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Study of Hepatotoxicity Induced By Anti-Tuberculosis Drugs in Patients Co -Infected With HIV and Tuberculosis at Coimbatore Medical College and Hospital.

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Abstract: *Human Immunodefieciency Virus (HIV) infection / Acquired Immuno Deficiency Syndrome (AIDS) is a global pandemic which has significant impact on the epidemiology of Tuberculosis. Progression of Mycobacterium Tuberculosis infection to active tuberculosis is more rapid and common in those infected with HIV than without HIV infection, so HIV/AIDS is an independent risk factor for TB disease progression[(1).]* ***Aim:*** *The purpose the study is to estimate the incidence of hepatotoxicity in peoples withco-infection of HIV and Tuberculosis and to determine the associated risk factors like alcohol consumption, age, gender, HBsAg, Anti HCV and CD4 count.****Method of the study****: 100 peoples with HIV and co infected with TB were studied in a tertiary care hospital in Coimbatore.* ***Result:*** *A substantial number of cases (14%), with majority of hepatotoxic events occurred in the intensive phase of treatment, alcohol intake, extra pulmonary tuberculosis, low CD4 count,Hepatitis B/C co-infection were identified as risk factors to the development of ATT induced hepatotoxicity withlow CD4 count, alcohol intake, and Hepatitis B/C virus infection passing as independent predictors.The findings suggest that HIV-TB co-infected patients presenting with alcohol intake, low CD4 count and Hepatitis B/C co-infection should be closely monitored by physicians especially during the intensive phase of Anti-Tuberculosis therapy for better patient management and for the prevention of morbidity and mortality.*

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I. Introduction

HIV-TB CO-INFECTION

The chances of getting active TB in a healthy person in his whole lifetime is 5% to 10%, whereas the same in HIV infected persons is 5% to 15% yearly[(2)]. 9.6 million Peoples are estimated to have been affected by TB worldwide in 2014. From this 9.6 million, 12% were positive for HIV. In worldwide the estimated TB deaths were 1.5 million in 2014. Among this 1.1 million were HIV negative people and 3,90,000 where HIV positive people[(3)].

HIV IMPACT ON TUBERCULOSIS

The interaction between TB and HIV is bidirectional. Those people infected with HIV not only contracting the active Tuberculosis, they are also found to have very high rate of treatment failure and relapse of TB. In a patient with TB/HIV co-infection, at the time of TB diagnosis found to have advanced stage of HIV disease as defined by high viral loads, low CD4+ T cell counts and are classified as WHO clinical Stage of HIV disease 3 or 4 [(4)].

ANTI-TUBERCULOSIS DRUG INDUCED HEPATOTOXICITY

Concomitant use of Anti-Tuberculosis drugs and Anti-Retroviral therapy were complicated by the adherence challenge of polypharmacy and overlapping side effects. Drug induced hepatotoxicity is one of the overlapping side effects of both the first line Anti-Tuberculosis drugs and Anti-Retroviral drugs leading to interruption of therapy. The major cause of hepatotoxicity are additive toxicity of ART and ATT, overlapping hepatitis B and C virus infections and other co-administered drugs, as well as alcohol abuse [(5)].

II. Aim & Objectives

1. To estimate the incidence of hepatotoxicity in peoples with co-infection of HIV and Tuberculosis.
2. To determine the associated risk factors like alcohol consumption, age, gender, HBsAg, Anti HCV and CD4 count.

III. Methodology

Source of data:
HIV-TB co-infected patients registered in ART (Anti Retroviral Treatment centre of Government Coimbatore Medical College and Hospital were taken up for study.

Study centre:
The study was conducted in Government Coimbatore Medical College and Hospital, Tamil Nadu.

Study period:
One year from February 2017 to January 2018.

Sample size:
100 HIV-TB co-infected patients meeting the criteria for the present study.

Inclusion criteria:
1. Patients co-infected with HIV and tuberculosis
2. Age above 18 yrs.
3. The participants comprised both who have been started on ART and who have not been started on ART before commencing ATT.

