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Original Article

Liver enzyme elevations in a cohort of HIV/AIDS patients on first-line antiretroviral therapy in Namibia: Findings and implications

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ABSTRACT

Introduction: All antiretroviral therapies (ARTs) are potentially toxic to the liver. In sub-Saharan Africa, the rising incidence of ART induced adverse events has complicated treatment leading to recent revisions of Namibian ART guidelines. Unfortunately there have been limited studies to date evaluating ART induced liver injury in Namibia to guide further revisions if needed.
Objective: Determine the current patterns and grades of ALT elevation in Namibia's HIV/AIDS.
Methods: Retrospective cohort analysis. Patterns of alanine amino transferase (ALT) liver enzyme elevation were determined in a cohort of ART naïve HIV patients on firstline ART regimen in a referral hospital in Namibia over a 1 year treatment period. Patterns of ALT changes at baseline, 3 months and 6 months were analyzed using ANOVA and Bonferroni test for pairwise comparisons.
Results: Of 79 eligible patients, 72 developed significant ALT elevation within 3 months of ART initiation ($F(3, 76) = 6.4$, $p = 0.002$, $\eta^2 = 0.193$). Four 4 (5.6%) and 1 (1.38%) patient respectively developed grade 2 and grade 3 ALT elevation by month 3. There was no significant difference between mean ALT levels at baseline and month 6. A CD4 count of <350 cells/mm^3; female gender and age over 40 years were the main factors associated with moderate or severe ALT elevation.
Conclusions: First line ART commonly induces mild self-limiting liver enzyme elevation in Namibian HIV patients especially in the first 3 months. Consequently, there is a need to monitor ALT levels for at least 3 months after initiation mainly in high risk patients to reduce side-effect concerns. This is already happening.

1. Introduction

HIV/AIDS has devastated public health in sub-Saharan Africa. This is a concern since this region despite being resource constrained hosts over 80% of the world's HIV patients.[1] Within Africa, UNAIDS ranks Namibia among countries with the highest prevalence of HIV/AIDS among adults aged 15–49 years (14.3%), with currently over 250,000 people out of a population of 2.3 million in Namibia living with the infection.[2,3] Since the rollout of antiretroviral therapy (ART) in Namibia in 2003, over 104, 531 (80%) HIV/AIDS patients have been initiated on treatment.[3,4] Recently the test and treat policy has led to a considerable scale up of patients on first-line ART regimens. Unfortunately scale-up of ART exposes some patients to adverse drug reactions (ADRs)[5–10] with liver damage characterized by an elevation of alanine aminotransferase (ALT) being the most common.[11–14] Pharmacovigilance reports in Namibia have shown an increasing incidence in adverse effects that parallel the scale-up of ART,[15] particularly with stratification by CD4 count,[15–20] female sex[12,20] and the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs).[19-25]

The high number of female patients initiating ART[15,26] is an important risk factor for ART induced adverse effects including renal impairment - with hormonal differences playing a part.[15,21] Despite these risk factors, ART initiation policies in Namibia has

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evolved based on increasing CD4 thresholds: 250 cells/mm^3 (2003); 350 cells/mm^3 (2010); 500 cells/mm^3 (2014) and currently to test and treat.[27–29] Unfortunately to date, there have been only a limited number of studies evaluating the grades and risk factors for ART induced hepatotoxicity among the Namibian HIV/AIDS population. This is particularly important as the risk for ART induced hepatotoxicity among HIV patients in Namibia may be heightened by the high rates of tuberculosis (TB),[30] high alcohol consumption per capita (12.28 L per person per year)[31] and the use of efavirenz and/or nevirapine based therapies as first line ART treatment in line with recommendations.[20,22–25,27–29] TB coinfection and co-medication is an important risk factor for hepatotoxicity.[32,33] Liver damage characterized by elevation in liver transaminases through alanine amino transferase (ALT) is the most reliable marker for hepatocellular toxicity[11,20,34–36]; however, it's measurement among patients on firstline ART in Namibia is currently unknown. The routine monitoring of ALT in Namibia is complicated by limited human resource capacity, which may negatively impact on treatment outcomes in some patients.

