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Hepatotoxicity and Anaemia Co-morbidity in Treated HIV Patients in Fundong Subdivision in the Northwest Region of Cameroon

Lem Edith Abongwa[1,2*], Anthony Kebira Nyamache[2], Nantia Akono[1], Stanley Sunjo[1], Vera Nange[1], Hebert Balan[1], Fokunang Charles[1,3], Judith Torimiro[3,4] and Paul Okemo[2]

[1]Department of Biological Sciences, Faculty of Science, University of Bamenda, P.O.Box 39, Bambili, N. W. Region, Cameroon.
[2]Department of Microbiology, School of Pure and Applied Sciences, Kenyatta University, P.O.Box 43844, Nairobi, Kenya.
[3]Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon.
[4]Chantal BIYA International Center for Research on the Prevention and Management of HIV / AIDS (CIRCB), Cameroon.

Authors' contributions

This work was carried out in collaboration between all authors. Authors LEA, NA and FC designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors VN, HB and SS took care of participants' recruitment and managed the literature searches. Authors LEA, AKN, FC and JT managed the analyses of the study. Authors AKN, JT, FC and PO supervised the work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Hepatotoxicity and anaemia are relevant adverse effects of highly active antiretroviral therapy (HAART) and can cause interruption of therapy and death. However, there is dearth of information on hepatotoxicity and anaemia co-morbidity especially in rural areas. The aim of the

**Corresponding author: E-mail: lemedith19@gmail.com;*

study was to identify the prevalence of Hepatotoxicity and Anaemia co-morbidity among HIV patients treated with either Zidovudine + Lamivudine + Efavirenz or Zidovudine + Lamivudine + Nevirapine or Tenofovir + lamivudine + Efavirenz in Fundong.
Study Design: In total, 150 drug naïve patients who have been followed up for 18 months with age between 15 and 74 years were recruited into the study. Baseline and 18 months levels of CD4 counts, alanine transaminase (ALT), and aspartate transaminase (AST) and Haemoglobin concentration (Hb) were determined.
Place and Duration of Study: Samples were collected from patients visiting the day hospital in Fundong District Hospital between January-March 2015.
Methodology: HIV was diagnosed using Alere determine HIV rapid test kit and Bioline or Oral Quick test kit for the confirmatory test. CD4 counts were determined using the Alere Pima™ CD4 cartridge machine. Hb, ALT and AST counts were determined by colometric enzymatic reaction using the urit 3300 machine and classified based on age and sex.
Results: The majority of patients were female 115(76.7%) and belonged to the <30 years age range 48(32%). The prevalence of anaemia decreased from 86(57.3%) to 69(45.6%) at the end of the study period. In all, 46(30.7%) patients had hepatotoxicity and anaemia co-morbidity which was higher in the age group <30 years 30(41.7%) and in female 37(32.2%). A total of 1(0.7%) and 10(6.7%) patients developed severe hepatotoxicity using ALT and AST respectively. The prevalence of hepatotoxicity was higher in male (31.4% and 62.9%) and in the age group 30-39years (29.5% and 68.2%) for ALT and AST, respectively. The prevalence of anaemia and elevated AST and ALT were higher in persons with CD4 <200cells/µl. There was a significant correlation (P<0.001) between CD4 and Hb (r=0.193), CD4 and ALT(r=-0.149) and CD4 and AST(r=-0.193).
Conclusion: Hepatotoxicity especially Grades 1-2 and not anaemia is a significant adverse effect of HAART upon time.

Keywords: Hepatotoxicity; anaemia; HIV; highly active antiretroviral therapy.

1. INTRODUCTION

Hepatotoxicity and anaemia are the most relevant adverse effects of antiretroviral therapy (ART) owing to their frequency and the fact that it can lead to treatment interruption and death [1,2]. In 2014, of the 69.1% (25.8 million) people living with Human Immunodeficiency Virus (HIV) worldwide, only about 40.4% (14.9 million) received ART [3] of which 65.1% (9.7 million) were from low and middle income countries including Cameroon [4]. The advent of ART has transformed the course of HIV infection in most individuals through the reconstitution of the immune system and the suppression of viral replication [5]. This has led to a substantial dramatic improvement in the survival of HIV-infected patients on treatment and decreased incidence of HIV/AIDS related opportunistic infections and death [6,7]. In the era of ART, ART-associated hepatotoxicity has emerged as an important cause of morbidity, mortality and treatment interruption in persons with HIV [1,8,9].

