Effect of anemia on hepatotoxicity of HAART in HIV patients in Benin city

Rose A. Ugiagbe, Emeka U. Eze

Department of Medicine, Gastroenterology Unit, †Dermatology Unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria

ABSTRACT

Background: Hepatotoxicity is a relevant adverse effect of highly active antiretroviral treatment owing to its frequency, and it can cause interruption of therapy, hepatitis, and death. There is dearth of information on hepatotoxicity arising from highly active antiretroviral therapy (HAART) in anemic patients. Anemia is the most common symptom in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome. We studied the effect of anemia on hepatotoxicity in HIV patients who were about to start HAART, attending clinic, or in the medical wards. Materials and Methods: This was a prospective study in which patients were recruited consecutively and followed up for 24 weeks. Results: In all, 84 patients were recruited and 42 were enrolled as controls. The mean ages of the cases and controls were 35.2±9.9 and 35.5±9.0 years, respectively. The age range of the cases was 18-68 years with a median age of 31.5 years, whereas the mean age of the controls was 20-57 years with a median age of 33.5 years. There was no difference (t=0.197, df=124, and P=0.844). There were 61 females (72.6%) and 23 males (27.4%) in the cases, whereas in the controls, there were 34 females (81.0%) and 8 males (19.0%). Among the cases, 30 (35.7%) were anemic, while 54 (64.3%) were not anemic. Six (20%) of the anemic patients had hepatotoxicity, and 9 (16.7%) of the patients with normal packed cell volume had hepatotoxicity. Among the controls, all 42 (100%) patients had normal packed cell volume. Four (9.5%) of the patients had hepatotoxicity. There was no association between hepatotoxicity and anemia (χ²=3.243, df=2, P=0.198). Conclusion: Anemia did not affect hepatotoxicity of HAART in this study.

Key words: Anemia, hepatotoxicity, hepatotoxicity of highly active antiretroviral treatment

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS), first recognized in 1981 is caused by human immunodeficiency virus (HIV)-1.1 Sequence analysis estimates that HIV was introduced into humans in the early 1930s, and it is the fourth leading cause of mortality worldwide. About 42 million people are living with HIV/AIDS, 70% are in Africa and 15% in Asia. The prevalence in sub-Saharan Africa is more than 8%.2 The seroprevalence of HIV/AIDS in Nigeria increased from 1.8% in 1991 to 5.8% in 2001.3 The current national seroprevalence (2008) is 4.6% in Benin city, Edo state. Thus, Nigeria with a population figure of 140,000,000 persons (2006 census) and 4.6% prevalence of HIV/AIDS ranks the third highest in the world.2

The introduction of highly active antiretroviral therapy (HAART)1-3 in 1996 led to a dramatic and sustained decrease in HIV-related morbidity and mortality.4 Nevertheless, issues on adherence and adverse effects have become evident as limiting causes of benefit in a substantial proportion of individuals.5 Indeed the use antiretroviral therapy (ART) is often complicated by drug-related toxicities.

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, clinical hepatitis, and death, and all antiretroviral drugs are potentially hepatotoxic.6-9 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%.10,11

There is dearth of information on hepatotoxicity of HAART in Nigeria as studies are hardly cited in the literature. A prospective cohort study conducted in Jos, Nigeria, reported a low incidence of hepatotoxicity of HAART of
Hepatotoxicity due to mitochondrial toxicity has been associated with all nucleoside analogs. Hepatotoxicity may also be due to hypersensitivity reactions mostly observed with non-nucleoside reverse transcriptase inhibitors. Other pathogenic mechanisms of hepatotoxicity include drug interactions and immune reconstitution disease. The possible explanation of the interaction of anemia with hepatotoxicity via any of these mechanisms is presently at best conjectural.

The risk factors associated with HAART-induced hepatotoxicity are similar for the different classes of antiretroviral drugs. They include higher baseline alanine aminotransferase levels, chronic hepatitis B virus (HBV) or HCV infection, antiretroviral therapy-naive patient undergoing their first HARRT regimens, recent start of a regimen of nevirapine or high-dose ritonavir, female sex, and in HBV co-infected patient, discontinuing lamivudine (3TC). Others include illicit drug or medication abuse and abnormal metabolic syndromes.

