Chronic Kidney Disease in a Large National Human Immunodeficiency Virus Treatment Program

Ninutcha Paengsai

Chiang Mai University

Kajohnsak Noppakun (✉ kajohnsak.noppakun@cmu.ac.th)

Chiang Mai University

Gonzague Jourdain

Institut de recherche pour le développement (IRD) MIVEGEC

Tim R. Cressey

Institut de recherche pour le développement (IRD) MIVEGEC

Nicolas Salvadori

Institut de recherche pour le développement (IRD) MIVEGEC

Romane Chaiwarith

Chiang Mai University

Apichat Tantraworasin

Chiang Mai University

Jean Yves Mary

Université Paris Diderot

Chureeratana Bowonwatanuwong

Mahidol University

Sorakij Bhakeechep

University of Phayao

Patrinee Traisathit

Chiang Mai University

Natapong Kosachunhanun

Chiang Mai University

Research Article

Keywords: Antiretroviral therapy, chronic kidney disease, HAART, HIV infection, tenofovir disoproxil fumarate

Posted Date: January 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1214201/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Introduction:

Tenofovir disoproxil fumarate (TDF) is associated with a risk of chronic kidney disease (CKD), especially when used with protease inhibitors or in Asian populations. Data from the Thai national health insurance system were used to assess the incidence of CKD in patients receiving antiretroviral therapy (ART) in real-world practice.

Materials and methods

We analyzed data from patients who initiated one of the following first-line ART regimens: (i) zidovudine+lamivudine+nevirapine (AZT+3TC+NVP); (ii) zidovudine+lamivudine+efavirenz (AZT+3TC+EFV); (iii) tenofovir+lamivudine+nevirapine (TDF+3TC+NVP); (iv) tenofovir+lamivudine/emtricitabine+efavirenz (TDF+3TC/FTC+EFV); and (v) tenofovir+lamivudine+lopinavir/ritonavir (TDF+3TC+LPV/r). CKD was defined as glomerular filtration rate <60 mL/min/1.73 m² for >3 months, or a confirmed 2010 WHO diagnosis (ICD-10 code N183, N184, or N185). Death competing risks survival regression models were used for the analysis.

Results

Among 27,313 participants, median age 36.8 years, body mass index 20.4 kg/m², and absolute CD4 cell count 146 cells/mm³, followed for a median 2.3 years, 245 patients (0.9%) were diagnosed CKD (incidence 3.2 per 1,000 patient-years of follow-up; 95% confidence interval [CI] 2.8-3.6). Compared with patients receiving AZT+3TC+NVP, the risk of CKD measured by adjusted sub-distribution hazard ratio (aSHR) was higher in patients on TDF+3TC+LPV/r (6.5, 95% CI 3.9-11.1), on TDF+3TC+NVP (3.8, 95% CI 2.3-6.0) and on TDF+3TC/FTC+EFV (1.6, 95% CI 1.2-2.3). Among patients receiving TDF, compared with those receiving TDF+3TC/FTC+EFV, the risk was higher on TDF+3TC+LPV/r (4.0, 95%CI 2.3-6.8) on TDF+3TC+NVP (2.3, 95%CI 1.4-3.6) .

Conclusions

This real-world study suggest that the role of TDF in increasing the risk of CKD, especially when combined with LPV/r or NVP.

Introduction

The Global Burden of Disease estimated that 1.2 million people died from chronic kidney disease (CKD) in 2017¹. With an improvement in the access to antiretroviral therapy (ART), the causes of death in human immunodeficiency virus (HIV)-infected individuals are shifting from infectious diseases to non-communicable diseases, including several conditions associated with the use of some antiretroviral agents. CKD has emerged as an important problem in HIV-infected individuals²⁻⁴. A large meta-analysis of studies in HIV-infected adults from over 60 countries showed that the overall prevalence of CKD defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² was 4.8% and 19.4% of patients with diabetes mellitus⁵. High levels of viral loads, low CD4 cells counts, diagnosis of acquired immunodeficiency syndrome (AIDS), and low body weight, and the use of some antiretroviral agents such as indinavir, tenofovir disoproxil fumarate (TDF) and ritonavir-boosted lopinavir (LPV/r) are well-documented risk factors for CKD in HIV-infected individuals⁶⁻⁹. Several studies have demonstrated an increased risk of CKD in patients receiving TDF, especially in combination with protease inhibitors, such as lopinavir/ritonavir. However, little is known about the actual burden of this problem in relation to first line antiretroviral combinations used in adults within large treatment programs in the real world, especially in Asia where bodyweights of adults with HIV tend to be lower than other high settings.

Since 2004, the Thailand National Health Security Office (NHSO) in charge of the National AIDS Program has provided free-of-charge health services and ART for HIV-infected individuals. Using data from adults registered with this program under the Universal Coverage Scheme (UCS)¹⁰, we investigated the association between the incidence of CKD in adults with HIV and first-line ART regimens to help inform clinicians when selecting a first line regimen recommended by the 2019 World Health Organization guideline¹¹.

Results

Study population and follow up

Of 152,664 HIV-infected adults, 100,081 were excluded from the study because their first-line ART regimens were not recommended by WHO guideline, in addition to 25,270 patients because of insufficient data. Thus, a total of 27,313 patients were included in this analysis, 15,389 (56.3%) were males.