Hepatotoxicity is as a result of elevated changes in normal levels of liver enzymes such as alanine transaminase (ALT), and aspartate transaminase (AST). The elevated levels of ALT and AST generally signify some form of liver (or hepatic) damage or injury and such levels may be acute indicating sudden injury to the liver or chronic suggesting ongoing liver injury [1]. Studies in developed and developing countries indicate that AST and ALT levels increased after initiation highly active antiretroviral therapy (HAART) to cause different Grades of hepatotoxicity that ranges from 1.1%-78% [2,10-13]. However there is limited information with respect to this in Cameroon.

Anaemia is also the most common heamatologic abnormality in HIV infected persons, affecting 60% to 80% of patients in late- stage disease [14]. The severity varies in some individuals as patients may experience different symptoms such as fatigue, dyspnea, and reduced exercise tolerance [15,16]. Studies have shown that there is a significant association between hepatotoxicity and anemia and the progression to AIDS and death [13,17]. However limited information is known on the effect of HAART on Hb concentration and the link with hepatotoxicity.

In Cameroon, there is paucity of data on HAART associated hepatotoxicity and anaemia as studies are hardly cited in the literature. Our

study therefore aimed to identify the prevalence of Hepatotoxicity and Anaemia co-morbidity among HIV patients treated with either Zidovudine + Lamivudine + Efavirenz or Zidovudine + Lamivudine + Nevirapine or Tenofovir + lamivudine + Efavirenz in Fundong Health District in the Northwest region of Cameroon. This study is beneficial to the HIV infected patients, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment by promoting the early recognition of potentially serious adverse effects.

2. MATERIALS AND METHODS

2.1 Study Design

A retrospective review was performed on concerted patients receiving first line HAART at a primary Healthcare facility between January 2015 and March 2015. Ethical clearance was obtained from the Institutional Ethical Committee. The minimum acceptable sample size was calculated using the Lorenz formula to be 117. In all 150 persons were recruited for the study. Inclusion criteria included confirm cases of HIV, with complete data on Hb, CD4 count, normal ALT and AST baseline values, has regularly been on HAART for at least 16 months, and their liver function tests monitored every 6-12 Months based on the current Cameroon antiretroviral guidelines [18].

2.2 Laboratory Procedues

HIV was diagnosed using Alere determine HIV rapid test kit. Bioline test (One step anti-HIV1/2 test) or Oral Quick Rapid HIV-1/2 Antibody test was used as the confirmatory test. CD4 counts were determined using the Alere Pima™ CD4 cartridge machine. Hb count was measured by enzymatic reaction with Drabkin's reagent using the Urit 3300 machine. ALT and AST were measured using colometric enzymatic kinetic method according to the manufacturer procedures using the Urit 3300 machine. The AST reference values for women were <32 IU/L and for Men <38 IU/L and that of ALT were <31 IU/L and for Men <41 IU/L [18]. The patients were administered Zidovudine + Lamivudine + Efavirenz or Zidovudine + Lamivudine + Nevirapine or Tenofovir + lamivudine + Efavirenz based on the Ministry of Public Health treatment guidelines.

ALT and AST were categorized using standardized toxicity Grade scale using the normal range of ALT and AST levels as being on upper limit of normal (ULN) value. Grade 0 (normal; <1.25 ULN), Grade 1(mild <1.25-2.5 ULN), Grade 2 (moderate 2.6-5.0 ULN), Grade 3(severe >5.0-10 ULN) and Grade 4(life threatening >10ULN). Grade 3 and 4 were considered as hepatotoxicity [1]. Anaemia was classified based on Hb levels with respect to sex and age reference standards as follows: Non-anaemic ≥12 (for female) and 13 (for male) g/dL, Mild anaemia=11.0-11.9 (for female) and 12.9 (for male) g/dL; Moderate anaemia =8-10.9 g/dL and Severe anaemia <8 g/dL [19].

