Factors Associated with New Onset Type 2 Diabetes Mellitus in HIV-Infected Patients at HIV Clinic, Ratchaburi Hospital

ปัจจัยที่มีความสัมพันธ์ต่อการเกิดเบาหวานชนิดที่สองรายใหม่ ในผู้ติดเชื้อเอชไอวี ในคลินิกเอชไอวี โรงพยาบาลราชบุรี

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Abstract

Objective: This is to evaluate risk factors associated with new onset type 2 diabetes mellitus and incidence of new onset type 2 diabetes mellitus in HIV clinic, including diabetic control and diabetic complication in this population.

Methods: A single center, retrospective case control study was conducted in HIV clinic Ratchaburi Hospital. A total of 75 HIV-infected patients with new-onset type 2 diabetes mellitus were selected as cases and compared with 75 consecutively patients without diabetes mellitus as controls. Data were collected from hospital electronic database from January 2009 to August 2019.

Results: During the study period, there were 1,023 patients in HIV-clinic and 91 HIV-infected patients were newly diagnosed type 2 diabetes mellitus. Incidence rate was 6.6 per 1,000 person-years of follow-up time. Median age was 50 years, 53.3% were male. From multivariate model, age (adjusted OR 1.11, 95% CI 1.04–1.18, p = .002), BMI ≥ 25 kg/m^2 (adjusted OR 4.10, 95% CI 1.44–11.63, p = .008), statin exposure (adjusted OR 3.42, 95% CI 1.29–9.10, p = .014), initial FBG 100–125 mg/dL (adjusted OR 5.23, 95% CI 1.81–15.06, p = .002), and initial CD4 cell count > 250/mm^3 (adjusted OR 3.73, 95% CI 1.16–12.03, p = .027) were significantly associated with new-onset type 2 diabetes mellitus. In addition, emtricitabine (FTC) exposure was associated with reduced risk of new onset type 2 diabetes mellitus (adjusted OR 0.023, 95% CI 0.08–0.65, p = .006).

Conclusions: There are multiple factors associated with new onset type 2 diabetes mellitus in HIV-infected patients including age, obesity, initial impaired fasting glucose, initial CD4 > 250 /mm^3, and statin exposure. Interestingly, emtricitabine exposure is a protective factor in this population.

Keywords: HIV, diabetes mellitus, antiretroviral therapy, risk factor.
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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่มีความสัมพันธ์ต่อการเกิดเบาหวานชนิดที่สองรายใหม่ ที่พบในผู้ติดเชื้อเอชไอวี ในโรงพยาบาลราชบุรี

วิธีการ: ผู้ป่วยติดเชื้อเอชไอวี แบ่งเป็น กลุ่มผู้ป่วยที่เกิดเบาหวานชนิดที่สองรายใหม่ 75 ราย และกลุ่มที่ไม่เกิดเบาหวาน 75 ราย โดยเก็บข้อมูลจากเวชระเบียนของผู้ป่วยที่เข้ารับการรักษาในคลินิกเอชไอวี โรงพยาบาลราชบุรี ตั้งแต่เดือนมกราคม พ.ศ. 2552 ถึง สิงหาคม พ.ศ. 2562

ผลการศึกษา: มีผู้ป่วยที่เกิดเบาหวานชนิดที่สองรายใหม่ 91 ราย คิดเป็นอัตราการเกิด 6.6 ต่อ 1,000 คน/ปี จากการวิเคราะห์แบบพหุตัวแปร พบว่าอายุที่เพิ่มขึ้น มีโอกาสเกิดเบาหวานมากขึ้น 1.11 เท่า, ภาวะอ้วนมีโอกาสเกิดเบาหวานมากกว่า 4.10 เท่า, ผู้ที่ได้รับยา statin มีโอกาสเกิดเบาหวานมากกว่า 3.42 เท่า, ระดับน้ำตาลในเลือดเริ่มต้นขณะวินิจฉัยติดเชื้อเอชไอวี 100–125 มิลลิกรัม/เดซิลิตร มีโอกาสเกิดเบาหวานมากกว่า 5.23 เท่า และผู้ป่วยที่มีระดับ CD4 เริ่มต้นมากกว่า 250 ต่อลูกบาศก์มิลลิเมตร มีโอกาสเกิดเบาหวานมากกว่า 3.73 เท่า นอกจากนี้ การได้รับยา emtricitabine มีโอกาสเกิดเบาหวานรายใหม่น้อยลง

