MAJOR ARTICLE

Prediction of Response to Pegylated Interferon plus Ribavirin by *IL28B* Gene Variation in Patients Coinfected with HIV and Hepatitis C Virus

Juan A. Pineda,[1] Antonio Caruz,[3] Antonio Rivero,[4] Karin Neukam,[1] Irene Salas,[3] Ángela Camacho,[4] José C. Palomares,[2] José A. Mira,[1] Antonio Martínez,[5] Carmen Roldán,[1] Julián de la Torre,[4] and Juan Macías[1]

Units of [1]Infectious Diseases and [2]Microbiology, Hospital Universitario de Valme, Seville, [3]Immunogenetics Unit, Faculty of Sciences, Universidad de Jaen, Jaen, and [4]Unit of Infectious Diseases and [5]Molecular Genetics Laboratory, Unit of Clinical Analysis, Hospital Universitario Reina Sofía, Cordoba, Spain

Background. Variation in the *IL28B* gene is associated with sustained virologic response (SVR) to pegylated interferon plus ribavirin in hepatitis C virus (HCV)–monoinfected patients with genotype 1. Data on other genotypes and on patients coinfected with human immunodeficiency virus (HIV) and HCV are more limited. We aimed to assess the predictive ability of variations in the single-nucleotide polymorphism rs12979860 for SVR in HIV/HCV-coinfected patients, regardless of HCV genotype.

Methods. The rs12979860 genotype was determined by polymerase chain reaction in 154 patients who had received therapy against HCV with pegylated interferon plus ribavirin.

Results. rs12979860 genotype was TT in 20 patients (13%), TC in 66 patients (43%), and CC in 68 patients (44%). Rates of SVR in patients with genotype CC and in those with genotype TC or TT, according to HCV genotype, were, respectively, 50% and 17% ($P < .001$) in patients with genotype 1, 80% and 25% ($P = .027$) in patients with genotype 4, and 93% and 77% ($P = .115$) in patients with genotype 3. The median (interquartile range) low-density lipoprotein cholesterol level in patients with rs12979860 CC was 89 mg/dL (73–120 mg/dL) versus 75 mg/dL (55–91 mg/dL) ($P = .001$) in those with TC or TT. Independent predictors of SVR were HCV genotype 2–3 (odds ratio [OR], 13.98; 95% confidence interval [CI], 4.87–40.1; $P < .001$), rs12979860 CC (OR, 5.05; 95% CI, 2.04–12.5; $P < .001$), baseline plasma HCV RNA load of ⩽600,000 IU/mL (OR, 1.99; 95% CI, 1.18–3.34; $P = .009$), and female sex (OR, 4.28; 95% CI, 1.08–16.96; $P = .039$).

Conclusions. *IL28B* gene variations independently predict SVR in HIV/HCV-coinfected patients with HCV genotype 1 and non–genotype 1 HCV infection. The association between rs12979860 and plasma low-density lipoprotein cholesterol suggests that the system low-density lipoprotein ligand/receptor might be involved in the effect of this genotype.

The likelihood of attaining a sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection depends on viral-, disease-, and host-related factors [1]. Among host-related factors, genetic factors may play a critical role. Thus, it has been proven that polymorphisms near the *IL28B* gene on chromosome 19, which encodes the type III interferon (IFN-λ3), predict SVR in HCV-monoinfected patients bearing genotype 1 who are treated with pegylated interferon plus ribavirin [2–5]. Specifically, the single-nucleotide polymorphism (SNP) rs12979860, located 3 kilobases upstream of the *IL28B* gene, is associated with more than a 2-fold difference in the rate of SVR [2]. Likewise, this polymorphism confers a 3-fold higher ability to spontaneously clear HCV [6]. The use of these genetic markers may help us to select patients who are more or less prone to respond to pegylated interferon plus ribavirin. The information on the predictive value of variations in the *IL28B* gene in patients harboring HCV genotypes other than 1 is more limited, but recent studies have shown that they are also associated with response to pegylated interferon plus ribavirin in ge-

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Reprints or correspondence: Dr Juan A. Pineda, Unidad de Enfermedades Infecciosas, Hospital Universitario de Valme, Avda de Bellavista, 41014 Sevilla, Spain (japineda@telefonica.net); or Dr Karin Neukam, Unidad de Enfermedades Infecciosas, Hospital Universitario de Valme, Avda de Bellavista, 41014 Sevilla, Spain (keule165@gmail.com).

