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Research Article

Effect of Highly Active Antiretroviral Drugs Therapy (HAART) on Serum Hepatic and Renal Function Indices on HIV Patients in Kano Metropolitan

***Yunusa Abdulmumin[1], Iman Usman Haruna[2], Hauwa Ibrahim Danjaji[3], Murtala Muhammad[1], Tasiu Abdulmumin Mikail[1], Zainab Rabiu[4] and Umma Lawan[4]**

[1]Department of Biochemistry, Aliko Dangote University of Science and Technology Wudil, Kano State, Nigeria
[2]Department of O and G, Northwest University, Kano, Nigeria
[3]Department of Science Laboratory Technology, Aliko Dangote University of Science and Technology Wudil, Kano State, Nigeria
[4]Department of Biochemistry, Northwest University, Kano, Nigeria

****Corresponding Author's email*:** yabdulmumin@kustwudil.edu.ng

ABSTRACT

Human immunodeficiency virus (HIV) remains a major public health challenge, with Sub-Saharan Africa bearing the highest burden. Highly Active Antiretroviral Therapy (HAART) has improved survival rates but is linked to liver and kidney toxicity, leading to treatment modifications. This study assessed the impact of HAART on liver and kidney function indices among HIV patients in Kano Metropolitan, Nigeria. A cross-sectional study was conducted with 200 participants (100 HIV-positive on HAART, 100 HIV-negative controls). Liver and kidney function markers were analyzed by gender and HAART duration. Data were analyzed at $p<0.05$ significance differences. The results show that the liver indices (ALT, AST, and bilirubin) and kidney parameters (creatinine, urea, Na^+, K^+, Cl-) were significantly higher in HAART patients compared to controls, indicating potential hepatic and renal dysfunction. Prolonged HAART use (>7 years) resulted in significantly elevated ALT, AST, and kidney parameters and decreased protein levels. Gender analysis revealed that males exhibited higher values for most parameters compared to females, except for Cl-, which was higher in females. Prolonged HAART use is associated with significant alterations in liver and kidney function indices, particularly after seven years of treatment. The findings underscore the need for regular monitoring of hepatic and renal functions in HIV patients on long-term HAART to mitigate potential complications. These results provide critical insights for clinicians and policymakers in optimizing HIV treatment strategies in resource-limited settings.

Keywords: HAART; HIV; Liver markers; Kidney Markers; Kano metropolis

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INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus that targets and destroys immune system cells, impairing their functionality and leaving the body vulnerable to opportunistic infections. Sub-Saharan Africa remains the epicenter of the global HIV epidemic, accounting for a significant share of infections. According to UNAIDS, the region hosts approximately 68% of all people living with HIV globally, despite constituting just 12% of the world's population (UNAIDS, 2021).

In Nigeria, the national HIV prevalence rate stands at 1.3% as of 2023, reflecting progress in reducing new infections but with significant regional disparities. The South-South geopolitical zone has historically recorded the highest prevalence, while the South-East reported the lowest (NACA, 2022). Age-specific data reveal that adults aged 35–39 are

most affected, with a prevalence rate of 3.6% (UNAIDS, 2023). Gender disparities in HIV prevalence remain minimal, with females slightly more affected (3.4%) compared to males (3.3%) (FMOH, 2022).

Heterosexual transmission remains the dominant route of HIV infection in Nigeria, accounting for over 80% of new cases. Additionally, key populations such as female sex workers (FSW), men who have sex with men (MSM), and people who inject drugs (PWID) contribute to a significant proportion of new infections, despite constituting only a small fraction (3.5%) of the adult population (NSP, 2022). In Kano State, the HIV prevalence was reported at 0.8% in 2022, which is below the national average. However, given Kano's large population size, it remains a critical region for targeted HIV prevention and management strategies (NACA, 2022).

