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# Changes in serum liver enzymes level after switching from stavudine/lamivudine to zidovudine/lamivudine in NNRTIs based anti-retroviral regimens in Hawassa, Southern Ethiopia

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**Abstract:** Background: During stavudine phase-out in a resource limited countries, Zidovudine or Tenofovir is used to substitute stavudine. However, data concerning any difference in liver enzymes level after therapy change (switching) in Ethiopia is very limited. Methods: This prospective cohort study was carried out from May 2013 to July 2014 at ART clinic of Hawassa University teaching hospital. Of hundred fifty HIV-infected; immunologically stable adults receiving triple antiretroviral therapy: 120 were patients receiving stavudine based regimen with either of efavirenz or nevirapine during ART initiation (switch group); and the rest 30 patients were receiving zidovudine based regimen with either of efavirenz or nevirapine and also never switched (control group). Lamivudine is common for both groups. Levels of serum liver enzymes were determined and hepatotoxicity assessed according to World Health Organization ART guideline. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 20. Results: Serum mean AST and ALT level in the switch group decreased significantly over the time observed (p=<0.0001 for both enzymes); however ALP level was significantly increased (p=<0.0001). Hepatotoxicity in the switch group was significantly decreased (AST grade $\geq$ 1 from 35.8% to15.8%; and ALT from 20.8% to 3.3%) after 12 month of therapy change. Conclusion: Significantly a decreased hepatotoxicity was observed at the 12 month of post switch and this indicated that a substitution of stavudine to Zidovudine could have a potential to reverse hepatotoxicity. However, significantly decreased white blood cells count and abnormally increased level of ALP enzyme should require periodic monitoring and further investigations.

**Keywords:** Hepatotoxicity, HAART Switching, HIV/AIDS, Hawassa, Ethiopia

## 1. Introduction

The introduction of highly active antiretroviral therapy (HAART) has led to a marked reduction in acquired immunodeficiency syndrome (AIDS) related morbidity and mortality [1]. Since its introduction patients have started to live longer however, co-morbid problems are challenging human immunodeficiency virus (HIV) infected patients. Among these, hepatotoxicity is the one which is associated with antiretroviral drugs and it may be life threatening [2]. Antiretroviral drugs-related liver injury is a common cause of morbidity, it may result treatment discontinuation in HIV-infected patients [1, 3]. Elevations in serum hepatic enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) have been described in association with all major classes of HAART [4]. However, the complexity of medication used in antiretroviral therapy (ART) complicates the understanding of the independent effects of each drug in the development of drug induced liver injury [4, 5]. All antiretroviral classes are associated with hepatotoxicity, though this is more commonly seen with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) [6, 7]. Nevirapine (NVP) increases the risk of hepatotoxicity and monitoring hepatic enzymes is recommended if feasible, especially for women with HIV who have CD4 cell counts >250 cells/mm3 and individuals with HIV who are co-infected with hepatitis-B virus (HBV) or hepatitis-C virus (HCV) [8]. However, hepatotoxicity due to hepatic steatosis

resulting from mitochondrial toxicity: more common with stavudine (d4T) than with other nucleoside reverse transcriptase inhibitors (NRTIs) [9].

The aim of the present study was to determine changes in serum liver enzymes level as markers of hepatotoxicity in HIV-infected patients those who switching from d4T-based regimen to zidovudine (AZT) antiretroviral (ARV) drugs in a resource limited setting.

# 2. Methods

### *2.1. Study Design*

This prospective cohort study was carried out from May 2013 to July 2014 at ART clinic of Hawassa University teaching hospital.

### *2.2. Study Setting and Study Population*

Eligible patients were HIV-infected, immunologically stable adults receiving only triple antiretroviral therapy that included d4T backbone with one of NNRTI (either EFV or NVP) during HAART initiation. Cases were only patients who came for switching from d4T to AZT based regimen; whereas control were patients using AZT based regimen with either of EFV or NVP during HAART initiation and those never switched before were included. Both groups were similar in duration of HAART exposure and age range. All participants included were $\geq$18 years of age, receiving HAART for a minimum of one year and have a good ART adherence (adherence rate $\geq$ 95%). A good adherence is defined by missing < 2 dose of 30 doses or < 3 dose of 60 doses; and it was adopted from Ethiopian Federal Ministry of Health (EFMOH), HIV Care/ART follow-up form. Participants receiving anti-Tuberculosis drugs, pregnant women, and jaundiced patients, patients with a known liver disease, HBV and HCV positives, and renal failures were excluded.

