HCV: Resistance, DAA Failures, and Other Difficult Situations

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Disclosures


- **Speaker Bureau:** AbbVie Inc., Bristol-Myers Squibb Company, Gilead, Janssen Pharmaceuticals, Inc., Merck & Co., Inc.
Note the common root name for each drug class
Resistance

- **RAV**: Resistance Associated Variant
  - Present prior to initiation of therapy
- May have baseline or treatment emergent variants to
  - NS3/4A
  - NS5A
  - NS5B
    - Nucleotide
    - Non-nucleotide
# Barriers to Genetic Resistance by Drug Class (GT 1)

<table>
<thead>
<tr>
<th>Drugs in Class</th>
<th>NS3/4A Protease Inhibitors</th>
<th>NS5B Nucleos(t)ide Polymerase Inhibitors</th>
<th>NS5B Nonnucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td></td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Ledipasvir</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td></td>
<td></td>
<td></td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td></td>
<td></td>
<td></td>
<td>Daclatasvir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elbasvir</td>
</tr>
<tr>
<td>Barrier to resistance</td>
<td>Medium (1a lower barrier than 1b)</td>
<td>High (1a=1b)</td>
<td>Very low (1a lower barrier than 1b)</td>
<td>Low (1a lower barrier than 1b)</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd generation PIs have higher barrier, pangenotypic</td>
<td>Single target Active site</td>
<td>Allosteric Many targets</td>
<td>Multiple antiviral Mechanism of Action</td>
</tr>
</tbody>
</table>

- RAVs to one drug are generally cross resistant to other drugs within a class, although this is not always the case
- Viral fitness of RAVs effects their persistence after discontinuation of therapy

Fitness: Resistant Variants Are Present Before and Can Be Selected During Treatment

- HCV is a mixture of related but distinct populations of virions in each patient\(^1\)
- Most resistant variants are unfit and may be undetectable prior to therapy\(^2,3\)

![Diagram](https://via.placeholder.com/150)

Antiviral therapy eliminates sensitive variants. Resistant variants expand.

NS5A RAVs:
Are Some RAVs More Impactful than Others?
Does GT 1a vs GT 1b Matter?
Baseline NS5A RAVs in DAA-Naïve Patients

- Baseline RAVs in GT1a (Q30, L31, and Y93) have the largest clinical impact
- Y93H in GT1b most common but little clinical impact
- Y93H in GT1b only ~100 fold-change while in GT1a ~10,000 fold shift

The subtype background has much to do with whether the RAV has a clinical impact

# Broad Cross-Resistance with "Early Generation" NS5As

<table>
<thead>
<tr>
<th>Fold-change</th>
<th>1a</th>
<th>1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T Q30R L31M/V Y93H/N L31V Y93H/N</td>
<td></td>
</tr>
<tr>
<td><strong>Ledipasvir</strong></td>
<td>20x &gt;100x &gt;100x/ &gt;100x &gt;1,000x/ &gt;10,000</td>
<td>&gt;100x/--</td>
</tr>
<tr>
<td><strong>Ombitasvir</strong></td>
<td>&gt;1000x &gt;100x &lt;3x &gt;10,000x/ &lt;10x 20x/50x</td>
<td></td>
</tr>
<tr>
<td><strong>Daclatasvir</strong></td>
<td>&gt;100x &gt;1000x &gt;100x/ &gt;1000x &gt;1,000x/ &gt;10,000x</td>
<td>&lt;10x 20x/50x</td>
</tr>
<tr>
<td><strong>Elbasvir</strong></td>
<td>20x &gt;100x &gt;10x &gt;1,000x/ &lt;10x &gt;100x/--</td>
<td></td>
</tr>
<tr>
<td><strong>Velpatasvir</strong></td>
<td>&lt;10x &lt;3x 20x/50x &gt;100x/ &gt;1000x</td>
<td>&lt;3x &lt;3x--</td>
</tr>
<tr>
<td><strong>ACH-3102</strong></td>
<td>30x 20x &lt;10x &gt;100x/ &gt;100x</td>
<td>&lt;3x &lt;3x/ &lt;3x</td>
</tr>
<tr>
<td><strong>ABT-530</strong></td>
<td>&lt;3x &lt;3x &lt;3x &lt;10x/ &lt;10x</td>
<td>&lt;3x &lt;3x/ &lt;3x</td>
</tr>
<tr>
<td><strong>MK-8408</strong></td>
<td>&lt;10x &lt;10x &lt;10x &lt;10x &lt;10x</td>
<td>&lt;10x</td>
</tr>
</tbody>
</table>

LDV/SOF ± RBV: Prevalence of NS5A Variants at Baseline and Impact on SVR

- Pooled data from GT1 patients with compensated cirrhosis who were treated with LDV/SOF ± RBV
- Deep sequencing (detection limit, 1%)
- 513 patients treated of whom 18 relapsed
P values represent differences in SVR12 rates between patients with and without NS5A RAVs. Presence of RAVs was evaluated by deep sequencing with assay cutoff of 1%.