Exclusion criteria:
1. Patient with already established liver diseases prior to the start of medication
2. Pregnancy and lactation

Study design:
This is a case control study. This study was conducted in HIV-TB co-infected patients, who was started on first line ATT. Patients base line liver function test, CD4 count, HBsAg, Anti HCV, sputum for AFB, chest X ray are performed before starting ATT.
If patient develop symptoms like nausea, vomiting and jaundice, LFT was done in between the normal interval.
The participants who develop hepatotoxicity are labeled as cases and the other participants who without hepatotoxicity are labeled as controls.
If patient developed moderate to severe hepatotoxicity ATT was stopped temporarily and reintroduced in low dose after complete recovery. No patient was discontinued ATT completely or changedregimen.

Patient's data collection:
A total of 100 cases of HIV-TB co-infection registered for ATT at RNTCP centre from February 2017 to January 2018 were analyzed. A detailed history taking and clinical examination was done. Various parameters like age, sex, BMI, alcohol intake, symptom and clinical signs were noted down for analysis.

Investigations performed:
1. Liver function test
2. Sputum for AFB
3. Chest X ray
4. CD4 count
5. HBsAg
6. Anti HCV

After getting nod of clearance from ethical committee of Coimbatore Medical College, study was done.

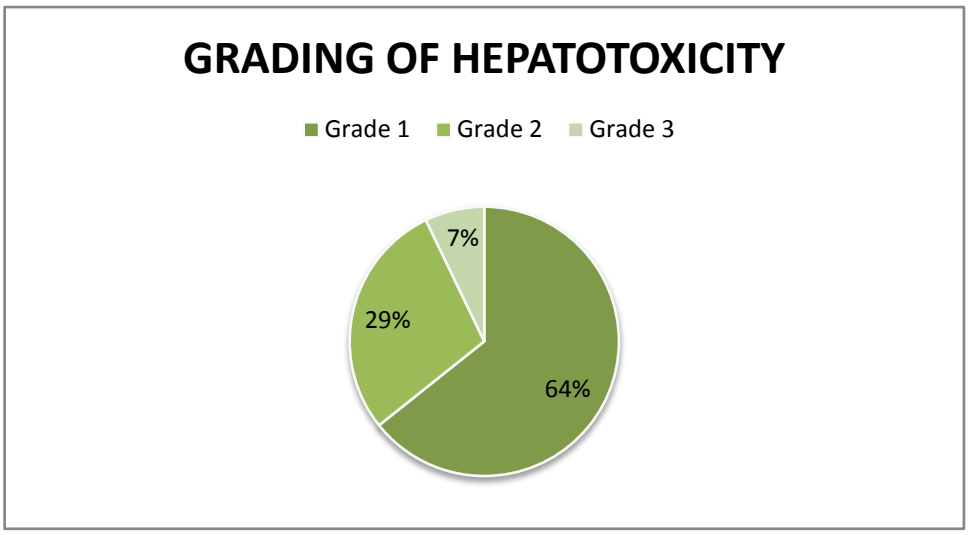
IV. Results And Analysis

In this study, a total of 100 HIV-TB co-infected patients were studied for hepatotoxicity. This study was analyzed in three stages.
Step 1. Independent influence of different factors like Age, Sex, alcoholconsumption and co infection with Hepatitis B and C on presence or absence of hepatotoxicity using **chi square test**
Step 2.Independent influence of same factors among patients with hepatotoxicity (N=14) using **ANOVA and Kruskal Wallis test** by using Grade of hepatotoxicity.
Step 3: To analysis influence of different factors and dependency on one another was using **multivariate regression analysis.**

HEPATOTOXICITY
In this study 14 peoples were developed ATT induced hepatotoxicity.

GRADING OF HEPATOTOXICITY

Figure 11: Shows grading of hepatotoxicity in pie chart



Out of 14 peoples 9 peoples developed grade 1 toxicity, 4 peoples developed grade 2 toxicity and 1 people developed grade 3 toxicity.In this study, 6 patients developed hepatotoxicity within 2 weeks, 4 patients within 4 weeks and 4 patients within 3 months.

ALANINE TRANSAMINASE LEVEL

ALT RANGE	No of cases
Less than 40	87
41-120	8
120-120	4
201-400	1
Above 400	0

ASPARTATE TRANSAMINASE LEVEL

AST Range	No of cases
Less than 37	87
37 – 120	8
120 – 200	4
201-400	1
Above 400	0

Classification of hepatotoxicity into grades 1-4 among the 14 cases

Severity	Level of liver enzymes	No of cases
Grade 1	1.25-2.5 xULN	9
Grade 2	2.6-5x ULN	4
Grade 3	5.1-10xULN	1
Grade 4	10x ULN	0

Out of 14 cases 13 cases showed raised ALT and 13 cases showed raised AST levels. No grade 4 hepatotoxicity was documented.