Hepatotoxicity in patients with HIV may be caused by multiple factors in addition to ART. These include HIV itself, HBV, HCV, systemic opportunistic infections, malignancies, and other hepatotoxic drugs, for example anti-bacteria and anti-convulsants. Others are illicit drug or medication abuse, alcohol consumption, and abnormal body mass index.

Several studies have shown anemia to be very common, in fact among the most common presenting symptom in HIV/AIDS patients. One study of 13,315 patients showed that incidence of anemia was associated with clinical stage of disease: 1-year incidence was 3.2% for 6,094 patients with HIV infection but not AIDS, 12.1% for 2,579 patients with immunologic AIDS (CD4 of <200/μL or CD4 percentage of <14), but not clinical AIDS, and 36.9% for 4,642 patients with clinical AIDS. In all groups there were 2,222 anemia diagnoses, of which 494 (22.2%) were drug related. Most diagnoses (1,311, 59%) were based only on low hemoglobin level; 505 diagnoses (23%) were based only on ICD-9 codes, and 406 diagnoses (18%) were based both on hemoglobin level and ICD-9 codes. The incidence of anemia differed by race/ethnicity, stage of disease, presence of concurrent illnesses, and prescription of chemotherapeutic agent. Anemia, whether drug-related or unrelated to drugs, was positively associated with clinical AIDS, a CD4 count of <200, bacterial septicemia, neutropenia, thrombocytopenia, prescription of ganciclovir, and prescription of fluconazole and negatively associated with the prescription of TMP-SMX. In addition, drug-related anemia was positively associated with prescription of ZDV. Anemia unrelated to drugs was also associated with black race, female sex, and lymphoma and was negatively associated with prescription of ZDV.

Despite its frequency of occurrence in HIV patients, anemia has not been shown in this locale to have any effect on the hepatotoxicity of HAART. There is paucity of data on this subject. This study therefore seeks to determine the effect of anemia on hepatotoxicity of HAART in Nigerian people living with HIV/AIDS.

**MATERIALS AND METHODS**

The study was carried out in the Department of Medicine, University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria. This hospital accepts referrals from Edo State and neighboring states including Delta, Ondo, Ekiti, Anambra, and Kogi States. It was carried out on patients with HIV starting HAART, attending Infectious Disease Clinic, Gastroenterology Clinic, or admitted into the medical wards. Age- and sex-matched patients with HIV but who were not yet qualified to be started on HAART, following the national guidelines, served as controls. Consent patients were recruited consecutively until the target study population was reached, and each patient was followed up for 24 weeks. The duration of the study was from July 2008 to June 2009. The study design was a prospective cohort study. Patients were eligible if they were newly diagnosed with HIV and normal liver function tests (LFTs), and commencing HAART. Exclusion criteria included patients with HIV and pulmonary tuberculosis, pregnant women, patients with HIV already on HAART, recent HBV or HCV infection. Patients with abnormal LFTs were also excluded. Informed and written consent was sought from each patient before enrolment into the study. The approval of the Hospital Ethics Committee was obtained. The sample size was determined using the Fisher formula. Thus, using a seroprevalence of HAART-induced hepatotoxicity of 5.6% found in a previous study, the minimum sample size was 81. However, 84 cases were used.

Each patient had a detailed history including alcohol use and drug history and a physical examination. Using a sterile disposable 10-mL syringe and needle, 10 mL of venous blood was collected from the cubital fossa of each patient and this was used for laboratory analysis. One milliliter of blood was collected in a K3 EDTA specimen bottle for total white blood cell count, differentials, absolute lymphocyte count, and packed cell volume (PCV) determination. The remaining blood sample was placed in lithium heparin and plain specimen bottles and sent to the chemistry laboratory for analysis.

The following investigations were carried out on each patient:

- PCV and white blood cell count (total, differential and absolute lymphocyte count) were done using Symex automated machine.
- LFTs (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, conjugated...
and unconjugated bilirubin, alkaline phosphatase and gamma glutamyl transpeptidase). ALT and AST were assayed using spectrophotometry. The normal reference values used in UBTH were 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 HCV were performed using the Global Diagnostic rapid tests and ELISA KITS.
- CD4 cell count was done using Cyflow automated machine.

All laboratory investigations were carried out at the University of Benin Teaching Hospital Haematology and Chemistry Laboratories according to standard procedures and manufacturer’s instructions.

