serum bilirubin, AST, ALT, ALP, total protein and albumin concentrations estimated by standard laboratory procedures. Malonaldehyde level (as indicator of oxidative stress), was determined as thiobarbituric acid reactive substances<sup>[20]</sup>. Total plasma antioxidant capacity was determined by FRAP (Ferric oxide reducing ability of plasma) method<sup>[21]</sup>. Colourless ferric tripyridyl triazine complex is reduced by plasma sample to blue ferrous complex due to the contained antioxidants. The change in absorbance is measured upon 4 minute reaction time at 593 nm which indicates total reducing power of electron donating antioxidants present in plasma.

Serum creatinine concentration was measured by Jaffe's method and glomerular filtration rate was estimated using the abbreviated equation of the 4 variable modification of diet in renal diseases (MDRD) formula<sup>[22]</sup>. The formula for uniform ethnicity is:

$$eGFR \text{ (mL/min/1.73 m}^2\text{)} = 186 \times \text{serum creatinine level} - 1.154 \times \text{age} \times 0.742 \text{ in case of women.}$$

Liver chemistry tests for serum bilirubin and enzymes were performed every month after starting the therapy and when patient reported with complaints. Peak estimated value reaching the defined range of hepatotoxicity or sub-hepatotoxicity, formed the basis of classifying individual patients as having no hepatotoxicity, sub-hepatotoxicity and hepatotoxicity. Whenever patient had 2 fold rise of transaminases over UNL (ALT 41 IU/L and AST 38IU/L), markers of acute viral hepatitis A, B, C and E<sup>[23]</sup>, were requisitioned. Abdominal ultrasonography was also sought to check presence of fatty liver or chronic liver disease. Intense enquiry was made in such cases of any alcohol use or self medication and in case of positive detection the patient would be excluded from study.

BMI of less than 20kg/m<sup>2</sup> was indicative of poor nourishment. Hypoalbuminaemia was defined as serum albumin level of less than 3.5 mg/dL. Upper normal level for ALT was 41 IU/L and AST 38 IU/L. ATT-DIH was defined by AST and ALT levels raised 5 times the UNL (upper normal limit, 40 IU/L) OR 3 times above UNL along with clinical symptoms viz. malaise, anorexia, nausea, fatigue, abdominal pain vomiting, jaundice etc. and negative serological tests for viral hepatitis A, B, C, E. Decline of raised transaminases at least to 50% within one month of ATT withdrawal finally provided confirmation. The patient was deemed to have served the study purpose and managed as per requirements. ATT medications, INH, RMP, and PZA were withheld till the transaminase levels normalized.

Patients showing rise of AST, ALT levels after starting ATT but not meeting the levels to hepatotoxicity definition, were made into a separate category of mild or subtoxic LFT alteration.

#### Statistical data analyses

The categorical data consisted distributions as present of absent and

distribution around a defined cut off or score or around common whole sample median. The serum bilirubin and enzyme levels were measured at baseline and consequent monthly intervals. All other parameters were determined once only at baseline. For statistical analyses, values of individual parameter in different patient categories (based on LFT abnormalities), were pooled and common median value was identified in 148 cases sample. Then segregation of number of patients from each category as those with above the median values and those at or below the common median value were tabulated. Only peak monitored value of cases showing defined abnormality were noted and compared to the baseline value. For bilirubin and serum enzyme parameters, the actual values are presented and difference from the baseline value of no hepatotoxicity group was examined by paired t-test. Comparative distribution of patients in different groups around common median value of given parameter was analyzed by Chi square (Moods median) test. In comparisons where number of observations in any cell were less than 5, Fisher's exact test was resorted to for analysis.

