ORIGINAL ARTICLE

Period of onset and lack of clinical manifestation of hepatotoxicity after commencing highly active antiretroviral therapy

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Abstract

Aim: The period of onset of hepatotoxicity varies between cohorts as do their clinical manifestations. Clinical manifestations of hepatotoxicity that have been previously reported include fatal portal hypertension, dress syndrome, and lipodystrophy syndrome. The aim of this study was to determine the period of onset and clinical manifestation of hepatotoxicity after commencing HAART.

Materials and Methods: This study was carried out on patients with HIV on HAART attending infectious disease clinic, gastroenterology clinic or admitted into the medical wards of University of Benin Teaching Hospital. Patients with HIV but not on HAART were used as controls. A clinical evaluation and relevant laboratory investigations were done. Hepatotoxicity was defined using a standardized toxicity grade scale.

Results: A total of 84 cases and 42 controls were studied. The mean ages were 35.2 ± 9.9 years and 35.5 ± 9.0 years for the cases and the controls respectively. Over 70% of the study population and controls were females. The overall incidence of hepatotoxicity was 17.85% and severe hepatotoxicity occurred in 10.71% of the patients. Over 80% of liver enzyme elevations occurred within 3 months, most of which were asymptomatic.

Conclusion: This study shows that over 80% of enzyme elevations occurred within 3 months and were mostly asymptomatic. There is a need for regular monitoring of liver function tests at short intervals in HIV patients starting HAART since most of the cases of hepatotoxicity found in this study occurred early and were asymptomatic.

Key words: Clinical manifestation, HAART, hepatotoxicity

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Introduction

The advent of antiretroviral therapy (ART) has resulted in a significant decrease in morbidity and mortality among HIV-infected patients.[1,2] However, ART is often complicated by drug-related toxicities.[3,4] Hepatotoxicity is one of the most relevant adverse effects of ART owing to its frequency and the fact that it can lead to interruption of therapy, hepatitis, and death.[5] Incidence rates of hepatotoxicity vary greatly with different locations and study designs. According to the different definitions used in each study the overall frequency of grade 3 or 4 liver toxicity induced by HAART in HIV patients ranges from 1% to 18%.[6,7] The period of onset of hepatotoxicity varies between cohorts[8,9] as do their clinical manifestations.[10,11] Clinical manifestations of hepatotoxicity that have been previously reported include fatal portal hypertension,[12] dress syndrome[11] (drug rash, eosinophilia and systemic symptoms), and lipodystrophy syndrome consisting of central obesity, buffalo hump, wasting of extremities, hyperlipidemia, and insulin resistance.[10] The aim of

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this study was to determine the period of onset as well as clinical manifestations of HAART-induced hepatotoxicity in HIV-infected patients.

Materials and Methods

The study was carried out in the Department of Medicine, University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria. It was carried out on patients with HIV about to be started on HAART, attending infectious disease clinic, gastroenterology clinic, or admitted into the medical wards. Patients with HIV but who were not yet qualified to be started on HAART, following the Nigerian National guidelines for initiating HAART,[13] served as controls. Consenting patients were recruited consecutively and each patient was followed up for 24 weeks. The duration of the study was from July 2008 to July 2009. The study design was a prospective cohort study. Patients were eligible if they were diagnosed with HIV and had normal liver function tests, commencing HAART. Exclusion criteria included patients with HIV and pulmonary tuberculosis, pregnant women, patients already on HAART, recent hepatitis B or C infection, and patients with abnormal liver function tests. Informed and written consent was sought from each patient before enrolment into the study. The approval of the Hospital Ethics Committee was obtained before commencement of the study. A questionnaire was administered.

Each patient had a detailed history taken from him including alcohol use and drug history, and a physical examination was conducted. The patient's height without shoes was measured with the patient standing erect and looking straight ahead (coronal plane) using the stadiometer and the result was recorded in meters to the nearest 0.01 m.

The body weight (without shoes on and wearing light clothing only) was measured using a weighing scale and recorded in kilograms to the nearest 0.01 kg.

The body mass index (BMI) was then calculated using the formula

$BMI = \text{Weight (kg)}/\text{Height (m)}^2$.

The following investigations were carried out on each patient

- Packed cell volume (PCV) and WBC count (total, differential, and absolute lymphocyte count) were done using the Symex automated machine.
- Liver function tests (AST, ALT, total bilirubin, conjugated and unconjugated bilirubin, alkaline phosphatase, and Gamma Glutamyl Transpeptidase- GGT). ALT and AST were assayed using spectrophotometry. The normal reference values used in UBTH are ALT ≤ 12 U/L and AST ≤ 12 U/L following the recommendations of the manufacturer of the kits. Like ALT/AST assays, other LFTs were done using spectrophotometry.
- Hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus were determined using the global diagnostic rapid tests and ELISA kits.
- CD4 cell count was done using Cyflow automated machine.

