Incidence and Risk Factors of Cardiovascular Diseases Among HIV Patients in Thailand

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Background: The antiretroviral therapy (ART) greatly reduces the mortality and morbidity of patients with HIV, however, the adverse effects of ART are related to abnormal metabolic changes including hyperglycemia and hyperlipidemia. Taken together with the systemic inflammatory states from HIV infection, the HIV-infected patients are now at a greater risk to develop cardiovascular diseases (CVD) in their lifetime.

Objective: To determine the incidence of CVD in HIV-infected patients in Thailand and their risk factors.

Materials and Methods: All HIV-infected patients aged 18 years or older that presented at either King Chulalongkorn Memorial Hospital or at The HIV Netherlands and Australia Thailand research (HIV-NAT) in 2010 were included. The incidence of CVD during 5-year follow-up and the possible risk factors were studied.

Results: One thousand eight hundred thirteen HIV-infected patients were included in the present study. The incidence of cardiovascular disease was 3.75 cases per 1,000 person-year. Major cardiovascular risk factors in HIV-infected patients included diabetes mellitus (adjusted odds ratio [adj OR] 4.3, 95% confidence interval [CI] 1.7 to 10.9), dyslipidemia (adj OR 4.1, 95% CI 1.7 to 9.8), previous cerebrovascular diseases (adj OR 34.7, 95% CI 5.1 to 233.5), and a family history of cardiovascular disease (adj OR 6.9, 95% CI 2.5 to 18.5).

Conclusion: Incidence of CVD in Thai HIV-infected patients was similar to other developed countries. Most of cardiovascular risk factors in non-HIV-infected patients are also common in HIV-infected patients.

Keywords: HIV, Cardiovascular disease, Risk factors

Cardiovascular diseases (CVD) are major health problems of the global population and the Thai people. Over the past 20 years, the death rate from CVD in Thai population has increased by more than 20 times[1]. The conventional risk factors of CVD in the HIV-infected patients include not only dyslipidemia, diabetes mellitus, and hypertension etc.[2], but also, the HIV infection has increased the risk of the CVD through inflammation of the blood vessels and the immune system disorders, or even the antiretroviral drugs causing side effects of several metabolic derangement including dyslipidemia, insulin resistance, abnormalities of glucose, and changes in fat distribution[3].

Although HIV infection has been associated with CVD, this problem has been often neglected. Typically, the doctors have simply focused on controlling the viral level, the rise of immune (CD4), and the opportunities infections. Furthermore, evidences on the incidence and risk factors for development of CVD in HIV-infected patients are somewhat limited, especially in Thai patients.

In the present study, the incidence of CVD assessment was examined in the HIV-infected patients as well as the risk factors causing the CVD leading to more effective prevention of the diseases and the improved quality of life for HIV-infected patients.

Materials and Methods
Design and population
The present report was a retrospective cohort

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study. The sample included all HIV-infected patients, aged 18 years and older that presented at either King Chulalongkorn Memorial Hospital or The HIV Netherlands and Australia Thailand research (HIV-NAT) between January and December 2010. The incidence of CVD between 2010 and 2015 and the possible risk factors were studied.

Variables

In the present study, certain variables with a prior examination were chosen to determine if they were associated with the CVD development including age, sex, body mass index (BMI), smoking, drinking, hypertension defined or taking antihypertensive drugs, diabetes mellitus or taking antidiabetics drugs, dyslipidemia or taking lipid-lowering drugs, and the family history of CVD.

In addition, the variables associated directly with HIV patients including the levels of HIV viral load, level of immune (CD4 level), taking/not taking antiretroviral drugs, type of antiretroviral drugs, the duration of taking antiretroviral drugs, lipodystrophy, and opportunistic infections or co-infections were examined.

Data collection

Patient medical records were gathered from the internal databases of the King Chulalongkorn Hospital and the HIV-NAT, using International Classification of Diseases Tenth Revision (ICD-10) for collecting and researching data. Data were collected from both the databases in computer and database in the outpatient and inpatient records.

Study endpoint

In the present study, data collected were to determine the incidence rate of CVD, the extent of the incidence rate of CVD in the participating patients between 2010 and 2015, and the risk factors associated with the CVD.

