

HOSTED BY



ELSEVIER

Contents lists available at ScienceDirect

Alexandria Journal of Medicine

journal homepage: <http://www.elsevier.com/locate/ajme>

Original Article

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

P.A. Mataranyika^a, D. Kibuule^a, F. Kalemeera^b, H. Kaura^c, B. Godman^{d,e,f,*}, T.W. Rennie^a^a School of Pharmacy, Department of Pharmacy Practice and Policy, Faculty of Health Sciences, University of Namibia, Box 13301, 340 Mandume Ndemufayo Avenue Pioneers Park, Windhoek, Namibia^b Department of Pharmacology and Therapeutics, Faculty of Health Sciences, University of Namibia, Box 13301, 340 Mandume Ndemufayo Avenue Pioneers Park, Windhoek, Namibia^c Institute of Pathology, Katutura Hospital Complex, Box 277, Windhoek, Namibia^d Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden^e Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, UK^f Liverpool Health Economics Centre, University of Liverpool Management School, Liverpool L69 7ZH, United Kingdom

ARTICLE INFO

Article history:

Received 31 December 2016

Revised 31 January 2017

Accepted 17 March 2017

Available online 13 April 2017

Keywords:

Liver enzyme elevation

ALT

Antiretroviral therapy

HIV/AIDS

Namibia

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 (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/mm³; 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.

© 2017 Alexandria University Faculty of Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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

Peer review under responsibility of Alexandria University Faculty of Medicine.

* Corresponding author at: Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden.

E-mail addresses: patsvadelaide@gmail.com (P.A. Mataranyika), dkibuule@unam.na (D. Kibuule), fkalemeera@unam.na (F. Kalemeera), Harold.kaura@nip.com.na (H. Kaura), Brian.Godman@ki.se, brian.godman@strath.ac.uk (B. Godman), trennie@unam.na (T.W. Rennie).

<http://dx.doi.org/10.1016/j.ajme.2017.03.002>

2090-5068/© 2017 Alexandria University Faculty of Medicine. Production and hosting by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

evolved based on increasing CD4 thresholds: 250 cells/mm³ (2003); 350 cells/mm³ (2010); 500 cells/mm³ (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 patients³⁷ 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 anaemia, and stavudine (d4T) based regimens from 2010 to 2015 was associated with peripheral neuropathy.^{27–29} The currently preferred Tenofovir-based regimens¹⁵ have been associated with renal insufficiency and bone demineralization.^{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 (≥ 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 (ALT) 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-hoc 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 ($< 2.5 \times \text{ULN}$); mild - moderate elevation or grade 2 ($2.5 - 5 \times \text{ULN}$); severe elevation or grade 3 ($> 5 \times \text{ULN}$) or grade 4 ($> 10 \times \text{ULN}$). 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 waived 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

Table 1
Baseline demographic and clinical characteristics of the study subjects (n = 79).

Characteristic	Total (%)	χ^2	P-value ^a
Sex			
Female	51(65)		
Male	28(35)	6.696	0.010
Age category			
20–30 years	11(14)		
31–40 years	41(52)		
41–50 years	20(25)		
>50 years	7(9)	36.359	0.000
ART regimen			
TDF/3TC/EFV	14(18)		
TDF/3TC/NVP	65(82)	21.525	0.000
Alcohol consumption			
Yes	17(22)		
No	62(78)	2.082	0.149
Clinical stage			
Stage 1	45(63)		
Stage 2	14(22)		
Stage 3	18(11)		
Stage 4	3(4)	30.490	0.000
CD4 categories			
<250 cells/mm ³	40(52)		
251–350 cells/mm ³	29(38)		
351–500 cells/mm ³	5(6.5)		
>500 cells/mm ³	3(3.5)	25.224	0.000
Co-infection 1st visit			
TB	7(2)		
No signs	72(98)	24.352	0.000
Adherence to ART			
>90%	64(92)		
70–87%	6(5)		
<90%	5(3)	11.109	0.004
Medicines on 1st visit			
Co-trimoxazole therapy	72(98)		
TB treatment & CTX	7(2)	24.352	0.000

^a Pearson chi-square test.

on a NVP based regimen (n = 53 (82%), p = 0.000); were WHO clinical state 1 or 2 (n = 59 (85%), p = 0.000) with a CD4 count of <350 cells/mm³ (n = 69 (89.6%), p = 0.000); did not have TB co-infection (n = 72 (98%), p = 0.000) and had an ART adherence level of >90% (n = 64(92%), p = 0.000) (Table 1).

