HCV: Resistance associated Substitution and Drug Interactions

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COI Disclosure Information

Advisory Board
BMS, Gilead, Novartis, Abbvie, MSD

Education and Research Funding
BMS, Gilead Novartis, Abbvie, Sanofi Aventis
Factors contributing to treatment failure:

1. Cirrhosis
2. Treatment experienced
3. Genotype 3
4. Resistance Associated Substitution (Variant)/ Polymorphism
HCV: Resistance Associated Substitution

- 9.5 kilobase RNA virus that replicates very rapidly (billions of viruses daily).
- RNA polymerase - 1 to 3 errors per replication cycle
- Transcription errors in critical coding region may confer decreased susceptibility to antiviral drugs.

Baseline associated substitution

- Can occur in up to 15% of patients. Significant for NS5A

Treatment related – due to selection especially if subtherapeutic doses

- Compliance
- Drug drug interaction
RAS are rarely seen (<1%) in NS5B inhibitors failure due to conservation highly conserved catalytic site region

NS5A  RAS are replication competent and can become dominant even after selection pressure is removed.
Resistance Associated Substitution

Every genotype/subtype has a defined aa sequence position

(Tyr) Y 93 H (His)

Physiological significance: in vitro testing for susceptibility – resistance associated substitution

Threshold of clinical significance

Polymorphism > 15% of virus population (Sanger or NGS at 15% prevalence correlates better with clinical significance.

RAS does not necessarily confer clinical significance

Dependent on HCV subtype, cirrhosis and Rx experience

Detecting genotypic resistance

1. Sanger sequence 15-25% sensitivity
2. NGS down to 1% sensitivity

Sarrazin C. Gastroenterology. 2010
<table>
<thead>
<tr>
<th>Resistance-associated substitutions</th>
<th>HCV Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
</tr>
<tr>
<td>K 24 E/R/N</td>
<td>M/L 28 M/G/T</td>
</tr>
<tr>
<td>M 28 A/T/G/V</td>
<td>R 30 H</td>
</tr>
<tr>
<td>Q 30 R/K/E/H/L/Y/G/T/D/I</td>
<td>L 31 V/M/F/I</td>
</tr>
<tr>
<td>L 31 M/V/F</td>
<td>P 58 S</td>
</tr>
<tr>
<td>H 54 R</td>
<td>Y 93 H/N/C/S/R</td>
</tr>
<tr>
<td>H 58 D/P/R</td>
<td></td>
</tr>
<tr>
<td>E 62 D</td>
<td></td>
</tr>
<tr>
<td>Y 93 H/N/C/S/F/L</td>
<td></td>
</tr>
</tbody>
</table>

Wyles HCV Drug Discovery 2017
## Fold-Changes in EC50 for Select Resistance-Associated Substitutions for HCV Drugs, by Genotype

<table>
<thead>
<tr>
<th>HCV Drug</th>
<th>M28T</th>
<th>Q30R</th>
<th>L31M</th>
<th>L31V</th>
<th>Y93H</th>
<th>Y93N</th>
<th>L31V</th>
<th>Y93H</th>
<th>Y93N</th>
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<tbody>
<tr>
<td>Daclatasvir</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&gt;1000×</td>
<td>&gt;10,000×</td>
<td>&lt;10×</td>
<td>20×</td>
<td>50×</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>20×</td>
<td>&gt;100×</td>
<td>&gt;10×</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&gt;1000×</td>
<td>&lt;10×</td>
<td>&gt;100×</td>
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<td>Ledipasvir</td>
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<td>&gt;100×</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&gt;10,000×</td>
<td>&gt;20×</td>
<td>&gt;100×</td>
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<td>Ombitasvir</td>
<td>&gt;1000×</td>
<td>&gt;100×</td>
<td>&lt;3×</td>
<td>&gt;100×</td>
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<td>&gt;10,000×</td>
<td>&lt;10×</td>
<td>20×</td>
<td>50×</td>
</tr>
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<td>Pibrentasvir</td>
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<td>&lt;3×</td>
<td>&lt;3×</td>
<td>&lt;3×</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
<td>&lt;3×</td>
<td>&lt;3×</td>
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<tr>
<td>Ruzasvir</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
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</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt;10×</td>
<td>&lt;3×</td>
<td>20×</td>
<td>50×</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&lt;10×</td>
<td>&lt;3×</td>
<td>NA</td>
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</table>
# Clinical Significance of RAS in HCV GT 1

