Assessment of Some Liver Enzymes of Human Immuno-Deficiency Virus (HIV) And Tuberculosis (TB) Subjects In Parts Of Esan Land, Edo State

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Abstract: Tuberculosis and Human Immunodeficiency Virus (HIV) infections are diseases which affect the immune system of the body. The aim of this study is to evaluate the activities of AST, ALT and ALP in Tuberculosis and HIV subjects. A total of one hundred and fifty subjects were recruited for this study which comprised of fifty (50) HIV infected subjects, fifty (50) tuberculosis infected subjects and fifty (50) apparently healthy subjects which served as control. Out of fifty (50) HIV infected subjects, twenty (20) subjects were newly diagnosed, fifteen (15) subjects were on drugs between 0-3 months and fifteen (15) were on drugs between 3-6 months. The same approach was used for recruitment of tuberculosis infected subjects. AST, ALT and ALP were determined using colorimetric method. The result obtain showed a significant increase ($p<0.05$) in the activities of AST in newly diagnosed HIV infected subjects (26.53±4.95u/l) as compared to the controls (22.17±10.34u/l). The activities of ALT were significantly increased ($p<0.05$) in newly diagnosed HIV subjects (13.62±2.20u/l) in comparison with the control (12.81±6.67u/l). On the same vein, the activities of ALP were significantly increased in the newly diagnosed HIV subjects (177.40±35.12u/l) as compared to the controls (76.22±17.55u/l). However, there were significant elevations in the activities of AST, ALT and ALP in HIV subjects under therapy within 0-3 months as compared to their respective controls. On the contrary, there was no significant difference in the activities of AST and ALT in HIV subjects under therapy within 3-6 months as compared to their respective controls. Though, there were was significant increase ($p<0.05$) in the activities of ALP in HIV subjects under therapy within 3-6 months (187.93±36.26u/l) as compared to their respective

controls (76.22±17.55u/l).The activities of ALP was significantly increase ($p<0.05$) in newly diagnosed TB infected subjects (114.50±40.29u/l) as compared to the controls (76.22±17.55u/l) while there was no significant difference observed in the activities of AST and ALT in newly diagnosed TB infected subjects. There was significant increase in the activities of AST, ALT and ALP in tuberculosis subjects under therapy within 0-3 months in comparison with the controls. Furthermore, there was significant increase in the activities of ALP in TB subjects under therapy for 3-6 months (103.93±32.70u/l) as compared to the controls (76.22±17.55u/l) while there was no significant difference observed for AST and ALT. This study however revealed that there were significant increase in the activities of AST, ALT and ALP which could possibly suggest predisposition liver impairment in these subjects.

Keywords: Liver, Enzymes, Immunity, Tuberculosis and Human Immunodeficiency Virus

INTRODUCTION

Tuberculosis is an infectious disease usually caused by the bacterium *Mycobacterium tuberculosis*. It generally affects the lungs but can also affects other parts of the body such as liver, bone, joint and central nervous system (WHO, 2015). Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak and sneeze (WHO and CDC 2015). Tuberculosis can be of pulmonary or extra-pulmonary. But it mostly occurs of pulmonary origin. The extra-pulmonary occurs outside the lungs (Dorlin *et al*., 2010). In 90% of pulmonary tuberculosis, the individual usually cough small amount of blood alongside the sputum. And also in rare case, the infection may erode into the pulmonary artery resulting in massive bleeding (Dorlin *et al*., 2010). Extra-pulmonary Tuberculosis occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases (Golden *et al*., 2005).

Human Immunodeficiency Virus (HIV) is a lentivirus that causes HIV infection and overtime acquired immunodeficiency syndrome (AIDS) (Douck *et al*., 2009). HIV infects vital cells in the human immune system such as helper T cells (specifically CD^4 T cells), macrophages, and dendritic cells (Cunmingham *et al*., 2010). HIV infection leads to low level of CD^4 T cells through a number of mechanisms, including pyroptosis of abortively infected T cells (Doltsh *et al*., 2014), apoptosis of uninfected bystander cells (Garg *et al*., 2012), direct viral killing of infected cells and killing infected CD^4 T cell by CD^8 cytotoxic lymphocytes that recognized infected cells (Kumar and Vinoy, 2012). When CD^4 members decline below a critical level, cell mediated immunity is lost and the body becomes progressively more susceptible to opportunistic infections.