LDV/SOF ± RBV: SVR12 in GT 1 Patients with Cirrhosis ± Baseline NS5A RAVs

LDV/SOF: Does Duration Matter? (12 vs 24 Weeks)

LDV/SOF x 12 Weeks: Does RBV Matter? (+/- RBV)

LDV/SOF: What About Longer Duration + RBV?

**12 Weeks**
- **LDV/SOF**
  - With RAVs: 23/26 (88%)
  - No RAVs: 86/91 (95%)

**24 Weeks**
- **LDV/SOF+RBV**
  - With RAVs: 14/14 (100%)
  - No RAVs: 44/44 (100%)

LDV/SOF ± RBV: SVR12 in GT 1 Patients with Cirrhosis ± Baseline NS5A RAVs

<table>
<thead>
<tr>
<th></th>
<th>With RAVs</th>
<th>No RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF 12 Weeks</td>
<td>88/23</td>
<td>95/66</td>
</tr>
<tr>
<td>LDV/SOF + RBV 12 Weeks</td>
<td>94/32</td>
<td>97/64</td>
</tr>
<tr>
<td>LDV/SOF 24 Weeks</td>
<td>85/17</td>
<td>100/113</td>
</tr>
<tr>
<td>LDV/SOF + RBV 24 Weeks</td>
<td>100/100</td>
<td>100/100</td>
</tr>
</tbody>
</table>

Only baseline HCV RNA >800,000 IU/mL and presence of baseline NS5A RAVs were identified as significant predictors of SVR12.

- Significant impact observed ONLY in patients with both factors
- Neither of these factors predicted SVR12 in GT1b treatment-naive patients
Among GT1a Treatment-naïve/Prior Relapsers with Baseline NS5A RAVS, the Efficacy of GZR/EBR (12 Weeks, No RBV) Varies from 58% to 91%, Depending on Methodology

Among GT1a PEG/RBV Non-responders With Baseline NS5A RAVs, the Efficacy of GZR/EBR (16/18 Weeks, With RBV) is High Regardless of Methodology

Impact of RAVs on Grazoprevir/Elbasvir Approved Label

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naive or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a: Treatment-naive or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†</td>
<td>ZEPATIER + ribavirin</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naive or PegIFN/RBV-experienced*</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡</td>
<td>ZEPATIER + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: Treatment-naive</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced*</td>
<td>ZEPATIER + ribavirin</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

*Peginterferon alfa + ribavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.
PRV/r/OMV + DSV + RBV (12 weeks in non-cirrhotics and 24 weeks in cirrhotics)

Figure 2. Impact of Baseline GT1a NS5A Class RAVs and Ombitasvir-specific RAVs on SVR Rate

Similar SVR rates were observed irrespective of the presence or absence of baseline variants

Sulkowski M et al., CROI 2016, Abstract 539LB
Do NS5A RAVs Persist After NS5A Treatment Failure?
Persistence of NS3, NS5A and NS5B Treatment Emergent Variants After Treatment with Ombitasvir/Paritaprevir/r + Dasabuvir ± RBV

- Pooled patients with virologic failure from all clinical trials (n=2510)
  - 67 patients with HCV genotype 1a
  - 7 patients with HCV genotype 1b (no long-term follow-up reported due to small numbers)

<table>
<thead>
<tr>
<th></th>
<th>Post-treatment 24 Weeks</th>
<th>Post-treatment 48 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A (any)</td>
<td>31/67 (46%)</td>
<td>5/57 (9%)</td>
</tr>
<tr>
<td>NS5A (any)</td>
<td>68/70 (97%)</td>
<td>49/51 (96%)</td>
</tr>
<tr>
<td>NS5B (non-nuc)</td>
<td>33/44 (75%)</td>
<td>20/35 (57%)</td>
</tr>
</tbody>
</table>

Long-Term Persistence of NS5A Variants After Treatment with LDV

- NS5A RAVs in patients who failed LDV treatment without SOF
- Positions 24, 28, 30, 31, 32, 58, 93 that confer >2.5-fold reduced susceptibility to LDV in vitro were included

Almost All Patients Who Failed Had Detectable NS5A RAVs at Treatment Failure

What Does AASLD/IDSA Guidance Document Recommend for NS5A Treatment-Experienced Patients??

