NEW YORK STATE
HCV PROVIDER CLASSIFICATION TRAINING
Part 1: Role of Resistance Testing, Adverse Effects of Therapy and Drug-Drug Interactions
Part 1: Role of Resistance Testing: 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

http://www.frontiersin.org/files/Articles/20092/fmicb-03-00054-HTML/image_m/fmicb-03-00054-g001.jpg
Direct Acting Antiviral (DAA) Therapy Targets

![Diagram showing viral protein structure and target sites for DAA therapy.](http://www.frontiersin.org/files/Articles/20092/fmicb-03-00054-HTML/image_m/fmicb-03-00054-g001.jpg)
Why Do People Fail Therapy?
Reasons for DAA Failure

- Non-compliance
- Resistance
DAA Failure Secondary to Resistance

• DAA failure rate 3-5%
• Two types
  – Baseline RAS
  – Treatment associated substitutions
• Development of RASs
  – Most common to NS5a inhibitor
  – Commercial testing available
What Are RASs?

- Resistance-associated substitutions/polymorphisms
- HCV infection consists of many genetically-distinct, closely-related viral populations
- Some develop antiviral resistance through mutation
Global Prevalence of Naturally Pre-existing, Pre-initial Treatment NS5A RASs

Numbers indicate NS5A prevalence with a 1% cut-off

Zeuzem et al, Hepatology 2015; 62(Suppl): 254A
Resistant Variants Can Also Be Selected During Treatment

Potent antiviral therapy eliminates sensitive variants

Resistant variants are uncovered which can then expand

Risks of RASs by DAA Class

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

• **Low** barrier to resistance (more RASs)
  - NS3/4A protease inhibitors (glecaprevir, grazoprevir, voxilaprevir)
  - NS5A inhibitors (elbasvir, ledipasvir, pibrentasvir, velpatasvir)
RASs 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 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
- RASs persist for 1-2 years in NS5A treatment failures

Resistance to Nucleotide NS5B Polymerase Inhibitor (Sofosbuvir)

- High barrier to resistance
- No cross-reactivity with non-nucleotide NS5B polymerase inhibitors
- Main variant is \textit{S282T}
- Resistant variants usually replaced by wild type virus quickly within weeks of stopping therapy
RAS Testing Prior To Therapy
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 $\geq 300$ 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.
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>
</tr>
</tbody>
</table>
Sample Genotype 1a NS5A

Hepatitis C Viral RNA Genotype 1 NS5a Drug Resist
Hepatitis C Viral RNA Genotype 1 NS5a Drug Resist

HCV NS5a SUBTYPE 1a
DACLATASVIR RESISTANCE NOT PREDICTED
LEDIPASVIR RESISTANCE NOT PREDICTED
OMEPITASVIR RESISTANCE NOT PREDICTED
ELBASVIR RESISTANCE NOT PREDICTED
VELPITASVIR RESISTANCE NOT PREDICTED
Mutations Detected: NONE

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
Where is Resistance Testing Recommended?

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

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

• Use the regimens listed below
  – SOF/VEL/VOX
  – GLE/PI
  – Consider adding ribavirin
Case 1

• 54 year-old man with Genotype 1A HCV
• Previously failed LDV/SOF
• NS5A resistance predicted by testing
• What are options for retreatment?
Case 1

- SOF/VEL/VOX
Case 2

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

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

- RASs are an important cause of treatment failures
- RASs predominate following treatment failure and can persist
  - Months (NS3/4A)
  - Years (NS5A)
- Certain RAVs should be tested for at baseline
  - NS5A prior to elbasvir in G1A
  - NS5A in cirrhotic patients with genotype 3
- Salvage therapies will likely overcome presence of RAVs
  - May need ribavirin
New York State HCV Provider Webinar Series
Part 2: Adverse Effects of Therapy
Part 2: Adverse Effects of Therapy: Objectives

- Review the currently available regimens for treatment of HCV
- Appreciate side effects related to specific medications
- Become aware of general side effects related to clearance of HCV
Case

- 56 year-old with genotype 1A hepatitis C, treatment-naive
- Noninvasive fibrosis testing consistent with mild fibrosis
- Good candidate for treatment
- PMH: atrial fibrillation, chronic kidney disease (GFR ~ 20 mL/min)
- Medications: ASA, amiodarone

