# DYSLIPIDEMIA AMONG THAI HIV-INFECTED ADULTS RECEIVING ANTIRETROVIRAL THERAPY: A HOSPITAL-BASED REPORT

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**Abstract.** The objective of this study was to determine the prevalence of dyslipidemia, pattern of lipid profiles, and risk factors for dyslipidemia. This study was a retrospective cross sectional study of the outpatient Thai HIV-infected patients receiving antiretroviral therapy (ART). Of 175 patients, 43% were male and median (IQR) age was 44 (40-51) years. Median (IQR) duration of HIV infection was 15 (13-16) years and median (IQR) duration of receiving ART was 11 (9-14) years. The prevalence of dyslipidemia was 51%. Dyslipidemia were associated with 76%, 55%, and 37% of patients receiving lopinavir/ritonavir-, efavirenz-, and nevirapine-based regimen, respectively. Medians serum low-density lipoprotein cholesterol (LDL-c) level for the corresponding regimens were 112, 136, and 107 mg/dl, respectively. The medians of serum triglycerides (TG) for the corresponding regimens were 162, 138, and 100 mg/dl, respectively. By multivariate analysis, risk factors associated with dyslipidemia included fasting blood glucose >110 mg/dl (OR=9.48), lopinavir/ritonavir-based regimen (OR=4.26), duration of receiving ART ≥12 years (OR= 2.69), and male (OR=2.29). Dyslipidemia associated ART was a common metabolic complication among even Thai HIV-infected patients, receiving ART in the outpatient clinic, especially patients received lopinavir/ritonavir-based regimen. Thus, clinicians should monitor these metabolic complications to improve quality of care.

**Keywords:** antiretroviral, dyslipidemia, Thailand

## INTRODUCTION

Antiretroviral therapy (ART) is recommended for all HIV-infected patients to reduce the risk of disease progression and burden of opportunistic infections (Sungkanuparph *et al*, 2010; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2012; WHO, 2013). However, antiretroviral drugs have a various adverse drug reactions (Tymchuk and Currier, 2008). One of those reactions is metabolic complication. The previous studies reported various metabolic complications, including hyperglycemia, dyslipidemia, and lipodystrophy (Friis-

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Moller *et al*, 2003; Behrens, 2005; Young *et al*, 2005; Mutimura *et al*, 2007).

In Thailand, a middle-income country, the widely prescribed antiretroviral regimens are 2 nucleoside reverse transcriptase inhibitors (NRTIs) as backbone drugs combined with one of the following drugs, *ie* efavirenz (EFV), nevirapine (NVP) and lopinavir/ritonavir (LPV/r) (Sungkanuparph *et al*, 2010). However, the knowledge regarding dyslipidemia and comparison of lipid abnormalities among those antiretroviral regimens was not well studied in Thai adult patients. Thus we aimed to determine the prevalence of and risk factor for dyslipidemia among HIV-infected patient receiving ART.

## MATERIALS AND METHODS

### Design and setting

This study was a cross sectional study conducting at Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Thailand. The protocol was approved by the Ethics Committee for Research in Human Subjects, Department of Disease Control, Ministry of Public Health.

### Participants and procedures

Data were collected in May-Jun 2013. The outpatient medical records of 175 patients were randomly selected. Inclusion criteria were >18 years old patients who had been receiving nevirapine (NVP)-, efavirenz (EFV)-, lopinavir/ritonavir (LPV/r)-based regimens for at least 6 months. The data were collected from the patient's medical records and an electronic database.

### Measures

**Lipid.** Lipid profile was measured by enzymatic colorimetric assay. Glucose was measured by hexokinase assay. All test performed on C501 Hitachi and Cobas Integra 400 plus analyzers (Roche Diagnostics: Rotkreuz ZG, Switzerland). If LDL-C was not directly measured, we calculated by use of the Friedewald formula when TG level <400 mg/dl (Warnick *et al*, 1990).

**Dyslipidemia.** Patients were defined as having dyslipidemia by 2 criteria: (1) those patients were prescribed lipid lowering drugs at any time or (2) abnormal serum lipid profile was compatible with the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) guidelines, 2001. Dyslipidemia was classified by NCEP-ATP III guidelines as follow: hypercholesteremia, TC level ≥240 mg/dl; high LDL-c, LDL-c level ≥160 mg/dl; hypertriglyceridemia, TG level ≥200 mg/dl or low HDL-c, HDL-c level <40 mg/dl.

### Statistical analyses

Categorical variables were compared using the Pearson chi-square test. Continuous variables were compared using Kruskal-Wallis test. To investigate relationship between independent variables and dyslipidemia, univariate analysis was performed by Pearson chi-square test. Variables with a $p$-value <0.05 by univariate analysis were included into multivariate analysis. Multivariate analysis was carried out using linear regression model. A $p$-value <0.05 was considered statistically significant. SPSS for Windows® (version 20; IBM, Armonk, NY) was used for statistical analysis.

