Effects of Highly Active Antiretroviral Treatment on Liver and Kidney Functions

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Authors' contributions

This work was carried out in collaboration among all authors. Authors WKBAO, CO, SAS and KOD conceived and designed the experiments. Authors SBB, YA, CO and KOD performed the experiments. Authors LQ, SBB, YA, CO and KOD analyzed the data. Authors SBB, YA, CO, SAS and KOD contributed reagents/materials/analysis tools and other logistics. The manuscript was written and edited by authors LQ, SBB, EA, WKBAO and KOD. Interpretation of results and appraisal of manuscript by authors PPMD, EA and BBNG. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: This study assesses the effects of HAART on liver and renal functions in HIV infected individuals on HAART.
Study Design: Cross sectional study.
Place and Methods: This study was conducted in Tamale, Ghana from August, 2015 to November 2017.

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Methodology: A total of 300 HIV infected participants with ages ranging from 19 to 79 years who have been administered with HAART for at least 6 months were recruited. Pre-HAART administration (baseline) demographic and clinical information, with initial liver and renal function test results were retrieved from the medical records of the participants present at the ART center. Post HAART administration blood sample (5 mLs) was taken from each participant into a gel separated vacutainer tube, allowed to clot and spun at 3000 rpm for 3 minutes to produce serum. The product (serum) was used for liver and renal function test analysis using a fully automated chemistry analyser (Vital Scientific Selectra Flexor XL).

Results: Of the study population, 72% were administered with AZT/3TC/EFV, 13% with AZT/3TC/NVP, 6.7% with TDF/3TC/LPV/r and TDF/3TC/NVP, 1% with AZT/3TC/EFV while 0.7% were administered with TDF/FTC/EFV. The following parameters were significantly increased post HAART administration; ALT (25.53 ± 16.90 to 30.87 ± 19.28 U/L), ALP (163.7 ± 141.0 to 215.2 ± 143.4 U/L), GGT (37.27 ± 25.21 to 53.19 ± 41.71 U/L), Total protein (73.97 ± 17.08 to 82.31 ± 11.62 g/L), Albumin (38.02 ± 9.331 to 41.01 ± 7.471 g/L), Globulin 38.02 ± 15.71 to 42.79 ± 25.20 (g/L). There were however significant reductions in Total bilirubin (12.13 ± 10.85 to 9.434 ± 4.560 µmol/L), Direct bilirubin (6.616 ± 5.770 to 4.184 ± 2.806 µmol/L), (Creatinine 73.19 ± 36.13 to 63.14 ± 27.14 µmol/L) and Urea (3.515 ± 2.552 to 3.011 ± 1.274 mmol/L).

Conclusion: HAART improves renal function, induces elevation in liver enzymes, stimulates the production of plasma proteins and reduces serum bilirubin concentration.

ABBREVIATIONS

Short term HAART users = Participants who have been on HAART for less than or equal to 52 months; Medium term HAART users = Participants who have been on HAART for more than 52 months but less than or equal to 104 months; Long term HAART users = Participants who have been on HAART for more than 104 months.

1. INTRODUCTION

HIV infection leading to immune deficiencies which allow fatal opportunistic infections has been a major public health concern of the 21st century. Globally, 36.9 million people are living with HIV whereas 21.7 million are on antiretroviral therapy (UNAIDS, 2017). About 35.4 million people have died of AIDS related illnesses since the start of the epidemic (UNAIDS, 2017). Research has shown significant renal impairment among HAART naïve HIV infected individuals [1]. HIV associated nephropathy (HIVAN) is the most common kidney disease amongst people living with HIV [2,3]. An estimated 5.9% of HAART naive people living with HIV present with acute renal failure [4]. Renal disorders ranging from electrolyte and fluid imbalances to end stage renal disease (ESRD) is evident in all stages of HIV infection [5]. In caring for individuals infected with HIV on HAART, managing liver and renal diseases remain very important. HAART induced liver disease is the most common non HIV associated cause of death amongst people living with HIV on HAART, causing about 14 to 18% of deaths in this population and about 50% of all hospitalized HIV infected individuals [6]. HAART related liver toxicity is one of the most important adverse events reported amongst people living with HIV [7]. It usually presents as mild abnormalities in liver function parameters to very pronounced liver failure [8].