<table>
<thead>
<tr>
<th>1b</th>
<th>Asunaprevir/ Daclatasvir L31F/I/M/V Y93H</th>
<th>SVR w RAS</th>
<th>SVR no RAS</th>
<th>Recomm.</th>
<th>Ref</th>
<th>AASLD recomm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>42%</td>
<td>88%</td>
<td>Rx only if no RAS</td>
<td>McPhee <em>Adv Ther.</em> 2015</td>
<td>NA</td>
</tr>
<tr>
<td>1a</td>
<td>Elbasvir/ Grazoprevir 28, 30, 31, 93</td>
<td>58%</td>
<td>98%</td>
<td>Add RBV Extend 16w</td>
<td>Zeuzem 2015 Jacobson 2015b</td>
<td>Recomm</td>
</tr>
<tr>
<td></td>
<td>Rx naïve</td>
<td>29%</td>
<td>97%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Rx Exp</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
AASLD suggest screening for RAS in GT1 treatment experienced patients with and without cirrhosis. If RAS are present
TE NC - add RBV; TE,C - extend 24/52

Zeuzem J Hep 2017
### Clinical significance of RAS GT3

<table>
<thead>
<tr>
<th></th>
<th>SVR w RAS</th>
<th>SVR no RAS</th>
<th>Recomm.</th>
<th>Ref</th>
<th>AASLD recomm</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT3</td>
<td>Sofosbuvir/daclatasvir Y93H</td>
<td>54%</td>
<td>97%</td>
<td>If Y93H + +RBV 12w +RBV 24w</td>
<td>ALLY-3 Nelson 2015</td>
</tr>
<tr>
<td></td>
<td>Rx Exp (12w) Cirrhotic(24w)</td>
<td>67%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cirrhotic(24w)</td>
<td>25%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir/Velpatasvir Y93H</td>
<td>88%</td>
<td>97%</td>
<td>+RBV or Rx 24w</td>
<td>ASTRAL 3</td>
</tr>
<tr>
<td></td>
<td>Rx Exp Cirrhotic Both (+RBV)</td>
<td>89%</td>
<td></td>
<td></td>
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</tbody>
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## Screen for RAS NS5A Rx failure

<table>
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<tr>
<th>RAS</th>
<th>Recomm.</th>
<th>SVR</th>
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</thead>
<tbody>
<tr>
<td>No NS5A</td>
<td>SOF + LDV</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>SOF + VEL +RBV 24w</td>
<td>97% GT1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85% GT3</td>
</tr>
<tr>
<td>NS5A</td>
<td>SMV+ SOF+ RBV 24w</td>
<td></td>
</tr>
<tr>
<td>No NS3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS5A</td>
<td>wait</td>
<td></td>
</tr>
<tr>
<td>NS3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### POLARIS-1: SVR12 Rates With 12-Wk SOF/VEL/VOX in Previous NS5A Failure

<table>
<thead>
<tr>
<th>SVR12, % (n/N)</th>
<th>SOF/VEL/VOX</th>
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<tbody>
<tr>
<td>Overall</td>
<td>96 (253/263)</td>
</tr>
<tr>
<td>Cirrhosis status</td>
<td></td>
</tr>
<tr>
<td>- No cirrhosis</td>
<td>99 (140/142)</td>
</tr>
<tr>
<td>- Cirrhosis</td>
<td>93 (113/121)</td>
</tr>
<tr>
<td>Baseline RAVs</td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>98 (42/43)</td>
</tr>
<tr>
<td>- Any</td>
<td>96 (199/208)</td>
</tr>
</tbody>
</table>

### SVR12, % (n/N) by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>96 (97/101)</td>
</tr>
<tr>
<td>1b</td>
<td>100 (45/45)</td>
</tr>
<tr>
<td>2</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>3</td>
<td>95 (74/78)</td>
</tr>
<tr>
<td>4</td>
<td>91 (20/22)</td>
</tr>
<tr>
<td>5</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>6</td>
<td>100 (6/6)</td>
</tr>
</tbody>
</table>

