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Profile of Liver Elevated Enzymes in People Living with HIV Followed at the Protestant Hospital of Garoua-Boulaï, East Region, Cameroon

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ABSTRACT

Background: *Human immunodeficiency virus (HIV) infection associated with Highly Active Antiretroviral Treatment (HAART) is considered a cause of many hepatobiliary disorders, including elevated liver enzymes, hepatomegaly, and fatty liver.*

Aim: *To highlight Liver Elevated Enzymes (LEE) in people living with HIV (PLHIV) under HAART treatment.*

Methods: *This study was cross-sectional and done between June 2022 to August 2022. Participants were PLHIV, adults over 21 years old, followed at the Protestant Hospital of Garoua Boulaï. Venous blood was collected from each participant Alanine aminotransferase (ALT), and aspartate aminotransferase (AST), were measured with a spectrophotometer. SPSS version 23.0. Was used to express proportions and adjusted odds ratios to identify risk factors.*

Results: *Overall, 131 participants were included in this analysis, all were HIV type 1, and 30% of participants have LEE. Of the 131 patients investigated, we found 69.6% of LEE with HBs Ag and 27.5% of this group found with Antibody HCV. A logistic regression analysis did not show any significant ($p<0.05$) association between LEE with socio-demographic and clinical variables.*

Conclusion: *This study shows that the occurrence of LEE is independently influenced by multiple risk factors.*

Keywords

Liver Elevated Enzyme, PLHIV, HAART, Protestant Hospital of Garoua Boulaï.

Introduction

Human immunodeficiency virus (HIV) is a member of the Lentivirus genus, the Reoviridea family, and the Orthoretrovirinae subfamily [1]. HIV is divided into two types based on genetic differences and viral antigen differences [2]. In 2022, an estimated 39.0 million people worldwide were living with HIV (PLHIV) [3], of these, sub-Saharan Africa alone contains an estimated 25.3 million Africans living with HIV [4,5], which makes HIV a major public health problem in the world, particularly in countries with limited resources, particularly those in Africa [6].

The availability of antiretrovirals for PLHIV has significantly improved their chances of survival [7], nevertheless, long-term use of Highly Active Antiretroviral Treatment (HAART) has toxic consequences that might be asymptomatic or symptomatic [8]. Yet, it has been demonstrated that the toxic effects of HAART are

connected to liver damage, which in turn is linked to the synthesis of hepatic transaminases [9]. These transaminases correspond to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) [10]. The function of transaminases is to catabolize amino acids so that they enter the citric acid cycle [11]. Transaminases are found in different organs [12] such as the liver, cardiac and skeletal muscles, pancreas, brain, kidneys, lungs, erythrocytes, and leukocytes for AST [13]. While ALT is found at a higher concentration in the liver compared to the kidneys, heart, and muscles [14]. This makes serum transaminases a good indicator of liver damage and HAART toxicity [15].

HIV infection is considered a cause of many hepatobiliary disorders, including elevated liver enzymes, hepatomegaly, and fatty liver [12]. Possible mechanisms of HIV-related liver injury include direct interaction of HIV and several liver cell types [16] and co-infection with viral hepatitis [17]. However, these mechanisms are not fully elucidated, making it difficult to separate drug-induced hepatotoxicity from viral infection-induced liver damage [18].

The evaluation of liver damage represents a critical step in the management of PLHIV [19]. Several studies have admitted that age, sex, HAART type, viral load, hypertriglyceridemia, hyperglycemia, history of anti-tuberculosis treatment and co-infection with hepatitis B and hepatitis C, alcohol abuse, continually elevated ALT or AST are risk factors for hepatotoxicity in PLHIV [15]. However, given the diversity of geographies, socioeconomic and cultural habits, human genetics, and the difficulty of extending literary data from one context to another, these aspects demand consideration. Since serum transaminases are regular clinical biochemical tests that are widely available and affordable in both developed and developing nations, further research into the clinical implications of high transaminases is needed among PLHIV patients receiving HAART.

Materials and Methods

Study design, population and ethical consideration

This study was a hospital-based cross-sectional, conducted at the Protestant Hospital of Garoua-Boulaï from June 2022 to August 2022. Participants were adults over 21 years old, previously diagnosed with HIV/AIDS on antiretroviral treatment for a period ≥ 06 months and followed at Protestant Hospital of Garoua Boulaï. All HIV-Tuberculosis co-infected participants were excluded.

