



HEPATOBIILIARY ABNORMALITIES AMONG PEOPLE LIVING WITH HIV/AIDS IN SOUTHERN ODISHA

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ABSTRACT

Background: Southern Odisha has nearly 40% of total PLHAs (People Living with HIV/AIDS) of the state. **Aims:** The aim was to explore the prevalence of Hepatobiliary abnormalities in PLHAs of southern Odisha with periodical follow up over a period of one year and nine months. **Settings and Design:** Prospective observational study. **Materials and Methods:** Fifty HIV infected patients enrolled in ART (Antiretroviral Therapy) centre, MKCG Medical College Hospital, Brahmapur, were included and prospectively followed up and analyzed every five months for liver enzymes and total bilirubin from January 2015 to September 2016. **Results:** The prevalence of hepatobiliary abnormalities was found to be 84%. Among the study subjects, 30% had raised aminotransferases, while 54% had isolated elevation of ALP (Alkaline Phosphatase). 20% had jaundice with raised bilirubin. Eight per cent were seropositive for HBsAg (Hepatitis B surface antigen), of which three-fourth had abnormal liver enzymes. Forty four percent were alcoholics; all had hepatobiliary abnormalities and half of them had isolated ALP elevation. Sixty per cent had tuberculosis (with completed DOTS), of which 24% had elevated liver enzymes and 32% had isolated ALP elevation. **Conclusions:** The prevalence of hepatobiliary involvement in PLHAs is quite high. Multiple factors can be attributed for this. Hence, physicians treating them should be more vigilant for monitoring of hepatotoxicity.

KEYWORDS: Southern Odisha, PLHAs, Hepatobiliary, HIV.

INTRODUCTION

HIV was identified in the early 1980's. Since then it has evolved into a pandemic. Due to its relentless destruction of the immune system, it has resulted in the deaths of over half of its victims. Globally, 36.7 million people were living with HIV at the end of 2015. An estimated 0.8% of adults aged 15–49 years worldwide are living with HIV.^[1] With the advent of HAART (Highly active antiretroviral therapy), there is improved survival rate among PLHAs. However, Liver disease, although usually asymptomatic has emerged as an important cause of both morbidity and mortality. Chronic Hepatitis B, Chronic Hepatitis C and HIV cholangiopathy are important hepatobiliary disorders that complicate the primary infection apart from alcohol, ART drugs and other hepatotoxic drugs.

Aim of The Study

The aim of the study is to assess the prevalence of hepatobiliary abnormalities among PLHAs in southern Odisha with periodic follow up over a period of one year and nine months.

Subjects and Methods

A prospective analysis of data collected regarding liver enzymes and total bilirubin of fifty PLHAs enrolled at ART centre of M.K.C.G. Medical College Hospital, Berhampur was carried out with periodic five monthly follow up over a period of one year and nine months (January 2015 to September 2016).

Inclusion Criteria

1. HIV-positive cases above 15 years and less than 70 years of age.
2. HIV-positive cases of both sexes.

Exclusion Criteria

1. Patients with HIV who died during follow up.
2. Patients lost to follow up (LFUs) and transferred cases.

HIV infection was diagnosed using simple rapid serological tests in the ICTC centre of the institute. The approach was consistent with WHO recommendations. A detailed clinical history and complete general physical and systemic examination findings of HIV infected patients wererecorded. Hepatobiliaryinvolvement was diagnosed based on elevation of liver enzymesand total bilirubin above upper limit of normal reference range. The data collected were analysed usingstatistical tests like chi-square test with SPSS 21. Descriptive statistics were used to calculate frequency mean, median, mode, and standard deviation.

RESULTS

Out of 50 patients, 72% were male and 28% were female. The mean age was 37.1 years with a standard deviation of 9.9842years. The median age was 36 years.

