Selecting HCV Treatment
Disclosures

- Research supported by Gilead Sciences Inc.:
  - Site investigator for HIV/HCV SWITCH Registry Study
  - Key personnel for FOCUS HCV Screening Program through Vanderbilt University Medical Center Emergency Department
Objective

At the end of this lecture, the learner will be able to:

- Describe the history of HCV treatment options
- Discuss past and current direct acting antiviral (DAA) therapies for HCV
- Navigate treatment selection for patients with HCV
Caveats

- Focus on treatment selection for genotypes 1, 2, and 3.
  - Majority of US population infected with GT 1, 2, or 3
  - GT 4 is relatively rare in the US and treatment closely reflects GT 1
  - GT 5 and 6 are rare in the US and treatment has relatively little clinical data

- Focus on treatment naïve and PEG-IFN/RBV treatment experienced patients.
  - Majority of patients who present for HCV care reflect these populations
  - When I refer to “treatment experienced” after this slide, assume I am referring to prior treatment with only PEG-IFN/RBV unless specified
Case: Bill

- Bill is a 39 y/o man with a medical history of HIV well controlled on abacavir/lamivudine/dolutegravir.
- He started a new job and moved to your area.
- He was screened for hepatitis C on intake at your clinic and was found to be antibody positive.
- He has never been evaluated nor treated for HCV.
Case: Bill

- HCV testing reveals RNA 3,500,000 copies with genotype 1a.
- Labs reveal:
  - CBC within normal limits (of note, Plt 206)
  - CMP within normal limits except AST 54 and ALT 88
  - INR 1.0
  - HBV sAg negative, cAb positive, sAb positive
  - HIV Ab positive, RNA <40
- He undergoes liver ultrasound and elastography.
  - No HCC is noted and elastography is consistent with F2 fibrosis.
Questions

- How has HCV treatment changed in recent years, and how does that impact Bill’s treatment?
- What factors define an appropriate DAA regimen and duration?
- How would his treatment change if his medical history or laboratory studies were different?
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
QUESTIONS ABOUT TREATMENT
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
History of HCV Treatment: The Bad, The Ugly, and The Good

- Early therapies had poor efficacy and poor tolerability:
  - Interferon (1986)
  - Ribavirin (1998)
  - Pegylated interferon (2001)
- Direct-acting antivirals (DAAs) improved efficacy with additional adverse effects and cost:
  - Telaprevir (2011)
  - Boceprevir (2011)
- New DAAs dramatically improve efficacy with few adverse effects at substantial cost:
  - Simeprevir and Sofosbuvir (2013)
  - Many others since 2014…

History of HCV Treatment: The Bad, The Ugly, and The Good

- Early therapies had poor efficacy and poor tolerability:
  - Interferon (1986)
  - Ribavirin (1998)
  - Pegylated interferon (2001)
- Direct-acting antivirals (DAAs) improved efficacy with additional adverse effects and cost:
  - Telaprevir (2011)
  - Boceprevir (2011)
- New DAAs dramatically improve efficacy with few adverse effects at substantial cost:
  - Simeprevir and Sofosbuvir (2013)
  - Many others since 2014…

History of HCV Treatment: The Bad, The Ugly, and The Good

- Early therapies had poor efficacy and poor tolerability:
  - Interferon (1986)
  - Ribavirin (1998)
  - Pegylated interferon (2001)

- Direct-acting antivirals (DAAs) improved efficacy with additional adverse effects and cost:
  - Telaprevir (2011)
  - Boceprevir (2011)

- New DAAs dramatically improve efficacy with few adverse effects at substantial cost:
  - Simeprevir and Sofosbuvir (2013)
  - Many others since 2014...

