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Analysis of Adverse Drug Reactions Combination of Zidovudine, Lamivudine, and Nevirapine Drugs in the Treatment of HIV/AIDS Patients in a Denpasar District Hospital

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Abstract

HIV/AIDS is a disease caused by infection with the Human Immunodeficiency Virus (HIV). Antiretroviral therapy is used for treatment. The three most commonly used combination antiretroviral regimens are zidovudine, lamivudine, and nevirapine. The problem that arises from the use of antiretroviral drugs is the emergence of adverse drug reactions (ADR). The purpose of this study was to identify and analyze the incidence of adverse drug reactions from the use of combination antiretroviral drugs in the treatment of HIV/AIDS patients in a Denpasar district hospital. This study is a descriptive study with prospective data collection on the patient's medical record. The sampling technique in this study uses a non-probability technique (Purposive Sampling). This study involved 102 patients. The results obtained were descriptive analysis for patient demographic data, duration of therapy and adverse drug reactions that occurred. The results showed that there was an adverse drug reaction in 50% of patients who used a combination of antiretroviral drugs zidovudine, lamivudine and nevirapine. The longest duration of ARV therapy in one of the hospitals in Denpasar Regency was the age > more than 2 years to 4 years, which was 33.3%. The types of ADR that occurred were nausea/vomiting (25 events), skin rash (23 events), headache (11 events), lethargy/fatigue (6 events), fever (6 events), muscle pain (5 events), diarrhea (4 events), neuropathy (2 events), anemia (2 events), and the least is nail hyperpigmentation (1 event).

Keywords
HIV/AIDS; antiretroviral (ARV); Adverse Drug Reaction (ADR)

I. Introduction

HIV/AIDS is an infectious disease caused by infection with the Human Immunodeficiency Virus (HIV) which attacks the immune system. The number of people living with HIV/AIDS in the world has increased. This can be seen from data from UNAIDS (United Nations Program on HIV/AIDS) at the end of 2015, which showed that there were 36.7 million people worldwide living with HIV. This number increased from the previous year which amounted to 35.9 million. The Directorate General of PP (Disease Control) and PL (Environmental Health) of the Indonesian Ministry of Health reported that cumulative HIV cases in Indonesia from April 1, 1987 to December 31, 2016 were 232,323 people, while AIDS cases were 86,725.

Antiretrovirals are drugs that inhibit the replication of the Human Immunodeficiency Virus (HIV). The goal of therapy with ARVs is to suppress HIV replication to the maximum,

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increase CD4 lymphocytes and improve the patient's quality of life. ARV therapy consists of a combination of several classes of ARV drugs, and usually consists of three drugs or so-called triple therapy, or often referred to as Highly Active Antiretroviral Therapy (HAART). One type of combination antiretroviral that is widely used by HIV/AIDS patients in a Denpasar district hospital is zidovudine, lamivudine, and nevirapine.

One of the problems that arise from the use of antiretroviral drugs is the emergence of unwanted drug reactions (adverse drug reactions). According to the National Department of Health (2004), the most common adverse drug reactions following the use of antiretroviral (ARV) drugs are nausea, rash, abdominal pain, hyperlactasemia, and lactic acidosis, lipodystrophy, hyperlipidemia, anemia or neutropenia. Research by Nur Rahmi Hidayati et al. (2013) conducted at a hospital in West Java found adverse drug reactions from the use of a combination of antiretroviral drugs zidovudine, lamivudine, and nevirapine in the form of headache, fatigue, anemia, itching, nausea/vomiting, diarrhea, skin rash, discoloration. skin and sleep disorders. In patient drug therapy, a pharmacist is expected to be able to identify problems related to the use of drugs, one of which is the adverse drug reaction (ADR). By decreasing the incidence of adverse drug reactions, it is expected to increase patient compliance in the use of drugs so that therapeutic success can be achieved.

Drugs are very important because drugs are a way to cure illnesses medically, but in fact, even patients who go to the hospital are not a guarantee that the patient is taking drugs in a safe condition, in fact it is the same as drugs that are freely traded in pharmacies. also does not guarantee comfort for the patient. Drug abuse is an endemic disease in modern society, a chronic disease that recurs, which until now has not been found to be universally satisfying, both from the point of prevention, therapy and rehabilitation. (Sitompul, R. 2021)

The hospital where the data was collected is one of the referral hospitals in Bali for people living with HIV and AIDS (PLWHA). This hospital has a VCT (Voluntary Counseling Test) clinic which functions as a place for voluntary counseling and testing for people living with HIV and AIDS.