3.2. Patterns of alanine amino transaminase (ALT) elevation among study subjects

The analysis of variance (ANOVA) of the mean ALT levels among study subjects at baseline, month 3 and month 6 after the initiation of first line, ART was statistically significant ($F(3, 76) = 6.4$, $p = 0.002$, $\eta^2 = 0.193$) (Table 2).

This suggests evidence to conclude there is a difference between the ALT levels by initiation and duration of ART treatment with an appreciable effect size ($\eta^2 > 0.14$). A post hoc comparison to evaluate pair wise difference between the mean ALT levels at baseline, month 3 and month 6, using the Bonferroni test to control for type I error, showed a significant increase in the mean ALT levels between baseline and month three ($p = 0.001$) as well as baseline and month six after the initiation of ART ($p = 0.02$). The ALT levels were higher at month three and month 6 compared to baseline (Table 3).

3.3. Prevalence of grades of ALT elevation among the study subjects

Out of the 79 patients at baseline, 77 (97.5%) and 2 (2.5%) had grade 1 and grade 2 ALT elevation respectively. At 3 months post ART initiation, out of the 72 (91.1%) patients who had their ALT results recorded; 67 (93.1%) had grade 1, 4 (5.6%) had grade 2 and 1 (1.34%) had grade 3 ALT elevation. At 6 months post ART initiation, out of the 66 (83.5%) patients who had their ALT determined; 62 (93.9%) had grade 1 and 4 (6.1%) had grade 2 ALT elevation. Out of the five 5 (6.9%) patients that developed grade 2 or 3 ALT elevation by month 3 post ART initiation, the majority were taking a NVP based regimen, had a baseline CD4 count <350 cells/mm³, were of the female gender, were aged more than

Table 2
Patterns of biomarkers for HAART efficacy and toxicity among the subjects.

Characteristic	Mean \pm SD	χ^2	F	η^2	P-value
ALT (IU/L)					
Baseline	29.85 \pm 23.977				
Month 3	50.62 \pm 41.035				
Month 6	44.12 \pm 35.461	2.810	6.940	0.193	0.002
CD4 (cells/mm³)					
Baseline	265.00 \pm 141.033				
Month 2	433.82 \pm 181.226	0.000	42.761	0.466	0.000
Haemoglobin (g/dL)					
Baseline	12.026 \pm 2.2339				
Month 6	13.617 \pm 1.8127				
Month 9	13.561 \pm 1.7188	2.970	9.975	0.487	0.001
Serum creatinine (mmol/L)					
Baseline	73.82 \pm 13.553				
Month 3	69.27 \pm 13.854				
Month 6	71.05 \pm 18.269				
Month 9	73.09 \pm 15.826	26.869	2.969	0.319	0.580
Body weight (kg)					
Baseline	63.552 \pm 13.5028				
Month 1	63.772 \pm 13.5840				
Month 2	64.400 \pm 13.9013				
Month 3	65.534 \pm 13.7929				
Month 4	66.085 \pm 13.3924				
Month 5	65.628 \pm 13.7351	109.262	3.330	0.217	0.010

NB: ALT: Alanine amino transferase.

Table 3
Pair wise comparison of ALT levels at base line, month 3 and month 6.

Characteristic	Mean difference	P ^a -value
ALT month 0		
ALT month 3	-20.767	0.001
ALT month 6	-14.267	0.020
ALT month 3		
ALT month 0	20.767	0.001
ALT month 6	6.500	0.500

^a Bonferroni post hoc test.

Table 4
Factors associated with elevation of ALT at month 3 (n = 5).

