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Cumulative tenofovir disoproxil fumarate exposure is associated with biomarkers of tubular injury and fibrosis in HIV-infected men

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Abstract

Tenofovir disoproxil fumarate (TDF) can cause kidney damage, but current clinical tests are insensitive for detecting toxicity. Among 884 HIV-infected men enrolled in the Multicenter AIDS Cohort Study, we measured urine biomarkers specific for tubular damage (interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), pro-collagen type III N-terminal pro-peptide (PIIINP)) and albuminuria. In adjusted analyses, each year of TDF exposure was independently associated with 3.3% higher IL-18 (95%CI: 0.8%,5.8%), 3.4% higher KIM-1 (1.1%,5.7%), and 3.1% higher

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PIIINP (0.8,5.5), but not with albuminuria (2.8%; −0.6%,6.2%). Biomarkers of tubular damage may be more sensitive than albuminuria for detecting toxicity from TDF and other medications.

Introduction

Tenofovir disoproxil fumarate (TDF) is widely prescribed for the treatment and prophylaxis of HIV infection.[1,2] Although early clinical trials suggested a favorable safety profile,[3] TDF is now a well-recognized contributor to acute and chronic kidney damage.[4-8] The primary site of TDF-associated nephrotoxicity appears to be the proximal tubular epithelium.[9-11] Elevations in serum creatinine, a marker of glomerular filtration, may be insensitive for the detection of TDF-associated proximal tubular damage.[12] In support of this hypothesis are recent studies demonstrating subclinical evidence of proximal tubular dysfunction among HIV-infected individuals receiving TDF.[13-17] However, the sample sizes of these studies were small, and proximal tubular dysfunction was variably defined.

Urine biomarkers specific for renal tubular injury and fibrosis may enable earlier detection of nephrotoxicity in HIV-infected individuals. In contrast to albuminuria, which is a marker of glomerular damage, interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1) are released by proximal tubular epithelial cells in response to injury, with urine levels rising by 10-20 fold in the setting of ischemic acute tubular necrosis.[18-20] We previously demonstrated that urine IL-18 and KIM-1 were each independently associated with longitudinal kidney function decline among HIV-infected women, in an era prior to the widespread use of TDF.[21] Pro-collagen type III N-terminal pro-peptide (PIIINP), a marker of tubulointerstitial fibrosis, is cleaved and released into urine during deposition of type III collagen in the kidney extracellular matrix.[22-24] Whether or not TDF exposure is associated with higher levels of these specific biomarkers of tubular injury and fibrosis is unknown.

In this cross-sectional study of HIV-infected men enrolled in the Multicenter AIDS Cohort Study, we evaluated associations of TDF exposure with four urine biomarkers: IL-18 and KIM-1, markers of kidney proximal tubular injury; PIIINP, a marker of tubulointerstitial fibrosis; and albumin-creatinine ratio (ACR), a clinical marker of glomerular injury. Our second objective was to evaluate antiretroviral medications (ARVs) other than TDF, to determine whether the nephrotoxicity was unique to TDF.

Methods

Study Population and Design

The Multicenter AIDS Cohort Study (MACS) is an ongoing, prospective cohort study designed to describe the natural history of HIV infection among men who have sex with men. Participants were enrolled between 1984 and 2003 from four sites in the United States: Baltimore, Chicago, Los Angeles and Pittsburgh.[25] This cross-sectional study included all 884 HIV-infected men with urine samples collected between October 1, 2009 and September 30, 2011. The institutional review boards of participating institutions approved the study protocol, and informed consent was obtained from all study participants.

Exposure Variables

Antiretroviral (ARV) medication exposure was ascertained for each participant using MACS visit questionnaires. Cumulative exposure included both current and historical exposure durations for each participant.

Outcome Variables

Urine biomarker levels were measured at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory. Commercially available ELISA kits were used to measure urine IL-18 (Medical & Biological Laboratories Co., Nagoya, Japan), KIM-1 (R & D Systems, Inc., Minneapolis, MN),[26] and PIIINP (USCN Life Sciences, Wuhan, Hubei, China). Urine albumin and creatinine were measured by immunoturbidimetry and colorimetric enzyme assay, respectively, using a Siemens Dimension Xpand plus HM clinical analyzer (Siemens, Munich, Germany).