## RESULTS

### Participants' characteristics

One hundred and seventy-five patients were included into the study. A summary and comparison of baseline characteristics among three antiretroviral

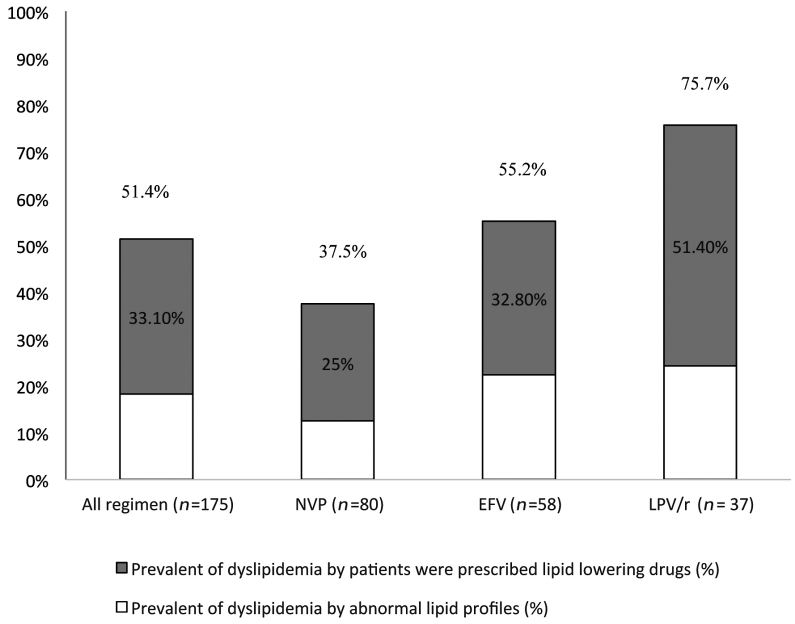


Fig 1–Prevalence of dyslipidemia in patients receiving NVP-, EFV-, and LPV/r-based regimens. All regimens, All patients receiving ART; EFV, efavirenz-based regimen; NVP, nevirapine-based regimen; LPV/r, lopinavir/ritonavir-based regimen.

regimens was shown in Table 1. Of which, 46% were prescribed NVP-based regimen, 33% were EFV-based regimen, and 21% were LPV/r-based regimen. Of 37 patients receiving LPV/r-based regimen, 95% were pre-exposed to NNRTI.

**The prevalence of dyslipidemia**

The prevalence of dyslipidemia was shown in Fig 1. Of all, the prevalence of dyslipidemia was 51%. Dyslipidemia were associated with 76%, 55%, and 37% of patients receiving LPV/r-, EFV-, and NVP-based regimen, respectively. Thai patients receiving LPV/r-based regimen had a higher frequency of dyslipidemia than EFV- and NVP-based regimen.

**The patterns of lipid profile**

The characteristics of serum lipid profile were examined among patients who were not taking lipid-lowering drugs. A summary of their lipid profile was shown in Table 1. The median serum HDL-c level was highest in the patients receiving NVP-based regimen. The median serum TG level was highest in the patients receiving LPV/r-based regimen and it was lowest in the patients receiving NVP-based regimen. The median serum TC and LDL-c levels were found to be highest in the patients receiving EFV-based regimen. The proportions of patients with hypercholesteremia, hypertriglyceridemia, and low HDL-c were highest in the patients receiving LPV/r-based regimen and they was lowest in patients receiving NVP-based regimen.

**Risk factors of dyslipidemia**

The potential risk factors associated with dyslipidemia were shown in Table 2. By univariate analysis, the association of possible independent variables with dyslipidemia were: receiving a NVP-based regimen or LPV/r-based regimen, having a systolic blood pressure ≥135 mmHg, having a diastolic blood pressure ≥85 mmHg, having a fasting blood sugar >110 mg/dl, having a duration of receiving ART of ≥12 years, having a waist circumference ≥81 centimeters, having a body mass index (BMI) ≥25 kg/m$^2$, male and aged ≥42 years. These variables were included into multivariate analysis.

