# HLA: ribavirin 2343

CI = confidence interval, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, NS = non-significant, OR = odds ratio, RR = relative risk, S = significant, SmPC = summary of product characteristics

**Brief summary and justification of choices:**

*HLA-B44*

Romero-Gómez 2003 points to a less frequent sustained virological response to ribavirin for HLA-B44-negative patients (i.e. a less frequent sustained virological response to treatment with interferon alpha and ribavirin (n = 105), but not to treatment with interferon alpha alone (n = 143)). However, two larger studies found no significant effect of HLA-B alleles on response to treatment with interferon alpha and ribavirin (Vidal-Castiñeira 2014 (811 patients), Vidal-Castiñeira 2012 (407 patients)). In addition, also none of the studies after 2008 with less than 300 patients, which were not included in this risk analysis, confir-med a role for HLA-B44. For this reason, the KNMP Pharmacogenetics Working Group concluded that there is insufficient evidence for a gene-drug interaction (no/no-interaction). You can find an overview of the observed clinical effects in the background information text of this gene-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

*HLA-C*

Results for HLA-C found in 3 studies were inconsistent. Suppiah 2011 found a less frequent response to interferon alpha and ribavirin for patients with the HLA-C2/C2 genotype and no effect of the HLA-C1/C1 and HLA-C1/C2 genotypes. However, Vidal-Castiñeira 2012 found this effect to be clinically insignificant. In this study, the HLA (and KIR) genotypes did not contribute significantly to a prediction model of treatment response. Vidal-Castiñeira 2014 found HLA-C*07 to have a positive influence on treatment response to interferon alpha and ribavirin and HLA-C*03 and HLA-C*05 to have no effect. However, Suppiah 2011 found HLA-C*03 to have a positive effect, HLA-C*05 to have a negative effect, and HLA-C*07 to have no effect. Although combination with genetic variants in the HLA-C ligands, the natural killer cell immunoglobulin-like receptors (KIRs), might improve strength and consistency of the effects, studies only investigated ribavirin in combination with interferon alpha. For this reason, there is no evidence that the effects are effects on ribavirin treatment, and so also hold for combinations of ribavirin with the newer antihepatitis C drugs, and not on interferon alpha treatment. In addition, considering the multiple reports of HLA affecting spontaneous hepatitis C virus clearance, there is actually no firm evidence that the effects are treatment dependent. They might just reflect the contribution of the host immune system to virus clearance. In the latter case, choosing an alternative drug will not resolve the problem. Finally, choosing an alternative for interferon alpha and ribavirin becomes less and less an option anyhow, because interferon alpha plus ribavirin is not the standard therapy for hepatitis C anymore. Because of the better efficacy and fewer adverse effects, the newer antihepatitis C medicines (with or without ribavirin) are generally preferred, independent of the HLA-profile of the patient. This means that they generally will have been considered before the patient was started on interferon alpha and ribavirin. Based on both the limited evidence for an effect of HLA-C on treatment response and on the probably limited clinical utility of HLA-C genotyping if this evidence would become firm in the future, the KNMP Pharmacogenetics Working Group decided not to introduce a new HLA-ribavirin interaction based on the HLA-C data.

*HLA-DRB1*04, HLA-E*0103, HLA-DMB rs23544 A>G, HLA-DMA rs1063478 C>T, HLA rs4273729 G>C, HLA-DOB rs2856997 T>G, HLA-DOA rs2284191 G>A, HLA-DOA rs1044429 G>A*

There is only one (large) study showing an effect of each of these HLA alleles or polymorphisms on the efficacy of the treatment. A second study confirming this effect is lacking. In addition, it is not possible to determine from the studies whether ribavirin or interferon alpha is responsible for this association (or whether the association is treatment independent). As for HLA-C, the KNMP Pharmacogenetics Working Group decided not to introduce new HLA-ribavirin interactions based on the data on these HLA alleles or polymorphisms, because of both the limited evidence for an effect on treatment response and on the probably limited clinical utility of HLA genotyping if this evidence would become firm in the future.

| Source | Code | Effect | Comments |
|---|---|---|---|
| **ref. 1**<br>Yao Y et al.<br>Association<br>between human | 4 | 346 chronic hepatitis C patients were treated with peginterferon alpha and ribavirin for 48 weeks. All patients were infected with hepatitis C virus genotype 1b.<br>Sustained virological response was defined as no detectable | Author's conclusion: "Genetic variations at HLA-DOA rs1044429 and |

