Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. DOI: 10.1056/NEJMoa1501315

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Renal Monitoring

Renal monitoring included serum creatinine, potassium, phosphate, bicarbonate, uric acid, urine beta-2 microglobulin, urine retinol binding protein, and urinalysis.

Although there was no clinically relevant interaction with atazanavir/ritonavir or darunavir/ritonavir alone and ledipasvir-sofosbuvir in healthy volunteer studies, we anticipated the potential for additional increase of tenofovir exposure in patients taking these drug combinations. Since drug interaction studies were not complete at the time of study initiation, antiretroviral regimens containing ritonavir-boosted HIV-1 protease inhibitors and cobicistat were not allowed.

Pharmacokinetic Analyses

Fifty-six patients enrolled in the pharmacokinetic substudy, for which intensive serial pharmacokinetic samples were collected over 24 hours between the week 2 and week 8 on-treatment visits. The population pharmacokinetic parameters for ledipasvir, sofosbuvir, GS-331007, and tenofovir were computed for all patients from concentration data from intensive and/or sparse samples using the previously established population pharmacokinetic models.*

*Kirby B, et al. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV-infected adult subjects. AASLD 2013.

Kirby B, et al. Population pharmacokinetics analysis of ledipasvir (GS-5885) in healthy and hepatitis C virus-infected subjects. IWCPHHT, 2014.

Table S1. Reasons for screen failure

Screened Patients	429
Patients Rescreened	1
Screen Failure Patients	94/429 (21.9%)
Screen Failure Patients Who Did Not Meet Eligibility Criteria	91/94 (96.8%)
Inclusion Criterion 13: Within specified laboratory ranges	49/91 (53.8%)
Exclusion Criterion 6: Clinically-relevant alcohol or drug abuse	20/91 (22.0%)
Inclusion Criterion 5: HCV GT1, 4	10/91 (11.0%)
Inclusion Criterion 8: HIV RNA <50 copies/mL, on protocol-approved ARV	5/91 (5.5%)
Inclusion Criterion 11: Liver imaging for HCC in patients with cirrhosis	5/91 (5.5%)
Exclusion Criterion 2: HBV infection	4/91 (4.4%)
Inclusion Criterion 16: Good general health	3/91 (3.3%)
Inclusion Criterion 17: Able to comply with study requirements	3/91 (3.3%)
Exclusion Criterion 1: Clinically-significant illness other than HCV/HIV	3/91 (3.3%)
Inclusion Criterion 4: HCV RNA >= 10^4 IU/mL at screening	2/91 (2.2%)
Inclusion Criterion 10: Cirrhosis status determination	2/91 (2.2%)
Inclusion Criterion 1: Signed ICF	1/91 (1.1%)
Inclusion Criterion 3: Body Mass Index(BMI) > =18 kg/m2	1/91 (1.1%)
Inclusion Criterion 9: Chronic HCV	1/91 (1.1%)
Screen Failure Patients Who Met Eligibility Criteria	3/94 (3.2%)
Reasons for Non-Enrollment of Patients Who Met Eligibility Criterion	
Withdrew Consent	2/3 (66.7%)
Lost to Follow-Up	1/3 (33.3%)

