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Long term renal function in Asian HIV-1 infected adults receiving tenofovir disoproxil fumarate without protease inhibitors

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SUMMARY

Objectives: The risk of kidney dysfunction on the WHO recommended first line regimens containing tenofovir disoproxil fumarate (TDF) without protease inhibitors (PI) remains unclear in Asian patients, especially those with low body weight.

Methods: Using data collected in a multicenter clinical trial in Thailand and proportional hazard regression models, we compared the risk of a >25% estimated glomerular filtration rate (eGFR) reduction in HIV naïve patients initiating TDF or zidovudine (AZT) containing non-PI regimen.

Results: Of 640 patients included in the analysis, 461 (72%) received a TDF-containing regimen for a median 6.7 years and 179 (28%) an AZT-containing regimen for 6.5 years. The risk of a >25% eGFR reduction was not associated with treatment (HR 1.11, 95% CI 0.84–1.47, $P = 0.46$). In multivariate analysis, the risk of >25% eGFR reduction form baseline was associated with body weight at baseline (HR 2.12, 95% CI 1.48–3.02 for <48 kg patients and HR 1.64, 95% CI 1.20–2.25 for 48–59.9 kg patients, compared to those with >60 kg, $P < 0.001$) and hypertension (HR 4.03, 95% CI 2.0–8.0, $P < 0.001$). The effect of baseline weight on >25% eGFR reduction did not significantly vary with treatment ($P = 0.27$).

Conclusions: The risk of eGFR reduction was not higher on TDF- versus AZT-based non-PI regimens. Although the risk of eGFR reduction was greater for patients of lower body weight, this risk was not significantly increased by TDF.

Introduction

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTIs) widely used as part of the initial antiretroviral therapy (ART) for HIV-1 infected patients in low- and high- income countries following the current World Health Organization (WHO) recommendations.[1] TDF is also used in combination with emtricitabine for pre-exposure prophylaxis of HIV infection[1] and, in monotherapy, for the treatment of hepatitis B virus infection.[2] The availability of highly potent antiviral therapy has dramatically improved the survival of HIV infected patients but chronic kidney disease (CKD) has been recognized as one of the major HIV infection comorbidities.[3] Although TDF appeared safe in most HIV infected patients in the short term,[4] its use has been

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associated with a broad spectrum of kidney tubular dysfunction.[5–7] In combination with a boosted protease inhibitor (PI), the use of TDF is also associated with a higher risk of eGFR reduction which could increase the long-term risk of CKD.[8–14]

Previous studies in Asian HIV infected-patients have shown a progressive decline of eGFR on TDF treatment, especially in adults with low body weight.[10,15–20] However, the eGFR formulas used in these studies have not been validated in Asian HIV-infected patients and the concomitant use of protease inhibitors may have increased the risk of eGFR decline and chronic kidney disease in these patients.[15–20] In south east Asia, national guidelines for HIV management recommend a first line regimen containing two NRTIs, such as TDF or zidovudine (AZT), in association with one non-NRTIs (NNRTIs).[21] PI are mostly restricted to second line regimens for patients with immuno-virologic failure or severe intolerance to NNRTIs. The risk of eGFR reduction in Asian HIV-1 infected adults initiating antiretroviral therapy containing TDF in association with NNRTIs remains unclear.

In this study, we compared the long-term evolution of eGFR in patients on TDF or AZT as part of their first line regimen with no protease inhibitors in Thailand, using an eGFR equation validated for HIV infected Thai patients, and analyzed the role of weight in the risk of eGFR reduction. We additionally compared the results to those obtained using standard creatinine clearance equation.

Methods

Study design and subjects

Data for the analysis were collected within a multicenter, randomized, clinical trial in antiretroviral naïve HIV-infected patients initiating ART in 21 public hospitals throughout Thailand (PHPT-3, ClinicaTrials.gov NCT00162682) and during post-trial follow-up within the PHPT cohort (NCT00433030). The objective of the trial was to compare the risk of clinical failure according to switching decisions based on HIV RNA load or CD4 cell count monitoring.[22] On April 1, 2006, during the enrollment period, access to TDF-emtricitabine (FTC) fixed dose combination became available in the trial. For this analysis, we included all patients who initiated ART with TDF-FTC and nevirapine or efavirenz between April 1, 2006 and April 11, 2007, the date of enrollment ended. We used a historical control group composed of all patients who initiated AZT-lamivudine (and nevirapine or efavirenz) in the trial, between May 4, 2005, the date of first enrollment, and March 30, 2006, when TDF-FTC became available. We excluded from this analysis all patients with an eGFR <60 ml/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) with Thai racial factor at ART initiation (baseline).

