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Effect of Anti-Retroviral Fixed-Dose Combination Tenofovir, Lamivudine, And Evafirenz on Lipid Profile in HIV/AIDS Patients

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ABSTRACT

Dyslipidemia has been recorded in antiretroviral therapy (HAART) naive HIV- and HAART HIV-patients. This study aimed to analyze the effect of Anti-Retroviral Fixed-Dose Combination (FDC) Tenofovir, Lamivudine, and Efavirenz on lipid profile in HIV/AIDS patients. This was a longitudinal observational study using one group pretest and posttest design. Subjects were measured for their lipid profile including total cholesterol, triglyceride, LDL, and HDL before and after 3 months receiving FDC ARV. Twenty subjects involved in this study. The mean total cholesterol before the treatment was 163.30±26.38 mg/dl and after 3-month treatment 183.15±26.36 mg/dl (p = 0.008). The mean of triglyceride before the treatment was 127.75±27.57 mg/dl and after 3 months 154.15±34.43 mg/dl (p = 0.003). The mean LDL before of the treatment was 92.90±27.30 mg/dl and after 3 months 109.95±22.49 mg/dl (p = 0.011) and mean of HDL before the treatment was 45.75±7.22 mg/dl and after 3 months 40.40±5.37 mg/dl (p = 0.003). FDC ARV had a significant effect on lipid profiles. Hence, a baseline lipid profile should be obtained in all HIV infected patients before and during antiretroviral treatment.

Keywords: Teoritin, Dyslipidemia; total cholesterol, triglyceride, LDL; HDL, HIV-naïve, anti-retrovirus

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INTRODUCTION

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) has become a world health problem and ranked number four in the world.(1) Besides, HIV compared with other diseases is rapidly growing, progressive, chronic, and serious illness.(2,3) Prevention of HIV using antiretroviral (ARV) therapy is a widely used strategy worldwide to prevent transmission of HIV.(4) ARV therapy requires high adherence and monitoring to suppress viral replication and prevent transmission in the blood, to improve immunology and clinical outcomes.(5,6)

Since the presence of ARV therapy, the mortality rate of HIV-infected patients has been reduced to 70% in the United States and 50% in Indonesia. (1,7) In line with the increase in the life expectancy of HIV patients, new problems arise, including dyslipidemia. Dyslipidemia in HIV patients may be related to the viral infection itself or due to the side effects of ARVs. In Indonesia, one of the most widely used ARV regimens as the first line is the FDC (fixed drug combination), consisting of Tenofovir, Lamivudine, and Efavirenz. However, until now it has not been known whether dyslipidemia occurs in HIV patients receiving FDC ARV therapy.(8–10)

Since the discovery of ARV, there has been a shift in the cause of the death of HIV/AIDS patients. There has been an increase in deaths from cardiovascular disease by 21.8% compared to that before the era of ARVs (8.4%).(8–10) The existence of this shift needs to be observed and anticipated thoroughly so that the death in patients with HIV/AIDS, especially due to cardiovascular disease, can be suppressed further.

Dyslipidemia plays an important role as the cause of disability and mortality.(11) Dyslipidemia due to the use of ARV is one of the factors that contribute to the incidence of cardiovascular disease in patients with HIV/AIDS. Based on the 2003 Data Collection on Adverse Events of the Anti-HIV Drugs (DAD) Study, the risk of the incidence of myocardial infarction in HIV patients was higher than that of non-HIV and the incidence increased by 2.5x in HIV patients who received ARV for more than 4 years.(12) Chronic inflammation through increased pro-inflammatory cytokines, endothelial changes and increased reactive oxidative species (ROS), may cause changes in lipid metabolism that results in dyslipidemia.(12) This effect is similar to other causes of infection.(13,14) The FDC ARV may also cause dyslipidemia through mitochondrial toxicity due to the inhibition of mitochondrial DNA polymerase-γ on fat and other tissues. This may affect respiratory chain complexes which may cause oxidative disturbances, resulting in the accumulation of lipids in the circulation. In addition, nucleoside analog drugs (Lamivudine, Tenofovir) can also deplete DNA in peripheral adipocyte tissue, resulting in apoptosis and decreased lipid reserve capacity.(15)

