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ASSESSMENT OF DRUG INDUCED HEPATOTOXICITY IN PATIENTS TREATED FOR TB/HIV CO-INFECTIONS IN AYDER REFERRAL HOSPITAL ART CLINIC, MEKELLE; ETHIOPIA

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ABSTRACT

Background: Concomitant use of treatment for tuberculosis and antiretroviral therapy is complicated by the adherence challenge of polypharmacy and overlapping side effect like drug-induced hepatotoxicity. **Objective:** To determine the prevalence of hepatotoxicity in patients treated for the co-infections of TB/HIV using serum ALT levels as marker of hepatotoxicity. **Result:** The most frequent type of hepatotoxicity grade observed was toxicity degree type one, which was observed in 45% of the patients. Five percent of female and 10% male on HAART and anti-TB medications developed hepatotoxicity. Patient in age between 19-62 year were develop almost double the prevalence i.e 10%, compared to 4% in </=18 year and only 1% in age >/=63 year. The prevalence of severe hepatotoxicity (grade 2 or more) was 15 (15%). There was no significant correlation in toxicity grade at baseline ALT measures, (Spearman Correlation Asymp. Sig. (2-sided) = .878). However, the ALT measure after three month showed that significant association with the grades of toxicity, (Spearman Correlation Asymp. Sig. (2-sided) = .000). HCV infection was significantly associated with the risk of hepatotoxicity, which occurred in 3 out of 4 of the study participants (OR, 22.7; P.value, 0.34). **Conclusion:** The prevalence of hepatotoxcity in the study area was comparable to other similar studies. HBV co-infection

was an independent risk factor for hepatotoxicity. Clinicians must consider the possibility of drug-induced liver injury in the management of HIV-infected patients, especially in those with certain risk factors such as co-infection with hepatitis B virus (HBV).

KEY WORDS: Drug induced hepatic injury, TB/HIV co-infections, Heptotoxicity.

INTRODUCTION

Worldwide, it is estimated that 14.8% of all new tuberculosis (TB) cases in adults are attributable to human immunodeficiency virus (HIV) infection. This proportion is much greater in Africa, where 79% of all TB/HIV co infections are found. In 2007, 456 000 people globally died of HIV-associated TB [1]. The advent of highly active antiretroviral therapy (HAART) in the treatment of HIV infection has significantly decreased the incidence of opportunistic infections as well as improved morbidity and mortality among HIV patients [2]. However, along with these positive outcomes, HAART is associated with a host of adverse reactions such as hepatotoxicity, hyperlipidemia, hyperglycemia, and lactic acidosis [3].TB is the most common opportunistic infection among people with HIV infection and their co-infection poses many problems with regard to diagnosis, treatment, drug resistance, adverse drug reaction, mortality and burdens on the health systems. Concomitant use of treatment for tuberculosis and antiretroviral therapy is complicated by the adherence challenge of polypharmacy and overlapping side effect profiles of antituberculosis (anti-TB) drugs and antiretroviral drugs. Drug-induced hepatotoxicity (DIH) is one of the overlapping side effects of both antiretroviral therapy (ART) and first line anti-TB drugs leading to interruption of treatment[2,4-7]. The major cause for these are: additive toxicity of the anti-TB and ART medications, overlapping hepatitis C (HCV) and hepatitis B virus (HBV) infections, and other co-administered medications like cotrimoxazole and anti-fungals, as well as alcohol abuse [8,9]. When Hepatotoxicity occur the liver shows an elevation in serum Aaspartate aminotransferase (AST) or Alanine aminotransferase (ALT) level from the normal range (AST = 0-37 and ALT< 41 IU/l) to >3x upper limit of normal in the presence of symptoms, or Serum AST or ALT >5x upper limit of normal in the absence of symptoms [1,10,11] . AST/ALT elevations instead of alkaline phosphatase (ALP) elevations favor liver cell necrosis as a mechanism over cholestasis. When AST and ALT are both over 1000 IU/L, the differential can include acetaminophen toxicity, shock, or fulminant liver failure. When AST and ALT are >3X of normal but not > 1000 IU/L, the differential can include alcohol toxicity, viral hepatitis, drug induced, liver cancer, sepsis, Wilson disease, post-transplant rejection of