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<td>leucocyte antigen-DO polymorphisms and interferon/ribavirin treatment response in hepatitis C virus type 1 infection in Chinese population: a prospective study.<br>BMJ Open 2018;8:e019406.<br>PubMed PMID: 29654010.</td>
<td>DOA rs1044429 GA and AA: AA#<br><br>DOA rs2284191 GA and AA: AA#<br><br>DOB rs2856997 TG and GG: D</td>
<td>hepatitis C virus RNA in serum 24 weeks after the end of treatment. Rapid virological response was defined as no detectable hepatitis C virus RNA in serum 4 weeks after start of treatment. Complete early virological response was defined as no detectable hepatitis C virus RNA in serum after 12 weeks of treatment.<br>ORs were adjusted for age, sex, baseline hepatitis C virus RNA level and glucose. False discovery rate corrections were applied for multiple comparisons.<br>The gene polymorphism rs1044429 is HLA-DOA rs1044429 G>A, rs2284191 is HLA-DOA rs2284191 G>A and rs2856997 is HLA-DOB rs2856997 T>G.<br><br>Results:
<table>
<tr><td colspan="4">Homozygous variant versus heterozygous versus homozygous wild type:</td></tr>
<tr><td colspan="4">% of patients with sustained virological response:</td></tr>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1044429</td><td>1.90 (S)</td><td>1.25-2.89</td><td>58%</td></tr>
<tr><td>rs2284191</td><td>2.70 (S)</td><td>1.59-4.61</td><td>60%</td></tr>
<tr><td>rs2856997</td><td>0.63 (S)</td><td>0.46-0.87</td><td>76%</td></tr>
<tr><td colspan="4">p-values were also significant after false discovery rate corrections, and multivariate regression analysis showed each of the three polymorphisms to be an independent predictive factor (S).</td></tr>
<tr><td colspan="4">The difference was also significant for (homozygous variant + heterozygous) compared to homozygous wild type and for heterozygous compared to homozygous wild type. The comparison between homozygous variant and homozygous wild type only reached significance for rs2856997.</td></tr>
<tr><td colspan="4">Interaction analysis showed the association between rs2856997 and sustained virological response to be stronger in females than in males (S).</td></tr>
<tr><td colspan="4">Baseline viral load did not differ between the genotypes. However, for rs2284191 (homozygous variant + heterozygous) compared to homozygous wild type, the viral load was lower after 4, 12, 24 and 48 weeks of therapy (S), but not after 8 weeks. For rs1044429 (homozygous variant + heterozygous) compared to homozygous wild type, the viral load was only lower after 12 weeks of therapy (S). For rs2856997 (homozygous variant + heterozygous) compared to homozygous wild type, there were no differences in viral load at any time point (NS).</td></tr>
<tr><td colspan="4">The percentage of patients with a response decreased with the number of risk genotypes (rs1044429 homozygous wild type, rs2284191 homozygous wild type and rs2856997 homozygous variant):<br>1 risk genotype: OR = 0.38 (95% CI: 0.17-0.83)<br>2 risk genotypes: OR = 0.22 (95% CI: 0.10-0.49)<br>3 risk genotypes: OR = 0.12 (95% CI: 0.04-0.37)</td></tr>
<tr><td colspan="4">% of patients with rapid virological response:</td></tr>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1044429</td><td colspan="2">trend for an OR > 1 (p = 0.074) (NS)</td><td>41%</td></tr>
<tr><td>rs2284191</td><td>2.44 (S)</td><td>1.52-3.91</td><td>42%</td></tr>
<tr><td>rs2856997</td><td>0.72 (S)</td><td>0.53-0.98</td><td>57%</td></tr>
<tr><td colspan="4">For all three polymorphisms, differences were significant for (homozygous variant + heterozygous) compared to homozygous wild type and for heterozygous compared to homozygous wild type. The comparison between homozygous variant and homozygous wild type did not reach</td></tr>
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<td>HLA-DOB rs2284191 and rs2856997 were independent predictors of hepatitis C virus treatment response in the Chinese Han population.”</td>
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<td>ref. 1, continuation</td>
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significance.<br>
% of patients with complete early virological response:
<table>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1044429</td><td>1.73 (S)</td><td>1.12-2.65</td><td>61%</td></tr>
<tr><td>rs2284191</td><td>2.83 (S)</td><td>1.63-4.94</td><td>63%</td></tr>
<tr><td>rs2856997</td><td>0.70 (S)</td><td>0.50-0.96</td><td>76%</td></tr>
<tr><td colspan="4">Differences were significant for (homozygous variant + heterozygous) compared to homozygous wild type. The comparison between heterozygous and homozygous wild type only reached significance for rs1044429 and rs2284191. The comparison between homozygous variant and homozygous wild type only reached significance for rs2856997.</td></tr>
</table>
<br>
Note: No significant effects on sustained virological response were found for DOA rs408036, rs3128935, rs3129304, rs376892, rs369150, rs86567, rs6913008, rs2582, rs416622 and rs453779, and for DOB rs2857111, rs1383258, rs2071472, rs7383287 and rs2071475.<br><br>
Note: The authors previously showed that the HLA-DOA rs2284191 genotype influenced susceptibility to hepatitis C virus infection and the HLA-DOB rs7383287 genotype influenced spontaneous viral clearance (Huang P et al. Genetic variants in antigen presentation-related genes influence susceptibility to hepatitis C virus and viral clearance: a case control study. BMC Infect Dis 2014;14:716).
