Original article

Low body weight and tenofovir use are risk factors for renal dysfunction in Vietnamese HIV-infected patients. A prospective 18-month observation study

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ABSTRACT

Background: The use of tenofovir has been rapidly increasing in Vietnam. Several studies identified low body weight as a risk factor for tenofovir-induced nephrotoxicity. However, little is known about the impact of tenofovir on renal function in HIV-infected Vietnamese with generally low weight.

Methods: An observational single-center cohort of adult HIV-infected patients on antiretroviral therapy at National Hospital of Tropical Diseases, Hanoi. Patients on tenofovir or with creatinine clearance \( \leq 60 \text{ ml/min} \) at baseline were excluded. The incidence of renal dysfunction was compared between patients who switched to tenofovir and those who did not. Renal dysfunction was defined as 25% decline of creatinine clearance from baseline. Time to renal dysfunction was analyzed by the Kaplan–Meier method between the two groups. The Cox hazard model was used to determine risk factors for renal dysfunction in uni- and multivariate analyses.

Results: Of 556 patients enrolled in this study, 403 were non-tenofovir group while 153 were the tenofovir-switched group. Renal dysfunction occurred at a higher rate in the tenofovir-switched group (92.5 per 1000 person-years) than the non-tenofovir group (47.8 per 1000 person-years) \( (p = 0.023, \text{ Log-rank test}) \). Multivariate analysis confirmed that tenofovir use, low body weight and glucosuria were significant risk factors for renal dysfunction (hazard ratio = 1.980; 95% confidence interval, 1.094–3.582, HR = 1.057; 95%CI, 1.016–1.098, HR = 5.202; 95%CI, 1.245–21.738, respectively).

Conclusions: Tenofovir use, low body weight and glucosuria were significant risk factors for renal dysfunction. We suggest close monitoring of renal function in patients with these risk factors even in resource-limited setting.

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Key points

Treatment with TDF and low body weight were significant risk factors for renal dysfunction in Vietnamese HIV-treated patients. Given that the average body weight of Vietnamese is small, close monitoring of renal function in HIV-1-infected patients is important during treatment with TDF.
1. Introduction

Although renal dysfunction is an important cause of morbidity and mortality in HIV-infected patients [1–7], only limited information is available on renal function in Vietnamese HIV-infected patients. Along with the 2010 WHO guidelines which phased out stavudine and recommended tenofovir (TDF) (URL: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf), the use of TDF had been increasing in Vietnam in recent years. TDF-associated nephrotoxicity is well known adverse effect. However, a meta-analysis study that evaluated the safety of TDF concluded that TDF-associated nephrotoxicity can be considered negligible and thus there is no need to restrict TDF use even when regular observation of renal function is not feasible [8]. Other experimental and clinical studies, however; provide a different scenario: one study of rhesus macaques described a dose-dependent nephrotoxic effect for TDF [9] and several studies reported cases of TDF-associated nephrotoxicity in low-body-weight HIV-infected patients [10,11]. Our group also reported that low body weight and use of TDF were significantly associated with chronic kidney dysfunction in Vietnamese HIV-infected patients in a cross-sectional study [12]. Since Vietnamese have a considerably smaller body weight compared with Caucasians, and the use of TDF in Vietnam is increasing throughout the country, the potential risk for TDF-related nephrotoxicity is a concern in Vietnam. This is also true in all countries in the region since the Asian population is, in general, of low body weight. To examine this issue in more detail, we conducted a longitudinal study to evaluate the incidence of renal dysfunction in Vietnamese HIV-infected patients and the risk factors of such morbidity, including use of TDF and low body weight.

2. Patients and methods

2.1. Study design

We performed a prospective observational study of a single-center cohort of Vietnamese HIV-infected patients on antiretroviral therapy (ART) to evaluate the impact of TDF and low body weight on renal function. This cohort was established in 2007 at the National Hospital of Tropical Disease (NHTD) in Hanoi, one of the biggest outpatient clinics for HIV infected-patients in Vietnam. The population of the cohort consists of Vietnamese HIV-infected patients on ART aged more than 17 years referred to NHTD.