Ethics statement

All enrolled patients provided written consent authorizing the use of their clinical and laboratory data for research purposes and publication. The study was approved by the Thai Ministry of Public Health and local Ethics Committees and has been conducted according to the principles expressed in the Declaration of Helsinki.

Data collection and management

After enrollment, patients attended the sites' clinics for routine physical examination, safety laboratory monitoring, drug refills and adherence counseling, monthly during the first 3 months of treatment, quarterly thereafter, or more often if needed. Baseline clinical and laboratory data included demographic variables (age, sex, weight, height, blood pressure), serum creatinine, CD4 cell count measured by flow cytometry, plasma HIV-RNA, history of any antiretrovirals drugs except for the prevention of mother-to-child transmission, presence of co-morbidities and AIDS defining events. In case of intolerance, the drug was replaced by another class of antiretroviral drugs. Hospital staff actively traced patients who missed visits through telephone calls and home visits. Data were collected prospectively at the hospital by nurses or physicians using case report forms sent to PHPT for double data entry and management. Adverse events were graded according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 and serious adverse events immediately reported to the Thai ministry of Public Health. Cause of death were reviewed by an independent committee.

Measurements

For each patient, the eGFR was estimated before initiation of antiretroviral therapy and quarterly thereafter. We used the original MDRD equation[23] corrected for Thais (using a "Thai racial factor") to estimate the GFR[24]:

$$\text{eGFR} = 186 \times \text{SCr}^{(-1.154)} \times \text{Age in years}^{(-0.203)} \times 0.724\ (\text{if female}) \times 1.129(\text{if Thai})$$

where serum creatinine (Scr) is expressed in mg/dL (creatinine measurements were performed before the implementation of the creatinine standardization program (National Kidney Disease Education Program). This equation has been demonstrated to be the most precise and accurate for the estimation of the eGFR in HIV-infected Thai patients.[25] We also estimated the creatinine clearance (CrCl) by Cockcroft & Gault equation adjusted by body surface area:

$$\text{CrCl} = [(140 - \text{Age in years}) \times \text{Body weight}/\text{SCr} \times 72]/\text{Body surface area} \times 0.85(\text{if female})$$

where Scr is expressed in mg/dL, body weight in kg and body surface area in square meters.

Study outcomes

In the comparison between treatment group (TDF versus AZT), the primary outcome measure was the time to >25% reduction in eGFR assessed by MDRD equation with Thai racial factor during the follow-up period. This threshold represents a clinically significant renal function decrease associated with an increased risk of end stage renal disease[26] and has been widely used in previous studies on the renal toxicity of ART.[15–18,27] The time to 25% decline in eGFR was calculated from baseline, i.e. the date of ART initiation. In a secondary analysis, we examined the same outcome in the following three weight categories: <48 kg, $\geq 48-<60$ kg and ≥ 60 kg, based on the lower and upper quartiles, following the method used in a previous study.[20] We chose to use weight rather than body mass index (BMI) in reference to previous studies showing that body weight was more strongly associated with a higher risk of significant eGFR reduction than BMI.[16,28] In order to explore the impact of a less accurate method to estimate eGFR on the results of the study, we compared our results with those obtained using Cockcroft and Gault equation. Finally, we estimated, between treatment group, the time to chronic kidney disease, the mean change in eGFR from baseline and the risk of deaths and adverse events.

Statistical analysis

Distribution of baseline characteristics of the patients were described, globally and per treatment group. Groups were compared using Fisher's exact test for categorical variables and the Wilcoxon rank-sum for continuous variables. Follow-up time from baseline

