Public Health Perspectives Journal 6 (2) 2021 124-133

Public Health Perspectives Journal

http://journal.unnes.ac.id/sju/index.php/phpj

Analysis of Factors Affecting CD4$^+$ Increase in HIV / AIDS Patients Receiving ARV Therapy

Dini Wurnaning Budi ✉, **Sri Ratna Rahayu, Ari Yuniastuti**

Universitas Negeri Semarang, Indonesia

Article Info

Article History:
Accepted
26 Desember 2020
Approved
24 February 2020
Published
20 August 2021

Keywords:
increase in CD4 +,
HIV / AIDS
ARVtherapy

Abstract

Acquired immunodeficiency syndrome (AIDS) is a collection of symptoms and infections that arise due to damage to the human immune system due to infection with the Human Immunodeficiency Virus (HIV). The number of HIV patients at Panti Wilasa Hospital continues to increase from every year in 2018 the number is 150 HIV / AIDS patients. The purpose of this study was to analyze the factors that influence the increase in CD4$^+$ levels of HIV / AIDS patients receiving ARV therapy at Panti Wilasa Citarum and Dr. Cipto Hospitals Semarang. This research is a quantitative study, with a cross-sectional approach. The minimum sample of the study was 38 respondents using simple random sampling technique. Data analysis in this study using Multiple Logistic Regression. The results of the study, the most influential variables were clinical stage (p=0.000), and concomitant disease tuberculosis (p = 0.14) on the increase in CD4$^+$ levels. The risk of HIV / AIDS transmission in Indonesia is the highest and until now, there is no cure for HIV. ARV therapy can inhibit the development of the HIV virus, giving ARVs is given if the CD4$^+$ level is less than 500 cells / mm^3, or there are other conditions in HIV patients. The importance of early awareness in ARV therapy for early initiation of ARVs is proven to be clinically beneficial, useful for prevention, increase life expectancy and reduce the incidence of HIV-related infections.

✉Correspondent Address:
Kampus Unnes Jl Kelud Utara III, Semarang, 50237, Indonesia
E-mail: dini261092@gmail.com

p-ISSN 2528-5998
e-ISSN 2540-7945

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a group of symptoms and infections (or: syndromes) that arise due to damage to the human immune system due to infection with the Human Immunodeficiency Virus (HIV). In 2015, there were 34 million cases of HIV / AIDS in the world. The world AIDS management agency (UNAIDS). gave the predicate that Indonesia is one of the countries in Asia with a fast growing epidemic (UNAIDS, 2013). According to the Directorate General of PP & PL Ministry of Health of the Republic of Indonesia (2015), HIV / AIDS cases in Indonesia in 2015 reached 69,197 people. Semarang City in 2018 achieved the highest case value from the previous years, namely 640 cases from 434 cases in the previous year (Menkes, 2014).

Semarang City is the city with the highest number of HIV / AIDS in Central Java, because it is a metropolitan city that has high mobility both socially and culturally, so this affects the pattern of community life, such as increasing risky behavior. Due to the high morbidity rate due to HIV, the Ministry of Health of the Republic of Indonesia appointed several hospitals as special referral hospitals for HIV and AIDS sufferers according to the Indonesian Ministry of Health No.782. Panti Wilasa Hospital is a type C hospital in the city of Semarang. This hospital is one of the hospitals designated as a referral hospital and received an award from the Ministry of Manpower and Transmigration of the Republic of Indonesia on December 7, 2012 as AIDS Care Hospital.

The number of HIV patients at Panti Wilasa Hospital continues to increase from year to year in 2018, as many as 150 HIV / AIDS patients registered at Panti Wilasa Citarum Hospital and Dr. Cipto, the number of HIV patients in both Panti Wilasa Hospitals tends to fluctuate due to patient mortality. High HIV, this is because patients who come to the hospital are already in a very low $CD4^+$ condition and many opportunistic infections. The Panti Wilasa Citarum Hospital is a referral place for taking ARV drugs, which is appointed directly by the Ministry of Health, and Dr. Cipto Panti Wilasa Hospital is a branch hospital of Panti Wilasa Citarum for HIV/ AIDS patients who want to seek treatment.

