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Adverse Effect of Anti-Retroviral Therapy in HIV/AIDS Patients at Merpati Clinic, Wangaya Hospital in Denpasar, Bali, Indonesia

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Abstract: ***The uses of Anti-retroviral therapy (ART) are rising due to the increase of newly diagnosed Human Immunodeficiency Virus (HIV) positive patients. HIV patient should take the medicine for lifetime to manage their disease. However, it is revealed from previous studies that poor adherence of ART usually caused by its adverse effect. The objective of this study is to learn about the adverse effect of ART and its association to other factors in HIV patients at Merpati Clinic Wangaya Hospital in Denpasar - Bali, Indonesia. A cross sectional study with retrospective review was conducted. All HIV patients on ART (regimen of tenovofir, zidovudine, lamivudine, nevirapine and efavirenz) were included on this study, except for pregnant woman. Data was taken from the patients' medical record. From 107 patients included in this study, 52 (48.6%) were complaining of adverse effect, and 9 (8.4%) of them experiencing more than one type of adverse effect. Neuropsychiatric-related symptoms found on 12 (19.7%) patients, gastrointestinal in 13 (21.3%) patients, dermatologic in 25 (41%) patients, and hematologic in 11 (18%). No relationship were found between age, sex, weight, and HIV staging to adverse effect, while types of regimen and CD4+ count have significant correlation to the adverse effect (p-value 0.001 and 0.049 respectively). Combination of ZDV/3TC/NVP found to be the most prone to adverse effect. Adverse effect of ART in HIV patient should be monitored carefully, to keep patient's adherence and better wellbeing. Treatment of adverse effect and change of regimen should always be considered in patients with adverse effect to ART.***

Keywords: adverse effect, anti-retroviral therapy, hiv patients

1. Introduction

As more people were diagnosed with HIV, the use of Anti-retroviral therapy (ART) also grows in number. World Health Organization (WHO) estimated that more than 37 million people worldwide are currently living with HIV/AIDS. More than twenty three millions of those people (62%) are receiving Anti-retroviral therapy (ART). The escalation of HIV prevalence also occurs in Indonesia. It is reported by Indonesian Ministry of Health that there are 48,300 cases in 2017, where the most case found in East Java (8,204). Bali is in the sixth position with 2,441 cases.[1] Early detection and administration of ART in HIV positive patients is suggested in this current era. [2]

Anti-retroviral therapy for HIV patient aims to suppress viral load and providing improvement of immunity, by increasing CD4+ count and preventing opportunistic infection. Patients with HIV should take this medicine for lifetime to maintain their health condition.[3], [4]

However, the benefit of anti-retroviral therapy is accompanied by adverse effect. Few studies have found that more than half of the HIV patient receiving ART experiencing mild to severe side effects. Oumar AA, et al reported that 61.2% patients receiving ART in Mali, West Africa experienced adverse drug reaction or adverse effect.[5] A study conducted in India shows that adverse effect experienced by 75.4% HIV patients on ART. [4] Several adverse effects that currently known related to ART including neuropsychiatric problem, gastrointestinal problem, dermatologic problem, hematologic problem, and hepatotoxicity.[4]-[6] The most frequent issue in early administration of ART is gastrointestinal problem such as bloating, nausea, and diarrhea. Fatigue, headache, dizziness, insomnia and nightmare are symptoms related to neuropsychiatric problem in HIV patients who received ART. Pruritus, rash, hypersensitivity and elevated liver enzyme are usually found in Nevirapine (NVP) takers. Efavirens (EFV) associated with central nervous system toxicity, nightmares, drowsiness, and rash. Hematologic problem such as anemia and leukopenia, accompanied by nausea, headache, rash, and elevated liver enzyme encountered in patients taking Zidovudine (ZDV). Most of the anti-retroviral agents carries hepatotoxic properties, but varies in severity. Adverse effect contributes to patient's poor adherence and prognosis. Identification and monitoring of the adverse effect should be done and treated to optimize patient's adherence. [2],[7]-[9] This study conducted to discover the prevalence and factors associated with adverse effect of ART in HIV patients at Merpati Clinic, Wangaya Hospital, Denpasar-Bali, Indonesia.