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<td>ref. 2<br>Sakhaee F et al. The impact of genetic variation in IL28B, IFNL4 and HLA genes on treatment responses against chronic hepatitis C virus infection. Infect Genet Evol 2017;54:330-7. PubMed PMID: 28739427.</td>
<td>4<br><br>rs4273729 GC and CC: D</td>
<td>
520 chronic hepatitis C patients were treated with peginterferon alpha-2a and ribavirin for 48 weeks (hepatitis C virus genotype 1) or 24 weeks (hepatitis C virus genotype 2 or 3). 223 patients (42.9%) were infected with hepatitis C virus genotype 1a, 80 (15.4%) with hepatitis C virus genotype 1b, 51 (9.8%) with hepatitis C virus genotype 2, and 166 (31.9%) with hepatitis C virus genotype 3a.<br>
Sustained virological response, rapid virological response, and complete early virological response were defined as in Yao 2018.<br>
ORs were determined with multivariate logistic regression.<br>
The gene polymorphism HLA rs4273729 is HLA rs4273729 G>C.<br>
There was an association between hepatitis C virus (HCV) genotypes and HLA rs4273729 genotypes (S). The percentage of patients having the HLA rs4273729 GG genotype was 65.7% for HCV genotype 3a, 53.8% for HCV genotype 1b, 47.1% for HCV genotype 2, and 40.4% for HCV genotype 1a. There was no association between baseline viral load and HLA rs4273729 genotypes.<br><br>
Results:
<table>
<tr><td colspan="4">Results compared to GG (wild type):</td></tr>
<tr><td colspan="4">% of patients with sustained virological response:</td></tr>
<tr><td>HCV genotype</td><td>CC</td><td>GC</td><td>value for GG</td></tr>
<tr><td rowspan="2">all</td><td>x 0.47</td><td>x 0.70</td><td rowspan="2">83%</td></tr>
<tr><td colspan="2">S for CC versus GC versus GG</td></tr>
<tr><td>1a</td><td colspan="2">OR = 0.41 (95% CI: 0.25-0.67) (S)</td><td></td></tr>
<tr><td>1b</td><td colspan="2">OR = 0.10 (95% CI: 0.04-0.39) (S)</td><td></td></tr>
<tr><td>2</td><td colspan="2">NS</td><td></td></tr>
<tr><td>3a</td><td colspan="2">OR = 0.58 (95% CI: 0.13-0.87) (S)</td><td></td></tr>
<tr><td colspan="4">% of patients with rapid virological response:</td></tr>
<tr><td>HCV genotype</td><td>CC</td><td>GC</td><td>value for GG</td></tr>
</table>
</td>
<td>Author’s conclusion: ”Beside IL28B SNPs and HLA rs4273729, IFNL4 ss469415590 was a powerful predictor factor for rapid, complete early and sustained virologic response. Genotyping these SNPs may be a helpful priority in the treatment of patients with hepatitis C virus infection, especially in countries where access to triple or double therapy with a viral protease inhibitor is limited.”</td>
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<td>ref. 2, continuation</td>
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<tr><td>all</td><td>x 0.45<br>S for CC versus GC versus GG</td><td>x 0.62</td><td>68%</td></tr>
<tr><td>1a</td><td colspan="2">NS</td><td></td></tr>
<tr><td>1b</td><td colspan="2">OR = 0.51 (95% CI: 0.36-0.73) (S)</td><td></td></tr>
<tr><td>2</td><td colspan="2">NS</td><td></td></tr>
<tr><td>3a</td><td colspan="2">NS</td><td></td></tr>
<tr><td colspan="4">% of patients with complete early virological response:</td></tr>
<tr><td>HCV genotype</td><td>CC</td><td>GC</td><td>value for GG</td></tr>
<tr><td>all</td><td>x 0.63<br>S for CC versus GC versus GG</td><td>x 0.81</td><td>85%</td></tr>
<tr><td>1a</td><td colspan="2">OR = 0.82 (95% CI: 0.56-0.98) (S)</td><td></td></tr>
<tr><td>1b</td><td colspan="2">OR = 0.28 (95% CI: 0.17-0.61) (S)</td><td></td></tr>
<tr><td>2</td><td colspan="2">NS</td><td></td></tr>
<tr><td>3a</td><td colspan="2">OR = 0.31 (95% CI: 0.21-0.57) (S)</td><td></td></tr>
</table>
<br>Note: Previous studies showed that the HLA rs4273729 genotype influenced spontaneous viral clearance in Europeans and Africans (Duggal P et al. Genome-wide association study of spontaneous resolution of hepatitis C virus infection: data from multiple cohorts. Ann Intern Med 2013;158:235-45) and in Chinese (Xu Y et al. A novel polymorphism near HLA class II region is associated with spontaneous clearance of HCV and response to interferon treatment in Chinese patients. J Hum Genet 2016;61:301-5). Also the association between hepatitis C virus (HCV) genotypes and HLA rs4273729 genotypes in chronically infected patients found in this study points to a treatment independent effect of HLA rs4273729.
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<td>ref. 3<br>Chen H et al. Polymorphisms of HLA-DM on treatment response to interferon/ribavirin in patients with chronic hepatitis C virus type 1 infection.<br>Int J Environ Res Public Health 2016;13:E1030.<br>PubMed PMID: 27775635.</td>
<td>4<br><br>DMA rs1063478 CT and TT: AA#<br><br>DMB rs23544 AG and GG: AA#</td>
<td>
336 chronic hepatitis C patients were treated with peginterferon alpha and ribavirin for 48 weeks. All patients were infected with hepatitis C virus genotype 1.<br>
Sustained virological response, rapid virological response, and complete early virological response were defined as in Yao 2018.<br>
ORs were adjusted for age, sex, baseline hepatitis C virus RNA level, γ-glutamyl transpeptidase, glucose, T3, T4, platelets, and α-foetal protein.<br>
The gene polymorphism rs1063478 is HLA-DMA rs1063478 C>T and rs23544 is HLA-DMB rs23544 A>G.<br><br>
Results:
<table>
<tr><td colspan="4">Homozygous variant versus heterozygous versus homozygous wild type:</td></tr>
