AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: IL-28B genotype and sustained viral clearance in HCV genotype 1 patients

A. S. Rangnekar & R. J. Fontana

Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA.

Correspondence to:
Dr R. J. Fontana, 3912 Taubman Center, Ann Arbor, MI 48109-0362, USA.
E-mail: rfontana@med.umich.edu

Publication data
Submitted 5 February 2012
First decision 22 February 2012
Resubmitted 27 April 2012
Accepted 1 May 2012
EV Pub Online 22 May 2012

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan.

SUMMARY

Background
Polymorphisms in the IL-28B region are a strong predictor of sustained virologic response (SVR) in individual studies of HCV genotype 1 patients receiving peginterferon (pegIFN) and ribavirin.

Aim
To obtain a pooled odds ratio (OR) of SVR in patients of varying race with the favourable IL-28B genotype compared to those with the unfavourable genotype.

Methods
A literature search was conducted using online databases and a review of conference abstracts. A random effects meta-analysis was performed and study heterogeneity and publication bias were assessed.

Results
There were 21 individual studies of HCV genotype 1 patients of varying ethnicity treated with pegIFN and ribavirin. The pooled prevalence of the favourable IL-28B genotype varied by race (73% vs. 41% vs. 13% in 2612 Asians, 3110 Caucasians and 452 African-Americans, respectively, $P < 0.001$). However, the strength of association of the IL-28B genotype with SVR was similar in all three racial groups (Caucasians: odds ratio (OR) 3.88, 2.75–5.49, African-Americans: OR 4.63, 2.52–8.50 and Asians OR 5.66, 3.99–8.02, all $P < 0.001$). The IL-28B genotype was also associated with SVR in 263 HIV/HCV co-infected Caucasians (OR 5.49, 3.02–9.96, $P < 0.001$). Study quality score and anti-viral treatment regimen did not impact the strength of the association in patient subgroups nor in the pooled population.

Conclusions
IL-28B genotype is significantly associated with SVR in HCV genotype 1 patients of varying race, as well as in HIV co-infected patients, receiving pegIFN and ribavirin. IL-28B testing in conjunction with other pre-treatment parameters may prove useful in counselling HCV patients.

Aliment Pharmacol Ther 2012; **36:** 104–114

doi:10.1111/j.1365-2036.2012.05145.x

INTRODUCTION

Long-term sequelae of untreated chronic hepatitis C virus (HCV) infection include the development of progressive hepatic necroinflammation and fibrosis which can lead to life-threatening decompensated cirrhosis and hepatocellular carcinoma (HCC).[1] Nearly 50% of HCV patients will achieve a sustained virologic response (SVR) after treatment with peginterferon (pegIFN) and ribavirin for 24–48 weeks that is associated with improved long-term clinical outcomes including survival compared with nonresponders.[2–5] However, the majority of HCV patients in western countries are infected with HCV genotype 1, wherein the observed SVR rate is lower (40%) after 48 weeks of full dose pegIFN and ribavirin treatment.[4]

As interferon therapy is associated with frequent and potentially serious side effects, it is important that clinicians be able to make accurate predictions regarding the likelihood of an SVR for individual patients with HCV genotype 1 infection. Clinical features associated with a lower likelihood of achieving SVR can be grouped into host, viral and treatment related factors.[3–9] Host factors associated with a poorer response include increasing patient age, male gender, higher body mass index (BMI), non-Caucasian race and greater degrees of hepatic steatosis and fibrosis on biopsy, whereas viral factors include HCV genotype 1/4 and a higher baseline viral load. In addition, the rate of decline in viral load at week 4 (i.e. rapid virologic response or RVR) and week 12 (i.e. early virologic response or EVR) provides additional prognostic value.[3, 6]

A single nucleotide polymorphism (SNP) upstream of the interleukin 28B (IL-28B) gene on chromosome 19 was recently shown to be strongly associated with SVR in previously untreated HCV genotype 1 patients.[7] The identified polymorphism in this gene, which encodes for interferon-λ-3, is associated with hepatic responsiveness to exogenously administered interferon as well as the rate of hepatocyte death.[8–10] In a cohort of treatment naïve HCV genotype 1 patients, the IL-28B SNP, rs12979860, was associated with a nearly two-fold higher SVR rate among patients with the favourable CC genotype compared to those with the CT or TT genotypes.[7] The IL-28B polymorphism may also explain at least half of the difference in SVR rates observed in Caucasians and African-Americans who received the same treatment with comparable adherence.[7, 11] Reliable estimates of the effect of IL-28B polymorphisms on SVR are not known, in part, due to the variable sample size and heterogeneity of HCV patients and treatment regimens used in many of the individual studies. Therefore, the current meta-analysis was undertaken to better quantify the effect of the IL-28B polymorphism on the likelihood of achieving SVR in HCV genotype 1 patients. In addition, evaluation of the impact of several host [i.e. subject race, human immunodeficiency virus (HIV) co-infection] and treatment factors (i.e. duration and dosing) on the utility of IL-28B testing in predicting SVR was undertaken.

METHODS

Literature search

A MEDLINE computer database search of manuscripts published between January 2000 and July 2011 was performed using the text-words IL-28B, IL28 and interleukin 28. A similar search was conducted using PUBMED and EMBASE for articles published during the same time period. Additional manual and electronic searches of abstracts presented at the annual American Gastroenterology Association from 2007 to 2011 and American Association for the Study of Liver Diseases meetings from 2007 to 2010 was undertaken. Finally, consultation with expert hepatologists as well as manual recursive searches of references from review articles and published studies were completed to identify any additional abstracts or unpublished data.

