Assessment of Liver Enzyme Abnormality Among HIV-Infected Patients on Antiretroviral Therapy in Asmara, Eritrea

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Abstract

Background

- Liver disease are predominant in HIV/AIDS patients and a wide range of the population have been affected. However, studies that have assessed the burden and risks of liver enzyme alterations among antiretroviral therapy experienced patients are hardly available in Eritrea. Thus, the present study targets to determine the prevalence and the risks related with abnormal liver enzymes among HIV-infected individuals.

Methodology

- a cross-sectional, observational study was conducted in two national referral hospitals, in Asmara, Eritrea. A structured predesigned questionnaire was employed to capture sociodemographic data of patients and blood sample was taken for analyses of liver enzyme profile tests. Data was analyzed using chi-square test and logistic regressions in SPSS software.

Result

- The study included 329 participants of whom majority were females. Participants' age ranges from 18 to 83 years with the mean age of 44.63(± 10.48). Patients had a history of taking first line regimen as either AZT, TDF, ABC or D4T based drug combinations with mean duration on drugs of 7.09(± 3.32) years. 88(26.7%) HAART experienced patients had significant alterations in their liver enzyme parameters. This abnormality was significantly associated with age (p-value = 0.022). HIV-1 patients with history of stavudine use as first line HAART medication had about three (AOR = 2.95; 95% CI = 1.19–7.27) times more elevated liver enzymes. Generally, liver enzymes were found to be higher in minority ethnic groups and rural areas (p value = 0.002).

Conclusion

-The results suggest that liver enzymes (ALT, AST) were significantly elevated in patients taking HAART medication. The finding of this study illustrates that HIV patients on antiretroviral medication are at increased risk of hepatotoxicity which necessitate for continuous and periodical clinical monitoring to reduce severe effects of liver injury.

Introduction

Liver disease are predominant in HIV/AIDS patients and a wide range of the population (25%-90%) have been reported to be affected [1, 2]. More than half of deaths that occur among hospitalized HIV infected patients admitted to hospitals after global initiation of HAART medication have been associated with liver

disorders [3, 4]. The main causes include consequent chronic hepatitis B and C infections, opportunistic infections, AIDS related neoplasms [5, 6], nonalcoholic fatty liver disease, alcohol abuse and medication-related hepatotoxicity. This leads to conditions ranging from asymptomatic moderate liver enzymes alterations to end stage liver disease and cirrhosis with its concomitant complications (i.e., hepatic encephalopathy, ascites and esophageal abnormality). An estimated overall prevalence of 8.3% of liver cirrhosis is observed in HIV population [7]. Moreover, cirrhosis incidence and liver disorder related deaths are substantially increased in hepatitis B and C infected HIV population [8, 9, 10]. Nevertheless, the burden and the risk factors of liver disorders might be distinct in various geographical locations including Eritrea.

Hepatotoxicity is often demonstrated by biochemical alterations in the liver function tests. Liver enzymes (aspartate aminotransferase or alanine aminotransferase) are often elevated by several HAART drugs including NRTIs, NNRTIs and PI groups [11, 12, 13]. Half of the patients does not manifest any clinical symptoms in spite of abnormalities in their liver enzymes, therefore, in many settings cases of HIV-patients with liver disorder are underreported [14].

Liver disorder treatment and management is an integral aspect of the HIV patients care. Previous studies which give information on the patterns of liver function health are hardly available in Eritrea. Thus, the present study targets to determine the prevalence and the risks related with abnormal liver enzymes among HIV-infected individuals.

Methods

Study setting and design

This was a cross-sectional, observational study carried out in Halibet National Referral Hospital (HNRH) and Orotta National Medical Surgical Referral Hospital (ONMSRH), in Asmara, Eritrea from March to June, 2018. They are the largest national referral hospitals with catchment area of over 814,000 inhabitants and with simultaneously large number referral patients visiting from around the country. The study population were known HIV/AIDS positive individuals who visited ONMSRH and HNRH for routine check-up and medication. The current number of patients who were on HAART in ONMSRH and HNRH was 1567 and 1162 respectively.

