Role of Resistance Testing
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Director of Inpatient Liver Services
Weill Cornell Medicine
Objectives

• Describe the Basics of Hepatitis C (HCV) Virology

• Explain the Direct Acting Antiviral Therapy Targets and Agents

• Describe Resistance to HCV Therapies

• Describe the role of Resistance Testing in HCV Therapy
HCV Viral Replication
Direct Acting Antiviral (DAA) Therapy Targets
WHY DO PEOPLE FAIL THERAPY?
Reasons for DAA Failure

• Non-compliance
• Resistance
DAA Failure Usually Secondary to Resistance

- DAA failure rate 3-5%
- Baseline versus treatment associated substitutions
- Development of resistance associated substitutions
  - Most common to NS5a inhibitors
    - Mostly genotypes 1a and 3
  - Commercial testing available
What Are RAVs?

- Resistance-associated variants or substitutions/polymorphisms
- HCV infection consists of many genetically-distinct, closely-related viral populations
- Some develop antiviral resistance through mutation
Resistant Variants Can Be Selected During Treatment

Potent antiviral therapy eliminates sensitive variants

Resistant variants are uncovered which can then expand
### Analysis of the Importance of RAVs: Definition and Sequencing Methods

#### Definition

| All substitutions | Each substitution within an HCV gene, which has been described as RAV, independent of the impact on resistance |
| Class-specific RAVs | All substitutions within an HCV Gene, which cause in vitro >2-fold resistance against an inhibitor of the gene |
| Substance-specific RAVs | Substitutions within an HCV gene which cause in vitro >2-fold resistance against a certain inhibitor of the gene |

#### Sequence analysis

- Direct sequencing versus deep sequencing (NGS)
Resistance Associated Variants

- Can occur:
  - Naturally, prior to any treatment exposure
  - During treatment (viral breakthrough)
  - Following treatment (viral relapse)
<table>
<thead>
<tr>
<th>RAV</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M204V/I</strong></td>
<td>The quintessential YMDD mutation in the HBV DNA polymerase that confers resistance to nucleotides (e.g. LAM)</td>
</tr>
<tr>
<td><strong>R155K</strong></td>
<td>A replicatively fit variant in the HCV protease that confers resistance to 1st generation protease inhibitors</td>
</tr>
<tr>
<td><strong>Q80K</strong></td>
<td>A variant present at baseline in many GT1a HCV patients reduces efficacy of simeprevir combined with PEG IFN+RBV</td>
</tr>
<tr>
<td><strong>Y93H</strong></td>
<td>One of several RAVs in the NS5A protein; Y93H has a many-fold effect on EC50- genotype 1a and 3</td>
</tr>
</tbody>
</table>
Global Prevalence of Naturally Pre-existing NS5A RASs

- Numbers indicate NS5A prevalence with a 1% cut-off

Zeuzem et al, Hepatology 2015; 62(Suppl): 254A
Most studies have found that NS5A RASs are present in approximately 10–20% of GT1-infected patients at baseline.

**OBV/PTV/r + DSV**

In a Phase 3 subset analysis:
BL NS5A RASs were detected in **22%** of patients

**LDV/SOF**

In a Phase 3 pooled analysis:
BL NS5A RASs were detected in **23%** of patients

**EBR/GZR**

In Phase 3 studies:
BL NS5A RASs were detected in **11–12%** of patients

- Viekira Pak PI, as approved in Jan 2016 (FDA Reference ID: 3878984);
How Do RAVs Emerge During Therapy?

- DAA exposure positively selects for the variants with resistance to that DAA
- At breakthrough or relapse, viral variants resistant to at least one DAA being used in treatment regimen
- Following treatment, RAVs may persist from weeks to years before being replaced by “wild-type” (non-mutated) virus
  - Wild-type virus generally more reproductively “fit” or able to replicate/survive better than mutated virus
Persistence of Selected RAVs in Treatment Failure
NS5A RAVs to LDV are Fit and Long-Lasting

The number of RAVs per patient declined (62% at baseline vs 34% at follow-up Week 96 had ≥3 RASs)

NS5A RAVs persisted in >95% of patients through to Week 48 and in 86% through to Week 96

FU = follow-up.