Previous research is used as a reference to compare research results based on the observations and findings of the researchers. The location of the difference in this study is adding several variables, namely comorbidities (Tuberculosis and hepatitis C), is there an effect on the increase in $CD4^+$ levels. In addition, the location of this research was carried out at Panti Wilasa Citarum Hospital and Dr. Cipto Semarang where previously, other researchers had never done it, especially in terms of what factors influenced the increase in $CD4^+$ levels.

The high transmission rate of HIV / AIDS in Indonesia and until now there has been no drug that can cure HIV. ARV therapy can inhibit the development of the HIV virus in the body of Host, ARVs are not able to kill the virus, but can slow its growth.

The purpose of this study was to analyze all the factors that could influence the increase in $CD4^+$ levels of HIV / AIDS patients receiving ARV therapy, then to determine the strength of the relationship and determine the factors that were very influential.

For the public, knowing the importance of early awareness in ARV therapy for early initiation of ARVs is proven clinically beneficial, useful for prevention, increasing life expectancy and reducing the incidence of HIV-related infections (Menkes, 2014).

METHOD

The study was conducted using a cross-sectional approach. The population are patients at Panti Wilasa Hospital. In this study were 96 patients. The minimum sample in this study was obtained by counting using the Lameshow formula, namely 38 respondents.

Gender, age, education, occupation, number of opportunistic infections, initial CD4+ level, duration of therapy, type of ARV regimen,

clinical stage, complementary diseases tuberculosis and Hepatitis C were independent, the dependent variable in this study was an increase in CD4+ levels. The instrument in this study used a questionnaire sheet and patient observation sheet.

In this study, multivariate analysis was carried out, namely to see the variables that had the most influence on the independent variables and the dependent variable using the Multiple Logistic Regression Test.

RESULTS AND DISCUSSION

This research was conducted at Panti Wilasa Citarum Hospital and Dr. Panti Wilasan Hospital. Cipto Semarang in October-November 2019 with the aim of knowing the factors that most influence the increase in $CD4^+$ levels

Table 1. Univariate Analysis

Variable	Category	Frequency	Presentation
Gender	Men	22	57.9
	Woman	16	42.1
Age	12-35 years	14	36.8
	36-65 years	24	63.2
Education	SD, SMP, SMA	14	42.2
	College	12	31.6
Profession	Work	21	55.3
	Unemployment	17	44.7
Opportunistic Infections	With IO	23	60.5
	No IO	15	39.5
Initial $CD4^+$ levels	< 350 cell/iu	20	52.6
	>350 cell/iu	18	47.4
Duration of Therapy	<12 Years	22	57.9
	>12 Years	16	42.1
Regimen Type	Line 1	20	52.6
	Line 2	18	47.7
Clinical Stage	Minor	21	55.3
	Major	17	44.7
Treatment Program Adherence	Disobedient Obedient	20	55.3
		18	44.7
Concomitant Diseases (Tuberculosis)	Yes	21	55.3
	No	17	44.7
Comorbidities (Hepatitis C)	Yes	14	36.8
	No	24	63.2
Increase in $CD4^+$ levels	<50 cell/ui	13	34.2
	>50 cell/ui	25	65.8

Based on table 1 shows that the male gender is 22 people (57%). At the time of observation in the field of gender affects the increase in $CD4^+$ levels both in positive and negative factors. A similar study conducted by Yogani et al (2015) shows that women tend to

have a good level of adherence than men. A study in 69 hospitals in Spain with a total number of respondents with 2620 people living with HIV / AIDS, showed that the mean $CD4^+$ value in women was higher than that of men, although on the other hand it also showed that men had a lower viral load value to "undetectable" (Levine et al, 2011).