<tr><td colspan="4">% of patients with sustained virological response:</td></tr>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1063478</td><td>1.96 (S)</td><td>1.29-2.96</td><td>59%</td></tr>
<tr><td>rs23544</td><td>1.78 (S)</td><td>1.23-2.56</td><td>56%</td></tr>
<tr><td colspan="4">Multivariate regression analysis showed each of the two polymorphisms to be an independent predictive factor (S).</td></tr>
<tr><td colspan="4">The difference was also significant for (homozygous variant + heterozygous) compared to homozygous wild type, for homozygous variant compared to (heterozygous + homozygous wild type), for heterozygous compared to homozygous wild type, and for homozygous variant compared to homozygous wild type.</td></tr>
<tr><td colspan="4">The percentage of patients with a response increased with the total number of gene variants of rs1063478 and rs23544:<br>1 gene variant: OR = 2.27 (95% CI: 1.10-4.63)<br>2 gene variants: OR = 2.91 (95% CI: 1.37-6.17)</td></tr>
</table>
</td>
<td>Author’s conclusion: ”The genetic variation of HLA-DMA rs1063478 and HLA-DMB rs23544 are associated with the treatment outcomes in the Chinese Han population.”</td>
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<td>ref. 3, continuation</td>
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<table>
<tr><td colspan="4">3-4 gene variants: OR = 45.12 (95% CI: 5.49-370.75)</td></tr>
<tr><td colspan="4">% of patients with rapid virological response:</td></tr>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1063478</td><td colspan="2">NS</td><td>48%</td></tr>
<tr><td>rs23544</td><td colspan="2">NS</td><td>46%</td></tr>
<tr><td colspan="4">For rs1063478, the difference was significant for homozygous variant compared to (heterozygous + homozygous wild type) (OR = 2.65; 95% CI: 1.16-6.06) (S), while homozygous variant compared to homozygous wild type showed a trend for an OR > 1 (p = 0.059) (NS).<br>For rs23544, none of the comparisons showed a trend (NS).</td></tr>
<tr><td colspan="4">% of patients with complete early virological response:</td></tr>
<tr><td></td><td>OR</td><td>95% CI</td><td>value for wild type</td></tr>
<tr><td>rs1063478</td><td>1.63 (S)</td><td>1.07-2.46</td><td>63%</td></tr>
<tr><td>rs23544</td><td colspan="2">NS</td><td>68%</td></tr>
<tr><td colspan="4">For rs1063478, the difference was also significant for (homozygous variant + heterozygous) compared to homozygous wild type (OR = 1.70; 95% CI: 1.02-2.82) (S), while both homozygous variant compared to homozygous wild type and heterozygous compared to homozygous wild type showed a trend for an OR > 1 (p = 0.053 and 0.092, respectively) (NS).<br>For rs23544, the difference was significant for homozygous variant compared to (heterozygous + homozygous wild type) (OR = 2.27; 95% CI: 1.02-5.04) (S), while homozygous variant compared to homozygous wild type showed a trend for an OR > 1 (p = 0.081) (NS).</td></tr>
</table>
<br>Note: No significant effects on virological response were found for DM-polymorphisms rs1050391 and rs3135029.<br><br>Note: The authors previously showed that the HLA-DMA rs1063478 genotype influenced susceptibility to hepatitis C virus infection (Huang P et al. Genetic variants in antigen presentation-related genes influence susceptibility to hepatitis C virus and viral clearance: a case control study. BMC Infect Dis 2014;14:716).
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<td>ref. 4<br>Vidal-Castiñeira JR et al.<br>Diversity of killer cell immunoglobulin-like receptor (KIR) genotypes and KIR2-DL2/3 variants in HCV treatment outcome.<br>PLoS One 2014;9:e99426.<br>PubMed PMID: 24927414.</td>
<td>4<br><br>C*07: AA#</td>
<td>811 chronic hepatitis C patients were treated with peginterferon alpha-2a or alpha-2b and ribavirin for 48 weeks. All patients were infected with hepatitis C virus genotype 1. Sustained virological response was defined as in Yao 2018. HLA-C*07 belongs to the HLA-C1 group.<br>The KIR2DL3 subtypes *001 and *002 were determined in 249 patients.<br><br>Results:
<table>
<tr><td>HLA-C*07 allele frequency in patients with sustained virological response compared to patients without sustained virological response (HLA-C*07 allele frequency = 17.2%):</td></tr>
<tr><td>OR = 1.49 (95% CI: 1.16-1.92) (S)</td></tr>
<tr><td>The association with HLA-C*07 was only significant in combination with the natural killer cell immunoglobulin-like receptor gene variant KIR2DL3 (OR = 2.17 (95% CI: 1.61-2.94) (S); carrier frequency of the combination 45.0% in responders compared to 27.3% in non-responders). There was no difference in the carrier frequency of HLA-C*07 in combination with KIR2DL2 in responders compared to non-responders (NS).</td></tr>
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<td>Author’s conclusion: ”KIR2DL3*001-HLA-C1 was also associated with sustained viral response (24.5% vs. 45.7%).”</td>
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<td>ref. 4, continuation</td>
<td>B: AA<br><br>C*03: AA<br>C*05: AA</td>
<td>
Carrier frequency of other KIR-HLA combinations in patients with sustained virological response compared to patients without sustained virological response (SVR):
<table>
<tr><th>combination or genotype</th><th>OR</th><th>95% CI</th><th>value for non-SVR</th></tr>
<tr><td>KIR2DS2-HLA-C1</td><td>0.68 (S)</td><td>0.51-0.92</td><td>51.2%</td></tr>
<tr><td>KIR2DL2/2DL2-HLA-C1/C1</td><td colspan="2">NS</td><td>4.1%</td></tr>
<tr><td>KIR2DL2/2DL2-HLA-C1/C2</td><td>0.35 (S)</td><td>0.19-0.64</td><td>12.2%</td></tr>