Wyles et al. J Hepatol 2015; 62(Suppl): S221
Risks of RAVs by DAA Class

- **High** barrier to resistance (few RAVs)
  - Nucleotide NS5B polymerase inhibitors (sofosbuvir)

- **Low** barrier to resistance (more RAVs)
  - Non-nucleotide NS5B polymerase inhibitors (dasabuvir)
  - NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir)
  - NS5A inhibitors (ledipasvir, daclatasvir, ombitasvir, elbasvir, velpatasvir)
## Activity of NS5A Inhibitors Against GT1 Resistance-Associated Variants

### Transient Replicon EC\(_{50}\) (pM)

<table>
<thead>
<tr>
<th></th>
<th>GT1a</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT</td>
<td>M28T</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>2.7</td>
<td>24,500</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>5.9</td>
<td>4050</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>51</td>
<td>1801</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>4</td>
<td></td>
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<tr>
<td>ABT-530</td>
<td>0.72</td>
<td>1.5</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Odalasvir</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Samatasvir</td>
<td>4.1</td>
<td>615</td>
</tr>
</tbody>
</table>

### Resistance Levels

- **< 10-fold resistance**
- **10-fold < resistance < 100-fold**
- **>100-fold resistance**
- **Data not available**

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*Activities of competitor compounds from public presentations and manuscripts*
### NS3 Inhibitor Activity Against GT1 Resistance-Associated Variants

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transient Replicon EC\textsubscript{50} (nM)\textsuperscript{a}</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>WT</td>
<td>R155K</td>
<td>A156T</td>
<td>D168A</td>
<td>D168V</td>
<td>WT</td>
<td>R155K</td>
<td>A156T</td>
<td>D168V</td>
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<tr>
<td>Paritaprevir</td>
<td>1.4</td>
<td>51</td>
<td>24</td>
<td>70</td>
<td>135</td>
<td>0.11</td>
<td>4.4</td>
<td>0.81</td>
<td>17</td>
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<tr>
<td>Simeprevir</td>
<td>2.8</td>
<td>45</td>
<td>164</td>
<td>147</td>
<td>8756</td>
<td>11</td>
<td>260</td>
<td>377</td>
<td>17917</td>
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<tr>
<td>Asunaprevir</td>
<td>0.76</td>
<td>16</td>
<td>17</td>
<td>283</td>
<td>0.86</td>
<td>23</td>
<td>5.4</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>0.3</td>
<td>1.3</td>
<td>97</td>
<td>29</td>
<td>27</td>
<td>0.5</td>
<td>1.1</td>
<td>104</td>
<td>5.9</td>
</tr>
<tr>
<td>ABT-493</td>
<td>0.21</td>
<td>0.16</td>
<td>290</td>
<td>0.84</td>
<td>0.93</td>
<td>0.54</td>
<td>0.32</td>
<td>300</td>
<td>1.3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Activities of competitor compounds from public presentations and manuscripts
RAVs Can Be Identified by Population-Based or Deep Sequencing Techniques

Population-based sequencing

- Sanger method
- Generates a consensus sequence of all of the viral substitutions in an individual
- Sensitivity of ≤20%

Deep sequencing also known as next-generation sequencing (NGS)

- High-throughput sequencing technique
- Whole-genome sequencing or analysis of a specific gene
- Sensitivity down to approximately 1%

A sensitivity cutoff of 15% may be more clinically relevant than a cutoff of 1% for the detection of viral substitutions that confer resistance to DAAs

Resistance to NS3/4A Protease Inhibitors

- Low barrier to resistance
- Cross-resistance between all agents
- Most RAVs rare and rapidly replaced by wild type virus
- Exception is Q80k variant
  - High frequency in genotype 1A
  - Up to 50% North Americans with 1A

