Metabolic abnormalities among HIV-infected patients: The rational of national health security for people living with HIV
Duangjai Duangrithi¹, Khuntikun Polsracoo², Titiwut Bhuddhataweekul²

¹Division of General Pharmacy Practice, Department of Pharmaceutical Care, Collage of Pharmacy, Rangsit University, Pathumtani, Thailand
²Department of Pharmaceutical Care, Collage of Pharmacy, Rangsit University, Pathumtani, Thailand

Corresponding author: Duangjai Duangrithi, Division of General Pharmacy Practice, Department of Pharmaceutical Care, Collage of Pharmacy, Rangsit University, Pathumtani, Thailand 12000. Tel: +66 81 8893557, Fax: +66 2 9972222 ext 1403, E-mail: dungjai.d@rsu.ac.th


ABSTRACT
In the era of highly active antiretroviral therapy (ART), traditional risk factors for metabolic syndrome are presented as increasing age. In low- and middle-income countries, the restricted benefit package of national health security for human immunodeficiency virus (HIV) does not facilitate the early detection of metabolic disorders. In order to assess the rational of national health security for metabolic abnormalities among people living with HIV (PLHIV), this retrospective study aims to determine the occurrence of metabolic abnormalities and its predicting factors. The study was approved by the hospital ethics committee and conducted at the internal medicine clinic, Pathum Thani Hospital, Thailand. Patients with HIV having had at least 1 year of first-line ART, and having their fasting glucose, fasting lipid profile, and blood pressure assessed before ART were recruited into the study. Those with any abnormal metabolic component prior to ART or absent history of ART were excluded. The metabolic abnormalities were defined as any of the following: elevated triglyceride, reduced high-density lipoprotein (HDL), elevated blood pressure, elevated fasting glucose, or on drug treatment for these metabolic abnormalities. The occurrence of metabolic abnormalities was found in 102 of 340 patients (30.0%). Hypertension (11.4%) was the most common abnormality. Age became the single predictor of metabolic abnormalities (odds ratio [OR] = 1.03, 95% confidence interval [CI] = 1.00–1.06). Aging patients with HIV should be the target group for monitoring.
and treating metabolic abnormalities. The revision of the benefit package on metabolic abnormalities is urgently needed to promote a better quality of life.

Keywords: HIV; HAART; metabolic syndrome; NRTIs; NNRTIs

INTRODUCTION

Human immunodeficiency virus (HIV) attacks the body’s immune system, specifically the CD4 cells. In 2017, 36.9 million people globally were living with HIV, and 59% of all people living with HIV (PLHIV) were provided with antiretroviral therapy (ART). Thailand, one of the countries with the highest prevalence of HIV in Asia and the Pacific, accounts for 9% of the region's total population of PLHIV. HIV incidence per 1000 population was 0.09 [0.08 – 0.10]. PLHIV were 480,000, and 75% of them are on ART. The incidence rate of metabolic syndrome (MetS) in patients on ART was 1.2 per 100 person-months, and most of them had a low level of high-density lipoprotein (HDL).

The development of highly active antiretroviral therapy (HAART), a treatment regimen of combined ART, improved the quality of life and increased the life expectancy of PLHIV. Only 49.6% of the deaths were due to acquired immunodeficiency syndrome while the rest was due to age-related illness, especially cardiovascular disease. This increases the importance of age-related illness among these patients. In the era of HAART, several traditional risk factors of MetS are presented, which finally lead to MetS, cardiovascular events, and mortality. In addition, both HIV infection and ART can cause metabolic abnormalities. The previous study showed that the highest prevalence of metabolic component in patients treated with the first-line HAART group and the ART-naive group were 53.2 and 14.8%, respectively. Prevalence of MetS in PLHIV, ranging from 11.2 up to 45.4%, was reported, and 24.2% of patients on first-line HAART regimens were diagnosed with MetS. Furthermore, MetS prevalences across subgroups were as follows; 23.7 and 26.7% in men and women, respectively, and 25.8, 17.2, and 17.9% in protease inhibitor (PI) users, nonnucleoside reverse transcriptase inhibitor (NNRTI) users, and nucleoside reverse transcriptase inhibitors (NRTI) users, respectively. However, there is no significant difference in the prevalence of MetS in high or low proportion of smokers, 8% versus 22.2%, P = 0.193.