The age is categorized into 2, namely the age of 12-35 years and 36-65 years as many as 24 respondents (63%) aged 36-65 years. PLWHA when infected with HIV aged more than 30 years had a better response to ARV than PLWHA who was 18-29 years old. Another study suggested Boniphace et al (2011), that older people living with HIV / AIDS tend to be more adherent to treatment, as evidenced by a lower detectable viral load and a faster increase in $CD4^+$ levels.

Education is categorized into 2 SD, SMP, SMA and Higher Education. A total of 14 (42.2%) on average have elementary, junior high school education. Research conducted by Adiningsih et al (2018) that knowledge about HIV and adherence to antiretroviral therapy is technical knowledge obtained through counseling activities by medical personnel, and not always obtained by PLWHA during formal education.

Jobs were categorized as working and not working as many as 21 (55.3%) of the respondents worked. The time a person spends doing activities including work can affect how often a person accesses health services. A similar study conducted by Adiningsih et al (2018) found a significant relationship between work status and a 2.9 higher risk of experiencing immunodeficiency than respondents who did not work. The existence of work pressure and fatigue are indicated as causes of immunodeficiency in working PLWHA. According to the results of research by Pettifor et al (2013), PLWHA with established jobs will have better mental health than PLHIV who do not have a job or PLWHA with temporary and high-risk jobs. Temporary and high-risk jobs can lead to job losses, future economic uncertainty, and stressful job pressures. The existence of work pressure and fatigue are indicated as causes of immunodeficiency in working PLWHA. The results of the research by Aprita et al (2010) showed that HIV / AIDS patients who visited the VCT Clinic at Arifin Achmad Hospital, Riau Province, based on the type of work, were mostly self-employed as many as 46 people (52.27%). The results of this study support the results of Purnama's (2010) research at the Tanjung Marowa Health Center, Medan which states that the largest type of work is self-employed as much as 46.0%.

Opportunistic infections are divided into 2, namely there are OIs and no OIs. A total of 23 (60.5%) had opportunistic infections on average. Opportunistic infections occur because of severely decreased immunity. The number of $CD4^+$ cells in the blood is a reliable indicator to monitor the severity of immune damage caused by HIV. Similar research conducted by Fajar (2013) that OIs can occur in people with HIV / AIDS, namely pulmonary tuberculosis, chronic diarrhea, etc., of all opportunistic infections found in HIV / AIDS sufferers, there is an increase in the incidence of OIs which is proportional to the decrease in CD4 + levels in patients. People with HIV and AIDS are at 26-31 times greater risk of developing opportunistic infections such as tuberculosis, compared to non-HIV infected individuals (Valdivia et al, 2017).

Initial CD^+ levels were categorized into 2 categories <350 cells / ui, totaling 10 respondents experienced an increase in $CD4^+$ levels <50 cells / ui and categories> 350 cells / ui 3 respondents experienced an increase in $CD4^+$ levels <50 cells / ui The results showed that PLWHA with population values $CD4^+$ levels <50 cells / mm3 had a fourfold risk of not increasing to> 200 cells / mm^3 during the 12 months of therapy. Longer therapy, which is up to 5 years, can increase the population value of $CD4^+$ levels to above 500 cells / mm. In the study, as many as 3 (4.47%) subjects who started therapy with CD^+ count values <50 cells / mm3 and all of them increased, but did not reach 350 cells / mm^3 with a duration of therapy between 10- 33 months (Hutapea et al, 2017).

Duration of therapy was categorized into 2 <12 years and> 12 years. A total of 22 (57.9%) length of therapy was received by respondents was <12 years. Research conducted by Adiningsih et al (2018) stated that the duration of therapy had an effect on increasing CD^+ levels, respondents who received ARV therapy for 13-24 months experienced the highest increase in $CD4^+$ levels compared to those who received ARV therapy for ≤12 months.

