original article

Elevated alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus coinfection

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BACKGROUND: Mortality related to human immunodeficiency (HIV) has improved with the use of antiretroviral therapy; however, liver disease–related mortality remains a major concern for the HIV population. Elevation of alanine aminotransferase (ALT) has been noted in HIV-infected persons even without viral hepatitis infection.

OBJECTIVE: The objective of this study was to determine the incidence and prevalence of chronic alanine ALT elevation among patients infected with HIV who are negative for hepatitis B or C infection.

DESIGN: Retrospective chart review.

SETTINGS: We reviewed the medical records of all patients infected with HIV who had been treated from November 2002 to December 2010.

PATIENTS AND METHODS: Patients with an unknown or positive HBV or HCV infection status were excluded. We identified patient demographics, route of transmission, peak viral load, and nadir CD4 count.

RESULTS: We followed 440 patients for up to 2265 person-years. A total of 123 patients developed chronically elevated ALT levels, with an incidence of 5.8 cases per 100 person-years. Chronically elevated ALT levels were associated with high HIV viral load, mean body mass index, and diabetes mellitus. We found exposure to lamivudine in 58% of the patients, efavirenz in 41%, and zidovudine in 38%. Abdominal ultrasounds revealed fatty liver in 20 of 39 (51%) of the patients.

CONCLUSION: Among patients without viral hepatitis coinfection, the prevalence and incidence of chronic elevated ALT levels were high and accompanied by high HIV RNA levels and increased BMI.

LIMITATIONS: The limitations of this report are its retrospective nature and lack of a control group.

Human immunodeficiency virus infection is a global health concern. By the end of 2013, the estimated number of HIV-infected patients was 35 million. Recent reports indicate that HIV-related deaths had fallen to 1.5 million by 2013, compared to 2.2 million in 2005.[1] The significant reduction in HIV-related deaths can be explained by improvement in universal access to combined antiretroviral therapy (cART), especially in highly HIV-endemic areas.[2] More HIV-infected people are now living and living longer. However, with the increase in number and availability of cART, liver disease has emerged as an important cause of morbidity and mortality among HIV-infected persons. The D:A:D study (Data collection on Adverse events of Anti-HIV Drugs) showed that liver disease was the second most common cause of death in HIV-infected patients after AIDS-related mortality.[3]

Elevated liver enzymes, which have been attributed to chronic viral hepatitis coinfection, are frequently seen in HIV patients. Many factors other than viral hepatitis might contribute to elevated liver enzymes, such as fatty liver infiltration, alcohol consumption, HIV cholangiopathy, and medications. Alanine aminotransferase (ALT) is a surrogate marker and predictor of liver disease and liver-related mortality. In a large retrospective analysis of patients without hepatitis B (HBV) or C (HCV) coinfection, ALT elevation was associated with increased liver disease-related mortality.[4]

HIV has been implicated as a direct cause of liver damage, with some reports showing a correlation between HIV viral load and the degree of liver-enzyme elevation.[5] In a large Swiss cohort study, the incidence of chronic elevation of ALT levels (defined as greater than the upper limit of normal at two or more consecutive semi-annual visits) in HIV-infected patients without hepatitis B or C coinfection was 3.9 cases per 100 person-years. In the same study, an elevated ALT was associated with high HIV RNA levels, increased BMI, alcohol use, and prolonged stavudine and zidovudine exposure.[6]

The epidemiology of liver disease varies according to ethnicity, lifestyle, alcohol-induced liver disease, and other systemic conditions. Non-alcoholic fatty liver disease (NAFLD) is more prevalent in populations with a high incidence of diabetes mellitus, obesity, and hyperlipidemia, which are all common in Saudi Arabia. Recent studies from Saudi Arabia indicate that the prevalence of diabetes, obesity, and hyperlipidemia is 23.7%, 35.5% and 54%, respectively.[7,8] NAFLD is an emerging cause of liver diseases among the Saudi population. As such, the prevalence of NAFLD was 16.6% in a recent prospective report that involved 1,312 patients.[9]

The latest report indicates that more than 10,000 people in Saudi Arabia have been infected with HIV.[10] Our hospital is one of the main HIV care centers in the country.[11] However, the prevalence of liver disease in HIV-infected persons in Saudi Arabia and the region remains unknown. The objective of this study was summarize data on the incidence and prevalence of chronic ALT elevation among patients infected with HIV who are negative for hepatitis B or C infection.

PATIENTS AND METHODS

Chronic elevated ALT was defined as an ALT level more than the upper limit of normal in two consecutive occasions 3 to 12 months apart. The upper limit of normal ALT is set at 40 IU/L for both men and women at our hospital laboratory. Diabetes mellitus was defined according to the American Diabetes Association's updated diagnostic criteria in 2010.[12] Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[13] Hypercholesterolemia and hypertriglyceridemia were defined as a total cholesterol >6.2 mmol/L (>240 mg/dL) and triglycerides >1.8 mmol/L (>160 mg/dL), respectively.[14]

In this retrospective study of medical records, all HIV-infected patients who were followed in our hospital from 1 November 2002, until 31 December 2010, were reviewed using an electronic data system, medical records, and the HIV database. Patients with an unknown or positive HBV (defined as positive hepatitis B surface antigen) or HCV (defined as positive antibody for hepatitis C virus) infection status and those less than 14 years old were excluded. We identified patient demographics, route of transmission, peak viral load, and nadir CD4 count, and other factors that might contribute to elevated ALT—medications, fatty liver infiltration, and risk factors for metabolic syndrome. The duration of follow-up was collectively used to determine the incidence of ALT elevation expressed as case per 100 person-years. The project was approved by the Institutional Review Board (RAC # 2111 042). As the study was observational and no patient identifiers were used, a consent form was waived by the IRB.

