The Correlation of Initial CD4 Cell Count with Increased Alanine Aminotransferase in Patients with Human Immunodeficiency Virus Who Have Received Nevirapine

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Abstract: Nevirapine is one of the most widely used antiretroviral drugs in developing countries. One of the current concerns is the high risk of hepatotoxicity associated with the use of Nevirapine in about 6-30% of patients and is the cause of discontinuation of antiretroviral therapy in 2-10% of patients due to severe liver disorders characterized by increased alanine aminotransferase (ALT). Hepatotoxicity in people with Human Immunodeficiency Virus (HIV) can be caused by many factors. Two mechanisms of nevirapine hepatotoxicity have been proposed. One of mechanisms is the immune-mediated hypersensitivity reaction that induces hepatotoxicity reactions that are thought to be associated with early CD4 counts. The aim of this study was to determine the correlation between initial CD4 count and elevated ALT levels in people infected with HIV who have received nevirapine for 3 months. This study was cross-sectional observational analytic research of 30 HIV-infected patients receiving nevirapine treatment. Each patient was assessed for initial CD4 cell count and initial ALT levels before receiving nevirapine treatment. After 3 months of nevirapine treatment, ALT re-examination was performed to determine elevated alanine aminotransferase levels, then correlation analysis was performed using Spearman's test. Spearman's correlation test results found a negative correlation between initial CD4 count and elevated ALT levels but not was statistically significant ($r = -0.107$; $p = 0.573$). In the sub analysis, a positive correlation was found between initial ALT level and ALT level increase ($r = 0.427$; $p = 0.019$). Initial CD4 count was not correlated with elevated ALT levels in HIV-infected patients receiving Nevirapine-based ARVs.

1 INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is a clinical syndrome caused by Human Immunodeficiency Virus (HIV) that has caused many deaths in various countries and it is estimated that 34 million people worldwide had been infected with HIV by the end of 2011 (Kanta, 2011; Hamza M, 2014). The morbidity and mortality of HIV decreases significantly after introduction of antiretroviral therapy (ART). With regard to the life expectancy of HIV-infected patients, ARV (antiretroviral) side-effects are of paramount importance (Bruck et al., 2008; Kovari et al., 2010). Nevirapine (NVP) is one of the most widely used antiretroviral drugs in developing countries and recommended by WHO since 2002 as part of first-line ART because of its high effectiveness and affordable price. However, NVP has a major limitation of a high risk of hepatotoxicity (Knobel et al., 2008; Manosuthi et al., 2008; Coffie et al., 2010; Shubber et al., 2013).

Hepatotoxicity is a serious NVP side-effect in HIV-infected patients. The incidence of mild to severe hepatotoxicity and the occurrence of liver failure are frequently reported in the use of NVP. Literature suggests that NVP hepatotoxicity occurs in 6-30% of patients and causes NVP to terminate in about 2-10% of patients (Manosuthi et al., 2008; Gao et al., 2010; Neuman et al., 2012; Itodo GE, 2015). NVP hepatotoxicity was assessed based on levels of alanine aminotransferase (ALT) and grouped according to the criteria of the Clinical Trial Group of AIDS (Kalyesubula et al., 2011; Chu et al., 2012). Several studies have reported an increase in baseline ALT levels of HIV patients − either those who have not or already have ARVs. Another study found that the group of HIV patients receiving ARV had higher baseline ALT than the naive ARV group

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(Shiferaw et al., 2016). Other studies have found an increased risk of hepatotoxicity in HIV patients receiving NVP-based treatment (Gao et al., 2010).

NVP is associated with several risk factors such as initial Cluster of Differentiation 4 (CD4) count, coinfection with HBV/HCV, ALT levels before treatment, elderly, etc. (Ugiagbe RA, 2011; Bello SI, 2014). There are two mechanisms of NVP hepatotoxicity that have been proposed. The first mechanism involves immune-mediated hepatotoxicity that is suspected to correlate with baseline CD4 count. The second mechanism is suspected to be related to the drug's intrinsic toxic effects and doses. Early onset hepatotoxicity occurs in the first 18 weeks, whereas late-onset hepatotoxicity occurs after 18 weeks of NVP (De Maat MMR, 2003; Bruck et al., 2008; Mbougua et al., 2010; Alfirevic A & Pirmohamed M, 2011). In the study, the median onset of NVP hepatotoxicity occurred at 12.43 weeks after NVP administration (Manosuthi et al., 2008), while other studies found a median onset of NVP hepatotoxicity occurring on the 137th day after NVP administration (Bruck et al., 2008). Another study found that HIV patients with a baseline CD4 count > 250 cells/mL were 10 times more likely to have NVP hepatotoxicity than those with a baseline CD4 count ≤ 250 cells/μL (Mafuru M & Kamuhabwa A, 2015).

