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THE CORRELATION BETWEEN ADHERENCE TO ANTIRETROVIRAL (ARV) MEDICATION AND CD4 COUNT IN THE OCCURRENCE OF VIROLOGICAL FAILURE AMONG INDIVIDUALS WITH HIV/AIDS

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ABSTRAK

Kegagalan virologi merupakan tantangan yang dihadapi oleh pasien human immunodeficiency virus (HIV) setelah memulai pengobatan, dan dipengaruhi oleh berbagai faktor. Modalitas terapi pada pasien HIV dilakukan dengan antiretroviral (ARV), dengan jumlah sel CD4 memainkan peran penting dalam menentukan waktu untuk memulai ARV. Oleh karena itu, tujuan dari penelitian ini adalah untuk menyelidiki hubungan antara kepatuhan terhadap ARV dan jumlah sel CD4 yang terkait dengan kegagalan virologi pada pasien HIV/AIDS yang telah diobati selama minimal 12 bulan dengan rejimen ARV. Penelitian analitik observasional dengan desain potong lintang dilakukan menggunakan teknik consecutive sampling pada 74 pasien berusia ≥ 17 tahun dan menjalani pengobatan ARV selama minimal 12 bulan di Departemen Rawat Jalan Konseling dan Pengujian Sukarela (VCT) dan Penyakit Menular Seksual (STD) Dermatologi, Venereologi, dan Estetika RSMH/FK UNSRI Palembang, serta Pusat Kesehatan Masyarakat Sukarami dan Dempo dari Juni hingga Agustus 2023. Dari total sampel penelitian sebanyak 74 pasien, 26 di antaranya (35,1%) mengalami kegagalan virologi. Kepatuhan terhadap antiretroviral (ARV) (p<0,001) dan jumlah sel CD4 (p<0,001) secara signifikan terkait dengan kegagalan virologi. Analisis multivariat menunjukkan bahwa kepatuhan terhadap ARV (p<0,001) dan jumlah sel CD4 (p<0,001) sangat terkait dengan kegagalan virologi. Penelitian ini menunjukkan bahwa kepatuhan terhadap ARV yang buruk dan jumlah sel CD4 yang rendah terkait dengan kegagalan virologi. Penguatan konseling kepatuhan ARV diperlukan untuk memperbaiki kondisi imunologis dan meningkatkan penekanan virus pada pasien HIV/AIDS.

Kata kunci: gagal virologic, HIV/AIDS, jumlah CD4**,** kepatuhan ARV

ABSTRACT

Virological failure is a challenge encountered by human immunodeficiency virus (HIV) patients once they commence treatment, and this arises from various contributing factors. Several methods have been utilized, encompassing therapeutic methods involving the use of antiretroviral therapy (ARV), with the CD4 cell count playing a crucial role in determining when to start ARV. Therefore, the aim of the study was to investigate the relationship between ARV adherence and CD4 count associated with virological failure in HIV/AIDS patients treated for at least 12 months with an ARV regimen. An observational analytic with a cross-sectional design study was conducted using a consecutive sampling technique on 74 patients aged ≥ 17 years old and on ARV treatment for at least 12 months at the voluntary counseling and testing (VCT) and sexually transmitted disease (STD) Outpatient Department of Dermatology, Venereology, and Aesthetics RSMH/FK UNSRI Palembang, Sukarami, and Dempo Public Health Center from June to August 2023. Out of the total study sample of 74 patients, 26 of them (35.1%) experienced virological failure. Antiretroviral (ARV) adherence (p<0.001) and CD4 count (p<0.001) were significantly associated with virological failure. Multivariate analysis showed that ARV adherence (p<0.001) and CD4 count (p<0.001) were strongly associated with virological failure. In conclusion, this study showed that poor ART adherence and low CD4 count were associated with virological failure. Strengthening ARV adherence counseling are needed to improve immunologic conditions and increase viral suppression in HIV/AIDS patients.