2.3 Data Analysis

The results obtained from this study was entered, double checked into a Microsoft Excel database and exported to SPSS version 16 for analysis. The Pearson χ^2 test was used to examine associations between gender, age group, CD4 cell count groups with anaemia and hepatotoxicity data at baseline, and 18 months after treatment. A bivariate correlation was used to assess the relationship between Hb, ALT AST and CD4. Mean and standard error of the mean (SEM) were used to describe continuous variables and student T test was used to compare the means at different drug duration. P value of <0.05 was considered statistically significant.

3. RESULTS

3.1 Patients

The age range of the patients was 15 to 74 years with a mean (SD) of 36.7 (13.3) years. The majority of patients were <30 years 48 (32%) and the least >50 years age group 27(18.0%). The female population 115 (76.7%) tripled that of the male 35 (23.3%).

3.2 Variation of CD4, Haemoglobin (HB), Alanine Transaminase (ALT), and Aspartate Transaminase (AST) Levels Overtime

Of the 150 patients at initiation, 89(59.3%) had CD4 levels less than 200 cells/µl and at the end of the study period 17 (2.7%) of patients showed constant CD4 decrease. Hb, CD4, ALT and AST significantly increased (P <0.05) 18 months after initiation of the treatment (Table 1). A positive significant correlation was seen between CD4 and Hb (r= 0.193 p< 0.001) and a negative significant correlation between CD4 and ALT (r= -0.149; p< 0.001) and CD4 and AST (r= -0.193 p= 0.034).

Table 1. CD4, Hb, ALT and AST at baseline and 18 months after treatment

Parameter	At baseline mean (SEM)	18 months after treatment mean (SEM)	T value	P value
CD4(cells/µL)	197.41(13.5)	500.48 (21.9)	15.49	< 0.001
Hb (g/dl)	11.46 (2.0)	12.53 (1.9)	2.50	0.014
ALT(IU/L)	24.69 (1.7)	34.20 (2.9)	3.36	< 0.001
AST(IU/L)	42.6(2.7)	59.3 (3.8)	5.06	< 0.001

There was a significant negative correlation between Hb and ALT (r=-0.136; p=0.019) and insignificant correlation between Hb and AST (r=-0.06; p=0.300). The prevalence of patients with both hepatotoxicity and anaemia co-morbidity increased to 46(30.7%) at the end of the study compared to the 36(24.0%) at baseline. There was no significant gender difference in co-morbidity (p=0.22) however co morbidity was higher in female 37(32.2%) than male 9(25.7%). Co-morbidity was highest in the < 30 years age range 20(41.7) and this difference was significant p=0.033. Of the 10 patients with severe hepatotoxicity, 9(90%) had CD4 <200(cells/µl) and 5 had severe anaemia. In addition 17(11.3%) of patients experienced a continuous decrease in the CD4 values.

3.3 Evolution of Anemia in Subjects

There was no statistically significant reduction (p=0.05) in anaemia prevalence from baseline 86 (57.30%) till the end of the study at 18months 69 (46.%) (Fig. 1a). At the end of the study period anaemia prevalence was significantly higher (p=0.002) in females 58 (50.4%) than in males 14 (40.0%) patients. The age range 30-39 years significantly (p=0.012) registered the highest prevalence of anaemia cases 29 (60.4%) while the lowest 8 (11.6%) was seen in the 40-49 years age range. There was no statistically significant reduction in anaemia prevalence with increase in CD4 (p=0.061) (Fig. 1b).

3.4 Biochemical Parameters in Severe Hepatotoxicity

At the end of the study period, patients on HAART presented with significantly levels (p =0.004) of hepatotoxicity due to elevated ALT and AST (Fig. 2a). Most of the patients had non severe (Grade 1 and 2) hepatotoxicity 36 (24.0%) and 80 (53.3%) for ALT and AST, 1(0.7%) vs. 10(6.7%) for Severe hepatotoxicity (Grade 3 and 4) respectively. Although male patients had higher prevalence 5 (14.6%) of severe hepatotoxicity compared to their female counterpart 5(4.3%), this difference was not significant (p=0.122). The age group 30-39 years had also recorded the highest prevalence of severe hepatotoxicity 6 (13.6%) with a significant difference of p=0.00 (Fig. 2b). The prevalence of elevated AST and ALT was lower in persons with CD4 >500 cells/µl compared to those <500 cells/µl. This difference was significant in AST (p<0.001) and not with ALT (p=0.053).

