



**PATTERNS AND CLINICAL CHARACTERISTICS OF PATIENTS ADMITTED WITH
ANTI-TB DRUG INDUCED LIVER INJURY AT THREE HOSPITALS IN ADDIS
ABABA, ETHIOPIA FROM JANUARY 2014-APRIL 2019**

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A thesis presented in Partial Fulfillment of specialty certificate in Internal
Medicine submitted to St. Paul's Hospital Millennium Medical College,
department of Internal Medicine

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**August 2019,
ADDIS ABABA,
ETHIOPIA**

Acknowledgement

My deepest gratitude goes to my clinical and public health advisors Dr. Yemisrach Chanie and Mr. Tewodros Fantahun, respectively for their support and guidance in doing this research. I thank the research office of SPHMMC for giving me this chance to do this research; I am also grateful to my colleagues who provided me with supportive ideas in proceeding with it.

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Acronyms

ALF-acute liver failure

ALP- alkaline phosphatase

ALT- alanine amino transferase

AST- aspartate amino transferase

ATS- American thoracic society

ATT- anti tuberculous treatment

DIH-drug induced hepatitis

DILI- Drug induced liver injury

EPTB- extra pulmonary TB

HBV- hepatitis B virus

HBVsAg- hepatitis B virus surface antigen

HIV- Human immune deficiency

INH- isoniazid

IQR-interquartile range

LFT- liver function test

MDR- multi drug resistant

PTB- pulmonary TB

PZA- pyrazinamide

RIF-rifampicin

SPHMMC- Saint Paul hospital millennium medical college

ULN-upper limit normal

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ABSTRACT

Background: New cases of TB-infected individuals are treated by a combination of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (E). However, a variety of adverse reactions of these drugs have been reported; one of the well-known toxic effects is hepatotoxicity. Little is known about the development of hepatotoxicity in TB. Because LFT is not routinely repeated following initiation of anti-TBs, patients with asymptomatic hepatotoxicity might have been missed and detected late after overt hepatotoxicity. There are only limited number of studies on anti TB drug hepatotoxicity in Ethiopia and this study will address the patterns of clinical characteristics of patients with anti TB drug induced liver injury.

Objective: To assess the patterns and clinical characteristics of patients admitted with anti TB drug induced liver injury in the medical wards at SPHMMC, St. Peter and Zewditu hospitals from January 2014-April 2019.

Method- A hospital based retrospective chart review study was conducted by reviewing charts of patients admitted with anti TB drug induced liver injury or who developed it after admission at medical wards of SPHMMC, St. Peter and Zewditu hospitals from January 2014 to April 2019. Charts of all patients with anti TB drug induced liver injury in the study period were reviewed. Data was collected using structured check list and entered into a computer using Statistical Package for Social Science (SPSS) software version 25. Descriptive statistics were used to summarize sociodemographic and clinical characteristics of the patients.

Result- Among 158 consecutive patients analyzed with anti TB DILI, the mean age was 39.7 yrs. There were 81 (51.3%) HIV positive and 77(48.7%) HIV negative patients with anti TB DILI. There were 16(10.1%) patients with HBV infection and 2 HCV infection. All patients took RHZE regimen and the minimum time to develop DILI was 1 week and the maximum was 12 weeks. The mean time was 2.82 weeks. Among the symptomatic patients, nausea and vomiting was the most common complaint (49.4%). There were 83 (52.5%) patients who developed jaundice and the time to develop it ranged from 1 week to 8 weeks, the mean time being 2.36 weeks. Anti TB drug was discontinued for 86(54.4%) patients and 75 of them showed clinical and biochemical improvement. Anti TB was restarted for 77(48.7%) of patients and the mean time it took was 10.47 days.

Conclusion- Anti TB drug induced hepatotoxicity continues to be a major problem among hospitalized patients taking the drug. Proper clinical and laboratorial monitoring of such patients starting from the early phases of treatment eases the detection of the problem before severe injury.

Key words: anti TB drugs; admitted patients with anti TB DILI; clinical characteristics.

1. INTRODUCTION

1.1. BACKGROUND

Tuberculosis (TB) continues to remain a significant infectious disease across much of the world. It poses a formidable socioeconomic burden on the individual and on the society. TB is a global public health priority, with 10.4 million people developing the disease in 2016 (10% among HIV co-infected individuals), 1.67 million deaths and 490 000 multidrug-resistant (MDR) plus an additional 110000 rifampicin-resistant cases. (1)

New cases of TB-infected individuals are treated by a combination of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol. (2) However, a variety of adverse reactions of these drugs have been reported; one of the well-known toxic effects is hepatotoxicity. (3)

Antituberculosis-drug-induced liver injury (anti-TB-DILI) may result from the direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature. (4)

ATT related hepatotoxicity ranges from hepatic adaptation to hepatocellular injury to acute hepatic failure. (5)

Asymptomatic transaminase elevations are common during ATT, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time. (6)

The most accepted and detailed document on ATT-induced DILI is provided by American Thoracic Society (ATS). ATS recognized risk factors that predispose patients to develop ATT-induced DILI include: Chronic ethanol consumption, Viral hepatitis, Pre-existing liver disease, Pregnancy/3 months post-partum, Concomitant hepatotoxic medications, baseline abnormal ALT/AST/Bilirubin, Concomitant HIV and age >35 years. (7)