HAART is a multi-drug combination regimen targeted to reduce HIV viral replication to undetectable concentrations and keep HIV viral replication suppressed for years in infected individuals. HAART has been able to significantly reduce mortality and morbidity associated with AIDS [9]. The advent of HAART has significantly improved the life expectancy of HIV infected individuals who are on it [3]. Over time however, the use of HAART results in hepatotoxicity and nephrotoxicity [10]. Renal dysfunction has been associated with tenofovir disoproxilfumarate which accumulates in the proximal tubule of the kidney [11]. HAART induces functional stress especially mitochondrial injury. Nevirapine and efavirenz may lead to hypersensitivity syndrome reactions that may lead to hepatotoxicity which leads to liver necrosis and death [12]. Reisler [13] reported the rate of hepatotoxicity associated with nucleotide reverse transcriptase inhibitors (NRTIs) as 12%, which brings to light the difficulty in managing HAART associated liver

and renal pathologies [14]. The aim of this study was to assess the effects of HAART on liver and renal functions in HIV infected individuals on HAART.

2. MATERIALS AND METHODS

2.1 Study Design

This was a cross sectional study carried out from August 2015 to November, 2017.

2.2 Study Population

A total of 300 HIV infected participants with ages ranging from 19 to 79 years have been administered with HAART for at least 6 months were recruited at the Tamale Teaching Hospital, Savelugu District Hospital, Tamale West and Central hospitals.

2.3 Data Collection

Pre-HAART administration (baseline) demographic and clinical information, with initial liver and renal function test results were retrieved from the medical records of the participants present at the ART centers. Post HAART information such as age, weight, HAART type and duration of HAART use were recorded using questionnaire which had been pre-tested among 10 HIV infected individuals administered with HAART to clear possible ambiguity and difficulty in answering the questions. Data from the pre-tested questionnaires were however not included in the results analysis.

Post HAART blood sample (5mLs) was taken from each participant into a gel separated vacutainer tube, allowed to clot, spun at 3000rpm for 3 minutes to produce serum which was used to perform liver and renal function tests using a fully automated chemistry analyzer, Vital Scientific Selectra Flexor XL. The HAART comprised two Nucleotide Reverse Transcriptase Inhibitor (NRTI) plus one Non-nucleotide Reverse Transcriptase Inhibitor (NNRTI) or two NRTIs and a Protease Inhibitor (PI). The participants were further stratified into short term (<52 months), medium term (≥52 but ≤104months), long term (>104 months) based on the duration of HAART.

2.4 Statistical Analysis

Data was entered into Microsoft excel 2016 and exported to GraphPad prism version 6.0 (www.graphpad.com) for analysis. Data was presented as number, percentages, means and standard deviation. Means were compared between groups using student paired t-test and ANOVA. A $p<0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Demographic Characteristics of the Study Population

According to the demographic data of the study population as captured in Table 1, A total of 300 subjects were recruited and were grouped into cases and controls. In all, 217 (72.3%) were classified as cases, while 83 (27.7%) were classified as controls. The cases were further classified into short-term, medium-term and long-term HAART users depending on the duration of HAART usage. Participants administered with HAART for 52 months or less months were classified as short-term HAART users, those who have been administered with HAART for more than 52 months but less than or equal to 104 months were classified as medium-term HAART users, while more 104 months were classified as long-term HAART users.

3.2 Distribution of HAART in the Study Population

The antiretrovirals administered to the study participants in this study included Zidovudine (AZT), Lamivudine (3TC), efavirenz (EFV), Nevirapine (NVP), tenofovir (TDF), lopinavir (LPV), NVP, emtricitabine (FTC) and ritonavir (r). HAART was administered as triple combinations as follows; AZT/3TC/EFV, AZT/3TC/NVP, TDF/3TC/EFV, TDF/3TC/LPV, TDF/3TC/LPV/r, TDF/3TC/NVP, TDF/FTC/EFV. Of all the participants, 3/300 (1%) were administered with AZT/3TC/EFV, 39/300 (13.0%) were administered with AZT/3TC/NVP, 216/300 (72%) of the participants were administered with TDF/3TC/EFV, 20/300 (6.7%), 20/300 (6.7%) and 2/300 (0.7%) were administered with TDF/3TC/LPV/r, TDF/3TC/NVP and TDF/FTC/EFV respectively.

3.3 Comparison of Liver and Renal Function Parameters Pre and Post HAART

There was an insignificant increase in the mean plasma concentration of AST, from 32.19 ± 21.68 U/L pre-HAART administration to 34.88 ± 26.70 U/L post HAART (p - 0.6110). The mean plasma ALT concentration increased significantly from 25.53 ± 16.90 U/L pre-HAART administration to 30.87 ± 19.28 U/L post HAART (p - 0.0440). Also, the mean plasma ALP increased significantly from 163.7 ± 141.0U/L to 215.2 ± 143.4 U/L post HAART (p - 0.0002). Mean plasma GGT concentration increased significantly from 37.27 ± 25.21 U/L to 53.19 ± 41.71 U/L at post HAART (p - <0.0001). Table 2 summarises the routine liver and renal function parameters pre and post HAART.

