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Effect of antiretroviral therapy to liver function of people living with HIV/AIDS patients in West Papua

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ABSTRACT

Background: Antiretroviral (ARV) therapy is one of the efforts to combat HIV/AIDS in Indonesia, especially West Papua. One of the side effects using ARV is impaired liver function in people living with HIV/AIDS (PLWHA). ARV therapy evaluation to liver disorders can be seen from the serum glutamic oxaloacetic transaminase (SGOT)/alanin transaminase (ALT) and serum glutamic pyruvic transaminase (SGPT)/aspartate transaminase (AST) level.

Objective: This study aims to determine the effect of ARV therapy to liver function of PLWHA patients in West Papua who receiving ARV for six months.

Methods: A cross sectional study, involving 110 respondent who were PLWHA patients receiving ARV at Voluntary Conseling and Testing (VCT) service of hospital in Manokwari, Sorong, and Fak-Fak. Laboratory test was used to examine the liver function. Demographic and clinical variable data were obtained from medical records. The Fisher's exact test with a significance level of $p<0.05$ was used to determine the effect of ARV to liver function.

Results: Respondent had no liver problems with normal SGOT and SGPT value: 72.7% and 76.4% respectively. While, the rest had mild and moderate toxicity. Respondent experiencing moderate toxicity was 2 patients who regularly took fixed dosed combination in Sorong. The result of fisher's exact test analysis showed there was significant relationship in the administration of FDC antiretroviral and regular ARV regimens with a value of SGOT enzyme with p value 0.20 and SGPT enzyme with p value: 0.31.

Conclusion: The use of antiretrovirals, both fixed dosed combination and release dose regiment did not significantly association with increase AST enzyme and ALT enzyme on PLWHA in West Papua.

Latar Belakang: *Terapi antiretroviral (ARV) merupakan salah satu upaya penanggulangan HIV/AIDS di Indonesia khususnya Papua Barat. Salah satu efek samping penggunaan ARV adalah gangguan fungsi hati pada orang dengan HIV/AIDS (ODHA). Evaluasi penggunaan terapi ARV terhadap gangguan fungsi hati dapat dilihat dari kadar SGOT/ASTdan SGPT/ALT.*

Tujuan: *Tujuan penelitian ini yaitu untuk mengetahui pengaruh pemberian antiretroviral terhadap fungsi hati pasien HIV/AIDS di papua barat yang telah mendapat terapi antiretroviral enam bulan.*

Metode: *Jenis penelitian cross sectional melibatkan 110 responden yaitu pasien HIV/AIDS yang mendapat ARV dilayanan VCT RSUD Manokwari, Sorong, dan Fak-fak. Analisis fungsi hati dilakukan melalui pemeriksaan laboratorum sedangkan data variabel demografi dan klinis didapatkan dari rekam medis.*

Analisis statistik untuk mengetahui pengaruh ARV terhadap fungsi hati menggunakan uji fisher exact test dengan level signifikansi p<0,05.

Hasil: *Responden tanpa gangguan fungsi hati dan memiliki nilai SGOT dan SGPT normal, secara berurutan yaitu sebanyak 72,7% dan 76,4%, sedangkan sisanya mengalami toksisitas ringan dan sedang. Dua responden yang mengalami toksisitas sedang adalah pasien yang mengonsumsi ARV kombinasi dosis tetap di kota sorong. Hasil analisis fisher exact test menunjukkan tidak ada hubungan yang signifikan pada pemberian antiretroviral kombinasi dosis tetap dan regimen ARV regular dengan nilai SGOT dengan nilai p=0,20 dan SGPT dengan nilai p=0,31.*

Kesimpulan: *Penggunaan antiretroviral baik kombinasi dosis tetap maupun regimen regular tidak berpengaruh terhadap peningkatan SGOT dan SGPT pasien HIV/AIDS di papua barat.*

INTRODUCTION

Globally, Human Immunodeficiency Virus (HIV) infection is one of the ten biggest health issues problem that burden and challenge the world.[1] World Health Organization (WHO) reported 38 million people are infected HIV worldwide. Then 1.7 milions of them are newly infected in 2019. There are 25.4 million people have accessed antiretroviral (ARV) therapy, this is still less than the number of HIV infected people reported.[2] In 2019, the Indonesian Ministry of Health released the cases data of HIV and Acquired Immunodeficiency Syndrome (AIDS) in West Papua Province as 5,243 and 1,741 people, respectively.[3] This is a big challenge in prevention and control of HIV/AIDS in West Papua, especially in certain district of West Papua Province which has the most HIV cases, sequentially as Sorong City (1,902 cases), Manokwari district (1,422 cases), Sorong District (1,023 cases) and Fak-Fak district (423 cases).[4]

