RISK OF CARDIOVASCULAR EVENTS PREDICTED BY THE RAMA-EGAT SCORE AMONG HIV-INFECTED PATIENTS IN THAILAND

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Abstract. Cardiovascular disease has become an important cause of death among HIV-infected patients. A cross sectional study was conducted to determine the risk for cardiovascular events among HIV-infected patients who visited the Infectious Disease Clinic at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The risk for cardiovascular events was determined using the Rama-EGAT risk score. Patients were categorized into two groups by score: high risk group with a Rama-EGAT score ≥ 6 and low risk group with a Rama-EGAT score <6. One hundred nine patients were included in the study. The mean age of participants was 47.3 years old, 73 (67%) were male. Mean duration of HIV infection among participants was 8.5 years and the mean CD_4 cell count was 485 cells/mm³. Nearly all the patients had received antiretroviral therapy. The mean body weight and body mass index (BMI) were 61.2 kg and 22.5 kg/m², respectively. Of the 109 participants, 12 (11%) had a high risk for cardiovascular events. On multivariate analysis, older age [odds ratio (OR) per 5 years increase = 8.6; p=0.005], diabetes mellitus (OR = 63.1; p=0.020) and lower HDL (OR per 5 mg/dl decrease = 4.3, p=0.020) were factors significantly associated with high EGAT risk score. Early screening for diabetes mellitus and HDL levels, as well as appropriate glycemic control and regular exercise are crucial for preventing cardiovascular events among HIV-infected patients receiving antiretroviral therapy in Thailand.

Keywords: HIV, risk, cardiovascular events, Rama-EGAT Score, Thailand

INTRODUCTION

Currently, many HIV-infected patients in Thailand are receiving antiretroviral therapy (ART), which decreases AIDS-related mortality and opportunistic infections and improves quality of life (Manosuthi *et al*, 2006). HIV-infected patients are now living longer (Manosuthi *et al*, 2006; Sungkanuparph *et al*, 2008). As this population grows older, cardiovascular disease has become more important. A Swiss HIV Cohort study found the incidence of cardiovascular disease increased with increasing age (Hasse *et al*, 2011). Factors contributing to cardiovascular risk include host factor, disease (virus) factors and treatment (ART) factors (Barbaro and Klatt, 2002; Das, 2010; Triant *et al*, 2007). HIV infection is associated with

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greater carotid intima media thickening and causes atherosclerosis (Grunfeld *et al*, 2009). HIV has been reported to infect smooth muscle cells and increase monocyte chemo-attraction which subsequently develop into foam cells, possibly resulting in increased cardiovascular risk (Malvestutto and Aberg, 2010). Host factor includes traditional risk factors such as aging, hypertension, smoking, dyslipidemia and diabetes mellitus. Treatment factors, such as anti-retroviral therapy (ART) may affect lipid metabolism and cause insulin resistance (Currier *et al*, 2008). Some studies have demonstrated ART, especially protease inhibitors (PIs), may increase the risk of acute myocardial infarction (Lang *et al*, 2010; Worm *et al*, 2010). The SMART study showed discontinuing ART or using it intermittently was associated with greater mortality, greater progression to AIDS and a greater risk of other major events, especially cardiovascular diseases [Strategies for Management of Antiretroviral Therapy (SMART) Study Group, 2006; Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups, 2008]. Therefore, evaluation of cardiovascular risk, myocardial infarction, is an important part of caring for HIV-infected patients.

In Thailand, the use of ART has increased over the past decade (Chasombat *et al*, 2006). Currently, more than 200,000 HIV-infected Thais are receiving ART (UNAIDS, 2010). ART has significantly reduced mortality and morbidity among HIV-infected patients in Thailand (Manosuthi *et al*, 2006; Jongwutiwes *et al*, 2007; Sungkanuparph *et al*, 2008). However, the risk of cardiovascular events among HIV-infected Thai patients has never been reported.

Scores can be used to predict the risk of coronary artery disease over 10 years; the Framingham heart score and Rama-EGAT score are examples. Recent studies have demonstrated that Rama-EGAT score is more appropriate for predicting coronary artery disease risk in the Thai population because the Framingham risk score may overestimate the risk in Thais (Sritara *et al*, 2003; Asia Pacific Cohort Studies Collboration *et al*, 2007; Sritara *et al*, 2007). This study evaluated the risk for cardiovascular events among HIV-infected patients attending Ramathibodi Hospital using the Rama-EGAT risk score and determining predictive factors that contributed to the high Rama-EGAT score.

