

Dyslipidemia among HIV-positive children receiving antiretroviral therapy in Indonesia

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Abstract

Introduction: Antiretroviral (ARV) therapy has changed the status of human immunodeficiency virus (HIV) infection from a high-mortality disease into a chronic one. One of the consequences of long-term use of ARV medications is dyslipidemia, which may progress to cardiovascular disease in the future. The aim of the study was to measure the rate of dyslipidemia among HIV-infected children receiving ARV therapy and related risk factors.

Material and methods: A cross-sectional study was conducted at pediatric outpatient clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from January to July 2019. Lipid profile was examined on 96 eligible subjects and data regarding nutritional status, clinical stage at diagnosis, latest immunosuppression status, latest viral load (VL) value, and latest ARV combination used were obtained from medical records. Bivariate and multivariate analysis were performed to find the association between dependent and independent variables using SPSS version 22.

Results: Of 96 subjects included, 52 (54.2%) subjects experienced dyslipidemia. The prevalence of dyslipidemia among those with second-line (containing protease inhibitors) and first-line (containing non-nucleoside reverse transcriptase inhibitors) ARV therapy were 80% and 39%, respectively. The use of second-line ARV therapy was associated with 6.3 times ($p < 0.01$; 95% CI: 2.4-17.1) increased risk of dyslipidemia compared to first-line ARV therapy.

Conclusions: Prevalence of dyslipidemia among HIV-positive children on ARV was high with second-line ARV therapy being a risk factor.

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Key words: children, HIV, dyslipidemia, HAART, protease inhibitors.

Introduction

Antiretroviral (ARV) therapy has changed the prognosis of HIV infection from a disease with high mortality rate into a controllable chronic disease. Before the introduction of ARV therapy, three-year survival rate of HIV-infected children was only 5-10% [1]. Suppressed viral replication followed by restored immunological competence caused by ARV therapy have contributed to the decrease of mortality

cases up to 70% [1]. One of the consequences of long-term ARV therapy use is dyslipidemia. Hyperlipidemia was reported in 50-70% of HIV-infected children treated with ARV therapy [2]. Lipid profile of HIV-infected children was reported to be similar with that of children diagnosed with heterozygous familial hypercholesterolemia with increased risk of early atherosclerosis. Protease inhibitors (PI), one type of antiretroviral drugs, has been associated with abnormal

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lipid profile [3]. Dyslipidemia is of primary concern as it is related to increased cardiovascular events in the future.

Studies describing the association between ARV therapy and dyslipidemia among HIV-infected children in developing countries were limited. The aim of this study was to describe the prevalence of dyslipidemia among HIV-infected children receiving ARV therapy and related risk factors.

Material and methods

Study design, place, and time

This was a cross-sectional study conducted at child outpatient clinic of rumah sakit umum pusat nasional Cipto Mangunkusumo (RSCM), the national referral hospital of Indonesia, from January to July 2019.

Participants

From 188 children with HIV, a total of 96 HIV-infected children were consecutively recruited. Inclusion criteria were HIV-infected children aged from 1 month to 17 years old who visited outpatient clinic for routine control, and have been receiving their current ARV therapy for at least six months. Exclusion criteria were applied to those who suffered from severe bacterial infection that needed hospitalization or any history of hospitalization within three months before sampling, those who have been consuming medication that could affect lipid profile, such as statin, and those who had any of the following conditions: familial hypercholesterolemia, hyperthyroidism, diabetes mellitus, storage disease, chronic kidney disease, or nephrotic syndrome, as known from history taking or written in medical record. Children were also excluded if they could not perform fasting prior to blood drawing.

Ethical approval

Ethical approval was obtained from the research ethics committees of the Faculty of Medicine, Universitas Indonesia. A signed informed consent form was taken from the parent/caregiver, and verbal consent from adolescents aged less than 18 years old after they have been adequately informed about the study.

Data collection

Eligible subjects were tested for lipid profile (total cholesterol, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) after consent had been obtained. Subjects were required to fast for at least six hours before blood sampling. Blood examination was conducted at clinical pathology laboratory, RSCM. Also, information regarding gender, age, body weight, body height, body mass index (BMI), nutritional status, the World Health Organization (WHO) HIV clinical stadium, latest CD4 absolute, and percentage value (immunosuppression status), viral load

(VL) if available (as it was not covered by either this study expenses or national health insurance), latest ARV therapy regimen, its combination, and duration were collected.

