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PROFILE OF ANTIRETROVIRAL RESISTANCE IN HIV/AIDS PATIENTS IN DR. SOETOMO GENERAL ACADEMIC HOSPITAL SURABAYA

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Abstract

Background: World HIV/AIDS prevalences reach to 36,9 million patient. Most patient located in Africa as much as 24,7 million. Meanwhile in Asia, 4,8 million people recorded suffered from HIV/AIDS. The first time HIV/AIDS was reported in Indonesia in 1987. The prevalence of HIV/AIDS in Indonesia since it first discovered until 2016 was spread in 80% districs/cities from all provinces in Indonesia. Dr. Soetomo general hospital is a referral hospital in the eastern part of Indonesia. It has HIV care unit which many HIV/AIDS patients were treated with antiretroviral. However, the data of profile of antiretroviral resistance is still limited.

Objective: This study aimed to identify the profile of antiretroviral resistance in patients treated with antiretroviral in Dr. Soetomo hospital in Surabaya.

Methods: This study used descriptive retrospective design. The data of antiretroviral resistance was obtained from treated patients by using medical record. The examined population was all patient diagnosed with HIV/AIDS in Dr. Soetomo Hospital Surabaya.

Results: Combination of Lamivudine, Zidovudine and Nevirapine of the first line antiretroviral was most often used (70.6%) to treat the patients. The highest drug resistance was found in Nevirapine and Efavirenz (members of Non-nucleoside reverce transcriptase inhibitors) (58.8%, respectively) with the associated mutation patterns of HIV polymerase included Y181C, V108I, V106I, G190GA (~ Nevirapine resistance) and Y181C, V108I, V106I (~ Efavirenz resistance); while the most resistant members of nucleoside reverce transcriptase inhibitors were Lamivudine and Emtricitabine (23.5%, respectively) (M184V and K65R), followed by Tenofovir (17.6%) (K65R) and Zidovudine (5.9%) (K219QE).

Conclusion: Most patients showed high resistance to Nevirapine and Efavirenz in non-nucleoside reverce transcriptase inhibitors group, followed by Lamivudine and Emtricitabine in nucleoside reverce transcriptase inhibitors group.

Keywords: *HIV, antiretroviral resistance*

Introduction

The human immunodeficiency virus (HIV) belongs to Ra retrovirus that infects immune system and causes over time acquired immunodeficiency syndrome (AIDS). AIDS is a condition in humans with progressive failure of the immune system [*Ammaranond P et al., 2003, Aji HS, 2010*].

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A global HIV/AIDS prevalence reached 36.9 million patients. Most patients were located in Africa as much as 24.7 million. Meanwhile in Asia, 4.8 million people were recorded as suffering from HIV/AIDS. Asia is predicted to have the highest rate of HIV infection globally. According to WHO and UNAIDS, the three countries reporting the highest rate of HIV are China, India, and Indonesia, which have the largest population in the world. [*UNAIDS, 2015*] In Indonesia, the first case of HIV/AIDS was reported in 1987. Since the first HIV case (1987) to 2016, HIV and AIDS spread over 407 (80%) of the 507 districts/cities across provinces in Indonesia. The first case was reported

in Bali province, and the last was reported in West Sulawesi province in 2012 [*MoH, 2017*].

According to Ministry of Health of Republic of Indonesia, HIV prevalence in Indonesia during January and March 2017 was 10,376 people, with the highest percentage of infections in the age group of 25-49 years (69.6%), and a much higher among males (male-female ratio of 2:1). In the province of East Java, cases of HIV/AIDS increased in 2009 by 4,504 patients while in 2016 there were 6,513 cases [*MoH, 2017*].

The introduction of highly active antiretroviral therapy (HAART) to HIV/AIDS patient improves quality of life, life expectancy, decrease rate of resistance and further decrease mortality to AIDS related causes. There are some antiretroviral (ARV) drugs in 6 classes licensed for the treatment of HIV-1: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitor, CC chemokine receptor 5 (CCR5) antagonist and integrase inhibitor [*Tang MW, Shafer RW, 2012*]. The 2010 World Health Organization (WHO) HIV treatment guidelines recommend zidovudine/lamivudine, tenofovir/lamivudine or tenofovir/emtricitabine (NRTIs) in combination with nevirapine or efavirenz (NNRTIs) as first line ARV therapy (ART). In 2016, WHO published the consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection and recommended tenofovir disoproxil fumarate+ lamivudine (or emtricitabine) +efavirenz as the preferred first-line ART [*WHO, 2008*].

