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Changes in Estimated Glomerular Filtration Rate in Naive HIV Patients with Fixed Drugs Combination Tenofovir Treatment in First 3 Months

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ABSTRACT

The treatment HIV/AIDS uses ARVs, one of which is FDC tenofovir. FDC tenofovir is associated with changes in kidney function. This study aimed to determine changes in serum creatinine levels and eGFR in naïve HIV patients who received FDC tenofovir therapy for 3 months. This prospective longitudinal study included naïve HIV patients who received tenofovir. Serum creatinine levels and eGFR was measured before administration of tenofovir and after 3 months administration of tenofovir. Among 30 patients, the subject consisted 20 (66,7%) males and 10 (33.3%) females. The median age was 37 with range 17-57 years. The mean serum creatinine before tenofovir treatment 0.89 ± 0.25 mg/dL and after 3 months treatment mean ± SD 0.92 ± 0.28 mg/dL. The mean eGFR before administration of tenofovir treatment 89.37 ± 33.54 ml/min/1.73m2 and after 3 months the mean ± SD 88.31 ± 33.56 ml/min/1.73m2. There were no significant changes in serum creatinine and eGFR after 3 months administration of tenofovir (p = 0.441; p = 0.771, respectively). Serum creatinine and eGFR were not change after administration of tenofovir in naïve HIV patients.

Keywords: HIV, tenofovir, serum creatinine, eGFR

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INTRODUCTION

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is rapidly growing, chronic, progressive and serious illness compared with other diseases.(1,2) HIV / AIDS treatment is growing rapidly with the discovery of antiretroviral drugs. The use of antiretroviral drugs increases the life expectancy of patients with HIV / AIDS. Treatment of HIV / AIDS in Indonesia began using combination therapy of lamivudine zidovudine (duviral®) and nevirapine (neviral®). Ministry of health in 2014 recommended one of the antiretroviral drugs used is the fixed drugs combination (FDC) consisting of a combination of lamivudine, tenofovir and efavirenz. FDC has several advantages compared to other antiretrovirals which can be given to pregnant women, patients with pulmonary tuberculosis (TB) and other opportunistic infections.(3)

The kidney function represents by glomerular filtration rate (GFR) because of glomerulus act as a filter.(4,5) When normal kidney function is reduced, ultrafiltration will be required to maintain volume control.(6) If kidney function is interrupted by any cause, the kidneys will not be able to maintain normal physiological functions.(7) Identification of kidney function is important because it is associated with a high morbidity and mortality.(8) The cause of the emergence of this kidney disorder itself, the HIV/AIDS, can lead to a chronic inflammatory process that affects the kidney functions, as similar with other infections.(9,10)

Currently the use of tenofovir as a component of FDC is feared to have side effects on the kidneys. Tenofovir was originally said to be safe against kidney function, but recent studies have shown controversy. Some studies show a significant decrease in kidney function while other studies show no changes in kidney function. The timing of changes in kidney function also differs, some guidelines recommend examining tenofovir use for a period of 1 year after tenofovir use, but some studies say changes in kidney function can occur in the first 3 months or 6 months after tenofovir use. A study conducted by John Hopkins University in the United States showed that changes in serum creatinine levels after administration of tenofovir in the first 90 days would tend to persist in the following months.(11)

Research evaluating the effect of tenofovir and serum creatinine in Indonesia is still minimal. Study on the effects of tenofovir on HIV naive conducted in the US did not show a decrease in GFR in long-term administration. Study in Taiwan showed that patients given combination antiretroviral therapy containing tenofovir or without tenofovir showed no significant differences. Research in Singapore showed no significant differences in patients given tenofovir at an evaluation every 3 months. Some even show an improvement in creatinine clearance as calculated by the GFR. While research conducted in Myanmar shows that only a few patients have decreased kidney function, which according to the study shows that the decline in kidney function is still very small.(11–14)

Current antiretroviral therapy is given regardless of CD4 levels where the most regimens given according to the program are antiretroviral containing lamivudine, tenofovir and efavirenz. Current guidelines in Indonesia currently recommend serum creatinine testing after 1 year of tenofovir use.(3) Other studies have shown a significant risk of kidney function decline so that there is still a lot of controversy regarding the administration of FDC contain tenofovir with changes in kidney function. Some studies show abnormalities of kidney function can occur more quickly even in the first 3 months. This study aimed to evaluate the effect of tenofovir FDC administration on changes in serum creatinine levels and eGFR for the first 3 months in HIV patients in the Outpatient Unit of IPIPI Hospital Dr. Soetomo Surabaya.

