EVALUATION OF ANTIRETROVIRAL ON HIV/AIDS PATIENTS AT 2012 -2013 PERIOD IN ONE HOSPITAL IN BANDUNG*

By:

Sri Adi Sumiwi, Anas Subarnas, and Pritasari Dwi A., Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia Email:sri.adi@unpad.ac.id

ABSTRACT

HIV/AIDS is a chronic disease that develops progressively and uses antiretroviral drugs as the therapy. For an HIV-positive patient, antiretroviral therapy is a lifelong treatment. Therefore, an evaluation of antiretroviral drug use in hospitals should be conducted. The aim of this study is to obtain information about antiretroviral drug use profile and the accuracy of antiretroviral drug use in RSUD in Bandung during the period of 2012 to 2013. This study was performed using an observational method and retrospective approach. The use of antiretroviral drug was calculated by Anatomical Theraupetic Chemical/Defined Daily Dose (ATC/DDD) and Drug Utilization 90% (DU90%) method. The result showed that the use of antiretroviral drugs tended to increase from 301.66 into 350.04 DDD/1000 inhabitants (outpatient) and there were 3 antiretroviral drugs (nevirapin, efavirenz, and lamivudin) which included in DU90% segment during 2012-2013 period. There was a presumed drug interaction (10%) between antiretroviral drugs (nevirapine) for tuberculosis and 2% of antiretroviral duplication.

Key words : Antiretroviral, ATC/DDD, DU90%, evaluation, HIV/AIDS

*Presented on The 14th Asian Conference on Clinical Pharmacy, October 31-November 3, 2014, Kuala Trengganu, Malaysia.

INTRODUCTION

Infection of *Human Immunodeficiency Virus* (HIV) increases in every year. It also becomes global health problem which becomes fifth rank after heart disease, respiratory infection, stroke, and diarrhea (Robert, 2013). Increasing of HIV/AIDS case also happens in Indonesia. The case which is reported in the end of 2013 reaches out 52.348 for AIDS and 127.416 for HIV. According to (Ditjen PP&PL Kemenkes RI, 2014) West Java is on the top fourth of 33 provinces in case of HIV/AIDS infection.

There are ten hospitals in Bandung which were recommended by government for providing antiretroviral therapy service for HIV/AIDS-positive patient. One of recommended hospital is RSUD Bandung. It is set in ministry of health decree Republic of Indonesia No.451/MENKES/SK/XII/2012 dealing with recommended hospital for HIV/AIDS-positive patient.

Antiretroviral therapy has to be given toward HIV-positive patients in their entirely life, so the choosing of antiretroviral drugs should be considered well and accorded towards condition of patient. It is done to minimalize site effect and give comfort for patient. According to Ramadian and Eky (2010), site effect and comfort are main factors relating to patient adherence in consuming antiretroviral drugs. If patient adherence becomes greater is expected the curing of outcome clinic to be better, therefore the virus mutation or drugs resistance can be prevented. Hence, in supporting the good curing, evaluation of using antiretroviral WHO standard method; Anatomical *Therapeutic* drugs by Chemical (ATC)/Defined Daily Dose (DDD) and Drug Utilization 90% (DU90%) is really required.

ATC/DDD method is a classification system and an evaluation drugs-used, while DU90% is a method describing drugs-used pattern. According to Sjoquist and Brikett (2003) this method is used to make classification of statistic data of drugs-used therefore, the quality of drugs-used can be measured. The beneficial of this method is able to compare the result of drugs-used evaluation in hospital easily. By knowing the comparison of drugs-used in different place will be used to detect substantial differentiation. Then, the further evaluation can be done if there is significant differentiation which leads to problem identification and repairmen of drugs-used system (WHO, 2009).

