A Stormy C: Challenges to Hepatitis C Management

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Target Audience: Pharmacists
ACPE#: 0202-0000-16-065-L01-P
Activity Type: Application-based

Learning Objectives

• Describe the clinical and economic burden associated with HCV infection
• Discuss the importance of early assessment of high risk patients and early treatment rationale
• Distinguish new and emerging HCV agents
• Use national algorithms and guidelines to guide treatment strategies for patients with HCV
• Examine manage care considerations in the management of HCV, including strategies for determining cost-effectiveness of treatment and the impact of changing treatment outcomes on managed care organizations

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Which of the following is not a benefit associated with the early initiation of HCV treatment?

A. Prevent progression to end stage liver disease
B. Reduction in liver disease related morbidity and mortality
C. Ability to shorten the duration of treatment with direct acting antiviral drugs to 8 weeks in all patients regardless of genotype and treatment experience
D. Reduction in the incidence of HCV disease transmission

Which HCV antiviral medication is no longer recommended alone or in combination as treatment for an HCV genotype 1 infection?

A. Ribavirin
B. Pegylated interferon
C. Simeprevir
D. Ledipasvir

HCV Treatment guidelines can assist the practitioner to help manage patients with chronic HCV infection because:

A. Only FDA approved regimens are included in the guidelines
B. Only the least expensive treatment regimens are included in the guidelines
C. Provides concise treatment recommendations based on the most current information from clinical trials
D. Includes experimental treatments and investigational protocols

Considerations for the treatment of HCV infection in a managed care situation include:

A. Due to the high cost of antivirals, treatment of HCV infection should be restricted only to patients with stage F4 fibrosis (cirrhosis)
B. Pharmacoeconomic models can be used to determine the cost-effectiveness of various HCV treatment regimens
C. Treatment cure is associated with an immediate cost savings by preventing liver-disease related complications
D. Expensive new antivirals are no more effective than previously used treatments such as peginterferon + ribavirin

Introduction

- Hepatitis C virus (HCV) infection is a major health problem (~500,000 die each year from HCV-related liver disease)
- Previous treatments (peginterferon + ribavirin)
  - Modest efficacy (~50%)
  - Significant side effects
- Recent development of direct acting antivirals (DAAs)
  - Very effective (>90% viral response)
  - Few side effects
  - Expensive (approximately $100,000 treatment/course)
- HCV infection can be cured
- Access to diagnosis and treatment is low

HCV 101

- HCV is a RNA virus (Hepacivirus genus, Flaviviridae family)
  - Discovered in 1989 (previously known as non-A, non-B)
  - Seven genotypes, varies by geographic distribution
    - US: Genotype 1 (70%), genotype 2 (20%), genotype 3 (10%)
  - Genotypes respond differently to treatment
  - Five unrelated hepatotrophic viruses, A, B, C, D, and E.
- Transmission
  - Blood-borne (injection drug use)
  - Blood products, solid organ transplant (rare with screening)
  - Vertical (mother to child)
- No vaccine available for hepatitis C

References:
Magnitude of HCV Infection

- 130 to 150 Million persons infected worldwide
- ~2 to 3% of population
- >10% in Egypt
- >5 Million in the USA have chronic hepatitis C infection
- 72% Of injection drug users were unaware of serostatus
- Most prevalent in those born between 1945 to 1965
- Birth-cohort screening

HCV Disease Progression

- Acute Infection
- Chronic Infection
- Cirrhosis

Consequences of Hepatitis C

- Chronic Hepatitis Cohort Study (CHeCS)
  - 2,143,369 patients (2006-2010)
  - Mean age of death 15 years younger
  - Age-adjusted mortality 12x higher
- Cause of death HCV > HIV in 2007
- Leading cause of hepatocellular carcinoma (HCC)
- Most common indication for liver transplantation
- Extra-hepatic manifestations:
  - Increased risk of cardiovascular disease
  - Risk factor for developing diabetes mellitus
  - Progressive loss of kidney function

Progression of Liver Disease

- Paired biopsy study:
  - 33% progression of fibrosis (over 3 years)
- HALT-C Study:
  - 10%/year with bridging fibrosis transition to cirrhosis
  - Cirrhosis: ~4%/year decompensation
- Increased risk of progression:
  - Alcohol consumption
  - HIV / HBV co-infection
  - Steatohepatitis
  - Organ transplantation