Data collection

An informed consent was taken from each participant after providing explanation of study and the procedures. Data were obtained with a pre-tested questionnaire. These include information on; age, sex, weight, level of education, monthly income, history of alcohol and cigarette use, type of HAART, concomitant use of other drugs within 4 weeks before enrollment, WHO clinical staging, and the year of the first diagnosis of HIV.

Laboratory analysis

About five milliliters (mL) of venous blood was collected from each participant and processed to obtain serum. Measurement of Alanine aminotransferase (ALT), aspartate aminotransferase (AST), was done using the SPINREACT commercial kits (Ctra Santa Coloma, Spain) as described by manual and spectrophotometer (RAL Clima MC-15). Detection of HBsAg was done with Fastep brand HBSAg strips.

Case definitions for hepatic transaminases were determined by sex. Normal values of AST (GOT) in men belong to the range 5-40 IU/L and in women, normal values belong to the range 5-38 IU/L. While normal ALT (GPT) values in men belong to the 5-45 IU/L range and in women, normal values belong to the 5-40 IU/L range.

Ethical Approval

The study was approved by Institutional Review Board of Protestant Hospital of Garoua-Boulaï (Ref. N°2022/100/UN/R/DFS/CD-SBM).

Statistical analysis

The clinical assessment and laboratory results were recorded and double-checked using Microsoft Excel software and analyzed using Statistical Package for the Social Sciences version 23.0. Categorical variables were expressed as frequencies and proportions while logistic regression as adjusted odds ratios to identify risk factors associated with liver elevated enzyme (LEE). The level of significance was set at 5% throughout the analyses.

Results

Distribution of participants

Overall, 131 participants were included in this analysis, all were HIV type 1, 30% of participants have LEE and 70% have normal liver enzymes (Figure 1).

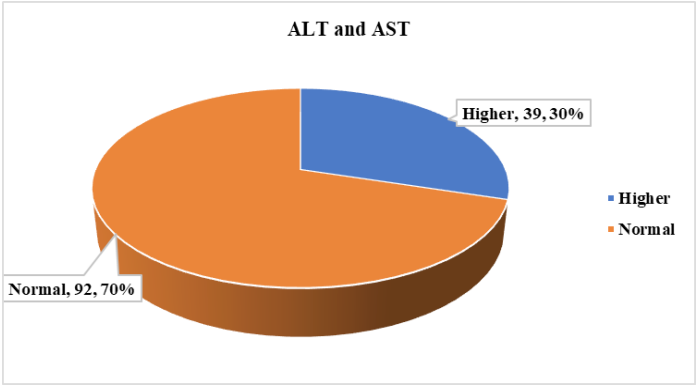

Figure 1: Distribution of study population.

Socio-Demographic Characteristics of the Study Population

Table 1 shows the socio-demographic characteristics of participants. Our study found 34.8% of women and 19.0% of men with LEE. We also found 31.8% aged between 21 to 29 years old have LEE. 29.7% of this group were married, 30.8% of this group stopped their education in primary school. 56.0% of the group with LEE were Muslim. 30.0% had been on HAART for 10 years. 64.7% of participants with LEE were on Dolutegravir (DTG) + Lamivudine (3TC) + Nevirapine (NVP) as treatment. 35.7% of the

group of LEE were at the second line of treatment. 29.5% of this group were at WHO 1 staging (Table 1).

Table 1: Characteristics of study population.