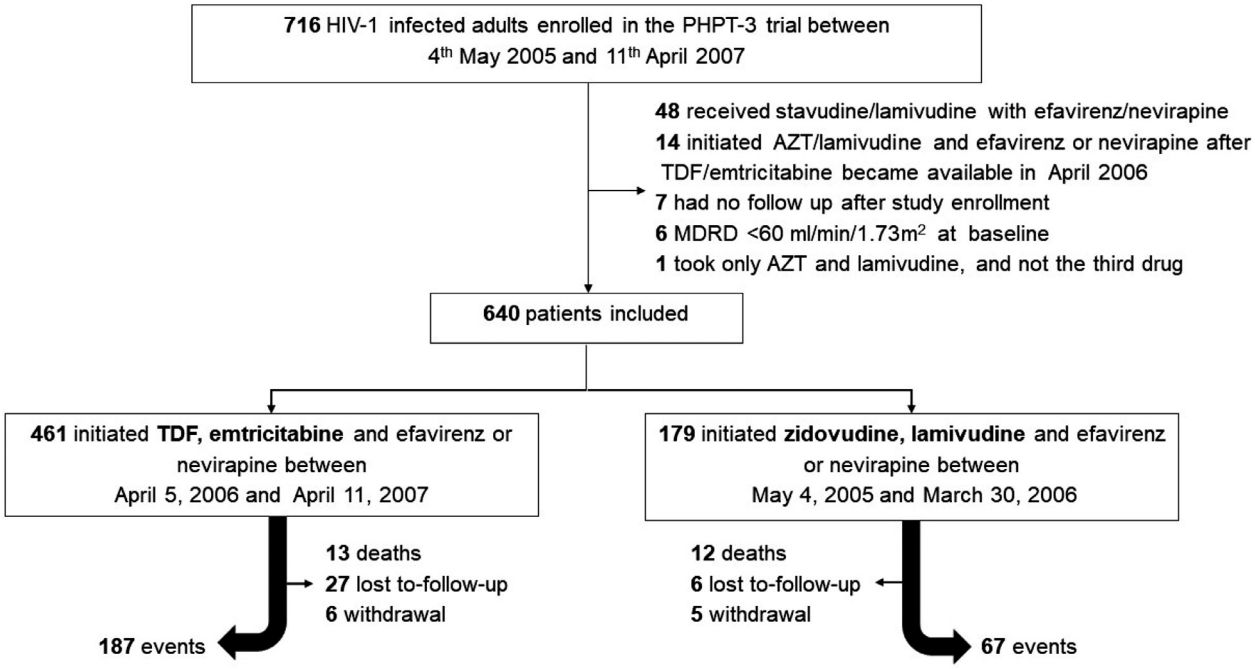

Fig. 1. Patient disposition.

was estimated through the reverse Kaplan-Meier method and time to >25% reduction in eGFR from baseline was estimated through Kaplan-Meier method. Cox proportional hazards models were used to compare the time to >25% reduction in eGFR from baseline. Patients were censored in the analysis at the time of death or loss to follow-up, or 3 months after last treatment when permanent discontinuation or switching of ART occurred. The effect of treatment, TDF versus AZT, baseline weight (categorized through first and third quartiles), gender, age (categorized through first, second and third quartiles), hypertension defined as blood pressure ≥140/90 mmHg and eGFR at baseline was studied through univariate Cox regression model. In addition, interaction between the effects of treatment group and of baseline weight as categorized was studied using Cox model with the variables drug, baseline weight and drug × baseline weight. Interaction was tested through likelihood ratio test. Then, the effects of treatment and of potential confounders including interaction between treatment and baseline weight were analyzed in a multivariate Cox model with a backward selection strategy based on the Wald test using covariates identified as possible predictors in the univariate analysis ($P < 0.20$). PASS software was used to estimate the sample size of a future study necessary to detect an interaction of the same magnitude as observed in this study with 80% power. Details are provided in the supplementary material. As a sensitivity analysis of the threshold of 25% used in the primary outcome, the same analyses were performed using either time to >20% or time to >30% reduction in eGFR from baseline. This analysis was repeated using the Cockcroft and Gault equation. Furthermore, Cox proportional hazards regression models were used to compute and compare the time to chronic kidney disease (CKD) defined as two consecutive measurements of eGFR <60 ml/min/1.73 m^2 at least 3 months apart. Finally, we estimated the mean change in eGFR between groups from baseline to 2, 5 and 7 years and collected deaths, adverse events and switches for toxicity during the follow-up. Statistical significance was considered if $P < 0.05$ (two-sided). Statistical analyses were performed using *SAS* software version 9.4.

Results

Patients and follow-up

Of the 716 HIV-1 infected adults enrolled in the PHPT-3 trial, 640 were eligible for this study including 461 (72%) who initiated an ART regimen containing TDF and 179 (28%) AZT (Fig. 1). Nineteen percent of the patients had an advanced stage of disease (stage C, CDC Classification System for HIV-infected adults). The baseline characteristics distribution were similar in the two treatment groups (Table 1): 62% were female, the median (interquartile range, IQR) age was 36 years (31–41), eGFR calculated by MDRD equation with Thai racial factor was 115 ml/min/1.73 m^2 (100–135). Patients who started TDF had a median (IQR) follow-up time of 6.7 years (5.5–6.9) and those on AZT 6.5 years (4.1–6.9). The last follow-up visit was on March 4, 2014.