Costs of Hepatitis C

- Per patient per year costs:
  - HCV without liver disease: $5,670
  - Advanced liver disease (decomp. cirrhosis): $27,845
  - Hepatocellular carcinoma:
    - Mean spending: $1,805
    - MELD score (5-10): $260
    - MELD score (35-40): $33,792
- Cost of liver transplant:
  - Hospital admission: $399,100

Hepatitis C Infection: Impact on the Healthcare System

- Large users of health services:
  - >2.3 million outpatient visits
  - 73,000 ED visits
  - 475,000 inpatient visits
- Resource use highest in baby boomers:
  - 2.8 million inpatient days
  - >$15 Billion annually
- Projected in the next 40-50 years:
  - 1.76 million persons will develop cirrhosis
  - 400,000 will develop HCC
  - 1 million will die from HCV-related complications
Economic Burden of Hepatitis C Infection

- Untreated HCV infection associated with economic loss:
  - Impairment at work:
    - Absenteeism: 5.03% vs. 2.82% (p=0.089)
    - Activity impairment: 41.16% vs. 27.29% (p<0.001)
  - Costs:
    - Direct costs: $22,818 vs. $15,361 (p=0.001)
    - Indirect costs: $10,316 vs. $5,468 (p<0.001)
  - Reduced quality of life:
    - Health Utility (SF-6D): 0.65 vs. 0.73 (p<0.001)

Benefits of HCV Treatment

- Improved renal and cardiovascular outcomes:
  - 8-year cumulative incidence of ESRD:
    - Treated: 1.1%
    - Untreated: 9.3%
  - 8-year cumulative incidence of stroke:
    - Treated: 3.1%
    - Untreated: 5.3%
- Lower all-cause mortality with SVR:
  - 10-year cumulative rate of liver-related mortality/transplant:
    - With SVR: 1.9%
    - Without SVR: 37.4%
  - 10-year cumulative rate of hepatocellular carcinoma:
    - With SVR: 5.1%
    - Without SVR: 21.8%

Hepatitis C is Curable

- New antivirals have revolutionized hepatitis C treatment
  - Highly effective
  - Very safe
  - Simple to take
  - Minimal drug-drug interactions
- HCV can be cured with distinct treatment course
- HBV/HIV can be suppressed with long-term/lifelong treatment
- Access to medications
- Diagnosis
- Linkage to care

Goals of HCV Treatment

- Eradicate virus (achieve SVR)
  - SVR = sustained virologic response
  - SVR12 = undetectable HCV RNA at 12 weeks post treatment
- Reduce all-cause mortality
- Reduce liver-related health adverse consequences

HCV Treatment: Who?

- All patients with chronic HCV infection
  - EXCEPT:
    - Those with short life expectancies that cannot be remediated by treating HCV or by transplantation

HCV Treatment: When?

- EARLY

Reduction in Morbidity

Reduction in Mortality

HCV Treatment Initiation and Degree of Fibrosis

10-year cumulative occurrence rates SVR No SVR

- All-cause mortality: 3.9% 26.0%
- Liver-related death or transplantation: 1.9% 21.4%
- Hepatocellular carcinoma: 3.1% 21.8%
- Liver failure: 2.1% 29.9%

HCV can be cured with distinct treatment course

HBV/HIV can be suppressed with long-term/lifelong treatment

Access to medications

Diagnosis

Linkage to care

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HCV Treatment: When?

• Benefits of EARLY treatment (cure)
  – Prevent disease progression
  – Reduce disease transmission
  – Improve quality of life
  – Improve extrahepatic and nonhepatic manifestations of chronic disease

Which Type of Treatment?

Hepatitis C Treatment Guidelines

• AASLD/IDSA
  www.hcvguidelines.org
• U.S. Department of Veterans Affairs
• European Association for the Study of the Liver (EASL)
• World Health Organization

AASLD/IDSA Treatment Guidelines

• AASLD Practice Guidelines Published in 2009
  www.hcvguidelines.org. Date accessed 1/30/16
• AASLD/IDSA joint venture (2014) 2
  – Online guidelines
  – "Living document" that is continuously updated
• Expert panel (volunteer)
  – Evidence-based review of information
    • Literature, scientific meetings, FDA safety warnings
  – Guidance to provide up-to-date recommendations
    • Screening
    • Treatment
    • Management

Treatment Considerations

- HCV genotype/subtype
- HCV stage
  - No fibrosis / fibrosis / cirrhosis / decompensated cirrhosis
- Prior treatment history
  - Naïve or experienced (PegINF/RBV + DAA)
- Concomitant conditions
  - Chronic kidney disease
  - Psychiatric disorders (for ribavirin or peginterferon)
- Potential for drug-drug interactions
- Insurance formulary

