

RENAL IMPAIRMENT IN HIV-1 INFECTED PATIENTS RECEIVING ANTIRETROVIRAL REGIMENS INCLUDING TENOFOVIR IN A RESOURCE-LIMITED SETTING

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Abstract. A retrospective cohort study was conducted among HIV-1 infected patients taking tenofovir as part of an anti-HIV drug regimen in a resource-limited setting in Thailand. One hundred thirty patients with a mean \pm SD age of 39.7 \pm 7.4 years, of whom 55% were male, were included in the study. Fifty-eight (45%), 48 (37%), and 24 (18%) patients concurrently received nevirapine-based, efavirenz-based, and protease inhibitor (PI)-based regimens, respectively. The median (IQR) value for serum creatinine was 0.8 (0.6-0.9) mg/dl, for eGFR was 103 (96-120) ml/min/1.73 m² and for CD4 was 302 (194-511) cells/mm³ at the time of tenofovir initiation. At 3-6 months, the median (IQR) eGFR was 100 (88-117) ml/min/1.73 m² ($p=0.002$, compared to baseline). The proportions of patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m² at baseline and 3-6 months were 0% and 2%, respectively ($p<0.001$). At 6-months follow-up, 2 patients (1.4%) were diagnosed with acute renal failure at 3 weeks and 9 weeks after tenofovir use, respectively. Both patients received a boosted PI in the regimen. Overall, the incidence of acute renal failure was 0.26 per 100 person-months. Renal function progressed to irreversible renal failure in one patient. In summary, tenofovir-associated renal impairment is not uncommon in a real-life practice. This report highlights the potentially irreversible adverse effect of this agent, particularly in patients with vulnerable kidneys and concomitant use of tenofovir and boosted PI.

Keywords: HIV, tenofovir, renal impairment, toxicity, Thailand

INTRODUCTION

Renal impairment in HIV-1 infected patients may be due primarily to HIV-1 infection itself or associated with preexisting co-morbidities, such as diabetes

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and hypertension, or be a complication of antiretroviral treatment; it increases the risk of morbidity and mortality (Szczepanek *et al*, 2004 a,b). Renal impairment has been previously reported in patients using protease inhibitors, such as indinavir, atazanavir and fosamprenavir, resulting in renal stones and renal dysfunction (Rho and Perazella, 2007; Harris, 2008; Jao and Wyatt, 2010). Tenofovir, a nucleotide reverse transcriptase inhibitor, is recommended for use in combination with other

antiretroviral agents, for the treatment of HIV-1 infection (Gazzard *et al*, 2008) and was recently approved for the treatment of hepatitis B virus infection (Keeffe *et al*, 2008). According to current HIV treatment guidelines, this drug is recommended for use in first-line HIV treatment regimens and is recommended for treatment of HIV-1 resistant to other nucleoside reverse transcriptase inhibitors, particularly in resource-limited settings (Hammer *et al*, 2008). Tenofovir has few side effects or toxicities; the most common adverse events reported among patients receiving tenofovir are mild gastrointestinal side effects, such as nausea, flatulence and diarrhea (Nelson *et al*, 2007). Severe renal toxicity, including impaired renal function, has been reported infrequently (Gallant *et al*, 2004; Jones *et al*, 2004; Nelson *et al*, 2007; Gallant *et al*, 2008; Smith *et al*, 2009). In many prospective clinical trials, where patients with significant pre-existing renal impairment were excluded, renal toxicity has been found to be very uncommon, and appears at similar rates to patients receiving regimens not including tenofovir (Ananworanich *et al*, 2008). However, many Thais and other Asians have a lower body weight than patients from western countries. Data regarding the frequency of renal impairment in HIV-infected patients receiving antiretroviral regimens including tenofovir in a real-life practice among Asians is limited. Therefore, we conducted a study to evaluate renal function among HIV-infected patients taking antiretroviral regimens including tenofovir.

