CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Interleukin-28B Polymorphism Improves Viral Kinetics and Is the Strongest Pretreatment Predictor of Sustained Virologic Response in Genotype 1 Hepatitis C Virus

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BACKGROUND & AIMS: We recently identified a polymorphism upstream of *interleukin* (*IL*)*-28B* to be associated with a 2-fold difference in sustained virologic response (SVR) rates to pegylated interferon-alfa and ribavirin therapy in a large cohort of treatment-naive, adherent patients with chronic hepatitis C virus genotype 1 (HCV-1) infection. We sought to confirm the polymorphism's clinical relevance by intention-to-treat analysis evaluating on-treatment virologic response and SVR. **METHODS:** HCV-1 patients were genotyped as CC, CT, or TT at the polymorphic site, rs12979860. Viral kinetics and rates of rapid virologic response (RVR, week 4), complete early virologic response (week 12), and SVR were compared by *IL-28B* type in 3 self-reported ethnic groups: Caucasians (n = 1171), African Americans (n = 300), and Hispanics (n = 116). **RESULTS:** In Caucasians, the CC *IL-28B* type was associated with improved early viral kinetics and greater likelihood of RVR (28% vs 5% and 5%; $P < .0001$), complete early virologic response (87% vs 38% and 28%; $P < .0001$), and SVR (69% vs 33% and 27%; $P < .0001$) compared with CT and TT. A similar association occurred within African Americans and Hispanics. In a multivariable regression model, CC *IL-28B* type was the strongest pretreatment predictor of SVR (odds ratio, 5.2; 95% confidence interval, 4.1–6.7). RVR was a strong predictor of SVR regardless of *IL-28B* type. In non-RVR patients, the CC *IL-28B* type was associated with a higher rate of SVR (Caucasians, 66% vs 31% and 24%; $P < .0001$). **CONCLUSIONS: In treatment-naive HCV-1 patients treated with pegylated interferon and ribavirin, a polymorphism upstream of *IL-28B* is associated with increased on-treatment and sustained virologic response and effectively predicts treatment outcome.**

Keywords: Genetics; IL-28B; Interferon-Lambda; Peg-Interferon-Alfa.

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One hundred and eighty million individuals worldwide are chronically infected with hepatitis C virus (HCV)[1] and at risk for related morbidity and mortality from cirrhosis and hepatocellular carcinoma. Curative antiviral therapy may prevent these complications. The current standard of

Abbreviations used in this paper: **ALT, alanine aminotransferase; BMI, body mass index; cEVR, complete early virologic response; CI, confidence interval; EVR, early virologic response; HCV, hepatitis C virus; HCV-1, hepatitis C virus genotype 1; IL, interleukin; ITT, intention-to-treat; pegIFN, pegylated-interferon; RBV, ribavirin; RVR, rapid virologic response; SNP, single nucleotide polymorphism; SVR, sustained virologic response.**

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care is pegylated-interferon-alfa (pegIFN-alfa) and ribavirin (RBV) combination therapy. However, of patients infected with genotype 1 HCV (HCV-1), the most common HCV genotype in North America, Europe, and Japan, only approximately 40% are cured by standard therapy.[2–6] Furthermore, therapy may be associated with considerable toxicity. Therefore, the ability to prospectively identify individual patients who are likely to respond to treatment would be clinically valuable.

A number of pretreatment host and viral factors have been associated with treatment outcome in HCV-1.[6] These include baseline viral load, age, sex, body mass index (BMI), insulin resistance, hepatic steatosis, and hepatic fibrosis. African American ancestry is a powerful negative predictive factor for sustained virologic response (SVR).[7,8] The rate of plasma HCV-RNA decline during treatment is predictive of treatment outcome, and virologic responses at week 4 (rapid virologic response [RVR]) and week 12 (early virologic response [EVR]) are additional key therapeutic milestones. However, our understanding of the genetic determinants of treatment outcome has been limited.

We recently performed a genome-wide association study to identify genetic determinants of treatment response in HCV-1 patients treated with pegIFN plus RBV.[9] We identified a single nucleotide polymorphism (SNP) upstream of the gene *IL-28B* on chromosome 19, coding for IFN-λ-3, which was associated with an approximately 2-fold difference in SVR rates in patients of European, African American, or Hispanic ancestry.[9] The analysis was restricted to 1137 of 1671 patients, in which nonresponders were required to have been more than 80% adherent to both pegIFN and RBV dosing, and ethnicity was defined by genetic ancestry.[9] The importance of this genetic region as a determinant of treatment response has now been confirmed by 2 independent genome-wide association studies.[10,11] *Interleukin* (*IL*)*-28B* polymorphism also has been shown to be associated with spontaneous clearance after HCV infection.[12,13]

In this intention-to-treat (ITT) analysis of the discovery cohort, we sought to interpret the *IL-28B* polymorphism in a more detailed clinical context to determine how knowledge of this genetic information might impact physician practice. We describe how the genotype of the *IL-28B* polymorphism influences on-treatment virologic responses, as well as relapse rates, and consider in detail the effect of the polymorphism in the context of other variables predictive of antiviral therapy outcome. Our analyses included all patients, regardless of their level of adherence to therapy, and ethnicity was determined by subject self-report, as it would be in a clinical practice setting.

Materials and Methods

Patients

The study population included 1604 of 3070 patients who were enrolled in the IDEAL study and consented to genetic testing (ClinicalTrials.gov number, NCT00081770).[6] In addition, 67 patients were included from a second randomized controlled trial.[7] For all 1671 patients, the protocol-specified treatment duration was 48 weeks, with an additional 24 weeks of follow-up evaluation. Clinical and laboratory data were collected as described previously.[6,7] Ethnicity was defined by patient self-report, and not genetically inferred ancestry as in the analysis of Ge et al.[9] A discrepancy between self-report and genetic ancestry was noted in 130 (8%) patients. All patients for whom the polymorphism of interest was genotyped successfully were included in this analysis, which therefore included 491 patients excluded from the analysis by Ge et al[9] (336 [21%] on the basis of nonadherence).

Genotyping

A total of 1671 patients were genotyped using the Illumina Human610-quad BeadChip (Illumina, San Diego, CA) as previously described.[9] We selected the discovery SNP, rs12979860, for this study. Genotype at the polymorphic site rs12979860 on chromosome 19 was suitable for analysis in 1628 patients. For simplicity, we refer to an *IL-28B* polymorphism throughout this article, noting that the association SNP actually lies 3 kilobases upstream of the *IL-28B* gene. Genotype was defined as CC, CT, or TT *IL-28B* type.

Treatment Efficacy Assessments

HCV-RNA levels were measured using sensitive reverse-transcription polymerase chain reaction assays. In the IDEAL study, the Cobas TaqMan assay (Roche Molecular Diagnostics, Pleasanton, CA) was used, which has a lower limit of quantitation of 27 IU/mL.[6] In the earlier study by Muir et al,[7] the NGI SuperQuant assay was used (National Genetics Institute, Culver City, CA), which has a lower limit of quantitation of 39 IU/mL. Viral load was measured at baseline; treatment weeks 2, 4, 12, 24, and 48; and follow-up evaluation weeks 4, 12, and 24 (patients from the study by Muir et al[7] did not have viral load measured at week 2 or week 4). On-treatment responses were defined by undetectable plasma HCV-RNA levels at the following time points: ultrarapid virologic response at 2 weeks; RVR at 4 weeks; complete EVR (cEVR) at 12 weeks; and end-of-treatment response at 48 weeks.[14] SVR was defined by undetectable HCV-RNA levels at 24 weeks posttreatment (or 12 weeks posttreatment if 24-week follow-up data were not available; n = 40). Relapse was defined as detectable HCV-RNA levels during follow-up evaluation in patients who achieved end-of-treatment response.

Statistical Analysis

Comparisons between groups were performed using a Wilcoxon test for the non-normal continuous variables, and for categoric data the Pearson chi-square test/Fisher exact test was used. Significance was defined at a *P*

value of less than .05. Analysis of on-treatment response by *IL-28B* polymorphism was performed in 3 separate ethnic populations: Caucasians, African Americans, and Hispanics (on-treatment responses for the 41 patients of "other" ethnicity are not described). A linear mixed-effects model that included subject-specific intercept and slope and accounted for the left censoring of the viral load measurements was built to analyze the association of *IL-28B* SNP genotype and race on the $\log_{10}$ viral load within the first 12 weeks of treatment.[15] Multivariable logistic regression with backward elimination was used to identify baseline factors in the entire cohort associated with SVR. Separate models were not constructed for each ethnicity; rather, ethnicity was included as a covariate in the model. Additional covariates considered for inclusion in the model included baseline viral load ($\log_{10}$ IU/mL), fasting blood sugar level, liver fibrosis stage, age, BMI, serum alanine aminotransferase (ALT) level, hepatic steatosis grade, ribavirin starting dose, sex, pegIFN (dose/type), *IL-28B* type, and *IL-28B* type by ethnicity interaction. *IL-28B* polymorphism was evaluated according to CC versus non-CC *IL-28B* type for the regression modeling. A significance level of 0.05 was used for removal from the model. A second model was built to consider the effect of *IL-28B* polymorphism for predicting SVR after adjusting for RVR, which included all subjects with measured covariates and virologic data at week 4 (1422 subjects). In addition to the covariates described earlier, we grouped week 4 response and *IL-28B* polymorphism as a 3-level variable: week 4 responders (RVR); week 4 nonresponders, CC genotype; and week 4 nonresponders, non-CC genotype; there were too few patients without the CC genotype who were also week 4 responders to subset the week 4 responders by genotype. All analyses were performed using R statistical software (R Foundation for Statistical Computing, http://www.R-project.org) and SAS version 9.1 (SAS Institute, Cary, NC).

Results

Characteristics of the Study Patients

A majority of the patients were male (61%) and older than 40 years of age (Table 1). Most patients were Caucasian (72%); African Americans comprised 18% of patients, and Hispanics comprised 7%. Compared with Caucasians, African Americans were older, more likely to have a BMI of 30 kg/m^2 or greater, and an increased baseline fasting glucose level, and less likely to have an abnormal serum ALT level. Allocation of pegIFN type was balanced between and within each ethnic group. African American patients were less likely to have been assigned an RBV dose greater than 13 mg/kg/day. The frequency of the *IL-28B* SNP genotype differed between ethnic groups ($P < .0001$) (Table 1), as previously described.[9] The CC genotype was observed most frequently in Caucasians (37%), followed by Hispanics (29%) and African Americans (14%). The TT genotype was more common in African Americans (37%) than Hispanics (22%) or Caucasians (12%).

Viral Kinetics

As previously reported, a small but statistically significant difference in median viral load at baseline was noted according to *IL-28B* type, with higher levels present in CC patients (Caucasians, 6.6 (6.1–6.9) vs 6.4 (6.0–6.7) vs 6.3 (5.9–6.6) $\log_{10}$ IU/mL for CC, CT, and TT patients, respectively, Supplementary Table 1).[9] However, when viral load was considered according to the threshold of 600,000 IU/mL, the proportion of patients with high baseline viral load did not differ by *IL-28B* type.

On-treatment, differences in viral load reduction between genotypes were detectable as early as week 2, the earliest time point evaluated (Figure 1; Supplementary Table 2). Among Caucasians, median reductions of viral load at week 2 were as follows: 2.6, 0.9, and 0.6 $\log_{10}$ IU/mL for patients with the CC, CT, and TT *IL-28B* types, respectively ($P < .0005$). Despite ongoing viral decline, the difference was of similar magnitude at weeks 4 and 12, corresponding to increased rates of RVR and cEVR in patients with the CC genotype (Figure 2 and Tables 2 and 3). The rate of viral load reduction in African American and Hispanic patients also was more rapid in those with the CC *IL-28B* type. However, among African American CC patients, the magnitude of viral decline was less than that observed in Caucasian CC patients at all times (weeks 2, 4, and 12; $P < .0020$; Figure 1, Supplementary Table 2). Linear mixed-effects modeling confirmed that viral load declined more for patients with the CC versus non-CC *IL-28B* type (delta, 0.6190; 95% confidence interval [CI], 0.5562–0.6817 $\log_{10}$ IU/mL/wk; Supplementary Table 3). This effect was independent of ethnic background, which also was associated with the rate of viral decline. There was no significant difference in the rate of decline between patients with the CT and TT genotypes ($P = .1468$).

Viral Clearance–On-Treatment and SVR

Within each ethnic group, the CC *IL-28B* type was associated with higher on-treatment response rates at all time points (4, 12, and 48 weeks) (Figure 2 and Table 2). In Caucasians who were CC, 87% attained a cEVR, 10% achieved a pEVR, and only 3% did not achieve a 2-$\log_{10}$ IU/mL reduction in viral load at week 12 of treatment.

