

Correlation Between Tenofovir Drug Levels and the Renal Biomarkers RBP-4 and β 2M in the ION-4 Study Cohort

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Background. Concomitant dosing of ledipasvir (LDV) and tenofovir disoproxil fumarate (TDF) results in an increased tenofovir (TFV) area under the curve (AUC). The aim of this study was to examine whether there was a correlation between the renal biomarkers retinol binding protein-4 (RBP-4) and β 2 microglobulin (β 2M) and tenofovir AUC.

Methods. The ION-4 trial enrolled HIV/hepatitis C virus–coinfected patients on nonpharmacologically boosted antiretroviral regimens with TDF-containing backbones. We assessed for a correlation between tenofovir AUC and urinary biomarkers and also for changes in serologic biomarkers with respect to clinically relevant changes in renal function (creatinine clearance decrease >25%, change in creatinine >0.2 mg/dL, change in proteinuria from negative/trace to \geq 1+).

Results. Three hundred thirty-five patients were enrolled in the ION-4 study; their demographic characteristics have been previously described. Both RBP-4 and β 2M exhibited positive correlations with tenofovir AUC. Baseline and study levels of RBP-4 and β 2M were higher for patients with increases in urine proteinuria and an absolute creatinine increase.

Conclusions. TFV exposure is associated with increased proximal tubule urine biomarkers in participants on ledipasvir/sofosbuvir and nonpharmacologically boosted TDF-based antiretroviral regimens. Baseline proximal tubule biomarkers may predict nephrotoxicity risk if events are prevalent. Further studies assessing the predictive role of these urine biomarkers may help guide medical decision-making and risk/benefit assessments in patients with risk factors for renal dysfunction.

Keywords. hepatitis C; HIV; ledipasvir; tenofovir; urinary biomarkers.

The primary challenge facing providers who treat patients with HIV and hepatitis C virus (HCV) coinfection is drug–drug interactions [1]. The combination drug ledipasvir/sofosbuvir (LDV/SOF) is 1 of many direct-acting antiviral (DAA) regimens that have revolutionized the treatment of HCV [2–5]. Overall, LDV/SOF has few clinically relevant drug–drug interactions with antiretrovirals (ARVs), with the exception of tenofovir disoproxil fumarate (TDF) [2, 5]. In healthy volunteer drug interaction studies and in the phase III ION-4 study in HIV/HCV-coinfected participants, LDV/SOF dosing was associated with increased exposure to tenofovir (TFV) for multiple ARV regimens containing TDF [6, 7]. The effect of increased tenofovir exposure on proximal tubule function in the setting of HCV treatment is unknown.

TDF is a widely prescribed antiretroviral medication and is a component of many different firstline regimens [8].

Tenofovir-related proximal tubule toxicity is a well-described phenomenon [9], and in severe cases, it can result in Fanconi's syndrome or acute kidney injury [10]. Renal tubular impairment has been previously associated with higher tenofovir plasma concentrations [11]. Retinol binding protein-4 (RBP-4) and β 2 microglobulin (β 2M) are reliable urinary biomarkers for detecting proximal tubule dysfunction [12–14]. Previous studies demonstrate that exposure to tenofovir is related to increased levels of these biomarkers [15, 16]. Retinol binding protein-4 is a carrier protein synthesized in the liver associated with vitamin A transport [17, 18], and β 2M is the light chain portion of the MHC I complex. Both are freely filtered by the glomerulus and are exclusively reabsorbed by transporters in the proximal tubule, making them excellent biomarkers for detecting tenofovir-mediated proximal tubule dysfunction [12, 19].

The objective of this study was to assess for a correlation between tenofovir area under the curve (AUC) and urinary biomarker level in the ION-4 study cohort.

METHODS

The ION-4 trial was a phase III, multicenter, prospective, single-arm, open-label study with centers in the United States, Canada, and New Zealand that assessed the safety and efficacy of LDV/SOF for 12 weeks in HIV/HCV-coinfected patients [6].

