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# STUDY OF CLINICAL AND ETIOLOGICAL PROFILE OF LIVER DYSFUNCTION IN PATIENT WITH RETROVIRAL DISEASE IN A TERTIARY CARE HOSPITAL A OBSERVATIONAL CROSS SECTIONAL STUDY

General Medicine

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## ABSTRACT

**Background-** Human immunodeficiency virus (HIV) infection is characterized by an irreversible and profound immunosuppression. Liver-related diseases are an important cause of morbidity and mortality in HIV patients. liver function tests (LFTs) derangement is common in people living with human immunodeficiency virus/acquired immune deficiency syndrome (PLHA). There are multifactorial causes of lft derangement. Drug-induced liver injury (DILI) is the commonest cause, mostly ATT induced.. others being alcohol abuse and concomitant viral hepatitis and other infections. **Aim And Objectives:** To study clinical profile, etiological profile of patient with liver dysfunction and retroviral disease, and its correlation with cd4 count specially in patient with Hepatitis B and Hepatitis C. **Materials And Methods:** It was a observational cross sectional study conducted on HIV patients who attended the medicine OPD and were hospitalised in medicine ward of our Tertiary care hospital over a period of 12 months. It included 120 pts. **Results:** The etiology of liver dysfunction observed in our study was ATT induced Hepatitis in 43(35.8%) patients, followed by Hepatitis B in 16 (13.3%) patients, 11 (9.20%) patients had alcoholic hepatitis / cirrhosis, 8 (6.70%) patients had ART induced Hepatitis followed by 6 (5.0%) patients had HIV cholangiopathy; 4 (3.30%) patients had NASH , 3 (2.50%) patients had Hepatitis A, 3 (2.5%) had Hepatitis C, 2 (1.70%) patients were diagnosed as dengue NS1 positive and developed dengue Hepatitis and 1(0.8%) patient was a case of primary biliary cirrhosis , 1 (0.85) patient had Liver abscess and 1 (0.8%) had coinfection of Hepatitis B and Hepatitis C. However in our study 21 (17.5%) patients had multifactorial etiology. **Conclusions:** In HIV-infected patients liver function abnormalities are very common. There are multiple causes of liver dysfunction in HIV patients. Drug induced liver injury due to ATT is most common. Many other causes like Coninfection with HBV infection, Alcoholism.. Liver-related disease is one of the leading causes of non-AIDS-related death.Therefore, early diagnosis of liver disease in its early stages is an essential component reduce morbidity and mortality in this population. The mechanisms of liver diseases in HIV somewhat depend on the function of the immune system.

## KEYWORDS

Cd4 count, Highly active antiretroviral therapy, Human immunodeficiency virus infection, Liver function

## INTRODUCTION:

HIV continues to be a major global public health issue.(1) Before introduction of HAART, liver dysfunction in HIV-infected patients mainly due to opportunistic infections (e.g., with cytomegalovirus [CMV] or mycobacteria and leishmaniasis), including AIDS-related cholangitis associated with parasitic infections (cryptosporidiosis and microsporidiosis), viral infections (e.g., with CMV), or mycobacterial infections; tumors (lymphoma and Kaposi sarcoma); and drug-related hepatitis (caused by trimetoprim-sulfamethoxazole and other antibiotics(2,3). All of these had very poor prognosis and reflected the severe immunodeficiency state of patients.

HAART has completely change the pattern of hepatic events in HIV patient. In treatment of HIV patient liver is one of the most important organs to consider. In HIV patient Liver disease is one of the leading causes of morbidity and mortality which includes several pathogenic processes that are drug-related hepato toxicities; chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; alcoholic liver disease ;other liver diseases, such as steatosis or non alcoholic steatohepatitis (NASH). Survival of HIV patient can be increase by early recognition and diagnosis of hepatic events by facilitating the safe and effective use of HAART.(4,5)

According to AIDS clinical trials group of liver toxicity (6)), hepatotoxicity is defined as patients with transaminases, ALT and AST rise above the upper limits of normal ranges. Severe hepatic injury classified as grade 3 or 4 changes when ALT, AST levels are 3-5 and greater than 5 times the upper normal limits, respectively. Also severe hyperbilirubinemia is classified as grade 3 or 4 and is treated independent of AST and ALT levels.