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Table 1. Main Demographic and Clinical Characteristics of the Population Included in the On-Treatment Analysis

Characteristics	On-Treatment Analysis Population (n = 154)
Age, median years (interquartile range)	42 (38–44)
Male sex	130 (85)
BMI, median value (interquartile range)	23 (21–26)
Former IDU	137 (89)
HCV genotype	
1	82 (53)
2	1 (0.6)
3	50 (32)
4	21 (14)
Plasma HCV RNA load, median $\log_{10}$ IU/mL (interquartile range)	6.1 (5.2–6.6)
Serum ALT level, median IU/L (interquartile range)	66 (46–99)
Fibrosis stage in liver biopsy (n = 108)	
0	1/108 (1)
1	16/108 (15)
2	48/108 (44)
3	29/108 (27)
4	14/108 (13)
Liver stiffness, median kPa (interquartile range)	8.8/87 (6.5–14)
Advanced fibrosis by biopsy or elastography[a]	58/150 (38)
Type of pegylated interferon	
Alfa-2a	110 (71)
Alfa-2b	45 (29)
Ribavirin dose/weight, median (interquartile range), (mg/kg)	15 (13–17)
Exposure to planned HCV therapy ⩾80%	144 (93)
HBsAg positive	5 (3)
Baseline plasma LDL-C level, median mg/dL (interquartile range)	81 (61–105)
CDC clinical category C	56 (36)
Undetectable HIV RNA load	128 (83)
$CD4^+$ cell count, median mm^3 (interquartile range)	495 (382–730)
Concomitant antiretroviral therapy	134 (87)
Use of zidovudine	20 (13)
Use of abacavir	24 (16)

NOTE. Data are no. (%) of population, unless otherwise indicated. ALT, alanine aminotransferase; BMI, body mass index, calculated as the square of height in meters divided by weight in kilograms; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IDU, injection drug user; LDL-C, low-density lipoprotein cholesterol.

[a] Fibrosis stage in biopsy of F3 or higher or liver stiffness ⩾11 kPa if biopsy had not been performed.

notype 1 or 4 carriers, considered as a whole, but not in those bearing genotype 2 or 3 [5, 7].

Patients who are coinfected with human immunodeficiency virus (HIV) and HCV have singularities regarding predictors of SVR. Thus, the overall rate of response in HIV/HCV-coinfected patients is lower than that in HCV-monoinfected patients [8]. Moreover, certain conditions that may have a negative impact on SVR are more common among or exclusive to HIV-infected patients, such as antiretroviral drugs interfering with hepatitis C therapy, $CD4^+$ cell depletion, insulin resistance, steatosis, or advanced fibrosis [8]. A recent study has suggested that the rs12979860 genotype also predicts SVR in HIV/HCV-coinfected patients with genotypes 1–4 considered together [7], but additional studies are required to confirm this point, to know the role of the *IL28B* genotype in patients with specific HCV genotypes, and to analyze the associations of the *IL28B* genotype with other factors that may influence SVR in HIV/HCV-coinfected patients.

In this study, we aimed to assess whether the polymorphism rs12979860 in the *IL28B* region independently predicts SVR in a cohort of HIV-infected patients with chronic hepatitis C who were treated with pegylated interferon plus ribavirin without HCV genotype restriction.

METHODS

Study cohort. From October 2001 through June 2008, a cohort of 169 HIV/HCV-coinfected patients, previously naive for

