Incidence of Acute Kidney Injury in Patients Coinfected with HIV and Hepatitis C Virus Receiving Tenofovir Disoproxil Fumarate and Ledipasvir/Sofosbuvir in a Real-World, Urban, Ryan White Clinic

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Abstract

Ledipasvir/sofosbuvir (LDV/SOF), an antiviral treatment for hepatitis C virus (HCV), and tenofovir disoproxil fumarate (TDF), an antiretroviral for treating human immunodeficiency virus (HIV), may be coadministered in patients coinfecting with these viruses. A drug interaction between LDV and TDF could increase TDF-associated nephrotoxicity rates; however, there is minimal clinical evidence describing acute kidney injury (AKI) rates in this population. This study was conducted at a Ryan White-funded facility in Atlanta, Georgia, that cares for over 5,000 patients with AIDS. This retrospective cohort used chart review to assess occurrence of and risk factors for AKI in HIV/HCV-coinfecting patients receiving LDV/SOF and antiretroviral therapy (ART). AKI rates were compared between TDF-containing and non-TDF-containing ART groups according to Kidney Disease Improving Global Outcomes (KDIGO) criteria. Additional evaluated risk factors for AKI included chronic kidney disease and use of boosted protease inhibitor-based ART. In the 117 included patients, the overall incidence of AKI was 27.3%. AKI occurred more frequently in the non-TDF group (13/86, 15.1% vs. 19/31, 61.3%, $p < .001$). All AKI was KDIGO stage 1. From multivariable logistic regression, the only independent predictor of AKI was treatment with non-TDF relative to TDF (adjusted odds ratio 6.51, 95% confidence interval 2.34–18.10, $p < .001$). In this real-world cohort of HIV/HCV-coinfecting patients, KDIGO-defined AKI was common, but occurred less frequently in patients receiving TDF-based ART. Our study suggests that patients with normal baseline renal function can be safely treated with TDF and LDV/SOF without significant nephrotoxicity if renal function is closely monitored.

Keywords: hepatitis C, HIV, tenofovir, ledipasvir, sofosbuvir, acute kidney injury

Introduction

APPROXIMATELY 25% OF PATIENTS with human immunodeficiency virus (HIV) in the United States are coinfecting with hepatitis C virus (HCV).¹ Ledipasvir/sofosbuvir (LDV/SOF), a once-daily oral antiviral regimen that treats HCV, achieves high rates of sustained virologic response with minimal adverse effects in HIV/HCV-coinfecting patients.^{2–7} The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America

(IDSA) list LDV/SOF among first-line treatment options for HCV in coinfecting patients.⁸ Tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir (TFV), is a nucleotide reverse transcriptase inhibitor (NRTI) commonly prescribed as part of the dual NRTI backbone antiretroviral therapy (ART) for HIV. Its toxicities include reduced estimated glomerular filtration rates (eGFR), acute kidney injury (AKI), and proximal renal tubule dysfunction (PRTD) or Fanconi syndrome.^{9–12}

TFV is a substrate of P-glycoprotein transporters. LDV inhibits these transporters, increasing serum concentrations

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of TFV by up to 2.6-fold, provoking concern that administering TDF-containing ART with LDV/SOF may yield higher rates of nephrotoxicity than without LDV/SOF.¹³ For this reason, the AASLD-IDSA guidelines recommend against concomitant LDV and TDF use in patients with creatinine clearance (CrCl) less than 60 mL/min.⁸ Similarly, the LDV/SOF package insert endorses close monitoring for TDF-associated adverse effects or considering alternative ART in candidates for both medications.¹⁴

Standard combination ART regimens include anchor drugs such as boosted HIV protease inhibitors (PIs) and efavirenz (EFV). Either or both agents may be prescribed with TDF for HIV treatment in HIV/HCV-coinfected patients who are otherwise candidates for LDV/SOF therapy. HIV PIs boost serum concentrations of both TDF and LDV, an effect potentiated by pharmacokinetic enhancers ritonavir and cobicistat.^{13,15,16} Although data do not support that EFV increases TFV concentrations in the absence of LDV/SOF, TFV concentrations are doubled with LDV/SOF use when given as EFV/TDF/emtricitabine.^{13,16,17}

Clinical trials have not demonstrated elevated rates of renal dysfunction in patients receiving both TDF and LDV/SOF. However, study subjects were in highly controlled trial settings, lacked concomitant kidney disease, and were not using HIV PIs as part of ART.^{5,6} The present study sought to assess incidence and risk factors for acute nephrotoxicity associated with concomitant TDF and LDV/SOF use in HIV/HCV coinfection in a real-world clinical setting.

