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Duration of HAART use: A key prognosticator for NAFLD in HAART experienced HIV patients

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Abstract

Background: The Human immunodeficiency disease (HIV) remains a global menace decades after its discovery and despite advances in therapeutics and use of Highly active antiviral therapies (HAART). HIV/AIDS patients now have longer lifespan with increased non-AIDS related morbidity and mortality. Non-alcoholic fatty liver diseases (NAFLD), a global public health challenge has been identified as one of the leading causes of morbidity and mortality in HIV infected persons. Our study aimed to identify the risk factors for NAFLD in HIV infected patients and to relate the liver enzymes derangement to NAFLD.

Method: we retrospectively analyzed data from 170 HAART experienced viral hepatitis sero-negative HIV patients. Sociodemographic, anthropometric, and laboratory characteristics were extracted. Hepatic steatosis was diagnosed by ultrasound scan.

Result: NAFLD was present in 27.9% of the patients and the duration of HAART use ($p<0.001$), elevated plasma glucose level ($p<0.001$), increased waist circumference ($p=0.004$), duration of HIV infection ($p=0.026$), and elevated serum triglycerides ($p=0.033$) were identified as the major risk factors for NAFLD. Using the Wald test of variables, duration of HAART use was identified as the key prognosticator of NAFLD in HIV patient [Wald value (WV) of 10.749 ($p= 0.001$)].

Reduced CD4 cell count and liver enzyme derangement were not identified as risk factors for NAFLD.

Conclusion: NAFLD is common in HAART experienced HIV patients and the duration of HAART use is the most important predictor for its occurrence. Early recognition and vigorous modification of these risk factors among HIV patients are necessary to prevent further progression of NAFLD.

Keywords: HIV; AIDS; Non-alcoholic fatty liver disease; HAART

1. Introduction

The Human immunodeficiency disease (HIV) remains a global menace decades after its discovery and despite technological advances in its diagnosis and therapeutics. Africa remains a locus of the pandemic being home to two-thirds of the global HIV population with 25.3 million infected persons [1] according to a 2020 report. Worldwide multiple concerted efforts involving leading global government organizations and Humanitarian corporations has led to an increased access to highly active antiretroviral therapy (HAART) in HIV infected persons from 7.8 million in 2010 to 27.4 million in 2020 [2]. Consequently, AIDS related mortality has declined by about 42% since 2010 [2] resulting in an increased life expectancy of the HIV population.

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Non-alcoholic Fatty Liver Disease (NAFLD) affects a large proportion of individuals worldwide with a global prevalence of 25.24% [3]. NAFLD is increasingly being identified as a leading public health challenge affecting individuals living in both developed and developing countries. NAFLD it is now being recognized as possibly the most common cause of chronic liver disease and the commonest cause of elevated liver enzymes [4, 5].

The Prevalence of NAFLD in persons living with HIV/AIDS is remarkably high ranging from 35% as reported by Maurice et al [6] to 50% [7] and can be due to the presence of HIV itself as well as its treatment [7]. The pathogenesis of NAFLD in HIV infected has not been fully understood however, insulin resistance, mitochondrial dysfunction and dyslipidemia seem to be the main drivers [7] .

1.1. Etiopathogenesis of NAFLD in HIV

Data from large population- based studies on the prevalence, predictors and natural history of NAFLD among HIV infected persons are sparse. HIV patients may be at particular risk for fatty liver disease due to increased prevalence for both risk factors proposed for the 'two-hit' pathogenesis of NAFLD. These are insulin resistance with release of free fatty acids from adipose tissue with subsequent hepatic triglyceride deposition as well as oxidative stress-cytokine mediated injury [8] .