Based on the description above, it is necessary to conduct an analysis to determine the type of adverse drug reaction that occurs in the treatment of HIV/AIDS patients who use a combination of antiretroviral drugs zidovudine, lamivudine, and nevirapine in a Denpasar district hospital.

II. Research Methods

Research design. This research is a descriptive research with prospective data collection. Descriptive research is research that describes the properties and actual conditions of an object of research. The goal is to collect facts and describe them thoroughly and thoroughly according to the problem to be solved.

Ingredients. The materials used in this study were medical records of HIV/AIDS patients who used a combination of antiretroviral drugs zidovudine, lamivudine, and nevirapine at a Denpasar district hospital.

Method. The sampling technique in this study uses a non-probability technique (Purposive Sampling). The collection of patient medical record data was carried out based on the number of visits by patients who had control at one of the Denpasar District hospitals on the day of the study. Data analysis was in the form of a frequency test (descriptive) of patient demographic data which included name, age, gender, type of ARV regimen, duration of ARV therapy, diagnosis, laboratory results and the type of adverse drug reaction that occurred in the treatment of HIV/AIDS patients in a hospital. Denpasar Regency using a combination of ARV drugs zidovudine, lamivudine, and nevirapine.

The inclusion criteria in this study are:

1. Outpatients who are diagnosed with HIV/AIDS and come for treatment regularly at a Denpasar district hospital.
2. Patient age > 17 years.
3. Patients who continue to use the ARV drugs zidovudine, lamivudine, and nevirapine since the beginning of the HIV infection until now.

The exclusion criteria in this study are:

1. HIV/AIDS patients with incomplete/missing medical records.
2. HIV/AIDS patients who were declared dead during the study.
3. HIV/AIDS patients with severe opportunistic infections.
4. HIV/AIDS patients who are referred to other hospitals.

III. Result and Discussion

Based on the research that has been carried out, 102 patients who met the inclusion criteria were diagnosed with HIV/AIDS and were undergoing treatment with a combination of antiretroviral drugs zidovudine, lamivudine and nevirapine in one of the hospitals in Denpasar. This study was conducted prospectively by collecting patient medical record data.

Table 1. Characteristics of HIV/AIDS Patientsone of the hospitals in Denpasar

Patient Characteristics	Category	Number of Patients	
		n = 102	%
Gender	Man	65	63.7
	Woman	37	36.3
Age group	17 – 25 years	1	0.9
	26 – 35 years old	45	44.1
	36 – 45 years	39	38.2
	46 – 55 years old	14	13.7
	> 56 years old	3	2.9
last education	SD	11	10.7
	junior high school	17	16.6
	senior High School	65	63.7
	D3	1	0.9
	S1	8	7.8
Marital status	Marry	66	64.7
	Not married yet	35	34.3
	Widow widower	1	0.9
Work	civil servant	5	4.9
	Private employees	50	49
	Entrepreneur/trader	15	14.7
	Housewife	10	9.8
	Etc	15	14.7
	Does not work	7	6.8

Description: PNS: Civil Servan

Table 1 shows the characteristics of HIV/AIDS patients receiving treatment inone of the hospitals in DenpasarBased on gender, there were more male patients than female patients. This is in line with the research conducted by Jef Gishard Kristo Kalalo, et al regarding the Study on Therapeutic Management of HIV/AIDS Patients at the Manado City Hospital VCT Clinic in 2012 which stated that the proportion of HIV/AIDS cases in men was higher than women because the majority of injecting needle users are male and most of the commercial sex customers are male.

Based on age group, most HIV/AIDS patients were found in the age group of 26-35 years, namely 44.1%. The same thing was also found in Kurnia Fitri Jamil's 2014 study, which stated that HIV/AIDS sufferers are most often found in the productive age (15 - 49 years), this is probably due to the influence of high sexual activity, environmental and work influences. Based on the level of education, it can be seen that the largest group is with a high school education level (SMA), which is 63.7%. Education is one of the factors that influence a person's perspective on life, especially regarding health. Research conducted by Amaruddin and Yanti (2011), explains the relationship between education level and the risk of contracting HIV/AIDS in street children. However, from the results of this study, it can be seen that respondents who have a higher level of education take greater risky actions than respondents with a low level of knowledge. This means that the higher the level of education, the more likely it is to take actions that are at risk of contracting HIV/AIDS.

