Chronic kidney disease incidence and survival of Thai HIV-infected patients

Wannarat Pongpirul[a], Krit Pongpirul[b,c], Jintanat Ananworanich[d], Virat Klinbuayaem[e], Anchalee Avihingsanon[d] and Wisit Prasithsirikul[a]

Objectives: As data on chronic kidney disease (CKD) incidence among Asian HIV patients has been limited, the present study aimed to estimate the CKD incidence in HIV-infected patients who received standard antiretroviral therapy in Thailand and to compare baseline demographics and clinical characteristics of the patients who developed CKD with those who do not.

Design: A multicenter, observational prospective cohort of HIV patients with normal kidney functions who received standard antiretroviral therapy.

Methods: CKD was diagnosed based on the KDIGO 2012 criteria, using Chronic Kidney Disease Epidemiology Collaboration based estimated glomerular filtration rate with and without urine protein. The cumulative probability of CKD incidence was analyzed using Kaplan–Meier estimation.

Results: Of 5552 patients, 96 patients with pre-existing CKD and 26 patients with incomplete data were excluded, and 5430 patients were analyzed. Their mean age was 39.87 years, 41.52% were women, and 49.45% were homosexual. They were followed up for 49.41 months on average, with 229 incident cases (4.22%) being identified during 22 035 person-years at risk. Overall CKD incidence rate was 10.39 per 1000 person-years. Average time to CKD was 26.4 months (95% confidence interval: 24.44–28.83). The adjusted relative hazard significantly increased by 8.6% and 10.3% for each additional year of patient age and each additional $\log_{10}$ copies/ml of HIV viral load, respectively. Patients with diabetes mellitus and hypercholesterolemia had significantly higher adjusted relative hazard (3.37 and 1.41; $P < 0.001$ and $P = 0.014$), respectively.

Conclusion: CKD incidence among the Thai HIV-infected patients was lower than in white and non-Southeast Asian populations. Diabetes, hypercholesterolemia, age, and HIV viral load were the significant risk factors.

Trial registration: ClinicalTrials.gov identifier: NCT01328275.

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[a]Department of Medicine, Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand, [b]Department of Preventive and Social Medicine, Chulalongkorn University, Bangkok, Thailand, [c]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, [d]The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand, and [e]Sanpatong Hospital, Chiang Mai, Thailand.

Correspondence to Krit Pongpirul, MD, MPH, PhD, Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Tel: +66 686 605 5088; e-mail: doctorkrit@gmail.com
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Introduction

Given longer survival from HAART [1], people living with HIV/AIDS have not only increasingly comparable risks of chronic diseases as a general population, but also HIV-specific risks. Chronic kidney disease (CKD) has been more prevalent in HIV-infected patients than the general population. In the United States, the CKD prevalence among HIV-infected patients varied from 2.4% [2] to 15.5% [3], compared with 5.6% in Spain [4]. In Asia, the CKD prevalence was 15.4% in Japan [5] and 16.8% in China [6].

Before the HAART era, HIV-associated nephropathy (HIVAN) was the major cause of end-stage renal disease potentially among the African patients with *APOL1* gene [7]. Evidence suggested that viral suppression by HAART resulted in significant reduction of HIVAN [8]. However, the renal protective effect of HAART has been inconclusive [9]. Regardless of HAART, HIVAN among Thai HIV-infected patients with low $CD4^+$ cell counts has never been identified, suggesting it does not exist in the Thai population [10].

Based on the Data Collection on Adverse events of Anti-HIV Drugs Study, a large prospective cohort collaboration across Europe, the United States, and Australia, CKD incidence among HIV-positive people was 1.76 per 1000 person-years [11]. The nephrotoxic effect of tenofovir disoproxil fumarate has been widely known [11], especially in patients with low body weight [12,13].