Typical mechanisms of liver disease in these patients include oxidative stress, mitochondrial injury, lipotoxicity, immune-mediated injury, cytotoxicity, toxic metabolite accumulation, gut microbial translocation, systemic inflammation, senescence and nodularregenerative hyperplasia (7)

The diagnosis of liver injury can be considered when abnormalities of liver-related biochemical tests (s. bilirubin, SGOT, SGPT, ALP) are identified. Laboratory tests and various investigations are used to assess for coinfections that increase risk of liver complications, measure markers of liver injury, and identify liver-related disease processes.(AST) are the most commonly used biomarkers of liver injury. .(8)

Liver biopsy is the gold standard method of identifying liver disease, but it has limitations.) Biopsy provides evidence of liver damage, but cannot identify the cause of damage,except in rare cases of drug hypersensitivity (histologic evidence of granulomas and eosinophils)) or mitochondrial injury (evidence of micro vesicular steatosis).(9,10)

A new and non-invasive transient elastography method (Fibro Scan; Echosens, Paris, France) it measures liver stiffness, which is a property of fibrotic or cirrhotic liver damage, and it has prognostic value for hepatitis. Transient elastography may offer even better predictability when combined with serum markers of fibrosis. (11)

## MATERIALAND METHODS:

This observational cross sectional study was conducted on 120 HIV patients with deranged liver dysfunction, who attended the medicine OPD and hospitalised in medicine ward of Tertiary care hospital over a period of 12 months. The study was initiated after obtaining approval from the institutional ethics committee and department of general medicine. Participants were selected based from the following selection criteria.

### Inclusion Criteria:

1. Males or Females with age 18 years of age.
2. Patients having retroviral disease
3. Patients with liver dysfunction
4. Patients having liver dysfunction either biochemically, clinically and/or imaging studies

### Exclusion Criteria:

1. Patients who do not give consent for the study
2. Patients with retroviral disease with no liver dysfunction

### Data Collection And Study Protocol:

In our study, total 120 cases were enrolled after fulfilling the inclusion criteria, these 120 cases were subjected to detailed history, physical examination Socio demographic data including age, sex, weight, marital status, alcohol use, drug history were documented. Baseline

clinical parameters and co-morbidities during therapy were studied. Baseline CD4 count and recent CD4 count were documented. Routine baseline investigations including CBC, RFT, LFT, fasting lipid profile, fasting blood sugar, alkaline phosphatase were carried out. Special investigations such as HBsAg,Anti HCV Ab, , IgM HAV, IgM HEV, USG abdomen, CXRAY were done. In some cases where diagnosis was uncertain further investigations like CT abdomen, MRCP, Liver biopsy, autoimmune workup, workup for Wilson disease, fibro scan, ascitic fluid analysis, fever profile were done as per indicated depending on the suspected diagnosis and clinical picture. In some cases who were present with associated other symptoms/ opportunistic infection, relevant investigation like MRI brain, CT brain, HRCT thorax was done. Opportunistic infections were documented among patients noted. In cases with drug induced hepatitis, the LFT were serially monitored after stopping the drug and improvement/ normalisation of LFT was documented. Thus, after a complete workup. Final diagnosis d regarding the cause of liver dysfunction was noted.

Collected Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation. p value (Probability that the result is true) of <0.05 was considered statistically significant.

## RESULTS:

In our study maximum number of cases were in the age group of 41-50 years contributing to Total of 52(43.3%), Mean age was 42.88 ± 9.7 years. Male preponderance of 90 (75%) as compared to 30 (25%) of females with male: female ratio of 3:1 was documented.HIV I subtype were 114 (95%) patients whereas 6 (5%) patients were HIV II subtype in study. The study population was divided into groups based on CD4 counts. 35 (29.1%) patients had CD4 count in range of 201-500 followed by 29 (24.20%) patients had CD4 count in range of 101-200, 20(16.6%) patients had CD4 count in range of 50-100, 19 (15.8%) patients had CD4 above 500, and 17 (14.20%) patients had CD4 count below 50. Mean CD4 count was 261.19.

In our study most common presenting symptom was vomiting observed in 67 (55.8%) patients followed by pain in abdomen in 60 (50%) patients, yellowish discoloration of sclera in 49 (40.8%) patients and abdominal distention in 20 (16.7%) patients.