Of the 36.7 million people living with HIV worldwide, 19.5 million people were accessing ART in 2016. Most of these people are doing well, with treatment proving highly effective in suppressing the HIV virus. But a growing number are experiencing the consequences of drug resistance. The effect of HAART in the treatment of HIV infection is usually measured by survival, CD4 lymphocyte counts, HIV-1 RNA viral load testing, and the occurrence of opportunistic infections [*Brechtl J et al., 2001*].

HIV resistance to ARV agents can be assessed by genotypic assays. Genotypic resistance testing relies on detecting known drug-resistance mutations in the enzymatic targets of ART i.e. protease and reverse transcriptase. The most common NRTI mutations are M184V/I, K65R, K70E/G, L74V, Y115F and the Q151M complex of mutations, while the most common NNRTI mutations are L100I, K101EP, K103NS, V106AM, Y181CIV, Y188L, G190ASE and M230L [*Tang MW, Shafer RW, 2012*].

Dr. Soetomo General Hospital Surabaya is a care referral center for HIV/AIDS patients in East Java province, however the data of antiretroviral (ARV) resistance is still limited. The study aimed to identify ARV resistance pattern in HIV/AIDS patients in Dr. Soetomo General Hospital Surabaya in the last 2 years.

Material and methods

This was a descriptive retrospective study using secondary data through medical records in Unit of Intermediate Care and Infectious Diseases (UPIPI) of Dr. Soetomo General Hospital, in Surabaya, Indonesia.

Samples were all patients diagnosed with HIV/AIDS in UPIPI of Dr. Soetomo General Hospital in the period 2016-2018. Patients were eligible for enrollment if they (i) had initiated (first line) ART at least 6 months, (ii) showed a resistance to ART, based on HIVDR (HIV Drug Resistance) genotyping test. Patients registered from January 2016 until December 2018 in the hospital were recruited.

The first line ART included Lamivudine (3TC), Zidovudine (AZT), Nevirapine (NVP), Emtricitabine (EFV), Tenofovir (TDF), and Efavirenz (FTC). The amino acid mutation type in HIV polymerase region associated with ARV resistance was determined based on the previous reports. The obtained data then was analysed descriptively.

Results

The demographic distribution of patients who underwent antiretroviral resistance test in UPIPI of Dr. Soetomo Hospital in period 2016 – 2018 is shown in Table 1.

The WHO clinical stages of HIV/AIDS are I, II, III, IV. The WHO clinical staging is used to manage patients with HIV/AIDS who attended Dr. Soetomo hospital (Table 2).

The distribution of a CD4+ count in patients with HIV/AIDS in Dr. Soetomo Hospital Surabaya is shown in Table 3.

All patients received the first line ARV. The data of CD4+ count, clinical staging and adherence to ARV of each patients is shown in table 4.

The patients had opportunistic infections (IO)

including Candidiasis, Pneumonia, Tuberculosis and cancer (Table 5).

The combinations of ARV therapy used by the patients included : 3TC + AZT + NVP, 3TC + AZT + EFV, 3TC + TDF + NVP, 3TC + TDF + EFV, FTC + TDF + NVP, and FTC + TDF + EFV (Table 6).

The available ARV types in Indonesia include Lamivudine, Emtricitabine, Tenofovir, Zidovudine, Nevirapine, and Efavirenz. The ARV resistance patterns are shown by the treated patients in this study (Table 7).

The NRTIs used by the patients included Lamivudine, Emtricitabine, Tenofovir and Zidovudine, while the used NNRTIs included Nevirapine and Efavirenz. The distribution of amino acid mutation pattern in HIV Polymerase region associated with ARV resistance is shown in Table 8.

Table 1.