Antiretroviral therapy (ART) refers to the use of pharmacological agents that have specific inhibitory effects on replication cycle of HIV. These agents are drugs used for the treatment of disease caused by retrovirus, primarily HIV. WHO shows that about 20.9 milion (18.4 - 21.7 million) people living with HIV are accessing antiretroviral drugs, which is the current effective management of HIV.[5] They are different classes of ARV drugs which include the nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, chemokine receptor antagonist and integrase inhibitors. Each of these classes of ARV drugs inhibits HIV replication at different stages in HIV life cycle.[6]

The advent of drug expansion program by pharmaceutical companies, research institutions and state agencies, has led to modification of ARV drugs to a fixed-dose combination (FDC) antiretroviral drugs generally referred to as combination antiretroviral therapy or highly active antiretroviral therapy (HAART), currently used in the treatment of HIV infection.[7] HAART have its potential to reduce progression of the disease in patients, they still have certain side effects which include liver toxicity, hematuria, decreased bone density, cardiovascular disease, gastrointestinal tract infection, hypersensitivity reaction, lactic acidosis, lipodystrophy, myopathy and Steven-Johnson syndrome. One of the major side effects caused by ART is hepatoxicity.[8]

Hepatoxicity, a case of liver disfunction or damage, is in a most cases associated with overload of drugs or xenobiotics, producing a wide variety of clinical and histopathological indicators of hepatic injury. Drug-induced liver damage due to exposure of the organ to certain allopathic medication including ARV drugs has been documented in many studies.[9] In fact, according to a recent report, AIDS-related illness account only around 50% of the deaths, whereas HAART-induced liver injury has appears as a primary cause of death in HIV infected patients.[10]

The long term use ARV contain some ARV drugs requires clinical special attention, such as liver function monitor. Serum glutamic oxaloacetic transaminase (SGOT) or aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT) or alanine aminotransferase (ALT) level were used to

monitor liver function. Sixth months monitoring for liver function should be conducted on people living with HIV/AIDS (PLWHA) taking ARV combined with other drugs such as antibiotic cotrimoxazole and antituberculosis drugs.[11] Based study in 2017, as 88% of HIV patients taking ARV had suffered mild liver malfunction. This occurred on patients who take nevirapine in their ARV regimen. Nevirapine is included in the group of non-nucleoside reverse transcriptase inhibitor. Using drugs from the group NNRTI and protease inhibitor may lead the unfortunate metabolic changes such as liver toxicity, lipodystrophy and insulin resistance.[11]

Now, currently in West Papua using ARV therapy regimen consist of 2 nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor regimen, but in several hospital in West Papua have used a lot of fixed dose combination. This is a tablet containing three kinds of drugs. FDC must be taken one tablet a day at the same hour. Thus, this is easier for patients to comply and do not forget consuming the drug.[12] The benefit using FDC in first line therapy treatment are less temporary side effect, less toxic, and simply, thereby increasing therapy adherence.[13] A research in America reported the hepatoxicity case, especially as hepatocellular damage which is signed by increasing aminotransferase level in blood on HIV patients taking FDC as their first line ARV regimen.[14] Also, some studies showed the liver damage increased on patients whose increasing amino transferase already before ARV initiation.

Blood test can be used to detect SGOT and SGPT in plasma. Normally, both of this transaminase enzyme are inside the cell. The increasing of transaminase level in blood is sign of tissue damage. Mild increase of SGOT and SGPT is the increase of enzyme less than 5 times of normal upper limit. Frequently, this is not significant case but could be a sign for chronic disease.[15] Therefore, this research aims to determine the effect of ARV therapy to liver function of PLWHA patients in West Papua who have received ARV for six months therapy.

METHODS

Study desain

A cross sectional study was conducted in Manokwari District, Sorong City, and Fak-fak District during May to July 2019. This study envolved 110 respondents, who were meet the inclusion, i.e. patients with HIV/AIDS diagnosed, 18-60 years old, had ARV therapy in VCT of Hospital in Manokwari, Sorong, and Fak-fak for 2018-2019 period and tested for liver function (SGOT and SGPT). While, the exclusion, i.e. patients had no complete medical record, dropped out for ARV therapy, passed away, and patients referred to other hospitals than site of study. HIV patients who have received ARV therapy either the usually regular regimen or a fixed dose combination for 6 months. WHO recommends monitoring of liver enzymes in response to therapeutic effects.[16] Regular monitoring (every 6 months) was carried out in this study the samples taken were patients who had received 6 months of therapy. This study was approved by Ethics Committee of National Institute of Health Research and Development, Indonesian Ministry of Health number LB.02.01/2/KE.008/2019.

