Hepatitis C: 
Emerging Treatment Recommendations

Disclosure
- Jordan Schultz has no actual or potential conflicts of interest to report

Learning Objectives for Pharmacists
- At the completion of this activity, the participant will be able to:
  - Describe the differences between past hepatitis C treatment regimens and newer preferred regimens
  - Discuss considerations that should be made when choosing therapy
  - Discuss the available literature regarding new hepatitis C regimens
  - Design an appropriate monitoring plan for patients with hepatitis C being treated with newer medications
  - Create an appropriate treatment strategy for someone who is a non-responder to past treatment regimens versus someone who is treatment naïve or a treatment relapser
Learning Objectives for Technicians

• At the completion of this activity, the participant will be able to:
  o Describe the role that the pharmacy technician plays in helping patients obtain financial assistance to afford specialty medications
  o Recognize signs of non-adherence to specialty medications
  o Recognize the differences between the various new hepatitis C treatment regimens

Glossary of Abbreviations

• CBC = complete blood cell count
• HCV = Hepatitis C virus
• IFN = interferon
• INR = international normalized ratio
• PEG = peginterferon alfa
• RBV = ribavirin
• SOF = sofosbuvir
• SMV = simeprevir
• SVR12 = sustained virologic response at 12 weeks

History of Present Illness

• HD is a 59 year old female
• CC: Chronic HCV
• "Diagnosed" with hepatitis in the 1970's
• First referred to UIHC in 2007 when HCV antibody test was positive
  o Diagnosed with chronic HCV, genotype 1a
Hepatitis C Overview

- Infectious virus affecting ~185 million worldwide
  - 3.4 – 4.4 million in the U.S.
- Presents as acute or chronic disease
  - 80% of acute infections lead to chronic HCV
  - 20% of chronic HCV patients develop cirrhosis within 25 years
- HCV is currently the primary cause of liver transplantations in the U.S.
- Six genotypes, with genotypes 1-3 accounting for 97% of all HCV cases in the United States

Hepatitis C Pathophysiology

- Enveloped, single-stranded RNA virus
- Member of the genus *Hepacivirus* within the *Flaviviridae* family
- Humans are the only known natural hosts for HCV

Transmission of HCV

- High transmission risk
  - Men who have sex with men (MSM) with high-risk sexual practices
  - Active IV drug use
  - Incarcerated persons
  - Persons on long-term hemodialysis
- Those who have achieved SVR (virologic cure) no longer transmit the virus to others
  - Treatment of high risk patients benefits public health
Diagnosis of HCV

- Standard immunoassay testing
  - High sensitivity and high specificity in newer assays
  - Ease of use
  - Low cost

- HCV RNA assay testing
  - Quantifies amount of HCV RNA
  - Used to assess initial management of disease

- Liver biopsy or imaging
  - Used to assess degree of fibrosis/cirrhosis
  - An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended – Class 1, level A

Fibrosis

- Occurs in response to chronic liver injury
  - Collapse of hepatic lobules
  - Formation of fibrous septae
  - Hepatocyte regeneration with nodule formation

- METAVIR Score
  - F0: No fibrosis
  - F1: Portal fibrosis without septa
  - F2: Few septa
  - F3: Numerous septa without cirrhosis
  - F4: Cirrhosis

  \[ \text{F2} = \text{significant fibrosis} \]

Cirrhosis

- **Compensated**
  - Asymptomatic
  - +/- gastroesophageal varices
  - No ascites
  - No jaundice
  - No hepatic encephalopathy
  - Transition to decompensated occurs at a rate of ~5-7% per year
  - Median survival is 9-12 years

- **Decompensated**
  - Defined by development of:
    - Jaundice
    - Ascites
    - Variceal hemorrhage
    - Hepatic encephalopathy
  - Should be considered for liver transplantation
  - Survival is poor
    - 1-year survival rate of <50%
  - Other complications:
    - Hepatorenal syndrome
    - Spontaneous bacterial peritonitis