US Prevalence: HCV Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (G1a and G1b)</td>
<td>72%</td>
</tr>
<tr>
<td>2 (G2)</td>
<td>17%</td>
</tr>
<tr>
<td>3 (G3)</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
</tbody>
</table>

McHutchison JG et al. NEJM 1998;339:1485

HCV Treatment Evolution

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Discovery of HCV</td>
</tr>
<tr>
<td>1997</td>
<td>Interferon α2a, α2b, αcon</td>
</tr>
<tr>
<td>1998</td>
<td>Interferon + Ribavirin</td>
</tr>
<tr>
<td>2001</td>
<td>Peginterferon α2a (Pegasys)</td>
</tr>
<tr>
<td>2002</td>
<td>Peginterferon α2b (PegIntron)</td>
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<tr>
<td>2011</td>
<td>Boceprevir (Victrelis)</td>
</tr>
<tr>
<td>2013</td>
<td>Paritaprevir/ritonavir, ombitasvir, dasabuvir (Viekira Pak)</td>
</tr>
<tr>
<td>2014</td>
<td>Ledipasvir/Sofosbuvir (Harvoni)</td>
</tr>
<tr>
<td>2015</td>
<td>Daclatasvir (Daklinza)</td>
</tr>
<tr>
<td>2016</td>
<td>Velpatasvir (Under FDA review)</td>
</tr>
</tbody>
</table>

McHutchison JG et al. NEJM 1998;339:1485

Interferon based regimens
- Long duration
- Complex
- Many adverse effects
- Low SVR rates

Targets for Direct Acting Antivirals (DAA)

<table>
<thead>
<tr>
<th>Core</th>
<th>E1</th>
<th>E2</th>
<th>p7</th>
<th>NS2</th>
<th>NS3</th>
<th>NS4</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
</table>

McHutchison JG et al. NEJM 1998;339:1485

Fried MW. NEJM 2002;347:975

INF = interferon
RBV = ribavirin
PegINF = peginterferon
Targets for Direct Acting Antivirals (DAA)

Core E1 E2 p7 NS2 NS3 NS4 NS4B NS5A NS5B

NS3/4A protease inhibitors
Telaprevir (TEL)
Boceprevir (BOC)
Grants approval

NS5A replication complex inhibitors
Ledipasvir (LDV)
Ombitasvir (OBV)
Daclatasvir (DCV)
Elbasvir (EBV)
Velpatasvir (VEL)

NS5B polymerase inhibitors
Sofosbuvir (SOF)

NS5B nucleos(t)ides (NI)
Dasabuvir (DAS)

NS5B non-nucleosides (NNI)
Simeprevir (SMV)
Paritaprevir (PTV)
Grazoprevir (GZV)

Characteristics of HCV antiviral classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Potency</th>
<th>Genotype Activity</th>
<th>Resistance Barrier</th>
<th>FDA Approved Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 protease inhibitors</td>
<td>High</td>
<td>1 and 4</td>
<td>Low - Intermediate</td>
<td>Sofosbuvir, Telaprevir, Boceprevir, Paritaprevir, Grazoprevir</td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>High</td>
<td>1, 3-6</td>
<td>Very Low</td>
<td>Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir, Velpatasvir*</td>
</tr>
<tr>
<td>NS5B NI inhibitors</td>
<td>Intermediate</td>
<td>1-6</td>
<td>High</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>NS5B NNI inhibitors</td>
<td>Intermediate</td>
<td>1</td>
<td>Low</td>
<td>Daclatasvir</td>
</tr>
</tbody>
</table>

*Under FDA review (1/30/16)

Sofosbuvir (Sovaldi, SOF)

- HCV-specific NS5B nucleotide polymerase inhibitor
- Potent antiviral activity against genotypes 1-6
- High resistance barrier
- Once-daily, 400 mg tablet (approved for use in combination)
- No food effect
- Renal elimination (avoid when CrCl < 30 ml/min)
- Well tolerated
- Low potential for drug interactions

FDA Approved Indications

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 4</td>
<td>SOF + PegINF + RBV</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>SOF + RBV</td>
<td>24</td>
</tr>
</tbody>
</table>

*Consider 24 weeks of SOF + RBV in genotypes 1 and 4 with PegINF at dose of 1,000-1,200 mg/week (if 25% of patients are HCV/HIV-1 co-infected)