- 7 virology failures; all cirrhotic pts (GT1a, n = 2; GT3, n = 4; GT4, n = 1)

Glecaprevir and Pibrentasvir GLE/PIB
MAGELLAN-1, Part 2: SVR12 (ITT) Analysis

SVR12 rate by cirrhosis
Cirrhosis: 85% (23/27)
No Cirrhosis: 91% (58/64)

12 or 16 Weeks in Patients with CHC GT1 or 4 and Prior DAA Treatment Failure

Poordad EASL 2017
SVR12 by Presence of NS3A or NS5A Substitutions

**Y93H/N at baseline:** 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

Key **NS3** positions: 155, 156, 168

Key **NS5A** positions: 24, 28, 30, 31, 58, 92, 93

OTVF: on-treatment virologic failure

5/9 of these patients achieved SVR12

Key baseline **NS3** and **NS5A** substitutions were only present in patients with prior failure to both PI and NS5A inhibitors
Summary I

- Baseline (i.e., prior to drug exposure) NS5A RASs are relatively prevalent (up to 18%)
- Clinical significance seen mainly in genotype 1a and 3 infections.
- Patient characteristics, including cirrhosis, prior HCV treatment, increase clinical impact of NS5A RASs.
- Treatment failure with NS5A regimens are due mainly to RASs that can persist for more than 2 years.
- The impact of NS5A RAS is relative and can often be overcome by increasing the length of therapy and/or by adding ribavirin.
Drug Drug Interactions

http://www.hep-druginteractions.org/
Drug Drug Interactions

I. Absorption
pH affect Drug dissolution

Ledipasvir, Velpatasvir, PRoD: solubility decreases as pH increases. Drugs that increase gastric pH (antacids, H2-receptor antagonists, proton pump inhibitors) are likely to decrease concentrations of ledipasvir. H2-receptor antagonists simultaneously or 12 h apart =< famotidine 40 mg proton pump inhibitors =< omeprazole 20 mg

AASLD guidelines 2017
Impact of PPI on HCV therapy

HCV-TARGET study with 1788 patients receiving ledipasvir-sofosbuvir

Use of PPI was associated with an approximately 2-fold lower odds of achieving SVR compared with those with no use of PPI (OR, 0.57; 95% CI, 0.25 to 0.67)

Terrault Gastroenterology 2016
### Real world impact on HCV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LDV/SOF (n = 1927)</th>
<th>LDV/SOF + RBV (n = 328)</th>
<th>Total (n = 2255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>1124 (58)</td>
<td>234 (71)</td>
<td>1358 (60)</td>
</tr>
<tr>
<td>PPI use, n (%)</td>
<td>550 (29)</td>
<td>122 (37)</td>
<td>672 (30)</td>
</tr>
<tr>
<td>PPI use at baseline, n (%)</td>
<td>506 (26)</td>
<td>115 (35)</td>
<td>621 (28)</td>
</tr>
<tr>
<td>Among PPI users, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI use for the entire treatment</td>
<td>396/444 (89)</td>
<td>90/109 (83)</td>
<td>486/553 (89)</td>
</tr>
<tr>
<td>Baseline PPI use ≤20 mg daily</td>
<td>258/440 (59)</td>
<td>64/109 (59)</td>
<td>322/549 (59)</td>
</tr>
</tbody>
</table>

This translates into an absolute difference in SVR between those on and off PPIs of 4%, still a small factor in real world data.
Drug Drug Interactions

Drugs that are hepatic P-gp inducers will increase efflux of drug into lumen and reduce bioavailability.

P-gp inducers: Carbamazapine, rifampin, St John’s wort are P-gp inducers.