Study selection criteria

Studies were selected based on the following inclusion criteria: (i) published studies of IL-28B genotyping in adults with chronic HCV genotype 1 infection; (ii) treatment with pegIFN and ribavirin and (iii) reported outcome of SVR. The following exclusion criteria were also used: (i) use of direct acting anti-viral agents (DAAs); (ii) treatment of patients who had undergone liver transplantation and (iii) use of IL-28B SNPs other than rs12979860 or rs8099917. All published studies regardless of the number of patients reported were included. After reviewing the titles and abstracts of all citations identified in the literature search, two investigators (AS, RF) independently applied the selection criteria and extracted data. Any disagreements were resolved by consensus, and agreement between investigators for selection of studies for this meta-analysis was greater than 95%.

Data extraction

Eligible studies were reviewed in a duplicate but independent manner by two investigators (AS, RF). For each study, the investigators collected the following data:

(i) Study: year, location, design, publication status; (ii) Patient factors: total number and mean age, baseline serum aspartate aminotransferase (AST), baseline alanine aminotransferase, BMI and per cent with diabetes mellitus, male gender, treatment naïve and HIV co-infection; (iii) HCV factors: HCV genotype, baseline HCV RNA level, total number of patients achieving RVR and SVR; (iv) Treatment factors: adherence to established HCV treatment guidelines,[12] duration of both pegIFN and ribavirin, type of pegIFN used, dose reduction in antiviral medications, use of growth factors for cytopenias and (v) IL-28B: IL-28B SNP tested and number of patients with each IL-28B genotype and number with each IL-28B genotype who achieved RVR and SVR. For subgroup analyses, full-dose therapy was defined as either pegIFN α-2a 180 mcg or pegIFNα-2b $\geq$1.0 mcg/kg/week in combination with ribavirin $\geq$800 mg daily. Any discrepancies in data extraction were resolved by discussion among the investigators.

IL-28B testing

The two IL-28B SNPs reported in the individual studies were rs12979860 and rs8099917 which are in linkage disequilibrium with each other. The favourable genotype for rs12979860 is CC, whereas the unfavourable genotypes are CT and TT. The favourable genotype for rs8099917 is TT, whereas the unfavourable genotypes are TG and GG. Data from studies using both SNPs were initially merged as they are highly concordant in almost all East Asians and the majority of Caucasians. However, separate sensitivity analyses were conducted after excluding Caucasian studies using rs8099917 as the two SNPs do not reliably provide comparable results in this population.[13] When individual studies reported data for both SNPs, only the most robustly studied SNP for each race was chosen (i.e. rs8099917 for Asians and rs12979860 for non-Asians).

Primary outcome

The primary outcome for this meta-analysis was achievement of SVR after pegIFN and ribavirin treatment, which was defined as undetectable serum HCV RNA by polymerase chain reaction testing 24 weeks after treatment.

Secondary outcome

A secondary outcome for this meta-analysis was achievement of RVR with pegIFN and ribavirin treatment. RVR was defined as an undetectable serum HCV RNA at week 4 of treatment. An additional secondary outcome included crude pooled rates of the IL-28B genotype by race.

Quality assessment

A study quality assessment scale was created based on previously validated tools designed for diagnostic accuracy studies.[14–16] This eight-item scoring system involved questions about sample purity (based on inclusion of only treatment naïve and HCV genotype 1 patients), reporting of other known pre-treatment host factors associated with SVR and use of well-established HCV treatment algorithms with validated stopping rules. A score $\geq$6 was defined as high quality and a score <6 as low quality.

Statistical analysis

A pooled odds ratio (OR) of SVR based on the favourable IL-28B genotype was the estimate of effect, and was determined using the DerSimonian and Laird method for a random effects method. Study heterogeneity was assessed by the I^2 test, where an I^2 >50% is suggestive of substantial heterogeneity. Publication bias was assessed using the Harbord and Peters tests. Influence analysis was performed by removing one study at a time from the model to see if there was undue influence by a single study. All statistics were computed using STATA 11.0 (StataCorp LP, College Station, TX, USA).

The data from the included studies were analysed separately by patient race. In addition, because the recommended dose of ribavirin is lower and the anticipated SVR rate is also lower in HIV co-infected patients compared with non-HIV patients, the HIV co-infection studies were analysed separately. Sensitivity and subgroup analyses were performed based on IL-28B SNP, treatment algorithm, treatment experience and overall study quality score. Specific comparisons were made using meta-regression.

RESULTS

Of the 180 published studies on IL-28B polymorphisms in HCV patients, 130 were eliminated due to the lack of reporting on virologic outcomes in treated patients. Among the 50 remaining studies, two involved the use of protease inhibitors with pegIFN and ribavirin, whereas three included liver transplant recipients. Of the 25 studies of HCV genotype 1 patients, four were reported in duplicate leaving a total of 21 analysable studies (Figure 1). Studies published only as abstracts were not included as they did not reliably provide extractable data for SVR stratified by IL-28B genotype.

