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Effects of Hepatitis B Virus Co-Infection and Antiretroviral Therapy on Disease Progression among HIV Patients Treated at the Buea Regional Hospital, Southwest Region, Cameroon: A Case-Control Study

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Abstract

In the era of "test and treat", when AIDS-defining events have been drastically reduced, chronic liver disease associated with viral hepatitis and antiretroviral therapy (ART) remains an important cause of non-AIDS morbidity and mortality among HIV-infected patients. Compared to the general population, HIV-infected patients are about 10-times at risk of hepatitis B virus infection. Additionally, several antiretroviral regimens are hepatotoxic. Therefore, effective monitoring and management of ART and HBV co-infection are essential to ending the AIDS epidemic and eliminating viral hepatitis by 2030. This was a hospital-based, matched (age and sex) case-control study. HIV patients (case patients) on ART for at least six months and "healthy" controls aged 18 years and older were enrolled. Blood samples were collected for immuno-hematologic indices and transaminases measurements. Data were presented as counts, percentages, median (IQR) and means (SD), and a p-value < 0.05 was considered significant. The comparisons of means were performed using ANOVA on SPSS version 23. Of the 212 participants, 106 were case patients (60 HIV only and 46 HIV/HBV co-infections). The median age of the study participants was 37 years (IQR: 33 - 44.8), and 69.3% were female. The median duration of ART in HIV patients was 43 months (IQR: 16 - 77.3 months) with most patients on efavirenz-based ART (75.5%). Overall, transaminase levels were higher in the case patients than in healthy controls, while

hematologic indices were lower in the case patients than in healthy controls. Transaminases levels in HIV/HBV co-infected patients were significantly higher than those of HIV mono-infected participants (ALT: 34.13 IU/l vs. 24.69 IU/l, p = 0.002; AST: 36.50 IU/l vs. 28.08 IU/l, p = 0.001). However, there was no significant difference in immune-haematologic indices (CD4, Hgb, WBC, RBC, platelet counts) of HIV mono-infected and HIV/HBV co-infected patients. HIV patients on nevirapine-based regimens had raised and sustained transaminase levels than those on efavirenz-based regimens throughout ART. Severe anaemia and advanced HIV disease (<200 cell/μL) significantly decline over the course of ART. The prevalence of significant (>1.5) and mild (0.6 - 1.5) liver fibrosis based on the APRI score was 0.5% and 8%, respectively. Significant fibrosis (>3.25) was 0.9%, while 18.4% had inconclusive fibrosis (1.45 - 3.25) based on the FIB-4 score. HIV/HBV co-infected patients had a higher occurrence of liver fibrosis (APRI: 0.5% vs FIB-4: 0.9%). Co-infections with HBV increase the risk of liver-related morbidity in HIV patients. Therefore, screening for serological markers of chronic HBV infection and hepatic transaminase levels in HIV patients remains crucial in the continuum of care.

Keywords

HIV/HBV Co-Infection, NVP-Based, EFV-Based, Antiretroviral Therapy, Fibrosis, Non-Invasive Markers (NIM)

1. Introduction

Scaling up of ART has dramatically reduced the episodes of the human immunodeficiency virus (HIV)-related morbidity and mortality and increased life expectancy among those living with HIV worldwide [1]. In the last year, access to ART has more than doubled considerably [2]. However, comorbidities with hepatitis infection currently pose significant clinical and public health challenges in managing HIV patients [3]. People infected with HIV are more at risk of being co-infected with hepatitis B virus (HBV), and hepatitis C virus (HCV) compared to the general population. These viruses share transmission routes, and up to 33% of those with HIV may be co-infected with HBV or HCV, especially in some people, such as injection drug users (IDUs) and men who have sex with men [4] [5].

In 2019, an estimated 296 million people lived with HBV infections, 1.5 million new infections per year, resulting in 820,000 deaths, mainly from complications such as cirrhosis and hepatocellular carcinoma [6]. Globally, approximately 5% to 20% of the 36.7 million people living with HIV are co-infected with chronic HBV infection, with sub-Saharan Africa bearing the highest burden [2] [7]. Chronic HBV rates in HIV-infected individuals vary significantly between regions and risk-based groups, reflecting different patterns of transmission [8] [9]. For example, in Vietnam, the prevalence of chronic HBV in HIV-infected individuals who inject drugs or are sex workers is 28% and 15%, respectively

[10]. In Cameroon, the burden of HBV infection in HIV-infected patients is enormous, with seroprevalence rates ranging from 12.6% [11] to 23.7% [12].

Studies have shown that HIV/HBV co-infected patients are at higher risk of developing complications of HBV-associated liver disease [13] and often have elevated HBV DNA viremia [14] than those with chronic HBV mono-infection. Elevated HBV DNA levels are associated with an increased risk of developing cirrhosis [15] liver decompensation [16], and hepatocellular carcinoma [17] and may contribute to ART-related hepatotoxicity [18] experienced by HIV/HBV co-infected patients.

Current guidelines for managing HIV patients recommend routine testing and monitoring of patients for hepatitis before initiating ART [7], a standard of care in developed countries, but it is not performed in most resource-limited settings due to cost [12]. Chronic liver disease associated with viral hepatitis remains a significant cause of AIDS and non-AIDS morbidity and mortality among HIV-infected patients. On the other hand, HIV increases the risk of HBV-related liver diseases, but the effects of viral hepatitis coinfection on the immune-haematological variables are not very unclear. Furthermore, the elevated liver enzyme has been reported to be a potential side-effect of most antiviral agents used to treat HIV infection. Therefore, people with HIV co-infected with HBV are at increased risk for severe life-threatening complications, which might most probably affect the treatment outcome of HIV infection. These facts are major public health concerns, particularly in resource-limited settings with relatively few studies that have addressed these concerns.