Characteristic	# of patients by ALT elevation		Total (%)	P-value
	Grade 2	Grade 3		
CD4 counts				
<250 cells/mm ³	2	-	2(40)	
251–350 cells/mm ³	2	1	3(60)	0.361
ART regimen				
TDF/3TC/EFV	1	-	1 (20)	
TDF/3TC/NVP	3	1	4(80)	0.576
Sex				
Male	1	-	1 (20)	
Female	3	1	4(80)	0.576
Age of patient				
41–50 years	3	-	3(75)	
>50 years	-	1	1(25)	0.046
Clinical stage				
Stage 1	3	1	4(80)	
Stage 3	1	-	1(20)	0.576
Alcohol intake				
Yes	1	-	1 (20)	
No	3	1	4(80)	0.576
TB coinfection				
Yes	1	-	1 (20)	
No	3	1	4(80)	0.576

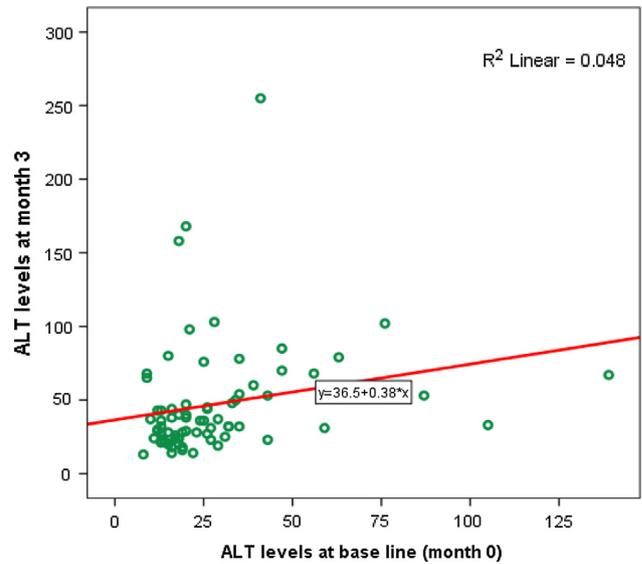


Fig. 2. Grades of ALT elevations by sex of patient after 3 months of ART initiation.

40 years and were classified by WHO HIV clinical stage I (Table 4). The study also found that the initiation of ART significantly increased mean CD4 counts, level of haemoglobin and the patient's body weight. The first ART regimen was associated with an increase in the mean serum creatinine levels also increased after the initiation of ART (Table 4; Fig. 3).

There were a higher number of female patients with normal – grade 1 and 2 – as well as with severe liver enzyme elevation (Fig. 1). The elevation in ALT at 3 months was associated with the baseline ALT levels (Fig. 2) and CD4 count. The elevation in ALT was negatively correlated with the baseline CD4 counts (Fig. 3).

4. Discussion

We found that first line ART regimens were associated with significant elevation of ALT from baseline to 3 months, with ALT levels

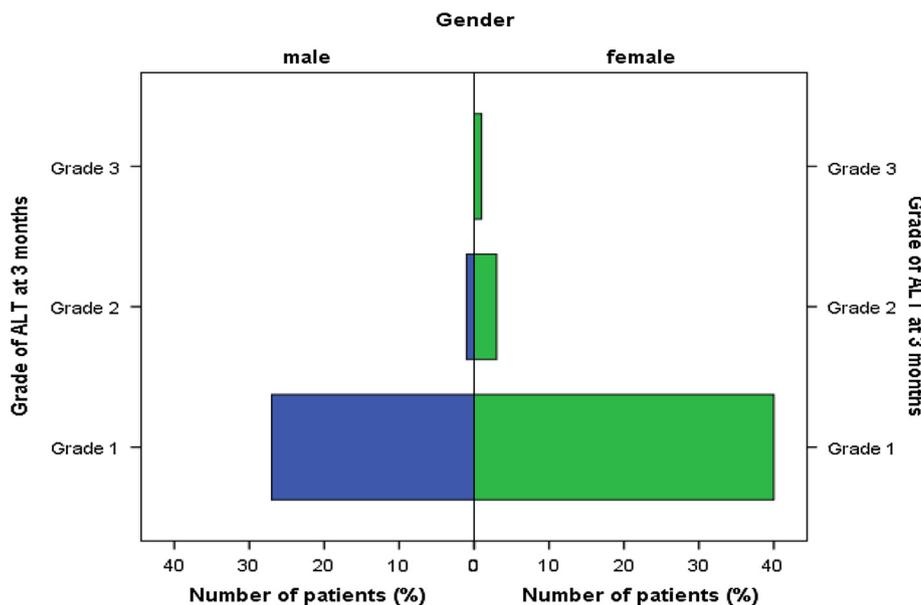


Fig. 1. Grades of ALT elevations by sex of patient after 3 months of ART initiation.

