



## CLINICALLY RELEVANT HCV DRUG RESISTANCE MUTATIONS FIGURE AND TABLES

### HCV Phenotype Working Group, HCV Drug Development Advisory Group

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Drug resistance information on direct-acting antivirals (DAAs) used to treat hepatitis C (HCV) infection is accumulating rapidly.<sup>1,2</sup> A systematic, comprehensive one-stop information source summarizing relevant data would benefit researchers, clinicians and the HCV community at large. The HCV resistance field is not yet as advanced as the HIV field, for which numerous resistance interpretation resources exist, including the well-known IAS-USA resistance mutation table<sup>3</sup> and the Stanford HIV Resistance database.<sup>4</sup> For HCV, initial clinical information is emerging and this publication is meant to provide current state-of-the-art information with respect to drug resistance.<sup>5,6</sup>

The Phenotype Analysis Working Group of the HCV Drug Development Advisory Group (HCV-DrAG), a project of the Forum for Collaborative HIV Research, undertook a review of resistance data for direct-acting antivirals (DAAs), concentrating on data for compounds which have entered phase 3 of clinical development or are already approved. A volunteer panel of expert stakeholders from academia, industry, and regulatory agencies reviewed published data and reached consensus on which mutations to include in this report.

This report of the Working Group summarizes available HCV drug resistance information in three formats: 1) a detailed table listing *in vitro* resistance information for all mutations observed with a compound ([Appendix 1](#)); 2) a summary of Appendix 1 listing important mutation-related parameters in an easily accessible format ([Table 1](#)) and; 3) a graphic summary of clinically relevant mutations observed with HCV drug therapy ([Figure 1](#)).

Reviewed data includes aggregate *in vitro* (based on site-directed mutagenesis and phenotypic resistance studies) and *in vivo* resistance information from phase 2 and phase 3 trials available through peer-reviewed publications and/ conference proceedings. Methodological details for *in vitro* and clinical trial analyses are available in the reference section. This revised version has newly submitted data included in the full-detail table (Appendix 1) and a new figure design.

The Tables - in detail ([Appendix-I](#)) and abbreviated form ([Table-I](#)) - provide resistance information on all mutations observed with a particular compound. The tables provide a listing of the compounds, their classification, viral enzyme targets, resistance mutations (position and number), replicon vector and subtype used, (cell type used for transfection, type of transfection, assay readout, and other key assay parameters). For each mutation, the mean fold-change in resistance ( $\pm$  SD) is shown. Please refer to the detailed phenotypic data in Appendix 1 for more information related to cross-resistance.

A summary of HCV resistance mutations detected in patients at virologic failure is shown in Figure 1. Black ovals depict key amino acid positions where substitutions were observed in at least 10% ( $\geq$  10%) of treatment failure patients; white ovals depict amino acid positions where substitutions have been observed in less than 10% ( $<$  10%) of treatment failure patients. Substitutions identified in  $\geq$  10% treatment failure patients are represented by encircled text, while those identified in  $<$  10% treatment failure patients are represented by un-encircled text. Importantly, Figure 1 does not yet include all mutations that contribute to resistance to a given drug. For example, a mutation selected by one protease inhibitor (PI) may lead to a reduction in susceptibility to a second PI, but if that mutation is not observed in patients treated with the second PI it is currently not displayed. Future versions of Figure 1 may include such information as the relevant data are gathered.



Many factors influence the selection of drug-resistant variants including genetic barrier for each drug in the combination, dose, treatment adherence, PK/PD for drugs, drug-drug interactions, etc. Hence, the data provided here should not be used as a means of predicting virologic failure in patients but as an aid in providing guidance on drugs that could or could not be combined based on observed resistance profiles.

Contributions for publication in the drug resistance figure and table, and comments can be made to [nmani@hivforum.org](mailto:nmani@hivforum.org).

#### ACKNOWLEDGMENTS

The HCV DrAG is grateful to Dr. Neil Parkin (Data First Consulting, Inc.) for initiating the table and figure for the project.

The HCV Drug Development Advisory Group (DrAG), a project within the Forum for Collaborative HIV Research, follows the same structure and composition, with representatives from the U.S. and European regulatory agencies, academic scientists, regulatory agencies, drug sponsors and patient advocates. The HCV DrAG receives funding from pharmaceutical companies which are listed at [www.hivforum.org](http://www.hivforum.org).