Sampling Technique

The study was carried out with a sampling method of convenience in the sense that, participants were patients who turned up voluntarily for their routine and subsidized semester check-up to which liver function profile tests were planned along with other laboratory monitoring tests. Study participants were HIV patients who were $\geq$ 18 years old and patients having good adherence to medication.

Sociodemographic Data Collection

A structured predesigned questionnaire was employed to gather sociodemographic information (sex, age, educational level, area of residence). Medical history of subjects (drug combination, CD4 count, viral load

count, duration of exposure to HAART, and drug history and side effects) were collected from patient's medical record with the help of hospital counselling staffs. It also incorporated questions related to the lifestyles of participants (dieting, exercise, smoking, and frequency of alcohol intake).

Specimen collection and analysis

After applying standard antiseptic technique, a total of 5ml of venous blood sample was obtained in a uniquely labelled chemistry tubes from each individual. Blood specimen were then allowed to clot and serum was separated by centrifugation at 3000 rpm for 3 minutes. The serum samples were stored at 6^0C and were analyzed within 24 hours of collection for Liver function tests including ALT, AST, ALP, and Bilirubin using AU480 Chemistry Analyzer (Beckman Coulter- AU480). An upper limit normal (ULN) values of 31IU/L and 35IU/L were specified for AST for women and men respectively. Similarly, upper limit normal for ALT was set as 45 IU/L for men and 34 IU/L for women. Abnormal Liver enzyme were defined values more than 1.25 of the upper limit of normal [15].

Statistical Analysis

The data were collected, cleaned and analyzed using SPSS version 20. Summary and descriptive statistics were computed. Bivariate and multivariate logistic regression analysis were employed to define the association between independent variables and the outcome variable. Moreover, Odds ratio calculations with 95%CI were used to determine the strength of association. A p-value <0.05 was set to hold statistical significance.

Ethical approval and consent to participate

Approval for the study was sought from the Asmara College of Health Science research ethical committee and Health Research Ethics and Protocol Review Committee of the Ministry of Health. Patients were given information regarding the nature and objectives of the study, then, a written and verbal consent was obtained from voluntary study participants upon the acquisition of the data and specimen.

Results

Sociodemographic characteristics. A total of 329 HIV/AIDS patients on HAART were enrolled in this study from whom majority were females and urban dwellers. The participants' age ranges from 18 to 83 years with the mean age of 44.63(±10.48). At least half of the study subjects were literate (Table 1). All of the patients had a history of taking first line regimen as either AZT, TDF, ABC or D4T based drug combinations with mean duration on drugs of 7.09(±3.32) years. Out of 329 patients enrolled in the study, 203(61.7%) patients had changed the drug combination they use while 126 patients adhered with only one drug combination since the initiation of HAART.

Prevalence of liver abnormalities. Eighty-eight (26.7%) HAART experienced patients were present with a significant alteration in their liver enzyme parameters (ALT and/or AST). AST, ALT, and both AST and ALT

were increased in 84 (25.5%), 35(10.6%), and 31 (9.4%) of HAART experienced groups, respectively. Majority of the patients CD4 cell count were in the range of 200 and 500, and 45 (28.8%) of the participants in this group were present with hepatotoxicity.

Factors associated with liver abnormalities. Presence of abnormal liver enzymes was significantly related with age (p-value = 0.022). Those patients in the age group of 40-50 were three (AOR= 3.29; 95% CI= 1.29-8.39) times more likely to have increased liver enzymes in comparison with other patients (Table 2). Different types of HAART regimen were also significantly associated with presence of liver injury. Generally, stavudine(D4T) based drug regimen use was present with higher proportion of liver enzyme abnormalities. HIV-1 patients with history of stavudine use as first line HAART medication had about three (AOR = 2.95; 95% CI = 1.19-7.27) times more elevated liver enzyme compared to their counterparts. Moreover, though attenuated in the adjusted regression analysis, presence of lamivudine and tenofovir in drug regimen was also related with increased AST values (p value= 0.04). Generally, liver enzymes were found to be higher in minority ethnic groups and rural areas (p value= 0.002).