4. DISCUSSION

The prevalence of HIV in our study group is higher in female than male. This is in line with the recent HIV/AIDS demographic data in Cameroon [20] and other studies carried by Isichei et al. [9] in Nigeria and Derbe et al. [20] in Ethiopia. This can also be attributed to the morphological differences between male and female and due to the fact that the higher percentage of women presents in the hospital than men consequently, females were more likely to be recruited than males [9,21]. Furthermore it is compulsory to test all women at antenatal care as such female tend to ignore the stigma associated with HIV/AIDS disease than male. Lastly it is a common practice that in couples that are both positive about 75% of the women come to the health facilities to pick up drugs for their spouses. On the other hand the most represented age group in this study population was <30 years 48(32.0%) which contradicts the 30-39 age group data from studies in Yaoundé-Cameroon [1]. This can be due to the fact that this age group is made up of youths that are of child bearing age as such are active in sexual activity which is a principal transmission route of HIV.

Anaemia is a common abnormality seen among HIV persons on HAART. This is similar to other studies carried out in Nigeria [9] and in Cameroon with children [22]. The rate of pre-ART anaemia 86(57.3%) in our study was higher compared to the 52.6% as reported by Adane et al. [23] but falls within the range of 1.3% to 95% as reported by Belperio and Rhew [11].

Our data reveals a significant decrease in the prevalence of anaemia (p= 0.05) from 86(57.3%)

at baseline and to 69(46%) after 18 months of treatment which is similar to the Multicenter retrospective studies carried in Sub-Saharan African which state that the prevalence of anaemia reduces in person on HAART [13]. The positive correlation between CD4 and Hb (r= 0.193 p<0.001) suggests that anaemia is associated with advanced HIV disease state and higher viral load [16]. This is in line with studies carried out elsewhere in Africa [11,24]. Anaemia in HIV can be due to opportunistic infections, or drugs such as Zidovudine, Retrovir, Foscavir that suppress bone marrow production [15,16,25]. The high prevalence of 86(57.3%) of anaemia at the baseline is a clear indication that the causes of anaemia is multi-factorial and need to be closely monitored. It is likely that in a rural area like Fundong individuals might suffer from malnutrition, malaria and helmintic infections which cause anaemia.

In terms of gender, anaemia was higher is female 56(48.7%) than in male 12(34.3%) similar to reports from Ethiopia by Adane et al. [23] this may be attributed to menstrual blood loss [26] or greater Iron requirements in pregnancy since majority of these women 92 (61.33%) were of child bearing age 16-42 years [27].