Kata kunci: *ARV adherence, CD4 count, HIV/ADIS, Virological Failure*

INTRODUCTION

Human immunodeficiency virus (HIV) remains a global health issue (Pandey & Galvani, 2019).Various local and international efforts have been made to combat this pandemic. Unfortunately, recent studies indicate an increasing trend in HIV/AIDS cases since 2010, following a decline from 2005. The global burden of HIV/AIDS was estimated at approximately 36.9 million cases in 2019, with a prevalence rate of 476 cases per 100,000 people (Govender et al., 2021). By 2030, it is hoped that the world can end the acquired immunodeficiency syndrome (AIDS) epidemic, however in 2018 virologic suppression in patients with HIV receiving antiretroviral therapy (ARV) was only around 85%. Based on data from the Indonesian Ministry of Health (Kemenkes) in 2022, data on HIV patients in Indonesia reached 519,158 (Rondonuwu, 2022).

The successful management of HIV remains a challenge for clinicians, and despite the success of antiretroviral therapy (ARV), a significant portion of HIV patients fail to achieve a satisfactory response (Pandey & Galvani, 2019). Patients experiencing therapy failure tend to have higher mortality and morbidity rates than those who do not. This necessitates close monitoring of ARV therapy to assess its success, identify adherence issues, and determine ARV regimen replacements in cases of treatment failure (Ahmed et al., 2019; Pandey & Galvani, 2019).

Treatment failure can be evaluated through three approaches: clinical, immunological, and virological; these provide an early and more precise indication of treatment failure. Patients experiencing treatment failure will have their antiretroviral (ARV) regimen modified to regain virological suppression (Ahmed et al., 2019; Kementerian Kesehatan Republik Indonesia, 2022). Virological failure is a condition where the plasma viral load (VL) is >1000 copies/mL after 12 months of ARV therapy with good medication adherence (Sumantri, 2013). A retrospective cohort study by Kurniawan et al., in 2017 in Jakarta on 197 patients receiving ARV, found that approximately 10.65% experienced virological failure, thus requiring a change in ARV drug regimen (Kurniawan et al., 2017). In addition, a retrospective cohort study by Fibriani et al., in 2013 in Bandung on 575 HIV patients receiving ARV therapy, found that approximately 9.1% experienced virological failure (Fibriani et al., 2013). A cross-sectional study by Megasari in 2023 in Surabaya showed a virological failure rate of approximately 15.5% among 63 HIV patients treated with ARV (Megasari & Wijaksana, 2023). This is still below the virological suppression target of the United Nations Program on HIV and AIDS (UNAIDS), which is 95% (Mesic et al., 2021).

Various studies have identified several significant factors that can influence virological failure. A retrospective cohort study by Mesic et al. in 2021, involving 51,010 patients with HIV, found several factors affecting virological failure, namely age at initiation of antiretroviral therapy (ART) >19 years, female sex, marital status, BMI <18.5 kg/m^3, WHO clinical stage 4, HIV-Tuberculosis (TB) co-infection, and ART duration (Mesic et al., 2021). Initiating ART in adolescence remains a challenge. This is due to the unstable psychological characteristics of adolescents and their higher-risk sexual behaviour. Both factors can affect adherence to ART (Nachega et al., 2009). Patients with high BMI are known to have increased leptin hormone levels. This hormone functions to increase T cell production. A body mass index <16 kg/mm^2 has a 4.2 times higher likelihood of virological failure compared to a BMI ≥18 kg/mm^2 (Ahmed et al., 2019). TB infection can increase TNF-α levels in the blood. These high TNF-α levels indicate that HIV activity and replication can also increase, thus worsening the progression of AIDS (Mulyadi & Fitrika, 2011). A meta-analysis by Getaneh et al. in 2022 found that viral load levels in HIV patients with TB co-infection were up to 2.46 times higher

compared to those without TB co-infection (Getaneh et al., 2022). HIV patients with advanced clinical stage have a decrease in CD4 count up to 7 times lower compared to the early stage (Ebonyi et al., 2014).