Time to ≥25% reduction in eGFR from baseline

Over the first seven years of treatment, 187 patients experienced a >25% reduction in eGFR in the TDF group and 67 in the AZT group, i.e. a cumulative incidence of 41% (95% confidence interval (95% CI) 36–45) and 37% (95% CI 30–45), respectively. In univariate analysis, the difference between the two groups was not statistically significant (hazard ratio (HR) 1.11, 95% CI 0.84–1.47, $P = 0.46$). There was no effect of efavirenz relatively to nevirapine on the risk of >25% in eGFR reduction (HR 0.95, 95% CI 0.73–1.23, $P = 0.67$) in the univariate analysis. There was a significant association between baseline weight and risk of a >25% reduction in eGFR from baseline. Compared to patients with a body weight ≥60 kg, those with a lower weight had a greater risk of a >25% eGFR reduction (<48 kg: HR 2.12, 95% CI 1.48–3.02, $P < 0.01$; 48–59.9 kg: HR 1.64, 95% CI 1.20–2.25; $P<0.01$) (Table 2). There was no significant interaction between the effects of treatment group and baseline weight ($P = 0.27$). An illustration of the cumulative risk of eGFR reduction with time from baseline by treatment arm and by weight categories is represented in Fig. 2. Patients with

Table 1
Patient characteristics at antiretroviral initiation according to antiretroviral regimen.

		Total ($n=640$)	TDF containing regimen ($n=461$)	AZT containing regimen ($n=179$)	*P*-value
Gender	female	394 (62%)	287 (62%)	107 (60%)	0.59[a]
Age (years)		36 (31,41)	36 (32,41)	35 (30,40)	0.25[b]
Weight (kg)	<48	140 (22%)	107 (23%)	33 (18%)	0.42[a]
	≥48–<60	312 (49%)	222 (48%)	90 (50%)	
	≥60	188 (29%)	132 (29%)	56 (31%)	
Body mass index (kg/m^2)	underweight (<18.5)	118 (18%)	97 (21%)	21 (12%)	0.02[a]
	normal (≥18.5–<25)	450 (71%)	309 (67%)	141 (79%)	
	overweight (≥25–<30)	63 (10%)	47 (10%)	16 (9%)	
	obese (≥30)	9 (1%)	8 (2%)	1 (1%)	
Creatinine (mg/dl)		0.78 (0.60,0.90)	0.78 (0.64,0.90)	0.80 (0.62,0.90)	0.35[a]
eGFR by MDRD equation with Thai racial factor (ml/min/1.73m^2)		115 (100,135)	114 (100,135)	115 (99,137)	0.11[b]
CrCl adjusted for BSA calculated using the Cockcroft-Gault equation (ml/min/1.73m^2)		104 (88,121)	103 (88,120)	106 (88,124)	0.17[b]
CDC stage	A	364 (57%)	260 (57%)	104 (58%)	0.91[a]
	B	153 (24%)	112 (24%)	41 (23%)	
	C	123 (19%)	89 (19%)	34 (19%)	
CD4 (cells/mm^3)		148 (92,202)	144 (93,209)	155 (91,197)	0.93[b]
HIV viral load ($\log_{10}$(c/mL))		4.8 (4.2,5.2)	4.8 (4.3,5.2)	4.8 (4.2,5.2)	0.75[b]
Blood pressure	≥140/90 mmHg	12 (2%)	8 (2%)	4 (2%)	0.67[a]
Switching strategy assigned by randomization in the parent study	Guided by CD4 monitoring	323 (50%)	233 (51%)	90 (50%)	0.92[a]
	Guided by viral load monitoring	317 (50%)	228 (49%)	89 (50%)	
Antiretroviral regimens	TDF-FTC-EFV	370 (58%)	370 (80%)		
	TDF-FTC-NVP	91 (14%)	91 (20%)		
	AZT-3TC-EFV	59 (9%)		59 (33%)	
	AZT-3TC-NVP	120 (19%)		120 (67%)	

n (%) for qualitative items or median (IQR) for quantitative one
[a] Fisher exact test.
[b] Wilcoxon rank sum test.BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CrCl, Creatinine Clearance; BSA, Body Surface Area; ART, antiretroviral treatment; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; NVP, nevirapine; AZT, zidovudine; 3TC, lamivudine.

Table 2
Time from baseline to >25% reduction in eGFR estimated by MDRD equation with Thai racial factor.

