Hepatitis C Treatment in the Direct Acting Antiviral Era - The Pharmacist’s Role

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Clinical investigator with research grants funded by Gilead Sciences, AbbVie, Merck, and Intercept Pharmaceuticals

- All grants paid to institution only
Learning Objectives

1) Describe the natural history and health burden of hepatitis C

2) Evaluate the current recommendations and treatment options available for hepatitis C

3) Identify areas in which pharmacists can play a significant role in hepatitis C care

4) Develop a basic understanding of what hepatitis C care will look like in the future
Hepatitis C Virus (HCV)

Discovered in 1989
- Previously known as Non-A / Non-B hepatitis

Blood-borne virus that causes inflammation of the liver
- Disease severity varies between mild short-lived illness to serious lifelong infection

HCV resides in the cytoplasm of hepatocytes
- Does not integrate into host DNA, unlike HIV
- Ability to achieve cure

HCV Viral Kinetics

Single-strand, enveloped, positive-sense RNA virus, ~60nm in size

High genetic diversity
- Error-prone HCV RNA-Polymerase
- High replication rate (100 to 3,000-fold greater than HIV)
- > 1 trillion viral particles produced per day

Trivia Question

If a patient’s daily HCV production was laid end-to-end, how many lengths of a football field would it span?

Answer = ~550 football fields
HCV Classification

6 Main Genotypes (GT) with greater than 50 subtypes

- Influences treatment response
- Variable disease progression (Increased with GT 3)
- Geographic distribution

Distribution of genotypes in Northern California Kaiser (> 10,000 patients)

<table>
<thead>
<tr>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5</th>
<th>GT 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>16%</td>
<td>12%</td>
<td>1%</td>
<td>&lt; 1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Epidemiology of Chronic HCV

3.2 million (1% to 1.5%) US persons living with HCV
  - ~50 to 75% are undiagnosed

Baby boomers (birth 1945-1965) account for 75% of infections
  - 5x greater risk of HCV infection
  - Majority of these HCV infections occurred in 1970’s and 80’s

Image Source (Accessed September 12, 2016): https://encrypted-tbn1.gstatic.com/images?q=tbn:ANd9GcTE6RbUtqXCDRqFU84Qaq515UcRlBOJ_UzirStQRI86qoYxY8xSEDOR
HCV as a Cause of Liver Damage

HCV causes inflammation and injury to the liver
- Result of which is the progression of fibrosis (essentially scarring)

METAVIR scoring for liver fibrosis
- F0 to F4 categorization
- F0 = No fibrosis
- F4 = Cirrhosis

Natural History and Progression of HCV

Image Source (Accessed September 12, 2016): Used with permission of Hepatitis C Online (Copyright © 2016 Hepatitis C Online – AWS)
http://www.hepatitisc.uw.edu/pdf/evaluation-staging-monitoring/natural-history/core-concept/all
## Factors Associated With Accelerated Fibrosis Progression

### Host Factors

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage</td>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Inflammation grade</td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>Older age at time of infection</td>
<td>Obesity</td>
</tr>
<tr>
<td>Male sex</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Organ Transplant</td>
<td></td>
</tr>
</tbody>
</table>

### Viral Factors

- HCV genotype 3
- Coinfection with hepatitis B virus or HIV
Complications of Cirrhosis

Portal hypertension
Ascites
Encephalopathy
Variceal bleeding
Coagulopathy
Spontaneous bacterial peritonitis (SBP)
Hepatocellular carcinoma (HCC)
Hepatorenal syndrome
Hepatic hydrothorax
Extrahepatic Manifestations

Hematological
- B-Cell Non-Hodgkin’s Lymphoma
- Thrombocytopenia
- Mixed cryoglobulinemia

Dermatological
- Lichen planus
- Porphyria cutanea tarda
- Pruritus

Endocrine Disorders
- Thyroid disease
- Type II Diabetes

Central Nervous System
- Depression
- Weakness / myalgia
- Peripheral neuropathy

Rheumatologic Disorders
- Polyarthritis
- Systemic Lupus Erythematosus
- Sjogren’s syndrome