To close the gap in achieving the UNAIDs 90-90-90 goal of ending the AIDS epidemic and eliminating hepatitis by 2030, effectively monitoring and managing the effects of ARTs, HBV coinfections and other comorbidities on HIV treatment outcomes are needed. Therefore, this study examines the impact of HBV comorbidity and ART on some immune-haematological indices and markers of liver disease in a cohort of HIV patients treated at Buea Regional Hospital compared to healthy controls. The study specifically evaluated the effects of HBV coinfection on liver enzymes and some immune-haematological parameters in HIV-infected patients; investigated ART-related hepatotoxicity in HIV-infected patients in the continuum of care and the prevalence of liver fibrosis in the study population based on Non-Invasive markers (APRI and FIB-4 scoring algorithms) (NIM).

2. Materials and Methods

2.1. Study Area

The Buea Regional Hospital (BRH) was selected as the study site, it is located in Buea in the Fako Division of the Southwest region of Cameroon at the foot of Mount Cameroon. By national classification, BRH is a 120-bed tertiary health facility with up to 22 departments/units that serve close to 30,000 clients per annum from Buea municipality and its environs and neighbouring towns (Mu-

yuka, Ekona, Mutengene, Tiko, Ombe, and Limbe). Participants were enrolled from a cohort of people living with HIV who visit the BRH HIV treatment center for clinical follow-up or antiretroviral drugs refills.

2.2. Study Design and Duration

This was a hospital-based matched (age and sex) case-control study that enrolled HIV-infected participants, as well as healthy controls who were ≥18 years of age. The study was carried out from May 2018-June 2019.

2.3. Study Population and Sampling Method

Case participants in this study were purposively selected from a cohort of people living with HIV (PLWHIV) treated at the Buea Regional Hospital HIV treatment center. These participants had been previously screened for HBV under the BioCollections Worldwide study protocol from 2015 to 2018. Cases were divided into two major groups: Mono-infected HIV patients and HIV/HBV co-infected. Retrospective data was collected from the treatment centre and blood samples were collected for each eligible participant who came for drug refill during the period of the research. Comparison of treatment outcomes were done between these groups of cases and inferences made.

The healthy controls were enrolled during an HIV, HCV and HBsAg free screening exercise that was conducted in the Buea Regional Hospital. Controls were considered physically strong and healthy people negative for HIV, HCV, HBsAg and anti-HBc with no history of liver disease, kidney disease or metabolic syndrome. The controls and cases were matched for age range and sex. Newly diagnosed HIV patients, HIV patients who were not yet on treatment and HIV/HCV co-infected patients were excluded from this study.

2.3.1. Data Collection

Individual patient files were reviewed for the following information: demography, clinical presentation, date of start of treatment, current and previous treatment regimen, duration of treatment and previous results for ALT, AST, WBC, Platelet, CD4 and Hgb. The retrospective results included those for the year 2015 to 2018.

2.3.2. Sample Collection and Preparation

About 10 ml of venous blood sample was collected from each participant using vacutainer needles into 2 tubes: dry tube for biochemical analysis of ALT and AST and EDTA tube for FBC and CD4 test. The samples in the dry tubes were centrifuged at 3000 rpm for 5 minutes to obtain sera. The sera were used to perform liver enzyme tests and rapid serology strip tests for HBV and HCV.

2.4. Laboratory Investigations

2.4.1. Rapid Detection of HBsAg and HCV

Screening for the presence of Hepatitis B surface Antigen (HBsAg) and HCV an-

tibody was performed using the rapid test kit, Acon® (Acon Laboratories Inc., USA) which follows an immunochromatographic principle. Essentially, 50 µL of plasma was pipetted and placed on the area designated for sample on the test strip. The result was read after 15 minutes following the migration of the sample along the strip. A positive test was considered when two precipitation bands appeared (one for the control band and the other for the test sample). A negative test was considered when the control band appeared and the test band was absent.

2.4.2. Full Blood Count

The haemoglobin (Hgb) concentration, white blood cell (WBC), red blood cell (RBC), and platelet counts were measured using the Auto Haematology Analyzer (Mindray model BC-2800, New York, USA) following the manufacturer's instructions. Anaemia was defined as haemoglobin concentration < 11 g/dL. Anaemia was further categorised as mild (9.6 - 10.9 g/dL), moderate (8 - 9.5 g/dL) and severe (<8 g/dL) [19].

2.4.3. Liver Aminotransferases

Liver aminotransferase was measured for each participant using aspartate aminotransferase (AST or GOT) human reagent and alanine aminotransferase (ALT or GPT) human reagent (Gmbh, Germany) by spectrophotometry (Mindray® BA-88 Biochemistry Analyzer), following the manufacturer's instructions. Biological reference ranges were considered as follows: ALT (Females: <32 U/l; Males: <41 U/l) and AST (Females: <31 U/l; Males: <37 U/l).

Calculation and interpretation of noninvasive markers (NIM)

Aspartate Platelet ratio index (APRI) score

To determine the level of fibrosis, the APRI score was used [20]. This was calculated by inserting the corresponding AST level, the upper limit normal (ULN) AST value, and the platelet count into Equation (1):

$$\text{APRI} = \frac{\dfrac{\text{AST level}}{\text{ULN}^{*}}}{\text{Platelet count}\left(\times 10^{9}/\text{L}\right)} \times 100 \quad [21]. \tag{1}$$

*ULN is the upper-level normal of AST for the reagent used.