<tr><td>KIR2DL2/2DL2-HLA-C2/C2</td><td colspan="2">NS</td><td>2.2%</td></tr>
<tr><td>KIR2DL2/2DL3-HLA-C1/C1</td><td colspan="2">NS</td><td>14.9%</td></tr>
<tr><td>KIR2DL2/2DL3-HLA-C1/C2</td><td colspan="2">NS</td><td>19.1%</td></tr>
<tr><td>KIR2DL2/2DL3-HLA-C2/C2</td><td colspan="2">NS</td><td>10.1%</td></tr>
<tr><td>KIR2DL3/2DL3-HLA-C1/C1</td><td>2.94 (S)</td><td>1.85-4.76</td><td>6.4%</td></tr>
<tr><td>KIR2DL3/2DL3-HLA-C1/C2</td><td colspan="2">NS</td><td>18.5%</td></tr>
<tr><td>KIR2DL3/2DL3-HLA-C2/C2</td><td colspan="2">NS</td><td>10.5%</td></tr>
<tr><td>KIR3DL1/S1-HLA-Bw480I/80T</td><td colspan="2">NS</td><td></td></tr>
<tr><td>KIR2DL3*001-HLA-C1</td><td>2.70 (S)</td><td>1.54-4.55</td><td>24.0%</td></tr>
<tr><td>KIR2DL3*002-HLA-C1</td><td colspan="2">NS</td><td>41.1%</td></tr>
<tr><td colspan="4">For KIR2DL2/2DL2, KIR2DL3/2DL3, and KIR2DL3*001, but not for KIR2DS2, the association was also significant for all HLA genotypes/gene variants together.</td></tr>
</table>
<br>
Note: Genotyping was for all HLA-B and HLA-C alleles. None of the HLA-B alleles and none of the 15 observed HLA-C alleles other than HLA-C*07 (including C*03 and C*05) showed an association with sustained virological response.<br><br>
Note: Previous studies showed that HLA-C was associated with hepatitis C virus clearance (McKiernan SM et al. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. Hepatology 2004;40:108-14) and viral load (Tseng KC et al. Effect of human leukocyte antigen class I and II alleles on hepatitis C viral load among chronic hepatitis C patients in Southern Taiwan. Hum Immunol 2013;74:978-82).
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<tr>
<td>ref. 5<br>Guzmán-Fulgencio M et al. HLA-E variants are associated with sustained virological response in HIV/hepatitis C virus-coinfected patients on hepatitis C virus therapy. AIDS 2013;27:1231-8.</td>
<td>4</td>
<td>321 patients co-infected with hepatitis C virus and HIV were treated with peginterferon alpha-2a or alpha-2b and ribavirin for 48-72 weeks (hepatitis C virus genotype 1 or 4) or 24-48 weeks (hepatitis C virus genotype 2 or 3). Early stopping rules were applied for individuals with suboptimal virological response after 12 weeks of treatment. 216 patients (67.5%) were infected with hepatitis C virus genotype 1 or 4 and 105 patients (32.5%) with hepatitis C virus genotype 2 or 3. Sustained virological response and rapid virological response were defined as in Yao 2018. Early virological response was defined as a drop in viral load by 99% (≥ 2 log reduction).<br>Bonferroni correction for multiple comparisons was applied. ORs per HLA-E*0103 allele were calculated. ORs were adjusted for the most significant co-variables, such as sex,</td>
<td>Author’s conclusion: ”The HLA-E*0101 allele was associated with increased odds of HCV clearance and could help to predict sustained virological response among HIV/HCV-coinfected patients on HCV therapy.”</td>
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<tr>
<td>PubMed PMID: 23811951.<br><br>ref. 5, continuation</td>
<td>E*0103: D</td>
<td>age, HCV genotype, HCV-RNA at baseline at least 500,000 IU/ml, significant fibrosis, IL28B rs8099917 TT genotype, and highly active antiretroviral therapy.<br>Patients with HLA-E*0103 had lower percentages of hepatitis C virus genotype 2 or 3 (10.9% of HLA-E*0103/*0103, 35.7% of HLA-E*0101/*0103, and 36.6% of HLA-E*0101/*0101) and the favourable IL28B rs8099917 TT genotype (37% of HLA-E*0103/*0103, 60% of HLA-E*0101/*0103, and 74% of HLA-E*0101/*0101), which are both relevant predictive factors of virological response.<br><br>Results:
<table>
<tr><td colspan="4">Results compared to HLA-E*0101/*0101 (wild type):</td></tr>
<tr><td colspan="4">% of patients with sustained virological response:</td></tr>
<tr><td>HCV or IL28B genotype</td><td>*103/*103</td><td>*101/*103</td><td>value for *0101/*0101</td></tr>
<tr><td rowspan="3">all</td><td>x 0.28</td><td>x 0.78</td><td rowspan="3">70%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td colspan="2">OR per *0103 allele = 0.49 (95% CI: 0.32-0.74) (S)</td></tr>
<tr><td rowspan="3">HCV 1/4</td><td>x 0.39</td><td>x 0.68</td><td rowspan="3">57%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td colspan="2">OR per *0103 allele = 0.63 (95% CI: 0.40-0.98) (S)</td></tr>
<tr><td rowspan="3">HCV 2/3</td><td>x 0.00</td><td>x 0.89</td><td rowspan="3">93%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td colspan="2">OR per *0103 allele = 0.15 (95% CI: 0.05-0.46) (S)</td></tr>
<tr><td rowspan="3">IL28B TT</td><td>x 0.41</td><td>x 0.96</td><td rowspan="3">72%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td colspan="2">OR per *0103 allele = 0.47 (95% CI: 0.25-0.86) (S)</td></tr>
<tr><td rowspan="3">IL28B GT/GG</td><td>x 0.22</td><td>x 0.53</td><td rowspan="3">62%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td colspan="2">OR per *0103 allele = 0.38 (95% CI: 0.19-0.75) (S)</td></tr>
<tr><td colspan="4">There was no significant interaction between HLA-E and IL28B genotypes regarding response.</td></tr>
<tr><td colspan="4">% of patients with rapid virological response:</td></tr>
<tr><td>HCV or IL28B genotype</td><td>*0103/*0103</td><td>*0101/*0103</td><td>value for *0101/*0101</td></tr>
