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BRIEF REPORT

Acute Kidney Injury in a Patient on Tenofovir Alafenamide Fumarate After Initiation of Treatment for Hepatitis C Virus Infection

David P. Serota,[1] Harold A. Franch,[2,3] and Emily J. Cartwright[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Emory University, Atlanta, Georgia; [2]Atlanta VA Medical Center, Veterans Health Administration, Atlanta, Georgia; [3]Division of Renal Medicine, Department of Medicine, Emory University, Atlanta, Georgia

HIV treatment with tenofovir alafenamide fumarate (TAF) has decreased renal toxicity compared with tenofovir disoproxil fumarate in clinical trials. We report the case of a patient with HIV/HCV coinfection who was started on a TAF-based HIV regimen and developed acute kidney injury that worsened with the addition of sofosbuvir-ledipasvir.

Keywords. acute kidney injury; hepatitis C; HIV infection; tenofovir alafenamide.

The advent of hepatitis C virus (HCV) direct-acting antivirals (DAAs) has drastically improved the prognosis for those living with HCV infection. This is of particular importance for patients coinfected with HIV as they have higher rates of HCV complications including cirrhosis, hepatocellular carcinoma, and extrahepatic organ dysfunction [1, 2]. As access to DAAs has expanded, treatment of HCV in coinfected patients is a priority [3]. Persons with HIV/HCV coinfection show similar efficacy and tolerability when treated with DAAs [4, 5].

The American Association for the Study of Liver Diseases (AASLD)–Infectious Diseases Society of American (IDSA) HCV guidelines recommend consulting a resource like the University of Liverpool's website (www.hep-druginteractions.org) to explore drug interactions before initiating HCV treatment. Ledipasvir (LED) is an HCV NS5A inhibitor coformulated with sofosbuvir (SOF), a nucleotide analogue NS5B polymerase inhibitor, and administered once daily as a fixed-dose combination tablet (SOF/LED). Administration of SOF/LED with tenofovir disoproxil fumarate (TDF) and ritonavir or cobicistat can lead to elevated TDF exposure and is not recommended [6].

Tenofovir alafenamide (TAF) was approved for HIV treatment in the United States in 2015. Compared with tenofovir disoproxil fumarate, TAF has an improved side effect profile and higher intracellular drug levels [7]. In phase III clinical trials comparing TAF- and TDF-based regimens, TAF-based treatment demonstrated improved renal and bone mineral density outcomes [8]. There have been few reported renal adverse events related to TAF; however, clinical trial participants lacked HCV co-infection [9]. There is no expected interaction between SOF/LED and TAF, and co-administration is encouraged.

We present the case of an older man with HIV/HCV coinfection with decompensated cirrhosis who developed acute kidney injury a few months after starting tenofovir alafenamide, emtricitabine, elvitegravir, and cobicistat (EVG/c/FTC/TAF), with the addition of SOF/LED. This case demonstrates potentially unreported risks of renal morbidity attributable to the combination of these medications in a frail patient.

CASE PRESENTATION

A 70-year-old man with HIV-1 infection, alcohol use disorder, chronic HCV infection, and Childs-Turcott-Pugh class B cirrhosis initially presented to establish HIV care in December 2016 (Figure 1). He was started on dolutegravir-abacavir-lamivudine (DTG/ABG/3TC) but was changed to EVG/c/FTC/TAF in February 2017 due to perceived neuropsychiatric side effects [10]. At the time of initiation of therapy, his HIV viral load was >1 million copies/mL and his absolute CD4 helper T-cell count was 100 cells/mL, with a CD4 percentage of 9%. He was diagnosed with HCV infection 12 years before presentation. He had a history of decompensated cirrhosis; his HCV was genotype 1b, and his viral load was 13 300 000 IU/mL. In February 2017, his serum creatinine level was 1.2 mg/dL, with an estimated creatinine clearance of 50 mL/min (using the Cockcroft-Gault equation). One month after initiating EVG/c/FTC/TAF, his serum creatinine increased to 1.65 mg/dL, with normal electrolyte levels. At the time, this increase was attributed to decreased excretion of creatinine associated with cobicistat initiation.