Over the 8-year study period, of these 27,313 patients, 817 (3.0%) were lost to follow up, 5,840 (21.4%) switched to a second-line ART regimen and 1,844 (6.8%) died (Fig. 1). The median duration of follow-up for the first line ARV drug regiment was 2.3 years (IQR 1.5-3.6), accounting for a total 76,168 PYFU.

At baseline, median age was 36.8 years (IQR, 30.8-43.3), body mass index 20.4 kg/m^2 (IQR, 18.6-22.6), and absolute CD4 cell count 146 cells/mm^3 (IQR, 49-244). The most common comorbidities were hypertension (3.9%), HBV infection (3.8%), tubulo-interstitial nephritis (1.9%) and DM (1.9%). Table 1 shows the distribution of baseline characteristics overall and by ART regimen.

Table 1
Baseline characteristics of HIV-infected adults who received recommended first-line antiretroviral therapy regimens

Baseline characteristics	Antiretroviral therapy regimens					Overall
	AZT+3TC+NVP	AZT+3TC+EFV	TDF+3TC+NVP	TDF+3TC/FTC+EFV	TDF+3TC+LPV/r	
	(n=12,084)	(n=6,519)	(n=888)	(n=7,351)	(n=471)	(n=27,313)
Fiscal year of antiretroviral initiation						
2007	757 (6.3%)	515 (7.9%)	59 (6.6%)	165 (2.2%)	27 (5.7%)	1,523 (5.6%)
2008	823 (6.8%)	477 (7.3%)	55 (6.2%)	228 (3.1%)	39 (8.3%)	1,622 (6.0%)
2009	901 (7.5%)	588 (9.0%)	78 (8.8%)	358 (4.9%)	46 (9.8%)	1,971 (7.2%)
2010	1,193 (9.9%)	726 (11.1%)	93 (10.5%)	667 (9.1%)	54 (11.5%)	2,733 (10.0%)
2011	2,656 (22.0%)	1,295 (19.9%)	190 (21.4%)	1,484 (20.2%)	88 (18.7%)	5,713 (20.9%)
2012	2,639 (21.8%)	1,395 (21.4%)	203 (22.9%)	1,901 (25.9%)	107 (22.7%)	6,245 (22.9%)
2013	3,115 (25.8%)	1,523 (23.4%)	210 (23.7%)	2,548 (34.7%)	110 (23.4%)	7,506 (27.5%)
Male sex, n (%)	6,014 (49.8%)	3,959 (60.7%)	463 (52.1%)	4,709 (64.1%)	244 (51.8%)	15,389 (56.3%)
Age – years						
median (IQR)	36.9 (30.8-43.4)	37.1 (31.5-43.3)	37.4 (31.8-44.3)	36.3 (30.1-43.2)	36.4 (30.9-43.1)	36.8 (30.8-43.3)
n (%)						
18-34	4,780 (39.6%)	2,448 (37.6%)	322 (36.3%)	3,048 (41.5%)	191 (40.6%)	10,789 (39.5%)
35-44	4,676 (38.7%)	2,668 (40.9%)	349 (39.3%)	2,707 (36.8%)	185 (39.3%)	10,585 (38.8%)
45-59	2,378 (19.7%)	1,274 (19.5%)	189 (21.3%)	1,429 (19.4%)	80 (17.0%)	5,350 (19.6%)
≥60	250 (2.1%)	129 (2.0%)	28 (3.2%)	167 (2.3%)	15 (3.2%)	589 (2.2%)
History of comorbidities, n (%)						
Type 2 diabetes	230 (1.9%)	120 (1.8%)	12 (1.4%)	147 (2.0%)	12 (2.6%)	521 (1.9%)
Hypertension	459 (3.8%)	255 (3.9%)	39 (4.4%)	307 (4.2%)	14 (3.0%)	1,074 (3.9%)
Ischemic heart disease	53 (0.4%)	33 (0.5%)	2 (0.2%)	61 (0.8%)	2 (0.4%)	151 (0.6%)

Abbreviations: 3TC, lamivudine; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.