To evaluate renal function, serum creatinine had been measured since October 2011, which is the baseline of this study. Entry criteria were patients who were registered in this cohort on October 2011. Patients taking TDF or with serum creatinine clearance (CrCl) of ≤60 ml/min at baseline were excluded. Also excluded from the study were patients whose creatinine was not obtained twice at least. The follow-up period was 18 months (between October 2011 and April 2013). All patients of this cohort received ART at baseline. ART included Zidovudine (AZT)/Lamivudine (3 TC), Stavudine (d4T)/3 TC or TDF/3 TC as nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with efavirenz (EFV), Nevirapine (NVP) or ritonavir boosted lopinavir (LPV/r). To estimate the incidence of renal dysfunction in this population, patients were divided into those who switched to TDF and those who did not. Laboratory data, including serum creatinine, were measured twice a year (in April and October) in this cohort. The study was approved by the Human Research Ethics Committee of NHTD. Each patient included in this study provided a written informed consent for the clinical and laboratory data to be used for publication. The study was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Measurements

Clinical and laboratory data included demographic variables (age, sex and weight), serum creatinine (mg/dl, measured by Jaffe method), CD4 cell count (cell/mm³, measured by flow cytometry), plasma HIV-RNA (copies/ml, measured by the Roche COBAS TaqMan HIV monitor assay), complete history of ART, use of cotrimoxazole, date of HIV diagnosis, and presence of other comorbidities such as hepatitis B and C virus, diabetes mellitus and AIDS defining diseases. Renal dysfunction was defined as 25% decline in CrCl estimated by the Cockcroft–Gault formula, relative to the baseline.

2.3. Statistical analysis

Baseline characteristics were compared between case patients and control patients by the Student’s t-test for continuous variables and by either the χ² test or Fisher’s exact test for categorical variables. The time from baseline to renal dysfunction was analyzed by the Kaplan–Meier method for patients who switched to TDF and those who did not, and the log-rank test was used to determine the statistical significance. Censored cases represented those who died, dropped out, or were referred to other facilities before the end of follow-up period. The Cox proportional hazards regression analysis was used to estimate the impact of TDF use on the incidence of renal dysfunction. The impact of basic demographics, baseline laboratory data, and other medical conditions was also estimated with univariate Cox proportional hazards regression. Variables significantly associated with renal dysfunction in univariate analysis (p < 0.05) were entered into multivariate analysis. Statistical significance was defined at two-sided p value < 0.05. We used the hazard ratio (HR) and 95% confidence interval (95%CI) to estimate the association of each variable with renal dysfunction. All analyses were performed in SPSS (version 22.0).

3. Results

At baseline, 793 Vietnamese HIV-infected patients on ART were registered in this study. However, 237 patients were excluded from the study due to existing renal dysfunction at baseline (CrCl < 60 ml/min, n = 72), had already been treated with TDF at baseline (n = 143), and lack of repeated measurements of CrCl (n = 22). Thus, 556 patients who received ART met the study criteria and were included in the study. Of these, 153 patients were switched to TDF during the study period, while 403 patients continued treatment with non-TDF-containing regimen. The criteria for switch to TDF were adverse event caused by ART or induction of treatment for chronic hepatitis B virus infection.

Table 1 compares the baseline demographics and clinical variables of patients of the TDF-switched group and the non-TDF group. The TDF-switched group was significantly more likely to be males, hepatitis B virus S antigen-positive and hepatitis C virus antibody-positive compared to the non-TDF group. The TDF-switched group had marginally significant trend to be older and have diabetes mellitus. Body weight, serum creatinine, CD4 count, HIV RNA viral load, duration of ART, frequency of proteinuria and glucosuria, use of ritonavir boosted lopinavir (LPV/r) and cotrimoxazole, and history of AIDS-defining disease were not significantly different between the two groups. The mean CD4 count was >300/mm³ and the mean HIV RNA load was <100 copies/ml in both groups.

During the observation period, renal dysfunction, defined as 25% decline in CrCl, was observed in 19 (12.4%) of the TDF-switched group and 27 (6.7%) of the non-TDF group, with an estimated incidence of 92.5 and 47.8 per 1000 person-years, respectively. Fig. 1 depicts the time from the baseline to the development of
renal dysfunction by Kaplan–Meier method in the two groups. The incidence of renal dysfunction was significantly higher in the TDF-switched group, compared with the non-TDF group ($p = 0.023$, Log-rank test). With regard to the time of switch to TDF, 109 (71.5%) patients of the TDF-switched group switched their nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) to TDF within 3 months from the baseline and additional 31 (20.0%) switched between 3 and 6 months. Furthermore, of the 19 patients of the TDF-switched group who developed renal dysfunction, 13 (71.2%) switched to TDF within 3 months from the baseline and additional 5 (23.5%) switched to TDF between 3 and 6 months.