SEX DISTRIBUTION

In this study the number of males (60%) participated was more than the females (40%)

SEX RATIO AND HEPATOTOXICITY

Table 1: shows Sex ratio and hepatotoxicity

	HEPATOTOXICITY	
SEX	Present (in percentage)	ABSENT
MALE	8 (13%)	52
FEMALE	6 (15%)	34

TOTAL	14 (14 %)	100

In this study, 8 males and 6 females were developed hepatotoxicity. Using Chi square test the chi square value is 0.055. p value is 0.814 shows no association was found between sex and development of hepatotoxicity

GRADING OF HEPATOTOXICITY

Sex	**Grade l**	Grade 2	Grade 3
Male	5	2	1
Female	4	2	0

Using Anova p value is 0.711, shows no significance was made between grading of hepatotoxicity and sex distribution.

AGE DISTRIBUTION

In this study, 10 patients were in less than 25 years of age,78 patients were in the age group of 25 to 49 years of age and 12 patients were more than 50 years of age.

AGE DISTRIBUTION AND HEPATOTOXICITY

Table 2: Shows age distribution of hepatotoxicity

Age (years)	**Hepatotoxicity**	
	Present	Absent
Less than 25	2	8
25-49	11	67
50 and above	1	11

GRADING OF HEPATOTOXICITY

Age (years)	**Grade 1 (N=9)**	**Grade 2 (N=4)**	**Grade 3 (N=l)**
Less than 25	**1**	**1**	0
25-49	**8**	**2**	1
50 and above	**0**	**1**	0

Using Anova p value is 0.933, shows no significance was made between grading of hepatotoxicity and age distribution.

ALCOHOL INTAKE:

Out of 100 cases 37 people were presented with alcohol intake.

ALCOHOL INTAKE AND HEPATOTOXICITY

Table 3: Shows alcohol intake and hepatotoxicity co-relation

Alochol intake	**Hepatotoxicity**	
	Present	Absent
Present	6	31
Absent	8	55

In this study using Chi square test (p value:0.562) showed no significant effect was caused by alcohol intake.

GRADING OF HEPATOTOXICITY

Alcohol intake	**Grade 1**	**Grade 2**	**Grade 3**
Present	**3**	**2**	1
Absent	**6**	**2**	0

Using Anova (p value is 0.480), in this study no association was found between alcohol intake and grading of hepatotoxicity

TYPE OF TUBERCULOSIS

In this study there are 66 sputum positive cases, 13 sputum negative cases and 21 extra pulmonary Tuberculosis cases were participated.

TYPE OF TB AND HEPATOTOXICITY

Table 4: Shows distribution of type of Tuberculosis and hepatotoxicity

Type of tuberculosis	Hepatotoxicity	
	Present	Absent
Sputum positive	5	61
Sputum negative	2	11
Extra pulmonary	7	14

Using chi square test, significant correlation was found between type of Tuberculosis and hapatotoxicity (Chi square value: 6.591,P value = 0.010). There was a significant difference between extra pulmonary Tuberculosis and others.

GRADING OF HEPATOTOXICITY

Type of TB	Grade 1	Grade 2	Grade 3
Sputum positive	**4**	**1**	0
Sputum negative	**1**	**1**	0
Extra pulmonary	**4**	**2**	1

Using Anova (p value is 0.433), in this study no association was found between type of TB and grading of hepatotoxicity

CD 4 COUNT

Table 5:Shows distribution of CD4 count

CD4count(cells/mm3)	No of cases
Less than 200	59
More than 200	41

Out of 100 cases 59 peoples were presented very low CD4 count(<200 cells/mm^3) and 41 peoples were presented with CD4 count of more than 200 cells/mm^3

CD4 COUNT AND HEPATOTOXICITY

CD4 count	Hepatotoxicity	
	Present	Absent
Less than 200	12	47
More than 200	2	39

Patients with CD4 count <200 cells/mm3 have significant impact on development of hepatotoxicity (P=0.048).