METHODOLOGY

This study design was observational longitudinal study, conducted from December 2018 to May 2019 in HIV/AIDS outpatient clinic Dr. Soetomo Hospital (Surabaya, Indonesia). We included patient with naïve HIV/AIDS who haven/t received antiretroviral, aged 16 to 60 years old, and willing to sign an informed consent. Patients were excluded if they received antiretroviral HIV before, creatinine serum more than 1,3 mg/dl, history of diabetes mellitus and hypertension, received antituberculosis drugs, NSAID, lopinavirm gancyclovir more than 2 weeks. Thirty patients with HIV/AIDS who fulfilled inclusion criteria and no exclusion criteria were included in this study. Ethical clearance was approved by the Ethics Committee of Dr. Soetomo Hospital (Surabaya, Indonesia)

We collected data with anamnesis, laboratory examination, full blood count, transaminase test, and CD4 as baseline characteristic. Creatinine serum was measured twice, before therapy and there months after therapy by Siemens Dimension DF33B and CRE2 methods. Estimated glomerular filtration rate (eGFR) was measured by Cockroft-Gault formula.

Statistical Analysis

The SPSS statistical software package version 23 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The categorical data were displayed as frequency and percent whereas normal distribution data were presented as mean±SD or median (range) if abnormal distribution data. Differential test was performed with paired t test. *P* value that considered to be significant was <0.05.

RESULTS

Baseline patient and clinical characteristic were shown in Table 1. Of the 30 patients recruited, 20 (66,7%) patients were males and 10 (33.3%) patients were females. The median age of subjects was 37 (range 17-57) years. Based on education, as much as 13 patients (43.3%) were senior high school level. Most of patients as much as 21 patients (70%) transmitted from sex men and women, and the most mean of CD4 levels was less than 200 as much as 22 patients (73.7%).

Creatinine serum before FDC tenofovir was 0.89 ± 0.25 mg/dl and after 3 months of FDC tenofovir 0.92 ± 0.28 mg/dl. The eGFR was 89.37 ± 33.54 ml/min/1.73m^2 and after three months of FDC tenofovir 88.31 ± 33.56 ml/min/1.73m^2. Statistical analysis result with paired t test FDC tenofovir for creatinine serum was p = 0.441 and eGFR p = 0.771. No significance statistical analysis result for creatinine serum and eGFR in FDC tenofovir administration for 3 months in this study (Table 2).

DISCUSSION AND CONCLUSION

Of the 30 patients recruited, there was no significant differences in creatinine serum and eGFR after FDC tenofovir administration for 3 months. No significant result in this study may be related with excluded diabetes mellitus, hypertension that make 40-60 percent renal failure. Short research time that disrupt the result. Renal failure may be occurred in a year or more so longer study may be needed.

FDC tenofovir is widely used for antiretroviral therapy in HIV/AIDS. The eGFR is the most frequently used for evaluating kidney function. The eGFR can measured in several ways. One of methods to measure eGFR using Cockroft-Goult formula that can be measured from creatinine serum. Creatinine serum detected from blood plasma. The risk of kidney failure related with FDC tenofovir use in HIV/AIDS patient is still controversial among several study. Tenofovir in some study shown toxicity in proximal tubule.

This study different from study in Padang, Indonesia that show tenofovir changed creatinine serum significance from baseline that include patient with sepsis and tuberculosis. Sepsis and tuberculosis influence creatinine serum by pre renal and renal abnormalities.(15) Study in Taiwan showed significance result in patient with tenofovir that can be related with low CD4, in this study no significance result may be caused with short term study.(13) In Myanmar show significance result can be related with diabetes mellitus and elderly patient that we exclude in this study.(14) Study in Singapore show similar result with this study that patient with tenofovir improve renal function, it can be related with improve clinical condition and reduce renal disruption.(12) Study in Lesotho show significance result that can be related with early CD4 result and elderly. In this study no association CD4 and renal disruption.(16) Study in Japan showed significance result with tenofovir use for renal failure. Factor related with changes creatinine serum are hypertension, use nephrotoxicity drugs and CD4 baseline.(17)