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All patients enrolled in this study had a baseline creatinine clearance (CrCl) >60 mL/min and were on a TDF-based regimen. Further baseline demographic descriptions were published previously [6]. Patients receiving an HIV-1 protease inhibitor with or without a pharmacologic boosting agent (ritonavir or cobicistat) were excluded from the study, as were those receiving elvitegravir/cobicistat. As a part of the ION-4 study protocol, plasma TFV concentrations were collected at on-treatment 12 and 24 hours and 4, 6, 8, 10, and 12 weeks. Urine RBP-4 and β 2M were collected at baseline, on-treatment weeks 2, 4, and 12, and post-treatment weeks 4, 8, and 12. Urine protein and serum creatinine were collected at baseline, entry, on-treatment weeks 1, 2, 4, 6, 8, 10, and 12, and post-treatment weeks 4, 8, and 12. All patients with available TFV levels and urine biomarkers were included in this study. For the purposes of this study, samples at baseline, all on-treatment samples, and post-treatment week 4 samples were included in the analysis. Tenofovir drug levels and urinary biomarker levels were performed as part of the parent ION-4 trial by the central Covance Laboratories.

The primary end points of the study were tenofovir AUC and absolute levels of urinary biomarkers. Tenofovir AUC was calculated as part of the pharmacokinetic analysis for the ION-4 study, and we used existing pharmacokinetic data for our analysis. Mean absolute biomarker levels were also calculated.

Study Objectives

The primary objective of this study was to assess for a correlation between TFV AUC and urinary biomarkers in the ION-4 study cohort. There were also multiple secondary objectives in the study, including (1) assessments of differences in urinary biomarkers over time and with respect to demographic factors defined a priori and (2) renal safety assessments for change in creatinine clearance, absolute creatinine, and proteinuria. For demographic categories, we compared the mean level of biomarkers with respect to race, gender, and ARV regimen from time point 0 to study week 16, 4 weeks after the end of LDV/SOF therapy. The ION-4 study protocol included 3 nephrotoxicity thresholds: decrease in CrCl to <50 mL/min, absolute creatinine increase from baseline of >0.4 mg/dL, and development of grade 2+ proteinuria or greater on urinalysis. For this study, more lenient but clinically relevant a priori renal safety end points were also evaluated. These end points were CrCl decrease of >25% from baseline, absolute creatinine increase of >0.2 mg/dL from baseline, and development of grade 1+ proteinuria or greater on urinalysis.

Statistical Analysis

Spearman correlation coefficients were calculated to assess the relationship between mean levels of absolute urinary biomarkers and tenofovir drug levels for all available time points from time point 0 to week 16. Plots were overlaid with a locally weighted smoother (Loess). Tenofovir drug levels were also stratified by quartiles. For the secondary objectives, the mean

biomarker levels for each subgroup, as defined by changes in creatinine clearance, creatinine level, and proteinuria, were compared using a Wilcoxon rank-sum test. Findings were considered significant if the *P* value was $\leq .05$. All analyses were conducted with SAS 9.4 (Cary, NC, USA) and R 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 335 patients enrolled in the ION-4 trial, and all had available TFV pharmacokinetic and urinary biomarkers available for analysis. As previously reported, the cohort was 82% male, 34% of participants were black, and the mean baseline CrCl was 101 mL/min (Table 1) [6]. The mean baseline RBP-4 was 147×10^3 μ g, and the mean baseline β 2M was 0.24×10^3 μ g. For the ION-4 protocol-defined renal safety end points, 10 patients met criteria for CrCl decrease (CrCl below 50 mL/min), 4 patients met the criteria for absolute creatinine increase (increase of ≥ 0.4 mg/dL), and 14 patients met the criteria for proteinuria (2+ or greater). Of the 4 patients with an absolute creatinine clearance increase of 0.4 or greater, 1 was switched off of tenofovir. Using the more lenient clinically relevant biomarker study end points as defined here, 19 patients met criteria for CrCl decrease (drop of 25% from baseline), 42 patients met criteria for absolute creatinine increase (increase of >0.2 mg/dL), and 114 patients met criteria for proteinuria (1+ or greater).