## OBSERVATIONS AND RESULT

As seen in table 1, sample median age is high, 47 years. No significant differences in age distribution among the non hepatotoxic and hepatotoxic categories were seen. Sample also comprised four fifths of males. Significant sex differences among patients distributed in various categories were not seen. The hepatotoxicity group had insignificant higher proportion of female patients. 63 of 148 cases (42.6%) had BMI less than 20kg/m<sup>2</sup> and were poorly nourished. The proportion of malnourished cases was significantly high (75%), among those developing hepatotoxicity. Extensive (severe) pulmonary disease was detected in 48 of studied 148 (32.4%) cases. Such proportion was significantly high (62.5%), among patients developing hepatotoxicity. Sputum smear AFB positive rate was 62.8% (93 of 148 cases) in general, while in patients developing hepatotoxicity it was significantly higher (81%). None of the patients spared of hepatotoxicity ever complained symptoms of hepatic illness. All 16 cases developing hepatotoxicity and 4 of 26 cases with sub-toxic LFT alterations complained symptoms of hepatic illness.

Table 2 depicts biochemical profiles at baseline before starting ATT in different categories. The patient's later developing hepatotoxicity frequently had lower plasma protein concentration. Albumin concentration was also significantly more often lower among hepatotoxicity and even subtoxicity group. Significantly high proportion of such cases had eGFR values on the lower side of general median. All study subjects however had eGFR above the critical 60 mL/min/1.73 m<sup>2</sup> level. There was no significant difference in relative prevalence of elevated oxidative stress levels indicated by malonaldehyde concentration. Median malonaldehyde concentration was high compared to that (under 2 micromoles/L), in healthy people. The patients who suffered hepatotoxicity had significantly lower baseline plasma antioxidant capacity indicated by the FRAP values. Median plasma antioxidant capacity value is quite low compared to over 1,000 micromoles/L value observed to prevail in healthy adults.

Tables 3 presents baseline and monitored peak estimate data of liver enzyme and bilirubin serum levels for different groups. As stated, the baseline values of all 148 cases were pooled to obtain common median value for each studied parameter. Consequent monitored peak estimate in the cases formed the basis of categorizing them as no hepatotoxicity; sub-hepatotoxic LFT alteration and hepatotoxicity groups. Distribution of patients in each group around the common baseline median value initially and also at peak estimate level is shown in table 4.

Proportion bearing higher baseline ALT and AST values were significantly higher among hepatotoxicity group. Serum bilirubin or serum ALP enzyme profiles at baseline did not significantly differ among the three categories of patients. Hepatotoxicity group also exhibited higher than median values of ALP activity at baseline, although not statistically significant.

## DISCUSSION

Identification of risk factors associating ATT-DIH in areas endemic in TB and liver disease is of major significance. Hepatotoxicity is major adverse effect of first line anti-TB drugs and causes significant morbidity and mortality often enforcing modification of ATT drug regimen. Identification of patients at increased risk of hepatotoxicity with clinical and feasible laboratory indicators is worthwhile. Published studies have reported 4.3% to 19% incidence of ATT-DIH. It is difficult to assess real incidence for any select patient community as context of host, disease, therapy and terms of defining toxicity vary. ATT-DIH incidence is reported to be higher in developing societies where older age of patients, concomitant viral hepatitis and

chronic liver disease, alcohol consumption, indiscriminate drug use, intestinal parasites and infections, malnutrition and extensive disease may be the determinants<sup>[24-26]</sup>. Hepatotoxicity incidence may depend upon ethnic susceptibility. Several studies have examined host factors, environmental factors or genetic factors as HLA typing<sup>[23]</sup> and specific cytochrome P450 E family or acetylator status<sup>[27]</sup>.

Present study differs from most referred studies in very restrictive patient selection viz. 20 to 65 year age group and careful exclusion of risk factors from past and personal history (past liver disease, alcoholism and other hepatotoxic drug intake, co-morbidities etc). Even extrapulmonary TB cases which are reportedly more vulnerable to ATT-DIH<sup>[28]</sup> were excluded in order to have uniform severity assessment with X-ray and sputum smear test. The design essentially selects examination of role of host constitutional and environmental (nutritional) factors and disease severity for bearing on ATT-DIH.