Compensated vs. Decompensated

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Compensated Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>No Varices No Ascites</td>
<td>Varices +/− Ascites</td>
</tr>
<tr>
<td>Stage 2</td>
<td>No Varices No Ascites</td>
<td>Ascites +/− Varices</td>
</tr>
<tr>
<td>Stage 3</td>
<td>20%</td>
<td>57%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>1%</td>
<td>3%</td>
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</tbody>
</table>

Death (at 1 year)

- Recommendations for HCV Testing
  - Anyone born between 1945 and 1965
  - Those with certain medical conditions
    - HIV infection
    - Unexplained chronic liver disease
  - Those with risk behaviors and exposures
  - Risk behaviors
    - Current or past injection-drug use
    - Intranasal illicit drug use
  - Risk exposures
    - Long-term hemodialysis
    - Tattoo in unregulated setting
    - Health care workers after exposure
    - Children born to HCV infected women
    - Prior recipients of transfusions or transplants
      - Recipient later notified they received blood from HCV positive donor
      - Transplant or blood transfusion before July 1992
      - Received clotting factor concentrate produced before 1987
    - Anyone who has ever been incarcerated

Recommendations for when to Treat HCV

- Those with chronic HCV
- Highest priority to patients with:
  o Advanced fibrosis
  o Compensated cirrhosis
  o History of liver transplant
  o Severe extrahepatic HCV
- Those at high risk of transmitting HCV or for those in which HCV treatment may reduce the risk of transmission


Back to HD

- Initiated treatment with PEG + RBV on 1/25/2008

<table>
<thead>
<tr>
<th>Date</th>
<th>1/25/08</th>
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<tbody>
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<td>HCV</td>
<td>609,000</td>
</tr>
<tr>
<td>Quant</td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>4.33</td>
</tr>
<tr>
<td>WBC</td>
<td>2.6</td>
</tr>
<tr>
<td>Platelets</td>
<td>68</td>
</tr>
</tbody>
</table>

PEG and RBV started

Ribavirin

- Mechanism of action: Unclear
- Indications: chronic HCV in combination with PEG for patients with compensated liver disease
- Dose and administration: 1,000mg (<75 kg) to 1,200mg (≥75kg) by mouth per day in divided doses
- Adverse effects: fatigue (65%), headache (43%), pyrexia (44%), irritability/anxiety/nervousness (35%), insomnia (30%)
- Interactions: Nucleoside reverse transcriptase inhibitors, zidovudine
**Peginterferon alfa-2a**

- **Mechanism of action:** Induction of innate antiviral immune response
- **Indications:** Chronic HCV in combination with other antiviral medications for patients with compensated liver disease
- **Dose and administration:** 180mcg SQ once weekly
- **Adverse effects:**
  - Fatigue/asthenia (56%)
  - Headache (54%)
  - Pyrexia (37%)
  - Myalgias (37%)
- **Interactions:** Relatively few

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**Back to HD**

- Initiated treatment with PEG + RBV on 1/25/2008

<table>
<thead>
<tr>
<th>Date</th>
<th>1/25/08</th>
<th>2/22/08</th>
<th>3/20/08</th>
<th>4/17/08</th>
<th>6/2/2008</th>
<th>7/16/2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Quant: (U/mL)</td>
<td>600,000</td>
<td>91,000</td>
<td>5,000</td>
<td>22,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC (x10^6)</td>
<td>4.33</td>
<td>3.65</td>
<td>3.36</td>
<td>3.52</td>
<td>3.97</td>
<td>3.89</td>
</tr>
<tr>
<td>WBC (x10^3)</td>
<td>2.6</td>
<td>2.0</td>
<td>1.4</td>
<td>2.1</td>
<td>2.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Platelets (x10^4)</td>
<td>68</td>
<td>50</td>
<td>34</td>
<td>22</td>
<td>42</td>
<td>29</td>
</tr>
</tbody>
</table>

