Liver Enzymes Abnormalities among Highly Active Antiretroviral Therapy Experienced and HAART Naïve HIV-1 Infected Patients at Debre Tabor Hospital, North West Ethiopia: A Comparative Cross-Sectional Study

Melashu Balew Shiferaw, Ketema Tafess Tulu, Amtatachew Moges Zegeye, and Amarech Asratie Wubante

1Bahir Dar Regional Health Research Laboratory Center, Bahir Dar, Ethiopia
2Department of Biomedical Science, School of Health and Hospital, Adama Science and Technology University, Asella, Ethiopia
3North Shoa Zone Health Department, Debre Berhan, Ethiopia
4West Gojjam Zone Health Department, Finote Selam, Ethiopia

Correspondence should be addressed to Melashu Balew Shiferaw; bmelashu@gmail.com

Received 26 February 2016; Revised 26 May 2016; Accepted 16 June 2016

Academic Editor: Patrice K. Nicholas

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Liver disease has emerged as the most common non-AIDS-related cause of death in HIV patients. However, there is limited data regarding this condition including our setting in Ethiopia. Hence, liver enzyme abnormalities among highly active antiretroviral therapy (HAART) experienced and HAART naïve patients were assessed in this study. A total of 164 HAART experienced and 164 HAART naïve patients were studied. Blood specimen was collected to determine alanine aminotransferase (ALT) and aspartate aminotransferase (AST), CD4 count, and viral hepatitis. The prevalence of liver enzyme abnormality was 20.1% and 22.0% among HAART experienced and HAART naïve patients, respectively. The HAART experienced patients had higher mean ALT than HAART naïve patients \((P = 0.002)\). Viral hepatitis (AOR = 6.02; 95% CI = 1.87–19.39), opportunistic infections (AOR = 2.91; 95% CI = 1.04–8.19), current CD4 count <200 cells/mm\(^3\) (AOR = 2.16; 95% CI = 1.06–4.39), and male sex (AOR = 1.83; 95% CI = 1.00–3.33) were associated with elevated ALT and/or AST. In conclusion, liver enzyme abnormalities were high in both HAART experienced and HAART naïve HIV-1 infected patients. Hence, monitoring and management of liver enzyme abnormalities in HIV-1 infected patients are important in our setting.

1. Introduction

Liver disease has emerged as the most common non-AIDS-related cause of death among HIV infected patients, accounting for 14–18% of all deaths [1, 2]. Nearly half of deaths among hospitalized HIV infected patients in the HAART era have been attributed to liver disease [3, 4]. It ranges from asymptomatic mild elevations of liver enzymes to cirrhosis and end stage liver disease with all its complications (e.g., ascites, esophageal varices, and hepatic encephalopathy). Liver cirrhosis is a more serious consequence with an estimated overall prevalence of 8.3% in HIV infected persons [5].
2.3. Data Collection Procedure and Quality Control.
The prescribed dosages for a regimen included a prescribed dose regimen. Good Adherence. HIV-1 patients had taken biomarkers (ALT and AST) were determined using a machine (BECTON DICKINSON, USA). Liver enzyme determination and viral hepatitis screening. In addition, around 3 mL of venous blood was collected in a vacutainer tube with Ethylenediaminetetraacetic Acid (EDTA) anticoagulant to measure CD4 count using BD FACS count machine (BECTON DICKINSON, USA). Liver enzyme biomarkers (ALT and AST) were determined using 5010 photometer (ROBERT RIELE GmbH & Co. KG, Germany). Upper limit normal values were defined as ALT = 34 IU/L and AST = 31 IU/L for women and ALT = 45 IU/L and AST = 35 IU/L for men. Liver enzyme abnormalities were graded as follows: 1.25–2.5X the upper limit of normal (ULN) (grade 1), 2.6–5X ULN (grade 2), 5.1–10X ULN (grade 3), and >10X ULN (grade 4) [16]. Viral hepatitis (HBV and HCV) was screened using commercially available test kits for HBsAg (Ameritech-China, Ltd., USA) and for anti-HCV (Wondfo Biotech Co., Ltd., Guanzhoun, China).