Covariates

The following characteristics were tested as candidate covariates in multivariable models: age, race/ethnicity, diabetes mellitus, systolic and diastolic blood pressure, hypertension, cigarette smoking status, LDL and HDL cholesterol, triglycerides, body mass index, waist circumference, and hepatitis C virus (HCV) infection. Candidate HIV-related characteristics included: current CD4 lymphocyte count, nadir CD4 lymphocyte count, history of clinical AIDS diagnosis,[27] current and peak plasma HIV RNA level , and time-averaged historical HIV RNA level. Glomerular filtration rate was estimated using the CKD-EPI equation for creatinine (eGFR).[28] The presence of CKD was defined by eGFR<60ml/min/1.73m^2. Multiple imputation with the Markov chain Monte Carlo method was used to impute missing covariates, with 5 imputations to yield ~95% relative efficiency.[29]

Statistical Analysis

We stratified men into three categories based on TDF use (current, past, and never) and used multivariable robust regression models with M-estimation and Huber weighting[30] to examine associations of TDF and other ARV medications with each biomarker outcome. ARV exposure was analyzed continuously (per year of cumulative and current duration) and categorically (current, past, or never exposure). Models were built separately for IL-18, KIM-1, PIIINP and ACR and adjusted sequentially for demographic characteristics, traditional kidney disease risk factors, and HIV-related factors, using stepwise backward selection (α=0.05) to remove candidate variables that were not associated with the outcome. Because urine creatinine is susceptible to bias by muscle mass and health status,[31,32] we did not normalize biomarker concentrations to urine creatinine. In sensitivity analyses, we adjusted for urine creatinine as a covariate, to account for urine tonicity. Biomarker outcomes were log-transformed to normalize their distributions; results were back-transformed to produce estimated percentage differences. Finally, we used the least absolute shrinkage and selection operator (LASSO) method to determine which of multiple ARVs were associated with each biomarker.[33]

Results

At the time of urine collection, the median age was 52 years among the 884 study participants, and one-third of participants were African-American. Hypertension was present in 42% (n=375) of the cohort. Diabetes and HCV infection were prevalent in 12% (n=110) and 10% (n=89), respectively. The median eGFR was 91 ml/min/1.73m^2 (interquartile range, IQR: 75, 103) and 9% (n=76) of participants had an eGFR<60ml/min/1.73m^2. Current TDF users comprised 65% (n=573) of participants, and 13% (n=112) were former TDF users. Median TDF exposure duration was 4.4 years among current users (IQR: 2.8, 6.4) and 2.4 years among former users (IQR: 1.0, 4.6).

After adjustment for demographics, traditional kidney risk factors, and HIV-related factors, cumulative TDF exposure was associated with incrementally higher levels of urine IL-18, KIM-1, PIIINP, and ACR (**Table**). Each year of cumulative TDF exposure was associated with 3.9% higher urine IL-18, 3.0% higher KIM-1, 2.9% higher PIIINP, and 3.8% higher ACR. TDF exposure remained associated with higher biomarker levels after additional adjustment for urine creatinine (urine IL-18: 2.7% per year; KIM-1: 2.5%; PIIINP: 2.0%, and albumin: 3.7%; all p≤0.025). Compared with never users, current and past TDF users had higher adjusted levels of IL-18, KIM-1, and PIIINP but these associations did not reach statistical significance. Associations of TDF with biomarker levels were similar after adjustment for eGFR and when analyses were restricted to individuals with eGFR≥60ml/min/1.73m^2.

