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TDF/3TC/EFV Regimen-Related Renal and Neuropsychiatric Toxicity in Vietnam HIV-Infected Patients

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Abstract

Introduction: ARV regimen constituting of tenofovir, lamivudine and efavirenz (TDF/3TC/EFV) has been selected as basic regimen for HIV treatment in Vietnam. Despite the increasing use of this regimen, available data about EFV-related neuropsychiatric toxicity and TDF-related renal dysfunction is still limited. Objectives: To determine incidence of neuropsychiatric and renal toxicity and to identify possible related risk factors. Materials and Methods: A prospective study was conducted at ten clinics in Vietnam, including adult HIV-infected patients initiated with TDF/3TC/EFV regimen. Neuropsychiatric toxicity was recorded by interviewing patients while renal toxicity was defined as a decrease of creatinine clearance (CrCl) by over 25% from the baseline level. Associating risk factors were identified using multivariate analyses. Results: There were 838 patients enrolled with a median of 10.4 months monitoring period. 324 (38.66%) experienced at least one neuropsychiatric adverse events, mainly in the first month of treatment (94.5%). Most patients only experienced mild ADR (76.9%). TDF-related renal dysfunction was identified in 78 (14.47%) patients. Multivariate analysis showed that EFV-related CNS toxicity was associated with higher age (HR=1.218; 95%CI 1.076-1.363), lower weight (HR=0.822; 95%CI 0.686-0.959), higher hemoglobin (HR=1.111; 95%CI 1.055-1.168) and TDF-related renal toxicity was associated with lower hemoglobin (HR=0.846; 95%CI 0.745-0.948), higher age (HR=1.363; 95%CI 1.062-1.672) and higher baseline CrCl (HR=1.177; 95%CI 1.140-1.214). Conclusion: The EFV-related CNS toxicity was common yet mild while the incidence of TDF-associated renal toxicity was relatively low. Some identified risk factors may be useful for clinical management.

Keywords: ART; TDF; EFV; adverse drug reactions.
1. INTRODUCTION

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) recommended widely in combination with two other nucleoside reverse transcriptase inhibitors (NRTI) in highly active antiretroviral therapy (HAART) [1], [2]. Research has shown that efavirenz is related to neuropsychiatric adverse reactions such as dizziness, vertigo and sleep disorders [3], [4]. Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse-transcriptase inhibitor (NRTI). Currently, TDF is widely recommended as a first choice in HIV treatment guidelines [5]. There are a number of reports on renal toxicity appearing in HIV patients treated with TDF[6], [7].

Since 2015, the Vietnam Ministry of Health has recommended the combination of TDF/3TC/EFV as first line regimen for naïve HIV-infected patients and it is expected that the use of TDF and EFV will increase in the near future in Vietnam. Although Vietnamese patients are likely to have lower body weight than Whites and African Americans, a limited number of studies reported the EFV-associated neuropsychiatric adverse effects and TDF-associated renal dysfunction data in Vietnam populations [8], [9]. This present study was conducted to determine incidence of neuropsychiatric and renal toxicity and to identify possible risk factors associated with these adverse effects.

2. METHODS

2.1. Study design

We conducted a prospective cohort study including HIV-infected patients in 10 clinics in 7 cities in Vietnam. Inclusion criteria were as follows: (1) age ≥18 years old, (2) antiretroviral naivety, (3) initiation of TDF/3TC/EFV regimen between March 16, 2015 and July 15, 2016 and (4) non-pregnant during monitoring period. Moreover, exclusion criteria were defined for each group as follow: (for EFV cohort) (1) did not have at least one follow-up visit at the HIV clinic after EFV initiation; (for TDF cohort) (1) did not have information on baseline weight and serum creatinine and (2) did not have at least one follow-up serum creatinine results after TDF initiation.

Basic demographic information and baseline laboratory parameters were considered as potential risk factors and recorded closest to and prior the initiation of HAART within 90 days from the medical records. These included (where possible): demographic variables (weight, sex and age); CD4 cell count (cell/mm$^3$); haemoglobin, alanine aminotransferase (ALT), serum creatinine (µmol/L); and clinical stage (based on WHO Guidelines) [5].

Adverse effects on neuropsychiatric system and renal were monitored and reported by trained healthcare professionals. EFV-related neuropsychiatric disorders were determined by physicians by interviewing patients on each visit. The severity of neuropsychiatric adverse events was classified by the Division of AIDS grading tables [10]. To assess the renal toxicity of TDF, follow-up parameters including body weight and serum creatinine were collected every 6 months after TDF initiation based on recommendation by Vietnam Ministry of Health. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula. Study endpoint definition, which was renal function decline, was defined by a 25% decline in CrCl from the baseline level.