Abnormal levels of liver enzymes are common among persons infected with human immunodeficiency virus (HIV) and may be caused by multiple factors, including medication toxicity and co infection with hepatitis B or C virus (Egger *et al., 2002*). A study conducted in southwest Nigeria showed that the activities of the transaminases in patients on HAART exceeded the upper limit of normal compared with the HIV patients that were not on HAART and the HIV negative subjects (Olubunmi, 2014). Transaminase diagnosis and management may be difficult because of the intricacies of the pathogenic mechanism involved. These include suspected hepatotoxicity related to highly active antiretroviral therapy, immune allergic mechanisms (Cacoub *et al.,* 2004). Or by the HIV itself influencing a direct damage on the hepatic cells leading to apoptosis and mitochondrial dysfunction of hepatic cells (Matamarin *et al.,* 2009). ALT and AST are hepatic enzymes that could be used as markers of hepatocellular injury (Zechini *et al.,* 2004). Hepatic toxicity is due to increased rate of cytolysis and significantly elevated serum transaminase level. It is usually a common complication in HIV-infected patients undergoing anti-retroviral therapy (Anthony, 2001) and approximately found in 6 - 30% of treated subjects. Hepatic toxicity may also lead to elevated serum levels of alkaline phosphatase and bilirubin, which may either occur early or later in the course of therapy (Bellini *et al.,* 2003).

The kidney plays a major role in the metabolism and excretion of waste products of metabolism including drug metabolites. HIV infection hurts the ability of the kidneys to function properly and some HIV medications may also harm the kidneys (Pataki, 2006) making it vulnerable to various types of renal damage including disturbances of fluid and electrolyte metabolism and disturbances in acid-base balance. Clinically, HAART can cause various kidney syndromes including various electrolyte and acid base disorders, acute kidney injury (AKI), lactic acidosis, and chronic kidney disease (Row, 2001). Renal toxicities including acute kidney injury (AKI), tubulopathies, chronic kidney disease (CKD), and end-stage renal disease are some of the adverse side-effects of HAART requiring renal replacement therapy (Ogundahunsi *et al.,* 2008).

The widespread of HIV infection as well as the extensive use of HAART in management of HIV infection and speculations of their effects such as nausea, vomiting, rash, abdominal pain, skin rashes, peripheral neuropathy, pancreatitis, diarrhea, indirect hyper bilirubinemia etc., has made it necessary to investigate the effect of ARVs to the patients. The number of people infected with HIV was estimated to be 33 million globally, and by increase in the accessibility of antiretroviral therapy, the number of patients persisting with the HIV increases and also increases in the presentation of liver and kidney diseases (Smith *et al.,* 2010). Hepatotoxicity and nephrotoxicity are the major side effect described for all antiretroviral drugs (Gisolf *et al.,* 2000; Sulkowski *et al.,* 2000; Reisler *et al.,* 2001).

The important role of the liver and kidney in metabolizing or detoxifying drugs and excreting waste products of metabolism cannot be overemphasized, hence these vital organs need to be monitored during therapies of different drug combinations and regimens. The aim of this study is to investigate the effect of highly active antiretroviral drugs therapy (HAART) on serum liver enzymes and kidney function indices on HIV patients in Kano metropolitan.

MATERIAL AND METHODS

Study Area, Design and Selection Criteria

This was a cross sectional study carried out at some selected General Hospital in Kano Metropolitant such as Murtala Muhammad General Hospital (MMGH), Muhammad Abdullahi Wase specialist hospital (MAWSH) and Sir Sunusi General Hospitals. The study involved two hundreds adult human volunteers males and females aged between 18-50 years from Kano metropolis. One hundred (100) HIV/AIDS positive subjects on HAART were used as test control and one hundreds (100) HIV/AIDS negative subjects as normal control. Informed consent was obtained from each participant. Questionnaires were distributed and duly filled by the participants.

Inclusion criteria

Apparently healthy male and females individuals that tested negative to HIV/AIDS aged between 18-

50 years were selected as control subjects, while those that tested HIV/AIDS positive on HAART medications selected as test subjects.