#### Phenotype Analysis Working Group

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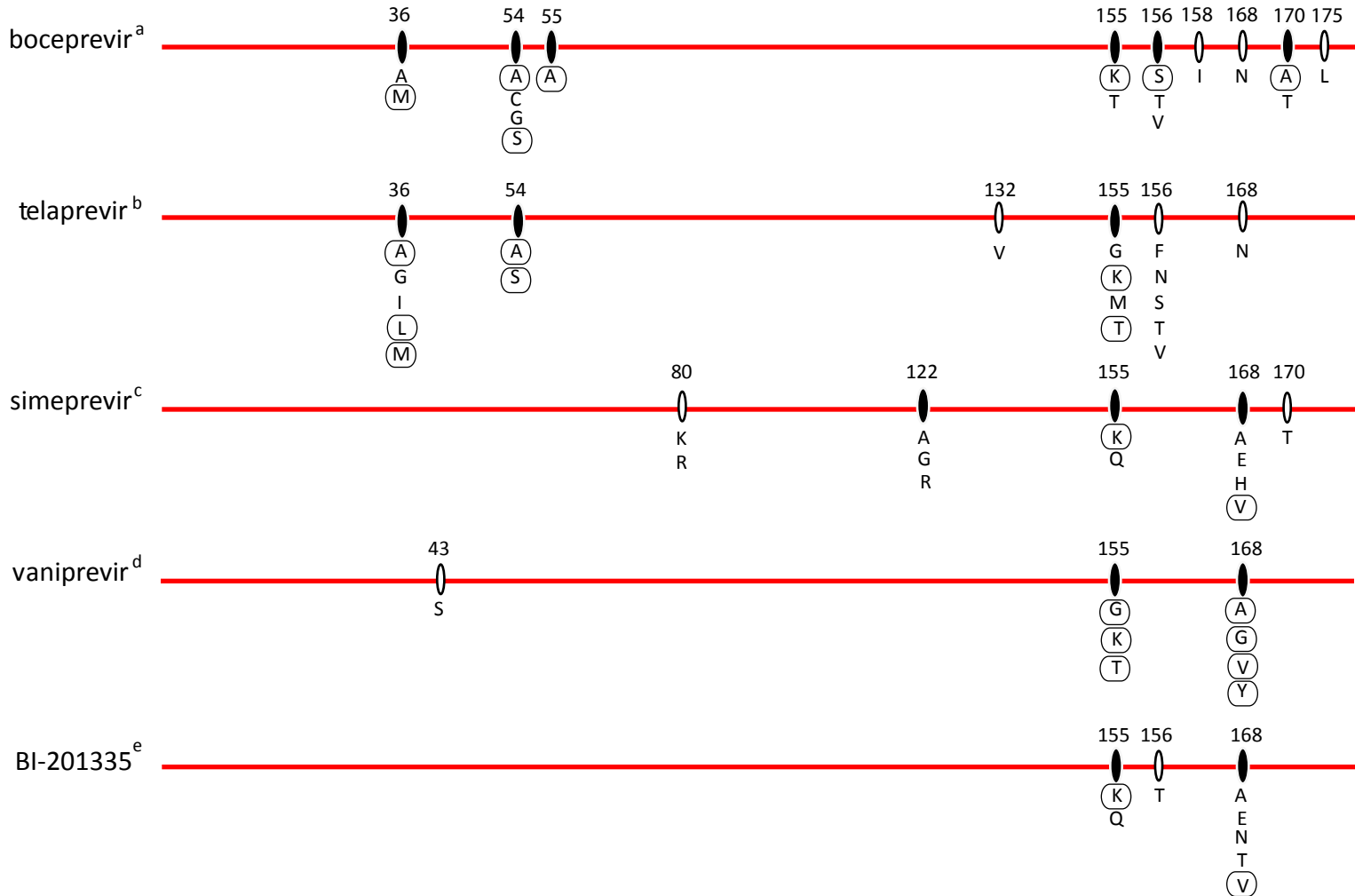
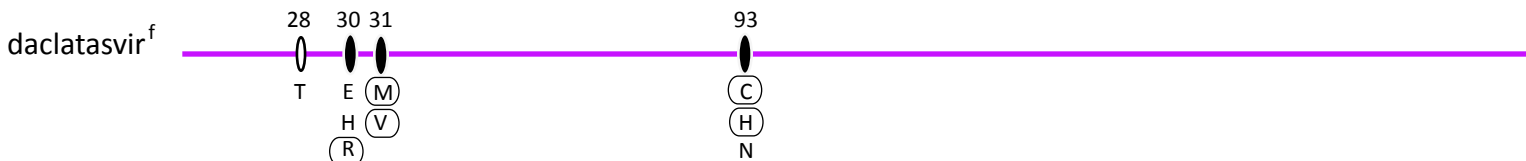
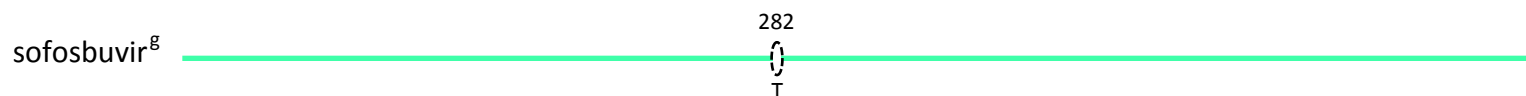
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†**Disclaimer:** The views represent the authors' and working group members' opinion and do not necessarily represent the views of the Food and Drug Administration or the Swedish Medical Products Agency/European Medicines Agency.

