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# Effects of HIV Infection and Highly Active Antiretroviral Therapy (HAART) on the Liver of HIV Patients

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## ABSTRACT

The use of Highly Active Antiretroviral Therapy (HAART) has improved the prognosis of HIV-infected individuals. However, the beneficial effect of reduced risk of early death from opportunistic infections and other consequences of HIV infection is reduced because Antiretroviral Therapy (ART) also carries negative side effects, including hepatotoxicity. The study examines hepatotoxic effect of HAART and hepatitis co-infection in HIV patients. Alkaline phosphatase, alanine transaminase, aspartate transaminase, gamma glutamyl transferase were determined from the serum of 100 HAART-experienced and 50 HAART-naïve HIV infected subjects enzymatically using Junior Flexor autoanalyser. Serum proteins were assayed by the biuret reaction and bilirubin determination was based on the diazo coupling reaction of Ehrlich method. HBV surface antigen (HBsAg) was detected by enzyme-linked immunosorbent assay. Globulins, total proteins, alkaline phosphatase, alanine transaminase, aspartate transaminase and gamma glutamyl transferase were significantly ($p<0.001$) elevated in the HIV HAART-experienced patients than the controls. Forty six percent of the HAART-experienced developed hepatotoxicity. Based on bilirubin levels, 11% of the HAART-experienced had hepatotoxicity. Nine percent of the HAART-experienced were co-infected with hepatitis B and 77% of them developed hepatotoxicity whilst 22% of the HAART-naïves were co-infected with hepatitis B and 73% of these developed hepatotoxicity. Hepatotoxicity was negatively correlated with alkaline phosphatase, alanine transaminase, aspartate transaminase, gamma glutamyl transferase and total plasma proteins. HAART induced hepatotoxicity in HIV patients more than HAART-naïve. There is an increased risk of hepatotoxicity in HIV patients' co-infection with hepatitis B virus and on antiretroviral therapy.

**Key words:** Hepatotoxicity, hepatitis B

## INTRODUCTION

HAART has produced a great deal of relieve for the HIV patients by decreasing the morbidity and mortality from opportunistic infections. However, this positive impact of Antiretroviral Therapy (ART) also carries negative side effects, including metabolic abnormal changes termed lipodystrophy syndrome and cardiovascular diseases (Farrugia *et al*., 2009; Nolan and Mallal, 2004) and hepatotoxicity which impede the management of HIV-infected patients. Among these, liver toxicity is the main focus since, it leads to HAART withdrawal especially when complicated by Hepatitis C Virus (HCV) and/or Hepatitis B Virus (HBV) co-infection. According to the AIDS Clinical Trials

Group scale of liver toxicity (AIDS Clinical Trials Group, 1996), hepatotoxicity is defined as patients with transaminases; ALT and/or AST rise above the upper limits of the normal range. Severe hepatic injuries are classified as grade 3 or 4 changes in AST and/or ALT levels during antiretroviral treatment when ALT, AST levels are 3-5 and greater than 5 times the upper normal limit, respectively. Also, severe hyperbilirubinaemia is classified as grade 3 or 4 and is treated independent of AST and ALT levels (Kontorinis and Dieterich, 2003).

Alkaline phosphatase is produced mostly from the liver and bone, its elevation is suggestive of biliary obstruction, injury to the bile duct or cholestasis when bone disease is excluded. Bone diseases such as paget disease, sarcoma, metastatic disease, hyperparathyroidism and rickets can increase plasma alkaline phosphatase levels. High plasma alkaline phosphatase level is also associated with the small bowel, kidneys and the placenta. Gamma Glutamyl Transferase (GGT) is a membrane bound enzyme that is a maker of hepatobiliary disease, it is not very specific and also a sensitive maker of alcohol and drugs such as phenytoin and phenobarbital which induce GGT (Magarian *et al*., 1992). However, its parallel elevations with alkaline phosphatase is a confirmation of hepatic source of damage (Lieberman and Phillips, 1990).

