Section: Biochemistry

Original Research Article

PROSPECTIVE STUDY OF LIVER FUNCTION TESTS IN HIV PATIENTS ON ANTIRETROVIRAL THERAPY AT A TERTIARY CARE HOSPITAL IN NORTH KARNATAKA

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ABSTRACT

Background: HIV patients treated with combination antiretroviral therapy (cART) are at increased risk of elevation of liver enzymes and bilirubin levels. As antiviral drugs are metabolized in the liver, patients with HIV infection are more prone to drug-induced liver injury due to reduced hepatocyte defence mechanisms. It is important that it be identified early to prevent further hepatic damage. **Objectives:** The present study was conducted to determine the effect of cART on liver function tests, that is, levels of serum ALT, AST, ALP, total bilirubin, total protein, and albumin levels before ART and after 3 months, 6 months, 9 months, and 12 months of ART. To compare serum ALT, AST, ALP, total bilirubin, total protein, and albumin levels before ART, after 6 months, and after 12 months of ART.
Materials and Methods: The study included 50 HIV-positive patients. Serum ALT, AST, ALP, total bilirubin, total protein, and albumin were analyzed before and after 3-month intervals of ART up to 12 months.
Results: The findings of our study showed a rise in ALT, AST, ALP, and total bilirubin levels with ART for up to 6 months. After 6 months, values showed a steady decline and reached normal level after 12 months. Levels of total protein and albumin declined initially up to 6 months and increased after 6 months of ART reached normal level after 12 months.
Conclusion: The present study shows that ART has significant effects on liver function. Therefore, it is recommended to monitor the liver functions of HIV patients regularly during early period of 3 to 6 months of ART.
Keywords: HIV, cART, ALT, AST, ALP, total bilirubin.

INTRODUCTION

India has the third largest number of people living with HIV (Human Immunodeficiency Virus), and there are about 2.4 million.[1] The adult prevalence rate is 0.21 percent. It is estimated that annual deaths due to HIV are about 39.6 thousand. The trend of annual AIDS (acquired immunodeficiency syndrome) deaths is showing a steady decline after the implementation of the free ART (antiretroviral therapy) program in India in 2004. There has also been a decrease in the incidence of new HIV cases in India after the introduction of free ART (antiretroviral therapy).[1]

Inhibiting HIV replication is crucial for extending and enhancing the quality of life for patients. It also helps to reduce the risk of transmission to others. Drugs used in the treatment of HIV are nucleoside & nucleotide reverse transcriptase inhibitors (NRTI). Non-nucleoside reverse transcriptase inhibitors (NNRTI), Protease inhibitors, Integrase strand transfer inhibitors, Viral entry or fusion inhibitors, CCR5 antagonists, CD4 antagonists and those that interfere with the viral capsid.[2]

Drug-induced liver injury (DILI) is defined as the elevation of liver enzymes with or without bilirubin levels in association with the use of a medication or drug. Liver fibrosis in human immunodeficiency

virus (HIV)-infected individuals is mostly attributable to co-infection with hepatitis B and C.[3] cART-associated hepatotoxicity can manifest during acute incidents like hypersensitivity responses, and lactic acidosis may be associated with advancing liver injury. Non-alcoholic steatohepatitis (NASH) and severe fibrosis develop gradually.[4] The effects of other factors, such as long-term combination antiretroviral therapy (cART), are unclear.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are hepatic enzymes that could be used as markers of hepatocellular injury. The objectives of our study were to estimate serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Total bilirubin, Total protein and Albumin before and after a 3-month interval of ART up to 12 months and to compare serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Total bilirubin, Total protein and Albumin before and after a 3-month interval of ART up to 12 months.

MATERIALS AND METHODS

The study design was a prospective cross-sectional study. The study included 50 HIV-positive patients between the ages of 30 and 75 years with a CD4 count < 350 cells/µl from ICTC (Integrated Counselling and Testing Centre) and the ART center of Belagavi Institute of Medical Sciences hospital, Belagavi. The diagnosis of HIV infection was done based on the symptoms, past history, and clinical examination and confirmed with an immunochromatographic test for HIV 1/2 antibodies.

Patients with a history of alcohol consumption, HIV-HBV co-infected patients, HIV-HCV co-infected patients, HIV-HBV-HCV co-infected patients, HIV patients with tuberculosis, HIV patients with muscular dystrophy, metabolic syndrome (non-alcoholic steatohepatitis), hemochromatosis and Wilson's disease were excluded from the study group. All HIV-positive patients were on treatment with Zidovudine (ZDV or AZT) 300 mg, Lamivudine (3TC) 150 mg, and Efavirenz (EFV) 600 mg. The present study was approved by the institutional ethical committee.

