

Research Article

The Effect of Antiretroviral Therapy (ART) Duration on CD4 Counts in Human Immunodeficiency Virus (HIV) Patients in dr. Doris Sylvanus Regional Hospital

Pengaruh Lama Terapi Antiretroviral (ARV) terhadap Jumlah CD4 pada Penderita Human Immunodeficiency Virus (HIV) di Rumah Sakit Umum Daerah dr. Doris Sylvanus

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ABSTRACT

Human Immunodeficiency Virus (HIV) attacks white blood cells, thereby reducing the immunity of infected patients. It attacks Cluster of Differentiation 4 (CD4) lymphocyte cells which have a role in the immune system. It has killed 36.3 million people worldwide. There were reported 222 cases in Central Kalimantan Province in 2019. The therapy given to suppress HIV is antiretroviral (ARV) which gradually recover CD4 cells of the patients. This study aims to determine the effect of duration of the antiretroviral therapy (ART) duration on CD4 counts in patients with HIV at the VCT (Voluntary, Counselling, and Test) Polyclinic, dr. Doris Sylvanus Hospital during 2019-2020. It is a descriptive retrospective study, extracting data from patients medical record data. Following total sampling and selected based on inclusion and exclusion criteria i.e. aged ≥ 18 years and diagnosed with HIV during 2019-2020, with complete CD4 count records prior and after ART, there were 45 patients included. The results showed that CD4 counts increased in patients with fixed dose combination (FDC) Tenofovir, lamivudine and efavirenz, with average value of 190.36 ± 220.92 cells/mm³ prior ART, became 259.93 ± 203.74 cells/mm³ at 12 month ART, and 310.82 ± 22.53 cells/mm³ at 24 month ART ($p = 0.000$). Thus, the longer ART duration the higher CD4 counts and recover the normal range.

Keywords: Cluster of differentiation 4, HIV, therapy duration

ABSTRAK

Human Immunodeficiency Virus (HIV) adalah virus yang menyerang sel darah putih sehingga dapat menurunkan kekebalan tubuh pasien yang terinfeksi. Virus HIV menyerang Cluster Differentiation 4 (CD4) sel limfosit yang berperan dalam sistem kekebalan tubuh. HIV telah membunuh 36,3 juta orang di dunia. Kasus HIV di Provinsi Kalimantan Tengah yang dilaporkan pada tahun 2019 sebanyak 222 pasien. Terapi yang diberikan untuk menekan virus HIV adalah antiretroviral (ARV) yang akan memulihkan sel CD4 secara bertahap. Tujuan dari penelitian ini adalah untuk mengetahui pengaruh lama terapi antiretroviral (ART) terhadap jumlah CD4 pada pasien HIV di Poli VCT RSUD dr. Doris Sylvanus pada tahun 2019-2020. Penelitian ini adalah studi deskriptif retrospektif, mengambil data dari medik pasien. Dengan teknik total sampling dan setelah seleksi berdasarkan kriteria inklusi dan eksklusi, yaitu usia ≥ 18 tahun dan didiagnosis pada 2019-2020 terinfeksi HIV, data lengkap jumlah CD4 sebelum dan sesudah ART, jumlah sampel total 45 pasien. Hasil penelitian menunjukkan bahwa rerata CD4 meningkat pada pasien HIV yang menerima ART Fixed Dose Combination (FDC) Tenofovir, Lamivudin, Efavirenz, dengan nilai CD4 pada awal diagnosis sebelum ART sebesar $190,36 \pm 220,921$ sel/mm³; menjadi $259,93 \pm 203,738$ sel/mm³; pada bulan ke 12 terapi, dan $310,82 \pm 221,526$ sel/mm³, pada bulan ke 24 terapi ($p = 0,000$). Kesimpulannya makin lama durasi ART makin tinggi nilai CD4 dan mencapai rentang nilai normal.