- What elements of her history impact which regimen you choose to treat her with?
## Currently Available Therapies

<table>
<thead>
<tr>
<th>Combination Therapies</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Grazeprevir</td>
<td>Zepatier®</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>Mavyret®</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni®</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>Epclusa®</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>Vosevi®</td>
</tr>
</tbody>
</table>
Medication-Specific Side Effects
# Common DAA Side Effects Overview

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Nausea</th>
<th>Diarrhea</th>
<th>Rash</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/ Sofosbuvir</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sofosbuvir/ Velpatasvir</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sofosbuvir/ Velpatasvir/ Voxilaprevir</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glecaprevir/ Pibrentasvir</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/ Grazeprevir</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Zepatier Package Insert MED Ireland 1/16; Harvoni package insert Gilead 6/16; Epclusa package insert Gilead 6/16; Vosevi PI Gilead 2017; Mavyret PI Abbvie 2017
Sofosbuvir Containing Regimens

• **Contraindicated** in severe renal impairment (GFR < 30 or dialysis)
  – Causes increased exposure to potentially nephrotoxic breakdown product

(Gilead Package Insert)
• **Contraindicated** in moderate-severe liver dysfunction, Child-Pugh B and C cirrhosis
• Due to the protease inhibitor

(Abbvie Package Insert)
Elbasvir/Grazoprevir

- **Contraindicated in moderate-severe liver dysfunction, Child-Pugh B and C cirrhosis**
- **Due to the protease inhibitor**
Reactivation of Hepatitis B

- Can occur on or after any DAA therapy
- Occurs in patients with prior, resolved, or active HBV infection
- FDA issued black box warning in 2016
  - 2 died, 1 required liver transplant
- Mechanism of reactivation unknown

Recommendations to Prevent Reactivation of Hepatitis B in Patients Starting DAA Therapy

• Prior to initiating DAA therapy, test for HBV with HBsAg, anti-HBs, and anti-HBc

• Check HBV DNA PCR in patients who are sAg positive or cAb positive/sAb negative

• Start HBV treatment prior to HCV treatment in those who meet criteria for treatment

• Follow HBV DNA PCR regularly (monthly) in those with low detectable HBV DNA or possibly those who are cAb positive but DNA negative at treatment start

http://www.hcvguidelines.org
Suggested Monitoring for HBV Reactivation During DAA for HCV

Test HBV Markers in All DAA Candidates:
1) HBsAg, 2) Anti-HBc, 3) Anti-HBs

HBV Markers NEGATIVE

HBsAg POSITIVE

HBV DNA Detectable

Meets AASLD criteria for initiation of HBV therapy

HBV DNA Low or UD

Initiate prophylactic antiviral therapy until 12 weeks after DAA completion

Monitor for HBVr:
- Check HBV DNA + LFTs q2 weeks during & after DAA therapy
- Start HBV Therapy if:
  - HBV DNA >10-fold above baseline or
  - HBV DNA >1000 IU/mL

HBsAg NEGATIVE anti-HBc POSITIVE (± anti-HBs)

Specific HBV monitoring not required unless change in liver enzymes or clinical status

HBV Markers NEGATIVE

VACCINATE

HBVr Standard Definition:
- Marked increased in HBV DNA (≥2 log increase from baseline levels) OR
- New appearance of HBV DNA to a level of > 100 IU/mL in a person with previously stable or undetectable levels.

Adapted from AASLD Guidelines

Lieber and Fried, 2017
New York State HCV Provider Webinar Series
Part 3: Drug-Drug Interactions
Part 3: Drug-Drug Interactions: Objectives

- Detail medications contraindicated with all DAA regimens
- Detail medications contraindicated with specific DAA agents
Medications Contraindicated with All Regimens

- **P-glycoprotein inducers**
  - St John’s Wart, rifampin, rifabutin, rifapentine

- **Anticonvulsants (strong cytochrome p450 [CYP] inducers)**
  - Carbamazepine, oxcarbazepine, phenytoin (CYP3A4, CYP2C19), phenobarbital
  - Levetiracetam and gabapentin are okay—no DDI’s
Individual Drug Interactions
Sofosbuvir Drug-Drug Interactions