HAART, generally consists of a combination of Nucleoside Analog Reverse Transcriptase Inhibitors (NRTI) plus a Protease Inhibitor (PI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) (Young, 2005). The extent to which each of these drugs induce or contributes to hepatotoxicity is varied. In some studies on PI's, full-dose ritonavir (RTV) has been found to be severely hepatotoxic (Sulkowski *et al*., 2000; Bonfanti *et al*., 2001), however, these results have been disputed by other researchers (Monforte *et al*., 2001; Cooper *et al*., 2002). RTV has also been reported to induce sever hepatotoxicity (Pai *et al*., 2000) and several cases of liver toxicity have also been reported associated with the use of indinavir (IDV) and saquinavir (SQV) (Flexner, 1998; Sulkowski, 2003). Many NRTI's induce mitochondrial damage and, thus, have also been associated with hepatotoxicity. Severe hepatic injury has been reported by the use of zidovudine, didanosine and stavudine (Brinkman *et al*., 1998; Gisolf *et al*., 2000). The hepatotoxic effect of NNRTI is also being contested. In some studies, the incidence of liver toxicity was similar to other antiretrovirals (Martinez *et al*., 2001; Palmon *et al*., 2002). While some researchers have found a higher liver toxicity for NVP than efavirenz (EFZ) (Sulkowski *et al*., 2002; Martin-Carbonero *et al*., 2003), others have failed to establish these findings (Palmon *et al*., 2002). Data also suggest that NNRTI's have a greater risk to induce immunoallergic effect on the liver soon after the start of therapy. With prolonged therapy, especially in HBV and/or HCV co-infected subjects, NNRTI have a tendency to induce a slight increase in the cumulative hepatotoxicity effect which may spontaneously abate over time (Sulkowski *et al*., 2002).

## MATERIALS AND METHODS

The study was carried out at the Kumasi South Hospital (Ghana) with the permission of the National Aids Control Programme. All procedures were approved by the Committee on Human Research Publication and Ethics of School of Medical Sciences, KNUST (CHRPE/Student/113/09). A written informed consent form was completed by all the participants, who were recruited into the study after the study was explained in a language they understood.

**Study design:** The study was descriptive, cross sectional and case-controlled and consisted of 100 patients on highly active antiretroviral therapy for at least six months constituting HAART-experienced and 50 HAART-naive patients constituted HIV-positive patients, not on

HAART and whose CD4 count was not below the critical value of 320 cell $mL^{-1}$. Personal information such as alcohol history, age, sex, pregnancy state for the females, duration of HAART and pulmonary tuberculosis history were obtained from their hospital folders and from pre-tested questionnaires. Patients with abnormal liver function tests before commencing HAART and patients who took more than an estimated 24 g alcohol per day, were considered high drinkers (Greenfield and Kerr, 2008), were excluded from the study. Patients with pretreatment serum AST and ALT levels within the normal range (AST, 35 IU $L^{-1}$ and ALT, 31 IU $L^{-1}$) were classified based on changes relative to the Upper Limit of Normal (ULN): Grade 0, less than 1.25 ULN; grade 1, 1.25-2.5 ULN; grade 2, 2.6-5.0 ULN; grade 3, 5.1-10 ULN; grade 4, greater than 10 ULN (Sulkowski *et al.*, 2002). Patients with a positive HBV surface antigen by immunoassay with neutralization (two or more occasions) were considered to have chronic infection.

WHO recommended antiretroviral medicines were used: Abacavir, combivir, lamivudine, efavirenz, tenofovir and nevirapine. All the HAART experienced participants involved in the study used a combination of these medicines grouped under NRTI consisting; lamivudine combivir, tenofovir and abacavir and NNRTI consisting of nevirapine and efavirenz. The study was limited to the Ministry of health approved antiretroviral drugs and their combinations at the research center. The various combinations at the site include the following; combivir plus either nevirapine or efavirenz or tenofovire plus lamivudine and either nevirapine or efavirenz and a third combination consisting of abacavir and lamivudine with either nevirqpine or efavirenz.