Treatment for his HCV infection was initiated with SOF/LED on May 1, 2017, for a planned 24-week duration based on IDSA/AASLD HCV guidelines for treatment-naïve patients with class B cirrhosis [3]. On May 17, he had a follow-up clinic appointment, at which time his serum creatinine had increased to 2.46 mg/dL with otherwise normal electrolyte levels. On May 22, his blood pressure was 128/89 mmHg, and he was euvolemic on examination. Spironolactone and furosemide were stopped

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Correspondence: D. P. Serota, MD, Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, 1518 Clifton Rd Northeast, GCR 420, Atlanta, GA 30322 (dserota@emory.edu).

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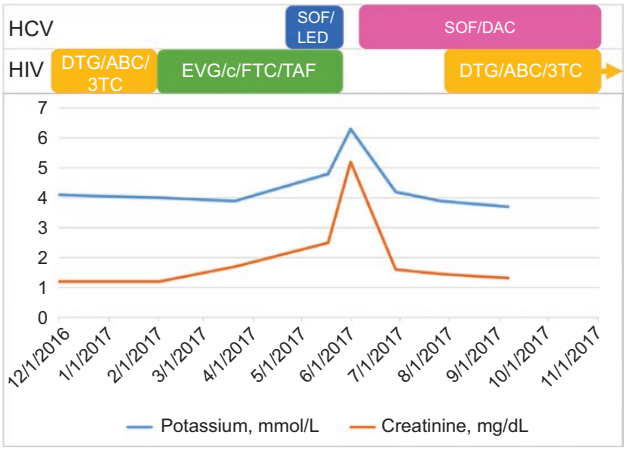

Figure 1. Timeline of medication administration and selected laboratory values: Serum creatinine (mg/dL) and potassium (mmol/L) levels are plotted over time with reference to HIV and hepatitis C virus medications taken by the patient. Abbreviations: DTG/ABC/3TC, dolutegravir, abacavir, and lamivudine coformulated tablet; EVG/c/FTC/TAF, elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide coformulated tablet; SOF/DAC, sofosbuvir and daclatasvir coformulated tablet; SOF/LED, sofosbuvir and ledipasvir coformulated tablet.

out of concern for prerenal azotemia. Ten days later, his serum creatinine was 5.2 mg/dL, and his potassium was 6.3 mmol/L. He was admitted to the hospital for evaluation and management of acute kidney injury and hyperkalemia.

He was asymptomatic and specifically denied dyspnea, orthopnea, or lower extremity swelling. He had no abdominal pain, distention, diarrhea, nausea, or vomiting. His wife noted no change in his behavior or cognition. His wife corroborated daily administration of EVG/c/FTC/TAF and SOF/LED without any missed doses. His other medications included aspirin, lisinopril, metoprolol, mirtazapine, thiamine, folic acid, and ferrous sulfate. He reported no recent use of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, illicit drugs, over-the-counter medications, or supplements. He reported consuming 1 small bottle of liquor in the preceding few weeks and had a negative urine alcohol metabolite panel 2 months before admission. His blood pressure was 137/71 mmHg, and he had no ascites, lower extremity edema, or asterixis noted on physical examination; he demonstrated normal cognition and attention.

Serum laboratory values included potassium of 6.3 mmol/L, bicarbonate 13 mmol/L, BUN 79 mg/dL, creatinine 5.2 mg/dL, and phosphorus 5.6 mg/dL. His anion gap was 10 mmol/L. His HCV viral load was undetectable. His urine studies showed 2 white blood cells, 3 red blood cells, 1+ protein, pH 5.0, and no casts. His urine sodium was 79 mmol/L, and his 24-hour urine protein was 6358 mg (ref <100 mg). On hospital day 2, his venous blood pH was 7.40 and lactic acid 1.6 mmol/L. A chest x-ray showed no abnormality. Ultrasonography of the kidneys showed normal kidneys measuring 10.9 cm (right) and 9.6 cm (left) with an absence of hydronephrosis.