The liver is the largest organ in the human body (Balisteri, 1996) weighing approximately 1.2 -1.5kg in the adult, and located in the right upper quadrant of the abdomen of the abdomen beneath the diaphragm, where it is held in place by ligamentous attachment. It is divided into four lobes which are supplied by the left right braches of the portal vein and the hepatics artery namely the right lobe, which is the largest. The left lobe, the smaller and wedge shape and the quadrant, nearly square in outline and the caudate lobe tail-like in appearance (Nsirim, 1999). The human liver organ performs a number of functions essential for life (Jau-shin, 2005). These functions includes receiving, processing and storage of materials absorbed from the digestive tract such as amino acids, carbohydrate, fatty acid ,cholesterol and vitamins; and it is capable of releasing metabolites of these compound on demand. Other functions include synthesis of plasma proteins, bile acid from cholesterol detoxification and site of metabolic conversion of endogenous and exogenous compounds (Balisteri, 1996).

The effect of TB on liver can be describes in three forms as described by Spiegel and Tuazon, (1984). The most common form is the diffuse hepatic involvement seen along pulmonary or military tuberculosis. The second

form is diffuse hepatic infiltration without recognizable pulmonary involvement. While the third form is much rear form presents as a focal/local tuberculoma or abscess. At the beginning of the HIV era, liver dysfunction in HIV-infected patients mainly corresponded with opportunistic infections (e.g with cytomegalovirus or mycobacteria and leishmaniasis), tumor (lymphoma and Kaposi sarcoma), drugs related hepatitis (caused by trimetiprim-sulfamethoxazole and other antibiotics). And Human immunodefiency virus itself infects the liver cells resulting in stimulation of immunological response by hepatic phagocytes against the infection leading to cells damage (Lebovics *et al*., 1988, Cappell, 1991 and Lefkowitch, 1994). On administration of antiretroviral therapy, liver toxicity increased (Spengler *et al*., 2002 and Raul *et al*., 2007).

Various studies done by different researcher have shown that serum liver enzymes are affected in HIV and TB individuals. In a research by Mayne, (1994) reported an increased Transaminase in newly diagnosed HIV infected subjects and administration of ART, Tranaminase was further increased. In contrast, Monitoring of the liver function in patients on anti-tuberculosis therapy indicated an increased Alkaline Phosphates serum activity, most frequently occurs during first three months of therapy but not in newly diagnosed. There is a tendency of enzymes values to return to normal irrespective of continuous treatment (Aldrich *et al.,* 2001*).*

Therefore, this study was carried out to assess serum levels of AST, ALT and ALP on drug naïve and chemotherapy subjects with TB and HIV infections

METHODOLOGY

STUDY AREA

This research was carried out in Irrua Specialist Teaching Hospital Edo state, Nigeria. Irrua lies longitudinally at 04ºE and 43ºE and Latitude 05º44ºN and 07º34ºN. Its geopolitical location is the South and it has a population of 3.1 million people (World Gazzetter, 2007).

SAMPLE SIZE

The number of subject sample sizes used in this research was guided by upper limit range to give 95% level of confidence at the expected prevalence of about 11% using the precise formular

$$N = \frac{Z^2pq}{D^2}$$

Where:

N = The desired sample size (when population is greater than 10,000).

Z = Constant given as 1.96 which corresponds to 95% confidence level.

P = Expected prevalence is11% (0.11).

q = 1.0 – p.

d = Acceptable error is 5% (Aroaye, 2004).

$$N = \frac{(1.96)^2 \times 0.11(1.0-0.11)}{(0.05)^2}$$

$$N = 150.44$$

A minimum of 150 samples was collected for this study.

RESEARCH PROTOCOL

The research was done to evaluate the serum level of Aspartate transterase (AST), Alanine transferase (ALT) and Alkaline phosphatase (ALP) in 150 subjects (50 HIV subjects, 50 TB subjects and 50 normal individual). The fifty (5)0 HIV infected subjects and fifty (50) TB infected subjects were compared with 50 controls

(normal subjects). The tuberculosis and HIV patient were grouped into drug naïve and those on drugs for the duration of 0-3 months and 3-6 months. The drug naïve were twenty (20), while those on drugs for 0-3 months were fifteen (15) and those on drugs for 3-6 months were fifteen (15). A validated, quantitative questionnaire was used to obtain their HIV and TB infection knowledge. During this period, HIV-negative and non TB infected volunteers from the same community was recruited for comparison. Ethical approval was given by institution ethical committee, of Irrua Specialist Teaching Hospital, Irrua. Blood samples were collect from these subjects and then centrifuged at 5,000rpm for 5 minutes after which it is then separated into plain container as serum labeled accordingly and kept frozen till the time of analysis. The data was analyzed using SPSS software, version 20.0 (SPSS), and the results will be expressed as mean values and standard deviations. Analysis of variance (ANOVA) was performed to test differences between groups. Differences was considered to be significant if the p- value <0.05.