**Table 1. Clinical Presentation Of Patients**

| Symptoms | cases | Percentage % |
|---|---|---|
| Vomiting | 67 | 55.8% |
| Abdominal pain | 60 | 50% |
| Yellowish discolouration of eye | 49 | 40.8% |
| Abdominal distention | 20 | 16.7% |

On general examination, maximum 68 (56.7%) patients had icterus, followed by pallor in 54 (45%) patients, oral thrush in 23 (19.2%), lymphadenopathy in 9 (7.5%). Most common finding on clinical examination was icterus followed by pallor. As on per abdomen examination abdominal examination most common finding was abdominal distention in 24 (20%) patients followed by hepatomegaly in 14 (11.70%),and splenomegaly was presented in 8 (6.70%) patients. Out of 120 patients 51 (42.5%) patient were alcoholics.

As per drug history 64 (48.30%) patient were on ATT (anti tubercular treatment) and 112 (93.3%) patients were on ART, 8 (6.7%) patients were on other drugs for opportunistic infection, 7 (5.8%) on pyrimethamine and sulphadiazine for treatment of Central nervous system toxoplasmosis and 1 (0.8%) patient was on trimethoprim and sulphamethoxazole for treatment of PCP. These 8 (6.7%) patients were also on ATT. 8 (6.7%) patients were newly diagnosed as HIV with event opportunistic infection of tuberculosis hence not yet started on ART medication at time of study.

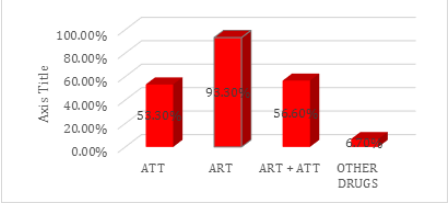



**Figure 1:** - Bar diagram showing Drug History among study groups

HIV-positive patients are at high risk for many viral infections. HIV patients are more prone for coinfection with HBV and HCV and/or both infections. In our study,20 (16.7%) patients were HBsAg positive, 3 (2.50%) patients were Anti HCV positive. 3 (2.5%) patients were positive for Hepatitis A (IgM Anti HAV) suggestive of Acute Hepatitis A and 1 (0.8%) patient had coinfection with Hepatitis B and C.. 2 (1.2%) patients who presented with fever were found to be Dengue NS 1 positive and had dengue hepatitis and 1 patient had CMV hepatitis (PCR to CMV positive).

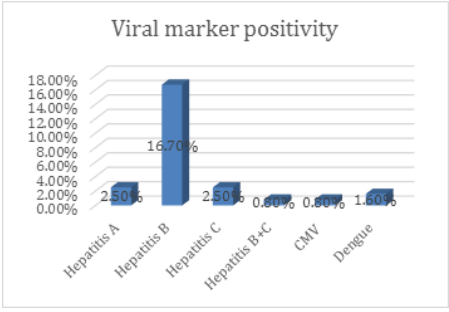
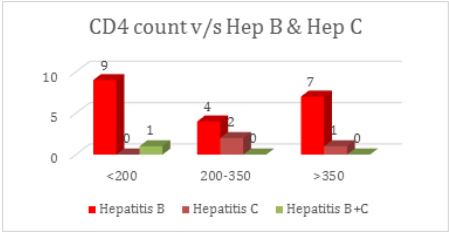



**Figure 2: -** Bar diagram showing Viral marker positivity among study group

Correlation of cd4 count with Hepatitis B and Hepatitis C was done. Out of Total 20 (16.6%) patients who were positive for HBsAg, 9 patients Had CD4 count below 200 and 4 had CD4 in dange of 201-350 and 1 patient had cd4 count more than 350 cell/mm3. Out of 3 (2.5%) patients who were positive for Anti HCV, 2 patient had CD4 count 201-350 and 1 patient had cd4 count more than 350 cells/mm3. 1 (0.8%) patient who had coinfection with HBsAg and anti HCV had CD4 count less than 200. In our study p value was 0.172 that was non-significant.




Bar diagram-3 showing Correlation between Hepatitis B & C and CD4 count

As per AIDS CLINICAL TRIALS Group (ACTG) has established a 1 to 4 grading system for hepatotoxicity; In our study 53 (44.20%) patients had grade 3 liver dysfunction; 27 (22.50%) had grade 2 liver dysfunction, 25 (20.80%) patients had grade 4 and 15 (12.5%) patients had grade 1 liver dysfunction.

