

# Effects of Intensive Phase Antituberculous Therapy on Hepatic and Haematological Parameters in Patients at the University Teaching Hospital in Lusaka, Zambia

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## ABSTRACT

**Objectives and study design:** Zambia is a high tuberculosis burden country. Antituberculous medicines are the mainstay of tuberculosis management. There have been several reports of antituberculous drug-related haematological and hepatic adverse effects noted in other settings. Adverse events have healthcare cost and morbidity implications. Prevalence and severity of these adverse effects is understudied in patients at University Teaching Hospitals hence the purpose of this study was to identify haematological and hepatic abnormalities and compare parameters before treatment and after completion of intensive phase among the patients. Factors associated with abnormalities were also determined. A prospective longitudinal study was undertaken at Chest Clinic between April 2018 and July 2018. Study patients were followed up for 2 months. Full blood count and liver function tests were recorded at base-line and at follow-up. Abnormalities were defined according to 2017 Department of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events. Data were analysed using SPSS version 22.0 Paired t-test and Wilcoxon matched - pairs signed rank test were used to compare parameters. Logistic regression was performed to determine factors that were predictive of abnormalities. A  $p < 0.05$  was considered statistically significant.

**Results:** A total of 37 patients were involved in the study. 56.8% of patients were male. Mean age of patients was 36.2 years (19 – 57 years) while body mass index was 21.9 kg/m<sup>2</sup>. Only 37.8% of patients were sputum smear positive at baseline. 56.8% of patients had HIV co-infection. 45.9% of patients were on antiretroviral therapy. 45.2% of patients had grade 1-3 aspartate transaminase derangements at follow-up compared to 29.7% at baseline. 5.4% of the patients had grade 1-3 alanine transaminase derangements at

baseline while 9.7% of patients had grade 1 at follow-up. Fewer patients (16.1%) had grade 1-2 anaemia at follow-up while 62.2% of patients at baseline had grade 1-4 anaemia. More patients (46.2%) had platelet derangements at follow-up compared to 25.8% at baseline. Fewer patients had differential white cell count derangements at follow-up compared to baseline. Statistically significant differences in haematological parameters: haemoglobin concentration, haematocrit, red, and white cell, eosinophil and neutrophil counts at baseline and follow-up were found. However, no statistical significant differences in red cell indices were observed. Changes in alanine transaminase levels at baseline and follow-up were statistically significant. Logistic regression was performed to determine the effects of age, gender, body mass index, HIV infection, antiretroviral therapy, sputum smear status, and appropriate baseline full blood count/liver function test parameters on the likelihood of study patients having deranged haemoglobin concentration, white cell count and alanine transaminase at follow-up. Logistic regression models to predict deranged haemoglobin concentration and white cell count were statistically insignificant. None of the predictor variables were associated with likelihood of derangements in alanine transaminase.

**Conclusion:** Findings of this study show that haematological and hepatic adverse effects were relatively fewer at follow-up and were mostly grades 1-3 in severity. Antituberculous therapy is relatively safe for patients during the initial phase.

**Keywords:** Adverse effects, antituberculous, haematological, hepatic, initial phase, intensive

## INTRODUCTION

In spite of the gradual reduction in the prevalence rate of tuberculosis (TB) since the 1990s<sup>[1]</sup>, one third of the world's population is still known to be infected with tubercle bacilli which can become active disease when conditions are favourable<sup>[2,3]</sup>. Zambia is amongst the top 30 countries with a high per capita burden of TB, with its prevalence at 319/100000 in individuals aged 15 years and older<sup>[3]</sup>.

First-line antituberculous medicines have been a successful mainstay of the treatment of drug-susceptible tuberculosis. However, these medicines are associated with several adverse effects. Haematological disorders and hepatotoxicity are among the widely reported adverse effects. For instance, Morris et al., reported that haematological and biochemical abnormalities were common among TB patients on antituberculous therapy in Mumbai<sup>[4]</sup>. These adverse effects may cause significant morbidity and compromise treatment regimens<sup>[5]</sup>. They may also lead to use of less active and occasionally more toxic medicines<sup>[6,7]</sup>. Adverse effects can also result in increased treatment costs, hospital visits and hospitalizations<sup>[5]</sup>.