**Table 1** Baseline demographic and clinical profile of cases in various categories.

Parameters	No-Hepatotoxicity (n = 106)	Mild LFT Alterations (n = 26)	Hepatotoxicity (n = 16)	Chi Square Analysis
<b>Age Median (47 years)</b>				
Median & below	58	09	07	
Above median	48	17	09	
<b>Gender</b>				
Male	83	22	12	
Female	23	04	04	
<b>BMI</b>				
20 kg/m <sup>2</sup> and below	41	10	12	
Above 20kg/m <sup>2</sup>	65	16	04	*
<b>X-ray grading</b>				
Mild	28	10	00	
Moderate	46	10	06	
Severe	32	06	10	*
<b>Sputum (AFB)</b>				
Positive	63	17	13	
Negative	43	09	03	

\*indicates statistically significant comparisons.

**Table 2** Distribution of patients under different categories around general median values of baseline biochemical parameters.

Parameters (Median value)	No-Hepatotoxicity (n = 106)	Mild LFT Alterations (n = 26)	Hepatotoxicity (n = 16)	Chi Square Analysis
<b>Total Protein (6.77g/dL)</b>				
Above M	61	09	04	
M and below	45	17	12	*
<b>Serum albumin (3.6 g/dL)</b>				
Above M	63	08	03	
M and below	43	18	13	*
<b>eGFR (83.2 ml/min/1.73 m<sup>2</sup>)</b>				
Above M	59	14	01	
M and below	47	12	15	*
<b>Plasma MDA (3.47 μmol/L)</b>				
Above M	50	13	11	
M and below	56	13	05	
<b>FRAP (612 μmol/L)</b>				
Above M	61	11	02	
M and below	45	15	14	*

\*indicated statistically significant differences

**Table 3** Liver function profiles in different patient categories.

Parameters	No-Hepatotoxicity (n = 106)	Mild LFT Alterations (n = 26)	Hepatotoxicity (n = 16)
<b>ALT IU/L (M ± SD)</b>			
Baseline	38 ± 11.2	38 ± 11.6	46 ± 12.2*
Peak	-	176 ± 96	670 ± 282*
<b>AST IU/L (M ± SD)</b>			
Baseline	32 ± 10.2	42 ± 12.3	51 ± 13.6*
Peak	-	192 ± 112	456 ± 274*
<b>ALP IU/L (M±SD)</b>			
Baseline	176 ± 80	183±68	180±72
Peak	-	232±102	268±126
<b>Serum Bilirubin mg/dl (M ± SD)</b>			
Baseline	0.67 ± 0.2	0.62 ± 0.23	0.69 ± 0.25
Peak	-	0.96 ± 0.6	2.36 ± 1.8*

\*Indicate statistically significant difference, student t test.

**Table 4** Distribution of patients of different groups around baseline common median values of Bilirubin and liver enzymes.

Parameters (Median value)	No-Hepatotoxicity (n = 106)	Mild LFT Alterations (n = 26)	Hepatotoxicity (n = 16)	Chi Square Analysis
<b>ALT (56 IU/L)</b>				
Baseline				
Above M	56	12	06	
M & Below	50	14	10	
Peak				
Above M	-	24	16	
M and Below	-	02	00	*
<b>AST (44 IU/L)</b>				
Baseline				
Above M	40	21	14	
M & Below	57	05	02	*
Peak				
Above M	-	26	16	
M & Below	-	00	00	*
<b>ALP (178 IU/L)</b>				
Baseline				
Above M	49	15	10	
M & Below	57	11	06	
Peak				
Above M	-	26	16	
M & Below	-	00	00	*
<b>Serum Bilirubin (0.7 mg/dL)</b>				
Baseline				
Above M	52	12	10	
M & Below	54	14	06	
Peak				
Above M	-	10	16	
M & Below	-	16	00	*

\*Indicates statistically significant differences

Higher age did not significantly associate ATT-DIH in present study, despite many such reports<sup>[23,29]</sup>. The median 47 year age indicates higher age profile of study sample than 35 year cut off used in most other reports, which may explain the divergence. Study sample also has excess four fifths comprised of male patients. No significant gender association to hepatotoxicity was manifest. Numerically the proportion of females to males in hepatotoxicity victims was 1: 3, i.e higher than overall 1: 4 proportion. Females are believed to differ from males in having lower BMI and slower pharmacokinetics including acetylation<sup>[30]</sup>, and thus at greater risk of DIH which may be more severe too.