MATERIALS AND METHODS

Study design and data collection

A cross sectional study was conducted among HIV-infected patients attending the Infectious Disease Clinic, Ramathibodi Hospital, Mahidol Univesity, Bangkok, Thailand between August and December 2011. This study was approved by the Ramathibodi Hospital Ethics Committee. All participants were aged >35 years. Patients were excluded if they had a history of a cardiovascular event, such as myocardial infarction or stroke. Lipodystrophy syndrome was diagnosed clinically. The patient risk for a cardiovascular event was calculated using the Rama-EGAT risks core (Table 1) (Sritara *et al*, 2003). The 10-year cardiovascular risk based on the Rama-EGAT score is shown in Table 2. Patients were classified into two groups based on their Rama-EGAT risk score.

The Rama-EGAT risk score came from the EGAT study (Sritara *et al*, 2003), which followed 3,499 Thais employed by the Electricity Generating Authority of Thailand (EGAT) from 1985 to 1997. Cardiovascular event risk for 10 years is given as a score and includes age, blood pressure

Table 1
Rama-EGAT Risk Score.

Variable	Score
Age	
< 35	-2
35-39	-1
40-44	0
45-49	1
50-54	2
55-59	3
60-64	4
65-69	5
70-74	6
≥75	7
Blood pressure	
SBP<120, DBP <80	0
SBP 120-129, DBP 80-84	0
SBP 130-139, DBP 85-89	1
SBP 140-159, DBP 90-99	1
SBP≥160, DBP ≥100	2
Waist circumference >90 cm	
No	0
Yes	1
Cholesterol	
<160	-2
160-199	0
200-279	0
≥280	2
HDL	
<35	2
35-49	0
50-59	-1
>60	-5
Diabetes mellitus	
No	0
Yes	1
Current smoker	
No	0
Yes	1
Alcohol drinker	
No	0
Yes	1

Table 2
Rama-EGAT Risk Score and 10-year
cardiovascular risk.

Total Rama-EGAT Score	10-year cardiovascular risk
≤-1	2%
0	3%
1	3%
2	4%
3	5%
4	7%
5	8%
6	10%
7	13%
8	16%
9	20%
10	25%
11	31%
12	37%
13	45%
≥14	≥53%

Rama-EGAT risk score is ≥ 6 (defined as a 10-year cardiovascular risk ≥ 10%) and a low Rama-EGAT risk score is < 6. The 10% 10-year risk is used as the cut-off point by the National Cholesterol Education Program (NCEP) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

The primary objective of this study was to evaluate the risk for cardiovascular events among HIV-infected patients using the Rama-EGAT score. The secondary objective was to determine the predicting factors that contributed to the high Rama-EGAT scores.

Statistical analysis

Mean (± standard deviation, SD), median (interquartile range, IQR) and frequency (%) were used to describe patient characteristic where appropriate. The Student's *t*-test and Fisher exact test were used to compare two means

and/or history of hypertension/antihypertensive drug use, total cholesterol level, HDL level, current smoking status, history of alcohol use, waist circumference and history of diabetic mellitus. A high

Table 3
Baseline characteristics of HIV-infected patients in high and low risk groups.