An APRI score > 1.5 denoted significant fibrosis (SF), between 0.6 and 1.5 denoted mild fibrosis (MF), between 0.5 and 0.6 denoted progressive fibrosis (PF) and APRI scores < 0.5 were considered to have no fibrosis [22] [23]. An APRI score of >2 was used to denote cirrhosis [20].

Fibrosis-4 score (FIB-4)

The FIB-4 score is used to estimate the degree of liver scarring [24]. This was calculated by incorporating the corresponding Age (years), AST level (U/L), Platelet count (10^9/L) and ALT level (U/L) in Equation (2).

$$\text{FIB-4} = \frac{\text{Age}\left(\text{years}\right) \times \text{AST level}\left(\dfrac{U}{L}\right)}{\text{Platelet count}\left(10^{9}/\text{L}\right)\sqrt{\text{ALT level}}\left(\dfrac{U}{L}\right)} \quad [24]. \tag{2}$$

Using a lower cut-off value of 1.45, a FIB-4 score < 1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4 - 6 that includes early bridging fibrosis to cirrhosis). On the contrary, a FIB-4 > 3.25 would have 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was initially validated, at least 70% of the patients had values < 1.45 or >3.25. The authors argued that these individuals could potentially have circumvented liver biopsy with an overall precision of 86% [24].

2.4.4. CD4$^+$ T-Cell Counts

CD4 counts in HIV patients were obtained using the Partec® CyFlow Counter (Partec Gmbh, Germany) according to the manufacturer's instructions. Basically, 20 µL of whole blood was added to a Partec tube. Thereafter, 20 µL of the reagent containing the CD4 – mAb PE (PE – conjugated monoclonal antibody to human CD4) was added to the tube. The contents were gently homogenized and the tube was incubated in the dark at room temperature for 15 minutes. After incubation, 800 µL of buffer was added and the tubes vortexed gently and placed on the Partec® CyFlow Counter for analysis. The results were printed automatically. CD4$^+$ T cell counts were classified as low or advanced stage (<200 cell/µL), moderate or chronic stage (200 - 499 cells/µL) and high or asymptomatic stage (≥500 cell/µL).

2.5. Data Management and Analysis

Data was first entered into a laboratory log book before entered into Epi info™ data sheet and these information was then exported to Microsoft excel 2013. The statistical package for social science (SPSS) version 23 was used for analysis. Statistical comparison between HIV mono-infections, HIV/HBV co-infections and each haematological and biochemical parameters were performed by ANOVA (one way). Data were presented as counts, percentages, median (IQR), means and standard deviation (SD). The level of significance was taken in the 95% confidence interval and a p-value < 0.05 was considered significant.

2.6. Ethical Consideration, Authorization and Consent

Ethical clearance for this was obtained from the Institutional Review Board of the Faculty of Health Sciences of the University of Buea (Reg No.859-08). Administrative authorization was obtained from the Southwest Regional Delegation of Public Health. This authorization was used to obtain clearance at the Buea Regional Hospital. All participants signed an informed consent form.

3. Results

3.1. Demographic Characteristics of Study Participants

A total of 212 participants, 106 cases, and 106 controls were enrolled after matching for age range and sex. Their ages ranged from 23 to 71 with a median

age of 37 years (Inter quartile range, IQR: 33 - 44.8 years). The participants were divided into four age groups and the most populated age group was 30 - 39 years (46.7%). Of the 212 participants, 147 (69.3%) were women (Table 1). The entire population constituted of 46 (21.7%) HIV/HBV co-infected patients, 60 (28.3%) HIV mono-infected patients and 106 (50.0%) healthy controls. The median ages of cases and control were 39.5 years (IQR: 34.0 - 48.0 years) and 36 years (IQR: 31.0 - 40.0 years) respectively. Based on the socio-economic status of the participants, 118 (55.7%) were currently married and 40.1% were single. A total of 105 (49.5%) were literate above the secondary school level and only 7 (3.4%) had never gone to school (Table 1).

3.2. Clinical Presentation of HIV Participants at Enrolment in to ART

Table 2 shows the clinical profile of HIV patients on ART at the time of ART initiation. Of the 106 HIV patients, 27 (25.5%) had herpes zoster, 11 (10.4%) had a history of TB at the time of initiation, and 2 persons (1.9%) had cerebral toxoplasmosis. Looking at risk factors, 16 (15.1%) had passed records of sexually transmitted infections (STIs), 15 (14.2%) had undergone surgery and less than 10% had received blood transfusion. Also, 42 (39.6%) HIV patients registered weight loss > 10%, 44.3% had fever for more than a month and 20 (18.9%) complained of having diarrhoea in the last 1 month. Forty-eight (45.3%) patients (45.3%) were recruited at stage 3 of HIV disease. At enrolment, most HIV patients were on EFV-based regimen (75.7%), 36.7% have had a changed of regimen with principal reason for change of treatment being drug stockout (33.0%).

Table 1. Socio-demographic characteristics of study participants.

