# Tenofovir-induced nephrotoxicity: A retrospective cohort study

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## ABSTRACT

**Background: Tenofovir (TDF) has been associated with renal function deterioration, but local data regarding the incidence and risk factors for this adverse event were lacking.**

**Objectives: To determine the incidence of nephrotoxicity in HIV-infected patients on tenofovir-based regimens and to evaluate risk factors involved in tenofovir-associated renal function decline.**

**Methods: This is a single-centre retrospective cohort study of 440 HIV-infected adults who were started on tenofovir-based antiretroviral regimens. Data were extracted from electronic medical and pharmacy records.**

**Results: A decline in eGFR of 25% or more was seen in 67 patients (15.2%) with an estimated incidence rate of 12 per 100 person-years. Among all 440 subjects, 22 discontinued TDF-based therapy due to renal complication. From multivariate analysis, the odds of developing >25% decrease in eGFR with tenofovir-containing regimen was three times higher for patients with baseline moderate renal impairment (HR 3.19; 95% CI, 1.43-7.12; p=0.005) and 14 times higher for patients with baseline severe renal impairment (HR 14.2; 95% CI, 11.20-170.7; p=0.036) as compared to those without pre-existing renal insufficiency. Age above 50 years and CD4 cell count of less than 50 were significantly associated with >25% decrement in eGFR.**

**Conclusion: The incidence rate of tenofovir-related renal dysfunction was found to be 12 per 100 person-years. Pre-existing renal impairment, age 50 and above, and CD4 cell count below 50 as were predictors for renal function decline. Given that the use of tenofovir is escalating in Malaysia, increased awareness about this adverse event is essential.**

**KEY WORDS:**
*Tenofovir, nephrotoxicity, renal dysfunction, risk factors, incidence*

## INTRODUCTION

Tenofovir (TDF) is a highly effective nucleotide analogue reverse-transcriptase inhibitor (NRTI) used with other antiretroviral (ART) agents for the treatment of human immunodeficiency virus (HIV) infection and hepatitis B co-infections. Despite the absence or lack of renal toxicity observed in earlier clinical trials of tenofovir,[1-4] there were various case reports on the manifestation of tenofovir-related nephrotoxicity.[5-9] A recent systematic review and meta-analysis that included data from 17 studies concluded that the association between tenofovir and nephrotoxicity as significant but modest.[10] Since its use in 2008 in Malaysia, there have been multiple cases of renal function deterioration attributed to tenofovir, but local data regarding the incidence and risk factors for this adverse event was lacking. Given that tenofovir has been increasingly prescribed as first line antiretroviral therapy as per recommendation by major guidelines,[11-12] a study on the effect of the drug on renal profile of patients on highly active antiretroviral therapy (HAART) was deemed necessary to guide future prescribing practice.

## MATERIALS AND METHODS

*Study design*

We conducted a single-centre retrospective cohort study of all HIV-infected adults who were started on tenofovir-based antiretroviral regimens at a local tertiary hospital from 1 January 2008 to 31 December 2010. The study was conducted from 1 March 2011 till 1 June 2011. Patients were followed through termination of tenofovir-based regime, death or the end of study on 1 June 2011. We evaluated the effect of tenofovir-containing regimens on renal function (defined as changes in glomerular filtration rate [GFR]) using data from electronic medical and pharmacy records. The objectives of the study were to determine the incidence of nephrotoxicity in HIV-infected patients on tenofovir-based regimens and to evaluate risk factors involved in tenofovir-associated renal function decline.

*Subjects*

Patients were eligible for inclusion in the study if they are HIV-infected individuals over 17 years of age, started on tenofovir-based regimens from 1 January 2008 to 31 December 2010, had been receiving TDF for a minimum of three months, had a baseline serum creatinine [SCr] (defined as serum creatinine measured within 90 days before or 30 days after regimen initiation), and had laboratory testing and medication collection done in Sungai Buloh Hospital. Patients were excluded if they had insufficient baseline or follow-up laboratory or pharmacy data. Our patient population comprised of Malaysians as well as non-Malaysians; the bulk of the latter were UNHCR Myanmar refugees. This study was registered with the National Medical Research Register of Malaysia (NMRR-14-1619-23794).