Within all populations, the CC *IL-28B* type was associated with a greater than 2-fold increase in SVR compared with the TT *IL-28B* type. The rate of SVR observed in Caucasians with the CC *IL-28B* type (69%) was higher than in either African Americans (48%) or Hispanics (56%) ($P = .0079$). The CT *IL-28B* type consistently was associated with numerically higher virologic responses than TT; however, the differences were small and not statistically significant (Figure 2 and Table 2). A detailed description of the SVR rates for

Table 1. Baseline Characteristics of the Clinical Cohort

Baseline characteristics	Caucasians	African Americans	Hispanics	Other[a]	*P* value[b]
N	1171	300	116	41	
Age, y	48 (43–52)	51 (47–54)	45 (39–51)	48 (42–53)	<.0001
Age, >40 y	997 (85%)	283 (94%)	80 (69%)	33 (80%)	<.0001
Male sex	713 (61%)	172 (57%)	77 (66%)	24 (59%)	.2226
BMI	27.4 (24.7–30.4)	29.4 (26.7–32.6)	28.8 (26.0–32.3)	25.5 (23.4–28.8)	<.0001
BMI ≥30 kg/m^2	328 (28%)	138 (46%)	44 (38%)	9 (22%)	<.0001
HCV–RNA level, $\log_{10}$ IU/mL	6.5 (6.0–6.8)	6.3 (5.9–6.7)	6.2 (5.7–6.6)	6.6 (6.2–6.9)	.0007
HCV–RNA level, >600,000 IU/mL	979 (84%)	244 (81%)	83 (72%)	35 (85%)	.0046
ALT level × ULN (range)	1.7 (1.2–2.6)	1.4 (1.0–2.0)	2.0 (1.3–3.5)	1.7 (1.2–2.8)	<.0001
ALT level >ULN	978 (84%)	223 (74%)	103 (88%)	36 (85%)	.0002
Fasting glucose level, mmol/L	5.1 (4.8–5.6)	5.2 (4.7–5.9)	5.1 (4.8–5.7)	5.0 (4.6–5.4)	.0903
Fasting glucose level, ≥5.6 mmol/L	336 (29%)	112 (37%)	31 (26%)	10 (24%)	.0102
Steatosis[c]					
Grade 0	443 (40%)	98 (35%)	29 (25%)	13 (35%)	.0006
Grade 1	516 (46%)	155 (55%)	55 (48%)	18 (49%)	
Grade 2	135 (12%)	26 (9%)	27 (23%)	6 (16%)	
Grade 3	23 (2%)	3 (1%)	3 (3%)	0 (0%)	
Grade 4	4 (4%)	0 (0%)	1 (1%)	0 (0%)	
Steatosis >grade 0	678 (60%)	184 (65%)	86 (74%)	24 (65%)	.0059
METAVIR fibrosis stage[c]					
F0	18 (2%)	2 (1%)	3 (3%)	1 (3%)	.2091
F1	795 (71%)	192 (68%)	81 (70%)	30 (81%)	
F2	175 (16%)	59 (21%)	15 (13%)	2 (5%)	
F3	60 (5%)	8 (3%)	7 (6%)	2 (5%)	
F4	73 (7%)	21 (7%)	9 (8%)	2 (5%)	
METAVIR F3–F4	133 (12%)	29 (10%)	16 (14%)	4 (11%)	.5715
PegIFN-alfa					
2b 1.0 ug/kg/wk	376 (32%)	88 (29%)	36 (31%)	16 (42%)	.7612
2b 1.5 ug/kg/wk	417 (36%)	118 (39%)	45 (38%)	4 (11%)	
2a 180 ug/wk	378 (32%)	94 (31%)	35 (30%)	18 (47%)	
RBV, mg/kg	13.2 (12.4–14.2)	12.8 (12.0–13.7)	13.5 (12.5–14.7)	14.3 (12.6–15.7)	<.0001
RBV >13 mg/kg	649 (55%)	123 (41%)	70 (61%)	29 (71%)	<.0001
rs12979860 genotype frequency					
CC	436 (37%)	42 (14%)	34 (29%)	26 (63%)	<.0001
CT	596 (51%)	146 (49%)	56 (48%)	13 (32%)	
TT	139 (12%)	112 (37%)	26 (22%)	2 (5%)	

NOTE. Data are presented as either median (25th-75th percentile), or n (%).
ULN, upper limit of normal.
[a]Ethnicities were as follows: Asian American (n = 19), American Indian (n = 7), and other (n = 15).
[b]Comparison across Caucasian, African American, and Hispanic patients (continuous data, Kruskal-Wallis Test; categoric data, chi-square test).
[c]Missing data: histology = 50 cases (Caucasian); 18 cases (African American); 1 case (Hispanic); 4 cases (other).

each genotype of the *IL-28B* polymorphism on the basis of individual and combinations of baseline characteristics and week 4 and week 12 on-treatment responses is presented in Supplementary Table 4.

SVR Rates According to Week 4 and Week 12 Responses

The CC *IL-28B* type increased the proportion of patients who attained RVR; in those who achieved this key therapeutic milestone, SVR rates were high, independent of *IL-28B* SNP genotype (Table 3). In contrast, in patients who did not achieve RVR, the effect of *IL-28B* SNP genotype was strikingly different—SVR rates were significantly higher in patients with the CC *IL-28B* type in all populations (Caucasian non-RVR:SVR = 66% for CC vs 31% for CT vs 24% for TT; $P < .0001$). In patients who were CC at the polymorphic site, the rate of cEVR was high in all populations (Table 2). Rates of SVR were higher post-cEVR than in patients attaining only pEVR, but the predictive utility of the *IL-28B* polymorphism was not strong once week 12 virologic response was available (Table 3).

Test Characteristics for IL-28B SNP Genotype Compared With RVR

The performance of the *IL-28B* SNP genotype (CC vs non-CC) as a binary predictor for SVR was evaluated in the 3 major population groups (Table 4). In Caucasian patients, having the CC *IL-28B* type was more sensitive and had a higher negative predictive value for SVR than RVR; however, RVR had superior positive predictive value and specificity for SVR. Importantly, the CC *IL-28B* type was present in 37% of the Caucasian population, whereas

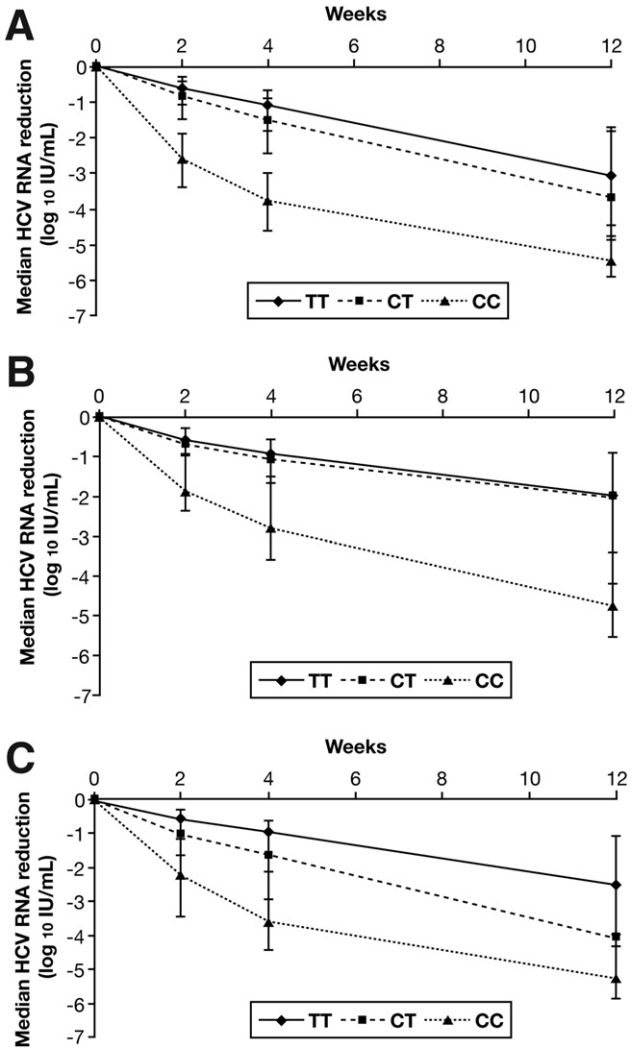

Figure 1. Median reductions in viral load from baseline on the basis of *IL-28B* type. (*A*) Caucasian, (*B*) African American, and (*C*) Hispanic patients. *Bars* represent 25th and 75th percentiles. $P < .001$ for all pairwise comparisons of median viral load for CC vs CT or TT using the Wilcoxon 2-sample test (see Supplementary Table 1 and 2).

only 14% attained an RVR. A similar pattern was observed in African American and Hispanic patients.

Multivariable Models

Regression modeling was used to identify pretreatment factors that were associated independently with SVR. Data from 1550 patients with a complete dataset of the covariates of interest were included in the model. We first modeled SVR considering all predictors as dichotomous variables (continuous and ordinal variables were dichotomized according to clinically relevant thresholds[6]). Multivariable logistic regression using backward selection identified *IL-28B* type, ethnic background, baseline viral load, hepatic fibrosis stage, and fasting glucose level as being associated independently with SVR (Table 5). *IL-28B* type had the greatest odds ratio favoring SVR in this model (CC vs non-CC: odds ratio, 5.2; 95% CI, 4.1–6.7; $P < .0001$). A second multivariate logistic regression model was built in which continuous and ordinal variables were not dichotomized, allowing us to use pseudo R-squared values to estimate the contribution of each variable to the variability observed in SVR. *IL-28B* type (CC vs non-CC) was estimated to explain 14.8% of the variability in treatment response in the cohort, after adjustment for the other independent predictors (Supplementary Table 5). Other independent predictors of SVR in this more powerful model included ethnic background, baseline viral load, hepatic fibrosis stage, fasting glucose level, BMI, and RBV starting dose (mg/kg). No other predictor explained more than 5% of the variability in SVR, and the *IL-28B* type therefore was the strongest pretreatment predictor of SVR.

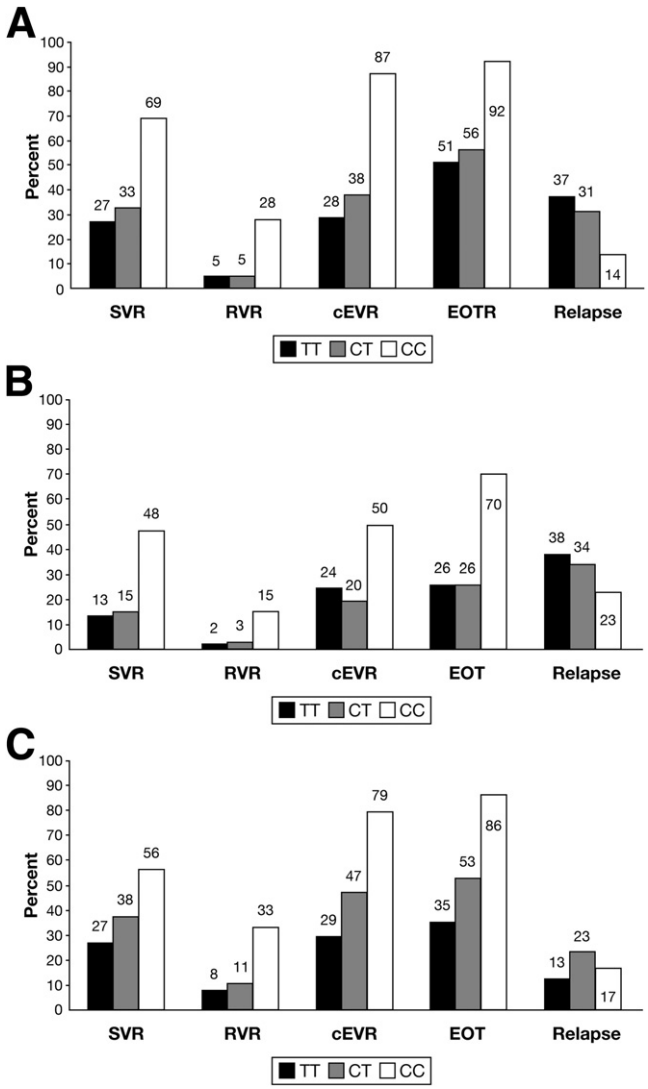

Figure 2. Virologic responses on treatment on the basis of *IL-28B* type and ethnicity. (*A*) Caucasian, (*B*) African American, and (*C*) Hispanic patients. EOTR, end-of-treatment response. Statistical comparisons are presented in Table 2.