METHOD

This study was performed using an observational method and retrospective approach. The data that used are antiretroviral drugs-used in 2012-2013 period and medical record of HIV/AIDS-positive patient (18-60 years old) who used antiretroviral in 2012-2013 period which fulfills inclusion criteria, belong to outpatient which has clear medical record and can be checked it easily. The exclusion criteria is medical record of patient which cannot be checked and the used of antiretroviral except used to HIV/AIDS therapy.

Types of collecting data include type of antiretroviral, dosage of antiretroviral, antiretroviral administration route, mount of outpatient in 2012-2013 period, age of

patient, sex of patient, educational background of patient, causes of HIV/AIDS infection, and opportunistic infection. The chosen data will be proceed and analyzed by using ATC/DDD method which includes in WHO Guideline Collaborating Center 2011 and DU90% for knowing the profile of antiretroviral-used 2012-2013 period. Here the calculation of DDD/1000 KPRJ and percentage of antiretroviral drugs-used

Calculation of DDD/1000 KPRJ

 $DDD = \frac{\text{Total of drug usage (g)}}{\text{DDD drug}}$ $DDD/1000 \text{ KPR} = \frac{\text{Total DDD (1 year)}}{\text{Total KPRJ}/1000}$

Calculation % Antiretroviral %

= Total of DDD/1000 KPRJ antiretroviral Total of DDD/1000 KPRJ entire antiretroviral

Antiretroviral which includes segment of DU90% is classified by measuring the percentage of each antiretroviral-used, then make the order position from high to low percentage. DU90% can be seen from total of 90% used of greater antiretroviral. The result of the data will be interpreted descriptively.

RESULT AND DISCUSSION

Based on the chosen data from medical record of patient that can be checked easy, there are 50 HIV/AIDS-positive patients who join antiretroviral therapy in 2012-2013 periods in RSUD Bandung. This data will be characterized based on Age, Sex, Educational background, Cause's factor, opportunistic infection, and antiretroviral drugs.

Characteristic of HIV/AIDS-positive patient Result 1.Age Grouping

Percentage HIV/AIDS positive patient based on age grouping can be seen in the Figure 1.



Figure 1. Percentage HIV/AIDS positive Patient Based on Age Grouping in RSUD Bandung 2012-2013 Period

Based on Figure 1. those HIV/AIDS patients who 26-30 years old has larger portion (44%) than other. Patients who infected HIV/AIDS largely involves in productive age category by range age from 18 to 55. This data are match which reported by Widyono (2008) that HIV/AIDS case are mostly happens towards people who has range age between 20 to 29 by 49,57%. It is caused by lifestyle relating to risk factor of patient like unsafe intercourse and using injection collectively.

2. Sex Grouping

Precentage of HIV/AIDS-positive patient based on the sex can be looked on Figure 2.



Figure 2. The Percentage of HIV/AIDS-Positive Patient is Based on The Sex in RSUD Bandung at 2012-2013 Period.

In Figure 2. shows that HIV/AIDS infects men greater (64%) than women (36%). It is caused the number of HIV/AIDS-positive patient in the hospital largely is men and relates to infection risk of HIV/AIDS in society which is usually caused by lifestyle, sexual activity, free sex, using of injection drugs, and tattoo-used.

3. Educational background of patient

Percentage of HIV/AIDS-positive patient is based on educational background. It is described in a Figure 3.



Figure 3. Percentage of HIV/AIDS-Positive Patient is Based on Educational Background in RSUD Bandung 2012-2013 period.

Figure 3. describes that 58% of HIV/AIDS-positive patient is high school education background. According to Pradipta (2012) higher education makes person easy to get capability in accepting the information dealing with health and it is hoped can create good habit to prevent HIV/AIDS.

4. Cause's Factor

Percentage of HIV/AIDS-positive patient bases on the cause's factor can be seen in Figure 4.



Figure 4. Percentage of HIV/AIDS-Positive Patient Based on The Cause's Factor in RSUD Bandung 2012-2013 Period.