Table 1. Demographic characteristics of the study population

Variables	Pre-HAART (n=300)	Post-HAART (n=300)
Age (years)*	35.4 ± 9.4	39.7 ± 10.0
Weight (Kg)*	58.8 ± 12.8	64.3 ± 25.6
Age Group (years)		
10—19	10 (3.3%)	3 (1%)
20-29	76 (25.3%)	36 (12%)
30-39	125 (41.7%)	120 (40%)
40-49	64 (21.3%)	96 (32%)
50-59	20 (6.7)	34 (11.3%)
60-69	5 (1.7%)	13 (4.3%)
70-79	0	1 (0.3%)
Gender		
Male	58 (19.3%)	58 (19.3%)
Female	242 (80.7%)	242 (80.7%)
HAART Duration (Months)		
Short-term	0	176 (58.7%)
Medium-term	0	96 (32%)
Long-term	0	28 (9.3%)

*Data are presented as frequencies and percentages, * - comparison between pre and post HAART, with p-value of paired t-test <0.001. P-values 0.05 were considered significant*

Table 2. Liver function tests parameters pre and post HAART

Parameters	Pre-HAART	Post-HAART	p - value
AST (U/L)	32.19 ± 21.68	34.88 ± 26.70	0.6110
ALT (U/L)	25.53 ± 16.90	30.87 ± 19.28	0.0440
ALP (U/L)	163.7 ± 141.0	215.2 ± 143.4	0.0002
GGT (U/L)	37.27 ± 25.21	53.19 ± 41.71	0.0001
Total protein (g/L)	73.97 ± 17.08	82.31 ± 11.62	<0.0001
Albumin (g/L)	38.02 ± 9.331	41.01 ± 7.471	<0.0001
Globulin (g/L)	38.02 ± 15.71	42.79 ± 25.20	0.0426
Total bilirubin (µmol/L)	12.13 ± 10.85	9.434 ± 4.560	0.0043
Direct bilirubin (µmol/L)	6.616 ± 7.570	4.184 ± 2.806	0.0002
Indirect bilirubin (µmol/L)	12.13 ± 10.85	9.434 ± 4.560	0.0043
Creatinine	73.19 ± 36.13	63.14 ± 27.14	0.0050
Urea	3.515 ± 2.552	3.011±1.274	0.0097

Data are presented as mean ± SD, shows the comparison of liver function test parameters between HAART users at pre-HAART and Post HAART, p-value <0.05 was considered statistically significant. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, GGT: Gamma Glutamyl Transferase

DISTRIBUTION OF HAART REGIMEN
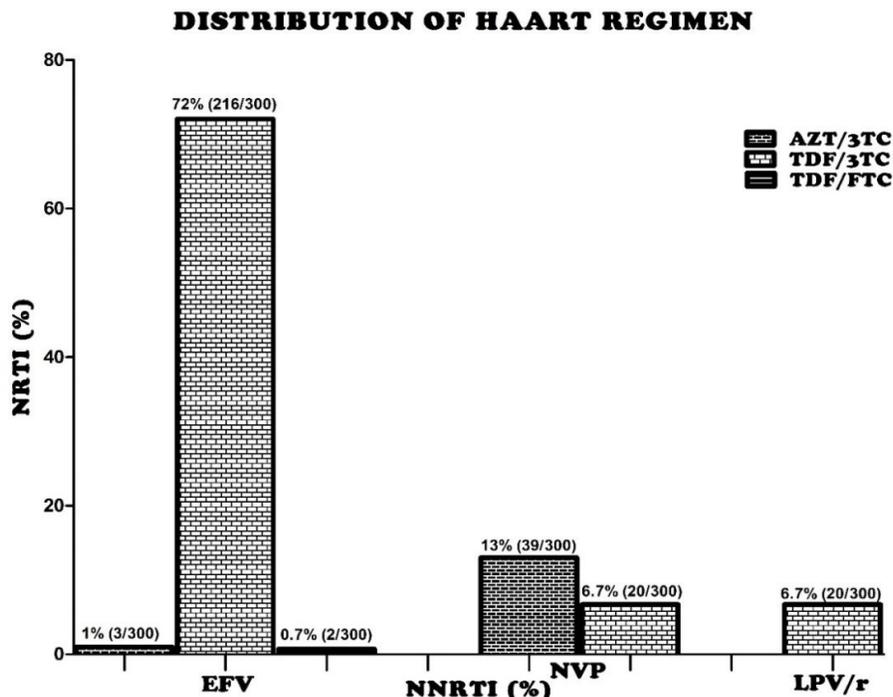
Fig. 1. Shows the percentage distribution of the various types of HAART regimen adminstered at the ART centers