In robust linear regression models that adjusted simultaneously for the LASSO-selected ARVs (**Figure**), cumulative TDF exposure remained independently associated with higher IL-18 (3.3% per year; 95%CI: 0.8%, 5.8%, p=0.011), KIM-1 (3.4% per year; 1.1%, 5.7%, p=0.004), and PIIINP (3.1% per year; 0.8, 5.5, p=0.008), but its association with ACR was attenuated (2.8% per year; −0.6%, 6.2%, p=0.10). Efavirenz exposure was associated with lower urine IL-18 (−3.0% per year; −4.8%, −1.3%, p<0.001) and KIM-1 (−3.9% per year; −5.7%, −2.2%, p<0.001), while lopinavir/ritonavir exposure was associated with higher urine IL-18 (3.7% per year; 0.8%, 6.7%, p=0.013) and ACR (6.8% per year; 2.6%, 11.1%, p=0.001). There were no statistically significant interactions for the associations of TDF exposure with the biomarker outcomes when TDF users were stratified by concurrent receipt of efavirenz (n=281) vs ritonavir (n=247).

Discussion

With widespread use of TDF for HIV treatment and prophylaxis, TDF-associated nephrotoxicity has become an increasingly important safety concern. We hypothesized that TDF exposure would be associated with more extensive kidney proximal tubular injury and fibrosis, measured by urine IL-18, KIM-1, and PIIINP, as compared with glomerular injury, measured by albuminuria. In this large contemporary cohort of HIV-infected men, we found that cumulative TDF exposure was incrementally associated with higher urine levels of IL-18, KIM-1, and PIIINP, independent of traditional kidney risk factors, HIV-related factors, and exposure to other ARV medications. Although cumulative TDF exposure was

also associated with higher ACR, the associations were not statistically significant after simultaneous adjustment for exposure to other ARVs.

In healthy patients, IL-18 and KIM-1 are present in urine at very low concentrations, with levels rising several-fold in the setting of acute kidney injury due to release from injured proximal tubular cells.[19,20] IL-18 is hypothesized to be a causal intermediate in the ischemia-reperfusion pathway, based on the observation that mice deficient in caspase-1, an activator of IL-18, are protected from acute kidney injury.[34,35] KIM-1 is also released into urine in response to ischemic injury, and administration of cisplatin to rats induces upregulation of KIM-1 in proximal tubular epithelial cells.[36,37] Finally, PIIINP is cleaved during synthesis and deposition of type III collagen in the kidney extra-cellular matrix, and urine PIIINP levels correlate with renal tubulointerstitial fibrosis.[22-24] To our knowledge, this is the first large study to utilize these specific markers of renal tubular damage in the quantification of TDF-associated nephrotoxicity. If our findings are validated in subsequent studies, urine IL-18, KIM-1, and PIIINP may yield a novel and more sensitive method for detecting TDF-associated tubular injury and fibrosis.

Among the other ARVs evaluated in this study, we observed an association of lopinavir/ritonavir exposure with kidney injury as manifested by higher IL-18 and ACR. This finding is supported by prior literature demonstrating higher rates of nephrotoxicity when lopinavir/ritonavir is co-administered with TDF.[38-40] Notably, pharmacokinetic studies have demonstrated higher plasma tenofovir concentrations among TDF users receiving lopinavir or ritonavir.[41-43] This drug interaction may occur through direct inhibition of tenofovir efflux into urine by protease inhibitors, or via enhanced intestinal absorption of tenofovir.[42,44,45] Our observed associations between efavirenz and lower urine IL-18 and KIM-1 levels were unexpected. Prior longitudinal studies have reported smaller reductions in eGFR when tenofovir is co-administered with efavirenz, as compared with ritonavir-boosted protease inhibitors.[46,47] Whether these differences are due to enhanced nephrotoxicity of tenofovir when combined with protease inhibitors or due to a renoprotective effect of efavirenz is unknown. Further studies are needed to verify our findings and identify potential underlying mechanisms.