Characteristics		Status n (%)		
		Cases	Control	Total
Age group (years)	20 - 29	13 (12.3)	13 (12.3)	26 (12.3)
	30 - 39	40 (37.7)	59 (55.7)	99 (46.7)
	40 - 49	33 (31.1)	27 (25.5)	60 (28.3)
	≥50	20 (18.9)	7 (6.6)	27 (12.7)
Sex	Female	75 (70.8)	72 (67.9)	147 (69.3)
	Male	31 (29.2)	34 (32.1)	65 (30.7)
Marital status	Currently married	46 (43.4)	72 (67.9)	118 (55.7)
	Single	54 (50.9)	31 (29.2)	85 (40.1)
	Widow/widower	6 (5.7)	3 (2.8)	9 (4.2)
Level of education	Did not go to school	6 (5.7)	1 (0.9)	7 (3.4)
	Primary	39 (36.8)	2 (1.9)	41 (19.3)
	Secondary	53 (50.0)	6 (5.7)	59 (27.8)
	Post-secondary	8 (7.5)	97 (91.5)	105 (49.5)

Table 2. Clinical characteristics of HIV participants on antiretroviral therapy.

Characteristics	Categories	n (%)
Opportunistic Infections		
	Herpes zoster	27 (25.5)
	Tuberculosis	11 (10.4)
	Cerebral toxoplasmosis	2 (1.9)
	Oral candidiasis	20 (18.9)
Risk factors for HIV		
	Previous STIs	16 (15.1)
	Scarification	45 (42.5)
	Surgical procedure	15 (14.2)
	Blood transfusion	8 (7.5)
Symptoms of HIV		
	Weight loss	42 (39.6)
	Fever in the last 1 month	47 (44.3)
	Diarrhoea in last 1 month	2 (1.9)
	Priorigo/Skin rash	16 (15.1)
WHO HIV staging		
	Stage 1	27 (25.5)
	Stage 2	23 (21.7)
	Stage 3	48 (45.3)
	Stage 4	8 (7.5)
ART regimen		
	NVP-based	**23 (21.7)**
	TDF-3TC-NVP	8 (7.5)
	AZT-3TC-NVP	15 (14.2)
	EFV-based	**80 (75.5)**
	TDF-3TC-EFV	77 (72.6)
	AZT-3TC-EFV	3 (2.8)
	2nd Line (ATV/r-TDF)	**3 (2.8)**
Change of ART regimen		
	No	67 (63.2)
	Yes	39 (36.7)
Reason for change of regimen		
	Drug stock out	35 (33.0)
	Suspected failure	3 (2.8)
	Allergic reaction	1 (0.9)

EFV-Efavirenz, NVP-Nevirapine, TDF-Tenofovir, 3TC-Lamividine, AZT-Zidovudine, ATV/r-Atazanavir/ritonavir.

3.3. Effects of HIV Infection and HBV Coinfection on Liver Enzymes and Some Immuno-Haematological Indices

The mean levels of ALT and AST were significantly higher ($p < 0.001$) in case-patients (ALT: 28.8 ± 13.3 SD, AST: 31.7 ± 11.4 SD) than in healthy controls (ALT: 22.2 ± 8.6, AST: 25.6 ± 8.9 SD) although the values were still lower than the normal upper limit of the reagents (ALT < 41 U/l and AST < 37 U/l). On the other hand, healthy controls had significantly higher mean values for Hgb, WBC, and platelet compared to case patients ($p < 0.001$) (Table 3).

When the case-patients were stratified into HIV mono-infected patients and HIV/HBV co-infected patients, there was no significant difference between the mean levels of levels of ALT ($p = 0.134$) and AST ($p = 0.116$) levels of healthy controls and HIV mono-infected patients. However, HIV/HBV coinfected participants recorded significantly higher mean values for AST ($p = 0.001$) and ALT ($p = 0.002$) as compared to HIV mono-infected patients (Table 4).

Meanwhile, the mean values of Hgb, WBC and platelet count of healthy controls were higher than those of HIV only and HIV/HBV co-infected patients, as seen in Table 4. The mean Hgb, WBC and platelets count levels of controls were significantly different from that of the HIV mono-infected participants but there were no significant differences when these measured parameters were compared between HIV mono-infected and HIV/HBV co-infected patients. The mean Hgb

Table 3. Comparison of mean liver enzymes and some haematologic measurements between healthy controls and case patients.

Parameters	Mean ± Standard deviation, SD		P-value
	Healthy control (n =106)	Case-patients (n =106)	
ALT (U/l)	22.2 ± 8.6	28.8 ± 13.3	**<0.001**
AST (U/l)	25.6 ± 8.9	31.7 ± 11.4	**<0.001**
Haemoglobin (g/dl)	13.6 ± 1.6	11.4 ± 1.5	**<0.001**
WBC (cells/mm^3) × 10^3	5.1 ± 1.2	4.3 ± 1.1	**<0.001**
Platelet (cells/mm^3) × 10	24.2 ± 6.1	21.0 ± 6.3	**0.004**

Table 4. Comparison of mean liver enzymes and some haematologic measurements between healthy controls, HIV-mono and HIV/HBV coinfected patients.