liver, autoimmune hepatitis, and steatohepatitis (non-alcoholic). When AST/ALT elevated are minor it may be due to rhabdomyolysis among many possibilities [12]. Therefore, AST/ALT tests could be used as markers of hepatocellular injury [13]. Hepatocellular injury has different grading scale from mild to severe based on the laboratory value of the ALT or AST [14,15]. Studies have revealed that 14-20 % of adults on ART had elevated serum liver enzymes as a marker of hepatocellular injury [16]. Liver enzyme elevations (LEEs) have been described in association with all major classes of antiretroviral therapy (ART)[4] and anti-TB drugs including isoniazid, rifampicin, pyrazinamide and ethambutol. Among the four anti-TB drugs, isoniazid, rifampicin, and pyrazinamide play major role in causing hepatotoxicity [17]. However, the complexity of medication used in both ART and anti-TB complicates the understanding of the independent effects of each drug in the development of drug induced liver injury [4]. Hepatotoxicity is the major problem associated with TB/HIV co infection. Thus, the purpose of this study was to determine the prevalence of hepatotoxicity in patients treated for TB-HIV co infection using the serum ALT level as marker of hepatotoxicity.

METHODS

Study area

The study was conducted in Ayder referral hospital of Tigray regional state, Northern Ethiopia, 786 km away from the capital city of Ethiopia, Addis Ababa.

Study Design

A case-control study was conducted. 'Cases' were those who develop change in their laboratory value for liver function tests with increment in ALT level from the baseline standards, while 'controls' were those who did not change their laboratory value for liver function tests of ALT measurements.

Sample Size Determination

The formula for calculating sample sizes

$$N = \frac{1}{(p-V)^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{(1-\beta)}\sqrt{p(1-p)/K + V(1-V)}\right]^2$$

and

$$U = \frac{p}{K+1}\left[K + \frac{R}{1+p(R-1)}\right]$$

$$V = \frac{pR}{1+p(R-1)}$$

Where

1. p is the Prevalence rate assumed in undiseased (control) groups global studies (14-20%) [7]. So, p = 0.2 0r 20% has been taken for this study.
2. K is 1 (control : case ratio = 3 :1)
3. R is the odds ratio Odds to be detected (R = 5)
4. α=0.05 (two-tailed)
5. β = 0.20 (power = 80%)
6. $Z_{1-\alpha}$ is the standard normal value at 95% confidence interval (±1.96)
7. $Z_{1-\beta}$ is the Z value corresponding to the power of 80% (0.842)

Substituting all the values, N becomes 25 (i.e. Triple this number would be included in the control group).

Data collection instrument

A prepared and pretested checklist was used to collect data from the patient charts and files. Socio-demographic, ART treatment regimen, other co-morbidities and laboratory values for liver function tests were components of the checklist.

Eligibility Criteria

Inclusion criteria

Both TB-HIV co-infected patient .

Exclusion Criteria

Patient with already established liver problem prior to the start of either of the medications.

Patient document lacking liver function test results .

Data Organization And Analysis

Data was compiled, processed, and analyzed using Statistical Package for Social Sciences (SPSS) for windows version 16. Descriptive statistics was used to summarize data and statistical analysis using logistic regression was carried out to determine whether there was any association between the dependent and independent variables. A 95% CI and p-value of <0.05 was considered to be statistically significant.

Ethical Consideration

A formal permission letter was secured from Mekelle University prior to obtaining any information from patients' medical records and charts.