**Sample preparation and biochemical assay:** Fasted blood samples (overnight fast between 8-12 h) were drawn from the median cubital vein on the anterior forearm into plain tubes; BD vacutainer®, (BD, Plymouth, PL6 7BP. UK). The clotted blood was centrifuged (Zentrifugen, D-78532, Tuttlingen, Germany) at 3000 rpm for 5 min to separate out the serum for Liver Function Test (LFT).

**Biochemical assay:** The sample analysis was done using Junior Flexor fully automated biochemistry analyzer. This analyzer uses Elitech brand of biochemistry reagents from vital scientific. The principle for the determination of AST and ALT, briefly are based on the AST catalysed transfer of amino group of L-aspartate to alpha-ketoglutarate to form L-glutamate and ALT catalysed transfer of amino group of L-alanine to alpha-ketoglutarate to give L-glutamate (Schumann *et al.*, 2002). Albumin estimation was based on its reaction with bromocresol green in the presence of succinate buffer (pH 4.2) to produce albumin-BCG complex (Doumas *et al.*, 1971). Alkaline Phosphatase assay (ALP) was based on its catalysed conversion of p-nitrophenylphosphate to p-nitrophenol and inorganic phosphate (German Society for Clinical Chemistry, 1972). While, Gamma-Glutamyl Transferase (GGT) assay was based on its catalytic conversion of L-gamma-Glutamylnitroalinide (GNPA) and glycylglycine to L-gamma glutamyl-glycylglycine and p-nitroanilide. The p-nitroanilide is proportional to the GGT activity (Szasz, 1974). Serum proteins form a coloured complex in the presence of copper salt in alkaline solution (Gornall *et al.*, 1949) and the determination of bilirubin was based on sulfanilic acid reaction with sodium nitrite to form diazotized sulfanilic acid. In the presence of cetrimide, conjugated and unconjugated bilirubin reacts with diazotized sulfanilic acid to form azobilirubin. In the absence of cetrimide, only conjugated bilirubin reacts (Sherwin and Thompson, 2003; Nosslin, 1960). The HBV surface

antigen (HBsAg) was detected by Enzyme-Linked Iimmuno Sorbent Assay (ELISA) using a commercially available test kit (Behringwerke AG, Marburg, Germany).

**Statistical analysis:** The data was analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0. The Mann-Whitney test was used for all the variables since they were not normally distributed according to the Kolmogorov-Smirnov normality test. Correlation studies of hepatotoxicity and liver function tests was carried out using Spearman rho correlation. The level of significance was set at $p<0.05$ and confidence level at 95%.

## RESULTS

Demographic and clinical characteristics of HIV HAART-experienced and HAART-naive patients are shown in Table 1. Of the 100 cases (HAART-experienced) analyzed, 54 (54%) were normal for hepatotoxicity while, 16(16%), 21(21%), 5(5%) and 4(4%) were of grade 0, 1, 2 and 3, respectively for hepatotoxicity. In contrast, none of the cases had grade 4 for hepatotoxicity. Also, significantly 22% of the controls had hepatitis B surface antigen as against 9% of the cases. Globulins, total proteins, AST, ALT, ALP and GGT were significantly ($p<0.001$) elevated in the HIV HAART-experienced patients than the controls 46% of the HAART-experienced developed hepatotoxicity. Eight out of 12, of those who have being on the drug for 1-6 months, had hepatotoxicity and also 8 out of 19 for 7-12 months, 20 out of 50 for 13-18 months, 10 out of 19 for >19 months as shown in (Table 2), 16 of the 46 cases of hepatotoxicity in the cases had grade 0, 21 of 46 cases had grade 1, 5 of 46 were grade 2 while the remaining 4 of 46 cases were grade 3 hepatotoxicity.