### *2.3. Data Collection and Measurements*

For all participants, data were collected on the socio-demographic information together with body weight and height. Blood sample was collected from each participant at the time of HAART switch and at 12 month of the switch by using Plain tubes and $K_2$EDTA anticoagulated tubes. $CD4^+$ lymphocyte count was done by using flow cytometry instrument (Becton Dickinson, CA, USA), and also CELL-DYN 1800 was used to perform haematological parameters. Clotted blood was centrifuged at 3000 cycles/ minute, and then serum was obtained for liver enzymes, total protein (TP) and albumin (ALB) tests. Serum AST, ALT and ALP were assayed by enzymatic method; and serum total TP and ALB through colorimetric method, (Human Gesellschaft für Biochemica und Diagnostica mbH, Germany). Hepatitis B virus (HBV) was done by two site sandwich immunoassay to determine surface antigen (HBsAg) from serum and for Hepatitis C virus (HCV) rapid immuno-chromatographic test was done using direct binding test for the visual detection of HCV antibodies in the serum. Severity grading of selected parameters of laboratory toxicities were assessed according to World Health Organization (WHO 2007) ART guideline, as follows:-

#### *2.3.1. Liver Enzymes (AST, ALT and ALP)*

Toxicity of degree-0: the level of toxicity which is considered as normal in which its value is $\leq$ 1.25 x ULN (upper limit normal) value. Toxicity of degree-1: the level of toxicity which is considered as weak in which its value is 1.25 – 2.5 x ULN value. Toxicity of degree-2: the level of toxicity which is considered as moderate in which its value is 2.5– 5 x ULN value. Toxicity of degree-3: the level of toxicity which is considered as severe in which its value is 5 –10 x ULN value. Toxicity of degree-4: the level of toxicity which is considered as severe in which its value is >10 x ULN value.

#### *2.3.2. Haematological Parameters*

The below table indicates the toxicity grading of haematological parameters (hemoglobin concentration and platelets count) for HIV-infected patients who were on ART.

*Haematological parameters toxicities*

| | Grade-1 | Grade-2 | Grade-3 | Grade-4 |
|---|---|---|---|---|
| Haemoglobin | 8.0-9.4 g/dl | 7.0.-7.9 g/dl | 6.6-6.9 g/dl | <6.6 g/dl |
| Platelets | (75-99) $x10^3/mm^3$ | (50-74.999)$x10^3/mm^3$ | (20-49.999)$x10^3/mm^3$ | <20 $x10^3/mm^3$ |

#### *2.3.3. Outcome Assessment*

The mean percentage changes of AST, ALT, ALP and other parameters at the switch time and at 12month of the switch for each individual was assessed by using Van Leth and colleagues' formula [10]. For each patient at specific study period we calculated this estimate as follows:

$$\%\ \text{Increase of each parameter} = \frac{-\text{Concentration at month (X)} - \text{Concentration at month (A)}}{\text{Concentration at month (A)}a} \times 100$$

Where, month-X is the study end point at which follow up takes place (12 month of HAART switch) and; month-A is the time of HAART switch or switch zero month.

### *2.4. Statistical Analysis*

Data entry and Database management was completed using EPI-INFO 2002. Statistical analyses were done using Statistical Package for Social Sciences (SPSS) Version 20. Both chi-square test and fisher exact test were used for categorical variables. Mean values and standard deviations were tabulated for normally distributed variables; median values and interquartile range (IQR) were tabulated for

skewed variables. Comparison of quantitative variables at the switch baseline and after 12 month of AZT replacement was performed with paired student *t*-test or Mann-Whitney *U*-test for those variables did not follow normal distribution. The alpha level was set at 0.05 for significance.

### *2.5. Ethical Considerations*

The study was approved by the institutional review board (IRB) of Hawassa University College of Medicine and Health Science, Written informed consent was obtained from all participants.

## 3. Results

### *3.1. General Characteristics of Study Population*

Of the 157 (100 females and 57 males) patients were enrolled in the study; 2 patients were lost to follow-up due to transferred out. Four patients were HBV positives and 1 was HCV positive. Therefore data of these 7 patients were not included in this analysis.