In the study population, 44% were alcoholics; 8% were HBsAgpositive; 10% had jaundice with elevated bilirubin; 64% suffered from comorbidity; 32% with Extrapulmonary Tuberculosis, 26%with Pulmonary

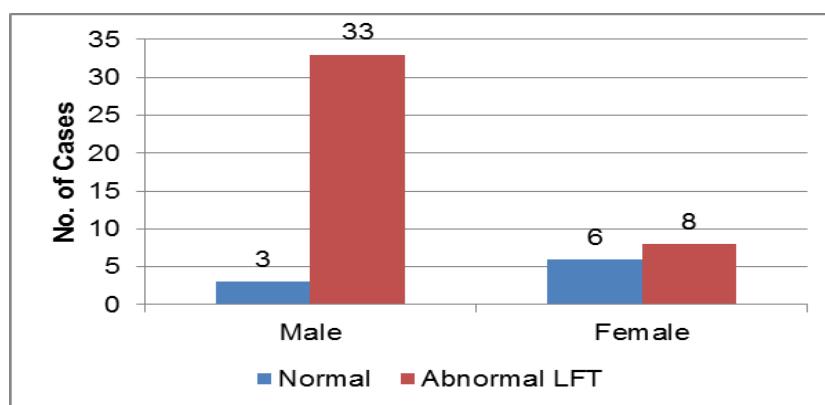
Tuberculosis, and 2% each with Miliary Tuberculosis, High Grade dysplasia of Tongue and Ovarian Cyst. Ninety-two per cent were only on single ART regimen with 58% on TLE [Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV)] and 28% on ZLN [Zidovudine (ZDV), Lamivudine (3TC) and Nevirapine (NVP)] regimens.

Out of the total study population, 30% had hepatobiliary disturbances based on raised AST (Aspartate Aminotransferase) /ALT (Alanine Aminotransferase) and 52% had isolated elevation of ALP. Hepatobiliary abnormality was statistically higher in males than females. Chi-square= 8.140; $p < 0.05$ [Figure 1, Table 1]. Among the HBsAg positive patients, three had elevated liver enzymes. There is no statistical significance in HBsAg status of patients with or without hepatobiliary abnormality. Forty-four per cent were alcoholics, of which 38% had isolated ALP elevation and 26% had elevated aminotransferases. Higher proportions of alcoholics had hepatobiliary involvement than non-alcoholics. This finding is statistically significant. Chi-square=8.624, $p < 0.05$ [Table 2, 3]. The trend of hepatobiliary involvement as seen above more in age group of 30-44 years is not statistically significant and occurred merely by chance; Chi-square=6.990, $p = 0.072$.

Table 1: Sex wise distribution of liver enzymes and total bilirubin.

Sex	AST*	ALT*	ALP*	Total* Bilirubin
Male	11	10	29	6
Female	1	0	8	4

*Abnormal LFT in any one of the observations.

**Figure 1: Sex wise distribution of hepatobiliary involvement.****Table-2. Distribution of hepatobiliary abnormalities in alcoholics and non- alcoholics.**

	Hepatobiliary abnormality	
	Present	Absent
Alcoholic	22	0
Non-alcoholic	21	9

Table 3: Distribution of liver enzymes and total bilirubin in Alcoholics and non- alcoholics.

	AST*	ALT*	ALP*	Total* Bilirubin
Alcoholic	7	5	19	5
Non-Alcoholic	5	5	18	5

*Abnormal LFT in any one of the observations.

Number of patients with elevated AST increased from 6 (12%) in first observation to 7 (14%) in last observation. Number of patients with elevated ALT decreased from 7 (14%) in first observation to 4 (8%) in last observation. Number of patients with elevated ALP increased from 1 (2%) in first observation to 37 (74%) in last observation. Number of patients with elevated Total Bilirubin decreased from 9 (18%) in first observation to 2(4%) in last observation. Sixty percent had tuberculosis (with completed DOTS), of which 24% had elevated

aminotransferases and 30% had isolated ALP elevation. Presence or absence of hepatobiliary abnormality across various comorbidities was not statistically significant. Presence or absence of hepatobiliary involvement across various ART regimens was not statistically significant. Alkaline Phosphatase (ALP) in the last observation was found to be significantly increased in patients on multiple ART regimens than on single ART regimen ($p=0.032$) [Figure 2].