Resistance to NS5A Inhibitors

- Low barrier to resistance
- Cross-resistance between most agents
- Occur frequently at baseline (no DAA exposure)
- G1A: substitutions at amino acid positions M28, Q30, L31, or Y93
- Most common: Y93H, L31M
- RAVs persist for 1-2 years in NS5A treatment failures

Resistance to Non-Nucleotide NS5B Polymerase Inhibitor (Dasabuvir)

- Low barrier to resistance
- No cross-resistance with nucleotide NS5B polymerase inhibitors
- RASs exist for both genotype 1A and 1B
- Most common M414T and S556G variants

Resistance to Nucleotide NS5B Polymerase Inhibitor (Sofosbuvir)

- High barrier to resistance
- No cross-reactivity with non-nucleotide NS5B polymerase inhibitors
- Main variant is S282T
- Resistant variants usually replaced by wild type virus quickly within weeks of stopping therapy
RAV TESTING PRIOR TO THERAPY: CURRENTLY AVAILABLE AND RECOMMENDED TESTS
Commercially Available Resistance Assays

• These are ordered as a plasma test

• Order by region not specific mutation
  – LabCorp/Monogram Biosciences
    • Regions: NS3/4A, NS5A, NS5B
  – Quest Diagnostics
    • Regions: NS3/4A, NS5A, NS5B
Quest NS5A Testing Options

Quest Diagnostics will be offering the following NS5A drug testing options:

- Test code 92447, Hepatitis C Viral RNA Genotype 1 NS5A Drug-resistance
- Test code 93871, Hepatitis C Viral RNA Genotype, LiPA with Reflex to HCV NS5A Drug-resistance

If the HCV genotype is 1a, NS5A drug-resistance test will be performed at additional charge.

- Test code 93873, Hepatitis C Viral RNA, Quantitative Real-Time PCR with Reflexes

If the HCV RNA is ≥300 IU/mL, the genotype (LiPA) test will be performed at additional charge. If the HCV genotype is 1a, the NS5A drug-resistance test will be performed at additional charge.
LabCorp Monogram NS3/4A testing

HCV GenoSure NS3/4A Provides Comprehensive Resistance Data for New HCV Protease Inhibitors

- Analyzes the genetic sequence for the nonstructural proteins NS3 and NS4A of HCV genotypes 1a and 1b
- **Identifies the Q80K polymorphism**
- Detects mutations in NS3 and NS4A and identifies drug-resistant variants for protease inhibitors grazoprevir, paritaprevir, and simprevir.
- Sensitivity to detect minor variant levels as low as 10% provides a detailed understanding of the patient’s viral population for informed treatment decisions

Download a [sample report](#).

<table>
<thead>
<tr>
<th>Test Name</th>
<th>HCV GenoSure NS3/N4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LabCorp Test Number</td>
<td>550540</td>
</tr>
<tr>
<td>Limitation</td>
<td>For patients with HCV genotype (subtype) 1a or 1b and a viral load ≥ 2000 IU/mL</td>
</tr>
<tr>
<td>Specimen Collection</td>
<td>3 mL plasma, EDTA or PPT tube, shipped frozen</td>
</tr>
<tr>
<td>Turnaround Time</td>
<td>7 to 10 days</td>
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</tbody>
</table>
Quest: Sample Recommendation for RAV testing

- **Genotype 1**: Consider NS3 (90924) and/or NS5A (92447) inhibitor resistance testing (see hcvguidelines.org)
- **Genotypes 2, 4-6**: Consider NS5A inhibitor resistance testing (93325)
- **Genotype 3**: Consider NS5A inhibitor resistance testing (93325)