- If previous failure of any NS5A inhibitor and non-cirrhotic, deferral preferred pending further data

- If cirrhosis or other need for urgent treatment, test for NS3 and NS5A RAVs and tailor retreatment regimen to results

- Applies to GT1a and 1b HCV infection

- Also applies to SOF + SMV treatment-experienced patients
Can we successfully retreat protease inhibitor (boceprevir, telaprevir or simeprevir) + PEG/RBV experienced patients?
Patients Who Previously Failed Boceprevir or Telaprevir + PEG/RBV Respond to LDV/SOF (ION-2)

Treatment History
- Failure of PEG/RBV
- Failure of PI + PEG/RBV

* Note the lower SVR rate with 12 weeks

Patients Who Previously Failed Boceprevir or Telaprevir + PEG/RBV Respond to DCV/SOF

- Another combination of DCV (NS5A inhibitor) + SOF (nuc polymerase inhibitor) highly efficacious in GT 1 PI failures
- RBV not necessary
- 12 weeks is equally efficacious

What About a Second Generation Protease Inhibitor + NS5A Inhibitor for Prior PI + PEG/RBV Failures (C-SALVAGE)?

- Grazoprevir (GZR) (protease inhibitor) + elbasvir (EBR) (NS5A inhibitor) + RBV
- 12 week treatment duration
- 43% cirrhotic

GT1 Patients who Failed Prior Protease Inhibitor (NS3) + PEG-IFN Regimen

No Cirrhosis
- LDV/SOF x 12 weeks
- DCV + SOF x 12 weeks
- EBR/GZR + RBV x 12 weeks* (*pts with BL high fold-change NS5A RAVs should receive 16 weeks)

Compensated Cirrhosis
- LDV/SOF + RBV x 12 weeks
- LDV/SOF x 24 weeks
- DCV + SOF ± RBV x 24 weeks
- EBR/GZR + RBV x 12 weeks* (*pts with BL high fold-change NS5A RAVs should receive 16 weeks)

*In patients with no high fold-change NS5A RAVs detected (Polymorphisms at amino acid positions 28, 30, 31 or 93).

www.hcvguidelines.org; accessed March 6, 2016.
What Is on the Horizon?
## Current and Next Generation NS3 Protease Inhibitors: Activity Against Various Subtypes *in vitro* Can Predict Lower Efficacy and Risk of RAVs

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Stable HCV Replicon EC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT1a</td>
</tr>
<tr>
<td>ABT-493</td>
<td>0.85</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>1.0</td>
</tr>
<tr>
<td>Simeprevir(^1,2)</td>
<td>13</td>
</tr>
<tr>
<td>Asunaprevir(^3)</td>
<td>4.0</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>0.38</td>
</tr>
<tr>
<td>GS-9451(^4)</td>
<td>13</td>
</tr>
<tr>
<td>GS-9857(^5)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

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\(^a\)Study conducted at Southern Research Institute.

NA, not available.


## Current and Next Generation NS5A Inhibitors: Activity Against Various Subtypes *in vitro* Can Predict Lower Efficacy and Risk of RAVs

<table>
<thead>
<tr>
<th>NS5A Inhibitor</th>
<th>Stable HCV Replicon EC₅₀ (pM)</th>
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<tbody>
<tr>
<td></td>
<td>GT1a</td>
</tr>
<tr>
<td>ABT-530</td>
<td>2</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>14</td>
</tr>
<tr>
<td>Daclatasvir¹</td>
<td>22</td>
</tr>
<tr>
<td>Ledipasvir²</td>
<td>31</td>
</tr>
<tr>
<td>Velpatasvir³</td>
<td>12</td>
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<tr>
<td>Elbasvir⁴</td>
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<tr>
<td>MK-8408⁵</td>
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<tr>
<td>ACH-3102⁶</td>
<td>26</td>
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<tr>
<td>IDX719⁷</td>
<td>8</td>
</tr>
</tbody>
</table>

*ᵃStudy conducted at Southern Research Institute.  
NA, not available.


NS3, NS5A and non-nuc polymerase inhibitor NS5B RAVs pre-exist at different frequencies in treatment-naïve patients

- Negative predictive factors important
  - GT1a
  - Cirrhosis
  - RAVs with high level resistance
- Addition of RBV and extending duration
- Future regimens may or may not have this issue

New DAA combinations are effective for first generation PI + PEG/RBV failures