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Association of Antiretroviral Regimens and CD4 Counts with Dyslipidemia in HIV Patients: Implications for Metabolic Management

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ABSTRACT

Background: Dyslipidemia, a key risk factor for cardiovascular disease, is prevalent among people living with HIV/AIDS receiving antiretroviral therapy. This study aims to evaluate the impact of different ART regimens on lipid profiles in HIV patients and identify regimens with better outcomes in lipid profile levels.

Subjects and Method: An observational study was conducted from June to August 2024 at Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia. A total of 110 participants were recruited using consecutive random sampling, including HIV patients on ART for at least three months. Independent variables included ART regimens and CD4 counts, while the dependent variable was dyslipidemia status. Data were collected via demographic forms, medical record reviews, and lipid profile analysis. Statistical analysis was performed using chi-square and t-tests, with significance set at $p < 0.05$.

Results: Of the 110 participants, 38.2% were identified with dyslipidemia. The highest dyslipidemia rates were observed in patients using the Duviral Alluvial regimen (80.0%), followed by Duviral Neviral (71.4%). Newer regimens, TLD and TLE, were associated with lower dyslipidemia rates (31.3% and 36.0%, respectively; p= 0.045). Patients with CD4 counts greater than 500 cells/µL were also significantly more likely to have dyslipidemia (OR= 2.5, 95%CI= 1.14- 5.58, p = 0.020).

Conclusion: Newer ART regimens such as TLD and TLE are associated with better lipid profile outcomes and lower dyslipidemia risk compared to older regimens. Higher CD4 counts may reflect an increased risk of lipid abnormalities, which highlights the need for lipid monitoring and regimen optimization in HIV care.

Keywords: HIV, ART, Dyslipidemia, CD4

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BACKGROUND

Dyslipidemia, characterized by abnormal lipid profiles, is a major risk factor for cardiovascular disease (CVD) (Jellinger et al., 2017; Mosca et al., 2022). People living with HIV/AIDS (PLWHA) receiving

antiretroviral therapy (ART) show an increased susceptibility to dyslipidemia and related metabolic complications (Grinspoon and Carr, 2005). Despite therapeutic advances, HIV continues to pose a significant global health challenge, with reports indicating 650,000 HIV-related deaths and 1.5 million new infections in 2021 (World Health Organization, 2023). In Indonesia, where HIV prevalence continues to rise, understanding ART-related complications becomes increasingly crucial for optimal patient care (Fahmi and Yona, 2019).

The management of HIV infection is frequently complicated by metabolic disorders, particularly dyslipidemia. Current theories suggest that antiretroviral medications, especially protease inhibitors (PI), nucleoside reverse-transcriptase inhibitors (NRTI), and non-nucleoside reverse-transcriptase inhibitors (NNRTI) (Ahmed, 2015), interfere with lipid metabolism through multiple pathways (Papantoniou et al., 2024). These regimes can elevate triglycerides, LDL, and total cholesterol while suppressing HDL levels (Sprinz et al., 2010). The clinical significance of these metabolic alterations is underscored by epidemiological evidence: HIV patients demonstrate substantially higher CVD rates compared to HIV-negative individuals, with a 1.8-fold increased risk of myocardial infarction and a 2.6-fold higher risk of stroke (Currier, 2023). While guidelines exist for ART selection (RI, 2019), there is limited data on the comparative effects of different regimens on lipid profiles in Indonesian populations.

This study aims to assess the impact of different antiretroviral regimens on lipid profiles in HIV patients and identify combinations associated with lower dyslipidemia risk in Indonesia. Through comparative analysis of lipid profiles across various ARV regimens, we seek to provide insights for optimal ART selection that minimizes dyslipidemia risk while maintaining therapeutic efficacy, ultimately reducing the risk of associated cardiovascular complications in Indonesian HIV patients.

SUBJECTS METHOD

1. Study Design

This observational study assessed lipid profiles in people living with HIV/AIDS (PLWHA) receiving antiretroviral therapy. The study was conducted from June 2024 to August 2024 at dr. Saiful Anwar Regional General Hospital (RSSA), Malang, Indonesia. Participants were recruited using consecutive random sampling during the study period.

2. Population and Sample

A total of 110 participants were recruited in this study. The study population included both outpatient and inpatient individuals who had received their HIV diagnosis either at RSSA or other referral healthcare facilities.

