DRUG UTILIZATION PROFILE IN HIV/AIDS PATIENTS
Study at Dr Soetomo Teaching Hospital Surabaya

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ABSTRACT

Increasing prevalence and mortality of HIV/AIDS led to a revolution in the care patients with HIV/AIDS. The accurate strategy of treatment was needed to solve any problems in related to opportunistic infections of AIDS. The treatments with antiretroviral (ARV) utilization are not a cure and present new challenges with respect to side effect and toxicity in the short therapy as well as ARV resistance which is used the long therapy due to viral mutation. The objective of this study was to analyze the drug profile in HIV/AIDS patients. The patients studied all were receiving antiretroviral and antimicrobial therapy who were hospitalized in Dr. Soetomo Teaching Hospital Surabaya during January 1st, 2004 until January 31st, 2006 (n=66 patients). This study was a descriptive analysis using patient's medical records. The results revealed that the patients' infection levels were in Stage III and IV (± 96% patients). Among the patients, about 82% using combination of the first line antiretroviral (ARV) drugs consisted of NRTIs (3TC, AZT) and NNRTIs (NVP, EFV). The ARV used in this study met the WHO guidelines as referred to the clinical condition of patients (stage III and IV) based on the total lymphocytes. There were 21% patients changing or stopping ARV treatment due to ADRs. Most patients' ADRs were caused by: (i) zidovudine (AZT) namely haematological toxicity as shown by decreasing Hb and WBC levels, (ii) Nevirapine (NVP) caused drug eruption or Steven Johnson's syndrome and hepatotoxicity with is shown by increasing SGOT and SGPT levels. The common opportunistic infections were chronic diarrhea (28%), lung tuberculosis (22%), oral candidiasis (15%), sepsis (14%), pneumonia (14%) and pneumocystic carinii pneumoniae (4%). The major prescribed antimicrobials were cotrimoxazole (13%), ceftriaxon (10%), levofloxacin (7%) and antifungal agents including nistatine (11 %), ketoconazole (7 %), fluconazole (6 %). The choice of antimicrobial agents based on the ability of the drugs to eliminate anaerob and aerob microorganisms and minimalizing the potential endotoxin release that could induce proinflammatory cytokines secretion (IL-1β, IL-6 and TNF-α), whereas antifungal agents used should be able to cover the broad spectrum fungal infection including aspergilosis. Potential drug interaction observed were the use of AZT with fluconazole or cotrimoxazole or rifampicin and NVP with rifampicin or ketoconazole. In conclusion, Drug profile used in HIV/AIDS patients were the first line ARV consisted of NRTIs (3TC, AZT) and NNRTIs (NVP, EFV); antimicrobial treatment including antibiotics and antifungal agents; and others to prevent or to treat opportunistic infections. ADRs was occurred in 21% patients receiving ARV therapy.

Keywords: *Drug Utility Study, DUS, HIV/AIDS, ARV/ART, opportunistic infection, antimicrobials*

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is a Human Immunodeficiency Virus (HIV) infection disease, which caused any symptoms and infections as result in depleting the immune system. HIV belongs to the family of human retroviruses and the subfamily of lentivirus. Prevalence and incidence of AIDS in the worldwide was accelerating within the past few years. According to the *United Nations Joint Program for HIV/AIDS* (UNAIDS), in 2005 approximately 40.3 million cumulative cases of HIV had been diagnosed in the worldwide, an estimated 4.9 million new cases of HIV infection, and 3.1 million deaths from AIDS. As of the last December, 2004, the HIV-infected cases in Indonesia were reported an estimated 3368 cases of HIV infection, 2682 cases of AIDS and ~ 740 AIDS-related deaths had occured (WHO 2005). AIDS caused a great many problems in an overall fields including health, economic and social aspects (Nasronudin 2007).

