Supplemental Table 1. Univariate and multivariable logistic regression model predicting rise in creatinine >= 0.3mg/dL during treatment

	Univariate Model		Multivariable Model 1		Multivariable Model 2	
Baseline Predictors of significant creatinine rise	Odds Ratio (95%CI)	P Value	Odds Ratio (95%CI)	P Value	Odds Ratio (95%CI)	P Value
Age, per 10 years	1.16 (0.66 - 2.0)	0.51	0.73 (0.37-1.45)	0.37		
Sex (male vs. female)	0.83 (0.28-2.5)	0.74	1.47 (0.42 - 5.2)	0.55		
Race (white vs. non-white)	0.89 (0.34 - 2.3)	0.81	0.89 (0.29-2.7)	0.83		
Diabetes (versus non-diabetic)	2.3 (0.88 - 6.0)	0.087	3.13 (1.0- 9.8)	0.051	2.9 (0.97 - 9.2)	0.055
Cirrhosis (versus non-cirrhotic)	2.14 (0.82 - 5.5)	0.12	1.58 (0.52 - 4.7)	0.41	1.5 (0.51 - 4.5)	0.46
Cryoglobulinemia	3.38 (0.97-12)	0.055	3.76 (0.82 - 17)	0.088	3.75 (0.85 - 16)	0.079
Ribavirin Use	0.70 (0.26 - 1.9)	0.47				
Prior transplant	0.41 (0.14 - 1.2)	0.11	0.59 (0.16 - 2.2)	0.43	0.66 (.19 - 2.3)	0.51
Hypertension	0.50 (-1.1 - 2.1)	0.54				
ACE or ARB use	1.3 (0.49 - 3.4)	0.59				
Baseline eGFR, per 10mL/min decrease in eGFR	1.28 (0.97 - 1.7)	0.079	1.39 (1.01 - 1.9)	0.043	1.29 (0.98-1.7)	0.067

Model 1 includes demographics and any predictor with P value < 0.2 in the univariate model. Model 2 includes only those variables with P Values < 0.2 in the univariate model.
Abbreviations: CI = confidence interval, ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate.

Supplemental Table 2. Summary of cases where creatinine rose 1.5 times baseline during therapy with sofosbuvir-based direct-acting antivirals

Demographics	Comorbidities	Regimen	Cured	Serum Creatinine (mg/dL)			Summary of AKI event
				BL	On-Tx	Post-tx Follow-up	
				Ave	Peak	First 6 months	
55 year old Black Male	HCV genotype 1b, HTN, DM, Cirrhosis	Sofosbuvir/Simprevir x 12 weeks	NO	1.4	3.6	X	Admitted to ICU with GI bleeding and AKI. SCr improved to baseline (1.3mg/dL) with hydration. Discharged, but died 1 week later; autopsy showed AMI.
50 year old White male	HCV genotype 2a, HTN, DM, decompensated cirrhosis	Sofosbuvir/Ribavirin x 12 weeks	NO	0.7	1.1	0.9	Admitted to ICU with N/V, AMS, hypotension and AKI 4 days after starting sofosbuvir/ribavirin. Given IVF and creatinine improved to 0.7mg/dL prior to discharge
60 year old White Male	HCV genotype 3, HTN	Sofosbuvir/Ribavirin x 24 weeks	NO	0.6	1.1	0.5	Asymptomatic SCr rise noted wk 8 of therapy, normalized to baseline on repeat (wk 12) without intervention.
80 year old Hispanic Male	HCV genotype 1 , HTN, DM, Cirrhosis	Sofosbuvir/Simprevir x 12 weeks	YES	1.1	1.7	1.1	Asymptomatic elevated SCr at end of therapy, normalized to baseline by SVR4 without intervention.
55 year old White Male	HCV genotype 1a, HTN	Sofosbuvir/Simprevir x 12 weeks	YES	1.1	2.5	1.2	Asymptomatic SCr rise noted wk 8 of therapy, normalized to baseline on repeat (wk 12) without intervention.
65 year old White Male	HCV genotype 1a, prior liver transplant	Sofosbuvir/Simprevir x 12 weeks	NO	1.7	3.4	X	Admitted due to AMS, fever, jaundice. Developed septic shock, ICH, died during hospitalization.
65 year old White Male	HCV genotype 2b, HTN, DM	Sofosbuvir/Rribavirin x 12 weeks	YES	1.4	2.9	1.4	Admitted with AKI due to obstructing nephrolithiasis, and hemolysis due to ribavirin. SCr improved with RBC transfusion, IVF and ureteral stent placement.