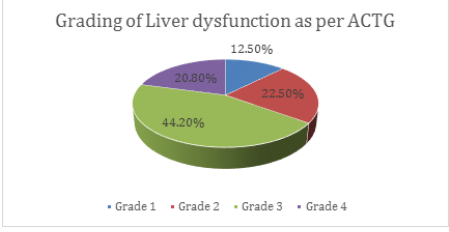



**Figure :-** Pie diagram showing grading of liver dysfunction as per aids clinical trails group

Correlation between severity of liver dysfunction and CD4 count was done. Total 15 patients had grade 1 liver dysfunction, in whom 6 (40%) had CD4 between 201-350, 5 (33.3%) had CD4 count below 200, 4 (26.7%) had CD4 >350 cells/mm3. 27 patients had grade 2 liver dysfunction, in whom, 16 (59.3%) had CD4 count below 200, 7 (25.9%) had CD4 between 201-350, 4 (14.8%) had CD4 >350 cells/mm3. 53 patients had grade 3 liver dysfunction, in whom, 32 (60.3%) had CD4 count below 200, 11 (20.5%) had CD4 >350 cells/mm3 ,10 (18.8%) had CD4 between 201-350. 25 patients had grade 4 liver dysfunction, in whom, 13 (52%) had CD4 count below

200, 7 (26.9%) had CD4 >350 cells/mm3, 5 (20%) had CD4 between 201-350. However, p value was 0.739 thus there was non-significant correlation found between CD4 count and severity of liver dysfunction in our study.

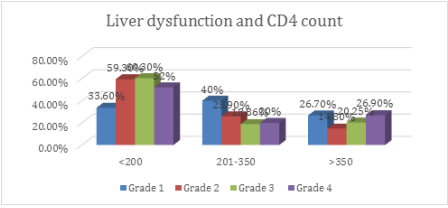



**Figure 4 : -** Bar diagram showing association between Correlation of severity of liver dysfunction with CD4 count

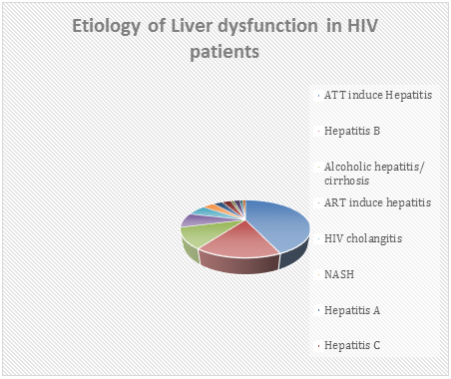
Most common opportunistic infection was tuberculosis in 64 (53.3%) patients, 23 (19.2%) patients had oral candidiasis that was 2nd most common opportunistic infection among study group, 7(5.8%) patients had central nervous system toxoplasmosis, 2 (1.7%) patients had herpes zoster, 2 (1.7%) patients had cryptococcal meningitis, 1(0.8%) patient had CMV pancreatitis and 1(0.8%) patient had PCP pneumonia, all these patients were on treatment for the respective opportunistic infection.

For investigation purpose USG abdomen was done in all 120 patients, maximum 49 (40.8%) patients had normal study in USG abdomen, abnormal findings were altered liver echotexture in 26 (21.6%), ascites in 16 (13.3%); abdominal lymphadenopathy in 11 (9.20%), hepatomegaly in 11 (9.20%), liver cirrhosis in 7 (5.80%), splenomegaly in 6 (5.0%) ; hepatosplenomegaly in10 (8.30%) , fatty liver in 6 (5.0%), dilated biliary radicles and dilated CBD findings was found on 5 (4.20%) patients, GB sludge in 2 patients and 2 patients had liver abscess whereas 1 patient was found to be liver hemangioma on USG finding

CT Abdomen was done in 15/120 patients for further investigations for confirming diagnosis and as per need of further investigation. Findings were overlapping, most common finding was altered liver echotexture in 5 patients, abdominal lymphadenopathy and dilated biliary radicals and dilated CBD each in 5 patients. For narrowing the diagnosis further investigations were done. 5 patients had undergone MRCP out of them 3 had papillary stenosis, 1 had sclerocholangitis and intrahepatic sclerosing cholangitis to confirm diagnosis of HIV cholangiopathy. 7 patients had undergone invasive procedure Liver biopsy out of them 3 cases had chronic hepatitis; 2 cases had hepatic steatosis and 2 had cryptogenic liver cirrhosis. Ascitic fluid examination was done in 15 patients, out of them 12 patients ascitic fluid examination was transudative in nature, whereas 3 patients were diagnosed as abdominal tuberculosis based on ascitic fluid examination. Autoimmune workup was done in total 18 patients,1 patient was positive for anti3E BPO that was specific for primary biliary cirrhosis