Decision to treat
  - Treatment selection (based in part on HCV genotype)
<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV GenoSure&lt;sup&gt;®&lt;/sup&gt;</th>
<th>Drug Resistance Associated Variants&lt;sup&gt;®&lt;/sup&gt; Detected</th>
<th>Assessment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCVNS5A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSAL</td>
<td></td>
<td></td>
<td>DCV</td>
<td>Resistance Possible</td>
</tr>
<tr>
<td>RAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Important Definitions**
- Resistant Variants: Drug-resistant variants are resistance variants that confer resistance to a particular drug or drug regimen. Drug-resistant variants can be associated with the development of drug resistance and failure to respond to treatment.
- Nucleoside Analogs: Nucleoside analogs are a class of antiviral drugs used to treat chronic HCV infection. They work by interfering with the replication of the virus.
- Important: It is essential to ensure that the appropriate drug-resistant variants are detected to avoid treatment failure.

**Region**
- Genotype:
  - 1a
  - 1b

**Summary of All Variants Detected**
- **HCVNS5A**
  - 3a

Contact Monogram NS5A RAV Testing for more information or to request a sample.
## Sample Monogram NS5A Testing

### HCV NS5A Drug Resistance Assay

<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV GenoSure</th>
<th>Assessment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3A</td>
<td>Yes</td>
<td>NS5A, DENV, FLAV, KF2, KB2, KF3, KB3, KF6, KB6, KF9, KB9, KF10, KB10, KF11, KB11, KF12, KB12</td>
<td>None/Undetermined</td>
</tr>
<tr>
<td>NS5B</td>
<td>Yes</td>
<td>NS5A, DENV, FLAV, KF2, KB2, KF3, KB3, KF6, KB6, KF9, KB9, KF10, KB10, KF11, KB11, KF12, KB12</td>
<td>None/Undetermined</td>
</tr>
</tbody>
</table>

### Important Definitions

- **Drug resistance** refers to the development of resistance to medication due to changes in the genetic makeup of the virus. This can affect the effectiveness of antiretroviral therapy (ART). Drug resistance can be monitored using molecular methods like the HCV NS5A Drug Resistance Assay.

- **Genotypic testing** involves assessing the genetic makeup of the virus to identify specific mutations that confer or confer resistance to treatment. This is typically performed using methods like the HCV NS5A Drug Resistance Assay.

- **Pharmacodynamics** refers to the actions of a drug on the body and the factors that influence these actions, such as drug metabolism and pharmacokinetics.

- **Pharmacokinetics** is the study of how a drug is absorbed, distributed, metabolized, and excreted in the body. This includes the time course of drug concentrations at the site of action.

- **Virologic response** is a virologic parameter that is used to assess the effectiveness of antiretroviral therapy. It can be measured by viral load reduction or undetectable viral load.

### Summary of All Variants Observed

<table>
<thead>
<tr>
<th>NS3A</th>
<th>None</th>
</tr>
</thead>
</table>

**Comments:** NS3A variants observed were NS3A_30_31 or NS3A_32. For testing on NS5A, consider a coinhibiting regimen. Please refer to the prescribing information or current guidelines to determine the appropriate treatment regimen and duration.

For more information on interpreting this report, please call Monogram Customer Service at 866-777-8778 between the hours of 9:00AM to 5:00PM Pacific Time, Monday through Friday.
Sample Monogram RAV Testing

[Image]

**HCV GenoSure**

**Monogram BIOSCIENCES**

**Drug Resistance Assay**

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**Patient**

- **Name:**
- **DOB:**
- **Medical Record:**
- **Date:**
- **Monogram Assessed:**

**Referring Physician:**

**Comments:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV GenoSure™ NS3/4A</th>
<th>Assessment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Region</td>
<td>Drug Resistance Associated Variants</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Region</td>
<td>Drug Resistance Associated Variants</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Region</td>
<td>Drug Resistance Associated Variants</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Region</td>
<td>Drug Resistance Associated Variants</td>
</tr>
</tbody>
</table>

**Important Definitions:**

- **Resistance Profile:** Resistance Associated Variants (RAVs) detected in the sample that are associated with resistance to specific antiviral agents.

- **Significant Treatment Resistance:** When the drug resistance associated variants are present and may significantly affect the clinical outcome.