Baseline characteristics	Antiretroviral therapy regimens					Overall
	AZT+3TC+NVP	AZT+3TC+EFV	TDF+3TC+NVP	TDF+3TC/FTC+EFV	TDF+3TC+LPV/r	
Tubulo-interstitial nephritis	258 (2.1%)	120 (1.8%)	16 (1.8%)	127 (1.7%)	6 (1.3%)	527 (1.9%)
Gout	42 (0.4%)	21 (0.3%)	5 (0.6%)	31 (0.4%)	1 (0.2%)	100 (0.4%)
Urolithiasis	78 (0.7%)	35 (0.5%)	3 (0.3%)	51 (0.7%)	3 (0.6%)	170 (0.6%)
Hepatitis B infection	92 (0.8%)	84 (1.3%)	69 (7.8%)	756 (10.3%)	33 (7.0%)	1,034 (3.8%)
Hepatitis C infection	71 (0.6%)	128 (2.0%)	13 (1.5%)	252 (3.4%)	15 (3.2%)	479 (1.8%)
Baseline absolute CD4 cell count - cells/mm³ (n= 17,662)						
median (IQR)	146 (49-244)	123 (39-250)	95 (33-248)	115 (37-253)	220 (65-399)	146 (49-244)
n (%)	8,524	4,194	454	4,300	190	17,662
<200	5,470 (64.2%)	308 (67.8%)	308 (67.8%)	2,798 (65.1%)	89 (46.8%)	11,403 (64.6%)
≥200	3,054 (35.8%)	1,456 (34.7%)	146 (32.2%)	1,502 (34.9%)	101 (53.2%)	6,259 (35.4%)
Variables with ≥ 20% missing values						
Body mass index - kg/m² (n= 9,266)						
median (IQR)	20.8 (18.8-22.8)	20.0 (18.2-22.2)	20.6 (18.8-23.4)	20.2 (18.2-22.4)	20.4 (18.8-22.8)	20.4 (18.6-22.6)
n (%)	4,528 (48.9%)	1,916 (20.7%)	371 (4.0%)	2,320 (25.0%)	131 (1.4%)	9,266
<18.5	968 (21.1%)	1,014 (52.9%)	174 (46.9%)	1,180 (50.9%)	74 (56.5%)	2,295 (24.8%)
18.5-22.9	2,451 (54.1%)	549 (28.7%)	89 (24.0%)	662 (28.5%)	27 (20.6%)	4,893 (52.8%)
23.0-24.9	557 (12.7%)	187 (9.8%)	53 (14.3%)	251 (10.8%)	18 (13.7%)	1,086 (11.7%)
≥25.0	532 (11.8%)	166 (8.7%)	55 (14.8%)	227 (9.8%)	12 (9.2%)	992 (10.7%)
Baseline serum creatinine - mg/dL (n=8,524)						
median (IQR)	0.90 (0.70-1.00)	0.85 (0.70-1.00)	0.83 (0.75-1.00)	0.86 (0.70-1.00)	0.79 (0.70-0.96)	0.82 (0.70-1.00)

Abbreviations: 3TC, lamivudine; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.

Baseline characteristics	Antiretroviral therapy regimens					Overall
	AZT+3TC+NVP	AZT+3TC+EFV	TDF+3TC+NVP	TDF+3TC/FTC+EFV	TDF+3TC+LPV/r	
Hyperlipidemia (n=4,868), n (%)	503 (21.6%)	231 (20.4%)	23 (17.3%)	203 (16.7%)	20 (35.1%)	980 (20.1%)
Abbreviations: 3TC, lamivudine; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.						

Incidence of CKD

During the total 76,168 PYFU, of 27,313 adults, 245 (0.9%) were diagnosed with CKD, leading to a cumulative incidence of 3.2 per 1,000 PYFU (95% CI 2.8-3.6). The incidence rate of CKD was lower during the first 2 years of follow-up compared to thereafter (S1 Table).

Incidence rate of CKD was higher in adults who received a TDF containing ART regimen (5.2 per 1,000 PYFU; 95% CI 4.4-6.3) compared to those receiving a non-TDF containing ART regimen (2.3 per 1,000 PYFU; 95% CI 2.0-2.8) (Table 2).

Table 2

Incidence per 1,000 Person-years of follow-up (PYFU) of chronic kidney disease according to baseline characteristics among 27,313 HIV-infected adults who received one of the first-line antiretroviral therapy regimens followed for a median 2.3 years in the study

	Number of patients with CKD	PYFU	Incidence per 1,000 PYFU (95% CI)
Overall	245	76,168	3.2 (2.8-3.6)
Fiscal year of antiretroviral initiation			
2007	13	8,846	1.4 (0.9-2.5)
2008	13	8,366	1.6 (0.9-2.7)
2009	29	8,660	3.3 (2.3-4.8)
2010	29	9,908	2.9 (2.0-4.2)
2011	72	16,682	4.3 (3.4-5.4)
2012	51	13,435	3.8 (2.9-5.0)
2013	38	10,272	3.7 (2.7-5.1)
Characteristics			
Sex			
Female	111	35,757	3.1 (2.6-3.7)
Male	134	40,410	3.3 (2.8-3.9)
Age – years			
18-34	17	30,800	0.6 (0.3-0.9)
35-44	55	29,961	1.8 (1.4-2.4)
45-59	117	13,990	8.4 (7.0-10.0)
≥60	56	1,416	39.5 (30.4-51.4)
History of comorbidities			
Type 2 diabetes			
No	217	75,068	2.9 (2.5-3.3)
Yes	28	1,100	25.5 (17.6-36.9)
Hypertension			
No	205	73,942	2.8 (2.4-3.2)
Yes	40	2,226	18.0 (13.2-24.5)
Ischemic heart disease			
No	242	75,867	3.2 (2.8-3.6)
Yes	3	301	10.0 (3.2-30.9)
Tubulo-interstitial nephritis			
No	234	74,961	3.1 (2.7-3.5)
Yes	11	1,208	9.1 (5.0-16.4)

Abbreviations: 3TC, lamivudine; AZT, zidovudine; CI, confidence interval; CKD, chronic kidney disease; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.