A rise in the liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are a common adverse effect leading to termination of therapy in patients treated with isoniazid, rifampicin and pyrazinamide<sup>[6]</sup>. When the serum liver enzyme concentration is less than 3 times above the upper limit, the drugs may be continued and patient monitored closely. If the liver enzyme concentration is 3 times above the upper limit and patient has symptoms of hepatotoxicity such as nausea, vomiting and jaundice, the drugs are withdrawn and reintroduced one by one when the liver enzymes revert to normal. The reintroduction starts with the least hepatotoxic drug. If hepatotoxicity recurs after initiation of a particular drug, the drug is permanently withdrawn. However, treatment with less than four drugs may delay time to smear conversion<sup>[8]</sup>.

Some studies have shown that antituberculous drugs induce haematological and hepatic abnormalities<sup>[9]</sup>. Hepatic abnormalities are amongst the common documented adverse effects<sup>[10-12]</sup> while haematological abnormalities are rare but both are serious adverse effects<sup>[13]</sup>.

There is variation in the reported prevalence of antituberculous therapy - related abnormalities in hepatic and haematological parameters and their associated risk factors. Variation in risk factors has been observed in different races. At the University Teaching Hospitals in Lusaka, there was no data on these adverse effects and the associated risk factors. Consequently, patients at higher risk of developing these abnormalities may not have been identified. Non identification of such patients could lead to poor outcomes of therapy including prolonged hospital stay, morbidity and mortality. Occurrence of adverse effects may lead to, increased healthcare costs, increased default rates and development of resistance to antituberculous therapy.

## MATERIALS AND METHODS

A prospective longitudinal study was done where study subjects were reviewed before commencing antituberculous therapy and at the end of two months. Patients' demographic information such as age, weight and gender were recorded. Venous blood samples were drawn from patients before initiation of the antituberculous medicines for full blood count (FBC) and liver function tests (LFTs) namely ALT and AST. Sputum samples were also obtained for direct microscopy. Patients' sputum smear status along with HIV status and current therapy were recorded.

The patients were then initiated on antituberculosis medicines. After two months, venous blood samples were again collected for FBC and LFTs. Clinical laboratory test results were noted.

The Department of AIDS (DAIDS) (Version 2.1 – March 2017) adverse events grading system shown in table 1 was used to grade the severity of the abnormalities<sup>[14]</sup>.

Data were analysed using GraphPad Prism version 8.0.1 (GraphPad Software Inc., La Jolla, CA, USA). Continuous variables such as age, hepatic and haematological parameters were expressed as mean with standard deviation or median. Categorical parameters such as sputum smear status, HIV status, HIV treatment status and gender were expressed as proportions and percentages.

The hepatic and haematological parameters at baseline and follow-up were compared using paired t - tests for normally distributed continuous variables and Wilcoxon matched - pairs signed rank test for non - normally distributed continuous

variables. Shapiro - Wilk test was used to test for normality of the data distribution. The ROUT (robust regression followed by outlier identification) method was used to detect outliers with Q (maximum desired false discovery rate) set to 1 per cent. Significant outliers were excluded from the data set and the results of the analyses of data without outliers were also reported. Binary logistics regression was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) to determine the effects of age, gender, BMI, HIV infection, ART, sputum smear status, and appropriate baseline FBC/LFT parameters on the likelihood of study patients having deranged Hb, WCC and ALT at follow-up. A p value < 0.05 was considered statistically significant.