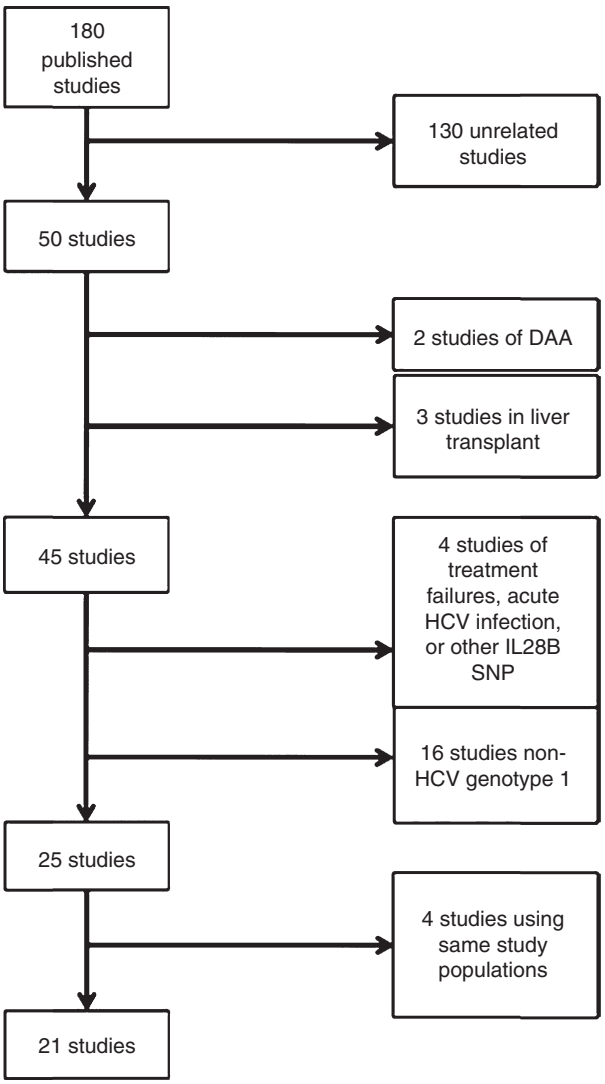

Figure 1 | Overview of study selection. There were 21 individual studies that met all of the inclusion and exclusion criteria.

Caucasians with HCV genotype 1

SVR outcome. There were nine studies of Caucasian patients with HCV genotype 1 who did not have HIV co-infection (Table 1).[11, 17–24] All of the studies included only HCV genotype 1 patients and six studies exclusively enrolled treatment naïve patients. To maximise power, the Alestig *et al.* study was included, which carries the risk of overlapping some patients from the Lindh *et al.* study.[23, 24] However, Caucasian patients from the McCarthy study were excluded from this analysis because 25% of them had nongenotype 1 HCV infection. The favourable IL-28B genotype (CC) was present in 41% of the 3110 pooled patients (Figure 2). Overall, 67% of the CC genotype patients achieved SVR compared to 37% of those with the unfavourable IL-28B genotype with a pooled OR of 3.88 (95% CI: 2.75–5.49, $P < 0.001$) (Figure 3). The moderate to high heterogeneity among these nine studies ($I^2 = 69\%$) was improved after removing the Suppiah study which was the only study to use the rs8099917 SNP, with a similar pooled OR of 4.34 (95% CI: 3.27–5.24, $P < 0.001$), but a lower heterogeneity ($I^2 = 31\%$). A subgroup analysis involving the five studies that used full dose pegIFN and ribavirin for 48 weeks vs. the four studies that did not led to a similar result (OR 4.65 vs. 3.39, $P = 0.45$). Pooling of the six high quality studies led to a pooled OR of 4.71 (95% CI: 3.37–6.57, $P < 0.001$). The six studies that only included treatment naïve patients had a significantly higher OR for SVR compared with the three studies that included a mixture of naïve and previously treated patients (4.71 vs. 2.44, $P = 0.01$).

RVR outcome. Data for the RVR outcome were available in five of the nine Caucasian studies, and the favourable IL-28B genotype (CC) was present in 35% of the 1861 pooled patients.[11, 19–21, 24] The rate of RVR was 32% in the CC patients compared to 8% in patients with the unfavourable IL-28B genotype with a pooled OR of 5.29 (95% CI: 3.75–7.48, $P < 0.001$) (supplementary Figure S1). Heterogeneity between studies was low ($I^2 = 26\%$). The OR of SVR in these same five studies was 4.40 (95% CI: 3.17–6.10, $P < 0.001$).

African-Americans with HCV genotype 1

SVR outcome. There were three studies of African-American patients with HCV genotype 1 infection, and they all utilised full dose pegIFN and ribavirin treatment for 48 weeks (Table 1).[11, 17, 25] These studies all reported data for the rs12979860 SNP. The favourable IL-28B genotype CC was present in only 13% of these 452 patients, which is significantly lower than that seen in the Caucasians and Asians (Figure 2). The SVR rate was 46% among CC patients compared to 19% among patients with the unfavourable IL-28B genotype with a pooled OR of 4.63 (95% CI: 2.52–8.50, $P < 0.001$) (Figure 3) and low study heterogeneity ($I^2 = 0\%$). Week 4 RVR data were only reported in one study.[11]

Asians with HCV genotype 1

SVR outcome. There were eight studies of Asian patients with HCV genotype 1 treated with pegIFN and ribavirin (Table 1).[26–33] These studies all used the rs8099917 SNP which is in strong linkage disequilibrium with rs12979860 in East Asians.[13, 29] The 73% prevalence of the favourable