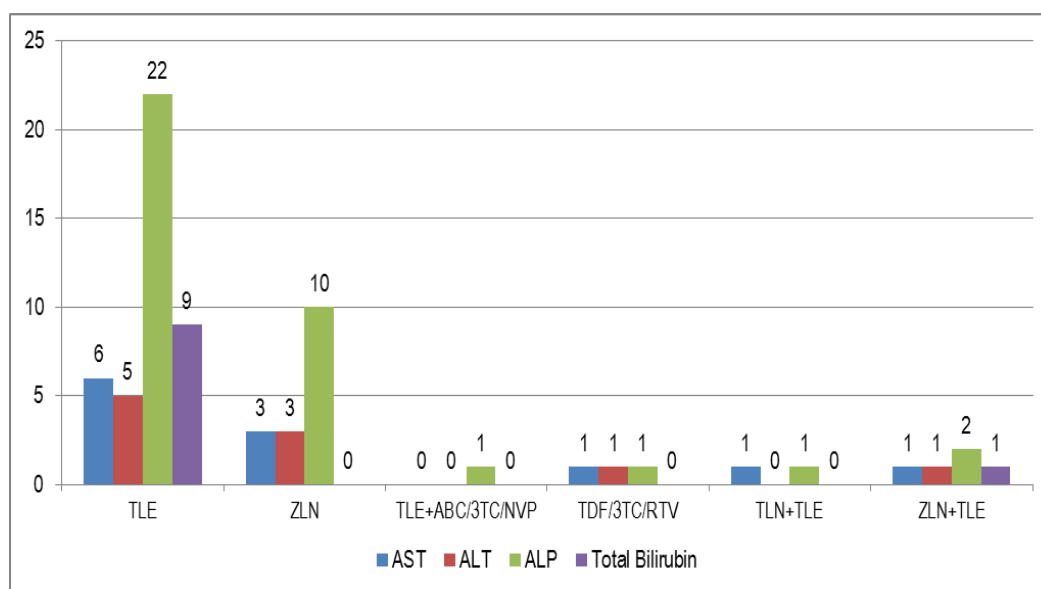


Figure 2: Distribution of liver enzymes and total bilirubin and ART regimen.

TLE - Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV); Abacavir (ABC); Ritonavir (RTV); ZLN- Zidovudine (ZDV), Lamivudine (3TC) and Nevirapine (NVP); TLN - Tenofovir (TDF), Lamivudine (3TC) and Nevirapine (NVP); TLE+ABC/3TC/NVP – TLE followed by ABC/3TC/NVP; TLN+TLE - TLN followed by TLE; ZLN+TLE – ZLN followed by TLE.

DISCUSSION

This study which was conducted for a period of one year and nine months revealed that hepatobiliary abnormality is substantial among the HIV infected population. Hepatobiliary diseases figure as the leading cause of morbidity and mortality among the PLHAs.

The high prevalence of HIV infection in males in this study must be due to the high rate of migration of the youth to other states in search of job opportunities where they are exposed to high risk activities. The main regions of migration include Surat, Mumbai, Chennai and Kerala. Another reason for the large male to female disparity may be because the females are often neglected and deprived of health care facilities resulting in an underestimation of their numbers. The high prevalence of hepatobiliary involvement in males must be due to concomitant use of alcohol and HBV (Hepatitis B virus) coinfection.

A study done by Kavita S. Joshi et al.^[2] in Mumbai showed that out of the total 102 patients, 78 (76.5%) patients were males and 24 (23.5%) patients were females. While the study by Ponsiano Ocama et al.^[3] concluded that out of 8,715 patients, 5,585 (64%) were females. In the Study by Jayeeta Sarkar et al.^[4], in HIV mono infected patients, 218 (70%) were males and 94 (30%) were females and among the HBV/HIV coinfecting patients 78.3 (61/78) and 21.7 per cent (17/78) were males and females, respectively. In the Study by Shamanna et al.^[5] 82% were males.

The major age group was 30-44 years which comprised of 58% of the study population. This clearly shows that the working population of the society is affected more than the rest as they are more sexually active. The decrease in number of elderly populations may be due to the high mortality of the HIV patients in the region.

In a study by Mark Wayne Sonderup,^[6] median age was 34 years. In the Study by Jayeeta Sarkar et al.,^[4] the median age was 35 years in both HIV mono infected and HIV-HBV coinfecting group. In The Shamanna et al.^[5], the median age of the patients was 40 years, most patients were in the middle age group of 20-39 years in the study by Abubakar et al.^[7]

In this study, the prevalence of hepatobiliary abnormality in PLHAs was 82%, of which 30% had raised AST/ALT and 52% had isolated elevation of ALP. A study by Jean Claude Dusingizeet al.^[8] showed prevalence of abnormal LFTs (liver function tests) (16.4%) in HIV infected Rwandan women. Study by Richard K. Sterling et al.^[9] showed the prevalence of elevated LFTs in those without HCV (Hepatitis C virus) /HBV were AST 20%, ALT 15%, and ALP 43%. Study by Ivan Nettoet al.^[10] studies serum transaminase levels (AST and ALT) in 40 HIV positive and 40 healthy and HIV negative control cases. It concluded that liver function tests were deranged in HIV positive patients as compared to control.