Table 3. One-way ANOVA of liver and renal function parameters based on the duration of HAART usage

Parameter	Duration of HAART			F test	p value
	Short term	**Medium term**	**Long term**		
AST	36.71 ± 27.98	30.07 ± 13.03	30.33 ± 12.09	2.853	0.0593
ALT	32.57 ± 21.29	27.15 ± 12.82	32.68 ± 22.80	2.525	0.0819
GGT	46.82 ± 29.17	45.17 ± 20.87	40.49 ± 15.13	0.6195	0.4923
ALP	219.5 ± 143.6	201.3 ± 153.3	299.0 ± 106.1	2.023	0.5389
Total Protein	82.72 ± 12.22	81.45 ± 10.27	81.87 ± 13.68	0.3658	0.6940
Albumin	40.23 ± 6.930*	42.72 ± 8.257	40.79 ± 7.273	3.433	0.0336
Globulin	44.82 ± 31.74	38.32 ± 9.405	42.93 ± 10.88	1.981	0.1398
Total bilirubin	9.234 ± 4.729	9.630 ± 4.472	11.7 ± 8.4	2.600	0.0760
Direct bilirubin	4.024 ± 2.786	4.299 ± 2.804	5.265 ± 2.824	2.071	0.1280
Indirect bilirubin	5.181 ± 3.158	4.299 ± 2.804	5.324 ± 2.490	2.859	0.0590
Creatinine	62.36 ± 27.26	64.23 ± 28.31	64.17 ± 22.57	0.1627	0.8500
Urea	3.086 ± 1.754	3.198 ± 1.374	3.336 ± 1.316	0.3501	0.7049

Data are presented as mean ± SD, shows One-way ANOVA of Liver and Renal Function Parameters in short, * represents significant comparison between Short-term and Medium-term HAART users. p-value <0.05 was considered statistically significant

3.4 Variations in Liver and Kidney Function Parameters with Duration of HAART

Table 3 shows how liver and kidney function parameters varied among short, medium- and long-term HAART users. Of all the parameters considered, only albumin varied significantly from 40.23 ± 6.930g/dL in short-term HAART users to 42.72 ± 8.257g/dL in the medium HAART users. Table 3 summarises the comparisons of liver and renal function parameters between short, medium- and long-term HAART users.

3.5 Discussion

The advent and administration of HAART comes along with HAART induced hepatotoxicity. As the life expectancies of HIV infected individuals improved, non-AIDS diseases became increasingly very important cause of morbidity and mortality in the HIV infected population [15]. Liver related diseases have become rampant in HIV infected populations [16,17]. Liver related diseases account for 13-18% of all mortality and one of the leading causes of non-AIDS related cause of death in HIV infected populations. The mechanisms involved in the cause of liver disease in HIV infected individuals on HAART include senescence nodular regenerative hyperplasia, systemic inflammation, cytotoxicity, immune related injury, mitochondrial injury, Oxidative stress, gut microbial translocation, lipotoxicity etc.

This study recorded elevated alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) post HAART administration. Shiferaw [18] and Owiredu [19] also recorded elevated ALT, ALP and GGT post HAART administration. These liver enzymes were associated with hepatocytes and were released into the plasma when the virus compromised the integrity of the hepatocytes. The elevated liver enzymes may be as a result of the toxic effects of HAART or direct inflammation on hepatocytes which increased the permeability of the cell and mitochondrial membranes [20,21]. The elevations in liver enzymes were reported to return to normal after the discontinuation of HAART [22,23]. NRTI incorporation terminated viral DNA maturation, inhibited mitochondrial DNA polymerase, damaged mitochondrial, depleted and impaired cellular respiration [24]. Studies by Kontorinis and Dieterich [24] showed that severe NRTIs induced mitochondrial toxicity which resulted in hepatomegaly and steatosis. NNRTIs, especially efavirenz and Nevirapine also increased the concentration or activity of other co-administered antiretroviral agent, thereby increased their toxicity effect on hepatocytes [25]. Kontorinis and Dieterich (24) recorded that, the activity of ritonavir was increased 20-fold when co-administered with saquinavir. Individuals on PIs recorded more incidences of hepatotoxicity than those on NRTIs [26]. The use of ritonavir recorded 48% hepatotoxicity [22]. It was noted that super therapeutic concentrations of HAART in serum altered its metabolism by the various isoforms of P450 systems [27]. Sulkowski (22) reported that increasing ritonavir exposure by 40% resulted in a mild hepatic impairment [28,29]. The statement 'the dosage of indinavir should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis' was contained in the prescriber information in the USA. This showed that the administration of HAART resulted in hepatotoxicity [30] as observed in this study.