INCLUSION AND EXCLUSION CRITERIA

Only subjects infected with TB and HIV between the ages of 18-65years of both sexes were sampled for this study. Healthy individuals within the age bracket were also sampled and used as controls. While individuals that are not within the age ranges of 18-65 years, haematological co-morbidities, sickle cell anemia and pregnant women were excluded from the study.

SAMPLE COLLECTION

Blood samples (5mls) were collected by clean venepuncture from the ante-cubital fossa into already labeled lithium heparin bottles, without undue pressure to either the arm or the plunger of the syringe. The samples were mixed by gentle inversion. The samples were centrifuged at 3000 rpm for 5 min to obtain the plasma. The plasma supernatants were separated into sterile bottles and stored frozen until analysis was done at room temperature.

BIOCHEMICAL ANALYSIS

Estimation of the activities of ALT, AST, and ALP was done using Randox Laboratory test kit (Antrim, UK). Specifically, ALT and AST activities were estimated using the method described by Reitman and Frankel (1957), while ALP was done using the methods described by Deutshe (1972)

STATISTICAL ANALYSIS

Statistical Package for Social Science (SPSS) version 20.0 software (SPSS Inc., Chicago, IL USA) windows was used and P<0.05 was considered as statistically significant using student t-test and ANOVA method of analysis.

RESULT

The results on socio demographic profile revealed that out of the total 50 HIV subjects enrolled for this study, 20 subjects were naïve (newly diagnosed), 15 subjects were on drugs between 0-3 months and 15 subjects were on drugs between 3-6 months. Out of the 20 HIV subjects naïve, 10 (50%) subjects were male and 10 (50%) subjects were female. Of out the 15 HIV subjects on drug for 0-3 months, 7 (46.7%) subjects were male and 8 (53.3%) were female. Out of the 15 HIV subjects on drugs for 3-6 months, 7 (46.7%) subjects were male and 8 (53.3%) subjects were female. A total of 50 Tuberculosis (TB) infected subject were enrolled in which 20 subjects were newly diagnosed (naïve), 15 subjects were on drugs for 0-3 months and 15 subjects were on drugs for 3-6 months. Out of 20 newly diagnosed TB subjects, 10(50%) subjects were male and 10(50%) were female. Out of the15 TB subjects on drugs for 0-3 months, 7(46.7%) subjects were male and 8(53.3%) were

female. And out of the 15 TB subjects on drugs for 3-6 months, 7(46.7%) subjects were male and 8(53.3%) were female (Table 1).

The results revealed a significant increase ($p<0.05$) in the activities of AST of HIV subjects (24.93±15.02) as compared to the controls (22.17±10.34 U/L). There was significant increase ($p<0.05$) in the activities of ALP of HIV subjects (197.70±66.42) as compared to the controls (76.22±17.55). There was no significant difference ($p>0.05$) when the activities of ALT in HIV subjects were compared with the controls (Table 2). Furthermore, there was a significant increase ($p<0.05$) in the activities of AST of TB subjects (36.32±21.21) as compared to the controls (22.17±10.34 U/L). There was significant increase ($p<0.05$) in the activities of ALP of TB subjects (128.70±39.60) as compared to the controls (76.22±17.55). There was no significant difference ($p>0.05$) when the activities of ALT in TB subjects were compared with the controls (Table 2)

The results obtained for liver enzyme activities of HIV subjects at different stages of infection revealed a significant increase ($p<0.05$) in the activities of AST in newly diagnosed HIV infected subjects (26.53±4.95u/l) as compared to the controls (22.17±10.34u/l). The activities of ALT were significantly increased ($p<0.05$) in newly diagnosed HIV subjects (13.62±2.20u/l) in comparison with the control (12.81±6.67u/l). On the same vein, the activities of ALP were significantly increased in the newly diagnosed HIV subjects (177.40±35.12u/l) as compared to the controls (76.22±17.55u/l). However, there were significant elevations in the activities of AST, ALT and ALP in HIV subjects under therapy within 0-3 months as compared to their respective controls. On the contrary, there was no significant difference in the activities of AST and ALT in HIV subjects under therapy within 3-6 months as compared to their respective controls. Though, there were was significant increase ($p<0.05$) in the activities of ALP in HIV subjects under therapy within 3-6 months (187.93±36.26u/l) as compared to their respective controls (76.22±17.55u/l) (Table 3).