Materials and Methods

Patients

Patients were eligible for inclusion if they were at least 18 years old, coinfecting with HIV/HCV, receiving ART, managed for HCV treatment at the Infectious Disease Program (IDP) clinic associated with Grady Health System, and initiated on LDV/SOF between October 1, 2014, and August 31, 2015. Patients were excluded if pregnant, received less than 4 weeks of LDV/SOF treatment, or did not have baseline laboratory results within 6 months before LDV/SOF initiation. To ensure stable ART before LDV/SOF initiation, patients were also excluded if they had baseline HIV RNA greater than 1,000 copies/mL or changed ART within 28 days before starting HCV treatment.

Study design

This retrospective study was conducted at the IDP clinic, a large, urban, Ryan White HIV/AIDS Program-funded facility in Atlanta, Georgia. A clinical database was utilized to identify eligible patients who were then divided into TDF and non-TDF groups based upon ART regimen. Chart review and clinical database query were used for data collection, including standard demographics; LDV/SOF duration; prescribed ART and nephrotoxic agents; diabetes mellitus; chronic kidney disease (CKD) including HIV-associated nephropathy (HIVAN); hypertension; baseline laboratory work including serum levels of creatinine (SCr), bicarbonate, and phosphate; glycosuria or proteinuria on urinalysis; renal replacement therapy; and TDF discontinuation.

Data regarding illicit substance use was not collected because patients were not qualified to receive LDV/SOF at the

study site if they were known active recreational injection drug or cocaine users. The Emory Institutional Review Board and Grady Research Oversight Committee approved the study protocol.

Endpoints

The primary endpoint for this study was rate of AKI of any degree as defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria.¹⁸ SCr of 1.5–1.9 times baseline or at least 0.3 mg/dL greater than baseline was considered stage 1 AKI. SCr of 2–2.9 times baseline was stage 2 AKI. SCr at least three times baseline, SCr of at least 4 mg/dL, or new renal replacement therapy were considered stage 3 AKI. CrCl was used for eGFR and was calculated for all patients included in the study using the Cockcroft-Gault equation. If actual body weight (ABW) was less than ideal body weight (IBW), ABW was used in the equation. If ABW was greater than 120% of IBW, an adjusted body weight (AdjBW) was utilized [$\text{AdjBW} = \text{IBW} + 0.4 \times (\text{ABW} - \text{IBW})$]. IBW was used if ABW was between 100% and 120% of IBW.

Each group was also assessed for achieving secondary endpoints during and up to 6 months after LDV/SOF treatment. These endpoints included stage and duration of AKI, time to AKI, rates of new onset PRTD, TDF discontinuation, LDV/SOF discontinuation before intended stop date, and new renal replacement therapy. The following risk factors were analyzed for an association with AKI: age, sex, race, boosted HIV PI use, CKD including HIVAN, hypertension, diabetes mellitus, proteinuria, and use of any other nephrotoxic agent during or within 6 months after LDV/SOF use. See Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/aid) for a comprehensive list of medications considered nephrotoxic for this study.

Finally, a *post hoc* logistic regression analysis was performed to determine whether CrCl or SCr above or below baseline medians modified the effect of treatment (non-TDF or TDF) on AKI incidence.

CKD was defined as a CrCl less than 60 mL/min present for at least 3 months before LDV/SOF initiation.¹⁹ HIVAN was documented if listed in the electronic medical record as biopsy confirmed. Hypertension was defined as systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg during at least two consecutive IDP clinic visits or at least one antihypertensive agent listed in the patient's home medication list. Diabetes mellitus was determined by diagnosis listed in the electronic medical record or use of at least one antihyperglycemic agent. PRTD was defined as an increase in SCr by at least 0.5 mg/dL from baseline and serum phosphate less than 2 mg/dL or either of these in addition to any two of the following: proteinuria of at least 100 mg/dL, glycosuria at least 250 g/dL, serum potassium of less than 3 mEq/L, or serum bicarbonate less than 19 mEq/L.²⁰

Statistical analyses

Baseline demographic and clinical characteristics were compared between groups with the two-sample *t*-test or Wilcoxon rank-sum test for continuous variables and the chi-square or Fisher's exact test for proportions. The incidence of AKI was estimated as a single-sample proportion.

