

Use of Tenofovir Disoproxil Fumarate and the Monitoring of Renal Function among HIV-1 Infected Patients in a Resource-limited Setting

Pichit Doungchalermwong, M.D.¹,
Somnuek Sungkanuparph, M.D.²

ABSTRACT

Tenofovir disoproxil fumarate (TDF) has recently been available in Asia and renal dysfunction in patients receiving TDF has been reported. This study was aimed to evaluate the use of TDF and the monitoring of renal function among HIV-1 infected patients in a resource-limited setting. We evaluated the use of TDF in a cohort of HIV-1 infected patients who were initiated TDF. Estimated creatinine clearance (CrCl) by Cockcroft-Gault calculation was used. We studied 205 patients with a mean age of 44.3 years and 61.5 percent were male. Mean body weight was 58.5 kgs. Median CD4 cell count was 389 cells/mm³. Of all, 22 percent had HBV co-infection and 8 percent had HCV co-infection. Prior to initiation of TDF, serum creatinine (Cr) and urinalysis were tested in 89 percent and 21 percent of patients, respectively. At baseline, mean CrCl was 85.7 ml/min and only 1 percent of patients had Cr >1.5 md/dl; 4 percent of patients had proteinuria. After initiation of TDF, 58 percent of patients had been followed up for serum Cr at a median duration of 4 months after initiation of TDF; mean CrCl was 82.7 ml/min and 3 percent of patients had Cr >1.5 mg/dl. Both CrCl and Cr were not significantly different from baseline ($p>0.05$). From linear regression analysis, only baseline Cr was associated with CrCl at follow-up after TDF initiation (Beta=0.844, $p<0.001$). In conclusion, TDF is commonly used for substitution of d4T and AZT when patients develop lipodystrophy in resource-limited setting. It appears that assessment of renal function prior to initiation of TDF and monitoring of renal function after initiation of TDF are inadequate and has to improve. Baseline Cr is a good predictor for CrCl change after initiation of TDF. (*J Infect Dis Antimicrob Agents* 2010;27:77-84.)

Note: The abstract of this study was presented in the 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Helsinki, Finland, 2009. P 1277.

¹Resident of Internal Medicine, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

²Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Received for publication: June 2, 2010.

Reprint request: Somnuek Sungkanuparph, M.D., Associate Professor, Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, 10400, Thailand.

Email: rasuy@mahidol.ac.th

Keywords: HIV, tenofovir, renal function, monitoring, creatinine clearance

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) infection is one of the major public health problems in Thailand and worldwide. Antiretroviral therapy (ART) has been proven to reduce morbidity and mortality in HIV-1 infected patients, both in resource-rich and resource-limited settings.^{1,2} Many regimens of ART such as non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens and protease inhibitor (PI)-based regimens can reduce the plasma HIV-1 RNA to below the limit of detection in most patients and result in immune restoration. However, some adverse effects from antiretroviral agents have been observed. These adverse effects can lead to ART non-adherence, drug resistance and virologic failure.

There are various antiretroviral agents that can be used in the ART regimens and nucleoside reverse transcriptase inhibitors (NRTIs) are commonly used as “backbone” in the regimens.³ Adverse effects and metabolic toxicity associated with NRTI use have been increasingly reported. These include short-term and long-term toxicity, such as nausea, anemia, renal function impairment, lactic acidosis, lipoatrophy and peripheral neuropathy.³⁻⁷

Tenofovir disoproxil fumarate (TDF) is the nucleotide analogue reverse transcriptase inhibitor that has been approved for the treatment of HIV infection⁸ and has recently been available in Asia. Renal dysfunction in patients receiving TDF has been reported.^{9,10} This study was aimed to evaluate the use of TDF and the compliance of monitoring of renal function among HIV-infected patients in a resource-limited setting.

MATERIALS AND METHODS

Patient population and study design

A retrospective cohort study was conducted

in HIV-infected patients who had been cared at Ramathibodi Hospital between September and December 2008. Inclusion criteria included HIV-infected patients who 1) had an age of >15 years old, 2) had been receiving TDF, 3) were not pregnant and 4) had medical record for data review. Exclusion criteria included patients who were referred to Ramathibodi Hospital and had incomplete medical record.