2.2. Statistical analysis

Mean (standard deviation, SD), median (interquartile range, IQR) and frequencies (%) were used to describe patients' characteristics. Censored cases represented those who died, dropped out, switched to non-EFV or non-TDF based regimen or were referred to other clinics before the end of follow-up period at 15 July 2016. The impact of basic demographics and baseline
laboratory data was estimated by multivariate analyses which was performed by using Bayesian Information Criterion (BIC) to find the most appropriate model. For the purpose of handling with a large number of missing values, the PMM method was used to create values replacing missing values of continuous variates. All statistical analyses were performed by using RStudio.

3. RESULTS

3.1. Baseline characteristics

From March 16, 2015 to July 15, 2016, a total of 838 HIV-infected patients were included in the study. All of 838 patients was eligible for inclusion in the analysis for neuropsychiatric toxicity (EFV cohort). Due to lack of baseline or follow up serum creatinine data, 299 patients were excluded from renal function monitoring cohort (TDF Cohort). Thus, 539 patients were included in the analysis for renal toxicity. Baseline characteristics and laboratory investigations were relatively similar between the two cohorts. These data were described in Table 1.

Table 1. Baseline demographics and laboratory investigations of EFV and TDF cohort

<table>
<thead>
<tr>
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<th>EFV cohort</th>
<th>TDF cohort</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>838 (100.0)</td>
<td>539 (100.0)</td>
</tr>
<tr>
<td>Age</td>
<td>Median (IQR)</td>
<td>33 (29, 38)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>561 (66.9)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>277 (33.1)</td>
</tr>
<tr>
<td>Weight</td>
<td>Median (IQR)</td>
<td>53 (48, 59)</td>
</tr>
<tr>
<td>ALT</td>
<td>Median (IQR)</td>
<td>30 (20-51) N=804</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>Median (IQR)</td>
<td>318 (122-478) N=801</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>Median (IQR)</td>
<td>131 (115-143) N=817</td>
</tr>
<tr>
<td>Crcl</td>
<td>Median (IQR)</td>
<td>86.0 (72.5-101.0)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>1</td>
<td>523 (62.4)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>109 (13.0)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>91 (10.9)</td>
</tr>
<tr>
<td>Follow-up time, months</td>
<td>Median (IQR)</td>
<td>4</td>
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### 3.2. EFV-associated neuropsychiatric toxicity
Median (IQR) duration of receiving EFV was 10.4 (7.9-12.8) months. The percentage of patients suffering at least one psychiatric disorder was 38.7% (324 patients). Among these patients, 94.5% experienced adverse events in the first month of treatment, median (IQR) time to EFV-associated neuropsychiatric adverse events was 7.0 (1.0-10.0) days. The most common manifestations of neuropsychiatric toxicity were dizziness, headache and fatigue, which were observed in at least 163 patients (50.3%), while nausea and hot flush occurred in at least 82 patients (25.3%). The number of patients experiencing mild and moderate adverse events were 249 (76.9%) and 72 (22.3%), respectively. Only 3 patients had severe symptoms.
By multiple logistic regression, higher age (per 10 years, HR=1.218; 95%CI, 1.076-1.363), lower weight (per 10kg increment, HR=0.822; 95%CI, 0.686-0.959), and higher hemoglobin at baseline (per 1g/dL increment, HR =1.111; 95%CI, 1.055-1.168) were statistically associated with EFV-related CNS toxicity.

### 3.3. TDF-associated renal toxicity
Median (IQR) duration of receiving TDF was 11.1 (8.7-13.0) months. There were 78 (14.5%) patients with renal dysfunction defined as a 25% decrease in CrCl from the baseline. Among these patients, median (IQR) time to a 25% decrease in CrCl was 6.2 (5.1-7.7) months, the earliest occurrence was in the first month of TDF initiation, and the latest occurrence was in the 16th month after TDF initiation. Among those experiencing TDF-related renal dysfunction, creatinine level in 60 (76.9%) remained normal, 18 patients (22.8%) had serum creatinine concentration exceeding normal limits, wherein 15 cases increased up to 1.5 times and 3 cases increased up to 3 times the normal upper limit.
By multiple logistic regression, lower haemoglobin at baseline (per 1g/dL increment, HR=0.846; 95%CI, 0.745 – 0.948), higher age (per 10 years increment; HR=1.363; 95%CI, 1.062 – 1.672) and higher baseline CrCl (per 10ml/min increment, HR=1.177; 95%CI, 1.140-1.214) were statistically associated with a 25% decrease in CrCl.