This study was expected to analyze the correlation between initial CD4 count and NVP hepatotoxicity to increase the awareness of in-depth physicians of NVP-related hepatotoxicity in HIV patients, especially in Dr. Soetomo General Hospital Surabaya.

2 METHODS

This study used an observational study with cross sectional analysis with the aim of measuring the correlation between baseline CD4 count and elevated ALT levels in HIV-infected patients receiving ART based on NVP of HIV/AIDS patients.

The research subjects were from the Outpatient Installation (medical record division) Intensive Care and Infectious Diseases Unit Dr. Soetomo General Hospital Surabaya, from January 1 to December 31, 2016. The sample was collected by using consecutive sampling from patients' medical records in accordance with the inclusion criteria, including HIV/AIDS patients who received ART based on NVP (first-line antiretroviral treatment) for 3 months with elevated levels ALT, aged > 18 - 60 years old, had never received antiretroviral treatment before, and had complete medical records according to the variables studied. On the other hand, the exclusion criteria were patients with Hepatitis B and/or Hepatitis C, and who received anti-Tuberculosis therapy two months before the start of ARV treatment up to three months after the first ARV treatment. Those with an initial level of ALT > 1.25 upper limit of normal values (> 1.25 ULN) received oral fluconazole treatment two weeks before ARV therapy and during the study observation.

Afterwards, CD4 was calculated at the start of the treatment, and ALT level elevation was examined before and after 3 months of ARV treatment. The data were then analyzed, and processed by using SPSS 18 statistical program (SPSS, Inc., Chicago, IL.).

3 RESULTS

From the 30 subjects enrolled in this study, there were more male subjects with more than 21 males (70%) versus 9 females (30%) with an average age of 33.67 years old. The age distribution of the study subjects was normal with the youngest age range of 20 years old and the oldest research subjects aged 48 years old. The average weight of the subjects was 56.73 kg which varied from 34 - 80 kg.

The subjects of the study were mostly (90%) receiving cotrimoxazole prophylaxis and only 3 subjects did not receive cotrimoxazole prophylactic treatment. Opportunistic infection (OI) was found in five subjects with one subject having toxoplasmosis infection, three subjects had oral candidiasis, and one subject had a toxoplasmosis infection accompanied by oral candidiasis. Five subjects were receiving Opportunistic Infection treatment: one subject was receiving pyrimethamine and clindamycin combination treatment, three subjects were receiving nystatin drop treatment, and one subject was receiving combination of pyrimethamine and clindamycin as well as nystatin drop treatment. The research subjects who were receiving nystatin drop treatment were included in the study because theorists did not find potential hepatotoxicity associated with the use of nystatin drops. The general characteristics data of the subjects can be seen in Table 1.

Table 1: The general characteristics of patients.

General Characteristics		Results
Gender	Female	9 (30%)

	Male	21 (70%)
Age (years)	Mean ± SD	33.67 ± 7.73
Body weight (Kg)	Mean ± SD	56.73 ±12.22
Use of cotrimoxazole	Yes	27 (90%)
	No	3 (10%)
Opportunistic Infection	No opportunistic	25 (83.3%)
	Toxoplasmosis	1 (3.3%)
	Oral candiasis	3 (10.0%)
	Toxoplasmosis and oral candiasis	1 (3.3%)
Other medication consumptions	None	25 (83.3%)
	Pyrimethamine and clindamycin	1 (3.3%)
	Nystatin drop	3 (10.0%)
	Pyrimethamine Clindamycin and Nystatin drop	1 (3.3%)

3.1 Initial CD4 Count in HIV/AIDS Patients

The initial CD4 count distribution was abnormal, with an initial median CD4 count of 45.0 cells/µL, with the lowest initial CD4 count of 6 cells/µL and the highest initial CD4 count value of 248 cells/µL. Initial CD4 count result for the study subjects can be seen in Table 2.

Table 2: Initial CD4 count in HIV/AIDS patients.