A case-control study by Ahmed et al. in 2019, involving 9,013 HIV patients, found that BMI, ART adherence, and CD4 count are risk factors associated with virological failure (Ahmed et al., 2019). CD4 count is inversely proportional to viral load. A CD4 count ≤200 mm^3 has a 2.4 times higher likelihood of virological failure compared to ≥200 mm^3. Good ART adherence can suppress viral replication in the blood. Poor ART adherence has a 5.2 times higher likelihood of virological failure compared to good ART adherence (Ahmed et al., 2019).

A cross-sectional study by Abubakari et al. in 2023 found that long-term ARV administration can improve viral suppression more effectively. This leads to a decrease in HIV/AIDS mortality rates. Several other factors associated with virological failure include age, duration of ARV administration, type of ARV combination, and ARV adherence (Abubakari et al., 2023). A duration of ARV administration of less than 1 year can increase the risk of poor medication adherence. This is suspected because, during therapy initiation, some patients do not take ARV therapy regularly or seek help from traditional healers (Abubakari et al., 2023). ARV use of less than 1 year can increase the incidence of virological failure by up to 0.27 times. The type of ARV therapy should be applicable for various co-infections and comorbidities commonly found in people living with HIV/AIDS (PLWHA) (Abubakari et al., 2023).

Given this background, this study aims to investigate the factors influencing virological failure in HIV/AIDS patients treated for at least 12 months with an ARV regimen in Palembang, South Sumatra of Indonesia.

METHOD

This study is observational analytic with cross-sectional design conducted in at the voluntary counseling and testing (VCT) and sexually transmitted disease (STD) Outpatient Department of Dermatology, Venereology, and Aesthetics RSMH/FK UNSRI Palembang, Sukarami, and Dempo Public Health Center from June to August 2023. The study subjects were patients aged ≥ 17 years old and on ARV treatment for at least 12 months. The sample size was calculated using a single-population formula, resulting in a minimum of 74 patients. The study was approved by the Health Research Ethics Committee Dr. Mohammad Hoesin General Hospital Palembang (DP.04.03/D.XVIII.6.11/ETIK/56/2023). Risk factors were collected through questionnaires and medical records, flow cytometry and polymerase chain reaction (PCR) were used to count CD4 T cells and determine viral load.

Virological failure was defined as a plasma viral load that did not decrease (>1000 copies/mL) after 12 months of ARV therapy. The CD4 count variable was defined as the CD4 cell count measured during viral load assessment. Antiretroviral (ARV) adherence was considered adequate if patients attended clinic visits regularly every two weeks to one month to pick up their medications and if there were no documented periods of missed doses in their medical records during the 6-12 months before viral load measurement.(Kurniawan et al., 2017)

Data were collected using a consecutive approach. Data analysis was performed using SPSS version 25. Descriptive statistics were presented as counts and percentages. Bivariate analysis was conducted using the chi-square test, with Fisher's exact test as an alternative. Multivariate analysis was performed using logistic regression.

RESULT

A total of 74 HIV patients were included in this study. Out of these 74 subjects, 26 (35.1%) experienced virological failure according to the previously defined operational criteria. The subjects were primarily aged 26 years and older (66,2%), most patient had a body mass index (BMI) above 18.5 kg/m² (59,5%) with stage I/II on WHO clinical stage (66,2%), CD4 cell count > 200 cell/mm^3 (59,5%), and without HIV- TB co- infection (54,1%). The most common therapy type found in patients was TLE (70,3%) with Duration > 12 months (54,1%) and having good ARV adherence (67,6%). The characteristics of the study subjects are displayed in Table 1.