After obtaining informed and written consent, 10 ml of venous blood samples were collected after 12 hours of fasting in a plain vacutainer under all aseptic precautions just before starting any treatment and after 3 months, 6 months, 9 months and 12 months of ART. Serum ALT, AST, ALP, total bilirubin, total protein and albumin were analyzed before and after 3-month intervals of ART up to 12 months. Serum ALT, AST, and ALP levels were estimated using the enzyme kinetic method. Total bilirubin levels were measured using the Diazo method. Total protein levels were analyzed using the Biuret method, and serum albumin levels were measured using the Bromocresol Green method. Analysis was done on the Erba XL 640 fully automated biochemistry analyzer.

Statistical Analysis: The values obtained were expressed as their mean + standard deviation. The significance of the difference between the means was calculated with repeated measures ANOVA. $p<0.05$ was considered statistically significant. SPSS 30 software was used for statistical analysis.

RESULTS

Table 1: Demographic data

Parameter	HIV patients	Males (%)	Females (%)
HIV patients	50	23 (46%)	27 (54%)
Age (years) (mean±SD)	41.60±8.48	42.78±9	40.6±8.1
<40 years	26 (58%)	13 (56.5%)	13 (48.1%)
40-49 years	18 (36%)	5 (21.7%)	13 (48.1%)
More than 50 years	6 (12%)	5 (21.7%)	1 (3.7%)

Values were expressed as percentage and mean±SD

Table 2: Serum parameters in HIV patients before and after 3 months interval of ART

Parameters	Before ART	3 months of ART	6 months of ART	9 months of ART	12 months of ART
ALT (IU/L)	21.4±4.41	23.25±5.24	24.7±5.4	18.85±2.94	16.43±1.74
AST (IU/L)	18.92±5.19	20.87±5.98	22.38±6.06	17.1±3.78	15.65±2.6
Alkaline phosphatase (IU/L)	66.78±11.92	72.14±12.4	77.33±12.5	61.38±11.1	56.18±10.2
Total bilirubin (mg/dl)	0.58±0.25	0.68±0.27	0.79±0.29	0.46±0.23	0.37±0.2
Total protein (gm/dl)	6.56±0.51	6.35±0.53	6.14±0.53	6.73±0.49	6.94±0.49
Albumin (gm/dl)	3.61±0.31	3.39±0.32	3.23±0.31	3.83±0.29	4.04±0.29
A:G ratio	1.28	1.21	1.17	1.39	1.46

All the values were expressed as mean±SD

Table 3: Significance of Difference of ALT, AST, Alkaline Phosphatase, Total Bilirubin, Total Protein, Albumin & A:G ratio Between before and After 6 & 12 Months of ART in HIV Patients

Parameters	F-Value	Before ART vs After 6 mths	Before ART vs After 12 mths	After 6 mths vs After 12 mths
ALT (IU/L)	1444.66	<0.0001	<0.0001	<0.0001
AST (IU/L)	836.66	<0.0001	<0.0001	<0.0001
Alkaline phosphatase (IU/L)	1672.73	<0.0001	<0.0001	<0.0001
Total bilirubin (mg/dl)	87.7	<0.0001	<0.0001	<0.0001
Total protein (gm/dl)	7890.08	<0.0001	<0.0001	<0.0001
Albumin (gm/dl)	7245.88	<0.0001	<0.0001	<0.0001
A:G ratio	729.16	<0.0001	<0.0001	<0.0001