It has been suggested that AIDS is significantly associated with development of hepatotoxicity. However, the reason for this association is currently unknown, but may reflect disease-induced alterations in bio activation or detoxification of reactive metabolites, as well as immune dysregulation. (8,9)

1.2. STATEMENT OF THE PROBLEM

Hepatotoxicity is one of the most important adverse drug reactions associated with anti-tuberculosis drugs that may limit their use.(10)

Literature reveals that rate of DILI during standard multidrug treatment ranges from 2.3% to 28% world over.(11) Hepatotoxicity caused by anti TB drugs due to the combined use of several medications and long therapy duration has been a major concern of clinical treatment. The risk of DILI is considerably higher for patients receiving the HRZE regimen than for those receiving single treatment. (12)

The reported mortality from DILI after the development of jaundice varies from 4% to 12%. (13)

It is to be noted that the frequency of anti TB DILI in different countries varies widely from 2% to 39 %.(14)

In resource limited countries, like Ethiopia, regular clinical and biochemical monitoring of pts after anti TB drugs initiation is not routinely practiced and when they develop hepatotoxicity, diagnosis usually is late, making the presentation fatal. It also has socioeconomic cost while monitoring them for the liver insult response so as to reinstitute the ATT drugs. Identifying risk factors might help prevent or monitoring patients more closely and it might decrease the burden related to hepatotoxicity. In Ethiopia, there are only few studies on anti TB DILI which are done on both retroviral infected and non-infected patients taking ATT and further studies should be done so as to prevent the hepatotoxicity early and identify associated risk factors for its development.(15)

2. Literature Review

2.1. Literature review

There is no universally agreed definition of anti-TB DILI and most definitions focus on ALT. Hence, monitoring of liver enzymes is important especially within the first 8 weeks of anti-tuberculosis treatment initiation. (16)

Among 1529 patients diagnosed with confirmed or presumed TB and put on treatment between April 2010 and May 2014 in UK, 105 (6.9%) cases of pDILI were identified. Among the pDILI cases, 92 (87.6%) had type 1 pDILI (ALT>3x ULN), one (0.1%) had type 2 pDILI (ALP>2X ULN and bilirubin>1xULN), and 12 (11.4%) had type 3 pDILI (bilirubin>2xULN). Seventy-seven of the pDILI cases fulfilled the ATS/BTS criteria for TB DILI: 52 (49.5%) type 1a and 25 (23.8%) had type 1b DILI. There were 34 hospital admissions amongst 32 patients (30% of total) with a median inpatient stay of 14 days (IQR 7–21). Of the seven (6.7%) deaths, the mean age was 55.1 years at diagnosis and mean baseline weight was 65.1 kg. One patient had HIV-1 co-infection, one had myeloma, one had chronic renal failure, one had severe emphysema, one was diabetic and had previous breast cancer. None had a history of alcohol excess, chronic liver disease, hepatitis B or C, or were on other hepatotoxic drugs. Five of the seven died with pDILI being a likely contributor to death giving an attributable mortality of 4.8%. The 77 patients had ALT 3-5xULN with symptoms or an ALT >5xULN, thereby meeting ATS/BTS criteria for stopping TB therapy. Baseline ALP was positively associated with a risk of DILI with an adjusted odds ratio (AOR) 7.33 (95% CI 1.46–36.8) per 10-fold increase in ALP, ($p=0.03$). Patient weight was inversely associated with reduced risk of DILI (AOR 0.96 (0.94–0.99) per kg, $p=0.003$). Alcohol intake (any amount) was associated with an increased risk of DILI (AOR 5.94 (95% CI 2.34–15.1), $p<0.001$). The small number (eight) of HIV-1 co-infected patients had a four-fold higher risk of DILI (AOR 4.40 (1.06–18.3), $p=0.04$). No positive association was found between increasing age and risk of DILI. More than half (53%) of pDILI occurred in the first 2 weeks and 87% occurred within the first 2 months of starting ATT. The duration of interruption of ATT in patients with pDILI was related to peak ALT and therefore may be shortened by

earlier identification of abnormal LTs through universal rather than risk factor based monitoring.(17)

As conclusion, this study demonstrated an overall DILI rate of 6.9% in this cohort and mortality with pDILI as a contributor in 4.8%. This study indicates that monitoring of LTs during the first 2 months of ATT should identify the majority of DILI earlier, possibly shortening treatment interruption and reducing mortality. (18)