***Table 1.*** *Characteristics of the 150 study population*

| Characteristic | Participant (n=150) |
|---|---|
| Sex: | |
| Female, n (%) | 100(66.7) |
| Male, n (%) | 50(33.3) |
| Age (years), mean ±SD | 39.2(8.7) |
| 20-30, n (%) | 24(16.0) |
| 31-40, n (%) | 59(39.3) |
| 41-50, n (%) | 51 (34.0) |
| 51-60, n (%) | 12 (8.0) |
| >60, n (%) | 4 (2.7) |
| Weight (Kg), mean ±SD (min-max) | 57.9 ±11.6 (38-91) |
| BMI ( $Kg/m^2$), mean ±SD (min-max) | 21.7 ± 3.3 (14.4-36.4) |
| Below 18 $Kg/m^2$, n (%) | 12(8.0) |
| 18-24.9 $Kg/m^2$, n (%) | 110 (73.3) |
| ≥ 25 $Kg/m^2$, n (%) | 18 (18.7) |
| HAART (months), mean ±SD (min-max) | 60.8 ±13.4 (17-91) |
| <24 months, n (%) | 1 (0.7) |
| 24-48 months, n (%) | 32 (21.7) |
| 49-72 months, n (%) | 89 (59.3) |
| ≥ 73 months, n (%) | 28 (18.7) |
| Hb (g %), mean ±SD | 14.0 (1.9) |
| PLT count (cells/$mm^3$), mean ±SD | 2787 (84.5) |
| WBC count (cells/$mm^3$), mean ±SD | 6.3 (1.9) |
| CD4+ count (cells/$mm^3$), median (IQR) | 548 (411-785) |
| CD4+ count <350, n (%) | 26(17.3) |
| CD4+ count 35-500, n (%) | 37 (24.7) |
| CD4>500, n (%) | 87 (58.0) |
| AST, mean ±SD | 38.1(8.8) |
| ALT, median (IQR) | 33 (24-44) |
| ALP, mean ±SD | 216.7(88) |
| TP, mean ±SD | 9.5(1.3) |
| ALB, mean ±SD | 4.49(0.46) |

N.B: BMI, body mass index; HAART, highly active antiretroviral therapy; Hb, hemoglobin; PLT, platelets; WBC, white blood cells; CD4+, clusters of differentiation-4 positive cells; SD, standard deviation AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; TP, Total protein; ALB, Albumin

Base line characteristics of 150 HIV-infected patients (females 66.7% and males 33.3%) had a mean age of 39.2 years. From 120 of the cases (switch-group), 44 (33.7%) were on d4T/3TC/EFV, and 76 (63.3%) were on d4T/3TC/NVP regimens before switching to AZT/3TC based regimens. Of 30 patients of control group, 13(43.3%) were on AZT/3TC/EFV and 17(56.7%) were on AZT/3TC/NVP. At the time of the AZT/3TC replacement, the mean BMI was 21.7 $Kg/m^2$ (range, 14.4-36.4 $Kg/m^2$), and the BMI was remained stable throughout the 12 months following up without showing a significant change..Majority of patients (81.3%) had BMI < 25 $Kg/m^2$ (Table 1).

### *3.2. Hepatotoxicity and Trends of Serum Liver Enzymes and Other Parameters (Switch Group vs. Control Group)*

At the switch 0 month serum levels of mean AST and ALT were significantly higher in the switch group when compared to control group (P=0.04 and P=0.02), respectively. However ALP and TP were significantly higher in control group when compared to the switch group (p=<0.0001 and p=0.005), respectively. On the other hand at the end of the study follow-up, the mean AST was significantly higher in the control group, p=0.01 (table2).