<tr><td rowspan="2">all</td><td>x 0.27</td><td>x 0.57</td><td rowspan="2">46%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td rowspan="2">HCV 1/4</td><td>x 0.44</td><td>x 0.40</td><td rowspan="2">33%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td rowspan="2">HCV 2/3</td><td>x 0.00</td><td>x 0.68</td><td rowspan="2">71%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
<tr><td rowspan="2">IL28B TT</td><td>x 0.34</td><td>x 0.67</td><td rowspan="2">49%</td></tr>
<tr><td colspan="2">S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td></tr>
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<td>ref. 5, continuation</td>
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<table>
<tr><td>IL28B GT/GG</td><td>x 0.24<br>S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td><td>x 0.41</td><td>41%</td></tr>
<tr><td colspan="4">% of patients with early virological response:</td></tr>
<tr><td>HCV or IL28B genotype</td><td>*0103/*0103</td><td>*0101/*0103</td><td>value for *0101/*0101</td></tr>
<tr><td>all</td><td>x 0.68<br>S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td><td>x 0.90</td><td>79%</td></tr>
<tr><td>HCV 1/4</td><td colspan="2">trend for a decrease ( p = 0.059) (NS)</td><td>69%</td></tr>
<tr><td>HCV 2/3</td><td colspan="2">NS</td><td>96%</td></tr>
<tr><td>IL28B TT</td><td colspan="2">NS</td><td>81%</td></tr>
<tr><td>IL28B GT/GG</td><td>x 0.54<br>S for *0103/*0103 versus *0101/*0103 versus *0101/*0101</td><td>x 0.75</td><td>71%</td></tr>
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<table>
<tr><td></td></tr>
<tr><td>93%</td></tr>
<tr><td>72%</td></tr>
</table>
Note: Genotyping was for HLA-E*0101 and HLA-E*0103.<br><br>Note: A previous study showed that the HLA-E*0101/HLA-E*0101 genotype might confer protection from hepatitis C virus infection (Schulte D et al. The HLA-E(R)/HLA-E(R) genotype affects the natural course of hepatitis C virus (HCV) infection and is associated with HLA-E-restricted recognition of an HCV-derived peptide by interferon-gamma-secreting human CD8(R) T cells. J Infect Dis 2009;200: 1397-401). Also the association between hepatitis C virus (HCV) genotypes and HLA-E genotypes found in this study points to a treatment independent effect of HLA-E genotypes.
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<td>ref. 6<br>Vidal-Castiñeira JR et al.<br>A predictive model of treatment outcome in patients with chronic HCV infection using IL28B and PD-1 genotyping.<br>J Hepatol 2012;56:1230-8.<br>PubMed PMID: 22322230.</td>
<td>4</td>
<td>407 chronic hepatitis C patients were treated with peginterferon alpha-2a or alpha-2b and ribavirin for 24-48 weeks according to hepatitis C virus genotype. 313 patients (76.9%) were infected with hepatitis C virus genotype 1, 8 (2.0%) with hepatitis C virus genotype 2, 73 (17.9%) with hepatitis C virus genotype 3, and 13 (3.2%) with hepatitis C virus genotype 4. The treatment was halted in patients whose hepatitis C virus RNA levels had not declined greater than 2 log after 12 weeks of therapy: these patients were classified as non-responders. Patients with hepatitis C virus RNA in serum at the end of the treatment were also included in the non-responder group. Sustained virological response was defined as in Yao 2018.<br>HLA genotype was determined in combination with the genotype of the natural killer cell immunoglobulin-like receptors (KIRs), which are the ligands of HLA-C.<br><br>Results:
<table>
<tr><td colspan="4">Carrier frequency of other KIR-HLA combinations in patients with sustained virological response (SVR) compared to patients without response:</td></tr>
<tr><td>genotype</td><td>OR</td><td>95% CI</td><td>value for non-SVR</td></tr>
<tr><td>KIR2DL2/2DL2-HLA-C1/C2</td><td>0.42 (S)</td><td>0.22-0.80</td><td>16.2%</td></tr>
<tr><td>KIR2DL3/2DL3-HLA-C1/C1</td><td>2.54 (S)</td><td>1.29-5.00</td><td>6.6%</td></tr>
</table>
</td>
<td>Author’s conclusion: ”In this prediction analysis of HCV treatment outcome, the KIR and HLA genotypes were not significant.”</td>
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<tr>
<td>ref. 6, continuation</td>
<td>B: AA<br>C: AA</td>
<td>Multivariate logistic regression analysis showed KIR-2DL3/2DL3-HLA-C1/C1 and KIR2DL2/2DL2-HLA-C1/C2 to be independent predictors of treatment outcome (S). However, the KIR and HLA genotypes did not contribute significantly to a prediction model of treatment response (NS).<br><br>Note: Genotyping was for all HLA-B and HLA-Cw alleles.</td>
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<td>ref. 7<br>Suppiah V et al. IL28B, HLA-C, and KIR variants additively predict response to therapy in chronic hepatitis C virus infection in a European cohort: a cross-sectional study. PLoS Med 2011;8:e1001092 PubMed PMID: 21931540.</td>
<td>4<br><br>Cw*03: AA#<br><br>Cw*05: D<br><br>Cw*07: AA<br>C1/C1: AA<br>C1/C2: AA<br><br>C2/C2: D</td>
<td>853 chronic hepatitis C patients were treated with peginterferon alpha and ribavirin for 48 weeks, except for the treatment being halted in patients whose hepatitis C virus RNA levels had not declined greater than 2 log after 12 weeks of therapy. All patients were infected with hepatitis C virus genotype 1.<br>Sustained virological response was defined as in Yao 2018.<br>HLA-Cw*03 and HLA-Cw*07 belong to the HLA-C1 group, HLA-Cw*05 belongs to the HLA-C2 group.<br>The natural killer cell immunoglobulin-like receptors (KIRs) are the ligands of HLA-C.<br><br>Results:<br>Carrier frequency in patients with sustained virological response (SVR) compared to patients without response:
<table>