Single center analysis of consecutive cases of anti-TB DILI patients following combination anti-TB drugs exposure from 1997–2011 was done at the Department of Gastroenterology, St. John's Medical College Hospital, Bangalore, India. There were 269 cases of anti-TB DILI among a cohort of 516 patients with DILI. Of these, 150 were males (55.8%). Mean age was 42.4 years (range 3–84). Twenty-five patients were <18 years (9.3%). Mean duration of receiving antituberculous drugs was 1.9 months (range 4 days to 16 months). Eighty-five patients received treatment for <15 days, and 142 patients <30 days. One hundred and ninety-one patients (71%) developed jaundice/icterus. Sixty-nine patients (25.7%) presented with encephalopathy and ascites each. Hepatitis B surface antigen (HBsAg) carrier state (inactive infection as reflected by absence of immunoglobulin M (IgM) anti HBc and low (<1000 copies/mL) or below the level of detectable DNA) and HIV infection were present in 13 (4.9%) and 21 (7.8%) patients, respectively. Eleven patients with concomitant hepatitis E, five with acute hepatitis B and one with hepatitis C were excluded from the analysis. One hundred and sixteen patients (43%) patients developed DILI during empiric treatment of tuberculosis. Fourteen percent of patients (n=38) developed DILI while on directly observed therapy schedule (DOTS) compared to 42% (n=113) with fixed dose combination drugs and 39% (n=105) with single drug formulations. In 5% (n=13) the formulation was not clear. Sixty-seven patients (25%) in the series were on additional drugs, which included antiepileptic drugs in 31 (11.5%) and anti-retroviral or cotrimoxazole in 18 of the 21 HIV infected individuals. Patients who experienced anti-TB drug-induced ALF were younger (37 years) than those without ALF (42 years) (P=0.02). Depending upon the pattern of

liver injury (16) hepatocellular hepatitis, cholestatic hepatitis and mixed hepatitis constituted 23.2%, 27.3% and 22.7% deaths, respectively. Ascites was more commonly present in non-survivors (35/61, 57.4%) than survivors (34/208, 16.3%) ($P < 0.001$). Univariate analysis identified total serum proteins, serum albumin, total and direct bilirubin as predictors of death. The presence of any grade of encephalopathy, ascites, white blood cell count, international normalized ratio (INR), serum creatinine and the MELD score were also significant after univariate analysis. Multivariate analysis identified encephalopathy, total bilirubin, INR, serum albumin and creatinine as independently predictive of death. Spontaneous recovery from ALF occurs only in a third of patients. Patients across all age groups including children and adolescents are at risk. All forms of formulation may be associated with anti-TB DILI. Paradoxically, empirical treatment with combination chemotherapy is associated with risk of DILI and potentially avoidable if the initial indication of treatment is critically scrutinized. Close observation for early signs and symptoms of hepatotoxicity is necessary throughout the course of treatment.(19)

A retrospective cohort study was carried out in patients aged >18 years seen at the medical wards of the Jos University Teaching Hospital, in Nigeria from January 2013 to June 2013. In this study, baseline characteristics of 110 patients were described and the characteristics of patients with symptomatic hepatitis were compared with those without.

There were 20 (18.2%) patients who developed symptomatic hepatotoxicity, in which 10 (50%) manifested with jaundice as part of the features of hepatotoxicity. Furthermore, 18 (16.4%) of the 20 patients met the stricter criteria for hepatotoxicity. Therefore, the cumulative incidence of hepatotoxicity based on clinical features alone was 18.2%, whereas it was 16.4% according to the ATS criteria. The median age of patients with hepatotoxicity was slightly lower than that of those without hepatotoxicity, although this difference was not significant, 35 (IQR 27–43) years vs. 37 (IQR 30–45) years; $p = .34$. Although the proportion of females (10, 50%) was higher among those with hepatotoxicity versus those without (40, 44%), the difference was not significant; $p = .65$. Similarly, the higher mean BMI of those with hepatotoxicity (18.8 kg/m², SD 3.4) was not significantly different from those without hepatotoxicity (18.4 kg/m², SD 3.8), $p =$

.70. Similarly, there was no significant difference between those with/without hepatotoxicity in HIV positive status (65% vs. 70.8%; $p = .61$), those on cART (55% vs. 52.8%; $p = .86$), alcohol consumption (35% vs. 32.6%; $p = .84$), HBsAg positivity (7.2% vs. 11.4%; $p = .35$), and HCV antibody positivity (0% vs. 2.9%; $p > .99$).

This study showed that the incidence of symptomatic hepatotoxicity among hospitalized patients is high and ALT levels were mostly in excess of 3 times ULN among cases. While doubts about the utility of LFT in preventing or detecting hepatotoxicity may exist, close clinical and laboratory monitoring are important in hospitalized patients. (20)

To assess anti-tuberculosis therapy-induced hepatotoxicity among HIV Positive and negative Patients in Ethiopia, a prospective study on 103 HIV positive (not on ART) and 94 HIV negative TB patients was done from August 2004 to March 2005 at St. Peter's hospital. In this study, the criteria for diagnosis was based on the Ethiopian National guideline for diagnosis of tuberculosis. The number of patients who had smear positive TB were 99, smear negative 39, extra pulmonary 32, and disseminated 17. Patients were excluded if they had a history of prior treatment for tuberculosis, did not consent for HIV testing, were less than 18 years of age and had clinical evidence of liver damage prior to starting medication.