		Univariable model		Multivariable analysis		Drug forced into the multivariable analysis	
	KM	HR (95% CI)	P^a	HR (95% CI)	P^a	HR (95% CI)	*P*
Drug							
AZT ($n=179$)	37%	1.00	0.46			1.00	0.46
TDF ($n=461$)	41%	1.11 (0.84,1.47)				1.11 (0.84,1.47)	
Baseline weight							
≥60 kg ($n=140$)	29%	1.00	<0.001	1.00	<0.001		
48–59.9 kg ($n=312$)	42%	1.64 (1.20,2.25)		1.74 (1.26,2.39)			
<48 kg ($n=188$)	49%	2.12 (1.48,3.02)		2.29 (1.59,3.29)			
Sex							
Male ($n=246$)	39%	1.00	0.38				
Female ($n=394$)	40%	1.12					
Age							
<31 years ($n=157$)	36%	1.00	0.96				
≥31 to <36 years ($n=176$)	41%	1.08 (0.63,1.53)					
≥36 to <41 years ($n=145$)	40%	1.08 (0.75,1.56)					
≥41 years ($n=162$)	42%	1.02 (0.72,1.45)					
Baseline eGFR adjusted for BSA (per 10 ml/min/1.73 m^2 increase)		0.99 (0.95,1.03)	0.52				
Baseline blood pressure							
<140/90 mmHg ($n=628$)	39%	1.00	0.02	1.00			
					P<0.001		
≥140/90 mmHg ($n=12$)	75%	2.99 (1.54,5.84)		4.01 (2.03,7.92)			

MDRD, Modification of Diet in Renal Disease; KM, Kaplan–Meier risk of failure at 7 years; HR, hazard ratio; 95% CI, 95% confidence interval; P^a, overall *P*-value; eGFR, estimated glomerular filtration rate; BSA, body surface area; AZT, zidovudine; TDF, tenofovir disoproxil fumarate.

hypertension also had a significantly higher risk of eGFR reduction than those with normal blood pressure (HR 2.99, 95% CI 1.54–5.84, $P=0.02$). Age, sex and baseline eGFR were not significantly associated with a greater risk of eGFR reduction (Table 2). In multivariate analysis, the risk of >25% eGFR reduction form baseline was only associated with a lower weight at baseline ($P < 0.001$) and hypertension (HR 4.01, 95% CI 2.03–7.92, $P<0.001$). The influence of treatment on >25% reduction in eGFR was not significant after adjustment on weight and hypertension (HR 1.11, 95% CI 0.84–1.47, $P=0.46$). The effect of the baseline weight on the risk of eGFR reduction was independent of the effect of the treatment in multivariate analysis with interaction (interaction $P=0.26$). The sample size necessary in a future study to detect a difference between the effect of weight on the risk of a >25% decrease in eGFR among

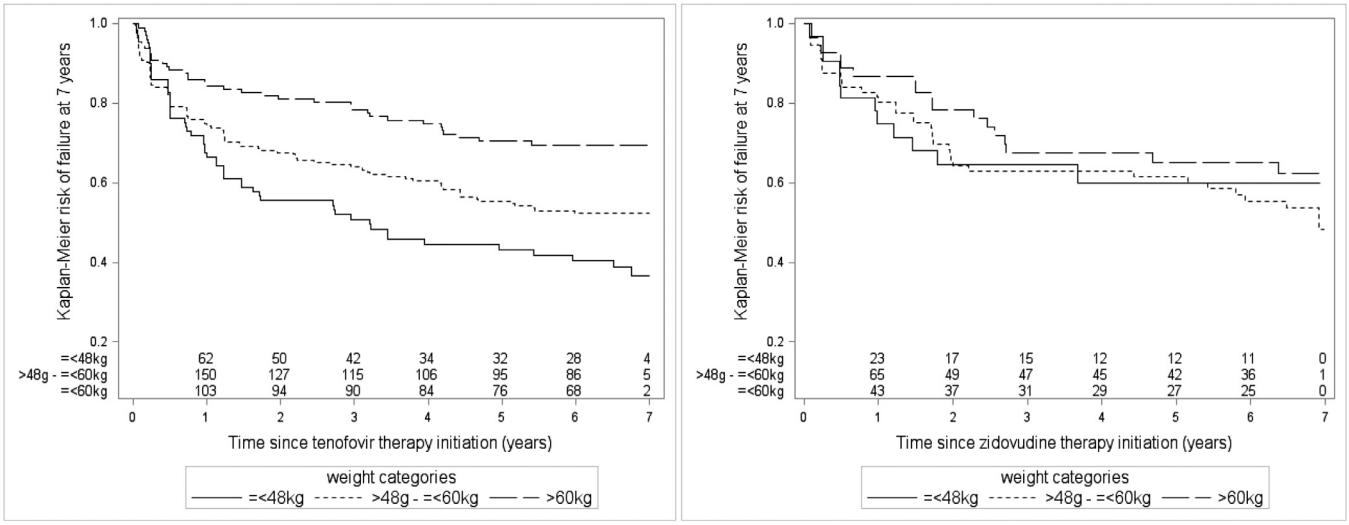

Fig. 2. Kaplan–Meier curves for time from baseline to >25% reduction in eGFR according baseline body weight in each treatment group.