Table 1 | Summary of the 21 individual studies included in the meta-analysis

Study	*N*	Age (mean)	Men (%)	BMI (kg/m^2)	Advanced fibrosis (%)*	Treatment duration (weeks)	Prevalence of favourable IL-28B genotype (%)	SVR in favourable IL-28B genotype (%)	SVR in unfavourable IL-28B genotype (%)
Caucasian (HIV−)									
Thompson (US)	1171	48	61	27	12	48	37	69	32
Darling (US)	111	48	65	n/a	19	48	49	91	63
Stattermayer (Austria)	372	45	61	n/a	31	24–72	35	79	43
Bochud (Europe/Israel)	170	41	70	25	35¶	24–72	26	66	48
Montes-Cano (Spain)	161	n/a	59	n/a	29	n/a†	39	54‡	30‡
Fattovich (Italy)	121	46	64	25	22	48	35	83	38
Suppiah (Australia/Europe)	848	43	62	26	n/a**	48	52	56‡	36‡
Alestig (Sweden)	50	47	60	n/a	6††	48	36	89	41
Lindh (Sweden)	106	45	61	n/a	23	24–72	36	79‡	49‡
Total	3110	46	62%		20%		41%	67%	37%
African-American (HIV−)									
Thompson (US)	300	51	57	29	10	48	14	48	14
McCarthy (US)	53	48	65	n/a	44	48	15	13§	9§
Darling (US)	99	48	65	n/a	19	48	9	67	36
Total	452	50	60%		24%		13%	46%	19%
Asian (HIV−)									
Hayes (Japan)	812	58	56	23	75	48	72	53‡	24‡
Kurosaki (Japan)	496	57	50	n/a	24	≥24	70	50‡	13‡
Tanaka (Japan)	314	57	54	n/a	29	n/a	62	64§	13§
Lin (Taiwan)	191	51	36	25	46	24	89	72	38
Sinn (Korea)	55	57	53	n/a	61	48	84	67§	44§
Huang (Taiwan)	226	52	62	n/a	n/a	24	83	65	26
Hayashi (Japan)	299	56	53	n/a	16	48	73	58‡	14‡
Akuta (Japan)	219	54	63	23	n/a	48†	68	63‡	26‡
Total	2612	56	54%		43%		73%	58%	20%
Caucasian (HIV+)									
Aparicio (Spain)	86	48	67	n/a	39	n/a	60	50‡	9‡
Pineda (Spain)	82	42	85	23	40	48	41	50	17
Rallon (Spain)	95	42	74	n/a	n/a	48–72	36	65	30
Total	263	44	75%		39%		46%	54%	20%

BMI, body mass index; n/a, not available; SVR, sustained virologic response.

Demographic data may be from all patients in the study population, including some who did not undergo IL-28B genotyping.

* Not all patients in each study underwent liver biopsy. In most studies, advanced fibrosis defined as Ishak score ≥4, METAVIR score ≥3.

† Some patients treated with either standard IFN + RBV or standard IFN alone.

‡ Study does not clearly state whether all patients were treatment naïve.

§ Some patients were not treatment naïve.

¶ Defined advanced fibrosis as Ishak score ≥2.

** Used Scheuer scoring system for liver fibrosis.

†† Used Ludwig and Batts scoring system for liver fibrosis.

IL-28B genotype (TT) among the 2612 patients was significantly higher than the prevalence in both the Caucasians ($P < 0.001$) and African-Americans ($P < 0.001$) (Figure 2). The pooled SVR rate was 58% in patients with the TT genotype compared to only 20% in patients with the unfavourable IL-28B genotype with a pooled OR of 5.66

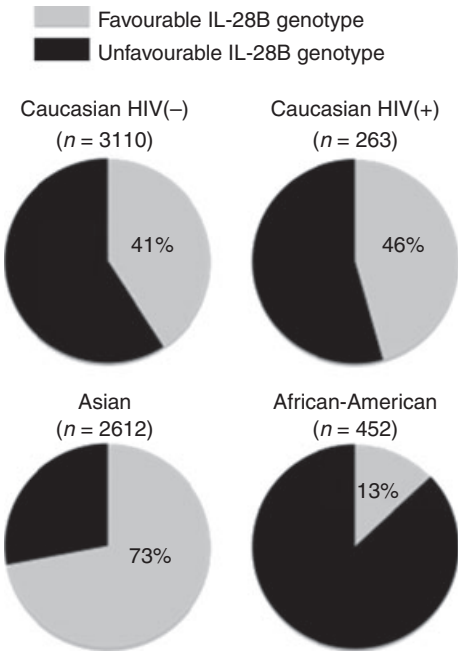

Figure 2 | Distribution of the favourable IL-28B genotype by ethnic group. The prevalence of the favourable IL-28B (rs12979860 CC or rs8099917 TT) was significantly higher in Caucasian vs. African-American patients (41% vs. 13%, $P < 0.001$) and in Asians vs. Caucasian (73% vs. 41%, $P < 0.001$) patients without HIV co-infection. In contrast, the prevalence was similar in the Caucasian HCV patients with and without HIV co-infection (46% vs. 41%, $P = 0.13$).

(95% CI: 3.99–8.02, $P < 0.001$) (Figure 3). There was moderate heterogeneity among studies ($I^2 = 56\%$). Removing the two studies that clearly included previously treated nonresponders[28, 30] resulted in a pooled OR of SVR in the TT genotype of 5.06 (95% CI: 3.77–6.79, $P < 0.001$) with lower heterogeneity ($I^2 = 32\%$). A subgroup analysis of the six high quality compared to the two low quality studies demonstrated similar OR (5.63 vs. 5.81, $P = 0.98$). Furthermore, the five studies that used full dose pegIFN and ribavirin for 48 weeks had a similar OR for SVR compared to the three studies that used alternative dosing and duration (6.14 vs. 4.87, $P = 0.57$).

RVR outcome. RVR data were reported in only two of the Asian studies.[27, 31] The favourable IL-28B genotype (TT) was present in 74% of the 722 pooled patients. The RVR rate was 25% in the TT patients as compared to 6% in the unfavourable IL-28B genotype patients, with a pooled OR of 4.07 (95% CI: 2.13–7.75, $P < 0.001$) (supplementary Figure S2).

HIV co-infected Caucasians with HCV genotype 1

SVR outcome. There were three studies of HIV (+) co-infected Caucasian patients with HCV genotype 1 treated with pegIFN and ribavirin (Table 1).[34–36] The favourable IL-28B genotype of CC was present in 46% of the 263 pooled patients, which was not significantly different from the Caucasian HCV patients without HIV co-infection (46% vs. 41%, $P = 0.17$) (Figure 2). Overall, 54% of the HIV (+) patients with the CC genotype achieved SVR compared to 20% of patients with the unfavourable IL-28B genotype with a pooled OR of 5.49 (95% CI: 3.02–9.96, $P < 0.001$) (Figure 4) and there was low heterogeneity ($I^2 = 0\%$). However, none of these studies reported week 4 viral kinetics.