Based on Figure 4. the larger factor of HIV/AIDS infection and spreading is consuming of narcotics injection (46%). The habit of using injection collectively makes narcotics addict are easy to be infected. It is based on data of HIV/AIDS case statistic in Indonesia reported in 2009. It is explained by PPL & PM health department, 2009 that the using of injection collectively by narcotics addict is largely done by men (92%) (PPL&PM Depkes, 2009).

5. Opportunistic Infection

The case of HIV/AIDS patient's opportunistic infection in 2012-2013 periods can be seen in Table 1. In this study, the opportunistic infection which mostly happens is tuberculosis (10%) and Candidiasis Oral (8%). Tuberculosis regimenused that allowed by health standard are combination of rifampisin, isoniazid, etambutol, and pirazinamid (RHEZ). While, antiretroviral regimen that suggested are combination of efavirenz it is chosen because neviarapine and rifampisisn are indicated to induce cytochrome enzyme P450 which decreases concentrate of nevirapine in blood. (Yunihastuti, 2005).

	0		
No	Nama	Obat	%
	Penyakit		
1.	Tuberculosis	rejimen obat	10
		tuberkulosis I	
2.	Herpes	acyclovir tablet	2
	Zooster	and krim	
3.		ambroxol;	4
	Cough, flu	cetirizine	
4.		cetirizine;	8
	cough phlegm,	ambroxol sirup	
5.	flu	neurodex	2
6.		ranitidine	2
7.	Joint pain	fluconazol;	8
	Dispepsia	nistatin	
8.	Candidiasis	benzadin	4
	oral	penisilin	
		(intramuscular);	
	Sifilis	doxicilin	
9.		fluconazol	4
		ciprofoxacin;	2
		betadine kumur	
	Stomatitis	klindamisin;	
10.	Gingivitis	kotrimoksazol	4
11.			
		kotrimoksazol	
12.	Toxoplasmosis	ranitidine	2
13.	Cerebri	-	2
14.			46
	Diare		
	Gastritis		
	without		
	opportunistic		

Tabel 1. The Characteristics of HIV/AIDS-positive Patient Based on Opportunistic Infections in RSUD Bandung 2012-2013 Period.

The data of HIV/AIDS patient's medical record in RSUD shows that combination of antiretroviral-used with tuberculosis drugs are zidovudin + lamivudin + nevirapine. The possibility of pharmacokinetic interaction could happen between antiretroviral (neviparin) with rifampisin. According to Nafrialdi (2012), using of rifampisin with nevirapine can decrease neviparin-content significantly, even though several patient the neviparin-content is still in therapeutic range.

6. Antiretroviral Drugs

Antiretroviral drugs-used for HIV/AIDS therapy can be looked on Table 2. There are 4 drugs types choices including in first line regimen category (2NRTI+1NNRTI): zidovudin + lamivudin + nevirapin; zidovudin + lamivudin + efavirenz; tenofovir+(lamivudin/emtricitabin)+

nevirapin; tenofovir + (lamivudin /emtricitabin) + efavirenz. Then, the second line regimen category consists of 2NRTI+*booseted-Protease Inhibitor* (PI). Consumption of the drugs should consider and pay attention toward patient's condition (Ministry of Health's, 2011).

No	Antiretroviral	%
1.	zidovudin+lamivudin+nevirapin	42%
2.	zidovudin+lamivudin+efavirenz	12%
3.	zidovudin+lamivudin+tenofovir	6%
4.	stavudin+lamivudin+efavirenz	18%
5.	stavudin+lamivudin+nevirapin	6%
6.	nevirapin+lamivudin+tenofovir	6%
7.	lamivudin+tenofovir+(lopinavir/ritonavir)	4%

lamivudin+efavirenz+tenofovir

nevirapine+efavirenz+tenofovir

Total

4%

2%

100

Table 2. The Characteristics of HIV/AIDS-positive Patient Based on Antiretroviral – Used in RSUD Bandung at 2012-2013 Period.