The patients were then commenced on any of the HAART regimens below based on the protocol used in PEPFAR clinic in UBTH, which corresponds with the Nigerian National guidelines for initiating HAART.[13]

Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV)

Zidovudine (ZVD\AZT) + Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV)

Tenofovir (TDF) or Abacavir (ABC) + Emtricitabine (FTC) or Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV)

Didanosine (ddI) + Lamivudine (3TC) or Emtricitabine (FTC) + Nevirapine (NVP) or Efavirenz (EFV).

After 4 weeks of therapy, 5 ml of venous blood was collected from each patient and this was used for analysis of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum bilirubin, and alkaline phosphatase. This was again repeated at the 12th and 24th week of therapy. The controls were followed up 3 monthly, during the period of the study, with CD4 counts for evidence of deterioration and possible commencement of HAART. Five milliliters of venous blood was also collected from the controls at baseline, 4, 12, and 24 weeks just as for the cases. Those patients that had elevated liver enzymes had a repeat screening for HBsAg and anti-HCV if they were negative at the initial screening.

Those who tested positive for HBsAg or anti-HCV on recruitment had a repeat screening at 24 weeks to establish persistence of infection. This was done for both the cases and controls.

Definition of Hepatotoxicity

A standardized toxicity grade scale, modified from that used by the AIDS clinical trial group which is now widely used,[3,10,14] was employed in this study. Patients' serum ALT or AST levels within normal range were classified based on changes relative to ULN (ALT ≤ 12 U/L, AST ≤ 12 U/L) as follows:

Grade 0 = value < 1.25 × ULN

Grade 1=value within 1.25 – 2.5×ULN
Grade 2=value within 2.6 – 5×ULN
Grade 3=value within 5.1 – 10×ULN
Grade 4=value>10×ULN.

Changes in serum total bilirubin (TBR) were classified based on changes relative to ULN:
Grade 0=value<1.1×ULN
Grade 1=value within 1.1 – 1.5×ULN
Grade 2=value within 1.6 – 2.9×ULN
Grade 3=value within 3 – 5×ULN
Grade 4=value>5×ULN.

For the purpose of analysis, grades 1 and 2 were grouped as mild-to-moderate hepatotoxicity and grades 3 and 4 as severe hepatotoxicity.[15]

Elevations in levels of alkaline phosphatase were interpreted as evidence of cholestasis.

Clinical Manifestations

The clinical features assessed include abdominal pain, nausea/vomiting, jaundice, and rash. This was recorded at baseline, 4, 12, and 24 weeks.

Statistical analysis

The data obtained were analyzed using the statistical package for social sciences (SPSS) version 15.0. The Chi-square test was used to compare the various ARV regimens and hepatotoxicity. It was also used to compare risk factors for hepatotoxicity such as hepatitis B or C coinfection, alcohol use, and underweight. The student *t*-test was used for continuous variables. Two-way analysis of variance (ANOVA) was used to compare means of variables involving more than two groups. The level of significance was set at *P* value<0.05 and confidence level at 95%.

Results

A total of 84 patients and 42 controls were used for the study. Each patient and control were followed up for 24 weeks and the results were analyzed. Baseline characteristics were recorded as median and interquartile range for continuous variables and percentages for categorical variables. The baseline characteristics of the cases and controls are summarized in Table 1. The controls had a significantly greater amount of alcohol consumption than the cases; however, both groups were similar regarding other factors such as BMI, HBsAg, anti-HCV, CD4 cell count, ALT, AST, ALP, TBR, PCV, sex, and age.

All 84 cases were commenced on HAART. The most commonly used regimens were Lamivudine, Zidovudine, Nevirapine (LZN) accounting for 50 (59.5%) of cases. This was followed by Lamivudine, Stavudine, Nevirapine (LSN) which were used in 14 (16.7%) of the cases. Tenofovir, Emtricitabine, Nevirapine (TEN), and Lamivudine, Zidovudine, Efavirenz (LZE) each were prescribed for 6 (7.1%) of cases. Tenofovir, Emtricitabine, Efavirenz (TEE), Lamivudine, Stavudine, Efavirenz (LSE), and Lamivudine, Emtricitabine, Effavirenz (LEE) each were used in 5 (6.0%), 2 (2.4%), and 1 (1.2%) of cases respectively as shown in Table 2.