Associations between baseline characteristics and AKI were evaluated using the chi-square or Fisher's exact test. Odds ratios (OR) were calculated to measure associations between risk factors and AKI. The adjusted OR and its 95% confidence interval (CI) were calculated for each risk factor in the presence of others in the final model. Data were analyzed in SAS (Cary, NC, version 9.4). Statistical significance was defined as a two-sided p value of less than 0.05. Additional details regarding statistical analyses can be found in Supplementary Data.

Results

Population and baseline characteristics

Figure 1 illustrates patient screening for inclusion. One hundred seventeen patients were included, 86 of whom received TDF-containing ART. Most patients had an intended LDV/SOF treatment duration of 12 weeks (79 TDF, 30 non-TDF). One patient in the TDF group received 8 weeks of LDV/SOF. Seven patients received LDV/SOF for 24 weeks (six TDF, one non-TDF).

Baseline characteristics were similar between groups (Table 1), except mean SCr was higher in the non-TDF group (1.03 mg/dL vs. 1.24 mg/dL, $p = .01$), mean CrCl was lower in the non-TDF group (86.4 mL/min vs. 69.1 mL/min, $p < .001$), baseline CKD was more common in the non-TDF group (11.6% vs. 41.9%, $p < .001$), and EFV was used more frequently in the TDF group (27.9% vs. 6.5%, $p = .01$). Data

on recreational drug use were not available. A complete list of prescribed antiretroviral agents and nephrotoxic medications can be found in Supplementary Tables S2 and S3. Sixty-six percent of patients were black males. No patient had PRTD or HIVAN at baseline. Laboratories assessing for PRTD at baseline can be found in Supplementary Table S4.

Outcomes

AKI was detected in 13 (15.1%) TDF patients and 19 (61.3%) non-TDF patients ($p < .001$) at some point during the study period. All AKI was stage 1 according to KDIGO criteria. When defined as an increase in SCr of greater than 1.5 times baseline, AKI occurred in two (2.3%) and three (9.7%) patients in the TDF and non-TDF groups, respectively ($p = .12$). The median days to AKI after LDV/SOF was initiated was 64 [interquartile range (IQR) 15–78] in the TDF group and 96 (IQR 46–159) in the non-TDF group ($p = .19$). The median number of days a patient experienced AKI was 55 (IQR 32–94) in the TDF group and 68 (IQR 34–95) in the non-TDF group ($p = .84$). The median amount of time between laboratories was 37 days (IQR 20–91) in the TDF group and 47 days (IQR 28–98) in the non-TDF group. No patient experienced PRTD or required new renal replacement therapy.

Figure 2 illustrates mean SCr and CrCl throughout the study period. SCr was consistently higher in the non-TDF group. Trends were not further subdivided since these results would not be clinically meaningful. The time to AKI onset

FIG. 1. Flow of participation for patients coinfecting with HIV/HCV by treatment (TDF or non-TDF). ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV/SOF, ledipasvir/sofosbuvir; TDF, tenofovir disoproxil fumarate.

TABLE 1. BASELINE CHARACTERISTICS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS/HEPATITIS C VIRUS COINFECTION RECEIVING LEDIPASVIR/SOFOSBUVIR AND EITHER TENOFOVIR DISOPROXIL FUMARATE-CONTAINING OR NON-TENOFOVIR DISOPROXIL FUMARATE-CONTAINING ANTIRETROVIRAL THERAPY (N=117)