Consequently, the aim of this paper was to determine the current patterns and grades of ALT elevation in Namibia's HIV/AIDS population to provide future guidance to the authorities in Namibia and other African countries with similar profiles of patients with HIV. This is because ADRs negatively impact on treatment adherence,[16] health related costs, and the social-psychological wellbeing of patients[37] as well as patient outcomes including their quality of life.[8,38–42] Increased morbidity and mortality related to ADRs is the main reason for revision and switching ART treatment as seen in the HIV guidelines in the Namibia.[8,9,27–29,43] The use of AZT based regimens from 2003 to 20,010 was associated with anemia, and stavudine (d4T) based regimens from 2010 to 2015 was associated with peripheral neuropathy.[27–29] The currently preferred Tenofovir-based regimens[15] have been associated with renal insufficiency and bone dimineralization.[15,20,43] Despite these risk factors for liver damage among the Namibian population, evidence on patterns and prevalence of liver toxicity remains limited.

2. Methods

2.1. Study subjects

The study adopted a retrospective cohort analysis of grades and risk factors for ALT elevation among patients on firstline ART regimens. The study population consisted of clinical and laboratory records of patients initiated on first-line ART at Katutura Intermediate Hospital (KIH). This is a teaching referral hospital in Windhoek; the capital city of Namibia, and cares for over 5800 patients on active ART from across the Khomas region and Namibia.

Retrospective data was collected over a 12 month period between 1st January 2013 and 1st January 2014. The study included records of all adult HIV/AIDS patients ($\geq$18 years) who completed at least 12 months of treatment of first line ART regimen.

The first line regimens in this study included tenofovir/lamivudine/nevirapine (TDF/3TC/NVP) or tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) combinations. For consistency and reliability, only records on ALT levels that had been provided by the National Institute of Pathology (NIP) laboratory at KIH were included. All the serum levels of ALT of records included in this study were determined by Architect ci8200 Dxc analyzer (Abbot Diagnostics) as per the International Federation Clinical Chemistry protocol (IFCC). Patients with severe ALT elevation at baseline and/or with missing laboratory records on ALT levels at 3 months and or 6 months were excluded from the study.

Out of the 123 patients who had the first line ART at KIH between January 2013 and 31 January 2014, 44 patients were excluded as their records did not have ALT measurements at month 3 or month 6. Consequently, a total of 79 patient records that met the eligibility criteria were included in the study.

2.2. Procedure

Laboratory data on the liver enzyme (AST) and (AST) profiles of ART naïve patients were collected using quantitative methods over a 12 month period and five time points - baseline and months 3, 6, 9 and 12 of treatment. Data from the patients' records were abstracted by the principal researcher (PAM) from patient ART treatment records over a 3 months study period - May 2014 to August 2014 using a pre-tested abstraction tool (Appendix A). Data abstracted includes demographic, clinical and laboratory data at baseline, 3 and 6 months. Data collection tools were designed to exclude patient identifiable data including patient names.

The main outcome variable was the grades and risk factors for ALT elevation at 3 months and 6 months of ART treatment. Data was double entered into Epidata® (version 3.1) entry software for management and exported to SPSS® (version 21) software for quantitative analysis. The grades of ALT elevation were determined using descriptive statistics such as frequencies (%), mean(X) and standard deviation (SD). The risk factors and patterns of ALT elevation were determined using a chi-square test (χ^2) for categorical variables and student *t*-test and/or ANOVA test for continuous variables. The Bonferroni pair-wise Post-hock test was used to compare the mean ALT levels at baseline with months 3 and month 6 post ART initiation. The significance level for a 95% confidence interval was set at a p value < 0.05. Missing data were excluded in the analysis.

2.3. Criteria for grading ALT elevation

The grades of ALT elevations were determined using the WHO toxicity scale based on the upper limits of normal (ULN) ALT levels,[35] that is normal or grade 1 (<2.5 $\times$ ULN); mild - moderate elevation or grade 2 (2.5–5 $\times$ ULN); severe elevation or grade 3 (>5 $\times$ ULN) or grade 4 (>10 $\times$ ULN). The normal limits of ALT levels were considered to be 0–40 IU/L.[34,44,45]

2.4. Ethics

The study was approved by the University of Namibia (UNAM), the Ministry of Health and Social Services (MoHSS) and Namibia Institute of Pathology (NIP) research and ethics committees. The need for informed consent was waved by the research committee as the study was based on patient records with no direct contact with patients. Patient codes or serial numbers were used instead of patient identifiers such as names to delink the patients from the data collected. All collected data was safely stored.

3. Results

A total of 79 patient records that met the eligibility criteria were included in the study. 44 patients were excluded as their records did not have ALT measurements at month 3 or month 6.

3.1. Baseline demographic and clinical characteristics

The majority of the study subjects were female (n = 51 (65%), p = 0.01) aged between 30 and 40 years (n = 41 (52%), p = 0.000); were not married (76%), (p = 0.000) and did not consume alcohol (n = 61(78%); p = 0.149). The majority of the subjects were initiated