### MAIN STUDY FINDINGS

A total of 37 patients were included in this study. 21 (56.8 percent) patients were male. The mean age of the patients was 36.2 years (19 - 57 years) while their mean BMI was 21.9 kg/m<sup>2</sup> (17 - 29.3kg/m<sup>2</sup>). Only 14 (37.8 percent) patients were sputum smear positive at baseline. 21 (56.8%) patients had HIV co-infection. Only 17 (45.9 percent) patients were on ART.

Increase in the proportion of patients with elevated ALT (grades 1 - 3) was noted, the number at baseline was 2 (5.4%) and 6 (16.2%) at follow - up the elevation was statistically significant (p= 0.025). There was also an increase in the proportion of patients with raised AST (grades 1-3) at follow- up. The values being 11 (29.7%) at baseline and 15 (40.5%) at follow, however, the increase was not statistically significant (p= 0.895). More patients had anaemia and leukopenia (grade 1 - 4) before drug therapy 23(62.2%) and 2 (5.4%) respectively compared to follow - up 5(13.5%) and 0% respectively. The raise in haemoglobin concentration and decrease in white cell count were statistically significant (p< 0.0001 and p= 0.006 respectively). The proportion of patients with thrombocytopenia increased at follow - up 6 (16.2%) at baseline and 13 (35.1%) at follow - up, however, the decrease in platelet count was not statistically significant (p= 0.127).

Age, sex, baseline hepatic and haematological parameters and BMI were not found to be associated with hepatic or haematological abnormalities.

### DISCUSSION

The study showed that the majority of TB patients were young adults with a mean age of 36.2 years and age range of 19 - 57 years signifying the most productive population. This is similar to the findings by Bashir et al. and Kassa et al. whose studies included patients with mean age of 33 and 34.8 years, respectively <sup>[9,15]</sup>. Yaranal et al. undertook a study in patients with a mean age of 41 years <sup>[16]</sup>. The reasons for the higher prevalence of TB in the young adult age group could be due to HIV infection, a known immunosuppressant which is also more prevalent in this age group <sup>[17]</sup>. In addition, younger adults could be exposed to other factors that might predispose them to TB infection such as tobacco smoke and overcrowded environments.

Most of the patients were males accounting for 56.8 percent. A similar finding has been reported by several other studies <sup>[15,16,18,19]</sup>. The findings of the present study are, however, different from those described by Marra et al. who included an equal number of male and female patients in their study <sup>[20]</sup>. The findings of the present study with respect to gender distribution are also similar to those reported by the Zambia TB prevalence survey which found more males with tuberculosis <sup>[17]</sup>. The similarity of the findings could be due to the fact that globally, more men have TB <sup>[21]</sup>. Nhamoyebonde and Leslie contend that the relationship between male sex and tuberculosis risk is less clear and is likely to involve a highly complex network of factors <sup>[21]</sup>. The differences in the findings may be because the degree of male bias varies by geographic location and by year, however, the overall trend is clear, and of the 20 high-burden countries for which data are available, more males have been recorded to have TB <sup>[21]</sup>.

A large number of the patients (56.8 percent) had HIV co - infection as highlighted by the Zambia TB prevalence survey. This could be due to lowered immune function among HIV patients which leads to activation of latent tuberculosis as HIV infection causes suppressed cell - mediated immunity <sup>[22]</sup>. The majority of patients (62.2 percent) had sputum smear negative tuberculosis. Montales et al. explain that HIV co-infection may alter the pathogenesis of tuberculosis and lead to negative sputum smear results <sup>[23]</sup>.

Tuberculosis generally presents with constitutional signs and symptoms such as cough which may be dry initially then productive later, night sweats, loss of appetite and weight loss. Therefore, it is anticipated that TB patients may have lower BMIs. The present study found that patients' BMI ranged from 17 Kg/m<sup>2</sup> to 29.3 Kg/m<sup>2</sup> with a mean BMI of 21.9 Kg/m<sup>2</sup>. These findings are similar to those reported by Abera et al. who found a mean BMI of 20.6 Kg/m<sup>2</sup> with a range of 17.08 Kg/m<sup>2</sup> to 24.06 Kg/m<sup>2</sup> [12]. The results of the present study, however, are in contrast to those found by Hassen Ali et al. and Nagu et al. where the majority of the patients (81.8 percent and 51 percent, respectively) had BMI less than 18.5 Kg/m<sup>2</sup> [11,24].

