ปัจจัยที่มีผลต่อการเกิดอาการไม่พึงประสงค์ทางไตของผู้ป่วยติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัส Tenofovir disoproxil fumarate ณ โรงพยาบาลดำเนินสะดวก
Factors Affecting Renal Adverse Reactions in HIV Infected Patients Receiving Tenofovir Disoproxil Fumarate at Damnoen Saduak Hospital

นิพนธ์ต้นฉบับ **Original Article**

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ2564;16(3):219-227.

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่มีผลต่อการเกิดอาการไม่พึงประสงค์ทางไตของผู้ป่วยติดเชื้อเอชไอวีที่ได้รับยา tenofovir disoproxil fumarate (TDF) และระยะเวลาที่พบอาการไม่พึงประสงค์ทางไตที่ได้รับยา TDF **วิธีการศึกษา:** เป็นการศึกษาเชิงวิเคราะห์แบบเก็บข้อมูลย้อนหลังจากเวชระเบียนในผู้ติดเชื้อเอชไอวีทุกรายของโรงพยาบาลดำเนินสะดวกที่ได้รับยา TDF ระหว่างวันที่ 15 พฤษภาคม 2553 ถึง 30 เมษายน 2564 จำนวน 415 คน ทดสอบความสัมพันธ์ระหว่างการเกิดอาการไม่พึงประสงค์ทางไต (ค่า glomerular filtration rate (eGFR) ลดลงมากกว่าร้อยละ 25 ก่อนเริ่มยา TDF) กับปัจจัยต่าง ๆ ด้วย multiple logistic regression และเวลาที่เกิดอาการไม่พึงประสงค์กับปัจจัยต่าง ๆ ด้วย multiple linear regression **ผลการศึกษา:** ผู้ป่วยมีอายุเฉลี่ย 41.63 ± 11.92 ปี พบผู้ที่มีค่า glomerular filtration rate (eGFR) ลดลงมากกว่าร้อยละ 25 ร้อยละ 9.64 ปัจจัยที่มีผลต่อการเกิดอาการไม่พึงประสงค์ต่อไตเพิ่มขึ้น ได้แก่ การมีค่า eGFR ก่อนเริ่มยา TDF น้อยกว่า 90 ml/min/1.73m² (adjusted OR or aOR = 4.14; 95% CI = 1.74, 9.89) มีเบาหวานเป็นโรคร่วม (aOR = 4.46; 95% CI = 1.65, 12.11) ส่วนการใช้ยาต้านไวรัสเอชไอวีนานกว่า 120 เดือน สัมพันธ์กับความเสี่ยงที่น้อยลง (aOR = 0.36; 95% CI = 0.13, 1.00) พบว่าระยะเวลาของการรับยาต้านไวรัสเอชไอวีที่นานมีผลต่อระยะเวลาที่พบอาการไม่พึงประสงค์ทางไตที่ช้าลง (B = 0.39; 95% CI = 0.13 – 0.65) **สรุป:** ปัจจัยที่เสริมความเสี่ยงการเกิดอาการไม่พึงประสงค์ได้แก่ ค่า eGFR ก่อนเริ่มยา TDF น้อยกว่า 90 ml/min/1.73m² และการมีเบาหวานเป็นโรคร่วม ปัจจัยที่ลดความเสี่ยง ได้แก่ การใช้ยาต้านไวรัสเอชไอวีนานกว่า 120 เดือน เมื่อใช้ยาต้านไวรัสเอชไอวีนานขึ้นเวลาที่พบอาการไม่พึงประสงค์ทางไตก็นานขึ้น

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Abstract

Objective: To examine factors affecting renal adverse reactions and onset of renal adverse reactions in HIV-infected patients receiving tenofovir disoproxil fumarate (TDF). **Methods:** In this retrospective analytical study, 415 patients with HIV-infected patients in Damnoen Saduak hospital who received TDF between 15 May 2010 and 30 April 2021 were recruited. Association between renal adverse reactions, i.e., glomerular filtration rate (eGFR) decrease of more than 25% before TDF initiation, and various factors was tested using multiple logistic regression analysis; while time to the renal adverse reactions with factors was tested using multiple linear regression. **Results:** Patients were 41.63 ± 11.92 years old by average. 9.64% of them had a significant decrease in eGFR more than 25%. Factors significantly associating with increased risk of renal adverse reactions included initial eGFR of less than 90 ml/min/1.73m² (adjusted OR or aOR = 4.14; 95% CI = 1.74, 9.89) and diabetes mellitus (aOR = 4.46; 95% CI = 1.65, 12.11); while antiretroviral (ARV) drug use of more than 120 months was associated with a reduced risk (aOR = 0.36; 95% CI = 0.13, 1.00). Longer duration of ARV drug use was associated with longer (or slower) onset of renal adverse reaction (B = 0.39; 95% CI = 0.13 – 0.65). **Conclusion:** Factors increased the risk of renal adverse reaction included eGFR before TDF initiation of leass than 90 ml/min/1.73m² and diabetes mellitus; while the use of ARV drug more than 120 months decreased the risk. The longer the ARV drug use, the longer the onset of the renal adverse reaction use.