Figure S1. Patient disposition

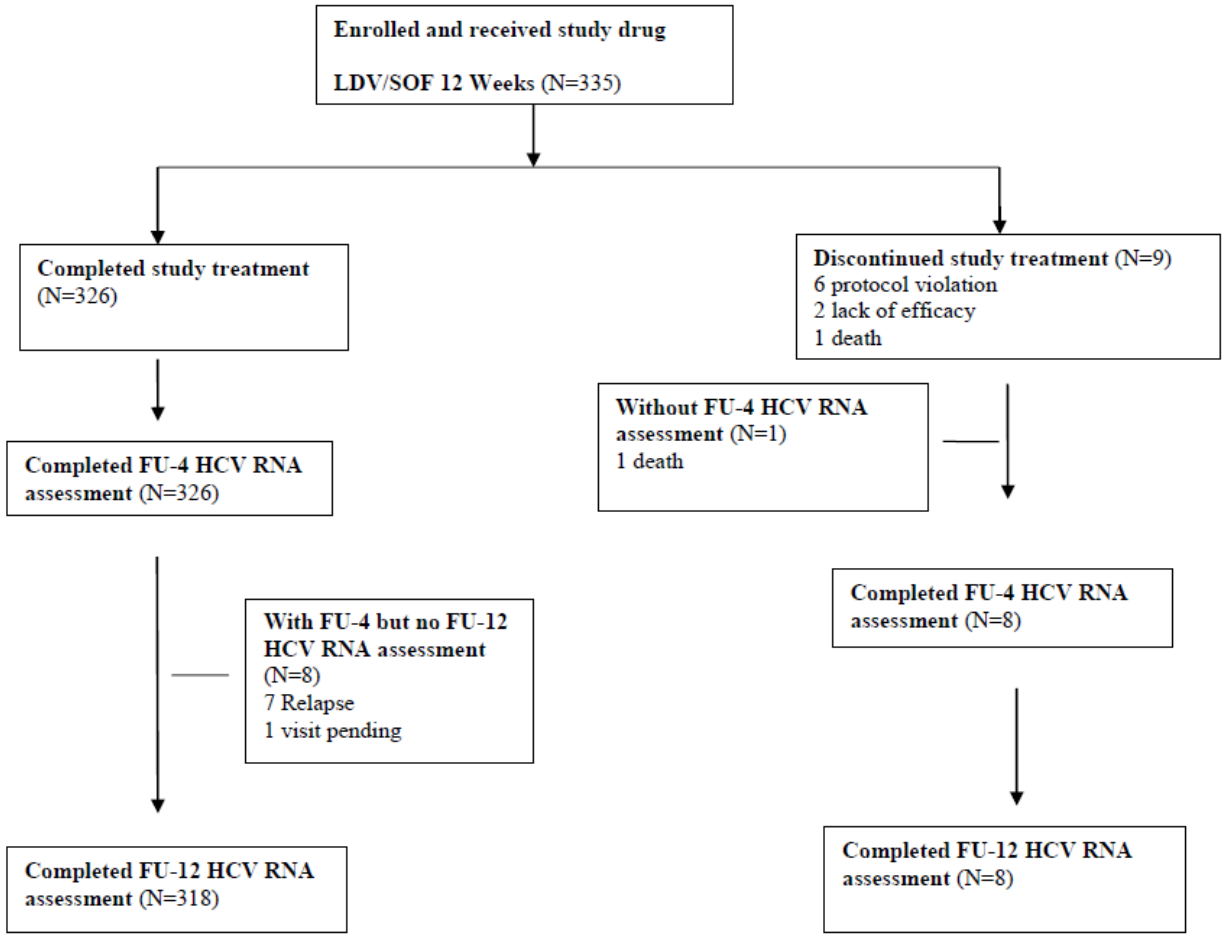


Table S2. Prior HCV treatment and response

	LDV-SOF (N=335)
Treatment-naïve	150 (49%)
Interferon eligible	132 (88%)
Interferon ineligible	18 (12%)
Treatment-experienced	185 (55%)
DAA+PEG+RBV	53 (29%)
Treatment intolerant	6 (11%)
Relapser/breakthrough	18 (34%)
Non-responder	29 (55%)
PEG+RBV	113 (61%)
Treatment intolerant	14 (12%)
Relapser/breakthrough	41 (36%)
Non-responder	58 (51%)
Null responder	40 (69%)
Partial responder or unknown	18 (31%)
DAA+RBV	14 (8%)
Relapser/breakthrough	14 (100%)
Other	5 (3%)
Treatment intolerant	1 (20%)
Non-responder	3 (60%)
Partial responder or unknown	1 (20%)
Undetermined	1 (20%)

Table S3. SVR12 by subgroup

	LDV/SOF+ EFV+FTC+TDF (N=160)	LDV/SOF+ RAL+FTC+TDF (N=146)	LDV/SOF+ RPV+FTC+TDF (N=29)	LDV/SOF Total (N=335)
Overall	151/160 (94.4%)	143/146 (97.9%)	28/29 (96.6%)	322/335 (96.1%)
95% CI	89.6% to 97.4%	94.1% to 99.6%	82.2% to 99.9%	93.5% to 97.9%
Age at Baseline (Years)				
<65	146/154 (94.8%)	134/137 (97.8%)	28/29 (96.6%)	308/320 (96.3%)
95% CI	90.0% to 97.7%	93.7% to 99.5%	82.2% to 99.9%	93.5% to 98.0%
≥65	5/6 (83.3%)	9/9 (100.0%)	0/0	14/15 (93.3%)
95% CI	35.9% to 99.6%	66.4% to 100.0%	24/24 (100.0%)	68.1% to 99.8%
Sex at Birth				
Male	120/128 (93.8%)	122/124 (98.4%)	85.8% to 100.0%	266/276 (96.4%)
95% CI	88.1% to 97.3%	94.3% to 99.8%	4/5 (80.0%)	93.4% to 98.2%
Female	31/32 (96.9%)	21/22 (95.5%)	28.4% to 99.5%	56/59 (94.9%)
95% CI	83.8% to 99.9%	77.2% to 99.9%	9/10 (90.0%)	85.9% to 98.9%
Race				
Black	52/61 (85.2%)	42/44 (95.5%)	55.5% to 99.7%	103/115 (89.6%)
95% CI	73.8% to 93.0%	84.5% to 99.4%	18/18 (100.0%)	82.5% to 94.5%
Non-Black	97/97 (100.0%)	101/102 (99.0%)	81.5% to 100.0%	216/217 (99.5%)
95% CI	96.3% to 100.0%	94.7% to 100.0%	28/29 (96.6%)	97.5% to 100.0%
HCV Genotype				
1a	101/108 (93.5%)	114/117 (97.4%)	25/25 (100.0%)	240/250 (96.0%)
95% CI	87.1% to 97.4%	92.7% to 99.5%	86.3% to 100.0%	92.8% to 98.1%
1b	43/45 (95.6%)	28/28 (100.0%)	3/4 (75.0%)	74/77 (96.1%)
95% CI	84.9% to 99.5%	87.7% to 100.0%	19.4% to 99.4%	89.0% to 99.2%
4	7/7 (100.0%)	1/1 (100.0%)	0/0	8/8 (100.0%)
95% CI	59.0% to 100.0%	2.5% to 100.0%		63.1% to 100.0%
Cirrhosis				
No	130/137 (94.9%)	104/105 (99.0%)	25/26 (96.2%)	259/268 (96.6%)
95% CI	89.8% to 97.9%	94.8% to 100.0%	80.4% to 99.9%	93.7% to 98.5%
Yes	21/23 (91.3%)	39/41 (95.1%)	3/3 (100.0%)	63/67 (94.0%)
95% CI	72.0% to 98.9%	83.5% to 99.4%	29.2% to 100.0%	85.4% to 98.3%
Prior HCV Treatment Experience				
Naive	69/72 (95.8%)	59/62 (95.2%)	15/16 (93.8%)	143/150 (95.3%)
95% CI	88.3% to 99.1%	86.5% to 99.0%	69.8% to 99.8%	90.6% to 98.1%
Experienced	82/88 (93.2%)	84/84 (100.0%)	13/13 (100.0%)	179/185 (96.8%)
95% CI	85.7% to 97.5%	95.7% to 100.0%	75.3% to 100.0%	93.1% to 98.8%
Baseline HCV RNA (IU/mL)				
<800,000	16/16 (100.0%)	19/19 (100.0%)	1/1 (100.0%)	36/36 (100.0%)
95% CI	79.4% to 100.0%	82.4% to 100.0%	2.5% to 100.0%	90.3% to 100.0%
≥800,000	135/144 (93.8%)	124/127 (97.6%)	27/28 (96.4%)	286/299 (95.7%)
95% CI	88.5% to 97.1%	93.3% to 99.5%	81.7% to 99.9%	92.7% to 97.7%