***Table 2.*** *Comparison of Serum liver enzymes and other parameters of study population.*

| Parameters | At switch baseline (0-month) | | | At the 12 month of post-switch | | |
|---|---|---|---|---|---|---|
| | Switch group | Control group | *p-value* | Switch group | Control group | *p-value* |
| AST (U/L), mean ±SD | 39.5(19.2) | 32.2(12.6) | *0.04* | 29.3(16) | 36.3(16.7) | *0.01* |
| AST ≥ grade-1 toxicity, n (%) | 43(35.8) | 5(16.7) | *0.03* | 19(15.8) | 7(23.3) | *0.23* |
| ALT (U/L), mean ±SD | 40(26.6) | 29(16.7) | *0.02* | 27.4(14.7) | 35.6(21) | *0.09* |
| ALT ≥ grade-1 toxicity, n (%) | 25(20.8) | 4(13.3) | *0.25* | 4(3.3) | 4(16.7) | *0.01* |
| ALP (U/L), mean ±SD | 201(73.8) | 280(112) | *<0.0001* | 245.5(83) | 257(98) | *0.47* |
| ALP ≥ grade-1 toxicity, n (%) | 2 (1.6%) | 5 (16.7) | *0.04* | 9(7.5) | 3(10.0) | *0.70* |
| (AST +ALT ) grade-1 toxicity, n (%) | 17 (14.1) | 4(13.3) | *0.96* | 3(2.5) | 2(6.7) | *0.59* |
| Hb (g %), mean ±SD | 14.5(1.7) | 12.2(1.7) | *<0.0001* | 14.6(1.9) | 13(1.5) | *<0.0001* |
| PLT count(cells/$mm^3$), mean ±SD | 279(81.5) | 269(97) | *0.94* | 279(97) | 260(61) | *0.52* |
| WBC count (cells/$mm^3$) mean ±SD | 6.4(1.9) | 6.1(2.1) | *0.38* | 5.9(1.9) | 6.1(1.6) | *0.71* |
| T/P (g/dl), mean ±SD | 9.3(1.3) | 9.9(1.5) | *0.005* | 10.1(0.8) | 9.9(1) | *0.52* |
| ALB (g/dl), mean ±SD | 4.5(0.4) | 4.5(0.7) | *0.10* | 4.9(0.32) | 4.6(0.72) | *0.006* |
| weight (Kg), mean ±SD | 57.4(11) | 60.1(13) | *0.30* | 56.9(11.5) | 56.4(11) | *0.78* |
| BMI ($Kg/m^2$), mean ±SD | 21.6(3.4) | 22(3.2) | *0.36* | 21.5(3.4) | 21.8(3.4) | *0.76* |

| Parameters | At switch baseline (0-month) | | | At the 12 month of post-switch | | |
|---|---|---|---|---|---|---|
| | Switch group | Control group | *p-value* | Switch group | Control group | *p-value* |
| CD4 count (cells/mm$^3$), mean ±SD | 613(268) | 485(243) | *0.01* | 593(290) | 532(222) | *0.41* |
| HAART duration (months) mean ±SD | 60.6(13.6) | 62(13.6) | *0.76* | - | - | - |
| Age in years, mean ±SD | 38.6(8.5) | 41.9(9.2) | *0.87* | - | - | - |

N.B: BMI, body mass index; HAART, highly active antiretroviral therapy; Hb, hemoglobin; PLT, platelets; WBC, white blood cells; CD4+, clusters of differentiation-4 positive cells; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; TP, Total protein; ALB, Albumin.

### *3.3. Within a Group Comparison of Hepatotoxicity and Trends of Serum Liver Enzymes and Other Parameters*

The serum mean AST and ALT level in the switch group decreased significantly over the time observed (p=<0.0001 at 12 month for both enzymes); however the mean ALP level was significantly increased (p=<0.0001). WBC count in the switch group was significantly decreased (p=0.002). On the other hand the mean CD4+ T lymphocyte count in the control group significantly increased (p=0.001). Moreover TP and ALB mean value showed significant change in the switch group (p=<0.0001). Hepatotoxicity of AST and ALT enzymes of grade-1 and above in the switch group was significantly decreased (AST from 35.8% to15.8% and ALT from 20.8% to 3.3%). conversely ALP toxicity was significantly raised from 1.6% to 7.5% (table-3 and figure 1).

