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# Incidence and clinical outcomes of diabetes mellitus in HIV-infected adults in Thailand: a retrospective cohort study

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## Abstract

**Background:** Since 2005, Thailand has scaled up one of the largest antiretroviral treatment (ART) programs in South East Asia. Although diabetes mellitus (DM) incidence is increasing in low and middle-income countries, its burden and contributing factors in the HIV infected population are not well known.

**Methods:** Using the Thai National AIDS Program data over a period of 8-years, we identified patients diagnosed with DM based on the following records: 1) fasting plasma glucose equal to or greater than 126 mg/dl following the 2013 American Diabetes Association criteria or 2) diagnosis codes E11-E14 of the 2010 WHO International Classification of Diseases, or 3) anti-diabetic drugs. Incidence was the number of new cases divided by that of person-years of follow-up (PYFU). Competing risks survival regression, treating death without DM as a competing event, was used to identify factors associated with DM. The risk of death in patients diagnosed with DM was estimated using Cox regression models.

**Results:** Data of 763,666 PYFU from 199,707 patients (54.2% male; median age 36.2 years at registration with the program) were available and 8383 cases were diagnosed with DM, resulting in an incidence rate of 11.0 per 1000 PYFU. New DM diagnosis was more likely in men (adjusted sub-distribution hazard ratio 1.2), older patients (compared to patients 18 to 34 years old: 1.8 for 35 to 44; 3.0 for 45 to 59; 3.8 for ≥60), and if ART was initiated (1.3). In 2014, 1313 (16.6%) of 7905 diabetic patients had DM complications (11.5% microvascular complications and 6.9% macrovascular complications). Patients diagnosed with DM were at higher risk of death compared to the others.

**Conclusions:** DM incidence was higher in this Thailand cohort of HIV infected adults than in the general population. Risk factors were similar to those in the general population, in addition to starting ART.

**Keywords:** HIV infection, Antiretroviral treatment, Diabetes mellitus, Incidence, Diabetic complications

## Background

The burden of diabetes prevalence is rising especially in low and middle-income countries [1]. In 2017, the International Diabetes Federation estimated that 425 million people worldwide, or 8.8% of adults 20–79 years, were affected by diabetes type 1 and type 2 (8.3% in Thailand) and that half (50.0%) of all people 20–79 years with diabetes are unaware of their disease [2].

Known risks factors of diabetes mellitus (DM) include older age, male sex, family history of DM, alcohol use, adiposity, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia [1]. Indeed, hyperlipidemia, insulin resistance and lipodystrophy are commonly observed in HIV-infected patients on antiretroviral treatment (ART) and several studies have suggested that HIV infection and/or antiretroviral drugs may increase the risk of DM [3–6]. The Thai national AIDS program database, which

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Paengsai *et al. BMC Public Health* (2018) 18:1079

Page 2 of 10

includes data on DM incidence, related mortality and prevalence of related complications, provided a unique opportunity to assess the importance of DM in a South-East Asian HIV infected adult population.

Since Fiscal Year (FY) 2005 (October 1, 2004 to September 30, 2005), Thailand has provided free health services, including ART and laboratory monitoring to HIV-infected patients through the Thailand National AIDS Program (NAP), under the National Health Security Office (NHSO). At each visit, or at the end of each month for hospitalizations, data from HIV-infected patients covered by these schemes are entered into the NAP database. We estimated the incidence of DM diagnosis, investigated associated risk factors and clinical outcomes using the data from adults registered with the NAP under the Universal Coverage Scheme (UCS), which covers about three-quarters of the Thai population [7].

## Methods

This study was a retrospective cohort study and an analysis of secondary data of the NHSO. A total of 199,707 HIV infected adults (≥18 years old) with no history of DM registered between FY2007 to FY2013 and follow up until September 30,2014 (end of FY2014) for care with the NAP and received care under UCS in 1035 hospitals throughout Thailand.

We extracted the following patient characteristics from the NHSO database: sex, date of birth, weight, height, fasting plasma glucose (FPG), triglycerides, hepatitis C virus infection, absolute CD4 cell count (including nadir) and date of ART initiation [7]. A patient not showing up for at least 7 months after last visit was considered lost to follow up (LTFU). The number of PYFU was calculated from date of NAP registration (baseline) to censoring date, i.e. 7 months after last visit date, date of death (within 7 months after last visit), date of first DM diagnosis, or September 30, 2014, which ever occurred first.

For this study, DM was considered diagnosed at the first date of at least two of the following records: 1) FPG ≥126 mg/dl following the 2013 American Diabetes Association criteria [8] or 2) confirmed diagnosis codes E11-E14 (which excludes type-1 diabetes mellitus) of the 2010 WHO International Classification of Diseases (ICD-10) [9], or 3) confirmed receipt of anti-diabetic drugs [8]. Hypertriglyceridemia was defined by triglycerides ≥200 mg/dl [4]. DM incidence rates were estimated by the number of new diagnoses divided by the total number of PYFU. The 95% confidence intervals (CIs) were calculated using the quadratic approximation to the Poisson log likelihood [10].