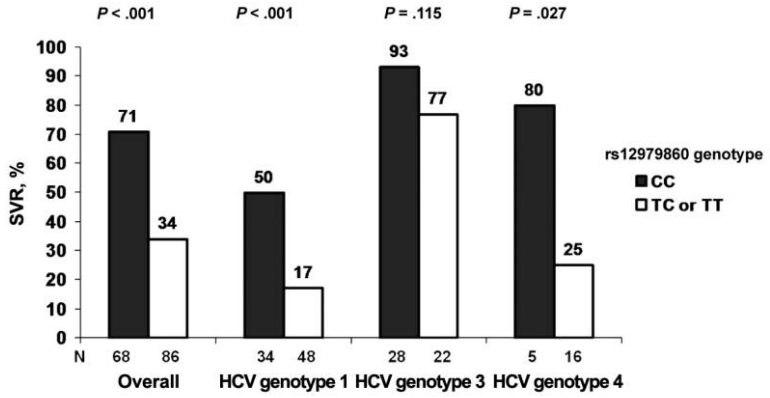

Figure 1. Rate of sustained virologic response (SVR) according to rs12979860 genotype in patients with hepatitis C virus (HCV) genotype 1, 3, and 4.

pegylated interferon and ribavirin, consecutively started therapy for chronic HCV infection in 2 tertiary care centers in southern Spain. Patients were prospectively followed up. Visits were scheduled at least every 4 weeks during the first 24 weeks of treatment and every 8–12 weeks thereafter. In addition, all patients were assessed 24 weeks after stopping therapy. At each visit, clinical, biochemical, and hematologic assessments were performed. A whole blood sample was collected from all patients and cryopreserved at −70°C for genetic determinations.

Drug therapy. All patients were given pegylated interferon alfa-2a at a dosage of 180 μg once per week or pegylated interferon alfa-2b at a dosage of 1.5 μg/kg once per week, both in combination with ribavirin at a daily dose of 800–1200 mg. Patients harboring HCV genotype 2 or 3 received HCV therapy for 24 weeks if they had an undetectable plasma HCV RNA load at week 4. The length of therapy was 48 weeks in the remaining patients. At weeks 12 and 24, HCV therapy was prematurely discontinued in nonresponders.

Definition of viral response. The outcome variable in this study was SVR, defined as undetectable HCV RNA in serum 24 weeks after the completion of HCV therapy. A decrease in plasma HCV RNA level $\geqslant 2$ $\log_{10}$ or below the detection threshold at week 12 was considered to be an early virologic response. An end-of-treatment response was defined as undetectable plasma HCV RNA at the completion of therapy. Patients without early virologic response, as well as those with detectable plasma HCV RNA at week 24, were considered to be nonresponders. Virologic breakthrough was defined as detectable plasma HCV RNA after week 24 of therapy in patients with a previous undetectable HCV load. Relapse was defined as a lack of SVR after having reached end-of-treatment response.

The plasma HCV RNA load was measured using a quantitative polymerase chain reaction assay according to the available technique (Cobas Amplicor HCV Monitor [Roche Diagnostic Systems], with a detection limit of 600 IU/mL; Cobas AmpliPrep-Cobas TaqMan [Roche Diagnostic Systems], with a detection limit of 50 IU/mL; and Cobas TaqMan [Roche Diagnostic Systems], with a detection limit of 10 IU/mL).

Determination of the* IL28B *genotype. DNA was extracted using the automated MagNA Pure DNA extraction method (Roche Diagnostics). The rs129679860 SNP was genotyped using a custom TAQMAN genotyping assay (Applied Biosystems) on DNA isolated from whole blood samples. The DNA was genotyped according to the manufacturer's instructions on a MX3005 thermocycler using MXpro software (Stratagene). The researchers responsible for genotyping procedures were unaware of other data from the patients.

Data analysis. Hardy-Weinberg equilibrium was calculated using Haploview software (http://www.broadinstitute.org/haploview/haploview) [9]. The association between SVR and rs12979860 genotype was analyzed. A dominant model (TT = TC < CC) was used. Likewise, we assessed the relationship between SVR rate and parameters that might have an impact on the response to HCV therapy. For this analysis, advanced fibrosis was defined as a stage of fibrosis of F3 or higher, according to Scheuer's scoring system [10], in patients who had undergone a pretreatment liver biopsy, or as a baseline liver stiffness of $\geqslant 11$ kPa, as determined by transient elastog-

Table 2. Viral Responses during Treatment According to rs12979860 Genotype

Type of response	Responses		*P*
	rs12979860 CC (*n* = 68)	rs12979860 TC/TT (*n* = 86)	
EVR	59 (87)	47 (55)	<.001
Nonresponse	9 (13)	41 (48)	<.001
Viral breakthrough	3 (4)	7 (8)	.351
ETR	56 (82)	38 (44)	<.001
Relapse	8 (12)	9 (10)	.798

NOTE. ETR, end-of-treatment response; EVR, early virologic response.