Renal
- Glomerulonephritis
- Nephrotic Syndrome

Chronic HCV: Silent but Deadly

HCV is the leading cause of:
- Cirrhosis
- HCC
- Liver transplantation
- Liver-related deaths

From 2003 to 2013 HCV-associated deaths surpassed 60 other nationally notifiable infectious diseases combined

People with chronic HCV live on average 15 years less than people without HCV

HCV-Associated Advanced Disease Outcomes

Projected Cumulative Incidence (2015 to 2050)

Economic Burden of Chronic HCV

Annual Healthcare Costs Between Non-HCV and Chronic HCV Patients

- No Chronic HCV: $5,676
- HCV Non-Cirrhotic: $19,596
- HCV Compensated Cirrhosis: $22,620
- HCV Decompensated Cirrhosis: $40,320
- HCV HCC: $94,848
- HCV Liver Transplant: $259,068

HCV TREATMENT

GOALS OF THERAPY AND TREATMENT RECOMMENDATIONS
Goals of HCV Treatment

Virologic cure
- Sustained Virologic Response (SVR) = No HCV detected 12 weeks after treatment completion

Health-benefits of achieving SVR
- 70% risk reduction for liver cancer
- 90% risk reduction in liver transplant and liver-related mortality
- Improvement in all-cause mortality and liver-related health adverse consequences
- Reduced mortality related to extrahepatic manifestations
HCV Treatment: Who and When

WHO
- **Everyone** with chronic HCV
- Exception = Short-life expectancy

Considerations in timing
- Extrahepatic manifestations
- Advanced liver disease
- Higher risk of accelerated fibrosis progression
- Earlier the better (Early fibrosis stages)
- Reduce risk of transmission

Pharmacy Directors in charge of the medication budget may want to cover their ears
### FDA Approved HCV Agents

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ interferon (IFN)</td>
<td>▪ NS3/4A Protease Inhibitor (PI)</td>
<td>▪ NS3/4A Protease Inhibitor (PI)</td>
<td>▪ NS5A Inhibitor</td>
<td>▪ Combination DAA’s</td>
</tr>
<tr>
<td>▪ peginterferon (PEG)</td>
<td>▪ telaprevir (TVR)</td>
<td>▪ boceprevir (BOC)</td>
<td>▪ simeprevir (SMV)</td>
<td>▪ PrOD Extended Release (XR)</td>
</tr>
<tr>
<td>▪ ribavirin (RBV)</td>
<td>▪ NS5B Polymerase Inhibitor</td>
<td>▪ sofosbuvir (SOF)</td>
<td>▪ ledipasvir / sofosbuvir (LDV/SOF)</td>
<td>▪ sofosbuvir / velpatasvir (SOF/VEL)</td>
</tr>
</tbody>
</table>

**Combination DAA’s**

- paritaprevir / ritonavir / ombitasvir + dasabuvir (PrOD)
- paritaprevir / ritonavir / ombitasvir (PrO)

History of HCV Treatment Response

- **1991**: IFN (24) and IFN (48)
- **1998**: IFN/RBV (24) and IFN/RBV (48)
- **2001**: PEG (48) and PEG/RBV (48)
- **2011**: PI + PEG/RBV (24-48)
- **2013 - Present**: DAA + PEG/RBV (12-48) and All Oral DAA (8-24)

**Treatment (Duration = Weeks)**

**SVR (%)**

Figure Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Last Updated July 6, 2016. Date Accessed September 12, 2016.
### DAA Class Properties

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitor</th>
<th>NS5B Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td>Nucleoside / Nucleotide</td>
<td>First Generation</td>
</tr>
<tr>
<td>DAA Agents</td>
<td>Non-Nucleoside</td>
<td>Second Generation</td>
</tr>
<tr>
<td>telaprevir boceprevir</td>
<td>sofosbuvir</td>
<td>ledipasvir daclatasvir ombitasvir</td>
</tr>
<tr>
<td>simeprevir paritaprevir grazoprevir</td>
<td>dasabuvir</td>
<td>elbasvir velpatasvir</td>
</tr>
<tr>
<td>Pangentotypic Coverage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrier to Resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral Potency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Good Profile**
- **Average Profile**
- **Least Favorable Profile**