Table 2. Rates of Virologic Response for Caucasian, African American, and Hispanic Populations

Rates of on-treatment response, SVR	Overall	CC	CT	TT	*P* value		
					CC vs CT	CC vs TT	CT vs TT
Caucasians							
SVR	535/1171 (46%)	301/436 (69%)	196/596 (33%)	38/139 (27%)	<.0001	<.0001	.2061
URVR/wk 2	61/1106 (6%)	48/414 (12%)	11/562 (2%)	2/130 (2%)	<.0001	.0005	1.000
RVR/wk 4	150/1091 (14%)	115/406 (28%)	29/556 (5%)	6/129 (5%)	<.0001	<.0001	.7930
cEVR/wk 12	599/1089 (55%)	354/407 (87%)	210/559 (38%)	35/123 (28%)	<.0001	<.0001	.0565
EOTR/wk 48	687/998 (69%)	345/374 (92%)	283/509 (56%)	59/115 (51%)	<.0001	<.0001	.4033
Relapse	159/687 (23%)	48/345 (14%)	89/283 (31%)	22/59 (37%)	<.0001	<.0001	.3835
African Americans							
SVR	57/300 (19%)	20/42 (48%)	22/146 (15%)	15/112 (13%)	<.0001	<.0001	.7035
URVR/wk 2	5/252 (2%)	3/33 (9%)	1/124 (1%)	1/95 (1%)	.0295	.0524	1.000
RVR/wk 4	11/251 (4%)	5/33 (15%)	4/126 (3%)	2/92 (2%)	.0195	.0138	1.000
cEVR/wk 12	69/269 (26%)	19/38 (50%)	26/133 (20%)	24/98 (24%)	.0002	.0041	.3675
EOTR/wk 48	82/250 (33%)	26/37 (70%)	32/122 (26%)	24/91 (26%)	<.0001	<.0001	.9811
Relapse	26/82 (32%)	6/26 (23%)	11/32 (34%)	9/24 (38%)	.3471	.2662	.8091
Hispanics							
SVR	47/116 (41%)	19/34 (56%)	21/56 (38%)	7/26 (27%)	.0888	.0249	.3473
URVR/wk 2	11/109 (10%)	6/31 (19%)	3/54 (6%)	2/24 (8%)	.0675	.4429	.6405
RVR/wk 4	18/111 (16%)	10/30 (33%)	6/55 (11%)	2/26 (8%)	.0115	.0197	1.000
cEVR/wk 12	54/104 (52%)	23/29 (79%)	24/51 (47%)	7/24 (29%)	.0048	.0002	.1421
EOTR/wk 48	58/100 (58%)	24/28 (86%)	26/49 (53%)	8/23 (35%)	.0038	.0001	.1475
Relapse	11/58 (19%)	4/24 (17%)	6/26 (23%)	1/8 (13%)	.7278	1.000	1.000

NOTE. Data for SVR include the entire ITT population. Data for on-treatment virologic milestones/relapse rates refer to the number of patients who had the evaluation performed. The trial protocol included a stopping rule for patients who did not attain EVR at week 12 (no EVR = reduction of serum HCV RNA <2 $\log_{10}$ IU at week 12).
EOTR, end-of-treatment response at week 48; URVR, ultrarapid virologic response at week 2.

A second important question relates to the informativeness of *IL-28B* status after viral response at week 4 is known. For those subjects attaining RVR, *IL-28B* type was not associated with SVR (CC vs non-CC genotype, $P = .6734$). However, for those who did not attain RVR, *IL-28B* type had a strong predictive value ($P < .0001$). A direct comparison between these 2 groups showed that the predictive value of the *IL-28B* polymorphism was significantly different (*P* value for interaction = .0023). A model then was built to consider the independent effects of the *IL-28B* polymorphism and RVR in the context of the other baseline predictors. RVR had the largest odds ratio for SVR (odds ratio, 9.1; 96% CI, 5.8–14.0 vs non-RVR non-CC genotype reference) (Table 5). In non-RVR patients, CC genotype was associated independently with SVR (odds ratio, 5.2; 95% CI, 3.9–6.9 vs non-CC genotypes). An additional term to divide patients who attained RVR by *IL-28B* polymorphism was not significant.

Analysis of Adherent Patients

We also analyzed the 1137 adherent patients used for the genetic association study[9] (Supplementary Tables 6–10, Supplementary Figures 1 and 2). The effect of the *IL-28B* type on treatment response was similar in this subset. SVR rates were higher, consistent with the role for adherence in treatment outcome.[16]

Table 3. Rates of SVR by Week 4, Week 12 Responses

Rates of SVR by wk 4, wk 12 responses	Overall	CC	CT	TT	*P* value CC vs CT	*P* value CC vs TT	*P* value CT vs TT
Caucasians							
RVR	126/150 (84%)	98/115 (85%)	22/29 (76%)	6/6 (100%)	.2654	.5932	.3113
Non-RVR	388/941 (41%)	193/291 (66%)	165/527 (31%)	30/123 (24%)	<.0001	<.0001	.1316
cEVR	473/599 (79%)	288/354 (81%)	158/210 (75%)	27/35 (77%)	.0842	.5456	.8083
Partial EVR	58/280 (21%)	11/40 (28%)	37/191 (19%)	10/49 (20%)	.2493	.4331	.8704
African Americans							
RVR	11/11 (100%)	5/5 (100%)	4/4 (100%)	2/2 (100%)	1.000	1.000	1.000
Non-RVR	43/240 (18%)	12/28 (43%)	18/122 (15%)	13/90 (14%)	.0008	.0013	.9497
cEVR	45/69 (65%)	16/19 (84%)	15/26 (58%)	14/24 (58%)	.0577	.0665	.9634
Partial EVR	11/79 (14%)	4/13 (31%)	6/41 (15%)	1/25 (4%)	.2296	.0382	.2391
Hispanics							
RVR	15/18 (83%)	8/10 (80%)	5/6 (83%)	2/2 (100%)	1.000	1.000	1.000
Non-RVR	32/93 (34%)	11/20 (55%)	16/49 (33%)	5/24 (21%)	.0844	.0190	.2946
cEVR	41/54 (76%)	17/23 (74%)	18/24 (75%)	6/7 (86%)	.9391	1.000	1.000
Partial EVR	5/20 (25%)	1/6 (17%)	3/9 (33%)	1/5 (20%)	.6044	1.000	1.000

NOTE. Data for SVR include the entire ITT population. Data for on-treatment virologic milestones/relapse rates refer to the number of patients who had the evaluation performed. The trial protocol included a stopping rule for patients who did not attain EVR at week 12 (no EVR = reduction of serum HCV RNA <2 $\log_{10}$ IU at week 12).
EOTR, end-of-treatment response at week 48; URVR, ultrarapid virologic response at week 2.

Discussion

We previously identified a polymorphism upstream of the *IL-28B* gene to be associated strongly with SVR in treatment-adherent HCV-1 patients.[9] In this ITT analysis, we present a number of novel insights. The clinical relevance of the genetic discovery was confirmed, irrespective of the degree of treatment adherence. The polymorphism was associated with improved SVR rates by enhancing early viral kinetics, increasing the rates of week 4, week 12, and week 48 viral clearance, and decreasing the rate of posttreatment relapse. Two major benefits of the polymorphism were observed: (1) a higher rate of RVR, which was followed in most cases by an SVR; and (2) a 2-fold increase in the rate of SVR in the majority of patients (>80%) who did not achieve an RVR. The effect of this polymorphism on treatment response was maintained in Caucasians, African Americans, and Hispanics, in whom the differing allele frequencies contributed very strongly to the racial disparity in overall response rates. Indeed, African American patients with the CC *IL-28B* type responded better than Caucasian patients with the non-CC *IL-28B* types. Finally, the strength of this

Table 4. *IL-28B* Type Versus RVR for Predicting SVR

Overall cohort		Sensitivity, %	Specificity, %	PPV, %	NPV, %
Caucasians	CC vs non-CC (n = 1171)	56 (52–60)	79 (76–82)	69 (65–74)	68 (65–71)
	RVR vs no RVR (n = 1091)	25 (21–29)	96 (94–97)	84 (77–89)	59 (56–62)
African	CC vs non-CC (n = 300)	35 (23–49)	91 (86–94)	48 (32–63)	86 (81–90)
Americans	RVR vs no RVR (n = 251)	20 (11–34)	100 (98–100)	100 (68–100)	82 (77–87)
Hispanics	CC vs non-CC (n = 116)	40 (27–56)	78 (66–87)	56 (38–72)	66 (54–76)
	RVR vs no RVR (n = 111)	32 (20–47)	95 (86–99)	83 (58–96)	66 (55–75)

NOTE. Test performance characteristics presented are for the use of *IL-28B* type (CC vs non-CC) or RVR (yes/no) as a binary predictor of SVR within each ethnic population. Data shown are the test statistic (95% CI).
PPV, positive predictive value; NPV, negative predictive value.

Table 5. Multivariable Logistic Regression Models for SVR

	Odds ratio	95% CI	*P* value
Model 1: baseline variables only			
CC *IL-28B* type vs non-CC	5.2	4.1–6.7	<.0001
HCV RNA ≤600,000 vs >600,000 IU/mL	3.1	2.3–4.1	<.0001
Caucasian vs AA ethnicity	2.8	2.0–4.0	<.0001
Hispanic vs AA ethnicity	2.1	1.3–3.6	.0041
METAVIR F0–2 vs F3–4	2.7	1.8–4.0	<.0001
Fasting blood sugar level <5.6 vs ≥5.6 mmol/L	1.7	1.3–2.2	<.0001
Model 2: considering *IL-28B* type and RVR in the same model			
RVR vs (non-RVR + non-CC)	9.1	5.8–14.0	<.001
(Non-RVR + CC) vs (non-RVR + non-CC)	5.2	3.9–6.9	<.001
METAVIR F0–2 vs F3–4	2.7	1.7–4.1	<.001
HCV RNA ≤600,000 vs >600,000 IU/mL	2.4	1.7–3.4	<.001
Caucasian vs AA ethnicity	2.3	1.6–3.3	<.001
Hispanic vs AA ethnicity	1.8	1.04–3.1	.0361
Fasting blood sugar level <5.6 vs ≥5.6 mmol/L	1.7	1.3–2.3	.0001

NOTE. Model 1: the baseline model considered *IL-28B*-type (CC vs non-CC) and the following covariates, previously identified to be associated independently with SVR in the IDEAL study population[6]: ethnic background, age (±40 y), sex, BMI (±30 kg/m^2), baseline HCV–RNA level (±600,000 IU/mL), ALT level (±ULN), fasting glucose level (±5.6 mmol/L), hepatic steatosis (absent vs present), hepatic fibrosis stage (METAVIR F0–2 vs F3–4), and RBV dose (±13 mg/kg/day). PegIFN type was not associated with SVR in univariable analysis (Supplementary Table 11). Variables not present in the final model were removed by backward selection. A significance level of 0.05 was used for removal from the model. Model 2: the week-4 model collapsed the week-4 response and *IL-28B* polymorphism as a 3-level variable (RVR vs non-RVR + CC *IL-28B* type vs non-RVR + non-CC *IL-28B* type). Otherwise, the same covariates were included as for the baseline model.

genetic factor as a predictor of treatment response was borne out in the multivariable analysis, where it was the strongest pretreatment predictor of SVR.

The key marker for improved treatment response was the CC *IL-28B* type. The rate of SVR was doubled in patients with the CC compared with the non-CC *IL-28B* type in all populations. The CC *IL-28B* type was associated with improved early viral suppression, such that by week 2 of treatment the median reduction in viral load was 2-log$_{10}$ IU/mL greater in Caucasian patients with CC versus non-CC genotypes. The more rapid reduction in viral load correlated with increased rates of RVR and cEVR. Relapse rates also were lower in Caucasian and African American patients with the CC *IL-28B* type.

All patients who attained RVR had a high rate of SVR, although it is important to note that patients with the CC genotype were most likely to reach RVR. In contrast, the *IL-28B* polymorphism was very important in the non-RVR patients, for whom having a CC genotype increased SVR rates 2-fold. Although viral load sampling was not performed between weeks 4 and 12 of treatment, the viral kinetics predicted that the majority of these CC patients who did not attain an RVR were likely to have become HCV-RNA negative soon after 4 weeks. The weak utility of *IL-28B* genotype for predicting SVR once the week 12 virologic response was determined, was also consistent with the fact that the major effect of the *IL-28B* polymorphism was to influence viral kinetics before week 12. Together, these observations emphasize that the major effect of this polymorphism was to increase the rate of early viral decline, leading to higher SVR rates.

The observation that the CC genotype is less frequent in African American patients advances our understanding of the poor response rates seen in this population.[7,8] However, even in African American patients with the CC genotype, viral kinetics were slower, and rates of RVR, cEVR, and SVR were lower. African American ancestry remained an independent negative predictor of outcome in the multivariable logistic regression. This could suggest the presence of other as yet undetected gene variants that influence treatment response in African Americans compared with Caucasians.

We believe that knowledge of *IL-28B* type will aid both clinicians and patients in making decisions about pegIFN and RBV therapy. Patients who have the good response CC *IL-28B* type have a high likelihood of attaining SVR and, in the absence of other concerns regarding suitability for therapy, should be considered ideal candidates. In contrast, patients with the non-CC *IL-28B* type, especially in the setting of other markers of poor response, such as African American ethnicity, advanced fibrosis, or high viral load, are unlikely to attain SVR. In this setting, the urgency for therapy should be weighed against the expected availability of direct antivirals in the near future.[17]

The clinical utility of *IL-28B* genotyping was compared with that of week 4 viral clearance. Although RVR had a higher positive predictive value for SVR, it cannot be evaluated before therapy and is uncommon in HCV-1 patients. In comparison, the CC genotype, present in 37% of Caucasians, was strongly predictive of SVR, even if RVR was not achieved. It is likely that RVR and *IL-28B* genotyping will have complementary roles in clinical practice, with *IL-28B* type having important utility at baseline, and at week 4 for non-RVR patients.

