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Original Research Article

Long-Term Effect of HAART on Biochemical Profiles of HIV/AIDS Patients in a Tertiary Health Facility in Benin City, Nigeria

Shakirat I Bello[1,3], Abel N Onunu[2], and Patrick O Erah[4]*
[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, [2]Department of Internal Medicine, University of Benin Teaching Hospital, [3]Department of Clinical Pharmacy & Pharmacy Practice, and [4]Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

For correspondence:* ***Email:* *patrick.erah@uniben.edu;* ***Tel:*** *+234-805-526-3622*

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Abstract

Purpose: *To assess the long-term effect of highly active antiretroviral therapy (HAART) on biochemical parameters of HIV-infected patients in University of Benin Teaching Hospital (UBTH), Benin City, Nigeria.*
Methods: *HIV/AIDS patients on HAART for 2 - 8 years (297), those who were not on HAART (112, positive control), and healthy subjects (103, negative control) were recruited in the Infectious Diseases Clinic (IDC) of UBTH. Their sera were assayed for biochemical parameters. WHOQoL bref instrument was used to assess patients' Quality of life (QoL).*
Results: *Patients who have been on HAART had significantly elevated ALT and AST levels ($p < 0.001$) but mild liver toxicity. QoL of these patients was not significantly different from that of the healthy controls. The levels of Na^+ (133.4 ± 5.2 mmol/l), K^+ (3.6 ± 0.4 mmol/l) and Cl^- (101.3 ± 4.0 mmol/l) were significantly lower in patients on HAART than those of the positive (137.5 ± 5.1, 3.9 ± 0.5, 104.3 ± 5.7 mmol/l respectively, $p < 0.001$). Also, levels of creatinine (0.8 ± 0.2 mg/dl), TBil (0.5 ± 0.2 mg/dl), and CB (0.3 ± 0.5 mg/dl) were significantly higher in patients on HAART than those of either the positive (0.7 ± 0.3, 0.4 ± 0.2, 0.2 ± 0.1 mg/dl) or negative (0.7 ± 0.3, 0.3 ± 0.1, 0.2 ± 0.1 mg/dl) controls respectively ($p < 0.001$).*
Conclusion: *Treatment with HAART for 2 - 8 years may not produce severe hepatotoxicity in HIV/AIDS patient though mild liver toxicity should be expected. The patients' QoL was not negatively affected by the use of HAART for 2 - 8 years.*

Keywords: *Biochemical parameters, HIV/AIDS, Long-term HAART, Quality of life (QoL).*

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INTRODUCTION

Acquired immune deficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV) is exemplified by progressive impaired body's immune system resulting in a number of opportunistic infections and biochemical complications [1]. The advent of highly active antiretroviral therapy (HAART) has enhanced long-term viral suppression, decrease of opportunistic infections and increased quality of life (QoL) of infected individuals [2]. However, the long-term treatment with HAART is associated with substantial toxicity, adherence difficulties and drug resistance [3]. A study conducted in Sagamu reported metabolic complications of hyperglyceridemia and hyperlipidaemia while hypercholesterolaemia, obesity and metabolic

syndrome were recorded in Kano [4,5]. Also, hepatotoxicity may occur with the use of all antiretroviral drugs (ARVs) classes and severe cases have been reported in a significant proportion of patients [6]. Hepatotoxicity may result from other factors, including the HIV infection itself, hepatitis B and C virus infections, and systemic opportunistic infections [7]. In addition, ART are known to cause symptoms that affect, to a greater or lesser degree, People Living with HIV/AIDS (PLWHA) and impacts on their QoL [8]. As part of the strategies to increase access to HAART for HIV-infected patients in Nigeria, various HIV/AIDS care centres were established across Nigeria with the support from international donors. One of such centres was established in University of Benin Teaching Hospital, Benin City, Nigeria (UBTH). In this centre, earlier reports showed that hepatotoxicity was observed in 17.9-36.7 % of patients on HAART with 10.7 % severe cases [7,9]. However, the long-term effect of HAART on biochemical parameters of HIV/AIDS patients has not been investigated in this facility. This study was therefore conducted to assess whether 2 - 8 years use of HAART in UBTH lead to severe hepatotoxicity, significant reduction in QoL or significant abnormalities in serum levels of biochemical parameters among HIV/AIDS patients.

EXPERIMENTAL

Setting

This study was conducted in the Infectious Diseases Clinic of the Consultant Out-Patient Department (IDCCOPD) in University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria. UBTH is an 800-bed tertiary health facility providing health care services to citizens of Edo State and neighbouring states. As at November 2013, 10440 HIV/AIDS patients were receiving treatment at IDCCOPD.

