The Correlation Between the Duration of Protease Inhibitor Therapy and Insulin Resistance and Triglyceride Levels in People with HIV/AIDS

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Abstract— The Human Immunodeficiency Virus (HIV) disease is a contagious disease and continues to be a global health issue. The widespread use of highly active retroviral therapy (HAART) led to a dramatic decrease in complications. However, on the other hand, the use of antiretroviral (ARV) drugs has raised concerns regarding metabolic disorders. Research on the effects of Protease Inhibitors (PIs), which are a type of HAART, on metabolic abnormalities is still very limited and controversial. Therefore, it is hoped that this study can be used as a reference in the management of HIV. An observational study with a cross-sectional design was conducted at the VCT outpatient clinic of Ngoerah General Hospital from March to July 2024. The study sample consisted of 70 HIV patients receiving protease inhibitor type ARV therapy. The statistical analysis used was the chi-square and logistic regression. The characteristics of the study subjects had the highest average age ranging from 40 - 44 years as many as 37 people (52.3%). The longest duration of use of antiretroviral drugs divided in the 6-12 months and more than 12 months. There was a significant correlation between the duration of ARV treatment with insulin resistance and increase in triglycerides level. There is a significant correlation between the duration of ARV treatment with insulin resistance and increase level of triglycerides. The longer duration of use of Protease Inhibitor, the further it will increase the insulin resistance and triglycerides level.

Key Words— Insulin Resistance, Protease Inhibitors, Triglyceride, HIV

I. INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a contagious disease whose progression remains a global health issue. According to data from the 2022 global HIV epidemic report by the United Nations Programme on HIV and AIDS (UNAIDS), there are 39 million people worldwide living with HIV, with 1.3 million new infections reported in 2022. The widespread use of highly active retroviral therapy (HAART) in the mid-1990s led to a

dramatic decrease in complications due to immunodeficiency for individuals with HIV infection, including mortality, thereby increasing life expectancy [1]. However, on the other hand, the use of antiretrovirals (ARVs) can create new problems. One type of ARV commonly used is the Protease Inhibitor (PI). PI drugs work by reducing the amount of virus in the body by blocking the enzymes that the virus uses to replicate, and they are often used as second-line treatment for patients who fail or are resistant to first-line therapy [2].

Based on the literature, the use of ARV drugs is associated with the occurrence of metabolic disorders. Some metabolic abnormalities commonly observed in patients include lipodystrophy, dyslipidemia, and insulin resistance. Regarding insulin resistance, several studies have shown that the use of protease inhibitors (PIs), including ritonavir, can acutely inhibit the activity of GLUT-4 (glucose transporter-4), leading to peripheral insulin resistance in both HIV-negative patients and HIV-positive patients with lipodystrophy [3,4].

Research on the effects of protease inhibitor (PI) administration on metabolic abnormalities is still very limited and controversial. Therefore, it is hoped that this study will provide results regarding the relationship between protease inhibitor therapy and insulin resistance and triglyceride levels in people with HIV/AIDS, which may serve as a reference for better HIV management.

II. METHOD AND PROCEDURE

A. Study Setting

An observational study with a cross-sectional design was conducted at the VCT outpatient clinic of Ngoerah General Hospital from March to July 2024. The study sample consisted of 70 HIV patients receiving protease inhibitor type ARV therapy.

B. Variables

Variables in the study are determined based on inclusion and exclusion criteria. Inclusion criteria for the study include patients diagnosed with HIV, patients who have received ARV therapy with a regimen that includes ritonavir/lopinavir, and individuals aged ≥ 18 years. Exclusion criteria for the study include patients with diabetes mellitus, patients with malignancies, pregnant patients, patients with chronic kidney disease, patients with autoimmune diseases, patients with chronic liver disease, patients in critical condition, and patients who refuse to participate.

C. Hypothesis and Analysis

We hypothesized There is a relationship between the duration of protease inhibitor administration and insulin resistance and increased triglyceride levels in patients with HIV.

We will first report separately all independent variables between the 2 groups. Hypothesis testing via chi square analysis will then be performed on nominal independent variables while logistic regression will be performed on numerical independent variables gathered to the dependent variables. Significant variables will then be further opted for multivariate logistic regression to find the impact and significance of each individual variables to critical clinical symptoms and mortality. All analysis were performed using IBM SPSS Statistics 25.

III. RESULT AND DISCUSSION

This study included a total of 70 subjects admitted to VCT clinic Ngoerah General Hospital between March to July 2024. Subjects ranged from 25 to 62 years old, with a mean (± SD) of 42.33 (± 9.33) years old. Male patients predominate females, constituting 52.9% patients admitted. Our patients are almost equally divided between using PI during 6 – 12 month and more than 12 months. A complete profile of total subjects analyzed is shown on Table 1.