To assure the quality of the data, the questionnaire was pretested. Two-day training was given to data collectors. Every day, the collected data were reviewed and checked for completeness. Standardized operating procedures and manufacturer's instructions were strictly followed for all laboratory procedures. Controls (Humatrol N and Humatrol P) were used for liver function tests in each test procedure. ELISA confirmed positive and negative samples were used in each test procedure for HBV and HCV testing kits performance checkup.

2.4. Data Processing and Analysis. The collected data were double-entered into EPI info version 7.0 to ensure data quality. The data were analyzed using SPSS version 20. Descriptive and summary statistics were calculated. ALT and AST enzyme levels were determined. The Mann Whitney U test and the independent t-test were used to compare non-parametric and parametric variables, respectively. Variables with P value ≤ 0.2 in the bivariate analysis were entered into multivariate analysis in backward LR method. P value < 0.05 in the multivariate analysis was taken as significant factor for elevated liver enzyme.

2.5. Ethical Consideration. Ethical clearance was obtained from University of Gonder School of Biomedical and Laboratory Sciences Ethical Review Committee. Official permission was obtained from Debre Tabor Hospital. Each study participant was informed about the purpose of the study and written informed consent was obtained from them. Results were kept confidential and abnormal results were reported to the physicians and professional nurses working at Debre Tabor Hospital HIV Clinic for management.

3. Results

3.1. Sociodemographic Characteristics. A total of 164 HAART experienced and 164 HAART naïve HIV infected patients participated in this study. The mean ages of the HAART experienced and HAART naïve groups were 36.29 ± 10.27 and 34.41 ± 10.73 years, respectively. Ninety (54.9%) HAART experienced and 111 (67.7%) HAART naïve patients were males. Most of the subjects were illiterate and married in 60 (36.6%) and 74 (45.1%) of HAART experienced groups, respectively (Table 1).

2.3. Data Collection Procedure and Quality Control. The HAART experienced group had 135 (±91.35) cells/mm³ mean
### Table 1: Sociodemographic characteristics of study participants, 2013.

| Characteristics   | HAART status |
|-------------------|--------------|
|                   | On HAART (%) | HAART naive (%) |
| Sex               |              |                |
| Male              | 74 (45.1)    | 53 (32.3)      |
| Female            | 90 (54.9)    | 111 (67.7)     |
| Age in years      |              |                |
| <25               | 12 (7.3)     | 32 (19.5)      |
| 25–34             | 59 (36.0)    | 58 (35.4)      |
| 35–44             | 59 (36.0)    | 43 (26.2)      |
| >44               | 34 (20.7)    | 31 (18.9)      |
| Education         |              |                |
| Illiterate        | 60 (36.6)    | 77 (47.0)      |
| Elementary        | 52 (31.7)    | 41 (25.0)      |
| High school       | 29 (17.7)    | 21 (12.8)      |
| College & above   | 23 (14.0)    | 25 (15.2)      |
| Marital status    |              |                |
| Single            | 32 (19.5)    | 30 (18.3)      |
| Married           | 74 (45.1)    | 72 (43.9)      |
| Divorced          | 29 (17.7)    | 39 (23.8)      |
| Widowed           | 29 (17.7)    | 23 (14.0)      |
| Residence         |              |                |
| Rural             | 32 (19.5)    | 50 (30.5)      |
| Urban             | 132 (80.5)   | 114 (69.5)     |

HAART: highly active antiretroviral therapy.