Table 1: Demographic and clinical characteristics of HIV HAART-experienced and HAART-naive patients as absolute count (frequency %)

| Parameters | Cases (100) | Control (50) | p-value |
|---|---|---|---|
| Age | 36 | 35 | 0.646 |
| **Sex** | | | |
| F | 64 (64%) | 35 (70%) | 0.465 |
| M | 36 (36%) | 15 (30%) | |
| **Proteine (g $L^{-1}$)** | | | |
| Albumin | 40.6 (9.1) | 41.4 (5.6) | 0.208 |
| Globulin | 47.64 (135.52) | 37.86 (50.44) | <0.001 |
| Total protein | 89.2 (23.6) | 78.9 (12.0) | <0.001 |
| **Enzyme level (IU $L^{-1}$)** | | | |
| ALP | 325.1 (182.4) | 188.1 (55.4) | <0.001 |
| ALT | 21.0 (16.5) | 11.5 (9.9) | <0.001 |
| AST | 32.3 (22.4) | 22.6 (12.2) | <0.001 |
| **Bilirubin (mg $dL^{-1}$)** | | | |
| Direct | 3.1 (3.4) | 4.0 (3.4) | 0.865 |
| Indirect | 2.2 (1.9) | 2.0 (1.6) | 0.304 |
| Total | 5.5 (4.9) | 5.4 (4.4) | 0.475 |
| **Tests** | | | |
| GGT (IU $L^{-1}$) | 46.5 (37.8) | 19.2 (12.8) | <0.001 |
| HBsAg | 9 (9%) | 11 (22%) | 0.027 |

Continuous data have been expressed as median (interquartile range) while, categorical data have been expressed as absolute count (frequency %), ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gamma glutamyl transferase, HBsAg: Hepatitis B surface antigen

Table 2: Comparison of hepatotoxicity among HAART-experienced using ALT and/AST with respect to duration on drug

| | Months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1-6 (12) | | 7-12 (19) | | 13-18 (50) | | >19 (19) | | Total | |
| Hepatotoxicity grade | No. | Percentage | No. | Percentage | No. | Percentage | No. | Percentage | No. | Percentage |
| Normal | 4 | 33.3 | 11 | 57.9 | 30 | 60.0 | 9 | 47.4 | 5 | 454.0 |
| 0 | 5 | 41.7 | 1 | 5.3 | 7 | 14.0 | 3 | 15.8 | 1 | 616.0 |
| 1 | 3 | 25.0 | 5 | 26.3 | 9 | 18.0 | 4 | 21.1 | 2 | 121.0 |
| 2 | 0 | 0.0 | 2 | 10.5 | 2 | 4.0 | 1 | 5.3 | 5 | 5.0 |
| 3 | 0 | 0.0 | 0 | 0.0 | 2 | 4.0 | 2 | 10.5 | 4 | 4.0 |

Values have been expressed as absolute number (incidence), duration on drug is expressed in months

Table 3: Comparison of hepatotoxicity among HIV HAART-experienced using total bilirubin with respect to duration on drug

| | Months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1-6 (12) | | 7-12 (19) | | 13-18 (50) | | >19 (19) | | Total | |
| Hepatotoxicity grade | No. | Percentage | No. | Percentage | No. | Percentage | No. | Percentage | No. | Percentage |
| Normal | 11 | 91.7 | 17 | 89.5 | 45 | 90.0 | 16 | 84.2 | 89 | 89.0 |
| 1 | 0 | 0.0 | 1 | 5.3 | 0 | 0.0 | 0 | 0.0 | 1 | 1.0 |
| 2 | 1 | 8.3 | 0 | 0.0 | 3 | 6.0 | 0 | 0.0 | 4 | 4.0 |
| 4 | 0 | 0.0 | 1 | 5.3 | 2 | 4.0 | 3 | 15.8 | 6 | 6.0 |

Values have been expressed as absolute number (incidence), duration on drug is expressed in months