Operational Definitions

The following WHO operational definitions were used in the study

1. Toxicity of degree 0: the level of toxicity which is considered as normal in which its value is <1.25 x normal value of ALT in serum
2. Toxicity of degree 1: the Level of toxicity which is considered as weak in which its value is 1.256 – 2.5 x normal value of ALT in serum
3. Toxicity of degree 2: the Level of toxicity which is considered as moderate in which its value is 2.6 – 5 x normal value of ALT in serum
4. Toxicity of degree 3: the Level of toxicity which is considered as severe in which its value is 5.1 – 10 x normal value of ALT in serum
5. Toxicity of degree 4: the Level of toxicity which is considered as severe in which its value is >10 x normal value of ALT in serum
6. Category I anti-Tb drugs: *Initial Phase* (8 weeks) *with* INH, RIF, PZA, EMB and *Continuation Phase* (26 weeks) *with* INH/RIF or INH/RPT
7. Category II anti-Tb drugs: *Initial Phase* (8 weeks) *with* INH, RIF, PZA, EMB and *Continuation Phase* (26 weeks)*with* INH/RIF or INH/RPT
8. Category III anti-Tb drugs: *Initial Phase* (8 weeks) *with* INH, RIF, PZA, EMB and *Continuation Phase* (26 weeks) *with* INH/RIF
9. Category IV anti-Tb drugs: *Initial Phase* (8 weeks) *with* INH, RIF, EMB and *Continuation Phase* (39 weeks) *with* INH/RIF

RESULT AND DISCUSSION

Background Characteristics Of The Study Subjects

In this study, 100 patient records were sampled and studied. The mean age of the study subjects was 33.6 + 17 years. The age range was between 4 and 70. More than half of the study subjects 55 (55 %) were females. The most frequent type of TB diagnosed was extra-pulmonary TB (59%) while category one anti-TB regimen was used almost in 85% of the study participants. Sixty two percent of the patients were on WHO HIV stage four and in 94% of the participants ART regiment containing NRTI + NNRTI was used. Only 4% of the patients were positive for hepatitis B surface antigen (HBsAg) test while 79% of them were on cotrimoxazole (CTM) prophylaxis (Table 1). According to the WHO category of HIV stages, the majority of our study participants 62 (62%) were in stage four (Table 1). In other study the majority were in stage III (71.4%) [4]. The toxicity grade observed in our study had similar pattern with previously conducted studies [4].

Table 1: The background characteristics of patients on anti-TB and HAART medications, Ayder referral hospital, Mekelle-Ethiopia; 2013.

Variables		Frequency	Percent
Age category	</=18	18	18.0
	19-62	69	69.0
	>/=63	13	13.0
Sex	Female	55	55.0
	Male	45	45.0
TB infection	Pulmonary TB	41	41.0
	Extra-pulmonary Tb	59	59.0
Anti-Tb drug regimen	Category one	85	85.0
	Category two	11	11.0
	Category there	4	4.0
WHO staging	Stage one	2	2.0
	Stage two	1	1.0
	Stage there	35	35.0
	Stage four	62	62.0
ART regimen	NRTI + NNRTI	94	94.0
	NRTI + PI	5	5.0
	NRTI + NRTI	1	1.0
HBV	Positive	4	4.0
	Negative	96	96.0
Co-trimoxazole prophylaxis	Yes	79	79.0
	No	21	21.0

Table 2: Mean, frequency and standard deviation of ALT, based on degree of toxicity of patients on anti-TB and HAART medications. Ayder referral hospital, Mekelle-Ethiopia; 2013.