Parameters	Healthy controls n = 106	HIV only n = 60	P-value	HIV/HBV n = 46	P-value
ALT	22.2 ± 8.6	24.7 ± 12.2	0.134	34.1 ± 12.9	**0.002**
AST	25.6 ± 8.9	28.1 ± 10.8	0.116	36.5 ± 10.3	**0.001**
Haemoglobin (g/dl)	13.6 ± 1.6	11.3 ± 1.6	**<0.001**	11.7 ± 1.2	0.166
WBC (cells/mm^3) × 10^3	5.1 ± 1.2	4.3 ± 1.2	**<0.001**	4.3 ± 1.1	0.724
CD4 × 10^2 (cells/µl)	-	4.4 ± 2.0	-	4.1 ± 2.0	0.498
Platelet (cells/mm^3) × 10	24.2 ± 6.2	22.1 ± 6.6	**0.041**	19.7 ± 5.9	0.061

and WBC levels of coinfected patients were higher than that of HIV mono-infected patients but this was the opposite for mean platelets count. When these means were compared with the normal ranges of the measured haematological parameters, they fell within the range of acceptance. However, the mean CD4 count of HIV/HBV patients was lower than that of HIV mono-infected patients but this difference was not statistically significant (p = 0.498).

3.4. The effects of HIV/HBV Coinfection on Liver Enzymes over the Course of ART

The mean AST and ALT levels of HIV mono-infected and HIV/HBV co-infected patients were compared overtime (at initiation of ART [baseline], ART duration of 12 and 24 months). The median duration of treatment of HIV patients was 43 months (IQR: 16 - 77.3 months). As shown in Figure 1, overall, HIV/HBV co-infected patients had higher mean AST and ALT levels than HIV mono-infected patients. The means of HIV/HBV co-infected patients were generally higher than the upper limit normal (ULN) of the test kit (ULN for AST < 37 IU/mL), while the ALT values were generally lower than the ULN test kit (UNL for ALT ≤ 41 IU/mL). There was a gradual increase in the mean enzyme levels, in both HIV mono-infected and HIV/HBV co-infected patients from the time of ART initiation until the median duration of 12 months which remained slightly stable for HIV-mono-infected patients, but significantly increased for HIV/HBV coinfected patients in the course of ART (AST, p = 0.002; ALT, p = 0.002].

3.5. The Effects of Regimen Type on Liver Enzyme over the Course of ART

Figure 2 shows the trends of mean AST and ALT levels of patients on EFV and

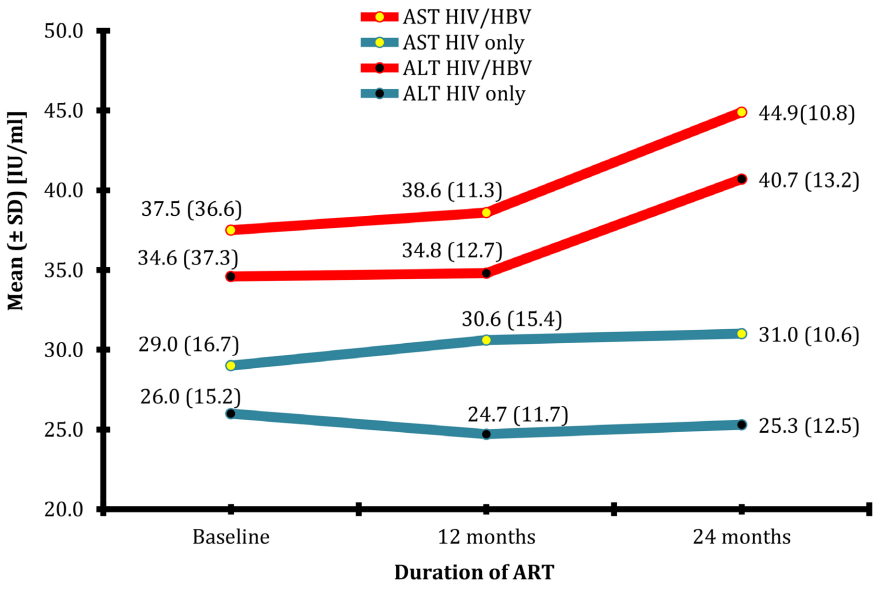

Figure 1. Trends in mean AST and ALT levels during treatment in HIV mono and HIV/HBV coinfected patients.

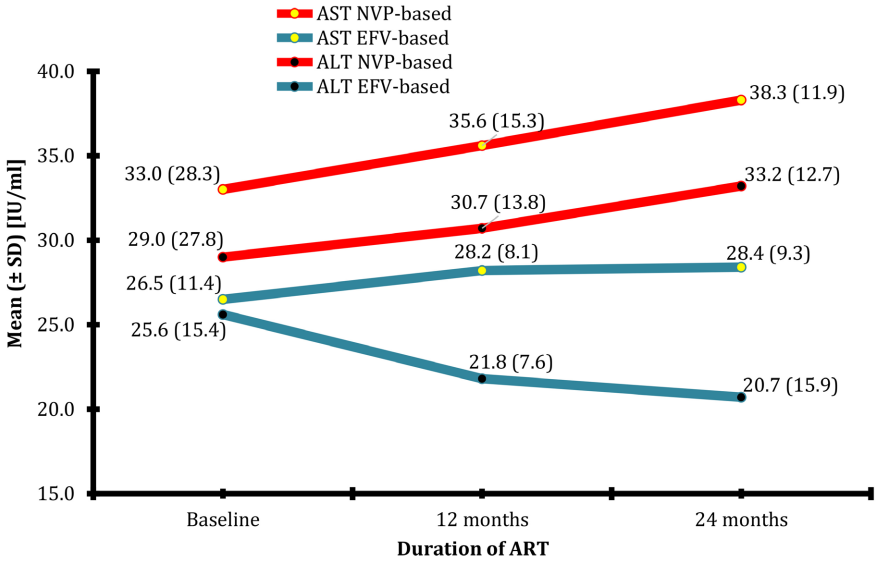

Figure 2. Trends in mean AST and ALT levels of HIV patients treated with NVP- and EFV-based regimens.