	TDF (n=86)	Non-TDF (n=31)	p
Male, n (%)	68 (79.1)	24 (77.4)	0.85
Age, years, mean (SD)	53 (8.6)	56 (6.7)	0.11
Weight, kg, mean (SD)	82 (16.2)	78 (16.6)	0.22
Height, inches, mean (SD)	69 (3.4)	69 (3.5)	0.96
Race, n (%)			
Black	72 (83.7)	27 (87.1)	0.92 ^a
White	11 (12.8)	3 (9.7)	
Other	3 (3.5)	1 (3.2)	
HIV viral load, n (%)			
<40 copies/mL	79 (91.9)	29 (93.5)	1.00 ^a
40–1,000 copies/mL	7 (8.1)	2 (6.5)	
CD4, cells/mm ³ , n (%)			
<200	9 (10.5)	1 (3.2)	0.10 ^a
200–349	17 (19.8)	10 (32.3)	
350–500	14 (16.3)	9 (29.0)	
>500	46 (53.5)	11 (35.5)	
Serum creatinine, mg/dL, mean (SD)	1.03 (0.24)	1.24 (0.43)	0.01
Creatinine clearance, mL/min, mean (SD)	86.4 (21.4)	69.1 (23.6)	<0.001
Concomitant disease states, n (%)			
Diabetes mellitus	11 (12.8)	6 (19.4)	0.37
Hypertension	47 (54.7)	23 (74.2)	0.06
CKD ^b	10 (11.6)	13 (41.9)	<0.001
ART administered with LDV/SOF, n (%) ^c			
Boosted PI	41 (47.7)	23 (74.2)	0.01
Efavirenz	24 (27.9)	2 (6.5)	0.01

^aFisher's exact test.^bCKD was defined as a calculated creatinine clearance of less than 60 mL/min.^cFour and one patients in the TDF and non-TDF groups, respectively, used both boosted PIs and efavirenz concomitantly with LDV/SOF. ART, antiretroviral therapy; CKD, chronic kidney disease; LDV/SOF, ledipasvir/sofosbuvir; PI, protease inhibitor; PRTD, proximal renal tubule dysfunction; SD, standard deviation; TDF, tenofovir disoproxil fumarate

was ~2 months in the TDF group and 3 months in the non-TDF group while duration of AKI was ~2 months in both groups.

AKI did not resolve by the end of the study period for three (3.4%) patients in the TDF group and six (19.4%) patients in the non-TDF group. For three of these patients, AKI was first detected from the final laboratory work included in the study, after LDV/SOF treatment was complete. Details for all nine patients are summarized in Supplementary Table S5.

One 52-year-old black male in the non-TDF group with baseline CKD and hypertension controlled with medications exhibited progressive renal dysfunction. His ART consisted of atazanavir/ritonavir, abacavir, and lamivudine, and he received 12 weeks of LDV/SOF. At baseline, his SCr was 3.1 mg/dL (CrCl 27 mL/min) and urinalysis showed proteinuria (100 mg/dL). Ninety-five days after completing LDV/SOF, his SCr was 5.4 mg/dL (CrCl 15 mL/min) with worsened proteinuria (500 mg/dL). Provider notes from the electronic medical record did not associate medications with his renal dysfunction nor was there a rationale for prescribing LDV/SOF in a patient with a baseline CrCl less than 30 mL/min.

Factors associated with AKI

Univariable logistic regression analysis demonstrated significant associations between stage 1 AKI and non-TDF ART

(OR 8.89, 95% CI 3.50–22.60, $p < .001$) and baseline CKD (OR 4.04, 95% CI 1.55–10.50, $p = .004$). A complete list of risk factors used in the univariable logistic regression analysis can be found in Supplementary Table S6. The *post hoc* logistic regression analysis suggested treatment group (non-TDF vs. TDF) might have affected AKI rates differently in patients with CrCl less than the median of 80 mL/min compared with higher baseline CrCl, but this was not significant ($p = .19$).

The risk of AKI among patients with CrCl above the median was higher in the non-TDF group compared with the TDF group (OR = 3.6; 95% CI 0.68–18.9, $p = .13$). The risk of AKI among patients with CrCl below the median was significantly higher in the non-TDF group compared with the TDF group (OR = 15.0; 95% CI 3.9–57.6, $p < .001$). A similar analysis for baseline SCr above or below the median of 1 mg/dL did not suggest the effect of treatment was modified by baseline SCr ($p = .88$). The risk of AKI among patients with SCr above the median was significantly higher in the non-TDF group compared with the TDF group (OR = 7.7; 95% CI 2.1–27.9, $p = .0018$). The risk of AKI among patients with SCr below the median was significantly higher for patients in the non-TDF group compared with those in the TDF group (OR = 8.9; 95% CI 0.2–33.7, $p = .0019$).