	Number of patients with CKD	PYFU	Incidence per 1,000 PYFU (95% CI)
Gout			
No	240	75,983	3.2 (2.8-3.6)
Yes	5	186	26.9 (11.2-64.7)
Urolithiasis			
No	237	75,823	3.1 (2.8-3.6)
Yes	8	346	23.1 (11.6-46.3)
Hepatitis B infection			
No	234	73,931	3.2 (2.8-3.6)
Yes	11	2,237	4.9 (2.7-8.9)
Hepatitis C infection			
No	236	75,115	3.1 (2.8-3.6)
Yes	9	1,054	8.5 (4.4-16.4)
Baseline absolute CD4 cell count - cells/mm³			
<200	99	27,084	3.7 (3.0-4.5)
≥200	58	15,771	3.7 (2.8-4.8)
First-line antiretroviral regimens			
AZT+3TC+NVP	79	34,130	2.3 (1.9-2.9)
AZT+3TC+EFV	46	19,105	2.4 (1.8-3.2)
TDF+3TC/FTC+EFV	80	18,889	4.2 (3.4-5.3)
TDF+3TC+NVP	23	2,599	8.8 (5.9-13.3)
TDF+3TC+LPV/r	17	1,445	11.8 (7.3-18.9)
Abbreviations: 3TC, lamivudine; AZT, zidovudine; CI, confidence interval; CKD, chronic kidney disease; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir.			

The estimated cumulative incidence of CKD at 8 years follow-up was 1.9% (95% CI 1.4-2.3). It was 1.5% (95% CI 0.1-2.2) in patients on AZT+3TC+NVP, 2.8% (95% CI 1.5-4.9) on TDF+3TC/FTC+EFV, 4.0% (95% CI 2.6-5.9) on TDF+3TC+NVP, 1.3% (95% CI 0.9-2.0) on AZT+3TC+EFV and 5.1% (95% CI 3.0-8.1) on TDF+3TC+LPV/r.

Association between first-line antiretroviral treatment regimen and chronic kidney disease

In univariable analyses, the risk of CKD diagnosis was associated with older age at baseline, history of type 2 diabetes, hypertension, tubule-interstitial nephritis, gout and urolithiasis at baseline, and time-updated absolute CD4 cell count <200 cells/mm³ (all $p \leq 0.05$, Table 3).

Table 3

Factors associated with the risk of chronic kidney disease in HIV-infected adults who received currently recommended first-line antiretroviral therapy regimens (number of patients 27,313, except if otherwise specified)

Variables	Univariable ^a		Multivariable ^a	
	SHR (95% CI)	p-value	aSHR (95% CI)	p-value
Fiscal year of antiretroviral initiation				
2007	reference			
2008	1.0 (0.5-2.2)	0.993		
2009	1.7 (0.9-3.3)	0.133		
2010	0.9 (0.4-2.0)	0.813		
2011	1.5 (0.8-2.8)	0.217		
2012	1.1 (0.6-2.1)	0.827		
2013	0.8 (0.4-1.7)	0.565		
Male sex	0.9 (0.6-1.4)	0.662	0.9 (0.6-1.5)	0.779
Age – years				
18-34	reference		Reference	
35-44	3.1 (1.8-5.4)	<0.001	2.9 (1.7-5.1)	<0.001
45-59	13.5 (8.1-22.5)	<0.001	11.6 (6.9-19.6)	<0.001
≥60	64.6 (37.4-111.6)	<0.001	47.6 (26.5-85.5)	<0.001
Baseline history of comorbidities				
Type 2 diabetes	6.6 (4.4-9.9)	<0.001	2.8 (1.7-4.5)	<0.001
Hypertension	4.9 (3.5-7.0)	<0.001	1.4 (0.9-2.1)	0.153
Ischemic heart disease	2.5 (0.8-7.7)	0.117		
Tubulo-interstitial nephritis	2.4 (1.3-4.5)	0.004		
Gout	6.4 (2.6-15.7)	<0.001	2.8 (1.1-7.0)	0.029
Urolithiasis	6.2 (3.0-12.8)	<0.001	3.6 (1.7-7.8)	0.001
Hepatitis B infection	0.6 (0.2-1.8)	0.391		
Hepatitis C infection	2.1 (0.8-5.5)	0.127		
Baseline absolute CD4 cell count <200 cells/mm³	0.9 (0.7-1.3)	0.572		
First-line antiretroviral regimens				
AZT+3TC+NVP	reference		Reference	
AZT+3TC+EFV	1.1 (0.7-1.5)	0.712	1.0 (0.7-1.5)	0.973
TDF+3TC/FTC+EFV	1.7 (1.2-2.3)	0.002	1.6 (1.2-2.3)	0.003
TDF+3TC+NVP	4.1 (2.6-6.6)	<0.001	3.8 (2.3-6.0)	<0.001
TDF+3TC+LPV/r	6.0 (3.5-10.2)	<0.001	6.5 (3.9-11.1)	<0.001

Abbreviations: 3TC, lamivudine; aSHR, adjusted sub-hazard ratio; AZT, zidovudine; CI, confidence interval; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; SHR, sub-hazard ratio; TDF, tenofovir.

^aThe analysis was adjusted by previous serum creatinine measurement and propensity score.