NVP-based treatments over time. The mean AST levels of patients on NVP-based treatment were higher than that of EFV. Generally, at initiation of ART, there was an increase in mean AST and ALT levels of NVP-based patients up to a median duration of 24 months. The mean AST ($p < 0.001$) level of NVP-based patients at ART initiation (33.0 ± 28.3 U/L versus 26.5 ± 11.4 U/L) and at ART duration of 24 months (38.3 ± 11.9 U/L versus 28.4 ± 9.3 U/L) were higher than those of EFV-based patients. This was similar with ALT ($p = 0.004$) levels.

3.6. The Effects of ART Duration on Immuno-Haematological Indices

Largely, the anaemic status of HIV-enrolled patients improved with treatment as seen in **Figure 3** below. At the time of initiation of ART, 6.6% had severe anaemia and this value decreased to 0.9% 24 months of ART. These changes in proportions were very obvious for the other stages of anaemia.

Figure 4 shows the clinical staging of CD4 of HIV patients over the course of treatment. Largely, there were improvement in the CD4 cell count of patients with treatment duration. At the start of ART, 43.4% had a $CD4^+$ count < 200 cells/μl. As patients continued with their treatments, the values improved and by the median duration of ART at 24 months, there were only 8.5% of patients with a CD4 count of <200 cells/μl.

3.7. Staging of Liver Fibrosis Using Non-Invasive Markers in HIV Mono and HIV/HBV Co-Infected Patients

According to APRI, significant fibrosis (SF) was observed in a HIV/HBV coinfected patient, 17 persons had mild fibrosis (MF) and 13 had progressive fibrosis (PF). Of the 17 persons with MF, 12 (5.6%) were HIV/HBV coinfected, 4 (1.9%) were HIV mono-infected patients and there was 1 (0.9%) healthy control. Of the

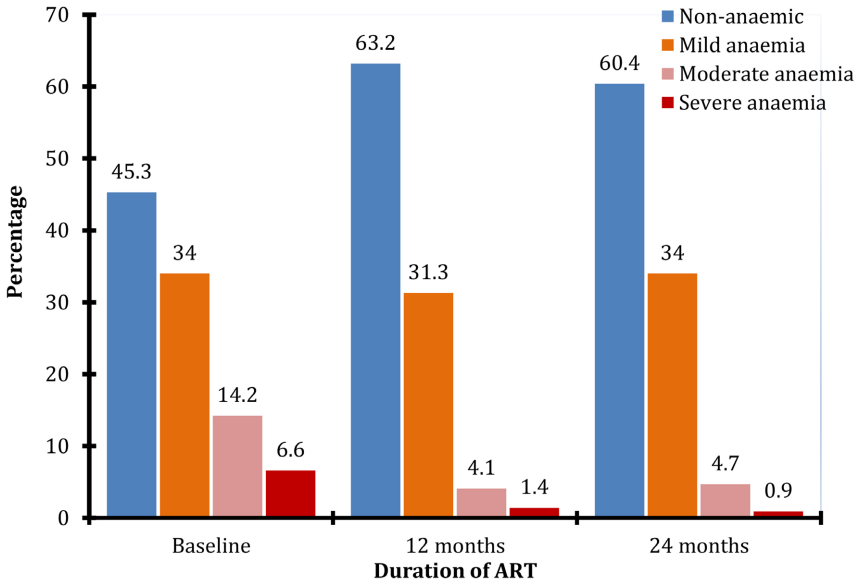

Figure 3. Variation in anaemia among HIV participants during the course of ART.

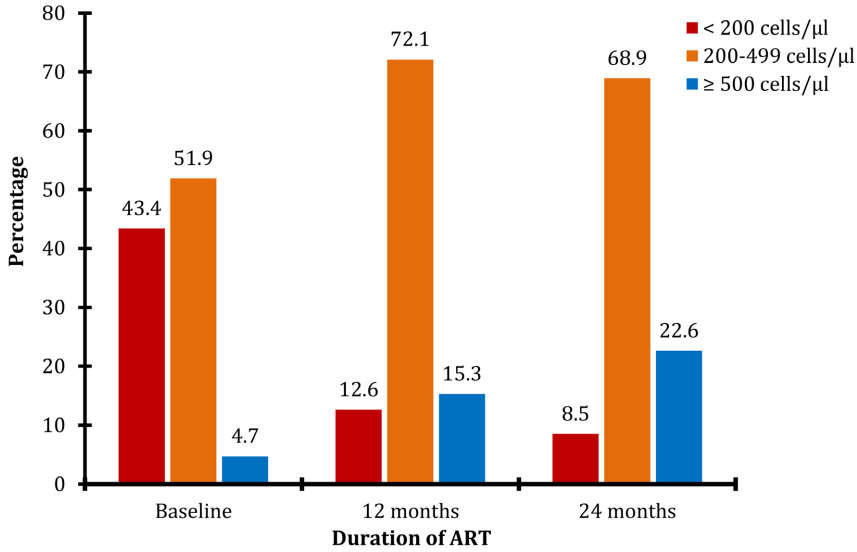

Figure 4. Variation of CD4 clinical staging during ART.

13 persons with PF, 5 (2.4%) were healthy controls, 6 (2.8%) HIV mono-infected, and 2 (0.9%) HIV/HBV coinfected patients (Table 5).