A p-value < 0.05 was considered for statistical significance

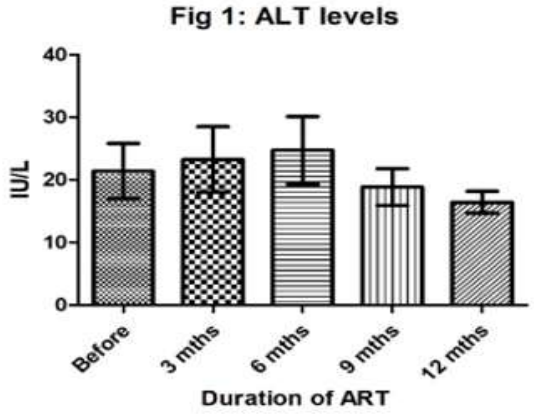


Figure 1: Shows levels of ALT

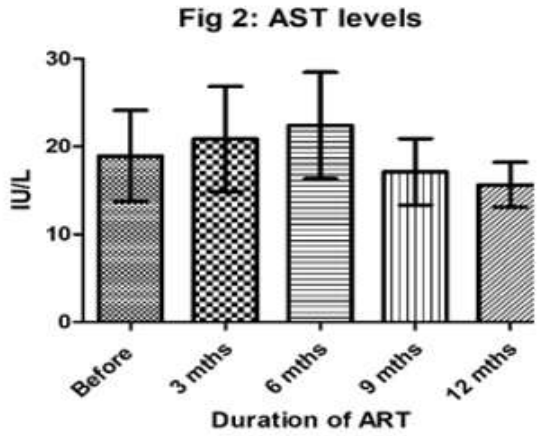


Figure 2: Shows levels of AST

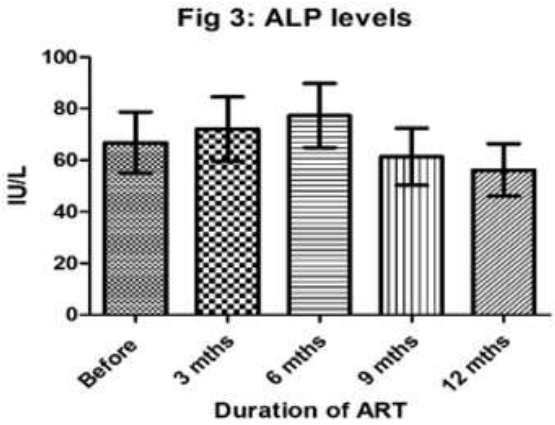


Figure 3: Shows levels of ALP

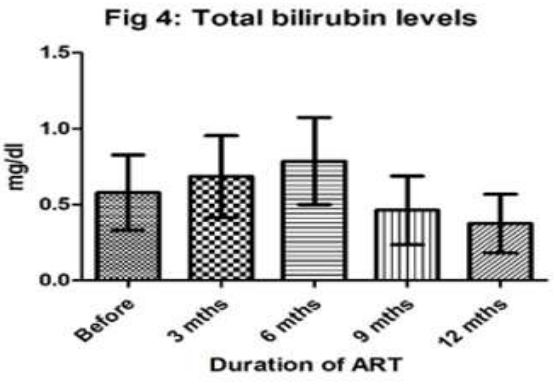


Figure 4: Total Bilirubin

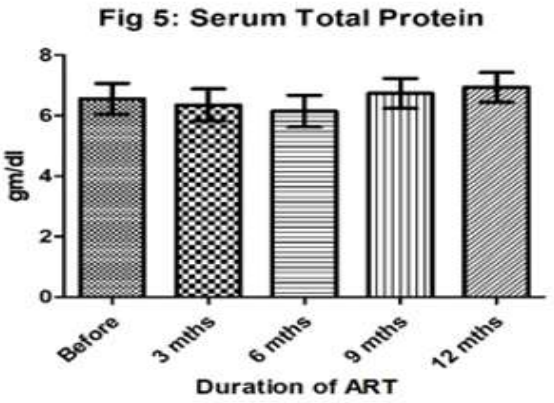


Figure 5: Serum Albumin

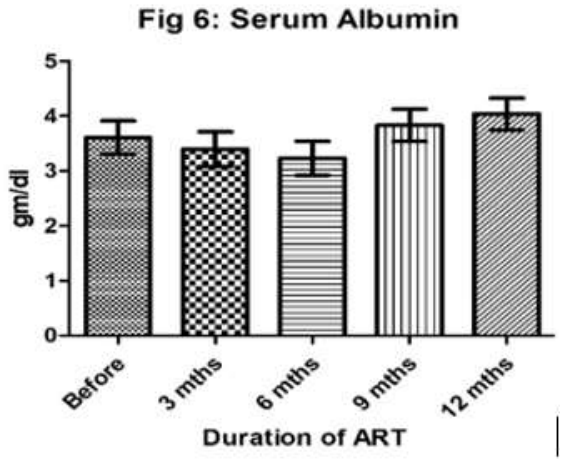


Figure 6: Total Protein. The graph displays values before and after 3 months, 6 months, 9 months, and 12 months of ART

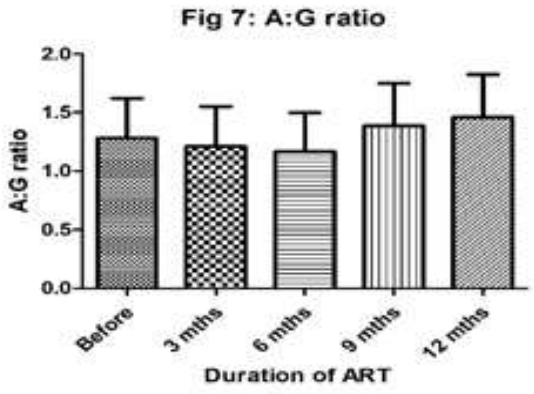


Figure 7: Show A:G ratio; The graph displays values before and after 3 months, 6 months, 9 months, and 12 months of ART