Treatment Response in Direct Acting Antiviral (DAA) Era

SVR (%)

IFN
PEG-IFN
IFN + RBV
P/R
TPV/BOC + P/R
DAA + P/R
DAA +/- RBV

0 20 40 60 80 100

IFN  PEG-IFN  IFN + RBV  P/R  TPV/BOC + P/R  DAA + P/R  DAA +/- RBV
## HCV Therapies: The Past, Present, and Future

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN</td>
<td>IFN</td>
<td>IFN</td>
<td>IFN</td>
<td>IFN</td>
<td>IFN</td>
<td>IFN</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
<td>PEG-IFN</td>
</tr>
<tr>
<td>RBV</td>
<td>RBV</td>
<td>RBV</td>
<td>RBV</td>
<td>RBV</td>
<td>RBV</td>
<td>RBV</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Telaprevir</td>
<td>Telaprevir</td>
<td>Telaprevir</td>
<td>Telaprevir</td>
<td>Telaprevir</td>
<td>Telaprevir</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Boceprevir</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Simeprevir</td>
<td>Simeprevir</td>
<td>Simeprevir</td>
<td>Simeprevir</td>
<td>Simeprevir</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
<td>Ledipasvir</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
<td>Paritaprevir</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>Elbasvir</td>
<td>Elbasvir</td>
<td>Elbasvir</td>
<td>Elbasvir</td>
<td>Elbasvir</td>
<td>Elbasvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
<td>Grazoprevir</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
<td>Pibrentasvir</td>
</tr>
</tbody>
</table>
FDA Approved HCV Therapies

**Nonspecific Antivirals**
- Interferon (IFN)
- Ribavirin (RBV)
- Pegylated Interferon (PEG-IFN)

**NS3/4 Protease Inhibitors**
- Telaprevir (TPV)
- Boceprevir (BOC)
- Simeprevir (SMV)
- Paritaprevir (PTV)
- Grazoprevir (GZP)
- Voxilaprevir (VOX)
- Glecaprevir (GLE)

**NS5A Inhibitors**
- Ledipasvir (LDV)
- Ombitasvir (OBV)
- Daclatasvir (DCV)
- Elbasvir (EBR)
- Velpatasvir (VEL)
- Pibrentasvir (PIB)

**NS5B Polymerase Inhibitors**
- Sofosbuvir (SOF)
- Dasabuvir (DBV)
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
Simeprevir (SMV; Olysio™)

- FDA Approval
  - 2013
- Class
  - NS3/4A protease inhibitor
- Genotypes (FDA approved for treatment)
  - 1 and 4
- Common Side Effects (≥10%)
  - Headache, fatigue, nausea, diarrhea, photosensitivity, rash, dizziness
- Notes:
  - No dose adjustment for renal function
  - Not recommended in patients with moderate/severe hepatic impairment
  - Negatively impacted by GT 1a NS3/4A protease polymorphisms (Q80K); thus, baseline HCV resistance testing is recommended
Sofosbuvir (SOF; Sovaldi™; half of Harvoni™; half of Epclusa™; 1/3 of Vosevi™)

- FDA Approval
  - 2013
- Class
  - NS5B polymerase nucleotide analogue inhibitor
- Genotypes (FDA approved for treatment)
  - 1-6
- Common Side Effects (≥10%)
  - None
- Notes:
  - Not recommended with severe renal impairment (GFR <30 ml/min/1.73m²)
  - Contraindicated with amiodarone
Ledipasvir (LDV; half of Harvoni™)

- FDA Approval
  - 2014
- Class
  - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
  - GT 1 and 4-6
- Common Side Effects (≥10%)
  - Headache, fatigue
- Notes:
  - Caution with acid blocking agents
PTV/r /OBV + DBV (Viekira Pak/XR™ and Technivie™)

- **FDA Approval**
  - 2014, 2015, and 2016

- **Class**
  - Paritaprevir (PTV)
    - NS3/4A protease inhibitor
  - Ombitasvir (OBV)
    - NS5A replication complex inhibitor
  - Dasabuvir (DBV; in Viekira Pak/XR™)
    - NS5B RNA non-nucleoside polymerase inhibitor

