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**Original Research**

# Are comorbidities and previous antiretroviral therapy associated with renal dysfunction in patients with HIV infection treated with tenofovir-based regimen?

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**Abstract**

**Background:** TLD, Tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/ dolutegravir (DTG), is one of the antiretroviral therapy (ART) for patients with HIV infection and can be used as the first-line treatment. The main concern of TLD is renal dysfunction. However, there is limited data if any comorbidities or previous ART was associated with renal dysfunction in patients with HIV infection treated with TLD.

Objective: To evaluate if any comorbidities or previous ART associated with renal dysfunction in this setting.

Methods: This study was a retrospective cohort study. The inclusion criteria were adult patients diagnosed as HIV infection, received treatment with TLD for at least 12 months, and had regular follow-up. The primary outcome was a decline of eGFR of 25% or more after treatment with TLD for 12 months. Factors associated with the primary outcome were computed by using logistic regression analysis.

Results: There were 1,340 patients met the study criteria. Of those, 461 patients (34.40%) had eGFR decline of 25% or more after TLD treatment for 12 months. Four factors were significantly related with eGFR decline of 25% or more: naïve patient with TDF, and previous treatment with TDFFTCEFV (TEEVIR), AZT3TCNVP (GPOZ), and AZT3TCEFV. Previous treatment with AZT3TCEFV had the highest adjusted odds ratio of 2.992 (95% confidence interval of 1.682, 5.322), while TDFFTCEFV (TEEVIR) and AZT3TCNVP (GPOZ) had the adjusted odds ratio of 1.898 and 1.967, respectively.

Conclusions: The prevalence of eGFR decline of 25% or more after TLD treatment for 12 months was 34.40%. Risk factors for eGFR decline of 25% or more included naïve patients to TLD or previously treated with tenofovir-based or zidovudine-based regimens.

**Keywords:** renal failure, antiretroviral therapy, risk factors

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## INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is a common sexually transmitted disease. A global burden of disease study reported that at least 40 million people were infected with HIV in 2021[1]. People living with HIV were more common in female (22 million vs 18 million) and lived in sub-Saharan countries (29.1 million). Antiretroviral therapy (ART) is the mainstay treatment for patients with HIV infection regardless of CD4 count. The benefits of ART include virologic suppression and near normal life expectancy.

TLD, Tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/ dolutegravir (DTG), is one of the ART for patients with HIV infection[2]. This regimen can be used as second-line treatment for those with nucleoside reverse transcriptase inhibitor (NRTI) resistance[3]. In some countries such as Thailand, TLD is the first-line ART treatment. A previous study showed that TLD treatment had virological suppression rate of 85% after 24 weeks of treatment[3]. However, the major side effect of TLD is renal dysfunction[4-6]. At least 12% of patients treated with Tenofovir disoproxil fumarate (TDF) had renal dysfunction[5]. Several risk factors for renal dysfunction by reduction of estimated glomerular filtration rate (eGFR) of 25% or over were age, smoking, or TDF treatment for 3 years or over with odds ratio of 2.851, 1.972, and 1.928, respectively. However, there is limited data if any comorbidities or previous ART was associated with renal dysfunction in patients with HIV infection treated with TLD. This study aimed to evaluate if any comorbidities or previous ART associated with renal dysfunction in this setting.

## METHODS

This study was a retrospective cohort study conducted at adult ART clinic, Phrachomklao Hospital, Phetchaburi province, a tertiary care hospital. The inclusion criteria were adult patients diagnosed as HIV infection, received treatment with TLD for at least 12 months, and had regular follow-up. Those who were treated with TLD as pre-exposure or post-exposure prophylaxis were excluded. The study period was between February 1st, 2023 and March 31st, 2025. The study protocol was approved by the institutional board review, Phrachomklao Hospital, Phetchaburi (17/2566).

All eligible patients were retrospectively reviewed baseline characteristics from the hospital database (HOSxP, version 4.0).