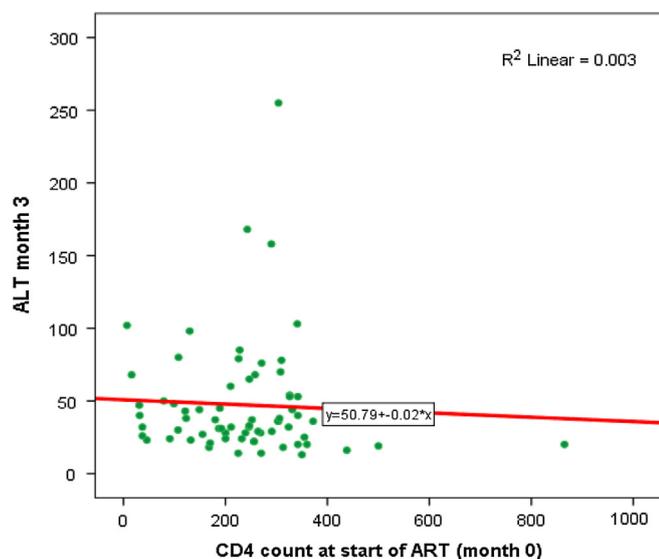


Fig. 3. Grades of ALT elevations by CD4 counts after 3 months of ART initiation.

normalized by the months 6 of therapy. These findings concur with studies by Lucien et al., Uberti-Foppa, Teklay et al. and De Maat et al. who found an increased ALT elevation following ART with in the first month of treatment.^{7,11,22,35} Studies have associated NNRTI based regimens with early onset of ALT elevations.^{16,39,45} However our findings differ from studies by Lucien et al., Splenger et al., and Bossi et al., regarding the patterns of the ALT elevation, which showed long term elevation of ALT with duration of treatment.^{6,11,17} These studies, unlike our study, evaluated regimens with thymidine analogues (AZT or d4T) that have been associated with long term mitochondrial toxicity related liver damage.³⁹ This is unlike this study where adenosine analogue (TDF) based regimens were used, and have been referred to as safe to the liver.⁸ TDF regimens were used as currently the recommended first line ART regimen in Namibia is TDF/lamivudine (3TC)/Nevirapine (NVP) or Efavirenz (EFV).²⁹

We also found a low incidence of moderate or grade 2 ALT elevation in 4 patients (5.6%) and severe or grade 3 elevation in only 1 patient (1.39%) who had ALT elevation at 3 months of ART initiation. Studies in Ethiopia, Zambia, and Palmon et al. also showed mild liver enzyme elevation in patients initiated on TDF based regimens.^{7,9,23} However these findings differ from those of Martinez et al., Sulkowsky, Verucchi et al., Tetrault et al. and Manfredi et al., whose incidence of severe ALT elevation were 8% and 17.5% for EFV and NVP respectively.^{18,24,25,46,47} A study in Cameroon by Lucien et al. found 22.67% (34/150) presented with transaminitis with respect to ALT,¹¹ with a study undertaken in the US among 352 subjects found 81 subjects developed elevated liver enzymes over the 96 week follow up period.¹⁹ In this US study, the cumulative incidence of liver enzyme elevation was 5.7% at month 1, 9.2% at month 2, 11.5% at month 3, 17.3% at month 6 and 19% at month 9.¹⁹ A slightly higher rate of efavirenz associated hepatotoxicity (12.5%) was observed in a prospective cohort study by Maggiolo et al. and Shubber et al.^{12,14} Whilst not statistically significant, our study found that grade 2 (moderate) and or grade 3 (severe) ALT enzyme elevations were associated with the use of NVP based regimens, initiation of ART in patients in the WHO Clinical Stage I, and older than 40 years. This was similar to the findings of Lucien et al., Spengler et al., and Hawkins et al., where ALT elevations were greater in patients >40 years, females and having a CD4 count of less than 350 cells.^{6,11,48} Previous studies have associated liver damage with the NVP based regimens^{20,22–25} and the female sex.¹⁶