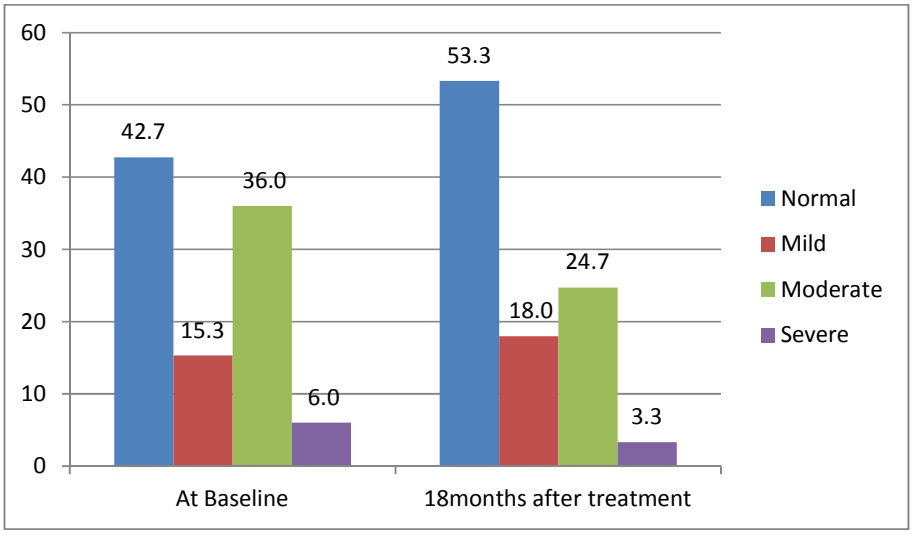

Fig. 1a. Evolution of anaemia (%) from baseline to 18 months after treatment

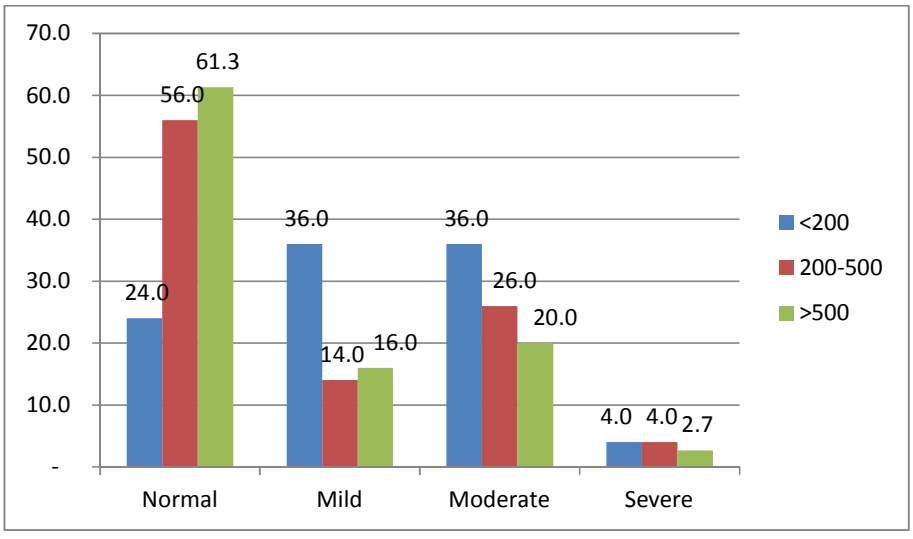

Fig. 1b. Prevalence of anaemia (%) by CD4 grouping (cell/µL) 18 months after treatment

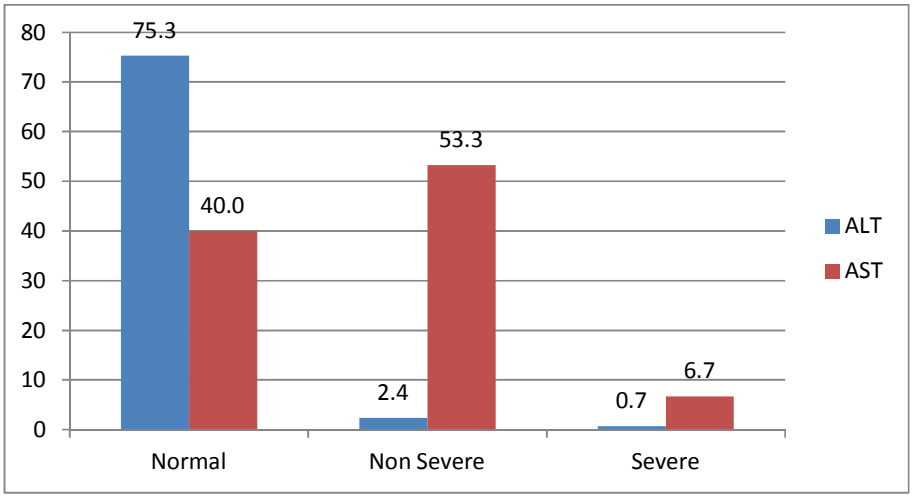

Fig. 2a. Prevalence of ALT and AST hepatotoxicity grade (%) after 18 months of treatment