RESULTS

A total of 440 patients were seen between November 2002 and December 2010 with 2265 person-years of follow-up. Fifty-three patients with viral hepatitis were excluded, while 387 patients had negative hepatitis B surface antigen (HBsAg) and negative hepatitis C virus (HCV) antibody. Of the 387 patients, 123 had chronic ALT elevation. The incidence of ALT elevation was 5.8 cases per 100 person-years with a prevalence of 32%.

Demographic data for patients with chronic ALT elevation are shown in **Table 1**. The male-to-female ratio was 3.4:1, which is almost equal to the gender distribution in our HIV clinic patients. In addition, the modes of disease transmission were 71% heterosexual, 13% blood or organ recipients, and 2.4% perinatal. As many as 29% of the patients had a BMI of more than 30; 11.4% had diabetes, and the same percentage had hypertension. A liver ultrasound was performed for 39 patients, and 20 had findings suggestive of fatty liver infiltration.

The median baseline CD4 count was 269 (3-1367) cells/μL, with a median nadir CD4 count of 147 (1-1965) cells/μL. Sixty-one percent of the patients had nadir CD4 counts of less than 200 cells/μL; 20% had CD4 counts of 200-350 cells/μL, and 19% had CD4 counts of more than 350 cells/μL. The median baseline of HIV RNA was 15 507 copies/mL (40-5 000 000 copies/mL) and peak HIV RNA was 60 906 (50-8 882 209 copies/mL). Forty percent of the patients had a peak viral load of more than 100 000 copies/mL.

Seventeen percent of the patients had never received combination antiretroviral therapy at the time of ALT elevation. Fifty-eight percent of the patients were taking lamivudine, 40.7% efavirenz and 38% were taking zidovudine.

Table 1. Clinical characteristics of 123 patients with elevated ALT.

Variable	
Age (years)	40.0
Male (n)	93
Female (n)	28
Peak BMI (kg/m^2)	27.0
Baseline CD4 (cells/μL)	268.5
Nadir CD4 cells/μL	147.0
Baseline HIV RNA (copies/mL)	15507.0
Peak HIV RNA (copies/mL)	60905.5
Cholesterol (mmol/L)	5.0 (3.88-5.15 mmol/L)
HDL (mmol/L)	1.0 (≥1.04 mmol/L)
Triglycerides (mmol/L)	1.7 (<2.82 mmol/L)
Peak ALT (U/L)	99.0 (0-40 IU/L)
AST (U/L)	63.0 (0-40 IU/L)
Bilirubin (mg/dL)	0.5 (0.3-1.2 mg/dL)
ALP (U/L)	90.0 (36-92 IU/L)

Values are median unless specified otherwise. Normal lab values in parenthesis. Tests for normality indicated the data were highly skewed and non-normal.

DISCUSSION

Our longitudinal cohort of 387 HIV patients without hepatitis B or C coinfection had a high prevalence of ALT elevation. The incidence of ALT elevation was 5.8 cases per 100 person-years, which is the highest reported incidence in the literature. The median viral load at presentation was 134 265 cells/μL; this figure is consistent with other reports, which found that elevated viral load at presentation is an independent risk factor for chronic ALT elevation.[6] Furthermore, our results show that 61% of the patients had a nadir CD4 count of less than 200 cells/μL, suggesting that the progression of HIV infection correlates with ALT elevation. Antiretroviral medications are implicated in elevated liver enzymes in HIV-infected patients.[15] In our report, lamivudine was the most frequently used medication at the time of ALT elevation, followed by efavirenz and zidovudine, but these data cannot establish causality with liver function.

More than two thirds of our patients were overweight or obese. Obesity plays a major role in the chronic ALT elevation in the Saudi population in general and HIV patients in particular. Although only 39 patients had a liver ultrasound, half had a finding suggestive of fatty liver infiltration, which is consistent with the risk of non-alcoholic fatty liver disease (NAFLD). Alcohol consumption is rare in Saudi Arabia. Therefore, the role of alcohol-induced liver injury is probably minimal in our patients, but no data on alcohol consumption was collected. In other studies, alcohol consumption was one of the major causes of chronic ALT elevation.[6]

This study is the first report from Saudi Arabia – or, for that matter, any Arab country – that describes the prevalence of chronic ALT elevation in HIV-infected patients. We know that ethnic, cultural, and environmental factors play a role in this disease. Also, this study will alert physicians to newly emerging medical issues in HIV patients like NAFLD. The findings are limited because the study was retrospective and lacked a control group.

In conclusion, among patients without viral hepatitis coinfection, the prevalence and incidence of chronic elevated ALT levels were high and accompanied by high HIV RNA levels and increased BMI that supports data from other studies indicating a statistical association between elevated ALT and the other factors.. Long-term follow-up is needed to assess whether chronic elevation of ALT levels will result in increased morbidity or mortality.

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Author Disclosure Statement

No competing financial interests exist.

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