***Table 3.*** *Within a group comparison of Serum liver enzymes and other parameters of study population*

| Parameters | Switch-group | | *p-value* | Control-group | | *p-value* |
|---|---|---|---|---|---|---|
| | Switch (0 month) | Switch 12-month | | 0 month | 12-month | |
| AST (U/L), mean ±SD | 39.5(19.2) | 29.3(16) | *<0.0001* | 32.2(12.6) | 36.3(16.7) | *0.27* |
| AST ≥ grade-1 toxicity, n (%) | 43(35.8%) | 19(15.8) | | 5(16.7) | 7(23.3) | |
| ALT (U/L), mean ±SD | 40(26.6) | 27.4(14.7) | *<0.0001* | 29(16.7) | 35.6(21) | *0.28* |
| ALT ≥ grade-1 toxicity, n (%) | 25(20.8) | 4(3.3) | | 4(13.3) | 4(16.7) | |
| ALP (U/L), mean ±SD | 201(73.8) | 245.5(83) | *<0.0001* | 280(112) | 257(98) | *0.41* |
| ALP ≥ grade-1 toxicity, n (%) | 2 (1.6%) | 9(7.5) | | 5 (16.7) | 3(10.0) | |
| (AST +ALT ) grade-1 toxicity, n (%) | 17 (14.1) | 3(2.5) | | 4(13.3) | 2(6.7) | |
| Hb (g %), mean ±SD | 14.5(1.7) | 14.6(1.9) | *0.71* | 12.2(1.7) | 13(1.5) | *0.02* |
| Hb ≥ grade-1 toxicity | 0(0.0) | 2(1.6%) | | 2(6.6) | 1(3.3) | |
| PLT count(cells/mm$^3$), mean ±SD | 279(81.5) | 279(97) | *0.96* | 269(97) | 260(61) | *0.70* |
| PLT ≥ grade-1 toxicity | 1(0.8%) | 3(2.5%) | | 1(3.3) | 1(3.3) | |
| WBC count (cells/mm$^3$) mean ±SD | 6.4(1.9) | 5.9(1.9) | *0.002* | 6.1(2.1) | 6.1(1.6) | *0.95* |
| T/P (g/dl), mean ±SD | 9.3(1.3) | 10.1(0.8) | *<0.0001* | 9.9(1.5) | 9.9(1) | *0.9* |
| ALB (g/dl), mean ±SD | 4.5(0.4) | 4.9(0.32) | *<0.0001* | 4.5(0.7) | 4.6(0.72) | *0.45* |
| weight (Kg), mean ±SD | 57.4(11) | 56.9(11.5) | *0.14* | 60.1(13) | 56.4(11) | *0.29* |
| BMI (Kg/m$^2$), mean ±SD | 21.6(3.4) | 21.5(3.4) | *0.79* | 22(3.2) | 21.8(3.4) | *0.74* |
| CD4 count (cells/mm$^3$), mean ±SD | 613(268) | 593(290) | *0.29* | 485(243) | 532(222) | *0.001* |

N.B: BMI, body mass index; HAART, highly active antiretroviral therapy; Hb, hemoglobin; PLT, platelets; WBC, white blood cells; CD4+, clusters of differentiation-4 positive cells; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; TP, Total protein; ALB, Albumin; Kg, kilogram.