		Transaminases	
		Liver elevated enzyme n(%)	Liver normal enzyme n(%)
Sex	Female	31 (34.8)	58 (65.2)
	Male	8 (19.0)	34 (81.0)
Age	21-29	14 (31.8)	30 (68.2)
	30-39	12 (22.2)	42 (77.8)
	40-49	7 (38.9)	11 (61.1)
	50 and over	6 (40.0)	9 (60.0)
Marital status	Bachelor	9 (25.0)	27 (75.0)
	Divorce	6(35.3)	11 (64.7)
	Bride	19 (29.7)	45 (70.3)
	Widower	5 (35.7)	9 (64.3)
Level of study	Unschooled	9 (25.7)	26 (74.3)
	Primary	20 (30.8)	45 (69.2)
	Secondary	9 (33.3)	18 (66.7)
	Tertiary	1 (25.0)	3 (75.0)
Religion	Other	4 25.0)	12 (75.0)
	Catholic	6 (15.0)	34 (85.0)
	Muslim	14 (56.0)	11 (44.0)
	Protestant	15 (30.0)	35 (70.0)
Duration of treatment	< 5 years	19 (28.8)	47 (71.2)
	5 to 10 years	14 (31.1)	31 (68.9)
	10 years and over	6 (30.0)	14 (70.0)
Treatment	ABC+3TC+DTG	//	10 (100.0)
	DTG+3TC+ NVP	11 (64.7)	6 (35.3)
	TDF+3TC+DTG	12 (17.9)	55 (82.1)
	TDF+3TC+EFV	16 (43.2)	21 (56.8)
Processing line	First line	34 (29.1)	83 (70.9)
	Second line	5 (35.7)	9 (64.3)
Clinical stage of the disease (WHO)	Stage 1	33 (29.5)	79 (70.5)
	Stage 2	5 (31.3)	11 (68.8)
	Stage 3	//	2 (100.0)
	Stage 4	1 (100.0)	//

3TC: Lamivudine; **ABC:** Abacavir; **DTG**: Dolutegravir; **EFV**: Efavirez; **NVP**: Nevirapine; **TDF**: Tenefovir

Coinfection with HBV and HCV

Overall, of the 131 patients investigated, we found 69.6% of LEE with HBs Ag and 27.5% of this group found with Antibody HCV (Table 2).

Table 2: HBs Ag and Antibody HCV serology among participants.

		Transaminases	
		Liver elevated enzyme n(%)	Liver normal enzyme n(%)
HBs Ag	Negative	23 (21.3)	85 (78.7)
	Positive	16 (69.6)	7 (30.4)
Anti-HCV	Negative	25 (31.3)	55 (68.8)
	Positive	14 (27.5)	37 (72.5)

Risks factors of liver elevated enzymes

Our study found that, age (30-39 year) (OR=1.1 at CI =95% [0.3-3.8]); gender (Male) (OR=1.9 at CI =95% [0.5-6.4]); year under HAART (10 years and more) (OR=2.7 at CI=95% [0.4-15.8]); WHO staging (Stage 2) (OR=1.5 at CI=95% [0.2-8.1]); alcohol consumption (OR=1.3 at CI =95% [0.1-9.5]); and positive anti-HCV (OR=1.9 at CI =95% [0.6-6.05]) were associated with LEE, but these associations were non-significant (Table 3).

Table 3: Risk factors of elevated transaminases.

	OR	95% confidence interval	p-value
Age			**0.6**
21-29			
30-39	1.1	[0.3-3.8]	0.8
40-49	0.5	[0.09-3.2]	0.5
50 and over	0.4	[0.08-2.2]	0.3
Sex			
Female			
Male	1.9	[0.5-6.4]	0.2
Duration of treatment			**0.4**
< 5 years			
5 to 10	1.05	[0.3-3.5]	0.9
10 years and over	2.7	[0.4-15.8]	0.2
Current treatment line			
Second			
First	0.4	[0.08-2.4]	0.3
Molecules used in treatment			**0.2**
ABC+3TC+DTG			
DTG+ 3TC+ NVP	0.0	0.0	0.9
TDF+3TC+EFV	0.0	0.0	0.9
WHO clinical stage			**0.9**
Stage1			
Stage2	1.5	[0.2-8.1]	0.6
Stage3	1.9	0.0	0.9
Stage4	0.0	0.0	1.0
Alcohol consumption			**0.5**
No			
Yes	1.3	[0.1-9.5]	0.7
Often	0.5	[0.1-1.7]	0.3
Tobacco consumption			
No			
Yes	0.6	[0.03-11.8]	0.7
Anti-HCV			
Negative			
Positive	1.9	[0.6-6.05]	0.2
Ag HBs			
Negative			
Positive	0.1	[0.03-0.3]	0.1

3TC: Lamivudine; **ABC:** Abacavir; **DTG:** Dolutegravir; **EFV:** Efavirez; **NVP:** Nevirapine; **TDF:** Tenefovir

Discussion

The current study aims to highlight transaminase differences in people living with HIV. This study is part of a series of continuous public health surveillance studies that look at the prevalence, risk factors, and hepatitis B and C virus coinfections associated with elevated transaminases in people living with HIV in resource-limited settings, with the goal of producing data that can help better manage the control of liver toxicity in people living with HIV. Liver toxicity, covering grades 1-4, is a critical health issue

that contributes significantly to morbidity, death, extended hospital admissions, and treatment [20,21].