Types of drug regimens were divided into 2, namely line 1 and line 2, as many as 22 (57.9%) on line 1 therapy. First-line ARV therapy aims to inhibit viral DNA transcription. A similar study conducted by Yogani et al (2015) stated that ARV therapy guidelines were divided into first and second lines depending on the success of therapy. Most of the respondents who underwent first-line ARV therapy experienced an increase in their $CD4^+$ count.

The clinical stage is divided into 2, namely mild and severe. A total of 22 (55.3%) respondents experienced a mild clinical stage. ARV therapy was started when the $CD4^+$ count was ≤350 cells / mm^3 or at clinical stage III / IV. In clinical stage III, it is usually accompanied by quite severe opportunistic infections, such as oral candidiasis and tuberculosis. In a previous study, clinical stage at first arrival was not associated with an increase in $CD4^+$ levels ($p = 0.188$). Initially, it was thought that the advanced clinical stage (Stage III and IV) would experience a slower increase in $CD4^+$ levels than the initial stage. This is based on the presence of a heavier number of opportunistic infections found at an advanced stage and usually an advanced stage tends to have a lower $CD4^+$ count compared to the early stage (Yogani et al, 2015).

Treatment program adherence in the non-adherent category 10 respondents experienced an increase in CD^+ levels <50 cells / ui. A similar study by Pearson's correlation test showed that there was a statistically significant relationship with a strong correlation strength ($r = 0.601$) between adherence level and CD4 cell count in HIV / AIDS patients at the VCT clinic of Sanglah Hospital in the period September - November 2014 ($p <0.05$) (Manuaba et al, 2017). Chalker et al (2010) conducted a similar study. In 78 facilities, we interviewed 1,631 patients and reviewed 8,282 records. Difficulty taking notes prevented data collection at two facilities. Overall, 94.2% of patients reported perfect adherence; dispensed drugs covered 91.1% of the days in the retrospective period of six months; 13.7% of patients had a distance of more than 30 days in their divided treatment, 75.8% patient comes to the clinic on or before the next appointment date and 87.1% of patients came within 3 hours.

Concomitant diseases (tuberculosis) in the respondents on average they have comorbidities (tuberculosis) as much as 21 (55%). People with HIV and AIDS are at 26-31 times greater risk for developing opportunistic infections such as tuberculosis, compared with non-HIV infected individuals (Valdivia et al, 2017).

Concomitant disease (Hepatitis C) in respondents on average they do not have comorbidities (Hepatitis C) as much as 24 (63.2%). Hepatitis C virus is the second cause of viral infection epidemics after human immunodeficiency virus (HIV) in the last two decades. Hepatitis C is most easily transmitted via parenteral routes such as injection narcotics and blood transfusions, but it is difficult to transmit via the sexual route (Adiningsih et al, 2018).

Adherence to taking medication is divided into 2 categories, namely adherence and non-compliance. As many as 20 (55.3%) respondents did not comply in taking the drugs that had been given. Patient adherence to medication was associated with an increase in $CD4^+$ counts ($p <0.001$) and the non-adherent group had a relative risk (RR) of 3.268 times for not experiencing an increase in $CD4^+$ levels (95% CI 2.450-4.359). The level of medication adherence is important in the management of HIV patients. This is because the level of adherence to taking medication that is less will be associated with the progression of HIV disease, which is marked by an increase in viral load and a decrease in $CD4^+$ cells. Non-compliance with taking medication is

also associated with viral mutations that will lead to drug resistance (Yogani et al, 2015)

Table 2. Univariate Analysis

Variable	P Value Increase in CD4 + Levels
Gender	0.016
Age	0.023
Education	0.033
Profession	0.009
Opportunistic Infections	0.028
Initial CD^4 + levels	0.031
Duration of Therapy	0.016
Regimen Type	0.031
Clinical Stage	0.009
Treatment Program Adherence	0.031
Concomitant Diseases (Tuberculosis)	0.009
Comorbidities (Hepatitis C)	0.023

In the bivariate analysis, the relationship between the independent variables was Gender, Age, Education, Occupation, Number of Opportunistic Infections, Initial CD^+ levels, Duration of Therapy, Type of ARV Regimen, Clinical Stage, Complementary Tuberculosis and Hepatitis C to the dependent variable, namely the increase in $CD4^+$ levels at HIV / AIDS patients receiving ARV therapy. Using the Chi Square test.