### Table 2: Clinical and immunological profile of HIV-1 patients at Debre Tabor Hospital, 2013.

| Variables          | HAART status |
|--------------------|--------------|
| WHO stage          |              |
| Stage I            | 34 (20.7)    | 97 (59.1)     |
| Stage II           | 40 (24.4)    | 44 (26.8)     |
| Stage III          | 64 (39.0)    | 19 (11.6)     |
| Stage IV           | 26 (15.9)    | 4 (2.4)       |
| OIs                |              |
| No                 | 150 (91.5)   | 134 (81.7)    |
| Yes                | 14 (8.5)     | 30 (18.3)     |
| BMI (kg/m^2)       |              |
| <18.5              | 39 (23.8)    | 40 (24.4)     |
| 18.5–25            | 113 (68.9)   | 116 (70.7)    |
| >25                | 12 (7.3)     | 8 (4.9)       |
| HBV                |              |
| Negative           | 156 (95.1)   | 152 (92.7)    |
| Positive           | 8 (4.9)      | 12 (7.3)      |
| HCV                |              |
| Negative           | 163 (99.4)   | 162 (98.8)    |
| Positive           | 1 (0.6)      | 2 (1.2)       |
| Regimen            |              |
| 1a                 | 52 (31.7)    | —             |
| 1b                 | 28 (17.1)    | —             |
| 1c                 | 40 (24.4)    | —             |
| 1d                 | 10 (6.1)     | —             |
| 1e                 | 18 (11.0)    | —             |
| 1f                 | 16 (9.8)     | —             |
| Hepatotoxicity     |              |
| Grade 1            | 11 (6.7)     | 17 (10.4)     |
| Grade 2            | 6 (3.7)      | 0             |
| Grade 3            | 5 (3.0)      | 1 (0.6)       |

WHO: World Health Organization; OI: opportunistic infection; BMI: body mass index; HBV: hepatitis B virus; HCV: hepatitis C virus; HAART: highly active antiretroviral therapy; 1a: d4T+3TC+NVP; 1b: d4T+3TC+EFV; 1c: AZT+3TC+NVP; 1d: AZT+3TC+EFV; 1e: TDF+3TC+EFV; 1f: TDF+3TC+NVP.

3.3. Liver Enzyme Abnormalities. Thirty-three (20.1%) HAART experienced and 36 (22.0%) HAART naive patients had elevated liver enzyme abnormalities in at least one biomarker (AST and/or ALT). ALT, AST, and both ALT and AST were elevated in 22 (13.4%), 25 (15.2%), and 14 (8.5%) of HAART experienced groups, respectively. In the HAART naive group, 97 (51.1%) were under WHO clinical stage I and 12 (7.3%) were positive for HBV infection (Table 2). The HAART experienced group had significantly higher mean CD4 count compared to HAART naive patients (HAART experienced: 356.88 cells/mm^3; HAART naive: 283.63 cells/mm^3) (P < 0.0001).

3.4. Factors for Liver Enzyme Abnormalities. Viral hepatitis (HBV and/or HCV), opportunistic infections, being male, and current CD4 count <200 cells/mm^3 were significantly associated with elevated liver enzymes. Accordingly, HIV-1 patients with HBV and/or HCV infections were about 6 (AOR = 6.02; 95% CI = 1.87–19.39) times more likely to have elevated ALT/AST levels. Those patients with history of opportunistic infections were 2.91 (AOR = 2.91; 95% CI = 1.04–8.19) times more likely to have raised ALT/AST levels. Those patients with current CD4 count <200 cells/mm^3 were 2.16 (AOR = 2.16; 95% CI = 1.06–4.39) times more likely to have elevated liver enzymes as compared to those patients with CD4 count >350 cells/mm^3 (Table 3).
Table 3: Multiple logistic regression analysis of factors for ALT and/or AST enzyme abnormalities in HIV-1 infected patients at Debre Tabor Hospital, 2013.