Table 2 shows the results of the Cox proportional hazards regression model. Univariate analysis identified body weight per 1 kg-decrement, use of TDF, and glucosuria as factors significantly associated with renal dysfunction. After adjustment by multivariate analysis, body weight per 1 kg-decrement (HR = 1.098; 95%CI, 0.006), use of TDF (HR = 1.980; 95%CI, 1.053–2.1738; $p = 0.024$), and glucosuria (HR = 5.202; 95%CI, 2.45–21.738; $p = 0.006$) were still associated significantly with renal dysfunction.

We also compared the incidence of renal dysfunction in the TDF-switched group according to body weight. Fig. 2 shows the time from baseline to renal dysfunction in patients with body weight of <55 kg, representing the average weight of this study population, and in those with ≥55 kg. The incidence of renal dysfunction was significantly more likely to develop renal dysfunction [12/66 cases (18.2%), 145.3/1000 person-year] compared to patients of the >55 kg group [7/87 cases (8.0%), 570/1000 person-year] ($p = 0.040$, Log-rank test).

Table 1
<table>
<thead>
<tr>
<th>Variables</th>
<th>Without TDF</th>
<th>With TDF</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>403 (72.5)</td>
<td>153 (27.5)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>35.6 ± 7.0</td>
<td>36.9 ± 6.8</td>
<td>0.064</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>167 (41.4)</td>
<td>45 (29.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Body weight</td>
<td>55.7 ± 8.3</td>
<td>56.5 ± 8.2</td>
<td>0.284</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.93 ± 0.13</td>
<td>0.93 ± 0.12</td>
<td>0.668</td>
</tr>
<tr>
<td>CD4+ cell count, cell/µl</td>
<td>394 ± 197</td>
<td>385 ± 166</td>
<td>0.651</td>
</tr>
<tr>
<td>Log 10 HIV-RNA level, copies/ml</td>
<td>1.48 ± 0.55</td>
<td>1.42 ± 0.41</td>
<td>0.190</td>
</tr>
<tr>
<td>Proteinuria, n (%)</td>
<td>48 (11.9)</td>
<td>21 (13.7)</td>
<td>0.522</td>
</tr>
<tr>
<td>Glucosuria, n (%)</td>
<td>3 (0.7)</td>
<td>2 (1.3)</td>
<td>0.617</td>
</tr>
<tr>
<td>HBVAg (+), n (%)</td>
<td>22 (5.5)</td>
<td>25 (18.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCVAb (+), n (%)</td>
<td>153 (38.0)</td>
<td>69 (45.1)</td>
<td>0.014</td>
</tr>
<tr>
<td>Duration of ART, years</td>
<td>1.14 ± 1.35</td>
<td>1.20 ± 1.47</td>
<td>0.650</td>
</tr>
<tr>
<td>Use of ritonavir boosted lopinavir, n (%)</td>
<td>7 (1.7)</td>
<td>5 (3.3)</td>
<td>0.326</td>
</tr>
<tr>
<td>Use of cotrimoxazole, n (%)</td>
<td>136 (33.7)</td>
<td>45 (29.4)</td>
<td>0.330</td>
</tr>
<tr>
<td>Prior AIDS-defining disease, n (%)</td>
<td>36 (8.9)</td>
<td>12 (7.8)</td>
<td>0.683</td>
</tr>
<tr>
<td>Diabetes mellitus (+), n (%)</td>
<td>31 (7.7)</td>
<td>19 (12.4)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

ART = Antiretroviral therapy; TDF = tenofovir.

The mean serum creatinine was higher in the TDF-switched group compared with the non-TDF group, and the difference in the mean serum creatinine between the two groups increased from 0 mg/dl at baseline, to 0.4 mg/dl at 6 month, 0.5 mg/dl at 12 months and 0.6 mg/dl at 18 months from the baseline.