All patients developing hepatotoxicity in our study sample complained of symptoms of hepatic illness and had liver enzyme and bilirubin alterations at instance of 1st or 2nd month monitoring which is in agreement to other reports. Shakya found median 28 days (15-61 days), latent period for occurrence of DIH after commencing ATT<sup>[31]</sup>. Mahmood *et al.*<sup>[32]</sup> reported DIH onset in most patients within 14 days of starting ATT and return of raised enzyme profiles fast in 2 weeks on withdrawing ATT. Shakya *et al.*<sup>[31]</sup> reported similar observation. In study by Makhoul *et al.*<sup>[33]</sup>, DIH occurred between 15 to 60 days (median 30 days), of initiating ATT and after stopping therapy, LFT normalized between 15 to 45 days. 72% of slow acetylators as opposed to 27% of fast acetylators exhibited raised transaminases in first week of commencing ATT<sup>[34]</sup>, but no differences occurred after 8 weeks. The duration of detection of hepatotoxicity in this study apparently exceeds the period predicable for difference of acetylator status leading to early INH toxicity. PZA toxicity occurs after longer periods of treatment. PZA hepatotoxicity, though high, are dose dependant. At 30 mg/kg prevalent dose, taken for 2 months, there are rare chances of DIH<sup>[35]</sup>. The hepatotoxicity in context is attributable primarily to INH therefore.

Both BMI and low albumin states significantly associated ATT-DIH in present study. Poor nutrition associates higher DIH risk<sup>[36,37]</sup>. ATT-DIH is increased in hypoalbuminaemia and low BMI. Protein energy malnutrition may hamper enzyme function including acetylation<sup>[38]</sup>. Poor nutrition implies lower glutathione storage and hence greater vulnerability to oxidative injury. Two thirds of subjects developing subsequent hepatotoxicity had higher than median malonaldehyde levels in contrast to even proportion among those not developing ATT-DIH. Oxidative stress is part of inflammation associated to tuberculous infection. The plasma antioxidant potential to protect organs against oxidative stress determines the extent of oxidative damage. Plasma antioxidant capacity in all patients measured as FRAP was lower than known for healthy adults, e.g. 1,000  $\mu$ moles/L. Significantly lower FRAP level prevailed in patients that suffered ATT-DIH.

Higher proportion of ATT-DIH cases had severe disease, consistent with other reports. Sputum smear positive cases are also reported to suffer more severe DIH; probably due to release of toxic contents of killed heavy bacterial load<sup>[39]</sup>. The ongoing immune inflammatory responses of tuberculous infection cause cachexia<sup>[40]</sup>. The disease sets in vicious circle of oxidative damage and nutrient erosion. Liver, the drug metabolizing high activity organ must bear the brunt of free radical damage. Slower drug metabolizing trait and high dose of ATT in relation to body weight may as well be important risk factor for hepatotoxicity<sup>[41]</sup>.

Serum levels of liver enzymes ALT and AST were significantly higher, although within normal limits, at baseline estimates in patients that developed hepatotoxicity. This observation suggests ability of ALT AST profiles to mark tuberculosis patients at increased risk of ATT-DIH even before starting therapy. Neither ALP nor serum

bilirubin profiles at baseline carried such hint. ALP primarily rises following cholestasis and bilirubin does not rise before significant liver damage has already occurred. The baseline imbalance of oxidative stress and deficient antioxidant status imparts vulnerability to develop ATT-DIH. Majority of ATT-DIH patients displayed lower normal values of baseline eGFR in significant contrast to other patients. Decline in renal function therefore indicates as risk factor.

## CONCLUSION AND EPILOGUE

The study findings collectively emphasize poor nutrition and extensive disease as evident risk factors for ATT-DIH. Their co-existence with subclinical elevations in ALT and AST liver enzyme levels should cause alarm. It implies serious cognizance and correction of nutritional deficit and intensive monitoring of liver function at fortnight, first month and second month of starting DOTS. Patients with baseline elevation of enzyme profile should be prescribed non-hepatotoxic ATT. Renal function declines should also caution on increased risk of ATT-DIH.