Initial CD4 Count		Results (cell/µL)
Initial CD4	Median	45.0
	Range	6 - 248

3.2 Increase in ALT Levels in HIV/AIDS Patients

Based on the results of the initial ALT level (months 0) examination on 30 HIV/AIDS subjects, it was found that the initial ALT level distribution was abnormal, with median baseline ALT values of 21.5 U/L, with the lowest initial ALT level of 4 U/L and the highest value of the initial ALT level of 59 U/L. On the other hand, the final ALT levels (month 3) showed that ALT level distribution was abnormal, with a median ALT level of 36.5 U/L, with the lowest ALT level of 14 U/L and the highest ALT level of 161 U/L as shown in Figure 1.

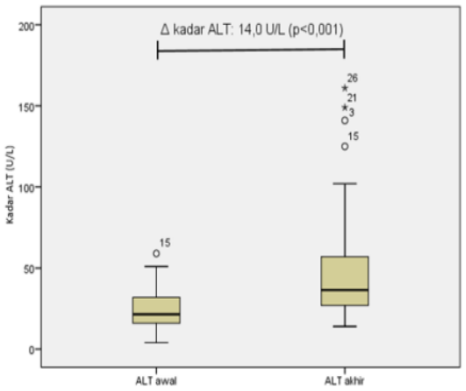

Figure 1: Box plot of increased ALT levels.

The increase of ALT level of the subjects after analysis using the Wilcoxon test was $p < 0.001$. There was a statistically significant difference in ALT level change. The figure above shows the influence of other factors that influence the increase of ALT levels except NVP administration.

Based on the results of the ALT level elevation test, the distribution was not normal. The results of elevated ALT levels of HIV/AIDS patients are shown in Table 3.

Table 3: Increased ALT levels in patients with HIV/AIDS.

Increased ALT Level		Results (U/L)
Increased ALT Level	Median	14.0
	Range	4 s/d 135

3.3 The Correlation of Initial CD4 Count with Increased Levels of ALT in HIV/AIDS Patients and the Correlation between its Components

The analysis of the correlation between initial CD4 count and elevation of ALT level in this study resulted in an r value of -0.107 with $p = 0.573$. It was concluded that there was no association between initial CD4 count and elevated ALT levels. The result of the association between baseline CD4 count and elevated ALT levels appears in the scatter diagram of Figure 2.

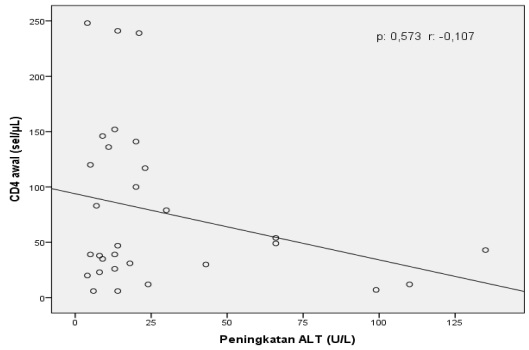

Figure 2: The scatter diagram of initial CD4 count in relation to the increase of ALT level.

In this study, there was a significant correlation (p = 0.019) between baseline ALT levels with elevated ALT levels with an r value of 0.427 indicating a moderate correlation. The association between baseline ALT levels and elevated ALT levels in this study was positive and significant.

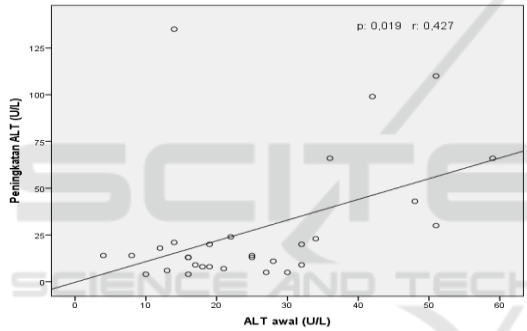

Figure 3: The scatter diagram of the initial ALT level in relation to increasing ALT levels.

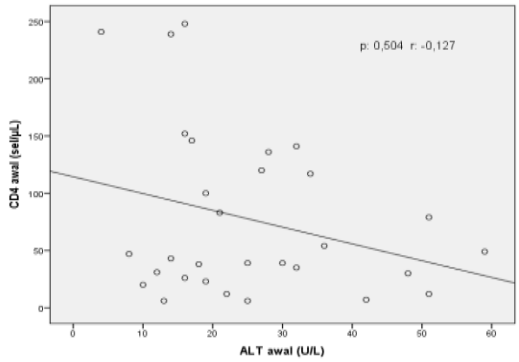

Figure 4: The scatter diagram of initial CD4 count in relation to initial ALT level.