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**Figure 1.** Summary of clinically relevant HCV drug resistance mutations.**NS3 Protease (180 aa)****NS5A Domain I (213 aa)****NS5B Polymerase (591 aa)- Nucleoside Analog**

● Amino acid positions where substitutions were detected in *at least* 10% of treatment failure patients

○ Amino acid positions where substitutions were detected in *less than* 10% of treatment failure patients

⋈ Amino acid positions where *in vitro* substitutions were detected; none observed in patients treated with sofosbuvir

x Amino acid substitutions identified in *at least* 10% of treatment failure patients

○ Un-encircled substitutions identified in *less than* 10% of treatment failure patients

See Footnotes for more detailed information.



## FOOTNOTES

## NS3 Protease Inhibitors

## a. boceprevir

- The NS3 amino acid substitutions observed most commonly in clinical trials with patients who did not achieve SVR were V36M, T54A/S, V55A, R155K and A156S and I/V170A.<sup>1</sup> These substitutions have been shown to reduce boceprevir anti-HCV activity in *in vitro* studies.<sup>2</sup>
- V36M, T54S and R155K substitutions predominate in HCV genotype 1a patients, while T54A/S, V55A, A156S and I/V170A variants predominate in genotype 1b patients.<sup>1</sup>

## b. telaprevir

- The NS3 amino acid substitutions observed most commonly in clinical trials with patients who did not achieve SVR were V36M/A/L, T54A/S, R155K/T and A156S/T.<sup>3</sup> These substitutions have been shown to reduce telaprevir anti-HCV activity in *in vitro* studies.<sup>4</sup>
- V36M and R155K substitutions predominate in HCV genotype 1a patients, while V36A, T54A/S and A156S/T variants predominate in genotype 1b patients.<sup>3</sup>

## c. simeprevir

- The emerging NS3 amino acid substitutions observed most commonly in clinical trials with patients who did not achieve SVR were R155K (alone or in combination with mutations at position 80, 122 or 168) in genotype 1a patients, while D168V was most common in genotype 1b patients.<sup>5,6</sup> These mutations have been shown to reduce TMC435 anti-HCV activity in *in vitro* studies.<sup>7</sup> Though not observed in patients treated with simeprevir, F43I, S, and V, and A156G, T and V confer >10-fold reductions in susceptibility to this drug.

## d. vaniprevir

- The NS3 amino acid substitutions observed most commonly in trials were R155K and D168V in genotype 1a patients, while D168T/V substitutions predominate in genotype 1b patients.<sup>8</sup> These mutations have been shown to reduce MK-7009 anti-HCV activity in *in vitro* studies.<sup>9</sup> Though not observed in patients treated with vaniprevir, A156T confers a 125-fold reduction in susceptibility to this drug.