Variables	Univariable ^a		Multivariable ^a	
Time-updated absolute CD4 cell count <200 cells/mm ³ (n=27,056)	2.1 (1.6-2.8)	<0.001	2.2 (1.7-2.9)	<0.001
Variables with ≥ 20% missing values				
Baseline body mass index - kg/m ² (n=9,266)				
<18.5	1.5 (0.9-2.5)	0.116		
18.5-22.9	reference			
23.0-24.9	0.9 (0.4-2.0)	0.883		
≥25.0	1.0 (0.5-2.2)	0.960		
Time-updated HIV-1 RNA load ≥ 1000 copies/mL (n=27,056)	1.3 (0.8-2.1)	0.303		
Abbreviations: 3TC, lamivudine; aSHR, adjusted sub-hazard ratio; AZT, zidovudine; CI, confidence interval; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; SHR, sub-hazard ratio; TDF, tenofovir.				
^a The analysis was adjusted by previous serum creatinine measurement and propensity score.				

Adjusting for sex, age, history of type 2 diabetes, hypertension gout, and urolithiasis at baseline, previous serum creatinine measurement and propensity score stratification, and compared to AZT+3TC+NVP, the following three regimens were associated with a higher risk of CKD: TDF+3TC+LPV/r (aSHR 6.5, 95% CI 3.9-11.1), TDF+3TC+NVP (aSHR 3.8, 95% CI 2.3-6.0) and TDF+3TC/FTC+EFV (aSHR 1.6, 95% CI 1.2-2.3) (Fig. 2). Among patients receiving TDF, compared to TDF+3TC/FTC+EFV, the risk was higher on TDF+3TC+LPV/r (aSHR 4.0, CI 2.3-6.8), or TDF+3TC+NVP (aSHR 2.3, CI 1.4-3.6).

Discussion

Using data from 27,313 HIV-infected adults on ART over a median follow up of 2.3 years (76,168 PYFU), the estimated incidence rate of CKD was 3.2 per 1,000 PYFU. Factors independently associated with CKD diagnosis were older age, type 2 diabetes, gout and urolithiasis, which are known risk factors in the general population^{12–15}, receipt of TDF-containing regimens and absolute CD4 cell count <200 cells/mm³, both factors related to HIV infection.

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study in Europe, the USA, and Australia reported a CKD incidence rate of 1.8 per 1,000 PYFU (95% CI 1.6–2.0) in HIV-positive adults¹⁶, lower than in our study. However, in our study, data on atazanavir and abacavir were too scarce to be analyzed and compared to D:A:D study. Two studies in Asia reported higher CKD incidence rates than in our study. The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) reported an overall CKD incidence rate of 10.4 per 1,000 PYFU but no breakdown by ART regimen was provided, limiting the possibility to compare¹⁷. The AIDS Clinical Center of National Center for Global Health and Medicine (NCGM) in Japan reported an overall CKD incidence rate of 20.6 per 1000 PYFU (95% CI 17.6–24.2), probably due to a high percentage of patients (83%) on ritonavir-boosted protease inhibitors¹⁸.

In our population, older age, T2DM, hypertension were associated with the risk of CKD like in the general population^{18–21}. HBV and HCV co-infections were not associated with the risk of CKD in our study although an association with HBV was found in other studies^{22,23} and HCV⁸.

Two studies in Africa reported that the risk of CKD preferably occurred during the first 3 years following HIV diagnosis and in case of low CD4 cell counts^{24,25}. In the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial, ART-naïve patients with CD4 cell counts ≤ 500 cells/μL had a higher prevalence of CKD than those with higher CD4 cell counts¹⁹. We also found an association with lower CD4 cell counts. Increased HIV-1 RNA load has also been reported as a significant risk factor¹⁷ but we could not analyze this association due to insufficient baseline HIV-1 RNA load data.

We found that TDF exposure increased the risk of CKD like in the EuroSIDA Study Group²⁶, the U.S. veterans study²⁷, a prospective cohort from France²⁸, the Canadian HIV Observational Cohort study⁸ and the D:A:D study¹⁶. However, the NCGM study found no increase in incidence of CKD among patients on TDF (despite a median observation duration of 5.1 years) but a higher drop in eGFR with longer exposure to TDF¹⁸. Interestingly, a retrospective study in Kenya²⁹ raised the question of a potential risk of CKD associated with NVP when in combination with TDF. To our knowledge only one other study, also in Thailand, showed that patients on TDF+3TC+NVP had a higher risk of renal impairment compared to patients on TDF+3TC+EFV³⁰. It is unclear whether this could be explained by confounding factors that were not taken into account.

As for the use of protease inhibitor, the Canadian HIV Observational Cohort study⁸ and the D:A:D study¹⁶ reported that the exposure to LPV/r was significantly associated with an increased risk of CKD, as in our study. In HIV-positive adults with kidney dysfunction, plasma TDF concentration in peripheral blood mononuclear cells has been shown significantly higher among patients receiving LPV/r compared with those receiving an NNRTI (NVP or EFV)³¹. A recent study from the USA National Historical Cohort of HIV-infected Veterans, reported that a incidence rate of CKD in patients on EFV+FTC+TDF of 39.3 per 1,000 PYFU (95% CI 34.0-45.3), significantly lower when compared to ritonavir-boosted PI (atazanavir, LPV or darunavir) +FTC+TDF (66.1 per 1,000 PYFU, 95% CI 55.7-77.9) (HR 0.6, 95% CI 0.5-0.7)³².