Table 1: Baseline characteristics of the study population

	Control *n*=42	Cases *n*=84	*P* value
Sex			
Male	8 (19%)	23 (27.4%)	0.306
Fmale	34 (81%)	61 (72.6%)	
Age (years)	34 (30–41)	32 (28–40)	0.439
PCV (%)	35 (33–37)	32 (28–35)	0.124
ALT (U/l)	8.5 (8–10)	8 (7–10)	0.133
AST(U/l)	11 (10–12)	11.5 (10–12)	0.324
ALP (U/l)	14 (10–28)	18 (14–25)	0.088
GGT (U/l)	14 (10–28)	20 (18–22)	0.085
TBR (mg/dl)	0.8 (0.2–1.0)	0.7 (0.4–1.0)	0.648
Conj BR (mg/dl)	0.4 (0.08–0.5)	0.4 (0.2–0.5)	0.324
Total protein (g/dl) 6 (5.8–6.6)	6 (5.6–6.5)	0.183	
Albumin (g/dl)	3.6 (3.5–4.0)	3.5 (3.2–3.8)	0.125
CD4 counts/ml	510 (431.8–656.3)	168 (88.8–250.5)	0.248
Total WBC. ($\times10^9$ counts/l)	5.2 (4.4–6.1)	3.8 (2.9–4.7)	0.124
Lymphocytes ($\times10^9$ counts/mm^3)	2.1 (1.8–2.8)	1 (0.9–1.6)	0.052
Neutrophils ($\times10^9$ counts/mm^3)	2.2 (1.6–2.9)	1.9 (1.6–2.6)	0.613
HbsAg	1 (2.4%)	2 (2.4%)	0.707
Anti-HCV	1 (2.4%)	1 (1.2%)	0.557
Alcohol (g/day)	31 (28–36)	9 (3–18)	0.030
BMI (kg/m^2)	24.5 (21.2–28.5)	22.5 (20.1–26.3)	0.462

Continuous variables are expressed as median (interquartile), and categoric variables are expressed as absolute numbers (%). PCV = Packed cell volume, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ALP = Alkaline phosphatase, GGT = Gamma glutamyl transpeptidase, TBR = Total bilirubin, Conj BR = Conjugated bilirubin, WBC = White blood cell count, HBsAg = Hepatitis B surface antigen, Anti HCV = hepatitis C virus antibodies

Table 2: Distribution of HAART regimens among cases

HAART regimen	Frequency
LZN	50
LSN	14
TEN	6
LZE	6
TEE	5
LSE	2
LEE	1
Total	84

LZN = Lamivudine+Zidovudine+Nevirapine, LZE = Lamivudine+Zidovudine+Efaviranz, TEE = Tenofovir+Emtricitabine+Efaviranz, LSE = Lamivudine+Starvudine+Efavirenz, LSN = Lamivudine+Stavudine+Nevirapine, TEN = Tenofovir+Emtricitabine+Nevirapine, LEE = Lamivudine+Emtricitabine+Effavirenz

Of the 84 cases analyzed, 10.71% (9 cases) had severe hepatotoxicity while 7.14% (6 cases) had mild-to-moderate hepatotoxicity. In contrast, of the 42 controls, none (0) had severe hepatotoxicity while 9.52% (4 cases) had mild-to-moderate hepatotoxicity as shown in Table 3. There was a statistically significant difference in severe hepatotoxicity between cases and controls (χ^2=4.846, df=1, P=0.028).

Five of the 15 cases of hepatotoxicity in the cases (33.3%) occurred by 4 weeks of therapy, 53.3% (8 of 15 cases) occurred by 12 weeks while the remaining 13.3% (2 of 15 cases) occurred by 24 weeks. This is depicted in Table 4. Thus 86.6% of cases of hepatotoxicity occurred within 12 weeks of therapy.

Of the 84 cases, 5 (6.0%) developed clinical symptoms after commencement of HAART; rashes occurred in 3 (3.6%) and 2 (2.4%) had nausea and vomiting. Hepatotoxicity (mild to moderate) was identified in one patient who developed rash at 4 weeks accounting for 6.7% (1 of 15 cases) of patients with hepatotoxicity. This is shown in Table 5. There was however no significant association between hepatotoxicity and clinical symptoms (χ^2=1.803, df=2, P=0.406).