Data analysis

In the present study, data analyses were performed using the SPSS version 18 and the descriptive statistics implemented included frequency, percentage, mean, and standard deviation. To describe the demographic characteristics and the incidence of CVD, the Chi-square test was adopted. To determine the relationship between risk factors and CVD, the logistic regression model was adopted. The results were presented in odd ratio 95% confidence interval (CI) with a p-value of 0.05 or smaller as being considered statistically significant.

The present study was approved by the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Definitions and ICD-10

In the present study:

1. A patient infected with HIV refers to a patient with HIV laboratory test and the lower level of CD4, the identified ICD-10 is B20 to B24, Z21.

2. Cardiovascular diseases refer to coronary artery disease and ischemic stroke.

2.1 Coronary artery diseases include:

• Acute coronary syndrome refers to a patient who was diagnosed by an increase in the cardiac enzyme with any of the following symptoms.

    - Symptoms of ischemia: angina.

    - Electrocardiogram (ECG) has been specifically characterized with cardiovascular ischemia: ST-T depression, ST-T elevation, inverted T wave, new left bundle branch block, or pathologic Q wave.

    - Radiological evidence (imaging) displays the new loss of viable myocardium or the regional wall motion abnormality by echocardiography.

    - Blood clots in blood vessels by coronary artery angiography (CAG, intracoronary thrombus by angiography or autopsy).

• Stable angina or chronic stable angina refers to a group of symptoms caused by chronic ischemic heart disease, the symptoms of angina are intermittent and not severe, lasting three to five minutes each time, rest or taking angioplasty drugs for more than two months.

• Patients with history of coronary artery extension (percutaneous coronary intervention) or coronary artery surgery (coronary bypass graft surgery).

• Patient records reported ICD-10 as I210 to 214, I200, I251, Z951, and Z955.

2.2 Ischemic stroke refers to a group of neurological symptoms caused by disorders of the circulation of blood to the brain, causing brain ischemia, brain cell damages and loss of function of the body parts of the respective brain that controls abruptly, leading to disability or death within 24 hours. The symptoms last more than 24 hours, confirmed by the computer tomography (CT) or ICD-10 I63 to I64.

3. Hypertension refers to the systolic blood pressure greater than 140 mmHg or the diastolic blood pressure over 90 mmHg[4] or in duration of treating high blood pressure.