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At baseline, studied variables were evaluated including age, sex, comorbidities, concurrent medications, previous treatment with TLD and other ART, body mass index, eGFR, CD4, and viral load. After treatment with TLD for 12 months, clinical outcomes were assessed including eGFR, CD4, and viral load. The primary outcome was a decline of eGFR of 25% or more after treatment with TLD for 12 months.

## Statistical analyses

Patients were categorized into two groups by the primary outcome: eGFR decline of 25% or more versus eGFR decline less than 25%. Descriptive statistics were used to show results of studied variables, inferential statistics either the student t test or Chi square test were used to compare differences of studied variables and clinical outcomes between the two groups. Factors associated with eGFR decline of 25% or more were computed by using univariate and multivariate logistic regression analysis. Studied variables were calculated for a p value by univariate logistic regression analysis, those studied variables with a p value of less than 0.05 or clinically important were put in the subsequent stepwise multivariable logistic regression analysis. Results were reported as unadjusted and adjusted odds ratio with 95% confidence intervals. Statistical analyses were performed by using STATA software, version 18.5 (College Station, Texas, USA).

## RESULTS

During the study period, there were 1,340 patients met the study criteria. Of those, 461 patients (34.40%) had eGFR decline of 25% or more after TLD treatment for 12 months. The average eGFR at baseline in the eGFR decline group was significantly higher than the eGFR decline less than 25% group (103.61 vs 96.68 ml/min/1.73m$^2$; p < 0.001). There were three factors significantly different between those two groups: proportions of previous ART treatment including AZT3TCEFV, TDF3TCNVP, and TDFAZTLPV/RTV as shown in Table 1. The eGFR decline of 25% or more group had a higher proportion of previous treatment with AZT3TCEFV than the eGFR decline less than 25% group (11.93% vs 8.08%; p = 0.022), while the previous treatments with TDF3TCNVP (1.71% vs 0.43%; p = 0.048) and TDFAZTLPV/RTV (2.05% vs 0.43%; p = 0.018) were significantly higher in the eGFR decline less than 25% group than the eGFR decline of 25% or more group. Other factors were comparable between both groups. Note that presence of diabetes had almost significant p value between both groups (10.13% vs 6.94%; p = 0.053).

After treatment with TLD for 12 months (Table 2), the eGFR decline of 25% or more group had significantly lower eGFR (71.44 vs 82.64 ml/min/1.73m$^2$; p < 0.001) and higher percentage of eGFR reduction from baseline (-32.17% vs -14.04%; p < 0.001) than the eGFR decline less than 25% group. CD4 level (671.90 vs 662.01 cells/mm$^3$; p = 0.553) and proportion of patients with viral load less than 20 copies/ml (95.66% vs 96.13%; p = 0.677) were comparable between both groups.

There were seven factors remaining in the predictive model for eGFR decline of 25% or more (Table 3). Only previous treatment with AZT3TCEFV was significant by univariate logistic regression analysis, but four factors were significantly related with eGFR decline of 25% or more by multivariable logistic regression analysis: naïve patient with TDF, and previous treatment with TDFFTCEFV (TEEVIR), AZT3TCNVP (GPOZ), and AZT3TCEFV. Previous treatment with AZT3TCEFV had the highest adjusted odds ratio of 2.992 (95% confidence interval of 1.682, 5.322), while TDFFTCEFV (TEEVIR) and AZT3TCNVP (GPOZ) had the adjusted odds ratio of 1.898 and 1.967, respectively. Note that the two latter factors were not significant in the univariate logistic regression analysis. The Hosmer-Lemeshow Chi square of the model was 11.11 with a p value of 0.434 indicating goodness of fit of the model.