Variables of interest

Dependent variable of this study was dyslipidemia. Dyslipidemia was defined as abnormality of at least one lipid parameter: total cholesterol ≥ 200 mg/dl, LDL ≥ 130 mg/dl, triglycerides ≥ 100 mg/dl for children aged 0-9 years or > 130 mg/dl for children aged 10-18 years, or HDL < 40 mg/dl [4]. Independent variable was ARV therapy regimen. The regimen consisted of first- and second-line therapy. First-line therapy was a combination of 2 nucleoside reverse transcriptase inhibitors (NRTI), including lamivudine (3TC), zidovudine (AZT), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC), and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), such as nevirapine (NVP) and efavirenz (EFV). For second-line therapy, a PI, lopinavir/ritonavir (LPV/r), replaced NNRTI.

Statistical analysis

Bivariate and multivariate analysis were performed to assess the association between dependent and independent variables. Only outcomes at a 20% significance level ($p \leq 0.2$) in the bivariate models were included in multivariable logistic regression models. Prevalence odds ratio with 95% confidence interval and p -value were considered. Only variables with a p -value < 0.05 remained in the final model. Statistical analyses were performed using Statistical Package for Social Studies (SPSS Inc., Chicago, Illinois, USA) version 22.

Results

Total of 96 participants were included in the study. Proportion of male and female subjects was almost equal (47.9 vs. 52.1%). Median age of subjects was 10 years old (IQR, 7-13 years old), and most of the subjects came from group aged 6-11 years old (43.8%). Most of them were well-nourished (60.4%) and only 3 patients were assessed as obese. Median BMI was 15.96 kg/m² (IQR, 14.53-17.97 kg/m²) (Table 1).

Based on the latest immunosuppression status, 78.1% of the subjects were immunocompetent. Viral load (VL) results were available in 39 patients, with 32 of them showing viral count of 1,000 copies/ml. Two third of subjects have been receiving first-line ARV therapy and the most common combination used was AZT+3TC+NVP (36 of 61 subjects). The most common combination of second-line ARV therapy used was ABC+3TC+LPV/r (28 of 35 patients). Two third of subjects have been consuming the ARV medications ≥ 24 months.

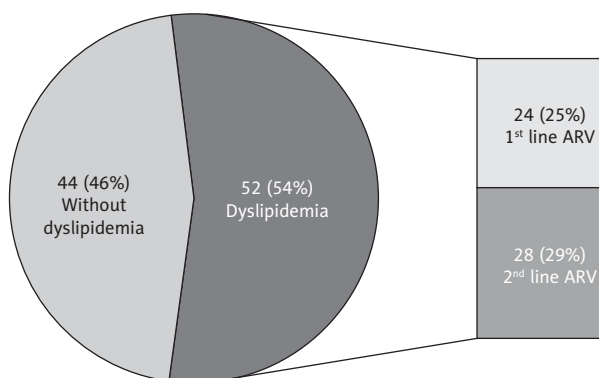
In this study, the prevalence of dyslipidemia was 54% (Figure 1). Table 2 shows that most of the subjects in the study population experienced hypertriglyceridemia (32.3%). Of all

Table 1. Baseline characteristics of subjects

Variables	Frequency (%) (n = 96)
Gender	
Male	46 (47.9)
Female	50 (52.1)
Age* (years)	10 (7-13)
Age group (years)	
< 2	1 (1.0)
2-5	19 (19.8)
6-11	42 (43.8)
> 12	34 (35.4)
Nutritional status	
Severely malnourished	0 (0)
Malnourished	24 (25.0)
Well-nourished	58 (60.4)
Overweight	11 (11.5)
Obese	3 (3.1)
BMI* (kg/m ²)	15.96 (14.53-17.97)
WHO clinical stage at diagnosis	
1	16 (16.7)
2	9 (9.4)
3	28 (29.2)
4	43 (44.8)
Immunosuppression status	
Without immunosuppression	75 (78.1)
Mild immunosuppression	6 (6.3)
Moderate immunosuppression	8 (8.3)
Severe immunosuppression	7 (7.3)
VL (copies/ml)	
≤ 1,000	32 (82.1)
> 1,000	7 (17.9)
Duration of ARV (months)	
< 24	32 (33.3)
≥ 24	64 (66.7)
ARV therapy regimen	
First-line	61 (63.5)
Second-line	35 (36.5)

*Mean

subjects with lipid abnormality, 61% demonstrated abnormality of only one lipid panel, while only three subjects presented abnormality of all lipid panels. The highest difference between median value and upper limit of a certain lipid panel was observed in patients with hypertriglyceridemia (47 mg/dl among subjects aged 0-9 years old, and 44 mg/dl among patients aged 10-18 years old). The difference was 31.5 mg/dl among the subjects with increased LDL.