There have been limited data on CKD incidence among the Asian HIV-infected population. A recent retrospective cohort conducted at a single Japanese institution reported an incidence of 20.6 per 1000 person-years [13]. Nonetheless, the study was predominated by male patients and the CKD diagnosis was based only on estimated glomerular filtration rate (eGFR) without urine protein. In the present study, we aimed (first) to estimate the incidence of CKD diagnosed, based on eGFR with and without urine protein, in HIV-infected patients who received standard antiretroviral therapy (ART) in Thailand and (second) to compare baseline demographics, clinical characteristics, and survival of the patients who developed CKD with those who do not.

Methods

Data from the HIV Progress Adult study, a multicenter, observational prospective cohort of Thai adult HIV patients who received standard ART (ClinicalTrials.gov identifier: NCT01328275) conducted during December 2007 to June 2015, was analyzed. The three centers were Bamrasnaradura Infectious Diseases Institute (BIDI), Department of Disease Control, Ministry of Public Health, Nonthaburi; Sanpatong Hospital, Chiang Mai; and the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok. Both BIDI (the largest referral center for infectious diseases) and Sanpatong hospital (a 120-bed community hospital in the North) had inpatient and outpatient facilities. HIV-NAT had only outpatient care for HIV-infected patients and research patients.

eGFR based on serum creatinine was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Proteinuria was defined as at least 1+ on urine dipstick examination. eGFR and proteinuria were assessed by at least two consecutive measurements performed 3 months apart. CKD stage was classified according to KDIGO 2012 guideline [14]. Hypertension was diagnosed in a patient with a systolic blood pressure of at least 140 mmHg or with a diastolic blood pressure of at least 90 mmHg or taking antihypertensive drugs prior to or at baseline.

The sample size was the same as the Thai HIV Progress Adult study. In addition to the patient inclusion criteria (adult aged at least 18 years currently receiving ART at the three centers), patients with eGFR lower than $60\,ml/min/1.73\,m^2$ or positive urine protein at study entry were considered presumed pre-existing CKD and therefore excluded.

All data were expressed as the mean and SD unless stated otherwise. Demographics, clinical characteristics, and laboratory values of the patients who developed CKD and those who did not develop CKD were compared using univariate analysis. Because including urine protein could result in a biased CKD incidence toward higher estimates than commonly reported in other studies, the diagnosis of CKD based on eGFR with and without urine protein was performed and compared. Categorical variables were analyzed using Pearson's chi-square or Fischer's exact test as appropriate. Continuous variables were analyzed using Student's *t*-test. The cumulative probability of CKD incidence was analyzed using Kaplan–Meier estimation. This study was approved by the Institutional Review Board, BIDI (IRB no. S028h/58). All patients provided written informed consent.

Results

Of 5552 patients in the HIV Progress Adult study, 96 patients with pre-existing CKD (1.73% CKD prevalence in HIV patients) and 26 patients with incomplete data were excluded, and 5430 patients were analyzed. Their mean age was 39.87 years, 41.52% were women, and 49.45% were homosexual (92.18% men). The detailed patient characteristics are presented in Table 1. Income, education, and health insurance profile of Sanpatong

Table 1. Patient characteristics by study sites.

	Overall	BIDI	HIV-NAT	Sanpatong
N	5430	3319	1312	799
Age (years)	39.96	40.42	37.50	42.08
Female	41.49%	41.97%	38.64%	44.18%
Income (Thai baht/month)				
<5000	28.63%	24.69%	24.21%	51.81%
5000–9999	23.38%	25.24%	20.99%	19.52%
10 000–14 999	18.74%	20.91%	19.26%	9.01%
15 000–19 999	11.80%	11.72%	14.31%	8.14%
≥20 000	17.45%	17.43%	21.23%	11.51%
Health insurance scheme				
Universal coverage	38.72%	27.61%	52.66%	61.95%
Civil servant medical benefits	17.14%	18.67%	8.67%	24.41%
Social security	36.05%	41.85%	36.64%	11.26%
Out-of-pocket	8.10%	11.87%	2.03%	2.38%
Education level				
No education	1.86%	2.32%	0.16%	2.63%
Less than bachelor degree	70.59%	71.18%	62.57%	80.80%
Bachelor degree	24.25%	23.08%	33.07%	15.14%
Master/doctoral degree	3.30%	3.42%	4.20%	1.38%
Smoking status				
Past	41.42%	41.91%	41.25%	39.74%
Current	26.75%	26.59%	22.94%	38.08%
CDC category				
A	28.88%	15.28%	54.99%	44.52%
B	18.52%	13.58%	31.38%	19.23%
C	52.60%	71.14%	13.63%	36.25%