## DISCUSSION

Even though diabetes was almost a significant factor between those with eGFR decline of 25% or more and those with eGFR decline of less than 25% (Table 1), it was not significant after adjusted by other factors (Table 3). Being diabetes had the adjusted odds ratio of 0.680 (95% confidence interval of 0.437, 1.058) for eGFR decline of 25% or more. Other comorbidities including dyslipidemia, hypertension, or psychosis were not included in the predictive model by stepwise method. These results indicate that comorbidities may not be related to renal dysfunction in patients with HIV infection treated with TLD. A previous study found that both diabetes and hypertension were associated with renal dysfunction[7]. The odds ratios for these two comorbidities were 0.614 (p = 0.001) and 0.397 (p = 0.007), respectively. These differences may be due to different criteria for identifying renal dysfunction. In this study, we used the decline of eGFR by 25% or more, while the previous study used eGFR grading as grade 3 or 4. Additionally, only 50.8% of patients were initially received TDF.

In this study, there were 90 naïve patients who never received any ART (6.72%), the other 93.28% had previously treated with ART. Among 20 previous ART treatments prior to TLD treatment, three regimens were associated with eGFR decline of 25% or more including TDFFTCEFV (TEEVIR), AZT3TCNVP (GPOZ), and AZT3TCEFV (Table 3). TEEVIR is comprised of tenofovir, emtricitabine, and efavirenz. Tenofovir is a component which may lead to significant renal dysfunction as previously reported[5,6]. These results may imply that previous treatment with tenofovir may have an additional adverse effect on renal function if switch therapy to TLD. The previous study found that duration of tenofovir treatment of three years was associated with renal dysfunction by 1.928 times[5]. Even though the previous study did not find that tenofovir naïve was not related to renal dysfunction (p = 0.624)[5], this study found that TLD naïve was the independent factor for eGFR decline with adjusted odds ratio of 2.182 (95% confidence interval of 1.075, 4.430) as shown in Table 3. Baseline eGFR may be a contributing factor for these findings. We performed an additional analysis

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**Table 1.** Baseline characteristics of patients with HIV infection who received TLD for 12 months categorized by estimated glomerular filtration rate (eGFR) decline of 25% or over from the baseline.

| Factors | eGFR decline < 25% | eGFR decline ≥ 25% | p value |
|---|---|---|---|
| | n = 879 | n = 461 | |
| **Age, years** | 46.90 (10.45) | 46.52 (11.16) | 0.534 |
| **Male sex, n (%)** | 446 (50.74) | 239 (51.84) | 0.701 |
| **Comorbidities, n (%)** | | | |
| Dyslipidemia | 331 (37.66) | 150 (32.54) | 0.064 |
| Hypertension | 153 (17.41) | 69 (14.97) | 0.254 |
| Diabetes | 89 (10.13) | 32 (6.94) | 0.053 |
| Psychosis | 9 (1.02) | 8 (1.74) | 0.269 |
| **Medications, n (%)** | | | |
| ACEI | 77 (8.76) | 28 (6.07) | 0.082 |
| ARB | 18 (2.05) | 10 (2.17) | 0.883 |
| **Naïve patients, n (%)** | 54 (6.14) | 36 (7.81) | 0.247 |
| **Previous ART, n (%)** | | | |
| AZT3TCNVP (GPOZ) | 254 (28.93) | 131 (28.42) | 0.844 |
| TDFFTCEFV (TEEVIR) | 410 (46.64) | 212 (45.99) | 0.819 |
| AZT3TCEFV | 71 (8.08) | 55 (11.93) | 0.022 |
| TDFFTCNVP | 10 (1.14) | 2 (0.43) | 0.193 |
| TDFAZTRPV | 1 (0.11) | 0 | 0.469 |
| TDF3TCEFV | 1 (0.11) | 2 (0.43) | 0.239 |
| TDF3TCRPV | 1 (0.11) | 0 | 0.469 |
| TDF3TCNVP | 15 (1.71) | 2 (0.43) | 0.048 |
| TDFFTCRPV | 1 (0.11) | 2 (0.43) | 0.239 |
| TDF3TCLPV/RTV | 15 (1.71) | 6 (1.30) | 0.571 |
| TDFFTCLPV/RTV | 6 (0.68) | 1 (0.22) | 0.261 |
| TDFAZTLPV/RTV | 18 (2.05) | 2 (0.43) | 0.018 |
| TDFAZT3TCLPV/RTV | 5 (0.57) | 2 (0.43) | 0.745 |
| AZT3TCDTG | 1 (0.11) | 1 (0.22) | 0.642 |
| AZTTDFDTG | 1 (0.11) | 0 | 0.469 |
| AZT3TCATZRTV | 1 (0.11) | 1 (0.22) | 0.642 |
| AZT3TCLPV/RTV | 8 (0.91) | 4 (0.87) | 0.938 |
| AZTABCLPV/RTV | 1 (0.11) | 1 (0.22) | 0.642 |
| AZT3TCATZRTVTDF | 2 (0.23) | 0 | 0.305 |
| DTG3TCLPV/RTV | 3 (0.34) | 1 (0.22) | 0.692 |
| **BMI, kg/m²** | 22.60 (5.10) | 22.19 (3.85) | 0.133 |
| **eGFR, ml/min/1.73m²** | 96.68 (17.24) | 103.61 (12.77) | < 0.001 |
| **CD4, cells/m$^m$3** | 604.91 (290.79) | 598.48 (293.75) | 0.701 |
| **Viral load < 20 copies/ml** | 759 (88.56) | 396 (88.99) | 0.819 |