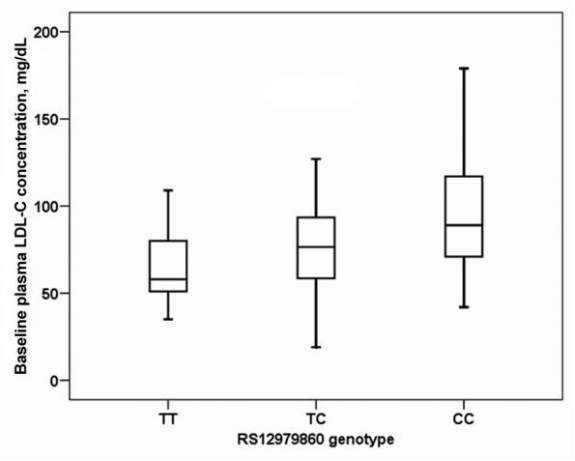

Figure 2. Relationship between *IL28B* genotype and baseline plasma levels of low-density lipoprotein cholesterol (LDL-C) level ($P < .001$).

raphy (FibroScan; Echosens), in those who had not undergone a pretherapy liver biopsy. Two sensitivity analyses were performed for estimating SVR. On the one hand, we conducted an intention-to-treat approach, considering all noncompleters or missing patients as having experienced treatment failure. On the other hand, an on-treatment analysis, excluding patients who dropped out or discontinued therapy because of adverse events, was performed. The associations between SVR and these variables were appraised on an on-treatment basis.

The frequencies were compared using the χ^2 test or Fisher's exact test. The Student's *t* test was used for comparisons among continuous variables in the 2 groups if a normal distribution was followed, and the Mann-Whitney *U* test was used if a normal distribution was not followed. For comparing continuous variables in >2 groups, the Kruskal-Wallis test was used. The median was used as the cutoff value when continuous variables were categorized, unless otherwise specified. Variables associated with SVR in the univariate analysis with $P < .20$ were entered in logistic regression models, where SVR was the dependent variable. The analysis was performed using the SPSS statistical software package, version 15.0 (SPSS), and the Stata/SE 9 package (Stata).

Ethical aspects. The study was designed and performed according to the Helsinki Declaration and was approved by the ethics committees of both participating hospitals. All patients provided written informed consent to participate in this study.

RESULTS

Features of the study population. All patients were of European ancestry. Nine (5%) of 169 patients who started therapy discontinued it because of adverse events, and 6 (4%) voluntarily dropped out. Consequently, 154 patients constituted the on-treatment population. The main baseline characteristics of this group are given in Table 1. Baseline plasma HCV RNA load was ≤600,000 IU/mL in 62 patients (40%). $CD4^+$ cell counts were <250 cells/mm^3 in 17 patients (11%).

Response to HCV therapy. In the intention-to-treat analysis, 77 patients (46%) attained SVR. Specifically, 33 (30%) of 111 patients with genotypes 1–4 and 44 (76%) of 58 patients with genotypes 2–3 ($P < .001$) achieved SVR. The corresponding figures in the on-treatment analysis were 50% for the overall population, 32% for genotype 1–4 carriers, and 86% for those harboring genotype 2–3 ($P < .001$).

IL28B *genotype.* rs12979860 genotypes were TT in 20 patients (13%), TC in 66 patients (43%), and CC in the remaining 68 patients (44%). These genotypes were in the Hardy-Weinberg equilibrium ($P = .97$). The frequency of the allele C was significantly higher among patients with SVR (75% vs 56%; $P = .005$). The rates of SVR according to the rs12979860 genotype were 50% in TT carriers, 29% in TC carriers, and 71% in CC carriers ($P < .001$). SVR was significantly more common among patients with genotype CC than among those with genotypes TC/TT, considered as a whole (71% vs 34%; odds ratio [OR], 4.7; 95% confidence interval [CI], 2.4–9.4; $P < .001$) (Figure 1). Differences between patients with rs12979860 CC and those with TC/TT regarding SVR were mainly seen in patients with HCV genotype 1 or 4 (Figure 1). The rates of SVR in patients with HCV genotype 1–4 were 54% in CC carriers and 19% in TC/TT carriers ($P < .001$). The corresponding rates in patients with HCV genotype 2 or 3 were 93% for genotype CC and 77% for TC/TT ($P = .104$).