BIDI, Bamrasnaradura Infectious Diseases Institute; CDC, Centers for Disease Control; HIV-NAT, HIV Netherlands Australia Thailand Research Collaboration.

hospital was compatible with public community hospitals in Thailand. One-quarter of the patients were current smokers at the time of data collection. Dominated by BIDI data, more than half were CDC Category C.

The average baseline eGFR was 104.93 mg/min/1.73 m^2 (Table 2). Mean $CD4^+$ cell count was 386.55 cells/μl, and three-quarter of the patients had $CD4^+$ cell count more than 200 cells/μl and less than 50 HIV RNA virus copies/ml. Hepatitis B antigen and anti-hepatitis C antibody were positive in 13.33 and 6.96% of the patients, respectively. The average BMI was 22.18 kg/m^2. The prevalence of hypertension and diabetes mellitus were 16.63% and 3.96%, respectively.

Of 229 patients who developed CKD, 60 and 58 patients were diagnosed with CKD stages 1 and 2, respectively, mainly because of the presence of proteinuria. One-hundred-and-six patients were categorized as stage 3 for their first CKD diagnosis (89 stage 3a and 17 stage 3b

Table 2. Baseline characteristics by study sites.

	Overall	BIDI	HIV-NAT	Sanpatong	*P*
Baseline eGFR (ml/min/1.73 m^2)	104.93	107.74	96.78	109.36	<0.001
$CD4^+$ cell count (cells/μl)	386.55	363.66	465.84	351.25	<0.001
$CD4^+$ cell count ≤200 cells/μl (%)	22.52	23.74	15.47	29.04	<0.001
HIV RNA viral load (log_{10} copies/ml)	4.34	4.52	3.91	4.62	<0.001
HIV RNA viral load ≤50 copies/ml (%)	86.59	85.42	98.84	79.60	<0.001
HIV RNA viral load ≤1000 copies/ml (%)	91.21	90.69	100.00	84.86	<0.001
HBsAg positive (%)	13.33	8.57	15.89	13.21	0.001
HBV DNA viral load (×107 copies/ml)	2.47	3.93	2.27	–	<0.001
Anti-HCV positive (%)	6.96	11.42	5.22	2.33	0.531
HCV RNA viral load (×106 copies/ml)	1.11	1.48	1.06	–	0.583
BMI (kg/m^2)	22.18	22.30	22.09	21.88	0.009
Hypertension (%)	16.63	14.94	17.20	22.90	<0.001
Diabetes mellitus (%)	3.96	4.55	3.05	3.00	0.021
Fasting plasma glucose (mg/dl)	98.36	100.58	94.49	95.16	<0.001
Hypercholesterolemia (%)	35.16	33.90	37.04	37.30	0.051
Total cholesterol (mg/dl)	203.89	202.25	212.32	198.31	<0.001
LDL-cholesterol (mg/dl)	130.83	132.91	117.76	128.15	<0.001
HDL-cholesterol (mg/dl)	53.37	55.11	50.78	49.42	<0.001
Triglyceride (mg/dl)	192.87	192.49	181.68	208.93	0.009

BIDI, Bamrasnaradura Infectious Diseases Institute; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-NAT, HIV Netherlands Australia Thailand Research Collaboration.