สรุป: การเกิดเบาหวานชนิดที่สองรายใหม่ในผู้ป่วยเอชไอวี เกิดจากหลายปัจจัยร่วมกัน การศึกษานี้พบความสัมพันธ์ระหว่างการเกิดเบาหวานรายใหม่กับอายุ ภาวะอ้วน ระดับน้ำตาลในเลือดสูง และระดับระดับเม็ดเลือดขาวชนิด CD4 เริ่มต้นก่อนรักษาโรคเอชไอวีมากกว่า 250 ต่อลูกบาศก์มิลลิเมตร ส่วนการได้รับยา emtricitabine ในการรักษาโรคเอชไอวีนั้นเป็นปัจจัยป้องกันการเกิดเบาหวานรายใหม่ในผู้ป่วยกลุ่มนี้

คำสำคัญ: เอชไอวี เบาหวาน ยาต้านไวรัส ปัจจัยเสี่ยง
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Introduction

Human immunodeficiency virus (HIV) infection had remained a major global public health concern. In 2015, Thailand, there were 276,434 HIV-infected patients who received antiretroviral therapy. Since October 2014, according to “Treatment as Prevention” concept, all HIV-infected Thai patients with any CD4 cell count could receive antiretroviral therapy (ART) to decrease the risk of AIDs and non-AIDs related events and also risk of HIV transmission[1].

Life expectancy of HIV-infected patients has increased after treatment with antiretroviral agents. Therefore, their comorbidities and non-communicable diseases (NCDs) were increased[2,3]. Diabetes mellitus (DM), one of important NCDs, is a major cause of morbidity and mortality among HIV-infected patients, especially cardiovascular diseases[2,4].

From previous studies, people living with HIV infection have higher incidence of DM[5]. Two studies in Thailand have reported high incidence rates of DM of 5.0 to 7.6 per 1,000 person-years[6,7]. The new cases of DM in HIV-infected patients were associated with several factors; for instance; age, body mass index (BMI), and some antiretroviral agents (stavudine, zidovudine, didanosine, and protease inhibitors)[3,6,7]. Nevertheless, didanosine, and stavudine were no longer use for the treatment of HIV infection in Thailand[8,9].

This study aims to evaluate factors associated with new onset type 2 diabetes mellitus (T2DM) in HIV-infected patients in Ratchaburi Hospital, one of the tertiary care centers in Thailand.

Objective

This is to evaluate factors associated with new onset T2DM in HIV-infected patients, incidence of new onset T2DM in HIV-infected patients, diabetic control, and diabetic complication in HIV clinic, Ratchaburi Hospital, Thailand.

Methods

We conducted the retrospective case-control study in HIV-infected patients who visited in HIV Clinic, Ratchaburi Hospital between January 2009 and August 2019. Case was defined as HIV-infected patients with new onset T2DM. The consecutive patients without T2DM who followed T2DM case were included as control.

HIV-infected patients who aged at least 18 years were eligible in this study. The patients were excluded if they had T2DM prior to diagnosis of HIV infection, type 1 DM, gestational diabetes, other type diabetes, and loss to follow-up more than 1 year.

Sample sizes

From Samad et al.[3] the year of HIV diagnosis was one of associated factor for new onset T2DM in HIV-infected patient with OR = 3.57, 80% power, and 0.05 type I error. When considering 10% drop-out rate, the sample size should be 75 cases in each group. The total population we had to collect in this study was 150.