We fitted competing risks survival regression models (Fine-Gray) [11–13], treating death without DM as a competing event (except in case of death after DM

diagnosis), to assess the association of new DM diagnosis occurrence with sex, baseline age (categories: 18–34, 35–44, 45–59 or ≥ 60 years [14]) and Body Mass Index (BMI) (≥25 or < 25 kg/m$^2$); and baseline and time-updated triglycerides (< 200 or ≥ 200 mg/dl), baseline absolute CD4 cell count (< 200 or ≥ 200 cells/mm$^3$), and time-updated ART initiation (yes/no) [4, 14]. All models were adjusted for the existence of at least a previous record of FPG (dichotomous, time-updated variable) and time-updated absolute CD4 < 200 cells/mm$^3$. We imputed missing data by multiple imputation with chained equations (MICE procedure, Stata Corp, College Station, Texas, USA) based on logistic regression for binary variables if they were ≤ 20% missing data (time-updated absolute CD4 values if there was a missing data more than 9 months after the previous known value) [15]. We conducted multivariable analyses using a backward selection approach starting with factors significantly associated with time to DM in the univariable analysis ($p \leq 0.20$), excluding variables with more than 20% missing values (baseline BMI, baseline and time-updated triglycerides, baseline absolute CD4 data) and sensitivity analyses [16] were conducted including each of these variables. The cumulative incidence function (CIF) at time t was defined as the probability of a new diagnosis from baseline using Gray's sub-distribution hazard technique [17, 18].

A Poisson distribution was assumed to calculate the 95% confidence intervals (CIs) of prevalence. We used the 2010 WHO ICD-10 [9] codes for microvascular diabetic complications: ophthalmic complications code E11-E14 with additional code ".3", diabetic retinopathy codes H36.0*, renal complications codes E11-E14 with additional external cause code ".2" or code N18, neurological complications codes E11-E14 with additional code ".4" (diabetic amyotrophy, autonomic neuropathy, mononeuropathy, polyneuropathy and autonomic), and macrovascular diabetic complications: ischaemic heart diseases (ICH) codes I00-I25, cerebrovascular disease (CVD) codes I60-I69, peripheral circulatory complication codes E11-E14 with additional code".5" (diabetic gangrene, peripheral angiopathy or diabetic ulcer), and amputation (The 2010 WHO ICD-9-CM procedure code 84.11, 84.12, 84.14, 84.15 and 84.17 [19]).

We analyzed the interaction between time-updated ART initiation and time-updated DM for the risk of death by year using a constant proportional hazard in univariable and multivariable Cox's survival regression analyses ($p \leq 0.05$). We tested the proportional hazards assumption of each model based on Schoenfeld residuals [20] and considered time-updated DM diagnosis as a time-varying variable [21, 22].

Analyses were performed using Stata software, version 13.1 (Stata Corp, College Station, Texas, USA). Patient

identifiers were encrypted by NHSO prior data management and analysis. The analysis plan was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University, Thailand on March 18, 2014 (114/2014, Research ID: COM-2557-02140).

## Results

### Study population and follow up

All 199,707 HIV-infected adults (54.2% male) with no history of DM, registered with the NAP through the UCS from FY2007 to FY2013, were included in the analysis. Baseline median age was 36.2 years (IQR 30.5 to 42.6), BMI 20.2 kg/m$^2$ (IQR 18.2 to 22.4), absolute CD4 cell count 120 cells/mm3 (IQR 33 to 324) and nadir CD4 cell count 119 cells/mm$^3$ (IQR 33 to 323); and 1408 of 199,707 (0.7%) had a history of hepatitis C infection. Of the 11,763 patients with available records, 2511 (21.4%) had triglycerides ≥200 mg/dl.

Data from a total of 763,666 PYFU were available from FY2007 to FY2014 (median follow-up time was 3.8 years [IQR 1.6 to 6.1]); 15,114 patients (7.6%) were lost-to-follow up, 8383 (4.2%) were diagnosed

with DM and 44,062 (22.1%) died (Fig. 1). 116,394 patients (58.3%) had at least one FPG measure. ART was initiated in 152,664 patients (76.4%) and the median duration from registration to ART initiation was 1.3 months (IQR 0.7 to 4.9). Of note, 24,539 (55.7%) of the patients who died had not initiated ART.