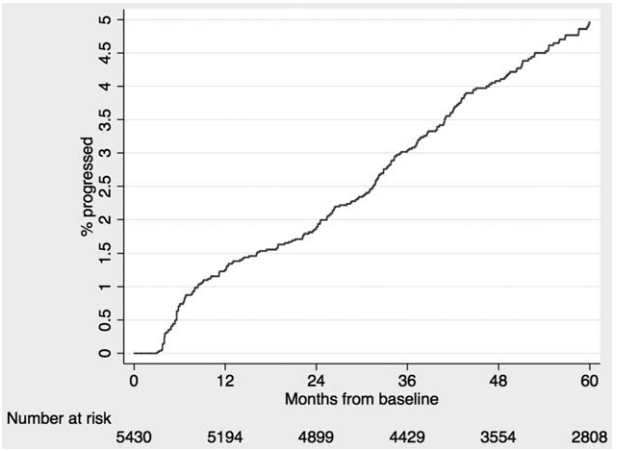

Fig. 1. Progression to chronic kidney disease, defined by estimated glomerular filtration rate and urine protein.

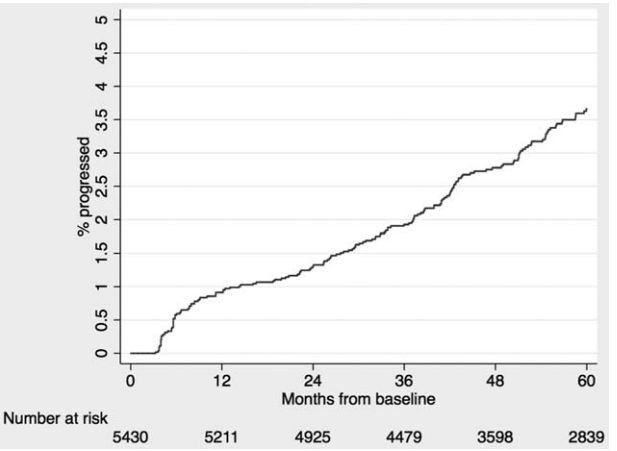

Fig. 2. Progression to chronic kidney disease, defined by estimated glomerular filtration rate.

patients). Four and one patients were diagnosed stages 4 and 5, respectively.

The patients were followed up for 49.41 months on average, with 229 incident cases (4.22%) were identified during 22 035 person-years at risk. Overall CKD incidence rate was 10.39 per 1000 person-years. Average time to CKD was 26.64 months (95% confidence interval: 24.44–28.83). The Kaplan–Meier progression to CKD is presented in Fig. 1: at 24 months, 1.82%; at 36 months, 2.85%; and at 48 months, 3.66%. If urine protein was not used for the CKD diagnosis, the average follow-up period became 49.74 months and only 165 incident cases (3.04%) were identified during 22 186 person-years at risk. Overall CKD incidence rate was 7.44 per 1000 person-years. The Kaplan–Meier progression to CKD is presented in Fig. 2: at 24 months, 1.27%; at 36 months, 1.82%; and at 48 months, 2.49%.

The crude CKD incidence significantly increased by 8.8% and 3.6% for each additional year of patient age and kg/m^2 of patient BMI (Table 3). Diabetes mellitus, hypertension, and hypercholesterolemia significantly increased the crude CKD incidence. After adjustment, the relative hazard significantly increased by 8.6% and 10.3% for each additional year of patient age and each additional log_{10} copies/ml of HIV viral load, respectively. Diabetes mellitus and hypercholesterolemia significantly increased the relative hazard for CKD.

Discussion

This prospective cohort study is the first to report the incidence of CKD, diagnosed based on both eGFR and urine protein, among Southeast Asian HIV-infected patients. As the known nephrotoxic drugs such as tenofovir disoproxil fumarate were not commonly prescribed to our patients during the study period, our findings could be an unconfounded representation of CKD progression among non-HIVAN patients. The findings could help to verify whether the known risk factors for CKD are applicable to the Southeast Asian HIV-infected population.

As data on CKD incidence among normal Thai population are not available, the magnitude of CKD epidemics has been assessed by using prevalence based on cross-sectional data. Our HIV-infected patients had a relatively good kidney function at study entry as suggested

Table 3. Univariate and multivariate analysis.