Exclusion Criteria

Patients who are suffering from renal disorder and are on medication that can induced renal disorder, long term smokers and alcoholic individuals were excluded from the study.

Ethical Considerations and Informed Consents

Ethical approval was duly obtained from the Kano State Ministry of Health, (No: 02233/11/2024). Written consent of willingness to participate in the study as subject was obtained from all the participants.

Sampling Techniques

Venous blood was collected into appropriately labelled five milliliters (5ml) plain tube. Sample was allowed to clot and retract, centrifuged at 5,000 rpm and the supernatant (serum) was separated into another labelled vial and stored at -20 °C until analyzed, and the analyses were carried out within 48 hours of collection.

Biochemical Analysis

Measurement of liver function indices

The blood serum collected from participants were used to determine the values of liver parameters such as; Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Total proteins, Albumin, total and direct Bilirubin.

Measurement of kidney function indices

The blood serum collected from the participants were used to measure the values of kidney indices such as; Creatinine (CREAT), Blood urea nitrogen (BUN), Sodium, Potassium and Chloride.

Data Analysis

Data obtained from this study were analyzed using the statistical package for social sciences (SPSS) for Windows Inc. Chicago, IL, USA. Significant differences between means were determined using Anova. Student's T- test was used to calculate differences between the means. Results were recorded as mean ± standard deviation. P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Demographic and Clinical Characteristics of the Study Participants

A total of two hundred (200) participants were recruited in the study, 100 were HIV-infected patients on HAART while 100 were HIV negative (control) subjects. There were 25 males and 75 females HIV patients while the normal control were 56 males and 44 females. Most of the HIV subjects participated were in the age group between 31-50 years (65%) while for the control, majority were in the age between 18-30 years. Most of the HIV-infected patients were on the Tenofovir, Lamivudine and Efavirenz; (TDF+3TC+EFV) (70%) and 30% were on Zidovudine, Lamivudine and Efavirenz and the HIV patients had been on medication for 4-12 years. Additionally, the HIV patients were not employed but independent engaging in activities such as food vendors, cook, managing small restaurant at car park or other social gathering within the city (65%) while the 35% were employed in most of the private organizations such as hotels, private offices, etc (Table 1).

Effect of HAART on liver function indices of HIV positive patients

The liver parameters such as ALT, AST, protein, albumin , direct and total bilirubin of HAART patients showed significant ($p<0.05$) higher mean values when compared with normal control (non HIV Participants) . While ALP showed no significant different between the HIV patient on HAART and the normal control. Similarly all the female patients on HAART showed significant different when compared with male counterpart except for ALP which indicate no any statistical difference (*$p<0.05$*) (Table 2).

Table 1, Demographic and clinical characteristics of the study participants

Characteristics		HIV patient on HAART (%) (n=100)	HIV negative control (%) (n=100)
Gender	Male	25 (25)	56 (56)
	Female	75 (75)	44 (44)
Age group (years)	18 – 30	14 (14)	67 (67)
	31 – 50	61 (61)	12(12)
	51 – 70	25 (25)	21 (21)
ARV therapy	TDF+3TC+EFV	70 (70)	Nil
	AZT/3TC+EFV	30 (30)	Nil
Duration of therapy	≤ 4 years	25 (25)	Nil
	4 – 12 years	65 (65)	Nil
	> 12 years	10 (10)	Nil
Occupation			
Employed		35(35)	Nil
Unemployed		65(65)	Nil

HAART= Highly Active Antiretroviral Drugs Therapy**,** ARV= ANTI- RETRIVIRUS, TDF+3TC+EFV =Tenofovir+ Lamivudine+ Efavirenz; AZT/3TC+EFV = Zidovudine+ Lamivudine+ Efavirenz; Nil = not applicable

Table 2: Effect of HAART on liver function indices of HIV positive patients.