The patients were then commenced on any of the HAART regimens below based on the guidelines used in PEPFAR clinic in UBTH which corresponds with those approved by the National Antiretroviral Drug Guidelines of Nigeria; 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 ALT, serum AST, and serum bilirubin. This was again repeated at the 12th and 24th weeks of therapy. This was applied to both the subjects and controls. Those patients who showed signs of hepatitis 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 (both cases and controls) had a repeat screening at 24 weeks to establish chronicity.

A standardized toxicity grade scale, modified from that used by the AIDS clinical trial group which is now widely used,6,12,15 was used in this study. Patients with pre-treatment serum ALT or AST levels within normal range (ALT≤12 U/L and AST≤12 U/L) were classified based on changes relative to upper limit of normal (ULN) 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 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.21

The data obtained were analyzed using the statistical package for social sciences (SPSS) version 15.0. Chi-square test was used to compare the various anti-retroviral drug regimens and hepatotoxicity. The Student’s t-test was used for continuous variables. Two-way analysis of variance 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 this study. Each patient was followed up for 24 weeks, and the results were analyzed.

The mean ages of the cases and controls were 35.2±9.9 and 35.5±9.0 years, respectively. The age range of the cases was 18-68 years with a median age of 31.5 years, whereas the age range of the controls was 20-57 years with a median age of 33.5 years. The age distribution of the cases and controls is as shown in **Figure 1**. There was no significant difference in the mean ages of the cases and controls (t=0.197, df=124, P=0.844). There were 61 females (72.6%) and 23 males (27.4%) in the case group, whereas in the control group, there were 34 females (81.0%) and 8 males (19.0%) as shown in **Figure 2**. There was no significant difference in the sex distribution between the cases and controls (χ²=1.048, df=1, P=0.306).

All 84 cases were commenced on HAART. The most commonly used regimen was Lamivudine, Zidovudine,

![Figure 1: Age distribution of cases and controls](image-url)
Table 1: Distribution of HAART regimens among cases

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

LZN = Lamivudine + Zidovudine + Nevirapine; LSN = Lamivudine + Stavudine + Nevirapine; TEN = Tenofovir + Efavirenz + Lamivudine + Stavudine; TEE = Tenofovir + Emtricitabine + Efavirenz; LSE = Lamivudine + Emtricitabine + Efavirenz; LSZ = Lamivudine + Stavudine + Zidovudine

Table 2: Incidence of hepatotoxicity in cases and controls

| Hepatotoxicity | Cases, n (%) | Control, n (%) |
|----------------|--------------|----------------|
| None           | 69 (82.14)   | 38 (90.48)     |
| Mild/moderate  | 5 (6.0%)     | 4 (9.52)       |
| Severe         | 2 (2.4%)     | 0              |
| Total          | 84 (100)     | 42 (100)       |

$\chi^2 = 4.846, df = 1, P = 0.028$

Table 3: Relationship between hepatotoxicity and alcohol intake

| Hepatotoxicity | Cases Alcohol intake | Controls Alcohol intake | $P$ values |
|----------------|----------------------|-------------------------|------------|
|                | Yes      | No       | Yes       | No       |            |
| None           | 10       | 59       | 2         | 36       | Cases, $P=0.019$ Controls, $P=0.0041$ |
| Mild to moderate| 3        | 3        | 2         | 2        |            |
| Severe         | 4        | 5        | 0         | 0        |            |
| Total          | 17       | 67       | 4         | 38       |            |

Table 4: Relationship between hepatotoxicity and chronic hepatitis B

| Hepatotoxicity | Cases HBsAg | Controls HBsAg | $P$ values |
|----------------|-------------|---------------|------------|
|                | Positive    | Negative      |            |
| None           | 0           | 69            | 0          | 38        | Cases, $P=0.0246$ Controls, $P=0.010$ |
| Mild to moderate| 0          | 6             | 1          | 3         |            |
| Severe         | 2           | 7             | 0          | 0         |            |
| Total          | 2           | 82            | 1          | 41        |            |

Among cases, 17 of 84 (20.2%) had taken alcohol (median 9 g/day, range 3-18 g/day) and 7 of the 17 (41.2%) developed hepatotoxicity, while 10 (58.8%) had no hepatotoxicity. Among controls, 4 of 42 (9.5%) had taken alcohol (median 31 g/day, range 28-36 g/day), and 2 of the 4 (50%) developed hepatotoxicity as shown in Table 3. There was a significant association between hepatotoxicity and alcohol intake in both the cases ($\chi^2=7.970, df=2, P=0.019$) and the controls ($\chi^2=8.406, df=1, P=0.004$) respectively. All patients, cases, and controls, who had taken alcohol during the study, had taken <20 g/day and <40 g/day, respectively.