Mild liver dysfunction (less than 5 fold ALT/AST rise and no symptoms), occurs in 20% of patients<sup>[19]</sup>. It is found to be reversible even on continuing treatment<sup>[42]</sup>. Severe liver disease occurs in 1 to 3% of patients but in India reported rates are 8 to 39%<sup>[43]</sup>. If that goes undetected, liver failure would occur and death unless liver transplant is an option.

Available guidelines indicate baseline LFT before starting ATT. Routine (regular) measurement of hepatic function during treatment is indicated in patients showing baseline abnormalities and those with documented viral hepatitis B or C or alcohol abuse<sup>[44,45]</sup>. Early identification may offer scope for applying interventions to improve prognosis. Other studies have confirmed such benefit of regular monitoring<sup>[46,47]</sup>. Rapid increase of ALT implies need to investigate viral hepatitis and toxicity to any other drugs and more frequent monitoring, e.g. on fortnightly basis. For patients with abnormal liver function at baseline, ATT be not started till normalization with rest, diet and hepatoprotective therapies.

Yet there is no consensus on frequency of LFT monitoring in ATT<sup>[48]</sup>. American thoracic society recommends monitoring every 2 to 4 weeks for patients at risk. JTC-British thoracic society<sup>[45]</sup> recommends monitoring every week for first 2 weeks, then every 2 weeks for 2 months. In Chinese, national programme, LFT done at baseline and after 2 months of starting ATT<sup>[49]</sup>. Standard approach to ATT-DIH is to stop INH if ALT raises at least 3 fold over UNL along with jaundice and/or symptoms of hepatic illness. In absence of symptoms ALT rise 5 times is deciding factor<sup>[50]</sup>. When ALT does not recover following ATT withdrawal, detailed investigations for autoimmune disease are indicated. Restoring of ATT depends on risk benefit assessment, which would mandate frequent liver function monitoring as errant drug is very likely to inflict injury again.

## REFERENCES

- 1 Pandit A. Tuberculosis: A basic discourse Apollo medicine, 2016; **13**: 86-90.
- 2 Pandit A. Tuberculosis control: Perspective and programmes, *Mintage Journal of Pharmaceutical and Medical Research*, 2016; **5**: 7-10.
- 3 Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients, *N Engl J Med* 2000; **342**(17): 1266-71. [PMID: 10781624 DOI: 10.1056/NEJM200004273421707]
- 4 Chitturi S, Ferrell G. Drug induced liver disease. In Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of Liver*, 9th ed.