In the present study, more patients had elevated ALT and AST levels at follow-up (Table ). These findings are different from those highlighted by Hassen Ali et al and Shang et al. [11,25]. In these two studies, only patients with normal baseline ALT and AST levels were enrolled. Hassen Ali et al found that 61.5% of the patients had elevated ALT at follow-up and 11.1% had elevated AST(11) and Shang et al. found 4.73% had elevated ALT at follow-up and 1.3% had elevated AST respectively[25]. The difference in the findings could be due to the fact that the study undertaken by Hassen Ali et al. had a larger sample size. Shang et al., found that the proportion of patients with elevated ALT was lower than that of the present study[25]. This could be because of differences in the metabolism of isoniazid as slow metabolizers are prone to hepatic abnormalities and fast metabolizers are less prone [26].

The findings of the present study show a decrease in the proportion of patients with anaemia at follow-up (13.5 percent) compared to 62.2 percent at baseline. This is in contrast with the findings of Enoh et al. and Kassa et al. who found that 37.1 percent and 72 percent of patients had anaemia at follow-up, respectively [9,19]. The differences in the findings could be due to differences in patients' genetic predisposition to adverse effects due to variable metabolism of antituberculous drugs in the different settings. Patients' anaemia in the current study improved as they may have had anaemia of chronic illness which improved as the infection resolved [15]. In the studies conducted by Enoh et al. and Kassa et al. the increase in the proportion of patients with anaemia at follow-up was attributed to the adverse effect of antituberculous drugs.

The present study did not find any association between age, gender, HIV status, HIV treatment status, BMI, sputum smear status and baseline ALT with the increase in ALT level at follow-up. These findings are similar to those reported by Abera et al. who found that age, gender and nutritional status were not associated with elevated liver enzymes [12]. The findings of the present study were, however, different from the findings of numerous other studies which found that age above 60 years was associated with increase in the ALT levels [5,6,20,27], although none of the patients in the current study was above 60 years old. Marra et al. also found that higher baseline ALT levels were associated with elevated ALT levels at follow-up [20]. Hassen Ali et al. established that lower BMI was a predictor of elevated ALT levels [11] whereas An et al. stated that female sex was associated with deranged ALT levels [10]. The differences in the findings of the present study and those of the other studies could be due to the fact that the oldest patient in the study was 57 years and as a consequence, none of the patients were above 60 years.

Although it is expected that the findings of the present study would be similar to those reported by other studies undertaken among African patients, who are generally considered slow acetylators of isoniazid and prone to developing isoniazid-induced hepatotoxicity which is characterised by raised liver enzymes [26], the findings of this study were contrary to this assertion.

The differences in the findings were probably due to the use of different study designs, however, the results of the current study would be expected to be similar to those found by Ekhabbazi et al. who carried out a prospective longitudinal study [28] like the present study but they found that age, gender, HIV status and baseline transaminase level were associated with elevated liver enzymes. The findings of a cohort study undertaken by Abera et al. in Ethiopia [12] were similar to those of the present study.

Regarding limitations of the study, one patient was lost to follow hence there was missing data which was not included in the data analysis. Data analysis was only carried out on complete paired data.

The researcher had no control on influence of other drugs taken by patients during follow-up which might affect hepatic and haematological parameters including other unidentified confounders.

The effects of individual antituberculous drugs on hepatic and haematological parameters were not explored.