In this study, 4 patients (8%) were HBsAg positive patients of which 3 patients had elevated liver enzymes and all were males. In a study by N.Rama Krishna et al.,^[11] HIV-HBV co-infection was detected in 11.48% and was higher in males. There was significantly higher AST, ALT, alkaline phosphatase, serum bilirubin values than the mono-infected group. In study by Ikeh et al., the prevalence of HIV-HBV coinfecting group was 9.8% with relatively high liver enzyme levels. Similarly, studies by Jayeeta Sarkar et al.^[4] Saroj Hooja et al.,^[12] and Richard K. Sterling et al.^[9] showed HIV-HBV coinfecting groups were associated with significantly elevated liver enzymes and bilirubin.

In this study, 44% were alcoholics and all had hepatobiliary involvement. In Study by Jayeeta Sarkar et al.^[4] alcohol use was noted in 60.3% of patients. In a study by Suryanarayana Bettadpura Shamanna et al.^[5] 35% of patients had alcoholic liver disease and after a median period of 8 months of follow up 30% had decompensated alcoholic liver disease, thus concluding that alcohol abuse is one of the causes of hepatobiliary diseases in PLHAs. In a retrospective study by V Wiwanitkit et al.,^[13] alcoholic liver disease appeared to be the most common cause of jaundice (42.31%).

In this study, 30 (60%) patients had history of tuberculosis and completed DOTS, of which 27 patients (90%) had hepatobiliary involvement while 3 patients (10%) did not have hepatobiliary involvement. However, presence or absence of hepatobiliary involvement across various comorbidities was not statistically significant. In a study by Mark Wayne Sonderup,^[6] 29% patients had granulomatous hepatitis, mostly non-necrotizing and predominantly due to Mycobacterium tuberculosis. In a study by Javier Lizardi-Cervera J. et al.^[14] main histologic diagnoses were granulomatous hepatitis (29%) and most frequent microorganism isolated was Mycobacterium tuberculosis (26.6%). In a study by Shamanna et al.,^[5] 11.76% of patients had probable hepatic involvement due to tuberculosis and 19.60% of patients had anti tuberculosis drug-induced hepatotoxicity. In a study by Ponsiano Ocama et al.^[3] probable granulomatous hepatitis due to tuberculosis was diagnosed in 9% of patients and all responded to anti-tuberculosis therapy.

In this study, alkaline phosphatase (ALP) in the last observation was found to be significantly increased in patients on multiple ART regimens than on single ART regimen ($p=0.032$). In a study done by Mark Wayne Sonderup,^[6] 61% of patients with drug induced liver injury were on HAART either individually or in combination with cotrimoxazole or TB drugs. In study by Chris Ngeny Kipngetch,^[15] the prevalence of hepatotoxicity based on elevated alanine aminotransferase above upper limit of normal was 18% in HAART treated and 8% in HAART naïve patients. However, the prevalence of hepatotoxicity cases did not vary significantly between HAART treated and HAART naïve subjects, thus concluding that prevalence of hepatotoxicity was 17.3% in all HIV positive subjects irrespective of HAART status. In study by Melashu Balew Shiferaw et al.,^[16] the prevalence of liver enzyme abnormality was 20.1% and 22.0% among HAART experienced and HAART naïve patients, respectively. The HAART experienced patients had higher mean ALT than HAART naïve patients ($p=0.002$), thus concluding that liver enzyme abnormalities were high in both HAART experienced and HAART naïve HIV-1 infected patients.

CONCLUSION

This study highlights significant liver dysfunction in PLHAs. Mostly males in middle age group are affected, considering the fact that they are sexually active, migrating, working population. Hence, they are more likely to be co-infected with HBV, TB and predisposed to the risk of toxicity of alcohol, ART and antitubercular drugs. Hence, physicians treating them should be more vigilant for monitoring of hepatotoxicity.

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