Subjects and study design

Following approval by the Ethics and Research Committee of UBTH (protocol number ADM/E 22/A/VOL.V11/833), the study was conducted between October 2012 and October 2013 in accordance with International Ethical Guidelines for Biomedical Research Involving Human Subjects (Declaration of Helsinki promulgation) [10]. HIV/AIDS patients who had been on HAART for 2-8 years (297) and those who were about to commence HAART (112, positive control) as well as 103 healthy individuals (healthy control) were recruited at random. The sample size of 297 used was calculated based on the number of HIV/AIDS patients receiving treatment in IDCCOPD as at October 2012 as earlier reported [11]. All patients included in the study had normal renal and liver functions which were determined and documented prior to HAART, and were at least 20 years old, not pregnant, and consented to participate in the study after verbal and written explanation of the procedures as appropriate. Severely ill patients and those with documented history of tuberculosis, hypertension, diabetes and hepatitis B or C, or drank alcohol were excluded. The patients on HAART were managed with combination of either Zidovudine + Lamivudine + Nevirapine (ZLN), Zidovudine + Lamivudine + Efavirenz (ZLE), Zidovudine + Lamivudine + Lopinavir/ritonavir (ZLA), Tenovofir + Emtricitabine + Efavirenz (TEE), Tenovofir + Emtricitabine + Nevirapine (TEN) or Tenovofir + Emtricitabine + Lopinavir/ritonavir (TEA). Health status of each patient and healthy controls was determined using both clinical and laboratory investigations, including CD4 count. According to written practice guidelines in the facility, all patients had standard laboratory evaluation before they were placed on HAART and at regular intervals. The standard clinic visit schedule was 4 weeks after initiation of HAART and 12 weeks thereafter.

On recruitment, the QoL of HIV/AIDS patients on HAART and the healthy control patients were assessed using WHOQoL-HIV Bref instrument. The instrument consists of 28 items, with each item using a 5-point Likert scale (ranges from 1 to 5). These items are distributed in four domains which include: physical, psychological, social and environmental. In calculating the QoL, the mean score of each item is converted to a scale of 0 to 100, where 100 was considered the highest QoL [12]. Venous blood (5 ml) each was then collected from each patient and healthy control into a plain test tube for biochemical analysis and EDTA (with anticoagulant) tube for immunological assays. Each blood sample was allowed to clot at room temperature for 45 min and then centrifuged to obtain serum using standard procedure [13].

Laboratory assays

Immunological analysis

Blood samples were assayed for CD4 cell count using flow cytometric analysis (Partec, GmbH, Germany).

Biochemical analysis

Sodium, potassium, chloride, bicarbonate, urea, creatinine concentrations were estimated from the serum samples of the venous blood. Sodium and potassium concentrations in the serum samples were estimated using flame photometer. The chloride ion, bicarbonate ion, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, total bilirubin and conjugated bilirubin in serum were determined using standard techniques as previously reported [14,15]. Any changes in serum ALT and AST of patients on HAART for 2-8 years from point of recruitment to the end of the follow-up were categorised using standardized toxicity grade scale as previously reported [6]. Using the normal range of ALT and AST levels as 9-50 iu/l, patients were classified as being on upper limit of normal (ULN, 50 iu/l), 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, 5.1-10.0× ULN), and grade 4 (life-threatening, > 10× ULN) [6].

Outcomes measured

The primary outcomes measured abnormality in serum levels of biochemical parameters (sodium, potassium, chloride, bicarbonate, urea, creatinine, ALT, AST, total bilirubin and conjugated bilirubin), presence of severe hepatotixicty defined as grade 3 or 4 change in AST and ALT levels, and significant reduction in QoL of those patients.

Statistical analysis

Data were entered into Statistical Package for Social Science (SPSS) version 18 (SPSS Inc, USA). Continuous data were expressed as mean ± standard deviation while categorical data were expressed as percentages. One-way ANOVA was used to compare patients' data while chi-square test was applied to analyse proportional data. At 95 % confidence interval, 2-tailed $p < 0.05$ was considered to be statistically significant.

RESULTS

The demographic characteristics of the patients and healthy controls are provided in Table 1. Majority of the subjects 68.0 % on HAART, 67.1 % not on HAART and 63.1 % healthy controls) were females, 73.4 % on HAART, 71.5 % not on HAART and 76.1 % healthy controls were 31– 50 yr old and 88.6 % on HAART, 86.8 % not on HAART and 82.5 % healthy controls were employed.