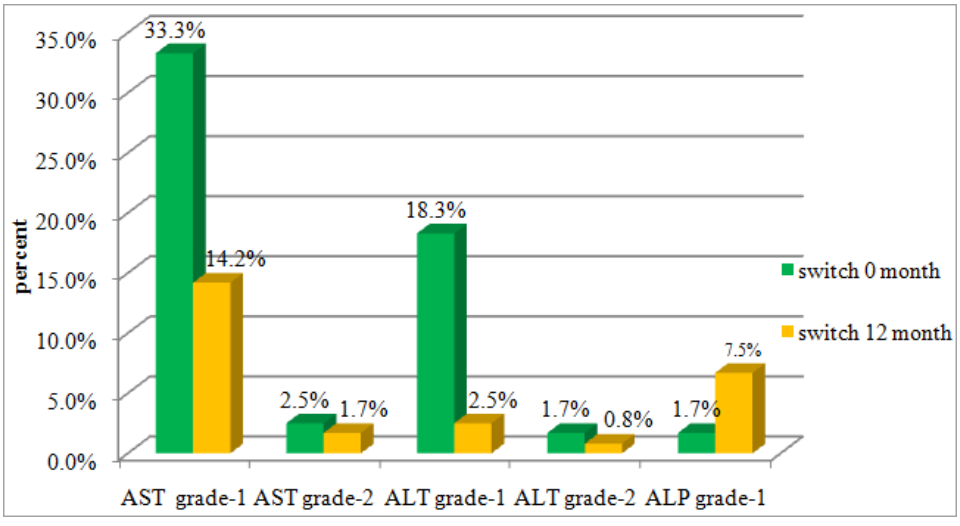


***Figure 1.*** *Hepatotoxicity indicator serum liver enzymes grade of the switch group.*

### *3.4. Comparison of Change of Parameters with Different Variables in the Switch-Group*

Males have significantly higher mean AST and ALT value at the switch 0 month when compared with females, (46.9 vs. 36.3 ±11.0; p=0.005 and 52.9 Vs. 34.3; p=<0.0001) respectively. Mean ALP was significant with age ≥ 40 years; however ALT was significant with patients using NVP (table 4).

Based on WHO hepatotoxicity grading, AST grade 1 in EFV group was 31.8% at the time of HAART switch and it was decreased to 13.6% after 12 month of post switch. However this AST grade 1 in NVP group also decreased from 34.2% to 14.6%. In contrast to AST and ALT, ALP grade-1 toxicity showed increasing trend at 12 month of post switch in EFV and NVP groups (figure 2).

***Table 4.*** *Change of parameters in some independent variables after 12 months*

| Variables | * mean | AST % (SE) | *mean | ALT % (SE) | *mean | ALP % (SE) | * mean | TP % (SE) | * mean | ALB % (SE) |
|---|---|---|---|---|---|---|---|---|---|---|
| Gender = female | 36.3 | -23.8(3.9) | 34.3 | -18.1(4.0) | 204.5 | 32.8(5.8) | 9.4 | 9.1(1.7) | 4.5 | 8.4(1.5) |
| male | 46.9 | -9.1(13) | 52.9 | -18.5(8.9) | 192 | 24.3(4.1) | 9.2 | 10.3(1.7) | 4.5 | 8.2(1.3) |
| *p value* | *0.005* | *0.20* | *<0.0001* | *0.95* | *0.41* | *0.35* | *0.32* | *0.66* | *0.24* | *0.94* |
| BMI= < 25 Kg/m$^2$ | 40.2 | -22(3.7) | 40.2 | -19.8(4) | 197 | 31.4(4.8) | 9.4 | 9.3(1.4) | 4.5 | 8.1(1.2) |
| ≥ 25 Kg/m$^2$ | 36.7 | 2.1(22) | 39.3 | -10(10.4) | 218 | 23.4(7.9) | 9.2 | 10.5(3.7) | 4.4 | 9.6(1.9) |
| *p value* | *0.45* | *0.12* | *0.89* | *0.35* | *0.22* | *0.53* | *0.46* | *0.71* | *0.36* | *0.62* |
| CD4+ cells <500 cells/mm$^3$ | 41.9 | -25.3(5.4) | 42.1 | -25.5(5) | 201 | 25.8(5.4) | 9.1 | 12.5(1.9) | 4.4 | 8.4(2.6) |