- **Genotypes (FDA approved for treatment)**
  - 1 and 4

- **Common Side Effects (≥10%)**
  - Fatigue, nausea, pruritus, insomnia, asthenia, skin reactions

- **Notes**
  - No dose adjustment with renal dysfunction
  - Not recommended in moderate/severe hepatic impairment
  - Contraindicated with many drugs due to strong CYP3A inhibition by ritonavir

Bagwell A and Chastain CA. *Current Treatment Options in Infectious Diseases* 2016.
Daclatasvir (DCV; Daklinza™)

- FDA Approval
  - 2015
- Class
  - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
  - 1 and 3
- Common Side Effects (≥10%)
  - Headache, fatigue
- Notes
  - No dose adjustment for renal impairment

Bagwell A and Chastain CA. *Current Treatment Options in Infectious Diseases* 2016.
Elbasvir/Grazoprevir (EBR/GZP; Zepatier™)

- FDA Approval
  - 2016

- Class
  - Elbasvir
    - NS5A replication complex inhibitor
  - Grazoprevir
    - NS3/4A protease inhibitor

- Genotypes (FDA approved for treatment)
  - 1 and 4

- Common Side Effects (≥10%)
  - Headache, fatigue, nausea

- Notes
  - No dose adjustment for renal impairment
  - Not recommended in moderate/severe hepatic impairment
  - Negatively impacted by GT 1a NS5A polymorphisms at M28, Q30, L31, Y93; thus, baseline HCV resistance testing is recommended

Bagwell A and Chastain CA. *Current Treatment Options in Infectious Diseases* 2016.
Velpatasvir (VEL; half of Epclusa™; 1/3 of Vosevi™)

- FDA Approval
  - 2016
- Class
  - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
  - 1-6
- Common Side Effects (≥10%)
  - Headache, fatigue
- Notes
  - First single-tablet, pangenotypic regimen available
Voxilaprevir (VOX; part of Vosevi™)

- FDA Approval
  - 2017
- Class
  - NS3/4A protease inhibitor
- Genotypes (FDA approved for treatment)
  - 1-6
- Notes
  - Part of SOF/VEL/VOX for prior DAA failure salvage
Glecaprevir/Pibrentasvir (GLE/PIB; Mavyret™)

- FDA Approval
  - 2017
- Class
  - Glecaprevir
    - NS3/4A protease inhibitor
  - Pibrentasvir
    - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
  - 1-6
- Notes
  - No dose adjustment for renal impairment
  - Not recommended in moderate/severe hepatic impairment
  - Recommended 8 weeks of treatment in treatment naïve without cirrhosis
  - Recommended 12 weeks of treatment for treatment experienced and/or cirrhosis
  - May be used for GT 1 salvage therapy after DAA failure
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- **Selecting HCV Treatment**
  - Genotype 1
  - Genotypes 2 and 3
  - Other Considerations
Primary Factors when Selecting HCV Treatment

- Genotype
- Degree of fibrosis
  - I.e. Non-cirrhotic vs. cirrhotic
- Treatment history
  - I.e. Treatment naïve vs. treatment experienced
  - Recommendations may differ depending on what therapies were used previously (i.e. PEG-IFN vs. DAA-based therapy)
Secondary Factors when Selecting HCV Treatment

- **Efficacy**
  - Relatively equal among recommended regimens
- **Safety**
- **Side effect profile**
  - Including need for PEG-IFN or RBV
- **Drug-drug interactions**
- **Access**
  - Cost
  - Formulary restrictions
Do Genotypes Matter Any More?