Kata Kunci: Cluster of differentiation 4, HIV, lama terapi

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INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that attacks white blood cells, thereby reducing the immunity of infected patients. According to the World Health Organization, HIV has killed 36.3 million people and is expected to kill another 1.5 million by 2020. By the end of 2020, an estimated 37.7 million people will be infected with HIV, with more than two-thirds living in Africa (1). The Directorate General of HIV/AIDS P2P Ministry of Health Information Systems and Sexually Transmitted Diseases have reported a continuous increase in HIV cases in Indonesia yearly. The Directorate General of HIV/AIDS P2P is the Directorate General of Disease Prevention and Control, which has the task of organizing the formulation and implementation of policies in the field of disease prevention and control in Indonesia, one of which is HIV/AIDS. Based on the research in 2019, the number of HIV diagnoses in the country reached a high record for the first time in 11 years, with 50,282 cases. Meanwhile, for the Central Kalimantan province, a total number of 222 patients was reported (2). HIV attacks the immune system and impairs the patient's ability to fight other infections. As HIV infection progresses, the CD4 cell count decreases and is often used to evaluate immunological function. CD4 is a molecule found on the T-helper lymphocyte cell surface, aiding the immune system.

ARV drugs are given to people with HIV infection with the aim of slowing down replication to reduce the amount of virus (viral load), increase immunity, and prevent the process of changing the HIV virus' genetic code from RNA to DNA. Three criteria can be used to determine the success of therapy: clinical, virological, and immunological progress (3,4). For instance, clinical progress in HIV patients includes weight gain; virological efficacy is defined as a reduction of viral load following ART; while immunological success is when their CD4 lymphocytes increase after ART. A previous investigation by Setyo Adiningsih showed an increase in CD4 count for patients with good adherence who had been on ARV therapy for 13-24 years (5). In contrast, Yoshikazu Mutoho revealed a lack of recovery from CD4 counts and CD4/CD8 ratios to levels in people who looked healthy after long-term ARV success in patients with suppressed viral loads (6). Probably, there is a minimal duration of time for ART before the increase in CD4 effect can be seen (5). Thus, this study aims to determine whether the duration of time, 1-2 years of ART, affects CD4 counts of HIV patients of underwent home treatment, specifically at VCT Polyclinic, dr. Doris Sylvanus Hospital, Palangka Raya, Kalimantan.

METHODS

Samples

Designed as a quantitative, descriptive, and retrospective study, this study was conducted in VCT Polyclinic, dr. Doris Sylvanus Hospital, Palangka Raya, Kalimantan. Data were collected from medical records of patients, and sampled employees. Total sampling technique, and selected using inclusion and exclusion criteria i.e. aged ≥ 18 years and diagnosed with HIV at dr. Doris Sylvanus Hospital in 2019-2020, receiving home treatment antiretroviral therapy FDC (Tenofovir, Lamivudine, and Efavirenz) collected from dr. Doris Sylvanus Hospital and had CD4 tested before and during undergoing ART at the 12th and 24th months.

Data Analysis

Data were statistically analyzed using univariate and bivariate Friedman tests where appropriate, and considered significant when $p < 0.05$.

RESULTS

HIV Patient Demographic Data

The total medical records used were from 45 patients. Most HIV patients who received ART were < 60 yo (93.3%), males (66.7%) and latest formal education high school 33.3% and undergraduate (33.3%), and employed (82.2%) (Table 1). Furthermore, 40% of patients were at stage 3 (Table 1). In more detail, there were seven patients from undergraduate groups in stage 1, one in stage 2, 5 in stage 3, and one in stage 4. In the senior high school group, two were in stage 1, nine were in stage 3, and four were in stage 4.

Table 1. Demographic data of HIV patients receiving antiretroviral therapy at dr. Doris Sylvanus Hospital in 2019-2020

Characteristic	Frequency	Percentage
Gender		
- Male	30	66.7%
- Female	15	33.3%
Age		
< 60 years old	42	93.3%
≥ 60 years old	3	6.7%
Profession		
- Unemployed	4	8.9%
- Employed	37	82.2%
- Housewife	4	8.9%
Formal Education		
- Elementary School	5	11.1%
- Junior High School	8	17.8%
- Senior High School	15	33.3%
- Undergraduate	15	33.3%
- No formal education	2	4.5%
Stadium WHO		
- Stage 1	13	28.9%
- Stage 2	4	8.9%
- Stage 3	18	40%
- Stage 4	10	22.2%

The most common opportunistic infection (OI) was Pneumocystis Pneumonia in 17 (37.38%) patients (Table 2). Other OIs were tuberculosis, oral candidiasis, and hepatitis, whether as sole OI and/or as combinations (Table 2).