The higher incidence may parallel the higher enrollment of female patients on ART programmes in African countries.^{15,26–29} Contrary to findings of this study (Fig. 2), liver toxicity of NVP base ART regimens has been associated with higher CD4 counts of >250 in female patients and >400 cell m³ in male patients.⁴⁵ This may be because these studies have traditionally been undertaken among Western countries with different patient populations and pharmacogenomics.²⁶

We accept that the main limitation of this study is the retrospective design – with a number of patients missing complete records on their ALT measurements; consequently, they were excluded. A prospective randomized clinical trial is ideal but may not be realistic in settings with limited resources. This is consistent with the fact that most studies in the African setting on ART induced liver damage have used retrospective data.^{5,11} However, we controlled for bias with paired samples in our study design. In addition, we were also aware that this study was undertaken in only one center in Namibia. Never-the-less we believe in view of the fact that we had 79 patients with paired ALT measurements (3 × 79 tests) for 3 months, and ANOVA analysis indicated significant differences at different treatment time points, that our findings are robust and would not have been different if we had included additional patients or additional centers in Namibia.

5. Conclusion

First line ART regimens commonly induce mild self-limiting liver enzyme elevation in Namibian HIV patients especially in the first 3 months of therapy. However, the incidence of moderate to severe first line ART induced liver toxicity is low. Patients of the female gender, aged over 40 years with a CD4 count of <350 and the use of NVP based regimens may be at greater risk of developing moderate to severe liver damage. Consequently, there is a need to monitor ALT levels for at least the first three months after initiation of therapy mainly in female patients, patients with grade >2 ALT elevations at baseline and patients with low CD4 counts, as well as patients on co-medication for tuberculosis.

In view of this, a different approach to monitoring liver toxicity may be warranted and should be incorporated in guidelines to monitor ART toxicity. This approach should be based on clinical signs and symptoms for hepatocellular injury such as jaundice as well as asymptomatic elevations in ALT at baseline and three months for all patients initiated on ART. We believe based on our findings that patients with high risk of hepatocellular damage such as low baseline CD4 count, of female sex, and >grade 2 ALT elevations, and patients who test positive for HBV/HCV, should be monitored for at least 6 months after initiation of NVP and EFV based antiretroviral therapy. The Ministry of Health in Namibia has started to implement these practices, and we will be monitoring the results in future research projects. These findings may also be of interest to other African countries.

Conflict of interest and funding

The authors hereby declare that they have no conflicts of interest to disclose. There was no external funding for this project.

Acknowledgements

The authors would like to acknowledge the contribution from the National Institute of Pathology of Namibia for the permission to use their data to conduct this study and the staff of the MoHSS ART clinic of Katutura State Hospital and the MoHSS for allowing us to undertake this research.

Laboratory results

Parameter	Base line	Mo nth 1	Mo nth 2	Mo nth 3	Mo nth 4	Mo nth 5	Mo nth 6	Mo nth 7	Mo nth 8	Mo nth 9	Mo nth 10	Mo nth 11	Mo nth 12
119. Haemoglobin(g/dl)													
120. Creatinine clearance(umol/L)													
121. ALT(u/L)													
122. Viral load													
123. CD4 count (cells/uL)													
124. Hematocrit (%)													
125. Neutrophils(x10 ⁹ /L)													
126. Lymphocytes(x10 ⁹ /L)													
127. Total WBC(x10 ⁹ /L)													
128. Platelets (x10 ⁹ /L)													