The high prevalence and mortality of HIV/AIDS led to a revolution in the care of patients with HIV/AIDS. The accurate strategy of treatment was needed to solve any problems in related to opportunistic infections of AIDS. The treatments with antiretroviral (ARV) utilization are not a cure and present new challenges with respect to side effect and toxicity in the short therapy as well as ARV resistance which is used the long therapy due to viral mutation. Therefore, this study performed was to analyze the drug utilization profile including ARV and antimicrobial agents in hospitalized HIV/AIDS patients

with opportunistic infections. The purpose of this study was to analyze drug profile in related to laboratory test and clinical data to determine when starting ARV therapy, stopping or changing therapy because of either side-effect/toxicity or treatment failure.

MATERIALS AND METHODS

This study used observasional method with deskriptive analysis. The subject observed was hospitalized HIV/AIDS patients at Department of Infectious Disease Intermediate Cure in Dr. Soetomo Teaching Hospital Surabaya-Indonesia. The patients studied all were receiving antiretroviral and antimicrobial therapy, during January 1st, 2004 until January 31st, 2006.

RESULTS

The number of samples in this study were 176 patients, whereas met criteria were 66 patients who aged 1 to 60 years. Most of the patients (n=56) were the male subjects of 21 to 30 years old. The major risk factor of HIV/AIDS transmission (± 48%) were injection drug use by druggiest. According to the WHO staging system for HIV infection and disease in adult and adolescent was divided into four stages or stadiums, that was namely stage I, II, III, and IV. The most of patients in this study were in the clinical stage III (30 patients) and IV (33 patients). There was a child to categorize into stage B (moderate symptoms) (Depkes RI 2003) or stage II as referred to WHO staging system for HIV infection and disease in children (WHO 2004). A patient was classified into stage I due to the labor caring pre-operation and a patient suffered a contact dermatitis that classified into stage II. The results shown that ± 96% of the HIV/AIDS patients who were hospitalized fall in the severe clinical stage with opportunistic infections.

The ARV utilization will depend on estimating a clinician, CD4 cell count, viral load (VL) and the clinical status of the patient. In the table 1, it was shown the clinical stage in related to the measurement of total lymphocytes count and an estimated CD4 cells from patients. The value of CD4 cell count in this table was calculated based on the equation : CD4 = 0.3 x total lymphocytes levels – 8.2 (Nasronuddin & Lydia 2003). Of 66 patients, there were only two patients who had CD4 count from laboratory test and were not the measurement of viral load because economic factor from the patients.

Tabel 1. Total Lymphocyte Count , CD4 Level, and The Clinical Stage of the HIV/AIDS Patients

Clinical Stage	Total lymphocytes (cells/mm^3)	An estimated CD4 count (cells/mm^3)	Number of patients	Percentage (%)
I	-	-	1*	1.54
II	-	-	1	1.54
III	>1200	>350	1	1.54
	>1200	<350	-	-
	<1200	>350	3	4.61
	<1200	<350	11	16.92
	-	-	17	26.15
IV	>1200	>350	3	4.61
	>1200	<350	-	-
	<1200	>350	-	-
	<1200	<350	10	15.15
	-	-	18	27.69
	Total		65	100,00

Note: 1* = A HIV patient who was in labor caring pre-operation
- = no patient or the total lymphocyte count or CD4 level was not available

ARVs are categorized into four classes based on their mechanism of action. They are Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs) and Entry Inhibitors (EIs) (Dong 2001; Fletcher 2002; Koda Kimble 2002). However, only two classes of ARV i.e. NRTIs and NNRTIs (both as first line therapy) are used for patients in Dr. Soetomo

Teaching Hospital Surabaya (Table 2). Side effect of ARV therapy is high (± 21% patients) which necessitates changing or stopping ARV therapy. A patient might take more than 2 side effects in this study. Table 3 shows frequency of ARV side effects. Frequency of an opportunistic infection observed was shown in Table 4 and phisical condition of HIV/AIDS patient to evaluate outcome therapy during treatment with ARV as demonstrated in Table 5.