- Philadelphia. *Lippincott Williams and Wilkins* 2002; 1059-1128.
- 5 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**(2): 284-289. [PMID: 830577]
  - 6 Kulkarni A, Madras NA. Relationship of nitric oxide and protein carbonyl in tuberculosis. *Indian J Tuberc* 2008; **55**(3): 138-44. [PMID: 18807745]
  - 7 Rai RR, Phadke MS. Plasma oxidant-antioxidant status in different respiratory disorders. *Indian J Clin Biochem* 2006; **21**(2): 161-164. [PMID: 23105636 PMCID: PMC3453974 DOI: 10.1007/BF02912934]
  - 8 Mitchell JR, Thorgeirsson UP, Black M, Timbrell JA, Snodgrass WR, Potter WZ, Jollow HR, Keiser HR. Increased incidence of isoniazid hepatitis in rapid acetylators: possible relation to hydrazine metabolites. *Clin Pharmacol Ther*, 1975; **18**(1): 70-79. [PMID: 1149365]
  - 9 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**(6): 1072-1075. [PMID: 3717759 DOI: 10.1164/arrd.1986.133.6.1072]
  - 10 Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis*. 1978; **117**(6): 991-1001. [PMID: 666111 DOI: 10.1164/arrd.1978.117.6.991]
  - 11 Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis*. 1992; **145**: 494-497. [PMID: 1736764 DOI: 10.1164/ajrccm/145.2\_Pt\_1.494]
  - 12 Byrne JA, Strautnieks SS, Mieli-Vergani G, Higgins CF, Linton KJ, Thompson RJ. The human bile salt export pump: characterization of substrate specificity and identification of inhibitors. *Gastroenterology* 2002; **123**(5): 1649-1658. [PMID: 12404239]
  - 13 Martínez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine (Baltimore)* 1999; **78**(6): 361-369. [PMID: 10575418]
  - 14 Rae JM, Johnson MD, Lippman ME, Flockhart DA. Rifampin is a selective, pleiotropic inducer of drug metabolism genes in human hepatocytes: studies with cDNA and oligonucleotide expression arrays. *J Pharmacol Exp Ther* 2001; **299**(3): 849-857. [PMID: 11714868]
  - 15 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**(44): 998-999. [PMID: 12455909]
  - 16 Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003 Jul 31; **349**(5): 474-85. [PMID: 12890847 DOI: 10.1056/NEJMra021844]
  - 17 Ferrell GC. Drug induced liver disease, Edinburgh. *Churchill Livingstone* 1993. P 1-673.
  - 18 Sharma SK, Mohan A. Antitubercular drug induced hepatotoxicity. In Venkataraman GS ed. *Medicine Update*, Vol. 14 Mumbai. Association of Physicians of India, 2004 p 298-306.
  - 19 Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, Fujiwara P, Grzemska M, Hopewell PC, Iseman MD, Jasmer RM, Koppaka V, Menzies RI, O'Brien RJ, Reves RR, Reichman LB, Simone PM, Starke JR, Vernon AA; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society: Treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003; **167**(4): 603-62. [PMID: 12588714 DOI: 10.1164/rccm.167.4.603]
  - 20 Sangeetha P, Das UN, Koratkar R, Suryaprabha P. Increase in free radical generation and lipid peroxidation following chemotherapy in patients with cancer. *Free Radic Biol Med* 1990; **8**(1): 15-19. [PMID: 2157633]
  - 21 Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power" the FRAP assay. *Anal Biochem* 1996; **239**(1): 70-76. [PMID: 8660627 DOI: 10.1006/abio.1996.0292]
  - 22 Leavy AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol*. 2000; **11**: A0828.
  - 23 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**(7): 916-919. [PMID: 12359646 DOI: 10.1164/rccm.2108091]
  - 24 Mehta S. Malnutrition and drugs: clinical implications. *Dev Pharmacol Ther* 1990; **15**(3-4): 159-165. [PMID: 2129200]
  - 25 Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; **51**(2): 132-136. [PMID: 8711642 PMCID: PMC473016]
  - 26 Gangadharam PR. Isoniazid, rifampin, and hepatotoxicity. *Am Rev Respir Dis* 1986; **133**(6): 963-965. [PMID: 3013057 DOI: 10.1164/arrd.1986.133.6.963]
  - 27 Garg PK, Tandon RK. Antituberculosis treatment induced hepatotoxicity, in Sharma SK, Mohan A, eds. *Tuberculosis*. 2nd ed. New Delhi, Jaypee Bros Medical Publ. 2009; 783-795
  - 28 Anand CAC. Risk Factors of Hepatotoxicity during Anti-tuberculosis treatment. *MJAFI (Medical Journal of the Armed Forces India)* 2006; **62**: 45-49.
  - 29 Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury-I, Performance characteristics of laboratory tests. *Clin Chem* 2000; **46**(12): 2027-2049. [PMID: 11106349]
  - 30 Marvin W. Impacts of gender on drug responses. *Drug Top* 1998; 591-600
  - 31 Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. *Ann Pharmacother* 2004; **38**(6): 1074-1079. [PMID: 15122004 DOI: 10.1345/aph.1D525]
  - 32 Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B, Salkeen S. Hepatotoxicity with Antituberculosis Drugs: The risk factors. *Pak J Med Sci* 2007; **23**: 33-38
  - 33 Makhlof 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 Int*. 2008; **2**(3): 353-360. [PMID: 19669265 PMCID: PMC2716885 DOI: 10.1007/s12072-008-9085-y]
  - 34 Grönhagen-Riska C, Hellstrom PE, Fröseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. *Am Rev Respir Dis* 1978; **118**(3): 461-466. [PMID: 707874 DOI: 10.1164/arrd.1978.118.3.461]
  - 35 Girling DJ. Adverse effects of antituberculosis drugs. *Drugs*. 1982; **23**(1-2): 56-74. [PMID: 6459920]
  - 36 Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy, Clinical profile and reintroduction of therapy. *J Clin Gastroenterol* 1996; **22**(3): 211-214. [PMID: 8724260]
  - 37 Krishnaswamy K, Prasad CE, Murthy KJ. Hepatic dysfunction in undernourished patients receiving isoniazid and rifampicin. *Trop Geogr Med* 1991; **43**(1-2): 156-60. [PMID: 1750106]
  - 38 Buchanan N, Eyberg C, Davis MD. Isoniazid pharmacokinetics in Kwashiorkor. *S Afr Med J* 1979; **56**(8): 299-300. [PMID: 550491]
  - 39 Paton NI, Chua YK, Earnest A, Chee CB. Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting. *Am J Clin Nutr*. 2004; **80**(2): 460-465. [PMID: 15277171]
  - 40 Burman WJ, Reves RR. Hepatotoxicity from rifampin plus pyrazinamide: lessons for policymakers and messages for care providers. *Am J Respir Crit Care Med* 2001; **164**(7): 1112-1113. [PMID: 11673194 DOI: 10.1164/ajrccm.164.7.2109052]