Keywords: tenofovir disoproxil fumarate, renal adverse reaction, HIV, risk factor

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Introduction

Tenofovir disoproxil fumarate (TDF) is one of nucleoside reverse transcriptase inhibitors (NRTIs). As a prodrug, TDF is phosphorylated to tenofovir -diphosphate (TFV-DP) in the plasma. TFV-DP, by competing with the natural substrate deoxyadenosine 5'-triphosphate, inhibits reverse transcriptase enzyme, therefore the formation of viral DNA strand is disrupted, and viral replication is inhibited. Frequent side effects of TDF include diarrhea, nausea and vomiting, stomach upset, flatulence, and kidney toxicity.[1,2]

In Thailand, TDF has been used as the first anti-retroviral viral (ARV) regimen in the National Guidelines on HIV/AIDS Diagnosis and Treatment of Thailand since 2010 to 2021.[3,4] TDF is used with other ARV medications in patients 12 years old or older with a dose of 300 mg per day. Recently, TDF products are available in combination pills with other ARV

medications for the patient's convenience such as efavirenz (EFV) + emtricitabine (FTC) + TDF (brand name of Teevir®) and FTC + TDF (Teno-EM®).

TDF is an effective ARV drug with its low resistance rate and high tolerance. However, with its long-term daily use, its adverse effect of renal impairment is prominent and causes TDF dose adjustment or regimen change. Renal impairment caused by TDF includes acute kidney injury, chronic kidney failure, Fanconi syndrome, diabetes insipidus, increased serum creatinine level, and albuminuria.[3-5] TDF in the parent form is excreted through kidney by glomerular filtration and tubular secretion.[1,2] The risk of kidney injury could be increased by any factors that cause TDF renal accumulation or decreased excretion.

TDF-related renal impairment could be acute and chronic in nature. Acute kidney failure (or acute renal failure) is developed in a short period of time starting with reduced urinary output, urinary retention, leg and foot edema, appetite loss, lethargy, back pain, and shortness of breath. Patients could be asymptomatic until symptoms of seizure and comatose state as severe acute state of kidney injury is reached. For TDF-related chronic kidney failure (or chronic renal failure), symptoms are gradually developed and manifested. Five stages of chronic kidney failure are based on estimated glomerular filtration rate (eGFR) which reflects the extent of waste filtrated from the blood with a normal function of 90 – 100 mL/min.[6] The Acute Dialysis Quality Initiative (ADQI) defines patients with the risk of renal impairment as those with a 1.5-folds increase in serum creatinine (SCr), at least 25% decrease of baseline GFR, or a urination rate of less than 0.5 mL/kg/hour for six hours.[7]

In addition to medications like TDF, renal impairment could be caused by other factors[8] such as polycystic kidney disease which is a genetic related disease. Long standing hypertension worsens kidney impairment. Diabetes mellitus contributes about 30% of chronic kidney disease. Geographically, in northern and northeastern parts of Thailand, kidney stone was more prevalent than other regions. Obesity also contributes to the cause of which obese persons had metabolism higher than their normal weight counterparts resulting in more burden of kidney excretion function. Physiologically, higher age is associated with decreasing the kidney function of which the decrease starts as early as 35 years of age. Long-term consumption of certain foods such as salty foods, fermented products, fatty meat, and beans could pose more burden on kidney excretion function. Certain occupations allow more chance of kidney injury than others. Boxers could be physically attacked on the body which could directly harm the kidney while factory workers could be exposed with chemicals accumulated to a level toxic to the kidney.

A review showed that incidence of TDF-related renal impairment was 10% to 22% among Europeans and 5% to 18% in Thais.[9] The review stated that based on studies in countries other than Thailand, renal impairment of TDF is increase with previous use of ARV drugs especially protease inhibitors (PIs). Fanconi's syndrome is the most found renal impairment of TDF. The most severe form of renal impairment related to TDF is acute kidney failure which is found in 0.5% to 1.5% of patients taking the drug. TDF-relate renal impairment could be normalized when the drug has been discontinue for 2 to 4 months. The onset of renal impairment has been found as early as 5 weeks to 16 months. Clearance creatinine level decreases after the start of TDF for 6 months to 3 years. Risk of renal impairment increases with the longer duration of TDF use. Severity of TDF-related renal impairment depends on accumulated amount of the drug in the cell of proximal renal tubules.[9]

In Thailand, incidence rates of TDF-related renal impairment were reported to be 30%, 26.60%, 19.30%, 13.98% and 5.68% in studies of Pengthina10, Petchkum and Suphanchaimat[11], Chayangsu[12], Suwan and Kornjirakasemsan[13] and Aswatiwong[14], respectively. In countries other than Thailand, incidence rate of 14.80% was reported in Korea[15], 5.6% in India[16], and 2.7% in China.[17] A vast difference of incidence of among studies could be attributable in part to differences in definition of the decrease in renal function. For example, while a study defined renal impairment as a decrease of ClCr of more than 25%[10], another one defined it as a decrease of eGFR of more than 50%.[11] Another study in Thai patients defined renal impairment in association with tenofovir when eGFR deceased to the levels of CKD stage 3 and 4.[16] Discrepancy in TDF-related renal impairment incidence was also differences in time of study conduct of which some studies were conducted many years ago, number of patients included and demographic and clinical status of the patients among studies.