4. Diabetes mellitus refers to fasting blood sugar for eight hours, greater than 126 mg/dl or blood

Table 1. Characteristics of the patients at baseline

	Total (n = 1,813)	Non-CVD (n = 1,779)	CVD (n = 34)	p-value
	n (%)	n (%)	n (%)	
Age (years), Median (range)	44 (38 to 50.2)	44 (38 to 50)	53.3 (46 to 68.7)	<0.001
Male	1147 (63.3)	1122 (63.1)	25 (73.5)	0.21
Weight (Kg), Median (range)	59.4 (52.5 to 67)	59.3 (52.5 to 67)	64 (52.7 to 72)	0.06
Body mass index (Kg/m^2), Median (range)	21.9 (19.9 to 24.1)	21.9 (19.9 to 24.1)	23.3 (21.5 to 24.4)	0.02
Current/Ex-smoked	628 (34.6)	614 (34.5)	14 (41.2)	0.19
Current/previous alcohol consumption	567 (31.3)	559 (31.4)	8 (23.5)	0.41
Family of cardiovascular disease	65 (3.6)	55 (3.1)	10 (29.4)	<0.001
Diabetes mellius	108 (6.0)	93 (5.2)	15 (44.1)	<0.001
Hypertension	218 (12)	210 (11.8)	8 (23.5)	0.001
Dyslipidemia	335 (18.5)	314 (17.7)	21 (61.8)	<0.001
Previous ischemic heart disease	13 (0.8)	10 (0.6)	3 (8.8)	<0.001
Previous ischemic stroke	6 (0.4)	3 (0.2)	3 (8.8)	<0.001
CD4 level (cell/dl), Median (range)	473 (313 to 651)	472 (312 to 650)	555 (424 to 775)	0.06
Viral load <50 copies/ml	1253 (69.1)	1222 (68.7)	31 (91.2)	0.01
Duration of diagnosed (years), Median (range)	11 (7 to 15)	11.5 (7 to 15)	10 (7 to 15)	0.58
Protease inhibitor exposed	687 (48.1)	674 (48.3)	13 (41.9)	0.48
Duration of protease inhibitor exposed (years), Median (range)	5 (2 to 7)	5 (2 to 7)	4 (2 to 5)	0.18
Duration of non-nucleoside reverse transcriptase inhibitor exposed years), Median (range)	5 (1 to 8)	5 (1 to 8)	8 (3 to 9)	0.06
Duration of nucleoside reverse transcriptase inhibitor exposed (years), Median (range)	7 (3 to 10)	7 (3 to 10)	9 (4 to 13)	0.13
Opportunistic infection	297 (18.6)	291 (18.6)	6 (17.7)	0.88
Hepatits B viral infection	123 (6.8)	123 (6.9)	0 (0.0)	0.02
Hepatits C viral infection	62 (3.4)	62 (3.5)	0 (0.0)	0.24
Cryptospirosis	2 (0.1)	2 (0.1)	0 (0.0)	0.84
Cryptococcosis	13 (0.7)	13 (0.7)	0 (0.0)	0.59
Tuberculosis	85 (4.7)	80 (4.5)	5 (14.7)	0.01
Toxoplasmosis	5 (0.3)	5 (0.3)	0 (0.0)	0.74
Mycobacterium Avium complex infection	4 (0.2)	4 (0.2)	0 (0.0)	0.77
Cytomegalovirus infection	11 (0.6)	11 (0.6)	0 (0.0)	0.62
Pneumocystis pneumonia	31 (1.7)	30 (1.7)	1 (2.9)	0.67
Syphillis infection	19 (1.1)	19 (1.1)	0 (0.0)	0.52
Lipodystrophy	603 (33.3)	586 (32.9)	17 (50.0)	0.04

glucose two hours after meal greater than 200 mg/dl[5], or in the duration of treating diabetes.

5. Dyslipidemia refers to total cholesterol greater than 200 mg/dl, LDL greater than 130 mg/dl[6], or in the duration of treating high cholesterol.

6. Lipodystrophy refers to the abnormal or degenerative conditions of the body's adipose tissue, lipoatrophy at the front of the limbs and buttocks while lipohypertrophy at other parts of the body including abdomen, back, neck, or breast, etc[7].

7. The family history of coronary heart disease refers to a family member was diagnosed with the coronary heart disease[8].

Results

Baseline data

The participants included 1,813 patients who had been followed-up at the King Chulalongkorn Hospital and the HIV-NAT between 2010 and December 2015. Of them, 34 patients were diagnosed with CVD, and 33 patients were lost follow up, representing 1.8% of the entire population.

In the present study, the participants' median age was 44 years. The patients had underlying disease as a risk factor for CVD, including family history of CVD, diabetes mellitus, hypertension, dyslipidemia, history of coronary heart diseases, and ischemic stroke

Table 2. Prevalence divided by type of cardiovascular events

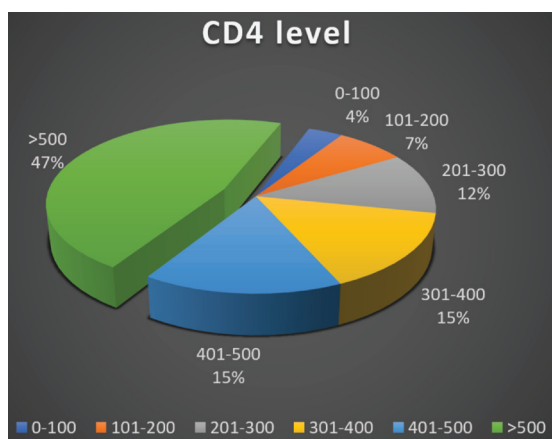| Type of cardiovascular events	Number of cases
Ischemic stroke	11
Acute coronary artery syndrome (ST segment elevation myocardial infarction)	5
Acute coronary artery syndrome (non-ST segment elevation myocardial infarction)	8
Unknown type of coronary heart diseases	10

Figure 1. Distribution of CD4 count in HIV-infected patients.

as shown in Table 1.