The results obtained for liver enzyme activities of TB subjects at different stages of infection revealed that the activities of ALP was significantly increased ($p<0.05$) in newly diagnosed TB infected subjects (114.50±40.29u/l) as compared to the controls (76.22±17.55u/l) while there was no significant difference observed in the activities of AST and ALT in newly diagnosed TB infected subjects. There was significant increase ($p<0.05$) in the activities of AST, ALT and ALP in tuberculosis subjects under therapy within 0-3 months in comparison with the controls. Furthermore, there was significant increase in the activities of ALP in TB subjects under therapy for 3-6 months (103.93±32.70u/l) as compared to the controls (76.22±17.55u/l) while there was no significant difference observed for AST and ALT (Table 4).

The classification of the HIV subjects based on the stages of infection revealed that out of 20 naïve HIV subject, 6(30%) subjects were on stage 1, 10(50%) subjects were on stage II and 4 (20%) subjects were on stage III. Out of the 15 HIV subjects on drugs for 0-3 months, 6(40%) subjects were on stage I, 9(60%) subjects were on stage II and none were on stage III. And out of the 15 HIV subjects on drugs for 3-6months, 10(66.7%) subjects were on stage I, 5(33.3%) subjects were on stage II and none were on stage III (Table 5).

Table 1: Sex Distribution of HIV and TB Subjects

Sex	Control	HIV naïve	HIV 0-3 months	HIV 3-6 months	TB naïve	TB 0-3 months	TB 3-6 months

Male	25(50%)	10(50%)	7(46.7%)	7(46.7%)	10(50%)	7(46.7%)	7(46.7%)
Female	25(50%)	10(50%)	8(53.3%)	8(53.3%)	10(50%)	8(53.3%)	8(53.3%)
Total	50	20	15	15	20	15	15

Table 2: Liver Enzymes Activities of HIV and TB Subjects

Parameters	Control (n=50)	HIV (n=50)	t-value	p-value	TB (n=50)	t-value	P-value
AST	22.17±10.34	24.93±15.02	10.44	0.006	36.32±21.21	50.56	0.000
ALT	12.81±6.67	18.27±14.80	8.44	0.327	15.04±13.85	12.10	0.308
ALP	76.22±17.55	197.70±66.42	36.25	0.000	128.70±39.6	42.74	0.000

KEY: P<0.05-Significant; P>0.05-Non significant; ALP-AlkalinePhosphatase; AST- Aspartate Aminotransferase; ALT-Alanine Aminotransferase.

Table 3: Liver Enzymes Activities of HIV Subjects at Different Stages of Drug Therapy

Parameters	Controls (n=50)	Naïve (n=10)	0-3 months (n=15)	3-6 months (n=15)	F-value	P-value
AST	22.17±10.34	26.53±4.95*	22.21±9.87*	23.52±23.33**	7.882	0.037
ALT	12.81±6.67	13.62±2.20*	19.88±4.34*	8.64±7.26**	20.104	0.028
ALP	76.22±17.55	177.40±35.12*	234.53±101.53*	187.93±36.26*	156.3	0.000

KEY: *-Significant; **-Not Significant; P<0.05-Significant; P>0.05-Non significant; ALP-AlkalinePhosphatase; AST- Aspartate Aminotransferase; ALT-Alanine Aminotransferase.

Table 4: Liver Enzymes Activities of TB Subjects at Different Stages of Drug Therapy

Parameters	Controls (n=50)	Naïve (n=10)	0-3 months (n=15)	3-6 months (n=15)	F-value	P-value
AST	22.17±10.34	30.10±19.51**	46.93±21.71*	34.00±20.12**	17.976	0.000
ALT	12.81±6.67	14.30±13.29**	17.60±4.80*	12.80±4.00**	1.050	0.000
ALP	76.22±17.55	114.50±40.2*	132.40±40.89*	103.93±32.70*	73.395	0.000

KEY: *-Significant; **-Not Significant; P<0.05-Significant; P>0.05-Non significant; ALP-AlkalinePhosphatase; AST- Aspartate Aminotransferase; ALT-Alanine Aminotransferase.