This study recorded significant increases in serum total protein post HAART administration. Serum total protein, albumin and globulins were all elevated post HAART administration. The elevation in albumin concentration was believed to be due to the general improvement in the health status of the individual. Globulins and total proteins were higher post haart administration. This confirms the presence of an infection which is able to stimulate the body's immune response leading to the production of antibodies which are immunoglobulins (plasma proteins) [31,32].This finding concurs with the report of Ngala [33] who also reported elevations in total protein, albumin and globulins in HIV infected individuals post HAART administration. HAART induced improvement in immune status helps in the prevention of opportunistic infection which impairs humoral immune response e.g. pneumococcal pneumonia [34]. According to Ngala [33] as the general immune status of the study population improved, more immune proteins such as antibodies against the disease and opportunistic infections were produced by the body. Improvements in B-cell number, coupled with increased B cell polyclonal activation led to increased serum globulin production post HAART administration. The serum globulins consisted of alpha globulins-1 (10%), alpha globulins-2 (30%), beta globulins (34%), gamma globulins (46%). Picker [35] reported increases in all fractions of globulins post HAART administration.

In this study, total, direct and indirect bilirubins were all reduced post HAART. This is consistent with findings of Mahato [36] who also reported reductions in bilirubin post HAART administration. However, this finding differs from the observations made by Sulkowski [26] and Ayelagbe [37] who found increases in bilirubin post HAART administration. They attributed the increases in bilirubin post HAART to drug mediated impairment of bilirubin conjugation by the bilirubin UDP-glucuronyltransferase which led to decreased conjugation and excretion of

bilirubin [38]. A decrease in bilirubin concentration post HAART administration as observed in this study may be a manifestation of an improvement in renal function which facilitated the rapid excretion of conjugated bilirubin from the body and an absence of opportunistic infections.

This study reported reductions in serum creatinine and urea post HAART administration. This observation contradicts the findings of Obirikorang [3] but corroborated the findings of Betjes and Verhagen [39] who also recorded improvements in serum creatinine and urea concentrations post HAART administration. The improvements in renal function noted in this study basically resulted from HAART's suppression of viral replication and a general improvement in the health status of the study population. The pathogenesis of HIV associated renal disease (HIVARD) includes the direct cytotoxic influence of HIV on renal cells. According to Schwartz [40], the invasion of renal cells by HIV caused structural changes particularly in podocytes which led to loss of differentiation, atrophy, cytolysis and loss of contact inhibition, collapsed glomerulosclerosis and proteinuria. The tubular cells also dedifferentiated, atrophied and underwent apoptosis, causing cystic dilatation [41]. Extensive fibrosis of the interstitium has been reported, with varying degrees of infiltration by mononuclear cells [41,42]. Renal insufficiency mostly occurs in advanced HIV infections with high viral load [42]. The results of this study show HAART-associated improvement in function. Considering the renal pathogenesis of HIVARD as aforementioned, HAART lowering of viral load may be considered best treatment for HIVARD. Monotherapy with a reverse transcriptase inhibitor like AZT was associated with a better renal prognosis especially early in the course of the disease [39,42]. The findings of this study suggest that commencement of HAART before renal complications develop may be the reason for the improved renal function noticed in this study.

4. CONCLUSION AND RECOMMENDA-TION

HAART administration improves renal function. HAART also causes elevations in liver enzymes, increases the production of plasma proteins and reduces bilirubin, probably as a result of increased excretion due to improvements in renal function.

CONSENT

Written informed consent was obtained from all participants for publication of this case control study.

ETHICAL APPROVAL

This study was approved by the Committee for Human Publication and Research Ethics (CHRPE) of the Kwame Nkrumah University of Science and Technology, Kumasi Ghana in a letter referenced CHRPE/AP/367/16. The study team also obtained institutional approval in a letter referenced GHS/NR/18-O. Written informed consent was obtained from all participants before recruiting them into the study. Consent form was given to each participant to sign or thumb-print and confidentiality was assured.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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