Toxicity of degree-ALT		ALT baseline	ALT after
0	Mean	33.45	38.30
	N	40	40
	Std. Deviation	17.840	21.042
1	Mean	36.87	68.64
	N	45	45
	Std. Deviation	20.141	45.491
2	Mean	45.12	161.00
	N	8	8
	Std. Deviation	29.479	95.367
3	Mean	26.14	142.43
	N	7	7
	Std. Deviation	16.446	95.446
Total	Mean	35.41	69.06
	N	100	100
	Std. Deviation	19.993	61.118

Table 3: **Range, mean and standard deviation of baseline ALT test result compared to after three months test of patients on anti-TB and HAART medications, Ayder referral hospital, Mekelle-Ethiopia; 2013.**

	Minimum	Maximum	Mean	Std. Deviation	Pearson's R and Spearman Correlation Asymp. Sig. (2-sided)
ALT baseline	7	91	35.41	19.993	.878*
ALT after 3month	10	301	69.06	61.118	.000*

Table 4: **Bivariate and multivariate results of binary logistic regression analysis of patient on co-medication for HIV/TB infections, Ayder referral hospital, Mekelle-Ethiopia; 2013**

Variables		Cases	Control	Hepato-toxicity		B	S.E.	Wald	df	Sig.	Exp(B)
				Yes	No						
Sex	Female	14	41	5	50						
	Male	11	34	10	35	.75	.694	1.165	1	.281	2.116
Age	</=18	3	15	4	14			.111	2	.946	
	19-62	19	50	10	59	.05	.879	.004	1	.952	1.054
	>/=63	3	10	1	12	-.37	1.148	.101	1	.750	.694
HIV stage	Stage one	1	1	0	2			.628	3	.890	
	Stage two	0	1	0	1	-19.62	.0004	.000	1	1.000	.000
	Stge there	6	29	4	31	-20.43	.0004	.000	1	1.000	.000
	Stage four	18	44	11	51	-.86	1.085	.628	1	.428	.423
Type of TB	Pul.TB	8	33	5	36						
	Extra-Pul. TB	17	42	10	49	-.89	1.046	.737	1	.391	.407
ART reg.	NRTI+NNRTI	25	69	14	80			.277	2	.871	
	NRTI +PI	0	5	1	4	.65	1.227	.277	1	.599	1.907
	NRTI +NRTI	0	1	0	1	.00	.00057	.000	1	1.000	1.000
TB drugs reg.	Cat I	18	67	12	73			.515	2	.773	
	Cat II	7	4	2	9	-.58	1.238	.223	1	.637	.558
	Cat III	0	4	1	3	.82	1.470	.311	1	.577	2.271
HBV	Positive	4	0	3	1						
	Negative	21	75	12	84	3.13	1.476	4.497	1	.034*	22.862
CTM	Yes	22	57	12	67						
	No	3	18	3	18	-.497	.781	.404	1	.525	.609