## CONCLUSION

The use of intensive phase antituberculous drugs was associated with haematological abnormalities such as anaemia (grade 1-3), leukocytosis and thrombocytopenia (grade 1-3) and elevation in ALT and AST levels. Statistically significant differences in haemoglobin concentration ( $p < 0.0001$ ), white cell count ( $p = 0.006$ ) and ALT level ( $p = 0.025$ ) were observed. However, the proportion of patients with derangements in haemoglobin level and white cell count decreased at follow-up. Factors such as age, gender, BMI, HIV infection, ART, sputum smear status, and appropriate baseline FBC/LFT parameters did not predict the likelihood of ALT derangements at follow-up. Based on the findings of this study, antituberculous drugs are safe for use in Zambian patients however, close monitoring is required for patients with initial mild elevation in liver enzymes.

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**TABLES AND FIGURES**

**Tables**

**Table 1: The 2017 DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events**

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
ALT/AST, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Hemoglobin, Low (g/dL) ≥ 13 years of age (male only)	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
≥ 13 years of age (female only)	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
WBC, Decreased (cells/L) > 7 days of age	2.000 x 10 <sup>9</sup> to 2.499 x 10 <sup>9</sup>	1.500 x 10 <sup>9</sup> to 1.999 x 10 <sup>9</sup>	1.000 x 10 <sup>9</sup> to 1.499 x 10 <sup>9</sup>	< 1.000 x 10 <sup>9</sup>
Platelets, Decreased (cells/L)	100 x 10 <sup>9</sup> to < 125 x 10 <sup>9</sup>	50 x 10 <sup>9</sup> to < 100 x 10 <sup>9</sup>	25 x 10 <sup>9</sup> to < 50 x 10 <sup>9</sup>	< 25 x 10 <sup>9</sup>

**Table 2: Summary of patient demographics.**

Gender	N (%)
Male	21 (56.8)
Female	16 (43.2)
Sputum smear status at baseline	
Positive	14 (37.8)
Negative	23 (62.3)
HIV status	
Positive	21 (56.8)
Negative	16 (43.2)
HIV treatment status	
On ART	20 (54.1)
Not on ART	17 (45.9)

**Table 3: Haematological and hepatic abnormalities among patients**

Parameter (grade)	Baselinen (%)	Follow-upn (%)
Normal ALT level	35 (94.6%)	31 (83.8%)
Increase in ALT level (grade 1- 3)	2 (5.4%)	6 (16.2%)
Normal AST level	26 (70.3%)	22 (59.5%)
Increase in AST level (grade 1-3)	11 (29.7%)	15 (40.5%)
Normal Hb level	14 (37.8%)	32 (86.5%)
Anaemia (grade 1-4)	23 (62.2%)	5 (13.5%)
Normal Platelet count	21 (56.8%)	24 (64.9%)
Thrombocytopenia (grade 1-4)	6 (16.2%)	13 (35.1%)
Thrombocytosis	10 (27%)	0 (0%)
Normal white cell count	29 (78.4%)	36 (97.3%)
Leukopenia (grade 1 – 4)	2 (5.4%)	0 (0%)
Leukocytosis	6 (16.2%)	1 (2.7%)

**Table 4a: Differences in haematological parameters among patients at baseline and follow-up (paired samples t-tests)**

Parameter	No. of pairs	Baseline Mean (SD)	Follow-up Mean (SD)	t (95% CI)	P value
Haemoglobin concentration (g/dl)	37	9.51 (3.25)	12.37 (1.67)	-5.59 (-3.89 - -1.83)	< 0.0001
Platelet count (x 10 <sup>9</sup> /L)	37	309.17 (169.2)	255.79 (125.89)	1.562 (-13.78 – 106.16)	0.127
White cell count (x 10 <sup>9</sup> /L)	37	7.26 (3.53)	5.33 (1.89)	2.93 (0.60 -3.27)	0.006

**Table 3b: Differences in hepatic parameters among patients at baseline and follow-up (Wilcoxon signed rank test)**

Parameter (units)	No. of pairs	Baseline Median	Follow-up Median	Z	P value
ALT level (IU/L)	37	18.4	26.7	-2.225	0.025
AST level (IU/L)	37	34.5	35.0	-1.075	0.896