2. Methods

An observational cross sectional study was conducted at Merpati Clinic in Wangaya Hospital, Denpasar – Bali, Indonesia. All HIV positive patient on 4 types of first line anti-retroviral therapy were included in this study. Four of the ART combinations were:

- TDF/3TC/EFV (FDC)
- TDF/3TC/NVP
- ZDV/3TC/EFV
- ZDV/3TC/NVP

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(TDF = Tenofovir, 3TC = Lamivudin, EFV = Efavirenz, FDC = Fixed Drug Combination, NVP = Nevirapine, ZDV = Zidovudine)

We exclude pregnant woman and other anti-retroviral therapy combination. Demographic characteristic, CD4 count, types of ARV regimen, other medication and the adverse effect were recorded. The adverse effect were categorized into 4 group, dermatological, gastrointestinal, neuropsychiatric, and hematologic based on patients sign and symptoms, also from diagnosis. Data was collected retrospectively from the medical record, then analyzed with SPSS windows version 21. The correlation between the characteristic and the adverse effect were analyzed with pearson chi-square with p-value of <0.05 and confidence interval (CI) 95% are considered significant.

3. Result

There were 107 of HIV positive patients on anti-retroviral therapy were included in this study. Demographic study shows the patients consisted of 51 (47.7%) female and 56 (52.3 %) male. Most of the subject 58 (54.2%) in age group of ≥38 years old. From the weights of the patient, 55 (51.4%) were ≥ 59 kilograms.

The TDF/3TC/EFV (FDC) is the most regimen taken by 49 (45.8%) patient. From HIV/AIDS staging, 99 (92.5%) were HIV and 8 (7.5%) were AIDS. Adverse effect happened in 52 (48.6%) patients, and among them, there were 9 patients experiencing more than one type of adverse effect.

Most common adverse effect were dermatological problem in 25 patients (41%), followed by gastrointestinal problem 13 (21.3%), hematologic problem (anemia) in 11 (18%) patients, and 12 (19.7%) had neuro-psychiatric related problem. The most combination with adverse effect observed is ZDV/3TC/NVP with 30 (71.4%) of the patient taking this regimen reported hypersensitivity or drug eruption, and anemia. (Shown in table 1).

Table 1: Demographic characteristic

Variables	n (%)
Sex	
Male	56 (52.3)
Female	51 (47.7)
Age*	
<38	49 (45.8)
≥38	58 (54.2)
Weight*	
<59	52 (48.6)
≥59	55 (51.4)
Education	
Elementary School	9 (8.4)
Junior High	17 (15.9)
Senior High	59 (55.1)
University	22 (20.6)
Marital Status	
Unmarried	18 (16.8)
Married	69 (64.5)
Widowed	20 (18.7)
HIV/AIDS staging	
HIV	99 (92.5)
AIDS	8 (7.5)
ART regimen	
TDF/3TC/EFV(FDC)	49 (45.8)
TDF/3TC/NVP	6 (5.6)
ZDV/3TC/EFV	10 (9.3)
ZDV/3TC/NVP	42 (39.3)
Adverse effect	
Yes	52 (48.6)
One type of adverse effect	43 (40.2)
More than one adverse effect	9 (8.4)
No	55 (51.4)
Type of Adverse Effect	
Dermatologic	25 (41)
Gastrointestinal	13 (21.3)
Neuro-psychiatric	12(19.7)
Hematologic	11 (18)
Opportunistic infection	
Yes	28 (26.2)
No	79 (73.8)
CD4 Count	
<400	94 (87.9)
≥400	13 (12.1)

**age and weight in median*

It is also found that age, sex, weight, staging, and opportunistic infection have no correlation with adverse effect, while types of regimen and CD4 count correlates with adverse effect with p-value of 0.049 and 0.001 respectively. (Shown in table 2)

Table 2: Association between variables

Variables	Adverse Effect n(%)	No Adverse Effect n(%)	*p-value***
Age (year)			
<38	23 (46.9)	26 (53.1)	0.752
≥38	29 (50)	29 (50)	
Sex			
Male	32 (57.1)	24 (42.9)	0.064
Female	20 (39.2)	31 (60.8)	
Weight			
<59 kg	25 (48.1)	27 (51.9)	0.916
≥59 kg	27 (49.1)	28 (50.9)	
Staging			
HIV	47 (47.5)	52 (52.5)	0.481
AIDS	5 (62.5)	3 (37.5)	
Regimen			
TDF/3TC/EFV(FDC)	14 (28.6)	35 (71.4)	0.001
TDF/3TC/NVP	2 (33.3)	4 (66.7)	
ZDV/3TC/EFV	6 (60)	4 (40)	
ZDV/3TC/NVP	30 (71.4)	12 (28.6)	
Opportunistic Infection			
Yes	13 (46.4)	15 (53.6)	0.789
No	39 (49.4)	40 (50.6)	
CD4 Count			
<400	49 (52.1)	45 (47.9)	0.049
≥400	3 (23.1)	10 (76.9)	