<tr><th>HLA allele or genotype</th><th>OR</th><th>95% CI</th><th>value for non-SVR</th></tr>
<tr><td>Cw*03</td><td>1.64 (S)</td><td>1.20-2.27</td><td>9.2%</td></tr>
<tr><td></td><td colspan="3">The association with Cw*03 (C1 group) was significant in combination with both KIR2DL2 (OR = 2.13 (95% CI: 1.33-3.45) (S); carrier frequency of the combination 16.7% in responders compared to 8.5% in non-responders) and KIR2DL3 (OR = 2.04 (95% CI: 1.39-3.03) (S); carrier frequency of the combination 25.6% in responders compared to 14.4% in non-responders).</td></tr>
<tr><td>Cw*05</td><td>0.70 (S)</td><td>0.49-1.0</td><td>10.4%</td></tr>
<tr><td></td><td colspan="3">The association with Cw*05 (C2 group) was only significant in combination with KIR2DL3 (OR = 0.51 (95% CI: 0.33-0.78) (S); carrier frequency of the combination 10.9% in responders compared to 19.5% in non-responders), not in combination with KIR2DL2 (NS).</td></tr>
<tr><td>Cw*07</td><td colspan="2">NS</td><td>34.0%</td></tr>
<tr><td>C1/C1</td><td colspan="2">NS</td><td>38.9%</td></tr>
<tr><td>C1/C2</td><td colspan="2">trend for an increase (p = 0.084) (NS)</td><td>41.5%</td></tr>
<tr><td>C2/C2</td><td>0.66 (S)</td><td>0.45-0.95</td><td>19.7%</td></tr>
<tr><td></td><td colspan="3">The association with C2/C2 was only significant in combination with KIR2DL3/2DL3 (OR = 0.52 (95% CI: 0.30-0.92) (S); carrier frequency of the combination 5.3% in responders compared to 9.6% in non-responders), not in combination with KIR2DL2/2DL3 (NS).</td></tr>
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<td>Author’s conclusion: ”Genotyping for IL28B, HLA-C, and KIR genes improves prediction of HCV treatment response.”</td>
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| **ref. 7, continuation** | | The association was also significant in association with KIR2DS1 (OR = 0.52 (95% CI: 0.29-0.94) (S); carrier frequency of the combination 4.7% in responders compared to 8.7% in non-responders).<br><br>Note: Genotyping was for all HLA-C alleles. None of the 13 observed HLA-C alleles other than HLA-Cw*03 and HLA-Cw*05 showed an association with sustained virological response.<br><br>Note: Previous studies showed that HLA-C1 and its receptor KIR2DL3 were associated with spontaneous hepatitis C virus clearance (Khakoo SI et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 2004;305:872-4 and Knapp S et al. Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. Hepatology 2010;51:1168-75).<br>When comparing 228 persons with spontaneous virus clearance to the 583 chronic hepatitis C patients, the authors of this study did not find a significant difference in the frequency of the C1/C1, C1/C2 and C2/C2 genotypes, but they found a trend for a lower C2/C2 frequency in persons with spontaneous virus clearance (p = 0.084; 12.3% versus 17.0%) (NS) (p = 0.07; 4.3% versus 7.7% in persons with KIR2DL3/KIR2DL3). | |
| **ref. 8**<br>Jiao J et al.<br>Hepatitis C virus genotypes, HLA-DRB alleles and their response to interferon-alpha and ribavirin in patients with chronic hepatitis C.<br>Hepatobiliary Pancreat Dis Int 2005;4:80-3. | 3<br><br>DRB1*04: AA[#] | A total of 25 Chinese patients were treated for 6-12 months with interferon-alpha ($3.10^6$ IU 3x per week) + ribavirin (1.2 g/day). Follow-up lasted 1-1.5 years. A possible link between HLA-DRB polymorphisms and the percentage of patients with a complete response was studied.<br>More HLA-DRB1*07-positive than HLA-DRB1*04-positive patients had a complete or partial response (S; 67% versus 0% and 33% versus 20% respectively).<br>Patients with a complete response were less likely to be HLA-DRB1*04-positive than patients without a response (0% versus 36%; OR = 0.03 (S; 95% CI 0.0009-0.9407)). | Authors' conclusion: "DRB1*07 allele was found to be closely related to complete response whereas DRB1*04 showed no response at all." |
| **ref. 9**<br>Romero-Gómez M et al.<br>HLA class I B44 is associated with sustained response to interferon + ribavirin therapy in patients with chronic hepatitis C.<br>Am J Gastroenterol 2003;98:1621-6. | 3<br><br>B44-negative: D<br><br>DRB1*03: AA | A total of 143 patients were treated with interferon-alpha 3x per week for one year and 105 patients with interferon-alpha ($3.10^6$ IU 3x per week) + ribavirin (1.0 - 1.2 g/day). A possible link between HLA polymorphisms and the percentage of patients exhibiting a sustained virological response (i.e. no detectable hepatitis-C-RNA in the serum 6 months after therapy) was studied.<br>More HLA-B44-positive than HLA-B44-negative patients had a sustained virological response to interferon + ribavirin (76.9% versus 41.7%; S; increase by 84%). Following correction, HLA-B44 was found to be an independent variable (OR = 4.84 (95% CI = 1.31-17.8)). For patients who were only treated with interferon, the percentage of HLA-B44-positive patients did not differ significantly between the patients with and without a sustained virological response.<br>Fewer HLA-DRB1*03-positive than HLA-DRB1*03-negative patients had a sustained virological response to interferon + ribavirin (30.4% versus 56.1%; S; decrease by 45%). However, following correction, HLA-DRB1*03 was not an independent variable. | Authors' conclusion: "HLA class I B44 is related to a higher rate of SR in combination therapy but not in interferon monotherapy, whereas HLA class II, tumor necrosis factor-α -238A or -308A seem not to influence response to the antiviral therapy." |