Identification of dyslipidemia in HIV-naïve patients and those receiving FDC-type antiretroviral therapy is very important to be the basis for providing blood lipid-lowering therapy or for replacing regimens that have lower lipotoxicity. Therefore, this study was conducted to determine the effect of FDC ARV therapy for at least 3 months on lipid profiles (total cholesterol, LDL, HDL, and triglyceride levels) of the patients in the outpatient clinic of the Intensive Care Unit for Infectious Diseases, Dr. Soetomo Hospital, Surabaya, Indonesia.

METHODOLOGY

This study was a longitudinal observational study using one group pretest and posttest design, involving 20 samples of HIV/AIDS patients who had not received ARV therapy and then received ARV FDC (Tenofovir, Lamivudine, Efavirenz) therapy for 3 months, who visited the Intensive Care Unit for Infectious Diseases, Dr. Soetomo Hospital, Surabaya, between May and September 2018.

The independent variable was FDC (Tenofovir, Lamivudine, Efavirenz) ARV and the dependent variable was total cholesterol, triglycerides, LDL and HDL. Total levels of cholesterol, triglycerides, LDL and HDL were measured using laboratory tests for blood lipids. Data on total cholesterol, triglyceride, LDL and HDL levels used mg/dl units and analysis of FDC ARV therapy effects on lipid profiles used computer-based statistical analysis. The normality of data distribution has been tested, so a paired t-test was used to determine the effect of FDC ARV after 3 months on the lipid profile. Different test results were stated significant if the p-value was below 0.05.

RESULTS

Descriptive analysis of research subjects showed in Table 1. The mean age of the subjects was 33± 9 years, with the youngest being 20 years and the oldest 50 years. The majority of the subjects were males, 15 (75%), and the most risk factor was vaginal sex as much as 11 subjects (55%). Subjects with a CD4 cell count of less than 200 were 12 (60%), 4 subjects (20%) were in CD4 range of 200-349, 4 subjects (20%) were in CD4 range of 350-499 and none of the subjects had CD4 above 500. The mean body mass index was 20.99±1.71 kg/m^2. The mean systolic and diastolic blood pressure were 117.2±7.68 and 76.8±5.74, respectively. The mean of the lipid profiles was mostly increased but decreased in HDL-c after 3 months of receiving FDC ARV. The mean total cholesterol, triglyceride, LDL-c, HDL-c before ARV treatment was 163±26, 128±28, 93±27, and 46±7, respectively. While after receiving ARV, the mean total cholesterol, triglyceride, LDL-c, HDL-c was 183±26, 154±39, 110±22, and 40±5, respectively (Table 2).

The effect of FDC ARV after 3 months on the lipid profile was analyzed used paired comparative T-test. The result showed significant effect in total cholesterol, triglyceride, LDL-c, and HDL-c with p = 0.008; p = 0.003; p = 0.011; p = 0.003 respectively, in HIV/AIDS patients after receiving FDC ARV for 3 months (Table 3).

DISCUSSION AND CONCLUSION

This study revealed that there was a significant effect in lipid profile after FDC ARV treatment. The total cholesterol, triglyceride, LDL-c was increased while HDL-c was decreased after 3 months of receiving FDC ARV. Changes in lipid metabolism in HIV patients who have received therapy are due to the release of proinflammatory cytokines/lipid peroxidases. IFN-α is believed to be the cause of increased triglyceride levels through a mechanism of reduced triglyceride clearance, increased lipogenesis in the liver and increased the synthesis of VLDL.(16) In addition, there is an increase in cholesterol ester transfer protein activity, resulting in increased cholesterol transfer from HDL-c to apoprotein-B which causes a decrease in HDL level.(17)