Liver Function indices	ON HAART		Normal control(n=100)	P-value
	Females (n=75)	Males (n=25)		
ALT (µ/L)	33.2±13.5	28.7±12.4	16.5±9.5	0.001*
AST (µ /L)	32.5±14	28.9±12	21.3±5.3	0.03*
ALP (µ /L)	99.5±46.8	101.2±35.3	103.3±35	0.15
Protein (g/L)	77.5±5.7	74.2±4.7	69.4±7.0	0.001*
Albumin (g/L)	46±3.9	44±2.9	38.5±3.4	0.001*
Direct bilurubin (µ /L)	1.62±0.5	1.36±0.5	1.0±0.6	0.003*
Total bilirubin (µ /L)	4.9±3.1	3.9±2.2	2.9±4.6	0.01*

*Results are presented in triplicate as Mean ±Standard Deviation. The * indicated significant difference between the sex at p<0.05. ALT= Alanine amino transferase, AST= Aspartate amino transferase, ALP=Alkaline phosphatase.*

The findings reveal significant alterations in liver function indices among HIV-positive patients on HAART compared to the normal control group, indicating a possible impact of antiretroviral therapy and HIV infection on liver physiology. The significantly higher mean values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in patients on HAART, compared to the control group, suggest liver stress or damage. Elevated transaminase levels are commonly reported in HIV-positive individuals undergoing HAART, attributed to direct hepatotoxic effects of antiretroviral drugs or immune-mediated hepatic injury (Lemoine *et al*., 2021). The increase in total protein levels could reflect chronic inflammation or immune activation commonly associated with HIV infection (Hoffman *et al*., 2020).

Albumin levels, though higher than in controls, were within clinically acceptable limits, indicating preserved liver synthetic function despite elevated inflammatory markers. The increased bilirubin (both direct and total) levels are consistent with studies suggesting HAART-induced hemolysis or impaired bilirubin metabolism, particularly with drugs like Zidovudine or Atazanavir (Gervasoni *et al*., 2020).

Interestingly, alkaline phosphatase (ALP) levels showed no significant difference between HAART patients and the control group. This indicates that bile duct injury or bone metabolism disturbances, commonly reflected in ALP, may not be significantly impacted. This finding is consistent with reports that liver enzyme disturbances in HAART patients are often more prominent in transaminases than ALP (Ganesan *et al*., 2019). The gender differences observed in liver function indices, where female patients exhibited significantly higher values for most parameters compared to males, could be attributed to hormonal differences or variations in drug metabolism and distribution (Monteiro *et al*., 2022). Female patients on HAART are known to exhibit higher susceptibility to drug-induced hepatotoxicity, which may explain this finding. The absence of significant gender differences in ALP levels further supports the conclusion that biliary or bone involvement may not differ substantially between genders.

Effect of HAART on Kidney parameters of HIV positive patients

The kidney parameters such as creatinine, urea and electrolytes (Na^+, K^+ and Cl^-) for the HAART patients were significantly higher when compared with non HIV patients (Normal control). However, the mean values for all the parameters were significantly higher in males compared to females with exception of Cl^- in female which was found to be higher than it male counterpart for the HAART patients (Table 3).

Table 3 Effect of HAART on kidney function indices of HIV positive patients

Kidney parameters	ON HAART		Normal control n=100	P-value
	Females (N=75)	Males (N=25)		
Creatinine (µmol/l)	78.98±26	89.22±26	65.0±17.0	0.001*
Urea (mmol/l)	3.96±0.77	4.55±1.0	2.7±1.1	0.001*
Na^+ (mmol/l)	139.7±2.6	141.1±2.9	124.3±10.8	0.08
K^+ (mmol/l)	4.9±0.38	5.4±0.41	3.1±0.58	0.06
Cl^- (mmol/l)	110.8±3.6	108.2±3.4	99.82±3.8	0.048*

Results are presented in triplicate as Mean ±Standard Deviation. The * indicated significant difference between the sex at p<0.05: Na=sodium, K=Potassium, Cl=Chloride

The findings of this study reveal significant alterations in kidney function parameters among HIV-positive patients on Highly Active Antiretroviral Therapy (HAART) compared to non-HIV individuals (normal control). Elevated levels of creatinine, urea, and electrolytes (Na+, K+, and Cl^-) in HAART patients indicate potential impacts of long-term antiretroviral drug use on kidney function. These alterations are consistent with previous studies reporting renal dysfunction as a common adverse effect associated with HAART, particularly regimens containing tenofovir disoproxil and fumarate (TDF) (Hoffman *et al*., 2020).