Liver Function

Liver function was evaluated based on SGOT dan SGPT data from laboratory test. Those data were analyzed to find out liver malfunction case. The data be classified based on ARV toxicity into 4 groups of degree of hepatoxicity; mild toxicity (SGOT/SGPT value is 1.25-2,5 x normal upper limit (NUL), moderate toxicity (SGOT/SGPT value is 2,5-5,0 x NUL), severe toxicity (SGOT/SGPT value is 5,0-10,0 x NUL), and potentially life-threatening toxicity (SGOT/SGPT value is>10.0 x NUL).

Clinical and demographic data

CD4 levels were classified as <350 cells/mm^3 or >350 cells/mm^3, while HIV were divided into (a) stage 1 and 2 and (b) stage 3 and 4. For TB infection status, subjects were divided into TB positive and TB negative. Other data that were collected were included gender

(male/female), age (<35 years/>35 years), occupation (working/not working), education (low: elementary-junior high school, high: high school-university), marital status (married/not), ethnicity (papua/non-Papua).

Data dan statistical analysis

Statistic test of Fisher exact with a significance level of <0.05 was used to analyse liver function to demographic variables (age, gender, education, employment, marital status, ethnicity) and clinical variables (CD4, HIV clinical stadium, tuberculosis (TB) status).

RESULTS

Most of the HIV/AIDS patients in West Papua were in HIV clinical stadium of III & IV. Also, most of them were taking FDC as their ARV therapy regimen (Table.1)

Most of the respondents had no hepatoxicity during ARV therapy, or no severe or life-threatening hepatoxicity events (Table.2)

Table 1. Demographic and clinical characteristic of HIV Patients in West Papua

Variables	Frequency	Percentage (%)
Gender		
Men	51	46.4
Women	59	53.6
Age		
< 35 years old	58	52.7
> 35 years old	52	47.3
Employment		
Unemployee	53	48.2
Employee	57	51.8
Education		
Elementary-secondary	73	66.4
High-university	37	33.6
HIV clinical stadium		
Stadium 1 & 2	32	29.1
Stadium 3 & 4	78	70.9
Total CD4		
<350 cells/mm3	55	50
>350 cells/mm3	55	50
TB Status		
No TB	60	54.5
TB	50	45.5
ARV therapy		
FDC (TDF +3TC + EFV)	96	87.3
Other	14	12.7

Based on Fisher exact test (significance level of <0.05) showed there was no significant relationship between the use of FDC therapy with an increase in SGOT and SGPT on HIV patients in West Papua (Table.3). The use of FDC and regular drug regiments did not significantly association with increase SGOT and SGPT enzyme.

Table 2. Degree of hepatoxicity based on SGOT and SGPT parameter on HIV patients in West Papua

Variables	Frequency	Percentage (%)
SGOT		
Normal	80	72.7
Mild toxicity	28	25.4
Moderate toxicity	2	1.9
SGPT		
Normal	84	76.4
Mild toxicity	24	21.8
Moderate toxicity	2	1.8

Table 3. Hepatoxicity analysis of FDC usage based on HIV patients's SGOT and SGPT in West Papua

Variables	FDC regiment	Other regimen	Total	p value
Normal SGOT	72	8	80	0.20
SGOT increased	24	6	30	
Total	96	14	110	
Normal SGPT	75	9	84	0.31
SGPT increased	21	5	26	
Total	96	14	110	

DISCUSSION

ARV's side effects or toxicity is essential to be considered during therapy. This side effects might be caused various factors, such as gender, drugs characteristic, and concurrent use of ARV's with other drug which has similar toxicity.[17] Based on the SGOT and SGPT value, this study showed almost respondents were in normal range value than whose had hepatoxicity. This suitable with the ARV guide from Indonesian Ministry of health about classification of ARV's side effect, which ARV NRTI group relatively had no side effects to liver, but ARV from NNRTI such as efavirenz and nevirapine might cause side effects.[17] Generally, HIV patients in West Papua took FDC as their first line ARV regimen. This FDC consist of lamivudine, tenofovir, and efavirenz. Beside, some patients use other first line ARV regimen than FDC which is less side effect and less toxic.[13]