- Historically have been important for predicting prognosis of infection and response to treatment
- More recently have allowed appropriate DAA selection
- May have minimal contribution in era with two first-line pangenotypic regimens depending on practice environment

Roles?
- Selection of cost-effective therapies
- Prognosis prediction (i.e. worse for GT 3)
- Tool for determining relapse vs. reinfection (in some cases)
QUESTIONS?
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
### Recommended Regimens for HCV GT 1 in Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Non-Cirrhotic</th>
<th>Comp. Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>8-12 Weeks*</td>
<td>12 Weeks</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>12 Weeks</td>
<td>12 Weeks</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>12 Weeks**</td>
<td>12 Weeks**</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>8 Weeks</td>
<td>12 Weeks</td>
</tr>
</tbody>
</table>

*8 weeks for non-African American, non-HIV co-infected patients with baseline viral load <6 million
**16 weeks + RBV if baseline GT 1a NS5A polymorphisms detected

## Recommended Regimens for HCV GT 1 in PEG-IFN Experienced Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Non-Cirrhotic</th>
<th>Comp. Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>12 Weeks</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>12 Weeks</td>
<td>12 Weeks</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>12 Weeks**</td>
<td>12 Weeks**</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>8 Weeks</td>
<td>12 Weeks</td>
</tr>
</tbody>
</table>

**16 weeks + RBV if baseline GT 1a NS5A polymorphisms detected**

QUESTIONS?
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
### Recommended Regimens for HCV GT 2 & 3 in Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>GT 2</th>
<th>GT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>8-12* weeks</td>
<td>8-12* weeks</td>
</tr>
<tr>
<td>*12 weeks for compensated cirrhosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recommended Regimens for HCV GT 2 & 3 in PEG-IFN Experienced Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>GT 2</th>
<th>GT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/Velpatasvir</td>
<td>12 weeks</td>
<td>12 weeks**</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>8-12* weeks</td>
<td></td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir + SOF</td>
<td>12 weeks***</td>
<td></td>
</tr>
<tr>
<td>SOF/Velpatasvir/Voxilaprevir</td>
<td>12 weeks***</td>
<td></td>
</tr>
</tbody>
</table>

*12 weeks for compensated cirrhosis **Without cirrhosis ***With cirrhosis
QUESTIONS?
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotypes 2 and 3
- Other Considerations
Treating Decompensated Cirrhosis

- Multiple considerations (stay tuned…)
- Optimizing Efficacy and Safety
  - RBV used in shorter (i.e. 12 week) regimens
  - If RBV ineligible, 24 weeks used
  - Regimens exclude protease inhibitors
- Regimens Include:
  - Daclatasvir + Sofosbuvir +/- RBV x 12-24 weeks
  - Ledipasvir/Sofosbuvir +/- RBV x 12-24 weeks
  - Sofosbuvir/Velpatasvir +/- RBV x 12-24 weeks

AASLD/IDSA HCV Guidelines. www.hcvguidelines.com
Resistance-Associated Substitutions

- Mutations abbreviated as RASs
- Present in variable amounts at baseline in the population
- Viral mutations may be selected in cases of treatment failure
- Evolving role of testing and impact on DAA selection
Resistance-Associated Substitutions: When to Test?

- **GT 1a**
  - When considering **elbasvir/grazoprevir**
  - *Consider* for DAA treatment experienced, GT 1a patients +/- cirrhosis when considering **ledipasvir/sofosbuvir**

- **GT 3**
  - Treatment-naïve patients with cirrhosis OR treatment-experienced patients without cirrhosis when considering **daclatasvir and sofosbuvir**
  - Treatment-naïve patients with cirrhosis OR treatment-experienced patients +/- cirrhosis when considering **sofosbuvir/velpatasvir**

- Testing at other times may or may not be beneficial. Review guidelines and/or discuss with HCV treatment expert(s).
Treating DAA Failures

- Often most complex patient population
- Resistance may or may not be helpful depending on prior as well as anticipated regimen
- Two approved regimens for retreatment
  - Sofosbuvir/velpatasvir/voxilaprevir
  - Glecaprevir/pibrentasvir
- Consult guidelines, literature, and HCV treatment experts
Summary

- HCV treatment has transformed over the past several years.
- High efficacy therapies with limited side effects are available for all genotypes.
- Select HCV treatment is based on primary (genotype, stage, treatment experience) and secondary factors.
QUESTIONS?