Table 5: CD^4 Count Distribution Frequency among HIV Infected Subjects

CD^4 count reference range: 548-1068

HIV	Total	HIV stage 1 (548-1068)	HIV stage 11 (200-499)	AIDS stage III (0-199)
Naïve	20	6(30%)	10(50%)	4(20%)
0-3	15	6(40%)	9(60%)	0
3-6	15	10(66.7%)	5(33.3%)	0

DISCUSSION

Various studies done by different researcher have shown that serum liver enzymes were affected in HIV and TB subjects. In a research carried out by Mayne, (1994), there was report in increased Transaminase activities in newly diagnosed HIV infected subjects and on administration of ART, Tranaminases were further increased. In addition, monitoring of the liver function in patients on anti-tuberculosis therapy indicated an increased Alkaline Phosphatase serum activity most frequently during the first three months of therapy but not in newly diagnosed. There is a tendency of the enzymes values to return to normal irrespective of continuous treatment (Aldrich *et al*., 2001).

In this study, a significant increase in the activities of AST, ALT and ALP were observed in newly diagnosed HIV subjects when compared with the control. This correlated with the research by carried out Abubakar *et al*., (2014). This could be attributed to the fact that HIV virus infects a wide range of non-hemaetopoietic cell including cells in the liver. This serve as a reason for the elevated liver enzymes observed in the newly diagnosed HIV subjects (Lebovies *et al*., 1988, Cappell, 1991 and Lefkowitch, 1994).

Results of liver enzymes level obtain from HIV infected subjects on antiretroviral therapy (ART) between 0-3 months showed a significant increase of AST, ALT and ALP level when compared to the control. This result agrees with the report of Abubakar *et al*., (2014). This may be due to hepatotoxicity caused by antiretroviral drug side effect (Sulkowski *et al*., 2000; Gisolf *et al*., 2000, Resier *et al*., 2001). The mechanism by which ART cause liver related toxicity particularly, NRTIs is through direct mitochondrial toxicity leading to abnormal liver function (Murphy *et al*., 2010), while NNRTIs may cause direct cell stress and distribution in lipid or sugar metabolism associated to protease inhibitor (Nunez, 2010).

After 3-6 month duration on ART, only ALP remained significantly increased when compared to control. But reduced when compare to newly diagnosed HIV subjects and HIV subjects on ART between 0-3 months. While AST and ALT were non-significant when compare to the control. This result is in contrast with the research by Ayelagbe *et al*., (2014). However, this partially correlates with the study of Abubakar *et al.*, (2014) where they reported that this reduction in serum level of Alkaline Phosphatase (ALP) might be due to absent of factors that were responsible for liver toxicity apart from ART. These factors include Alcohol, illicit drugs or medication abuse, other disease conditions that affect the liver such as HBC or HCV, abnormal metabolic syndrome and HIV virus liver inflammation. In addition, in the absence of all these factors and ability of ART to reduced viral load or HIV virus liver inflammation, the liver enzymes activities gradually return to normal.

The CD^4 count in newly diagnosed HIV subjects was decreased when compared to reference range. This agrees to research by Alimont *et al.*, (2003) where they reported that HIV virus has negative effect on CD^4 Lymphocyte cells which is the cause of decreased CD^4 count in naïve HIV subjects. The CD^4 count increases on initiation of ART treatment.

This study also showed that ALP was significantly increased when compare to control while there were no significant changes in the activities of AST and ALT when compare to control in newly diagnosed TB infected Subject. This could be aligned with the fact that *Mycobacterium tuberculosis* which causes pulmonary tuberculosis might have diffused into other organs such as bone, pleural and liver (Extra-pulmonary tuberculosis); therefore leading to increased concentration of ALP (Anantnaryan and Panikar, 2013).

It was also observed that there was significant increase in the activities of AST, ALT and ALP in TB subjects on therapy between 0-3 months. This increase could be attributed to the fact that on initiation of Antituberculosis Therapy, ATT (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide), hepatotoxicity occur leading to an increased AST,ALT and ALP level (Preeti *et al*., 2013). Isoniazid first undergoes acetylation and get converted into acetyl isoniazid which further hydrolyzed into two products acetyl hydrazine and isoniotinic acid. Some part is converted into hydrazine. Hydrazine is responsible for hepatotoxicity that led to the increased in liver enzymes activities (Preeti *et al*., 2013).

Only ALP was significantly increased while there was no significant change in the activities of AST and ALT in TB subjects under therapy between 3-6 months. This is in line with the study of Dinesh and Rao, (2005) where they reported that the combination of Rifampicin and Ethambutol have potent activities against *Mycobacterium tuberculosis* but along with that it induced hazardous side effects on patient liver like hepatitis and jaundice.

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