Nine nonresponders (18%) had the CC genotype, and 41 (82%) had the TC/TT genotype ($P < .001$). No statistically significant difference was found in terms of viral breakthroughs or relapses in relation to rs12979860 (Table 2). The rates of response at each time point of the follow-up with respect to the *IL28B* genotype are given in Table 2.

The distribution of rs12979860 genotypes in carriers of different HCV genotypes was not uniform. Thus, 34 patients (41%) with HCV genotype 1, 1 (100%) with genotype 2, 28 (56%) with genotype 3, and 5 (24%) with genotype 4 harbored rs12979860 CC ($P = .049$). Median (interquartile range) baseline HCV viral load among patients with rs12979860 CC was 6.11 $\log_{10}$ IU/mL versus 6.09 $\log_{10}$ IU/mL among those with genotype TC/TT ($P = .467$). There was a strong relationship between rs12979860 genotype and the baseline level of plasma low-density lipoprotein cholesterol (LDL-C) level (Figure 2). Thus, the median (interquartile range) LDL-C level in patients with rs12979860 CC was 89 mg/dL (73–120 mg/dL) versus 75 mg/dL (55–91 mg/dL) ($P = .001$) in those with genotype TC/TT.

Predictors of SVR. Beside HCV genotype 2–3 and rs12979860 genotype CC, female sex, baseline HCV RNA level

Table 3. Predictors of Sustained Virologic Response in the Univariate and Multivariate Analyses

Variable	No. (%) of subjects with SVR	Univariate *P*	Adjusted OR (95% CI)[a]	Multivariate *P*
Age				
⩽42 years	45 (52)			
>42 years	32 (47)	.560		
Sex				
Male	60 (46)			
Female	17 (71)	.026	4.28 (1.08–16.96)	.039
BMI				
⩽23	40 (52)			
>23	37 (48)	.653		
IDU				
Yes	70 (51)			
No	7 (44)	.578		
CDC clinical category				
A–B	48 (49)			
C	29 (51)	.867		
Advanced liver fibrosis[b]				
Yes	24/105 (41)			
No	51/105 (55)	.090	1.99 (0.82–4.83)	.129
HCV genotype				
1–4	33 (32)			
2–3	44 (86)	<.001	13.98 (4.87–40.11)	<.001
Baseline HCV RNA load				
⩾600,000 IU/mL	36 (39)			
<600,000 IU/mL	41 (66)	.001	1.99 (1.18–3.34)	.009
Daily dose of ribavirin				
⩽15 mg/kg	36 (44)			
>15 mg/kg	41 (56)	.123	2.19 (0.81–5.51)	.124
Type of pegylated interferon				
Alfa-2a	56 (51)			
Alfa-2b	21 (48)	.721		
Exposure to planned HCV therapy				
<80%	2 (20)			
⩾80%	75 (52)	.050	4.78 (0.77–30.30)	.094
rs12979860 genotype				
TC/TT	29 (34)			
CC	48 (71)	<.001	5.05 (2.04–12.5)	<.001
Baseline LDL-C level				
⩽100 mg/dL	42 (44)			
>100 mg/dL	29 (58)	.149	2.85 (0.73–11.1)[c]	.130[c]
Concomitant antiretroviral therapy				
Yes	63 (47)			
No	14 (70)	.055	2.22 (0.51–9.61)	.286
Abacavir therapy				
Yes	7 (29)			
No	70 (54)	.026	3.66 (0.92–14.52)	.064
Zidovudine therapy				
Yes	7 (35)			
No	70 (52)	.150	1.36 (0.30–6.08)	.688

NOTE. BMI, body mass index, calculated as the square of height in meters divided by weight in kilograms; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HCV, hepatitis C virus; IDU, injection drug user; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SVR, sustained virologic response.