Pooled analysis

As the impact of IL-28B genotype on SVR appeared similar in all four of the analysed groups (Figures 3 and 4), the data were pooled to increase the ability to determine the impact of other study features. After combining all 21 studies with a total of 6437 patients, the pooled OR of SVR for patients with the favourable IL-28B genotype remained significant at 4.68 (95% CI: 3.75–5.83, $P < 0.001$). There was moderate heterogeneity between studies ($I^2 = 58\%$), which was minimised with removal of the Suppiah study ($I^2 = 30\%$). Similar results were obtained when subgroup analyses were performed using the 14 studies of full dose pegIFN and ribavirin for 48 weeks vs. the 7 with other treatment regimens (OR 5.20 vs. 3.94, p = 0.25), the 14 high quality vs. 7 low quality studies (OR 5.05, vs. 3.93, $P = 0.23$) and the 10 studies of only treatment naïve vs. the 11 studies of both treatment naïve and treatment experienced patients (OR: 4.74 vs. 4.65, $P = 0.85$) (supplementary Table S1). There was no evidence of publication bias based on the Harbord and Peters tests ($P = 0.29$ and $P = 0.48$ respectively).

DISCUSSION

This meta-analysis clearly demonstrates that the prevalence of the favourable IL-28B polymorphism (CC) is significantly influenced by subject race (Figure 2). In addition, a consistent and significantly higher SVR rate was noted in all of the patient groups analysed among the patients with the favourable IL-28B genotype (Figure 3). These observations indicate that the IL-28B region plays a fundamental role in the response of all HCV genotype 1 patients to interferon-based therapy. In addition, the similar OR of the favourable IL-28B genotype in predicting SVR in the HIV co-infected Caucasian

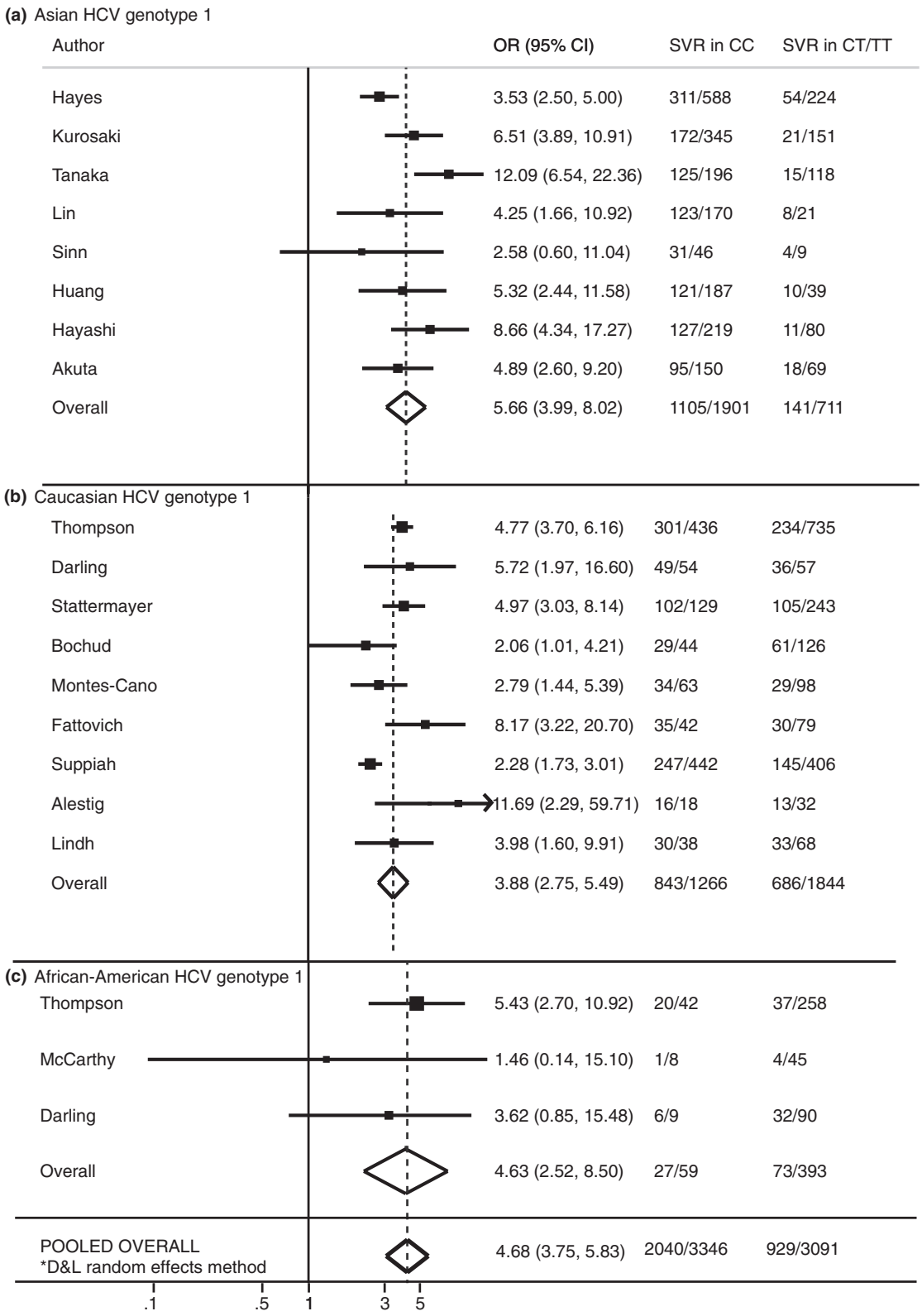

Figure 3 | Forest plots of the IL-28B genotype and SVR in HCV genotype 1 patients of varying race without HIV co-infection. (a) Asian HCV genotype 1, (b) Caucasian HCV genotype 1 and (c) African-American HCV genotype 1.