| Characteristics | All (n=109) | Rama-EGAT score | | p-value |
		High risk group (n=12)	Low risk group (n=97)	
Age in years, mean ±SD	47.3 ± 9.7	61.5 ± 9.2	45.6 ± 8.3	<0.001
Gender, number (%)				0.330
Male	73 (67)	10 (83)	63 (65)	
Female	36 (33)	2 (17)	34 (35)	
Current smoking, number (%)	29 (27)	4 (33)	25 (26)	0.730
Alcoholic drinking, number (%)	16 (15)	1 (8)	15 (16)	>0.99
Body weight in kg, mean ±SD	61.2 ± 10.6	65.5 ± 8.3	60.7 ± 10.8	0.141
BMI in kg/m^2, mean ±SD	22.5 ± 3.0	23.8 ± 2.9	22.3 ± 3.0	0.115
Waist circumference in cm, mean ±SD	80.9 ± 8.4	87.2 ± 8.7	80.2 ± 8.1	0.006
Blood pressure in mmHg, mean ±SD				
Systolic	132 ± 18	144 ± 20	130 ± 17	0.008
Diastolic	77 ± 11	80 ± 12	77 ± 11	0.449
Hypertension, number (%)	20 (18)	8 (67)	12 (12)	<0.001
Diabetes mellitus, number (%)	14 (13)	7 (58)	7 (7)	<0.001
Lipid levels in mg/dl, mean ±SD				
Triglycerides	215 ± 164	259 ± 164	209 ± 164	0.328
Total cholesterol	225 ± 54	234 ± 36	224 ± 56	0.567
HDL cholesterol	47 ± 14	40 ± 9	48 ± 15	0.075
LDL cholesterol	137 ± 40	130 ± 31	138 ± 41	0.519
Non-HDL cholesterol	177 ± 42	189 ± 28	176 ± 38	0.067
Total cholesterol/HDL cholesterol ratio	4.7 ± 1.2	5.8 ± 1.1	4.6 ± 1.2	0.078
Use of lipid lowering drugs, number (%)	15 (14)	2 (17)	13 (13)	0.670
Duration of known HIV infection, years, mean ±SD	8.5 ± 4.2	8.8 ± 3.3	8.5 ± 4.3	0.852
CD$_4$ cell count in cells/mm^3, mean ±SD	485 ± 193	502 ± 144	483 ± 199	0.748
Lipodystrophy, number (%)	20 (18)	4 (33)	16 (17)	0.227
ART regimens				0.990
NNRTI-based	80 (73)	9 (75)	71 (73)	
PI-based	29 (27)	3 (25)	26 (27)	
Duration of ART in years, mean ±SD	8.1 ± 4.0	8.3 ± 3.3	8.0 ± 4.3	0.823

SD, standard deviation; ART, anti-retroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

of continuous variables. The chi-square test was performed to compare categorical variables. Multivariate analysis was used to determine factors predictive of a high risk Rama-EGAT score. Variables with p-value < 0.10 were included in the multivariate analysis model. All analyses were performed using the SPSS program version 16.0. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

One hundred nine HIV-infected patients were included in the study. The

Table 4
Multivariate analysis of predicting factors for high Rama-EGAT score.

Variables	Odds ratios	95% confidence intervals	p-values
Age (per 5 year increase)	8.6	1.9-38.3	0.005
Diabetes mellitus	63.1	1.9-206.9	0.020
Hypertension	3.2	0.3-38.3	0.356
Waist circumference (cm)	2.4	0.9-6.3	0.081
HDL (per 5 mg/dl decrease)	4.3	1.1-10.0	0.020

mean (±SD) age of subjects was 47.3 (±9.7) years; 67% were males. The mean (±SD) CD_4 cell count was 485 (±193) cells/mm^3. The mean (±SD) duration of known HIV infection was 8.5 (±4.2) years. Twenty patients (18%) had lipodystrophy. Twenty patients (18%) had hypertension and were using anti-hypertensive drugs. Fourteen patients (12.8%) had diabetes mellitus. The means (±SD) body weight and body mass index (BMI) were 61.2 (±10.6) kg and 22.5 (±3.0) kg/m^2, respectively (Table 3).

Rama-EGAT risk scores

The mean (±SD) Rama-EGAT score was 1.5 (±3.3). Twelve HIV-infected patients (11%) had a high Rama-EGAT score (high risk group) (Table 3). The mean age of the high risk group was significantly higher than the low risk group (61.5 *vs* 45.6 years, $p < 0.001$). The mean (±SD) waist circumference was significantly higher in the high risk group than in the low risk group (87.2 *vs* 80.2 cms, $p=0.006$). The mean systolic blood pressure was higher in the high risk group (144 *vs* 130 mmHg, $p=0.008$). The proportion of patients with hypertension was higher in the high risk group (67% *vs* 12%, $p<0.001$) and the proportion with diabetes mellitus was also higher in the high risk group (58% *vs* 7%, $p<0.001$). Gender, current smoking, alcohol use, duration of known HIV

infection, CD_4 cell count, lipodystrophy, diastolic blood pressure, and antiretroviral regimen were not significantly different between the high and low risk groups. The mean HDL cholesterol level was nonsignificantly lower in the high risk group (40 *vs* 48 mg/dl, $p=0.075$). On multivariate analysis, age [odds ratio (OR) per 5 years had an increase of 8.6, $p=0.005$], diabetes mellitus (OR 63.1, $p=0.020$) and HDL (OR per 5 mg/dl decrease = 4.3, $p=0.020$) were factors significantly associated with a high Rama-EGAT score (Table 4).