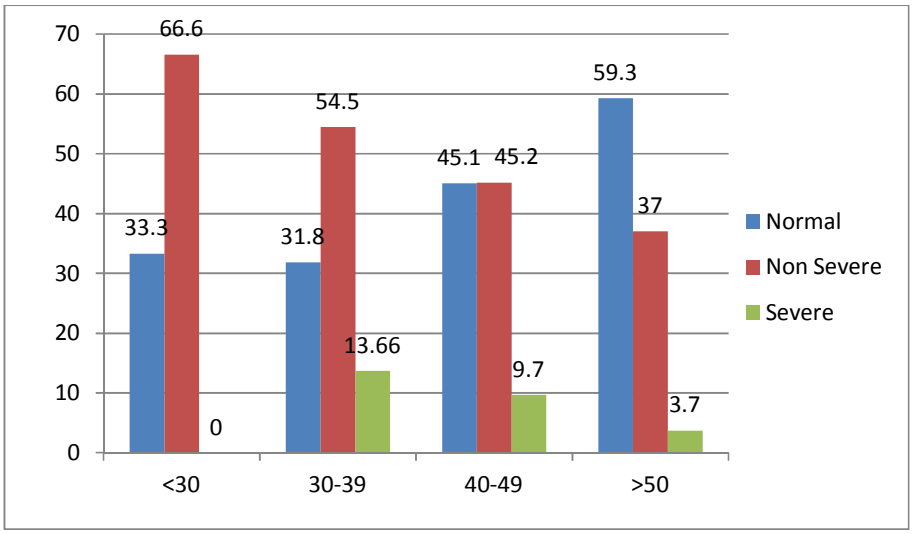

Fig. 2b. Hepatotoxicity (%) by age group (years) after 18 months of treatment

The assessment of hepatotoxicity in patients with HIV infection when dealing with elevations of transaminases is complex, because many factors such as mitochondrial damage and hypersensitivity reactions or direct toxicity as a result of drugs metabolized in the liver through the cytochrome pathways may contribute to liver disease [28]. The overall prevalence mild to moderate (Grade 1 and 2) hepatotoxicity was 80(53.3%) and 36 (24.0%) while that of severe hepatotoxicity (Grade 3) was 10(6.7%) vs. 1(0.7%) for AST vs. ALT, respectively. These values of severe hepatotoxicity were lower compared to similar to studies carried out in Tanzania (13%) [29], Nigeria (10.7%) [2], Spain (9%) [24]. However severe hepatotoxicity due to elevated AST was higher compared to the prevalence of 1.84 % in Ethiopia [7]. These high results tie with those obtained in a previous retrospective review in Boston, where researchers confirmed that long time antiretroviral therapy is associated with high rate of severe hepatotoxicity regardless of drug class or combination [10]. However, it is inconsistent with other reports from Nigeria which state that patients on HAART for 2 - 8 years treatment will present with only mild and moderate hepatotoxicity [5].

The association between hepatotoxicity and gender is conflicting in other African studies. Though not statistically significant male patients

had a higher prevalence of hepatotoxicity compared to female which is similar to studies carried in Uganda [30] India [5] and Netherlands [31]. However this result contradict other finding in Ethiopia [7] Cameroon [32] South Africa [33], Swiss [34] and Nigeria [35] which state that hepatotoxicity are experienced more by women. Since the courses of HIV pathogenesis and drug metabolism in humans are not sex dependent [7] the reasons for this gender discrepancy are not yet explained most probably could due to the difference in population density.

Transaminase levels were insignificantly highest in the 30-39 years. This findings are similar to the study carried out in Yaoundé-Cameroon [1] and but contradict the significant high prevalence in those >50 years age group in Douala-Cameroon [12]. Similar results were recorded in Nigeria [31] and South Africa [36]. This study supported the fact that age is not a risk factor for development of hepatotoxicity in patients taking ART drugs as reported in similar studies carried out elsewhere [7,31,34]. These differences in age can be attributed to the fact that characteristics of the population, duration of treatment, definitions of severe hepatotoxicity varies in the different studies since hepatotoxicity and adverse effects occurred early after starting treatment at mean interval of 2 weeks [17].