Table S3. SVR12 by subgroup (continued)

Baseline BMI (kg/m2)				
<30	120/127 (94.5%)	108/109 (99.1%)	22/23 (95.7%)	250/259 (96.5%)
95% CI	89.0% to 97.8%	95.0% to 100.0%	78.1% to 99.9%	93.5% to 98.4%
≥30	31/33 (93.9%)	35/37 (94.6%)	6/6 (100.0%)	72/76 (94.7%)
95% CI	79.8% to 99.3%	81.8% to 99.3%	54.1% to 100.0%	87.1% to 98.5%
Baseline ALT				
≤1.5 x ULN	95/98 (96.9%)	79/81 (97.5%)	18/19 (94.7%)	192/198 (97.0%)
95% CI	91.3% to 99.4%	91.4% to 99.7%	74.0% to 99.9%	93.5% to 98.9%
>1.5 x ULN	56/62 (90.3%)	64/65 (98.5%)	10/10 (100.0%)	130/137 (94.9%)
95% CI	80.1% to 96.4%	91.7% to 100.0%	69.2% to 100.0%	89.8% to 97.9%
IL28B				
CC	37/37 (100.0%)	39/40 (97.5%)	4/4 (100.0%)	80/81 (98.8%)
95% CI	90.5% to 100.0%	86.8% to 99.9%	39.8% to 100.0%	93.3% to 100.0%
Non-CC	114/123 (92.7%)	104/106 (98.1%)	24/25 (96.0%)	242/254 (95.3%)
95% CI	86.6% to 96.6%	93.4% to 99.8%	79.6% to 99.9%	91.9% to 97.5%
CT	79/82 (96.3%)	83/84 (98.8%)	19/19 (100.0%)	181/185 (97.8%)
95% CI	89.7% to 99.2%	93.5% to 100.0%	82.4% to 100.0%	94.6% to 99.4%
TT	35/41 (85.4%)	21/22 (95.5%)	5/6 (83.3%)	61/69 (88.4%)
95% CI	70.8% to 94.4%	77.2% to 99.9%	35.9% to 99.6%	78.4% to 94.9%
Baseline CD4 Counts (cells/μL)				
<350	13/14 (92.9%)	18/19 (94.7%)	4/4 (100.0%)	35/37 (94.6%)
95% CI	66.1% to 99.8%	74.0% to 99.9%	39.8% to 100.0%	81.8% to 99.3%
≥350	138/146 (94.5%)	125/127 (98.4%)	24/25 (96.0%)	287/298 (96.3%)
95% CI	89.5% to 97.6%	94.4% to 99.8%	79.6% to 99.9%	93.5% to 98.1%
Prior HCV Treatment Experience for Cirrhotic Subjects				
Naive	5/6 (83.3%)	11/13 (84.6%)	1/1 (100.0%)	17/20 (85.0%)
95% CI	35.9% to 99.6%	54.6% to 98.1%	2.5% to 100.0%	62.1% to 96.8%
Experienced	16/17 (94.1%)	28/28 (100.0%)	2/2 (100.0%)	46/47 (97.9%)
95% CI	71.3% to 99.9%	87.7% to 100.0%	15.8% to 100.0%	88.7% to 99.9%
Most Recent HCV Treatment Regimen				
DAA+PEG+RBV	18/19 (94.7%)	32/32 (100.0%)	2/2 (100.0%)	52/53 (98.1%)
95% CI	74.0% to 99.9%	89.1% to 100.0%	15.8% to 100.0%	89.9% to 100.0%
PEG+RBV	52/57 (91.2%)	45/45 (100.0%)	11/11 (100.0%)	108/113 (95.6%)
95% CI	80.7% to 97.1%	92.1% to 100.0%	71.5% to 100.0%	90.0% to 98.5%
DAA+RBV	11/11 (100.0%)	3/3 (100.0%)	0/0	14/14 (100.0%)
95% CI	71.5% to 100.0%	29.2% to 100.0%		76.8% to 100.0%
Other	1/1 (100.0%)	4/4 (100.0%)	0/0	5/5 (100.0%)
95% CI	2.5% to 100.0%	39.8% to 100.0%		47.8% to 100.0%

Figure S2. Rates of Sustained Virologic Response by Subgroup and Baseline Factors

The position of the square indicates the rate of virologic response 12 weeks after the end of treatment in the subgroup. Horizontal lines indicate 95% confidence intervals. The vertical line represents the overall rate of sustained virologic response.