Cat=category Reg. =regimen CTM=cotrimoxazole *=significant

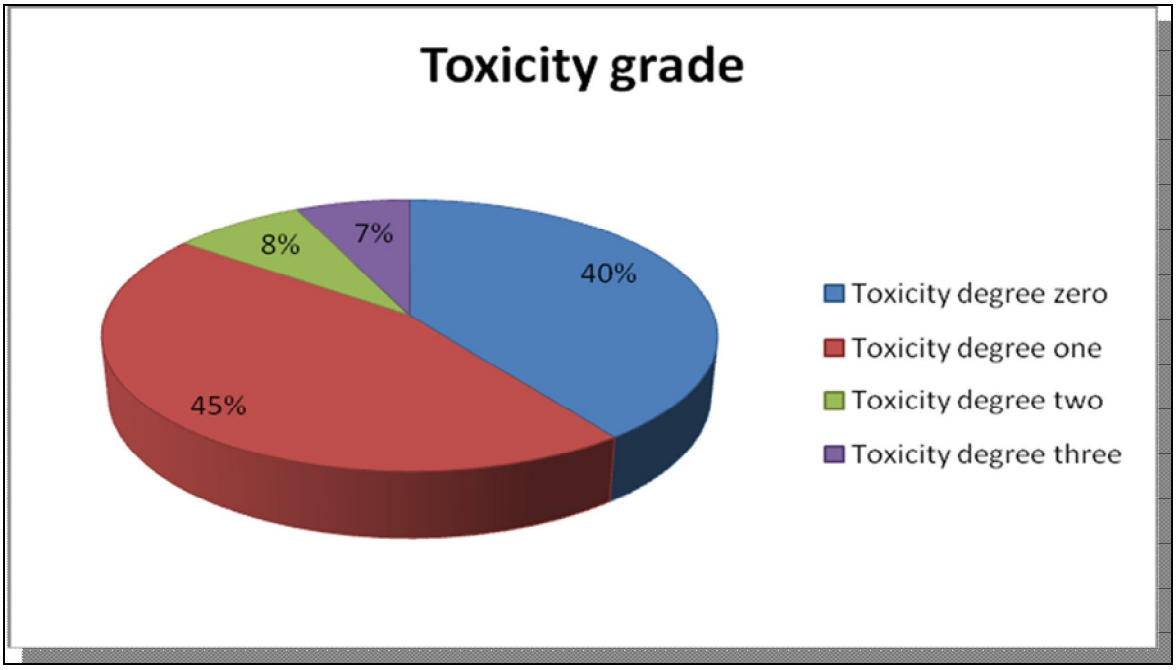

Figure 1: **Grade of toxicity based on ALT test result of patient on co-medication for HIV/TB infections, Ayder referral hospital, Mekelle-Ethiopia; 2013.**

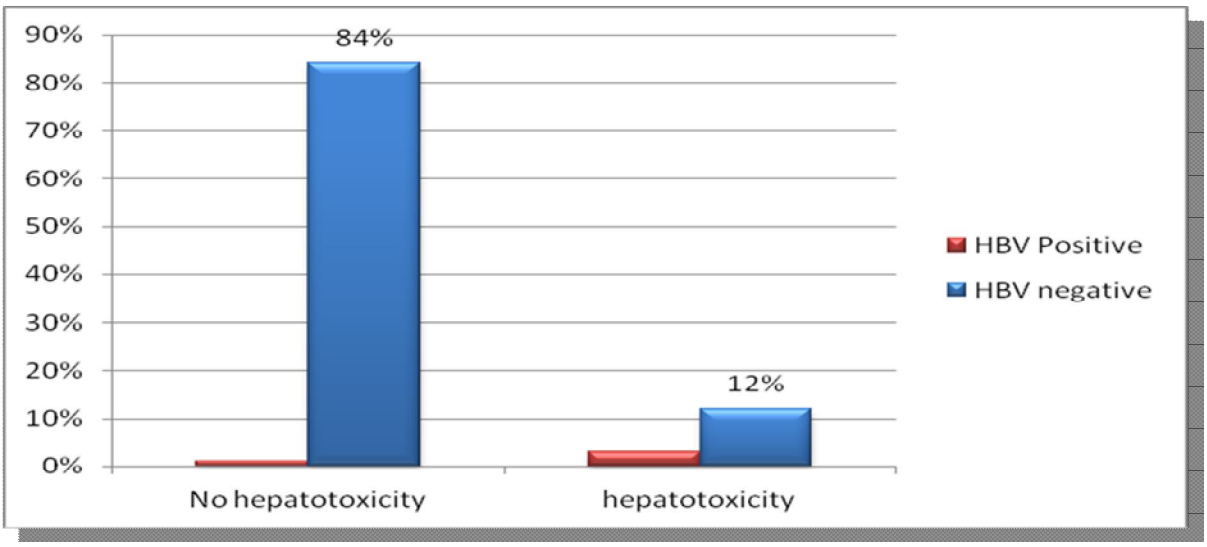

FIgure 2: **The prevalence of hepatotoxicity in HBV infected and non infected patients of patients on anti-TB and HAART medications, Ayder referral hospital, Mekelle-Ethiopia; 2013.**

Characteristics Of Liver Function Test (ALT Test)