Out of the 197 study participants 105 (52.8%) were male and 92 (47.2%) were female; the median age of the patients was 26 years (range, 18 to 67 years). Out of these patients, 103 (52.3%) patients were HIV positive and 94 (47.7%) patients were negative. CD4 count was done for 87 of the 103 HIV positive patients. Eighty percent of the patients had CD4 count less than 200 cells/mm³. Fourteen (7.2%) were positive for HBsAg and only 4 (2.2 %) were positive for anti-HCV. Only 55 (27.9%) patients from the 197 took other drugs concomitantly and these drugs were: Vitamin B6(7 patients), codeine phosphate (5 patients), promethazine (4 patients) amoxicillin (13 patients), antacids syrup (13), albendazole (3 patients), tetracycline (2 patients), phenobarbitone (2 patients), ampicillin and gentamycin (2 patients), phenobarbitone plus antacid syrup (1 patient), ketoconazole (1 patient), and trimethoprim/sulfamethoxazole (2 patients). Thirty four (17.3%) study participants had sub-clinical hepatotoxicity of which 8 (4.1%) developed clinical

hepatotoxicity with all of them having jaundice and necessitated discontinuation of their anti-tuberculosis therapy. Out of the 34 patients 14 (41.2%) were males and 20 (58.8%) were females. Twenty six (76.5%) were HIV positive and 8 (23.5%) were negative. Twenty two (66.7%) patients were, 35 years of age and the mean time for the development of sub-clinical DIH was 2.8 weeks (Range 1–8 weeks). The mean duration of stay of the elevated ALT was 2.2 weeks (Range 1–7 weeks). The effect of confounders such as age, sex, HBsAg, concomitant drug intake, HIV status, body mass index, CD4 count and anti-HCV antibody was controlled. The results of the analyses showed that the odds of developing biochemical hepatotoxicity in patients taking other drugs concomitantly was 2.7 with a 95% CI of 1.2–5.8. The odds of developing biochemical hepatotoxicity in HIV positive patients was 3.6 with a 95% CI of 1.5–8.5 as compared to that of HIV negative patients. Three (21.4%) of the HBsAg positive and 31 (17.1%) of the HBsAg negative study participants developed sub-clinical hepatotoxicity whereas none of the 4 anti-HCV positive patients had hepatotoxicity and no patient was positive for concomitant HBsAg and anti-HCV Ab. The proportion of DIH in HIV positive and HIV negative patients was statistically significant where HIV positive patients are at a higher risk than HIV negative ones. This may be partly explained by the different drugs used by these patients for the treatment of AIDS-related opportunistic infections before the diagnosis of TB was made.

Unlike other studies which showed that patients in the older age group are at increased risk for development of hepatotoxicity, (21, 22, 23) in this study, such a finding was not observed and this could be due to a larger proportion of study participants being in the age group below 35 years which will make comparison difficult. Unlike other studies no association between Anti-HCV and HBsAg positivity and development of hepatotoxicity was observed. This may be attributed to the small number of patients who are positive for Anti-HCV antibody and HBsAg in this study. This study recommended that patients with HIV infection, low CD4 count and those on other concomitant drugs have initial screening with liver function test and closely monitored with subsequent tests during treatment. (24, 25)

2.2 Significance of the study

Hepatotoxicity is one of the most frequent and serious adverse effects of anti-TB medications and may reduce treatment effectiveness by compromising treatment regimens. However, little is known about the development of hepatotoxicity in TB. Because LFT is not routinely repeated following initiation of anti-TBs, patients with asymptomatic hepatotoxicity might have been missed.

It is also not possible to determine if this group of patients are at increased risk of progressing to the more clinically relevant overt hepatotoxicity.

At SPHMMC, there is no special TB care Centre and once patients are started on anti TB drugs, they will be linked to nearby health facilities and won't be appointed for follow up to know the outcomes. The same is true for the other two hospitals except that MDR TB patients at St. Petr's hospital have strict monitoring. This study is expected to fill the gaps in physicians' practice of initiating anti TB medications and trend of monitoring for possible drug toxicity as well as screening and detecting other risks of synergy.

3. Objectives

3.1. General

To assess the patterns and clinical characteristics of patients admitted with anti TB drug induced liver injury in the medical wards at SPHMMC, St. Peter and Zewditu hospitals from January 2014-April 2019.

3.2. Specific

To assess the clinical presentation of patients admitted with anti TB drug induced liver injury in the medical wards at SPHMMC, St.Peter and Zewditu hospitals

To describe the pattern and level of aminotransferase elevation of patients admitted with anti TB drug induced liver injury in the medical wards at SPHMMC, St Peter and Zewditu hospitals

4. Methods and Materials

4.1. Study area and period

The study was conducted in the medical wards of 3 hospitals in Addis Ababa, Ethiopia namely, Saint Paul Hospital Millennium Medical College (SPHMMC), St Peter and Zewditu hospitals. In Addis Ababa, the higher level health care delivery is from general hospitals (staffed by around 234 persons) and specialized hospitals (staffed by around 440 persons) and the above study sites are among such hospitals.

SPHMMC is located in Swaziland Street of Gullele Sub-city in the northern part of the capital city of Ethiopia, Addis Ababa. Saint Paul Hospital, established in 1961 G.C., became a medical college, now known as SPHMMC, in 2007 G.C. and currently gives health services in different departments. The medical ward of SPHMMC has 47 beds and provides services to admitted patients coming both from Addis Ababa and outside. Patients are being followed and managed by subspecialists, internists, internal medicine residents and interns.