Data collection

The patients' clinical and laboratory parameters were collected from the hospital electronic database (HOSxP). Baseline characteristics (age, gender, weight, and height), history of smoking and alcohol drinking, family history of DM, date of HIV infection and T2DM diagnosis, ART regimen, history of opportunistic infection, diabetic nephropathy and neuropathy, type of antidiabetic medication, CD4 cell count, fasting blood glucose (FBG), HbA1C, LDL, HDL, serum

triglyceride, GFR, and urine microalbumin were also collected and analyzed. Case and control were sorted by ascending order from hospital numbers.

The definitions in this article are defined as:

1. HIV infection was defined as having positive serum anti-HIV.

2. T2DM was defined as one of the followings.

2.1 HbA1C was more than 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

2.2 FBG was more than 126 mg/dL (fasting is defined as no caloric intake for at least 8 hours).

2.3 Two-hour plasma glucose was more than 200 mg/dL during an OGTT.

2.4 Random plasma glucose was more than 200 mg/dL in patient with classic symptoms of hyperglycemia or hyperglycemic crisis[10].

3. Hypertension (HT) was defined as systolic blood pressure (SBP) more than 140 mmHg or diastolic blood pressure (DBP) more than 90 mmHg on two or more clinic visits over a 6-month period and/or initiation of antihypertensive therapy.

4. Chronic kidney disease (CKD) was defined as two consecutive (more than 6 months apart) estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2,[11] using the CKD-EPI formula.

5. BMI was calculated as weight in kilograms divided by the square of the height in meters.

6. Hepatitis C was defined as having positive serum anti-HCV antibody.

7. Chronic hepatitis B virus infection was defined as having positive for hepatitis B surface antigen on study visits, more than 6 months apart.

Statistical analysis

Categorical variables were reported as frequencies and percentage. Mean ± standard deviation was used for normally distributed continuous variables and median with interquartile range (percentile 25 and 75) for non-normally distributed variables. Normality of distribution of variables was examined by Kolmogorov-Smirnov test. For demographic data, comparisons of categorical variables were performed using chi-square or Fisher's exact test and continuous variables were compared by using Student's t test or Mann-Whitney U test.

To determine factors associated with new onset type 2 diabetes mellitus, univariate analysis was performed and reported by odds ratio and 95% confidence intervals. Logistic regression was used to perform multivariate analysis. For all tests performed, a two-tailed p-value less than .05 was considered statistically significant. PASW Statistics 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis.

This study was reviewed and approved by the Institutional Review Boards of Ratchaburi Hospital, Thailand (COA-RBHEC 030/2023), approved date 17 Jul 2023.

Results

From January 2009 to August 2019, there were 1,023 HIV-infected patients had visits in HIV-clinic, Ratchaburi Hospital. Out of this, 91 patients were newly diagnosed T2DM. An incidence was 6.6 per 1,000 person-years of follow-up.

The baseline characteristics of the 150 patients were shown in Table 1 and 2.

Table 1. Baseline characteristics of 150 study participants with and without diabetes at the time of HIV infection diagnosis

Factors	Total N = 150 N (%)	DM n = 75 n (%)	Non DM n = 75 n (%)	p-value
Gender				
• Male	80 (53.3)	39 (26.0)	41 (27.3)	
• Female	70 (46.7)	36 (49.3)	34 (44.2)	.527
BMI (kg/m^2)				
• <18.5	13 (8.7)	0 (0)	13 (8.7)	< .001
• 18.5–24.9	97 (64.7)	47 (31.3)	50 (33.3)	
• ≥25	40 (26.7)	28 (18.7)	12 (8.0)	.034
Initial CD4 cell count (/mm^3)				
• <100	60 (40)	26 (17.3)	34 (22.7)	
• 100–250	45 (30)	19 (12.7)	26 (17.3)	.909
• >250	45 (30)	28 (18.7)	17 (11.3)	.057
Family history of DM	59 (39.3)	39 (26.0)	20 (13.3)	.006
Alcohol used	34 (22.7)	22 (14.7)	12 (8)	.036
Smoking	11 (7.3)	7 (4.7)	4 (2.7)	.309
Initial fasting blood glucose (mg/dL)				
• <100	102 (68.0)	35 (23.3)	67 (44.7)	
• 100–125	48 (32.0)	40 (26.7)	10 (5.3)	< .001