***p-value in chi-square test*

4. Discussion

Adverse effect of ART can be found in any of the regimen and have a broad spectrum of sign and symptoms. These adverse effects are the main cause of the low adherence in patients living with HIV/AIDS. [3],[5] From this study, we

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found that 52 (48.6%) of the patient experiencing adverse effect, while in other studies it varies greatly. One study from Luma HN et al, reported only 19.5% adverse effect of ART. [10] Isa AM et al, in his study found 58.7% patient experienced adverse effect, while Bhatnagar S et al, reported adverse effect in 61.2% patients, and Oumar A et al found it on 75.4% of HIV patient on ART. [3]-[5] Shet A et al reported 90% of 321 people in their study experienced at least 1 adverse effect. [11]

Change of ART regimen was done in our patient. In 2 (1.39%) case, the adverse effect was found in the new regimen as well. When this happened, we try to change the regimen again until we found suitable regimen for the patient. Patient should be encouraged strongly to keep their adherence in taking medication even after this situation happened.

Khan KU et al, reported that age did not have any significance to the adverse effect with p-value of 0.51, while body weight have p-value of <0.001 which indicates correlation with adverse effect.[12] Luma HN et al had mutual finding with this study, in which they found no correlation between age and body weight with adverse effect.[10] This study reported no correlation between the age (p-value = 0.752) and weights (p-value = 0.916) of the patients.

Men were more prone to adverse effect 57.1% than women 39.2% in this study, although we found no significance of gender (p-value = 0.064) to the adverse effect. This finding correspond to Khan KU et al who found that adverse effect were more common in men (31.9%) than women (10.9%), but the study shows p-value of 0.002 which indicate there's a correlation between gender and adverse effect.[12] In contrast to Luma HN et al, that reported 21.6% of women and 16.3% of men and found there is no significance (p-value = 0.23) between the two variables.[10]

Regimen types is associated with the adverse effect, with the p-value of 0.001. This finding is also reported similarly in previous study by Luma HN et al, which found p-value of 0.010 which indicates significance between regimen types and adverse effect.[10] Chelkeba L et al also reported mutual finding with the p-value of 0.001.[13]

We also found the significance between CD4+ count and adverse effect (p-value = 0.049). The CD4+ count is related to the adverse effect in other study. The higher the CD4 count, the less adverse effect found in the patients.[12,13] The types of adverse effect also varies, Luma HN et al, Vagani SV et al, and reported that the most common adverse effect was peripheral neuropathy, followed by gastrointestinal problem.[10,14] Chowta MN et al reported that it was gastrointestinal problem like nausea, followed by gastritis and diarrhea are the most common.[15] Rozin C also reported that gastrointestinal problem is mostly seen and followed by neurologic symptoms, then hypersensitivity.[16] Chioma AD et al, shows different order of the side effect, with hematological problem in the first place (34%), and gastrointestinal problem in second place (21.8%) and skin manifestation in third place (20%).[17]

This study found dermatological problem (41%) is the most common finding in patients, followed by gastrointestinal problem in 21.3% patient, neuro-psychiatric problem accounts for 19.7%, and the last were hematologic problem (anemia) in 18% of the adverse effect. In our study, dermatological problem is consisted mostly of hypersensitivity reaction (rash, pruritus) in patient taking NVP. Hematological problem commonly found in patient taking ZDV, and neuropsychiatric problem found in EFV regimen takers. FDC contributes to equal amount of gastrointestinal, neuro-psychiatric, and dermatological symptoms, except for hematologic (anemia) which we found none of the participant taking FDC diagnosed with anemia.

5. Conclusion

Adverse effect in HIV patients on ART appear in various types of problem. The type of regimen correlates with the adverse effect, with ZDV/3TC/NVP is the most prone combination to cause such effect. More research with larger amount of participants should be done to evaluate another factors contributing to the adverse effect of ART.

6. Study Limitation

Small sample size is one of the limitation in this study. The prevalence of ART adverse effect may have been under or over reported. No other laboratory investigations or diagnostic test for ruling out other causes were done.

7. Acknowledgment

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8. Authors Contribution

Ketut Suryana contributes in constructing the idea, research methodology, organizing and supervising the course of the research, logical interpretation, literature review, constructing the manuscript and reviewing before article submission.

9. Conflict of Interest

Authors reported no conflict of interest in this study

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