Demographic Distribution

Characteristic	Number of Male n (%)	Number of Female n (%)	Total n (%)
Gender	11 (66.7)	6 (33.3)	-
Age (y.o)			
20 - 29	1 (5.9)	1 (5.9)	2 (11.8)
30 - 39	9 (52.9)	2 (11.8)	11 (66.8)
40 - 49	2 (11.78)	-	2 (11.8)
50 - 59	-	2 (11.8)	2 (11.8)
Level of Education			
High School	8 (47)	4 (23.5)	12 (70.6)
Bachelor	4 (23.5)	-	4 (23.5)
Uneducated	-	1 (5.9)	1 (5.9)
Marital Status			
Married	9 (52.9)	5 (29.4)	14 (82.3)
Unmarried	3 (17.6)	-	3 (17.65)
Transmission Pattern			
Heterosexual	5 (29.4)	5 (29.4)	10 (58.8)
Homosexual	3 (17.6)	-	3 (17.6)
Drug Injection *	4 (23.5)	-	4 (23.5)

*Notes: * - Intravenous drug user*

Discution

The sociodemographic characteristics of the enrolled patients in this study including gender, age, education level, marital status and transmission ways are as follows.

The male patients with HIV/AIDS were predominant (66.67%). According to MoH RI (2014), since 2008 until 2014, the pattern of HIV transmission based on sex has a similar pattern which is more common in the male group. Rüütel K et al. (2009) showed that HIV patients were still dominated by male with 53.2% and 46.8% of female patients. This was also in line with the study by Saktina P, Satriyasa B (2017), which stated that the patients with AIDS in Sanglah Hospital Denpasar consisted of 67.6% of males and 32.4% of females. The total number of patients treated in HIV and AIDS treatment care on August 2009 in Dr.Kariadi Hospital Semarang were 697, and males were pre-

Table 2.

Distribution of HIV Clinical Staged based on WHO

WHO Clinical Staging	Number of Males n (%)		Number of Females n (%)		Total n (%)	
	Pre ARV	Post ARV	Pre ARV	Post ARV	Pre ARV	Post ARV
Stage II	2 (11.8)	1 (5.9)	4 (23.5)	2 (11.8)	6 (35.3)	3 (17.7)
Stage III	9 (52.9)	8 (47.1)	1 (5.9)	1 (5.9)	10 (58.8)	9 (52.9)
Stage IV	1 (5.9)	2 (11.8)	0 (0)	0 (0)	1 (5.9)	2 (11.8)
Stage Unknown	0 (0)	1 (5.9)	0 (0)	2 (11.8)	0	3 (17.7)

Table 3.

Distribution of CD4+ Count

CD4+ Count (cells/mcl)	Number of Males (%)		Number of Females (%)		Total (%)	
	Pre ARV	Post ARV	Pre ARV	Post ARV	Pre ARV	Post ARV
< 200	10 (58.9)	5 (29.4)	0 (0)	1 (5.9)	10 (58.8)	6 (35.3)
201 – 350	1 (5.9)	2 (11.8)	1 (5.9)	0 (0)	2 (11.8)	2 (11.8)
> 350	0 (0)	3 (17.6)	1 (5.9)	1 (5.9)	1 (5.9)	4 (23.5)
Untested	4 (23.5)		5 (29.4)		9 (52.9)	

TABLE 4.

CD4+ Count, WHO Clinical Staging and Adherence to ARV of Each Patient

Patient No.	CD4+ Count (cells/mcl) Pre ARV	CD4+ Count (cells/mcl) Post ARV	CD4+ change	WHO Staging Pre ARV	WHO Staging Post ARV	WHO Staging Change	Adherence to ARV
1.	19	-	-	3	3	NC	No
2.	183	46	Dec.	3	3	NC	No
3.	33	139	Inc.	3	4	Inc.	No
4.	33	139	Inc.	3	3	NC	No
5.	352	352	NC	3	2	Dec	No
6.	167	376	Inc.	3	3	NC	Yes
7.	66	199	Inc.	4	4	NC	No
8.	-	-	-	3	-	-	No
9.	-	-	-	2	-	-	No
10.	291	116	Dec.	2	2	NC	No
11.	79	117	Inc.	3	3	NC	No
12.	90	331	Inc.	3	3	NC	Yes
13.	242	451	Inc.	3	3	NC	Yes
14.	-	-	-	2	3	Inc.	No
15.	43	381	Inc.	3	3	NC	Yes
16.	-	-	-	2	-	-	No
17.	8	298	Inc.	2	2	NC	No

NOTES: *Dec- Decrease, Inc.- Increase, NC- No Change*

TABLE 5.