According to table 2, it describes that the most of using antiretroviral drugs is zidovudin+lamivudin+nevirapine (42%) while the second rank is placed by combination of stavudin + lamivudine + efavirenz (18%). Combination of zidovudin + lamivudin + nevirapine has larger percentage because it will be the first recommendation that used by government for implementing in patient who does not have heart and blood dysfunction (Tjay and Rahardja, 2007). Duplication case of antiretroviral happens around 2 % between evirapin and efavirenz-used which includes in NNRTI type.

Calculation DDD

8.

9.

Antiretroviral drug-use data obtained from the hospital pharmacy room in RSUD Bandung, then calculated the value of DDD and DU90%. During 2012-2013, there are 10 types of antiretroviral drugs used. The number of outpatient visit in 2012 was 84.724 and by 2013 as much as 98.518. Total of DDD/1000 NOV usage of antiretroviral drug-used in RSUD Bandung 2012-2013 periode can be seen in Table 3.

 Tabel 3. Total of DDD Antiretroviral Usage in RSUD Bandung at 2012-2013

 Period

Period	Туре	Total of	DDD/1000
	Antiretroviral	DDD	KPRJ
		Usage	
2012	9	25561.36	301.66
2013	7	34486.14	350.04
	Total	60047.50	651.70

Table 3 shows an increase of antiretroviral usage in 2013 amounted to 48,38 DDD/1000 KPRJ, then followed by an increase number of outpatient visits (NOV) in 2013 amounted to 13794 visits. NOV is not only includes the number of HIV outpatient visit but also all outpatient with other diseases. The increase of antiretroviral usage in 2013 may be affected by an increase of HIV patients themselves. It may be influenced by the increasing affordability of HIV/AIDS Prevention Commission and Health Departement in detecting patients at risk so people can get early treatment.

Profile of Antiretroviral Usage

The profles of each antiretroviral usage in RSUD Bandung can be seen in Table 4. and 5. Based on Table 4 and 5., the largest of antiretroviral usage during two consecutive periods is nevirapine at 60,17 DDD/1000 NOV and 72,02 DDD/1000 NOV. Almost all antiretroviral usage in 2013 have quantity increased (DDD/1000 NOV) than in 2012, excepting for stavudine drug-use that decreased in 4,72 DDD/1000 NOV.

Table 4. Profile of Each Antiretroviral Usage in RSUD Bandung at 2012

	In 2012		
Antiretroviral	DDD/1000	%	
	KPRJ	Usage	
nevirapin	60,17	28,83	
efavirenz	59,48	28,49	
lamivudin	42,01	20,12	
stavudin	29,03	13,91	
tenofovir	17,40	8,34	
zidovudin	0,64	0.31	
Total	208.73	100,00	

Table 5. Profile of Each Antiretroviral Usage in RSUD Bandung at 2013

	13	
Antiretroviral	DDD/1000	%
	KPRJ	Usage
nevirapin	72,02	27,96
efavirenz	63,27	24,57

lamivudin	56,51	21,94
tenofovir	41,46	16,09
stavudin	24.31	9,44
Total	257,57	100,00

Profile of fixed dose combination of antiretroviral usage in RSUD Bandung 2012-2013 period can be seen in Table 6 and 7. Based on Table 6. and 7. Total of fixed dose combination of antiretroviral usage in 2012 and 2013 was 92,93 DDD/1000 NOV dan 92,47 DDD/1000 NOV.