MATERIALS AND METHODS

A retrospective cohort study was conducted among HIV-infected patients taking tenofovir as part of either a first-

line or second-line antiretroviral regimen between January 2007 and December 2007 at Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand. Patient identification numbers were obtained from the database of the institute and the data were extracted from the medical records. All patients were followed for 6 months of tenofovir use to study the prevalence of renal impairment or acute renal failure. The final decision regarding whether an adverse event occurred was determined by the attending physician note in the medical record. All data regarding concurrent use of antiretroviral drugs and other prescribed drugs were collected. Study inclusion criteria were: 1) HIV-infected patients aged >15 years, 2) use of a tenofovir-containing antiretroviral regimen, 3) receiving a dose of tenofovir at 300 mg/day. Exclusion criteria were: 1) not following up after starting tenofovir, 2) not having a serum creatinine measured at baseline, within 1 month of initiating tenofovir. The primary outcome of interest was estimated glomerular filtration rate (eGFR) at 3-6 months after onset of tenofovir use by comparing the baseline eGFR with the eGFR at 3-6 months. We also studied the incidence of acute renal failure 6 months after starting tenofovir and described the characteristics of patients who developed tenofovir-related acute renal failure. The eGFR was calculated by the Modification in Diet in Renal Disease (MDRD) Study formula (Levey *et al*, 1999). Acute renal failure was defined as an abrupt or rapid decline in renal filtration function, measured by a decline in eGFR >50% from baseline at 3 months.

Mean (\pm standard deviation, SD), median (interquartile range at 25th and 75th, IQR) and frequencies (%) were used to describe patient characteristic where ap-

Table 1
Baseline characteristics of 130 patients.

Baseline characteristics	Number (percent)
Gender: Male	72 (55.4%)
Age, years, mean \pm SD	39.7 \pm 7.4
Body weight, kilograms, mean \pm SD	56.3 \pm 10.4
CD4 count, cells/mm ³ , median (IQR)	302 (104-511)
Serum creatinine, mg/dl, median (IQR)	0.8 (0.6-0.9)
eGFR, ml/min/1.73 m ² , median (IQR)	103 (96-120)
Combined with protease inhibitor	24 (19%)
Combined with nevirapine	58 (45%)
Combined with efavirenz	48 (37%)

propriate. The Wilcoxon signed-rank test was used to compare the eGFR between baseline and at 3-6 months after initiating tenofovir. In patients who had more than 1 measurement during the period 3-6 months after initiating tenofovir, the first measurement was used for analysis. All analyses were carried out using SPSS software version 15.0 (SPSS, Chicago, IL). A *p*-value > 0.05 was considered statistically significant. The study was reviewed and approved by the ethical review board of the Bamrasnaradura Infectious Diseases Institute and the Department of Disease Control, Ministry of Public Health.

RESULTS

A total of 146 patients met inclusion criteria and all medical records were retrieved and reviewed. Sixteen patients were excluded due to lack of serum creatinine measurements. The remaining 130 patients were included in the final analysis. The mean \pm SD age was 39.7 \pm 7.4 years; 55% were males. All patients were ethnic Thais. Table 1 summarizes the characteristics of the 130 patients. Fifty-eight (45%), 48 (37%), and 24 (18%) patients re-

ceived nevirapine-based, efavirenz-based, and protease inhibitor-based regimens, respectively. Of the 122 patients who used tenofovir in a second-line regimen, the reasons for switching the regimen were metabolic complications (92%) and HIV-1 drug resistance (8%). All patients who used tenofovir in a first line regimen received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral regimen. The median (IQR) serum creatinine was 0.8 (0.6-0.9) mg/dl and the median (IQR) eGFR was 103 (96-120) ml/min/1.73 m² at the time of tenofovir initiation. The median (IQR) CD4 cell count was 302 (194-511) cells/mm³. A comparison of the median eGFR at baseline and at 3-6 months after tenofovir onset is shown in Fig 1. The median eGFR was significantly lower at 3-6 weeks compared to baseline (100 vs 103 ml/min/1.73 m², *p*=0.002). The median (IQR) serum creatinine at 3-6 months was 0.8 (0.7-0.9) mg/dl which was significantly lower than baseline (*p*=0.017). The proportions of patients who had an eGFR \geq 90, 60-89, 30-59, 15-29, and <15 ml/min/1.73 m² at baseline and 3-6 months were 80.0% vs 73.8%, 17.7% vs 18.5%, 2.3% vs 6.2%, 0% vs 0%, and 0% vs