Based on Table 2, the gender p-value is 0.016, which means that there is a significant relationship to the increase in CD^+ levels. Several studies have assessed the factors that have an effect on increasing $CD4^+$ levels, both positive and negative factors. Factors that have a positive effect on the increase in CD^+ levels in HIV patients based on previous studies are gender, most of the HIV transmission that occurs in female subjects is through sexual intercourse and usually only gets treatment at an advanced stage. (Yogani et al, 2015).

Age has a p-value of 0.023, which means that there is a significant relationship with an increase in CD^+ levels. This condition is described in Yuliandra (2017) study, that older people living with HIV / AIDS tend to be more adherent to treatment, as evidenced by a low viral load that is not detectable, as well as a faster increase in CD^+ levels.

Education has a p-value of 0.033, which means that there is a significant relationship to the increase in CD^+ levels. Research conducted by Adiningsih et al (2018) states that there is no significant relationship between the education level of respondents and the number of $CD4^+$ levels during antiretroviral therapy. According to the results of research by Zipursky et al (2013), PLWHA with established jobs will have better mental health than PLHIV who do not have a job or PLWHA with temporary and high-risk jobs. Temporary and high-risk jobs can lead to job losses, future economic uncertainty, and stressful job pressures. The existence of work pressure and fatigue are indicated as causes of immunodeficiency in working PLWHA.

Employment has a p-value of 0.009, which means that there is a significant relationship with the increase in $CD4^+$ levels. According to the results of the research by Bhatti et al (2015), PLWHA with established jobs will have better mental health than PLHIV who do not have a job or PLWHA with no job. Fixed and high risk. Temporary and high-risk jobs can lead to job losses, future economic uncertainty, and stressful job pressures. The existence of work pressure and fatigue are indicated as causes of immunodeficiency in working PLWHA.

Opportunitic infections have a p-value of 0.028, which means that there is a significant

relationship to the increase in $CD4^+$ levels. Opportunistic infections occur because of a severely decreased immune system. The number of $CD4^+$ cells in the blood is a reliable indicator to monitor the severity of the immune damage caused by HIV, and makes it easier for us to make decisions about giving antiretroviral treatment. Opportunistic infection patterns differ in various countries depending on the pattern of microorganisms present in the patient's body or environment (Thigpen et al, 2012).

Initial $CD4^+$ levels have a p-value of 0.031, which means that there is a significant relationship to the increase in $CD4^+$ levels. The results showed that people living with HIV with a population value of CD^+ levels <50 cells / mm^3 had a 4 times risk of not increasing to> 200 cells / mm^3. During the 12 month therapy period. Longer therapy, which is up to 5 years, can increase the population value of CD^+ levels to above 500 cells / mm. In the study, as many as 3 (4.47%) subjects who started therapy with CD^+ count values <50 cells / mm^3 and all of them increased, but did not reach 350 cells / mm^3 with a duration of therapy between 10-33 months (Hutapea et al, 2017).

The duration of therapy has a p-value of 0.016, which means that there is a significant relationship to the increase in CD^+ levels. This is in line with research in Yogyakarta by Yasin et al (2011), which showed an increase in $CD4^+$ levels was in line with the duration of ARV therapy from 6 months, 12 months, 24 months.