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| **ref. 9, continuation** | A29, A33, B7, DRB1-*11 and 39 other alleles: AA | No significant association was found for 44 other HLA antigens, including HLA-A29, A33, B7, and DRB1*11.<br>The authors indicated that previous studies found an effect of HLA class II polymorphisms on both the spontaneous clearance of hepatitis C infection and the response to interferon-α.<br><br>NOTE: The phenotype, not the genotype, was determined for HLA-A and HLA-B. | |

AA[#]: A negative effect on the efficacy of the treatment was found, but it is not possible to determine from the study whether ribavirin or interferon-alpha is responsible for this association.

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| Risk group | - |

**Comments:**

- For the period after 2008 only studies with more than 300 patients were included in the risk analysis. Smaller studies did not contribute enough to the evidence. One study with more than 300 patients was not included in the risk analysis, because the article was not available in the Netherlands (de Rueda PM et al. Importance of host genetic factors HLA and IL28B as predictors of response to pegylated interferon and ribavirin. Am J Gastroenterol 2011;106:1246-54. PubMed PMID: 21670772). In addition, Smith 2011 was not included in the risk analysis, because it concerns the same patients as Suppiah 2011, but examines the effect of HLA-C only in combination with IL28B polymorphisms (Smith KR et al. Identification of improved IL28B SNPs and haplotypes for prediction of drug response in treatment of hepatitis C using massively parallel sequencing in a cross-sectional European cohort. Genome Med 2011;3:57. PubMed PMID: 21884576).
- The SmPC Copegus (ribavirin) 20-01-19 does not contain any information.
- Possible relationship between HLA polymorphisms and spontaneous hepatitis C virus clearance:
  Multiple studies have shown that gene variants in the HLA region were correlated with spontaneous clearance of the hepatitis C virus:
  - the review Rauch A et al. Host genetic determinants of spontaneous hepatitis C clearance. Pharmacogenomics 2009;10:1819–37.
  - the editorial on HLA-DPA1 and HLA-DPB1 Tamori A et al. HLA class II associated with outcomes of hepatitis B and C infections. World J Gastroenterol 2013;19:5395-401.
  - the study on HLA-DMA, HLA-DOA, and HLA-DOB Huang P et al. Genetic variants in antigen presentation-related genes influence susceptibility to hepatitis C virus and viral clearance: a case control study. BMC Infect Dis 2014;14:716.
  - the study reporting an association for HLA-DQB1*0301 and for HLA rs4273729 in Europeans and Africans Duggal P et al. Genome-wide association study of spontaneous resolution of hepatitis C virus infection: data from multiple cohorts. Ann Intern Med 2013;158:235-45.
  - the meta-analysis on DQB1*0301 and DRB1*1101 Hong X et al. Human leukocyte antigen class II DQB1 *0301, DRB1*1101 alleles and spontaneous clearance of hepatitis C virus infection: a meta-analysis. World J Gastroenterol 2005;11:7302-7.
  - the study on HLA-DRB1*1101, HLA-DQB1*0301, HLA-DRB1*0701, and HLA-DRB4*0101 Thursz M et al. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. The Lancet 1999;354: 2119-24.
  - the study on HLA rs4273729 in Chinese Xu Y et al. A novel polymorphism near HLA class II region is associated with spontaneous clearance of HCV and response to interferon treatment in Chinese patients. J Hum Genet 2016;61:301-5.
  - the study on HLA-A*03, HLA-B*27, HLA-DRB1*0101, HLA-DRB1*0401, HLA-DRB1*15, and DQB1*0201 McKiernan SM et al. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. Hepatology 2004;40:108-14.
  - the study on HLA-C*15 Tseng KC et al. Effect of human leukocyte antigen class I and II alleles on hepatitis C viral load among chronic hepatitis C patients in Southern Taiwan. Hum Immunol 2013;74:978-82.
  - the study on HLA-C1 (and KIR2DL3) Khakoo SI et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 2004;305:872-4.
  - the study on HLA-C1 (and KIR2DL3) Knapp S et al. Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. Hepatology 2010;51:1168-75.

Date of literature search: 2 January 2023.

| | Genotype | Code | Gene-drug interaction | Action | Date |
|---|---|---|---|---|---|
| KNMP Pharmacogenetics Working Group decision | B44-negative | 4 D | no | no | 7 February 2023 |

**Mechanism:**
The mechanism of the effect of HLA on the efficacy of interferon alfa/ribavirin treatment is not known. An effect on the immune response against hepatocytes infected with the hepatitis virus is likely to play a role.