patients when compared with the HIV (−) Caucasian patients (5.49 vs. 3.88, $P = 0.36$) (Figures 3 and 4) indicates that this factor is equally important in immunosuppressed individuals who generally have a lower likelihood of SVR due to higher baseline levels of HCV RNA and more severe liver disease.[37–39]

The SVR rate with a 48-week course of pegIFN and ribavirin treatment has traditionally been highest in Asian populations, lowest in African-Americans and intermediate in Caucasians.[6, 40] In our analysis, the pooled SVR rates were substantially lower in African-Americans (22%) as compared with the other two groups, but similar in Asians (48%) and Caucasians (49%). We noted a particularly lower than expected pooled SVR in the Asian IL-28B favourable patients (58%) compared with the unfavourable Asian IL-28B genotypes (20%) (Table 1). This finding may, in part, be related to the inclusion of Asian patients who had previously failed pegIFN and ribavirin therapy in up to six of the studies. Although we were unable to determine the exact proportion of previously treated patients, one would anticipate that this may be a biased population towards general nonresponders who may have a lower than expected response to treatment as was noted in our subgroup analysis of Caucasian patients. In addition, the use of shorter durations of combination therapy in three of the Asian studies, lower doses of ribavirin in five of the studies and a higher overall proportion of patients with advanced liver fibrosis may have played a role (Table 1).

Multivariate regression analyses conducted in several of the individual studies confirmed that IL-28B genotype remains a significant pre-treatment predictor of SVR even after controlling for other well-known host and viral factors.[11, 17, 21, 25–27, 29, 31, 33–36] However, because these data were not provided in an analysable format, we were unable to combine the IL-28B data with other clinical variables to develop a robust mathematical model from the pooled results. How to use IL-28B data with other pre-treatment predictors to accurately estimate an individual patient's chance of response to therapy remains a clinically important, but unresolved issue.[41–44] The data from the current meta-analysis suggest that the impact of IL-28B appears to be similar in all of the patient subgroups analysed and was not greatly influenced by duration of therapy or other study characteristics, except in Caucasian mono-infected patients. Nonetheless, additional large prospective studies involving the full spectrum of HCV patients that are likely to be encountered in clinical practice, including patients of Hispanic ethnicity, are needed to provide more robust models for clinicians to use.

The choice of which IL-28B SNP to use in testing varies by patient race. A recent retrospective database study demonstrated that while there is a high concordance between rs12979860 and rs8099917 in Asians, the rate of concordance is substantially lower in non-Asian populations.[13] Several of the Asian studies included in this meta-analysis confirmed this finding by genotyping patients at both SNPs.[26, 29, 30] In contrast, it appears that

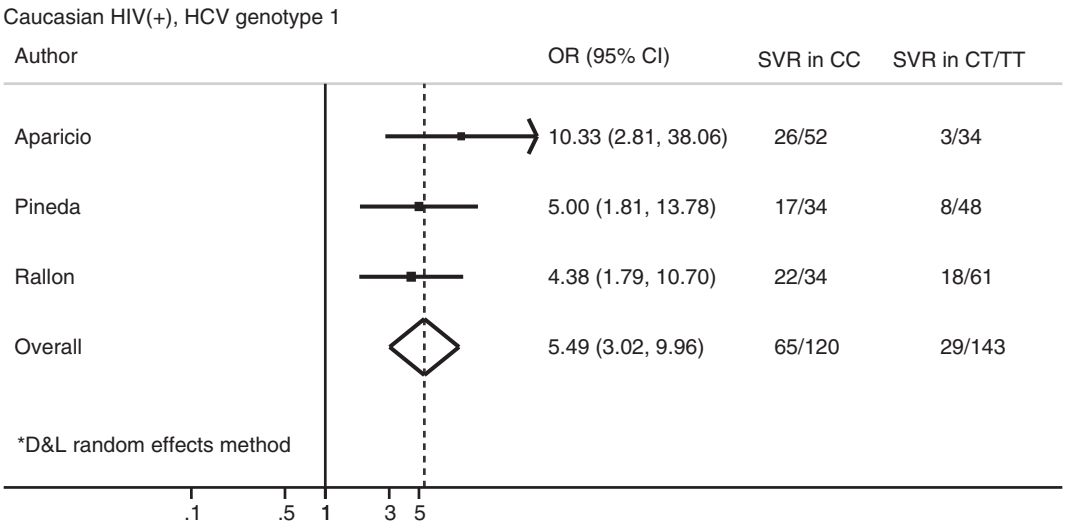

Figure 4 | Forest plot of the IL-28B genotype and SVR in Caucasian HCV genotype 1 patients with HIV co-infection.

a larger proportion of patients are classified as the favourable IL-28B genotype when the rs8099917 SNP is utilised in Caucasian studies.[19, 20, 24] Therefore, use of the rs8099917 SNP in non-Asian populations may lead to misclassification of IL-28B genotype and reduce the ability to accurately predict SVR.

The role of IL-28B genotyping also needs to be better defined in the era of DAAs, such as telaprevir and boceprevir. The DAAs in combination with pegIFN and ribavirin are associated with significantly higher SVR rates in genotype 1 patients compared with dual therapy. However, the role of IL-28B genotyping in DAA treated patients remains unclear as uniform testing for this parameter was not conducted in the phase 3 multicenter licensing trials. Nonetheless, IL-28B genotype has been shown to be a predictor of SVR in smaller subgroups of patients undergoing triple therapy with a DAA, PegIFN and ribavirin.[45, 46] However, triple therapy is also associated with greater costs and more side effects including rash and anaemia, and current regimens using DAAs may increase the risk of developing viral resistance. Furthermore, a recent analysis demonstrated that triple therapy is not cost-effective in subjects with an IL-28B CC genotype due to their excellent response to dual therapy.[47] Therefore, our pooled data of the strength of association between IL-28B genotype and SVR in different patient populations receiving only pegIFN and ribavirin may prove important to regulatory agencies, clinicians, patients and third party payers.