 Table 6. Fixed Dose Combination of Antiretroviral Usage in 2012

Combination	DDD/1000
	KPRJ
zidovudin + lamivudin	88.34
tenofovir + emtricitabine	1.98
tenofovir+emtricitabine+	2.61
efavirenz	

Table 7. Fixed Dose Combination of Antiretroviral Usage in 2013

Kombinasi	DDD/1000		
		KPRJ	
zidovudin	+	87.52	
lamivudin		4.95	
lopinavir + ritonavir			

This combination antiretroviral was formed in *Fixed Dose Combination* (FDC) therefore it had to been calculated separately. In 2012-2013 period, the most of using FDC was zidovudin+lamivudine. Lamivudine can strengthen the power and extend the work of zidovudine with side effect tend to be mild. Using zidovudin+lamivudin (FDC) is usually added by NNRTI class such as nevirapin or efavirenz. These drug initiation is appropriated with patient condition. NNRTI includes in the combination regimen most widely used for initial therapy because of its strong efficacy and effective drug (Ditjen PPM and PL DepKes RI, 2004).

Tenofovir + emtricitabine and tenofovir + emtricitabine + efavirenz fixed dose combination was only used in 2012. The decline drug of both FDC usage is because patients prefer other antiretroviral combinations as appropriate. Whereas in 2013 appeared ritonavir + lopinavir FDC which is Protease Inhibitor (PI) classes. Ritonavir+lopinavir is a second line antiretroviral treatment. The aim of using combination low dose ritonavir (PI/r) is to increase the drug concentration in plasma. The use of this class is indicated for patients whose their CD4 still low due to poor medication adherence. The drug is usually combined with tenofovir which not induce CYP3A4 activity therefore lopinavir concentration will not decrease in the blood.

Drug Utilizing 90% (DU90%)

The profiles of antiretroviral usage based on the antiretroviral type that is included in the DU90% segment in Bandung Hospital period 2012-2013 can be seen in Table 8 and 9.

.Table 8. The profile of Antiretroviral Usage based on the Antiretroviral Type included in DU90% segment in RSUD Bandung at 2012.

Antiretroviral	DDD/1000	%	Segment
	NOV	Usage	
nevirapine	60,17	28,83	
efavirenz	59,48	28,49	DU
lamivudine	42,01	20,12	90%
stavudine	29,03	13,91	
tenofovir	17,40	8,34	
zidovudine	0,64	0.31	
Total	208.73	100,00	

Table 9. The profile of Antiretroviral Usage based on the Antiretroviral Type included in DU90% segment in RSUD Bandung at 2013

Antiretroviral	DDD/1000	%	Segment
	NOV	Usage	
nevirapin	72,02	27,96	
efavirenz	63,27	24.57	
lamivudin	56,51	21,94	DU
tenofovir	41,46	16,09	90%
stavudin	24.31	9,44	
Total	257,57	100,00	

Based on Table 8. and 9., antiretroviral, which annually enter the DU90% segment, is nevirapine, efavirenz, lamivudine. DU90% illustrates the use of the drug most widely used. The profile of antiretroviral usage, which includes in DU90% segment in 2012 and 2013 have changed. In 2012, stavudine includes in to the DU90% segment but the opposite occurred in 2013.

The changes of the profile of antiretroviral usage, is caused by the change of antiretroviral treatment guidelines HIV / AIDS by both the WHO and the National in 2010 and 2011, to reduce the use of stavudine gradually. The government recommends replacing the use of stavudine with the use of tenofovir gradually and the government will not provide stavudin anymore after the drug is stocked-out (Ministry of Health, 2011).

This problem is related to the side effects caused by peripheral neuropathy and lipodystrophy stavudine after 6 months of usage (Ministry of Health, 2011). Even, the side effects are known to be a key determinant of compliance people to HIV / AIDS (PLWHA). Whereas, to lower the amount of virus in accordance with the desired target levels of adherens needs at least 95%, because poor adherens actually increase the risk of mutation and antiretroviral drug resistance. Consequently, the need of these drugs will increased (Ramadian, O. & Eky, R. 2010). Based on the medical records of patients in Bandung Hospital, it is found that 2% of patients have experienced *lip dystrophy*.