Discussion

Elevations in liver enzymes are frequent in HIV population, however, because of the complexities related to pathophysiologic mechanisms of liver function, diagnosis or general management of cases may be challenging [16]. The degree of liver cell toxicity is usually evaluated by measuring serum transaminase enzymes levels or activity [17]. It is obvious that Liver is the synthesis organ of the major body enzymes and when there is any injury on the liver, variable concentrations of those enzymes are released into the blood due to raised permeability [18].

AST and ALT are the primarily sensitive biomarkers of liver cell injury and used for the detection of hepatocellular disorders [19]. ALT is principally synthesized in liver cells, whereas AST is secreted in liver and other complementary tissues including heart, brain, lungs, kidneys, pancreas, skeletal muscles, erythrocytes and leukocytes [18]. Different research outputs indicated that patients on different HAART drugs had demonstrated raised levels of AST and ALT [19, 20, 21].

In this study, the prevalence of liver injury was 26.7% in general agreement with studies in Sub-Saharan Africa (SSA) [22, 23]. However, this outcome is higher to studies on HIV infected patients conducted in Cameroon(22.6%), South Africa (23%) and Brazil (19.7%) [21, 24, 25]. This might be attributable to different factors including traditional risks such as hepatitis B and C virus co-infections [11], increased alcohol intake [12], use of illicit regimens, the time period of treatment [26], older age, genetic predispositions and geographic conditions [27].

In concordance with other similar studies, this study indicated that liver injury was observed more in males than in females which could be due to the effect of alcohol consumption [28]. Also studies carried out in Thailand [29], US community [30] and Italy [31] indicated a parallel association. Analysis of other sociodemographic and clinical factors also showed a more significant association ($p<0.05$) between liver

enzyme elevations and HAART regimen in addition to age of participants. Liver enzyme abnormalities were higher in the age group 40 to 50 years. This is comparable to several findings elsewhere [32, 33].

Different HAART regimen have been directly implicated in alterations of liver enzyme activity [11, 34]. In this study, zidovudine and tenofovir were used by large portion (83%) of study participants as first line regimen for their HAART medication. But a high proportion of the liver enzyme abnormality (13.3%) was present in HIV patients who had history of stavudine based medication (aOR=2.95; 95% CI = 1.19-7.27). This is consistently supported by previous animal study and clinical trials conducted demonstrating induction of some extent of long term mitochondrial toxicity [35, 36]. WHO guidelines strictly urge the termination of wide use of stavudine in first-line regimens for reason related to its well documented metabolic toxicities [37]. A complete phasing out of stavudine as preferred drug regimen has been obtained in Eritrea recently. However, still less than 5% of the HIV population on antiretroviral treatment uses this drug worldwide [37].

Limitations

In this study, several limitations can be mentioned. Regardless of very low national prevalence of HCV and HBV, hepatitis virus coinfection along with other opportunistic diseases were not evaluated in this study. A typical liver function parameter such as albumin activity and INR was not included which could have enabled for an elaborate analysis in the organ mechanisms. Ultrasound analysis and platelet count were not assessed for the detection of liver fibrosis and ascites. It is hugely understood that those tests are expensive and for very low income countries like Eritrea, it is impractical to implement all the tests.

Conclusion

In this study, liver enzymes (ALT, AST) were markedly raised in patients on antiretroviral medication. Moreover, hepatotoxcity was noticed in a considerable number in older HIV participants and on those who had history of stavudine medication, imparting an inevitable issue to be addressed. The results of this study point out that HIV patients on HAART medication are at eminent risk of liver toxicity which necessitate for continuous clinical monitoring to reduce complicated form of liver injury.

Abbreviations

ART
Antiretroviral therapy
EFV
Efavirenz
HBV
Hepatitis B virus
HCV
Hepatitis C virus

NNRTI
Nonnucleoside reverse transcriptase inhibitor
NRTI
Nucleoside reverse transcriptase inhibitor
NVP
Nevirapine
PI
Protease inhibitor
SSA
Sub-Saharan Africa

Declarations

Data Availability

The dataset supporting the conclusions of this article is available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no conflict of interest to declare on this study.