In the present study, the median CD4 of the patients was 473 cell/ml, and 47% of the patients had CD4 level greater than 500 cell/ml as shown in Figure 1. In addition, 69.1% of the patients could suppress the viral load to less than 50 copies /ml.

Incidence of diseases

After the follow-up of the HIV-infected patients between 2010 and 2015, there were 34 patients with CVD. The incidence proportion represented 3.75 cases per 1,000 person-years. As factored by age, the patients in the age range of 45 years or less, the incidence proportion represented 0.44 cases per 1,000 person-years, the patients in the age range of 45 to 55 years, the incidence proportion represented 3.3 cases per 1,000 person-years, and the patients in the age range of 55 years or higher, the incidence proportion represented 14 cases per 1,000 person-years.

The analysis was performed over the group of the patients with CVD. It found ischemic stroke in 11 cases representing 32% of the patients with CVD, coronary heart diseases in 23 cases representing 68% of overall patients, acute coronary syndrome with abnormal ECG of ST segment elevation in five cases, acute myocardial infarction without abnormal ECG

ST segment elevation in eight cases, and unknown-type of coronary heart diseases in ten cases as shown in Table 2.

Risk factors of cardiovascular diseases

The univariate analysis of data from the HIV-infected patients demonstrated that risk factors caused the development of CVD included age range of 45 years or higher (adjusted odds ratio [adj OR] 5.67, 95% CI 2.34 to 13.77), history of heart disease and stroke (adj OR 15, 95% CI 3.93 to 57.19), had history of ischemic stroke (adj OR 50.23, 95% CI 9.75 to 258.75), family history of CVD (adj OR 11.98, 95% CI 5.46 to 26.26), diabetes (adj OR 12.45, 95% CI 6.13 to 25.3, dyslipidemia (adj OR 6.41, 95% CI 3.17 to 12.94), hypertension (adj OR 4.38, 95% CI 1.71 to 11.24), and lipodystrophy (adj OR 2.65, 95% CI 1.2 to 5.82).

Afterward, a selection criterion for variables into the multivariate was to choose the variables p value smaller than 0.1 from univariate. This could eliminate the confounding factors to some degrees. Then, using the stepwise backward likelihood ratio to choose the factors in the final model, obtaining four risk factors of the CVD including history of ischemic stroke (adj OR 34.69, 95% CI 5.15 to 233.45), family history of heart disease and stroke (adj OR 6.89, 95% CI 2.57 to 18.48), diabetes mellitus (adj OR 4.27, 95% CI 1.67 to 10.9), and dyslipidemia (adj OR 4.09, 95% CI 1.7 to 9.83) as shown in Table 3 and 4.

Discussion

To the incidence of cardiovascular disease in HIV-infected patients, the change in cutting off age has affected the incidence of the diseases substantially. In analyzing the different range in ages, the incidence of the CVD has increased dramatically. Thus, the longer the life expectancy of the HIV-infected patient is, there an increasing chance of developing CVD. In addition, the incidence of CVD substantially varies from study to study. The incidence rate in CVD was in range of 3.5 to 11.18 cases per 1,000 person-years[9-12]. The cause of the difference of incidence among studies may be the group of patients age range rather than the

Table 3. Risk factors of cardiovascular diseases in HIV-infected patients

	Univariate			Multivariate		
	OR	95% CI	p-value	Adj OR	95% CI	p-value
Age >45 years	5.67	2.34 to 13.77	<0.001			
Male	1.63	0.75 to 3.51	0.21			
Body mass index ≥23 kg/m²	2.41	1.2 to 4.84	0.01			
Smoking/smoked	1.69	0.78 to 3.69	0.19			
Alcoholing/alcoholed	0.74	0.32 to 1.72	0.49			
Previous ischemic heart disease	15.00	3.93 to 57.19	<0.001			
Previous ischemic stroke	50.23	9.75 to 258.75	<0.001	34.69	5.15 to 233.45	<0.001
Family history of cardiovascular disease	11.98	5.46 to 26.26	<0.001	6.89	2.57 to 18.48	<0.001
Diabetes mellitus	12.45	6.13 to 25.3	<0.001	4.27	1.67 to 10.9	0.002
Dyslipidemia	6.41	3.17 to 12.94	<0.001	4.09	1.7 to 9.83	0.002
Hypertension	4.38	1.71 to 11.24	0.002			
Protease inhibitor exposed	0.77	0.38 to 1.59	0.49			
Opportunistic infection	0.94	0.38 to 2.29	0.89			
Lipodystrophy	2.65	1.2 to 5.82	0.02			
CD4 cell <350 cell/dl	0.21	0.11 to 0.90	0.03			
Viral load ≥50 copeis/ml	0.21	0.06 to 0.69	0.01			