Sofosbuvir prescribing information (8/2015)

Sofosbuvir (Sovaldi, SOF)

- FDA approved 2013 (initial)
  - G1, 2, 3 and 4

- Treatment naive or experienced
- HCV/HIV-1 confection
- HCC awaiting liver transplantation

Sofosbuvir prescribing information (8/2015)
**Sofosbuvir (Sovaldi, SOF)**

- Potential for drug interactions
  - Substrate of P-glycoprotein and BCRP
- Avoid coadministration
  - Amiodarone
  - Anticonvulsants
  - Antimycobacterials (rifampin)
  - St. John’s wort

**Simeprevir (Olysio, SMV)**

- 2nd generation HCV NS3/4A protease inhibitor
- FDA approved 2013 (Genotypes 1,4)
  - Naïve, experienced (PegINF + RBV; avoid if failed PI)
    - G1 or 4: with PegINF + RBV (24-48 weeks)
    - G1: with SOF (12-24 weeks)
- Once-daily, 150 mg tablet (administer with food)

**Simeprevir (Olysio, SMV)**

- Rash and Photosensitivity
  - Can occur any time, most common within first 4 weeks
  - Recommendations
    - Limit sun exposure and when outdoors use sun protective measures
    - Monitor rash progression
    - May need to consider dermatologic consult
    - Discontinue therapy if severe rash
  - Hyperbilirubinemia (direct and indirect elevations)
    - Occur early, commonly peak by week 2
    - Reverse upon discontinuation

**Simeprevir (Olysio, SMV)**

- Potential for drug interactions
  - CYP 1A2 and CYP 3A4 (intestinal)
  - Inhibitor of P-glycoprotein and OATP1B1/B3 transporters
  - Coadministration not recommended

**Simeprevir (Olysio, SMV)**

- Selected drug interactions
  - Monitor recommended
    - Calcium channel blockers
    - Digoxin
    - Phosphodiesterase inhibitors (PDE-6)
    - HMG CO-A reductase inhibitors
      - Rosuvastatin: do not exceed 10 mg/day
      - Atorvastatin: do not exceed 40 mg/day
      - Others: use lowest possible dose
**Ledipasvir/Sofosbuvir (Harvoni, LDV/SOF)**

- HCV NS5A inhibitor
- Co-formulated
  - Ledipasvir (90 mg)/Sofosbuvir (400 mg) + food
- FDA approved 2014 (Genotypes 1, 4-6)
  - Treatment naive and experienced + cirrhosis
  - Duration: typically 12 weeks
    - 8 weeks (naïve/no cirrhosis) - baseline HCV RNA <6 million IU/mL
    - 24 weeks (experienced/cirrhotic) - failed SOF or RBV intolerant
- Adverse effects
  - Common: fatigue, headache, nausea, insomnia

**Adverse effects**

- **Common:** fatigue, headache, nausea, insomnia
- **NS5A**
- **NS5B**
- **NI**

**Ledipasvir/Sofosbuvir prescribing information (11/2015)**

http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

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**Daclatasvir (Daklinza, DCV)**

- 1st generation NS5A inhibitor
- FDA approved (with SOF)
  - December 2015 (G3: naive and experienced + cirrhosis)
  - February 2016 (G1, 4-6 naïve/experienced + compensated cirrhosis)
- Once daily
  - 30 mg tablet
- **Adverse effects**
  - Common: headache, fatigue, nausea, diarrhea

**Daclatasvir prescribing information (2/2016)**

http://packageinserts.bms.com/pi/pi_daklinza.pdf

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**Summary: DAA Regimens with SOF**

- **SOF** + **PI (Simeprevir)**
  - 2 tablets daily + food
    - Population: Genotype 1, 4, 5
    - 12-24 weeks
    - SVR: 90-97%

- **SOF** + **NS5A (Ledipasvir)**
  - 1 tablet daily
    - Population: Genotype 1 and 4-6
    - 8-24 weeks
    - SVR: 85-100%

- **SOF** + **NS5A (Daclatasvir)**
  - 2 tablets daily
    - Population: Genotype 1 and 3
    - 12 weeks
    - SVR: 90%

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**Daclatasvir (Daklinza, DCV)**

- **Potential for drug interactions**
  - No CYP450 Involvement
  - Substrate of P-glycoprotein and BCRP transporters
- **Selected drug interactions**
  - Digoxin: ↑ effect (monitor levels)
  - Tenofovir: ↑ effect (monitor toxicity)
  - Acid reducing agents