**Figure 1.** Prevalence of dyslipidemia among HIV-infected children receiving antiretroviral therapy (N = 96)**Table 2.** Distribution of lipid profile

Lipid	Dyslipidemia		
	n	Median (mg/dl)	IQR (mg/dl)
Total cholesterol	21	215	207-240
Triglyceride	14*	147	123.8-207.3
	17**	174	152-223
HDL	22	35	28.5-37.3
LDL	10	161.5	133.3-196.5

*Subjects aged 0-9 years old. **Subjects aged 10-18 years old

Bivariate analysis showed that gender ($p = 0.11$) and ARV therapy regimen ($p < 0.01$) were the only variables associated with dyslipidemia (Table 3). When multivariate analysis was performed, only ARV therapy regimen had an association with dyslipidemia (Table 4). The use of second-line ARV medications was associated with 6.34 times higher risk of dyslipidemia compared to first-line therapy ($p = 0.00$; 95% CI: 2.35-17.1). The prevalence of dyslipidemia among subjects treated with second-line therapy was 80%, and those with first-line therapy was 39%. Abnormal lipid profile was observed mostly in subjects with combination of ABC+3TC+LPV/r (40.4%) (Table 5).

Discussion

In children < 14 years old, HIV infection is mostly caused by vertical transmission with high mortality early in life. In this study, 80% of the subjects were 6 years old or older. Improved life span in HIV-infected children may be influenced by ARV therapy, which suppresses viral replication and has been associated with decreased HIV-related mortality cases up to 70% [1]. Studies in El Salvador and Uganda also reported similar mean age in their study population indicating good survival rate [5, 6]. Restoration of well-functioned immune system contributes to decreased HIV-related morbidities, such as tuberculosis and chronic diarrhea, allowing

Table 3. Bivariate analysis of dyslipidemia risk factors

Variables	Dyslipidemia		POR	95% CI	p-value
	Yes	No			
Gender					
Male	21	25	0.52	0.23-1.16	0.11
Female	31	19			
Age					
< 0-11	35	27	1.30	0.56-3.00	0.54
> 12	17	17			
Nutritional status					
Malnourished	19	19	0.76	0.33-1.72	0.51
Well-nourished	33	25			
HIV clinical stage					
3-4	40	31	1.40	0.56-3.48	0.47
1-2	12	13			
Immunosuppression status					
Immunosuppressed	13	8	1.50	0.56-4.04	0.42
Immunocompetent	39	36			
VL (copies/ml)					
> 1,000	4	3	0.91	0.17-4.77	0.91
≤ 1,000	19	13			
Duration of ARV (months)					
≥ 24	33	31	0.73	0.31-1.72	0.47
< 24	19	13			
ARV regimen					
Second-line	28	7	6.17	2.33-16.34	0.01
First-line	24	37			

POR – prevalence odd ratio

Table 4. Multivariate analysis of dyslipidemia risk factors

Variable	Dyslipidemia		POR	95% CI	p-value
	Yes	No			
Gender					
Male	21	25	0.49	0.20-1.18	0.11
Female	31	19			
ARV regimen					
Second-line	28	7	6.34	2.35-17.1	0.00
First-line	24	37			

POR – prevalence odd ratio

children to grow up optimally. Most of the participants in the present study fell into well-nourished children category, and none was severely malnourished. Studies by Nampijja in Uganda and Brewinski in Latin America population also showed high prevalence of subjects with good nutrition status [6, 7]. Although dyslipidemia is one of the morbidities related to excess weight, only small percentage of the subjects in this study was in that category.

Table 5. Combination of antiretroviral therapy and dyslipidemia

ARV	Dyslipidemia	
	Yes Frequency (%)	No Frequency (%)
Total	52	44
First-line		
AZT+3TC+NVP	15 (28.8)	21 (47.7)
AZT+3TC+EFV	7 (13.5)	10 (22.7)
ABC+3TC+NVP	1 (1.9)	3 (6.8)
ABC+3TC+EFV	0	1 (2.3)
TDF+3TC+NVP	1 (1.9)	1 (2.3)
TDF+3TC+EFV	0	1 (2.3)
Second-line		
AZT+3TC+LPV/r	1 (1.9)	0
ABC+3TC+LPV/r	21 (40.4)	6 (13.6)
TDF+3TC+LPV/r	3 (5.8)	1 (2.3)
TDF+FTC+LPV/r	3 (5.8)	0

The effectiveness of HIV infection treatment was reflected by the number of subjects who were not immunosuppressed based on their latest CD4 results and low level of VL, which were found in high number in this study. Similarly, Sonogo *et al.* in their study conducted in El Salvador observed that proportion of immunocompetent subjects and subjects with undetected VL were 89% and 77.5%, respectively [5].