Dyslipidemia, insulin resistance, and diabetes mellitus (DM) have been observed among patients treated with HAART, especially PIs. Furthermore, the annual cumulative incidence of events related to coronary artery disease was significantly higher in patients treated with PI than patients treated with other ART. Therefore, the World Health Organization (WHO) recommended first-line ART regimens for adults consisting of two NRTIs plus one NNRTI. However, it was reported that NRTI and NNRTI can increase the risk of DM. Dyslipidemia has been observed in NNRTI-based therapy, although to a lesser degree when compared to PI. Therefore, prevention of MetS by monitoring metabolic components appears to be an effective strategy. However, there are some limitations in this regard in low- and middle-income countries.

According to the universal health coverage in Thailand, the benefit package for patients with HIV is the free basic medical services available to all HIV patients. The basic blood chemistry testing, consisting of fasting plasma glucose (FPG), serum total cholesterol, and serum triglyceride, have been performed in patients with HIV taking into consideration age and comorbidities as follows: age <35 years without any comorbidity: annually; age
The true value. The sample size calculation was as follows:
\[ n = \frac{z^2 \times p \times (1 - p)}{d^2} \]

where
\( n = \) sample size
\( z = 1.96 \) (\( \alpha = 0.05 \))
\( p = \) the prevalence of impaired fasting glucose
\( d = \) error allowance

Therefore, a sample size of at least 339 patients with HIV was required for this study.

Intensive training was provided for two data collectors, Pharm D students, using a set of practice medical records before the study started. The electronic predefined case record forms (eCRFs) were prepared for data collection with the electronic log book for patients’ confidentiality and patient tracking. The electronic medical records were screened by a medical statistician according to inclusion and exclusion criteria before random sampling by data collectors. Patients with HIV having had at least 1 year of the first-line ART, and having FPG, fasting lipid profile, and blood pressure assessment before starting ART were recruited into the study. Those with any abnormal metabolic component prior to ART or absent history of ART were excluded.

Clinical characteristics were obtained from electronic medical records and laboratory data were obtained from the electronic laboratory report using the eCRFs. The scheduled meetings were arranged to resolve data clarification and conflicts.

**Methods**

This retrospective study was conducted at the internal medicine clinic at the outpatient department of Pathum Thani Hospital, from September 2018 to February 2019. The study was conducted in accordance with the principles for human experimentation, as defined in the Declaration of Helsinki and approved by the hospital ethics committee on 06 September 2018 (approval number: 0032.203.3/16076). The privacy of the research participants was ensured with an adequate level of confidentiality. The study conducted in the South West region of Cameroon showed that the highest prevalence of metabolic component in patients treated with the first-line HAART group and the ART-naive group were 53.2 and 14.8%, respectively.\(^9\)

In order to determine the occurrence of metabolic abnormalities in patients with HIV after first-line HAART, the incidence was estimated to be 33% with a 95% CI and the precision to be within 5% of the true value. The sample size calculation was as follows:

\[ n = \frac{z^2 \times p \times (1 - p)}{d^2} \]

where
\( n = \) sample size
\( z = 1.96 \) (\( \alpha = 0.05 \))
\( p = \) the prevalence of impaired fasting glucose
\( d = \) error allowance

Therefore, a sample size of at least 339 patients with HIV was required for this study.

Intensive training was provided for two data collectors, Pharm D students, using a set of practice medical records before the study started. The electronic predefined case record forms (eCRFs) were prepared for data collection with the electronic log book for patients’ confidentiality and patient tracking. The electronic medical records were screened by a medical statistician according to inclusion and exclusion criteria before random sampling by data collectors. Patients with HIV having had at least 1 year of the first-line ART, and having FPG, fasting lipid profile, and blood pressure assessment before starting ART were recruited into the study. Those with any abnormal metabolic component prior to ART or absent history of ART were excluded. Clinical characteristics were obtained from electronic medical records and laboratory data were obtained from the electronic laboratory report using the eCRFs. The scheduled meetings were arranged to resolve data clarification and conflicts.

**The outcomes of interest**

The outcomes of interest were the occurrence of metabolic abnormalities after at least 1 year of the first-line HAART and its predicting factors among patients with HIV.

**Definition**

The metabolic abnormalities were defined as at least one metabolic component of the following: blood
pressure over 130/85 mmHg or hypertension, fasting triglyceride level over 150 mg/dL or dyslipidemia, and fasting blood sugar over 100 mg/dL or DM.  

**Statistical analysis**

Data analysis was performed by Statistical Package for the Social Sciences 15.0 (SPSS, Chicago, IL). Categorical variables were summarized as frequencies and percentages, and then analyzed using the chi square test or the Fisher’s exact test. Continuous variables were summarized as mean ± standard deviation (SD) or median and interquartile range (IQR) values, and compared using t-test or the Mann–Whitney U-test where appropriate. Then, all variables with statistically significant relationships with metabolic abnormalities were included in the logistic regression model. The variables with statistical significance in this model indicated “the predictor” to the metabolic abnormalities. All tests for significance were two-sided, and P < 0.05 was considered to be of statistical significance.