Authors' Contributions

All authors were creditworthy for conception of the study, collection, analysis, interpretation of the data and writing of the proposal and final draft manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Patients characteristics and frequency of liver injury, Eritrea 2018

Variables	Category	Liver enzyme alteration		p-value
		Normal	Abnormal	
		N(%)	*N(%)*	
Gender	Male	77(72.6)	29(27.4)	0.863
	Female	164(73.5)	59(26.5)	
Age	18-39	67(70.5)	28(29.5)	**0.022**
	40-50	99(67.8)	47(32.2)	
	51- 60	61(87.1)	9(12.9)	
	>60	14(77.8)	4(22.2)	
Education	Illiterate	22(71.0)	9(29.0)	0.389
	Primary	108(77.1)	32(22.9)	
	Secondary	111(70.3)	47(29.7)	
BMI	Under weight	50(63.3)	29(36.7)	0.093
	Normal Weight	143(75.7)	46(24.3)	
	Over weight	34(75.6)	11(24.4)	
	Obese	10(90.9)	1(9.1)	
CD4	>500	97(74.6)	33(25.4)	0.690
	200-500	111(71.2)	45(28.8)	
	<200	33(76.7)	10(23.3)	
HAART Combination	AZT BDC	104(73.2)	38(26.8)	**0.028**
	ABC BDC	6(85.7)	1(14.3)	
	TDF BDC	21(87.5)	3(12.5)	
	D4T BDC	14(51.9)	13(48.1)	
Duration of drug taken	1-5 Years	69(68.3)	32(31.7)	0.402
	5-10 Years	134(75.3)	44(24.7)	
	>10 Years	38(76.0)	12(24.0)	
No. of Drug used	1 drug	93(73.8)	33(26.2)	0.286
	2 drugs	85(73.9)	30(26.1)	
	3 drugs	55(68.8)	25(31.2)	
	4 drugs	8(100)	0(0)	

AZT: Zidovudine; ABC: Abacavir; TDF: Tenofovir; BDC: Based Drug Combination; BMI: Body Mass Index

Table 2 Multivariate logistic regression analysis of factors associated with liver injury in HIV-1 infected patients in Asmara, Eritrea 2018

Variables	Total (%)	Abnormal Liver enzyme (%)	COR(95% CI)	P-value	AOR(95% CI)	P-value
Sex	165(89.7)	19(10.3)				
Male	42(79.2)	11(20.8)	Ref		Ref	
Female	108(83.3)	21(16.7)	0.96(0.56-1.60)	0.86	0.74(0.35-1.55)	0.42
Age	16(88.9)	2(11.1)				
18-39	210(88.2)	28(11.8)	2.27(0.81-6.34)	0.12	3.61(0.78-16.5)	0.09
40-50	115(89.1)	14(10.9)	3.29(1.29-8.39)*	0.013	4.57(1.17-17.8)*	0.03
51-59	138(85.7)	23(14.3)	2.35(0.88-6.20)	0.08	2.5(0.64-9.67)	0.19
>60	115(89.1)	14(10.9)	Ref		Ref	
BMI	138(85.7)	23(14.3)				
Under weight	115(89.1)	14(10.9)	5.8(0.7-47.6)	0.10	4.8(0.51-47.0)	0.17
Normal Weight	138(85.7)	23(14.3)	3.21(0.40-25.81)	0.27	2.7(0.30-25.6)	0.37
Over weight	115(89.1)	14(10.9)	3.23(0.37-28.2)	0.29	2.7(0.25-30.6)	0.41
Obese	138(85.7)	23(14.3)	Ref		Ref	
HAART Combination	115(89.1)	14(10.9)				
AZT BDC	142(71)	38(26.8)	Ref		Ref	
ABC BDC	7(3.5)	1(14.3)	0.45(0.05-3.91)	0.47	0.46(0.05-4.29)	0.49
TDF BDC	24(12)	3(12.5)	0.39(0.11-1.38)	0.14	0.39(0.11-1.44)	0.15
D4T BDC	27(13.5)	13(48.1)	2.54(1.09-5.89)*	0.03	2.95(1.19-7.27)*	0.02

* Significant at $p<0.05$; AZT: Zidovudine; ABC: Abacavir; TDF: Tenofovir; BDC: Based Drug Combination; BMI: Body Mass Index