| CD4+cells ≥ 500cells/mm$^3$ | 38 | -14.5(7.1) | 38.7 | -13.7(5.4) | 200 | 32.8(5.9) | 9.5 | 7.7(1.7) | 4.5 | 8.3(0.8) |
| *p value* | *0.28* | *0.29* | *0.50* | *0.14* | *0.98* | *0.42* | *0.18* | *0.074* | *0.29* | *0.96* |
| Hb <12 g% | 30.7 | -6.7(18.2) | 26.7 | 21.9(40.2) | 186 | 32.8(19.7) | 9.5 | 9.8(3.5) | 4.4 | 13.6(5) |
| Hb ≥ 12 g % | 39.8 | -19(5) | 40.5 | -19(3.8) | 201 | 30.1(4.3) | 9.3 | 9.5(1.3) | 4.5 | 8.1(1.1) |
| *p value* | *0.35* | *0.65* | *0.31* | *0.06* | *0.68* | *0.91* | *0.80* | *0.96* | *0.49* | *0.39* |
| PLT < 150 x10$^3$ cells/mm$^3$ | 37.2 | 22.3(24.2) | 44.2 | -1.9(21.2) | 184 | 29.7(30.9) | 9.0 | 18.9(9.2) | 4.3 | -9.2(28) |
| PLT ≥150 x10$^3$ cells/mm$^3$ | 39.6 | -20(4.9) | 39.9 | -18.7(3.9) | 201 | 30.2(4.2) | 9.4 | 9.1(1.3) | 4.5 | 8.9(0.75) |
| *p value* | *0.81* | *0.12* | *0.75* | *0.44* | *0.65* | *0.97* | *0.62* | *0.18* | *0.22* | *0.003* |
| WBC < 4x10$^3$ cells/mm$^3$ | 38.5 | -30.9(8.6) | 33.2 | -2.8(17.7) | 186.9 | 34.8(15.2) | 9.4 | 7.1(4.4) | 4.4 | 9.4(2.7) |
| WBC ≥ 4x10$^3$ cells/mm$^3$ | 39.7 | -16.8(5.4) | 41 | -20.3(3.7) | 202.8 | 29.5(4.3) | 9.3 | 9.8(4.5) | 4.5 | 8.2(1.2) |
| *p value* | *0.82* | *0.34* | *0.28* | *0.14* | *0.42* | *0.68* | *0.58* | *0.48* | *0.22* | *0.71* |
| NNRTI =EFV based | 36.8 | 26.6(4.5) | 33.7 | -20.1(4.1) | 188.6 | 28.6(4.9) | 9.4 | 7.1(1.9) | 4.4 | 8.6(1.0) |
| NVP based | 41.2 | -13.9(6.9) | 43.7 | -17.0(5.7) | 207 | 31.1(6.0) | 9.3 | 10.9(1.7) | 4.5 | 8.2(1.6) |
| *p value* | *0.22* | *0.22* | *0.04* | *0.71* | *0.17* | *0.78* | *0.95* | *0.16* | *0.07* | *0.71* |
| Age < 40 years | 40.3 | -22.4(4.2) | 40.3 | -13.5(6) | 184 | 35.3(4.9) | 9.2 | 10.7(1.7) | 4.5 | 8(1.9) |
| Age ≥ 40 years | 38.7 | -15.3(9.5) | 39.7 | -23.6(4) | 220 | 24.1(7) | 9.5 | 8.1 (1.9) | 4.5 | 8.7(0.9) |
| *P value* | *0.65* | *0.54* | *0.90* | *0.19* | *0.006* | *0.18* | *0.27* | *0.31* | *0.96* | *0.75* |