Table 4: Comparison of hepatotoxicity among cases and controls

| | Cases (100) | | Control (50) | | Total | |
|---|---|---|---|---|---|---|
| Hepatotoxicity grade* | No. | Percentage | No. | Percentage | No. | Percentage |
| Normal | 54 | 54.0 | 42 | 84.0 | 96 | 64.0 |
| 0 | 16 | 6.0 | 1 | 2.0 | 17 | 11.3 |
| 1 | 21 | 21.0 | 6 | 2.0 | 27 | 18.0 |
| 2 | 5 | 5.0 | 1 | 2.0 | 6 | 4.0 |
| 3 | 4 | 4.0 | 0 | 0.0 | 4 | 2.7 |

Values have been expressed as absolute number (incidence), *Hepatotoxicity grade of ALT and/AST is used

In using bilirubin levels as an index of hepatotoxicity, 89% were normal whilst 11% had hepatotoxicity of different grades as depicted in Table 3. One of the 11 cases of hepatotoxicity occurred within 1-6 months of therapy, 2 of 11 cases occurred within 7-12 months, 5 of 11cases occurred within 13-18 months while the remaining 3 of 11 cases occurred after >19 months therapy. Of the 50 controls 8 had hepatotoxicity in which there were one each in grade 0 and 2 whiles 6 had grades 1 and none had grade 3 (Table 4) while 46 of the cases had hepatotoxicity.

In Table 5, 7 of the 9 cases co-infected with HBsAg had hepatotoxicity of which 5 were of grade 2 and 3 while 8 of 11 of the controls co-infected with HBsAg had hepatotoxicity in graded 0-2 but no grade 3.

There was a negative significant correlation between ALT and/AST hepatotoxicity and TPT, ALP, ALT, AST TBIL and GGT. Also bilirubin hepatoxicity index was negatively correlated to ALP, ALT, AST, TBIL and GGT and positively correlated with total proteins.

Table 5: Comparison of incidence of hepatotoxicity among cases and controls with HBsAg co-infection

| | Cases (100) | | Control (50) | | Total | |
|---|---|---|---|---|---|---|
| Hepatotoxicity grade* | No. | Percentage | No. | Percentage | No. | Percentage |
| Normal | 2 | 22.2 | 3 | 27.3 | 5 | 25.0 |
| 0 | 1 | 11.1 | 1 | 9.1 | 2 | 10.0 |
| 1 | 1 | 11.1 | 6 | 54.5 | 7 | 35.0 |
| 2 | 3 | 33.3 | 1 | 9.1 | 4 | 20.0 |
| 3 | 2 | 22.2 | 0 | 0.0 | 2 | 10.0 |

Values have been expressed as absolute number (incidence), *Hepatotoxicity grade of ALT and/AST is used

## DISCUSSION

Toxicities linking to the use of antiretrovirals are expressed by the elevation of plasma transaminases. Liver toxicity may lead to morbidity, mortality and sometimes, treatment discontinuation in HIV-infected patients. Several antiretrovirals have been reported to cause fatal acute hepatitis (Manegold *et al*., 2001) and most often, they cause asymptomatic elevations of liver transaminases (Saves *et al*., 1999). Liver toxicity is also associated with subjects with chronic hepatitis C and/or B infection or co-infection with HIV and on HAART (Melvin *et al*., 2000). The incidence of antiretroviral-induced liver toxicity is still debatable. The contribution of each particular drug to the development of hepatotoxicity in a HAART regimen is varied. Lamivudine and Abacavir (NRTI) have been shown to be less hepatotoxic (Kontorinis and Dieterich, 2003), whilst PI's, e.g., ritonavir and zidovudine have been associated with severe hepatotoxicity (Sulkowski *et al*., 2000; Aceti *et al*., 2002).