Table 2. Opportunistic Infection in Patients with ART at dr. Doris Sylvanus Hospital in 2019-2020

Characteristic	Frequency	Percentage
Opportunistic Infections		
Tuberculosis (TB)		
Yes	14	31.1%
No	31	68.9%
Pneumocystis Pneumonia (PCP)		
Yes	17	37.8%
No	28	62.2%
Oral Candidiasis		
Yes	9	20%
No	36	80%

Table 2. Opportunistic Infection in Patients with ART at dr. Doris Sylvanus Hospital in 2019-2020

Characteristic	Frequency	Percentage
Hepatitis B		
Yes	2	4.4%
No	43	95.6%
Combination of Oral Candidiasis + PCP		
Yes	2	4.4%
No	43	95.6%
PCP + pulmonary TB combination		
Yes	4	8.8%
No	41	91.2%
Combination of Oral Candidiasis + PCP + Pulmonary TB		
Yes	5	11.1%
No	40	88.9%

Effect of Antiretroviral Therapy Duration on CD4 Count in HIV Patients

CD4 count at the first diagnosis, prior to ART, was 190.36 ± 220.92 cells/mm³ prior ART, with a range value of 3-964 cells/mm³. Following ART, in months 12 and 24, CD4 counts increased, and became 259.93 ± 203.74 cells/mm³ and 310.82 ± 22.53 cells/mm³ ($p=0.000$), respectively (Table 3). At 24 months of ART, 37.7% of patients have CD4 counts less than 250 cells/mm³.

Table 3. CD4 counts before and during ART

Duration	N	Means \pm SD (cells/mm ³)	Minimum (cells/mm ³)	Maximum (cells/mm ³)
0th month	45	190.36 ± 220.921	3	964
12th month	45	$259.93 \pm 203.738^*$	17	756
24th month	45	$310.82 \pm 221.526^*$	9	744

Note: *: $p=0.000$ (Friedman test)

DISCUSSION

Age

Based on the age group of HIV patients receiving antiretroviral therapy in 2019-2021 as shown in Table 1, 42 (93.3%) people are <60 years old, and 3 (6.7%) are ≥ 60 years. From the medical record data we collected, it was found that the youngest patient diagnosed with HIV was 18 years old and the oldest was 76 years old. This is due to the behavior of people in the age group (7). Others also reported that the youngest and oldest samples of HIV patients were aged 18 and 76, respectively. Meanwhile, the CD4 months of 0, 12, and 24 obtained for both young and old groups were 404; 411, and 469 as well as 103; 126, and 240, while the standard deviation was 220.921; 20,738; and 221.526, respectively. Although the recovery rate was quite good, at old age, it is still below 250 cells/mm³, which is probably due to comorbidities associated with chronic activation of the immune system (8).

Gender

Our sampled study showed that most patients were male (Table 1), which is in line with a Brazil study showing a

trend of incidence increase in males and a decrease in HIV in females (9). Many factors influence why HIV cases are found mostly in men, this is due to educational, economic, and sociocultural factors, and changing sexual habits (10).

Education

Our data showed that mostly highest educational backgrounds of the patients were senior high school and undergraduate (Table 1). Such findings were also reported in Dr. H. Abdul Moeloek Hospital Bandar Lampung (11). Our data also showed that the undergraduate group is mostly at stage 1, whereas the senior high school group is mostly in stage. Probably the patient's education level affects the awareness of patients to check their health early, thus the diagnosis of HIV infection can be established during an earlier stage (12).