There were several limitations in our study. The NAP database was primarily designed to facilitate the reimbursement of costs incurred by hospitals for the delivery of HIV related medical services, and risk factors for CKD were not systematically recorded. Another limitation is that some variables such as laboratory results at ART initiation were not recorded in the database (cholesterol, triglycerides, HIV-1 RNA load) and could not be fully assessed in our analysis. Nevertheless, this national database provides a unique source of information reflecting the actual CKD burden in people living with HIV.

In conclusion, based on the analysis of a large national dataset from HIV-infected patients treated in the real world, the risk of CKD was relatively low overall and mostly concentrated in patients receiving TDF with a higher incidence in those also on NVP or LPV/r.

Methods

Study design and participants

We performed a retrospective cohort study using data from the National AIDS Program, covering HIV-infected individuals who received ART. This program is under the Universal Coverage Scheme (UCS), which covers about three-quarters of the Thai population (~47 millions). Participants eligible for inclusion were as follows: (i) aged 18 years or older having registered for ART between October 2006 and September 2013 (Fiscal Years (FY) 2007 to 2013); (ii) received a first-line ART regimens recommended by the 2010 World Health Organization guideline¹¹; and (iii) did not have, when they initiated treatment, chronic kidney disease (CKD) defined by the estimated glomerular filtration rate (eGFR) (estimated using the Chronic Kidney Disease Epidemiology Collaboration equation³³) and ICD-10 code. We excluded participants who did not receive ART or had incomplete baseline or follow-up information.

Exposure

The exposure of interest was one of the first-line ART regimens: (i) zidovudine, lamivudine, and nevirapine (AZT+3TC+NVP); (ii) zidovudine, lamivudine, and efavirenz (AZT+3TC+EFV); (iii) tenofovir, lamivudine, and nevirapine (TDF+3TC+NVP); (iv) tenofovir, lamivudine or emtricitabine, and efavirenz (TDF+3TC/FTC+EFV); and (v) tenofovir, lamivudine, and lopinavir/ritonavir (TDF+3TC+LPV/r)¹⁰.

Outcomes

The outcome of interest was the diagnosis (confirmed within 3 months) of conditions defined by the 2010 WHO ICD-10³⁴ as codes N183, N184, N185 i.e. CKD stage 3, 4 or 5 (kidney damage with moderately to severely decreased GFR [15-59 mL/min] or chronic uremia or end stage kidney disease³⁴); or eGFR <60 mL/min/1.73 m² for >3 months³⁵.

Patients were followed from the date of ART initiation to last patient visit, switching of ART regimen, loss to follow up, end of study (September 30, 2014), death, or confirmed diagnosis of CKD; whichever occurred first.

Covariates

We extracted the following variables at time of ART initiation: sex, age, weight, height, serum creatinine levels, fasting plasma glucose, serum triglycerides, serum total cholesterol, absolute CD4 cell count, HIV-1 ribonucleic acid (RNA) load and history of comorbidities including type 2 diabetes, hypertension, ischemic heart disease, tubulo-interstitial nephritis, gout, urolithiasis, hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection.

We considered that a patient was diagnosed with type 2 diabetes if either of the following records were available: confirmed fasting plasma glucose ≥ 126 mg/dL according to the 2013 American Diabetes Association criteria³⁶, or WHO diagnosis (ICD-10 code E11-E14)³⁴, or receipt of anti-diabetic drugs at least twice of medical services. Hyperlipidemia was defined by either total cholesterol ≥ 240 mg/dL or triglycerides ≥ 200 mg/dL³⁷. Hypertension was defined by a confirmed WHO diagnosis (ICD-10 code I10-I15) or receipt of anti-hypertensive drugs. WHO ICD-10 was used to identify history of comorbidities: ischemic heart disease (codes I20-I25), tubulo-interstitial nephritis (codes N10-N12), gout (code M10), urolithiasis (codes N20-N23), HBV infection (codes B16, B170, B180 and B181), and HCV infection (codes B171 and B182)³⁸.

Statistical analyses

Characteristics of participants in the study were presented as medians and interquartile ranges (IQR) for continuous variables, and as counts and percentages for categorical variables. The number of person-years of follow-up (PYFU) was calculated from the date of ART initiation to censoring date. For descriptive purposes, the overall CKD incidence rate was estimated by the number of newly diagnosed individuals divided by the total number of PYFU, and the 95% confidence interval (CI) was calculated using the quadratic approximation to the Poisson log-likelihood.

Covariates associated with risk of CKD were analyzed. These included fiscal year of ART initiation, sex, age categories (18-34, 35-44, 45-59, or ≥ 60 years), body mass index (<18.5 , $18.5-22.9$, $23.0-24.9$ or ≥ 25 kg/m²) and history of comorbidities at treatment initiation, time updated absolute CD4 cell count (<200 or ≥ 200 cells/mm³) and HIV-1 RNA load (<1000 or ≥ 1000 copies/mL). All models were adjusted for the availability of serum creatinine measurement records at baseline and during follow up. We imputed missing data by multiple imputation with chained equations (MICE) based on logistic regression for variables with $\leq 20\%$ missing data, and for time-updated absolute CD4 cell count values if data were missing for more than 9 months after the previous known value³⁹. Baseline body mass index and time-updated HIV-1 RNA load were excluded from the main analysis because more than 20% of the values were missing. To minimize the possible bias of the choice of ART by the physician in charge, all models were stratified by groups defined by a propensity score for each first-line ART regimen. This score was generated using multinomial logistic regression based on a fiscal year of ART initiation, sex, age group, and history of comorbidities (HBV and HCV infection, hypertension, type 2 diabetes, ischemic heart disease, tubulo-interstitial nephritis, gout, urolithiasis) (see S1 Fig).