**RESULTS**

A total of 340 patients were recruited into this study. The first patient was recruited on 10 September 2018 and of the last patient was recruited on 11 January 2019. After at least 1 year of first-line ART, 30% (102/340) of patients had metabolic abnormalities. The demographic characteristics of patients with and without metabolic abnormalities were shown in Table 1. In both the groups, most of the patients were male. Patients with metabolic abnormalities were significantly older than those without metabolic abnormalities (42.45 ± 10.34 years old vs. 38.76 ± 10.24 years old; P value = 0.003). Proportions of those who were married (45.1% vs. 30.5%; P = 0.010) and had an occupation (100.0% vs. 94.5%, P value = 0.016) were significantly higher in patients with metabolic abnormalities. Traditional risk factors such as smoking (9.7% vs. 17.2%; P value = 0.139) and alcohol consumption (9.7% vs. 17.3%; P value = 0.134) were slightly higher

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Bivariate Analysis of Demographic and Clinical Characteristics Associated with Metabolic Abnormalities after ART (n = 340).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Total (n = 340)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>200 (58.80)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>39.76 ± 10.75</td>
</tr>
<tr>
<td>Married</td>
<td>118 (34.90)</td>
</tr>
<tr>
<td>Having an occupation</td>
<td>372 (96.20)</td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (14.90)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>35 (15.00)</td>
</tr>
<tr>
<td>% Weight change&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>+3.96 ± 10.74</td>
</tr>
<tr>
<td>Having comorbidities</td>
<td>59 (24.70)</td>
</tr>
<tr>
<td>Having opportunistic infection</td>
<td>135 (39.70)</td>
</tr>
<tr>
<td>Duration between diagnosis and initial treatment (year)</td>
<td>4.01 ± 0.84</td>
</tr>
<tr>
<td>ART&lt;sup&gt;c&lt;/sup&gt; duration (months)</td>
<td>41.14 ± 9.68</td>
</tr>
<tr>
<td>Baseline CD4 (cell/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>336.56 ± 242.14</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean ± SD.

<sup>b</sup>Weight differences between the latest measurement and before starting ART.

<sup>c</sup>ART, antiretroviral therapy

<sup>*</sup>statistical significance
in those without metabolic abnormalities while weight differences between the latest measurement and before ART initiation was slightly higher in the metabolic abnormality group (4.9% ± 10.36 vs. 3.9% ± 10.74; P value = 0.570). Furthermore, these patients had significantly longer average duration between diagnosis and initial treatment (4.21 ± 0.82 years vs. 4.05 ± 0.81 years; P value = 0.008) as well as ART duration (43.03 ± 10.05 months vs. 41.55 ± 9.27 months, P value = 0.018). Baseline blood chemistries and CD4 were similar in both groups.

The distribution of metabolic abnormalities was shown in Figure 1. Of 102 patients, hypertension (39; 11.5%) was the single most common metabolic abnormality while the combination of hypertension and hypertriglyceridemia was the most common combination of metabolic abnormalities (9; 2.7%). MetS was found in one patient (0.3%).

ART in these patients was similar except the proportion of patients treated with either efavirenz or nevirapine in the regimen containing lamivudine and stavudine, which was significantly greater in the metabolic abnormality group (3; 2.98 vs. 0, P value = 0.011) (Table 2).

Logistic regression analysis showed that age was the single predictor of metabolic abnormalities in these patients (OR = 1.03, 95% CI = 1.00, 1.06, P value = 0.024).

**DISCUSSION**

This is the first finding of the occurrence of metabolic abnormalities in patients with HIV after first-line ART in Thailand. About one-third of them had metabolic abnormalities, and it was likely to be underestimated due to the restricted benefit package for PLHIV. The fact that gender was of no consequence in patients with and without metabolic abnormalities supported a previous study in Thailand. However, in Western and African countries, females are at a higher risk of MetS, compared to males. Living with family and having an occupation tend to increase the occurrence of metabolic abnormalities in this study. Similarly, previous studies showed that marriage is associated with weight gain in both men and women and is strong predictor for MetS. In addition, MetS was significantly increased in the unemployed. In line with a previous finding, no association was found between current smoking and alcohol consumption. The inconsistent research findings were found among non-HIV patients. Mild-to-moderate alcohol consumption of beer and wine had a positive effect on lipids and fasting insulin. Moderate weight gain observed in our patients may increase the risk of MetS, as shown in a previous study. Generally, PLHIV are motivated to engage in health-promoting behaviors because intensive lifestyle modification significantly improved cardiovascular risk indicators in patients with HIV and MetS. Therefore, the traditional risk factors of MetS were found in small proportions and were not associated with metabolic abnormalities. Although there were significant differences in duration between HIV diagnosis and the initial treatment, and ART duration between the two groups, they were nonsignificantly different after logistic regression analysis. It was supported by a previous finding that the prevalence of...
Metabolic abnormalities among HIV-infected patients