The significantly higher creatinine and urea levels in HAART patients suggest impaired renal function, likely due to drug-induced nephrotoxicity. Studies have shown that TDF, widely used in HAART regimens, is associated with proximal tubular dysfunction, leading to elevated serum creatinine and reduced creatinine clearance (Monteiro *et al*., 2022). Such changes emphasize the need for regular monitoring of kidney function in HIV patients on HAART, particularly those on TDF-based regimens.

Gender-specific differences in kidney parameters were also observed. Male HAART patients exhibited significantly higher creatinine, urea, and electrolytes (Na+ and K+) compared to their female counterparts. This aligns with existing literature suggesting that men are more susceptible to HAART-related nephrotoxicity due to factors such as higher lean body mass and differing pharmacokinetics (Gervasoni *et al*., 2020). Interestingly, the higher mean Cl^-levels observed in female patients may point to gender-specific variations in electrolyte handling, potentially influenced by hormonal factors or dietary differences (Ganesan *et al*., 2019).

These findings also highlight the importance of comprehensive clinical management strategies for HIV patients on HAART. Regular assessment of kidney function and electrolyte balance should be integral to HIV care to identify early signs of nephrotoxicity and mitigate long-term complications. Clinicians should also consider individual patient factors, including gender and baseline renal function when prescribing HAART regimens to minimize adverse renal effects.

The significantly higher values of kidney function indices compared to normal controls emphasize the dual impact of HIV infection and long-term HAART on renal health. While HAART has revolutionized HIV management by improving survival and reducing viral load, its long-term adverse effects, such as renal dysfunction, underscore the need for safer antiretroviral options and individualized treatment approaches (Lemoine *et al*., 2021).

Impact of HAART Duration on Liver and Kidney Function Indices in Patients

The influence of Highly Active Antiretroviral Therapy (HAART) duration on liver and kidney function indices was assessed across three treatment intervals: 1–3 years, 4–6 years, and >7 years. The results revealed that the mean levels of ALT and AST were significantly elevated in patients on HAART for over 7 years, compared to those in the early stage of treatment (1–3 years). Conversely, mean protein levels were significantly lower in patients on HAART for more than 7 years relative to normal control subjects. No statistically significant differences were observed in the mean values of albumin, alanine aminotransferase, direct bilirubin, or total bilirubin with respect to HAART duration. However, these indices showed significant variations when compared with normal controls (Table 4).

Effect of HAART on Kidney Parameters and Duration of Medications

The mean values for all kidney indices analyzed were significantly higher in the HAART group compared to normal control. There were significant increases of all the parameters observed when compared to normal ranges of kidney indices. The increases observed from 4-6 years and higher at 7 years on HAART treatment (Table 5).

Table 4: **Effect of HAART on liver parameters and Duration of Medications**

Liver function indices (units)	HAART-duration (years)				P-value
	Normal control (n=100)	1-3 yrs (n=25)	4-6 yrs (n=55)	>7 yrs (n=20)	
ALT (μ/L)	16.5±9.5	27.2±12.1*	32.34±13.3*	33.4±11.2	0.002
AST (μ /L)	21.3±5.3	29.21±20.2*	33±16.1*	34.34±14	0.03
ALP (μ /L)	103.3±35	106.21±50.3	106.34±41.2 *	106.6±33.5	0.08
Protein (g/L)	69.4±7.0	74.6±5.8	74.3±4.2*	70.6±4.1*	0.03
Albumin (g/L)	38.5±3.4	43.12±2.9	43.1±3.7	43.2±3.1	0.14
Direct bilirubin(μ/L)	1.0±0.5	1.29±0.62	1.30±0.6	1.30±0.5	0.83
Total bilirubin(μ/L)	2.9±4.6	4.3±2.7	4.2±3.2	4.3±4.0	0.52