The result of the correlation between initial CD4 count and initial ALT level was r = -0.127 with p = 0.504. It was concluded that there was no correlation between initial CD4 count and initial ALT level. The result of the association between baseline CD4 count and baseline ALT levels is shown in the scatter diagram of Figure 4.

4 DISCUSSION

This study enrolled 30 subjects with HIV/AIDS who received NVP-based ART with an average age of 33.67 years old, which is similar to the previous research involving 63 patients with HIV/AIDS in the Outpatient Installation Intensive Care and Infectious Diseases Unit of Dr. Soetomo General Hospital Surabaya with an average age of 32.81 years old (Prayitno JH, 2010). Other studies were also in line with 206 HIV/AIDS patients receiving NVP-based ART with a median age of 33 years old (ranging from 29-38 years old) (Manosuthi et al., 2008). The results of this study are also in line with UPIPI internal data which record that 80.0% of patients age was between 25-49 years old. Also, the Directorate General of Communicable Disease Control & Environmental Health confirmed that the cumulative number of AIDS cases by age group of 20-29 years old was 31.5%, followed by the age group of 30-39 years old (29.6%) (Kementerian, 2016).

The subjects of the study were mostly male, with the ratio of 2.3: 1. The gender ratio in this study was in line with the study by the Directorate General of Communicable Disease Control & Environmental Health for Statistics of HIV/AIDS Cases in Indonesia reported up to March 2016 by gender. Male patients numbered 42,838 while female patients numbered 24,282 (1.8: 1) (Kementerian, 2016). The results of this study are also in accordance with Intensive Care and Infectious Diseases Unit's internal data recorded until the end of September 2016 for 6,019 (67.4%) male patients and 2,915 (32.6%) female patients (2.1: 1).

The highest percentage of factors causing HIV transmission were unsafe heterosexual sex (61.5%), unsterile needle syringe use by drug users (15.2%), perinatal transmission (2.7%) and homosexual sex (2.4%). Based on the survey, the report of drug abuse in Indonesia conducted by the National Narcotics Agency (BNN) in 2008 estimated the number of drug abusers to be as much as 3.1 - 3.6 million people. Male patients (88%) were much higher in number than women (12%). From a number of AIDS patients treated at the Intensive Care and Infectious Diseases Unit of Dr. Soetomo General Hospital Surabaya in 2005, there was 63% transmission of HIV through the use of intravenous

narcotics (Nasronudin, 2007). Based on gender, males are more at risk of HIV/AIDS than females because males are more mobile than females (Nandasari F & Hendrati LY, 2015). Males have a tendency to have HIV-risk-bearing behaviors greater than females, which explains the higher ratio of males to females.

The mean weight of the subjects was 56.73 kg varying from 34 kg to 80 kg. However, in this study, there were no data on the height of the study subjects so that the researchers could not obtain BMI data of the subjects who had more clinical benefit in relation to hepatotoxicity of the liver related to NVP administration. Most subjects in this study (90%) were receiving cotrimoxazole prophylaxis and only three subjects were not receiving cotrimoxazole prophylactic treatment. The treatment of Cotrimoxazole prevention is administered to clinical HIV/AIDS patients regardless of CD4 count < 200 cells/μL or WHO clinical stage 2, 3 or 4 with any CD4 count. The high percentage of patients receiving cotrimoxazole prophylaxis treatment in this study's subjects (90%) was in accordance with the Intensive Care and Infectious Diseases Unit's internal data which accounted for 79.9% of patients receiving cotrimoxazole preventive treatment.

Opportunistic infections were found in five subjects with a single subject having toxoplasmosis infection treated with a combination of pyrimethamine and clindamycin, three subjects with oral candidiasis were receiving nystatin drop treatment, and one subject with toxoplasmosis infection accompanied with oral candidiasis was receiving the combination treatment of pyrimethamine and clindamycin as well as nystatin drop treatment.

Nystatin is not absorbed through the gastrointestinal tract, and works locally in the mouth area; thus, there is no potential for hepatotoxesis. Pyrimethamine also has a low hepatotoxic potential. A common side-effect of pyrimethamine is cytopenia. Clindamycin is a drug that is metabolized in the liver and has a half-life of 2-2.5 hours. In patients with liver disorders, it may result in a prolonged half-life but clindamycin-related hepatotoxicity is very rare and occurs 1-3 weeks after clindamycin.