Table 3
Classification of patients with and without a >25% reduction in renal function depending on the method used for the estimation of the glomerular filtration rate.

		CrCl by Cockcroft–Gault equation		Total
		>25% reduction in creatinine clearance	≤25% reduction in creatinine clearance	
eGFR by MDRD equation with Thai racial factor	>25% reduction in MDRD equation	195	60	255
	≤25% reduction in MDRD equation	5	380	385
	Total	200	440	640

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

patients treated by TDF and among patients treated by AZT, at a level of 0.40, similar to the one observed in our data, was 2635. When using time to >20% or time to >30% in eGFR reduction from baseline, very similar results were obtained in the univariate and multivariate analyses, baseline weight and hypertension remaining the two independent risk factors associated to the risk of eGFR reduction, whereas treatment remained not associated (Table S1).

Time to ≥25% reduction in creatinine clearance from baseline using the cockcroft and gault equation

The mean baseline clearance calculated using the Cockcroft and Gault equation was 11 mL/min/1.73 m² lower than when using MDRD equation with Thai racial factor (Table 1). In univariate analysis, the risk of a >25% reduction was not significantly different between treatment groups (HR 1.11, 95% CI 0.81–1.53, $P=0.50$) (Supplementary Table 1). The risk of a >25% reduction was lower in patients with a higher eGFR at baseline (HR=0.99, 95% CI 0.99–1, $P=0.03$) (Table S2), in contrast with the lack of association when using eGFR equation (HR 0.99, 95% CI 0.95–1.03, $P=0.52$) (Table 2). As observed with eGFR equation, there was no significant interaction between the effects of treatment group and baseline weight ($P=0.53$).

Comparisons between Cockcroft and Gault and MDRD equation with Thai racial factor

Table 3 shows the risk of a >25% reduction in creatinine clearance depending on the choice of method used for estimation of the glomerular filtration rate. The classification differed for a total of 65 patients (10%). Cockcroft and Gault equation underestimated the proportion of patients with >25% eGFR reduction in this population. On these 65 patients, 60 had > 25% eGFR reduction not detected by the Cockcroft and Gault equation. Using the MDRD equation with Thai racial factor as the reference, the sensitivity of the Cockcroft and Gault equation to detect >25% reduction in GFR from baseline would be 76% and the specificity 99%.

Changes in eGFR from baseline and risk of chronic kidney disease after art initiation

After two years of ART, there was a mean eGFR increase of 4.10 ml/min/1.73 m^2 (95% CI 1.02–7.18) on TDF and 6.15 ml/min/1.73 m^2 (95% CI 0.98–11.31) on AZT ($P=0.81$) followed by a decrease in each group, so that seven years after ART initiation there was a mean decrease of 2.53 ml/min/1.73 m^2 (95% CI −2.29–5.20) in the TDF group and 1.47 ml/min/1.73 m^2 (95% CI −4.82–−0.24) in the AZT group ($P=0.30$). Over the first seven years of follow-up, the cumulative risk of CKD was 4.5% in the TDF group and 1.1% in the AZT group (HR 3.67, 95% CI 0.90–16.5, $P=0.07$).

Deaths, adverse events and switches for toxicity

Over follow-up, 12 patients died in the TDF group (3%) and 12 (7%) in the AZT group. The cumulative risk of death was 2.30 (95% CI 1.05–5.03) times higher in the AZT group compared to the TDF group (Log-rank $P=0.04$). Eight discontinuations of TDF were related to kidney toxicity (permanent or temporary) (Table 4) and none in the AZT group. There were no kidney-related deaths in either group. In the TDF group, 95 patients (21%) experienced at least one grade 3/4 adverse event, compared to 39 (22%) in the AZT group ($P=0.19$). The risk of grade 3/4 kidney-related adverse events was 1.2% in the TDF group and 1.6% in the AZT group ($P=0.65$). A total of 122 (19%) permanent discontinuations were reported: 45 (10%) in the TDF group and 77 (43%) in the AZT group ($P<0.01$). In the AZT group this was mainly driven by neutropenia and anemia, and in the TDF group by virologic failure.

Table 4
Deaths, adverse events and switches for toxicity.