Forty six percent of the HAART-experienced subjects had hepatotoxicity, 5 and 4% graded as 2 and 3, respectively, whilst only 16% of the controls had hepatotoxicity with none having grade 3 hepatotoxicity and 2% grade have 2 hepatotoxicity (Table 4). This statistical observation further strengthens the assertion that HAART accelerates the development of hepatotoxicity (Aranzabal *et al*., 2005). Globulins, total proteins, AST, ALT, ALP and GGT were significantly ($p<0.001$) elevated in the HIV HAART-experienced patients than the controls (Table 1). The AST, ALT, ALP and GGT are associated with hepatocytes and are released into plasma when the hepatocyte is attacked by the virus or HAART (Lansing *et al*., 1967). Globulins and total proteins on the other hand, are usually elevated as a result of immunological response in most infections (Stiehm and Fudenberg, 1966; Rossen *et al*., 1970). Hence, even though globulins and total proteins were lower in the HAART-naïve compared to the HAART-experienced, they were all higher than physiological values of 31 and 60-80 g $dL^{-1}$ (Rowe *et al*., 1968; Doumas, 1975), confirming an infection. The results of the study evaluated the risk for liver toxicity associated with the use of some antiretroviral drugs. World Health Organization (WHO) recommended antiretroviral medicines were administered. All the HAART-experienced participants involved in the study used a combination of antiretrovirals, grouped under NRTI consisting; llamivudine combivir, tenofovir and abacavir and NNRTI consisting of nevirapine and efavirenz.

Even though lamivudine and abacavir are known to have less hepotoxic effect, yet all HAART experienced subjects had significantly raised liver enzymes, may be this is the effect of the other drugs they were co-administered with. The pathogenic mechanisms involved in hepatotoxicity are varied, including direct drug toxicity, immune reconstitution in the presence of HCV and/or HBV co-infections, hypersensitivity reactions with liver involvement and mitochondrial toxicity (Nunez, 2006). However, the exact mechanism by which these drugs have induced hepatotoxicity

is unclear. In general, nucleoside analoques have been shown to act by incorporating into viral nucleic acid and thereby inhibiting viral replication, resulting in the depletion of mitochondria DNA and impaired cellular respiratory chain (Lewis and Dalakas, 1995). Severe NRTI mitochondrial toxicity is associated with hepatomegaly and steatosis (Kontorinis and Dieterich, 2003; Lewis and Dalakas, 1995). NNRTI's particularly nevirapine and efavirenz are metabolized through cytochrome P450. Cytochrome P450 enzymes are known to increase the activities/concentration of co-administered retroviral drugs and therefore, increasing their toxicity effect (Birkus *et al*., 2002), e.g., saqunavir concentration is increased by 20 fold when it is co-administered with ritonavir (Kontorinis and Dieterich, 2003).

Total bilirubin, a by-product of the breakdown of red blood cell in the liver, is a good indicator of liver function and high levels causes jaundice and are indicative of liver and bile duct damage (Ostrow *et al*., 1962). Hyperbilirubinemia has been observed in nevirapine and efavirenz users (Sulkowski *et al*., 2002). There was no significant change in bilirubin concentration between the HAART-experienced patients and the controls (Table 1). Bilirubin levels have been shown to be raised in patient on PI. Severe hyperbilirubinemia was associated with severe hepatotoxicity in a high percentage of subjects on indinavir than there were in the non indinavir treatment (Zucker *et al*., 2001). It can, therefore, be inferred that the non PI's use did not have damaging effect on the red cells in the liver as similarly reported by Zucker and Goessling (2000).

Viral Hepatitis has been shown to be an independent risk factor for the development of hepatotoxicity (Melvin *et al*., 2000). The toxicity effect is more pronounced when there is a co-infection with HIV and most particularly when the HIV patients are on HAART (Monforte *et al*., 2001; Greub *et al*., 2000). Only 9% of the HAART-experienced were co-infected with Hepatitis B and a significantly high 22% of the HAART-naïve controls were co-infected with Hepatitis B (Table 1). Table 5 depicts the statistical numbers of subjects co-infected with Hepatitis B. Even though, there was more infection in the controls, hepatoxicity was less. Indeed 22% of the HAART-experienced subjects had grade 3 hepatotoxicity whilst the controls had no grade 3 hepatotoxicity and a further 33% of the HAART-experienced had grade 2 hepatotoxicity as against 9.1% of the HAART-naïve (Table 5). This further strengthens the poor prognosis of the effect of hepatitis infection and HAART on HIV patients.