He was started on an infusion of sodium bicarbonate, and both his HIV and HCV medications were temporarily discontinued. He was nonoliguric throughout his hospital stay. His serum creatinine improved to 1.91 mg/dL on hospital day 6. Features of proximal renal tubular acidosis, including elevated fractional excretion of phosphate (40%) and persistently low serum bicarbonate, were observed. He was transitioned to oral sodium bicarbonate and started on DTG/ABC/3TC, and his HCV therapy was changed to sofosbuvir-daclatasvir (SOF-DAC) given concern for reduced ledipasvir absorption in the setting of increased gastric pH from the sodium bicarbonate. Twelve weeks after hospital discharge, his creatinine was 1.32 mg/dL, and his serum bicarbonate and electrolytes were within normal limits. His HIV viral load decreased to 171 copies/mL, and he achieved an undetectable HCV viral load at the end of therapy but has since been lost to follow-up.

DISCUSSION

We present a case of AKI in a patient on tenofovir alafenamide and cobicistat worsened by the initiation of SOF/LED. This patient likely had previously undiagnosed chronic kidney disease, with CrCl at antiretroviral therapy (ART) initiation of 50 mL/min, which is likely an overestimate in the setting of his advanced liver disease. His creatinine worsened after initiating EVG/c/FTC/TAF. He then presented with AKI and nonanion gap metabolic acidosis 1 month after initiation of SOF/LED. Ledipasvir is not itself nephrotoxic, but it leads to increased levels of TDF in healthy volunteers [6]. This effect was demonstrated in a case report of AKI precipitated by the addition of SOF-LED to a patient's stable HIV regimen of TDF-emtricitabine-efavirenz [11]. In that case, the patient's AKI resolved with discontinuation of TDF and transition to an alternative ART regimen.

Cobicistat inhibits CYP-mediated metabolism of elvitegravir (EVG), leading to increased peak levels and half-life. Cobicistat also increases levels of ledipasvir by a similar mechanism [6, 12]. Thus, when cobicistat, ledipasvir, and TDF are taken together, a double boosting of TDF levels can be expected. The University of Liverpool drug interaction website does not note an interaction between LED and EVG/c/FTC/TAF, which implies that it is a safer alternative than LED and EVG/c/FTC/TDF. Michal and colleagues showed no increased rate of AKI in patients taking TDF vs non-TDF regimens in a real-world cohort of HIV/HCV-infected patients receiving LED/SOF; however, only 1 patient was also taking cobicistat [13].

To date, there are few pharmacologic or empirical data on the expected interaction of SOF/LED and EVG/c/FTC/TAF. This patient had many established risk factors for TDF-related renal toxicity, including age >65 years, impaired baseline renal function, use of other renally cleared medications, and low body mass index [14]. As his creatinine decreased during the hospitalization, signs of proximal tubule injury, a hallmark of

TDF-related renal injury, became apparent. This clinical syndrome is consistent with tenofovir-induced kidney injury, and a biologically plausible mechanism exists with the aforementioned drug interactions. His renal function improved with discontinuation of his HIV and HCV medications, along with administration of sodium bicarbonate. Other potential contributors to his AKI include his diuretics and angiotensin-converting enzyme inhibitor; however, he had no recent dose changes, presented normotensive without tachycardia, and had no evidence of hypovolemia on physical examination. Alternative causes of AKI including sepsis, hepatorenal syndrome, and ingested nephrotoxins are less likely based on his clinical presentation.

Novick and colleagues published a report of a patient with HIV/HCV on an HIV regimen containing both TAF and cobicistat who developed AKI [15]. Renal biopsy showed mitrochondrial abnormalities consistent with the histologic pattern of tenofovir-induced nephrotoxicity. This patient's AKI resolved with discontinuation of TAF but required hemodialysis before improvement. In contrast to our case, the patient was not receiving LED.

Although initial studies of TAF indicate a statistically significant decrease in renal impact compared with TDF, this patient would have been excluded from clinical trials based on his HCV status, baseline CrCl, and his prior ART experience [9]. As TAF becomes ubiquitous in the landscape of treatment for HIV and hepatitis B virus, it is important to note that "less nephrotoxic" does not necessarily mean "not nephrotoxic" and that caution should be taken in using the combination of SOF/LED and EVG/c/FTC/TAF in patients with baseline CKD, low body mass index, older age, and concomitant renally excreted medications.

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