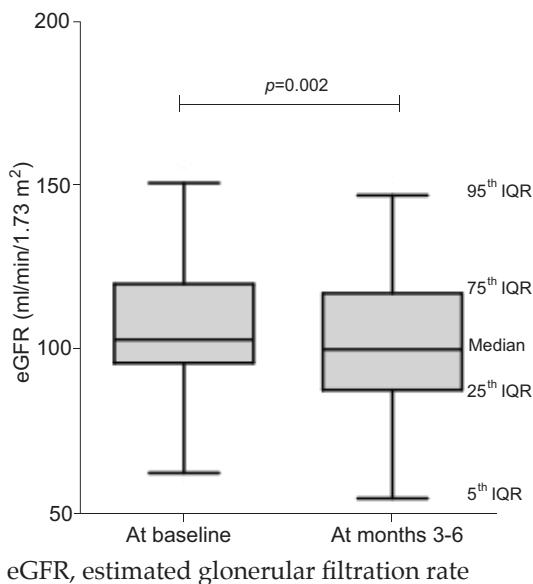


Fig 1-Box plot comparing estimated glomerular filtration rates at baseline and at 3-6 months in $\text{ml}/\text{min}/1.73 \text{ m}^2$.

1.5%, respectively ($p < 0.001$).

At 6-months follow-up, 2 patients (1.4%) were diagnosed with acute renal failure associated with the use of tenofovir. The overall incidence of acute renal failure was 0.26 per 100 person-months. The first case, a 51-year-old male with a CD4 count of 28 cells/ mm^3 and a baseline serum creatinine of 0.7 mg/dl, presented with an abrupt rise in serum creatinine of 11.6 mg/dl and progression to irreversible renal failure while on a regimen of tenofovir, lamivudine and ritonavir-boosted lopinavir for 2.3 months. His concomitant medication included sulfamethoxazole/trimethoprim 400/80 mg/day for *Pneumocystis pneumonia* prophylaxis and fluconazole 400 mg/week for cryptococcosis prophylaxis. He had neither diabetes mellitus nor hypertension. This patient required permanent renal replacement therapy with hemodialysis

due to irreversible renal impairment. The second case, a 69-year-old diabetic male with a CD4 count of 294 cells/ mm^3 and a baseline serum creatinine of 1.6 mg/dl, presented with an abrupt rise in serum creatinine of 6.4 mg/dl while receiving a regimen of tenofovir, lamivudine and ritonavir-boosted lopinavir for 3 weeks. He had received glipizide, pioglitazone and enalapril for 2 years prior to initiation of the tenofovir-containing regimen. The urinalysis revealed 3+ proteinuria, 3+ glycosuria and few red blood cells at the time of renal failure. A renal biopsy revealed evidence of diabetic nephropathy with interstitial nephritis and tubular epithelial damage. Details of the pathological findings are shown in Fig 2. Tenofovir was immediately discontinued on this visit. Temporary hemodialysis was carried out. His serum creatinine returned to baseline 4 months afterward. Both patients received ritonavir-boosted lopinavir and lamivudine until the end of the follow-up period.