	Total ($n=640$)	TDF ($n=461$)	AZT ($n=179$)	P-value
Deaths	24 (4%)	12 (3%)	12 (7%)	0.04[a]
Possibly related to drug	4	2	2	
Not related to drug	20	10	10	
HIV related	5	4	1	
Infection	4	3	1	
Renal failure	1	1		
Not HIV related	14	5	9	
Accidental injury/suicide	5	3	2	
Hepatocarcinoma (HBV+)	1	1		
Cardiovascular	3	1	2	
Liver failure	2		2	
Asthma	1		1	
Ethylic coma	1		1	
Breast cancer	1		1	
Possibly HIV related	1	1		
Hepatic encephalopathy	1	1		
All adverse events (maximum grade)				0.19[a]
≤1	66 (10%)	53 (11%)	13 (7%)	
2	387 (61%)	284 (62%)	103 (58%)	
3	134 (21%)	95 (21%)	39 (22%)	
4	41 (7%)	21 (5%)	20 (11%)	
Adverse events related to the kidney (maximum grade)				0.65[a]
≤1	586 (92%)	422 (92%)	164 (92%)	
2	32 (5%)	24 (5%)	8 (5%)	
3	8 (1%)	6 (1%)	2 (1%)	
4	2 (0.3%)	1 (0.2%)	1 (0.6%)	
Study drug discontinuation				<0.01[a]
Remained on study drug	454 (71%)	373 (81%)	81 (45%)	
Temporarily discontinued study drug	53 (8%)	36 (8%)	17 (9%)	
For toxicity	18	10	8	
Kidney	2	2		
Lipodystrophy	1		1	
Other	15	8	7	
For immunological or virologic failure	1	1		
For other reasons	34	25	9	
Interruption	27	19	8	
Pregnancy	4	4		
Other	3	2	1	
Permanently discontinued study drug	122 (19%)	45 (10%)	77 (43%)	
For toxicity	71	12	59	
Kidney	6	6		
Lipodystrophy	5		5	
Neutropenia	15		15	
Anemia	23		23	
Other	22	6	16	
For immunological or virologic failure	22	12	10	
For other reasons	29	21	8	

[a] Log rank test; TDF, tenofovir disoproxil fumarate; AZT, zidovudine.

Discussion

In this large population of HIV-infected patients followed in a clinical trial, initiating a TDF-containing regimen in combination with an NNRTI did not result in a higher risk of a >25% eGFR reduction from baseline over a median period of follow-up of 6.7 years compared to patients initiating a AZT containing regimen. This was observed using the MDRD equation with Thai racial factor as well as using the Cockcroft and Gault equation although the latter seemed less sensitive to detect eGFR reduction than the former in this population. Our study also demonstrated that Asian patients with a low body weight have a higher risk of significant eGFR reduction independent of the ART regimen used.

To the best of our knowledge, this is the first study to compare the risk of long-term eGFR reduction on two first line ART regimens used in low and middle income countries. Going against previous studies conducted in Asia on the renal toxicity of TDF,[15–20] our study demonstrates that TDF-FTC containing regimens are not associated with an increased risk of significant eGFR reduction than other NRTIs based regimens in combination with NNRTIs as the third agent. Over the 7 years of follow-up, the cumulative risk of a >25% eGFR reduction on TDF was 41%, a risk similar to that observed in a Japanese cohort of HIV-infected patients on TDF-FTC: 22.1% after 3 years of follow-up[17] and 40.8% after 10 years.[18] The risk to experience CKD on TDF over 7 years was 4.5%, apparently lower than in a recent study in Thailand where it was 4.2% after 3 years,[29] though, in this study, the components of the ART combination were not specified. For comparison, the risk of CKD on TDF-FTC in combination with PI after twelve years of follow-up was 10.8% in a Japanese cohort,[20] and 2.97% after 3 years on TDF treatment in a cohort of non-Asian patients.[27]

Several studies have reported that the use of PIs is associated with a higher risk of kidney dysfunction.[9,11–14] PIs may adversely affect the renal function directly either through mitochondrial damage[30] or tubulo-interstitial nephritis,[31] and/or indirectly by increasing the TDF concentration in plasma[32,33] and decreasing its urinary secretion.[9,34] When 300 mg of TDF is administered with a ritonavir boosted PI, the tenofovir area under curve (AUC)

increases by a factor 1.22–1.37.[35] It is likely that this increase is more pronounced in individuals with low body weight, which explains previous reports from Asia and Europe, where patients of low body weight on TDF treatment had a greater risk of eGFR reduction than others NRTI regimen.[10,15–18,20,28] In the main Japanese cohort comparing a TDF- versus abacavir- (ABC) PI containing regimen, patients with a body weight <60 kg at baseline had a higher risk of eGFR reduction on TDF than ABC.[17] In contrast, our study showed that patients of low body weight had a greater risk of eGFR reduction independent of whether TDF or AZT was used, even though the median body weight was 10 kg lower than the Japanese study. Although the study lacks the power to evidence an interaction between treatment and weight on the risk of a >25% reduction in eGFR and even if Fig. 2 strongly suggests that the effect of weight on the risk of a >25% reduction in eGFR is not the same among patients treated by TDF than among patients treated by AZT, this differential effect could not be demonstrated in our study. It is likely that a low body weight, in absence of PI, is not a sufficient factor to cause a significant increase of TDF concentrations which could lead to eGFR reduction.