4. Discussion

In this 18-month prospective study of a single-center cohort, we evaluated the impact of TDF on renal function in Vietnamese HIV-infected patients with low body weight of approximately 55 kg. The Kaplan–Meier curve showed that the cumulative incidence of renal dysfunction was significantly higher among the patients who switched to TDF than among those who did not ($p = 0.023$). Cox proportional hazards regression model identified the use of TDF, low body weight and glucosuria as significant high risk factors for renal dysfunction. In sub-analysis of the TDF-switched group, we confirmed that the cumulative incidence of renal dysfunction was significantly higher in patients with body weight <55 kg compared to those weighing ≥55 kg.
We reported previously that low body weight and TDF use were factors significantly associated with chronic kidney disease in a cross-sectional study of this cohort in Hanoi [12]. The present study confirmed that TDF exposure and low body weight bear a causative relationship to renal dysfunction. We also reported low body weight (<59 kg) as a risk factor for renal dysfunction in Japanese patients treated with TDF [10], whereas high body weight of >67 kg was not the risk, similar to the body weight of the patients reported by Cooper et al. [8]. In light of the fact that the average body weight of the patients in this cohort was 55 kg, which is around 30 kg lighter than that of average American males (88 kg) (URL:http://www.cdc.gov/nchs/data/nhsr/nhsr010.pdf), the impact of these risk factors on renal function remain unknown in patients with low body weight in the long-run, thus, observational studies will need to be continued for a longer term.

In addition to low body weight, the presence of glucosuria at baseline was identified as a risk factor for renal dysfunction. This result is consistent with the most recent WHO guidelines which suggest urinary glucose as one of the cost-effective screening test for serious TDF-induced kidney injury (URL: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf). Since the number of patients with glucosuria was small in this study (about 1% of total population), and glucosuria was not followed until the end of the observation period, further evaluation of this factor is necessary.

Other risk factors for renal dysfunction described in previous studies, such as cotrimoxazole, LPV/r, hepatitis C virus coinfection and diabetes mellitus [13–16] were not identified as risk factors in this study. This discrepancy could be explained by the fact that patients who could be affected by these factors were already excluded according to the study design, which excluded patients with renal dysfunction. With regard to the use of LPV/r, which is known as a risk for renal dysfunction [14,17], especially in cases of co-use with TDF, a number of patients with LPV/r were excluded from the study since most of the patients with LPV/r were co-treated with TDF at baseline. Thus, the impact of co-use of LPV/r and TDF on renal function could be underestimated in this study. Given that LPV/r is used as a salvage regimen and often administrated with TDF in Vietnam, long-term monitoring of renal function is required in patients treated with both LPV/r and TDF.

The present study has several limitations. First, data on hypertension, which is a risk factor for renal dysfunction, were not available in this study. Although the average age of patients in this study was around 36 years and the prevalence of hypertension may not high, measurement of blood pressure could lead to better management of renal dysfunction and hypertension should be evaluated for potential risk. Regarding diabetes mellitus as well, the degree of diabetes mellitus was not checked in detail. However, severe patients such as insulin dependence were not in this study, thus, the lack of data could be limited. Second, the observation period of 18 months is relatively short to evaluate long-term adverse event for renal function as mentioned above. Some studies advocated stabilization of decline in eGFR later after the first 6 months of TDF exposure [18] and reversibility of eGFR decline after cessation of TDF therapy [19], while several studies argued incomplete reversibility of eGFR decline following TDF exposure [20–22]. In this study, most of the patients who developed the decline in Crcl continued the same ART regimen because of their moderate and/or stabilized renal dysfunction. However, the observational period of the present study is relatively short compared to other studies, thus, whether or not the stabilization and reversibility will be observed in this cohort of averagely small body weight should be evaluated in the longer period.

Third, the timing of switch to TDF and total duration of ART were not unified in the present study, since the study was an observational cohort in which patients were already on ART at enrollment. The reasons for switch to TDF were mainly related to adverse events caused by d4T and AZT or treatment for HBV infection, thus the timing of switch to TDF was not strictly controlled. However, more than 70% and 90% of the patients were switched to TDF within 3 and 6 months from baseline, respectively, thus influence of this limitation on the result of this study could be restricted.

Despite concern on nephrotoxicity, TDF remains an important drug with enough anti-HIV potency and less mitochondrial toxicity among NRTIs. In order to use it safely in the long term, serum creatinine should be monitored in patients with aforementioned risk factors even in resource-limited situations. Further longitudinal studies are required to determine the impact of TDF, low body weight and glucosuria on renal function in Vietnamese and other Asian people with low body weight.

Conflict of interest

S.O. has received honoraria and research grants from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Pfizer, Co., and Roche Diagnostics K.K.; received honoraria from Astellas Pharmaceutical K.K., Bristol-Myers K.K., DaiichiSankyo, Co., Dainippon Sumitomo Pharma, Co., GlaxoSmithKline, K.K., Taisho Toyama Pharmaceutical Co., Torii Pharmaceutical Co., and Viiv Healthcare. H.G. has received honoraria from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Torii Pharmaceutical Co., and Viiv Healthcare, Co. All other authors declare no conflict of interest.

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References