The type of drug regimen has a p-value of 0.031, which means that there is a significant relationship to the increase in $CD4^+$ levels. Adiningsih et al. Showed that most respondents who underwent first-line ARV therapy experienced an increase in $CD4^+$ levels, but 18 (22.2%) among them had decreased $CD4^+$ counts. First-line ARV therapy is still effective but needs evaluation for respondents who have decreased $CD4^+$ levels. First-line ARV therapy aims to inhibit viral DNA transcription. Respondents who experience decreased CD4 + levels may fail first-line ARV therapy, and are advised to switch to second-line ARVs (Adiningsih et al, 2018).

Clinical stage has a p-value of 0.009, which means that there is a significant relationship with an increase in $CD4^+$ levels. In a previous study conducted by Yogani et al (2015), the clinical stage when it first arrived was not associated with an increase in $CD4^+$ levels (p = 0.188). Initially, it was thought that the advanced clinical stage (Stage III and IV) would experience a slower increase in $CD4^+$ levels than the initial stage.

Concomitant disease (TB) has a p-value of 0.009, which means that there is a significant relationship to an increase in $CD4^+$ levels. In a previous study conducted by Yogani et al (2015), TB and HIV caused the relationship between tuberculosis infection and increased $CD4^+$ levels. Similar to using cellular immunity response in clinical response. In patients with HIV, low $CD4^+$ counts increase the risk of acute infection and reactivation from TB. In addition to decreasing numbers, HIV infection also makes the function of $CD4^+$ and CD8 cells abnormal. TB-HIV co-infection also accelerates the progression of HIV from initially asymptomatic to AIDS stage until death.

Concomitant disease (Hepatitis C) has a p-value of 0.023, which means that there is a significant relationship to the increase in $CD4^+$ levels. Have conducted analysis with different $CD4^+$ count limits but still not found a significant relationship. This is not in accordance with the study of Fevrier et al (2017), who reported that the $CD4^+$ count in 4 hemophilia couples transmitting HIV and HCV was 125 cells / mul.

Adherence in taking medication has a p-value of 0.031, which means that there is a significant relationship with the increase in $CD4^+$ levels. Patients with poor adherence to medication had a 5 times higher risk of experiencing worse disease progression than those with moderate medication adherence (p = 0.007) or patients with good medication adherence (p = 0.001). The level of good medication adherence was also associated with the duration of virological failure (p <0.001) and

a faster $CD4^+$ increase (p = 0.004) and a reduced risk of death (p <0.007) (Yogani et al, 2015).

Tabel 3. Multiple Linear Regression Analysis

Variable	*P Value* Increase in $CD4^+$ Levels
Gender	0.075
Age	0.992
Education	0.928
Profession	0.763
Opportunistic Infections	0.928
Initial CD^4 + levels	0.159
Duration of Therapy	0.572
Regimen Type	0.693
Clinical Stage	0.015
Treatment Program Adherence	0.668
Concomitant Diseases (Tuberculosis)	0.040
Comorbidities (Hepatitis C)	0.646

In multivariate analysis, the effect of the independent variables was gender, age, education, occupation, number of opportunistic infections, initial $CD4^+$ levels, duration of therapy, type of ARV regimen, clinical stage, comorbidities of tuberculosis and hepatitis C on the dependent variable, namely the increase in $CD4^+$ levels at HIV / AIDS patients receiving ARV therapy. Using the Multiple Linear Regression test, which aims to get the most influential variable among other variables.

After analyzing all the dependent variables included in the modeling, then removing the independent variable which has the largest p value, so that the initial model is obtained with the determining factor variable which has a p value <0.05.

Tabel 4. The most influential factor

Variable	P *Value* Increase in CD4 + Levels
Clinical Stage	0.000
Concomitant Diseases (Tuberculosis)	0.014

The multivariate test result which has a p value <0.05 is the final model of the determinants of the factors that most influence the increase in $CD4^+$ levels in HIV / AIDS patients.