DISCUSSION

Although tenofovir is generally well tolerated, the potential for renal toxicity exists. Tenofovir is not metabolized by CYP450 enzymes, but is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure, declining renal function and Fanconi syndrome, have been reported in association with the use of tenofovir (Rifkin and Perazella, 2004). The present study demonstrates decreases in eGFR over time in patients receiving tenofovir. A previous large dataset evaluating the safety of tenofovir showed the incidence of serious renal adverse events was 0.5% (Nelson *et al*, 2007). The rate of renal impairment is relatively high compared

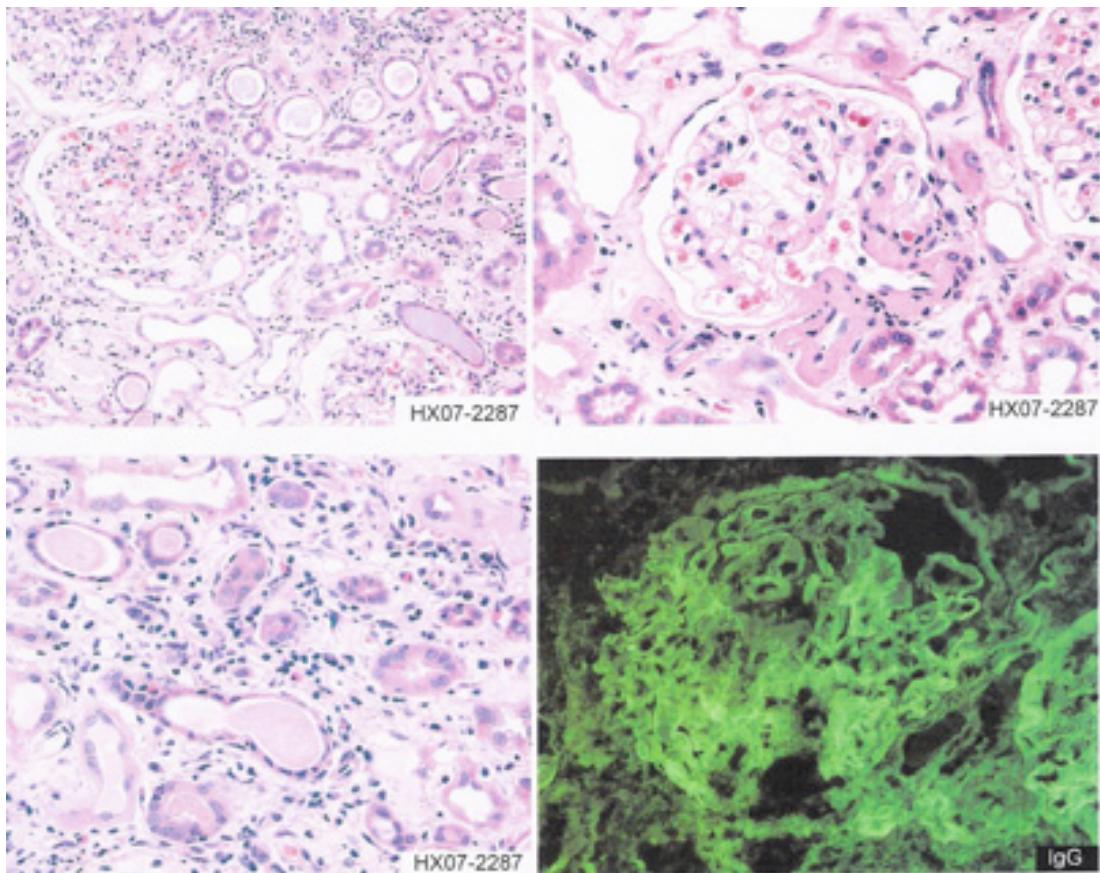


Fig 2—Pathological finding of kidney biopsy. Light microscopy findings: 16 glomeruli are present per section level; 4 glomeruli are globally hyalinized; 12 glomeruli show an irregular increase of the matrix in the mesangium with irregular thickening of the capillary wall. Hyaline arteriolosclerosis is severe in both afferent and efferent arterioles. There are tubular epithelial degeneration, necrosis, and regeneration and tubulitis, together with irregular thickening of the basement membrane of some tubules. Interstitial edema, fibrosis, diffuse with focal dense plasma cells, lymphomonocytic cells and mild eosinophils infiltration are identified. Arteriosclerosis is prominent. Immunofluorescence microscopy findings: frozen sections show a small fragment of renal tissue with 2 glomeruli and two cores of striated muscle. Both glomeruli show trace IgG linear deposits along the glomerular capillary wall. No deposition of IgM, IgA, C3 Ciq fibrin or kappa/lambda L.C. is present in both glomeruli. Deposit of C3 in the arteriolar wall is present.