Multivariable logistic regression analyses for the entire cohort and TDF group only are shown in Tables 2 and 3, respectively. Treatment with non-TDF ART relative to TDF-

FIG. 2. Mean serum creatinine and creatinine clearance by study group over time. **(a)** The difference in serum creatinine at each time point was statistically significantly different when analyzing TDF versus non-TDF groups. Baseline $p = .001$, weeks 0 to <4, $p = .001$; weeks 4 to <8, $p = .0004$; weeks 8 to <12, $p = .0045$; weeks 12 to <24, $p < .0001$; and >24 weeks, $p = .0008$. Serum creatinine in the two study groups changed in significantly different ways (i.e., different temporal patterns over time) during follow-up ($p = .01$). **(b)** The difference in creatinine clearance at each time point was statistically significantly different when analyzing TDF versus non-TDF groups. Baseline $p = .0003$; weeks 0 to <4, $p = .002$; weeks 4 to <8, $p = .0002$; weeks 8 to <12, $p = .0007$; weeks 12 to <24, $p < .0001$; and >24 weeks, $p = .0002$. Creatinine clearance in the two study groups changed in significantly different ways (i.e., different temporal patterns over time) during follow-up ($p = .05$). Data shown represents model-based mean with 95% confidence intervals. The vertical lines are 95% confidence intervals.

containing ART (adjusted OR 6.51, 95% CI 2.34–18.10, $p < .001$) was an independent predictor of AKI. The model suggested no association between AKI and boosted HIV PI (adjusted OR 0.88, $p = .82$) or EFV use (adjusted OR 0.40, $p = .22$). Neither baseline SCr (OR 1.14, 95% CI 0.92–1.41, $p = .24$) nor CrCl (OR 1.10, 95% CI 0.93–1.29, $p = .27$) were associated with AKI after adjusting for treatment group. Details

regarding the multivariable logistic regression analyses can be found in Supplementary Tables S7 and S8.

Discontinuations and loss to follow-up

Neither TDF nor LDV/SOF were discontinued due to renal dysfunction in any patient. Two patients discontinued LDV/

TABLE 2. MULTIVARIABLE LOGISTIC REGRESSION OF RISK FACTORS POTENTIALLY ASSOCIATED WITH ACUTE KIDNEY INJURY AMONG PATIENTS COINFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS/HEPATITIS C VIRUS RECEIVING ANY ANTIRETROVIRAL REGIMEN (N=117)

Factor	AKI, n (%)	No AKI, n (%)	Adjusted OR	95% CI	p
All patients	32 (27)	85 (73)			
Treatment (non-TDF/TDF) ^a	19/32 (59)	12/85 (14)	6.51	2.34–18.10	<0.001
EFV (yes/no)	3/32 (9)	23/85 (27)	0.40	0.09–1.71	0.22
Boosted PI (yes/no)	20/32 (63)	44/85 (52)	0.88	0.31–2.49	0.82
CKD (yes/no)	12/32 (38)	11/85 (13)	2.31	0.76–7.02	0.14

^an (%) where the numerator of the fraction is the “at risk” category (i.e., the number patients treated with non-TDF). AKI, acute kidney injury; CI, confidence interval; EFV, efavirenz; OR, odds ratio.

SOF before the intended stop date. One patient in the TDF group received 4 weeks LDV/SOF and was lost to follow-up. One patient in the non-TDF group received 8 weeks of LDV/SOF as limited by the payer source.

Discussion

Nephrotoxicity has been reported in up to 10% of the general HIV-infected population.^{21,22} This compares to ~5% of HCV mono-infected patients with one study reporting the odds of renal dysfunction to be 1.39 times more likely in HCV-positive patients than in HCV-negative patients.²³ Literature supports that up to 2.5% of patients receiving TDF experience some form of acute TDF-associated nephrotoxicity with onset documented anywhere from 8 to 96 months after initiation.^{11,22,24–26}

TDF-associated nephrotoxicity rates are proportional to the severity of preexisting CKD. One study reported that patients with moderate CKD (baseline CrCl 30–59.9 mL/min) were 15 times more likely to experience nephrotoxicity than those with baseline CrCl of at least 90 mL/min, although only 46 (5.2%) of the included patients were considered to have moderate renal dysfunction.²⁶ While data exists for these subpopulations, there are few reports examining kidney-related outcomes in real-world cohorts of patients with a combination of these characteristics, as seen in our cohort.