### Patients diagnosed with DM

Over the study period, 8383 patients were diagnosed with DM leading to an estimated cumulative incidence of DM of 11.0 per 1000 PYFU (CI 10.7 to 11.2). The incidence rate of DM was 10.8 per 1000 PYFU during the first year, reached 13.0 per 1000 PYFU during the third year and tended to decrease thereafter. The incidence was 12.5 per 1000 PYFU in men (CI 12.2 to 12.9) and 9.5 per 1000 PYFU in women (CI 9.1 to 9.8) ($p < 0.001$). Male sex, age above 35 years, baseline BMI ≥25 kg/m$^2$, triglycerides ≥200 mg/dl, absolute CD4 cell count < 200 cells/mm$^3$ and hepatitis C infection were associated with a higher incidence rate of DM (Table 1). The estimated cumulative incidence of DM was 3.8% (CI 3.7 to 3.9) at 4 years follow-up. It was about 3.4% (CI 3.3 to 3.5)
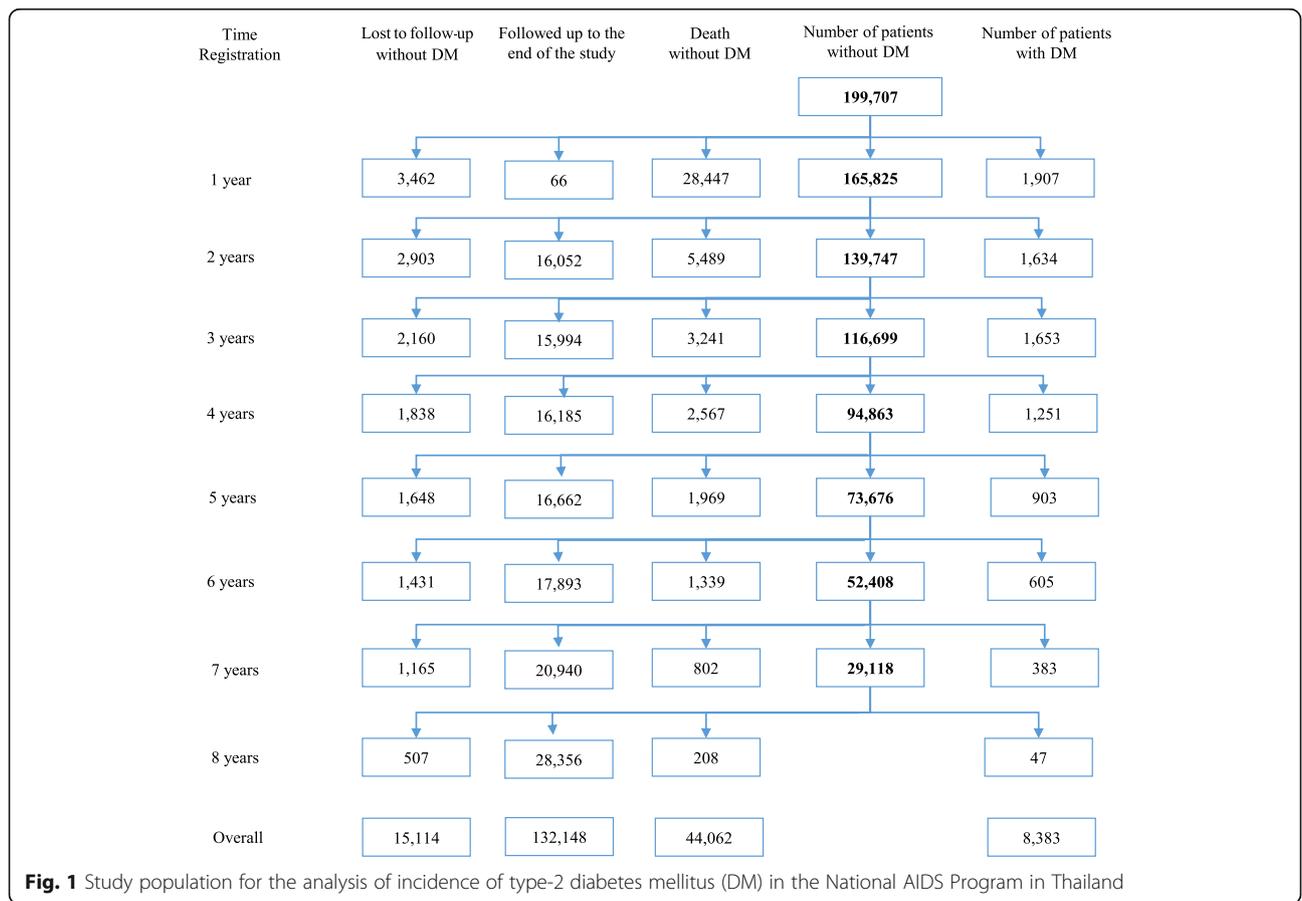


**Fig. 1** Study population for the analysis of incidence of type-2 diabetes mellitus (DM) in the National AIDS Program in Thailand