Results are presented in triplicate as Mean ±Standard Deviation. The * Significant difference in analyte values in the respective HAART duration categories at $p<0.05$. ALT= Alanine amino transferase, AST= Aspartate amino tansferase, ALP=Alkaline phosphatase

Table 5: Effect of HAART on Kidney Parameters and Duration of Medications

Kidney Parameters	HAART-duration (years)				P-value
	Normal control (n=100)	1-3 yrs (n=25)	4-6 yrs (n=55)	>7 yrs (n=20)	
Creatinine (μmol/l)	65.0±17.0	68.8±24.3	76.8±22.3	77.2±22.3	0.001*
Urea(mmol/l)	2.7±1.1	3.3±1	3.8±0.8	3.9±0.3	0.28*
Na^+ (mmol/l)	124.3±10.8	140±0.3	143.6±0.2	148.8±0.4	0.82*
K^+ (mmol/l)	3.1±0.58	4.2±0.36	4.36±0.35	4.41±0.38	0.09*
Cl^- (mmol/l)	99.82±3.8	106.9±3.5	107.6±2.5	108.9±1.7	0.36*

Results are presented in triplicate as Mean ±Standard Deviation. The * Significant difference in analyte values in the respective HAART duration categories at $p<0.05$

The findings highlight significant alterations in liver and kidney function indices with prolonged HAART therapy, emphasizing the need for ongoing biochemical monitoring in HIV patients. For liver function, ALT and AST levels were significantly elevated in patients who had been on HAART for over 7 years compared to those in the earlier stages of treatment (1–3 years). This suggests cumulative hepatocellular stress or damage associated with long-term therapy. Similarly, protein levels were significantly reduced in patients with extended HAART exposure (>7 years), which may indicate progressive liver dysfunction affecting protein synthesis. These observations align with studies showing that antiretroviral drugs, particularly non-nucleoside reverse transcriptase inhibitors, can induce hepatotoxicity over time (O'Brien *et al*., 2021; Mbunkah *et al*., 2022).

Regarding kidney function, all indices analyzed such as creatinine, urea, and electrolytes were significantly elevated in HAART-treated patients compared to controls and increased progressively with longer treatment durations. Patients on therapy for 4–6 years showed elevated values, with the highest levels observed in those on HAART for more than 7 years. These findings are consistent with reports of nephrotoxicity related to tenofovir-containing regimens, which impair renal tubular function and glomerular filtration (Ramana *et al*., 2022). Electrolyte imbalances, particularly elevated sodium and potassium levels, further suggest potential tubular dysfunction or early renal injury (Nguyen *et al*., 2023).

The gender-based differences observed in both liver and kidney indices underscore the physiological variations in drug metabolism and toxicity. Female patients exhibited lower levels of creatinine and urea compared to males, potentially reflecting differences in muscle mass or hormonal influences on renal function (Kariuki *et al*., 2020).

CONCLUSION

This study highlights the significant impact of HAART on liver and kidney function indices among HIV patients in Kano Metropolitan. Elevated levels of ALT, AST, and bilirubin suggest HAART-induced hepatotoxicity, while increased creatinine and urea indicate potential nephrotoxicity. Gender

differences were evident, with males showing higher kidney function indices while females exhibiting greater liver enzyme alterations than the males. Age also influenced biochemical variations, with middle-aged individuals (31–50 years) being the most affected. Additionally, prolonged HAART use (>7 years) was associated with more pronounced liver and kidney dysfunction. These findings emphasize the need for continuous monitoring of liver and kidney health in HIV patients on long-term HAART therapy.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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