Data collection and calculation

Clinical data including demographics, history of smoking, history of alcohol drinking, body weight, concomitant medications, antiretroviral regimens, lipodystrophy and other adverse events were reviewed from medical record and collected. The results of laboratory investigations including hematology, blood chemistries, CD4 cell count, HIV RNA, HBsAg, anti-HCV antibody, lipid profiles and urinalysis were retrieved from medical records.

Estimated creatinine clearance (CrCl) was calculated using Cockcroft-Gault formula, i.e. $\text{CrCl (ml/min)} = [(140 - \text{age in years}) \times \text{body weight in Kgs}] / 72 \times \text{creatinine}$. For females, the formula requires multiplication by 0.85.

Statistical analysis

Mean (\pm SD), median (interquartile range, IQR) and frequencies (percentage) were used to show the patients' characteristics. Continuous data between groups was compared by Student's *t*-test and the Mann-Whitney *U* test as appropriate. Categorical data was compared by the Chi-square or Fisher exact test where appropriate. Paired *t*-test was used to compare the continuous variables between two different time points in the same group. Linear regression analysis was used to examine risk factor associated with CrCl after initiating TDF. Statistical

significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS program version 14.0 (SPSS Inc, Chicago, IL).

RESULTS

We studied 205 patients with a mean (SD) age of 44.3 (9.4) years and 61.5 percent were male. Mean (SD) body weight was 58.5 (10.5) kg. Baseline characteristics of the study patients are shown in Table 1.

Prior to the initiation of TDF, 162 of 205 (79%) patients were found to have lipodystrophy. Median (IQR) CD4 cell count was 389 (218-514) cells/mm³. Of all, 162 (79.0%) patients had been screened for hepatitis B virus (HBV) co-infection by testing HBV surface antigen (HBsAg) and 35 of 162 (21.6%) patients had HBV co-infection. Regarding hepatitis C virus (HCV) co-infection, 119 (58.0%) patients had been tested with anti-HCV antibody and 10 from 119 (8.4%) patients had HCV co-infection.

Of all, 183 (89%) patients had been tested for serum creatinine. The mean (SD) baseline creatinine (Cr) and creatinine clearance (CrCl) were 0.9 (0.2) mg/dl and 85.7 (23.3) ml/min, respectively. Of all, 2 (1%) patients had Cr. >1.5 md/dl and 8 (3.9%) patients had proteinuria ranging from trace to 1+. The results of laboratory investigation prior to initiation of TDF were summarized in Table 2.

Reasons for using TDF in the 205 study patients included lipodystrophy from d4T and/or AZT (51%), regimen simplification (20%), HBV co-infection (13%), virologic failure (10%), and adverse events from other NRTIs (6%).

After initiation of TDF, 118 of 205 (57.6%) patients had been followed up for serum Cr. at a median (IQR) duration of 4 (2-7) months after initiation of TDF; mean (SD) CrCl was 82.7 (25.3) ml/min and 3 percent of patients had Cr >1.5 md/dl.

Both CrCl and Cr were not significantly different from baseline ($p > 0.05$). The second follow-up had been performed in only 34 (16.6%) patients and at a median (IQR) of 11 (7-18) months. Table 3 shows the baseline and followed up serum creatinine, and creatinine clearance.

Regarding antiretroviral regimens, 71 percent of patients used TDF in NNRTI-based regimens while the others used PI-based regimens. Lamivudine was the most common NRTI used together with TDF (86%). Table 4 shows the antiretroviral agents used with TDF in study patients.

When study patients were categorized into two groups according to the baseline serum creatinine level that was less than 1.5 mg/dl and equal or more than 1.5 mg/dl. Serum Cr and CrCl in the latter group was significantly higher than the former group ($p < 0.05$). However, there were no differences in changes from baseline for both Cr and CrCl.

From linear regression analysis, only baseline Cr was associated with CrCl at follow-up after TDF initiation (Beta=0.844, $p < 0.001$). Other factors including age, gender, weight, plasma glucose and concomitant use of PI were not associated with CrCl after TDF initiation ($p > 0.05$).