Paengsai *et al. BMC Public Health* (2018) 18:1079

Page 4 of 10

**Table 1** Incidence of diabetes mellitus according to patient baseline characteristics

| Baseline characteristics | Category | Total | Number of patients with diabetes mellitus | PYFU | Incidence per 1000 PYFU | 95% CI | P value* |
|---|---|---|---|---|---|---|---|
| Total | | 199,707 | 8383 | 763,666 | 10.98 | 10.74–11.21 | |
| Fiscal year of registration | 2007 | 41,537 | 2852 | 248,385 | 11.48 | 11.07–11.91 | < 0.001 |
| | 2008 | 34,100 | 1729 | 165,818 | 10.43 | 9.95–10.93 | |
| | 2009 | 28,872 | 1343 | 119,249 | 11.26 | 10.68–11.88 | |
| | 2010 | 26,026 | 916 | 89,424 | 10.24 | 9.60–10.93 | |
| | 2011 | 24,270 | 699 | 66,880 | 10.45 | 9.70–11.26 | |
| | 2012 | 22,861 | 443 | 46,229 | 9.58 | 8.73–10.52 | |
| | 2013 | 22,041 | 401 | 27,682 | 14.49 | 13.14–15.98 | |
| Sex | Female | 91,407 | 3604 | 381,552 | 9.45 | 9.14–9.76 | < 0.001 |
| | Male | 108,300 | 4779 | 382,114 | 12.51 | 12.16–12.87 | |
| Age (years) | 18–34 | 87,948 | 2076 | 354,196 | 5.86 | 5.61–6.12 | < 0.001 |
| | 35–44 | 74,610 | 3521 | 288,739 | 12.19 | 11.80–12.60 | |
| | 45–59 | 33,154 | 2428 | 110,286 | 22.02 | 21.16–22.91 | |
| | ≥60 | 3995 | 358 | 10,444 | 34.28 | 30.90–38.02 | |
| History of hepatitis C infection | No | 198,299 | 8327 | 760,649 | 10.95 | 10.71–11.18 | < 0.001 |
| | Yes | 1408 | 56 | 3017 | 18.56 | 14.28–24.12 | |
| Variables with more than 20% missing data | | | | | | | |
| Body mass index (kg/m$^2$) | < 25 | 59,249 | 2154 | 218,284 | 9.87 | 9.46–10.29 | < 0.001 |
| | ≥25 | 7296 | 509 | 29,241 | 17.41 | 15.96–18.99 | |
| Triglycerides (mg/dl) | < 200 | 9252 | 289 | 30,352 | 9.52 | 8.48–10.69 | 0.0021 |
| | ≥200 | 2511 | 111 | 8280 | 13.41 | 11.13–16.15 | |
| Absolute CD4 cell count (cells/mm$^3$) | ≥200 | 36,877 | 1283 | 144,795 | 8.86 | 8.39–9.36 | < 0.001 |
| | < 200 | 58,570 | 2114 | 183,322 | 11.53 | 11.05–12.03 | |
| Nadir CD4 cell count (cells/mm$^3$) | ≥200 | 36,877 | 1279 | 144,522 | 8.85 | 8.38–9.35 | < 0.001 |
| | < 200 | 58,671 | 2118 | 183,721 | 11.53 | 11.05–12.03 | |

Abbreviations: *CI* confidence interval, *PYFU* Person-years of follow-up
*Chi-square test

in women and 4.1% (CI 4.0 to 4.3) in men; 2.0% (CI 1.9 to 2.1) in patients aged 18–34 years, 4.2% (CI 4.0 to 4.3) in patients aged 35–44 years, 7.0% (CI 6.7 to 7.3) in patients aged 45–59 years and 9.4% (CI 8.5 to 10.5) in patients aged ≥60 years (Fig. 2).

Table 2 provides the results of the univariable and multivariable analyses using competing risks survival models. In the univariable analyses, DM diagnosis was associated with male sex, older age at baseline, higher BMI at baseline, hypertriglyceridemia at baseline and time-updated, and time-updated ART initiation (all $p \leq 0.05$). In the multivariable analysis, DM diagnosis was associated with male sex, age above 35 years at baseline, and time-updated ART initiation. The sensitivity analyses restricted to cases with available baseline BMI and hypertriglyceridemia data showed similar associations with the factors identified in the main analyses (Additional file 1: Table S1).