Our population was at significant risk for nephrotoxicity, and the rates of KDIGO-defined AKI in our patients were much higher than renal dysfunction estimates reported for the general HIV-infected population, regardless of TDF-containing ART, or HCV mono-infected patients. Sixty-six percent of patients were black males, known for their higher risk of HIVAN and other non-HIV-related renal disease.^{27,28} Twenty percent of the cohort had CKD at baseline, 60% had hypertension, and 15% had diabetes mellitus. While the incidence of acute renal dysfunction was high in this study, AKI never led to discontinuation of LDV/SOF or TDF, thus

resulting in minimal clinical impact. This finding was consistent even among the 41 patients receiving boosted HIV PIs in addition to TDF and LDV/SOF.

The ION-4 and ERADICATE trials also examined LDV/SOF treatment in patients coinfecting with HIV/HCV; however, neither allowed boosted PI-based ART due to concerns for increasing the risk of TDF-associated nephrotoxicity by increasing serum concentrations of TFV, and both excluded patients with clinically significant illnesses or major medical disorders.^{5,6} Both trials monitored for renal dysfunction using multiple measurements from serum and urine samples.

ION-4 excluded patients with calculated CrCl less than 60 mL/min and utilized ABW for CrCl calculations. Adverse effects were graded according to a 4-point scale, the Gilead Sciences, Inc., Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. Four patients experienced SCr increases of at least 0.4 mg/dL, although none was considered grade 3 or 4 elevations.⁵ TDF was discontinued in one, dose reduced in a second, and was not changed in two patients.

ERADICATE utilized a 5-point scale to grade severity of adverse effects using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events and reported no significant changes in SCr or eGFR over time, although one patient experienced increased SCr that resolved.⁶

We defined renal dysfunction differently than in ERADICATE or ION-4; however, when using similar definitions, we still found higher rates of renal dysfunction compared with these trials. ERADICATE had no patients with treatment-emergent eGFR less than 50 mL/min or eGFR decreases greater than 25%, while our study had 10 (3 TDF, 7 non-TDF) and 15 (6 TDF, 9 non-TDF) instances, respectively. ION-4 reported no grade 3 or 4 elevations in SCr, whereas our study found 7 of 640 (1.1%) SCr values greater than 3 mg/dL, although all were from the same patient in the non-TDF group. Furthermore, there were four patients in ION-4 with treatment-emergent SCr increases of at least 0.4 mg/dL compared with 14 patients in our study (3 TDF, 11 non-TDF).

TABLE 3. MULTIVARIABLE LOGISTIC REGRESSION OF RISK FACTORS POTENTIALLY ASSOCIATED WITH ACUTE KIDNEY INJURY AMONG PATIENTS COINFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS/HEPATITIS C VIRUS RECEIVING TENOFOVIR DISOPROXIL FUMARATE (N=86)

Factor	AKI, n (%)	No AKI, n (%)	Adjusted OR	95% CI	p
All patients	13 (15)	73 (85)			
EFV (yes/no)	2/13 (15)	22/73 (30)	0.41	0.08–2.17	0.29
Boosted PI (yes/no)	6/13 (46)	35/73 (48)	0.81	0.22–2.95	0.75
CKD (yes/no)	3/13 (23)	7/73 (10)	2.54	0.53–12.18	0.24

Higher rates of renal dysfunction in our study compared with the ION-4 and ERADICATE trials may be attributed to worse baseline renal function in our cohort. Patients receiving ART in ERADICATE had a median baseline SCr of 0.91 mg/dL (eGFR 93 mL/min), lower than our study; however, CKD rate was not reported. ION-4 did not report baseline SCr values or CKD rates.

Despite high rates of AKI, our cohort had fairly stable renal function throughout the study duration (Fig. 2), similar to other studies examining TDF and LDV/SOF coadministration.^{7,29} A recently published observational, real-world cohort examining oral antiviral regimen effectiveness in HIV/HCV coinfecting patients included a predominantly male ($n=981$, 99%) African American ($n=667$, 67%) population with a median baseline SCr of 1.01 mg/dL (IQR 0.90–1.20), most of whom received LDV/SOF without ribavirin ($n=757$, 76%) for HCV treatment.⁷ CKD rates were not reported. The median maximum SCr change in the entire cohort was 0.16 mg/dL (IQR 0.05–0.30), approximately half that seen in our study.