Abbreviation: BMI, body mass index; DM, diabetes mellitus; kg/m^2, kilograms/square meter; mg/dL, milligram/deciliter; mm^3, cubic millimeters

Of 150 patients, 53.3% were male and 26.7% had BMI ≥ 25 kg/m^2. Initial CD4 cell count < 100 /mm^3 were 40% and 30% had Initial CD4 cell count > 250 /mm^3, 39.3% had family history of diabetes, 22.7% had alcohol used, 7.3% had smoking, and 32% were impaired FBG.

At the time of analysis, participants had median age of 50 (IQR 45–56) years. Median BMI was 22.2 (IQR 19.9–25) kg/m^2. Median duration of diagnosis of HIV infection was 11 years (IQR 9–13) years. Median current CD4 cell count was 459 (IQR 345–625) /mm^3. All participants had HIV viral load < 20 copies/mL. From all of the ART-received patients, 99.3% had exposed to nucleoside reverse transcriptase inhibitors (NRTIs), 90.7% non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 17.3% protease inhibitors (PIs). Cardiovascular diseases in diabetes and non-diabetes group showed no significant difference.

Table 2. Baseline characteristics of 150 study participants with and without diabetes at the time of analysis

Factors	Total N = 150	DM n = 75	Non DM n = 75	p-value
Age, years (median [IQR])	50 (45–56)	54 (50–57)	46 (43–54)	< .001
BMI, kg/m^2 (median [IQR])	22.2 (19.9–25)	23 (21–27.3)	20.7 (19.03–23.43)	< .001
HIV viral load <20 copies/mL, n (%)	150 (100)	75 (100)	75 (100)	1.000
Duration of HIV infection diagnosis, years [median (IQR)]	11 (9–13)	12 (10–14)	11 (7–13)	.003
CD4 cell count, /mm^3 (median [IQR])	459 (345–625)	505 (389–732)	402 (338–538)	.002
ART regimen exposure, n (%)				
NRTIs				
Zidovudine (AZT)	58 (38.7)	36 (24.0)	22 (14.7)	.010
Didanosine (ddI)	5 (3.3)	3 (2.0)	2 (1.3)	.609
Stavudine (d4T)	99 (66.0)	52 (34.7)	47 (31.3)	.531
Tenofovir (TDF)	80 (53.3)	28 (18.7)	52 (34.7)	< .001
Emtricitabine (FTC)	53 (35.3)	18 (12.0)	35 (23.3)	.001
Lamivudine (3TC)	138 (92.0)	74 (49.3)	64 (42.7)	.019
Abacavir (ABC)	2 (1.3)	0 (0.0)	2 (1.3)	< .001
NNRTIs				
Efavirenz (EFV)	99 (66.0)	43 (28.7)	56 (37.3)	.014
Nevirapine (NVP)	61 (40.7)	32 (21.3)	29 (19.3)	.442

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high density lipoprotein; kg/m^2, kilograms/square meter; LDL, low density lipoprotein; mg/dL, milligram/deciliter; mL/min/1.73 m^3, milliliter/minute/1.73 cubic meter; mm^3, cubic millimeters; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

Table 2. Baseline characteristics of 150 study participants with and without diabetes at the time of analysis (Ext.)