Despite the significantly high percentage of HAART-naïve co-infected with Hepatitis B, their liver transaminases and total proteins were significantly lower compared to the case subjects. This may be because viral hepatitis alone may take a longer time to induce hepatatoxicity but HIV infection accelerates the rate of HBV-induced liver fibrosis probably because of loss of HBV-specific immune function as has been reported for HCV infection (Vento *et al*., 1998). But the effect of HAART is more hepatotoxic than the accelerated effect of HIV co-infection with hepatitis (Table 1).

HAART-induced hepatotoxicity is cumulative and time dependent. Grade 3 hepatoxicity was observed after 13 months of HAART (Table 2). Only 4% of the subjects developed grade 3 hepatoxicity whilst none developed grade 3 hepatotoxicity before 13 months. None of the subjects developed even grade 2 hepatotoxicity before 6 months but 5% developed hepatoxicity between 7-19 months of HAART. Similarly in none related studies, it has been shown that HAART-induced dysglycaemia and dyslipidaemia and cardiovascular risk is time dependent (Ngala and Fianko, 2013, 2014).

In using plasma bilirubin as an index of hepatoxicity, the trend was similar to that observed with the plasma enzymes. Hepatotoxicity as depicted by the bilirubin was time dependent. Eleven percent of the HAART-experienced developed hepatotoxicity with 6% acquiring grade 4

Table 6: Correlation between liver function test and hepatotoxicity using two different protocols

| Hepatotoxicity | TPT | ALP | ALT | AST | TBIL | GGT |
|---|---|---|---|---|---|---|
| ALT r and/AST | -0.285** | -0.289** | -0.604** | -0.695** | -0.203* | -0.349** |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 | 0.013 | <0.001 |
| Total r bilirubin | 0.041 | -0.244** | -0.289** | -0.346** | -0.486** | -0.252** |
| p-value | 0.619 | 0.003 | <0.001 | <0.001 | <0.001 | 0.002 |

*,**Significant at 0.05 and 0.01 level, respectively (2-tailed), r: Spearman rho coefficient, TPT: Total protein, ALP: Alkaline phosphatase, ALT: Alkaline transaminase, AST: Aspartate transaminase, TBIL: Total bilirubin, GGT: Gamma glutamyl transferase

hepatotoxicity between 7-19 months, one patient between 7-12 months, 2 between 13-18 months and 3 after 19 months. Severe hyperbilirubinemia was found associated with grade 3 and 4 hepatotoxicity in 30% of subjects on indinavir, showing asymptomatic elevations in indirect bilirubin in a high percentage of subjects. The incidence of severe hyperbilirubinemia was higher among HCV-infected patients (Sulkowski *et al*., 2002).

There was a significant but negative correlation between total proteins, AST, ALT, ALP and GGT and hepatotoxicity using AST and ALT index. Also, AST, ALT, ALP and GGT were significantly negatively correlated with hepatotoxicity whilst total proteins were positively but nonsignificantly correlated using bilirubin as a toxicity index (Table 6).

## CONCLUSION

Hepatotoxicity was induced in HAART-experienced HIV patients, even in patient who were treated with antiretroviral drugs not known to be associated with hepatotoxicity. The effect of HAART on hepatotoxicity was time dependent. There is strong evidence that co-infection with hepatitis B virus increases the risk of hepatotoxicity while taking antiretroviral therapy. Regular monitoring of transaminases is therefore recommended when HIV patients are being treated with antiretroviral drugs even if they do not include PIs. This will help to decide on discontinuation of treatment if toxicity levels become too high.

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