The mechanisms through which *IL-28B* SNP genotype influences antiviral response to pegIFN and RBV remain unclear. The protein product of *IL-28B* is IFN-λ-3, 1 of the 3 members of the recently described type 3 IFN family (IFN-λ-1/2/3 = *IL-29*, *IL-28A*, and *IL-28B*).[18,19] In experimental models, IFN-λ inhibits both HCV and HBV replication.[20] In co-stimulation experiments, IFN-λ and IFN-alfa have an additive antiviral effect.[21] Antiviral activity of recombinant IFN-λ-1 (IL-29) has been confirmed in HCV-1 patients.[22] The discovery is therefore biologically plausible, and suggests the IFN-λ signaling axis as an important new direction for studying natural viral defenses.

The data raise a number of important issues. Future studies should address whether *IL-28B* SNP genotyping may be used to personalize duration of therapy. Whether the *IL-28B* polymorphism has a role in predicting treatment outcome with the addition of direct antivirals in future HCV treatment regimens needs to be established. The delayed viral kinetics seen in patients with the non-CC genotypes, apparent as early as treatment week 2, might suggest a particular role for the direct antivirals in these patients. The relevance of the *IL-28B* polymorphism to non–HCV-1 infection is not known. Finally, because the polymorphism is the strongest baseline factor predictive of response, and profoundly effects viral kinetics as early as week 2, current clinical trials investigating direct antivirals on a pegIFN/RBV backbone should be analyzed by *IL-28B* type, and stratification of patients will need to be considered in the future to balance treatment arms according to *IL-28B* type.

In conclusion, *IL-28B* type is the strongest baseline predictor of SVR to pegIFN plus RBV in treatment-naive patients with HCV-1. The good response CC *IL-28B* type is associated with improved viral kinetics and increased rates of RVR, cEVR, and end-of-treatment response, as well as reduced relapse. Even in patients who do not attain RVR, the CC *IL-28B* type is associated with high rates of SVR. The data strongly support a future role for *IL-28B* SNP genotyping as part of a clinical assessment before standard antiviral therapy in individuals chronically infected with HCV-1.

Appendix

Other participants and members of the IDEAL study group included the following: Abdullah Al-Osaimi, Luis Balart, Michael Bennett, David Bernstein, Edmund Bini, Martin Black, Joseph Bloomer, Hector Bonilla, Terry Box, Thomas Boyer, Norbert Brau, Kimberly Brown, Robert Brown, Christine Bruno, William Cassidy, Raymond Chung, David Clain, Jeffrey Crippin, Douglas Dalke, Charles Davis, Gary Davis, Franco Felizarta, Roberto Firpi-Morell, Steven Flamm, Jose Franco, Alexandra Gibas, Eliot Godofsky, Fredric Gordon, John Gross, Stephen Harrison, Jorge Herrera, Steven Herrine, Robert Herring, Ke-Qin Hu, Jonathan Israel, Shobha Joshi, Mandana Khalili, Alan Kilby, Paul King, Alvaro Koch, Edward Krawitt, Marcelo Kugelmas, Louis Lambiase, Edward Lebovics, James Levin, Robert Levine, Steven Lidofsky, Michael Lucey, Mark Mailliard, Luis Marsano, Paul Martin, Thomas McGarrity, Dennis Mikolich, Timothy Morgan, Kevin Mullen, Santiago Munoz, Donald Nelson, Frederick Nunes, Anders Nyberg, Sangik Oh, Prashant Pandya, Mary Pat Pauly, Craig Peine, Robert Perillo, Gary Poleynard, Anthony Post, John Poulos, David Pound, Mordechai Rabinovitz, Natarajan Ravendhran, Joanna Ready, Rajender Reddy, Adrian Reuben, Lorenzo Rossaro, Lawrence Rothman, Raymond Rubin, Vinod Rustgi, Michael Ryan, Warren Schmidt, William Semon, Thomas Sepe, Kenneth Sherman, Maria Sjogren, Robert Sjogren, Coleman Smith, Lawrence Stein, Robert Strauss, Mark Swaim, Gyongnyi Szabo, Joseph Thurn, Myron Tong, John Vierling, George Wu, Rockford Yapp, Ziad Younes, and Atif Zaman.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.04.013.

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Conflicts of interest

The authors disclose the following: Drs McHutchison, Goldstein, Muir, Afdhal, Jacobson, Esteban, Poordad, Lawitz, McCone, Shiffman, Galler, Lee, Reindollar, King, Kwo, Ghalib, Freilich, Nyberg, Patel, Zeuzem, Poynard, and Sulkowski report having received research and grant support from Schering-Plough; Drs McHutchison, Goldstein, Muir, Afdhal, Jacobson, Esteban, Poordad, Lawitz, Shiffman, Reindollar, Kwo, Zeuzem, Poynard, and Sulkowski have received consulting fees or acted in an advisory capacity for Schering-Plough; Drs Brass, Koury, Pedicone, and Albrecht are employees of Schering-Plough (now Merck & Co, Inc) and are stockholders in this entity; Dr Noviello is a former employee of Schering-Plough and is now a consultant to Merck & Co, Inc; and Drs Goldstein, Ge, Fellay, Shianna, Urban, McHutchison, and Thompson are co-inventors of a patent application based on this finding. David Vock and Karen Pieper declare that they have had access to all data and independent statistical support to allow them to analyze the data independently of the sponsor of the study.

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Supplementary Table 1. HCV–RNA Levels at Baseline

Baseline HCV–RNA level, log_{10} IU/mL	CC	CT	TT	*P* value[a] CC vs CT	CC vs TT	CT vs TT
Caucasians						
N	436	596	139			
Median (25th–75th percentile)	6.6 (6.1–6.9)	6.4 (6.0–6.7)	6.2 (5.9–6.5)	<.0001	<.0001	.0012
HCV–RNA level > 600,000 IU/mL, N (%)	367/436 (84.2%)	502/596 (84.2%)	110/139 (79.1%)	.9813	.1690	.1476
African Americans						
N	42	146	112			
Median (25th–75th percentile)	6.7 (6.2–6.9)	6.4 (5.9–6.8)	6.2 (5.8–6.6)	.0183	<.0001	.0197
HCV–RNA level, >600,000 IU/mL, N (%)	38/42 (90.5%)	118/146 (80.1%)	88/112 (78.6%)	.1423	.0880	.6552
Hispanics						
N	34	56	26			
Median (25th–75th percentile)	6.5 (5.9–6.9)	6.1 (5.7–6.5)	6.0 (5.4–6.3)	.0160	.0016	.1571
HCV–RNA level > 600,000 IU/mL, N (%)	28/34 (82.3%)	39/56 (69.6%)	16/26 (61.5%)	.1801	.0708	.4674

[a]Pairwise comparisons of median viral load were performed using the Wilcoxon 2-sample test for continuous data or the chi-square test for categoric data.

Supplementary Table 2. Median On-Treatment Reduction of HCV–RNA Levels

Median on-treatment HCV–RNA reduction, log_{10} IU/mL	CC	CT	TT	*P* value[a] CC vs CT	CC vs TT	CT vs TT
Caucasians						
Week 2 (n = 1106) median (25th–75th percentile)	2.6 (1.9–3.4)	0.9 (0.4–1.5)	0.6 (0.3–1.1)	<.0001	<.0001	.0003
Week 4 (n = 1091) median (25th–75th percentile)	3.8 (3.0–4.6)	1.5 (0.9–2.4)	1.1 (0.7–1.8)	<.0001	<.0001	.0003
Week 12 (n = 1089) median (25th–75th percentile)	5.5 (4.7–5.9)	3.7 (1.8–4.9)	3.1 (1.7–4.4)	<.0001	<.0001	.0447
African Americans						
Week 2 (n = 252) median (25th–75th percentile)	1.9 (1.0–2.4)	0.7 (0.3–1.1)	0.6 (0.3–0.9)	<.0001	<.0001	.3013
Week 4 (n = 251) median (25th–75th percentile)	2.8 (1.5–3.6)	1.1 (0.6–1.7)	0.9 (0.6–1.7)	<.0001	<.0001	.4004
Week 12 (n = 269) median (25th–75th percentile)	4.7 (3.4–5.5)	2.0 (1.1–4.0)	2.0 (0.9–4.2)	<.0001	<.0001	.4957
Hispanics						
Week 2 (n = 109) median (25th–75th percentile)	2.2 (1.6–3.5)	1.0 (0.4–2.0)	0.6 (0.3–1.1)	<.0001	<.0001	.0963
Week 4 (n = 111) median (25th–75th percentile)	3.6 (3.0–4.4)	1.6 (1.0–3.1)	1.0 (0.6–2.1)	<.0001	<.0001	.0503
Week 12 (n = 104) median (25th–75th percentile)	5.3 (4.3–5.8)	4.1 (1.2–5.1)	2.5 (1.1–4.0)	.0005	<.0001	.0337

[a]Pairwise comparisons of median viral load were performed using the Wilcoxon 2-sample test.

Supplementary Table 3. Linear Mixed Effects Modeling[15] of Viral Kinetics to Week 12 in the Overall Cohort

Parameter	Estimate	95% CI, lower–upper boundary	*P* value
Week∗CC	−0.5872	−0.6328 to -0.5416	<.0001
Week∗Caucasian	−0.1702	−0.2220 to -0.1184	<.0001
Week∗Hispanic	−0.1840	−0.2713 to -0.0967	<.0001

NOTE. For the comparison of median viral load reductions at weeks 2, 4, and 12 of treatment (Figure 1 and Supplementary Table 1), a value of 10 IU/mL (1 $\log_{10}$ IU/mL) was substituted for HCV–RNA counts that were below the limit of detection (27 IU/mL). This practice of imputing 1 $\log_{10}$ IU/mL for all left-censored values will introduce bias to comparisons between genotypes and races, potentially underestimating effect. To reduce the bias, a linear mixed-effects model for longitudinal left-censored data was fit to the log HCV–RNA data with race and genotype as covariates.[1] The results suggest that HCV–RNA level declined 0.5872 $\log_{10}$ IU/mL/wk more for patients with the CC vs non-CC *IL-28B* type (95% CI, 0.5416–0.6328). Even after accounting for *IL-28B* type, race was still a significant factor in the rate of viral decline. On average, Caucasians and Hispanics decreased their HCV–RNA value 0.1702 and 0.1840 $\log_{10}$ IU/mL more per week, respectively, than African Americans (95% CI, 0.1184–0.2220 and 0.0967–0.2713, respectively). African American ethnic background and the non-CC *IL-28B* type were used as the reference groups. The estimate describes the average difference in the rate of change in the viral load per week compared with the reference group. Week∗CC describes the average difference between the slope of patients with the CC *IL-28B* type vs the non-CC *IL-28B* types. Week∗Caucasian describes the average difference between the slope of African Americans and Caucasians.

