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ORIGINAL ARTICLE

Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients

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KEYWORDS
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Abstract *Background/Purpose:* Tenofovir disoproxil fumarate (TDF) is associated with kidney tubular dysfunction, for which the risk may vary among patients of different ethnicities. Data are limited, however, on the association between renal function changes and TDF exposure in human immunodeficiency virus (HIV)-infected Taiwanese patients.

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nucleotide reverse-transcriptase inhibitor;
proximal renal tubulopathy;
tenofovir

Methods: Medical records of HIV-infected Taiwanese patients seeking HIV care at a university hospital from 2011 to 2014 were reviewed. The change of estimated glomerular filtration rate (eGFR) was compared between patients not receiving combination antiretroviral therapy (cART) and those starting cART with or without TDF. The determinants of annual eGFR changes and factors associated with greater annual eGFR decline in TDF-exposed patients were explored.
Results: A total of 775 patients were included: 140 were cART-naïve, 393 received TDF-containing cART, and 242 received cART without TDF. Compared with cART-naïve patients, the annual eGFR decline was greater in TDF-exposed patients (0.57 ± 8.6 mL/min/1.73 m^2 and 2.7 ± 8.9 mL/min/1.73 m^2, $p = 0.012$). The annual eGFR decline between patients receiving cART with or without TDF was similar (2.7 ± 8.9 mL/min/1.73 m^2 and 1.8 ± 8.3 mL/min/1.73 m^2, $p = 0.567$). Diabetes was associated with worsening eGFR decline in all studied patients. TDF exposure correlated with an additional annual eGFR decline of 2.73 mL/min/1.73 m^2 (95% confidence interval 0.139—5.326, $p = 0.039$) in patients with CD4 count < 350 cells/μL. Among TDF-exposed patients, the factors associated with annual eGFR decline of > 3 mL/min/1.73 m^2 were higher baseline eGFR and lower CD4 counts.
Conclusion: Among HIV-infected Taiwanese patients, cART exposure correlated with the decline of renal function. However, TDF-exposed patients are more likely to have prominent eGFR decline, especially those with higher baseline eGFR, advanced HIV disease, and diabetes.

Introduction

Tenofovir disoproxil fumarate (TDF) is a widely used nucleotide reverse-transcriptase inhibitor, and is an important component of combination antiretroviral therapy (cART) for patients with human immunodeficiency virus (HIV) infection.[1,2] With the introduction of cART, survival of HIV-infected patients has significantly improved. However, aging, multiple comorbidities, complex medications, and prolonged cART may increase the risk of kidney injury. In recent years, kidney dysfunction has become a clinically relevant and important issue.[3—5]

Since its introduction for clinical use, TDF has been found to be associated with an increased risk of kidney tubular dysfunction including Fanconi syndrome, diabetes insipidus, or osteomalacia.[6,7] Decline in renal function was also reported in patients with exposure to TDF, experiencing either acute or chronic kidney injury, or merely a decrease of estimated glomerular filtration rate (eGFR) when compared with baseline values.[8]

The magnitude and clinical impact of TDF on renal function are still being debated. Variable degrees of eGFR loss have been reported, ranging from < 5 mL/min/1.73 m^2 to $>$ 10 mL/min/1.73 m^2 annually.[8—10] In a 10-year longitudinal prospective follow-up study, there was only a mild decline of eGFR that was attributable to TDF.[11] By contrast, a study on a cohort of Japanese patients showed that the loss of eGFR increased continuously for up to 5 years.[12] Moreover, increased frequency of proteinuria has been observed in patients receiving TDF-containing cART.[13,14] Because proteinuria may often precede GFR loss, measurements of biomarkers, such as urine β-2-microglobulin, have been proposed for early detection of renal tubular dysfunction.[15]

Previous studies have shown different incidences and profiles of adverse effects of cART in Asian populations compared with those reported in Western countries.[16,17] The predictive factors of TDF-related kidney injury have been recognized, which vary among patients of different ethnicities. For Asian people, a lower weight[18,19] and certain genetic variability[20] may contribute to the development of kidney injury. A few studies have reported on the change in renal function in TDF-exposed Asians,[19,21—24] however, most of the studies had short observation periods. This study aimed to assess the eGFR changes and to identify the risk factors for decline of renal function associated with TDF exposure in HIV-1-infected Taiwanese patients.

Methods

Patient population

This retrospective cohort study was conducted between January 2011 and December 2014 at a university hospital that is the largest designated hospital for HIV care in Taiwan. Because TDF was not introduced into clinical use in Taiwan until 2011, the study population included all HIV-infected patients who regularly sought HIV care at the hospital since 2011. Three groups of patients were defined according to their treatment status: those not receiving cART, those receiving TDF-containing cART, and those receiving cART not containing TDF.

Patients were included if they were aged ≥ 20 years with at least two serum creatinine measurements with an interval of 90 days or more. The exclusion criteria included receipt of ART < 90 days, intermittent or unknown duration of ART exposure, and end-stage renal disease on dialysis. ART was initiated and prescribed according to the national treatment guidelines for HIV infection proposed by the Taiwan Centers for Disease Control.[25] The decision to