With reference to the first 'hit', HIV infected individuals have an increased rate of lipid and glucose abnormalities resulting from the effect of the HIV infection itself or as a potential metabolic side effect of anti-retroviral drugs. Highly active antiviral therapy with Protease inhibitors may result in hepatic steatosis via the over expression of the sterol regulatory protein-SREBP-1, [9] Zidovudine and Stavudine which are examples of nucleoside analogues may cause direct hepatotoxicity and steatosis due to inhibition of mitochondrial DNA polymerase-γ, [10] and Non-nucleoside reverse transcriptase inhibitors such as Nevirapine may cause damage to the liver via direct drug toxicity and hypersensitivity reaction. [10] .

In relation to the second 'hit', HIV patients may be at an increased risk of NAFLD due to a chronic inflammatory state induced by the virus which results in an increased level of tumor necrosis alpha (TNF-α levels) as well as a rise in gut-derived lipopolysaccharide that promote hepatic damage [11] .

The increasing levels of diabetes and obesity among HIV-infected persons, [12,13] which is similar to that of the general population, may also contribute to NAFLD in this population. Hepatic steatosis can progress rapidly to cirrhosis in HIV infected persons, even in the absence of co-infection with the hepatitis virus, and despite effective control of HIV replication [14,15] .

1.2. Changing morbidity and mortality in HAART experienced HIV infection

The introduction of Highly Active Antiretroviral Therapy (HAART) has significantly reduced the morbidity and mortality due to HIV/AIDS in persons living with the disease [16–18] resulting in a near normal life expectancy in HIV infected individuals on treatment [19,20]. A 2009 Chinese study [21] comparing the excess mortality in HIV infected individuals to that of the general population reported a substantial decline in mortality in HIV patients on HAART.

A 2008 multicenter retrospective Canadian study reported a 36% decline in AIDS related mortality, a 17% increase in non-AIDS related cancer and concluded that liver disease is the most frequent non-AIDS defining cause of death in the HAART era among HIV positive individuals [22]. HIV patients receiving HAART now more commonly have non-infectious and non-opportunistic (Non-AIDS) complications of their disease [23]. The introduction of these antivirals has also reportedly changed the scope of Liver diseases among HAART experienced HIV patients from opportunistic infections and AIDS related neoplasm to concomitant infection with chronic Hepatitis C (HCV), chronic Hepatitis B (HBV), medication-related hepatotoxicity, alcoholic steatohepatitis, and non-alcoholic fatty liver disease (NAFLD). [22,24,25].

2. Material and methods

We retrospectively analyzed a prospectively collected data from 170 HIV sero-positive patients attending the antiretroviral therapy (ART) clinic at the University of Port Harcourt Teaching, Port Harcourt, Nigeria (2011-2012). We collected data of the anthropometric and laboratory characteristics of the HIV patients sonographically classed into those with and without hepatic steatosis in order to determine the risk factors for NAFLD amongst them.

Informed consent was given by the participants and ethical approval was obtained from the ethical board of the hospital.

2.1. Participants

We included adult HIV patients seen at the ART clinic who admitted to an ingestion of <20g/day of alcohol and were sero-negative for viral hepatitis B and C. diabetics as well as pregnant women were excluded from the study.

2.2. Data collection

We extracted the dermographs and anthropometric characteristics of the HIV positive patients with and without NAFLD including their age, sex, body mass index (BMI), waist circumference, and laboratory parameters such as Aspartate transaminase (AST), Alanine transaminase (ALT), fasting blood glucose and lipid parameters. In this study, Diagnosis of hepatic steatosis was based on the increased echogenicity of the liver parenchyma as compared to the right kidney's cortex, and Hepatic steatosis found on abdominal ultrasound scan was graded as grade 1-mild, grade 2- moderate and grade 3-severe steatosis. Mild steatosis is when there is a slightly brighter liver as compared to the renal cortex, clear visualization of diaphragm, and interface of hepatic veins with sharp contours, Moderate steatosis is defined as brighter liver with attenuated ultrasound beam at deeper parts of the liver, diaphragm, and hepatic veins still visible but with blunted contours and finally, severe steatosis is the finding of very bright liver, severe ultrasound beam attenuation, diaphragm, or hepatic veins not visible on abdominal ultrasound scan [26,27].