**Daclatasvir prescribing information (7/2015)**

http://packageinserts.bms.com/pi/pi_daklinza.pdf

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**Paritaprevir-ritonavir/Ombitasvir plus Dasabuvir**

(Viekira/Technivie, PTV-r/OMV + DAS, 3D, PROD)

- **SOF** + **NS5A**
  - Dasabuvir
  - Paritaprevir (with ritonavir boosting)
  - Ombitasvir

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**Paritaprevir-ritonavir/Ombitasvir plus Dasabuvir (Viekira/Technivie, PTV-r/OMV + DAS, 3D, PROD)**

- **FDA approved December 2014**
  - G1 - naive and experienced + compensated cirrhosis
  - Liver transplant recipients (normal hepatic function, mild fibrosis)
- **Adverse events**
  - Most common
  - Without dasabuvir: nausea, pruritus, insomnia
  - With dasabuvir: fatigue, nausea, pruritus, insomnia, asthma, pruritus and other skin reactions
  - | Treatment | Duration (weeks) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a (naive, experienced)</td>
<td>PTV-r/OMV + DAS + RBV</td>
</tr>
<tr>
<td>Genotype 1b (naive, experienced)</td>
<td>PTV-r/OMV + DAS</td>
</tr>
<tr>
<td>Genotype 1b (naive, experienced)</td>
<td>PTV-r/OMV + DAS + RBV</td>
</tr>
<tr>
<td>Liver transplant recipients (MACTAVIR ≤ 20)</td>
<td>PTV-r/OMV + DAS + RBV</td>
</tr>
</tbody>
</table>
- **Laboratory abnormalities**
  - ALT elevations > 5 times ULN in ~1% (↑ with ethinyl estradiol containing medications)
  - Bilirubin elevations > 2 times ULN in 2% (↑ to 15% with ribavirin)
  - ↑ in special populations (i.e. HCV/HIV coinfected, liver transplant)
  - ↑ when treated 24 weeks compared to 12 weeks

**Concomitant Drug Class Drug Names**

- **Sedatives/hypnotics**
  - Alprazolam
  - Midazolam (oral), triazolam
- **Phosphodiesterase Type 5 (PDE-5) Inhibitors**
  - Sildenafil when dose d for pulmonary hypertension
- **Neuroleptics**
  - Pimozide
- **HMG CO-A Reductase Inhibitors**
  - Simvastatin
  - Lovastatin
- **HIV therapies**
  - Efavirenz
  - Darunavir/ritonavir
  - Lopinavir/ritonavir
  - Rilpivirine
- **Herbal supplements**
  - St. John’s wort
- **Ethyinyl estradiol-containing products**
  - Ethinyl estradiol products such as oral contraceptives
- **Ergot derivatives**
  - Ergotamine, dihydroergotamine
- **Antimycobacterials**
  - Rifampin
- **Antihyperlipidemic agent**
  - Gemfibrozil
- **Anticonvulsants**
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
- **Anti-gout**
  - Colchicine
- **Alpha 1 adrenoreceptor antagonist**
  - Alfuzosin HCL

1 Refer to paritaprevir/ribavirin/ombitasvir and dasabuvir prescribing information for full details (10/2015)

**Select Drug Interactions and Management Recommendations**

<table>
<thead>
<tr>
<th>Concurrent Drug Class</th>
<th>Drug Names</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Lamivudine (oral), tenofovir (oral), emtricitabine (oral), zidovudine (oral)</td>
<td>Caution; monitor concentration if possible</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Quinine</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Pyrimethamine</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Sulfadoxine, pyrimethamine</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Chloroquine</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Hydroxychloroquine</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Mefloquine</td>
<td>Monitor, consider dose reduction</td>
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<tr>
<td>Antimalaria</td>
<td>Nifurtimox</td>
<td>Monitor, consider dose reduction</td>
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<tr>
<td>Antimalaria</td>
<td>Primaquine</td>
<td>Monitor, consider dose reduction</td>
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<tr>
<td>Antimalaria</td>
<td>Peripheral blood mononuclear cells (PBMCs)</td>
<td>Monitor, consider dose reduction</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>Mefloquine</td>
<td>Monitor, consider dose reduction</td>
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<td>Monitor, consider dose reduction</td>
</tr>
<tr>
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<td>Pyrimethamine</td>
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<tr>
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<td>Monitor, consider dose reduction</td>
</tr>
</tbody>
</table>
Elbasvir/Grazoprevir (Zepatier, EBV/GZV)