The findings of this study highlight the need for a modernized approach for the detection and monitoring of drug-induced nephrotoxicity in HIV-infected and uninfected individuals. In contrast to prior studies,[48-50] which examined associations of TDF with clinical manifestations of tubular dysfunction or low molecular weight proteinuria, elevations in urine IL-18, KIM-1 and PIIINP indicate direct tubular injury and fibrosis, and likely represent more extensive kidney damage. Future longitudinal studies should examine whether combinations of biomarkers specific for tubular dysfunction, injury, and fibrosis can improve the safety of patients receiving nephrotoxic medications. Recognition of nephrotoxicity at its earliest stages is particularly important for the growing population of HIV-uninfected individuals receiving TDF as pre-exposure prophylaxis. Finally, recent phase II/III clinical trials suggest that a newer preparation of tenofovir, tenofovir alafenamide fumarate (TAF), may be less nephrotoxic than TDF.[51,52] However, the long-term kidney safety of TAF has not been established. Rigorous studies utilizing urine

biomarkers are needed to determine whether switching from TDF to TAF leads to improved kidney tubular health in the real-world setting.

There are several limitations to this study. First, although the clinical reasons for TDF discontinuation were unavailable, the presence of lower eGFR and higher prevalence of CKD in former TDF users, as compared with current or never TDF users, suggests that nephrotoxicity may have led to the discontinuation of TDF. Future longitudinal studies are required to specifically investigate the relationships between HIV duration, overall health status, and susceptibility to nephrotoxicity from antiretroviral medications. Second, we did not have access to serum levels of IL-18, KIM-1 and PIIINP. Although urine IL-18, KIM-1 and PIIINP are not known to be filtered or secreted by the kidney, we cannot exclude the possibility that higher serum levels contributed to our observations. Finally, because this was a study of men, the results may not be directly generalizable to women. However, there is no known pathophysiologic basis for a gender-based interaction between TDF exposure and kidney injury.

In conclusion, among HIV-infected men, cumulative TDF exposure was associated incrementally with higher urine levels of IL-18, KIM-1, and PIIINP. Future longitudinal studies should evaluate the potential roles of these tubular damage markers in the earlier detection of TDF-associated nephrotoxicity and quantification of longitudinal kidney risk among HIV-infected and uninfected individuals.

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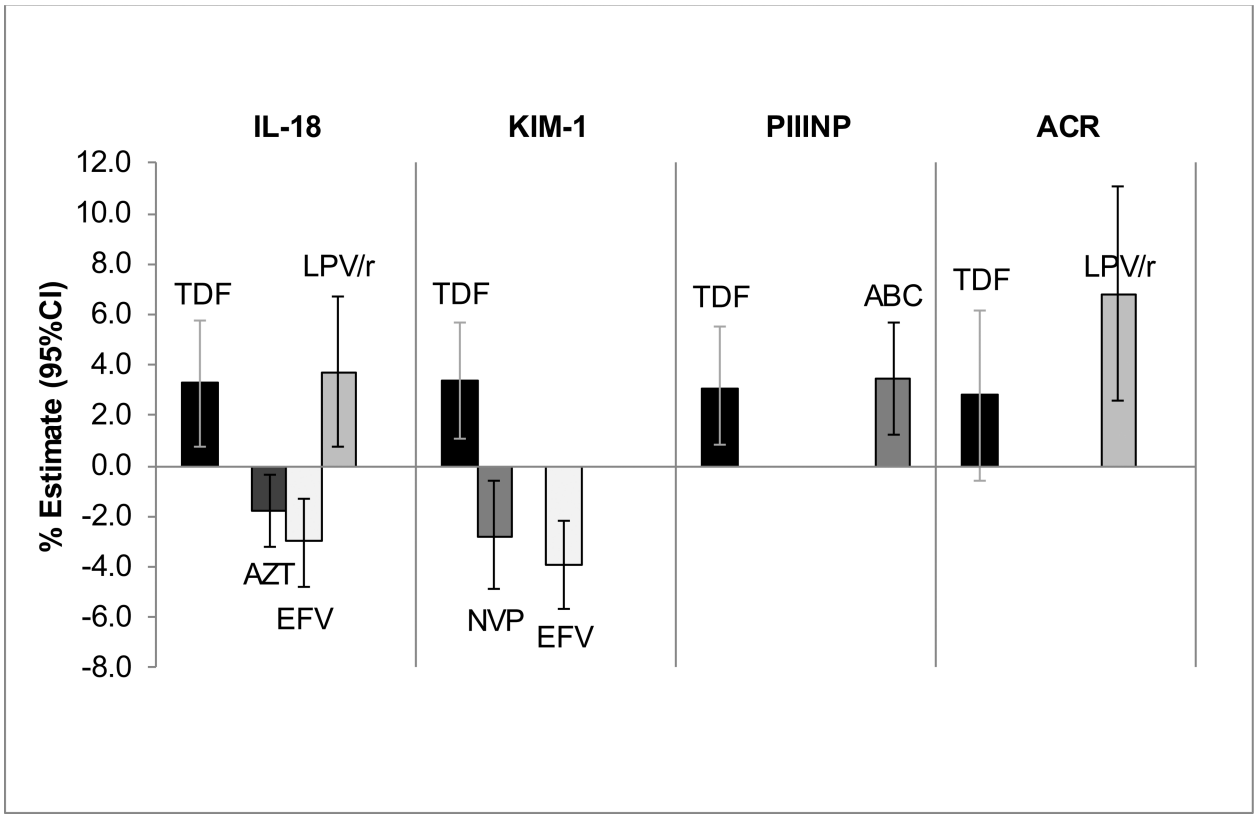