Supplementary Table 4. SVR Rates for Each Genotype of the *IL-28B* Polymorphism in the Overall Cohort, According to Baseline Characteristics and Week 4 and Week 12 On-Treatment Responses

Caucasians	Overall	CC	CT	TT
Overall	535/1171 (46%)	301/436 (69%)	196/596 (33%)	38/139 (27%)
Baseline factors				
Age ≤ 40 y	98/174 (56%)	47/67 (70%)	42/86 (49%)	9/21 (43%)
Age > 40 y	437/997 (44%)	254/369 (69%)	154/510 (30%)	29/118 (25%)
Female	209/458 (46%)	102/148 (69%)	90/247 (36%)	17/63 (27%)
Male	326/713 (46%)	199/288 (69%)	106/349 (30%)	21/76 (28%)
HCV–RNA level, ≤600,000 IU/mL	130/192 (68%)	58/69 (84%)	57/94 (61%)	15/29 (52%)
HCV–RNA level, >600,000 IU/mL	405/979 (41%)	243/367 (66%)	139/502 (28%)	23/110 (21%)
METAVIR F0–2	471/988 (48%)	263/365 (72%)	173/505 (34%)	35/118 (30%)
METAVIR F3–4	37/133 (28%)	21/51 (41%)	14/64 (22%)	2/18 (11%)
Fasting glucose level, <5.6 mmol/L	419/835 (50%)	230/318 (72%)	159/415 (38%)	30/102 (29%)
Fasting glucose level, ≥5.6 mmol/L	116/336 (35%)	71/118 (60%)	37/181 (20%)	8/37 (22%)
BMI < 30	383/843 (45%)	206/306 (67%)	149/430 (35%)	28/107 (26%)
BMI ≥ 30	152/328 (46%)	95/130 (73%)	47/166 (28%)	10/32 (31%)
RBV dose, >13 mg/kg/day	313/649 (48%)	162/227 (71%)	124/334 (37%)	27/88 (31%)
RBV dose, ≤13 mg/kg/day	222/521 (43%)	139/208 (67%)	72/262 (27%)	11/51 (22%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	113/164 (69%)	48/56 (86%)	51/81 (63%)	14/27 (52%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	7/17 (41%)	5/8 (63%)	2/8 (25%)	0/1 (0%)
HCV–RNA level, >600,000 IU/mL and F0–2	358/824 (43%)	215/309 (70%)	122/424 (29%)	21/91 (23%)
HCV–RNA level, >600,000 IU/mL and F3–4	30/116 (26%)	16/43 (37%)	12/56 (21%)	2/17 (12%)
On-treatment responses				
RVR	126/150 (84%)	98/115 (85%)	22/29 (76%)	6/6 (100%)
Non-RVR	388/941 (41%)	193/291 (66%)	165/527 (31%)	30/123 (24%)
≥4-log reduction in HCV–RNA level at wk 4	173/220 (79%)	137/175 (78%)	32/40 (80%)	4/5 (80%)
<4-log reduction in HCV– RNA level at wk 4	362/951 (38%)	164/261 (63%)	164/556 (30%)	34/134 (25%)
cEVR	473/599 (79%)	288/354 (81%)	158/210 (75%)	27/35 (77%)
Partial EVR	58/280 (21%)	11/40 (28%)	37/191 (19%)	10/49 (20%)
Combination of wk 4 response + baseline factors				
RVR + baseline HCV–RNA level, ≤ 600,000	66/77 (86%)	47/52 (90%)	14/20 (70%)	5/5 (100%)
RVR + baseline HCV–RNA level, >600,000	60/73 (82%)	51/63 (81%)	8/9 (89%)	1/1 (100%)
Non-RVR + baseline HCV–RNA level, ≤ 600,000	58/97 (60%)	9/12 (75%)	41/64 (64%)	8/21 (38%)
Non-RVR + baseline HCV–RNA level, >600,000	330/844 (39%)	184/279 (66%)	124/463 (27%)	22/102 (22%)

Supplementary Table 4. Continued

Caucasians	Overall	CC	CT	TT
RVR + F0–2	112/135 (83%)	86/102 (84%)	20/27 (74%)	6/6 (100%)
RVR + F3–4	7/8 (88%)	7/8 (88%)	*	*
Non-RVR + F0–2	343/792 (43%)	169/241 (70%)	147/449 (33%)	27/102 (26%)
Non-RVR + F3–4	25/108 (23%)	12/36 (33%)	11/54 (20%)	2/18 (11%)
RVR + baseline HCV–RNA level, ≤600,000 + F0–2	58/69 (84%)	40/45 (89%)	13/19 (68%)	5/5 (100%)
RVR + baseline HCV–RNA level, ≤600,000 + F3–4	4/4 (100%)	4/4 (100%)	*	*
RVR + baseline HCV–RNA level, >600,000 + F0–2	54/66 (82%)	46/57 (81%)	7/8 (88%)	1/1 (100%)
RVR + baseline HCV–RNA level, >600,000 + F3–4	3/4 (75%)	3/4 (75%)	*	*
Non-RVR + baseline HCV–RNA level, ≤600,000 + F0–2	49/82 (60%)	6/7 (86%)	36/56 (64%)	7/19 (37%)
Non-RVR + baseline HCV–RNA level, ≤600,000 + F3–4	3/9 (33%)	1/3 (33%)	2/5 (40%)	0/1 (0%)
Non-RVR + baseline HCV–RNA level, >600,000 + F0–2	294/710 (41%)	163/234 (70%)	111/393 (28%)	20/83 (24%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	22/99 (22%)	11/33 (33%)	9/49 (18%)	2/17 (12%)
African Americans				
Overall	57/300 (19%)	20/42 (48%)	22/146 (15%)	15/112 (13%)
Baseline factors				
Age ≤ 40 y	4/17 (24%)	1/2 (50%)	2/11 (18%)	1/4 25%)
Age > 40 y	53/283 (19%)	19/40 (48%)	20/135 (15%)	14/108 (13%)
Female	27/128 (21%)	9/17 (53%)	10/61 (16%)	8/50 (16%)
Male	30/172 (17%)	11/25 (44%)	12/85 (14%)	7/62 (11%)
HCV–RNA level, ≤ 600,000 IU/mL	21/56 (38%)	4/4 (100%)	8/28 (29%)	9/24 (38%)
HCV–RNA level, >600,000 IU/mL	36/244 (15%)	16/38 (42%)	14/118 (12%)	6/88 (7%)
METAVIR F0–2	51/253 (20%)	17/35 (49%)	20/125 (16%)	14/93 (15%)
METAVIR F3–4	3/29 (10%)	1/3 (33%)	1/14 (7%)	1/12 (8%)
Fasting glucose level, <5.6 mmol/L	42/188 (22%)	15/29 (52%)	16/90 (18%)	11/69 (16%)
Fasting glucose level, ≥5.6 mmol/L	15/112 (13%)	5/13 (38%)	6/56 (11%)	4/43 (9%)
BMI < 30	25/162 (15%)	8/21 (38%)	11/81 (14%)	6/60 (10%)
BMI ≥ 30	32/138 (23%)	12/21 (57%)	11/65 (17%)	9/52 (17%)
RBV dose, >13 mg/kg/day	22/123 (18%)	8/18 (44%)	6/56 (11%)	8/49 (16%)
RBV dose, ≤13 mg/kg/day	35/176 (20%)	12/24 (50%)	16/90 (18%)	7/62 (11%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	19/48 (40%)	3/3 (100%)	7/22 (32%)	9/23 (39%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	0/4 (0%)	*	0/4 (0%)	*
HCV–RNA level, >600,000 IU/mL and F0–2	32/205 (16%)	14/32 (44%)	13/103 (13%)	5/70 (7%)

Supplementary Table 4. Continued

African Americans	Overall	CC	CT	TT
HCV–RNA level, >600,000 IU/mL and F3–4	3/25 (12%)	1/3 (33%)	1/10 (10%)	1/12 (8%)
On-treatment responses				
RVR	11/11 (100%)	5/5 (100%)	4/4 (100%)	2/2 (100%)
Non-RVR	43/240 (18%)	12/28 (43%)	18/122 (15%)	13/90 (14%)
≥4-log reduction in HCV–RNA level at wk 4	13/14 (93%)	7/7 (100%)	4/5 (80%)	2/2 (100%)
<4-log reduction in HCV–RNA level at wk 4	44/286 (15%)	13/35 (37%)	18/141 (13%)	13/110 (12%)
cEVR	45/69 (65%)	16/19 (84%)	15/26 (58%)	14/24 (58%)
Partial EVR	11/79 (14%)	4/13 (31%)	6/41 (15%)	1/25 (4%)
Combination of wk 4 response + baseline factors				
RVR + baseline HCV–RNA level, ≤600,000	8/8 (100%)	3/3 (100%)	3/3 (100%)	2/2 (100%)
RVR + baseline HCV–RNA level, >600,000	3/3 (100%)	2/2 (100%)	1/1 (100%)	* *
Non-RVR + baseline HCV–RNA level, ≤600,000	12/35 (34%)	*	5/18 (28%)	7/17 (41%)
Non-RVR + baseline HCV–RNA level, >600,000	31/205 (15%)	12/28 (43%)	13/104 (13%)	6/73 (8%)
RVR + F0–2	10/10 (100%)	4/4 (100%)	4/4 (100%)	2/2 (100%)
RVR + F3–4	*	*	*	*
Non-RVR + F0–2	39/203 (19%)	11/24 (46%)	16/105 (15%)	12/74 (16%)
Non-RVR + F3–4	2/22 (9%)	0/1 (0%)	1/11 (9%)	1/10 (10%)
RVR + baseline HCV–RNA level, ≤600,000 + F0–2	7/7 (100%)	2/2 (100%)	3/3 (100%)	2/2 (100%)
RVR + baseline HCV–RNA level, ≤600,000 + F3–4	*	*	*	*
RVR + baseline HCV–RNA level, >600,000 + F0–2	3/3 (100%)	2/2 (100%)	1/1 (100%)	*
RVR + baseline HCV–RNA level, >600,000 + F3–4	*	*	*	*
Non-RVR + baseline HCV–RNA level, ≤ 600,000 + F0–2	11/30 (37%)	*	4/14 (29%)	7/16 (44%)
Non-RVR + baseline HCV–RNA level, ≤ 600,000 + F3–4	0/3 (0%)	*	0/3 (0%)	*
Non-RVR + baseline HCV–RNA level, > 600,000 + F0–2	28/173 (16%)	11/24 (46%)	12/91 (13%)	5/58 (9%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	2/19 (11%)	0/1 (0%)	1/8 (13%)	1/10 (10%)
Hispanics				
Overall	47/116 (41%)	19/34 (56%)	21/56 (38%)	7/26 (27%)
Baseline factors				
Age ≤ 40 y	13/36 (36%)	4/10 (40%)	6/19 (32%)	3/7 (43%)
Age > 40 y	34/80 (43%)	15/24 (63%)	15/37 (41%)	4/19 (21%)
Female	14/39 (36%)	2/6 (33%)	9/24 (38%)	3/9 (33%)
Male	33/77 (43%)	17/28 (61%)	12/32 (38%)	4/17 (24%)
HCV–RNA level, ≤600,000 IU/mL	17/33 (52%)	5/6 (83%)	7/17 (41%)	5/10 (50%)
HCV–RNA level, >600,000 IU/mL	30/83 (36%)	14/28 (50%)	14/39 (36%)	2/16 (13%)

Supplementary Table 4. Continued

Hispanics	Overall	CC	CT	TT
METAVIR F0–2	44/99 (44%)	17/29 (59%)	20/51 (39%)	7/19 (37%)
METAVIR F3–4	2/16 (13%)	1/4 (25%)	1/5 (20%)	0/7 (0%)
Fasting glucose level, <5.6 mmol/L	34/85 (40%)	14/25 (56%)	14/43 (33%)	6/17 (35%)
Fasting glucose level, ≥5.6 mmol/L	13/31 (42%)	5/9 (56%)	7/13 (54%)	1/9 (11%)
BMI < 30	31/72 (43%)	13/20 (65%)	13/37 (35%)	5/15 (33%)
BMI ≥ 30	16/44 (36%)	6/14 (43%)	8/19 (42%)	2/11 (18%)
RBV dose, >13 mg/kg/day	29/70 (41%)	11/18 (61%)	13/35 (37%)	5/17 (29%)
RBV dose, ≤13 mg/kg/day	18/45 (40%)	8/15 (53%)	8/21 (38%)	2/9 (22%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	15/27 (56%)	3/3 (100%)	7/16 (44%)	5/8 (63%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	1/5 (20%)	1/2 (50%)	0/1 (0%)	0/2 (0%)
HCV–RNA level, >600,000 IU/mL and F0–2	29/72 (40%)	14/26 (54%)	13/35 (37%)	2/11 (18%)
HCV–RNA level, >600,000 IU/mL and F3–4	1/11 (9%)	0/2 (0%)	1/4 (25%)	0/5 (0%)
On-treatment responses				
RVR	15/18 (83%)	8/10 (80%)	5/6 (83%)	2/2 (100%)
Non-RVR	32/93 (34%)	11/20 (55%)	16/49 (33%)	5/24 (21%)
≥4-log reduction in HCV–RNA level at wk 4	13/19 (68%)	7/11 (64%)	6/8 (75%)	*
<4-log reduction in HCV–RNA level at wk 4	34/97 (35%)	12/23 (52%)	15/48 (31%)	7/26 (27%)
cEVR	41/54 (76%)	17/23 (74%)	18/24 (75%)	6/7 (86%)
Partial EVR	5/20	1/6	3/9	1/5
Combination of wk 4 response + baseline factors				
RVR + baseline HCV–RNA level, ≤600,000	10/11 (91%)	5/5 (100%)	3/4 (75%)	2/2 (100%)
RVR + baseline HCV–RNA level, >600,000	5/7 (71%)	3/5 (60%)	2/2 (100%)	*
Non-RVR + baseline HCV–RNA level, ≤ 600,000	7/22 (32%)	0/1 (0%)	4/13 (31%)	3/8 (38%)
Non-RVR + baseline HCV–RNA level, > 600,000	25/71 (35%)	11/19 (58%)	12/36 (33%)	2/16 (13%)
RVR + F0–2	13/16 (81%)	6/8 (75%)	5/6 (83%)	2/2 (100%)
RVR + F3–4	1/1 (100%)	1/1 (100%)	*	*
Non-RVR + F0–2	31/78 (40%)	11/17 (65%)	15/44 (34%)	5/17 (29%)
Non-RVR + F3–4	1/15 (7%)	0/3 (0%)	1/5 (20%)	0/7 (0%)
RVR + baseline HCV–RNA level, ≤ 600,000 + F0–2	8/9 (89%)	3/3 (100%)	3/4 (75%)	2/2 (100%)
RVR + baseline HCV–RNA level, ≤ 600,000 + F3–4	1/1 (100%)	1/1 (100%)	*	*
RVR + baseline HCV–RNA level, > 600,000 + F0–2	5/7 (71%)	3/5 (60%)	2/2 (0%)	*
RVR + baseline HCV–RNA level, >600,000 + F3–4	*	*	*	*