The scatter plot and line of best fit for mean RBP-4 for all study time points (week 0 to week 16) per patient vs tenofovir AUC and mean β 2M vs tenofovir AUC are shown in Figure 1. Mean absolute values of RBP-4 per patient through week 16 were found to have a positive correlation with tenofovir AUC, with a Spearman correlation coefficient of .34 (*P* < .001). Mean absolute values of β 2M through week 16 were also found to have

Table 1. Baseline Characteristics and Demographics

Characteristics	ION 4 Study Cohort (n = 335)
Median age (IQR), y	52 (48–58)
Male, No. (%)	276 (82)
Black, No. (%)	115 (34)
Mean BMI (IQR), kg/m ²	27 (24–30)
Mean baseline RBP-4, mcg	147
Mean baseline β 2M, mcg	0.24
Mean creatinine clearance (SD)	101.6 (30.79)
HIV ARV regimen, No. (%)	
Efavirenz + FTC + TDF	160 (48)
Raltegravir + FTC + TDF	146 (44)
Rilpivirine + FTC + TDF	29 (9)
Comorbidities	
Hypertension, No. (%)	130 (39)
Diabetes mellitus, No. (%)	31 (9)

Abbreviations: ARV, antiretroviral; β 2M, β 2 microglobulin; BMI, body mass index; FTC, emtricitabine; IQR, interquartile range; RBP-4, retinol binding protein-4; TDF, tenofovir disoproxil fumarate.

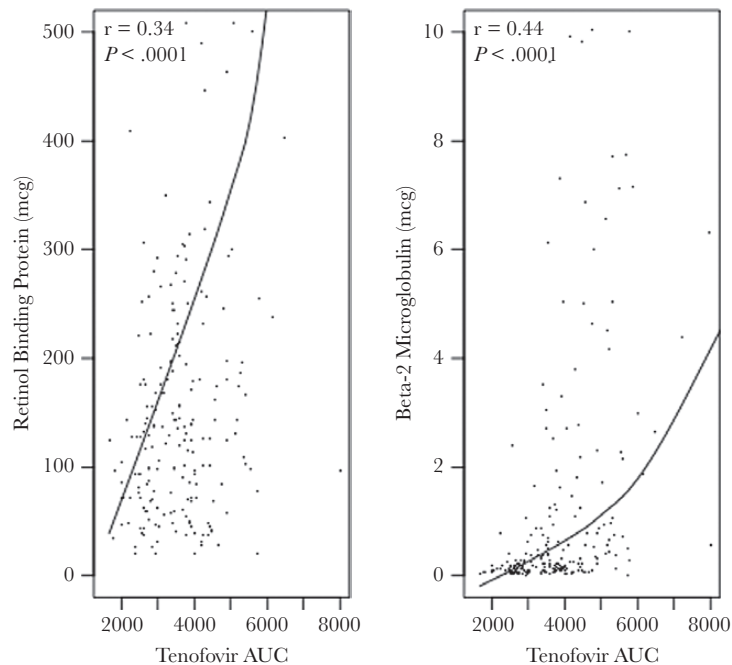


Figure 1. Scatter plot and line of best fit for mean RBP-4 (left) and β 2M (right) through study week 16 vs tenofovir AUC. Abbreviations: AUC, area under the curve; β 2M, β 2 microglobulin; r , Spearman correlation coefficient; RBP-4, retinol binding protein-4.

a positive correlation with tenofovir AUC, with a Spearman correlation coefficient of .44 ($P < .001$). Tenofovir AUC quartile vs RBP-4 level and β 2M are shown in [Figures 2](#) and [3](#), respectively. For the lower 75% of values of both biomarkers, there was no significant correlation between tenofovir AUC and urinary biomarker level ([Figures 2](#) and [3](#)). In the highest quartile of tenofovir AUC, there was a positive correlation for RBP-4 and β 2M, with a Spearman correlation coefficient of .40 for both biomarkers ($P = .0007$ and $.0007$, respectively).