GRADING OF HEPATOTOXICITY

CD4 count	Grade 1	Grade 2	Grade 3
Less than 200	**7**	**4**	1
More than 200	**2**	**0**	0

Using Anova (p value is 0.650), grading of hepatotoxicity does not show any correlation with CD4 count.

HEPATITIS B/C INFETION

Table 5: Shows hepatitis B/C distribution in bar diagram

Hepatitis B/C	No of cases
Yes	8
No	92

Out of 100 patients 8 patients had Hepatitis B/C co-infection.

HEPATOTOXICITY AND HEPATITIS B/C

Table 6: Shows hepatitis B/C and hepatotoxicity distribution

Hepatitis B/C	Hepatotoxicity	
	Present	Absent
Yes	3	5
No	11	81

Significant correlation was detected between Hepatitis B/C co-infection and hepatotoxicity (Chi square value: 6.591, P value = 0.046)

GRADING OF HEPATOTOXICITY

Hepatitis B/C	Grade 1	Grade 2	Grade 3
Yes	**2**	0	1
No	**7**	4	0

Using Anova, no correlation was found between grading of hepatotoxicity and Hepatitis B/C co-infection (P=0.102).

Multivariate regression analysis

Hepatotoxicity	P value	Odds ratio (Exp B)	Significance
Age	0.752	2.012	Non-significant
Sex	0.360	.759	Non-significant
Alcohol intake	0.042	2.518	Significant
Type of TB	0.035	1.259	Significant
CD4 count	0.018	4.891	Significant
Stage	0.085	1.834	Non-significant
Hepatitis B/C	0.017	1.382	Significant

V. Discussion

In this study, HIV-TB co-infected 100 patients who were newly started on ATT were studied and documented for ATT induced hepatotoxicity. There were 60 male patients and 40 female patients in the study population. The majority (78%) of the HIV-TB co-infected patients belongs to the age group of 25 to 49 years, suggesting that the incidence and prevalence of the disease is more common in the sexually active age group.

Out of 100 persons 14% peoples developed ATT induced hepatotoxicity. In these 14 peoples 43% were females and 57% were males. Out of 60 males 13% developed hepatotoxicity and out of 40 females 15% developed hepatotoxicity. Overall incidence was 14%.

In this study no significant difference was observed with gender and also no association was found between the age groups and hepatotoxicity manifestations.

In this study population, 37% of people were presented with alcohol intake. In this study alcohol intake showed significant impact on development of drug induced hepatotoxicity in multivariate regression analysis (p value- 0.014).

This study showed that CD4 count had significant impact (p value -0.018) on development of drug induced hepatotoxicity. This may be due to the presence of a range of disseminated opportunistic infections in patients with low CD4 count that may have direct subclinical involvement of liver leading to cell death.

Sputum positive AFB was *66%*, sputum negative AFB was 13% and extra pulmonary TB was 21%. Patients with extra pulmonary tuberculosis had disproportionately higher risk of developing hepatotoxicity. So patients with extra pulmonary tuberculosis needed regular monitoring of liver function test while taking ATT.

In this study Hepatitis B/C co-infection had significant impact on development of hepatotoxicity in patients taking ATT (p value -0. 017).

VI. Conclusion

HIV- TB co-infection is increasing at a rapid rate now, such that all patients with any one of this infection should be search for other. So that mortality and morbidity rates produced by the co-infection can be reduced with an effective and well co-ordinated manner.

In patients co-infected with HIV-TB, low grade hepatotoxicity induced by Anti-Tuberculosis was not uncommon. A substantial number of cases (14%), with majority of hepatotoxic events occurred in the intensive phase of treatment, alcohol intake, extra pulmonary tuberculosis, low CD4 count,Hepatitis B/C co-infection were identified as risk factors to the development of ATT induced hepatotoxicity withlow CD4 count, alcohol intake, and Hepatitis B/C virus infection passing as independent predictors.

The findings suggest that HIV-TB co-infected patients presenting with alcohol intake, low CD4 count and Hepatitis B/C co-infection should be closely monitored by physicians especially during the intensive phase of Anti-Tuberculosis therapy for better patient management and for the prevention of morbidity and mortality.

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