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*Measurements*

Demographic data and potential risk factors for renal dysfunction were collected from computerised medical records. They included age, gender, ethnicity, co-administration with protease inhibitors (PI) or didanosine (DDI), presence of diabetes mellitus or hypertension, baseline CD4 cell count, baseline serum creatinine (SCr) and estimated glomerular filtration rate (eGFR), period on TDF-based regimen, duration of HIV diagnosis, and treatment experience prior to initiation of TDF-based regimen (treatment naive or experienced). Baseline laboratory values were values recorded closest to or within 90 days before regimen initiation. Potential risk factors were predetermined according to previous studies.[5,6,8,9]

Follow-up laboratory serum SCr and eGFR were collected at study endpoint which is termination of TDF-containing regimen, death or end of study on 1 June 2011.

We estimated glomerular filtration rate, eGFR using the four-variable Modification in Diet in Renal Disease (MDRD) equation without consideration of racial adjustments in multiracial Asian populations.[13-14]

Four-variable Modification in Diet in Renal Disease (MDRD) equation:

$186 \times (SCr/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female})$

where SCr = serum creatinine in µmol/l, and age is expressed in years

Baseline renal function was categorised based on estimated GFR as follows: normal (eGFR ≥90 mL/min/1.73m$^2$), mild (eGFR 60-89 mL/min/1.73m$^2$), moderate (eGFR 30-59 mL/min/1.73m$^2$), and severe renal impairment (<30 mL/min/1.73m$^2$).

The primary endpoints of the study included changes in serum creatinine (SCr) levels and corresponding estimated glomerular filtration rate (eGFR) from baseline, and the rate of tenofovir discontinuation due to development of renal dysfunction. Renal dysfunction was defined as 25% or more decrease in eGFR relative to baseline.[8,15]

*Data Analysis*

Baseline characteristics and relevant laboratory parameters were summarised. Dichotomous variables were expressed using proportions; continuous variables were expressed as medians with interquartile ranges (IQRs) and means with standard deviation (SD), where appropriate. Changes in eGFR over time were also assessed using median. Incidence of renal impairment was determined as the proportion of patients with 25% or more decline in eGFR to the total study population at risk.

Potential predictor variables included demographics (age, sex, race), baseline creatinine, CD4 cell count, history of diabetes mellitus, hypertension, concomitant ART regimen class (protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or mixed), and treatment history. The influence of these covariates on eGFR over time was estimated using univariate and multivariate logistic regression, in which crude and adjusted hazard ratios (HRs) with 95% confidence interval (95% CI) were determined.

All statistical analysis was performed with STATA/SE 12.1 for Windows. All tests were two-sided and used a statistical significant threshold of 0.05.

## RESULTS

A total of 490 patients were started on tenofovir-based antiretroviral regimen during the study period, of which 440 patients were included in the study. Fifty patients were excluded due to insufficient baseline or follow-up laboratory data. Baseline demographics and clinical characteristics of study population were shown in Table I. The majority of the study population were males (n=332, 75.5%), below 50 years of age (n=329, 74.8%) and were of Chinese ethnicity (n=241, 54.8%). More than 90% of patients had baseline eGFR of above or equal to 60 ml/min/1.73m2 with a median eGFR of 100 ml/min/1.73m2 (IQR 81-118). The majority of subjects started on tenofovir-based regimen were treatment experienced (391 of 440, 88.9%).

A decline in eGFR of 25% or more was seen in 67 patients (15.2%) with an estimated incidence rate of 12 per 100 person-years. Out of these 67 patients, 16 (24%) of them had their eGFR dropped by 50% or more after starting on tenofovir-containing regimen. Among all 440 subjects, 43 discontinued TDF-based therapy. Half of these patients had their treatment discontinued due to TDF-related renal toxicity whereas the others had reasons other than renal complication such as death, case transferred out to a different facility, treatment default and individual patient's preference. Median time from commencement to discontinuation of TDF-based regime was 444.5 days (range, 2-1604 days).