Based on marital status, the largest group is married marital status, which is 64.7%. The high number of AIDS sufferers who are married can be caused by HIV transmission through sexual contact with their partners (husband/wife) but they also engage in risky sex. Then their partners will be infected thereby increasing the number of HIV/AIDS patients. Based on the type of work, the most results were working in the private sector as much as 49%, this can happen because in the private sector there are many things that can trigger infected sufferers, among others, because of having sex alternately, stress factors for work, far from being infected. from the family, lack of knowledge about HIV/AIDS and low awareness of HIV transmission prevention measures (Putri and Bagus, 2014).

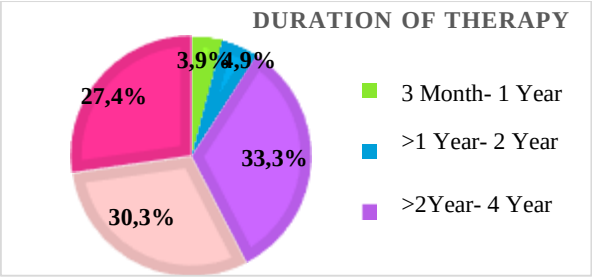

Figure 1. *Duration of Antiretroviral Therapy for HIV/AIDS Patients in one of the hospitals in Denpasar*

Based on the duration of ARV therapy, the types of adverse drug reactions that occur can be seen in table 2 below:

Table 2. The most common types of ADR seen from the length of ARV therapy

No.	Duration of ARV therapy	The most common types of ADR
1.	3 months – 1 year	Nauseous vomit
2.	> 1 year – 2 years	Anemia, headache
3.	> 2 years – 4 years	Skin rash, neuropathy, lethargy/fatigue
4.	> 4 years – 6 years	Nausea, vomiting, fever, muscle aches
5.	> 6 years	Skin rash, diarrhea

In the data of the research subjects, the description of the duration of ARV therapy was obtained one of the hospitals in Denpasarthe most are patients with a duration of therapy > 2 years - 4 years, which is 33.3%. Adverse drug reaction (ADR) is a fairly common occurrence in HIV patients and generally occurs in the first three months after ARV initiation, although long-term adverse drug reactions are also common afterward. The timing of adverse drug reactions varies from individual to individual. This adverse drug reaction often causes drug withdrawal cases in some patients.

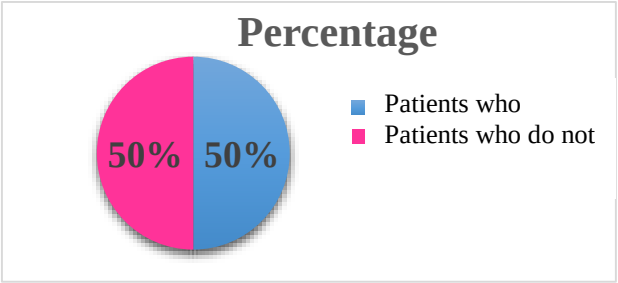

Figure 2. *Percentage of Patients Experiencing Adverse Drug Reactions (ADR)*

The number of Adverse Drug Reactions experienced by HIV/AIDS patients can be seen in table 3.

Table 3. Classification of Data Based on the Number of Adverse Drug Reactions experienced by HIV/AIDS Patients

ADR	Number of patients	Percentage
1 type of ADR	27	52.9%
2 types of ADR	16	31.4%
3 types of ADR	6	11.8%
4 types of ADR	2	3.9%
Total	51	100%

Based on the results of the study, there were 51 HIV/AIDS patients who experienced ADR (50%) from 102 patients. During treatment, it was found that most HIV/AIDS patients experienced 1 type of ADR, namely 27 people. Antiretroviral drugs can cause adverse drug reactions which in some patients can provide significant symptoms. One of the factors causing adverse drug reactions is the use of two or more drugs with the same side effects, such as zidovudine and lamivudine, both of which can cause nausea/vomiting. Thus, early detection of adverse drug reactions is very important, because these adverse drug reactions can reduce drug compliance (Ministry of Health, 2006).

Table 4. Types and number of ADR (Adverse Drug Reactions) events

No.	ADR Type	Number of ADR events
1.	Nauseous vomit	25
2.	skin rash	23
3.	Headache	11
4.	Fever	6
5.	Lethargic/tired	6
6.	Muscle ache	5
7.	Diarrhea	4
8.	Anemia	2
9.	Neuropathy	2
10	Nail hyperpigmentation	1
Total ADR Events		85