2.3. Outcome measures

The primary aim of our study is to identify and prognosticate the risk factors for NAFLD in this HIV positive cohort as well as to assess the relationship if there be any between the grades of NAFLD and liver transaminases.

2.4. Statistical analysis

All data were analyzed using the commercially available statistical package for social sciences (SPSS) version 21 analytic software. Data were expressed as mean ± standard deviations and frequencies as a percentage. Continuous variables were compared using the Students t-test, or one-way analysis of variance as considered appropriate. Categorical parameters were compared using the chi-square test. We performed the Wald test on variables to identify the major risk factor for NAFLD and relations among variables were assessed using Pearson correlation coefficient, odds ratio and odds logistic regression analysis. All tests were considered to be statistically significant at the P-value < 0.05.

3. Results

3.1. Comparison of clinical, anthropometric and laboratory characteristics of the HIV patients with and without NAFLD.

Out of the 170 HIV patients, Hepatic steatosis diagnosed by ultrasonography was detected in 44 patients giving a prevalence of 25.9%.

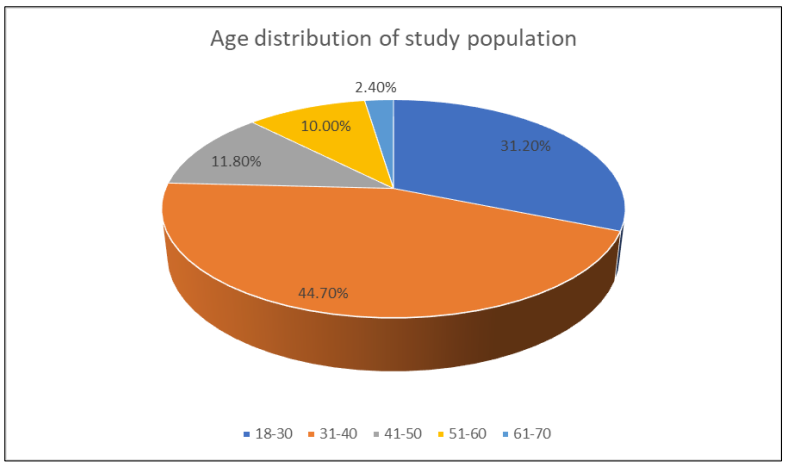

Figure 1 Comparison of risk factors in patients with NAFLD and without NAFLD

There were more females than males in the study population with a ratio of 2.2:1 (117 -68.8% females and 53-31.2% males). The age distribution of the study population is as shown in figure 1. Comparing the mean age of the 44 HIV patients with NAFLD to those without NAFLD, mean age for the NAFLD positive patients was 37.8 ± 9.7 years compared

to 36.37 ± 10.1 years and this was not statistically significant (p =0.410). There were 14(31.8%) males and 30 (68.18%) females with NAFLD and this was not statistically significant. (p = 1.000).

As shown in table 1, the mean duration of HAART use was higher among the 44 patients with NAFLD compared to those without NAFLD (5.1±1.6years vs 3.7±2.2years) and this was statistically significant. (p =0.000). The mean BMI and waist circumference were also significantly higher in the HIV cases with NAFLD than in those without NAFLD. (BMI was 26.1 ± 5.0kg/m2 and 24.4 ± 3.7kg/m2 respectively; p=0.022) (Waist circumference was 91.3 ± 11.0cm and 88.7 ± 10.1cm respectively; p =0.000).

Dyslipidemia was found in 39 (88.6%) of the cases who had NAFLD while 82 (65%) of the cases without NAFLD had dyslipidemia. Comparing the mean fasting blood glucose of patients with NAFLD versus those without, we found that they had a higher value (NAFLD vs without NAFLD 5.0 ± 1.2mmol/l versus 4.3 ± 1.0mmol/l. p < 0.001). Of the blood lipid parameters, the total cholesterol, triglycerides, and low-density lipoprotein cholesterol were all significantly higher in the HIV cases with NAFLD than in those without NAFLD.