We estimated the cumulative incidence rate of CKD and corresponding 95% CI using a cumulative incidence function accounting for deaths without CKD diagnosis as competing events⁴⁰. We analyzed the association between first-line ART regimens and risk of CKD using Fine and Gray competing risks survival regression^{41,42}. In multivariable analyses, the associations were expressed in adjusted sub-distribution hazard ratio (aSHR) and we used a backward elimination approach regression analysis using the Wald chi-square test starting with all variables associated with CKD in the univariable analysis at the P level of 0.20 or less. All analyses were performed using Stata software, version 15.1 (Stata Corp, College Station, Texas, USA).

Patient Consent Statement

This was a retrospective analysis using anonymized records collected for quality and financial purposes by the insurance system managed by the National Health Security Office (NHSO) in Thailand. The Ethical Committee of the Faculty of Medicine, Chiang Mai University, Thailand waived the requirement for patient consent and approved the design of the work on March 18, 2014 (114/2014, Research ID: COM-2557-02140). The work was performed in accordance with the Declaration of Helsinki.

Declarations

Funding

The authors did not receive any funding or scholarship for this study.

Acknowledgments

We would like to thank the National Health Security Office (NHSO), Thailand for providing the data, in particular Winai Sawasdivorn, Jadej Thammatacharee, Yolsilp Suchonwanich, Sinchai Tawwuttanakidgul, Suchada Chaivooth, Chirod Narkpaichit, Artit Pusamang, Pornpimol Sirimai, Sumitra Daengprasert, Sumalee Hiranmongkholkul, Traithep Fongthong, Kanjana Sirigomon, and Jutatip Thungthong. This research was supported by Chiang Mai University.

Authors contributions

N.P., K.N., G.J., A.T., N.K. and R.C. originally designed the study, which was discussed and reviewed by all co-authors. N.P., K.N., N.S. and J.Y.M. analyzed the data. N.P., K.N. and G.J. interpreted the analysis results and contributed to review the literature. N.P., K.N., G.J. and T.R.C. wrote the first draft of the manuscript, which commented and edited by all co-authors. G.J., K.N. and N.K. supervised the whole study process. All authors approved the final manuscript of this article prior to submission.

Funding acquisition: None reported

Competing Interests Statement

The authors declare that they have no competing interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Lond. Engl.* **395**, 709–733 (2020).
2. Calza, L. *et al.* Prevalence of chronic kidney disease among HIV-1-infected patients receiving a combination antiretroviral therapy. *Clin. Exp. Nephrol.* **23**, 1272–1279 (2019).
3. Vassalotti, J. A. & Winston, J. A. CKD in HIV-Infected Patients: From the New Plague to Chronic Care Management. *Am. J. Kidney Dis.* **65**, 823–825 (2015).
4. Winston, J. A. HIV and CKD epidemiology. *Adv. Chronic Kidney Dis.* **17**, 19–25 (2010).
5. Ekrikpo, U. E. *et al.* Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PloS One* **13**, e0195443 (2018).
6. Fernando, S. K., Finkelstein, F. O., Moore, B. A. & Weissman, S. Prevalence of chronic kidney disease in an urban HIV infected population. *Am. J. Med. Sci.* **335**, 89–94 (2008).
7. Liegeon, G. *et al.* Long Term Renal Function in Asian HIV-1 Infected Adults Receiving Tenofovir Disoproxil Fumarate Without Protease Inhibitors. *J. Infect.* (2019) doi:10.1016/j.jinf.2019.08.006.
8. Rossi, C. *et al.* Hepatitis C co-infection is associated with an increased risk of incident chronic kidney disease in HIV-infected patients initiating combination antiretroviral therapy. *BMC Infect. Dis.* **17**, 246 (2017).
9. Swanepoel, C. R. *et al.* Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* **93**, 545–559 (2018).
10. Chaivooth, S. *et al.* The challenges of ending AIDS in Asia: outcomes of the Thai National AIDS Universal Coverage Programme, 2000–2014. *J. Virus Erad.* **3**, 192–199 (2017).
11. World Health Organization. Update of recommendations on first- and second-line antiretroviral regimens. <https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/>.
12. Hsieh, M.-H. *et al.* Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan. *J. Microbiol. Immunol. Infect. Wei Mian Yu Gan Ran Za Zhi* **48**, 256–262 (2015).
13. Aekplakorn, W. *et al.* A risk score for predicting incident diabetes in the Thai population. *Diabetes Care* **29**, 1872–1877 (2006).
14. Jiamjarasrangsri, W. & Aekplakorn, W. Incidence and predictors of type 2 diabetes among professional and office workers in Bangkok, Thailand. *J. Med. Assoc. Thai. Chotmaihet Thangphaet* **88**, 1896–1904 (2005).
15. Jiamjarasrangsri, W., Lohsoonthorn, V., Lertmaharit, S. & Sangwatanaroj, S. Incidence and predictors of abnormal fasting plasma glucose among the university hospital employees in Thailand. *Diabetes Res. Clin. Pract.* **79**, 343–349 (2008).