The result indicated that risk factors associated with dyslipidemia included

Table 1
Characteristics of the patients.

| Baseline characteristics | NVP-based regimen (*n*=80) | EFV-based regimen (*n*=58) | LPV/r based regimen (*n*=37) | *p*-value |
|---|---|---|---|---|
| Age, years, median (IQR) | 43 (40-48) | 48 (42-55) | 45 (41-49) | 0.004 |
| Male (%) | 31 | 47 | 62 | 0.006 |
| BMI (kg/m$^2$), median (IQR) | 21.9 (19.9-24.7) | 21.6 (20.0-23.8) | 21.5 (19.7-23.2) | 0.795 |
| Waist circumference (cm), median (IQR) | 78 (72-86) | 78 (72-84) | 82 (76-86) | 0.185 |
| Duration of known HIV infection (yrs), median (IQR) | 15 (13-16) | 15 (13-17) | 15 (13-16) | 0.557 |
| Duration of receiving AR, years, median (IQR) | 10 (9-12) | 11.5 (10-15) | 12 (10-15) | 0.001 |
| Percent of CD4 cell count, percent, median (IQR) | 26 (22-30) | 25 (22-31) | 24 (20, 28) | 0.039 |
| Fasting blood glucose, mg/dl, median (IQR) | 96 (91-103) | 103 (95-115) | 94.5 (89, 99.75) | 0.001 |
| Systolic blood pressure, mmHg, median (IQR) | 124 (115-138) | 125 (110-140) | 120 (108, 133) | 0.625 |
| Diastolic blood pressure, mmHg, median (IQR) | 77 (68-85) | 78 (69-86) | 74 (63, 86) | 0.713 |
| Characteristics of co-morbid conditions (%) | | | | |
| Hypertension, % | 16 | 14 | 22 | 0.603 |
| Diabetes mellitus, % | 3 | 9 | 8 | 0.242 |
| Undetectable viral load, % | 95 | 96 | 84 | 0.039 |
| Type of NRTI prescribed as part of regimen (%) | | | | |
| Tenofovir disoproxil fumarate | 49 | 65 | 46 | 0.086 |
| Zidovudine | 44 | 21 | 35 | 0.019 |
| Stavudine | 7 | 3 | 0 | 0.174 |
| Didanosine | 2 | 3 | 0 | 0.542 |
| Abacavir | 2 | 10 | 0 | 0.031 |
| Lamivudine | 92 | 90 | 84 | 0.355 |
| Emtricitabine | 2 | 7 | 5 | 0.459 |
| Amount of NRTI in the regimen (%) | | | | |
| No NRTI | 0 | 0 | 3 | 0.153 |
| One NRTI | 1 | | 30 | <0.001 |
| Two NRTIs | 97 | 97 | 62 | <0.001 |
| Three NRTIs | 1 | 2 | 5 | 0.035 |

Table 1 (Continued).

| Baseline characteristics | NVP-based regimen (*n*=80) | EFV-based regimen (*n*=58) | LPV/r based regimen (*n*=37) | *p*-value |
|---|---|---|---|---|
| Characteristic of serum lipid | | | | |
| TC, *n*, median (IQR) | (58) 186 (172-210) | (37) 203 (188-222) | (17) 176 (166.0-222.0) | 0.071 |
| LDL-c, *n*, median (IQR) | (38) 107 (98-136) | (36) 136 (104-149) | (16) 112 (102.0-150.0) | 0.192 |
| TG, *n*, median (IQR) | (60) 100 (67-150) | (39) 138 (74-182) | (18) 162 (106.0-231.0) | 0.022 |
| HDL-c, *n*, median (IQR) | (36) 64 (54-75) | (34) 50 (44-74) | (15) 50 (37.0-61.0) | 0.017 |
| TC/HDL-c, *n*, median (IQR) | (36) 2.9 (2.5-3.8) | (34) 3.9 (2.9-4.6) | (15) 4 (2.9-5.2) | 0.006 |
| Hypercholesteremia *n* (%) | 58 (5) | 37 (11) | 17 (18) | 0.25 |
| Hypertriglyceridemia *n* (%) | 60 (10) | 39 (21) | 18 (28) | 0.135 |
| High LDL-c, *n*, (%) | 38 (10) | 36 (11) | 16 (12) | 0.98 |
| Low HDL-c, *n*, (%) | 36 (3) | 34 (12) | 15 (27) | 0.039 |

BMI, body mass index; NRTI, nucleoside reverse transcriptase inhibitors; TC, total cholesterol; LDL-c, low density lipoprotein level; TG, triglyceride level; HDL, high density lipoprotein level; TC/HDL-c, ratio of serum total cholesterol and high density lipoprotein. *p*-value compared among three regimens.

having a fasting blood glucose >110 mg/dl (OR=9.48), receiving a LPV/r-based regimen (OR=4.26), having a duration of receiving ART of ≥12 years (OR=2.69), male (OR=2.29). There was no significant relation with body mass index, systolic blood pressure, diastolic blood pressure, waist circumference and age.