**Notes:**

- RAVs are resistant variants that confer resistance to the drug.
- Resistance is defined as resistance associated variants.
- Resistance may be associated with the selected drug.
- Treatment options may be limited by the presence of resistant variants.
- Treatment decisions should be made based on the presence of resistant variants.

**Summary of All Variants Observed:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Genotype</th>
<th>Summary of All Variants Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5A</td>
<td>1a</td>
<td>Certain</td>
</tr>
<tr>
<td>NS5A</td>
<td>2a</td>
<td>Certain</td>
</tr>
<tr>
<td>NS5A</td>
<td>3a</td>
<td>Certain</td>
</tr>
<tr>
<td>NS5A</td>
<td>4a</td>
<td>Certain</td>
</tr>
<tr>
<td>NS5A</td>
<td>5a</td>
<td>Certain</td>
</tr>
<tr>
<td>NS5A</td>
<td>6a</td>
<td>Certain</td>
</tr>
</tbody>
</table>

**Comments:**

- Certain: The drug-resistant variants detected in the sample may significantly affect the clinical outcome.

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**For more information or to arrange an appointment, please call Monogram’s Customer Service at 800-777-0077 between the hours of 8:00 A.M. to 5:00 P.M. Pacific Time Monday through Friday.**
**Sample Genotype 1a NS5A**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>NS5a</td>
<td></td>
</tr>
<tr>
<td>NS5a Subtype 1a</td>
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</tr>
<tr>
<td>DACLATASVIR RESISTANCE</td>
<td>NOT PREDICTED</td>
</tr>
<tr>
<td>LEDIPASVIR RESISTANCE</td>
<td>NOT PREDICTED</td>
</tr>
<tr>
<td>OMEDITASVIR RESISTANCE</td>
<td>NOT PREDICTED</td>
</tr>
<tr>
<td>ELBASVIR RESISTANCE</td>
<td>NOT PREDICTED</td>
</tr>
<tr>
<td>VELPASVIR RESISTANCE</td>
<td>NOT PREDICTED</td>
</tr>
<tr>
<td>Mutations Detected</td>
<td>NONE</td>
</tr>
</tbody>
</table>

This assay is designed to amplify HCV genotypes 1a and 1b and may not successfully amplify other HCV genotypes.

This test utilizes RT-PCR and DNA sequencing to detect the presence of treatment-emergent HCV NS5a variants associated with NS5a inhibitor antiviral therapy.

The clinical significance of NS5a resistance associated variants for antiviral therapy may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient. Testing for NS5a resistance-associated variants prior to initiation of treatment with elbasvir plus grazoprevir in HCV genotype 1a infected patients is recommended.

For further guidance consult with the package inserts of the applicable direct acting agents and guideline documents such as the AASLD and IDSA guidelines available at http://hcvguidelines.org.
RAV Testing Prior to Therapy: Currently Available and Recommended Tests

- **Genotype 1A**
  - **NS3/4A** Resistance Assay Testing (especially in cirrhotics)
  - Prior to consideration of **simeprevir**
  - Identification of **Q80K** polymorphism
  - If identified, do not use simeprevir-containing regimen
RAV Testing Prior to Therapy: Currently Available and Recommended Tests

- Genotype 1A (cont.)
  - **NS5A** Resistance Assay Testing
    - Prior to consideration of elbasvir*/grazoprevir
    - If high-fold (> 5 fold) RASs present, use alternate regimen or extend to 16 weeks + weight-based RBV

www.hcvguidelines.org
RAV Testing Prior to Therapy: Currently Available and Recommended Tests

- Genotype 1A (cont.)
  - **NS5A** Resistance Assay Testing
    - In any patient *previously treated* with NS5A-containing regimen
    - If RAVs present, use dual DAA therapy including sofosbuvir + RBV for 24 weeks or triple/quadruple sofosbuvir-containing therapy 12-24 weeks
Sample NS5A Genotype 3 Resistance Reports