Distribution of Opportunistic Infection

No	Number of IOs	Number of Patients n (%) Pre ARV	Number of Patients n (%) Post ARV
1.	0	0 (0)	0 (0)
2.	1 - 3	5 (29.4)	3 (17.6)
3.	> 3	0 (0)	0 (0)
4.	Unknown	12 (70.6)	14 (82.3)

TABLE 6.

Distribution of ARV Combination

No.	ARV Combination NRTI	ARV Combination NNRTI	The Number of Patients n (%)
1.	3TC + AZT	+ NVP	12 (70.6)
2.	3TC + AZT	+ EFV	1 (5.9)
3.	3TC + TDF	+ NVP	3 (17.6)
4.	3TC + TDF	+ EFV	1 (5.9)
5.	FTC + TDF	+ NVP	0 (0)
6.	FTC + TDF	+ EFV	0 (0)
	TOTAL		17 (100)

NOTE : *3 TC - Lamivudine, AZT - Zidovudine, NVP - Nevirapine, EFV - Efavirenz, TDF - Tenofovir, FTC - Emtricitabine*

TABLE 7.

Distribution of ARV Resistance

No	ARV Type	ARV Group	Number of Patients (%)
1.	Lamivudine (3TC)	NRTI	4 (23.5)
2.	Emtricitabine (FTC)		4 (23.5)
3.	Tenofovir (TDF)		3 (17.6)
4.	Zidovudine (AZT)		1 (5.9)
5.	Nevirapine (NVP)	NNRTI	10 (58.8)
6.	Efavirenz (EFV)		10 (58.8)

TABEL 8

Distribution of Mutation Pattern in HIV Polymerase

No	ARV Type	ARV Group	Mutation Pattern in HIV Polymerase	Number of Mutation (%)
1.	Lamivudine	NRTI	M184V, K65R	29.4
2.	Emtricitabine		M184V, K65R	29.4
3.	Tenofovir		K65R	11.8
4.	Zidovudine		K219QE	5.9
5.	Nevirapine	NNRTI	Y181C, V108I, V106I, G190GA	47
6.	Efavirenz		Y181C, V108I, V106I	41.2

dominant because they tend to have more than one partner in the heterosexual and homosexual groups [*Shafer RW, et al, 2007*].

The highest proportion of the patients based on age was obtained in a group of 30 – 39 years old (66.7%). This is in line with the previous report in Spain, that among 865 patients, the average age of the patients with HIV/AIDS was 37 years old [*Domingo P et al, 2107*]. Also found that the highest percentage of AIDS patients in Sanglah Hospital Denpasar was in the age group of 30 – 39 years old (39.7%.) In the Youth Group *Kuldesak* in Depok, patients with age group of 31-40 years old were predominant (57.5%), followed by those with age group of 21 – 30 years old (35%) [*Shafer RW, 2007*]. Stated that from 2010 to September 2014, mostly, people with HIV infection were in the productive age group of 25-49 years old, followed by those with the age group of 20 -24 years old [*Ministry of Health RI, 2014*]. The younger group has a higher risk of having unsafe sexual behaviour than the older group, it makes them less aware in HIV transmission. In some cases, the older group can also have unsafe sexual behaviour [*Yeni P, 2006*].

The patient education level was mostly high

school (70.59%), followed by university/college (25.32%). It is in line with the previous study, which reported that the highest percentage was patients with high school education level (53.8%) [*Moyle G, 2005*]. However, the different result was reported that education level of patients was dominated by elementary school (37.1%), followed by high school education (34.3%) and diploma and master (2.9%) [Anissa L et al., 2014; Wesnawa M, Putra I, 2016]. Another showed that patient education level was dominated by secondary education (46.2%) and lower education (44.2%) [*Bennet DE et al., 2008*]. People living with HIV/AIDS (PLWHA) who had secondary education (high school/equivalent) up to higher education more often utilize health services than those with low education level [*Clavel F, Hance AJ, 2004*]. Understanding an information or knowledge is affected by education level. The higher level of education of a person is the easier to understand information. However, reported that the risk of getting HIV and AIDS was not influenced by education level. A comprehensive literature review in Africa Sub-Sahara, showed that education remains the only hope to combat HIV/AIDS transmission [*Tuntufye SW, 2014*].