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- 41 Pandit A. Treatment outcomes in tuberculosis at TB/DOTS unit of tertiary care centre. *Mintage Journal of Pharmaceutical and Medical Research* 2016; **5**: 15-16
- 42 Tost JR, Vidal R, Caylà J, Díaz-Cabanela D, Jiménez A, Broquetas JM, Study Group for Severe Hepatotoxicity due to Anti-tuberculosis Drug. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. *Int J Tuberc Lung Dis.* 2005; **9(5)**: 534-40. [PMID: 15875925]
- 43 Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991; **99(2)**: 465-71. [PMID: 1824929]
- 44 [No authors listed] Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society, *Thorax.* 1998; **53(7)**: 536-48. [PMID: 9797751 PMCID: PMC1745276]
- 45 Migliori GB, Raviglione MC, Schaberg T, Davies PD, Zellweger JP, Grzemska M, Mihaescu T, Clancy L, Casali L. Tuberculosis management in Europe. Task Force of the European Respiratory Society (ERS), the World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region, *Eur Respir J.* 1999; **14(4)**: 978-992. [PMID: 10573254]
- 46 Agal S, Baijal R, Pramanik S, Patel N, Gupte P, Kamani P, Amarpurkar D. Monitoring and management of antituberculosis drug induced hepatotoxicity. *J Gastroenterol Hepatol.* 2005; **20(11)**: 1745-1752. [PMID: 16246196 DOI: 10.1111/j.1440-1746.2005.04048.x]
- 47 Byrd RB, Horn BR, Solomon DA, Griggs GA. Toxic effects of isoniazid in tuberculosis chemoprophylaxis. Role of biochemical monitoring in 1,000 patients. *JAMA* 1979; **241(12)**: 1239-1241. [PMID: 762788]
- 48 Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, Gordin FM, Nunes D, Strader DB, Bernardo J, Venkataramanan R, Sterling TR; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Sub-committee, An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174(8)**: 935-52. [PMID: 17021358 DOI: 10.1164/rccm.200510-1666ST]
- 49 Xia YY, Hu DY, Liu FY, Wang XM, Yuan YL, Tu DH, Chen YX, Zhou L, Zhu LZ, Gao WW, Wang HY, Chen da F, Yang L, He PP, Li XT, He YJ, Sun F, Zhan SY. Design of the anti-tuberculosis drugs induced adverse reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS). *BMC Public Health.* 2010; **21(10)**: 267. [PMID: 20492672 PMCID: PMC2893093 DOI: 10.1186/1471-2458-10-267]
- 50 Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria, *Am J Respir Crit Care Med* 2016 Jun 22. [PMID: 27331880 DOI: 10.1164/rccm.201602-0402OC]

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