Adverse drug reactions due to the use of a combination of antiretroviral drugs zidovudine, lamivudine and nevirapine in HIV/AIDS patients in Indonesiaone of the hospitals in Denpasarthere are several types. The results showed that the number of adverse drug reactions experienced by HIV/AIDS patients was 25 cases of nausea/vomiting, then 23 cases of skin rash, 11 incidents of headache, lethargy/fatigue and fever, the same results were obtained as many as 6 events, muscle pain as many as 5 events, diarrhea as many as 4 events, neuropathy and anemia also obtained the same results as many as 2 events and the least is a patient who has nail hyperpigmentation as much as 1 event. A similar type of adverse drug reaction was also found in Dr. M. Muneer Kanha and Dr. Sk. Sharmila in 2006-2008 in India involving 325 HIV/AIDS patients who used a regimen of zidovudine, lamivudine,

Adverse drug reaction Nausea and vomiting can be caused by the use of zidovudine and lamivudine, this often happens because the route of ARV administration is orally where ARVs can irritate and increase stomach acid (Nur Rahmi et al., 2013). This can be overcome by giving symptomatic drugs such as ondansetron and domperidone.

Many skin rashes are experienced by HIV/AIDS patients during treatment with antiretrovirals. The patient's complaint is that the skin appears red which can be accompanied by itching. Skin rashes can be caused by the use of the drug nevirapine. In cases of mild skin rash, antihistamines such as cetirizine can be given. If the administration of antihistamines does not show a good response, the patient can be given corticosteroids such as hydrocortisone. Moderate rash that is not widespread and without mucosal involvement and systemic signs may be considered for replacing one NNRTI (NVP instead of EFV). In moderately severe cases, antiretroviral therapy was discontinued and supportive therapy was given. After recovery, the antiretroviral combination was replaced with 3 NRTIs in children or 2 NRTIs + PI in adults (Ministry of Health, 2015).

Adverse drug reactionDiarrhea can occur due to the use of the drug lamivudine, but will usually go away on its own without having to stop ARVs. If necessary, symptomatic therapy and oral rehydration can be given to maintain fluid and electrolyte balance. Likewise with ADR headaches which can also be caused by the use of the drug lamivudine, patients can be given symptomatic therapy, such as giving paracetamol as a pain reliever. While the adverse drug reaction of fever can be caused by the use of the drug zidovudine, the fever that occurs can disappear but can reappear. Fever will usually recover with the administration of antipyretics such as paracetamol.

Anemia can occur due to ADR from zidovudine or can also occur due to infection from HIV itself. People with advanced HIV often develop anemia because their bodies no longer (for various reasons) produce the hormones needed to stimulate the production of red blood cells. To confirm anemia caused by ADR from zidovudine, further blood tests are needed by looking at the shape and size of the erythrocytes. Because zidovudine inhibits DNA synthesis in the process of forming blood cells (erythropoiesis), the anemia caused is megaloblastic anemia.

On antiretroviral use there is a 1.5-2.3 times greater risk of anemia but usually occurs in the first year of antiretroviral therapy. ARV drugs that are often cited as one of the causes of anemia are nucleoside reverse transcriptase inhibitors, namely zidovudine, because they have a higher myelotoxicity effect than drugs in the same group and the protease inhibitor group. Manifestations of toxic side effects of zidovudine on the bone marrow include anemia, neutropenia, and siderosis caused by its inhibition of heme and goblin synthesis along with impaired iron availability. The treatment taken by doctors when anemia occurs in HIV/AIDS patients is to prescribe supplements or perform blood transfusions if deemed necessary. For anemia, if the Hb value < 6.5 g% and/or the total number of neutrophils <

Nail hyperpigmentation can occur in HIV-infected patients, which can be caused by the use of the drug zidovudine. But this rarely happens. Hyperpigmentation usually affects several nails and is reversible, but takes several years after discontinuation of the drug (Yuri, 2014). Adverse drug reactions lethargy / fatigue can be caused by the use of drugs zidovudine and nevirapine. While adverse drug reactions muscle pain can be caused by the use of drugs nevirapine and zidovudine. Adverse drug reaction neuropathy can be caused by the use of the drug lamivudine. The patient's complaint is tingling in the palms of the hands and feet that only occasionally appears. If there is severe neuropathy, the use of ARV drugs is discontinued.

IV. Conclusion

Based on the research that has been done, it can be concluded that:

1. There were 51 patients (50%) out of 102 patients with HIV/AIDS who had experienced adverse drug reactions. The duration of ARV therapy inone of the hospitals in Denpasar the most are > 2 years – 4 years, which is 33.3%.
2. The most common types of ADR were nausea/vomiting (25 events) followed by skin rash (23 events), headache (11 events), lethargy/fatigue (6 events), fever (6 events), muscle pain (5 events), diarrhea (4 events), neuropathy (2 events), anemia (2 events), and the least is nail hyperpigmentation (1 event).

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