<table>
<thead>
<tr>
<th></th>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV NS 5A Subtype</td>
<td>3a</td>
<td>3a</td>
</tr>
<tr>
<td>Daclatasvir resistance</td>
<td>Probable</td>
<td>Not predicted</td>
</tr>
<tr>
<td>Velpatasvir resistance</td>
<td>Probable</td>
<td>Not predicted</td>
</tr>
<tr>
<td>Mutations Detected</td>
<td>Y93H</td>
<td>None</td>
</tr>
</tbody>
</table>
DAA-naïve:
- LDV/SOF
- PTV/r/OMV + DSV
- DCV + SOF
- SMV + SOF
  - Baseline test for Q80K in GT1a in cirrhotics
- GZR/EBR
  - Baseline testing suggested for GT1a, independent of naïve or PR experience, cirrhosis vs no cirrhosis
  - GZR/EBR 12 weeks if no high-level RAVs (28,30,31,93)
  - GZR/EBR + RBV 16 weeks if RAVs present ("alternative")
Who Do We Recommend Testing for Resistance?

• Genotype 1a
  – Being considered for GRZ/ELB
  – Cirrhosis
  – Failed previous DAA therapy

• Genotype 3
  – Cirrhotics
  – Failed previous therapies
Strategies to Overcome RAVs in DAA Treatment Failures

• Use DAAs from other classes
• Use newly approved regimens
  – SOF/VEL/VOX
  – GLE/PIB
Case 1

- 54 year-old man with Genotype 1A HCV
- Previously failed LDV/SOF
- NS5A resistance predicted by testing
- What are options for retreatment?
### Classes of Medications Used for HCV Treatment

<table>
<thead>
<tr>
<th>NS3-4A Protease Inhibitors (&quot;Previr&quot;)</th>
<th>NS5A Inhibitors (&quot;Asvir&quot;)</th>
<th>NS5B Inhibitors: (&quot;Buvir&quot;)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nucleoside Analogues</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Nucleoside Analogues</td>
<td></td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>Daclatasvir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
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<tr>
<td>Grazoprevir</td>
<td>Elbasvir</td>
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<td></td>
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<tr>
<td>Paritaprevir</td>
<td>Ledipasvir</td>
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<td></td>
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<td>Simeprevir</td>
<td>Ombitasvir</td>
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<td>Voxilaprevir</td>
<td>Pibrentasvir</td>
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<td></td>
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</tr>
<tr>
<td>Velpatasvir</td>
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</tbody>
</table>

### Combination Therapies

<table>
<thead>
<tr>
<th>Combination Therapies</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir / Pibrentasvir</td>
<td>Mavyret®</td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir</td>
<td>Zepatier®</td>
</tr>
<tr>
<td>Paritaprevir/Ombitasvir/Dasabuvir</td>
<td>Viekira XR®</td>
</tr>
<tr>
<td>Sofosbuvir/Ledipasvir</td>
<td>Harvoni®</td>
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<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>Epclusa®</td>
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<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>Vosevi®</td>
</tr>
</tbody>
</table>
Case 1

- SOF/VEL/VOX
- A two DAA combination extended to 24 weeks with RBV
Case 2

- 64 year-old woman with Genotype 1A HCV
- Treatment-naïve
- Insurance will approve GZR/EBR
- Does she need resistance testing?
Case 2

- Yes, as baseline RAVs will impact duration of treatment
- NS5A resistance testing indicated
- If high-fold RAVs then treat for 16 weeks with RBV (instead of 12 weeks if none)
Summary

- RAVs are an important cause of treatment failures
- RAVs predominate following treatment failure and can persist
  - Months (NS3/4A)
  - Years (NS5A)
- Certain RAVs should be tested for at baseline
  - NS3/4A Q80K prior to simprevir in G1A
  - NS5A prior to elbasvir in G1A
  - NS5A in cirrhotic patients with genotype 3
- Newly approved salvage therapies will likely overcome presence of RAVs