Anti-retroviruses also play a role in changing lipid metabolism in HIV/AIDS patients. Tenofovir, which is a class of NRTIs, causes DNA depletion in peripheral adipocyte tissue, resulting in apoptosis and decreased lipid reserve capacity. In addition, this drug also causes mitochondrial toxicity by inhibiting mitochondrial DNA polymerase-γ on fat and other tissues that will affect respiratory chain complexes. As a result, fatty acid oxidation is disturbed and the accumulation of TG and intracellular lactate is taking place, which eventually enters the systemic circulation.(15,18) Efavirenz, which is a class of NNRTI, causes a decrease in regulatory expression of Sterol Regulatory Enhancer Binding Protein-1 (SREB-1) which acts as a regulator in the process of glucose synthesis and adipocyte differentiation so that the inhibition of SREBP-1 located in adipocyte tissue will cause a decrease in adipocyte differentiation, increased lipogenesis and VLDL processes, resulting in dyslipidemia.(19)

Commonly, the decision to start ARV therapy is based on immunological criteria, as defined by the level of CD4 count. Thus ARV therapy should only begin when the patient is committed to long term treatment.(20) However, the atherogenic profile of lipids in HIV patients increases with ARV administration and increases more along with the duration of ARV administration. The prolonged antiretroviral treatment causes the patients to have a higher risk of cardiovascular disease due to dyslipidemia resulting from the side effects of ARV administration and metabolic effects produced by the viral infection itself.(21)

This study has several limitations, ie the small number of samples that were not able to represent the situation in Indonesia, the short observation period so that it was less optimal to observe the side effects of the antiretroviral drugs, and many factors that influence changes in lipid profile before and after receiving FDC ARVs.

FDC ARV after 3 months has a significant effect on lipid profiles (high total cholesterol, high triglycerides, high LDL, and low HDL). Examination of lipid profiles should be performed before and during ARV therapy to minimize the risk of cardiovascular disease.

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Table 1. General characteristics of HIV/AIDS patients in Intensive Care Unit for Infectious Diseases, Dr. Soetomo Hospital, Surabaya

Characteristics	Results (n=20)
Age (year)	
Mean±SD	33±9
Range (min. - max)	(20-53)
Age group (year)	
<20 years, n (%)	0 (0)
20-29 years, n (%)	7 (35)
30-39 years, n (%)	9 (45)

40-49 years, n (%)	3 (15)
≥50 years, n (%)	1 (5)
Gender	
Male, n (%)	15 (75)
Female, n (%)	5 (25)
Risk factors	
Risk anal sex	9 (45)
Risk vaginal sex	11 (55)
Injected narcotics	0 (0)
CD4 groups	
CD4 < 200, n (%)	12 (60)
CD4 200-349, n (%)	4 (20)
CD4 350-499, n (%)	4 (20)
CD4 ≥500, n (%)	0 (0)
Body Mass Index (kg/m^2)	
Mean±SD	20.99±1.71
Range (min – max)	(23.5-18.5)
Sistolic Blood Pressure (mm/Hg)	
Mean±SD	117.2±7.68
Range (min – max)	(130-98)
Diastolic Blood Pressure (mm/Hg)	
Mean±SD	76.8±5.74
Range (min – max)	(88-68)

Table 2. Mean lipid profile before and after receiving FDC ARV for 3 months

	Total cholesterol	Triglyceride	LDL-c	HDL-c
Before ARV Mean±SD	163±26	128±28	93±27	46±7
3 months after FDC ARV Mean±SD	183±26	154±39	110±22	40±5

Table 3. Analysis the effect of FDC ARV after 3 months on lipid profile

Variable	Mean	Δ Mean	p*
Total cholesterol pre (mg/dl)	163.30±26.38	19.85±29.80	0.008
Total cholesterol post (mg/dl)	183.15±26.36		
Triglyceride pre (mg/dl)	127.75±27.57	26.40±34.36	0.003
Triglyceride post (mg/dl)	154.15±34.43		
LDL-c pre (mg/dl)	92.90±27.30	17.05±27.05	0.011
LDL-c post (mg/dl)	109.95±22.49		
HDL-c pre (mg/dl)	45.75±7.22	5.35±7.16	0.003
HDL-c post (mg/dl)	40.40±5.37		

*Analyzed by paired samples T-test (2-tailed significance)