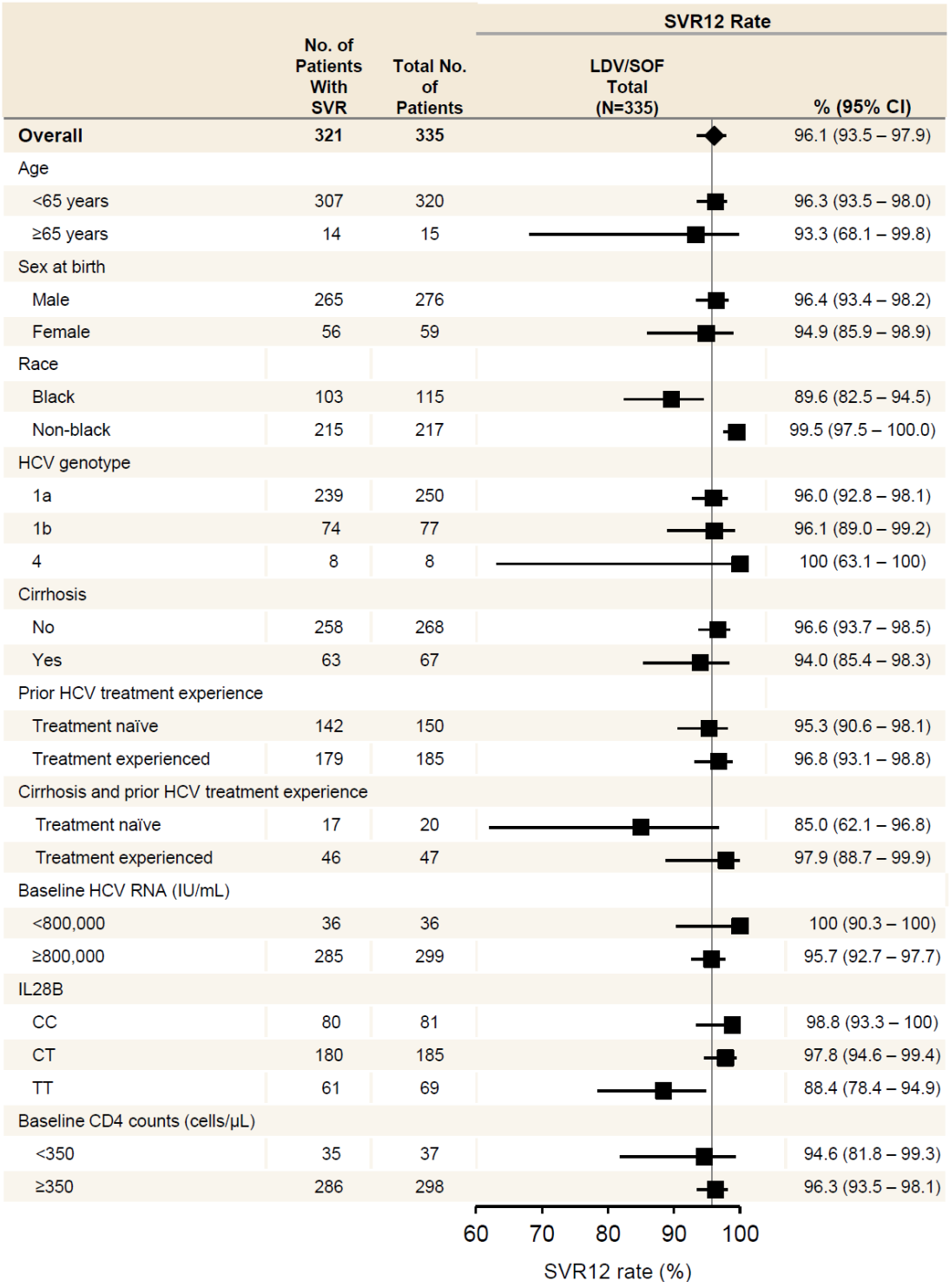


Table S4. Characteristics of patients who did not achieve SVR12

Response	Age	Sex	Race	BMI	Genotype	Baseline CD4 count	Cirrhosis	IL28B	HCV RNA	Timing of VF	Prior HCV treatment	ARV Regimen
Breakthrough/ rebound	60	F	Black	22.5	1b	837	No	TT	6.4	Week 8	N/A	RPV+FTC+TDF
	53	M	Black	23.7	1a	391	No	CT	6.4	Week 6	N/A	EFV+FTC+TDF
Relapse	35	M	Black	24.1	1a	308	No	CT	7.3	FU Week 4	N/A	EFV+FTC+TDF
	58	M	Black	28.2	1a	553	No	TT	7.5	FU Week 4	PEG+RBV	EFV+FTC+TDF
	61	M	Black	22.4	1a	504	Yes	TT	7.0	FU Week 4	N/A	EFV+FTC+TDF
	61	F	Black	26.8	1a	144	Yes	CT	6.4	FU Week 12	PEG+RBV	RAL+FTC+TDF
	51	M	Black	30.0	1a	964	No	TT	6.5	FU Week 4	NS5A+PEG+RBV*	EFV+FTC+TDF
	65	F	Black	24.8	1b	904	Yes	TT	7.0	FU Week 4	N/A	EFV+FTC+TDF
	60	M	Black	32.3	1a	435	No	TT	7.4	FU Week 4	N/A	RAL+FTC+TDF
	63	M	Black	42.7	1a	690	No	TT	7.3	FU Week 12	PEG+RBV	EFV+FTC+TDF
	55	M	Black	32.5	1a	933	No	CT	6.7	FU Week 4	PEG+RBV	EFV+FTC+TDF
	58	M	Black	24.8	1b	2069	No	TT	7.3	FU Week 4	PEG+RBV	EFV+FTC+TDF

*Prohibited prior HCV regimen resulting in an important protocol violation

Table S5. SVR12 by Race and Antiretroviral Regimen

	LDV/SOF+ EFV+FTC+TDF (N=160)	LDV/SOF+ RAL+FTC+TDF (N=146)	LDV/SOF+ RPV+FTC+TDF (n=29)	LDV/SOF Overall (N=335)
Black patients (%)	52/61 (85)	42/44 (95)	9/10 (90)	103/115 (90)
95% CI	74 to 93	85 to 99	56 to >99	83 to 95
Non-black patients (%)	97/97 (100)	100/102 (98)	18/18 (100)	215/217 (99)
95% CI	96 to 100	93 to 99	82 to 100	96 to >99