Renal impairment was manifested as early as 1 week after the start of TDF.[10] Previous studies revealed that TDF-related renal impairment was associated with concomitant use of

protease inhibitors[10,14,18], comorbidities of diabetes, hypertension or hyperlipidemia[13,14], body mass index (BMI) of 18.50 kg/m^2 or lower[13,16], CD4 cell count of less than 200 cell/mm^3 before TDF initiation[13,16], eGFR of less than 60 ml/min/1.73 m^2 before TDF initiation.[14] A study reported that creatinine clearance (Clcr) level of 50-89 ml/min and less than 50 ml/min before TDF initiation was associated with a lower risk of renal impairment than those with Clcr level of 90 ml/min or higher.[10] Another study found that patients who were older than 50 years and those receiving angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) concomitantly with TDF were more likely to develop renal impairment than their counterparts.[13]

Studies on the association between the use of TDF and its renal impairment in Thailand have certain limitations. Some studies used retrospective design with a relatively short duration of follow-up, or patients included had relatively normal kidney function. Certain studies included patients 16 years old or older while others included those 18 years old or older. At present, it is recommended that TDF could be started in patients 12 years old or older with a dose of 300 mg once daily. In the past, based the recommendation in 2010, patients were given ARV drugs when CD4 cell count was less than 350 cell/mm3 while present guideline recommended ARV drugs initiation regardless of CD4 cell count. In addition, different factors affecting the renal impairment of TDF with different levels of risk were reported by these studies. There is a need to determine a comprehensive set of factors simultaneously affecting TDF-related renal impairment.

At present, renal impairment is defined as a decrease of eGFR of 25% or higher. More studies on incidence of TDF-related renal impairment based on new definitions have been needed. In addition, time since TDF initiation to the renal impairment has not been clear, so we wanted to examine the time to the occurrence the renal toxicity. Specifically we retrospectively examined potential factors that could affect the renal toxicity of TDF and factors potentially affecting the time to the occurrence of the toxicity. Findings could be useful in vigilance on renal toxicity associated with TDF and modification of certain factors to delay the occurrence.

In our present study, we aimed to determine renal adverse reaction, specifically renal impairment, among HIV infected patients receiving TDF who were 12 years old or older with the TDF dose of 300 mg once daily regardless of their kidney function and CD4 cell count as recommended. The initiation of TDF regardless of CD4 cell count allows early treatment with ARV drugs which could in turn lead to more chance of renal impairment. Longer duration of TDF treatment could be expected to relate to a higher risk of renal impairmen but no studies have been conducted to prove such association. In addition, based on our experience in clinical practice at Damnoen Saduak Hospital, some patients developed TDF-related renal impairment within a short period of TDF use while others have not experienced such event even with a long duration of use. Factors affecting the onset time of developing TDF-related renal impairment which is a renal adverse reaction was of great concern. Specifically, we aimed to determine factors associated with renal impairment incidence defined as a glomerular filtration rate (eGFR) decrease of more than 25% before TDF initiation, and factors associated with the onset time of developing such renal impairment. These factors included age, occupation, body mass index, comorbidity, concomitant use of drugs with renal impairment potential, time since ARV drugs initiation, use of TDF as the first regimen, time since TDF initiation, PI as a concomitant ARV drug, baseline CD4 cell count, eGFR before TDF initiation, and Scr level before TDF initiation.

Methods

In this retrospective study, data from medical records and computerized database were used for analysis. Study population was all HIV infected patients of Damnoen Saduak Hospital who took TDF 300 mg tablet or any combined tablets containing TDF. Treatment of HIV and AIDs in Damnoen Saduak Hospital was initiated in April 2002. TDF has been available at this hospital since December 2008. For individual patients, date of their first TDF exposure was verified. For those whose HIV treatment was switched from other regimens to TDF, their previous ARV regimen was recorded. These patients were those who had ARV resistance, contraindication to certain ARV drugs for example contraindication to zidovudine (AZT) because of anemia, or regimen changes guided by new guidelines. A total of 486 HIV infected or AIDS patients who had used TDF as our study population.

From the 486 patients as study population, patients who were eligible were 12 years old or older, with or without co-morbid diseases, with at least one eGFR result within one year before TDF initiation, and with at least one eGFR result each year after TDF initiation. Patients who were lost to regular

appointed visits at Damnoen Saduak Hospital for more than 6 months were excluded. The sample size was estimated based on the equation of n = 10k/p where k = number of independent variables and p was the proportion of main study outcome which was the proportion of patients using TDF who experienced renal impairment. With 15 independent variables to be tested, and proportion of 5.68% to 30.00% of TDF-related renal impairment reported by studies in Thailand[11-14], the required sample was from 500 to 2641 patients. With a study population of 486 patients, this study could be underpowered. However, in the final analysis, if not all independent variables were tested simultaneously, the required sample size for such number of independent variables was re-evaluated.

Outcome and factors measurement

In this study, the outcome of kidney function impairment was defined as a decrease of eGFR by more than 25% of the eGFR before TDF initiation. Time to the kidney function impairment was measured in months. Measures of study potential factors included age, occupation, and body mass index before TDF initiation, comorbidity before TDF initiation and during its use, drugs with renal impairment potential used concomitantly with TDF, duration of ARV drugs use including TDF until the end of study (i.e., April 30, 2021) or the occurrence of TDF-related renal impairment (in months), use of TDF as the first or switched regimen, time since TDF initiation in months, PI used concomitantly with TDF, and latest CD4 cell count, eGFR level and Scr level before TDF initiation as the baseline values.