3. Study Variables

The independent variable in this study was a positive HIV diagnosis in individuals who had undergone antiretroviral therapy treatment. The dependent variables included gender, the type of ART regimen used, CD4 cell count, and total cholesterol levels. To ensure appropriate patient selection, we included participants who had received antiretroviral therapy for at least three months and provided written informed consent. However, to minimize confounding factors that could affect lipid metabolism independently of HIV treatment, we excluded patients with conditions known to influence lipid profiles, including those using oral contraceptives, patients with polycystic ovary syndrome, diabetes mellitus, or chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus.

4. Study Instruments

Data collection involved three main approaches. First, participants provided demographic information through a standardized form after giving written informed consent. Second, medical records were reviewed to gather details about participants' current ARV regimens and treatment history. Third, blood samples (3 cc) were collected at the RSSA clinical pathology laboratory for laboratory analysis. These samples were tested for lipid profile parameters, including total cholesterol, and CD4 cell counts. Lipid abnormalities were defined as total cholesterol levels greater than 200 mg/dL, indicating dyslipidemia (Lin et al., 2018).

5. Data analysis

Data analysis was performed using the SPSS version 25.0. Descriptive statistics were used to characterize the study population, with continuous variables presented as means and standard deviations and categorical variables as frequencies and percentages. The relationship between categorical variables was analyzed using chi-square tests, while comparisons of variables between groups were conducted using independent T-tests. Statistical significance was set at $p < 0.05$ for all analyses.

6. Research Ethics

This study was approved by the ethical committee from the Faculty of Medicine Universitas Brawijaya, Malang Indonesia (Ethical approval number: 63/EC/KEPK/-03/2024 and approved in March 1st, 2024). All participants signed the informed consent before participation in this study.

RESULTS

1. Characteristic of Subjects

A total of 110 HIV patients participated in the study, with 54 males (49%) and 56 females (50.9%). Most participants were on the TLE ARV regimen (45.5%), followed by those on other regimens (see Table 1).

Table 1. Sample characteristics

Characteristics	Category	Frequency	Percentage
Sex	Male	54	49%
	Female	56	50.9%
ART Regimens	Duviral Alluvial	5	4.5%
	Duviral Neviral	7	6.3%
	TLE	50	45.5%
	TLD	48	43.6%
Dyslipidemia Status	Dyslipidemia	42	38.2%
	Non-dyslipidemia	68	61.8%

2. Association between ARV regimens, CD4 counts and dyslipidemia status

As shown in Table 2, there was a significant relationship between ARV drug regimen and dyslipidemia status (p= 0.045). Respondents on the Duviral Alluvial regimen are 8.8 times more likely to have dyslipidemia compared to those on TLD (p= 0.031). Respondents on the Duviral Neviral regimen are 5.5 times more likely to have dyslipidemia compared to those on TLD (p= 0.039). In contrast, respondents on the TLE regimen are 0.8 times less likely to have Dyslipidemia compared to those on TLD (p = 0.619). In addition, CD4 count shows a significant association with dyslipidemia (p= 0.02). Respondents with CD4 >500 are 2.5 times more likely to have dyslipidemia than those with CD4 <500.

Table 2. Association Between ARV Regimen, CD4 Counts and and Dyslipidemia Status

Variables	Dyslipidemia Status				p	OR (95% CI)	p
	Yes		No				
	N	%	N	%			
ARV Regimens							
Duviral Alluvial	4	80.0	1	20.0	0.045	8.8 (0.90-85.58)	0.031
Duviral Neviral	5	71.4	2	28.6		5.5 (0.95-31.64)	0.039
TLD	15	31.3	33	68.8			
TLE	18	36.0	32	64.0		0.8 (0.34-1.87)	0.619
CD4 Counts (cells/µL)							
>500	23	51.1	22	48.9	0.020	2.5 (1.14-5.58)	
<500	19	29.2	46	70.8			

DISCUSSION

The significant relationship between ARV regimen and dyslipidemia (p = 0.045) in our study shows the importance of regimen selection when considering metabolic side effects. Respondents on the Duviral Alluvia regimen exhibited the highest rate of dyslipidemia (80%), followed by those on Duviral Neviral (71.4%). Alluvia consists of Lopinavir/Ritonavir, and Ritonavir, as part of older protease inhibitor (PI) regimens, is known to cause metabolic disturbances, including dyslipidemia (Sarkar and Brown, 2023).