St. Peter's specialized hospital is also found in Addis Ababa, Guilele sub city and currently gives tremendous health cares with both inpatient and outpatient services. Especially, after global health committee (GHC) initiated the countrywide program for drug resistant TB, it has increased the adherence rates and decreased mortality in the very sick population of patients. The medical ward has more than 32 beds for admission.

Zewditu Memorial hospital is also another hospital in central Addis Ababa which was built, owned and operated by seventh day Adventist church initially but nationalized in about 1976. It is Ethiopia's leading hospital in the treatment of HIV patients (treats >6000 patients each month. It also gives many inpatient services including for neurological patients. The medical ward has 34 beds for admission currently.

This study was conducted from January 2014 to April 2019.

4.2 Study design

A hospital based retrospective chart review study was conducted in patients admitted with anti TB associated DILI at SPHMMC, St Peter and Zewditu hospitals from January 2014 to April 2019

4.3 Population

4.3.1. Source population:

All patients admitted in the medical wards of SPHMMC, St Peter and Zewditu hospitals from January 2014 to April 2019.

4.3.2. Study population:

All patients admitted with anti TB DILI at SPHMMC, St.Peter and Zewditu hospital medical wards from January 2014 to April 2019 and who fulfil inclusion criteria.

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

-Patients admitted with anti TB drug induced liver injury or developed the anti TB DILI after admission at medical ward from January 2014 to April 2019 and age ≥ 18 years.

4.4.2. Exclusion criteria

-Patients with evidence of active hepatitis due to any cause at the time of anti TB treatment initiation.

-Patients with significantly incomplete data

4.5. Sample size determination and sampling technique

4.5.1. Sample size determination:

Patients who developed anti TB DILI from the three sites within the study period (158 patients) were analyzed.

4.5.2 Sampling technique:

Charts of all patients who were admitted with anti TB drug induced liver injury at the medical wards of the three hospitals from January 2014 to April 2019 was reviewed.

4.6 Measurement and study variables

4.6.1 Instrument

Data was collected using a modified structured checklist. The checklist has two parts. First part contains socio-demographic data. Second portion includes data about the clinical and biochemical characteristics of the patients. The check list is prepared after reviewing previously done similar articles and based on American Thoracic Society guidelines. (6, 11)

4.6.2 Study variables

4.6.2.1 Dependent variables

- Clinical and biochemical characteristics of anti TB DILI

4.6.2.2 Independent variables

- Age, sex, type of tuberculosis, duration of treatment, anti TB regimen, HBV and HCV infection, RVI status, alcohol consumption, other comorbidities.

4.7 Operational Definitions:

Tuberculosis: an infectious disease caused by *Mycobacterium tuberculosis*

First line Anti TB drugs: ethambutol, rifampicin, isoniazid and pyrazinamide

Anti TB drug induced liver injury: Development of liver injury after anti TB drug initiation

Subclinical anti TB drug induced hepatotoxicity: Elevation of liver enzymes without signs and symptoms after anti TB drug initiation

Clinical hepatotoxicity: biochemical hepatotoxicity plus symptoms of DIH including: nausea, vomiting, weakness and jaundice

Initiation phase: first 2 months of anti TB treatment

Continuation phase: the remaining months of anti TB treatment

Jaundice: yellowish discoloration of the eyes

Liver enzymes: alanine aminotransferase and aspartate aminotransferase

4.8. Data collection procedure

Charts of patients who were admitted in the medical wards of SPHMMC, St. Peter and Zewditu hospitals from January 2014 to July 2019 with anti TB associated DILI were reviewed and data was collected manually using a pre-tested structured checklist. The data was collected by data collectors, internal medicine residents and interns after they were trained by the investigator. Then the data was filled by the data collectors in to the checklist.

4.9. Data quality management

Data quality was managed through training the data collectors, and filling the structured checklist with the appropriate data from patient charts. There was supervising personnel for the quality of data other than the collectors. Pretest was done two weeks before actual data collection to check its clarity, length and completeness and the necessary correction was done accordingly.

4.10. Data processing and analysis

The data collected was cleared and entered into a computer using Statistical Package for Social Science (SPSS) software version 25. The data is summarized and described using tables. Descriptive statistics was conducted to describe socio-demographic and the other clinical variables.

4.11. Dissemination of result

Finally, the result of the research will be reported to the department of internal medicine so that all clinicians will understand the burden of the problem as well as improve the quality of clinical monitoring at our set up. It will also be documented in the library of SPHMMC. The finding will be presented to staffs and students of SPHMMC and others, as possible.

4.12. Ethical issues

Ethical clearance was obtained from the Institutional Research Board (IRB) of SPHMMC and the other two hospitals as well. Letter of co-operation was obtained from each level as necessary. Privacy of patients will be kept by writing patients' card number only, not mentioning their names and returning their charts to the card office.

5. RESULTS

During the study period, cards of 158 patients from the three study sites with anti TB drug induced liver injury were traced. There were 90 (57%) female and 68 (43%) male patients. The minimum age was 18 yrs and maximum was 90 yr. but the mean age was 39.7 yr with standard deviation of 12.4. From the total, 81 patients (51.3%) were HIV positive and 77 (48.7%) were HIV negative. There were 16 patients (10.1%) who had surface antigen positive for HBV and only 2 patients who were positive for HCV antibody. There were 27 patients (17.1%) who had alcohol consumption history irrespective of the amount they took.