References

- UNAIDS. Report on the Global AIDS Epidemics. Ps 16-29. <http://www.unaids.org/documents/20101123_globalreport_em.pdf>; 2010.
- UNAIDS. Namibia Report on AIDS Epidemics update. <http://www.unaids.org/en/resources/documents/2014/20140716_UNAIDS_epidemiologydata>; 2013.
- Republic of Namibia, Ministry of Health and Social Services. Directorate of special programmes Surveillance report of the 2014 national HIV sentinel survey. <http://www.mhss.gov.na/files/downloads/12f_2014%20National%20HIV%20Sentinel%20Survey.pdf>; 2014.
- Global HIV/AIDS response progress report 2014. UNICEF, UNAIDS. <http://www.unaids.org/sites/default/files/media_asset/GARPR_2014_guidelines_en_0.pdf>.
- Mwamakimbula NWR, Prevalence and severity of adverse drug reactions among adult patients using default first line and modified antiretroviral combinations in Mbeya region, Tanzania. <http://ihi.eprints.org/1627/1/William_Ndimbumi_Mwamakimbula_Reuben.pdf>; 2012.
- Spengler U, Lichtenfeld M, Rockstroh JK. Antiretroviral drug toxicity – a challenge for the hepatologist? *J Hepatol.* 2002;36(2):283–294.
- Teklay G, Legesse B, Legesse M. Adverse effects and regimen switch among patients on antiretroviral treatment in a resource limited setting in Ethiopia. *J Pharmacovigilance.* 2013;1:4.
- Cassetti I, Madruga JV, Suleiman JM, et al.. The safety and efficacy of Tenofovir DF in combination with lamivudine and Efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. *HIV Clin Trials.* 2007;8:164–172.
- Chi BH, Mwango A, Giganti M, et al.. Early clinical and programmatic outcomes with Tenofovir-based antiretroviral therapy in Zambia. *J Acquired Immune Deficiency Syndrome.* 2010;54:63–70.
- Woldemedhin B, Wabe NT. The reason for regimen change among HIV/AIDS patients initiated on first line highly active antiretroviral therapy in southern Ethiopia. *N Am J Med Sci.* 2012;4:19–23.
- Lucien KFH, Clement ANJ, Fon NP, Weledji P, Ndikvu CP. The effects of antiretroviral treatment on liver function enzymes among HIV-Infected out-patients attending the central hospital of Yaounde, Cameroon. *Afr J Clin Exp Microbiol.* 2010;11(3):1595–1689.
- Shubber Z. Adverse events associated with Nevirapine and Efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS.* 2013;27:1403–1412.
- Kontorinos N, Dieterich D. Hepatotoxicity of antiretroviral therapy. *AIDS Rev.* 2003;5(1):36–43.
- Maggiolo F, Arici C, Airoidi M, et al.. Reasons for discontinuation of Nevirapine containing HAART. *J Antimicrob Chemother.* 2007;59:569–572.
- Kalemeera F, Mbango C, Mubita M, Naikaku E, Gaida R, Godman B. Effect of changing from first- to second-line antiretroviral therapy on renal function: a retrospective study based on data from a single health facility in Namibia. *Exp Rev Anti-infective Ther.* 2016;14(8):777–783.
- Wakibi S, Ng'ang'a Z, Mbugua G. Factors associated with non-adherence to highly active antiretroviral therapy in Nairobi, Kenya. *AIDS Res Ther.* 2011;5(8):43.
- Bossi P, Colin D, Bricaire F, Caumes E. Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infectious Diseases.* 2000;30:227–228.
- Martinez E, Blanco JL, Arnaiz A, et al.. Hepatotoxicity in HIV-1-infected patients receiving Nevirapine-containing antiretroviral therapy. *Acquired Immune Deficiency Syndrome.* 2001;15:1261–1268.
- Oforokun I, Smithson SE, Lu C, Easley KA, Lennox JL. Liver enzymes elevation and immune reconstitution among treatment-naïve HIV-infected patients instituting antiretroviral therapy. *Am J Med Sci.* 2007;334(5):334–341.
- Sabolic I, Asif AR, Budach WE, Wanke C, Bahn A, Burckhardt G. Gender differences in kidney function. *Pflugers Archiv.* 2007;455(3):397–429.
- Barlett J. Severe liver toxicity in patients receiving two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor. 8th Conference on Retroviruses & Opportunistic Infections. Chicago, IL. 2001; Abstract 19.
- De Maat MM, ter Heine R, Van Gorp EC, et al.. Case series of acute hepatitis in a non-selected group of HIV-infected patients on nevirapine-containing antiretroviral treatment. *AIDS.* 2003;17(15):2209–2214.