The most patient marital status was married (82.3%) followed by unmarried (17.7%). However, the results were different with the study that showed the predominant patients was unmarried (50.6%) followed by married (35.1%).

The most pattern of HIV transmission was heterosexual (58.8%), followed by IVDU (23.5%) and homosexual (17.6%). This is in line with the previous study [*Astindari A, 2014*], which found that the heterosexual transmission pattern was predominant (71.9%), followed by IDU (35.4%) [*Booth CL, Geretti AM., 2007*].

The effect of HAART in the treatment of HIV infection of the patients is shown by data of clinical stage, CD4+ counts, and the occurrence of opportunistic infections before and after ARV therapy, as follows.

World Health Organization (WHO) classify HIV into 4 clinical stages namely; stadium I, II, III, and IV, where in the last stage (stage IV) used as AIDS indicator [*WHO, 2008*]. Most of them got opportunistic infection (IO). Even without laboratory tests, the WHO clinical staging is useful for predicting the prognosis in people with HIV. The clinical staging is helpful for areas with limited access to laboratory facilities [*Malamba SS et al., 1999*]. Before ART, patients with WHO clinical stage III was predominant (58.8% consisted of 52.9% of male and 5.9% of females), followed by those with stage II (35.3%, consisted of 11.8% of males and 23.5% of females). Also showed that among 73 samples from Voluntary Counseling and Testing Clinic (VCT) in dr. Zainoel Abidin Hospital Banda Aceh, the highest percentage was found in patients with stage III (60.27%), followed with those with stage I (30.14%). On the contrary, reported that the highest percentage was found in patients with stage IV (72,9%), followed by those with stage III (10.4%). Melesse (2015) stated that at the initiation of ART; 76.2% patients at Wukro Hospital in Ethiopia, had stage III or IV clinical stage (advance stage of the disease). The highest order in the post-ART group in this study was the same as the highest order in the pre ART group.

Fear of stigma and discrimination or the lack of decentralization of HIV clinics can be a barrier for the patients to get HIV care service. Based on the East Java province health profile report, the new cases of AIDS in 2012 decreased to 822 cases from 1,052 cases in 2011. The existence of VCT (voluntary counseling and testing) clinic and health service unit (UPK) that are useful for early detection of HIV and also the existence of CST (care support treatment) clinic which aims to follow up the finding of new HIV cases might contribute the improved condition. In period 2005-2012, the new cases of HIV were higher compared with those of AIDS, it means that UPK was successful in reducing the number of AIDS cases year by year so the the mortality rate can reduced. During 2009-2012, there was a progress in implementation of HIV control program in Indonesia [*WHO, 2008*]. Many HIV care units have been developed and there is a sharp increase of their utilization. Although the new case finding of HIV/AIDS in rural areas was limited, the development of HIV care units have not been expanded in all provinces. The main goals of the program are to increase the effectiveness, quality, accessibility, and ARV availability of HIV/AIDS management. This is a great challenge to reach the goals, especially in remote, inaccessible areas.

Before ART, the majority of CD4+ count was <200 *cells/mcl* (58.8%), followed by 201-350 *cells/mcl* (11.8%) and >350 *cells/mcl* (5.9%). Meanwhile after ART, the majority of CD4+ count of the patients was <200 *cells/mcl* (35.3%), fol-

lowed by >350 *cells/mcl* (23.52%) and 201-350 *cells/mcl* (11.8%). It showed an increase percentage in high CD4+ (>350 *cells/mcl*) and a decrease percentage in low CD4+ (<200 *cells/mcl*). Kurniawan (2017) also found the high percentage of patients with an increase in CD4+ (77.7%, 153/197) 6 months after ART at the outpatient clinic at Dr. Cipto Mangunkusmo hospital, Jakarta.