Patients who had been on 2-8 years treatment with HAART had significantly elevated ALT and AST levels ($p < 0.001$) with the values of ALT and AST ranging from 58.6 to 103.4 iu/l irrespective of the HAART used (Table 2). As shown in Figure 1, the elevation in the levels of the transferases was irrespective of duration (2-8 years) of treatment before the study. However, on a standard toxicity scale, the elevation was at grade 1 (mild toxicity) and not severe toxicity. The mean QoL of these patients was not significantly different from that of the healthy controls (Table 3).

Table 1: Demographic characteristics of HIV/AIDS patients and healthy controls

Variable	On HAART (N=297) n (%)	Not on HAART (N=112) n (%)	Normal control N=103) n (%)
Gender			
Male	95 (32.0)	37 (32.9)	38 (36.9)
Female	202 (68.0)	75 (67.1)	65 (63.1)
	χ^2 *=0.83, df=2, p=0.660*		
Age (years)			
20-30	30 (10.1)	18 (15.6)	22 (20.8)
31-40	129 (43.4)	41 (37.7)	43 (42.1)
41-50	95 (32.0)	38 (33.8)	35 (34.0)
51^+	43 (14.5)	15 (12.9)	3 (3.1)
	χ^2 *=17.60, df=6, p<0.001*		
Occupation			
Unemployed	34 (11.5)	15 (13.2)	18 (17.5)
Employed	263 (88.6)	97 (86.8)	85 (82.5)
	χ^2 *=2.45, df=2, p=0.293*		

Table 2: Transferase and antiretroviral drugs of HIV/AIDS patients on HAART

Parameter	Highly active antiretroviral therapy (HAART) combination						*P*-value
	TEN n=2	ZLE n=37	ZLN n=208	ZLA n=27	TEA n=3	TEE n=20	
ST (iu/l)	98.00 ±1.41 [a]	102.30 ±2.44 [a]	102.00 ±4.83 [a]	103.00 ±5.59 [a]	103.44 ±1.53 [a]	102.00 ±10.52 [a]	0.095
ALT (iu/l)	59.31 ±3.53 [a]	59.27 ±4.16 [a]	58.58 ±5.02 [a]	63.92 ±6.24 [a]	58.94 2.91 [a]	59.73 ±5.71[a]	0.345

Data with same superscript are not significantly different at 0.05 level of significance.
Key: *TEN = tenofovir+emtricitabine+nevirapine; ZLE = zidovudine+lamivudine+efavirenz; ZLN = zidovudine+lamivudine+nevirapine; TEE = tenofovir+emtricitabine+efavirenz; ZLA = zidovudine+lamivudine+lopinavir/ritonavir; TEA = tenofovir+emtricitabine+lopinavir/ritonavir*

Table 3: Quality of life mean scores for HIV/AIDS patients on HAART and healthy controls

Quality of life domain	Patients on HAART	Healthy controls	P-value
Physical	76.71±7.06	76.95±6.80	0.777
Psychological	76.33±6.75	77.42±7.48	0.299
Social	61.30±8.51	62.70±9.23	0.354
Environmental	70.90±6.26	71.20±5.44	0.680

Table 4: Biochemical and immunological parameters of HIV/AIDS patients and normal control

Parameter	Not on HAART[a] (n=112, mean±SD)	On HAART[b] (n=297, mean±SD	Control[c] (n=103, mean±SD)	Normal range	*P*-value
CD_4 count (cells/µl)	388.5±215.7	507.9±275.0	799.3±273.7	440-1500	$<0.001^{ac}$*, 0.001^{bc}*, $<0.001^{ab}$*
Urea (mg/dl)	31.9±22.9	25.1±8.0	32.5±22.7	15-50	$<0.001^{bc}$*,$<0.001^{ab}$*
Creatinine (mg/dl)	0.7±0.3	0.8±0.2	0.7±0.3	0.8-1.4	$<0.001^{bc}$*, $<0.001^{ab}$*
Sodium (mmol/l)	137.5±5.1	133.4±5.2	133.5±5.3	135-145	$<0.003^{ac}$*, $<0.001^{ab}$*
Potassium (mmol/dl)	3.9±0.5	3.6±0.4	4.1±0.6	3.5-5.0	$<0.001^{ac}$*, $<0.001^{bc}$*, $<0.001^{ab}$*
Bicarbonate ion (mmol/dl)	21.2±2.3	25.1±2.2	21.8±3.3	20-30	$<0.001^{bc}$*,$<0.001^{ab}$*
Chloride ion (mmol/dl)	104.3±5.7	101.3±4.0	101.4±7.5	96-106	$<0.002^{ac}$*, $<0.001^{ab}$*
Total bilirubin (mg/dl)	0.4±0.2	0.5±0.2	0.3±0.1	0.1-1.2	$<0.001^{ac}$*,$<0.001^{bc}$*, $<0.028^{ab}$*
Conjugated bilirubin (mg/dl)	0.2±0.1	0.3±0.5	0.2±0.1	0-0.4	$<0.001^{bc}$*,$<0.001^{ab}$