Table 1 Comparison of risk factors for NAFLD in the 170 HIV cases with/without NAFLD

Risk Factor	NAFLD Present	NAFLD Absent	P Value
AGE (yrs.)	37.8±9.7	36.4±10.1	0.410
BMI (kg/m^2)	26.1±5.0	24.4±3.7	0.022
WC (cm)	91.3±11.0	83.7±10.1	0.000
HAARTDURATION (yrs.)	5.1±1.6	3.7±2.2	0.000
FPG (mmol/l)	5.0±1.2	4.3±1.0	0.000
DYSLIPIDEAMIA	39 (88.6%)	82 (65%)	0.003

Values expressed as mean ± SD; SD= standard deviation; BMI= body mass index; WC= waist circumference; AST=aspartate transaminase; ALT=alanine transaminase; FPG=fasting plasma glucose; TC= total cholesterol, TG= triglycerides, HDL-c= high density lipoprotein cholesterol, LDL-c= low density lipoprotein cholesterol.

Table 2 distribution of laboratory parameters among the patients with and without NAFLD

Variable	NAFLD present	NAFLD absent	P value
TOTAL BILIRUBIN µmol/l	7.3±1.8	7.9±2.1	0.084
AST iu/l	26.5±20.3	29.0±21.9	0.507
ALT iu/l	19.8±17.5	24.7±22.4	0.190
CD4COUNT cells/µl	326.6±241.6	351.3±242.1	0.561
FPG mmol/l	5.0±1.2	4.3±1.0	<0.001
TC mmol/l	5.5±1.1	5.1±1.0	<0.001
TG mmol/l	1.5±0.6	1.3±0.5	<0.001
HDL-C-c mmol/l	1.2±0.4	1.3±0.4	0.360
LDL-C-c mmol/l	3.6±1.1	3.4±0.9	<0.001

Values expressed as mean ± SD; SD= standard deviation; BMI= body mass index; WC= waist circumference; AST=aspartate transaminase; ALT=alanine transaminase; FPG=fasting plasma glucose; TC= total cholesterol, TG= triglycerides, HDL-c= high density lipoprotein cholesterol, LDL-c= low density lipoprotein cholesterol

3.2. Odds logistics regression analysis of patients with and without NAFLD

In standard odd logistic regression analysis, the duration of HAART use, the duration of HIV infection, the waist circumference, BMI, total cholesterol, triglycerides and LDL-C all explained 53.361 of the variances observed in HIV patients with NAFLD. (p<0.001). Using the Wald test of variables, the most important risk factors for NAFLD in HIV cases is the duration of HAART use with a Wald value (WV) of 10.749 and a significance of 0.001. Other risk factors

found to make a significant contribution include fasting plasma glucose (WV=10.518, p=0.001), waist circumference (WV=8.217, p=0.004), duration of HIV infection (WV=4.978, p=0.026) and triglycerides (WV=4.533, p=0.033).

Using the omnibus test of model coefficients, it was observed that the goodness of fit test for the model is highly significant at a p-value of 0.000 (significant value should be <0.05) and a chi-square of 63.421+9 degrees of freedom.

From the Odds logistic analysis, the specificity of the risk factors for NAFLD was 96.8% and the sensitivity was 56.8%. The positive predictive value calculated was 86.2% (i.e. 86.2% of HIV cases predicted to have NAFLD were accurately picked by the model). See table 3.

Table 3 odds logistic regression analysis of risk factors for NAFLD.