Additionally, Bhattacharya *et al.* evaluated the impact of TDF on SCr with and without concomitant HIV PIs. Median maximum SCr changes in these groups were 0.17 mg/dL (IQR 0.04–0.30) and 0.18 mg/dL (IQR 0.08–0.30), respectively. This value was 0.15 mg/dL (IQR 0.00–0.30) for patients receiving non-TDF-containing ART. From this, they concluded that ART containing both TDF and HIV PIs may be used with LDV/SOF. This was congruent with findings from our study indicating no association between AKI and boosted HIV PI use in patients receiving TDF and LDV/SOF.

While TDF use was not associated with AKI in our study, SOF is not recommended for patients with severe renal dysfunction due to concerns for metabolite accumulation, although there are no descriptions in the literature of toxicities related to elevated SOF metabolite concentrations.³⁰ SOF has been associated with worsening renal function in patients with baseline CrCl less than or equal to 45 mL/min, although the cohort study reporting this did not examine LDV/SOF as one of the SOF-based treatment regimens.³¹ Our study included five patients with baseline CrCl less than 45 mL/min (one TDF, four non-TDF), one of whom had a baseline CrCl less than 30 mL/min. Of these, all four patients in the non-TDF group experienced AKI (peak SCr increase of 0.3–0.5 mcg/mL, three resolved after a range of 49–210 days), whereas the patient in the TDF group did not experience changes in renal function.

There are reports of SOF being well tolerated despite moderate-to-severe renal dysfunction,^{32–35} and several prospective trials are ongoing examining safety and efficacy of SOF-containing HCV treatment in this patient population. One case series noted that worsening renal function was more common in CKD stage 3 patients and recommended careful renal function monitoring during SOF treatment.³⁶

Finally, while most patients in the literature had stable renal function, there are reports of worsening CrCl in HCV-monoinfected patients with kidney transplants treated with LDV/SOF, but no instance was directly attributed to LDV/SOF even with baseline CrCl less than 30 mL/min in one patient.^{37–43} The underlying etiology for worsening renal function in patients treated with SOF-containing therapies remains unclear; however, SOF use alone cannot explain the findings in our study given that all patients received LDV/SOF yet the non-TDF group experienced much higher rates of KDIGO-defined AKI.

There are several limitations to the present study. First, there are inherent limitations with retrospective studies. The intervals at which laboratory work was completed were not well controlled, and only 89 patients had follow-up laboratory work accessible through the electronic medical record at least 6 months after completing treatment with LDV/SOF. AKI may have occurred more often or resolved more rapidly than detected by chart review. For this reason, it was not possible to accurately differentiate between acute renal dysfunction and progression of baseline CKD. Not all patients received consistent or complete laboratory monitoring to assess for PRTD, and this study was likely too small to detect changes in PRTD rates.

More patients in the TDF group were lost to posttreatment follow-up than in the non-TDF group. Of these, 11 patients received primary care for HIV at outside facilities. This must be considered when interpreting rates of AKI and AKI resolution during this time period, especially if there is concern for post-LDV/SOF-related AKI in patients taking TDF.

Finally, it is not surprising that AKI rates were lower in the TDF group when comparing baseline characteristics between groups. Fewer patients receiving TDF had CKD at baseline. This mimics real-world prescribing patterns but provides significant selection bias in this retrospective study, impacting the association between TDF and AKI rates since patients were not randomized to receive TDF- or non-TDF-containing ART.

While TDF remains a commonly utilized antiretroviral agent, tenofovir alafenamide (TAF), a newer TFV prodrug, is available and associated with lower rates of nephrotoxicity than TDF. While TAF is currently available in the United States and coformulated with other antiretroviral medications, most patients in the current study did not have access to TAF-containing medications at the time of LDV/SOF treatment. As long as TDF remains available, patients receiving TDF-based ART could receive concomitant LDV/SOF for HCV treatment, highlighting the relevance of our findings.

Conclusion

This retrospective analysis of a real-world HIV/HCV-coinfecting cohort starts to address the concern for clinically significant AKI associated with the drug–drug interaction between LDV/SOF and TDF in patients with normal baseline renal function. TDF use should not be the sole reason for avoiding LDV/SOF treatment in patients coinfecting with HIV/HCV, nor should patients with stable renal function already receiving TDF necessarily change ART before starting LDV/SOF, even with concomitant boosted HIV PI or EFV use. Our results support ongoing, close monitoring of renal function during treatment with LDV/SOF due to our high rates of KDIGO-defined AKI regardless of ART regimen, especially in individuals with CKD.

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