Data collection instrument

Data collection form was designed by the researcher based on literature review. We collected gender, age at TDF initiation, occupation, body mass index at TDF initiation, comorbidity before TDF initiation and during its use, drugs with renal impairment potential used concomitantly with TDF including angiotensin-converting enzyme inhibitors (ACEIs). angiotensin receptor blockers (ARBs), and non-steroidal anti-inflammatory drugs (NSAIDs), duration of ARV drugs use including TDF until the end of study (i.e., April 30, 2021) or the occurrence of TDF-related renal impairment, use of TDF as the first or switched regimen, time since TDF initiation in months, time since TDF initiation in months before discontinuation or dose reduction if any, PI used concomitantly with TDF, and latest CD4 cell count, and eGFR and Scr levels before TDF initiation as the baseline values till the end of the study which was April 30, 2021.

The form was examined for content validity in relation to research objectives by three experts including an internal medicine specialist practicing in the HIV clinic of Damnoen Saduak Hospital, a university instructor specialized in research methodology, and a hospital pharmacist well experienced in clinical pharmacy practice and research.

Data collection procedure

Data from medical records both paper-based records and electronic database were extracted. Since there were no patient's information on social behavior, dietary behavior, and family history involved in our study, the patient was not interviewed.

Ethics consideration

The study protocol was approved by the Ethics Committee for Human Study of Damnoen Saduak Hospital (Approval number: 17/2564; approval date: May 17, 2021; expiration date: May 17, 2022). The conduct was permitted by the hospital director.

Data analysis

Descriptive statistics including frequency with percentage and mean with standard deviation (SD) or median with inter-quartile range (IQR) as appropriate were used to present demographic and clinical status data (i.e., age, occupation, body mass index, comorbidity, concomitant use of drugs with renal impairment potential, duration of ARV drugs use including TDF until the end of study (i.e., April 30, 2021) or the occurrence of TDF-related renal impairment, use of TDF as the first regimen, time since TDF initiation, PI as a concomitant ARV drug, baseline CD4 cell count, eGFR before TDF initiation, and Scr level before TDF initiation).

Since certain factors have been inconclusively determining the occurrence of TDF-related renal impairment, we tested each of all of these factors in the univariate logistic regression analysis. The likelihood of renal impairment associated with each factor was reported as crude and adjusted odds ratio (OR and aOR, respectively) with 95% confidence interval (CI). A multiple logistic regression analysis to the test all factors together was also conducted. To test the effect of each of all factors mentioned above on time to the occurrence of TDF-related renal impairment, linear regression analyses, both univariate and multiple variable, were conducted. In this linear

regression, duration of TDF use was not put in the regression as a factor since it was identical to the duration until the TDF-related renal impairment occurred which was the dependent variable. Statistical significance was set a type I error of 5% (i.e., *P*-value < 0.05). All analyses were performed using STATA version 14 (copyright of Faculty of Pharmaceutical Sciences, Chiang Mai University).

Results

Of the 486 patients in the database, 415 patients were eligible for the study (Table 1). Patients excluded were those with no eGFR prior to TDF initiation, no eGFR result after TDF initiation and lost to regular appointed visit for more than 6 months. Of these 415 patients, the majority were in their 41 – 60 years of age (53.49%). Their mean age was 41.63 ± 11.92 years old. The youngest and oldest patients were 12 and 75 years old, respectively. Slightly more than half of them were men (54.22%). The majority were general labors (59.52%). Almost two-thirds had their BMI in the range of 18.50 - 24.90 kg/m^2 (61.45%) with a mean BMI of all patients of 21.70 ± 4.32 kg/m^2. Almost half of them had at least one comorbid illness (44.58%). Of these with co-morbidities, hyperlipidemia was found in 36.87%, hypertension in 17.35%, and diabetes mellitus in 7.95%. Most patients did not use any medications with renal impairment potential (90.84%). The majority had taken ARV drugs for more than 120 months (40.24%). Their median duration of ARV drug use was 86 months (IQR: 110 or 39 - 149). Almost three-quarters had taken TDF for 13 – 60 months (73.25%). Their median duration of TDF use was 37 months (IQR: 31 or 21 - 52). The shorted duration of TDF use was 0.47 months or 14 days while the longest one was 149 months. Slightly more than half of the patients were ARV naïve, i.e., TDF was their first ARV drug (57.35%). Other ARV medications used concomitantly with TDF were mostly non-nucleoside reverse transcriptase inhibitors (NNRTIs) (87.47%). The majority had CD4 cell count before TDF initiation of more than 350 cells/μL (54.37%). Median of CD4 cell count of all patients prior to TDF initiation was 382 cells/μL (IQR: 412 or 183 - 595). Most of the patients had eGFR before TDF initiation of 90 ml/min/1.73 m^2 or higher (83.37%) with a mean from all patients of 106 ± 17.94 ml/min/1.73 m^2. These patients had a mean Scr lelvel before TDF initiation of 0.78 ± 0.19 mg/dL with the majority of them had Scr level of less than 1 mg/dL (93.25%).

In terms of the study outcome, 40 of 415 patients experienced a decrease of eGFR of 25% or higher (9.64%). In addition to the study outcome, there were 6.99% (29 of 415 patients) having Scr increase more than 1.5 folds from baseline and 6.51% (27 of 415 patients) having both eGFR decrease of at least 25% and Scr increase of more than 1.5 folds from baseline (Table 1).