Factors influencing selection of recommended regimens

- Efficacy
- Treatment history
- Extent of liver disease
- Genotype
- Resistance Associated Variants (RAVs)
- Drug Interactions
- Patient comorbidities
- Side effect profile
AASLD / IDSA Recommended Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
</tr>
<tr>
<td>elbasvir / grazoprevir</td>
<td>X</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>X</td>
</tr>
<tr>
<td>PrOD ± ribavirin</td>
<td>X^</td>
</tr>
<tr>
<td>PrO + ribavirin</td>
<td></td>
</tr>
<tr>
<td>simeprevir + sofosbuvir</td>
<td>X</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>X</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir</td>
<td>X</td>
</tr>
</tbody>
</table>

^ RBV included

# AASLD / IDSA Recommendations

## Treatment Naïve & Previous PEG/RBV Failure (Genotype 1)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype (GT) (1a / 1b)</th>
<th>Non-Cirrhotic</th>
<th>Compensated Cirrhosis</th>
<th>Treatment Length (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>elbasvir / grazoprevir</td>
<td>GT1a / GT1b</td>
<td>+</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir ± RBV</td>
<td>GT1a / GT1b</td>
<td>+</td>
<td>+</td>
<td>8 - 12</td>
</tr>
<tr>
<td>PrOD + RBV</td>
<td>GT1a only</td>
<td>+</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>PrOD</td>
<td>GT1b only</td>
<td>+</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>simeprevir + sofosbuvir</td>
<td>GT1a / GT1b</td>
<td>+</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>GT1a / GT1b</td>
<td>+</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir</td>
<td>GT1a / GT1b</td>
<td>+</td>
<td>-</td>
<td>12</td>
</tr>
</tbody>
</table>

- **elbasvir / grazoprevir** - GT 1a check for baseline NSSA RAVs, if present, consider alternative treatment or lengthen treatment to 16 weeks with Ribavirin
- **ledipasvir / sofosbuvir** - Alternative regimen of 8 weeks treatment duration in non-cirrhotic patients with baseline HCV viral load < 6 million copies
- **ledipasvir / sofosbuvir + ribavirin** used in Genotype 1a and 1b patients with cirrhosis and previous failure to PEG / RBV
# AASLD / IDSA Recommendations

## Treatment Naïve & Previous PEG/RBV Failure (Genotypes 2-6)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype(s)</th>
<th>Non-Cirrhotic</th>
<th>Compensated Cirrhosis</th>
<th>Treatment Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Naïve</td>
<td>PEG/RBV</td>
<td>Naïve</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>2, 3, 4, 5, and 6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir ± RBV</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PrO + RBV</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>elbasvir / grazoprevir</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>5, 6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- Baseline RAV testing in GT 3 non-cirrhotic, treatment experienced and compensated cirrhotic, treatment naïve patients. If Y93H RAV present add Ribavirin to regimen
- Ribavirin addition to regimen in GT 3 compensated cirrhotic, treatment experienced patients and in GT 4 (same population) using ledipasvir / sofosbuvir
- For GT 4 patients using elbasvir / grazoprevir extend duration to 16 weeks and add RBV in previous PEG/RBV experienced patients with on-treatment virologic failure

# Notes

## Regimen

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Treatment Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>ledipasvir / sofosbuvir + RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>Treatment Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclatasvir + sofosbuvir ± RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir + RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>Treatment Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclatasvir + sofosbuvir + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir + RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
### AASLD / IDSA Recommendations

**Retreatment Previous Protease Inhibitor + PEG/RBV Failures**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment Length Non-cirrhotic</th>
<th>Treatment Length Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir + RBV</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>N/A</td>
<td>24 weeks</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir ± RBV</td>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>elbasvir / grazoprevir + RBV</td>
<td>12 – 16 weeks</td>
<td>12 - 16 weeks</td>
</tr>
</tbody>
</table>

- Previous Protease Inhibitors = telaprevir, boceprevir, simeprevir
- elbasvir / grazoprevir extend duration to 16 weeks in previous PEG/RBV experienced patients with on-treatment virologic failure

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AASLD / IDSA Recommendations

Retreatment Regimens Containing Multiple DAAs

Previous simeprevir + sofosbuvir OR NS5A Inhibitor containing regimens (GT1)