## e. BI-201335

- The NS3 amino acid substitutions observed most commonly in phase 2 trials were R155K in genotype 1a, and D168V in genotype 1b patients.<sup>10,11</sup> R155Q was only detected in combination with a D168 variant

in <1% of treated patients with virologic failure. D168N was only detected in combination with R155Q and only in <1% of treated patients with virologic failure. D168E emerged alone or in combination with R155K in <3% of treated patients with virologic failure. A156T was only detected once (< 1%) and only in combination with D168E. These substitutions have been shown to reduce BI-201335 anti-HCV activity in *in vitro* studies.<sup>11,12</sup>

## NS5A Inhibitors

## f. BMS-790052

- The NS5A amino acid substitutions observed most commonly in proof-of-concept monotherapy clinical trials in genotype 1a patients included M28T, Q30E/H/R, and Y93H.<sup>13</sup> In dual-DAA studies, the most common NS5A amino acid substitutions detected included Q30R, L31M/V, and Y93C/N.<sup>14</sup>
- The NS5A substitutions observed most commonly in trials in genotype 1b patients were L31M/V linked with Y93H.<sup>13,15</sup>

## NS5B Inhibitors

## Nucleoside Analogs

## g. sofosbuvir

- The S282T substitution in NS5B has not been observed in trials of patients treated with sofosbuvir.<sup>16</sup>
- The S282T substitution has been detected very rarely in trials with other drugs of this class.<sup>17,18</sup>

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**Table I**  
HCV Drug Resistance Table (Abbreviated)

Generic Name (aka)	Manufacturer	Target Enzyme; Compound Class	Mutation	Fold Resistance*	Replicon Vector Genotype	References
boceprevir	Merck	NS3; PI	V36M	2.9	1b	1
			F43S	3.5		
			T54A	6.7		
			R155K	3.6		
			A156S	24		
			A156T	128		
			V170A	19		
telaprevir	Vertex	NS3; PI	V36A	7.4	1b	2-5
			V36G	11		
			V36I	0.3		
			V36L	2.2		
			V36M	7.0		
			T54A	6.3		
			T54S	4.2		
			I132V	1.8	1a	
			R155G	7.4	1b	
			R155K	7.4		
			R155M	5.6		
			R155T	20		
			A156F	>62	1b	
			A156N	>93		
			A156S	9.6		
			A156T	>62		
			A156V	>62		
D168N	0.63	1a				
V36M+R155K	~64					
BI-201335	Boehringer Ingelheim	NS3; PI	R155K	360	1a	6,7
			R155K	350	1b	
			R155Q	60		
			A156T	270		
			A156V	150		
			D168A	690		
			D168G	80		
			D168V	970		
			D168V	620	1a	
			V36M	2.1	1b	
			T54A	0.9		
			T54S	3.5		
			Q80K	2.2		
			Q80L	1.2		
Q80N	0.6					
Q80R	2.6					



Generic Name (aka)	Manufacturer	Target Enzyme; Compound Class	Mutation	Fold Resistance*	Replicon Vector Genotype	References
simeprevir	Janssen R & D	NS3; PI	Q41R	1.9	1b	8
			F43I	89		
			F43S	11		
			F43V	99		
			Q80H	3.4		
			Q80K	7.8		
			Q80R	6.4		
			R109K	0.5		
			R155K	32		
			S122A	0.9		
			S122G	0.5		
			S122R	21		
			A156G	19		
			A156T	37		
			A156V	196		
			D168A	784		
			D168E	38		
			D168H	401		
			D168I	1800		
			D168N	5.5		
			D168T	334		
			D168V	3100		
			D168Y	651		
F43S+Q80R	286					
F43S+D168E	792					
Q80K+R155K	420					
Q80R+R155K	305					
Q80R+D168E	453					
Q80H+D168E	145					
Q80R+D168A	2660					
vaniprevir	Merck	NS3; PI	Q41R	3.3	1b	9
			F43S	4.9		
			R155K	219		
			A156T	125		
			D168Y	269		
sofosbuvir	Gilead	NS5B; NI	S282T	13	1a	10
			S282T	9.5	1b	
daclatasvir	Bristol-Myers Squibb	NS5A; RCI	Y93H	19	1b	11
			L31V	23		
			Y93H	19		
			L31V+Y93H	8336		
			M28T	683	1a	11,12
			Q30E	24933		
			Q30H	1450		
Q30R	1217					



Generic Name (aka)	Manufacturer	Target Enzyme; Compound Class	Mutation	Fold Resistance*	Replicon Vector Genotype	References
Continued - daclatasvir	Bristol-Myers Squibb	NS5A; RCI	L31M	3350	1a	11,12
			L31V	233		
			P32L	1850		
			Y93C	5367		
			Y93H	47477		
			Y93N	103767		
			M28T+Q30H	8336		

\*Compared to wild type replicon RNA

Please refer to [Appendix I](#) for more detailed information.

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