With regard to the type of tuberculosis irrespective of the diagnostic modality, 93 (58.9%) patients had pulmonary TB, 15(9.5%) patients had disseminated TB involving the peritoneum and GIT, and 50 (31.6%) patients had disseminated TB involving other sites than GIT. Patients with initial liver involvement were not included.

All patients were started on RHZE as an initial regimen and no patient took second line anti TB drugs. There were patients being managed and followed for MDR TB at St. Peter hospital but their site was isolated, not admitted in the medical wards. The minimum time to develop anti TB DILI was 1 week and the maximum was 12 weeks. Among the total, 48.8% of the patients developed DILI within 2 weeks. The mean time was 2.82 weeks with standard deviation 1.67. Symptomatic patients had the following complaints when they develop the toxicity: Nausea only (15.2%), vomiting (5.1%), nausea and vomiting (49.4%), abdominal pain (4.4%), nausea, vomiting and abdominal pain (11.4%). There were 46.2% of the total patients who did not complain any symptom for the DILI.

There were 83 patients (52.5%) who had yellowish discoloration of the eyes but for 5 patients, jaundice was noticed by physicians. The minimum time to develop the jaundice was 1 week and the maximum was 8 weeks. The mean time was 2.36 weeks.

Fig.1. Histogram of age distribution of patients admitted with anti TB DILI at SPHMMC, St. Peter and Zewditu hospitals from January 2014-April 2019, (N=158)

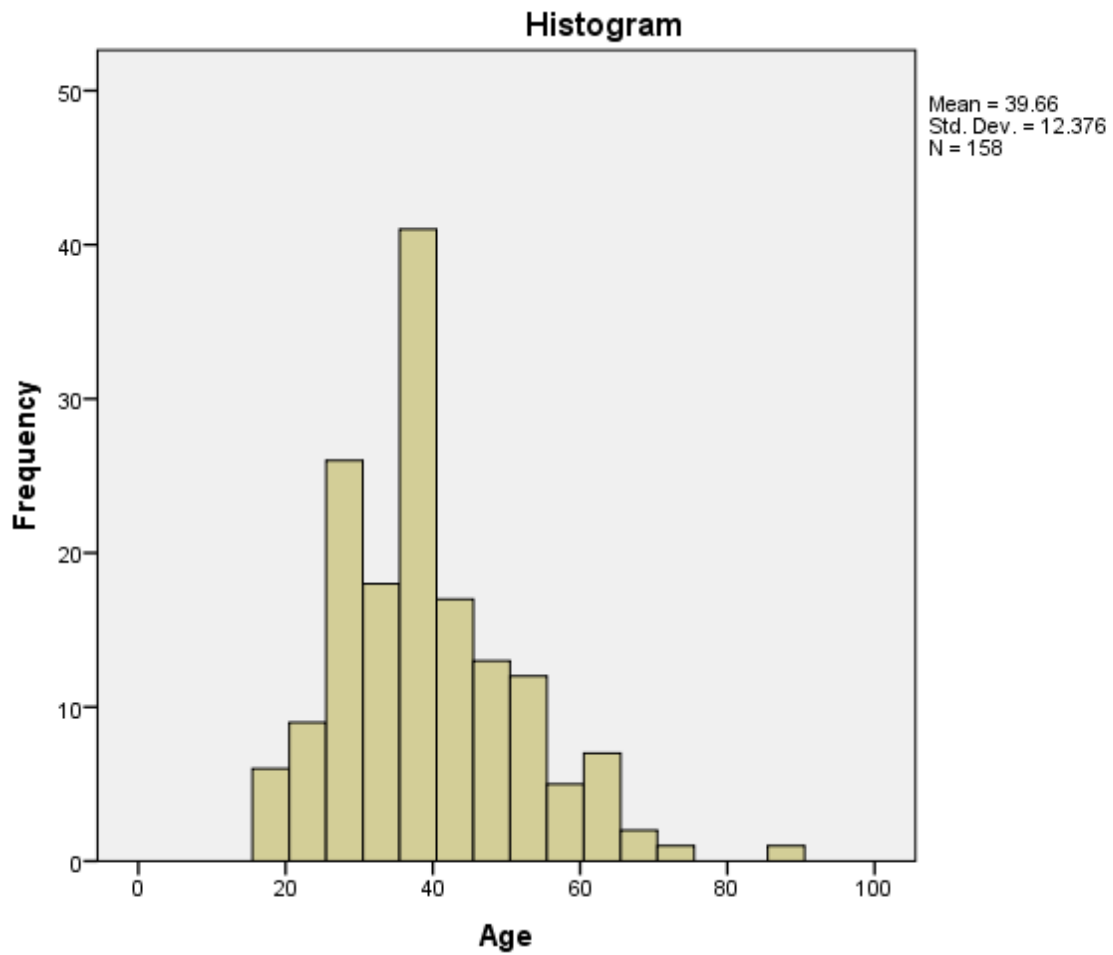


Table 1) Duration (in weeks) of anti TB drug till developing DILI in patients admitted with anti TB DILI at SPHMMC, St. Peter and Zewditu hospitals from January 2014-April 2015 , (N=158)