There was variation in the prevalence of hepatotoxicity when using AST compared to ALT indicating that both enzymes could be evaluate or hepatotoxicity. The high prevalence of Hepatotoxicity seen with AST is likely because AST is an enzyme not only present in Liver but also in the heart, muscle, brain and Kidney therefore it is less specific for liver disease compared to ALT is an enzyme primarily liver; trace amounts in skeletal muscles and heart [37]. The high prevalence seen with AST 90(60.0%) compare to ALT 37(24.7%) is similar to other studies in Cameroon (76.81% for AST and 53.33% for ALT) by Lucien et al. [12] and contradicts those of Spengler et al. [10]

Even though we did not record any life-threatening hepatotoxicity in our study, nevertheless the high prevalence of non severe 80(53.3%) with AST and 36(24.0%) for ALT is a warning for physicians caring for patients on ART and a call for concern because it may resolve to severe and potentially life-threatening clinical manifestations in the presence of other risk factors that would contribute towards the development of severe liver injury [13]. The high elevated AST and ALT values may be due to Co-infection with hepatitis B or/and C virus infections, high alcohol intake, systemic opportunistic infections, other medical conditions such as treatment of tuberculosis anti-convulsants, malignancies or herbal concoctions taken as additional means of fighting the infection [2,5,12,38]. Furthermore the high prevalence of non severe hepatotoxicity 53(35.3%) for AST and 19(12.6%) for ALT before drug initiation can attest to this. In addition the low values of severe hepatotoxicity suggests that HAART is well tolerated considering that we did not test for the presence of hepatitis C virus and/or hepatitis B virus confection that has shown to contribute towards the development of severe liver injury [2,5,38]. Furthermore patients with HIV often consume combination of different drugs that have the potential to damage the liver in association with the HAART regimen with the aim of controlling the infection [39]. As such it is of prime importance to always screen for hepatitis B and C in patients to be initiated on HAART.

Although the prevalence of patients with both hepatotoxicity and anaemia co-morbidity was high 46(30.7%) at the end of the study, there was no significant association between hepatotoxicity and anaemia (P=0.32) this is similar to what was has been reported by [2,40] and could be attributed to their difference in their metabolic path way.

At base line majority of the patients 89(59.35%) had CD4 count of >200cells/µl. Even though the treatment guideline stipulate that HAART should be administer as early as when the >500cells/µl [4] most people still find it difficult to accept treatment and their HIV status when diagnosed as such will come to the health facilities when the CD4 cell count is very low. Our result showed significant negative associations between CD4+ cell count and elevated AST and ALT. The higher the CD4 cell counts the lower the AST and ALT values. This study contradicts results of Shah [41] in Benin and Hawkins et al. [42] in Kenya who state that high CD4 counts are predictor of ART toxicity. This might be due to immune activation and pro-apoptotic effects on hepatocytes [29]. Although improvement in CD4 was greatly seen after 18 months of treatment 17(11.3%) experience a decrease which can be as a result of non compliance with ART or treatment failure. Thus there in need to assess drug resistance mutation in these sub set of people.

5. CONCLUSION

This study showed that the presence of hepatotoxicity especially Grades 1-2 and not anaemia is a significant adverse effect of the use of HAART upon time. Secondly, using AST value, gender was identified as determinant factor for hepatotoxicity.

6. RECOMMENDATIONS

There is a need to standardize the definitions of hepatotoxicity and anaemia in order to improve comparability of results. Furthermore it will be of prime importance to compare elevated liver enzyme and liver biopsy to investigate changes in the histological structure design of the liver to a normal functioning liver.

7. LIMITATIONS OF STUDY

The findings from this study should be interpreted with caution. Firstly, the cross sectional design did not allowed us to establish age and gender balance ratio at recruitment. Secondly specific drug could not be assessed because drugs were issue to patients base on the availability and drug expiring date. It was not possible to test for HBV, HCV, drugs combination or alcohol consumption which are important risks factors for elevated ALT and AST. Lastly we did not assess the type of anaemia to actually conclude on the difference in anaemia prevalence in gender.

CONSENT

All authors declare that verbal informed consent was obtained from the patient (or other approved parties) for publication of this paper.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the institutional ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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