The mean levels of both biomarkers through post-treatment week 4 (study week 16) are shown in [Figure 4A](#). Patients who had a CrCl decrease of >25% had higher levels of RBP-4 ($P = .048$) but not β 2M ($P = .12$) at baseline and throughout the study ([Figure 5](#)). Patients who had an absolute increase in creatinine of 0.2 mg/dL or greater had higher levels of both RBP-4 ($P = .017$) and β 2M ($P = .004$) at baseline and throughout the study ([Figure 5](#)). Both urinary biomarkers in patients with a creatinine increase of >0.2 mg/dL exhibited a steep decline at week 2 before increasing again. Patients who developed grade 1+ proteinuria or greater had a higher level of both RBP-4 and β 2M at baseline and through study week 16 ([Figure 4B](#)). All clinical subgroups exhibited a sharp drop in RBP-4 at post-treatment week 4; a pattern not replicated with β 2M. There were no differences in mean biomarker level based on age, race, or ARV regimen.

DISCUSSION

This study is one of the most comprehensive samplings of tenofovir drug levels and urinary biomarker levels to date. There was

a positive correlation between tenofovir AUC and levels of both RBP-4 and β 2M that appears to be driven primarily by the highest quartile of tenofovir AUC. These findings suggest that above a certain threshold of drug level, biomarker levels increase in a dose-dependent manner. These findings would suggest that tenofovir-mediated proximal tubule toxicity may be dose-dependent and potentially exacerbated by higher concentrations, consistent with existing data [20]. For the ION-4 study cohort, there were few clinically significant nephrotoxic events despite the increased exposure to tenofovir. These findings may have implications for LDV/SOF co-administration with pharmacologically boosted ARV regimens, in which tenofovir levels were noted to be higher than when co-administered with LDV/SOF alone, or in patients with CrCl <60 mL/min and/or other risk factors for renal dysfunction [7].

The mean biomarker levels for the entire study cohort appear to have dropped sharply at week 2. Levels of β 2M also appear to have trended downward throughout the study, whereas RBP-4 levels returned to baseline at post-treatment week 4. Though the exact etiology of the week 2 drop is unclear, it is possible that this is in part reflective of HCV clearance. HCV-associated renal disease such as membranoproliferative glomerulonephritis and membranous nephropathy is well described [21, 22] and may be exerting a subclinical effect on the kidney in the absence of an overt disease process. The normalization of RBP-4 in those patients who have elevated RBP-4 at baseline and worsening renal function during study dosing also supports this hypothesis. Of note, serum RBP-4 is elevated in certain types of liver