Exact logistic regression analysis for evaluating associations between baseline characteristics and virologic relapse

Univariate exact logistic regression analysis was performed to assess the relationship between virologic relapse and 15 baseline demographic and clinical factors: (<65 or ≥65 years old), sex, race (black or non-black), ethnicity (Hispanic/Latino or not Hispanic/Latino), HCV genotype (1a vs 4 or 1b vs 4), cirrhosis (yes or no), prior HCV treatment (treatment naive or treatment experienced), baseline HCV RNA viral load (<800,000 IU/mL or ≥800,000 IU/mL), BMI (<30 or ≥30 kg/m^2), baseline ALT (≤ or >1.5 × ULN) IL28B allele (TT or non-TT), CD4 cell count (<200 or 200-349, <200 or 350-500, <200 or >500 cells/μL), ARV (FTC+TDF with EFV or non-EFV) and platelets (<125 or ≥125 × 10^3/μL) and baseline creatinine clearance. Race, IL28B genotype, and ARV were included in the multivariate logistic regression model

Table S6. Univariate Exact Logistic Regression in Assessing Factors Associated with Virologic Relapse

Variable	Odds Ratio	95% Confidence Limit	2-Sided P-Value
Age group (Years): <65	0.409	0.05, 19.13	0.75
Sex: female	1.19	0.12, 6.19	1.000
Race: Black	28.95	4.59, infinity	**<0.001**
Ethnicity: Hispanic or Latino	0.34	0, 2.18	0.3
HCV Genotype: 1a or 4	0.352	0.047, infinity	1.000
HCV Genotype: 1b or 4	0.25	0.019, infinity	1.000
Cirrhosis: Yes	1.17	0.28, 7.84	0.65
Prior HCV Treatment: Treatment Experienced	1.21	0.28, 5.92	1.000
Baseline HCV RNA (IU/mL): <800,000	0.58	0, 3.73	0.63
Baseline BMI (kg/m^2): <30	0.68	0.15, 4.19	0.82
Baseline ALT (U/L): ≤1.5 × ULN	0.46	0.093, 1.97	0.36
IL28B: TT	9.92	2.19, 61.16	**0.0016**
Baseline CD4: <200 or 200-349 cells/μL	0.107	0.001, 9.8	0.41
Baseline CD4: <200 or 350-500 cells/μL	0.058	<0.001, 5.3	0.24
Baseline CD4: <200 or >500 cells/μL	0.094	0.007, 5.5	0.26
Baseline ARV: EFV or Non-EFV	4.54	0.887, 44.51	0.0766
Baseline platelets (×10^3/μL): ≥125	1.95	0.3, infinity	0.55
Baseline CRCL (mL/min) (continuous)	0.999	0.978, 1.02	0.92

Table S7. Multivariate Logistic Regression to Assess Association of Race, IL28B and ARV with Virologic Relapse

Variable	Odds Ratio	95% Confidence Limit	2-Sided P-Value
Race: Black	17.73	2.66, infinity	**0.0012**
IL28B: TT	4.27	0.89, 27.5	0.0751
ARV: EFV	3.26	0.59, 33.63	0.241

Table S8. Serious adverse events

	LDV/SOF+ EFV+FTC+TDF (N=160)	LDV/SOF+ RAL+FTC+TDF (N=146)	LDV/SOF+ RPV+FTC+TDF (n=29)	LDV/SOF Overall (N=335)
Number (%) of Subjects Experiencing Any SAE	4 (2.5%)	3 (2.1%)	1 (3.4%)	8 (2.4%)
Hepatocellular carcinoma	1 (0.6%)	1 (0.7%)	0	2 (0.6%)
Portal vein thrombosis	1 (0.6%)	1 (0.7%)	0	2 (0.6%)
Arthralgia	1 (0.6%)	0	0	1 (0.3%)
Azotaemia	1 (0.6%)	0	0	1 (0.3%)
Clostridium difficile colitis	0	1 (0.7%)	0	1 (0.3%)
Cough	1 (0.6%)	0	0	1 (0.3%)
Diarrhoea	0	0	1 (3.4%)	1 (0.3%)
Ileus	1 (0.6%)	0	0	1 (0.3%)
Peritonitis bacterial	1 (0.6%)	0	0	1 (0.3%)
Respiratory tract infection	0	1 (0.7%)	0	1 (0.3%)
Sepsis	0	1 (0.7%)	0	1 (0.3%)
Substance abuse	1 (0.6%)	0	0	1 (0.3%)