Table 1 Demographic characteristics and clinical status of participants (N = 415).

Factors	N (%) of all 415 patients	N (%) of patients with eGFR decrease ⩾ 25% from baseline	
		No (n = 375)	Yes (n = 40)
Gender			
Men	225 (54.22)	204 (90.67)	21 (9.33)
Women	190 (45.78)	171 (90.00)	19 (10.00)
Age (years),			
Mean ± SD (min - max)	41.63 ± 11.92 (12 - 75)	41.01 ± 11.80 (12 - 75)	47.42 ± 11.67 (12 - 72)
Age group (years)			
≤ 20	25 (6.02)	23 (92.00)	2 (8.00)
21–40	151 (36.93)	145 (96.03)	6 (3.97)
41–60	222 (53.49)	194 (87.39)	28 (12.61)
≥ 60	17 (4.10)	13 (76.47)	4 (23.53)
Occupation			
General labors	247 (59.52)	223 (90.28)	24 (9.72)
Small business	42 (10.12)	36 (85.71)	6 (14.29)
Agriculture	41 (9.88)	39 (95.12)	2 (4.88)
Freelance/business employees	33 (7.95)	31 (93.94)	2 (6.06)
Government employees	6 (1.45)	5 (83.33)	1 (16.67)
No occupation	44 (10.60)	39 (88.64)	5 (11.26)
Unknown	2 (0.48)	2 (100.00)	0
Body mass index (kg/m^2)			
Mean ± SD (min - max)	21.70 ± 4.32 (11.28 - 46.68)	21.68 ± 4.32 (11.28 - 46.68)	21.91 ± 4.32 (14.36 - 34.96)
Body mass index group (kg/m^2)			
< 18.50	89 (21.45)	872 (92.13)	7 (7.87)
18.50 – 24.90	255 (61.45)	230 (90.20)	25 (9.80)
≥ 25.00	71 (17.11)	63 (88.73)	8 (11.27)
Co-morbidity			
No	230 (55.42)	223 (96.96)	7 (3.04)
Yes (number of diseases)	185 (44.58)	152 (82.16)	33 (17.84)
1	112 (2.99)	95 (84.82)	17 (15.18)
2	58 (13.98)	47 (81.03)	25 (9.80)
3	14 (3.37)	10 (71.43)	8 (11.27)
Type of co-morbidity			
Hyperlipidemia			
No	262 (63.13)	249 (95.04)	13 (4.96)
Yes	153 (36.87)	126 (82.35)	27 (17.65)
Hypertension			
No	343 (82.65)	318 (92.71)	25 (7.29)
Yes	72 (17.35)	57 (79.17)	15 (20.83)
Diabetes mellitus			
No	382 (92.05)	352 (92.15)	30 (7.85)
Yes	33 (7.95)	23 (69.70)	10 (30.30)
Concomitant use of drugs with renal toxicity potential			
No	377 (90.84)	344 (91.25)	33 (8.75)
Yes (on ACEIs/ARBs found)	38 (7.71)	31 (81.58)	7 (18.42)
Duration of ARV drug use[$] (months)			
Median duration of ARV drug use			
Median (IQR)	86 (110 or 39 - 149)	84 (110 or 38 - 148)	92 (115 or 49.5 – 164.5)
(min - max)	(0.47 - 229)	(3 - 229)	(0.47 - 220)
Duration of ARV drug use[$]			
≤ 12	3 (7.47)	28 (90.32)	3 (9.68)
13 – 60	144 (34.70)	136 (94.44)	8 (5.56)
61 – 120	73 (17.59)	60 (82.19)	13 (17.81)
> 120	167 (40.24)	151 (90.42)	16 (9.58)

(continued)

[$] Duration of ARV drug use including TDF until occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021) (months).

Table 1 Demographic characteristics and clinical status of participants (N = 415). **Continued**