Table 2. Profile of ARV in HIV/AIDS patients

ARV Classes	Type	Frequency of Administration	Percentage (%)
NRTIs	Lamivudine/3TC	61	32.6
	Zidovudine/AZT/ZDV	60	32.1
	Stavudine/d4T	3	1.6
	Didanosine/ddI	1	0.5
NNRTIs	Nevirapine/NVP	57	30.5
	Efavirene/EFV	5	2.3

Table 3. Frequency of Side Effects of ARV Therapy

ARV	Side Effect	Number of Patients	Percentage (%)
Zidovudin	Anaemia (Decreasing Hb level)	13	19.70
	Decreasing Leucocytes	13	19.70
Nevirapin	*Drug eruption*	1	1.51
	Steven Johnson's Syndrome	2	3.03
	Increasing SGOT level	7	10.60
	Increasing SGPT level	7	10.60

Table 4. Type of Oportunistic Infections in HIV/AIDS Patient

Type of oportunistic infection	Number of Cases	Percentage (%)
Chronic Diarrhea	24	28.6
Lung Tuberculosis	19	22.6
Oral candidiasis	13	15.5
Pneumonia	12	14.3
Sepsis	12	14.3
PCP*	4	4.8

*PCP = Pneumocystic carinii pneumoniae

DISCUSSION

CD4 count is the best indicator to know the immune system damage as well as to determine when starting ARV therapy and to categorize the clinical stage of HIV infection of the patients, then can be determine the time accurately giving prophylaxis antimicrobial agents to prevent the further opportunistic infections (i.e *pneumocystic carinii pneumoniae* (PCP) or TB). CD4 cell count is a most important part of the immune system because its cells produce a chemical substance that play a role in stimulating the other cells to grow and to develop as well as antibodies forming. In this case, viruses could infect CD4+ T lymphocytes and replicated in this cells so declined CD4+ T cells count had occured. When CD4+ T lymphocytes < 200 cells/mm^3, the

immune system of the patients was fall in the lowest level, and a patient was too susceptable to the opportunistic infections at this condition. Antimicrobial treatment as prophylaxis therapy was needed to prevent further opportunistic infections. To decide when starting ARV treatment, total lymphocytes count and the clinical symptoms evaluating can be used to substitution CD4 cells level. Both can also be used to monitor the immune response of the patients in the caring, which can not doing the CD4 cells testing. (Depkes RI 2003).

Table 5. The Change of Total Lymphocyte Count and Outcome State in HIV/AIDS Patient

The Change of Total Lymphocyte Count	Outcome			Number of patients
	Improve	Forced Discharge	Death	
Increase (10-500 cells per mm^3)	5	1	6	12
Decrease (10-2000 cells per mm^3)	13	-	6	19
Inconsistance value (10-1000 cells per mm^3)	2	1	2	5
No record *	21	2	7	30
Number of HIV/AIDS patient	41	4	21	66

*= the total lymphocyte data was not available

A total limphocyte count, CD4 level estimation, and the clinical stage of HIV/AIDS patients during the use of ARV are shown in Table 1. Of 65 patients, 63 patients used ARV which met the WHO guidelines where ARV was provided to patient with stage III and IV without considering the total lymphocyte count. Furthermore, although WHO guidelines recommend the inisiation of ARV therapy, it is still adjusted to the clinical situation with considering risks and benefits to the patient and thus ARV therapy can be started early or delayed (Hoffman & Mulcahy 2005).

Combination use of ARV therapy is common, however, some situations such as concommitant diseases, other drugs consumed, pregnancy, child birth, or lactation require single ARV therapy. In this study, the most common combination of ARV (± 82% patients) was Zidovudine + Lamivudine + Nevirapine. All ARV route of administration was oral. Table 2 shows the use of ARV in Dr. Soetomo General Hospital Surabaya. Since the doses of ARV therapy is critical to the goal of HIV/AIDS therapy, this study also examined the doses of ARV used in patients. Besides, the incidence of side effects and some clinical situations or diseases require dosage adjustment. In this study, the doses of ARV therapy met WHO guidelines (WHO 2004). Side effect of ARV therapy is high (± 21% patients) which necessitates changing or stopping ARV therapy. A patient might take more than 2 side effects in this study. Table 3 shows frequency of ARV side effects.