Major impact on metabolic abnormalities in our patients. Age was the single predictor of metabolic abnormalities, which was supported by a previous study, especially in patients treated with regimens not based on PI. In the era of HAART, the life expectancy of PLHIV and people with age-related illness has increased. With increasing age, the risk of hypertension increased, which is supported by the highest rate of hypertension in this study. Furthermore, it is recommended to screen for hyperlipidemia and hyperglycemia at the inception of HIV care, after treatment initiation and modification. However, laboratory testing provided by the benefit package for PLHIV is not sufficient for an early detection of all metabolic components. Delayed detection of metabolic abnormalities may lead to adverse cardiovascular outcomes. Our result highlighted that the national benefit package for aging patients with HIV should be revised in order to promote effective screening for metabolic abnormalities. FPG and/or HbA1c should be monitored within 1–3 months after initiation or modification of ART.

**TABLE 2.** ART in HIV-infected Patients with and without Metabolic Abnormalities (n = 340).

<table>
<thead>
<tr>
<th>ART</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>Metabolic abnormalities after HAART (n, %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NVP</td>
<td>EFV</td>
<td>No (n = 238)</td>
<td>Yes (n = 102)</td>
</tr>
<tr>
<td>TDF</td>
<td>FTC</td>
<td>EFV</td>
<td>111 (46.64)</td>
<td>39 (38.24)</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>1 (0.42)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>EFV</td>
<td>57 (23.95)</td>
<td>30 (29.41)</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>3 (1.26)</td>
<td>3 (2.94)</td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>EFV</td>
<td>4 (1.68)</td>
<td>1 (0.98)</td>
<td>0.642</td>
</tr>
<tr>
<td>d4T</td>
<td>EFV</td>
<td>1 (0.42)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ddI</td>
<td>EFV</td>
<td>1 (0.42)</td>
<td>1 (0.98)</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>AZT</td>
<td>EFV</td>
<td>29 (12.18)</td>
<td>12 (11.76)</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>25 (10.50)</td>
<td>12 (11.76)</td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td>NVP</td>
<td>6 (2.52)</td>
<td>1 (0.98)</td>
<td>0.011*</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>0</td>
<td>3 (2.98)</td>
<td></td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine; AZT, zidovudine; d4T, stavudine; ddI, didanosine.

*statistical significance.
ART, and then once or twice a year. In patients having impaired FPG or DM, FPG should be monitored every 3 months or HbA1c should be monitored every 6 months. Fasting lipid profile should be monitored within 3 months after initiation or modification of ART, then every 3 months in the first year, and once or twice a year thereafter. In patients having a triglyceride level of > 200 mg/dL, fasting lipid profile should be monitored within 3 months after initiation of ART and within 6–8 weeks after initiation or dose increases for statins, and subsequently every 6–12 months. Due to the economic burden in this resource-constrained country, patients aged ≥ 35 years should be prioritized as the finding in HIV-1-infected Thai adults showed that they are at high risk for MetS. In addition, waist circumference and body mass index should be monitored at each visit. Lifestyle modification consisting of diet control, exercise, smoking cessation, and alcohol abstinence is strongly recommended.

There are some limitations to this study due to incomplete entries in the electronic medical records such as marital status, waist circumference, height, and weight. The metabolic abnormalities may be underestimated because of the limitation of laboratory testing according to national health security for PLHIV. Furthermore, the result might have limited generalizability as the study was conducted only among Thai patients with HIV.

CONCLUSION

Age-related risk factors should be monitored and treated in order to prevent or slow down metabolic disorders in PLHIV. Therefore, improvement of the benefit package for aging PLHIV, especially blood tests for metabolic abnormalities, is urgently needed to promote a better quality of life and to diminish the long-term cost of health services.

CONFLICTS OF INTEREST

All authors have disclosed no conflicts of interest.

FUNDING

This study received no financial support.

ACKNOWLEDGEMENT

We would like to express our special thanks to Dr. Arthit Ourairat, President of Rangsit University. We also thank Mrs. Prakywan Krobsanit for her support to this study.

REFERENCES