Table 1. Characteristics of Subjects

Characteristics	Number (n)	Percentage (%)
Age at ARV initiation		
• 17-25 years	25	33,8
• ≥ 26 years	49	66,2
Body Mass Index (BMI)		
• Underweight	30	40,5
• Normoweight/overweight/obesity	44	59,5
WHO Clinical Stage		
• Stage III/IV	25	33,8
• Stage I/II	49	66,2
CD4 Cell Count		
• ≤ 200 cell/mm^3	30	40,5
• > 200 cell/mm^3	44	59,5
HIV- TB Co- infection		
• Yes	34	45,9
• No	40	54,1
ARV Type:		
• TLD	22	29,7
• TLE	52	70,3
ARV Duration:		
• 12 months	34	45,9
• >12 months	40	54,1
ARV Adherence:		
• Poor	24	32,4
• Good	50	67,6
Virological Failure:		
• Yes	26	35,1
• No	48	64,9

The bivariate analysis, utilizing the Pearson Chi-square test, encompassed an examination of 8 risk factors among HIV/AIDS patients. These factors included the age at which ARV treatment was initiated, BMI, WHO clinical stage, CD4 count, HIV-TB co-infection, type of ARV therapy, duration of ARV administration, and adherence to ARV medication. The results of this analysis revealed that two variables exhibited a significant association with virological failure in HIV/AIDS patients. Firstly, individuals with poor adherence to ARV treatment were found to have a substantially higher risk of virological failure when compared to those with good adherence (COR=4.688; 95% CI=2.385-9.214, p<0.001). Secondly, individuals with a CD4 count of ≤ 200 cells/mm^3 were at a significantly higher risk of virological failure when compared to those with a CD4 count of >200 cells/mm^3 (COR=4.889; 95% CI=2.229-10.723, p<0.001) (Table 2).

In multivariate analysis, the most important risk factors were ARV adherence (AOR=13.052, 95% CI=3,151-54,073, p<0,001), and CD4 count (AOR=16,224, 95% CI=3,790- 69,445, p<0,001). The results of multivariate analysis are displayed in Table 3.

Table 2. Relationship Between ARV Adherence and CD4 Count with Virological Failure

Variable	Virological Failure n (%)		p-Value*	COR	CI (95%)
	Virological Failure	Non- Virological Failure			
ARV Adherence:					
• Poor	18 (75,0)	6 (25,0)	<0,001	4,688	2,385-
• Good	8 (16,0)	42 (84,0)			9,214
CD4 Cell Count					
• ≤ 200 cell/mm^3	20 (66,7)	10 (33,3)	<0,001	4,889	2,229-
• > 200 cell/mm^3	6 (13,6)	38 (86,4)			10,723

*p-Value considered significant if <0.05; COR: Crude; CI: Confidence Interval

Table 3. Multivariate Analysis Results of the Relationship Between ARV Adherence and CD4 Count with Virological Failure

Variable	Beta Coefficient	SE	p-Value*	AOR	CI (95%)
ARV Adherence	2,569	0,725	<0,001	13,052	3,151-54,073
CD4 Count	2,787	0,742	<0,001	16,224	3,790-69,445

*p-Value considered significant if <0.05; SE: Standard Error; AOR: Adjusted Odds Ratio

DISCUSSION

This study was cross-sectional specifically designed to examine factors related to virological failure in HIV/AIDS patients, focusing on ARV adherence and CD4 count as variables. The study found that the rate of virological failure in the population of study subjects was 35.1%. This is in line with findings in some African countries, where virological failure rates range from 32% to 51.5% (Gidey Brhane et al., 2017; Gupta-Wright et al., 2020). However, when compared to virological failure rates in Asian countries, the virological failure rate in this study is much higher. A study conducted in 10 Asian countries in 2017 found a virological failure rate of 7% in adult HIV patients. This difference can be explained by the population used in the multivariate study, which consisted of adult HIV patients who had been on second-line ARV therapy for at least 6 months (Ross et al., 2021).

In this study, poor ARV adherence was found to significantly increase the risk of virological failure by 4.688 times on bivariate and 13,052 times on multivariate which aligns with the findings of a case-control study by Ahmed et al. on 9013 HIV patients, which reported that poor ARV adherence increased the risk of virological failure by 5.2 times (Ahmed et al., 2019). Other studies have found that the risk of treatment failure in populations with poor ARV adherence ranged from 3.9 to 16.37 times (Ahmed et al., 2019; Derseh et al., 2020; Hailu et al., 2018; Negash et al., 2020).