Antiretroviral drug metabolized in the liver through cytochrome and its metabolizing enzyme which may even cause liver toxicity due its polymorphism. Antiretroviral drugs inhibit the human mitochondrial DNA resulting in inhibition of normal mitochondrial replication which in turn decrease cellular respiratory chain thereby inhibits fatty acid β-oxidation pathway.[18] This study found 6 patients had ARV therapy regimen were not FDC,i.e. combination of lamivudine+tenofovir+nevirapine and lamivudine+zidovudine_nevirapine. Those patients were experiencing an increase of SGOT and SGPT but in mild toxicity level. This is relevant with study by Ogedegbe et all, who conducted the clinical trial that showed NRTI related to 7% of hepatoxicity on zidovudine usage.[19] Other study found the newest NRTI, such as tenofovir related to low increase of aminotransferase and no symptoms.[20]

Nevirapine is a non-nucleoside reverse transcriptase inhibitor commonly prescribed as a part of combination with other ARV drugs in the treatment of HIV/AIDS.[21] It is commonly used ARV drug to treat HIV-1 infection in pregnant women to prevent gestational transmission. The nevirapine induced hepatoxicity is manifested as elevation of serum marker enzymes, bile

duct obstruction and jaundice, hepatic necrosis, hepatitis and hepatic failure.[22] NNRTI class other than nevirapine namely is efavirenz. Efavirens is a non-nucleoside reverse transcriptase inhibitor which causes hepatoxicity by blocking the bile acid transport. Efavirenz when administered in combination with tenofovir (one of the first-line agents for the treatment of HIV), causes hepatoxicity characterized by high levels of hepatic aminotransferase.[14] The mechanism related to hepatoxicity induced by efavirenz are not clear, nevertheless, a recent study has reported that the mitochondrial toxicity of this drug is accompanied by an induction of ER stress in human hepatocytes.[23] In light of above literature, a recent study has confirmed the role of mitochondrial and ER stress to be the key factor for efavirenz-induced hepatoxicity.[24] However, as we seen earlier the mechanism of efavirenz-induced hepatoxicity is not well characterized till date but it is considered to occur less frequently than with nevirapine.[25]

HIV patients in West Papua also received the Nucleoside Reverse Transcriptase inhibitor class of ARV, namely lamivudine and zidovudine. Zidovudine induced hepatoxicity could be suggested due to the impairment of mitochondrial DNA transcription and inhibition of DNA polymerase γ in hepatocytes.[18] The severity of zidovudine induced hepatoxicity is reported in experimental animals and such studies found that the mild and transient elevation of marker enzyme of hepatoxicity to severe manifestation like inflammation, ER stress, fatty infiltration, lactic acidosis and hepatic failure leading of death. For this reasons, the clinical use of zidovudine is limited.[26,27] Lamivudine is an L-enantiomer, substituted analogue of cytidine is said to be effective against both HIV and hepatitis B infections. Recent experimental studies have proved that chronic lamivudine administration consequently leads to an elevation in hepatoxic and lipid marker enzymes in plasma of rats. The study also showed that ethanol intake could aggravate the lamivudine induced hepatoxicity in rats.[18]

This study also found two HIV patients receiving FDC had experienced the hepatoxicity on moderate level. Based on their medical record, they were suffering the tuberculosis as opportunistic infection and also often consume alcohol. As known, alcohol was toxic for liver. Its usage had relationship with the liver damage during taking antiretroviral. The continuous usage of alcohol might raise up the risk of liver damage through the oxidative damage on mitochondria DNA and also reduce the glutathione storage and the important free radical molecules.[28] Moreover, the severe of liver damage because of the ARV usage could be occurred when the patients consumed both the tuberculosis drugs and ARV simultaneously. In addition, the alcohol consumption and the presence of hepatitis virus coinfection on HIV/AIDS patients might be worsen the liver damage condition.[29]

However, the incident of drug side effects must not be barrier to initiate the ARV therapy. Noteworthly, all patients will not experience with the drug side effects. Beside, those side effects oftenly able to be managed well. ARV therapy was much more profitable for HIV patients compare to the risk of death which would be happened if the patients was not receiving ARV therapy.

We suggest, there is no need to change the FDC regimen usage during ARV therapy for patients in West Papua because this has mild toxicity and almost normal effects to patients liver function. SGOT/ALT and SGPT/AST enzyme measurement should be done at the beginning before measurements are carried out 6 months after therapy to determine how much increase in liver enzymes occurs.

CONCLUSION

In conclusion, the FDC usage by HIV Patients in West Papua was not significantly effect the SGOT and SGPT increase value.

CONFLICT OF INTEREST

The authors have declared that no conflict of interests.

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