Table 1 shows demographic data for the HIV patients included in the study. The present study included 50 HIV-positive patients. 23 patients were males, and 27 patients were females. The mean age of patients included in the study was 41.6 years. Thus, the data suggests that the incidence of HIV infection is more common among sexually active patients. Table 2 shows mean values of ALT, AST, ALP, total bilirubin, total protein, albumin levels and A:G ratio at 0, 3, 6, 9, and 12 months after starting cART. Total protein and albumin levels showed a decline after three months of starting ART up to 6 months. Total protein and albumin showed a steady rise after 6 months of ART and reached normal levels after 12 months of cART [Fig. 5, Fig. 6]. A:G ratio decreased 3 months after initiation of ART till 6 months. A:G ratio improved gradually after 12 months of cART [Fig. 7] Values of ALT, AST, ALP, and total bilirubin show a rising trend for up to 6 months. Serum levels of ALT, AST, ALP, and total bilirubin started declining after 6 months of ART and reached normal range at 12 months. [Fig 1, Fig 2, Fig 3, Fig 4].

Changes in levels of ALT, AST, ALP, total bilirubin total protein, albumin and A:G ratio at different intervals of cART were statistically significant in themselves and before ART levels. ($p<0.05$) [Table 3].

DISCUSSION

Results of our study revealed levels of serum AST, ALT, and ALP and Total bilirubin were significantly raised after a 3-month interval of ART up to 6 months and after 12 months these increased parameters came to normal levels. This indicates hepatocellular injury with initiation of ART.

Findings were similar to the study by Ikekpeazu E J et al., which reported that a significant increase in enzyme levels was noted at three and six months in the NNRTI group and at only three months in the NRTI and PI groups, when compared with the controls.[5] A study conducted by Vermehren J et al. determined that chronic elevation of liver enzymes was observed in up to 45.5% of HIV monoinfected patients on cART.[3]

Wondimeneh et al. showed elevated liver enzymes (AST and ALT) and lowered mean CD4 cell counts in HIV, HIV-HBV, and HIV-HBV-HCV co-infections.[6,7] Otegbayo J A et al. showed a rise in baseline ALT and AST; there was gradual normalization of enzyme levels with cART after 18 months both in monoinfected and HBV co-infected patients.[8]

Trivedi AP et al. found elevation in levels of serum globulin, total protein, ALT, AST, ALP, total bilirubin, and leukocyte count in HIV patients compared to healthy controls. They also report elevated levels of total bilirubin and albumin and a reversal of the A/G ratio in HIV patients compared to healthy controls.[9] Shah R.P. et al. reported decreased serum albumin levels in the protein electrophoresis of the serum of HIV and TB (tuberculosis-) infected patients.[10]

Bialy et al. highlighted the importance of cART for maintaining liver metabolic health. They recommended that individualized therapy and monitoring be implemented.[11] Peluso et al. showed LFT abnormalities in patients treated for acute HIV infection.[12]

Coinfection with the hepatitis C virus and other comorbidities, such as nonalcoholic fatty liver disease (NAFLD), can exacerbate liver dysfunction in HIV-infected individuals.[13,14] A systematic review conducted by Mohammed O et al. revealed the pooled prevalence of hepatotoxicity in HIV/TB co-infected patients was higher than that of non-co-infected patients.[15] Hodowanec AC showed IL-10 was elevated in HIV and HIV/HCV coinfected patients compared to HCV-monoinfected individuals. Immune activation in coinfected patients is primarily due to HIV infection.[16]

A study by Patel PD et al. demonstrated only a few subjects had moderate to severe liver enzyme elevations, and the incidence of severe hepatotoxicity was low.[17] While initiating or modifying ART regimens, it is important to monitor liver function. Early identification and management of hepatotoxicity reduce progression to advanced liver disease.[18]

Limitations: We could not correlate laboratory parameters with clinical and immunological status of subjects.

CONCLUSION

This research provides invaluable insights into the hepatotoxicity of ART. The study clearly demonstrates that liver enzymes increase for up to 6 months after ART. Further, after 6 months, LFT improves, suggesting recovery. Hence, it is very much necessary to follow up with patients on cART for hepatic injury to prevent progression of hepatic damage. The contribution of a particular drug needs to be evaluated. We recommend indicating LFT as

one of the follow-up investigations, especially in the early period of 3 to 6 months of ART.

Conflict of interest: The authors declare that they have no conflict of interest.

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