**Note:** Data shown as mean (SD) unless indicated otherwise; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ART: antiretroviral therapy; TLD, Tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/ dolutegravir (DTG); AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; EFV: efavirenz; RPV: rilpivirine; LPV/RTV: lopinavir, ritronavir; ABC: abacavir; DTG: dolutegravir; RTV: ritonavir; ATZ: atazanavir.

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**Table 2.** Laboratory results of patients with HIV infection who received TLD for 12 months categorized by estimated glomerular filtration rate (eGFR) decline of 25% or over from the baseline

| Factors | eGFR decline < 25% | eGFR decline ≥ 25% | p value |
|---|---|---|---|
| | n = 879 | n = 461 | |
| **eGFR, ml/min/1.73m²** | 82.64 (17.86) | 71.44 (12.51) | < 0.001 |
| **eGFR difference from baseline, %** | -14·04 (7·95) | -32·17 (7·07) | < 0.001 |
| **CD4, cells/mm³** | 662.01 (286.86) | 671.90 (293.18) | 0.553 |
| **Viral load < 20 copies/ml, n (%)** | 845 (96.13) | 441 (95.66) | 0.677 |

**Note:** Data shown as mean (SD) unless indicated otherwise; TLD, Tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/ dolutegravir (DTG).

**Table 3.** Factors remaining in the logistic regression model to predict estimated glomerular filtration rate (eGFR) decline of 25% or over from the baseline in patients with HIV infection who received TLD for 12 months.

| Factors | Unadjusted odds ratio (95% confidence interval) | Adjusted odds ratio (95% confidence interval) |
|---|---|---|
| **Diabetes** | 0.662 (0.434, 1.008) | 0.680 (0.437, 1.058) |
| **ACEI** | 0.673 (4.30, 1.054) | 0.742 (0.465, 1.183) |
| **Naïve patients** | 1.294 (0.835, 2.004) | **2.182 (1.075, 4.430)** |
| **Previous antiretroviral therapy** | | |
| TEEVIR (TDFFTCEFV) | 0.973 (0.776, 1.220) | **1.898 (1.172, 3.072)** |
| GPOZ (AZT3TCNVP) | 0.975 (0.759, 1.251) | **1.967 (1.193, 3.242)** |
| ZilavirEFV (AZT3TCEFV) | 1.541 (1.063, 2.235) | **2.992 (1.682, 5.322)** |
| TenoEMRPV (TDFFTCRPV) | 3.825 (0.345, 42.302) | 7.021 (0.610, 80.787) |