Etiology of derange liver function test was, ATT induce Hepatitis in maximum 43 (35.8%) patients , followed by Hepatitis B in 16 (13.3%) patients, 11 (9.20%) patients had alcoholic hepatitis / cirrhosis. 8 (6.70%) patients had ART induced Hepatitis followed by 6 (5.0%) patients had HIV cholangiopathy; 4 (3.30%) patients had NASH , 3 (2.50%) patients had Acute Hepatitis A, 3 (2.5%) had Hepatitis C, 2 (1.70%) patients were diagnosed as dengue with dengue Hepatitis and 1(0.8%) patient was a case of primary biliary cirrhosis , 1 (0.85) patient had Liver abscess and 1 (0.8%) had coinfection of Hepatitis B and Hepatitis C. however in our study 21 (17.5%) patients had multifactorial etiology.

21 (17.5%) patients had multifactorial contributory factors for liver dysfunction. In 21 patients, 11 (9.2%) patients were due to drug induced hepatotoxicity, 3(2.5%) patients were on ATT and nevirapine. 7 (5.8%) patients were on ATT and sulphadiazine for treatment of CNS toxoplasmosis and 1 (0.8%) patient was on ATT and trimethoprim and sulphamethoxazole for treatment of PCP pneumonia. 5 (4.2%) patients had alcoholic liver disease and ATT induce hepatitis, both were etiological factor for deranged liver function test. 2 (1.7%) patients had Hepatitis B, Alcoholic liver disease and ATT induce hepatitis, 2 (1.7%) patients had Hepatitis B and AKT induce hepatitis.1 (0.8% patient was on ATT and also had CMV PCR positive, in this patient ATT induce hepatitis and CMV hepatitis was factors for liver dysfunction.




## DISCUSSION

Liver enzyme abnormalities are commonly reported in HIV-infected populations. Data from resources reach setting countries demonstrated that about 10% of patients who started antiretroviral drug developed significant liver injury, also associated with ATT with risk factors being hepatitis C infection, older age group, and alcohol [12) .

In this study, median population ages were 42.8.years, Majority of cases were in the age group of 41 to 50 years. , and the liver dysfunction in HIV patients observed was higher 90 (75%) cases were males and 30(25%) cases were females. Male: female ratio was 3:1.

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HIV I subtype were 114 (95%) cases whereas 6 (5%) cases were HIV II subtype. In our study as per personal history, 51 (42.5%) patients were found to be alcoholic.

In this study as per clinical profile most common presentation was vomiting in 67 (55.8%) patients, followed by pain in abdomen 60 (50%) patients, followed by yellowish discoloration in 49 (40.8%) patients followed by abdominal distention was in 20 (16.7) patients, however 86 (71.7%) patients had other symptoms (fever, altered sensorium, bilateral pedal oedema, loss of appetite, breathlessness etc. In study HIV patients were on multiple drugs like ATT, ART and others, 64 (48.30%) patients were on ATT and 112 (93.3%) patients were on ART,56 (46.6%) patients were on both ART and ATT, 8 (6.7%) patients were not started on ART medication. 8 (6.7%) patients were on other drugs for opportunistic infection.

Viral infection are common in HIV patients, Total 29 patients were positive for viral infections. In hepatotropic viruses 20 (16.7%) patients were HBsAg positive, 3 (2.50%) patients were Hepatitis C. 3 (2.5%) patients were Hepatitis A and 1 (0.8%) patient had coinfection with Hepatitis B and Hepatitis C. In non-hepatotropic viruses, 2(1.7%) patients were Dengue NS 1 positive and had dengue hepatitis and 1 patient had CMV hepatitis (PCR to CMV positive). In 20(16.6%) Hepatitis B patients, 10 (8.3%) patients had grade 1 liver dysfunction, 4 (3.3%) patients had grade 3, 3 (2.5%) patients had grade 2 and 3 (2.5%) had grade 4 liver dysfunction. Mean CD4 count was 261.19 cells/mm3. 66 (55%) patients were severe immnuno compromised had CD4 count below 200 cell/mm3.