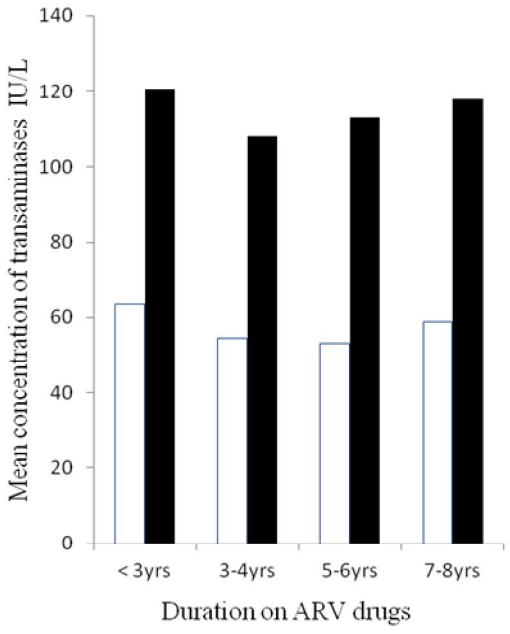

Figure 1: Mean levels of transferases of HIV/AIDS patients on HAART treatment. ***Key:*** ALT = aspartate aminotransferase; AST = alanine aminotransferase; Normal range of ALT and AST: 9-50 IU/L; ALT (□); AST (■)

Although the other biochemical parameters were all within normal range, the levels of Na^+ and TBil were significantly higher in HIV seropositive patients who were about to commence HAART than the healthy controls, unlike the level of K^+ which was significantly lower than those of the controls, $p < 0.001$. Also, the mean values of CRE, HCO3-, TBil and CB were significantly higher in patients on HAART when compared to the controls, while the concentrations of URE and K^+ were observed to be significantly lower in HAART patients than the controls, $p < 0.001$. Among the positive controls (patients yet to commence HAART), the levels of URE, Na^+, K^+ and Cl^- were significantly higher than those on HAART, $p < 0.001$. Furthermore, significantly lower levels of CRE, HCO3-, TBil and CB were found in patients that were yet to commence HAART when compared to the values for patients on HAART, $p < 0.001$ (Table 4). In Table 3, the mean scores in the domains of QoL revealed that physical, psychological, social and environmental of HIV/AIDS patients on HAART were not significantly different from those of normal controls, $p > 0.05$.

DISCUSSION

This study has revealed that none of the patients on 2 - 8 years treatment with HAART developed severe hepatotoxicity as their serum ALT and AST levels were within the grade 1 level in the liver toxicity grade scale [6], irrespective of the drugs taken and the duration of use. The measured QoL of the patients was equally not significantly different from that of the healthy control indicating the good-well being of the patients. The transferase levels in the patients are inconsistent with earlier reports, including those from the facility where this study was carried out, where a reasonable proportion of the patients developed severe/life threatening hepatotoxicity [9,15,16]. These results are however consistent with known fact that ARVs often cause liver toxicity even though the level of toxicity may be different for different ARVs [17]. Nevertheless, there is a report that the hepatotoxic effects of HAART may resolve with time in some cases in patients with direct injury to a HAART-naive liver when the organ gets used to the drug.

Although the changes in biochemical parameters, other than transferases, in this study were within the normal levels, significant changes in creatinine, sodium, potassium and conjugated bilirubin concentrations have been reported among HIV/AIDS patients in earlier studies [4,18-20]. In earlier studies in Nigeria, increase in creatinine concentration, total and conjugated bilirubin as well as mild hyponatraemia and hypokalaemia were reported in some patients on HAART [4,19]. On the contrary, decrease in levels of creatinine and urea was also reported [18, 20]. As these changes in biochemical parameters (other than transferases) were independent of the duration the patients have been on HAART for the 2-8 years, continuous monitoring of patients is necessary as required in the treatment guidelines for HIV/AIDS patients.

A lesson learned from this study is that it is unlikely that a patient on long-term HAART treatment will develop severe liver toxicity if treatment is started before any organ damage occurs. Nevertheless the interpretation and application of these data may be limited to the relatively small number of patients involved in this study.

CONCLUSION

Treatment with HAART for 2 - 8 yr may not produce severe hepatotoxicity in HIV/AIDS patient even though mild liver toxicity should be expected. Such patients will usually have good QoL. However, continuous monitoring of biochemical parameters for assessing liver and kidney functions are paramount in the management of HIV/AIDS patients on long term HAART to enhance their quality of life and prolong survival of these patients.

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