		Univariate			Multivariate		
		IRR	95% CI	*P*	RH	95% CI	*P*
Age	Per 1 year older	1.088	1.075–1.101	<0.001	1.086	1.072–1.100	<0.001
BMI	Per 1 kg/m^2	1.036	1.008–1.066	0.012	1.001	0.965–1.038	0.962
Sex	Male vs. female	1.078	0.828–1.403	0.576	0.873	0.663–1.150	0.334
Hypertension	Yes vs. no	1.983	1.486–2.647	<0.001	1.190	0.867–1.633	0.283
Diabetes mellitus	Yes vs. no	5.215	3.694–7.361	<0.001	3.372	2.338–4.864	<0.001
Hypercholesterolemia	≥200 vs. <200 mg/dl	1.499	1.156–1.944	0.002	1.405	1.072–1.840	0.014
$CD4^+$ cell count	≤200 vs. >200 cells/μl	0.932	0.672–1.291	0.671	0.816	0.567–1.172	0.271
HIV viral load	Per log_{10} copies/ml higher	1.036	0.986–1.087	0.159	1.103	1.043–1.166	0.001

CI, confidence interval; IRR, incidence rate ratio; RH, relative hazard.

by the relatively low baseline CKD prevalence (1.73%) compared to that reported for the Thai population (17.5%) [15]. Similar to the non-HIV population, age, diabetes, and hypercholesterolemia were the major determinants of CKD among Asian HIV-infected patients. The relative hazard of CKD progression among diabetic patients in our study was higher than that previously reported in a recent retrospective population-based Thai non-HIV cohort [16]. The findings should be incorporated into the estimated prediction of CKD burden.

Significantly, the CKD incidence from this Thai multicenter prospective cohort was much lower than in the recent single-center retrospective cohort from Japan who received more nephrotoxic drugs (7.44 vs. 20.6 per 1000 person-years) [13]. Given similar baseline prevalence, diabetes contributed to a larger relative hazard of CKD progression among the Thai than among the US HIV-infected population cohort (3.37 vs. 2.17) [17]. The findings suggested that a rigorous diabetes prevention and management program is crucial for the HIV-infected population.

Our study asserted that the HIV viral load increased the CKD risk. Kalayjian *et al.* [17] reported a hazard ratio of 1.96 for each additional $\log_{10}$ copies/ml among the US HIV-infected population. In China, Cao *et al.* [18] conducted a cross-sectional study on 538 untreated HIV-infected patients and reported a significant association between high viral load and CKD development.

The CKD incidences, based on eGFR with and without urine protein, were 10.39 and 7.44 per 1000 person-years, respectively, compared with 11.2 (Johns Hopkins HIV Clinical Cohort, USA) [19], 10.50 (EuroSIDA) [20], and 10.1 (Center for AIDS Research Network of Integrated Clinical Systems Cohort, CNICS) [17] per 1000 person-years for a white population based only on eGFR. This suggested that urine protein could be a significant contributor to the measurement of CKD epidemics and clinical outcomes. Hence, the CKD incidence in these studies in a white population [17,19,20] would be higher if urine protein is included in the diagnosis of CKD.

HIV and CKD have been the two separate chronic disease-specific programs financially supported under the Universal Coverage scheme in Thailand. The findings from our study also suggested a potentially close relationship between the two diseases. The high CKD incidence among HIV-infected patients should be included in the resource preparation and budget allocation for the years to come.

Some limitations of the present study should be noted. First, as only three centers participated in the main study, the findings reported here might not be generalizable to the other sites. Second, the urine protein used in the CKD diagnosis was qualitatively assessed and therefore might result in an underestimated incidence. Third, the potential effect of ART on the kidney function was not explored in our study. However, known nephrotoxic ARTs such as TDF were prescribed in a small number of patients and during the latter phase of the study.

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Conflicts of interest

There are no conflicts of interest.

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