Univariate analysis showed significant association between baseline renal function and >25% decrement in eGFR (HR 1.57; 95% CI, 1.11-2.23; p=0.01) (Table II). The odds of developing >25% decrease in eGFR with tenofovir-containing regimen was 3.4 times higher for patients with baseline moderate renal impairment (HR 3.44; 95% CI, 1.64-7.20; p = 0.001) and 11.8 times higher for patients with baseline severe renal impairment (HR 11.8; 95% CI, 1.05-133.18; p = 0.046) as compared to those without pre-existing renal insufficiency. Patients above 50 years of age were twice more likely to be associated with renal impairment compared to younger ages (HR 2.05; 95% CI 1.19-3.55; p=0.01). When stratified by gender, males aged 50 and above were more likely than their female counterpart to develop a significant drop in eGFR (HR=2.16; 95% CI 1.17-3.97; p=0.013). Furthermore, CD4 cell count at initiation of tenofovir treatment were found to be a significant predictor of >25% deterioration in eGFR (HR 1.64; 95% CI 1.34-2.03; p<0.001). After stratifying by CD4 groups, CD4 cell count of less than 50 was found to be significantly associated with >25% decrement in eGFR (HR 4.41; 95% CI 2.36-8.24; p<0.001). Race, duration of HIV infection, pre-existing diabetes mellitus, hypertension, use of PI or DDI, and prior HAART experience were not associated with >25% decrement in eGFR.

Multivariate analysis of predictors identified pre-existing renal impairment (moderate to severe renal impairment), age 50 and above, and CD4 cell count below 50 as significant risks for >25% decline in eGFR (Table III).

**Table I: Baseline characteristics of study population (N = 440)**

| Characteristic | n (%) unless otherwise specified |
|---|---|
| Age (years), mean (SD) | 44.4 (9.9) |
| Gender | |
| Male | 332 (75.5) |
| Female | 108 (24.5) |
| Race | |
| Malay | 136 (30.9) |
| Chinese | 241 (54.8) |
| Indian | 50 (11.4) |
| Others | 13 (3) |
| Duration of HIV infection (years), mean (SD) | 6.7 (4.4) |
| Treatment history[a] | |
| Naive | 49 (11.1) |
| Experienced | 391 (88.9) |
| HAART regimen | |
| NNRTI-based regimen | 323 (73.4) |
| PI-based regimen | 111 (25.3) |
| Others | 6 (1.3) |
| Treatment period (years), median (IQR)[b] | 1.2 (0.7, 2.2) |
| Baseline clinical parameters[c] | |
| eGFR (ml/min/1.73m$^2$), | |
| Median (IQR) | 100 (81, 118) |
| >/= 90 | 283 (64.3) |
| 60-89 (mild renal impairment) | 116 (26.4) |
| 30-59 (moderate renal impairment) | 38 (8.6) |
| <30 (severe renal impairment) | 3 (0.7) |
| CD4 cell count (cells/mm3), median (IQR) | 264 (111, 454) |
| Prior medical history | |
| Diabetes mellitus | 29 (6.6) |
| Hypertension | 61 (13.9) |
| Prior history of PI use | 65 (14.8) |
| Prior history of DDI use | 83 (18.9) |

[a]Treatment naïve referred to patients who had never been on HAART prior to tenofovir-based regimen initiation whereas treatment experienced referred to patients who had been on non-tenofovir containing regimen prior to switching to tenofovir-based regimen.
[b]Treatment on tenofovir-based HAART regimen
[c]Serum creatinine measured within 90 days before or 30 days after tenofovir regimen initiation; CD4 cell count measured just before tenofovir regimen initiation.
HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; DDI, didanosine

**Table II: Univariate analysis of risk factors for more than 25% decrease in eGFR**

| | HR | 95% CI | P value |
|---|---|---|---|
| Baseline eGFR per 1 ml/min/1.73m$^2$ | 1.57 | 1.11-2.23 | 0.010 |
| Baseline eGFR 60-89 ml/min/1.73m$^2$ | 0.56 | 0.27-1.15 | 0.115 |
| Baseline eGFR 30-59 ml/min/1.73m$^2$ | 3.44 | 1.64-7.20 | 0.001 |
| Baseline eGFR <30 ml/min/1.73m$^2$ | 11.8 | 1.05-133.1 | 0.046 |
| Age 50 and above | 2.05 | 1.19-3.55 | 0.010 |
| Age 50 and above, female gender | 1.57 | 0.44-5.60 | 0.490 |
| Age 50 and above, male gender | 2.16 | 1.17-3.97 | 0.013 |
| Duration of HIV infection per 1 year | 1.01 | 0.95-1.07 | 0.801 |
| Baseline CD4 cell count per 1 µl | 1.64 | 1.34-2.03 | <0.001 |
| Baseline CD4 cell count 100-199 µl | 1.02 | 0.43-2.44 | 0.965 |
| Baseline CD4 cell count 50-99 µl | 2.46 | 0.98-6.22 | 0.056 |
| Baseline CD4 cell count <50 µl | 4.41 | 2.36-8.24 | <0.001 |
| Diabetes mellitus | 2.06 | 0.88-4.83 | 0.095 |
| Hypertension | 1.63 | 0.83-3.21 | 0.157 |
| Concurrent use of PI | 1.55 | 0.79-3.05 | 0.200 |
| Concurrent use of DDI | 1.34 | 0.71-2.52 | 0.363 |
| Prior HAART experience | 0.51 | 0.25-1.03 | 0.059 |