- Adverse effects
  - Most common:
    - Without ribavirin: fatigue, headache, nausea
    - With ribavirin: anemia, headache
  - ALT elevations:
    - ~1% experienced elevations > 5x ULN
    - Onset: at or after treatment week 8
  - Asymptomatic:
    - Resolved with ongoing treatment or therapy completion
  - Recommended monitoring:
    - Hepatic panel: baseline, week 8, then as needed

Elbasvir/Grazoprevir (Zepatier, EBV/GZV)

- Potential for drug interactions
  - CYP3A: elbasvir, grazoprevir
  - P-glycoprotein: elbasvir, grazoprevir
  - OATP1B1/B3: grazoprevir

- Contraindications:
  - Moderate to severe hepatic impairment (Childs Pugh class B or C)
  - Coadministration of the following drugs:
    - Anticonvulsants: carbamazepine, phenytoin
    - Antimycobacerials: rifampin
    - Herbals: St. John’s wort
    - HIV medications: Efavirenz, tazanavir, darunavir, lopinavir, saquinavir, tipranavir
    - Cyclosporine

Elbasvir/Grazoprevir (Zepatier, EBV/GZV)

Select Drug Interactions and Management Recommendations

<table>
<thead>
<tr>
<th>Concomitant Drug Class</th>
<th>Drug Names</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Nafcillin</td>
<td>Coadministration not recommended</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Ketoconazole</td>
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<tr>
<td>Endothelin antagonists</td>
<td>Bosentan</td>
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<tr>
<td>HIV therapies</td>
<td>Etravirine</td>
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</tr>
<tr>
<td>HIV therapies</td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir (disoproxil fumarate or alafenamide)</td>
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<tr>
<td>Modafinil</td>
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</tr>
<tr>
<td>Tacrolimus</td>
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<td>Monitor drug concentrations, renal function and adverse effects</td>
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<tr>
<td>HMG CO-A Reductase inhibitors</td>
<td>Atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin</td>
<td>Atorvastatin: max dose: 20mg/day; Rosuvastatin: max dose: 10mg/day; Others: not studied; use lowest necessary dose</td>
</tr>
</tbody>
</table>

*Refer to elbasvir/grazoprevir prescribing information for full details (1/2016).*

Elbasvir/Grazoprevir (Zepatier, EBV/GZV)

Summary: Oral DAA Regimens

- Single-tablet, once daily regimen
- No NS5B
- SVR > 90% in both genotype 1a and 1b
- Duration: 12-16 weeks
- Decreased potency
- Requires ritonavir boost
- Usually requires RBV
- Twice daily regimen
- Duration: 12-24 weeks
- Avoid if > mild hepatic impairment
- Increased adverse effects (RBV)
- Drug interactions (PI)
- FDA approved Jan. 28, 2016 - combination product
- Elbasvir (50 mg): NSSA inhibitor
- Grazoprevir (100 mg): NS3/4A protease inhibitor
- Dose: 1 tablet orally per day ± RBV
- G 1 and 4; naïve, experienced (including PI regimens)

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment History</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
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</thead>
<tbody>
<tr>
<td>Genotype 1a1</td>
<td>Naïve/experienced</td>
<td>EBV/GZV</td>
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<tr>
<td>NS5A polymorphism positive</td>
<td>Naïve/experienced</td>
<td>EBV/GZV + RBV</td>
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<tr>
<td>Genotype 1b</td>
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<tr>
<td>Genotype 1a1 or 1b</td>
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<td>EBV/GZV + RBV</td>
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<tr>
<td>Genotype 4</td>
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<td>Genotype 1a1 or 1b</td>
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<td>EBV/GZV + RBV</td>
<td>16</td>
</tr>
</tbody>
</table>

1 Testing patients with HCV genotype 1a for NS5A resistance-associated polymorphisms is recommended
Summary: Renal/Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>PGT</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>GTV</td>
<td>Yes</td>
<td>*</td>
</tr>
<tr>
<td>DCV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PGTV+DNV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>EVG+GSV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>RBV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Risk information based on prescribing information for each product as of 1/30/16
*Hep = use is contraindicated;
*SAF = use is safe to use in patients with impaired renal function;
*CPA, CPA = Child Pugh class, A, B, C