Optimal ARV adherence has been proven to increase CD4 counts and reduce hospitalization rates. A cross-sectional study by Rihaliza et al. of 320 HIV patients reported that optimal ARV adherence lead to a 64% increase in CD4 counts for patients (Rihaliza et al., 2020). Several factors can influence an individual's adherence level, including age, psychosocial factors, neurocognitive ability, the number of pills to be taken, and potential side effects (Schaecher, 2013; Unzila et al., 2017). Psychosocial factors and neurocognitive ability are often correlated; a clinical trial by Stilley et al. in 2004 found that lower Intelligence Quotient (IQ) was associated with depression, which decreased ARV adherence (Stilley et al., 2004). Antiretroviral (ARV) adherence rates of 95% or higher were found in 47% of patients

taking one pill per day, 41% of patients taking two pills per day, and 34% of patients taking three or more pills per day (Sax et al., 2012). A systematic review by Al-Dakkak et al. in 2013 found that side effects such as anxiety, confusion, diarrhea, nausea, skin rash, muscle pain, upper abdominal pain, fatigue, taste disturbances, and loss of appetite were among the factors contributing to decreased ARV adherence. Gastrointestinal side effects were the main reason for treatment discontinuation (Al-Dakkak et al., 2013).

The CD4 count is a risk factor often found to be strongly linked to virological failure. In this study, individuals with a CD4 count of ≤ 200 cells/mm³ had a 4,889 times increased risk in the bivariate analysis and a substantially higher 16,224 times in the multivariate analysis of experiencing virological failure. This finding aligns with earlier studies. A cohort study conducted by Okoboi et al. on 1000 HIV patients found that a CD4 count ≥ 200 cells/mm³ was significantly associated with a lower occurrence of virological failure ($p < 0.05$) (Okoboi et al., 2022). Several studies have reported that individuals with low CD4 cell counts have a risk of virological failure ranging from 2.4 to 2.81 times higher (Ahmed et al., 2019; Derseh et al., 2020; Hailu et al., 2018).

Previous studies have established a clear relationship between CD4 count and treatment failure. CD4 count is considered to have a negative correlation with viral load, with low sensitivity and specificity (Haokip et al., 2018; Keiser et al., 2009). The lower the CD4 count, the higher the viral load, and conversely, the higher the CD4 count, the lower the viral load in HIV/AIDS patients. The mechanisms underlying this phenomenon can encompass various aspects, including direct HIV infection leading to CD4 T cell death, disruption of protein synthesis within cells by intracellularly replicating HIV, and damage to CD4+ T cells caused by cytotoxic T cells (Ma et al., 2018).

Several researchers have found that CD4 count can serve as a measure of virological failure occurrence. A prospective cohort study by Jose et al. discovered that virological failure and lower ARV resistance were more common in-patient populations with CD4 counts >350 cells/μL at the start of ARV therapy (Jose et al., 2016). Another prospective cohort study by Lodi et al. found lower treatment failure rates in patients with initial CD4 counts ranging from 350 to 500 cells/μL (Lodi et al., 2013).

Nevertheless, this study has certain limitations. including the use of a cross-sectional research method, which resulted in a relatively small sample size. Additionally, the research subjects were less homogeneous due to the majority of the samples being sourced from hospitals.

CONCLUSION

In summary, virological failure rate among HIV/AIDS patients undergoing ARV treatment for a minimum of 12 months stands at 35.1%. The present study revealed that risk factors associated with the occurrence of virological failure were low CD4 count and poor adherence to antiretroviral treatment. Improving nutritional status by increasing nutrition education and support and strengthening ARV adherence counseling are needed to improve immunologic conditions and increase viral suppression in HIV/AIDS patients.

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