Employment

Most of the patient studied in this report was employed (82.2%), although another study from HKBP Balige AIDS Committee, North Sumatra, showed that there was no effect of employment on the incidence of HIV infection with $p = 0.283$ albeit the group of patients who work is 72.4%, and those who do not work were 27.6% (13). Employment, especially the type of profession may be one of the risk factors, as drivers, traders, police and security officers, and hospitality staff service industry place people at greater risk of being infected with HIV (14).

WHO Stage

Based on the WHO stage, stage 3 was the most common stage found in our sampled patients, similar results were reported in DR. H. Abdul Moeloek Hospital Bandar Lampung (11). This is because HIV patients usually come when they already have symptoms of a weakened immune system such as oral candidiasis, pneumonia, and other long-time infectious diseases.

Opportunistic Infection

Opportunistic Infection (OI) is an infection that occurs in people with a low immune system, therefore, there is an opportunity for microorganisms to infect. OI found in his study was also reported by others from different hospitals, including Abdul Moeloek Hospital in Bandar Lampung (15), Dr. M. Djamil Hospital Padang in 2017 (16), Addis Ababa, Ethiopia (17). Untreated HIV infection will progressively reduce the CD4 count, which increases the risk of other microorganism infections. Other factors that also caused high risk include the level of population density, where HIV patients will more often come into contact with other people with symptomatic and/or carrier/latent cases (18).

The risk of various infectious and non-infectious pulmonary complications varies based on the level of immunosuppression that can be assessed by the number of CD4+ T cells. Lung infections occurred when the CD4+ count fell below 200 cells/ μ l, including Pneumocystis pneumonia and lung infections due to Cryptococcus, cytomegalovirus (CMV), and non-tuberculous mycobacteria (NTM). Meanwhile, bacterial pneumonia and tuberculosis can occur at any CD4+ count, but disease severity tends to increase as the CD4+ count declines. Non-infectious pulmonary complications such as chronic obstructive pulmonary disease (COPD), asthma, and pulmonary arterial hypertension can occur at any CD4 count (19). PCP (Pneumocystis Pneumonia) is a life-threatening disease that occurs mainly in individuals with

systemic immune disorders. The significant increase in PCP cases is in line with the decrease in CD4 counts in HIV patients (20). The attachment of Pneumocystis to the alveoli is not the main cause of alveolar damage, but also the host's inflammatory response. This can cause significant lung injury and impaired gas exchange, leading to the potential for hypoxia and respiratory failure (21).

The Effect of Antiretroviral Therapy Duration (ARV) on CD4 Counts

Our results showed that during 2 years ART CD4 counts increased with time ($p=0.000$), which is similar to other studies (5,22). Our study found that the maximum value at months 0, 12, and 24 was 964 cells/mm³, 756 cells/mm³, and 744 cells/mm³, respectively. Despite this in most patients CD4 counts increase with time and reach normal range within 24 months ART, 37.7 % of patients did not reach the target (CD4 still less than 250 cells/mm³). It is possible that longer time ART duration is needed to achieve normal CD4 counts in the latter patients. Although the inability of patients to respond to an immunological improvement is not fully understood, in general, it has been discovered that about 20% of all HIV patients do not achieve immune recovery despite the suppression of viral replication (23). These patients are referred to as immunological non-responders (INRs). INRs present with severely altered immunological functions,

including malfunction and diminished production of cells within lymphopoietic tissue, perturbed frequencies of immune regulators such as regulatory T cells and T-Helper (Th17) cells, and increased immune activation, immunosenescence, and apoptosis. Importantly, INRs have an increased risk of morbidity and mortality compared to HIV-infected patients with optimal immune reconstitution. Adding different ARV that may improve immune reconstitution has been investigated but results thus far have proved disappointing. The reason for immunological nonresponse is incompletely understood (24). INR has been associated with a number of factors, such as older age, a long duration of the HIV infection prior to HAART, coinfection with hepatitis C, and a low CD4 count nadir. The CD4 count nadir appears to be most critical for the recovery of CD4+ cells (24,25).

In conclusion, our study showed that in 73 % of patients during 24 months of ART, there is an association between the duration of ART with CD4 counts, that is the longer duration of ART the higher the CD4 counts and achieved target therapy normal range.

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