Factors	N (%) of all 415 patients	N (%) of patients with eGFR decrease ⩾ 25% from baseline	
		No (n = 375)	Yes (n = 40)
Duration of TDF use till renal impairment (months)			
Median duration of TDF use			
Median (IQR)	37 (31 or 21 - 52)	38 (29 or 22 - 51)	34.5 (50.5 or 19.5 - 70)
(min - max)	(0.47 - 149)	(3 - 149)	(0.47 - 125)
Duration of TDF use			
≤ 12	40 (9.64)	35 (87.50)	5 (12.50)
13 – 60	304 (73.25)	281 (92.43)	23 (7.57)
61 – 120	54 (13.01)	44 (81.48)	10 (18.52)
> 120	17 (4.10)	15 (88.24)	2 (11.76)
TDF as first ARV regimen			
Yes	177 (42.65)	165 (93.22)	12 (6.78)
No	238 (57.35)	210 (88.24)	28 (11.76)
ARV drugs used concomitantly with TDF			
NNRTIs based regimen	363 (87.47)	333 (91.74)	30 (8.26)
PIs based regimen	52 (12.53)	42 (80.77)	10 (19.23)
Median CD4 cell count before TDF initiation (cells/μL)			
Median (IQR)	382 (412 or 183 - 595)	381 (400 or 183 - 583)	417.5 (440 or 176 - 616)
(min - max)	(5 - 1,518)	(5 - 1,518)	(37 - 877)
CD4 cell count before TDF initiation (cells/μL)			
≤ 50	41 (9.95)	40 (97.56)	1 (2.44)
51 - 200	66 (16.02)	55 (83.33)	11 (16.67)
201 - 350	81 (19.66)	74 (91.36)	7 (8.64)
> 350	224 (54.37)	203 (90.63)	21 (9.38)
eGFR before TDF initiation (ml/min/1.73m²)			
Mean ± SD (min - max)	106 ± 17.94	107.71 ± 16.64	89.95 ± 21.63
	(49.37 - 159.03)	(56.25 - 159.03)	(49.37 - 128.34)
eGFR before TDF initiation (ml/min/1.73m²)			
≥ 90.00	346 (83.37)	322 (93.06)	24 (6.94)
89.99 - 60.00	65 (15.66)	51 (78.46)	14 (21.54)
59.99 - 45.00	4 (0.96)	2 (50.00)	2 (50.00)
Scr before TDF initiation (mg/dL)			
Mean ± SD (min - max)	0.78 ± 0.19	0.76 ± 0.18	0.91 ± 0.27
	(0.24 - 1.67)	(0.24 - 1.42)	(0.38 - 1.67)
Scr before TDF initiation (mg/dL)			
≤ 1.00	387 (93.25)	351 (90.70)	36 (9.30)
> 1.00	28 (6.75)	24 (85.71)	4 (14.29)
Increase in Scr after TDF initiation (mg/dL)			
≤ 1.5 folds	386 (93.01)	373 (96.63)	13 (3.37)
> 1.5 folds	29 (6.99)	2 (6.90)	27 (93.10)

$ Duration of ARV drug use including TDF until occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021) (months).

Factors affecting TDF-related renal impairment

In examining individual factors on TDF-related renal impairment, occupation was not included since no occupations that could harm the kidney were found in this group of participants. Based on univariate logistic regression, risk of renal impairment among patients aged more than 40 years old was 3.25 folds of their younger counterparts (OR = 3.25; 95% CI = 1.46 - 7.23). Significant increase in risk of renal impairment was also found in patients with diabetes mellitus (OR = 5.10; 95% CI = 2.22 - 11.70), hypertension (OR = 3.35; 95% CI = 1.66 - 6.74), hyperlipidemia (4.10; 95% CI = 2.05 - 8.23), TDF use of more than 60 months (OR = 2.30; 95% CI = 1.10 - 4.77), concomitant use of TDF with PIs (OR = 2.64; 95% CI = 1.21 - 5.79), baseline eGFR of less than 90 ml/min/1.73m² before TDF initiation (OR = 4.05; 95% CI = 2.02 - 8.13) (Table 2).

Based on multivairate logistic regression analysis, the risk of TDF-related renal impairment was significantly increased with diabetes mellitus (aOR = 4.46; 95% CI = 1.65 - 12.11) and baseline eGFR before TDF initiation of less than 90 ml/min/1.73m² (aOR = 4.14; 95% = CI 1.74 - 9.89). The risk was significantly decreased with the use of ARV drugs of more than 120 months (aOR = 0.36; 95% = CI 0.13 - 1.00) (Table 2).

Table 2 Factors affecting TDF-related renal impairment based on univariate and multiple logistic regression analysis* (N = 415).

Factors	N (%) of patients with eGFR decrease ⩾ 25% from baseline		Crude OR† (95% CI)	Adjusted OR‡ (95% CI)
	No (n = 375)	Yes (n = 40)		
Gender				
Men	204 (54.40)	21 (52.50)	1.00	
Women	171 (45.60)	19 (47.50)	1.08 (0.56-2.07)	1.08 (0.52 – 2.26)
Age (years)				
≤ 40	168 (44.80)	8 (20.00)	1.00	
> 40	207 (55.20)	32 (80.00)	3.25 (1.46 - 7.23)	1.92 (0.74 – 4.96)
Body mass index (kg/m²)				
18.50 – 24.90	230 (61.33)	25 (62.50)	1.00	
< 18.50	82 (21.87)	7 (17.50)	0.78 (0.33 - 1.88)	1.15 (0.42 – 3.18)
≥ 25.00	63 (16.80)	8 (20.00)	1.17 (0.50 – 2.71)	1.44 (0.53 – 3.91)
Co-morbidity				
Hyperlipidemia				
No	249 (66.40)	13 (32.50)	1.00	
Yes	126 (33.60)	27 (67.50)	4.10 (2.05 – 8.23)	2.28 (0.98 – 5.32)
Hypertension				
No	318 (84.80)	25 (62.50)	1.00	
Yes	57 (15.20)	15 (37.50)	3.35 (1.66 – 6.74)	1.65 (0.58 - 4.67)
Diabetes mellitus				
No	352 (93.87)	30 (75.00)	1.00	
Yes	23 (6.13)	10 (25.00)	5.10 (2.22 – 11.70)	4.46 (1.65 - 12.11)
Concomitant use of drugs with renal toxicity potential				
No	344 (91.73)	33 (82.50)	1.00	
Yes (on ACEIs/ARBs found)	31 (8.27)	7 (17.50)	2.35 (0.96 – 5.76)	0.88 (0.24 – 3.25)
Duration of ARV drug use$ (months)				
≤ 120	224 (59.73)	24 (60.00)	1.00	
> 120	151 (40.27)	16 (40.00)	0.99 (0.51 – 1.92)	0.36 (0.13 – 1.00)
Duration from TDF initiation till renal impairment (months)				
≤ 60	327 (87.20)	31 (77.50)	1.00	
> 60	48 (12.80)	8 (22.50)	2.30 (1.10 – 4.77)	2.64 (0.96 – 7.22)
TDF as first ARV regimen				
Yes	165 (44.00)	12 (30.00)	1.00	
No	210 (56.00)	28 (70.00)	1.83 (0.90 – 3.71)	1.76 (0.60 – 5.22)
ARV drugs used concomitantly with TDF				
NNRTIs based regimen	333 (88.80)	30 (75.00)	1.00	
PIs based regimen	42 (11.20)	10 (25.00)	2.64 (1.21 – 5.79)	2.51 (0.95 – 6.70)
CD4 cell count before TDF initiation (cells/μL)				
> 200	279 (74.60)	28 (70.00)	1.00	
≤ 200	95 (25.40)	12 (30.00)	1.25 (0.61 – 2.56)	1.46 (0.59 – 3.64)
eGFR before TDF initiation (ml/min/1.73m²)				
≥ 90.00	322 (85.87)	24 (60.00)	1.00	
< 90.00	53 (14.13)	16 (40.00)	4.05 (2.02 – 8.13)	4.14 (1.74 – 9.89)
Scr before TDF initiation (mg/dL)				
≤ 1.00	351 (93.60)	36 (90.00)	1.00	
> 1.00	24 (6.40)	4 (10.00)	1.62 (0.53 – 4.94)	0.49 (0.12 – 2.06)