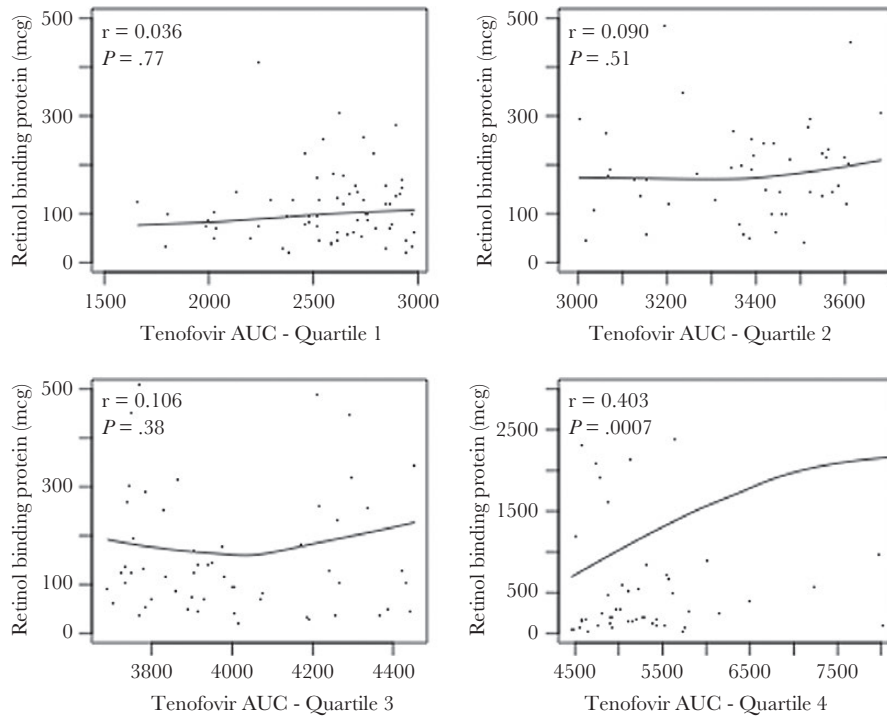


Figure 2. Scatter plots with lines of best fit for RBP-4 vs tenofovir AUC divided into quartiles by increasing tenofovir AUC through week 16. Quartile 1 corresponds to the lowest levels of tenofovir AUC, whereas quartile 4 corresponds to the highest. Abbreviations: AUC, area under the curve; β 2M, β 2 microglobulin; r , Spearman correlation coefficient; RBP-4, retinol binding protein-4.

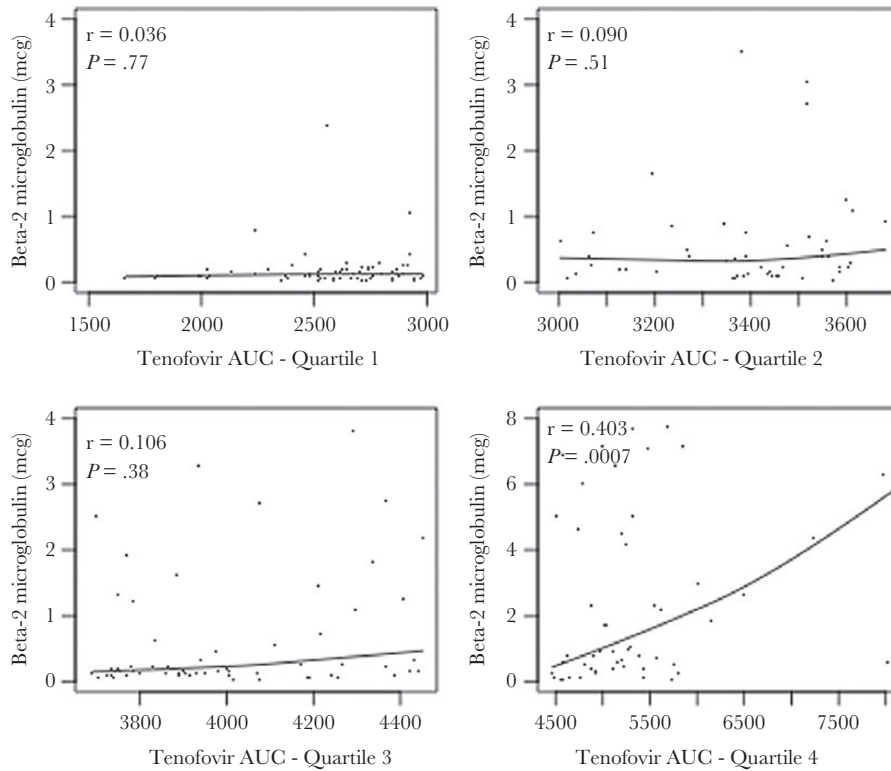


Figure 3. Scatter plots with lines of best fit for β 2M vs tenofovir AUC divided into quartiles by increasing tenofovir AUC through study week 16. Quartile 1 corresponds to the lowest levels of tenofovir AUC, whereas quartile 4 corresponds to the highest. Abbreviations: AUC, area under the curve; β 2M, β 2 microglobulin; r , Spearman correlation coefficient; RBP-4, retinol binding protein-4.