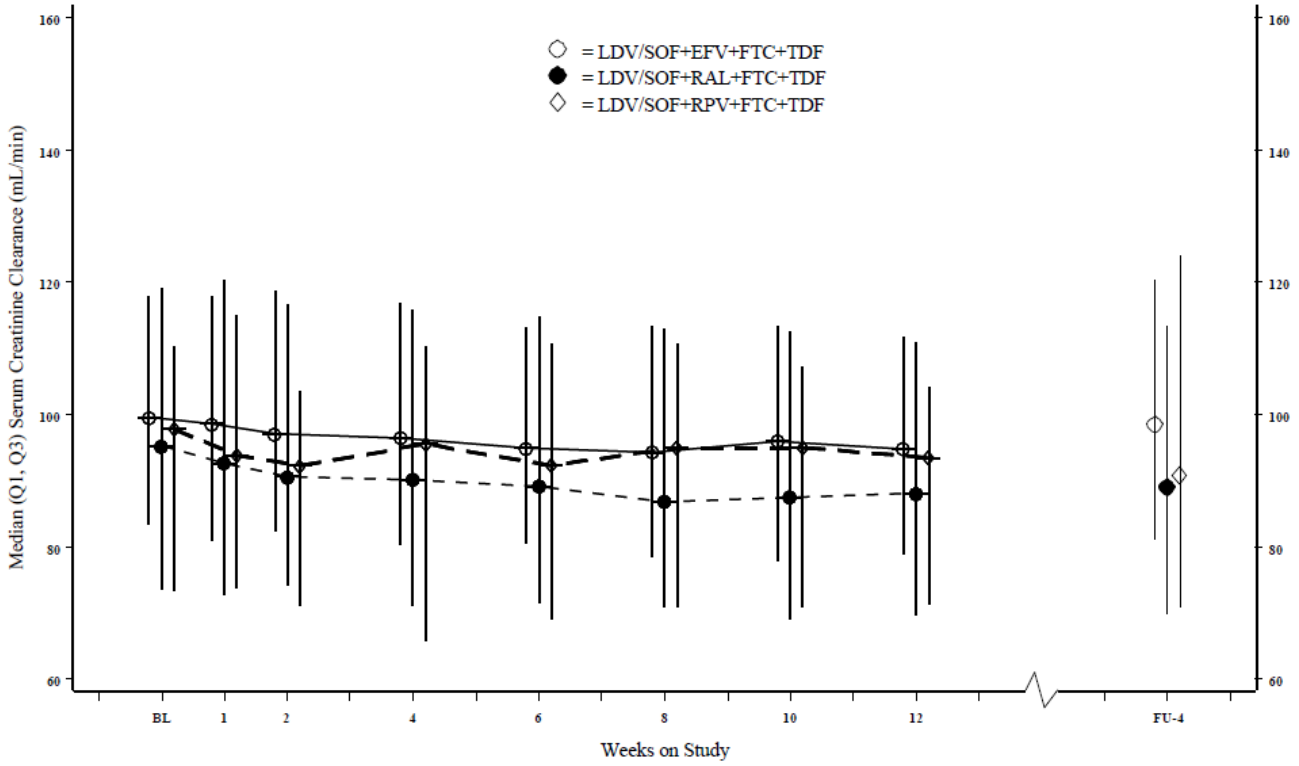
Table S9. Grade 3 and 4 laboratory abnormalities

	LDV/SOF+ EFV+FTC+TDF (N=160)	LDV/SOF+ RAL+FTC+TDF (N=146)	LDV/SOF+ RPV+FTC+TDF (n=29)	LDV/SOF Overall (N=335)
MAXIMUM POSTDOSE TOXICITY GRADE	160	146	29	335
Grade 3	14 (8.8%)	13 (8.9%)	3 (10.3%)	30 (9.0%)
Grade 4	3 (1.9%)	3 (2.1%)	0	6 (1.8%)
HEMATOLOGY				
Hemoglobin	160	146	29	335
Grade 3	1 (0.6%)	0	0	1 (0.3%)
Grade 4	0	0	0	0
Neutrophils	160	146	29	335
Grade 3	1 (0.6%)	0	0	1 (0.3%)
Grade 4	0	0	0	0
Platelets	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
WBC	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
COAGULATION				
APTT	157	144	29	330
Grade 3	0	0	0	0
Grade 4	0	0	0	0
INR	157	144	29	330
Grade 3	0	0	0	0
Grade 4	0	0	0	0
CHEMISTRY				
ALT	160	146	29	335
Grade 3	1 (0.6%)	0	0	1 (0.3%)
Grade 4	0	0	0	0
AST	160	146	29	335
Grade 3	0	1 (0.7%)	0	1 (0.3%)
Grade 4	0	0	0	0
Albumin	160	146	29	335
Grade 3	0	0	0	0

Grade 4	0	0	0	0
Alkaline Phosphatase	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Creatine Kinase (CK)	160	146	29	335
Grade 3	2 (1.3%)	1 (0.7%)	0	3 (0.9%)
Grade 4	1 (0.6%)	1 (0.7%)	0	2 (0.6%)
Creatinine	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Lipase	160	146	29	335
Grade 3	4 (2.5%)	4 (2.7%)	1 (3.4%)	9 (2.7%)
Grade 4	2 (1.3%)	2 (1.4%)	0	4 (1.2%)
Phosphate (Hypophosphatemia)	160	146	29	335
Grade 3	0	1 (0.7%)	0	1 (0.3%)
Grade 4	0	0	0	0
Serum Bicarbonate	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Serum Glucose (Hyperglycemia)	160	146	29	335
Grade 3	0	5 (3.4%)	0	5 (1.5%)
Grade 4	0	0	0	0
Serum Glucose (Hypoglycemia)	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Serum Potassium (Hyperkalemia)	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Serum Potassium (Hypokalemia)	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Serum Sodium (Hypernatremia)	160	146	29	335
Grade 3	0	0	0	2 (0.6%)
Grade 4	0	0	0	0
Serum Sodium (Hyponatremia)	160	146	29	335
Grade 3	0	0	0	2 (0.6%)