| Variables       | Liver enzyme |                | COR (95% CI)     | AOR (95% CI)     |
|-----------------|--------------|----------------|------------------|------------------|
|                 | Normal (%)   | Abnormal (%)   |                  |                  |
| Education level | Illiterate   | 130 (42.8)     | 7 (29.2)         | 0.59 (0.17–2.12) | 0.52 (0.14–1.97) |
|                 | Elementary   | 82 (27.0)      | 11 (45.8)        | 1.48 (0.44–4.91) | 1.54 (0.44–5.41) |
|                 | High school  | 48 (15.8)      | 2 (8.3)          | 0.46 (0.08–2.63) | 0.34 (0.06–2.078) |
|                 | College & above | 44 (14.5) | 4 (16.7) | 1 | 1 |
| Marital status  | Single       | 53 (17.4)      | 9 (37.5)         | 1 | — |
|                 | Married      | 136 (44.7)     | 10 (41.7)        | 0.43 (0.17–1.13) | — |
|                 | Divorced     | 66 (21.7)      | 2 (8.3)          | 0.18 (0.04–0.86) | — |
|                 | Widowed      | 49 (16.1)      | 3 (12.5)         | 0.36 (0.09–1.41) | — |
| Sex             | Male         | 100 (36.5)     | 27 (50.0)        | 1.74 (0.98–3.13) | 1.83 (1.00–3.33)* |
|                 | Female       | 174 (63.5)     | 27 (50.0)        | 1 | 1 |
| CD4 count/cells/mm³ | <200 | 73 (26.6)      | 24 (44.4)        | 2.10 (1.04–4.22) | 2.16 (1.06–4.39)* |
|                 | 200–350      | 99 (36.1)      | 14 (25.9)        | 0.90 (0.42–1.95) | 0.91 (0.42–1.98) |
|                 | >350         | 102 (37.2)     | 16 (29.6)        | 1 | 1 |
| OIs             | No           | 266 (87.5)     | 18 (75.0)        | 1 | 1 |
|                 | Yes          | 38 (12.5)      | 6 (25.0)         | 2.33 (0.87–6.25) | 2.91 (1.04–8.19)* |
| HAART status    | No           | 154 (50.7)     | 10 (41.7)        | 1 | — |
|                 | Yes          | 150 (49.3)     | 14 (58.3)        | 1.44 (0.62–3.34) | — |
| HBV or HCV      | Positive     | 17 (5.6)       | 5 (20.8)         | 4.44 (1.48–13.35) | 6.02 (1.87–19.39)* |
|                 | Negative     | 287 (94.4)     | 19 (79.2)        | 1 | 1 |

* Significantly associated; OI: opportunistic infection; HBV: hepatitis B virus; HCV: hepatitis C virus; HAART: highly active antiretroviral therapy; AOR: adjusted odds ratio; COR: crude odds ratio; CI: confidence interval.

4. Discussion

The prevalence of liver enzyme abnormalities in this study was 20.1% in HAART experienced and 22.0% in HAART naïve HIV patients. This finding is similar to other studies conducted on HIV infected patients in Cameroon (22.6%), South Africa (23%), and Brazil (19.7%) [17–19]. However, it was higher compared to the 11% prevalence in the general population of Australia [20]. The elevated liver enzyme in HIV infected patients might be due to direct inflammation of hepatocytes by HIV through apoptosis, mitochondrial dysfunction, and permeability alteration in mitochondrial membrane that stimulate an inflammatory response [12, 21–23].

Adverse drug reactions due to HAART are common. Its severity may range from mild to life-threatening conditions. They usually occur within the first 6–12 weeks but metabolic toxicities happen following prolonged use of antiretroviral therapy. Severe hepatotoxicity is a life-threatening condition (silent killer) that could affect patients on HAART. Patients with grade 3 hepatotoxicity should be immediately linked to ART physicians to substitute offending drug without stopping the HAART whereas HAART experienced patients with grade 4 hepatotoxicity should immediately discontinue all antiretroviral drugs and reintroduce modified regimen when the patient stabilized after supportive therapy [16]. In this study, 5 (3.1%) HAART experienced HIV infected patients had severe hepatotoxicity (Grade 3). Hence, regular monitoring of liver enzyme abnormalities is essential to manage such patients on HAART.