Renal failure related with proximal tubule disruption. Pathology anatomy result from 13 patient with renal failure related tenofovir use in HIV AIDS show disruption in proximal tubule similar with pathology anatomy for acute tubular necrosis. Acute tubular necrosis is acute and reversible when drugs terminated. Proximal tubule toxicity related with mitochondria apoptosis in proximal tubule when tenofovir accumulate in proximal tubule accumulate in mitochondria.(18–20)

The limitations in this study were no control group that for comparison with tenofovir group, time study may be too short, and further study need to exclude hepatitis B that can be change the result of renal failure related with hepatitis B, renal function test may be more sensitive and not only creatinine serum so we know kidney disorder early.

In conclusion, the creatinine serum and glomerular filtration rate had no significance different from statistical analysis after three months administration. Further may be needed for longer time study and comparison with control group.

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Table 1. Baseline patient and clinical characteristics

Variable		Frequency (%)	Mean ± SD
Sex			
–	Men	20 (66.7)	
–	Women	10 (33.3)	

Age			Median 37	(17-57)
–	20-29 year	9 (30)		
–	30-39 year	9 (30)		
–	40-49 year	6 (20)		
–	50-59 year	6 (20)		
Education				
–	Elementary	3 (10)		
–	Junior High	9 (30)		
–	Senior HIgh	13 (43.3)		
–	University	5 (16.6)		
Transmission				
–	Anal Sex	9 (30)		
–	Vaginal Intercourse	21 (70)		
CD4				
-	<200	22 (73.7)	124.7 ± 117.2	
-	>200	8 (26.7)		
Cotrimoxazole				
-	Yes	19 (63.3)		
-	No	11 (36.6)		

Table 2. Comparation Test

Variables	Before FDC (mean±SD)	After FDC (mean±SD)	p
Creatinine serum (mg/dl)	0.89 ± 0.25	0.92 ± 0.28	0.441
eGFR (ml/min/1.73m^2)	89.37 ± 33.54	88.31 ± 33.56	0.771

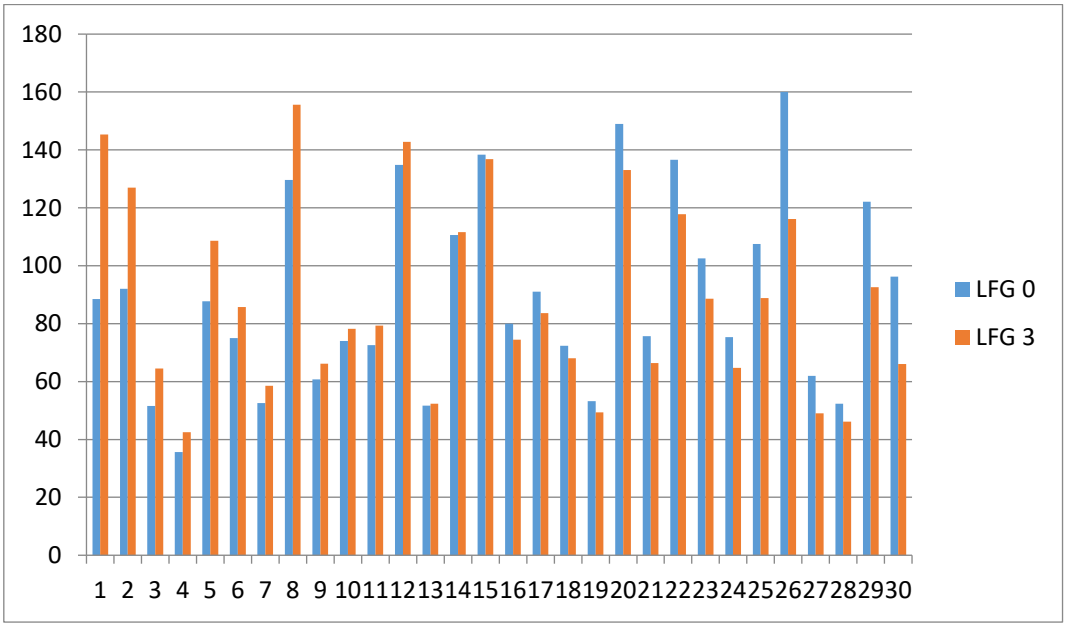

Figure 1. Bar Diagram Changes Glomerular Filtration Rate each Subject