*Age Rounded to the nearest 5 years to maintain anonymity. Abbreviations: BL = baseline, Ave = average, HCV = hepatitis C virus, HTN = hypertension, DM = diabetes mellitus, , ICU = intensive care unit, GI = gastrointestinal, AKI = acute kidney injury, SCr = serum creatinine AMI = acute myocardial infarction, wk = week, SVR4 = sustained virological response at 4 weeks, ICH = intracranial hemorrhage, RBC = red blood cell.

Supplemental Table 3. Serious Adverse Events

Age+/ race/ gender	Cirr-hosis	Treatment/ Planned Duration	HIV	Prior txplnt	Baseline serum creatinine	BL eGFR	Description	Early DC	Sustained Virologic Response	Level of Care
60/Wh/M	N	SOF+ SIM + RBV 12 weeks	Y	Liver	0.9	> 60	Presented to ED week 7 of DAA therapy with itching inside of the mouth, tongue and neck swelling, redness of face and palms. Diagnosed with angioedema attributed to lisinopril	No	Y	ED
55/Bl/M	Y	SOF + SIM 12 weeks	N	N	1.4	> 60	Presented to ED week 1 of DAA therapy with syncope, coffee-ground emesis and melena. Found to have hyperkalemia 7.8mEq/L, AKI, hypotension. Admitted to ICU with UGIB and shock requiring vasopressor support. Transferred to general medicine floor on day 2, and discharged to home 2 days later. Died of sudden cardiac death 3 days after discharge.	Died	N	Hosp/ICU
50/Wh/M	N	SOF + RBV 12 weeks	N	N	0.7	> 60	Presented to ED 4 days after initiating DAA therapy with AMS, nausea, vomiting, dizziness. Hyperammonemic and in shock with SBPs in the 60s requiring ICU stay and vasopressors. DAAs were discontinued upon admission. Transferred to general medicine floor 2 days after admission. MS cleared with lactulose. Discharged to home 4 days later.	Yes Day 5	N	Hosp/ICU
55/Bl/F	Y	SOF + LDV 12 weeks	N	N	1.1	> 60	Three ED visits for abdominal pain, then admitted to OSH week 6 of DAA therapy with hyperglycemia and decompensated LD, hepatic encephalopathy. Discharged after 5 days with ongoing fluid retention requiring intermittent urgent care visits. Completed treatment.	No	Y	Hosp
65/Bl/F	Y	SOF + RBV 12 weeks	N	N	1.3	52	Presented to ED week 3 of DAA therapy with epistaxis and blood-tinged sputum, Hgb 5.7g/dL, AKI, and potassium 7.6mEq/L with T wave changes on ECG due to hemolytic anemia requiring 2 units PRBCs. DAAs were discontinued upon admission.	Yes Day 18	Y	Hosp
65/Hi/M	Y	SOF + LDV 24 weeks	N	N	1.6	46	Presented to ED week 4 of DAA therapy following unexplained syncope with fall and LOC with intracranial hemorrhage. Admitted to ICU for non-operative management, discharged with short-term home care and recovery	No	Y	Hosp/ICU

60/Hi/M	N	SOF + SIM 12 weeks	N	Kidney, liver	1.5	49	Presented to ED week 7 of DAA therapy after syncope, found to have sinus node dysfunction with HR 32; BP 72/42mmHg, underwent pacemaker implantation. Was on amiodarone.*	No	Y	Hosp
65/Wh/M	Y	SOF + SIM 12 weeks	N	Liver	1.7	41	Presented to ED on day 7 of DAA therapy with elevated bilirubin (18.3mg/dL) and abnormal LFTs. Admitted for 5 days. Returned to ED 2 days later with jaundice, fever, AMS, and AKI. Hospitalized for 68 days in ICU, and died.	Died	N	Hosp/ICU
80/Wh/M	Y	SOF + SIM 12 weeks	N	N	1.6	40	Presented to ED week 4 of therapy with recurrent SBO and PNA. Admitted and discharged after 5 days. Experienced ongoing confusion, which had begun one month prior to initiation of DAAs with an increase in antidepressant dose. No evidence for HE. Week 8 he fell down the stairs. DAAs were DC'd for worsening confusion and cognitive decline.	Yes Week 8	Y	Hosp
55/Wh/F	N	SOF + RBV 24 weeks	N	Liver	1.8	31	Presented to ED one week after completing DAA therapy, with progressive CKD, hospitalized, underwent kidney biopsy showing lupus nephritis. Improved with steroids and mycophenolate mofetil but HCV relapsed**	No	N	Hosp
55/Wh/M	N	SOF + RBV 12 weeks	N	Liver	1.5	52	Developed severe anemia week 4 of therapy (Hgb 6g/dL) requiring 2 unit blood transfusion and ESA initiation	No	Y	Outpatient
75/Wh/M	N	SOF + RBV 24 weeks	N	N	1.3	52	Presented to ED week 13 of DAA therapy due to syncope after experiencing persistent dizziness and nausea	No	Y	ED
65/Wh/M	N	SOF + RBV 24 weeks	N	Liver	1.1	> 60	Presented to ED week 2 of DAA therapy with n/v and weakness. Developed CP and ECG changes in the ED. Admitted to the hospital and diagnosed with demand NSTEMI when stress test showed mild ischemia near a prior scar.	Yes Week 2	N	Hosp
70/Wh/M	Y	SOF + LDV 24 weeks	N	N	2.0	34	Admitted four times during therapy: During week 5 and week 13 of DAA therapy he complained of fall and SOB and was diagnosed with NSTEMI that was medically managed. During week 20 and 23 of DAA therapy he complained of SOB was diagnosed with CHF exacerbation.	No	Y	Hosp
65/Wh/M	N	SOF + RBV 12 weeks	N	N	1.4	53	Presented to ED week 4 of treatment with kidney stone, AKI, hemolytic anemia. Treated with 1 unit blood transfusion, ESA, and ureteral stent placed and AKI resolved.	No	Y	Hosp