Summary: Drug Interaction Potential

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A</th>
<th>CYP2C</th>
<th>P-glycoprotein</th>
<th>BCRP</th>
<th>OATP1B1/B3</th>
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<tbody>
<tr>
<td>EBRV</td>
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</tr>
<tr>
<td>OPRV</td>
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<td>PTVV</td>
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<td>RBV</td>
<td>X</td>
<td></td>
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<tr>
<td>SMV</td>
<td>X</td>
<td>X</td>
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<tr>
<td>LEDV</td>
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<td>X</td>
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<td></td>
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<tr>
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<td>VELP</td>
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<tr>
<td>DASB</td>
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<tr>
<td>SMV</td>
<td>X</td>
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</tbody>
</table>

DAA and DDI: Real World Data

Assessment of drug interaction potential amongst patients’ regular outpatient medications and currently approved PegIF therapy

Targets for Direct Acting Antivirals (DAA)

Drug Interaction Management

- Evaluate potential for drug interactions prior to initiating HCV treatment
- Modify doses and medication regimen as necessary before, during, and after HCV treatment
- Educate on proper medication administration and adherence
- Requires vigilant and continuous monitoring during HCV treatment course
- Resources:
  - AASLD/IDSA guidance recommendations
  - Prescribing information
  - Drug interaction websites (i.e. www.hep-druginteractions.org)
**Summary: Treatment Recommendations**

### Genotype 1: Treatment Naïve

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Regimen Duration</th>
<th>Regimen Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>EBV/GZV + LDV/SOF</td>
<td>EBV/GZV + LDV/SOF</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>DAS + RBV</td>
<td>DAS + RBV</td>
</tr>
<tr>
<td>1b</td>
<td>EBV/GZV + LDV/SOF</td>
<td>EBV/GZV + LDV/SOF</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>12</td>
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<tr>
<td></td>
<td>PAR + OMV + DAS</td>
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</tr>
<tr>
<td></td>
<td>12</td>
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<tr>
<td></td>
<td>SMV + SOF</td>
<td>SMV + SOF</td>
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<td></td>
<td>12</td>
<td>12</td>
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<tr>
<td></td>
<td>DCV + SOF</td>
<td>DCV + SOF</td>
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<td></td>
<td>12</td>
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</tr>
</tbody>
</table>

**NOTE:**
- DAS = dasabuvir; DCV = daclatasvir; EBV = elbasvir; GZV = grazoprevir; LDV = ledipasvir; OMV = ombitasvir; PAR = paritaprevir; SMV = simeprevir; SOF = sofosbuvir; r = ritonavir.
- In patients with genotype 1a infection without baseline high fold-change NS5A RAVs for EBV.

### Genotype 1: Treatment Experienced

<table>
<thead>
<tr>
<th>Subtype</th>
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<tr>
<td></td>
<td>DAS + RBV</td>
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</tr>
<tr>
<td>1b</td>
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<td></td>
<td>12</td>
<td>12</td>
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<tr>
<td></td>
<td>PAR + OMV + DAS</td>
<td>PAR + OMV + DAS</td>
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<td></td>
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</tr>
<tr>
<td>Failed</td>
<td>PegINF + RBV</td>
<td>PegINF + RBV</td>
</tr>
<tr>
<td>1a or 1b</td>
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### Genotype 2 or 3

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<td>SOF + Peg + RBV</td>
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<tr>
<td></td>
<td>DCV + SOF</td>
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### Summary: Treatment Recommendations

#### Genotype 1: Treatment Experienced

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</tr>
</tbody>
</table>

### Which populations are still difficult to cure?

- No Longer difficult
  - Genotype 1
  - Black race
  - Null responders
  - Failures (PI + Peg/RBV)
  - Post liver transplant
  - HCV/HIV
  - Genotype 3

- Remain challenging
  - Decompensated cirrhosis
  - Renal disease
  - DAA failures
Next Generation – DAA Strategies

- Combine multiple potent DAAs with high barrier to resistance and unique mechanisms of action
- Remove genotypic specificity
- Decrease therapy duration
- Simplify regimens
- Improve tolerability

Clinical Practice Guidelines: Why Now?