P-gp inhibitors: amiodarone, erythromycin, ketoconazole, quinidine.
# HCV drugs and transporters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate transporter</th>
<th>Metabolism</th>
<th>Inhibit transporter</th>
<th>effect CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asunaprevir</td>
<td></td>
<td>CYP3A</td>
<td>P-gp and OATP1B1</td>
<td>Inhibit CYP2D6 Induce CYP3A4</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>P-gp, BCRP</td>
<td>CYP3A4/5</td>
<td>OATP1B</td>
<td></td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>P-gp OATP1B1</td>
<td>CYP3A</td>
<td>BCRP</td>
<td>Inhibit CYP3A</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td></td>
<td>CYP3A</td>
<td>P-gp</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>P-gp</td>
<td>Minimally</td>
<td>P-gp</td>
<td></td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>P-gp BCRP</td>
<td>Amide hydrolysis</td>
<td>P-gp and BCRP</td>
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</tr>
<tr>
<td>Elbasvir</td>
<td>P-gp</td>
<td>CYP3A</td>
<td>BCRP, P-gp</td>
<td></td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>P-gp, BCRP, OATP1B1, OATP1B3</td>
<td>CYP2B6 CYP2C8 CYP3A4</td>
<td>P-gp, BCRP, OATP1B1, OATP1B3</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>P-gp BCRP</td>
<td>phosphorylated to active-form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>P-gp BCRP</td>
<td>CYP2C8 CYP3A, CYP2D6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>P-gp, BCRP OATP1B1/3</td>
<td>CYP3A</td>
<td>P-gp, BCRP, OATP1B1/3 BSEP</td>
<td>Inhibit CYP 3A UGT 1A1</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>P-gp BCRP</td>
<td>CYP3A</td>
<td>P-gp, BCRP,</td>
<td>Inhibit CYP 3A</td>
</tr>
</tbody>
</table>
Drugs that are P450 inducers will increase first pass metabolism and decrease drug bioavailability: rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital, phenytoin, St John’s wort.

Drugs that are P450 inhibitors will increase toxicity due to increase in levels of alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot derivatives, lovastatin, simvastatin, atorvastatin, oral midazolam, triazolam, quetiapine, quinidine, salmeterol.

EASL 2016
Drug Drug Interactions

Oral DAA are themselves potent inducers and inhibitors of transporters and P450 systems

Inhibition of P-gp and BCRP will increase levels of drugs that utilise these pathways and increases the risk of toxicity

Drugs that may have narrow therapeutic indices may cause toxicity
Rouvastatin, digoxin, dabigatran, ticagrelor, carvedilol, amlodipine, diltiazem, aliskiren
Toxicity with amiodarone

FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug
Important class of drugs to screen

• Cardiovascular drugs
  • Antiplatelet, amiodarone, carvedilol, Ca blocker

• Lipid lowering drugs

• CNS drugs

• Recreational drugs
Important Interactions - comorbidity

HIV-HCV coinfected

HCV post liver transplant

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

<table>
<thead>
<tr>
<th>Drug</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>3D</th>
<th>GZR/EBR</th>
<th>DCV</th>
<th>SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azatovir</td>
<td></td>
<td></td>
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<tr>
<td>Emtricitabine</td>
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<tr>
<td>Tenofovir</td>
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<td>Efavirenz</td>
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<td>Nevirapine</td>
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<td>Ritonavir</td>
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<tr>
<td>Atazanavir; atazanavir; atazanavir/ritonavir</td>
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<tr>
<td>Darunavir; darunavir/ritonavir</td>
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<tr>
<td>Lopinavir</td>
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<td>Dolasetravir</td>
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<tr>
<td>Eptinezavir/ritonavir/tenofovir/dosed inj.</td>
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<td>Eptinezavir/tenofovir/ritonavir</td>
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<tr>
<td>Darunavir/ritonavir</td>
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<td>Maraviroc</td>
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<td>Raltegravir</td>
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</tbody>
</table>

Table 4F. Drug-drug interactions between HCV DAAs and immunosuppressants.

<table>
<thead>
<tr>
<th>Drug</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>3D</th>
<th>GZR/EBR</th>
<th>DCV</th>
<th>SIM</th>
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Colour legend:
- Green: No clinically significant interaction expected.
- Yellow: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. These drugs should not be co-administered.
Summary II

1. Screening for Drug Drug Interactions is an integral part of HCV therapy with oral DAAs
2. PPI can reduce absorption of DAA and reduce bioavailability.
3. HCV drugs are substrates of cell transporters that moves drug in and out of the cell as well cytochrome P450 metabolism pathway- levels may change with other inducers/ suppressors
4. They are in turn inducers/suppressors of cell transporters/ P450 enzymes and may cause toxicity or underdose of other drugs
Thank You