## Prevalence of diabetes mellitus and diabetes-related complications

Of 8383 DM patients, the median follow-up time since DM diagnosis until end of study was 2.7 years (IQR 1.2 to 4.3). In the last year of the study (FY2014), of 157,980 alive patients on follow-up, 7905 patients (5.0%, CI 4.9 to 5.1) had DM. It was higher in men and increased with age. Of 7905, 1313 (16.6%, CI 15.7 to 17.5) patients had DM-related complications. The overall prevalence of microvascular complications was 11.5% (CI 10.8 to 12.3); renal (nephropathy) 7.8% (CI 7.2 to 8.4), ophthalmic 3.1% (CI 2.7 to 3.5) (diabetic retinopathy 0.6% [CI 0.5 to 0.8]), and neurological (neuropathy) 2.1% (CI 1.8 to 2.4). The overall prevalence of macrovascular complications was 6.9% (CI 6.3 to 7.5); ischemic heart diseases 3.1% (CI 2.7 to 3.5), cerebrovascular disease 2.7% (CI 2.3 to 3.1) and peripheral circulatory 1.6% (CI 1.3 to 1.9) (amputation 0.3% [0.2 to 0.5]) (see Table 3).
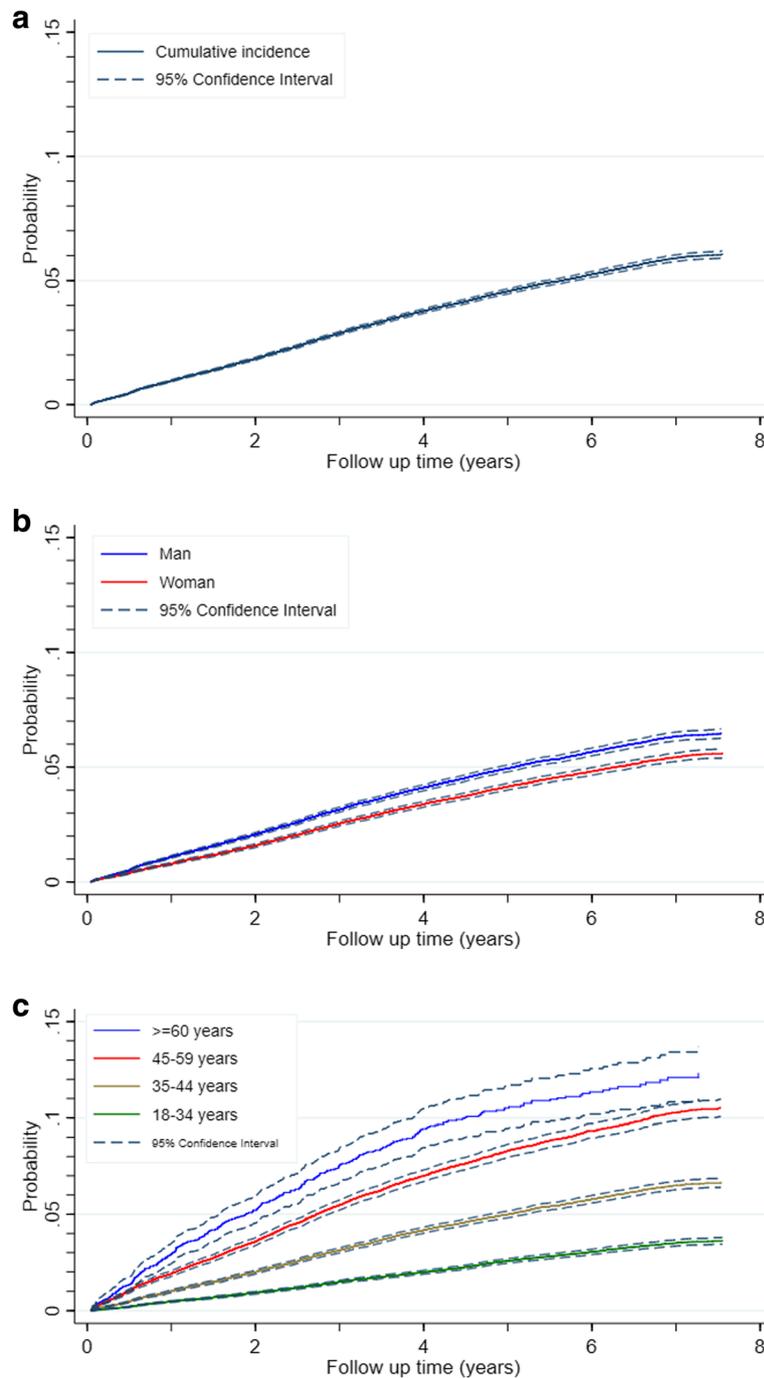
Paengsai *et al. BMC Public Health* (2018) 18:1079

Page 5 of 10



**Fig. 2** The estimate cumulative incidence function of diabetes mellitus in HIV-infected adults (**a**) overall (**b**) by sex and (**c**) by age at baseline. Legend text: (**a**) Cumulative incidence, 95% Confidence Interval (**b**) Man, Woman (**c**) > = 60 year, 45–59 year, 35–44 years, 18–34 year, 95% Confidence Interval

## Diabetes mellitus and mortality

During the study period, from a total of 199,707 patients, 46,252 died, including those who died after a diagnosis of DM. During the first year of follow-up, patients not diagnosed with DM had a higher risk of death than those with DM diagnosis, adjusting for sex, age, time-updated absolute CD4 cell count and time-updated ART initiation, with a strong interaction between time-updated DM and ART initiation (aHR 9.3, CI 6.3 to 13.7 in patients not receiving ART; aHR 2.6, CI 1.7 to 4.0 in patients receiving ART). In the following 3 years, the risk of death was similar in those with and without

Paengsai et al. BMC Public Health (2018) 18:1079

Page 6 of 10

**Table 2** Univariable and multivariable competing risk regression analyses of potential risk factors for diabetes mellitus (treating death without diabetes mellitus as a competing event)