* Occupation was not included since no occupations that could harm the kidney were found in this group of participants.

$ Duration of ARV drug use including TDF until occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021)

† Univariate logistic regression.

‡ Multiple logistic regression adjusting for gender, age, BMI, hyperlipidemia, hypertension, diabetes mellitus, concomitant drugs with renal impairment potential, Duration of ARV drug use including TDF until occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021), duration since TDF initiation, having TDF as first ARV regimen, concomitant ARV drugs, CD4 cell count before TDF initiation, eGFR before TDF initiation, Scr before TDF initiation.

‡ Multiple logistic regression: *P*-value < 0.001, R^2 = 0.199. OR = odds ratio, CI = confidence interval.

Factors affecting time to the occurrence of TDF-related renal impairment

Since duration of TDF use was identical to the duration until the occurrence of TDF-related renal impairment which was the dependent variable, it was exclude from the linear regression analysis. Based on multiple linear regression analyses, only duration of ARV drugs use was significantly, positively correlated with time to the occurrence of TDF-related renal impairment (coefficient or B = 0.39; 95% CI = 0.13 – 0.65 in multiple linear regression analysis with R^2 = 0.541 and *P*-value = 0.030) (Table 3). This duration of ARV use was defined as the duration since the first ARV drug and all other ARV drugs including TDF until the occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021).

Table 3 Factors affecting time to the occurrence of TDF-related renal impairment based on univariate and multiple linear regression analysis* (N = 415).

Factors	Univariate regression analysis			Multiple regression analysis		
	B	95% CI	*P*-value	B	95% CI	*P*-value
Gender (women)	-1.76	-24.68, 21.17	0878	-16.22	-60.32, 27.88	0.456
Age	-0.33	-1.32, 0.65	0.500	-0.74	-2.52, 1.03	0.395
BMI	0.70	-1.97, 3.38	0.597	1.16	-1.53, 3.85	0.383
Co-morbidity						
Hyperlipidemia	13.13	-10.93, 37.20	0.276	18.63	-11.65, 48.92	0.217
Hypertension	4.62	-18.98, 28.23	0.694	24.79	-5.87, 55.46	0.109
Diabetes mellitus	-9.74	-36.00, 16.50	0.457	-23.84	-52.23, 4.56	0.096
Concomitant use of drugs with potential renal impairment	-11.25	-41.16, 18.66	0.451	-20.62	-56.09, 14.84	0.243
Duration of ARV drug use†	0.31	0.15, 0.46	< 0.001	0.39	0.13, 0.65	0.004
TDF as not the first ARV regimen	20.96	-3.06, 44.98	0.085	-27.27	-60.46, 5.91	0.103
PI used concomitantly with TDF	13.85	-12.20, 39.90	0.289	-1.21	-33.90, 31.48	0.940
CD4 cell count before TDF initiation	0.02	-0.02, 0.07	0.259	-0.02	-0.08, 0.03	0.341
eGFR level before TDF initiation	0.68	0.19, 1.17	0.007*	-0.41	-2.70, 1.88	0.713
Scr level before TDF initiation	-49.62	-89.09, 10.14	0.015*	-77.55	-330.45, 627.31	0.530

† Duration of ARV drug use including TDF until occurrence of TDF-related renal impairment or end of study (i.e., April 30, 2021).

* Multiple linear regression analysis: P-value = 0.030, R^2 = 0.541.

* Duration of TDF use was not put in the regression as a factor since it was identical to the duration until the TDF-related renal impairment occurred which was the dependent variable.