Risk Factor	Score	P-Value	Exp B (Odds Ratio)	95% CI
AGE (yrs.)	0.687	0.407	1.011	0.905-1.060
YRSPOSITIVE	3.895	0.048	0.221	6.059-0.832
HAART (yrs.)	14.721	0.000	1.825	1.275-2.614
BMI (kg/m^2)	5.223	0.022	0.924	0.789-1.082
WC (cm)	16.298	0.000	1.096	1.029-1.167
FPG (mmol/l)	12.902	0.000	2.122	1.347-3.343
TC (mmol/l)	17.144	0.000	1.175	0.328-4.207
TG (mmol/l)	11.733	0.001	3.076	1.093-8.632
LDL-c (mmol/l)	16.290	0.000	1.662	6.521-5.297

BMI= body mass index, WC= waist circumference, FBG=fasting blood glucose; TC= total cholesterol, TG= triglycerides, HDL-c= high density lipoprotein cholesterol, LDL-c= low density lipoprotein cholesterol. Yrs=years

Table 4 Wald test of variables showing the major risk factors for NAFLD

NAFLD predictor	WALD value	P-value
HAART DURATION (yrs.)	10.749	0.001
FPG (mmo/l)	10.518	0.001
WC (cm)	8.217	0.004
HIV DURATION (yrs.)	4.978	0.026
TG (mmol/l)	4.533	0.033

3.3. Relation of degree of liver enzymes derangement to the grade of NAFLD

Table 5 comparison of ALT category to the grades of NAFLD

NAFLD GRADE	ALTCAT0	ALTCAT1	ALTCAT2	ALTCAT3	ALTCAT4	TOTAL
None	58	23	39	6	1	127
Mild	6	2	1	1	0	10
Moderate	12	5	5	1	0	23
Severe	5	4	1	0	0	10
Total	84	34	46	8	1	170

LEGEND:0=<1.25XULN; 1=1.25-2.5XULN; 2=>2.5-5.0XULN; 3= >5.0-10XULN; 4= >10XULN; AST= aspartate transaminase; ALT=alanine transaminase

No significant relationship was established between the grades of ALT and AST derangement and the presence/grades of NAFLD. (p=0.914 and 0.160 respectively). See table 5,6 7.

Table 6 comparison of AST category to the grade of NAFLD

NAFLD GRADE	ASTCAT0	ASTCAT1	ASTCAT2	ASTCAT3	ASTCAT4	TOTAL
None	47	27	44	9	0	127
Mild	5	1	3	1	0	10
Mod	8	8	6	1	0	23
Severe	3	6	0	1	0	10
Total	63	42	53	12	0	170

LEGEND:0=<1.25XULN; 1=1.25-2.5XULN; 2=>2.5-5.0XULN; 3= >5.0-10XULN; 4= >10XULN; AST= aspartate transaminase; ALT=alanine transaminase

Table 7 Comparison of liver enzyme categories to grades of NAFLD

NAFLD GRADE	ABN LFTs	NORMAL LFTs	P-VALUE
NONE	72	55	0.212
MILD	6	4	
MODERATE	16	7	
SEVERE	9	1	

ABN LFTS= liver transaminases >43iu/l. NORMAL LFTs= liver transaminases <43iu/l.

3.4. Correlation of NAFLD with its risk factors

Using the bivariate Pearson correlation available on SPSS, we determined the correlation between NAFLD on abdominal USS and its risk factors identified in the study. We observed that the duration of HAART use, body mass index, waist circumference, fasting blood glucose, and lipid parameters (total cholesterol, low density lipoprotein, triglycerides) correlated positively (r = 0.294, P=0.000, r = 0.175, P = 0.022, r= 0.310, P < 0.001, r = 0.276, P < 0.001, r=0.318, P=0.000, r=0.310, P=0.000, r=0.263, P=0.001 respectively). Liver transaminases ALT and AST however correlated negatively with the diagnosis of NAFLD and were not statistically significant. (r= -0.101, P=0.190, r= -0.051, P=0.507). (see table 8)

Table 8 correlation between variables and NAFLD

Variables	Correlation Coefficient (r)	P-Value
HAART DURATION (yrs)	0.294	0.000
BMI (kg/m^2)	0.175	0.022
WC (cm)	0.310	0.000
FBS (mmol/l)	0.276	0.000
TC (mmol/l)	0.318	0.000
TG (mmol/l)	0.263	0.001
LDL-c (mmol/l)	0.310	0.000
AST (iu/l)	-0.051	0.507
ALT (iu/l)	-0.101	0.190

Legend: BMI= body mass index; WC= waist circumference; TC= total cholesterol, TG= triglycerides, LDL-c= low density lipoprotein cholesterol; FBS=fasting blood sugar; AST=aspartame transaminase; ALT= alanine transaminase.