According to FIB-4, 171 (80.7%) persons had F0 - F1 fibrosis in which 95 (44.8%) were healthy controls, 44 (20.8%) were HIV mono-infected and 32 (15.1%) were HIV/HBV coinfected patients. Two (0.9%) HIV/HBV coinfected patients had F2 - F4 fibrosis and 39 persons had inconclusive results. Based on FIB-4 classification of fibrosis, 2 (0.9%: CI 0.16 - 3.73) participants had fibrosis both were HIV/HBV coinfected (Table 6).

4. Discussion

In HIV-infected patients, coinfection with HBV and antiretroviral (ARVs) may

Table 5. Different stages of liver fibrosis of study participants according to the APRI score.

APRI score	Stages of Fibrosis	Participant status n (%)			
		Healthy control n = 106	HIV only n = 60	HIV/HBV n = 46	Total N = 212
>1.5	SF	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
0.6 - 1.5	MF	1 (0.5)	4 (1.9)	12 (5.6)	17 (8.0)
0.5 - 0.6	PF	5 (2.4)	6 (2.8)	2 (0.9)	13 (6.1)
<0.5	NF	100 (47.1)	50 (23.6)	31 (14.6)	181(85.3)

NF = No fibrosis, PF = progressive fibrosis, MF = mild fibrosis, SF = significant fibrosis.

Table 6. Different stages of liver fibrosis base on FIB-4 score.

FIB-4 score range	FIB-4 interpretation	Hepatitis status n (%)			Total N (%)
		Healthy controls n = 106	HIV only n = 60	HIV/HBV n = 46	
<1.45	F0 - F1	95 (44.8)	44 (20.8)	32 (15.1)	171(80.7)
1.45 - 3.25	Inconclusive	11 (5.2)	16 (7.5)	12 (5.7)	39 (18.4)
>3.25	F2 - F4	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)

complicate or adversely affect clinical course and management. Hepatic toxicity is also a well-known complication of the treatment of HIV infection. An accurate assessment of HBV infection in HIV-co-infected individuals is necessary to make therapeutic decisions [25]. WHO encourages testing for HBsAg, especially in endemic regions, but testing for HBV markers such as HBeAg, HBV DNA and tests to assess the stage of liver disease (e.g. liver enzymes, liver biopsy, etc.) may not be widely available in many resource-limited countries [7]. These tests guide the physician to make appropriate therapeutic decisions to avoid severe hepatotoxicity in patients who already have derangement of the liver function and to prescribe ART that is also effective against HBV in coinfected patients.

A diverse degree of immunopathogenesis in HIV-infected patients carries enormous haematological and biochemical consequences [26]. This study showed that serum ALT and AST levels are significantly higher in HIV/HBV coinfected patients compared to HIV mono-infected patients and healthy controls. This is consistent with previous studies done by Shenge *et al.* [27], Ballah *et al.* [28] and Ibeh *et al.* [26]. These results suggested that the abnormal liver enzymes away from being due to HIV infection are further compounded in HIV/HBV coinfections. Specifically, the mean serum ALT level of HIV/HBV coinfected patients was significantly higher than that of HIV mono-infected patients ($p = 0.002$), similar to studies carried out in Ghana [29] and France [30]. Likewise, the mean AST level of HIV/HBV coinfected patients was significantly higher than that of HIV-mono-infected patients in line with a study reported in Northern India [31], but it was contrary to the findings of a study in Nigeria [32]. In HIV-positive

patients, the increase in hepatic enzymes could be secondary to multiple factors such as alcoholism, lipid-lowering drugs, antibiotics, coinfection with hepatotropic viruses or opportunistic infections, and direct hepatic damage caused by HIV [33]. Additionally, the variations in transaminase enzyme levels in the various studies could also reflect the difference in sociodemographic and clinical characteristics of the study populations involved [34].

ART regimen type also significantly impacted serum AST and ALT levels, notably higher in patients treated with nevirapine (NVP)-based compared to efavirenz (EFV)-based regimen, which increases throughout ART. This finding is very much in line with that of Mbuagbaw *et al.* [35], who reported that NVP-based treatment is likely to raise transaminase levels compared to EFV-based treatments with increased risk of mortality. Several long-term and short-term toxicities of the different antiretroviral drugs affect many body organs [36] [37]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are the drugs most commonly implicated in hepatotoxicity yet these drugs are frequently used as part of the triple combination first-line ART regimen [35]. The greatest risk of NNRTI-associated severe hepatotoxicity are observed in patients taking nevirapine, those with hepatitis B or C coinfection, and those co-administered protease inhibitors [38]. In particular, nevirapine use has been associated with severe hepatotoxicity in other studies, which, in some cases, was associated with an early (12 weeks) hypersensitivity reaction [38].

Despite significant reduction in all complications of human immunodeficiency virus (HIV) infection since the introduction of ART, haematological anomalies remain common problems [39]. This study has shown that compared to a healthy population, levels of haemoglobin, PLT and WBC were significantly lower in HIV patients (both HIV only and HIV/HBV co-infections), which is in accordance with other studies that highlight the adverse effects of HIV disease on the haematologic profile, primarily due to the enormous assault of the virus on haemopoietic cells/system [40] [41]. This occurs in addition to hepatotoxicity and nephrotoxicity of antiretroviral drugs [42]. However, coinfection of HIV patients with HBV does not significantly further compound the reduction of these parameters, although HIV/HBV coinfected patients had lower mean PLT levels in this study, it was not significant. A study by Shaukat *et al.* [43] showed that decreased Hgb levels are more common in HIV/TB and HIV/HCV than among HIV/HBV coinfections, while other studies demonstrate contrary views [34] [44].