PEG and RBV started
PEG and RBV d/c ed

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**Relapsers**

- Virologic rebound after achieving SVR at end of treatment
- Relapse usually occurs within 24 weeks after completion of treatment
- Retreatment of previous relapsers is the same as treatment naïve patients

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*Ramers CB. Initial Evaluation of Persons with Chronic Hepatitis C. Accessed on 11/1/2014 from http://www.hepatitisc.uw.edu/pdf/initial-evaluation-chronic/core-concept/all*
Non-Responders

Patients never cleared HCV from their serum during treatment

Null responders: failed to achieve a 2-log reduction in HCV viral load after 12 weeks

Partial responders: achieved a 2-log decrease in HCV at week 12, but the HCV RNA level remained detectable at week 24

Sofosbuvir (Sovaldi®)

- Mechanism of action: Nucleotide analog NS5B polymerase inhibitor
- Indications: Chronic hepatitis C as a component of combination antiviral therapy, established in genotypes 1, 2, 3, and 4 infections
- Efficacy has been established in genotype 1, 2, 3, and 4 infections
- Dose and route: 400mg tablet by mouth daily
- Adverse effects: fatigue, headache (≥20%)
- Interactions: Potent intestinal P-glycoprotein inducers (rifampin)
- Administration: With or without food
- Cost: ~$1,000/day = $84,000 for 12 week course
Simeprevir (Olysio®)

- **Mechanism of action:** NS3/4A protease inhibitor
- **Indications:** treatment of chronic HCV as a component of combination antiviral therapy
- **Dose and route:** 150 mg capsule by mouth daily
- **Adverse effects:** Photosensitivity/rash (28%), pruritus (22%), nausea (22%)
- **Interactions:** Mild CYP3A4 inhibition and P-gp transporters
- **Administration:** Once daily by mouth with food
- **Cost:** ~$1,000/day = $84,000 for 12 weeks course

### Trial Name | Design and Purpose | SVR12 | 95% CI, p-value
--- | --- | --- | ---
**QUEST** Genotype 1: Treatment-naive | SMV + pIFN + RBV (12 weeks) | 80% | (20.1% - 38.6%), p<0.001
 placebo + pIFN + RBV (12 weeks) | 50% |
**PROMISE** Genotype 1a and 1b: Previous non-responders to pIFN-based therapy | SMV + pIFN + RBV (12 weeks) | 79% | (34.6% - 53.0%), p<0.001
 placebo + pIFN + RBV (12 weeks) | 37% |

Cost: ~$1,000 per day

### COSMOS Trial

- 1st trial to evaluate IFN-free regimens in genotype 1
- Randomized, open-label, multi-center trial done between 11/2/2011 and 1/29/2014
- Previous non-responders to PEG + RBV with genotype 1

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td><strong>Group 2</strong></td>
</tr>
<tr>
<td>SMV + SOF + RBV (24 weeks)</td>
<td>SMV + SOF + RBV (24 weeks)</td>
</tr>
<tr>
<td>N=20</td>
<td>N=27</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td><strong>Group 3</strong></td>
</tr>
<tr>
<td>SMV + SOF (24 weeks)</td>
<td>SMV + SOF (24 weeks)</td>
</tr>
<tr>
<td>N=14</td>
<td>N=16</td>
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<tr>
<td><strong>Group 3</strong></td>
<td><strong>Group 4</strong></td>
</tr>
<tr>
<td>SMV + SOF + RBV (12 weeks)</td>
<td>SMV + SOF + RBV (12 weeks)</td>
</tr>
<tr>
<td>N=27</td>
<td>N=26</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
<td></td>
</tr>
<tr>
<td>SMV + SOF (12 weeks)</td>
<td>SMV + SOF (12 weeks)</td>
</tr>
<tr>
<td>N=14</td>
<td>N=13</td>
</tr>
</tbody>
</table>