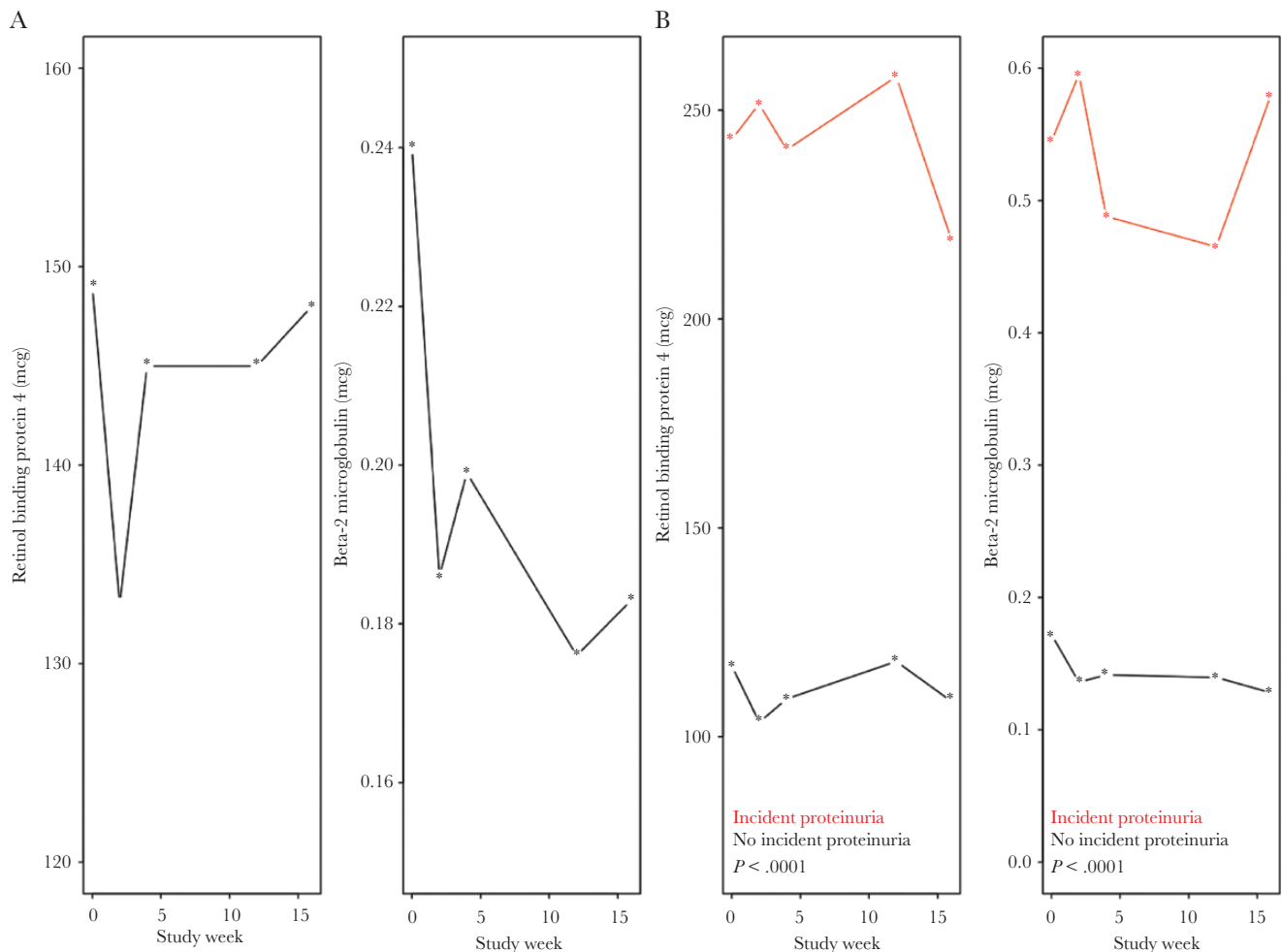


Figure 4. A, Pooled mean biomarker level for the study cohort through study week 16. Each point represents a pooled mean value for that study time point. B, Pooled mean biomarker level for study outcome of incident proteinuria over the study time period. The red line represents the subgroup that developed incident proteinuria based on study criteria. Abbreviations: AUC, area under the curve; β 2M, β 2 microglobulin; r , Spearman correlation coefficient; RBP-4, retinol binding protein-4.

disease such as nonalcoholic fatty liver disease; however, the data are limited with respect to RBP-4 and HIV, and RBP-4 and cirrhosis. Further study is needed to determine the etiology of this improvement.

Additionally, baseline urinary biomarker levels may play a role in the prediction of nephrotoxic events. With the exception of β 2M in the CrCl outcome group, there were higher levels of RBP-4 and β 2M at baseline and throughout the study for all other renal safety subgroups. These biomarkers were originally developed as both diagnostic and predictive tools in the setting of acute kidney injury (AKI) [19, 23]. Checking biomarker levels at baseline in certain high-risk patient populations may help stratify the risk of developing nephrotoxic events from co-administration of TDF and LDV/SOF and could help identify patients who may need more frequent renal monitoring. For the recently approved formulation of tenofovir, TAF, the approved dose is dependent on whether it is part of a fixed-dose combination with a pharmacologic booster. The approved dose when part of a pharmacologically

boosted regimen is 10 mg, whereas 25 mg is approved in the absence of a pharmacologically boosted regimen. There are no data to support this approach with TDF-based regimens at this time.

Due to significantly lower TFV systemic exposures, tenofovir alafenamide is unlikely to have the same challenge of increased TFV exposure when dosed with LDV. Pharmacokinetic data suggest that tenofovir serum levels with TAF are much lower than for TDF, and healthy volunteer data of concomitant dosing of TAF and LDV confirm this finding [24]. For patients receiving TAF as a treatment for hepatitis B viral infection, there is a smaller increase in urinary biomarkers over time as compared with TDF [25]. Although a switch to a TAF-containing regimen before HCV therapy with LDV/SOF can address any potential risk, the findings from this study remain relevant for several reasons. TDF is no longer under patent, resulting in a major cost differential between these 2 tenofovir prodrugs [25, 27]. In addition, in some countries, access to TAF may still be limited, whereas access to LDV/SOF has increased.