Factors	Total N = 150	DM n = 75	Non DM n = 75	p-value
PIs				
Ritonavir (RTV)	26 (17.3)	14 (9.3)	14 (9.3)	.778
Lopinavir (LPV)	26 (17.3)	14 (9.3)	14 (9.3)	.778
Atazanavir (ATV)	1 (0.7)	0 (0.0)	0 (0.0)	1.000
Opportunistic infection & co-infection, n (%)				
Candidiasis	4 (2.7)	0 (0.0)	4 (2.7)	1.000
Cryptococcosis	3 (2.0)	3 (2.0)	0 (0.0)	1.000
Histoplasmosis	4 (2.7)	0 (0.0)	4 (2.7)	1.000
Tuberculosis	31 (20.7)	13 (8.7)	18 (12.0)	.401
Pneumocystis pneumonia	9 (6.0)	5 (3.3)	4 (2.7)	.350
Toxoplasmosis	2 (1.3)	1 (0.7)	1 (0.7)	.970
HBV infection	8 (5.3)	4 (2.7)	4 (2.7)	.938
HCV infection	6 (4.0)	4 (2.7)	2 (1.3)	.379
Hypertension, n (%)	43 (28.7)	31 (42.5)	12 (15.6)	< .001
Dyslipidemia, n (%)	84 (56.0)	57 (38.0)	27 (18.0)	<.001
Cardiovascular disease, n (%)	9 (6.0)	4 (2.7)	5 (3.3)	.731
Chronic kidney disease, n (%)	8 (5.3)	4 (2.7)	4 (2.7)	1.000
Statin exposure, n (%)	65 (43.3)	46 (30.7)	19 (12.7)	< .001
Fasting blood glucose, mg/dL (median [IQR])	112 (92–132)	132 (122–150)	95 (88–104)	< .001
eGFR, mL/min/1.73 m^2 (median [IQR])	92 (78–103)	90 (77–100)	97 (78–107)	.537
Serum LDL, mg/dL (median [IQR])	112.5 (95.2–134.6)	110 (87–136)	113 (97–131)	.231
Serum HDL, mg/dL (median [IQR])	50.5 (43–59.25)	51 (41–56)	51 (43–63)	.083
Serum triglyceride, mg/dL (median [IQR])	145 (113.8–211)	152 (121–212)	139 (92–200)	.025

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high density lipoprotein; kg/m^2, kilograms/square meter; LDL, low density lipoprotein; mg/dL, milligram/deciliter; mL/min/1.73 m^3, milliliter/minute/1.73 cubic meter; mm^3, cubic millimeters; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

In DM group, median FBG was 132 mg/dL (IQR 122–155) with median HbA1C 6.76% (IQR 6.43–7.79). Median current CD4 cell count was 505 (IQR 389–732) /mm^3 and median duration of DM diagnosis was 3 years (IQR 2–5) after diagnosis of HIV infection. In 75 cases of new onset type 2 diabetes mellitus patients, 9 patients (6.0%) had diabetic nephropathy and 5 (3.3%) had diabetic retinopathy.

Factor associated with new onset T2DM

According to baseline characteristics in Table 1 and 2, factors associated with new onset T2DM were older age, higher BMI, higher CD4 cell count, higher serum triglyceride, exposure to statin drugs, alcohol drinking, longer duration of HIV infection, and family history of diabetes.

In multivariate logistic regression models (Table 3.) factors associated with new onset T2DM were age, BMI ≥ 25 kg/m^2, statin exposure, initial impaired FBG (100–125 mg/dL) and initial CD4 cell count > 250 /mm^3. Emtricitabine (FTC) exposure was associated with reduced risk of new onset T2DM.

Table 3. Univariate and multivariate binary logistic regression model for factors associated with new onset type 2 diabetes mellitus in HIV infected patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	adjusted OR	95% CI	p value
Age	1.10	1.05–1.16	< .001	1.11	1.04–1.18	.002
BMI ≥ 25 kg/m^2	2.30	1.06–4.99	.034	4.10	1.44–11.63	.008
Initial FBG 101–125 mg/dL	7.27	3.24–15.31	< .001	5.23	1.81–15.06	.002
Duration of HIV infection	1.16	1.05–1.28	.003	1.064	0.92–1.23	.400
Initial CD4 cell count > 250 /mm^3	2.15	0.98–4.75	.057	3.73	1.16–12.03	.027
Emtricitabine (FTC) exposure	0.30	0.15–0.62	.001	0.023	0.08–0.65	.006
Statin exposure	4.05	2.04–8.04	< .001	3.42	1.29–9.10	.014

Abbreviations: BMI, body mass index; kg/m^2, kilograms/square meter; mg/dL, milligram/deciliter; mm^3, cubic millimeters

Discussion

In this retrospective case control study, from January 2009 to August 2019, incidence rate of new onset T2DM was 6.6 per 1,000 person-years of follow-up which was similar to the previous studies in Thailand[6,7].