DISCUSSION

The results from the present study have demonstrated that more than half of the patients had used TDF because of having lipodystrophy from other NRTIs. This feature has become more and more common since stavudine has been widely used in Thailand and other resource-limited settings.⁵ According to the pre-existing data, there are various adverse events that can be caused by different NRTIs. Although TDF has the least lipodystrophy, other adverse events especially renal impairment is still a concern.

Table 1. Baseline characteristics of 205 patients receiving TDF.

Characteristics	Values
Gender, number (%)	
- male	126 (61.5)
- female	79 (38.5)
Age, years, mean \pm SD	44.5 \pm 9.3
Body weight, kgs, mean \pm SD	58.5 \pm 10.5
History of smoking, number (%), (n=98)	42 (42.9)
Alcohol drinking, number (%), (n=104)	51 (49.0)
Underlying disease, number (%)	
- Diabetes mellitus	10 (4.9)
- Hypertention	20 (9.8)
- Dyslipidemia	59 (28.8)
- Anemia	11 (5.4)
- Malignancies	5 (2.4)
- Heart disease	4 (2.0)
- Others*	13 (6.3)
Previous opportunistic infections, number (%)	
- Tuberculosis	45 (22.0)
- Pneumocystis pneumonia	25 (12.2)
- CMV retinitis	18 (8.8)
- Cryptococcosis	14 (6.8)
- Herpes zoster	10 (4.9)
- Herpes simplex	6 (2.9)
- Toxoplasmosis	3 (1.5)
- Others**	11 (5.4)

*including neuropathy, hyperthyroidism, mixed connective tissue disease, benign prostate hyperplasia and idiopathic thrombocytopenic purpura

**including *Mycobacterium avium* complex infection, cryptosporidiosis, isospora infection, esophageal candidiasis, salmonellosis and progressive multifocal leucoencephalopathy

Table 2. Baseline laboratory investigations of 205 patients receiving TDF.

Characteristics	Values
Hemoglobin, g/dl, mean \pm SD	13.1 \pm 1.9
Hct, %, mean \pm SD	38.6 \pm 5.3
White blood cell count, cells/mm ³ mean \pm SD	
- Neutrophil, %, mean \pm SD	49 \pm 13
- Lymphocyte, %, mean \pm SD	38 \pm 11
- Monocyte, %, mean \pm SD	9 \pm 3
- Eosinophil, %, mean \pm SD	4 \pm 3
- Basophil, %, mean \pm SD	1 \pm 0.7
Platelet, cells/mm ³ , mean \pm SD	265,990 \pm 84,000
Blood urea nitrogen, mg/dl, mean \pm SD	12.3 \pm 5.3
Creatinine, mg/dl, mean \pm SD	0.9 \pm 0.2
CD4 cell count, cells/mm ³ median (IQR)	389 (218-514)
CD4 percent, %, median (IQR)	16 (11-22)
AST, μ /L, median (IQR)	25 (20-46)
ALT, μ /L, median (IQR)	46 (35-80)
Albumin, g/L, median (IQR)	44 (42-48)
Total bilirubin, mg/dl, median (IQR)	0.5 (0.4-0.7)
Direct bilirubin, mg/dl, median (IQR)	0.2 (0.2-0.3)
Total cholesterol (mg/dl), Median(IQR)	214 (175-246)
LDL, mg/dl, median(IQR)	129 (106-160)
HDL, mg/dl, median (IQR)	43 (35-50)
Triglycerides, mg/dl, median (IQR)	175 (106-252)
Glucose, mg/dl, median (IQR)	94 (85-103)
HbA1C, median (IQR)	6.4 (5.4-6.7)
Positive HBsAg, number (%), (n=162)	35 (21.6)
Positive anti-HCV, number (%), (n=119)	10 (8.4)
Proteinuria, number (%), (n=44)	8 (18.2)
Glucosuria, number (%), (n=44)	1 (2.3)

Table 3. Baseline and followed up creatinine and creatinine clearance of 205 patients receiving TDF.