N.B: BMI, body mass index; HAART, highly active antiretroviral therapy; Hb, hemoglobin; PLT, platelets; WBC, white blood cells; CD4+, clusters of differentiation; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; TP, Total protein; ALB, Albumin; ; NNRTI, non-nucleoside reverse transcriptase inhibitors; EFV, Efavirenz; NVP, Nevirapine; NRTI, nucleoside reverse transcriptase inhibitors; AZT, Zidovudine; TDF, Tenofovir ; *mean, mean at switch 0 month

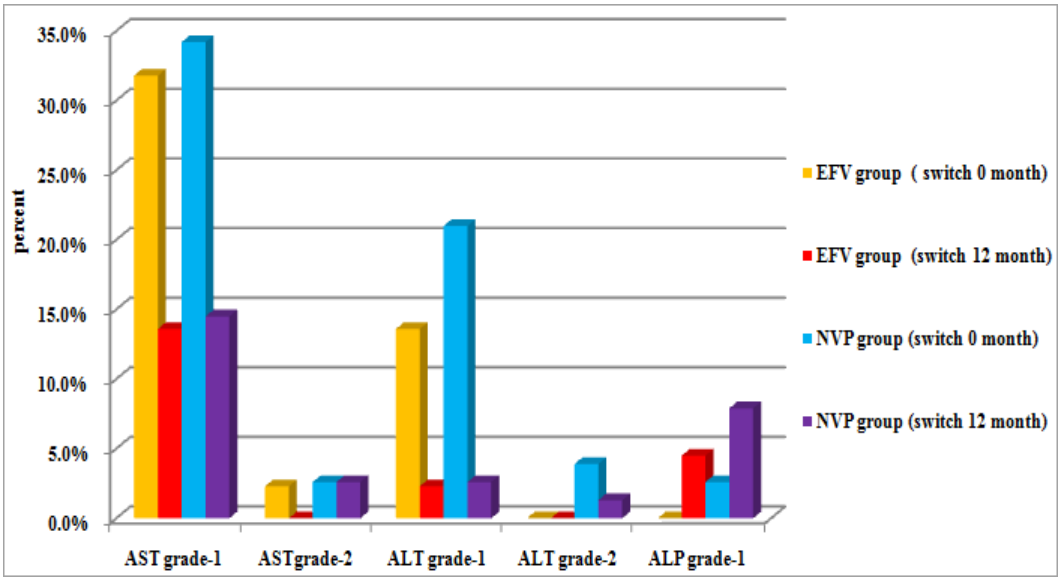


***Figure 2.*** *Comparison of hepatotoxicity indicator serum liver enzymes grade of the switch group with use of NNRTIs*

## 4. Discussion

Following recommendations from WHO 2010 guidelines, in 2013 d4T was phased-out in Ethiopia from adults' treatment [11].The replacing of d4T + lamivudine (3TC) with Zidovudine (AZT) + 3TC is not as a result of immunological failure but for the risks of metabolic and anthropometric alterations in HIV-infected patients. Therefore as expected, effectiveness of immunologic competence remained steady after therapy change. The present study result shows insignificant difference in CD4 cell count of the switch group when compared to control group at the 12 month of therapy change and which was similar with a study conducted in Germany [12].

Our study indicates that serum mean AST and ALT level in the switch group decreased significantly over the time observed (p=<0.0001 for both enzyme); the mean ALP level was significantly increased (p=<0.0001). And hepatotoxicity in the switch group was significantly decreased (ALT grade $\geq$ 1 was 3.3%) after one year of post switch. This finding is in line with the reports of incidence of drug-related hepatitis in US and European trials (ranged from 1% to 10%) [13-16].

We found that the proportions of hepatotoxicity after 12 month of post switch, which was higher among patients using NVP-based regimen when compared to EFV but not significant (ALT $\geq$ grade-1 was 3.9% vs.2.3%). Ogedegbe *et al.* have reported that all classes of antiretrovirals have been associated with increases in serum transaminases, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) appear most commonly associated with inducing liver enzyme, [17]. Our finding is comparable with cohort studies report from Haiti, Thailand, India, Zambia, and Malawi: which was ranging from <1% to 7% for NVP-associated hepatotoxicity [18,19-23]. Also in similar with our finding, studies have shown higher frequencies of hepatotoxicity in patients using NVP-based regimen (4-18%) when compared to those using EFV (1-8%) [6, 9, 24-26].

A study from South African reported that 17% incidence of serious hepatotoxicity (i.e., ALT and AST levels 5times upper limit normal (5xULN)) [27]. Contrary to this report, our cohort indicates no patients were seen with AST and ALT level greater than 2xULN.

Our study indicates patients switched from d4T/3TC to AZT/3TC had drastically reduced hepatotoxicity when compared with switch baseline. Moreover, hepatotoxicity due to hepatic steatosis resulting from mitochondrial toxicity was more common with d4T than other NRTIs [9] and Ogedegbe *et al.* report also reflected similar suggestion [17].

The mean AST and ALT were significantly higher in males when compared to females at the switch baseline but no significant hepatotoxicity was observed in patients BMI. On the contrary to our findings, one study revealed that female patients with a BMI <18.5 $Kg/m^2$ had a 50% incidence of serious hepatotoxicity [28].

## 5. Conclusion

In summary, the proportions of abnormally raised liver enzymes (AST and ALT) were significantly decreased at 12 months of post switch. These significant improvements in hepatotoxicity indicator serum liver enzymes suggest that a substitution of d4T to AZT may reverse hepatotoxicity in HIV-treated patients whereas immunologic change remained stable.

However a significant decrease in WBC count after therapy replacement should be requiring strict observation; and a significantly raised ALP enzyme should be monitored periodically to observe the progress and also have a need of further investigations: like bone function tests and 5'-nucleotidase enzyme test to identify the source of this enzyme.

## Competing Interests

We announce that we have no any competing interests.

## Authors' Contributions

D. Assegu generated and designed the study, A. Tadewos performed analysis and interpretation of data including with manuscript drafting and the critical appraisal.

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