Despite their increased potency, DAAs are not currently approved in many important subgroups including HCV patients with genotype 2/3 infection and all HIV co-infected patients. In HIV co-infected patients, there is a particular concern for drug-drug interactions between the available protease inhibitors and several of the commonly used antiretroviral agents. Therefore, IL-28B testing may play a particularly important role in HIV/HCV co-infected patients contemplating pegIFN and ribavirin therapy until additional DAAs are developed and tested. Recent data suggest that IL-28B genotyping in conjunction with baseline HCV viral load may help identify HIV co-infected patients who are likely to achieve SVR.[48, 49]

A limitation of the current study includes our inability to directly compare the role of IL-28B genotyping to other host, viral and therapeutic factors in a multivariate manner. Therefore, additional studies that incorporate multiple pre-treatment predictors with genetic data in a large cohort of prospectively treated patients who are given the same treatment regimen are needed. Nonetheless, robust and consistent associations of IL-28B genotype and SVR were shown in all of the groups analysed (Figures 3& 4). In addition, our results support recent reports of low concordance between the two major IL-28B SNPs in some Caucasian populations.[13] For this meta-analysis of a predictive genetic test, we had to create our own study quality assessment scale which has not been independently validated. Furthermore, studies of the IL-28B polymorphisms in the African-American population remain limited (Table 1). Nonetheless, the current meta-analysis represents the largest pooling of IL-28B genotype data in pegIFN and ribavirin treated patients to date. Lastly, all of the studies of HIV co-infected patients were from Spain, and whether the results will be generalisable to other HIV co-infected patients treated in other countries requires further study.

In conclusion, the current meta-analysis shows that the favourable IL-28B genotype is associated with a significantly higher SVR rate in HCV genotype 1 patients treated with pegIFN and ribavirin. Furthermore, this finding is consistent across different racial groups who have varying distributions of the IL-28B polymorphism as well as in Caucasian HCV patients with HIV co-infection. IL-28B genotype was also significantly associated with the likelihood of achieving RVR in a limited number of studies. Although further studies are needed to develop a more comprehensive predictive model of SVR, IL-28B genotyping will likely play an important role in guiding treatment decisions for HCV genotype 1 patients seeking pegIFN and ribavirin based therapy.

ACKNOWLEDGEMENTS

Declaration of personal interests: Dr Rangnekar has no financial conflicts of interest. Dr Fontana has served as a consultant to Merck, GlaxoSmithKline, Bristol-Meyers Squibb, Tibotec, Vertex Pharmaceuticals and Medtronic in the past year. *Declaration of funding interests*: Dr Rangnekar is supported by the T32 DK62708-01, NIDDK, Training Grant in Gastrointestinal Epidemiology, and a Clinical and Translational Science Award from the Michigan Institute for Clinical and Health Research.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Forest plot of the IL-28B genotype and RVR in HCV genotype 1 Caucasian patients without HIV co-infection.

Figure S2. Forest plot of the IL-28B genotype and RVR in HCV genotype 1 Asian patients without HIV co-infection.

Table S1. Quality assessment of the 21 studies included in the meta-analysis.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

REFERENCES

1. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35–50.
2. Manns MP, McHutchison JG, Gordon SC, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.
3. Fried MW, Shiffman ML, Reddy KR, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
4. Hadziyannis SJ, Sette H Jr, Morgan TR, *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346–55.
5. Morgan TR, Ghany MG, Kim HY, *et al.* Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; **52**: 833–44.
6. Conjeevaram HS, Fried MW, Jeffers LJ, *et al.* Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006; **131**: 470–7.
7. Ge D, Fellay J, Thompson AJ, *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399–401.
8. Balagopal A, Thomas DL, Thio CL. IL28B and the control of hepatitis C virus infection. *Gastroenterology* 2010; **139**: 1865–76.
9. Scott J, Holte S, Urban T, *et al.* IL28B genotype effects during early treatment with peginterferon and ribavirin in difficult-to-treat hepatitis C virus infection. *J Infect Dis* 2011; **204**: 419–25.
10. Honda M, Sakai A, Yamashita T, *et al.* Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology* 2010; **139**: 499–509.
11. Thompson AJ, Muir AJ, Sulkowski MS, *et al.* Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010; **139**: 120–9.
12. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
13. Faruki H, Albrecht J, Morrison P, *et al.* Genotype frequencies of IL28B genetic polymorphisms rs12979860 and rs809917 in a large genetic database of various ethnic/racial origin individuals. *Hepatology* 2011; **54**: 816A.
14. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; **3**: 25.
15. Whiting PF, Rutjes AW, Westwood ME, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529–36.
16. Owens DK, Lohr KN, Atkins D, *et al.* AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions – agency for healthcare research and quality and the effective health-care program. *J Clin Epidemiol* 2010; **63**: 513–23.
17. Darling JM, Aerssens J, Fanning G, *et al.* Quantitation of pretreatment serum interferon-gamma-inducible protein-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response. *Hepatology* 2011; **53**: 14–22.
18. Suppiah V, Moldovan M, Ahlenstiel G, *et al.* IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100–4.
19. Stattermayer AF, Stauber R, Hofer H, *et al.* Impact of IL28B genotype on the early and sustained virologic response in treatment-naive patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011; **9**: 344–50.
20. Bochud PY, Bibert S, Negro F, *et al.* IL28B polymorphisms predict reduction of HCV RNA from the first day of therapy in chronic hepatitis C. *J Hepatol* 2011; **55**: 980–8.
21. Fattovich G, Covolo L, Bibert S, *et al.* IL28B polymorphisms, IP-10 and viral load predict virological response to therapy in chronic hepatitis C. *Aliment Pharmacol Ther* 2011; **33**: 1162–72.
22. Montes-Cano MA, Garcia-Lozano JR, Abad-Molina C, *et al.* Interleukin-28B genetic variants and hepatitis virus infection by different viral genotypes. *Hepatology* 2010; **52**: 33–7.
23. Alestig E, Arnholm B, Eilard A, *et al.* Core mutations, IL28B polymorphisms and response to peginterferon/ribavirin treatment in Swedish patients with hepatitis C virus genotype 1 infection. *BMC Infect Dis* 2011; **11**: 124.
24. Lindh M, Lagging M, Arnholm B, *et al.* IL28B polymorphisms determine early viral kinetics and treatment outcome in patients receiving peginterferon/ribavirin for chronic hepatitis C genotype 1. *J Viral Hepat* 2011; **18**: e325–31.
25. McCarthy JJ, Li JH, Thompson A, *et al.* Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. *Gastroenterology* 2010; **138**: 2307–14.
26. Hayes CN, Kobayashi M, Akuta N, *et al.* HCV substitutions and IL28B polymorphisms on outcome of peg-interferon plus ribavirin combination therapy. *Gut* 2011; **60**: 261–7.
27. Kurosaki M, Tanaka Y, Nishida N, *et al.* Pre-treatment prediction of response to pegylated-interferon plus ribavirin for chronic hepatitis C using genetic polymorphism in IL28B and viral factors. *J Hepatol* 2011; **54**: 439–48.
28. Tanaka Y, Nishida N, Sugiyama M, *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105–9.
29. Lin CY, Chen JY, Lin TN, *et al.* IL28B SNP rs12979860 is a critical predictor for on-treatment and sustained virologic response in patients with