4. Discussion

Fatty liver is the leading cause of non-HIV related mortality in HIV/AIDS patients with a prevalence of 30-50% [28]. This study set out to elucidate the risk factors for NAFLD in HIV infected patients and to determine the relationship between abnormal liver enzymes and the presence of NAFLD in HIV patient. The prevalence of NAFLD in HIV infected persons varies depending on the diagnostic modality employed and the type of study. The prevalence of non-alcoholic fatty liver disease in this cohort of HIV mono-infected patients was 27.9%. This is comparable to the prevalence obtained elsewhere.

In this study, several factors were found to be associated with NAFLD in the cases and these include anthropometric measurements such as body mass index (BMI) and waist circumference (WC), the duration of HAART use, fasting plasma glucose (FPG), and the lipid parameters including the total cholesterol (TC), low density lipoprotein (LDL-C), triglycerides (TG) and high density cholesterol (HDL levels. Prolonged ART results in adverse metabolic disorders and drug toxicities. Prolonged HAART duration in longstanding HIV infection has been linked to the maldistribution of fat [29] resulting in HIV related lipoatrophy of fat from areas of the body such the face, buttocks, extremities and lipoaccumulation of fat in dorsocervical, abdominal neck and breast regions of the body.

In this study the mean duration of HAART use was significantly longer in the pat6ients with NAFLD (5.1years) compared to those without NAFLD (3.7 years) and this may have contributed to the etiopathogenesis of NAFLD in this population. Notably, 97.7% and 2.3% of the patients who had NAFLD were on nucleoside reverse transcriptase inhibitors-NRTIs (lamivudine plus stavudine) and Protease inhibitors respectively.

Guaraldi et al [30] in their work on HIV patients reported that cumulative NRTI exposure was an independent predictor of NAFLD, with each year of NRTI exposure increasing the risk of NAFLD by 11%. Gaslightwala et al [31] in a study of HIV-HCV co-infected patients found that longer duration of antiretroviral therapy use (≥ 4 years) was found to be an independent predictor of steatosis. Prolonged use of antiretroviral drugs such as Protease inhibitors and Nucleoside analogue reverse transcriptase inhibitors rather than HIV infection itself has been associated with the development of Hepatic steatosis [32].

The components of metabolic syndrome such as increased waist circumference, a high BMI play a key role in the development fatty liver in HIV infected persons and in this study both indices were significantly higher in the patients who had NAFLD. table 1. This has also been reported by Guaraldi et al 2008 [30] where they observed that increased waist circumference and male sex were significantly associated with NAFLD. This trend was also observed in our study were despite the lower number of male participants, more males than females developed NAFLD.

The association between elevated Liver enzymes and the occurrence of NAFLD has been variedly described [33,34].

In our study, we did not observe a positive relationship between elevated Liver Transaminases and the diagnosis of non-alcoholic fatty liver however, more patients with moderate to severe NAFLD were observed to have abnormal liver enzymes. (See Table 7).

5. Conclusion

Liver disease is the most frequent non-AIDS defining cause of death in the HAART era among HIV positive individuals and Non-alcoholic fatty liver disease remain a leading cause of Liver disease globally. Our study showed that NAFLD is common among HIV patients and the duration of antiviral therapy in HAART-experienced HIV patients is a major risk factor for its development.

Compliance with ethical standards

Disclosure of conflict of interest

The Authors declare no conflict of interest.

Statement of ethical approval

Ethical approval was obtained from the University of Port Harcourt Teaching Hospital Ethical Committee (reference number UPTH/ADM/90/S.11VOLX/90).

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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