Based on Table 4, the clinical stage p-value is 0.000, which means that the variable with the most significant influence on the increase in $CD4^+$ levels. Another study conducted by Yogani *et al* (2015) stated that the clinical stage at the time the subject first arrived also had no effect on the increase in $CD4^+$ cells (p = 0.188). Initially, it was thought hat the advanced clinical stage (Stage III and IV) would experience a slower $CD4^+$ rise than the early stage. This is based on the presence of a heavier number of opportunistic infections found at an advanced stage and usually an advanced stage tends to have a lower $CD4^+$ cell count compared to the early stage.

Complementary diseases (tuberculosis) p-value 0.014, which means the variable with the most significant influence on the increase in $CD4^+$ levels. Another study conducted by Yogani *et al* (2015) TB infection had an effect on the increase in $CD4^+$ cell count (p = 0.010). The association between tuberculosis infection and $CD4^+$ increase was due to both TB and HIV using the cellular immune response in their clinical response. In patients with HIV, a low $CD4^+$ count increases the risk of developing acute infection and reactivation from TB. In addition to decreasing numbers, HIV infection also makes the function of $CD4^+$ and CD8 cells abnormal. TB-HIV co-infection also accelerates the

progression of HIV from initially asymptomatic to AIDS stage until death.

CONCLUSION

Based on the results of the study, it can be concluded that gender, age, occupation, education, opportunistic infections, initial $CD4^+$ levels, length of therapy, type of regimen, clinical stage, adherence to treatment programs, comorbidities of tuberculosis and hepatitis c have a relationship with an increase in $CD4^+$ counts in patients. HIV / AID doing ARV therapy. There were variables that had the most influence among the other variables on the increase in $CD4^+$ levels, namely clinical stage ($p = 0.000$) and comorbidities ($p = 0.014$).

REFERENCES

Adiningsih, S., Widiyanti, M., Natalia, E. I., & Wahyuni, T. (2018). $CD4^+$ dan Faktor yang Mempengaruhi Kepatuhan Terapi Antiretroviral dengan HIV/AIDS di Jayapura. *Buletin Penelitian Kesehatan,* 46(2), 87-96

Aptriani, R., Fridayanti., & Barus, A. (2014). Gambaran Jumlah Cd4 Pada Pasien Hiv/Aids Di Klinik Vct Rsud Arifin Achmad Provinsi Riau Periode Januari-Desember 2013. *Jom FK*, 1, 1-12

Bhatti, A. B., Usman, M., & Venkataramana, K. (2015). Current Scenario of HIV/AID, Treatment Option, and Major Challenges with Compliance to Antiretroviral Therapy. *Cureus*, 8(3), 515.

Boniphace, I., Minzi, O., Rumisha S. F., & Mugus F., & Tanner M. (2011). HIV/AIDS Clinical Manifestations and the Implication for Patient Clinical Staging in Resource Limited Settings in Tanzania. *The Open AIDS Journal*, 5(4), 9-16.

Chalker, J. C., Anddualem, T., Gitau, L. N., Ntaganira, J., Obua, C., Tadeg, H., Waako, P., Degnan, D. F. (2010). Measuring adherence to antiretroviral treatment in resource-poor settings: The feasibility of collecting routine data for key indicators. *BMC Health Services Research*, 10(1), 34-37.

Fajar, E. P. P. (2013). Hubungan Antara Stadium Klinis, Viral Load Dan Jumlah CD4 Pada Pasien Human Immunodeficiency Virus (HIV) / Acquired Immuno Deficiency Syndrome (AIDS) Di RSUP Dr. Kariadi Semarang. *Jurnal Media Medika Muda,* 3(5), 1-12

Fevrier, M., Dorgham, K., & Rebollo, A. (2017). $CD4^+$ T Cell Depletion in Human Immunodeficiency Virus (HIV) Infection: Role of Apoptosis. *Jurnal Viruses*, 3(2), 586-612

Hutapea, H. M. L., Mirino, Y., Widiyanti, M., Fitriana, E., Maladan, Y., & Oktavian, A. (2017). Penurunan CD4 Pada ODHA Setelah Terapi ARV Lebih Dari 39 Bulan. *The Indonesia Journal of Public Health*, 13(3).