Here, first-line ARV therapy was mostly a combination of AZT+3TC+NVP. This was in line with guidelines that for combination of 2 NRTI and 1 NNRTI, the first choice was NRTI started with 3TC, followed by another NRTI usually AZT, and NVP as the first choice of NNRTI [8]. A combination of ABC+3TC+LPV/r was the common option for second-line therapy in this study. According to guidelines, in case of first-line therapy failure, PI replaces NNRTI [8].

Infection of HIV and use of PI have been known to be associated with abnormal lipid profile [1, 6, 7]. Chronic inflammation caused by HIV and ARV therapy stimulate homeostasis response to stress at cellular level, leading to metabolic disturbance of adipocyte cells [9]. The prevalence of dyslipidemia in this study was 54.17%. Around the globe, the prevalence of dyslipidemia among HIV-infected children receiving ARV therapy differs. Papi *et al.* in Brazil reported a 37% prevalence, while Mandal *et al.* in India found the prevalence to be 38.3% [1, 10]. Sonogo *et al.* in El Salvador and Tadewos *et al.* in Ethiopia showed a 60% and 82.3% prevalence, respectively [5, 11]. Different criteria used for dyslipidemia may explain such variation. A study by Yuniarti *et al.* revealed similar prevalence rate of 47% but in their study, the proportion of subjects treated with second-line ARV therapy was smaller and subjects were limited to pre-pubertal children [12].

Hypertriglyceridemia was the most common findings of dyslipidemia in this study. Elevated triglyceride level was caused by disturbed triglyceride clearance, increased triglyceride biosynthesis related to HIV infection, and use of PI [9]. Hypertriglyceridemia as the most common form of dyslipidemia was also reported by other studies [1, 5, 7, 12]. Median value of LDL in the present study fell into a category that needs intervention. According to guidelines, individuals with LDL value of 160-189 mg/dl with risk factors, including HIV-infection, need to have a diet modification and be administered with lipid-lowering agents [13].

Logistic regression analysis showed ARV therapy as the only factor associated with dyslipidemia. This finding was in line with reports from other studies. Yuniarti *et al.* reported PI as the only variable related to dyslipidemia with POR of 6.9 (95% CI: 2.03-23.7) [12]. Sonogo *et al.* also found PI to be related with hypertriglyceridemia with prevalence ratio of 2.8 (95% CI: 2.0-3.8) [5]. Brewinski *et al.* described an increased risk of hypertriglyceridemia and hypercholesterolemia among subjects receiving PI-based therapy, with adjusted odds ratio of 3.5 (95% CI: 1.9-6.4) and 2.7 (95% CI: 1.3-5.6) [7]. Protease inhibitors interfere with lipoprotein lipase activity causing ineffective triglyceride uptake by adipocyte cells and increase sterol response element binding

protein (SREBP) in hepatocytes, which play a role in gene regulation related to lipid metabolism. Both mechanisms result in elevated triglyceride serum level. Among NRTI, AZT was associated with poor lipid profile [14]. This could explain why dyslipidemia was also found higher in subjects treated with AZT-based first-line therapy compared to other combination without AZT.

Limitation of this study was that no cause-effect relationship between ARV therapy and dyslipidemia could be drawn due to study design. Other factors, which could have been confounding factors, such as familial hypercholesterolemia, hyperthyroidism, diabetes mellitus, storage disease, chronic kidney disease, or nephrotic syndrome, were not evaluated objectively and relied only on history taking or medical records. The number of sub-population participants with dyslipidemia was not sufficient to demonstrate an association between combination of ARV therapy and dyslipidemia in a logistic regression model.

Conclusions

In the present study, the prevalence of dyslipidemia among HIV-infected children was high (54.17%). Among those on second-line ARV therapy, the prevalence was 80%, while in those treated with first-line therapy, the prevalence was 39%. The patients receiving second-line ARV therapy were 6.34 times more likely to have abnormality in their lipid profile.

Lipid profile examination should be conducted regularly to evaluate dyslipidemia in children receiving ARV therapy. Those with abnormality of serum lipid profile should be managed according to guidelines.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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