In addition to weight, the second risk factor associated with eGFR reduction was the presence of hypertension at baseline. Despite a small number of patients, the results obtained for this factor in all models studied has been very stable. Hypertension is a well-known risk factor of eGFR decline and CKD. Patients with hypertension at baseline could benefit of a non TDF-containing regimen when they cannot access to antihypertensive drug. Close monitoring of the renal function is warranted in Asian patients with low body weight or hypertension.

Several factors in HIV patients can impact creatinine production, renal secretion and extra-renal elimination, thus alter the relationship between serum creatinine level and GFR. Compared to healthy controls, the body composition of HIV-infected patients may experience a lower fat-free mass,[39,40] malnutrition or lipodystrophy and therefore a decreased creatinine production.[36] A strength of the study is that, for these reasons, we used an eGFR equation specifically validated in a cohort of HIV-infected Thai patients.[25] Among creatinine-based eGFR equations, it was the most precise and accurate to estimate GFR with a median underestimation of 6.2 mL/min/1.73 m^2 compared to the reference method using an isotopic plasma clearance measurement, while the Cockcroft and Gault formula underestimated the GFR by a median 30.4 mL/min/1.73 m^2. We showed that the interpretation of the results depends on the choice of the method to estimate GFR, which highlight the need to use validated equation of eGFR to conduct studies in this specific population.

Another strength of the study is that the data were collected within a clinical trial conducted in small and medium sized public hospitals closely monitored for quality over a long duration of time. The study population was probably more representative of HIV infected adults initiating ART in Thailand than studies conducted in highly specialized settings. The sex ratio male and female was more balanced than in studies conducted in Japan, where men, who are probably more at risk of eGFR decline than women, are over represented.[37,38]

A limitation for the conclusions of our study may be that AZT side-effects were a significant cause of discontinuation, which may have underestimated the risk of renal dysfunction in the AZT group that could have occur if AZT was not discontinued. Second, all the measures of creatinine were performed before the implementation of creatinine standardization measurement with calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure. The lack of standardization between laboratories may have caused variability in the measurement of creatinine level. It has been shown that the MDRD equation for non IDMS creatinine is less precise than MDRD equation calibrated for IDMS method.[39] and that calibration improves GFR estimates for high levels of GFR.[40] Third, most of our patients at ART initiation were significantly immunocompromised, a known risk factor for renal dysfunction.[41] Our results especially apply to this population. Fourth, the >25% decrement in eGFR used as the criterion for renal dysfunction excluded patients with chronic proteinuria or glycosuria on TDF treatment without eGFR decline. Thus, the incidence of TDF toxicity may have been underestimated but this allows for comparisons with other studies using the same criterion.

In conclusion, HIV infected-patients initiating TDF-containing antiretroviral combinations without protease inhibitors did not have at a higher risk of eGFR reduction or CKD compared with AZT containing regimens in Thailand. Our data did not show that patients with low weight had an increased risk of eGFR reduction on TDF compared to AZT.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Geoffroy Liegeon: Investigation, Writing - original draft, Writing - review & editing. **Linda Harrison:** Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Anouar Nechba:** Investigation, Data curation, Formal analysis, Writing - review & editing. **Guttiga Halue:** Data curation, Writing - review & editing. **Sukit Banchongkit:** Data curation, Writing - review & editing. **Ampaipith Nilmanat:** Data curation, Writing - original draft, Writing - review & editing. **Naruepon Yutthakasemsunt:** Writing - review & editing. **Panita Pathipvanich:** Writing - review & editing. **Suchart Thongpaen:** Writing - review & editing. **Rittha Lertkoonalak:** Data curation, Writing - review & editing. **Thomas Althaus:** Investigation, Writing - original draft, Writing - review & editing. **Marc Lallemant:** Data curation, Writing - review & editing. **Jean-Yves Mary:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Gonzague Jourdain:** Investigation, Writing - original draft, Writing - review & editing.

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Supplementary materials

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