Although the usual risk factors of DM were common in this populations (age, BMI, impaired fasting blood glucose), there were several factors associated with new onset T2DM.

Dyslipidemia is one of non-communicable disease (NCDs) in HIV-infected patients and statins are commonly used as lipid lowering agents. Sixty-five (43.3%) patients had statin exposure and 46 (30.7%) were in DM group. This finding emphasized that statin exposure increased risk of new onset DM (adjusted OR 3.42, 95% CI 1.29–9.10, p = .014), similar to the previous studies in general population and HIV-infected patients[12–14]. In contrast to the study by Spagnuolo et al.[15], statin was associated with a non-significant increase of the risk of DM among HIV-infected patients. The difference between results may be from difference of incidence of new onset T2DM. The association of statin and new onset T2DM might be from statin itself or from patients who were potential at risk of metabolic syndrome.

From several previous studies[16,17], the association of CD4 cell count and blood glucose was unclear. On the other hand, in our study, current CD4 cell count was higher in HIV-infected patients with DM (median 505/mm^3, IQR 389–732) than without DM group (p = .002) and initial CD4 level > 250/mm^3 was related with increasing the risk of new onset DM (adjusted OR = 3.73, 95% CI 1.16–12.03, p = .027). The design of this study makes it difficult to specify the reasons for the relationships between CD4 count and type 2 diabetes mellitus. This issue might be an interesting topic for further research.

According to WHO guidelines for the use of antiretroviral drugs that published in 2016[8], emtricitabine (FTC) is one of the drugs in NRTIs group in first-line ART regimens. TEEVIR is a fixed drug combination, which comprises of tenofovir, emtricitabine, and efavirenz that previously used in Thailand as a first-line therapy. Our study found that new onset type 2 diabetes mellitus was significantly reduced with the use of emtricitabine (FTC) (adjusted OR = 0.023, 95% CI 0.08–0.65, p = .006). The result was consistent with previous data[8,9,18]. The mechanism of this protective effect was unclear.

Protease inhibitors and some NRTIs (didanosine) that have well known associated with risk factor of DM are longer widely used in our populations. However, these agents are non-significant association in our study.

In our HIV clinic, 75 cases of new onset T2DM had median HbA1C 6.76% (IQR 6.43–7.79), however HbA1C may underestimate about glycemic control in people with HIV[19,20]. In DM group, 6.0% of patients had diabetic nephropathy and 3.3% had diabetic retinopathy but the majority of patients were not evaluated for these diabetic microvascular complications in our clinic.

Our study has strength that was the complete medical record in our electronic database had benefit for the data collection about patients' baseline characteristics (e.g., initial CD4 cell count and initial FBG).

There were some limitations in this literature. First, our study was a retrospective. Second, small sample size (75 patients in DM group) was a limitation for multivariate analysis, we had studied only 7 associated factors. Third, this was a single-center study, so our patients might not represent general population in Thailand. Fourth, patients with ART drug resistance and had detectable virus were not available. Finally, from current Thai HIV guideline 2021/2022, the first-line ART have changed to integrase-based regimen and our study did not have patients who received integrase inhibitors. Therefore, these agents are the limitation of our study.

Conclusions

In this retrospective case control study, there are multiple factors associated with development of new onset T2DM in HIV-infected patients including ages, BMI, initial impaired fasting glucose, and initial CD4 count > 250 / mm^3. Interesting that emtricitabine exposure is a protective factor for developing T2DM in this population. However, the appropriate screening and control of the risk factors of T2DM are always essential.

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