hepatitis C virus genotype-1 infection. *PLoS One* 2011; **6**: e18322.
30. Sinn DH, Kim YJ, Lee ST, *et al.* Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in Asian patients. *J Gastroenterol Hepatol* 2011; **26**: 1374–9.
31. Huang CF, Huang JF, Yang JF, *et al.* Interleukin-28B genetic variants in identification of hepatitis C virus genotype 1 patients responding to 24 weeks peginterferon/ribavirin. *J Hepatol* 2012; **56**: 34–40.
32. Hayashi K, Katano Y, Honda T, *et al.* Association of interleukin 28B and mutations in the core and NS5A region of hepatitis C virus with response to peg-interferon and ribavirin therapy. *Liver Int* 2011; **31**: 1359–65.
33. Akuta N, Suzuki F, Hirakawa M, *et al.* Amino acid substitution in HCV core/NS5A region and genetic variation near IL28B gene affect treatment efficacy to interferon plus ribavirin combination therapy. *Intervirology* 2012; **55**: 231–41.
34. Aparicio E, Parera M, Franco S, *et al.* IL28B SNP rs8099917 is strongly associated with pegylated interferon-alpha and ribavirin therapy treatment failure in HCV/HIV-1 coinfected patients. *PLoS One* 2010; **5**: e13771.
35. Pineda JA, Caruz A, Rivero A, *et al.* Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfected with HIV and hepatitis C virus. *Clin Infect Dis* 2010; **51**: 788–95.
36. Rallon NI, Naggie S, Benito JM, *et al.* Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. *AIDS* 2010; **24**: F23–9.
37. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, *et al.* Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351**: 438–50.
38. Soriano V, Puoti M, Sulkowski M, *et al.* Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS* 2007; **21**: 1073–89.
39. Ballesteros AL, Franco S, Fuster D, *et al.* Early HCV dynamics on Peg-interferon and ribavirin in HIV/HCV co-infection: indications for the investigation of new treatment approaches. *AIDS* 2004; **18**: 59–66.
40. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004; **350**: 2265–71.
41. Costa JM, Telehin D, Munteanu M, *et al.* HCV-GenoFibrotest: a combination of viral, liver and genomic (IL28b, ITPA, UGT1A1) biomarkers for predicting treatment response in patients with chronic hepatitis C. *Clin Res Hepatol Gastroenterol* 2011; **35**: 204–13.
42. O'Brien TR, Everhart JE, Morgan TR, *et al.* An IL28B genotype-based clinical prediction model for treatment of chronic hepatitis C. *PLoS One* 2011; **6**: e20904.
43. Ochi H, Hayes CN, Abe H, *et al.* Toward the establishment of a prediction system for the personalized treatment of chronic hepatitis C. *J Infect Dis* 2012; **205**: 204–10.
44. Ladero JM, Martin EG, Fernandez C, *et al.* Predicting response to therapy in chronic hepatitis C: an approach combining IL28B gene polymorphisms and clinical data. *J Gastroenterol Hepatol* 2012; **27**: 279–85.
45. Chayama K, Hayes CN, Abe H, *et al.* IL28B but not itpa polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. *J Infect Dis* 2011; **204**: 84–93.
46. Akuta N, Suzuki F, Hirakawa M, *et al.* Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010; **52**: 421–9.
47. Gellad ZF, Naggie S, Reed SD, *et al.* The cost-effectiveness of a telaprevir-inclusive regimen as initial therapy for genotype 1 hepatitis C infection in individuals with the CC IL-28B polymorphism. *Hepatology* 2011; **54**: 417A–8A.
48. Neukam K, Camacho A, Lopez-Biedma A, *et al.* Prediction of response to pegylated interferon plus ribavirin in HIV/hepatitis C virus (HCV)-coinfected patients using HCV genotype, IL28B variations and HCV-RNA load. *J Hepatol* 2012; **56**: 788–94.
49. Labarga P, Barreiro P, Mira JA, *et al.* Impact of IL28B polymorphisms on response to peginterferon and ribavirin in HIV-hepatitis C virus-coinfected patients with prior nonresponse or relapse. *AIDS* 2011; **25**: 1131–3.