65/Wh/F	N	SOF + RBV 12 weeks	N	N	1.1	55	Presented to ED on day 11 of treatment with CP and mildly elevated cardiac enzymes. Hospitalized briefly following cardiac catheterization and stent placement.	No	Y	Hosp
60/W/M	Y	SOF + RBV 24 weeks	N	Liver	1.3	> 60	Presented to ED week 6 of therapy with diplopia and radiating upper back pain. Admitted for 2 days for neurologic work-up. Brain MRI and CT were unrevealing. Diplopia improved with RBV dose decrease and completely resolved after completing DAAs.	No	Y	Hosp

+ Age rounded to the nearest 5 years to maintain anonymity

Abbreviations: txplnt, transplant; HIV, Human Immunodeficiency Virus; BL, baseline; eGFR, estimated glomerular filtration rate; DC, discontinuation; Wh, white; M, male; N, no; SOF, sofosbuvir; SIM, simeprevir; RBV, ribavirin; Y, yes; ED, emergency department; DAA, direct-acting antiviral; Bl, black; ICU, intensive care unit; UGIB, upper gastrointestinal bleed; Hosp, hospitalized; AMS, altered mental status; MS, mental status; F, female; LDV, ledipasvir; OSH, outside hospital; LD, liver disease; SOB, shortness of breath; Hgb, hemoglobin; ECG, electrocardiogram; PRBCs, packed red blood cells; Hi, Hispanic; LOC, loss of consciousness; HR, heart rate; BP, blood pressure; LFTs, liver function tests; AKI, acute kidney injury; SBO, small bowel obstruction; PNA, pneumonia; HE, hepatic encephalopathy; CKD, chronic kidney disease; HCV, hepatitis C virus; ESA, erythropoietin stimulating agent; GI, gastrointestinal; URI, upper respiratory tract infection; UTI, urinary tract infection; NSTEMI, non-ST segment elevation myocardial infarction; CHF, congestive heart failure; CP, chest pain; MRI, magnetic resonance imaging; CT, computed tomography.

* Patient initiated combination SOF/SIM therapy Prior to FDA Black box warning regarding risk of coadministration with amiodarone.

** Case first reported Sise et al. Use of Sofosbuvir-Based Direct-Acting Antiviral Therapy for Hepatitis C Viral Infection in Patients with Severe Renal Insufficiency. Infect Dis (Lond). 2015; 47(12): 924–929.