CD4 count is used to determine the stage of HIV disease, the risk of opportunistic infections, to assess the prognosis, measure immunity status and as a guide to decide when to start ART (Itodo GE, 2015; Leticia OI, 2014). Generally, a person with normal immune status has a CD4 count of 800-1,200 cells/μL of blood. When the CD4 count falls to < 500/μL, mild infections including herpes simplex, condyloma, yeast infections, thrush and candidiasis can occur (Klimas et al., 2008).

In this study, we found an initial CD4 cell count with a median of 45.0 cells/μL, with a minimum value of 6 cells/μL and a maximum value of 248 cells/μL, and 90% of the study subjects had an initial CD4 count < 200 cells/μL. These results are similar to those for 206 HIV patients who received baseline CD4 counts with a median of 40 (14-111) cells/μL (Manosuthi et al., 2008). Different results were obtained for a mean CD4 cell count of 266.35 ± 203.11 cells/μL (Prayitno JH, 2010). The low median CD4 count in this study could be due to HIV/AIDS patients mostly coming for treatment and starting ARV therapy at the Intensive Care and Infectious Diseases Unit of Dr. Soetomo General Hospital at the clinical stage of HIV/AIDS with a low CD4 count (stage 3 and stage 4).

ALT and AST are enzymes that are released into the body in increasing amounts when liver cell damage occurs. ALT has been shown to be more specific for evaluating liver disease than AST because it is found in larger concentrations in the liver while concentrations in heart, skeletal muscle, adipose, intestine, prostate, brain and kidney tissue than in the liver (Upadhyay R & Kalla A, 2011; Liu et al., 2014).

A moderate increase in liver enzymes such as ALT often occurs in people with HIV/AIDS (Denue BA, 2013). Increased liver enzymes in HIV patients can be caused by HIV itself or other factors. Other factors include co-infection with HBV, HCV, opportunistic infections, malignancy, hepatotoxic drugs, high ALT/AST levels before treatment, alcohol abuse, elderly, females, use of ART (Price JC & Thio CL, 2009; Ugiagbe RA, 2011; Bello SI, 2014).

In this study, an initial ALT level was found with an initial median ALT of 21.5 U/L, with the lowest initial ALT of 4 U/L levels and a high score of baseline ALT of 59 U/L. These results were similar to those in Kenya and in Thailand that obtained median baseline ALT levels of 22 (17-32) U/L and 27 (17-44) U/L (Manosuthi et al., 2008; Makori J, 2015).

In this study, median baseline ALT levels of the subjects were lower than the mean ALT levels obtained by the study subjects with ALT > 1.25 Upper limit of normal (ULN) (62.5 U/L) levels that were excluded from this study with the aim of minimizing liver function impairment of the subjects prior to NVP therapy that could affect initial CD4

count correlation with NVP-related hepatotoxicity events.

In this study, we found a median value of final ALT level of 36.5 U/L, with the lowest value range of final ALT level of 14 U/L and highest value of end ALT value of 161 U/L. The increase of ALT level of the study subjects after being analyzed using the Wilcoxon test showed a statistically significant difference in ALT change with a median increased ALT level of 14.0 U/L.

HIV / AIDS patients tend to have higher baseline ALT levels than individuals without HIV. This often happens even before ARV therapy is given. High levels of initial ALT level suggest a liver intrinsic disorder that can result from HIV of cells in the liver or may be due to high systemic inflammation that can also be caused by the presence of IO requiring potentially hepatotoxic drugs for the treatment of IO. The severity of HIV can be judged by the high viral load of the patient. This is in line with the research finding results of an association between viral load ≥ 100,000 copies/mL with ALT levels (Kovari et al., 2010). CD4 count is generally inversely proportional to an increase in patient viral load. There were no patient viral load data in this study so that the association of baseline ALT levels and viral load could not be evaluated.

Based on the previous analysis, it can be concluded that elevated ALT levels in this study were influenced by baseline ALT levels, while elevated ALT levels could be due to NVP toxic effects that were elevated due to impaired liver function prior to NVP treatment.

5 CONCLUSION

There was no correlation between baseline CD4 cell count and elevated ALT levels (p = 0.573) in HIV/AIDS patients receiving NVP-based ARV in the Outpatient Installation, Intensive Care and Infectious Diseases Unit, Dr. Soetomo General Hospital Surabaya.

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