Grade 4	0	0	0	0
Total Bilirubin (Hyperbilirubinemia)	160	146	29	335
Grade 3	0	1 (0.7%)	1 (3.4%)	0
Grade 4	0	0	0	0
Uric Acid (Hyperuricemia)	160	146	29	335
Grade 3	2 (1.3%)	0	0	2 (0.6%)
Grade 4	0	0	0	0
Uric Acid (Hypouricemia)	160	146	29	335
Grade 3	0	0	0	2 (0.6%)
Grade 4	0	0	0	0
URINALYSIS				
Hematuria (RBC counts)	57	43	12	112
Grade 3	2 (3.5%)	0	0	2 (1.8%)
Grade 4	0	0	0	0
Urine Blood	160	146	29	335
Grade 3	4 (2.5%)	0	0	4 (1.2%)
Grade 4	0	0	0	0
Urine Glucose (Glycosuria)	160	146	29	335
Grade 3	0	3 (2.1%)	1 (3.4%)	4 (1.2%)
Grade 4	0	0	0	0
Urine Protein (Proteinuria)	160	146	29	335
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Figure S3. Creatinine clearance



LDV/SOF+EFV+FTC+TDF (n=):	160	157	160	159	158	152	156	155	131
LDV/SOF+RAL+FTC+TDF (n=):	146	144	143	146	143	144	143	139	124
LDV/SOF+RPV+FTC+TDF (n=):	29	28	29	29	29	29	28	26	23

Details regarding the four patients who had confirmed treatment-emergent increases of ≥0.4 mg/dL in serum creatinine

One patient required discontinuation of tenofovir disoproxil fumarate during the study period. This patient was a 54 year-old man with diabetes mellitus type 1 since 1965, hypertension and hyperlipidemia. Since 1998, pre-study serum creatinine ranged 1.0-1.3 mg/dL and he had intermittent low level proteinuria and glycosuria. He entered the study on efavirenz/ tenofovir disoproxil fumarate/emtricitabine and developed worsening renal function and a clinical picture suggestive of renal tubular disease (see table below). This patient entered the study with baseline urine retinol binding protein/serum creatinine and urine beta-2 microglobulin/serum creatinine ratios significantly greater than that of the overall study population. Both urine biomarkers increased from baseline at weeks 2 and 4 but showed significant improvement by week 12. Following the switch to efavirenz, raltegravir, and renally dosed emtricitabine, renal function improved and there was some improvement in proteinuria; glucosuria persisted.

Analysis Visit	Urine Glucose	Serum Glucose (mg/dL)	Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Serum Phosphate (mg/dL)	Urine Protein
Baseline	+4 (G3,H)	138 (G1,H)	79.5 (L)	1.18	3.3	+2 (G2,H)
Baseline	+4 (G3,H)	162 (G2,H)	78.8 (L)	1.18	2.6	+1 (G1,H)
Week 1	+4 (G3,H)	107 (H)	72.9 (L)	1.26	2.5	+2 (G2,H)
Week 2	+4 (G3,H)	173 (G2,H)	69.0 (L)	1.33	2.7	+2 (G2,H)
Week 4	+4 (G3,H)	150 (G1,H)	53.4 (L)	1.71 (G1,H)	2.4	+2 (G2,H)
Week 4	+4 (G3,H)	132 (G1,H)		1.88 (G1,H)	2.5	+2 (G2,H)
Week 6	+4 (G3,H)	123 (G1,H)	58.1 (L)	1.60 (G1,H)	2.0 (G1,L)	+2 (G2,H)
Week 8	+4 (G3,H)	107 (H)	64.2 (L)	1.45 (H)	2.3	+1 (G1,H)
Week 10	+4 (G3,H)	166 (G2,H)	65.6 (L)	1.43 (H)	2.8	+1 (G1,H)
Week 12	+3 (G2,H)	189 (G2,H)	68.4 (L)	1.36 (H)	2.8	+1 (G1,H)
FU-4	+4 (G3,H)	231 (G2,H)	63.3 (L)	1.47 (H)	2.4	+1 (G1,H)

One patient who entered the study on efavirenz/tenofovir disoproxil fumarate/emtricitabine with baseline chronic kidney disease and proteinuria developed trace-grade 1 glucosuria with

worsening renal function (see table below). This patient was a 47 year old man with no significant past medical history. His creatinine clearance remained >60 mL/min throughout the study and no changes in treatment for HIV or HCV was required. This patient entered the study with baseline urine retinol binding protein/serum creatinine ratio significantly greater than that of the overall study population and both urine retinol binding protein/serum creatinine and urine beta-2 microglobulin/serum creatinine ratios increased for this subject during the first two weeks of dosing and a peak at week 12; these biomarkers were trending down at the last follow-up visit.

Analysis Visit	Urine Glucose	Serum Glucose (mg/dL)	Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Serum Phosphate (mg/dL)	Urine Protein
Baseline	Normal	78	85.1	1.50 (H)	2.6	+1 (G1,H)
Baseline	Normal	90	88.7	1.42 (H)	3.3	+1 (G1,H)
Week 1	Normal	85	81.1 (L)	1.56 (G1,H)	3.8	+1 (G1,H)
Week 2	Normal	86	82.8 (L)	1.55 (G1,H)	3.2	+2 (G2,H)
Week 4	Normal	94	76.6 (L)	1.65 (G1,H)	2.9	+2 (G2,H)
Week 6	Normal	92	72.7 (L)	1.74 (G1,H)	2.9	+1 (G1,H)
Week 8	Trace (H)	99	76.4 (L)	1.67 (G1,H)	2.7	+1 (G1,H)
Week 10	Trace (H)	91	67.0 (L)	1.88 (G1,H)	2.6	+1 (G1,H)
Week 12	Trace (H)	87	74.1 (L)	1.70 (G1,H)	2.8	+2 (G2,H)
FU-4	Trace (H)	87		1.80 (G1,H)	2.9	+2 (G2,H)

One patient who entered the study on efavirenz/tenofovir disoproxil fumarate/emtricitabine and with baseline chronic kidney disease and had sudden increase in serum creatinine to 2.40 mg/dL at Week 8 (see table below) with coincident elevations in creatine kinase, and urine blood without hematuria. There was no associated glucosuria and there was an isolated increase in proteinuria from 1+ at baseline to 2+ at week 8. The lab abnormalities were consistent with mild rhabdomyolysis in the setting of reported cocaine use. Laboratory abnormalities improved with hydration and no change in study drug. This was felt by the investigator to be unrelated to the study medication.

