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Original Article

Tenofovir disoproxil fumarate co-administered with lopinavir/ritonavir is strongly associated with tubular damage and chronic kidney disease

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ABSTRACT

Backgroud: With expanding antiretroviral therapy (ART) in a resource-limited setting, the use of second line ART with ritonavir boosted lopinavir (LPV/r) is increasing. However, little is known regarding the renal safety of tenofovir (TDF) co-administered with LPV/r.

Methods: In total 1382 HIV-infected patients were enrolled and data were recorded twice (October 2014 and 2015) in Vietnam. Tubular dysfunction (TD) was defined as urinary beta 2 microglobulin (β2MG) > 1000 μg/L at both timepoints or increase in β2MG by > 2000 μg/L. Chronic kidney disease (CKD) was defined as creatinine clearance ≤60 ml/min or urinary protein/creatinine ratio ≥ 0.15 g/gCre at both timepoints.

Results: The patients'mean weight and age were 55.9 kg and 38.4 years, respectively, and 41.5% were female. Additionally, 98.2% were on ART, 76.3% were on TDF (mean exposure duration was 35.4 months), and 22.4% had never TDF exposure. TD and CKD were diagnosed in 13% and 8.3% of all patients, respectively. In multivariate analyses, age (OR = 1.057; 95%CI, 1.034–1.081), being female (OR = 0.377; 95%CI, 0.221–0.645), HBsAg positive (OR = 1.812; 95%CI, 1.134–2.894), HCVAb positive (OR = 1.703; 95% CI, 1.100–2.635), TDF exposure (OR = 9.226; 95%CI, 2.847–29.901) and LPV/r exposure (OR = 5.548; 95% CI, 3.313–9.293) were significantly associated with TD. Moreover, age (OR = 1.093; 95%CI, 1.068–1.119), being female (OR = 0.510; 95%CI, 0.295–0.880), weight (OR = 0.909; 95%CI, 0.879–0.939), hypertension (OR = 3.027; 95%CI, 1.714–5.347), TDF exposure (OR = 1.963; 95%CI, 1.027–3.7 53) and LPV/r exposure (OR = 3.122; 95%CI, 1.710–5.699) were significantly associated with CKD.

Conclusions: TDF and LPV/r exposure were strongly associated with TD and CKD, in addition to their known risks. Therefore, attention to renal safety for patients on second line ART is necessary.

1. Introduction

Renal dysfunction is fast becoming one of the major comorbidities among HIV-infected patients since widespread use of antiretroviral therapy (ART) has decreased AIDS-associated mortality [1,2]. Antiretroviral drugs (ARVs) can cause renal dysfunction in addition to HIV infection itself. Among various ARVs which affect renal function [3–5], tenofovir disoproxil fumarate (TDF) is the only ARV that WHO guidelines recommend as the first line nucleotide reverse transcriptase inhibitor (NRTI) in combination with lamivudine (3 TC) or emtricitabine (FTC) [6]. Thus, TDF is being commonly used as the first choice in many countries. Furthermore, in resource limited settings TDF is frequently co-administered with the protease inhibitor ritonavir-boosted lopinavir (LPV/r), which is also a known risk factor for

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renal dysfunction, as a salvage regimen recommended by WHO guidelines [4]. Although clinical trials and a meta-analysis reported that TDF-associated nephrotoxicity is only modest [7], several studies suggest that TDF causes renal proximal tubular dysfunction and renal dysfunction in a clinical setting, such as when TDF is co-administered with LPVr [8,9]. In many resource limited settings, the frequency of co-administration of TDF and LPV/r and the period of exposure has been increasing. The long term renal safety of TDF and LPV/r is of concern in this context.

The mechanism of TDF-induced renal dysfunction is not fully understood. One hypothesis is that accumulated TDF in renal proximal tubule cells causes mitochondrial toxicity, which is a well-known adverse effect of NRTIs, and leads to tubular dysfunction [10]. Subsequently, the renal tubular dysfunction could develop into renal dysfunction which presents as a decrease in estimated glomerular filtration rate or increase in urinary protein. Thus, to detect tubular dysfunction caused by TDF before renal dysfunction develops is clinically important. Several studies reported that urinary beta 2 microglobulin (β2MG) is a useful marker for TDF-associated tubulopathy in HIV-infected patients [11–15]. In contrast, regarding the mechanism of LPV/r-associated nephrotoxicity, although the influence of LPV/r on renal function remains controversial, it is thought to be due to increased TDF concentration in renal proximal tubular cells rather than a direct effect of LPV/r itself on renal function [16,17].