| Variables | Category | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|---|
| | | SHR | [95% CI] | P value | aSHR | [95% CI] | P value |
| Sex | Female | 1 | Reference | | 1 | Reference | |
| | Male | 1.22 | 1.17–1.27 | < 0.001 | 1.13 | 1.08–1.18 | < 0.001 |
| Age (years) at baseline | 18–34 | 1 | Reference | | 1 | Reference | |
| | 35–44 | 1.88 | 1.78–1.99 | < 0.001 | 1.83 | 1.73–1.93 | < 0.001 |
| | 45–59 | 3.17 | 2.99–3.37 | < 0.001 | 3.1 | 2.92–3.29 | < 0.001 |
| | ≥60 | 4.41 | 3.93–4.94 | < 0.001 | 4.32 | 3.85–4.84 | < 0.001 |
| History of hepatitis C infection at baseline | No | 1 | Reference | | 1 | Reference | |
| | Yes | 1.24 | 0.95–1.62 | 0.106 | 1.09 | 0.84–1.43 | 0.515 |
| Time-updated antiretroviral treatment initiation | No | 1 | Reference | | 1 | Reference | |
| | Yes | 1.26 | 1.19–1.35 | < 0.001 | 1.26 | 1.18–1.34 | < 0.001 |
| Baseline body mass index (kg/m$^2$) (n = 66,529) | < 25 | 1 | Reference | | | | |
| | ≥25 | 1.97 | 1.78–2.17 | < 0.001 | | | |
| Baseline triglycerides (mg/dl) (n = 11,762) | < 200 | 1 | Reference | | | | |
| | ≥200 | 1.41 | 1.14–1.76 | 0.002 | | | |
| Baseline absolute CD4 cell count (cells/mm$^3$) (n = 95,432) | ≥200 | 1 | Reference | | | | |
| | < 200 | 1.04 | 0.96–1.12 | 0.33 | | | |
| Nadir CD4 cell count (cells/mm$^3$) (n = 95,476) | ≥200 | 1 | Reference | | | | |
| | < 200 | 0.89 | 0.83–0.96 | 0.002 | | | |

Abbreviations: *CI* confidence interval, *n* number of patients with available data, *SHR* sub-distribution hazard ratio, *aSHR* adjusted sub-distribution hazard ratio
Note: impute time-updated CD4 (18.0% of values); Univariable and multivariable analysis were adjusting for previous fasting plasma glucose measurement and time-updated absolute CD4 < 200 cells/mm$^3$

DM diagnosis (aHR 1.0, CI 1.0 to 1.1) but tended to increase thereafter in patients with DM (5th to 8th year: aHR 1.2, CI 1.0 to 1.5, $p$ = 0.05).

## Discussion

The incidence of new DM diagnosis during the follow up of 199,707 of HIV infected adults over 8 years in Thailand (763,666 PYFU) was 11.0 per 1000 PYFU with slight variations over time. The study population included 45.8% females and was relatively young (median 36.2 years), with a lean baseline body shape (median 20.2 kg/m$^2$) and a low absolute CD4 cell count (median 120 cells/mm$^3$). In multivariable analyses, risk factors associated with DM diagnosis were male sex and older age, which are known risk factors in the general population. In addition, initiation of antiretroviral treatment was associated with DM, as previous reported [14, 23–25].

Our overall DM incidence estimate was similar to or slightly lower than that reported in several studies conducted in population with similar characteristics (sex, age, CD4, ART): 11.35 per 1000 PYFU in a study of 6816 HIV-infected patients registered with the South Carolina Medicaid system [3] in the USA (43% women, median age 39.0 years, and 80.4% on ART); 14.1 per 1000 PYFU (95% CI, 11.6 to 17.0) in the French Aproco-Pilote cohort [6] (78.5% men, median age 37.0 years, median CD4 cell count 280 cells/mm$^3$, all on ART, men 14.6 per 1000 PYFU versus women 12.6 per 1000 PYFU); 13.1 per 1000 PYFU in the National Taiwan University Hospital study [26] (86.0% men, median age 34.0 years, median CD4 cell count 92 cells/mm$^3$, all patients on ART). The incidence rate of DM and the risk factors for DM in our study were similar to 13.7 per 1000 PYFU, the pooled incidence rate estimated in a meta-analysis [27].

Male sex and older age, which are known factors of DM [1] may account for the differences in estimated incidence reported by previous studies of HIV infected patients, for instance 5.0 per 1000 PYFU in a younger population composed of 76% women in Thailand [28], or 26.0 per 1000 PYFU in older HIV-infected men (median 46 years) participating in the US Multicenter AIDS Cohort Study [29]. ART initiation was identified as a risk factor of DM in our study, similarly to that reported in the Data Collection on Adverse events of Anti-HIV Drugs study (relative risk of 1.1 per year of exposure) [5]. It is possible that, even after adjustment for age and treating death as a competing event, improved survival on ART is a confounder for this

Paengsai et al. BMC Public Health (2018) 18:1079

Page 7 of 10

**Table 3** Prevalence of diabetes related complications among HIV-infected adults with diabetes during last year of follow-up (Fiscal Year 2014)