Keputusan Menteri Kesehatan Republik Indonesia, (2011). *Tentang Rumah Sakit Rujukan Bagi Orang Dengan HIV dan AIDS No. 782 Tahun 2011*. Jakarta: Menteri Kesehatan.

Kurniawan, F., Djauzi, S., Yunihastuti, E., & Nugroho, P. (2017). Faktor Prediktor Kegagalan Virologis Pada Pasien HIV Yang Mendapatkan Terpai ARV Lini Pertama Dengan Kepatuhan Berobat Baik. *Jurnal Penyakt Dalam Indonesia*, 4(1), 29–34

Levine, D., Madsen, A., Wright, E., Barar R. E, Santelli J, & Bull S. (2011). Formative research on MySpace: online methods to engage hard-to-reach populations. *Journal of health communication*, 16(4), 448–54.

Manuaba, I. A. K. W., & Yasa, I. W. P. S. (2017). Tingkat Kepatuhan Mengkonsumsi Obat Antiretroviral Dengan Jumlah CD4 Pada Pssien HIV/AIDS Di Klinik VCT RSUP Sanglah Dalam Periode September-November 2014. *E-Jurnal Medika*, 6(1), 2303-1395

Menteri Kesehatan, (2014). *Peraturan Menteri Kesehatan Republik Indonesia nomor 87 Tahun 2014 tentang Pedoman Pengobatan Antiretroviral*. Jakarta: Menteri Kesehatan

Purnama, S. (2010). Karakteristik penderita HIV/AIDS di Puskesmas Tanjung Morawa Agustus 2006 – Mei 2010. Medan. *Tesis* Fakultas Kesehatan Masyarakat Universitas Sumatra Utara.

Pettifor, A., Linda, G. B., Sybil, H., Molly, R., & Seana, B. (2013). Preventing HIV among Young People: research priorities for the future. *J Acquir Immune Def Syndr*, 2, 155-S160.

Thigpen, M. C., Kebabetswe, P. M., & Paxton, L .A. (2012). Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med,* 367(5), 423–34.

Valdivia, A., Ly, J., Gonzalez, L., Hussain, P., Saing, T., Islamoglu, H., Pearce, D., Ochoa, C., & Venketaraman, V. (2017). Restoring Cytokine Balance in HIV-Positive Individuals with Low CD4 T Cell Counts. *Aids Research and Human Retroviruses*, 33(9), 905-918

World Health Organization, (2016). Consolidated guideline on the use of antiretroviral drugs for treating and preventing HIV infection 2nd ed. Geneva: World Health Organization, 91-154.

Yasin, N. M., Maranty, H., & Ningsih, W. R. (2011). Analisis respon terapi antiretroviral pada pasien HIV/AIDS. *Majalah Farmasi Indonesia*, 22(3), 212-222

Yogani, I., Karyadi, T. H., & Koesnoe, S. (2015). Faktor-faktor yang Berhubungan dengan Kenaikan CD4 pada Pasien HIV yang Mendapat *Highly Active Antiretroviral Therapy* dalam 6 bulan Pertama. *Jurnal Penyakit Dalam Indonesia.* 2(4), 217-222

Yuliandra, Y., Nosa, U. S., Raveinal., & Almasdy, D. (2017). Terapi Antiretroviral pada Pasien HIV/AIDS di RSUP. Dr. M. Djamil Padang: Kajian Sosiodemografi dan Evaluasi Obat. *Jurnal Sains Farmasi & Klinis*, 4(1), 1-8.

Zipursky, A. R., Gogolishvili, D., Rueda, S., Brunetta, J., Carvalhal, A., McCombe, J. A., & Rourke, S. B. (2013). Evoluation of brief screening tools for neurocognitive imparment in HIV/AIDS. *AIDS*, 27(15), 2385-2401