Defer treatment = Non-cirrhotic and no other reasons for urgent treatment

Consideration for retreatment in cirrhosis or other reason for urgent treatment

- RAV Testing for both NS3/4A Protease Inhibitor and NS5A Inhibitors

<table>
<thead>
<tr>
<th>RAV Testing Results</th>
<th>Retreatment Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NS5A Resistance</td>
<td>(SOF/LDV or SOF/VEL) + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>No NS3 / Yes NS5A Resistance</td>
<td>SOF + SMV + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Yes NS3 / Yes NS5A Resistance</td>
<td>Clinical Trial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF + (PrOD or EBR/GZR) ± RBV x 12-24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

### AASLD / IDSA Recommendations

**Renal, Decompensated Cirrhosis & Post-Liver Transplant**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Decompensated Cirrhosis</th>
<th>Severe Renal Impairment (CrCl &lt; 30 mL/min)</th>
<th>Recurrent HCV Post-Liver Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>elbasvir / grazoprevir</td>
<td>No</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>Yes</td>
<td>No</td>
<td>Genotypes 1 and 4</td>
</tr>
<tr>
<td>PrOD ± ribavirin</td>
<td>No</td>
<td>Yes</td>
<td>Alternative</td>
</tr>
<tr>
<td>simeprevir + sofosbuvir</td>
<td>No</td>
<td>No</td>
<td>Alternative</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>daclatasvir + sofosbuvir</td>
<td>Yes</td>
<td>No</td>
<td>Genotypes 1, 2, 3 and 4</td>
</tr>
<tr>
<td>sofosbuvir + ribavirin</td>
<td>No</td>
<td>No</td>
<td>Genotype 2</td>
</tr>
</tbody>
</table>

- Decompensated cirrhosis and recurrent HCV post-liver transplantation: RBV eligible - Add RBV x 12 weeks / RBV ineligible - No RBV x 24 weeks
- PrOD is recommended in severe renal impairment for GT 1b and as an alternative with RBV in GT 1a
- Sofosbuvir + ribavirin is the preferred option in RBV eligible patients with GT 2 post-liver transplant recurrent HCV infection and decompensated cirrhosis

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Priority population for treatment
- Increased risk of liver disease progression

SVR rates similar to HCV monoinfected

Do not interrupt HIV treatment
- PrO and PrOD use only for patients on HIV therapy
- Stable on HIV therapy for 1 month before starting

<table>
<thead>
<tr>
<th>HCV DAA(s)</th>
<th>Antiretroviral Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclatasvir</td>
<td>Efaverinz; Etravirine; Nevirapine; Cobicistat; Atazanavir boosted-ritonavir</td>
</tr>
<tr>
<td>elbasvir / grazoprevir</td>
<td>Efaverinz; Etravirine; Nevirapine; Protease Inhibitors; Cobicistat</td>
</tr>
<tr>
<td>sofosbuvir / velpatasvir</td>
<td>Efaverinz, Etravirine, Nevirapine Regimens containing TDF</td>
</tr>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>Regimens containing TDF</td>
</tr>
<tr>
<td>PrOD</td>
<td>Efaverinz; Etravirine; Nevirapine; Rilpivirine; Cobicistat; Darunavir</td>
</tr>
<tr>
<td>simeprevir</td>
<td>Efaverinz; Etravirine; Nevirapine; Protease Inhibitors; Cobicistat</td>
</tr>
</tbody>
</table>
Pill Burden and Administration

- PrO + RBV
- PrOD ± RBV
- PrOD XR ± RBV

- 3-10 tabs total daily scheduled Qday or BID

- daclatasvir + sofosbuvir
- simeprevir + sofosbuvir

- 1 tab Qday
- elbasvir / grazoprevir
- ledipasvir / sofosbuvir
- sofosbuvir / velpatasvir

- With Food
- Without Regards to Food

Reference – Individual medication package insert (available on reference slide)
Warnings and Precautions

**Serious Symptomatic Bradychardia**
- Amiodarone with sofosbuvir and ledipasvir, velpatasvir, simeprevir, or daclatasvir