Lower HIV/AIDS patient's Hb and WBC level in this study showed that the use of ARV depress bone marrow. HIV can infect bone marrow's progenitor cell because this cell has CD34CD4 which can express CD4 as well as CXCR4 and CXR5 chemokine receptor. Consequently, they can destruct progenitor cell. Moreover, the infected CD4+ T lymphocytes induces cytokine secretion and inhibit the production of blood cell. The destruction and disturbance of bone marrow's progenitor cell as well as decreasing WBC level can be caused by decreasing CD4 cell level of an infected lymphocyte and monocyte, neutrophil autoimmune process, drug use such immunosupressant and zidovudine. Also, lowering Hb level is assosiated with erythrocyte autoimmune process; malnutrition and duodenal bacterial infection which cause absorption disturbance, folat and vitamin B_{12} deficiencies; destruction of kidney cells which cause decreasing erythropoeitin production; and the use of drug such as cotrimoxazole and zidovudine. In this study, 13 patients had Hb level of < 10 g/dl whereas 7 patients had Hb level of < 7 g/dl during their hospital admission. According to data, the prevalence of anemia in HIV/AIDS patients range from 63-95% and patient with lower CD4 <200 cells/mm3 has high risk of anemia of 86%. The risk of death in HIV/AIDS patient with CD4 > 200 cells/mm3 with anaemia is 48% compared to patient without anaemia whereas the risk of death gain to 56% patient with CD4 < 200 cells/mm3 with anemia compared to patient without anemia. This condition requires Hb level that is important predictor of death due to anemia so blood transfusion or recombinant erythropoeitin and nutritional therapy are a necessities (Fauci & Lane 2005).

Cytokine may also stimulate protein kinase C activity and can mobilize calsium into the systemic circulation, then will increase ATP and *reactive oxygen species* (ROS) production in mitochondria. ROS may cause cell destruction and develop to the severe progresifity of disease (Nasronuddin 2003). Liver cell dysfunction due to ROS elevate SGOT and SGPT levels which is caused by alcohol, drug abuse, an infected B and C viral hepatitis as well as the use of drug i.e nevirapine, stavudine, cotrimoxazole, and rifampicin. In the other hand, kupffer cell in the liver serve as a filter for bacterial, endotoxin, toxin and metabolite agents. This cell dysfunction due to an infected HIV will cause these agents through into the systemic circulation. Increasing SGOT over SGPT because SGOT is not only in the liver but be also in the heart and the muscle, so liver cell damage as result in elevating ROS and SGOT level. In this study, there was 7 patients in elevating SGOT level and 3 patients in elevating SGPT level. In this case, it might be caused by side effect of nevirapine as result in immune reaction but the mechanism not clear. It was frequently observed in the patients starting treatment with the higher CD4 cell count due to have more immune reaction (Depkes RI 2003).

Frequency of an opportunistic infection observed was shown in Table 4 and most of the opportunistic infection was chronic diarrhea. Declining immune system in HIV/AIDS patients made them susceptable to opportunistic infections which was on the attacking any organs, particularly the most important organs including respiratory tract, gastrointestinal track and neurologic system.

