Selecting HCV Treatment
Caveats

- Focus on treatment selection for genotypes 1, 2, and 3.
  - Majority of US population infected with GT 1, 2, or 3
  - GT 4 treatment closely reflects GT 1 treatment
  - GT 5 and 6 are rare 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
  - Patients who have failed DAA-based regimens should be assessed by experienced HCV treatment providers
Case: Sam

- Sam is a 56 y/o man with a medical history of hypertension.
- He established care with a new primary care provider recently and was screened for HCV based on his age.
- His antibody returned positive and he was referred to you for further care.
- He has never been evaluated nor treated for HCV.
Case: Sam

- HCV testing reveals RNA 7,250,000 copies with genotype 1a.
- Labs reveal:
  - CBC within normal limits (of note, Plt 256)
  - CMP within normal limits except AST 67 and ALT 88
  - INR 1.0
  - HBV sAn negative, cAb positive, sAb positive
  - HIV negative
- 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 Sam’s treatment?
- What factors define an appropriate DAA regimen and duration?
- How would his treatment differ if his medical history or laboratory studies were different?
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotype 2
- Genotype 3
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
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  - Genotype 3
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…
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Treatment Response in Direct Acting Antiviral (DAA) Era

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

SVR (%)
# HCV Therapies: The Past, Present, and Future

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# FDA Approved HCV Therapies (2/2017)

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

## NS3/4 Protease Inhibitors
- Telaprevir (TPV)
- Boceprevir (BOC)
- Simeprevir (SMV)
- Paritaprevir (PTV)
- Grazoprevir (GZP)

## NS5A Inhibitors
- Ledipasvir (LDV)
- Ombitasvir (OBV)
- Daclatasvir (DCV)
- Elbasvir (EBR)
- Velpatasvir (VEL)

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

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotype 2
- Genotype 3
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™)

- 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
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
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
Velpatasvir (VEL; half of Epclusa™)

- 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
Overview

- History of HCV Treatment
- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
  - Genotype 1
  - Genotype 2
  - Genotype 3
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
Overview

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# HCV GT 1a, Treatment Naïve (2/2017)

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* - If no NS5A resistance-associated variants detected. ** - Consider 8 weeks in select patients.
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AASLD/IDSA HCV Guidelines. [www.hcvguidelines.com](http://www.hcvguidelines.com)
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QUESTIONS?
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- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
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HCV GT 2, Treatment Naïve (2/2017)

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### HCV GT 2, P/R Treatment Experienced (2/2017)

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QUESTIONS?
Overview

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- Direct Acting Antiviral (DAA) Review
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- Genotype 2
- Genotype 3
## HCV GT 3, Treatment Naïve (2/2017)

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<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL (Epclusa™)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>F4 (Cirrhotic)</td>
<td>DCV (Daklinza™) + SOF (Sovaldi™) +/- RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL (Epclusa™) +/- RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
## HCV GT 3, P/R Treatment Experienced (2/2017)

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Recommended Treatment</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F3 (Non-cirrhotic)</td>
<td>DCV (Daklinza™) + SOF (Sovaldi™)</td>
<td>12 weeks</td>
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</tr>
</tbody>
</table>
QUESTIONS?
Resistance Associated Variants

- Present in variable amounts at baseline in the population
- May be selected in cases of treatment failure
- Evolving role in timing of testing and impact on DAA selection
Resistance Associated Variants: When to Test?

- **Genotype I**
  - Simeprevir treatment (GT 1a only)
  - Elbasvir/grazoprevir treatment (GT 1a only)
  - Prior DAA treatment failure (who have cirrhosis or have urgent indications for treatment)

- **Genotype 3**
  - Treatment-naïve patients with cirrhosis OR treatment-experienced patients without cirrhosis when considering:
    - Daclatasivir and sofosbuvir treatment
    - Sofosbuvir/velpatasvir treatment

- Consider discussion with HCV treatment expert in these and other situations
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.