**Hepatic Decompensation and Hepatic Failure (Moderate / Severe Hepatic Impairment)**
- Not Recommended: simeprevir / Contraindicated: PrOD, PrOD XR, PrO, elbasvir/grazoprevir

**ALT Elevations**
- PrOD, PrOD XR, PrO, elbasvir/grazoprevir

**Photosensitivity / Rash / Sulfa Allergy**
- simeprevir

Reference – Individual medication package insert (available on reference slide)
Common Adverse Events

PrOD; PrOD XR

- Insomnia, pruritus, skin reactions, GI related
  - < 10% Incidence
  - > 10% Incidence
  - N/A

elbasvir/grazoprevir; ledipasvir/sofosbuvir*; sofosbuvir/velpatasvir*; daclatasvir + sofosbuvir; simeprevir + sofosbuvir

- Insomnia*, Asthenia*, GI related
  - < 10% incidence
  - > 10% incidence

Fatigue, Headache

Reference – Individual medication package insert (available on reference slide)
Ribavirin Warnings and Side Effects

- **Black Box Warning**
  - Cardiac Events
  - Pregnancy Category X

- **More Common**
  - Anemia
  - Fatigue
  - Nausea
  - Pruritus
  - Insomnia
  - Headache

- **Less Common**
  - Asthenia
  - Skin Reactions
  - Irritability
  - Myalgia

Reference – Individual medication package insert (available on reference slide)
Drug Interactions

- P-glycoprotein
- Acid Soluble
- CYP3A4 inducers
- OATP1B13 Inhibitors
- DCV + SOF
- SMV + SOF
- P-glycoprotein
- CYP3A4
- CYP2C8
- PrO & PrOD

Increasing

SOF/LDV
SOF/VEL
EBR/GZR

Reference – Individual medication package insert (available on reference slide)
Optimizing Care

PHARMACIST’S INVOLVEMENT
HEPATITIS C CLINIC

**Pharmacist’s Primary Responsibilities**

- Treatment referral review
- Patient treatment scheduling
- Patient education visit to review treatment plan
- Follow up on treatment
- Treatment outcomes

**Clinic Team**

**Pharmacists** R. Andy Rathbun, Lubna Kazi, Chrislynn Chew, Cindy Ngo

**MDs** Heather Patton, Mamie Dong, Lisa Nyberg, Anders Nyberg

**PAs** Debbie Muratet, Brian Farb

**RN Coordinators** Joyce Kreutzberg, Beth Walters

**LVN** Julita Dioquino

**Support Coordinator** RaChae Tudara

**Pharmacy Leadership** Jennigrace Bautista, Lina Delosreyes
Pretreatment Evaluation

Medical history
- Previous HCV treatment / response
- Liver disease staging
- Transplant status
- Drug interaction evaluation

Treatment Readiness
- Comorbidities
- Adherence to care
- Substance abuse
- Coverage, expected costs, and financial assistance

Labs (within 12 weeks of treatment)
- CBC, INR, AST, ALT, total and direct bilirubin, ALK Phos, Scr and calculated CrCL
- HIV serology
- Hepatitis A and B serology (Immunization)
- HCV genotype / subtype (anytime)
- Quantitative HCV viral load
- Pregnancy testing
- RAV testing as appropriate
- Substance abuse panel as appropriate

Monitoring During Treatment

Regular clinic visits and/or telephone contact
- Adherence; Adverse Events; Drug Interactions

Labs including HCV viral load after week 4 and as appropriate

Early Discontinuation
- On-treatment virologic failure
- Drug specific recommendations for monitoring of liver toxicity or decompensation
  - elbasvir / grazoprevir
  - PrO and PrOD based regimens
Monitoring After Treatment Completion

Monitoring of cirrhosis, regardless of treatment response
- HCC screening every 6 months
- Endoscopic esophageal varices screening

Failed to achieve SVR
- Disease progression assessment every 6 to 12 months
- Continued evaluation of retreatment appropriateness

Achieved SVR
- No advanced fibrosis = No additional follow up necessary
Regimen Cost