DISCUSSION

Eleven percent of HIV-infected Thai patients studied had a high 10-year cardiovascular risk based on their Rama-EGAT score. This emphasizes the importance of evaluating cardiovascular risk in HIV-infected patients. This cardiovascular risk is higher than the 2% found in a previous study conducted in Thailand during 1996-2009 (Edwards-Jackson *et al*, 2011). The higher risk in our study could be due to: the present study was conducted more recently than the previous study, the mean age of patients in the present study was older than the previous study (47.3 *vs* 41.0 years old) and the proportion of male patients in the present study was higher than the previous study (67% *vs* 55%).

On multivariate analysis, diabetes mellitus was a strong high risk predictor. Patients with diabetes mellitus had a 60 times higher chance of having high cardiovascular risk. For every 5 year increase in age the subjects had an 8.6 times higher chance of having high cardiovascular risk. A high HDL level was a protective factor. Every 5 mg/dl increase in HDL was associated with a 23% decrease of being in the high risk group. This information is useful for clinicians to help identify HIV-infected patients at high risk for cardiovascular disease and to modify the risk factors for these patients.

A limitation of the present study was the relatively small sample size, which may not allow the identification of some risk factors, such as family history of cardiovascular disease, duration of HIV infection, antiretroviral regimen, and lipodystrophy. However, the results of the present study provide important information for physicians caring for HIV-infected patients.

In conclusion, the Rama-EGAT score found 11% of HIV-infected patients studied had a high risk for cardiovascular events. The predicting factors for high caridovasvular risk among HIV-infected patients were older age, presence of diabetes mellitus, and low HDL level. Early screening for diabetes mellitus, glycemic control, regular exercise to increase HDL levels and modifying other traditional risk factors are cardiac risk modification strategies important for HIV-infected patients.

REFERENCES

Asia Pacific Cohort Studies Collaboration, Barzi F, Patel A, *et al*. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health* 2007; 61: 115-21.

Barbaro G, Klatt EC. HIV infection and the cardiovascular system. *AIDS Rev* 2002; 4: 93-103.

Chasombat S, Lertpiriyasuwat C, Thanprasertsuk S, Suebsaeng, Lo YR. The national access to antiretroviral program for PHA (NAPHA) in Thailand. *Southeast Asian J Trop Med Public Health* 2006; 37: 704-15.

Currier JS, Lundgren JD, Carr A, *et al*. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation* 2008; 118: e29-35.

Das S. Risk of cardiovascular disease in HIV-infected patients. *J Antimicrob Chemother* 2010; 65: 386-9.

Edwards-Jackson N, Kerr S, Tieu H, *et al*. Cardiovascular risk assessment in persons with HIV infection in the developing world: comparing three risk equations in a cohort of HIV-infected Thais. *HIV Med* 2011; 12: 510-15.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-97.

Grunfeld C, Delaney JA, Wanke C, *et al*. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS* 2009; 23: 1841-9.

Hasse B, Ledergerber B, Furrer H, *et al*. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011; 53: 1130-9.

Jongwutiwes U, Kiertiburanakul S, Sungkanuparph S. Impact of antiretroviral therapy on the relapse of cryptococcosis and survival of HIV-infected patients with cryptococcal infection. *Curr HIV Res* 2007; 5: 355-60.

Lang S, Mary-Krause M, Cotte L, *et al*. Impact

of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med* 2010; 170: 1228-38.

Malvestutto CD, Aberg JA. Coronary heart disease in people infected with HIV. *Cleve Clin J Med* 2010; 77: 547-56.

Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006; 43: 42-6.

Sritara P, Cheepudomwit S, Chapnan N, *et al*. Twelve-year changes in vascular risk factors and their associations with mortality in a cohort of 3499 Thais: the Electricity Generating Authority of Thailand Study. *Int J Epidemiol* 2003; 32: 461-8.

Sritara P, Patoomanunt P, Woodward M, *et al*. Associations between serum lipids and causes of mortality in a cohort of 3,499 urban Thais: The Electricity Generating Authority of Thailand (EGAT) study. *Angiology* 2007; 58: 757-63.

Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; 355: 2283-96.

Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; 22: F17-24.

Sungkanuparph S, Chakriyanuyok T, Butthum B. Antiretroviral therapy in AIDS patients with CMV disease: impact on the survival and long-term treatment outcome. *J Infect* 2008; 56: 40-3.

Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; 92: 2506-12.

Worm SW, Sabin C, Weber R, *et al*. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010; 201: 318-30.

UNAIDS. UNAIDS report on the global AIDS epidemic. Geneva: UNAIDS, 2010. [Cited 29 Feb 2012]. Available from: URL: http://www.unaids.org/globalreport/Global_report.htm