Discussions and Conclusion

In the present study, the incidence of TDF-related renal impairment among patients at Damnoen Saduak Hospital was 9.64%. It seems our finding is toward the lower end of what were found from previous studies in Thailand ranging from 5.68%[14], to 13.98%[13], 19.30%[12], 26.60%[11] and 30%.[10] Our finding is relatively consistent with those in other countries, specifically from 2.7% in Sechuan, China[17], to 5.6% in the souther India[16], and 14.80% in Pusan, South Korea.[15] This discrepancy in the incidence of TDF-related renal impairment could be attributable in part to different definition of renal impairment by setting and time. For example, in Thailand, the study of Pengthina defined renal impairment as a decrease in ClCr of more than 25%[10], while the study of Petchkum and Suphanchaimat defined it as a decrease om eGFR of more than 50%.[11] In India, the study of Kumarasmy et al defined TDF-related renal impairment as eFR respective with CKD stage 3 and 4.[16] In addition, we suspected that differences in time of study conduct, number of participants, and demographic and clinical characteristics of participants could also contribute such discrepany among studies.

Among common co-morbid diseases, only diabetes mellitus was found to significantly associated with a higher risk of TDF-related renal impairment in our study (aOR = 4.46; 95% CI = 1.65 - 12.11). The risk associated with diabetes mellitus found in our study was higher that of 2.58 folds in a previous study[13] those of 2.71 and 2.16 folds among those with diabetes and those with co-mobid illnesses (either diabetes, hypertension or hyperlipidemia), respestively.[14] Our study analyzed each of co-morbid illnesses and found the contribution of diabetes on the TDF-related renal toxixicty.

We found that eGFR before TDF initiation of less than 90 ml/min/1.73m² was significantly associated with an increased risk of TDF-related renal impairment (aOR = 4.14; 95% CI = 1.74 – 9.89). The previous study revealed that eGFR of less than 60 ml/min/1.73m² was associated with an increased risk of renal toxicity, with no exact risk was specified.[14] Our finding was consistent with another study among Thai patients of whichh patienst with Clcr before TDF inititation of less than 90 ml/min were more likely to have renal toxicity compared to their counterparts.[10]

We found that patients who had beentaking ARV drugs including TDF for more than 120 months were 0.36 folds less likely to experience renal toxicity (aOR = 0.36; 95% CI = 0.13 – 1.00). This finding is opposite to what was expected and has not been presented in any previous studies.

Our study found no association of increased risk of TDF-related renal impairment with gender, age, BMI, hyperlipidemia, hypertension, use of ACEIs/ARBs, use of ARV drugs other than TDF as first regimen, long use of TDF, concomitant use of PIs, CD4 level before TDF intiation, and Scr before TDF initiation. These findings were different from previous studies where there were associations of renal toxicity with TDF use with PIs[10] and with increasing age, ACEIs and ARBs use and CD4 cell count before TDF initiation

of less than 200 cell/mm^3.[13] Contribution of some of these factors deserves further investigation.

Time to the occurrence of TDF-related renal impairment was significantly associated only with longer use of ARV drugs including TDF. Such association has not been reported before. A study in Thai patients reported that the use of ARV drugs before TDF was associaed with the time to renal toxicity shortened by 3.13 folds. [13] However, the use of other ARV drugs was not associated time to the occurrence of TDF-related renal impairment in our study.

In this present study, the shortest duration to the occurrence of TDF-related renal impairment was 14 days after TDF initiation which was longer than 7 days found in a study in Thai patients.[10] We found the median time to the occurrence of TDF-related renal impairment of 34.50 months which was longer than 16 months found in another study in Thai patients[14] but shorter than 5.10 years reported from the study in Indian patients.[16] Discrepancy in time to the occurrence of TDF-related renal impairment could be due to different follow-up time in these studies.

For the patient with 14 days to the occurrence of TDF-related renal impairment, we found that the patient had eGFR before TDF initiation of 49.37 ml/min/1.73 m² and hyperlipidemia as factors influencing the incidence, and the use of TDF with PIs as the factor influencing the time to the incidence. The patient had cancer which was not an influencing factor in our study. However, anti-cancer drugs could have a detrimental effect on kidney function. A study of Belete and colleagues reported that cancer was associated with a 18.20-fold risk of renal toxicity (95% CI = 1.22 - 271.77, *P*-value = 0.035).[20]

Our findings could be useful in monitoring renal impairment among HIV patients taking TDF. eGFR espeically in patients with eGFR of less than 90 ml/min/1.73m² before TDF inititaion should be closely monitored with regular check-ups. In addition, regular monitoring on kidney function shuld also be done for patients with diabetes mellitus, hypertension, concomitant use of PIs with TDF, no TDF use as the first regimen, and use of TDF of more than 60 months. This close renal function monitoring could prevent acute kidney injury and chronic kidney failure. For patients with declining renal function, a change from TDF to other ARV drugs with less renal toxicity or the reduction of TDF drug could be done in a timelyfashion.

For future studies, we recommend more studies on patients with a decrease in eGFR of less than 25% for early renal impairment prevention. Studies with TDF dose adjustment to lessen renal toxicity should also be conducted. In addition, studies with adequate sample size are needed.

In conclusion, an incidence of 9.64% of TDF-related renal impairment was found in HIV patients of Damnoen Saduak Hospital. The incidence was positively associated with diabetes mellitus and eGFR before TDF initiation of less than 90 ml/min/1.73m² and negatively associated with ARV drug use of more than 120 months. Duration of ARVdrug use was positively associated with time untill the occurrence of TDF-related renal impairment.

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