CONCLUSION AND RECOMMENDATIONS

Conclusion

Based the results of this study, we can conclude that the profile of antiretroviral usage changes in 2013 where the stavudine does not enter the DU90% segment. The use of antiretroviral has increased from 301.66 DDD / 1000 NOV to 301.66 DDD / 1000 KPRJ. Antiretroviral drugs included in the DU90% segment of the period 2012-2013 are nevirapine, efavirenz, lamivudine. The use of antiretroviral in Bandung Hospital has been appropriated to the treatment guidelines, but there is an interaction between drug of tuberculosis with nevirapine antiretoviral (10%) and 2% of cases of antiretroviral duplication.

Recommendations

Based on the results of this study, firstly we suggested that the hospital staffs have to evaluate the use of drugs regularly to ensure antiretroviral usage appropriately, safely and effectively. Secondly, the hospital staffs need to monitor the possible side effects and the use of antiretroviral progressively and conduct advanced studies on the use of antiretroviral drugs at a referral hospital for patients with HIV / AIDS in Bandung.

REFERENCES

Ditjen PPM & PL Depkes. 2004. *Pedoman Nasional Terapi Antiretroviral*. Direktorat Jenderal Pemberantasan Penyakit Menular dan Penyehatan Lingkungan, Departemen Kesehatan Republik Indonesia. Jakarta.

Ditjen PPM & PL Depkes RI. 2009. *Statistik Kasus HIV di Indonesia, Dilaporkan s/d September 2009*. Departemen Kesehatan Republik Indonesia. Jakarta.

Ditjen PP & PL Kemenkes RI. 2014. Statistik Kasus HIV/AIDS di Indonesia. Tersedia di

http://spiritia.or.id/Stats/StatCurr.pdf [diakses 17 Juni 2014]

Ministry of Health. 2011. Pedoman Nasional Tatalaksana Klinis Infeksi HIV dan Terapi Antiretroviral Pada Orang Dewasa. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan. Jakarta.

Nafrialdiet.al.2012.InfluenceofRifampicinonNevirapinePlasmaConcentration in HIV-TBCoinfectedPatients.ActaMedIndones-IndonesJInternMed:4(2).Availableathttp://www.inaactamedica.org/archives/2012/22745144.pdf[Diakses 25 Juni 2014]

Pradipta, Marliya Niken. (2012). Faktor-Faktor yang Berhubungan dengan Konsistensi Pemakaian Kondom pada Waria Binaan Puskesmas Bogor Timur dalam Upaya Pencegahan HIV/AIDS Tahun 2012. [Skripsi]. Universitas Indonesia. Depok.

Ramadian, O. & Eky, R. 2010. Pengaruh Efek Samping Antiretroviral Lini Pertama Terhadap Adherens pada ODHA di Layanan Terpadu HIV RSCM. [Laporan Penelitian]. Jakarta tersedia di <u>www.aidsindonesia.or.id/repo/ARV-RSCM.pdf</u> [diakses 24 Juni 2014]

Robert, C. 2013. Angka Kematian Terkait HIV Meningkat di 98 Negara. Tersedia di <u>http://www.voaindonesia.com/content/angka-kematian-terkait-hiv-meningkat-di-98-negara/1733733.html</u> [diakses 17 juni 2014]

Sjoquist, F. Birkett D 2003. *Drug Utilization. In : Introduction to Drug Utilization Research.* WHO office of publications. P.76-84

Tjay, T.H. dan Rahardja, R. 2007. *Obat-Obat Penting*. Jakarta : Elex Media Komputindo.

WHO. 2009. The Purpose of the ATC/DDD System. Available at http:// www.whocc.no.atc ddd methodology/purpose of the act ddd system/ [diakses 4 November 2013].

Widoyono. 2008. *Penyakit Tropis : Epidemiologi, Penularan, Pencegahan dan Pemberantasannya*. PT. Gelora Aksara Pratama, Jakarta.

Yunihastuti, E. dkk. 2005. Infeksi Oportunistik Pada AIDS. Balai Penerbit FKUI. Jakarta.

l