Furthermore, low body weight was reported to be a risk factor for tubular and renal dysfunction caused by TDF in Japanese studies with an average body weight of approximately 65 kg [18,19]. In Japan, tenofovir alafenamide (TAF), which possesses a safer renal function profile compared with TDF, is therefore being substituted for TDF. However, due to budgetary constraints, TDF is still the predominantly used ARV in the majority of the world, including Asian countries, where body weight is smaller still than that of the Japanese. We previously reported that low body weight and use of TDF are risk factors for renal dysfunction in Vietnamese HIV-infected patients, where the average body weight was approximately 55 kg [20,21]. In these populations with smaller body weight, evidence on tubular and renal dysfunction caused by TDF is limited.

Therefore, we conducted a cross-sectional study to evaluate the prevalence of tubular and renal dysfunction and their associated factors, and to estimate the association between tubular and renal dysfunction and exposure of TDF and LPV/r in Vietnamese HIV-infected patients.

2. Patients and methods

2.1. Study design

We conducted a cross-sectional study in an observational single-center cohort of Vietnamese HIV-infected patients. This study was performed at the National Hospital for Tropical Disease (NHTD), Hanoi, Vietnam, one of the largest out-patient clinics for HIV infected-patients in Vietnam. The study population included Vietnamese HIV-infected patients aged more than 17 years, who presented at NHTD from October 2014 to October 2015. The study was approved by the Human Research Ethics Committee of the National Hospital for Tropical Disease and Hanoi city, Hanoi. All patients recruited in the study provided written informed consent for their clinical and laboratory data to be used and published for study purposes. The study has been performed according to the principles expressed in the Declaration of Helsinki.

2.2. Measurements

Data collection was performed twice, in October 2014 and October 2015, for every patient registered in the cohort. Data included demographic variables (height, weight, sex and age); systolic and diastolic blood pressure (mmHg); a complete history of ART; use of drugs for prophylaxis against opportunistic infections; fasting blood sugar (mg/dL); CD4 cell counts (cells/mm^3, measured by flow cytometry); plasma HIV-RNA (copies/ml, measured by the Roche Cobas Taqman analyzer; Roche Molecular Diagnostics, Pleasanton, CA); Hepatitis B virus surface antigen and hepatitis C virus antibody were both measured by ECLIA method; serum creatinine (sCre) (mg/dl, measured by the Jaffe method); urinary beta 2 microglobulin (β2MG) (μg/L; DENKA SEIKEN Co. Ltd., Tokyo, Japan); urinary protein (g/L) and urinary creatinine (g/L). Hypertension was defined as systolic pressure greater than 140 mmHg or diastolic pressure greater than 90 at both timepoints. Diabetes mellitus was defined as fasting blood glucose concentration greater than 126 mg/dL at both timepoints. Tubular dysfunction was defined as β2MG levels greater than 1000 μg/L at both timepoints or an increase in β2MG of more than 2000 μg/L. CKD was defined as Ccr less than 60 ml/min at both timepoints or urinary protein/creatinine ratio (uP/C) more than 0.150 g/gCre at both timepoints. Ccr was assessed using the Cockcroft-Gault equation.

2.3. Statistical analysis

Statistical analysis included descriptive (mean and standard deviation), univariate and multivariate analyses. Absolute and relative frequencies were used for continuous and categorical variables, respectively. To evaluate the association between TD, CKD and categorical variables, Chi-square or Fisher's exact tests were applied as required. Independent t tests or one way ANOVA were used to compare means and, in case of asymmetry, Mann Whitney or Kruskal-Wallis tests were also used. Variables significantly associated with TD and CKD in univariate analysis were included in the multivariate analysis. Poisson Regression was used to determine the factors associated with TD and CKD in univariate analysis and multivariate analysis. Statistical significance was defined as a two-sided p value < 0.05. We used odds ratios (OR) and 95% confidence intervals (95% CIs) to estimate the association of each variable with TD and CKD. All statistical analyses were performed with SPSS ver. 22.0 (IBM SPSS, Chicago, IL).

3. Results

Table 1 shows the baseline characteristics of the study participants. 1382 Vietnamese HIV-infected patients fulfilled the study criteria. They were on average 38.4 years old and 41.5% of the patients were female. The average body weight and body mass index were 55.9 kg and 21.3 kg/m^2, respectively, which represents a population with considerably low body weight. The prevalence of hypertension and diabetes mellitus were 9.4% and 1.6%, respectively. Of the total patients, 1357 patients were on ART and 1036 patients (76.3%) were taking TDF, 17 patients (1.3%) had been taking TDF and then discontinued previously, and 304 patients (22.4%) had never been exposed to TDF. Apart from TDF, zidovudine (AZT) or stavudine (d4T) were mainly used in combination with 3 TC. The average duration of TDF administration was 35.4 months, which is relatively short compared with that of ARV administration, which was 63.3 months. 10% of the patients on ART were taking LPVr and the rest of the patients were taking NNRTIs, either efavirenz (EFV) or nevirapine (NVP). More than 95% of the patients on ART achieved viral suppression.

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