Analysis Visit	Urine Glucose	Serum Glucose (mg/dL)	Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Serum Phosphate (mg/dL)	Urine Protein
Baseline	Normal	95	65.0 (L)	1.47 (H)	3.9	+1 (G1,H)
Baseline	Normal	92	49.0 (L)	1.77 (G1,H)	3.5	Trace (H)
Week 1	Normal	95	48.9 (L)	1.77 (G1,H)	3.5	+1 (G1,H)
Week 2	Normal	90	49.3 (L)	1.77 (G1,H)	3.1	+1 (G1,H)
Week 4	Normal	82	50.7 (L)	1.73 (G1,H)	3.3	+1 (G1,H)
Week 6	Normal	97	52.3 (L)	1.68 (G1,H)	3.1	+1 (G1,H)
Week 8	Normal	109 (H)	35.7 (L)	2.40 (G2,H)	3.0	+2 (G2,H)
Week 8	Normal	92	39.1 (L)	2.24 (G2,H)	2.7	+1 (G1,H)
Week 10	Normal	91	47.6 (L)	1.80 (G1,H)	2.9	+1 (G1,H)
Week 12	Normal	92	45.4 (L)	1.89 (G1,H)	2.8	+1 (G1,H)
FU-4	Normal	88	49.0 (L)	1.75 (G1,H)	3.4	+1 (G1,H)

One patient who entered the study on raltegravir and tenofovir disoproxil fumarate/emtricitabine had chronic kidney disease and a baseline creatinine clearance of 54.7 mL/min, which decreased to 45.1 mL/min at Week 2 (see table below). He did not develop glucosuria nor worsening of his baseline trace proteinuria. Per the package insert, this patient's tenofovir disoproxil fumarate/emtricitabine was changed to every other day dosing at that time. He was monitored closely during the study and completed without other changes to the ARV regimen or study drug.

Analysis Visit	Urine Glucose	Serum Glucose (mg/dL)	Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Serum Phosphate (mg/dL)	Urine Protein
Baseline	Normal	63 (G1,L)	60.6 (L)	1.09	2.3	Trace (H)
Baseline	Normal	97	54.7 (L)	1.19	3.1	Trace (H)
Week 1	Normal	108 (H)	54.7 (L)	1.19	2.4	Trace (H)
Week 2	Normal	94	49.2 (L)	1.34	3.7	Negative
Week 2		87	45.1 (L)	1.45 (H)	2.3	
Week 4	Normal	67 (L)	46.9 (L)	1.40 (H)	3.3	Trace (H)
Week 6		83	47.8 (L)	1.38 (H)	3.0	
Week 6	Normal	86	47.8 (L)	1.38 (H)	3.0	Negative
Week 8		81	48.5 (L)	1.36 (H)	2.7	
Week 8	Normal	88	44.6 (L)	1.51 (G1,H)	3.3	Trace (H)
Week 10		100	48.0 (L)	1.40 (H)	3.0	
Week 10	Normal	92	49.8 (L)	1.33	3.8	Trace (H)
Week 12	Normal	90	58.7 (L)	1.16	3.6	Negative
FU-4	Normal	92	52.0 (L)	1.31	3.0	Trace (H)

Table S10. Pharmacokinetic Parameters of Ledipasvir, Sofosbuvir, GS-331007, and Tenofovir by ARV regimen and Overall

Mean (%CV)	LDV/SOF+ EFV+FTC+TDF 12 Weeks (N = 160)	LDV/SOF+ RAL+FTC+TDF 12 Weeks (N = 146)	LDV/SOF+ RPV+FTC+TDF 12 Weeks (N = 29)	LDV/SOF Total 12 Weeks (N = 335)
SOFOSBUVIR				
AUC_{tau} (ng•hr/mL)	1303.6 (23.1)	1328.8 (24.5)	1374.8 (23.0)	1320.7 (23.7)
C_{max} (ng/mL)	704.7 (24.1)	696.0 (28.5)	647.2 (31.4)	695.9 (26.7)
GS-331007				
AUC_{tau} (ng•hr/mL)	13048.2 (27.2)	13836.6 (27.7)	13655.0 (27.7)	13444.3 (27.6)
C_{max} (ng/mL)	821.6 (27.3)	859.1 (29.2)	822.3 (30.9)	838.0 (28.5)
LEDIPASVIR				
AUC_{tau} (ng•hr/mL)	6076.8 (52.0)	5719.5 (56.5)	6433.4 (50.3)	5951.9 (53.7)
C_{max} (ng/mL)	282.0 (48.5)	251.8 (46.6)	281.9 (49.5)	268.8 (48.1)
C_{tau} (ng/mL)	179.5 (57.4)	162.3 (55.0)	187.3 (53.3)	172.7 (56.3)
TENOFOVIR				
AUC_{tau} (ng•hr/mL)	3,600.7 (30.3)	4,010.0 (30.9)	4,286.6 (30.8)	3,838.5 (31.2)
C_{max} (ng/mL)	335.7 (20.2)	378.9 (29.9)	379.5 (25.4)	358.3 (26.5)
C_{tau} (ng/mL)	86.7 (47.5)	99.8 (45.1)	111.7 (42.4)	94.6 (46.6)