In the present study, HAART experienced HIV-1 patients had higher mean ALT (P value: 0.002). A recent study conducted by Owiredu et al. [24] has reported higher ALT level on HAART experienced HIV patients. The possible reason might be due to class-specific effects of drugs and cause direct mitochondrial toxicity of the liver as well as other organs that may lead to liver failure and lactic acidosis [25, 26].

In this study, current CD4 count <200 cells/mm³ was associated with elevated liver enzyme. Contradicting data were reported by different investigators [27, 28] which might be related to the fact that enhancement of immunity could...
be deleterious in diseases that involve immune-mediated mechanisms, such as autoimmune diseases or chronic viral hepatitis, or to the fact that enhanced immunity could also on the other hand decrease the opportunistic infection during HIV infection contributing to the reduction of liver enzymes.

In this study, we found significantly higher prevalence of elevated liver enzyme in HIV-1 patients coinfected with viral hepatitis (HBV and HCV). Previous studies also found significant association of viral hepatitis with hepatotoxicity [8, 29–31]. Viral cytopathic effect [32], raised HBV DNA viral load [33, 34], and mutation in the HBV precore and overlapping core genes (often associated with higher HBV DNA concentrations) [35] might contribute to elevated liver enzymes in those coinfected patients.

In this study, we found three times more elevated liver enzyme in male HIV-1 patients. Studies conducted in Italy [36], US community [37], and Thailand [38] reported similar association.

Immune abnormalities contribute to an increased risk of opportunistic infection among HIV infected patients. Although HIV infection is most closely associated with altered cell-mediated immunity, a number of additional immune deficiencies may occur in association with HIV infection. It usually includes a poor antibody response due to B cell dysfunction and defects in chemotaxis, phagocytosis, and intracellular killing by monocytes, macrophages, and neutrophils. Impairment of local defenses, manifested by a depression of specific IgA at the mucosal surfaces, also contributes to increased opportunistic infections [39]. In this study patients with history of opportunistic infections had significantly higher prevalence of elevated liver enzyme. Previous findings reported elevated liver enzyme in HIV patients with opportunistic infections [9, 40, 41]. This might be due to the fact that opportunistic infections such as viruses from the herpesviridae family (HSV, CMV), parasites (Toxoplasma gondii), mycobacteria (M. tuberculosis, M. avium complex), and fungi (Cryptococcus, Histoplasma) can all affect liver and manifest mostly as elevated liver enzymes [11].

**Limitations.** Patients with elevated liver enzyme were not confirmed by ultrasound whether their liver was really abnormal or not, a number of disease conditions were not fully addressed about whether they elevate liver enzyme, and HIV negative controls were not used due to budget constraint.

5. **Conclusions**

We found higher liver enzyme abnormalities in both HAART experienced and HAART naïve HIV-1 infected patients. The risk of developing liver enzyme abnormality was high among those with HBV and/or HCV infections, those with opportunistic infections, male patients, and those with low CD4 count. Therefore, monitoring and management of liver enzyme abnormalities in HIV infected patients are essential in our setting.

**Abbreviations**

AIDS: Acquired Immunodeficiency Disease Syndrome
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
HBsAg: Hepatitis B surface antigen
HVB: Hepatitis B virus
HCV: Hepatitis C virus
HIV-1: Human Immunodeficiency Virus 1.

**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Authors’ Contributions**

Melashu Balew Shiferaw participated in the design of the study and data collection, performed the statistical analysis, and drafted the paper. Ketema Tafess Tulu, Amtatachew Moges Zegeye, and Amarech Asratie Wubante analyzed the data and helped to draft the paper. All authors read and approved the final paper.

**Acknowledgments**

The authors thank the Amhara Regional State Health Bureau for funding this study. They also thank the Debre Tabor Hospital laboratory staff members, ART nurses, and case managers for their kind cooperation during the data collection.

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