### 4. DISCUSSIONS
To our knowledge, the present study was one of the first multicentre studies regarding EFV-related neuropsychiatric disorders and TDF-associated renal dysfunction among Vietnamese HIV-infected patients.
The percentage of patients experiencing neuropsychiatric adverse events related to EFV was 38.7% (324 patients). This incidence rate was lower than the results in other studies, which reported that the prevalence rates fluctuated from 40% to 70% [2], [3]. This difference may be due to different study designs, including sample size, patient selection criteria, definition of adverse events on the neuropsychiatric system and the method of investigation and assessment [2]. The majority of reactions were mild, transient, and easily confused with clinical symptoms, particularly on IDU patients. As a result, they might be ignored and not recorded in the medical record.
The most common neuropsychiatric adverse effects were dizziness, headache and fatigue while some severe adverse effects including depression and suicidal intention were reported rarely. Most of the adverse effects were mild or moderate (99.1%). Only 3 cases were severe (0.9%). This result was similar to the data in some reviews and medical literature [1], [11], [12].

In our study, the ADR in the neuropsychiatric system mainly appear within the first month of initiation (94.5%). This lag period was also reported in other studies, wherein the most severe of adverse effects were recorded within the first 2–4 weeks [2]. Results from multivariate analysis in this study suggested that lower weight, higher age, or higher hemoglobin at baseline were the factors significantly associated with EFV toxicity on neuropsychiatric system. Lower body weight may lead to high EFV plasma concentration and increased risk of toxicity. The association between plasma concentration of EFV and neuropsychiatric disorder was well documented but does not always occur [13]. In addition, it was recommended by WHO that physicians should consider to reduce the dose of EFV to 400mg/day to reduce CNS adverse events when the symptoms occurred. This finding put an emphasis on monitoring for neuropsychiatric disorder for an appropriate and effective consultancy and treatment for lighter patients, which are common among Asian populations. The reason why older patients and those who had high haemoglobin level at baseline are associated with higher risk of neuropsychiatric disorder remains unclear to us. Future study is needed to explore this association.

We found that 14.5% of the patients developed a TDF-associated renal function decline defined by a 25% decrease in CrCl from the baseline. This proportion seemed to be higher than other studies in Asian population with different definitions of nephrotoxicity [8][14] and lower than those having similar definitions of adverse events [15]. In addition to the difference in definitions of nephrotoxicity, this can be explained by difference in the formula used to estimate CrCl, patients’ characteristic and duration of observation [16]. Factors associated with renal dysfunction were higher baseline CrCl, lower haemoglobin level at baseline and higher age. The mechanism of the association between high baseline renal function (or CrCl) and TDF-related renal dysfunction was not clearly known. However, this finding was also observed in other cohort studies on Asian populations [15][17]. It can be explained by the predefined criteria detecting nephrotoxicity in this study estimated by a 25% decrease in CrCl from baseline. Therefore, patients with higher baseline CrCl are more sensitive to suffer a decrease in renal function [18]. Old age was also suggested as a risk for TDF-induced renal dysfunction, which is similar to previous data [17][8].

The study had several important limitations. Firstly, there was noticeable amount of missing data, especially information of concurrent nephrotoxic drugs and comorbidities, which were potential risk factors for neuropsychiatric or renal toxicity. However, this was predicted in view of the routine of examining and recording patient data in HIV care practice, especially in resource-limited settings in Vietnam. Secondly, renal function was estimated at 6-months interval, additionally, some patients did not follow the recommended schedules of serum creatinine test. Thus, this might not represent the exact incidence and time-to-onset of the nephrotoxicity. Thirdly, other TDF associated nephrotoxicity, such as Fanconi syndrome were not observed because other laboratory tests including urine analysis and serum electrolyte levels were not collected.
5. CONCLUSIONS

Our study shows that proportions of EFV-associated neuropsychiatric toxicity was common yet mild while the incidence of TDF-associated renal toxicity was relatively low among Vietnam HIV-infected patients. Careful consulting and close monitoring is essential for early detection and appropriate management for both toxicities, especially among high risk patients. Further research is needed to confirm the impact of age or haemoglobin level on neuropsychiatric disorder and renal dysfunction.

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