OR=odds ratio; Adj OR=adjusted OR; CI=confidence interval

Table 4. Combine of risk factors of cardiovascular diseaes

Risk factors	Adj OR	95% CI
Diabetes mellitus plus dyslipidemia	17.2	7.8 to 38.3
Family history of CVD plus diabetes mellitus plus dyslipidemia	22.2	4.1 to 118.5

Adj OR=adjusted OR; CI=confidence interval

patients examined in the study of the lower incidence rate of CVD[13].

The multivariate analysis indicated that the risk factors caused the CVD in HIV-infected patients are the traditional risk factors such as hypertension, and diabetes mellitus, which are the same as non-HIV infected patient. In addition, HIV-infected patients with more risk factors are more likely to develop CVD, and this tendency is not different from non-HIV patients.

However, the results did not demonstrate that the non-traditional risk factors in the HIV-infected patients such as the level of CD4 and HIV viral load level have associated with CVD. It is anticipated that first, caring the HIV-infected patients from both healthcare services, King Chulalongkorn Memorial hospital and the HIVNAT, have been of adequate quality where it could control the level of CD4 and HIV viral load level. Second, 69% of HIV-infected patients had HIV viral load lower than 50 copies/ml, and only 11% of HIV-infected patients had the level of CD4 below 200 and high HIV viral load. Third, the follow-up

period in the present study had not been long enough and the size of the population had not been sufficient to represent the results of the non-traditional risk factors, resulting in the increased incidence of CVD. Fourth, it's possible that CVD in patients with HIV in Thailand have not associated with risk factors specific to these patients.

Limitation

The present study may have several limitations. First, the sources of the information came from only two institution and may not represent the entire population of the country because most population are well controlled non-traditional risk factor. Second, the incidence of the disease is relatively low, and the follow-up period is only five years, thus, not long enough to represent the result of all risk factors in the HIV-infected patients. Third, the patients infected with HIV in the present study are well-looked after and differ from the overall population of the country, by the infectious disease and CVD specialists. Fourth, this is a retrospective study where some data are incomplete,

and mistakes can occur in the recording.

With the restrictions mentioned above, the present study is a good starting point for the doctors who take care of HIV-infected patients to become aware and pay more attention caring for the HIV-infected with cardiovascular disease. In addition, thorough data collection about the patients is expected to be useful in caring for the patients.

Conclusion

The incidence of CVD in the HIV-infected patients in Thailand is similar to other developed countries and rising with increased age of the patients.

The results demonstrated that risk factors for CVD in the HIV-infected patients are preventable and controllable, for examples, the control of blood sugar levels and the level of lipid. In addition, when taking care of patients with a family history of CVD, the caregivers should pay more attention to control the risk factors for CVD. Importantly, in the HIV-infected patients with a history of previous ischemic stroke, the caregivers should focus on diseases prevention for other areas of CVD.

The results of the present study imply that HIV-infected patients who have well controlled CD4 and HIV viral load level have the same traditional risk factors to develop CVD as non-HIV infected patients.

What is already known on this topic?

In HIV patient, conventional risk factors (dyslipidemia, diabetes mellitus, and hypertension) and HIV-related risk factors (CD4 level and viral load level) are associated with the incidence of cardiovascular diseases among HIV patients.

What this study adds?

The incidence of cardiovascular diseases among of HIV-infected in Thailand, and among well-controlled CD4 and HIV viral load patients as well as the risk factors to developed cardiovascular disease are the same as non-HIV infected patients.

Conflicts of interest

The authors declare no conflict of interest.

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