TABLE 1. PROFILE OF SUBJECTS ANALYZED (N = 70)

Characteristic Respondents	Mean	n (%)
Age (Mean)	42,33± 9,3	
Sex		
• Male		37 (52,9)
• Female		33 (47,1)
Body Mass Index (BMI) (kg/m2)	23,94 ± 1,57	
Triglyceride (mg/dL)	229,47 ± 54,9	
HOMA IR	2.20 ± 0.2	
• Insulin Resistance		57 (81,4)
• Not Insulin Resistance		13 (18,6)

TABLE 2. CORRELATION DURATION OF PROTEASE INHIBITOR THERAPY AND INSULIN RESISTANCE ANALYZED

Variable	Insulin Resistance n(%)		*P*
	Yes	No	
Duration of Treatment			
> 12 Months	35 (100)	0 (0)	<0,001
6 – 12 Months	22 (62,1)	13 (37,9)	

Based on Table 2, subjects with ARV treatment duration of > 12 months experienced insulin resistance at 100%, while subjects with ARV treatment duration of 6-12 months experienced insulin resistance at 62.1%. Thus, it can be concluded that subjects with a treatment duration of > 12 months have a higher percentage of insulin resistance compared to those with a treatment duration of 6-12 months. Based on the chi-square test, it was found that there is a significant relationship between ARV treatment duration and insulin resistance (p=<0.001).

TABLE 3. CORRELATION DURATION OF PROTEASE INHIBITOR THERAPY AND INCREASE OF TRIGLYCERIDE LEVEL ANALYZED

Variable	Triglyceride n(%)		*P*
	High	Normal	
Duration of Treatment			
> 12 Months	35 (100)	0 (0)	<0,001
6 – 12 Months	31 (88,5)	4 (11,5)	

Based on Table 3, subjects with ARV treatment duration of > 12 months experienced an increase in triglyceride levels at 100%, while subjects with ARV treatment duration of 6-12 months experienced an increase in triglyceride levels at 88.5%. Thus, it can be concluded that subjects with a treatment duration of > 12 months have a higher percentage of triglyceride level increase compared to those with a treatment duration of 6-12 months. Based on the chi-square test, it was found that there is a significant relationship between ARV treatment duration and the increase in triglyceride levels (p=<0.001).

The characteristics of the study subjects based on gender in this study showed that there were more males than females. The results of this study are consistent with research conducted by Mulyati et al in 2017, which reported that males (67%) are more likely to suffer from HIV compared to females (33%), with an overall average age of 37.1 ± 10.7 years [5].

The average HOMA-IR value for the study subjects is 2.2. A total of 57 subjects (81.4%) in this study experienced insulin resistance. The prevalence in this study is slightly higher compared to previous research conducted by Guillen et al. in 2018, which reported an insulin resistance prevalence of 34%, twice as high as that in a population of patients without HIV with a HOMA-IR value of ≥ 2.1.6 In line with this, Salazar et al. in 2019 reported that a HOMA-IR value > 2 is associated with insulin resistance [7].

The average triglyceride value for the study subjects is 229. A total of 66 subjects (94.2%) in this study experienced an increase in triglyceride levels. Insulin resistance is a compensatory mechanism in most patients that can trigger clinically significant hyperglycemia in patients predisposed to diabetes mellitus (DM). Hypertriglyceridemia is one of the contributing factors to DM [8]. In line with this, Giearch et al. in 2018 reported that a triglyceride level < 150 mg/dL is considered optimal [9].

Several studies indicate a relationship between the use of protease inhibitors (PIs) and the occurrence of lipodystrophy, dyslipidemia, and insulin resistance. At physiological concentrations, there are also varying levels of metabolic effects of PIs. Darrajal et al. reported that among HIV patients receiving PI therapy, 22% experienced insulin resistance after 48 weeks of PI administration, with effects beginning to appear in the fourth week and increasing to 25% at 96 weeks [10]. Carr et al stated that patients receiving PI-based ARV therapy who experience body fat redistribution have high levels of triglycerides, cholesterol, insulin, and C-peptide. Insulin resistance is a compensatory mechanism in most patients that can trigger clinically significant hyperglycemia in patients predisposed to diabetes mellitus [11].

IV. CONCLUSION

In conclusion, A significant relationship was found between the duration of PI use and insulin resistance, as well as increased triglyceride levels, with a p-value of <0.001.

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