[a] Values provided by a model where LDL-C was not included. The model explained 84% of cases. The Nagelkerke r^2 value was 0.702 and the *P* value for the Hosmer-Lemeshow test was .539.

[b] Fibrosis stage in biopsy of F3 or higher or liver stiffness ⩾11 kPa if biopsy had not been performed.

[c] Values yielded by a model including just 127 patients with LDL-C and advanced fibrosis determinations available. The adjusted OR for the remaining variables included in the final model did not substantially change.

≤600,000 IU/mL, an exposure to the planned dosage of HCV therapy ≥80%, lack of concomitant antiretroviral treatment, and lack of treatment with abacavir were associated with SVR in the univariate analysis (Table 3). The median baseline level of plasma LDL-C was 90 mg/dL (interquartile range, 74–117 mg/dL) in patients who achieved SVR and 73 mg/dL (interquartile range, 61–97 mg/dL) in those who did not ($P = .033$). In the multivariate analysis, HCV genotype 2–3, rs12979860 genotype CC, plasma HCV level ≤600,000 IU/mL, and female sex independently predicted SVR (Table 3).

Thirty-nine patients (25%) carried HCV genotype 1–4, rs12979860 TC/TT, and a plasma HCV load ≥600,000 IU/mL. Only 4 (10%) of these individuals attained SVR.

DISCUSSION

The results of this study show that the *IL28B* genotype is a strong predictor of SVR to pegylated interferon plus ribavirin in HIV/HCV-coinfected patients with genotype 1 and non–genotype 1 HCV infection. Specifically, rs12979860 genotype CC is associated with a 2-fold higher rate of SVR than TC/TT genotype. *IL28B* gene variation predicts SVR independently from other well-defined factors that are associated with this outcome in HCV-monoinfected and HIV/HCV-coinfected patients, such as HCV genotype, baseline plasma HCV RNA burden, and sex [1, 11]. After viral genotype, *IL28B* is the strongest predictor of SVR, being even more potent than HCV RNA load.

The effect of rs12979860 variation on SVR had been proven in HCV-monoinfected patients with HCV genotype 1 [2] or in those harboring genotype 1 or 4 as a whole [5]. The present study shows that the impact of rs12979860 genotype is more potent in patients with HCV genotype 1 and in HCV genotype 4 carriers. However, the effect also appears to be exerted in patients with genotype 3. Statistically significant differences were not reached in terms of SVR between patients with HCV genotype 3 who bore rs12979860 CC and those who did not in this study, although there was a difference of 16% in the rate of SVR. Recently, an association has also been reported between rs12979860 CC in HIV/HCV-coinfected patients with HCV genotype 1–4 but not in those with genotype 3 [7]. However, both in this case and in our study, this finding might be merely a matter of statistical power.

The distribution of rs12979860 genotypes according to the HCV genotypes that the patients harbored was notable. Indeed, rs12979860 genotype CC was significantly more common in patients with genotype 3 than in patients with HCV genotype 1 or 4, similar to what has been reported in HCV-monoinfected patients [12]. The underlying mechanism for this finding is not clear. Whether genotype CC leads the individual to be more prone to infection with HCV genotype 3 or whether infection with HCV genotype 3 becomes chronic more often than does infection caused by other genotypes in patients with rs12979860 CC are topics to be investigated.

The mechanisms whereby rs12979860 has an impact on the response to pegylated interferon plus ribavirin is not completely understood. In previous studies involving HCV-monoinfected patients, allele C was unexpectedly associated with a higher baseline plasma HCV RNA level [2]. This finding has not been confirmed in this study. In any case, rs12979860 CC does not seem to negatively influence the replication of HCV, at least in untreated patients. This SNP has a strong linkage disequilibrium with a nonsynonymous coding variant in the *IL28B* gene (213A>G, K70R; rs81031142) [2]. Thus, it is possible that changes in rs12979860 genotype are associated with abnormalities in the IFN-λ3 signal transduction pathway, although functional data are lacking. IFN-λ1, another type III interferon, inhibits HCV replication, increases the levels of interferon-stimulated genes, and enhances the antiviral effect of interferon alfa [13]. It is conceivable that IFN-λ3, a closely related cytokine with activity against other viruses comparable to that of IFN-λ1 [14], works in a similar way against HCV [6]. However, the lack of association between rs12979860 genotype CC and lower baseline plasma HCV RNA burden argues against this hypothesis.