Supplementary Table 4. Continued

Hispanics	Overall	CC	CT	TT
Non-RVR + baseline HCV–RNA level, ≤ 600,000 + F0–2	7/18 (39%)	*	4/12 (33%)	3/6 (50%)
Non-RVR + baseline HCV–RNA level, ≤ 600,000 + F3–4	0/4 (0%)	0/1 (0%)	0/1 (0%)	0/2 (0%)
Non-RVR + baseline HCV–RNA level, >600,000 + F0–2	24/60 (40%)	11/17 (65%)	11/32 (34%)	2/11 (18%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	1/11 (9%)	0/2 (0%)	1/4 (25%)	0/5 (0%)

Supplementary Table 5. Multivariable Logistic Regression Models for SVR

Covariates	Odds ratio	95% CI	R^2	χ^2	*P* value
Model 1					
CC genotype vs non-CC	5.93	4.57–7.69	0.148	179.84	<.0001
Caucasian vs AA ethnicity	2.77	1.96–3.92	0.026	34.5	<.0001
Hispanic vs AA ethnicity	2.03	1.20–3.43			
Other vs AA ethnicity	1.65	0.73–3.75			
HCV–RNA level, per 1-log unit increase	0.46	0.37–0.56	0.046	56.53	<.0001
Metavir F0 vs F4	4.94	1.77–13.75	0.008	28.02	<.0001
Metavir F1 vs F4	3.78	2.16–6.64			
Metavir F2 vs F4	3.09	1.67–5.72			
Metavir F3 vs F4	1.73	0.80–3.73			
Fasting blood sugar level, per 1-unit decrease	1.30	1.12–1.51	0.004	11.51	.0007
BMI, per 5-unit increase	1.20	1.03–1.40	0.004	5.36	.0206
RBV, per 1-unit increase	1.10	1.01–1.20	0.003	4.54	.0332
Model 2					
RVR vs (non-RVR + non-CC)	8.45	5.44–13.12	0.182	200.93	<.0001
(Non-RVR + CC) vs (non-RVR + non-CC)	6.01	4.45–8.13			
Caucasian vs AA ethnicity	2.26	1.57–3.27	0.016	20.37	.0001
Hispanic vs AA ethnicity	1.82	1.05–3.14			
Other vs AA ethnicity	1.31	0.57–3.00			
HCV–RNA level, per 1-log unit increase until 7.0	0.55	0.44–0.69	0.02	25.96	<.0001
Metavir F0 vs F4	4.70	1.61–13.67	0.021	25.32	.0001
Metavir F1 vs F4	3.83	2.12–6.93			
Metavir F2 vs F4	2.95	1.53–5.68			
Metavir F3 vs F4	1.79	0.78–4.12			
Fasting blood sugar level, per 1-unit decrease	1.33	1.13–0.89	0.009	11.4	.0005

NOTE. Model 1: the baseline model included *IL-28B* type (CC vs non-CC) and the following covariates, previously identified to be associated independently with SVR in the IDEAL study population: ethnic background, age (continuous data), sex, BMI (continuous data), baseline HCV–RNA level (continuous data, $\log_{10}$ IU/mL), ALT level (continuous data), fasting glucose level (continuous data), hepatic steatosis (grade 0/1/2/3/4), hepatic fibrosis stage (METAVIR F0/F1/F2/F3/F4), and RBV dose (continuous data). PegIFN type was not associated with SVR in univariable analysis (Supplementary Table 11). Variables not present in the final model were removed by backward selection. A significance level of 0.05 was used for removal from the model.

Model 2: the week-4 model collapsed week-4 response and *IL-28B* polymorphism as a 3-level variable: (RVR vs non-RVR + CC IL-28B-type vs non-RVR + non-CC *IL-28B* type). Otherwise, the same covariates were included as for the baseline model.

Supplementary Table 6. Baseline Characteristics of the Adherent Subset

Baseline characteristics	Caucasians	African Americans	Hispanics	*P* value[a]	*P* value[b]	*P* value[c]
N	871	191	75			
Age, >40 y	755 (87%)	182 (95%)	53 (71%)	.0008	.0002	<.0001
Male sex	542 (62%)	120 (62%)	46 (61%)	.8769	.8783	.8209
BMI, ≥30 kg/m^2	250 (29%)	87 (46%)	31 (41%)	<.0001	.0216	.5334
HCV–RNA level, >600,000 IU/mL	727 (83%)	159 (83%)	54 (72%)	.9406	.012	.0388
ALT level, >ULN	732 (84%)	148 (78%)	66 (88%)	.0295	.3652	.0517
Fasting glucose level, ≥5.6 mmol/L	245 (28%)	75 (39%)	16 (21%)	.0024	.2065	.0055
Steatosis[d]	517 (59%)	127 (67%)	51 (68%)	.0676	.1426	.8141
METAVIR F3–4	101 (12%)	17 (9%)	12 (16%)	.2831	.2591	.0946
Peginterferon-alfa						
2b 1.0 ug/kg/wk	289 (33%)	59 (31%)	23 (31%)	.3175	.8154	.4771
2b 1.5 ug/kg/wk	310 (36%)	79 (41%)	26 (35%)			
2a 180 ug/wk	272 (31%)	53 (28%)	26 (35%)			
RBV, >13 mg/kg	475 (55%)	70 (37%)	49 (65%)	<.0001	.071	<.0001
rs12979860 Genotype frequency						
CC	336 (39%)	30 (16%)	26 (34%)	<.0001	.2091	.0006
CT	433 (49%)	91 (47%)	35 (47%)			
TT	102 (12%)	70 (37%)	14 (19%)			

[a]Caucasians vs African Americans.
[b]Caucasians vs Hispanics.
[c]African Americans vs Hispanics.
[d]Steatosis > 0% hepatocytes.

Supplementary Table 7. HCV–RNA Levels at Baseline and During Treatment in the Adherent Subset

				P value[a]		
Baseline viral load, $\log_{10}$ IU/mL	CC	CT	TT	CC vs CT	CC vs TT	CT vs TT
Caucasians						
N	336	433	102			
Median (25th–75th percentile)	6.6 (6.1–6.9)	6.4 (6.0–6.7)	6.3 (5.9–6.6)	<.0001	<.0001	.0117
HCV–RNA level, >600,000 IU/mL, N (%)	280/336 (83.3%)	368/433 (85.0%)	79/102 (77.5%)	.5318	.176	.0647
African Americans						
N	30	91	70			
Median (25th–75th percentile)	6.6 (6.2–6.9)	6.4 (6.0–6.7)	6.1 (5.8–6.5)	.0295	.0003	.0140
HCV–RNA level, >600,000 IU/mL, N (%)	28/30 (93.3%)	77/91 (84.6%)	54/70 (77.1%)	.3522	.0858	.2274
Hispanics						
N	26	35	14			
Median (25th–75th percentile)	6.5 (6.2–7.0)	6.1 (5.6–6.6)	6.0 (5.3–6.3)	.0243	.0245	.4621
HCV–RNA level, >600,000 IU/mL, N (%)	22/26 (84.6%)	23/53 (65.7%)	9/14 (64.3%)	.1423	.2338	1.000

[a]Pairwise comparisons of median viral load were performed using the Wilcoxon 2-sample test for continuous data or the chi-square test for categoric data.

Supplementary Table 8. Median On-Treatment Reduction of HCV–RNA Levels in the Adherent Subset

				P value[a]		
Median on-treatment viral load reduction, $\log_{10}$ IU/mL	CC	CT	TT	CC vs CT	CC vs TT	CT vs TT
Caucasians						
Week 2 (n = 826), median (25th–75th percentile)	2.5 (1.9–3.3)	0.9 (0.4–1.5)	0.6 (0.3–1.1)	<.0001	<.0001	.0031
Week 4 (n = 832), median (25th–75th percentile)	3.7 (3.0–4.7)	1.5 (0.9–2.5)	1.0 (0.7–2.0)	<.0001	<.0001	.0035
Week 12 (n = 865), median (25th–75th percentile)	5.5 (4.8–5.9)	3.7 (1.7–5.0)	3.2 (1.7–6.6)	<.0001	<.0001	.1005
African Americans						
Week 2 (n = 157), median (25th–75th percentile)	1.7 (0.5–2.3)	0.7 (0.4–1.1)	0.5 (0.3–0.8)	.0014	.0002	.0999
Week 4 (n = 162), median (25th–75th percentile)	2.7 (1.1–3.6)	1.1 (0.6–2.0)	0.9 (0.5–1.5)	.0013	.0003	.1615
Week 12 (n = 190), median (25th–75th percentile)	4.7 (2.3–5.4)	1.7 (1.0–4.0)	1.8 (0.9–4.0)	.0001	.0003	.9521
Hispanics						
Week 2 (n = 74), median (25th–75th percentile)	2.3 (1.6–3.7)	0.8 (0.4–1.3)	0.4 (0.1–1.1)	<.0001	.0002	.1629
Week 4 (n = 75), median (25th–75th percentile)	3.5 (2.7–4.8)	1.3 (0.7–2.4)	0.7 (0.4–1.8)	<.0001	.0001	.1012
Week 12 (n = 74), median (25th–75th percentile)	5.4 (4.8–5.9)	3.6 (1.1–4.9)	1.3 (0.6–3.3)	<.0001	<.0001	.0398

[a]Pairwise comparisons of median viral load were performed using the Wilcoxon 2-sample test.

Supplementary Table 9. Rates of Virologic Response for Caucasian, African American, and Hispanic Populations in the Adherent Subset

					P value		
	Overall	CC	CT	TT	CC vs CT	CC vs TT	CT vs TT
Rates of on-treatment response, SVR							
Caucasians							
SVR	488/871 (56%)	274/336 (82%)	180/433 (42%)	34/102 (33%)	<.0001	<.0001	.1266
URVR/wk 2	49/826 (6%)	40/321 (12%)	7/409 (2%)	2/96 (2%)	<.0001	.0030	.6824
RVR/wk 4	117/833 (14%)	91/321 (28%)	20/413 (5%)	6/99 (6%)	<.0001	<.0001	.6201
cEVR/wk 12	500/865 (58%)	295/334 (88%)	173/431 (40%)	32/100 (32%)	<.0001	<.0001	.132
EOTR/wk 48	604/846 (71%)	310/331 (94%)	241/418 (58%)	53/97 (55%)	<.0001	<.0001	.5887
Relapse	116/604 (19%)	36/310 (12%)	61/241 (25%)	19/53 (36%)	<.0001	<.0001	.1186
African Americans							
SVR	45/191 (24%)	16/30 (53%)	17/91 (19%)	12/70 (17%)	.0002	.0002	.8012
URVR/wk 2	3/157 (2%)	2/25 (8%)	0/77 (0%)	1/55 (2%)	.0582	.2288	.4167
RVR/wk 4	7/162 (4%)	3/25 (12%)	3/81 (4%)	1/56 (2%)	.1186	.085	.6447
cEVR/wk 12	48/190 (25%)	14/30 (47%)	18/90 (20%)	16/70 (23%)	.0042	.0173	.6612
EOTR/wk 48	63/186 (34%)	21/30 (70%)	23/86 (27%)	19/70 (27%)	<.0001	<.0001	.9555
Relapse	18/63 (29%)	5/21 (24%)	6/23 (26%)	7/19 (37%)	.8617	.3691	.453
Hispanics							
SVR	38/75 (51%)	20/26 (77%)	15/35 (43%)	3/14 (21%)	.0078	.0007	.0160
URVR/wk 2	10/74 (14%)	6/26 (23%)	3/34 (9%)	1/14 (7%)	.1574	.387	1.000
RVR/wk 4	13/75 (17%)	10/26 (38%)	2/35 (6%)	1/14 (7%)	.0015	.0344	.8505
cEVR/wk 12	40/74 (54%)	22/25 (88%)	15/35 (43%)	3/14 (21%)	.0004	<.0001	.2024
EOTR/wk 48	47/73 (64%)	25/26 (96%)	19/34 (88%)	3/13 (38%)	.0005	<.0001	.0438
Relapse	9/47 (19%)	5/25 (20%)	4/19 (21%)	0/3 (0%)	.9317	.3927	.3796
Rates of SVR by wk 4, wk 12 responses							
Caucasians							
RVR	112/117 (96%)	87/91 (96%)	19/20 (95%)	6/6 (100%)	.9061	.5999	.5765
Non-RVR	355/716 (50%)	177/230 (77%)	152/393 (39%)	26/93 (28%)	<.0001	<.0001	.0537
cEVR	435/500 (87%)	264/295 (89%)	146/173 (84%)	25/32 (78%)	.1061	.0762	.3812
Partial EVR	50/184 (27%)	8/27 (30%)	34/124 (27%)	8/33 (24%)	.8163	.6387	.7141
African Americans							
RVR	7/7 (100%)	3/3 (100%)	3/3 (100%)	1/1 (100%)	1.000	1.000	1.000
Non-RVR	35/155 (23%)	10/22 (45%)	14/78 (18%)	11/55 (20%)	.0076	.0235	.7656
cEVR	37/48 (77%)	13/14 (93%)	13/18 (72%)	11/16 (69%)	.1379	.0996	.8245
Partial EVR	7/45 (16%)	3/9 (33%)	3/20 (15%)	1/16 (6%)	.2595	.0762	.4065

Supplementary Table 9. Continued

					P value		
	Overall	CC	CT	TT	CC vs CT	CC vs TT	CT vs TT
Hispanics							
RVR	12/13 (92%)	9/10 (90%)	2/2 (100%)	1/1 (100%)	.6404	.7401	1.000
Non-RVR	26/62 (42%)	11/16 (69%)	13/33 (39%)	2/13 (15%)	.0539	.0041	.7656
cEVR	34/40 (85%)	19/22 (86%)	12/15 (80%)	3/3 (100%)	.6696	1.000	1.000
Partial EVR	3/9 (33%)	0/3 (0%)	3/5 (60%)	0/1 (0%)	.1964	1.000	1.000

NOTE. Data for SVR include the entire adherent subset. Data for on-treatment virologic milestones/relapse rates refer to the number of patients who had the evaluation performed. The trial protocol included a stopping rule for patients who did not attain EVR at week 12 (no EVR = reduction of serum HCV RNA < 2 $\log_{10}$ IU at week 12).