| Type of complications | Category | Sub category | Number of patients with complications | Total | P-value[a] | Annual prevalence (%) | 95% CI |
|---|---|---|---|---|---|---|---|
| MICROVASCULAR OR MACROVASCULAR | | | 1313 | 7905 | | 16.61 | 15.72–17.53 |
| | Sex | | | | 0.144 | | |
| | | Female | 596 | 3444 | | 17.31 | 15.94–18.75 |
| | | Male | 717 | 4461 | | 16.07 | 14.92–17.29 |
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 81 | 770 | | 10.52 | 8.35–13.07 |
| | | 35–44 | 321 | 2901 | | 11.07 | 9.89–12.34 |
| | | 45–59 | 658 | 3543 | | 18.57 | 17.18–20.05 |
| | | ≥60 | 253 | 691 | | 36.61 | 32.24–41.41 |
| MICROVASCULAR | | | 911 | 7905 | | 11.52 | 10.79–12.30 |
| Ophthalmic | | | 246 | 7905 | | 3.11 | 2.74–3.53 |
| | Sex | | | | 0.122 | | |
| | | Female | 119 | 3444 | | 3.46 | 2.86–4.13 |
| | | Male | 127 | 4461 | | 2.84 | 2.37–3.39 |
| | Age in years | | | | 0.004 | | |
| | | 18–34 | 25 | 770 | | 3.25 | 2.10–4.79 |
| | | 35–44 | 71 | 2901 | | 2.45 | 1.91–3.09 |
| | | 45–59 | 115 | 3543 | | 3.25 | 2.68–3.90 |
| | | ≥60 | 35 | 691 | | 5.07 | 3.53–7.04 |
| *Diabetic retinopathy* | | | 49 | 7905 | | 0.62 | 0.46–0.82 |
| | Sex | | | | 0.443 | | |
| | | Female | 24 | 3444 | | 0.7 | 0.45–1.04 |
| | | Male | 25 | 4461 | | 0.56 | 0.36–0.83 |
| | Age in years | | | | 0.072 | | |
| | | 18–34 | 2 | 770 | | 0.26 | 0.03–0.94 |
| | | 35–44 | 13 | 2901 | | 0.45 | 0.24–0.77 |
| | | 45–59 | 26 | 3543 | | 0.73 | 0.48–1.08 |
| | | ≥60 | 8 | 691 | | 1.16 | 0.50–2.28 |
| Renal | | | 615 | 7905 | | 7.78 | 7.18–8.42 |
| | Sex | | | | 0.174 | | |
| | | Female | 284 | 3444 | | 8.25 | 7.31–9.26 |
| | | Male | 331 | 4461 | | 7.42 | 6.64–8.26 |
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 24 | 770 | | 3.12 | 2.00–4.64 |
| | | 35–44 | 149 | 2901 | | 5.14 | 4.34–6.03 |
| | | 45–59 | 305 | 3543 | | 8.61 | 7.67–9.63 |
| | | ≥60 | 137 | 691 | | 19.83 | 16.65–23.44 |
| Neurological | | | 163 | 7905 | | 2.06 | 1.76–2.40 |
| | Sex | | | | < 0.001 | | |
| | | Female | 101 | 3444 | | 2.93 | 2.39–356 |
| | | Male | 62 | 4461 | | 1.39 | 1.07–1.78 |

Paengsai *et al. BMC Public Health* (2018) 18:1079

Page 8 of 10

**Table 3** Prevalence of diabetes related complications among HIV-infected adults with diabetes during last year of follow-up (Fiscal Year 2014) *(Continued)*

| Type of complications | Category | Sub category | Number of patients with complications | Total | P-value[a] | Annual prevalence (%) | 95% CI |
|---|---|---|---|---|---|---|---|
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 4 | 770 | | 0.52 | 0.14–1.33 |
| | | 35–44 | 32 | 2901 | | 1.1 | 0.75–1.56 |
| | | 45–59 | 86 | 3543 | | 2.43 | 1.94–3.00 |
| | | ≥60 | 41 | 691 | | 5.93 | 4.26–8.05 |
| MACROVASCULAR | | | 545 | 7905 | | 6.89 | 6.33–7.50 |
| Ischaemic heart diseases | | | 243 | 7905 | | 3.07 | 2.70–3.49 |
| | Sex | | | | 0.681 | | |
| | | Female | 109 | 3444 | | 3.16 | 2.60–3.82 |
| | | Male | 134 | 4461 | | 3 | 2.52–3.56 |
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 14 | 770 | | 1.82 | 0.99–3.05 |
| | | 35–44 | 45 | 2901 | | 1.55 | 1.13–2.08 |
| | | 45–59 | 116 | 3543 | | 3.27 | 2.71–3.93 |
| | | ≥60 | 68 | 691 | | 9.84 | 7.64–12.48 |
| Cerebrovascular disease | | | 212 | 7905 | | 2.68 | 2.33–3.07 |
| | Sex | | | | 0.002 | | |
| | | Female | 70 | 3444 | | 2.03 | 1.58–2.57 |
| | | Male | 142 | 4461 | | 3.18 | 2.68–3.75 |
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 10 | 770 | | 1.3 | 0.62–2.39 |
| | | 35–44 | 45 | 2901 | | 1.55 | 1.13–2.08 |
| | | 45–59 | 109 | 3543 | | 3.08 | 2.53–3.71 |
| | | ≥60 | 48 | 691 | | 6.95 | 5.12–9.21 |
| Peripheral circulatory | | | 123 | 7905 | | 1.56 | 1.29–1.86 |
| | Sex | | | | 0.174 | | |
| | | Female | 61 | 3444 | | 1.77 | 1.35–2.28 |
| | | Male | 62 | 4461 | | 1.39 | 1.07–1.78 |
| | Age in years | | | | < 0.001 | | |
| | | 18–34 | 10 | 770 | | 1.3 | 0.62–2.39 |
| | | 35–44 | 24 | 2901 | | 0.83 | 0.53–1.23 |
| | | 45–59 | 70 | 3543 | | 1.98 | 1.54–2.50 |
| | | ≥60 | 19 | 691 | | 2.75 | 1.66–4.29 |
| *Amputation* | | | 25 | 7905 | | 0.32 | 0.20–0.47 |
| | Sex | | | | 0.719 | | |
| | | Female | 10 | 3444 | | 0.29 | 0.14–0.53 |
| | | Male | 15 | 4461 | | 0.34 | 0.19–0.55 |
| | Age in years | | | | 0.214 | | |
| | | 18–34 | 4 | 770 | | 0.52 | 0.14–1.33 |
| | | 35–44 | 5 | 2901 | | 0.17 | 0.06–0.40 |
| | | 45–59 | 12 | 3543 | | 0.34 | 0.18–0.59 |
| | | ≥60 | 4 | 691 | | 0.58 | 0.16–1.48 |