Protease inhibitors have been well-documented for their effects on lipid metabolism, primarily by increasing triglycerides and total cholesterol (Meena et al., 2020). The greatest increases in total cholesterol were observed significantly in patients using Ritonavir (Meena et al., 2020; Riddle et al., 2002; Sarkar and Brown, 2023). The use of older generation PIs, such as Ritonavir, is associated with a high incidence of dyslipidemia in 70% to 80% of patients (Ahmed et al., 2022; Riddle et al., 2002). A study by Esther et al. demonstrated that the use of Lopinavir/ Ritonavir was independently associated with increased total cholesterol (p < 0.001) (Muya and Kamuhabwa, 2019). Protease inhibitors activate endothelial function and promote atherosclerosis. It is possible that HIV infection, immune reconstitution response, and antiretroviral therapy (ART) may promote early endothelial activation, representing pro-atherogenic factors and accelerators of atherosclerosis (Martini et al., 2023). In a recent review in 2021, Vos et al. concluded that PIs are associated with metabolic disturbances and an increased risk of cardiovascular disease (CVD) (Vos and Venter, 2021).

Participants on newer antiretroviral regimens, such as TLE (Tenofovir/ Lamivudine/ Efavirenz) and TLD (Tenofovir/ Lamivudine/ Dolutegravir), exhibited significantly lower rates of dyslipidemia, with incidences of 36% and 31.3%, respectively. This finding aligns with studies suggesting that regimens containing efavirenz and tenofovir are associated with better lipid profiles (Li et al., 2023). For instance, a study conducted in China reported that the percentage of patients with dyslipidemia was significantly higher in the LPV/r (Lopinavir/Ritonavir) group compared to the EFV (Efavirenz) group (84.0% vs. 52.6%, P < 0.001) (Dai et al., 2019). Moreover, 10% of patients on LPV/r-based regimens developed severe dyslipidemia, and these patients had increased odds of

hypercholesterolemia (odds ratio [OR]= 1.709, p= 0.038) (Dai et al., 2019).

Recent research indicates that antiretroviral therapy (ART) regimens containing dolutegravir are associated with more favorable lipid profiles than those containing efavirenz (Papantoniou et al., 2024). Efavirenz has been linked to increased production of reactive oxygen species (ROS) and reduced ATP synthesis due to inhibition of mitochondrial complex I, as well as induced hepatic cell apoptosis mediated by alterations in cytochrome c and caspase 9 activity. Additionally, efavirenz acts as a potent agonist of the pregnane X receptor (PXR), leading to upregulation of genes such as CD36, a fatty acid transporter, resulting in increased lipid uptake and cholesterol biosynthesis in cells (Papantoniou et al., 2024)

Conversely, dolutegravir, an integrase strand transfer inhibitor (INSTI), appears to have minimal impact on lipid levels even after long-term use. This underscores the beneficial role of INSTIs in managing dyslipidemia, especially when switching from other highly active antiretroviral therapy (HAART) regimens, as recommended by current guidelines. (MacInnes et al., 2011) DTG is increasingly favored for their better lipid profiles and lower incidence of metabolic side effects, making them particularly suitable for HIV patients with pre-existing cardiovascular risk factors. (Khemla et al., 2023)

Our study revealed a significant relationship between CD4 count and dyslipidemia (p= 0.02), with patients exhibiting dyslipidemia having a higher CD4 count (>500 cells/μL). While higher CD4 counts generally indicate effective immune recovery—a positive outcome of antiretroviral therapy (ART)—our findings suggest that this immune restoration may be associated with an increased risk of lipid disturbances. This could be due to prolonged ART exposure or the cumulative effects of certain drug classes on lipid metabolism (Ombeni and Kamuhabwa, 2015)

Supporting our results, Pefura Yone et al. reported an increasing trend in the prevalence of dyslipidemia among HIV-positive individuals receiving highly active antiretroviral therapy (HAART) as their CD4 T cell counts improve. They attribute this trend to partial immune system restoration and improved nutrition, both leading to higher blood lipid levels. Additionally, they emphasize that the toxicity of HAART significantly contributes to the development of poor lipid profiles, despite the increase in CD4 counts associated with the treatment (Pefura Yone et al., 2011).

In conclusion, this study highlights the significant association between ARV regimen type, CD4 count, and dyslipidemia in HIV patients in Indonesia. Our findings suggest that newer ARV regimens, such as TLD and TLE, are associated with lower rates of dyslipidemia compared to older regimens like PIs, which are linked to higher lipid abnormalities. Additionally, higher CD4 counts, often reflecting longer ART use, were found to increase the risk of dyslipidemia. Clinicians should consider prioritizing newer ARV regimens to reduce the risk of metabolic complications, particularly in patients with pre-existing cardiovascular risk factors. Regular monitoring of lipid profiles, especially in patients with higher CD4 counts, is essential to identify and manage dyslipidemia early, thereby reducing the long-term risk of cardiovascular diseases in HIV patients.

AUTHORS CONTRIBUTION

All authors have contributed in writing this article.

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CONFLICT OF INTEREST

There are no conflicts of interest

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