ART was associated with a reduction in anaemia in this study throughout treatment. We observed an over three-quarter decrease in the proportion of severe anaemia (6.6% to 0.9%) at 24 months of ART. Correspondingly, non-anaemic cases increased from 45.3% at initiation to 60.4% by the second year of ART. This finding agrees with the reports from North-eastern Nigeria [45] and South Africa [46]. Various studies have pointed out multiple potential factors that are associated with anaemia among HIV patients [47] [48]. Although there are numerous possible causes of anaemia in HIV infections, it is commonly attributed

to bone marrow failure, peripheral destruction, opportunistic infections, and HAART therapy [49]. The various direct and indirect impact of effective ART can explain these positive outcomes. One plausible explanation is that ART suppress HIV, that affects the bone marrow directly; therefore, by thwarting the viral load, ART could prevent anaemia. The other explanation could be related to the indirect effect of ART, which is expected to improve the immunity of HIV patients, thus decreasing the appearance of multiple opportunistic infections potentially associated with anaemia [50].

In line with studies in developing [51] and developed countries [52] viral hepatitis coinfected did not significantly affect CD4 levels, although it is contradictory to a report from Ghana by Olawumi *et al.* [29]. The results of our study indicated that the CD4 count of HIV patients improved with treatment duration. Less than five per cent (4.7%) of study participants at the initiation of ART had CD4 count > 500 cells/μl, which increased to 22.6% at 24 months of ART. Furthermore, patients with a CD4 count < 200 cells/μl decreased from 43.4% at initiation to 8.5% at 24 months of ART. This was in concordance with findings a study carried out in Canada [53]. In this Canadian study, CD4 counts from 350 - 500 cells/mm^3 were associated with risks of ≤5% across all age and HIV-RNA strata, while the risk of progression to AIDS increases substantially at CD4 counts < 350 cells/mm^3. The most significant risk increase occurs as CD4 counts fall below 200 cells/mm^3. It also highlighted that the risk of disease progression at 200 cells/mm^3 and the threshold for ART initiation in resource-limited settings is generally double the risk at 350 cells/mm^3 and the treatment threshold in resource-rich countries [53]. Baseline CD4 count, previously a standard requirement for commencement of antiretroviral therapy, may also be used as a surrogate marker for liver function, especially in coinfected patients. Therefore, even if ALT is normal, a low CD4 count below 200 cells/mm^3 may be a signal to perform a more sensitive or invasive test to assess liver function.

The effect of HIV infection on developing liver disease in those co-infected with viral hepatitis is complex. The mechanism has primarily been postulated as immunosuppression and possibly a direct or indirect (microbial translocation) effect of HIV in those co-infected with HBV leading to an accelerated natural course of viral hepatitis infection and more rapidly progressive liver fibrosis and cirrhosis. In this study, the highest rate of fibrosis was observed among HIV/HBV coinfected patients compared to their HIV mono-infected counterparts. The cut-off values of 1.5 and 3.25 were used for diagnosing significant fibrosis by APRI and FIB-4 scores, respectively. The prevalence of liver fibrosis was 0.5% when APRI was used and 0.9% with the FIB-4 score, and they were both common among patients with hepatitis B coinfection. This agrees with a similar study conducted in Tanzania [54]. In another study from Nigeria, liver fibrosis was also more common among HIVHBV-co-infected patients. The study reported higher liver fibrosis by APRI score (17% versus 4%) and the FIB-4 score (13% versus 2%) among HBV coinfected compared to HIV mono-infected participants [55].

We acknowledged some limitations to this study. A comparator HBV mono-infected group could have been included in the analysis. Only three-time points (baseline, 12, 24 months) were used to estimate the impact of coinfection and ART over the course of treatment because these were intervals with very few missing data.

5. Conclusion

Given the high incidence of HBV infections among HIV patients and because HBV/HIV coinfected patients are likely to have significant adverse effects, rapid detection of these coinfections may attract better treatment to avoid further complications. Haematological and biochemical profiling could serve as pointers for early detection of liver disease and renal function in HIV patients. The NVP-based regimen is more associated with a higher liver enzyme level. We recommend that HIV patients receive a free routine evaluation of liver enzymes, viral hepatitis and assessment of liver fibrosis using the NIM (APRI and FIB-4) at ART initiation and in the continuum of care.

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Conflicts of Interest

The authors declare that they have no competing interests.

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List of Abbreviations and Acronyms

3TC—Lamivudine; ALT—Alanine aminotransferase; APRI—Aspartate aminotransferase/Platelet Ratio Index; AIDS—Acquired immunodeficiency syndrome; ART—Antiretroviral therapy; AST—Aspartate Aminotransferase; EFV—Efavirenz; FIB-4—Fibrosis Index-4; HBsAg—Hepatitis B Surface Antigen; HBV—Hepatitis B Virus; HCV—Hepatitis C Virus; HIV—Human Immunodeficiency Virus; MF—Mild Fibrosis; NF—No Fibrosis; NNRTI—Non-Nucleoside Reverse Transcriptase Inhibitors; NRTI—Nucleoside Reverse Transcriptase Inhibitors; NVP—Nevirapine; PF—Progressive Fibrosis; PLHIV—People living with HIV; PLT—Platelet; SF—Significant Fibrosis; UNAIDS—United Nations Acquired Immunodeficiency Syndrome; WBC—White Blood Cell.