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; PI, protease inhibitor; DDI, didanosine; HAART, highly active antiretroviral therapy

**Table III: Multivariate analysis of predictors for more than 25% decrease in eGFR**

| | Adjusted HR | 95% CI | P value |
|---|---|---|---|
| Baseline eGFR 30-59 ml/min/1.73m$^2$ | 3.19 | 1.43-7.12 | 0.005 |
| Baseline eGFR <30 ml/min/1.73m$^2$ | 14.2 | 1.20-170.7 | 0.036 |
| Age 50 and above | 2.26 | 1.22-4.17 | 0.009 |
| Baseline CD4 cell count <50 µl | 4.81 | 2.49-9.28 | <0.001 |

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate

## DISCUSSION

In this multi-ethnic cohort, 15.3% of the patients had eGFR decline of more than 25% from the baseline after the initiation of tenofovir. The incidence of tenofovir-associated renal dysfunction was 12 per 100 person years. The strongest predictor for nephrotoxitiy is having moderate (HR 3.99, 95% CI 1.43-7.12) or severe renal dysfunction (HR14.2, 95% CI 1.20-17.07) at the time of commencement of tenofovir. Older individuals (age>50) and also those with advanced HIV disease (CD4 count 50 copies/ml) were also at higher risk.

The incidence on tenofovir-related renal dysfunction was higher than previously reported randomised controlled trials and cohort studies from western countries.[10,16] However retrospective cohort studies from Asian region have shown similarly high rates of renal dysfunction. A study on Japanese cohort showed eGFR decline in 19.6% (Incidence: 10.5 per 100 person years).[8] Likewise in Thailand, Chaisiri et al. (2010) showed 25% decline in renal function in 19.3% of the patients (incidence of 16.2 per 100 person years).[17] One of the postulated explanations for this is the lower BMI of the patients in Asia.

Similar to our study, several studies have concluded that the risk factors for renal toxicity include advanced HIV infection, advancing age and baseline renal impairment.[18,19] Study in South Africa by Brennan et al., has shown similar correlation between increasing baseline renal impairment and the incidence of renal dysfunction.[18] Besides the ones identified in this study, other reported risk factors for renal function decline with tenofovir include low BMI, other nephrotoxic drugs, concomitant protease inhibitors.[6]

It is important that we avoid starting tenofovir in patients with impaired baseline eGFR. In this study the patients were not followed-up after discontinuation of tenofovir. However, Jose et al. have shown that only one third of the decline in eGFR is completely reversible. Patients with higher GFR at baseline, lower GFR at the time of discontinuation and longer duration on tenofovir were associated with incomplete recovery of renal function.[20]

Our study has several limitations besides being a retrospective observational cohort study. Tenofovir renal toxicity can manifest as proximal tubular damage or as deterioration in renal clearance. Since the criteria for evaluating proximal renal tubular function is not established, we have used changes in eGFR only as marker of tenofovir-associated renal damage. When closely monitored, mild subclinical tubular dysfunction with low level proteinuria and phosphaturia has been reported in up to 22% of patients.[21] So our results might have underestimated the incidence of tenofovir-associated renal damage. In addition data on concurrent self-medication with over-the-counter or traditional medicine, BMI and information about appropriate dose reduction of tenofovir were not available.

In conclusion, renal dysfunction due to tenofovir is not uncommon. Given that the use of tenofovir is escalating in Malaysia, increased awareness about this adverse event is essential. We should avoid starting tenofovir in patients with baseline renal impairment. Doctors have to be trained to regularly monitor renal function by calculating eGFR at baseline and at regular intervals. Prompt withdrawal or dose reduction at the first sign of renal dysfunction is essential to avoid long term disability.

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## POTENTIAL CONFLICT OF INTEREST

All authors: no conflicts

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