EOTR, end-of-treatment response at week 48; URVR, ultrarapid virologic response at week 2.

Supplementary Table 10. SVR Rates for Each Genotype of the *IL-28B* Polymorphism in the Adherent Subset, According to Baseline Characteristics and Week 4 and Week 12 On-Treatment Responses

	Overall	CC	CT	TT
Caucasians				
Overall	488/871 (56%)	274/336 (82%)	180/433 (42%)	34/102 (33%)
Baseline factors				
Age ≤ 40 y	82/116 (71%)	38/45 (84%)	37/58 (64%)	7/13 (54%)
Age > 40 y	406/755 (54%)	236/291 (81%)	143/375 (38%)	27/89 (30%)
Female	189/329 (57%)	91/107 (85%)	83/180 (46%)	15/42 (36%)
Male	299/542 (55%)	183/229 (80%)	97/253 (38%)	19/60 (32%)
HCV–RNA level, ≤600,000 IU/mL	113/144 (78%)	51/56 (91%)	48/65 (74%)	14/23 (61%)
HCV–RNA level, >600,000 IU/mL	375/727 (52%)	223/280 (80%)	132/368 (36%)	20/79 (25%)
METAVIR F0–2	452/770 (59%)	254/296 (86%)	166/384 (43%)	32/90 (36%)
METAVIR F3–4	36/101 (36%)	20/40 (50%)	14/49 (29%)	2/12 (17%)
Fasting glucose level, <5.6 mmol/L	381/626 (61%)	210/247 (85%)	145/301 (48%)	26/78 (33%)
Fasting glucose level, ≥5.6 mmol/L	107/245 (44%)	64/89 (72%)	35/132 (27%)	8/24 (33%)
BMI < 30	142/250 (57%)	87/101 (86%)	45/123 (37%)	10/26 (38%)
BMI ≥ 30	346/621 (56%)	187/235 (80%)	135/310 (44%)	24/76 (32%)
RBV dose, >13 mg/kg/day	282/475 (59%)	147/176 (84%)	111/238 (47%)	24/61 (39%)
RBV dose, ≤13 mg/kg/day	206/396 (52%)	127/160 (79%)	69/195 (35%)	10/41 (24%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	106/129 (82%)	46/48 (96%)	46/59 (78%)	14/22 (64%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	7/15 (47%)	5/8 (63%)	2/6 (33%)	0/1 (0%)
HCV–RNA level, >600,000 IU/mL and F0–2	346/641 (54%)	208/248 (84%)	120/325 (37%)	18/68 (26%)
HCV–RNA level, >600,000 IU/mL and F3–4	29/86 (34%)	15/32 (47%)	12/43 (28%)	2/11 (18%)
On-treatment responses				
RVR	112/117 (96%)	87/91 (96%)	19/20 (95%)	6/6 (100%)
Non-RVR	355/716 (50%)	177/230 (77%)	152/393 (39%)	26/93 (28%)
≥4-log reduction in HCV RNA at wk 4	157/167 (94%)	125/134 (93%)	28/28 (100%)	4/5 (80%)
<4-log reduction in HCV RNA at wk 4	331/704 (47%)	149/202 (74%)	152/405 (38%)	30/97 (31%)
cEVR	435/500 (87%)	264/295 (89%)	146/173 (84%)	25/32 (78%)
Partial EVR	50/184	8/27	34/124	8/33
Combination of wk 4 response + baseline factors				
RVR + baseline HCV–RNA level, ≤ 600,000	59/60 (98%)	42/42 (100%)	12/13 (92%)	5/5 (100%)
RVR + baseline HCV–RNA level, >600,000	53/57 (93%)	45/49 (92%)	7/7 (100%)	1/1 (100%)
Non-RVR + baseline HCV–RNA level, ≤600,000	48/71 (68%)	7/10 (70%)	34/45 (76%)	7/16 (44%)
Non-RVR + baseline HCV–RNA level, >600,000	307/645 (48%)	170/220 (77%)	118/348 (34%)	19/77 (25%)

Supplementary Table 10. Continued

Caucasians	Overall	CC	CT	TT
RVR + F0–2	105/109 (96%)	80/83 (96%)	19/20 (95%)	6/6 (100%)
RVR + F3–4	7/8 (88%)	7/8 (88%)	*	*
Non-RVR + F0–2	331/637 (52%)	166/204 (81%)	141/352 (40%)	24/81 (30%)
Non-RVR + F3–4	24/79 (30%)	11/26 (42%)	11/41 (27%)	2/12 (17%)
RVR + baseline HCV–RNA level, ≤600,000 + F0–2	55/56 (98%)	38/38 (100%)	12/13 (92%)	5/5 (100%)
RVR + baseline HCV–RNA level, ≤600,000 + F3–4	4/4 (100%)	4/4 (100%)	*	*
RVR + baseline HCV–RNA level, >600,000 + F0–2	50/53 (94%)	42/45 (93%)	7/7 (100%)	1/1 (100%)
RVR + baseline HCV–RNA level, >600,000 + F3–4	3/4 (75%)	3/4 (75%)	*	*
Non-RVR + baseline HCV–RNA level, ≤600,000 + F0–2	45/64 (70%)	6/7 (86%)	32/42 (76%)	7/15 (47%)
Non-RVR + baseline HCV–RNA level, ≤600,000 + F3–4	3/7 (43%)	1/3 (33%)	2/3 (66%)	0/1 (0%)
Non-RVR + baseline HCV–RNA level, >600,000 + F0–2	286/573 (50%)	160/197 (81%)	109/310 (35%)	17/66 (26%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	21/72 (29%)	10/23 (43%)	9/38 (24%)	2/11 (18%)
African Americans				
Overall	45/191 (24%)	16/30 (53%)	17/91 (19%)	12/70 (17%)
Baseline factors				
Age ≤ 40 y	3/9 (33%)	0/1 (0%)	2/5 (40%)	1/3 (33%)
Age > 40 y	42/182 (23%)	16/29 (55%)	15/86 (17%)	11/67 (16%)
Female	20/71 (28%)	7/11 (64%)	7/29 (24%)	6/31 (19%)
Male	25/120 (21%)	9/19 (47%)	10/62 (16%)	6/39 (15%)
HCV–RNA level, ≤600,000 IU/mL	14/32 (44%)	2/2 (100%)	6/14 (43%)	6/16 (38%)
HCV–RNA level, >600,000 IU/mL	31/159 (20%)	14/28 (50%)	11/77 (14%)	6/54 (11%)
METAVIR F0–2	42/174 (24%)	15/28 (54%)	16/83 (19%)	11/63 (17%)
METAVIR F3–4	3/17 (18%)	1/2 (50%)	1/8 (13%)	1/7 (14%)
Fasting glucose level, < 5.6 mmol/L	32/116 (28%)	11/19 (58%)	12/57 (21%)	9/40 (23%)
Fasting glucose level, ≥ 5.6 mmol/L	13/75 (17%)	5/11 (45%)	5/34 (15%)	3/30 (10%)
BMI < 30	21/104 (20%)	6/14 (43%)	9/51 (18%)	6/39 (15%)
BMI ≥ 30	24/87 (28%)	10/16 (63%)	8/40 (20%)	6/31 (19%)
RBV dose, >13 mg/kg/day	16/70 (23%)	5/10 (50%)	5/29 (17%)	6/31 (19%)
RBV dose, ≤13 mg/kg/day	29/121 (24%)	11/20 (55%)	12/62 (19%)	6/39 (15%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	14/30 (47%)	2/2 (100%)	6/12 (50%)	6/16 (38%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	0/2 (0%)	*	0/2 (0%)	*

Supplementary Table 10. Continued

African Americans	Overall	CC	CT	TT
HCV–RNA level, >600,000 IU/mL and F0–2	28/144 (19%)	13/26 (50%)	10/71 (14%)	5/47 (11%)
HCV–RNA level, >600,000 IU/mL and F3–4	3/15 (20%)	1/2 (50%)	1/6 (17%)	1/7 (14%)
On-treatment responses				
RVR	7/7 (100%)	3/3 (100%)	3/3 (100%)	1/1 (100%)
Non-RVR	35/155 (23%)	10/22 (45%)	14/78 (18%)	11/55 (20%)
≥4-log reduction in HCV RNA at wk 4	9/9 (100%)	5/5 (100%)	3/3 (100%)	1/1 (100%)
<4-log reduction in HCV RNA at wk 4	36/182 (20%)	11/25 (44%)	14/88 (16%)	11/69 (16%)
cEVR	37/48 (77%)	13/14 (93%)	13/18 (72%)	11/16 (69%)
Partial EVR	7/45 (16%)	3/9 (33%)	3/20 (15%)	1/16 (6%)
Combination of wk 4 response + baseline factors				
RVR + baseline HCV–RNA level, ≤600,000	4/4 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
RVR + baseline HCV–RNA level, >600,000	3/3 (100%)	2/2 (100%)	1/1 (100%)	*
Non-RVR + baseline HCV–RNA level, ≤600,000	9/19 (47%)	*	4/8 (50%)	5/11 (45%)
Non-RVR + baseline HCV–RNA level, >600,000	26/136 (19%)	10/22 (45%)	10/70 (14%)	6/44 (14%)
RVR + F0–2	7/7 (100%)	3/3 (100%)	3/3 (100%)	1/1 (100%)
RVR + F3–4	*	*	*	*
Non-RVR + F0–2	33/145 (23%)	10/22 (45%)	13/73 (18%)	10/50 (20%)
Non-RVR + F3–4	2/10 (20%)	*	1/5 (20%)	1/5 (20%)
RVR + baseline HCV–RNA level, ≤600,000 + F0–2	4/4 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
RVR + baseline HCV–RNA level, ≤600,000 + F3–4	*	*	*	*
RVR + baseline HCV–RNA level, >600,000 + F0–2	3/3 (100%)	2/2 (100%)	1/1 (100%)	*
RVR + baseline HCV–RNA level, >600,000 + F3–4	*	*	*	*
Non-RVR + baseline HCV–RNA level, ≤600,000 + F0–2	9/18 (50%)	*	4/7 (57%)	5/11 (45%)
Non-RVR + baseline HCV–RNA level, ≤600,000 + F3–4	1/1 (100%)	1/1 (100%)	*	*
Non-RVR+ baseline HCV–RNA level, >600,000 + F0–2	24/127 (19%)	10/22 (45%)	9/66 (14%)	5/39 (13%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	2/9 (22%)	*	1/4 (25%)	1/5 (20%)
Hispanics				
Overall	38/75 (51%)	20/26 (77%)	15/35 (43%)	3/14 (21%)
Baseline factors				
Age ≤ 40 y	12/22 (55%)	5/6 (83%)	5/12 (42%)	2/4 (50%)
Age > 40 y	26/53 (49%)	15/20 (75%)	10/23 (43%)	1/10 (10%)
Female	13/29 (45%)	2/4 (50%)	10/20 (50%)	1/5 (20%)
Male	25/46 (54%)	18/22 (82%)	5/15 (33%)	2/9 (22%)
HCV–RNA level, ≤600,000 IU/mL	12/21 (57%)	4/4 (100%)	6/12 (50%)	2/5 (40%)
HCV–RNA level, >600,000 IU/mL	26/54 (48%)	16/22 (73%)	9/23 (39%)	1/9 (11%)