In our study total 20 (16.6%) patients were positive for HBsAg, out of these patients 9 patients Had CD4 count below 200 and 4 had CD4 201-350 range and 1 patient had cd4 count more than 350 cell/mm3. 3 (2.5%) patient were positive for Anti HCV, 2 patient had CD4 count 201-350 and 1 patient had cd4 count more then 350 cells/mm3. 1 (0.8%) patient had coinfection with HBsAg and anti HCV that had CD4 count less than 200. In our study p value was 0.172 that was non significance. In HBsAg positive patients,10(8.3%) patients had grade 1 liver dysfunction, 4 (3.3%) patients had grade 3, 3 (2.5%) patients had grade 2 and 3 patients had grade 4 liver dysfunction.

our study 84.2% patients had CD4 below 500 and 55.1% patients had advanced immunosuppression with CD4 below 200. Correlation of severity of liver dysfunction with CD4 count.

In our study group correlation between severity of liver dysfunction and CD4 count was done. Total 15 patients had grade 1 liver dysfunction, whom 6(40%) had CD4 between 201-350, 5 (33.3%) had CD4 count below 200, 4 (26.7%) had CD4 >350 cells/mm3. 27 patients had grade 2 liver dysfunction, whom, 16 (59.3%) had CD4 count below 200, 7 (25.9%) had CD4 between 201-350, 4 (14.8%) had

CD4 >350 cells/mm3.52 patients had grade 3 liver dysfunction, whom, 32 (60.3%) had CD4 count below 200, 11 (20.5%) had CD4 >350 cells/mm3 ,10 (18.8%) had CD4 between 201-350.25 patients had grade 4 liver dysfunction, whom, 13 (52%) had CD4 count below 200, 7 (26.9%) had CD4 >350 cells/mm3, 5 (29%) had CD4 between 201-350. However, p value was 0.739 thus there was non-significant correlation found between CD4 count and severity of liver dysfunction in our study.

In our study 53 (44.20%) patient had grade 3 liver dysfunction; 27 (22.50%) had grade 2 liver dysfunction, 25 (20.80%) patient had grade 4 and 15 (12.5%) patient had grade 1 liver dysfunction.AIDS CLINICAL TRIALS Group (ACTG) has established a 1 to 4 grading system forhepatotoxicity; grades 3 and 4 are usually used as identifiers of drug-related toxicity(associated respectively with >5-fold and >10-fold elevations of ALT/ AST abovenormal pretherapy levels whereas grade 1 have 1.25-2.5 ULN and group 2 have 2.5- 5 the ULN.(6) In our study maximum no of cases are due to drug induce hepatotoxicity, hence maximum cases were in grade 3 and grade 2.

Aetiological profile of liver dysfunction in our study, Maximum 43 (35.8%) patients had liver dysfunction due to AKT induce Hepatitis followed by Hepatitis B in 16 (13.3%) patients, alcoholic Liver disease in 11 (9.20%) patients, ART induce Hepatitis in 8 ,(6.7%) patients, all these patients were due to efavirenz induced hepatotoxicity. In all these 8 patients liver dysfunction in form of derange LFT occurred after initiation of ART regimen, in a time span ranging from 4 weeks to 24 weeks. Ifollowed by 6 (5.0%) patients had HIV cholangiopathy, 4 (3.30%) patients had NASH, 3 (2.50%) patients had Hepatitis A and 3 (2.5%) patients had Hepatitis C, 2 (1.70%) patients had dengue Hepatitis, 1(0.8%) had primary biliary cirrhosis,1 (0.8%) had Liver abscess and 1(0.8%) patient was coinfection of Hepatitis B and Hepatitis C. however in our study 21 (17.5%) patients had multifactorial aetiology. In these patients there were varying combination of ATT induce hepatitis, Hepatitis B and alcoholic liver disease.

## CONCLUSION:

HIV-infected patients liver function abnormalities are very common. There are multiple etiologies of liver dysfunction in HIV patients. HIV patients should be screened for basic LFT. In HIV patients Tuberculosis is common opportunitistic infectionand many patients are on ATT there Drugs causes liver injury. Many other causes like Coninfection with HBV infection, Alcoholism.. Liver-related disease is one of the leading causes of non-AIDS-related death.Therefore, early diagnosis of liver disease in its early stages is an essential component reduce morbidity and mortality in this population.

**Conflict Of Interest:** None

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