## DISCUSSION

In the present study, a high prevalence of dyslipidemia in Thai HIV-infected patients receiving ART was found. Our finding corresponded to a previous study in Thais (51% versus 54%) (Hiransuthikul *et al*, 2007). The studies from other countries reported prevalence of abnormal serum lipid up to 60% (Friis-Moller *et al*, 2003; Fontas *et al*, 2004). Therefore, ART-associated dyslipidemia was considered to be a common treatment complication in HIV-infected patients. Moreover, exposure to LPV/r-based regimen was a significant risk factor associated with having dyslipidemia. This finding is consistent with a previous large cohort study, showing that patients receiving first-line PI-based regimens had high TC and TG levels and TC:HDL-c ratios (Fontas *et al*, 2004).

Comparing among three regimens, patients who were prescribed LPV/r had more derangement of serum TG level. In addition, proportion of patients with hypercholesteremia, low HDL-c, and hypertriglyceridemia were found to be more frequent in patients receiving PI-based regimen when compared to those receiving NNRTI-based regimen. PI- and NNRTI-based regimens are associated with different risks of dyslipidemia. HDL-c is well

Table 2
Univariate and multivariate analysis of factors associated dyslipidemia.

| Independent variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value |
| Fasting blood glucose >110 mg/dl | 3.18 (1.33-7.60) | 0.007 | 9.48 (2.17-41.53) | 0.003 |
| Receiving a LPV/r-based regimen | 3.81 (1.68-8.68) | 0.001 | 4.26 (1.20-15.19) | 0.025 |
| Duration of receiving ART of ≥12 yr | 2.00 (1.09-3.68) | 0.024 | 2.69 (1.10-6.56) | 0.030 |
| Male | 3.00 (1.61-5.60) | <0.001 | 2.29 (1.01-5.23) | 0.049 |
| BMI ≥ 25 kg/m$^2$ | 2.47 (1.09-5.60) | 0.027 | 3.27 (0.96-11.11) | 0.058 |
| Systolic blood pressure ≥ 130 mmHg | 2.36 (1.24-4.48) | 0.008 | 1.54 (0.53-4.47) | 0.431 |
| Diastolic blood pressure ≥ 85 mmHg | 2.13 (1.04-4.36) | 0.036 | 1.14 (0.36-3.54) | 0.828 |
| Waist circumference ≥81 cm | 2.13 (1.09-4.16) | 0.026 | 0.99 (0.39-2.54) | 0.980 |
| Aged ≥ 42 years | 2.02 (1.07-3.81) | 0.029 | 0.83 (0.33-2.06) | 0.687 |
| Receiving a NVP-based regimen | 0.35 (0.19-0.65) | 0.001 | 1.02 (0.38-2.76) | 0.962 |

NVP-based regimen, nevirapine-based regimen; LPV/r-based regimen, Lopinavir/ritonavir-based regimen, BMI, body mass index.

known as good cholesterol (Berrougui *et al*, 2012). The main HDL function is transport cholesterol from peripheral cells to the liver and then excreted in bile (Berrougui *et al*, 2012). Thus patients who have low HDL-C level are potential burden of dyslipidemia. Our results suggest that various regimen related to different alteration of serum lipid. Exposure of NVP-based regimen is associated with a more favorable lipid profile than EFV- or LPV/r-based regimens. This finding was concordant to the results from the previous studies (Fontas *et al*, 2004; Young *et al*, 2005).

By multivariate analysis, risk factors associated with dyslipidemia included having high fasting blood glucose, receiving a LPV/r-based regimen, having a long time to receive ART and male sex. Relationship between having fasting blood glucose more than 110 mg/dl and dyslipidemia is a widely known. The patients had high blood sugar level in a parallel increasing risk of dyslipidemia (Pinto Neto *et al*, 2013).

With regard to the period of exposure to antiretroviral drug, we found the longer period of treatment the patients received, the higher chance of dyslipidemia occurred. This circumstance explained by the proportion of patients having duration of receiving ART more than12 years were prescribed in the LPV/r-based regimen more than in the NNRTI-based regimen (62% versus 39%). In terms of gender, male sex was three-time more likely to develop dyslipidemia than female sex. This finding is in line with the result from previous studies (Mooser and Carr, 2001; Hiransuthikul *et al*, 2007). Male receiving ART had higher serum TG and lower HDL-c than females.

The present study had some limitations. Firstly, this study did not consider lipid profile before receiving ART. Therefore, we did not know alteration of serum lipid after treatment in each receiving

treatment regimen. Secondly, this study has a relative small sample size. Finally, the present study is a retrospective cross sectional study. Some parameters might be missing.

Dyslipidemia was highly prevalent among Thai adult HIV-infected patients receiving ARV at an outpatient clinic in a middle-income country. LPV/r-based regimens were associated with a significantly higher risk of dyslipidemia than were NNRTI-based regimens. In addition, patients with high fasting blood glucose, a long period of ART, and male also had a risk of a dyslipidemia. Our results provide the data for the clinician to improve patients' quality of care.

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