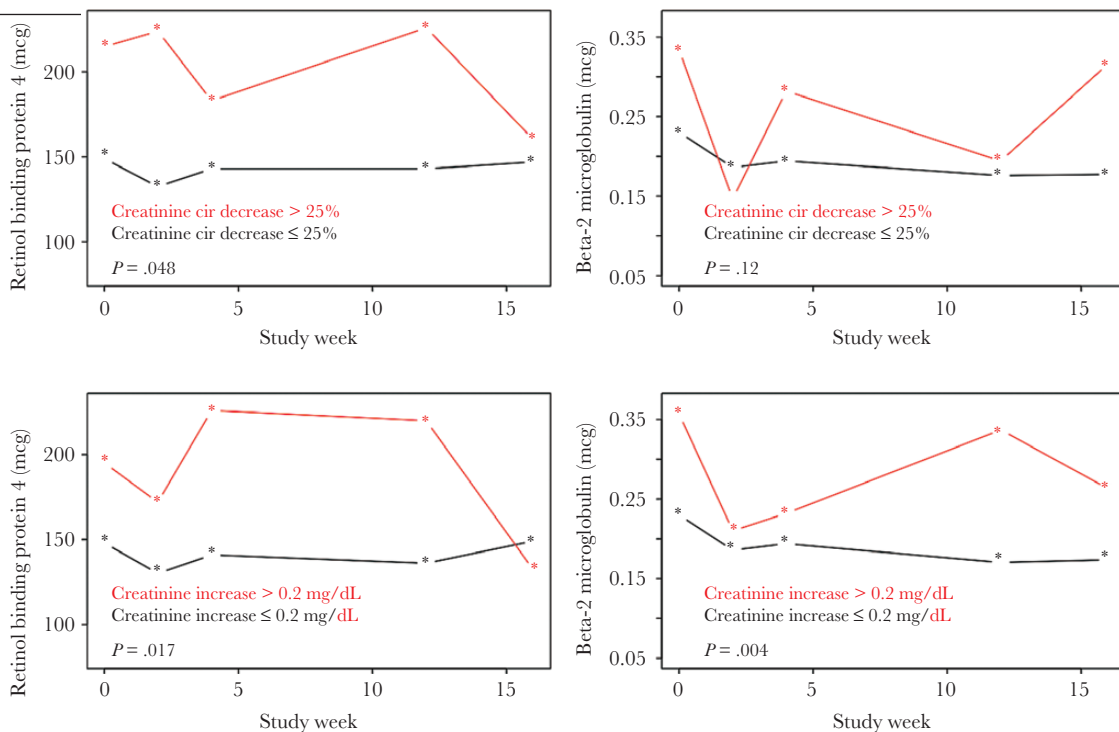


Figure 5. Pooled mean biomarker level through study week 16 for study outcome of creatinine clearance. The red line represents the subgroup with a decrease >25% in creatinine clearance. For absolute creatinine, the red line represents the subgroup with an absolute increase >0.2 from baseline over the study period. Each point represents a pooled mean value for that study time point.

This study has several limitations. This is a post hoc analysis of existing data and was not developed as an a priori outcome of the ION-4 study. In addition, absolute values for RBP-4 and β 2M were used. These biomarkers have traditionally been reported as ratios over urine creatinine to normalize biomarker values for volume status and urine concentration [12, 13]. However, many of these biomarkers were developed as diagnostic and prognostic tests in the setting of acute kidney injury. Normalization using urine creatinine is done as a surrogate for urine flow in the setting of AKI, where oliguria or polyuria is often present. Urine flow remains the gold standard for biomarker testing given the interindividual variability in urine creatinine secretion [23]. These limitations are attenuated by the intensive sampling regimen and by the participants having been otherwise at steady state with respect to urine output. Lastly, the ION-4 excluded participants on pharmacologically boosted ARV regimens. This particular subgroup of patients would have been an ideal group to study due to their increased tenofovir exposures in healthy volunteer studies. Thus, the data reported here cannot be extrapolated to such patients.

In conclusion, tenofovir exposure is associated with increased absolute levels of proximal tubule urine biomarkers in participants on LDV/SOF and nonpharmacologically boosted TDF-based ARV regimens. Extra caution should be used for boosted ARV regimens as these may increase tenofovir drug levels more than was observed in the ION-4 trial.

TAF-based regimens likely do not face such concerns, though they may not be as cost-effective in the future. In HIV/HCV-coinfected participants with CrCl >60 mL/min, increased exposure to TFV for 12 weeks during LDV/SOF therapy does not result in significant nephrotoxic events. Further studies assessing the predictive role of these biomarkers in HIV/HCV-coinfected patients with CrCl <50 mL/min or with multiple risk factors for nephrotoxic events may help guide medical decision-making and risk/benefit assessments for choosing DAA regimens.

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