to the report of a tenofovir expanded access program and post-marketing safety studies conducted in western countries. Post-marketing studies tend to under-report and reporting bias. Thais generally have a lower average body weight than

patients from western countries. However, no change in eGFR was found after tenofovir initiation among Thais in the Staccato trial (Gayet-Ageron *et al*, 2007). This discordant finding may be explained by the fact that patients with pre-existing

renal impairment were usually excluded from the clinical study.

Previous reports have shown the onset of tenofovir-associated nephrotoxicity is relatively common (Zimmermann *et al*, 2006). In the present study, two patients receiving ritonavir-boosted lopinavir and tenofovir developed acute renal failure after the first few months of tenofovir use. Concomitant administration of ritonavir-boosted lopinavir may have enhanced tenofovir exposure by up to 59%; markedly increases in the area under the curve and concentrations for tenofovir when the drug is used concurrently with ritonavir-boosted lopinavir have been described (Pruvost *et al*, 2009). Tenofovir is principally secreted in the urine via multidrug resistance protein MRP2, which is located on the apical surface of proximal cells of the renal tubules. Ritonavir is a potent inhibitor of MRP2-mediated transport (Miller, 2001). Thus, ritonavir potentially can increase proximal tubular concentrations of tenofovir and promote its toxicity by decreasing its apical efflux. The mechanism of renal toxicity is not well understood. Tenofovir, when combined with ritonavir-boosted lopinavir, should be monitored for tenofovir-associated adverse events. The majority of these cases occur in patients with underlying systemic or renal dysfunction, in patients concurrently receiving other nephrotoxic drugs, having a low CD4 cell count or having a low body weight (Coca and Perazella, 2002; Peyriere *et al*, 2004; Gallant *et al*, 2005). Previously reported risk factors associated with nephrotoxicity include concurrent use of other nephrotoxic medications; comorbidities associated with nephrotoxicity, such as hypertension and diabetes, chronic pain and the presumed use of nonsteroidal anti-inflammatory drugs, current and even previous

use of a protease inhibitor, and a history of opportunistic infections. In resource-limited settings both drugs may be recommended as a second-line regimen but in many countries baseline renal function screening and follow-up of renal function are not available. This may contribute to problems in the future. The integration of renal monitoring into the HIV treatment program is urgently warranted since this drug is widely prescribed.

There were a number of limitations in the present study. First, some selection bias may have occurred due to the nature of a retrospective study. Second, the confounding factors related to alteration of eGFR may not have been controlled. Third, although the eGFR of patients decreased over a 6-month study period, the majority were in the normal range. Using eGFR equations may result in inaccuracies when the GFR is within the normal range. Fourth, the final pathological diagnosis was not confirmed in one patient who developed acute renal failure. Fifth, the follow-up period of this study was relatively short. Thus, a long-term study is needed. The incidences of hypophosphatemia and proteinuria were not reported because serum phosphorus levels and urinalyses were not monitored in a large proportion of patients. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed, especially in patients at risk for renal impairment.

In conclusion, tenofovir-associated renal impairment was not uncommon in real-life practice. This study highlights the potentially irreversible adverse effects, on a vulnerable kidney of concomitant tenofovir and boosted protease inhibitor. Further studies regarding the pathophysiology of renal impairment need to be explored.

ACKNOWLEDGEMENTS

The authors wish to thank all the physicians who cared for these patients and the patients in the study.

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