*Source:* [Lancet](http://www.thelancet.com)
COSMOS Trial Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Cohort 1 METAVIR F0-F2</th>
<th>Cohort 2 METAVIR F3-F4</th>
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</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>SMV + SOF + RBV (24 weeks)</td>
<td>SVR12 = 79% (19/24)</td>
<td>SVR12 = 95% (28/30)</td>
</tr>
<tr>
<td>Group 2</td>
<td>SMV + SOF (24 weeks)</td>
<td>SVR12 = 93% (14/15)</td>
<td>SVR12 = 100% (16/16)</td>
</tr>
<tr>
<td>Group 3</td>
<td>SMV + SOF + RBV (12 weeks)</td>
<td>SVR12 = 96% (26/27)</td>
<td>SVR12 = 93% (25/27)</td>
</tr>
<tr>
<td>Group 4</td>
<td>SMV + SOF (12 weeks)</td>
<td>SVR12 = 93% (13/14)</td>
<td>SVR12 = 93% (13/14)</td>
</tr>
</tbody>
</table>

COSMOS Conclusions

- Combining SOF + SMV lead to high rates of SVR12
  - Even in patients with multiple factors that are generally associated with non-response (cirrhosis, previous treatment failure, etc)
  - “Treatment for 24 weeks and the addition of RBV did not clearly improve SVR rates in patients with advanced fibrosis or compensated cirrhosis.”
  - POSSIBLY some benefit to extending treatment to 24 weeks in certain patients
- Did not include patients that had previous non-response to other protease inhibitors

Back to HD

- Recommended that she receive SOF + SMV for 12 weeks
- Rejected by insurance
  - Combination of SOF + SMV is NOT FDA approved
  - PA submitted and denied
  - Appeal submitted and denied
- Treatment deferred until FDA-approved combination regimens are approved?!
**Ledipasvir + Sofosbuvir (Harvoni®)**

- **Mechanism of action:**
  - NS5A inhibitor (ledipasvir) + NS5B polymerase inhibitor (sofosbuvir)

- **Indications:**
  - Chronic hepatitis C genotype 1 infection

- **Dose and route:**
  - One tablet daily (90mg of ledipasvir + 400mg of sofosbuvir)

- **Adverse effects:**
  - Fatigue (13%)
  - Headache (14%)
  - Nausea (7%)

- **Interactions:**
  - Acid reducing agents and P-glycoprotein inducers

- **Administration:**
  - With or without food at the same time each day

- **Cost:**
  - ~$1,125/day = $94,500 for 12 week course

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**Trial Name**

<table>
<thead>
<tr>
<th>Design and Purpose</th>
<th>SVR12</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td></td>
<td></td>
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<tr>
<td>ION-1*</td>
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<td></td>
</tr>
<tr>
<td>N=865</td>
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<tr>
<td>Genotype 1</td>
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<tr>
<td>Treatment Naïve</td>
<td></td>
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<tr>
<td>LDV/SOF (12 weeks)</td>
<td>99%</td>
<td>95% CI: 96% - 100%</td>
</tr>
<tr>
<td>LDV/SOF + RBV (12 weeks)</td>
<td>97%</td>
<td>95% CI: 95% - 99%</td>
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<tr>
<td>LDV/SOF (24 weeks)</td>
<td>98%</td>
<td>95% CI: 95% - 99%</td>
</tr>
<tr>
<td>LDV/SOF + RBV (24 weeks)</td>
<td>99%</td>
<td>95% CI: 97% - 100%</td>
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</tbody>
</table>

*SVR12 rates in all treatment groups were superior to historical cohort rate of 60% (p<0.001)

**ION-2^**

| N=440             |        |                |
| GENotype 1        |        |                |
| Treatment failure on IFN+RBV +/− protease inhibitor |        |                |
| LDV/SOF (12 weeks)| 94%    | 95% CI: 87% - 97% |
| LDV/SOF + RBV (12 weeks)| 96%| 95% CI: 91% - 99% |
| LDV/SOF (24 weeks)| 99%    | 95% CI: 95% - 100% |
| LDV/SOF + RBV (24 weeks)| 99%| 95% CI: 95% - 100% |