Two of the 84 cases (2.4%) were positive for HBsAg at the beginning and at 24 weeks. One had severe hepatotoxicity at 4 weeks and the second at 12 weeks. In comparison, 1 of the 42 controls (2.4%), who was positive at the beginning and at 24 weeks, also developed mild to moderate hepatotoxicity (4 weeks). This is shown in Table 4. There was a significant association between hepatotoxicity and chronic hepatitis B in the cases ($\chi^2=17.073, df=2, Fisher’s P=0.0146$) and in the controls ($\chi^2=9.732, df=1, P=0.010$).

One of the 84 cases (1.2%) that was positive for anti-HCV at the beginning and at 24 weeks developed severe hepatotoxicity at 4 weeks. One of the 42 (2.4%) controls who tested positive to anti-HCV at the beginning and at 24 weeks developed mild to moderate hepatotoxicity (4 weeks). This is shown in Table 5. There was no association between hepatotoxicity and chronic hepatitis C infection in the cases ($\chi^2=8.434, df=2$, Fisher’s $P=0.179$) and in the controls ($\chi^2=9.732, df=1$, Fisher’s $P=0.095$), respectively.

Table 6 shows that among the cases, 30 (35.7%) were anemic, while 54 (64.3%) were not anemic. Six (20%) of

Figure 2: Sex distribution of cases and controls

Nevirapine (LZN) accounting for 50 (59.5%) of the cases. This was followed by Lamivudine, Stavudine, Nevirapine (LSN) which was used in 14 (16.7%) of the cases. Tenofovir, Emtricitabine, Nevirapine (TEN) and Lamivudine, Zidovudine, Efavirenz (LZE) each was prescribed for 6 (7.1%) of the cases. Tenofovir, Emtricitabine, Efavirenz (TEE), Lamivudine, Stavudine, Efavirenz (LSE), and Lamivudine, Stavudine, Zidovudine (LSZ) each was used in 5 (6.0%), 2 (2.4%), and 1 (1.2%) of the cases, respectively, as shown in Table 1.

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

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In this study, the overall incidence of hepatotoxicity of HAART was 17.9%. This includes severe (grades 3 and 4 ALT/AST elevation) and mild to moderate (grades 1 and 2 changes) hepatotoxicities. Severe hepatotoxicity occurred in 10.7% of the patients, while mild to moderate accounted for 7.1%. 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%. 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.

Hepatotoxicity was associated with alcohol intake in this study both in the cases and controls. The association of hepatotoxicity with alcohol intake in this study where no patient took >40 g/day suggests that HIV patients would appear to be more sensitive to alcohol toxicity. Hepatitis B but not C infection was associated with hepatotoxicity in this study. The low frequency of occurrence of the infections, 2.4% and 1.2% for hepatitis B and C, respectively, limits the interpretation of data. The low frequencies of these infections recorded in this study may be because of exclusion of patients with abnormal LFTs at baseline from the study which may have led to exclusion of some patients with chronic hepatitis B and/or C from the study.

Anemia unrelated to drugs is associated with black race, female sex, and lymphoma. Despite its frequency of occurrence in HIV patients, anemia has not been shown in this locale to have any effect on the hepatotoxicity of HAART. There is paucity of data on this subject. Several other studies done relating to this subject looked at anemia as a result of hepatotoxicity, not as a factor influencing hepatotoxicity. They found that HAART could cause anemia. No study was found in literature looking at anemic HIV-positive, HAART-naive patients, and the incidence of hepatotoxicity to HAART in them. This study, however, looked at anemic HIV patients starting HAART and followed them up to see if they had more or less hepatotoxicity.

There was no significant association between hepatotoxicity and anemia ($\chi^2=3.243$, df=2, $P=0.198$). Anemia did not affect hepatotoxicity of HAART in this study. There is a paucity of studies on this subject and this finding is important because several HIV/AIDS patients are anemic and it shows that the anemia in HIV does not increase the risk of hepatotoxicity when HAART is introduced.

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