After ART, there were 4 patients who showed a rise in CD4+ count. Based on WHO clinical staging, only 1 patient who showed improvement (decrease in staging), while 2 patients showed being worse condition (increase in staging) and the rest were no change in clinical condition. Adherence percentage for these patients in this study was only 23.5% (4/17). Extra attention and support should be warranted to counter this problem. Adherence is crucial and is strictly associated with virologic suppression Low levels of adherence increase disease progression as well as viral resistance, and limit the therapeutic options [*Betancur MN et al, 2017*].

Before ART, the percentage of patients who had opportunistic infection (OI) was 29.4%, while post ART, only 17.6% patients had OI. All of them had 1-3 OIs. However, most of the patients (pre and post ARV) were not known whether they had OIs or not (70.6% and 82.3%, respectively). Reported 31 patients died from AIDS and OIs in Dr. M. Djamil Hospital in period 2010-2012, which included 11 patients in 2010, 13 patients in 2011 and 7 patients in 2012.

The first line drugs combination used by the patients is dominated by Lamivudine, Zidovudine and Nevirapine (70.6%), followed by combination of Lamivudine, Tenofovir, Nevirapine (17.6%), and the combination of Lamivudine, Zidovudine, Efavirenz and also Lamivudine, Tenofovir, Efavirenz (5.9% respectively).

The highest drug resistance was found in NNRTIs included Nevirapine and Efavirenz (NNRTIs) (58.8% respectively), followed by NRTIs included Lamivudine and Emtricitabine (NRTIs) (23.5% respectively), Tenofovir (17.6%) and Zidovudine (5.9%). The most detected mutations (47%) was associated with Nevirapine (NNRTI) resistance, which included Y181C, V108I, V106I, G190GA, followed by those associated Efavirenz (NNRTI) resistance (41.2%) which included Y181C, V108I, V106I. Among NRTI group, the most mutations were associated with Lamivudine and Emtricitabine resistance (29.4%) which included M184V and K65R, followed by mutation associated with Tenofovir (K65R) (11.8%) and Zidovudine resistance (K219QE) (5.9%). The previous study reported that ART failure develops in about 20% of people with HIV receiving first-line ART in low resource settings [*Zhang F et al., 2009*] The second-line ART should be considered to encounter this problem.

Other related studies in some countries showed varied number of ARV resistance. In Saudi Arabia, 41% of treatment-experienced patients were reported to have NRTI resistance mutations, 16% had NNRTI resistance mutations, and 13% had PI resistance mutations [*Jamjoom GA et al., 2010*]. In Iran, the prevalence of NRTI, NNRTI, and PI resistance mutations was reported to be ~50, 29, and 6.5%, respectively [*Baesi K et al., 2014*]. In Kuwait, resistance-associated mutations were detected in 26.2% of the patients. M184V and K103N were the most commonly detected mutations associated with resistance to NRTIs and NNRTIs, respectively [*Chehadeh W et al., 2018*]. In Panama, the NNRTI mutations (K103N and P225H) were more prevalent in both ARV drug-naïve and ARV treated patients. The NRTI mutation M184V was more frequent in ARV treated patients. Therefore, there is a high level of resistance (>73%) to Efavirenz/Nevirapine, Lamivudine and Azidothymidine in ARV treated patients [*Mendoza Y et al., 2016*]. Monitoring ARV resistance in treated patients is crucial to avoid treatment failure. Moreover, ARV adherence should also be considered, because drug resistance is likely to occur in patients with non-adherence to ARV, particularly to drugs with low genetic barrier to resistance [*Chehadeh W et al., 2018*].

CONCLUSION

Nevirapine and Efavirenz (NNRTIs) resistance was detected in a large proportion (58.8%, respectively), with the associated mutation patterns in HIV polymerase included Y181C, V108I, V106I, G190GA (~Nevirapine reistance) and Y181C, V108I, V106I (~Efavirenz resistance). Meanwhile, the most resistant members of NRTIs were Lamivudine and Emtricitabine (23.5%, respectively) (M184V and K65R), followed by Tenofovir (17.6%) (K65R) and Zidovudine (5.9%) (K219QE).

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