23. Palmon R, Koo BC, Shoulz DA, et al. Lack of hepatotoxicity associated with non-nucleoside reverse transcriptase inhibitors. *J Acquired Immune Deficiency Syndrome*. 2002;29:340–345.
24. Sulkowsky MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine- or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *J Hepatol*. 2002;35:182–189.
25. Verucchi G. Incidence of liver toxicity in HIV infected patients receiving isolated dual nucleoside analogue antiretroviral therapy. *J Acquired Immune Deficiency Syndrome*. 2003;33:546–548.
26. Gaida R, Truter I, Grobler C, Kotze T, Godman B. A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications. *Exp Rev Anti-infective Ther*. 2016;14(4):377–388.
27. Republic of Namibia, Ministry of Health and Social Services Directorate of Special Programmes. National Guidelines for Antiretroviral Therapy First Edition; 2003.
28. Republic of Namibia, Ministry of Health and Social Services Directorate of Special Programmes. National Guidelines for Antiretroviral Therapy second Edition; 2010.
29. Republic of Namibia, Ministry of Health and Social Services Directorate of Special Programmes. National Guidelines for Antiretroviral Therapy Fourth Edition; 2014.
30. Ministry of health and Social Services (MoHSS), National Tuberculosis and leprosy Control Program 2009/2010 Annual Report, Windhoek MoSS.
31. World Health Organization. Global Status Report on Alcohol. <http://www.who.int/substance_abuse/publications/global_status_report_2004_overview.pdf>; 2004.
32. Veira DEO, Gomes M. Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. *J Bras Pneumol* 2008; 34. <http://www.scielo.br/pdf/jbpneu/v34n12/en_v34n12a10.pdf>.
33. Javari M, Shalviri G, Gholami, Salamzadeh J, Maghooli G, Mirsaeedi. Adverse reactions of anti-tuberculosis drugs in hospitalized patients. *PDS*. 2007;16(10):1104–1110.
34. WHO Toxicity Grading Scale for Determining. The Severity of Adverse Events. <www.icssc.org/Documents/Resources/AEMannual2003Appendices>; 2003.
35. Uberti-Foppa C, De Bona A, Gali L, et al.. Liver fibrosis in HIV-positive patients with hepatitis C virus: role of persistently normal alanine aminotransferase levels. *J Acquired Immune Deficiency Syndrome*. 2006;41:63–67.
36. Carter M. ALT levels may not give true picture of liver disease in HIV/HCV co-infected, suggests study. <<http://www.aidsmap.com/ALT-levels-may-not-give-true-picture-of-liver-disease-in-HIVHCV-coinfected-suggests-study/page/1422831/>>; 2006.
37. Bose S, Varanasi A, Mo G. Demographic, socio-economic and psychological determinants of HIV treatment: a community out-patient experience. *BJMP*. 2009;2(2):42–45.
38. Nunez MJ, Martin-Carbonero, Moreno V, Valencia E, Garcia-Samaniego J, Gonzalez-Castillo J. Impact of antiretroviral. *AIDS*. 2006;22:825–829.
39. Lewis JH. The rational use of potentially hepatotoxic medications in patients with underlying liver disease. *Informa Healthcare*. 2002;1:159–172.
40. Aronson JK, Torpey K, Lartey M. Side effects of drugs annual 2011; 33: 577–88. <https://www.elsevier.com/books/book-series/side-effects-of-drugs-annual_>.
41. Bonjoch A. High rate of reversibility of renal damage in a cohort of HIV-infected patients receiving Tenofovir-containing antiretroviral therapy. *Antiviral Res*. 2012;96:65–69.
42. Moore RD. Anaemia and human immunodeficiency virus disease in the era of highly active antiretroviral therapy. *Semin Hematol*. 2000;7:18–23.
43. Njuguna C, Orrell C, Kaplan R, Bekker LG, Wood R, Lawn SD. Rates of switching antiretroviral drugs in a primary care service in South Africa before and after introduction of tenofovir. *PLOS One*. 2013;8(5):e63596.
44. Bimenya GS. International system of units in clinical sciences: reference values for analytes in clinical chemistry, vol. 44, 1st ed., Kampala; 2000.
45. Loanou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999–2002. *Am J Gastroenterol*. 2006;101:76–82.
46. Tetrault JM, Tate JP, McGinnis KA, et al.. Veterans Aging Cohort Study Team. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. *Alcohol Clin Exp Res*. 2012;36(2):318–324.
47. Manfredi R, Calza L. Recent availability of two novel, fixed formulations of antiretroviral nucleoside analogues: a 12-month prospective, open-label survey of their practical use and therapeutic perspectives in antiretroviral-naïve and -experienced patients. *AIDS Patient Care STDs*. 2008;22:279–290.
48. Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. *JAIDS*. 2007;45(3):304–310.