- **Amiodarone**: causes severe symptomatic bradycardia (unclear effect on sofosbuvir concentrations)
- **Tipranivir/ritonavir**: decreases sofosbuvir concentrations
PPIs and DAAs

- **SOF/LED**
  - no more than 20 mg omeprazole daily due to reduced levels of ledipasvir

- **SOF/VEL and SOF/VEL/VOX**
  - Avoid PPIs

- **GLE/PIB**
  - No restrictions

Harvoni PI Gilead, Epclusa PI Gilead, Vosevi PI Gilead, Mavyret PI Abbvie
**DAAs and Antacids**

- **SOF/LED, SOF/VEL, SOF/VEL/VOX**
  - H2 blocker such as ranitidine or famotidine can be taken simultaneously or 12 hours apart, at doses not exceeding 40 mg famotidine twice daily
  - Antacids (such as aluminum and magnesium hydroxide) must be separated from ledipasvir/sofosbuvir by 4 hours

- **GLE/PIB**
  - No restrictions

Harvoni PI Gilead, Epclusa PI Gilead, Vosevi PI Gilead, Mavyret PI Abbvie
### Table 5. Dose equivalence among proton pump inhibitors and H2 antagonists.

<table>
<thead>
<tr>
<th>Drug family</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td>Omeprazole</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>(dose equivalent to omeprazole 20 mg once daily)</td>
<td>Lansoprazole</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>H2 antagonists</td>
<td>Famotidine</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>(dose equivalent to famotidine 20 mg twice daily)</td>
<td>Ranitidine</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>300 mg three-four times daily</td>
</tr>
<tr>
<td></td>
<td>Nizatidine</td>
<td>150 mg twice daily</td>
</tr>
</tbody>
</table>

Drug Classes with Possible DDIs with DAAs

- Lipid lowering agents
- Anti-depressants
- Anti-psychotics
- Cardiovascular agents
- Anti-platelet agents
- Anti-coagulants
- Medications used to treat HIV
- Calcineuron inhibitors
# Examples of Absolute DDI Contraindications with Select DAAs

<table>
<thead>
<tr>
<th></th>
<th>SOF/LDV</th>
<th>SOF/VEL</th>
<th>SOF/VEL/VOX</th>
<th>GLE/PIB</th>
<th>ELB/GZR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Interaction Checker
Access our free, comprehensive and user-friendly drug interaction charts

Educational Videos
Prescribing Resources

Twitter
@hepinteractions
Case Revisited

- 56 year-old lady with genotype 1A hepatitis C, treatment-naive
- Noninvasive fibrosis testing consistent with mild fibrosis
- Good candidate for treatment
- PMH: atrial fibrillation, chronic kidney disease (GFR ~20 mL/min)
- Medications: ASA, amiodarone

What elements of her history impact which regimen you choose to treat her with?
Case

- 56 year-old lady with genotype 1A hepatitis C, treatment-naive
- Noninvasive fibrosis testing consistent with **mild fibrosis**
- Good candidate for treatment
- PMH: atrial fibrillation, **chronic kidney disease (GFR ~ 20 mL/min)**
- Medications: ASA, **amiodarone**
Case (Continued)

• What elements of her history impact which regimen you choose to treat her with?

• Mild fibrosis
  – *Protease inhibitors not contraindicated*

• GFR ~ 20 mL/min
  – *Sofosbuvir contraindicated*

• Amiodarone
  – *Sofosbuvir contraindicated*
Summary

- Most DAA side effects are mild and rarely lead to discontinuation.
- DAA therapy has been associated with HBV reactivation.
- Protease inhibitor-containing regimens are contraindicated in cirrhotic patients with moderate to severe hepatic dysfunction.
- Each HCV regimen has unique drug-drug interactions and a careful review of each patient’s medical history and medication list is essential prior to initiating HCV therapy.
- It is essential to consult the package insert or the drug interactions website for potential drug interactions.
- Sofosbuvir-containing regimens are contraindicated in patients taking amiodarone and those with GFR < 30 or on dialysis.
- Withhold any vitamins/herbal supplements and statins during HCV treatment.