Weeks from starting of anti TB until development of DILI	Number of patients	Percent
1.00	32	20.3
2.00	45	28.5
3.00	36	22.8
4.00	29	18.4
5.00	7	4.4
6.00	6	3.8
8.00	1	.6
10.00	1	.6
12.00	1	.6
Total	158	100.0

Table 2) symptoms complained by patients when admitted with anti TB DILI at SPHMMC, St. peter and Zewditu hospitals from January 2014-April 2019 , (N=158)

Symptoms	Number of patients	Percent
Nausea	24	15.2
Vomiting	8	5.1
Abdominal Pain	7	4.4
Nausea + Vomiting	23	14.6
No Symptoms	73	46.2
Nausea + Abdominal Pain	5	3.2
Nausea + Vomiting + Abdominal Pain	18	11.4
Total	158	100.0

Table 3) duration (in weeks) of anti TB drug to develop jaundice for patients admitted with anti TB DILI at SPHMMC, St. Peter and Zewditu hospitals from January 2014- April 2019 (n=78)

Duration of anti TB until jaundice (in weeks)	Number of patients with jaundice	Percent	Valid Percent
1.00	23	14.6	29.5
2.00	30	19.0	38.5
3.00	13	8.2	16.7
4.00	6	3.8	7.7
5.00	2	1.3	2.6
6.00	2	1.3	2.6
8.00	2	1.3	2.6
Total	78	49.4	100.0
Missing System	80	50.6	
Total	158	100.0	

The minimum value for ALT elevation was 1.3 times and the maximum was 23.5 times. The mean value was 4.06 times. The mean values for AST and ALP elevations were 5.4 and 2.47 times respectively. There were 30 patients with no symptom complaint but ALT was >5 times elevated. There were 3 patients with no AST and 43 patients with no ALP but all had ALT documented.

Table 4) Degree of aminotransferase elevations (in folds) in patients admitted with anti TB DILI at SPHMMC, St. Peter and Zewditu hospitals from January 2014-April 2019 (N=158)

Values for aminotransferases elevation		AST	ALT	ALP
N	Valid	155	158	115
	Missing	3	0	43
Mean (in fold)		5.3988	4.0570	2.4677
Std. Deviation		5.73932	3.74083	1.47877
Minimum (in fold)		1.10	1.30	1.20
Maximum(in fold)		50.00	23.50	9.80

There were 128 patients who had different comorbidities other than tuberculosis. The top five comorbidities were RVI (51.3%), diabetes (4.4%), hypertension (3.8%), chronic kidney disease (3.2%) and inflammatory bowel disease (2.5%).

Anti TB was discontinued for 86 (54.4%) of patients and among these, 75 of them showed biochemical improvement after discontinuation. Anti TB was restarted for 77(48.7% of the total) patients. The minimum time to restart anti TB was 2 days and the maximum was 23 days. The mean was 10.47 days. Anti TB was restarted for 2 patients despite no improvement in amino transferase elevations.

Table 5) Duration of anti TB drug discontinuation until re-initiation (in days) for patients admitted with anti TB DILI at SPHMMC, St. Peter and Zewditu hospitals from January 2014- April 2019 (n=75)

Duration of anti TB drug discontinuation (in days)	Number of patients	Percent	Valid Percent
2	1	.6	1.3
4	1	.6	1.3
5	6	3.8	8.0
6	5	3.2	6.7
7	23	14.6	30.7
8	1	.6	1.3
9	1	.6	1.3
10	10	6.3	13.3
12	2	1.3	2.7
13	3	1.9	4.0
14	10	6.3	13.3
15	2	1.3	2.7
18	1	.6	1.3
20	1	.6	1.3
21	7	4.4	9.3
23	1	.6	1.3
Total	75	47.5	100.0
Missing System	83	52.5	
Total	158	100.0	

6. DISCUSSION

There are not many studies done about anti TB DILI which clearly establish when to diagnose it and common clinical characteristics of such patients in Ethiopia, and Africa at large. In this study, therefore, we assessed the common clinical characteristics of patients with anti TB DILI with some demographic and clinical variables from three hospitals. All the patients assessed were having DILI based on the ATS guideline which importantly uses elevation of ALT level than AST and ALP because of relatively lack of specificity for AST and TB can cause granulomatous hepatitis with raised ALP. With normal baseline aminotransferases and any elevation after starting anti TB plus clinical symptoms were criteria for diagnosis of DILI and biochemical improvement after drug discontinuation supported the diagnosis.

The median age from this study was 38.0 yrs which was higher than the median age in one of the previous studies done in Ethiopia which was 26 yrs but was due to large proportion of younger participants in that study (25). The proportion of HIV patients in this study was 51.3 %. In a previous study which was done in Ethiopia to see the prevalence of anti TB DILI among Ethiopian HIV positive and negative patients, the proportion of HIV patients was 76.5% (25) but a study done at a large TB center in United kingdom(UK) showed that the proportion of HIV patients among anti TB DILI patients was 7.6% (18). This difference may be explained by the different drugs given previously for the treatment of opportunistic infections and high prevalence of HIV infection in our country than in UK. There were 16 HBV positive and 2 HCV positive patients in this study but all had neither deranged liver enzymes nor were symptomatic at the time of anti TB drug initiation. There were 27 (17.1%) patients who had history of alcohol intake irrespective of the amount of intake but all had no evidence of liver injury at the time of anti TB initiation.