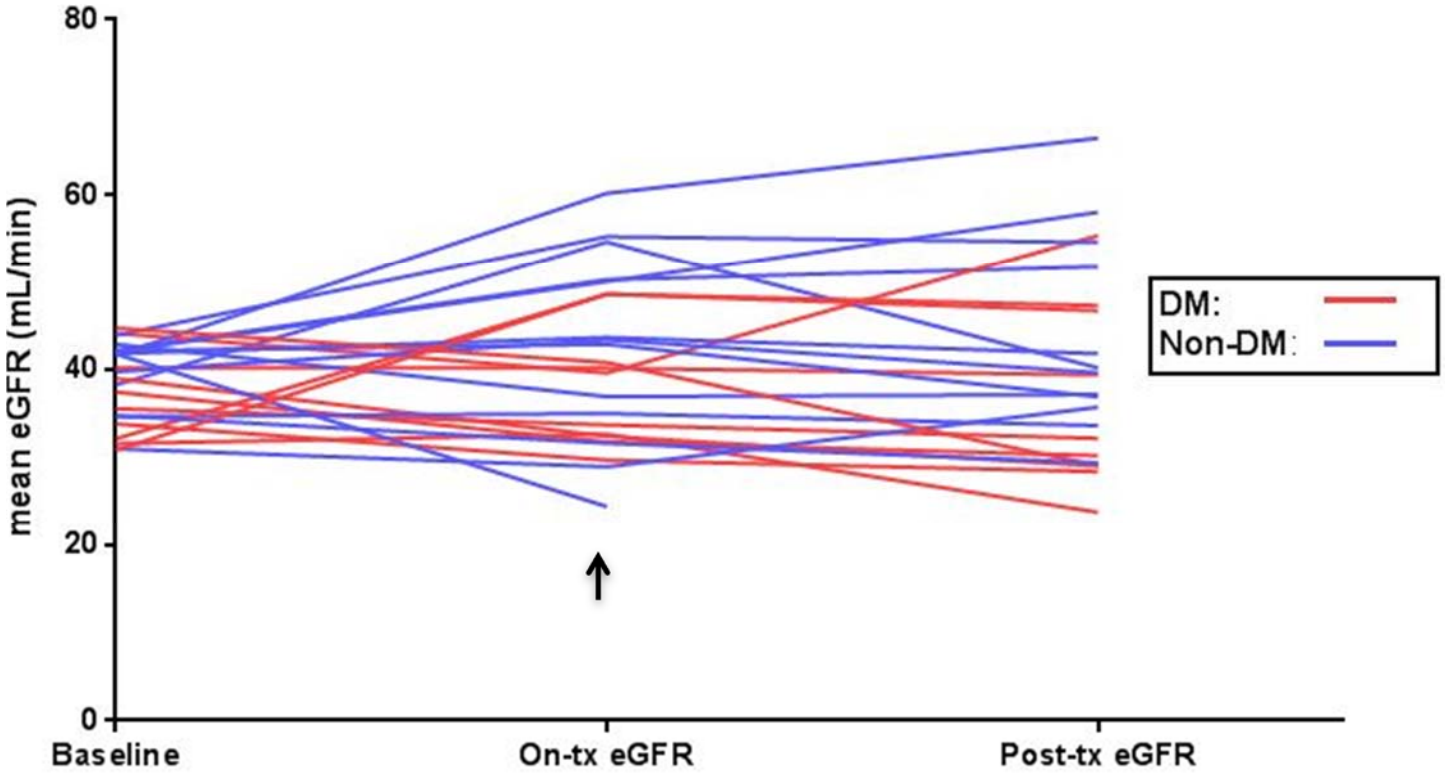
Note: Estimated GFR was calculated with the CKD-EPI equation(21)

Supplemental Table 4. Univariate and multivariable logistic regression model predicting SAEs during treatment

	Univariate Model		Multivariable Model	
Baseline Predictors of SAE	Odds Ratio (95%CI)	P Value	Odds Ratio (95%CI)	P Value
Age, per 10 years	1.05 (0.55 - 2.0)	0.89	0.95 (0.42-2.2)	0.90
Sex (male vs. female)	1.18 (0.30-4.6)	0.81	1.45 (0.29 - 7.4)	0.65
Race (white vs. non-white)	1.07 (0.34 - 3.4)	0.90	0.62 (0.16-2.4)	0.49
Diabetes (versus non-diabetic)	2.4 (0.74 - 7.5)	0.14	4.5 (1.2- 18)	0.028
Cirrhosis (versus non-cirrhotic)	1.5 (0.51 - 4.7)	0.44		
Cryoglobulinemia	0.45 (0.05 - 3.8)	0.47		
Ribavirin Use	2.3 (0.80 - 6.4)	0.12	3.5 (0.96 - 13)	0.056
Prior transplant	2.0 (0.66 - 6.2)	0.21	2.5 (0.66 - 9.3)	0.18
Hypertension	2.1 (0.26 - 17.9)	0.48		
ACE or ARB use	1.2 (0.39 - 3.9)	0.73		
Treatment length (24 weeks vs. 12 weeks)	2.95 (0.86 - 10.2)	0.085	2.0 (0.46 - 8.4)	0.35
Baseline eGFR, per 10mL/min decline	1.18 (0.86 - 1.6)	0.29	1.31 (0.88 - 1.9)	0.17

Supplemental Table 4. The multivariable model includes demographics and any predictor with P value < 0.3 in the univariate model. Abbreviations: SAEs = serious adverse events CI = confidence interval, ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate.

Supplemental Figure 1. Mean eGFR values at baseline, on-treatment (on-tx) and post-treatment (post-tx) in patients with baseline eGFR < 45mL/min/1.73m^2



Supplemental Figure 1. Each line corresponds to an individual patient's values. The arrow indicates one patient who experienced AKI in the context of decompensated cirrhosis and died during the hospitalization.