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Urine alpha1-microglobulin is a better marker for early tubular dysfunction than beta2-microglobulin among tenofovir-exposed human immunodeficiency virus-infected men who have sex with men☆

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ABSTRACT

Objectives: Men who have sex with men are at risk of tenofovir nephrotoxicity due to its wide use in both treatment and prophylaxis for human immunodeficiency virus infection, but little is known about the urinary biomarkers of early renal dysfunction in this population. This study aims to identify useful biomarkers of early renal dysfunction among human immunodeficiency virus-infected men who have sex with men exposed to tenofovir.

Methods: In a cross-sectional study urinary alpha1-microglobulin, beta2-microglobulin, N-acetyl-β-D-glucosaminidase and albumin were measured and expressed as the ratio-to-creatinine in 239 human immunodeficiency virus-infected men who have sex with men who were treatment naïve or receiving antiretroviral therapy with tenofovir-containing or non-tenofovir-containing regimens. Additionally, 56 patients in the non-antiretroviral therapy group started a tenofovir-containing regimen and were assessed after 3 and 6 months on antiretroviral therapy.

Results: Both the frequency of alpha1-microglobulin proteinuria (alpha1-microglobulin-creatinine ratio >25.8 mg/g) and the median urinary alpha1-microglobulin-creatinine ratio were higher in the tenofovir disoproxil fumarate group than the other two groups

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(all $p < 0.05$). A higher frequency of beta2-microglobulin proteinuria (beta2-microglobulin-creatinine ratio >0.68 mg/g) was also observed in the tenofovir group (28.9%) compared to the non-tenofovir group (13.6%, $p = 0.024$). There were no significant differences between groups for N-acetyl-β-D-glucosaminidase and albumin. In the longitudinal study, the median urinary alpha1-microglobulin-creatinine ratio after 3 and 6 months on tenofovir-containing therapy (16.8 and 17.3 mg/g) was higher than baseline (12.3 mg/g, $p = 0.023$ and 0.011, respectively), while no statistically important changes were observed in urinary beta2-microglobulin-creatinine ratio or in the other biomarkers after 3 and 6 months on antiretroviral therapy (all $p > 0.05$).

Conclusion: Urinary alpha1-microglobulin seems to be a more sensitive and stable indicator of tubular dysfunction than urinary beta2-microglobulin for assessing tenofovir-related nephrotoxicity and can be significantly altered after tenofovir exposure.

Introduction

The prevalence of HIV-associated kidney disease has decreased in the era of antiretroviral therapy (ART), but drug-induced nephrotoxicity is emerging.[1] Long-term exposure to nephrotoxic antiretroviral drugs, such as tenofovir disoproxil fumarate (TDF), may lead to progression of renal dysfunction and incomplete reversibility of toxicity, even after drug withdrawal.[2,3] Moreover, some urinary biomarkers of early kidney injury were found to be associated with important clinical outcomes, such as mortality and severe heart disease.[4,5] Therefore, it is important to detect early renal dysfunction in HIV-infected individuals, particularly in those exposed to TDF.

TDF is widely used as a preferential drug for ART according to worldwide guidelines, and it is also part of the only approved regimen for pre-exposure prophylaxis to HIV infection.[6] The drug is excreted through glomerular filtration and proximal tubular secretion, and its use has been related to an increased risk of rapid decline in renal function and chronic kidney disease.[2] Clinically, renal insufficiency is usually assessed by an estimated glomerular filtration rate (eGFR),[7] but proximal tubular dysfunction is more common and specific for TDF-induced toxicity[8] and can occur with the absence of glomerular defects.[9]

The evaluation of urinary biomarkers, such as α1-microglobulin (α1M), β2-microglobulin (β2M) and N-acetyl-β-D-glucosaminidase (NAG), may improve the identification of those at risk of tubular toxicity and may detect early stages of renal dysfunction.[10,11] However, the evaluation criteria of these proteins in tubular dysfunction have not been established and little is known about the change of these new biomarkers during ART. The role of the aforementioned biomarkers in diagnosing and monitoring early tubular damage still needs to be explored.

HIV transmission is increasing markedly faster among MSM than other high-risk groups in China and some other countries.[12,13] MSM are at risk of TDF toxicity due to its comprehensive role in treatment and pre-exposure prophylaxis. However, most biomarkers of early renal dysfunction have not been validated in HIV-infected patients let alone in specific key-populations, such as MSM. Our study aims to investigate the presence of early renal dysfunction among HIV-infected MSM and to find the indicators of early renal injury in MSM with TDF exposure.

Materials and methods

Study population

We performed a cross-sectional study and a longitudinal study with a single-center cohort of HIV-infected MSM at the First Hospital of China Medical University in Shenyang, a major city in northern China that has a rapidly increasing incidence of HIV infection among MSM.[14] A total of 239 MSM receiving care at the AIDS clinic were enrolled in a cross-sectional study between August 2012 and June 2014. All participants in the study were adults (age ≥18 years) who were treatment-naïve or had received the current ART regimen for no less than six months. The patients who had used other non-ART nephrotoxic drugs in the previous two months before enrollment were excluded from the study.

The ART regimens were based on either Efavirenz (EFV) or Lopinavir/ritonavir (LPV/r). The other two ART drugs were lamivudine (3TC) plus TDF (TDF group) and 3TC plus zidovudine (AZT) (non-TDF group). Fifty-six patients in the non-ART group who started TDF/3TC/EFV were enrolled in a longitudinal study and were assessed after 3 and 6 months on ART. This study was approved by the Medical Research Ethics Committee of the First Hospital of China Medical University. Written informed consent for participation in this study was obtained from each participant.

Data collection

Demographic characteristics; medical history, such as diabetes, hypertension, and prior AIDS-defining illness; and other clinical and laboratory data of each subject were obtained from the clinical records and laboratory database. Body weight was also measured. Fasting blood and mid-stream urine specimens were collected at the routine morning consultation. Blood samples were assayed for full blood count, CD4T cell count, HIV RNA level, β2M, and routine biochemistry levels,