The most common clinical complaint of the DILI patients in our study was nausea and vomiting (49.4%). These frequency of symptoms were comparable to one of the studies done in London (18). In this study, 54.3% of patients complained nausea and vomiting. From our study, 83(52.5%) patients had jaundice but this was a higher proportion when compared to the other studies (18, 19, 20). This may be due to the fact that all our patients were from inpatient (admitted) or partly for late detection of the DILI in our set up due to lack of close follow up. Among all the anti TB DILI patients, 46.2% didn't complain any symptom but had biochemical evidence of DILI.

From our study, there were 128 (81%) patients who had other comorbidities than any form tuberculosis the higher 3 proportions being RVI (51.3%), diabetes (4.4%) and hypertension (3.8%). (Table 5 for the other lists). But there were no significant co-administered known hepatotoxic drugs at the time of anti TB drug initiation.

Anti TB was discontinued for 86 (54.4%) patients based on the ATS criteria and 75 of them showed biochemical and symptomatic improvement which also strengthened the initial diagnosis of DILI. Anti TB was restarted for 77 patients implying that there were 2 patients for whom the drug was restarted despite not improving clinically or biochemically which probably may be due to underlying fatal form of tuberculosis which itself may be a killer than the DILI. The median time from discontinuation of anti TB to the re-initiation was 10 days which was shorter duration than a previously done study in England at one of TB Centre hospitals (18). The median time to full re challenge from that study was 28 days. This may be due to that we usually restart the full regimen early and once when the patients show improvement and will be discharged soon to be linked as outpatient.

7. Limitation of the study

- This research is only descriptive study and because all the patients included were those with anti TB DILI, it does not describe the association of some risk factors which are supposed to increase the risk for toxicity.
- Because this study is based on secondary data by reviewing charts of the patients from the three hospitals, the top challenge was lack of documenting DILI as part of the patient's diagnosis on the health management information system (HMIS) log book. So, the option was to see the cards of all patients who were admitted and started on anti TB within the study period and picking the patients with anti TB DILI.
- Lack of thorough initial clinical evaluation (documentation) by physicians so as to fill all clinical variables in the prepared check list
- Difficulty of knowing the exact dates of successive aminotransferase elevations and failure to document bilirubin together.
- The outcome of the patients was not addressed in this study because patients don't have follow up in our hospital and instead, they will be linked to the nearby health facility.

8. Conclusion

In conclusion, there are significant number of hospitalized patients who developed hepatotoxicity after they were started on anti TB drugs in our hospitals and their presentation ranged from mere elevation of aminotransferases to becoming symptomatic. Nausea and vomiting was the most common complaint of the patients. Significant proportion of the patients had jaundice. More than ninety percent of the DILI patients got improved after drug discontinuation.

9. Recommendation

This study revealed that there significant proportion of patients who develop anti TB hepatotoxicity and here are recommendations based on the findings:

- ✓ Further analytic and case control studies are crucially important to be done so as to identify and establish different risk factors to develop anti TB DILI.
- ✓ Health care providers should be trained about the side effects of anti TB drugs and how to monitor the patients taking anti TB drugs for early detection of complications before advancing.
- ✓ Loose forms (preparations) of anti TB drugs should be available in our country so that the incriminated hepatotoxic drug will be held during rechallenging.
- ✓ Patients taking anti TB drugs should have serial determination of liver enzymes and bilirubin at least for the first four weeks and there should be TB clinic in the hospitals for outpatient follow up after discharge.
- ✓ There should be proper documentation starting from diagnosis and dates of management started, profiles of done investigations and when intervened if side effects happened.

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Annex 1: Check list format

1. Chart No. _____
2. Age _____
3. Sex: 1. Male 2. Female
4. Area of residence 1. Addis Ababa 2. Other (specify)_____
5. Marital status 1. Married 2. Single 3. Divorced 4. Widowed
6. Type of tuberculosis? 1. Pulmonary 2.extra pulmonary (mention site) ----
7. Anti TB regimen mention _____
8. Duration of anti TB treatment Mention in weeks _____
9. RVI sero status? positive_____ negative_____
10. HBV positive? 1. Yes 2. No
11. HCV positive? 1. Yes 2. No
12. History of alcohol consumption (irrespective of amount)? 1. Yes
2. No
13. Presenting complaint during anti TB DILI? 1. Nausea 2. Vomiting
3.Abdominal pain 4. Others , specify_____
14. History of yellowish discoloration of the eyes? 1. Yes 2. No
15. If yes to Q14, When did it occur? Specify_____
16. Degree of GOT elevation? Mention in folds_____
17. Degree of GPT elevation? Mention in folds_____
18. Degree of ALP elevation? Mention in folds_____
19. Other comorbidities than mentioned above? Specify_____

20. Was anti TB treatment discontinued? 1. Yes 2. No
21. If yes for Q20, was there Clinical and biochemical improvement after drug discontinuation? 1. Yes 2. No
22. Anti TB restarted? 1. Yes 2. No
23. If yes for Q22, when after discontinuation? Mention number of days_____