Variables	Values
Baseline	
Creatinine, mg/dl, mean \pm SD	0.90 \pm 0.24
Creatinine clearance, ml/min, mean \pm SD	85.70 \pm 23.34
First follow-up (n=118)	
Median (IQR) time from baseline to first follow-up, months	4 (2-7)
Creatinine, mg/dl, mean \pm SD	0.95 \pm 0.27
Change of creatinine from baseline, mg/dl, mean \pm SD	0.04 \pm 0.17
Creatinine clearance, ml/min, mean \pm SD	82.70 \pm 25.32
Change of creatinine clearance from baseline, mg/dl, mean \pm SD	-2.59 \pm 15.49
Second follow-up (n=34)	
Median (IQR) time from baseline to first follow-up, months	11 (7-18)
Creatinine, mg/dl, mean \pm SD	1.10 \pm 0.55
Change of creatinine from baseline, mg/dl, mean \pm SD	0.15 \pm 0.32
Creatinine clearance, ml/min, mean \pm SD	76.09 \pm 26.83
Change of creatinine clearance from baseline, mg/dl, mean \pm SD	-8.01 \pm 15.07

Unfortunately, the data from the present study has shown that serum Cr had been tested in 89 percent of patients prior to the initiation of TDF but only 58 percent of patients had been followed up for serum Cr after initiation of TDF. This data reflects that physicians have had an insufficient concern about this important adverse event from TDF. Some interventions should be performed to improve this situation. Serum Cr and CrCl should be monitored every 3-6 months in patients using TDF.

The results from the present study have also shown that only baseline Cr is the factor predicting

CrCl after initiation of TDF. This emphasizes the importance of routine Cr screening prior to the initiation of TDF. Lamivudine was the most common NRTI used together with TDF. This may inform the National AIDS Program that the combined pill of TDF and lamivudine should be available in our setting, to simplify the ART regimen and improve adherence.

There were some limitations in the present study. The nature of retrospective study may not allow us to get complete data of Cr and CrCl particularly in our setting because only 58 percent of patients had been followed up for Cr and CrCl.

Table 4. Antiretroviral agents used with TDF in 205 patients.

Antiretroviral agents	Number (%)
NRTIs	
Lamivudine	176 (85.9)
Zidovudine	16 (7.8)
Stavudine	5 (2.4)
Didanosine	5 (2.4)
Abacavir	3 (1.5)
NNRTIs	
Nevirapine	53 (25.9)
Efavirenz	93 (45.4)
PIs	
Indinavir/ritonavir	9 (4.4)
Lopinavir/ritonavir	34 (16.6)
Atazanavir/ritonavir	14 (6.8)
Saquinavir/ritonavir	1 (0.5)
Nelfinavir	1 (0.5)

However, this result may be good data to inform clinicians how to better care for HIV-infected patients by screening and monitoring renal functions before and after initiation of TDF.

In conclusion, TDF is commonly used for substitution of d4T and AZT when patients develop lipodystrophy in resource-limited setting. It appears that assessment of renal function prior to initiation of TDF and monitoring of renal function after initiation of TDF are inadequate. Baseline Cr is a good predictor for CrCl change after initiation of

TDF; this test should not be omitted in resource-limited settings.

References

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853-60.
2. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006;43:42-6.
3. Sungkanuparph S, Anekthananon T, Hiransuthikul N, et al. Guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents: the recommendations of the Thai AIDS Society (TAS) 2008. *J Med Assoc Thai* 2008;91:1925-35.
4. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;354:1112-5.
5. Chuapai Y, Kiertiburanakul S, Malathum K, Sungkanuparph S. Lipodystrophy and dyslipidemia in human immunodeficiency virus-infected Thai patients receiving antiretroviral therapy. *J Med Assoc Thai* 2007;90:452-8.
6. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS* 2008;22:99-103.
7. Manosuthi W, Prasithsirikul W, Chumpathat N, et al. Risk factors for mortality in symptomatic hyperlactatemia among HIV-infected patients receiving antiretroviral therapy in a resource-limited setting. *Int J Infect Dis* 2008;12:582-6.
8. Fung HB, Stone EA, Piacenti FJ. Tenofovir disoproxil

- fumarate: a nucleotide reverse transcriptase inhibitor for the treatment of HIV infection. *Clin Ther* 2002;24:1515-48.
9. Rodriguez-Novoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. *Clin Infect Dis* 2009;48:e108-e116.
10. Szczech LA. Renal dysfunction and tenofovir toxicity in HIV-infected patients. *Top HIV Med* 2008;16:122-6.