From data revealed that the opportunistic infections eventually developed in the HIV/AIDS-infected patients as shown in Table 4. The major of its infection types are chronic diarrhea, lung tuberculosis, oral candidiasis, pneumonia, sepsis and *Pneumocytstic carinii pneumoniae* (PCP). It is important to note that the diarrhea was resulted by not only a manifestation of HIV infection or sepsis but also infection of bacteria (*Salmonella, Shigella, Campylobacter),* protozoa (*Cryptosporidia, Microsporodia, Isospora beili*), or fungal (*Histoplasmosis, Coccidioiodomycosis, Penicilliosis*). The choice of antimicrobial agents based on the ability of the drugs to eliminate anaerob and aerob microorganisms and minimalizing the potential endotoxin release that could induce proinflammatory cytokines secretion (IL-1β, IL-6 and TNF-α), whereas antifungal agents used should be able to cover the broad spectrum fungal infections including aspergilosis. Antifungal was administered to the HIV/AIDS patient that they were also infected by fungal or in CD4 cell count < 200 cells/ mm3 (Nasronuddin 2003). The major antimicrobial agents used in clinical treatment for HIV/AIDS patient were cotrimoxazole (13.4%), ceftriaxone (10.1%), levofloxacin (7.7%), nistatin (11.2%), ketoconazole (7.6%) and fluconazole (6.9%). Cotrimoxazole is an antimicrobial agent with broad spectrum activity that effective for treatment gastrointestinal tract infections, toxoplasmosis and first line for prophylaxis therapy and treatment for PCP (Depkes RI 2003; Raffanti 2001).

Combination ARV and other drugs are taken concurrently, there is a chance to make an interaction among the drugs in the several steps of fate into body including pharmaceutic, pharmacokinetic and pharmacodinamic phases. The interaction may increase or decrease the effectiveness and/or the side effects of the drugs. Some methods were applied to avoid the drug interaction such as regulation of dosage form, interval administration and meal setting. Potential drug interactions observed in this study were between AZT with fluconazole or cotrimoxazole or rifampicin and NVP with rifampicin or ketoconazole (Burnham 2001; Mc Evoy 2002).

The improving condition of HIV/AIDS patient clearly appear from clinical and laboratory data. The successful strategy of therapy in the HIV/AIDS patient was signed by either an increasing of body weight, total lymphocyte count and CD4 cell count or a decreasing viral load. In the present study, we observed total lymphocyte count and phisical condition of HIV/AIDS patient to evaluate outcome therapy during treatment with ARV as demonstrated in Table 5. Regarding to these indicators, the failure of ARV treatment in HIV/AIDS patient were marked a lost of body weight during ARV therapy, rebound the previous opportunistic infections or occuring the new ones.

The increasing of CD4 cell count during ARV therapy at 100-200 cells/mm3 for initially year and 100 cells/mm3 for consecutively years indicated a progress response for HIV/AIDS patient. On the contrary, the failure therapy was marked a decreasing the CD4 cell count until 30% from the highest value during ARV therapy. Decreasing VL at 32-100 copies per ml in the first month and at 50 copies per ml in 80-90 % cases for 24 weeks was wished during treatment of ARV. Treatment failure was observed if VL continuously increase over than 5000 copies per ml, diminish less than 10 copies per ml during 6-8 weeks in the starting ARV therapy and raising over than 4 copies per ml of the lowest levels or rebound to 50% from the previous treatment (Depkes RI 2003; WHO 2004).

In the present study, outcome of the progress ARV therapy only observed on the level of total lymphocyte count and improving the physical condition of patients

when they discharge from hospital. As shown in Table 5, 12 patients have a degradable extend of their total lymphocyte level to 10-2000 cells per mm3, 19 patient to 10-1000 cells per mm3 and 30 patients no recording. From all of the patient that receiving ARV treatment (66 patients), 62% (41 patients) getting improvement, 6% (4 patients) forced-discharge from hospital with no progress and 32 % (21 patients) were died.

CONCLUSION

Drug profile used in HIV/AIDS patients are the first line ARV consisted of NRTIs (3TC, AZT) and NNRTIs (NVP, EFV); antimicrobial treatment including antibiotics and antifungal agents; and others to prevent or to treat opportunistic infections. ADRs occurred in 21% patients receiving ARV therapy.

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