^SVR12 rates in all treatment groups were superior to historical cohort rate of 60% (p<0.001)

**ION-3^**

| N=647             |        |                |
| GENotype 1 w/o cirrhosis |        |                |
| Treatment naïve |        |                |
| LDV/SOF (8 weeks)  | 94%    | 95% CI: 90% - 97% |
| LDV/SOF + RBV (8 weeks) | 93%| 95% CI: 89% - 96% |
| LDV/SOF (12 weeks)| 95%    | 95% CI: 92% - 98% |

<table>
<thead>
<tr>
<th>SVR12</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>ION-1*</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>ION-2^</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>ION-3^</td>
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**ABT-450/ritonavir-ombitasvir (3D Regimen)**

<table>
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<th>Design and Purpose</th>
<th>SVR12</th>
<th>95% CI</th>
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<tr>
<td>SAPPHIRE-1*</td>
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<tr>
<td>N=631</td>
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<tr>
<td>Genotype 1</td>
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<tr>
<td>Treatment naïve</td>
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</tr>
<tr>
<td>(ABT-450+ritonavir)+-ombitasvir +/- RBV (12 weeks)</td>
<td>94.6%</td>
<td>(94.3% - 95.0%)</td>
</tr>
<tr>
<td>Historical cohort</td>
<td>69%</td>
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</tr>
</tbody>
</table>

*SVR12 rates in all treatment groups were superior to historical cohort rate of 60% (p<0.001)

**SAPPHIRE-2**

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<tr>
<th>Design and Purpose</th>
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<th>95% CI</th>
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<tbody>
<tr>
<td>N=394</td>
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<tr>
<td>Genotypes 2 or 3</td>
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<tr>
<td>Prior Relapsers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ABT-450+ritonavir)+-ombitasvir +/- RBV (12 weeks)</td>
<td>95.3%</td>
<td>(94.2% to 98.4%)</td>
</tr>
<tr>
<td>Partial Responders</td>
<td>100%</td>
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<tr>
<td>(ABT-450+ritonavir)+-ombitasvir +/- RBV (12 weeks)</td>
<td>95.2%</td>
<td></td>
</tr>
<tr>
<td>Null Responders</td>
<td>95.2%</td>
<td></td>
</tr>
<tr>
<td>Historical cohort</td>
<td>64%</td>
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</tbody>
</table>

**SAPPHIRE-2**

<table>
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</tr>
<tr>
<td>Historical cohort</td>
<td>64%</td>
<td></td>
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</tbody>
</table>

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1. NEJM. 2014; 370:1889-98
2. NEJM. 2014; 370:16:1483-93
3. NEJM. 2014; 370:1879-89
4. NEJM. 2014; 370:16:1483-93
**Monitoring During Anti-Viral Therapy**

- **Recommended within 6 weeks prior to starting therapy**
  - Complete blood cell (CBC) count
  - International normalized ratio (INR)
  - Hepatic function panel
    - Albumin
    - Total and direct bilirubin
    - Alanine aminotransferase
    - Aspartate aminotransferase
    - Alkaline phosphatase
  - Thyroid-stimulating hormone
  - If PEG is used
    - Calculated glomerular filtration rate

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**Monitoring During Anti-Viral Therapy**

- **Recommended within 12 weeks prior to starting therapy**
  - HCV genotype and quantitative HCV viral load

**Recommended monitoring during antiviral therapy**

- **Every 4 weeks**
  - CBC count
  - SCr level
  - GFR
  - Hepatic function panels
- **Every 12 weeks**
  - TSH for patients on IFN
- **More frequent assessment for drug-related toxic effects as clinically indicated**

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**QUESTIONS?**