16. Mocroft, A. *et al.* Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. *Lancet HIV* **3**, e23-32 (2016).
17. Pongpirul, W. *et al.* Chronic kidney disease incidence and survival of Thai HIV-infected patients. *AIDS Lond. Engl.* (2017) doi:10.1097/QAD.0000000000001698.
18. Suzuki, S. *et al.* Effect of Tenofovir Disoproxil Fumarate on Incidence of Chronic Kidney Disease and Rate of Estimated Glomerular Filtration Rate Decrement in HIV-1-Infected Treatment-Naïve Asian Patients: Results from 12-Year Observational Cohort. *AIDS Patient Care STDs* **31**, 105–112 (2017).
19. Achhra, A. C. *et al.* Kidney disease in antiretroviral-naïve HIV-positive adults with high CD4 counts: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Med.* **16 Suppl 1**, 55–63 (2015).
20. Lapadula, G. *et al.* Risk of Chronic Kidney Disease among Patients Developing Mild Renal Impairment during Tenofovir-Containing Antiretroviral Treatment. *PloS One* **11**, e0162320 (2016).
21. Kalyesubula, R. *et al.* Kidney disease in Uganda: a community based study. *BMC Nephrol.* **18**, 116 (2017).
22. Si, J. *et al.* Chronic hepatitis B virus infection and risk of chronic kidney disease: a population-based prospective cohort study of 0.5 million Chinese adults. *BMC Med.* **16**, 93 (2018).
23. Fabrizi, F., Cerutti, R. & Ridruejo, E. Hepatitis B virus infection as a risk factor for chronic kidney disease. *Expert Rev. Clin. Pharmacol.* **12**, 867–874 (2019).
24. Rwegerera, G. M., Bayani, M., Taolo, E. K. & Habte, D. The prevalence of chronic kidney disease and associated factors among patients admitted at princess marina hospital, Gaborone, Botswana. *Niger. J. Clin. Pract.* **20**, 313–319 (2017).
25. De Waal, R. *et al.* Changes in estimated glomerular filtration rate over time in South African HIV-1-infected patients receiving tenofovir: a retrospective cohort study. *J. Int. AIDS Soc.* **20**, 1–8 (2017).
26. Mocroft, A. *et al.* Chronic renal failure among HIV-1-infected patients. *AIDS Lond. Engl.* **21**, 1119–1127 (2007).
27. Scherzer, R. *et al.* A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. *AIDS Lond. Engl.* **28**, 1289–1295 (2014).
28. Flandre, P. *et al.* Risk factors of chronic kidney disease in HIV-infected patients. *Clin. J. Am. Soc. Nephrol. CJASN* **6**, 1700–1707 (2011).
29. Ambetsa, M. O. *et al.* Incidence and risk factors of renal dysfunction among HIV positive patients on Nevirapine based regimens at Kenyatta National Hospital. (University of Nairobi, 2014).
30. Manosuthi, W. *et al.* Renal impairment after switching from stavudine/lamivudine to tenofovir/lamivudine in NNRTI-based antiretroviral regimens. *AIDS Res. Ther.* **7**, 37 (2010).
31. Cressey, T. R. *et al.* Plasma and Intracellular Pharmacokinetics of Tenofovir Disoproxil Fumarate 300 mg Every 48 Hours vs 150 mg Once Daily in HIV-Infected Adults With Moderate Renal Function Impairment. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **61**, 633–639 (2015).
32. LaFleur, J. *et al.* Brief Report: Tenofovir-Associated Nephrotoxicity Among a US National Historical Cohort of HIV-Infected Veterans. *J. Acquir. Immune Defic. Syndr.* **1999** (2017) doi:10.1097/QAI.0000000000001608.
33. Levey, A. S. *et al.* A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **150**, 604–612 (2009).
34. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision, Version for 2010. <http://apps.who.int/classifications/icd10/browse/2010/en>.
35. Chapter 1: Definition and classification of CKD. *Kidney Int. Suppl.* **3**, 19–62 (2013).
36. American Diabetes Association. Standards of medical care in diabetes–2013. *Diabetes Care* **36 Suppl 1**, S11-66 (2013).
37. Jellinger, P. S. *et al.* American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* **18 Suppl 1**, 1–78 (2012).
38. Roger, V. L. *et al.* Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation* **125**, e2–e220 (2012).
39. Royston, P. & R. White, I. *Multiple Imputation by Chained Equation (MICE): Implementation in Stata*. vol. 45 (2011).

40. Loader, C. *Local regression and likelihood*. (Springer, 1999).
41. Lim, H. J., Zhang, X., Dyck, R. & Osgood, N. Methods of competing risks analysis of end-stage renal disease and mortality among people with diabetes. *BMC Med. Res. Methodol.* **10**, 97 (2010).
42. Fine, J. P. & Gray, R. J. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J. Am. Stat. Assoc.* **94**, 496–509 (1999).

Figures

Figure 1

Patients disposition

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Figure 2

Cumulative incidence function of chronic kidney disease with death as a competing risk by antiretroviral treatment regimen.

Data were adjusted for sex, age, history of type 2 diabetes, hypertension, gout, urolithiasis, serum creatinine levels, and propensity score stratification.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [S1.tif](#)
- [NinutchaPs3.6HIVCKDDMSupplementaryTable20211220.docx](#)