Supplementary Table 10. Continued

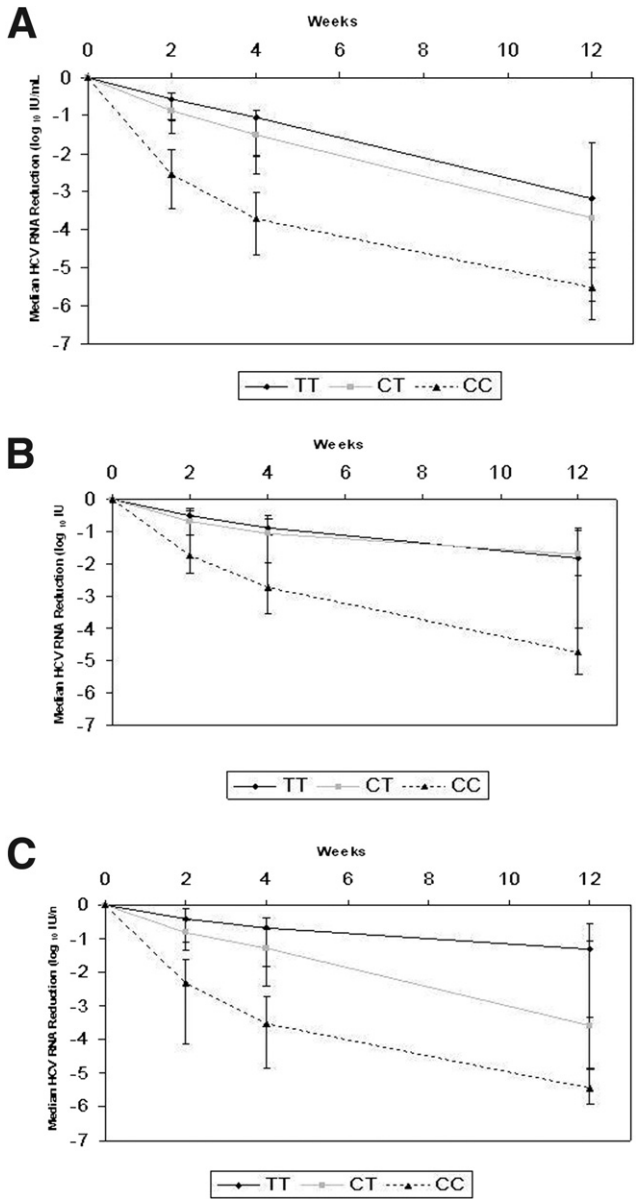
Hispanics	Overall	CC	CT	TT
METAVIR F0–2	35/63 (56%)	18/22 (82%)	14/31 (45%)	3/10 (30%)
METAVIR F3–4	3/12 (25%)	2/4 (50%)	1/4 (25%)	0/4 (0%)
Fasting glucose level, <5.6 mmol/L	29/59 (49%)	17/21 (81%)	9/28 (32%)	3/10 (30%)
Fasting glucose level, ≥5.6 mmol/L	9/16 (56%)	3/5 (60%)	6/7 (86%)	0/4 (0%)
BMI < 30	24/44 (55%)	15/17 (88%)	6/18 (33%)	3/9 (33%)
BMI ≥ 30	14/31 (45%)	5/9 (56%)	9/17 (53%)	0/5 (0%)
RBV dose, >13 mg/kg/day	26/49 (53%)	14/18 (78%)	9/22 (41%)	3/9 (33%)
RBV dose, ≤13 mg/kg/day	12/26 (46%)	6/8 (75%)	6/13 (46%)	0/5 (0%)
Combination of baseline factors				
HCV–RNA level, ≤600,000 IU/mL and F0–2	10/17 (59%)	2/2 (100%)	6/11 (55%)	2/4 (50%)
HCV–RNA level, ≤600,000 IU/mL and F3–4	2/4 (50%)	2/2 (100%)	0/1 (0%)	0/1 (0%)
HCV–RNA level, >600,000 IU/mL and F0–2	25/46 (54%)	16/20 (80%)	8/20 (40%)	1/6 (17%)
HCV–RNA level, >600,000 IU/mL and F3–4	1/8 (12.5%)	0/2 (0%)	1/3 (33%)	0/3 (0%)
On-treatment responses				
RVR	12/13 (92%)	9/10 (90%)	2/2 (100%)	1/1 (100%)
Non-RVR	26/62 (42%)	11/16 (69%)	13/33 (39%)	2/13 (15%)
≥4-log reduction in HCV RNA at wk 4	10/11 (91%)	8/9 (89%)	2/2 (100%)	*
<4-log reduction in HCV RNA at wk 4	28/64 (44%)	12/17 (71%)	13/33 (39%)	3/14 (21%)
cEVR	34/40 (85%)	19/22 (86%)	12/15 (80%)	3/3 (100%)
Partial EVR	3/9 (33%)	0/3 (0%)	3/5 (60%)	0/1 (0%)
Combination of wk 4 response + baseline factors				
RVR + baseline HCV RNA ≤ 600,000	6/6 (100%)	4/4 (100%)	1/1 (100%)	1/1 (100%)
RVR + baseline HCV–RNA level, >600,000	6/7 (86%)	5/6 (83%)	1/1 (100%)	*
Non-RVR + baseline HCV–RNA level, ≤600,000	6/15 (40%)	*	5/11 (45%)	1/4 (25%)
Non-RVR + baseline HCV–RNA level, >600,000	20/47 (43%)	11/16 (69%)	8/22 (36%)	1/9 (11%)
RVR + F0–2	10/11 (91%)	7/8 (88%)	2/2 (100%)	1/1 (100%)
RVR + F3–4	2/2 (100%)	2/2 (100%)	*	*
Non-RVR + F0–2	25/52 (48%)	11/14 (79%)	12/29 (41%)	2/9 (22%)
Non-RVR + F3–4	1/10 (10%)	0/2 (0%)	1/4 (25%)	0/4 (0%)
RVR + baseline HCV–RNA, ≤600,000 + F0–2	4/4 (100%)	2/2 (100%)	1/1 (100%)	1/1 (100%)
RVR + baseline HCV–RNA level, ≤600,000 + F3–4	2/2 (100%)	2/2 (100%)	*	*
RVR + baseline HCV–RNA level, >600,000 + F0–2	6/7 (86%)	5/6 (83%)	1/1 (100%)	*
RVR + baseline HCV–RNA level, >600,000 + F3–4	*	*	*	*

Supplementary Table 10. Continued

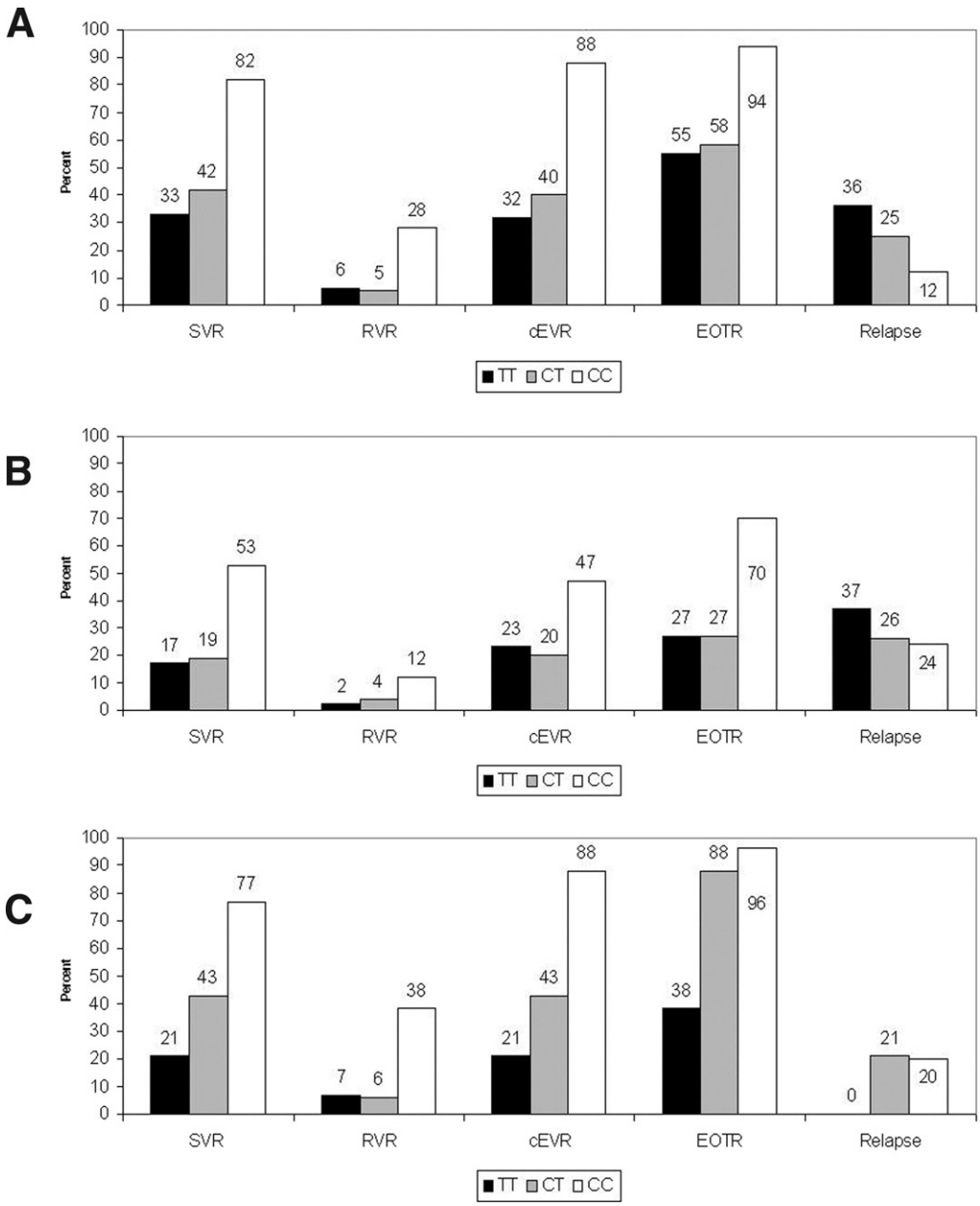
	Overall	CC	CT	TT
Non-RVR + baseline HCV–RNA level, ≤60,0000 + F0–2	6/13 (46%)	*	5/10 (50%)	1/3 (33%)
Non-RVR + baseline HCV–RNA level, ≤600,000 + F3–4	0/2 (0%)	*	0/1 (0%)	0/1 (0%)
Non-RVR + baseline HCV–RNA level, >600,000 + F0–2	19/39 (49%)	11/14 (79%)	7/19 (37%)	1/6 (17%)
Non-RVR + baseline HCV–RNA level, >600,000 + F3–4	1/8 (13%)	0/2 (0%)	1/3 (33%)	0/2 (0%)

Supplementary Table 11. SVR Rates for Each Genotype of the *IL-28B* Polymorphism in the Overall Cohort, According to PegIFN Type

						P value		
Population	*IL-28B* type	N	PegIFN-2b 1.0	PegIFN-2b 1.5	PegIFN-2a	PegIFN2-b1.0 vs PegIFN-2b1.5	PegIFN-2b1.0 vs PegIFN-2a	PegIFN-b1.5 vs PegIFN-2a
Caucasians	CC	436	106/148 (72%)	106/151 (70%)	89/137 (65%)	.7865	.2270	.3427
	CT	596	62/184 (34%)	63/218 (29%)	71/194 (37%)	.3006	.5548	.0959
	TT	139	7/44 (16%)	18/48 (38%)	13/47 (28%)	.0200	.1761	.3064
African Americans	CC	42	6/13 (46%)	6/14 (43%)	8/15 (53%)	.8632	.7047	.5726
	CT	146	6/49 (12%)	7/53 (13%)	9/44 (20%)	.8842	.2825	.3384
	TT	112	2/26 (8%)	4/51 (8%)	9/35 (26%)	1.000	.0967	.0323
Hispanics	CC	34	4/10 (40%)	7/13 (54%)	8/11 (72%)	.6802	.1984	.4225
	CT	56	3/16 (19%)	9/22 (41%)	9/18 (50%)	.1780	.0796	.7504
	TT	26	2/10 (20%)	3/10 (30%)	2/6 (33%)	1.000	.6044	1.000



Supplementary Figure 1. Median reductions in viral load from baseline on the basis of *IL-28B* genotype in the adherent subset. (*A*) Caucasians, (*B*) African Americans, and (*C*) Hispanics. *Bars* represent 25th and 75th percentiles. Statistical comparisons are presented in Supplementary Tables 7 and 8.



Supplementary Figure 2. Virologic responses on treatment on the basis of *IL-28B* SNP genotype and ethnicity in the adherent subset. (*A*) Caucasians, (*B*) African Americans, and (*C*) Hispanics. EOTR, end-of-treatment response. Statistical comparisons are presented in Supplementary Tables 7 and 8.