[a]Fisher's exact test

Paengsai et al. BMC Public Health (2018) 18:1079

Page 9 of 10

association, i.e. patients who survive longer are more likely to develop DM. Also, the risk may vary according to specific antiretroviral drugs [28].

The incidence of DM in HIV-infected adults aged 35 to 59 years in our study was 14.9 per 1000 PYFU, higher than in the Thai general adult population (7.8 to 11.4 per 1000 PYFU) [23, 24], suggesting a contribution of HIV infection or ART in the risk of DM.

At the end of study period, the overall estimated prevalence of DM was lower than in the Thai general population (5.0% versus 8.9%) [30]. This may have resulted from several differences between our population and the general population: lower median age, lower BMI, or regular medical follow-up and FPG assessments in our cohort. Also, DM-related complications seemed less prevalent [7, 30, 31], likely for similar reasons. Generally, microvascular complications develop 5 years after diagnosis [32, 33]. However, with a median follow-up of 2.7 years in our study the prevalence of microvascular complications was 11.5% and the most common was diabetes nephropathy. HIV infection or/and antiretroviral drugs may also have affected the kidneys or accelerated microvascular complications.

Our study showed that the risk of death in patients diagnosed DM tended to be higher after 4 years of follow-up, a finding similar to that reported by a previous study in Thailand [34]. Although causes of death were not available, we hypothesized that the increasing risk of death with DM may have been related to cardiovascular and renal complications as well as HIV infection itself.

A limitation of our study is that the NAP database has been primarily designed for overall monitoring of the program with missing data not systematically tracked as in clinical studies. Importantly, the NAP database represents a unique source of information that likely reflects the actual DM burden in the HIV infected population. Also, the lack of systematic FPG assessments in some patients may have led to an underestimation of DM incidence. This issue is now addressed by a specific program [35] which promotes systematic DM screening in at risk patients [14].

## Conclusion
HIV infected adults in Thailand had a slightly higher incidence of DM than that estimated in general population with similar common risk factors. Antiretroviral treatment may contribute to the risk of DM but to a lesser extent than the common risk factors of DM.

## Additional file

**Additional file 1: Table S1.** Sensitivity analysis for variable with missing data using multivariable competing risk regression analyses of potential risk factors for diabetes mellitus only complete cases (treating death without diabetes mellitus as a competing event). (XLSX 12 kb)

## Abbreviations
aHR: Adjusted hazard ratio; ART: Antiretroviral treatment; aSHR: Adjusted sub-distribution hazard ratio; BMI: Body mass index; CI: Confidence interval; CIF: Cumulative incidence function; DM: Diabetes mellitus; FPG: Fasting plasma glucose; FY: Fiscal year; ICD: International classification of diseases; LTFU: Lost to follow up; MICE: Multiple imputation with chained equations; NAP: The Thailand National AIDS Program; NHSO: The National Health Security Office; PYFU: Person-years of follow-up; SHR: Sub-distribution hazard ratio; UCS: Universal Coverage Scheme; WHO: World Health Organization

## Availability of data and materials
According to the agreement of the first author with the NHSO, the datasets analyzed for the study are not publicly available.

## Author's contributions
NP, NK, RC and GJ wrote the proposal and designed the study. NP, AT, NS and JYM analyzed data. NP, GJ, SB, CB and NK interpreted data. NP, NK and NS search literature. NP, TRC, AT, GJ and NK wrote the manuscript, and edited the final draft for publication. NK and GJ supervised the whole study process and edited the final draft for publication. All authors approved the final manuscript of this article prior to submission.

## Ethics approval and consent to participate
The analysis plan was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University, Thailand on March 18, 2014 (114/2014, Research ID: COM-2557-02140). The use of the database was authorized by the NHSO only for this study. Patient identifiers were encrypted by NHSO prior data management and analysis.

## Consent for publication
The use of the data analyzed was authorized by the NHSO exclusively for this paper.

## Competing interests
The authors declare that they have no competing interests.

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Paengsai *et al. BMC Public Health* (2018) 18:1079

Page 10 of 10

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