Figure. Associations of cumulative ARV exposure with urine biomarker levels

Bars represent percentage change in biomarker level per year of ARV exposure, with 95% confidence intervals displayed. Estimates are derived from multivariable linear regression models, adjusting for demographics, traditional kidney risk factors, HIV-related factors, and LASSO-selected ARVs. Abbreviations: ABC, abacavir; ACR, albumin-creatinine ratio; ARV, antiretroviral medication; AZT, zidovudine; IL-18, interleukin-18; EFV, efavirenz; LASSO, least absolute shrinkage and selection operator; LPV/r, lopinavir/ritonavir; KIM-1, kidney injury molecule-1; NVP, nevirapine; PIIINP, procollagen type III amino-terminal pro-peptide; TDF, tenofovir disoproxil fumarate.

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Table

Associations of TDF use with biomarker levels among HIV-infected MACS participants (n=884), without adjustment for exposure to other ARVs

	IL-18[1]		KIM-1[2]		PIIINP[3]		ACR[4]	
TDF Exposure[5]	**% Estimate[6] (95% CI)**	**P Value**	**% Estimate (95% CI)**	**P Value**	**% Estimate (95% CI)**	**P Value**	**% Estimate (95% CI)**	**P Value**
Cumulative TDF exposure (y)	3.9 (1.4, 6.4)	0.002	3.0 (0.7, 5.4)	0.012	2.9 (0.6, 5.3)	0.015	3.8 (0.6, 7.2)	0.021
Current TDF duration (y)	2.7 (0.3, 5.1)	0.029	2.1 (−0.1, 4.4)	0.063	1.5 (−0.8, 3.8)	0.20	2.1 (−1.1, 5.3)	0.20
Current vs never TDF use	13.9 (−3.6, 34.6)	0.13	2.9 (−11.9, 20.1)	0.72	7.3 (−8.1, 25.4)	0.37	18.2 (−5.0, 47.0)	0.13
Past vs never TDF use	18.4 (−5.5, 48.5)	0.14	7.6 (−13.5, 33.9)	0.51	21.4 (−2.7, 51.5)	0.085	36.2 (0.1, 85.4)	0.049

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; PIIINP, procollagen type III amino-terminal pro-peptide; TDF, tenofovir disoproxil fumarate; y, years.

[1] Models for IL-18 included age, race, HDL, HIV viral load, CD4 lymphocyte count, hepatitis C infection, and TDF

[2] Models for KIM-1 included age, race, waist circumference, CD4 lymphocyte count, hepatitis C infection, and TDF

[3] Models for PIIINP included age, race, CD4 lymphocyte count, hepatitis C infection, and TDF

[4] Models for ACR included age, race, current smoking, SBP, anti-hypertensive medication use, triglycerides, CD4 lymphocyte count, hepatitis C infection, and TDF

[5] TDF exposure variables enter the model individually, not simultaneously

[6] Estimated percentage difference in biomarker attributable to TDF exposure