The most frequent type of hepatotoxicity grade observed was toxicity degree type one, which was observed in 45% of the patients. No hepatotoxicity was observed in 40% of the study participants while only 7% were developed toxicity degree type three, which could result in

regimen change, discontinuation or drug desensitization, if it is symptomatic (Fig.1). A number of studies reported that the rates of severe hepatotoxicity in TB/HIV co-infected patients receiving both NNRTI based ART and rifampin containing anti-TB drugs concurrently range from 0.6% to 13% [18,19]. In our study the rate of severe hepatotoxicity (grade 2 or more) was 15 (15%) (Table 1), which is a little bit higher. Previous studies from Thailand reported that the rate of anti-TB drug induced hepatitis was 9.2% [20] and the rate of NNRTI associated severe hepatotoxicity was 14% [21]. Another study reported that the rate of NNRTI induced severe hepatotoxicity was 20% [7], which is in fact a little bit higher compared to our study [22].Many patients 40 (40%) had no significant transaminitis at baseline. This result is lower than other similar studies [23]. However, the prevalence of transaminitis at baseline with toxicity grade one in our study was 45%, which is a higher compared to other similar studies [23]. There was no Grade four transaminitis occurred in our study (Figure 1, Table 2).

Determinants Of Heptotoxicity

Five percent of female and 10% male on HAART and anti-TB medications developed hepatotoxicity. Patient in age between 19-62 year were develop almost double the prevalence i.e 10%, compared to 4% in </=18 year and only 1% in age >/=63 year respectively (Table 2). This result may be comparable to the number of participants involved in the study. When we compare the prevalence of hepatotoxicity based on the WHO stage of HIV classification, 11% percent of the patients who develop hepatotoxity were found in stage IV. Fourteen percent of patient develop hepatotoxicity were also on ART combination of NRTIs and NNRTIs. From anti-TB medication category majority i.e 12% were on category one anti-Tb medications. The mean and S.D of ALT at baseline in hepatotoxicity grade zero patients was (33.45, $\pm$ 17.84). This result was changed to (38.3, $\pm$ 21.042) after three months in the same population group. The mean and S.D of ALT change in heptotoxcity grade one patients at baseline and after three months were (36.87, $\pm$ 20.14 and 68.64, $\pm$ 45.491) respectively (Table 2). The present study showed that there was no significant correlation in toxicity grade at baseline ALT measures, (Spearman Correlation Asymp. Sig. (2-sided) = .878). However, the ALT measure after three month showed that significant association with the grades of toxicity, (Spearman Correlation Asymp. Sig. (2-sided) = .000) (Table 3). The prevalence of HBsAg positive serology in our study was 4% (Figure 2), that was lower than previous conducted study 30 (11.2%) [4]. HBV co-infection is a known risk factor for NNRTI induced hepatotoxicity in HIV infected patients [22]. In our study HCV infection was significantly

associated with the risk of hepatotoxicity, which occurred in 3 out of 4 of the study participants (OR, 22.7; P.value, 0.34) (Table 4). This figure was lower compared to other previous studies [7]. The difference may be due to the variation in study designs. The mechanism of liver injury mediated by HBV infection is related to immune restoration after ART, but the mechanism by which HBV leads to elevated liver enzymes is unclear. It may induce liver damage by a direct cytotoxic effect or by stimulatnoion of immune response [24].

CONCLUSIONS AND RECOMMENDATION

In our study the main factor determining the risk of hepatotoxicity in HIV-TB co-infected patients apart from the inherent hepatotoxic nature of first line anti-TB and ART medications was HBV infection. Therefore, we can conclude that HBV co-infection is an independent risk factor for hepatotoxicity in our study of TB-HIV co-infected patients. Clinicians must therefore consider the possibility of drug-induced liver injury in the management of HIV-infected patients, especially those with certain risk factors such as co-infection with hepatitis B virus (HBV) or hepatitis B virus (HBV).

Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ARH	Ayder Referral Hospital
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aaspartate Aminotransferase
CTM	cotrimoxazole
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immune Deficiency Virus
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
TB	Tuberculosis
ULN	Upper Limit of Normal

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