The association between rs12979860 genotype and plasma levels of LDL-C is striking [15]. In vitro studies have shown that LDL may competitively inhibit the binding of HCV to the LDL receptor, which functions as one of the cellular receptors for HCV [16, 17]. This competitive blockade would hamper the infection of hepatocytes with HCV [18]. Accordingly, higher levels of plasma LDL-C have been shown to be an independent predictor of SVR, both in HCV-monoinfected [19, 20] and in HIV/HCV-coinfected patients [21], in studies specifically designed to appraise this issue. Likewise, SNP in LDL receptor, similar to rs12979860 variations, are associated with both response to treatment and spontaneous clearance of HCV [22]. How variations in rs12979860 could determine the levels of LDL-C is unclear. Certain soluble LDL receptor isoforms are induced in response to interferon stimulation [23]. We could speculate that an rs12979860 genotype other than CC could induce soluble isoforms of the LDL receptor, which join to plasma LDL, decreasing LDL levels and allowing an easier entrance of HCV into the hepatic cell. Studies aimed to search for a genetic interaction between the *IL28B* locus and the LDL receptor or the LDL ligands and LDL receptor system are warranted. In the meantime, an effect on this system should be regarded as one of the putative underlying mechanisms that explain the impact of *IL28B* gene variations on the spontaneous and drug-induced clearance of hepatitis C virus.

This study has several limitations. A pretherapy liver biopsy and a determination of baseline LDL-C level were not available in all patients. Concerning preexisting advanced liver fibrosis,

an assessment of this parameter could be performed in most participants using either biopsy or transient elastography. In any case, the potential impact of LDL-C level and advanced liver fibrosis on the probability of SVR was much lower than that of rs12979860 genotype. In addition, insulin resistance, a factor that has been reported to be associated with a lower rate of SVR [24], was not measured here. However, the role of insulin resistance in response to HCV therapy in HIV-coinfected patients is controversial [25, 26]. Because of all these reasons and the results of previous studies, it is extremely unlikely that the association between the *IL28B* genotype and SVR found in this study is the result of confounding factors. On the other hand, these results provide data on the predictive value of *IL28B* gene variations coming from daily clinical practice, outside randomized clinical trials. Moreover, we provide specific data on this factor in HCV genotype 3 and 4 infections. These are strengths of this study.

Determinations of the *IL28B* genotype should be incorporated into daily clinical care soon. In fact, the rs12979860 genotype allows us to select a subpopulation with a high likelihood to respond to therapy, and more importantly, used along with other predictors of SVR, it identifies patients with a very low probability of SVR. Thus, just 10% of patients with HCV genotype 1 or 4, a baseline plasma HCV RNA load >600,000 IU/mL, and rs12979860 TC/TT achieved SVR in the population included herein. According to these findings, therapy with pegylated interferon plus ribavirin in patients with the former profile could be deferred until new options are available, at least in patients without advanced fibrosis. This is important because a course of therapy with a low likelihood of success could be spared in almost one-quarter of all patients, because 25% of the participants in this study carried HCV genotype 1 or 4, an HCV RNA load >600,000 IU/mL, and rs12979860 genotype TC/TT. Moreover, the *IL28B* genotype, along with other baseline predictors of response or the viral kinetics in the early stages of treatment, might allow us to design models to accurately predict SVR or lack thereof, at least in some of the candidates treated with pegylated interferon plus ribavirin.

In summary, variation in the *IL28B* locus is a more potent predictor of response in HIV/HCV-coinfected patients than others currently used, such as plasma HCV RNA load. Its effect is evident not only in patients with HCV genotype 1 but also in those with HCV genotype 4 and, probably, in genotype 3 carriers. The SNP rs12979860 correlates with plasma LDL-C level, which might play a role in the mechanism of action of this polymorphism. The use of this genotype in routine clinical practice may select patients with very high or very low likelihood of therapy success.

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Potential conflicts of interest. All authors: no conflicts.

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