The increase in the enzyme levels of HIV-treatment naïve patients and those on HAART is well documented [22]. The prevalence of LEE in this study was 30% (39/131) in HAART, this finding is higher like other studies conducted on HIV infected patients in Cameroon (22.6%) [23], South Africa (23%) [24] , Ethiopia (20.1%) [25] , Europe and North America, where rates vary between 19–29% [24,26-28]. In contrast, the prevalence of LEE found in our study is different in one side to that reports from Africa which estimates LEE around 13% [29-31] and to the other side to the 11% of prevalence of LEE in the general population of Australia [32]. The elevated liver enzyme in HIV infected patients might be due to direct inflammation of hepatocytes by HIV through apoptosis, mitochondrial dysfunction, and permeability alteration in mitochondrial membrane that stimulate an inflammatory response [32]. Indeed, ALT is a sensitive marker, primarily secreted in liver cells, while AST is produced in liver and other tissues like; heart, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes [33]. These enzymes are released into the plasma in greater amounts when there is an injury to the liver cell membrane resulting in increased permeability. Nevertheless, many studies found that HAART medications caused varying degrees of liver enzyme increase or hepatotoxicity (such as; mild, moderate and severe) [34]. This could be due to a variety of factors such as co-infection with the hepatitis virus, the habit of consuming alcohol, the drug regimen, the duration of treatment, the presence or absence of comorbid conditions, geographic location, and genetic polymorphisms [22,35-37], which may have contributed to the differences in the level of liver injury among the participants of this study.

Female was related with LEE in our investigation, despite the fact that HIV pathogenesis and drug metabolism in humans are not sex dependent in general. This conclusion differs from prior research conducted in other situations, including Ethiopia [20], Nigeria [38], Cameroon [23], South Africa [39], Swiss [40] and Brazil [41]. There are several reasons for this difference. First, in these studies males represented between 63–94% of the study population compared to our study where females accounted for 67% of our study population. Second, an inverse relationship between black ethnicity and chronic liver enzyme elevation has been reported in several studies of HIV infected patients [29,42-44]. Third, a high prevalence of viral hepatitis B and C infections respectively 69.6% and 27.2% participants in our study population, all of which have been shown to be associated with LEE. In these factors we can add, drugs, toxins, HIV, endogenous metabolites, alcohol and certain social behaviours such as the use of herbal remedies may lead to LEE among PLHIV [22,45-50].

Our findings indicate that age is not a predictor of LEE. This might be because our research cohort was youthful, ranging from 18 to 50 years old. This conclusion is consistent with previous findings that age is not a risk factor for the development of hepatotoxicity in HAART patients [20,40,51,52].

In the present study, LEE in grade 1 and 2 defined by the WHO were observed respectively in 29.5% and 31.3% of the study participants. This finding was consistent with very high rate of LEE reported in other studies conducted on HIV patients under HAART by Sulkowski et al. [35] and Mankhatithan et al. [53] that indicated 10.4% and 17.7%, respectively. However when considering studies carried out in Ethiopia by Mulu et al. [20], in Uganda by Kalyesubula et al. [54] and in Thailand by Law et al. [55], These studies showed lower rate of LEE respectively 1.84%, 2.9% and 1.3% in different grade of HIV defined by the WHO [56]. These wide variations in the rate of LEE reported in our study and previous studies is probably due to differences in the population characteristics, different definitions of LEE and the frequency of patient follow-up, monitoring and duration of therapy.

In this study, logistic regression analysis did not show any significant ($p<0.05$) association between LEE with socio-demographic and clinical variables, yet Tesfa et al. showed that that BMI was correlated with the drug metabolism of the patient in Northeast Ethiopia [22]. Whether the study design is changed to a cohort, this cross-sectional study gains strength. Because of the small number of study participants, we cannot draw general conclusions regarding the impact of HAART on liver enzymes in HAART patients. Owing to funding constraints, this study did not include all significant liver enzymes used in the diagnosis of liver damage.

Conclusion

Despite the fact that there we did not find significant association between socio-demographic and clinical variables and LEE in this study, it is obvious that the occurrence of LEE is independently influenced by multiple risk factors.

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