12 Week Treatment Course

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Wholesale Acquisition Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBR/GZR</td>
<td>$54,600</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>$74,760</td>
</tr>
<tr>
<td>PrO</td>
<td>$76,608</td>
</tr>
<tr>
<td>PrOD</td>
<td>$83,328</td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>$94,500</td>
</tr>
<tr>
<td>DCV + SOF</td>
<td>$147,000</td>
</tr>
<tr>
<td>SMV + SOF</td>
<td>$150,360</td>
</tr>
</tbody>
</table>

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Financial Considerations

**Wholesale Acquisition Cost (WAC) treatment range**
- $54,600 to >$300,000

**Average national negotiated discount from WAC**
- 2014 = 22%
- 2015 = 46%

**Numerous cost-effective analysis demonstrate**
- Increased quality-adjusted life expectancy (QALY)
- Cost-effectiveness in early and late-stage HCV disease

Patient Affordability

Formulary Restrictions

Reviewing expected co-pay with patient before treatment

Patient co-pay assistance

- Manufacturer programs
- Patient Access Network Foundation
- Patient Advocate Foundation (Co-Pay Relief)
Pharmacist Optimizing Care

**Treatment evaluation**
- Financial considerations
- Readiness to start treatment
- Regimen selection

**Patient education**
- Side effects, Drug interactions, Medication administration

**Treatment monitoring**
- Safety, Adherence, Effectiveness
Looking Forward

FUTURE OF HEPATITIS C
In Pursuit of “Perfectovir”

- Drug Interactions
- SVR > 95%
- Minimal Toxicity
- 1 pill Qday
- Special Populations
- Pangenotypic Activity
- Short Duration
- HCV Resistance
- Retreatment Options
- Affordability
- Decompensated Cirrhosis

Room for Improvement

Treatment Needs Met

<table>
<thead>
<tr>
<th>Investigational Agents</th>
<th>Drug Class</th>
<th>Dosing</th>
<th>Estimated Availability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABT-493 + ABT-530</strong></td>
<td>NS3/4A PI + NS5A</td>
<td>PO Qday</td>
<td>2017</td>
<td>Pangenotypic, Potential for 8 wk treatment course, Renal Impairment, Retreatment</td>
</tr>
<tr>
<td><strong>sofosbuvir + velpatasvir + voxilaprevir (GS-9857)</strong></td>
<td>NS5B + NS5A + NS3/4A PI</td>
<td>PO Qday</td>
<td>2017 / 2018</td>
<td>Pangenotypic, Potential for 8 wk treatment course, Retreatment</td>
</tr>
<tr>
<td><strong>MK-3682 + grazoprevir + (elbasvir OR MK-8408)</strong></td>
<td>NS5B + NS3/4A PI + NS5A</td>
<td>PO Qday</td>
<td>2018</td>
<td>Pangenotypic, Potential for 8 wk treatment course</td>
</tr>
</tbody>
</table>
Summary

- HCV is a chronic liver disease with potential long-term health implications
- Treatment options are now available for almost every patient, offering much improved cure rates, with better tolerability and ease of use
- Multiple treatment options will be available over the coming years that should increase access to cure and reduce treatment cost
- Fiscal responsibility through quality optimization
Test Question 1

What percentage of patients would be expected to develop cirrhosis after 20 to 30 years of being infected with chronic HCV?

a) 5%
b) 25%
c) 50%
d) 75%
Test Question 2

Which FDA approved HCV regimen has an 8 week treatment duration as an alternative option available for some patients?

a) sofosbuvir / ledipasvir
b) daclatasvir + sofosbuvir
c) elbasvir / grazoprevir
d) sofosbuvir / velpatasvir
Test Question 3

Which of the following options would be expected to have reduced efficacy when co-administered with omeprazole 40mg twice daily?

a) paritaprevir / ritonavir / ombitasvir + dasabuvir
b) daclatasvir + sofosbuvir
c) elbasvir / grazoprevir
d) sofosbuvir / velpatasvir
References

3) Schooley RT. Top Antivir Med 2014; 21(5):148-15
5) MMWR 2012;61(No. RR-4)
7) Sherman KE. Top Antivir Med 2011; 19(3):121-125
16) van der Meer, et al. JAMA 2012;308(24):2584-2593
19) Figure Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.
References (continued)

35) Kwo PY, et al. EASL 2016. Abstract LBO1
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2. To claim credit: Go to www.cshp.org/cpe before December 1, 2016.