Table 3: Incidence of hepatotoxicity in cases and control

Hepatotoxicity	Cases (%)	Control (%)	*P* value
None	69 (82.14)	38 (90.48)	0.028
Mild/moderate	6 (7.14)	4 (9.52)	
Severe	9 (10.71)	0	
Total	84 (100)	42 (100)	

Table 4: Comparison of grades of ALT/AST with TBR and ALP

Grades	ALT and/or AST (4 weeks)	ALT and/or AST (12 weeks)	ALT and/or AST (24 weeks)	TBR (weeks 4–24)	ALP
Normal	73	64	69	84	84
Grade 0	6	7	0	0	0
Grade 1	1	2	3	0	0
Grade 2	1	3	3	0	0
Grade 3	3	8	9	0	0
Grade 4	0	0	0	0	0
Total	84	84	84	84	84

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBR = Total bilirubin. Between hepatotoxicity and chronic hepatitis B in the cases, χ^2=17.073, df=2, Fisher's P=0.0146, and in controls, χ^2=9.732, df=1, P=0.010

Table 5: Clinical manifestation of hepatotoxicity

Clinical manifestation	Hepatotoxicity			*P* value
	Yes	No	Total	
None	14	65	79	0.406
Rash	1	2	3	
Nausea and vomiting	0	2	2	
Total	15	69		84

Discussion

In this study, the overall incidence of hepatotoxicity of HAART was 17.85%. This includes severe (grade 3 and 4 ALT/AST elevation) and mild to moderate (grades 1 and 2 changes) hepatotoxicities. Severe hepatotoxicity occurred in 10.71% of the patients while mild to moderate accounted for 7.14%. The overall finding contrasts with a study conducted in Madrid, Spain, where the overall incidence of hepatotoxicity was 31% but severe hepatotoxicity is similar to their finding of 9%.[16] A similar study was carried out in New York where hepatotoxicity was analyzed as mild to moderate (grades 1 and 2) and severe (grades 3 and 4) and a low incidence of 1.1% was reported for severe hepatotoxicity.[15] The analysis of hepatotoxicity as severe and mild-to-moderate hepatotoxicity is often ignored by most investigators because mild-to-moderate hepatotoxicity resolves whether antiretroviral therapy is continued or not and are of limited clinical relevance.[3] The incidence of severe hepatotoxicity after HAART as reported by most clinical trials ranges between 1% and 18%.[6,7,16] The finding of 10.7% in this study falls within that range. Among controls, 4.8% (4 of 42) had mild-to-moderate hepatotoxicity, none had severe hepatotoxity. This contrasts sharply with the finding of severe hepatotoxicity of 10.7% and mild-to-moderate hepatotoxicity of 7.1% in cases. One explanation for the occurrence of hepatotoxicity in controls would be the consumption of alcohol (median 31 g/day) in these patients. Others include a flare up of viral hepatitis, HIV itself and probably the small sample size of the controls. There was a statistically significant difference between the frequency of severe hepatotoxicity in the cases compared with the controls (χ^2=4.846, df=1, P=0.028).

In this study 33.3% (5 of 15) of cases of hepatotoxicity occurred at 4 weeks of therapy, 53.3% (8 of 15) at 12 weeks while 13.3% (2 of 15) occurred at 24 weeks. This shows that 86.6% of cases occurred within 12 weeks of therapy. This finding compares favorably with the study done in South Africa where 80% of their patients developed hepatotoxicity within the first 12 weeks.[9] In contrast, the study conducted in Spain reported 60% of cases of hepatotoxicity occurring after the first 12 weeks and suggested that liver enzyme elevations occurred as a consequence of a toxic cumulative effect. The finding in this study strengthens previous definition of drug-induced hepatotoxicity as an acute event occurring within the preceding 3 months of commencement of the drug.[17,18] This has made some investigators to separate the first 12 weeks of therapy from the complete treatment episode.[3] The occurrence of five cases of hepatotoxicity at 4 weeks and eight cases at 12 weeks would suggest different mechanisms, the former due to hypersensitivity reaction and the latter due to mitochondrial toxicity.[15] Two cases still occurred at 24 weeks suggesting that in HIV patients on HAART, hepatotoxicity still occurs after 12 weeks though with a decreasing frequency.

This study shows that over 94% of patients with hepatotoxicity were asymptomatic. This is similar to previous reports where the majority of HIV patients on HAART had asymptomatic enzyme elevations.[4,19] However, this study did not show manifestation of hepatotoxicity in the form of clinical features such as abdominal pain, nausea and vomiting, rash or jaundice. This contrasts sharply with a report from South Africa where rash and nausea were independently associated with hepatotoxicity.[9] On the other hand, most other studies did not relate clinical manifestations with hepatotoxicity.[8,14,16]

In summary, over 80% of liver enzyme elevations occurred within 3 months and were mostly asymptomatic. There is a need for regular monitoring of liver function tests (ALT/AST), at short intervals, in HIV patients starting HAART because of the risk of early hepatotoxicity and asymptomatic presentations.

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