**Note:** Factors included in the stepwise method including age, sex, body mass index, dyslipidemia, hypertension, psychosis, CD4 level at baseline, ALT level at baseline, proportions of viral load less than 20 copies/ml, treatment with angiotensin receptor blocker, previous treatment with TDF3TCNVP, and AZTTDFKLT; TLD, Tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/ dolutegravir (DTG).

of baseline eGFR between TLD naïve and those previously treated with ART. The average baseline eGFR for TLD naïve patients was significantly higher than those previously treated with ART (104·19 vs 98·70 ml/min/1·73m$^2$; p = 0·002). These findings may imply that TLD may cause renal dysfunction even in those TLD naïve patients with normal baseline eGFR. Note that average eGFR in those with eGFR decline of 25% or more was significantly lower than those with eGFR decline of less than 25% after 12 months treatment with TLD despite the higher baseline eGFR (103·61 vs 96·68 ml/min/1·73m$^2$). Additionally, those withe eGFR decline of less than 25% also had average percentage of eGFR decline by -14·04%. These findings may indicate that treatment with TLD may be harmful in those patients naïve to tenofovir and those previously treated with tenofovir. In addition to nephrotoxicity of tenofovir in TLD, a previous report also showed that dolutegravir caused a decline of eGFR in 54% of patients treated with dolutegravir-based regimen[8].

The other two previous ART regimens that caused eGFR reduction after switching therapy to TLD were AZT3TCNVP (GPOZ) and AZT3TCEFV (ZilavirEFV). The explanation for these findings was unclear. Based on the similarity of both regimens, the renal dysfunction may be due to zidovudine, nevirapine, or efavirenz. A previous review showed that zidovudine may lead to mitochondrial toxicity which is a pre-requisite condition for tenofovir-induced tubular damage[9]. A rat model showed that nevirapine may have nephrotoxicity by evidence of histoarchitectural damage in the glomerular apparatus[10]. Several case reports also showed the possible association of efavirenz and renal dysfunction including hypersensitivity or direct nephrotoxicity[11-13]. Current evidence may support the renal safety of these three medications. The results of this study may acknowledge renal dysfunction if these two regimens were given prior to TLD switching therapy.

Pharmacists in any level of hospital with ART clinic may use the results of this study to prevent renal dysfunction in patients with HIV infection who are treated with TLD. First, patients with HIV infection who are naïve to TLD or previously treated with TDFFTCEFV (TEEVIR), AZT3TCNVP (GPOZ), and AZT3TCEFV are at risk for renal dysfunction. These results are helpful to identify high risk patients. Second, those who are at risk should be closely renal function monitoring as well as urinalysis and urine albumin-creatinine ratio such as every 3 months. NSAIDs or other renal toxicity medications should be avoided. Automatic pop-up in the electronic medical record for the nephrotoxic agents should be implemented. Third, an alternative ART regimen may be preferred. Finally, pharmacist-led medication review or medication reconcile system may be needed to prevent TLD-associated renal toxicity.

There are some limitations in this study. First, some factors associated with renal dysfunction may not be evaluated particularly nephrotoxic agents. However, patients with HIV infection were advised to avoid any additional medications at the clinic. The HIV clinic in our hospital was a multidisciplinary approach comprised of physicians, a special nurse and a special pharmacist. This study was initiated by a special pharmacist based on clinical observation. Second, sample size calculation was not performed as we collected all patients treated at the clinic. Finally, some variables may not be evaluated or data availability due to retrospective data collection such as duration or control of diabetes or hypertension. Additionally, it might be possible confounding factors or interaction effects which were not evaluated or controlled. Baseline eGFR was not included in the predictive model as it was collinear with the outcome of the study. Note that previous treatment with TDF3TCNVP,

and TDFAZTLPV/RTV were significantly different between both groups in Table 1. But, these two factors were not included in the predictive model as both factors had small numbers.

## CONCLUSION

In conclusion, the prevalence of eGFR decline of 25% or more after TLD treatment for 12 months was 34.40%. Risk factors for eGFR decline of 25% or more included naïve patients to TLD or previously treated with tenofovir-based or zidovudine-based regimens.

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