- HCV care is rapidly changing
  - Emerging data from clinical trials
  - New drugs coming to market
- Most current knowledge of best practices
- Improve clinical decision making and quality of care
  - Concise recommendations
  - Discourage ineffective practices
- Increase efficiency by standardizing practice

Treatment Guidelines

- Recommendations are just that…recommendations
- Regimens may or may not be FDA approved
- Unique populations
  - Decompensated cirrhosis
  - Multiple drug-drug interactions (transplant, HIV-co-infection)
  - Treatment experienced (resistance)
- Guidelines change
  - New drugs that come to market
  - Emerging data from clinical trials, meetings (e.g. AASLD, EASL)
  - New tools and treatments become available
- Keep checking for updates

Patient Case
HCV Genotype 1

67 YO male with HCV genotype 1a infection. Liver biopsy (earlier this year) fibrosis (F3). Never been treated for hepatitis C before

Labs:
- Scr = 0.9
- INR = 1.0

PMH:
- Hypercholesterolemia
- Hypertension

Meds:
- Pravastatin 20mg PO daily
- Lisinopril 10mg PO daily

AASLD/IDSA Treatment Guidelines
Genotype 1a

www.hcvguidelines.org accessed 1/15/16

HCV Genotype 1 Efficacy and Costs


Patient Case
HCV Genotype 3
53 YO male with HCV genotype 3, treatment naïve.
Stage F4 fibrosis = cirrhosis (Fibroscan).
Labs: Scr = 1.1 INR = 1.1 Plts = 167K
PMH: GERD
Meds: Omeprazole 20mg PO daily
Insurance: Managed Medicaid
Prescribed: Sofosbuvir + Daclatasvir + Ribavirin x24 weeks
Prior authorization: Denied recommend alternative regimen: Sofosbuvir + Peginterferon + Ribavirin x12 weeks
Alternate regimen discussed with provider → patient switched 2nd Prior authorization: Accepted

AASLD/IDSA Treatment Guidelines
Genotype 3
www.hcvguidelines.org. accessed 1/15/16

Patient Case:
Changing Guidelines
59 YO female with HCV Genotype 1a infection (treatment naïve).
Labs: Platelets: 50K Creatinine: 1.3 (CrCl = 44mL/min)
Hemoglobin 9.2 g/dL Hematocrit 30%
Medical history: Hepatic encephalopathyAscitesEsophageal varices (last bleed was 2 yrs ago)Bipolar disorder
Decompensated cirrhosis, ribavirin intolerant/ineligible:
Old guidelines1: Sofosbuvir/Ledipasvir x24 weeks
Current guidelines2,3: Sofosbuvir + Daclatasvir x24 weeks
2. Welzel TM. EASL 2015. Abstract #P0772

Decompensated Cirrhosis (GT 1)
Old and Current Guidelines
- Efficacy for both is >90%
Old guidelines: SOF/LDP x24 wks = $226,800
Current guidelines: SOF+DAC x24 wks = $351,360
Adapted from Bourliere M. AASLD 2014. Abstract #82.
Welzel TM. EASL 2015. Abstract #P0772
www.hcvguidelines.org. Accessed 1/10/16

HCV in Managed Care
Scylla and Charybdis
- Chronic disease
  - Consume healthcare resources
  - Progressive (liver transplant)
- High cost of treatment
  - Expensive but finite
- Curable
  - Decrease clinical events
  - Decrease all-cause mortality
- Big investment
  - Save lives and save resources

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New Patients 2014
Insurance Type

<table>
<thead>
<tr>
<th>New HCV Treatment (thousands)</th>
<th>Payor Mix (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>161</td>
</tr>
<tr>
<td>2012</td>
<td>157</td>
</tr>
<tr>
<td>2013</td>
<td>152</td>
</tr>
<tr>
<td>2014</td>
<td>137</td>
</tr>
</tbody>
</table>

Drug Dashboard 2014
Part D Drug Spending

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Spending</th>
<th>Beneficiary Count</th>
<th>Tot. Annual Spending/User</th>
<th>Avg. Annual Beneficiary Cost/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sovaldi</td>
<td>$3,106,960,981</td>
<td>33,033</td>
<td>$94,056</td>
<td>$5,054</td>
</tr>
<tr>
<td>Nexium</td>
<td>$2,660,421,777</td>
<td>1,405,799</td>
<td>$1,892</td>
<td>$250</td>
</tr>
<tr>
<td>Crestor</td>
<td>$2,543,786,426</td>
<td>1,752,704</td>
<td>$1,451</td>
<td>$309</td>
</tr>
<tr>
<td>Adria</td>
<td>$2,377,319,032</td>
<td>405,161</td>
<td>$6,238</td>
<td>$352</td>
</tr>
<tr>
<td>Spina</td>
<td>$2,276,374,746</td>
<td>1,420,746</td>
<td>$1,602</td>
<td>$352</td>
</tr>
<tr>
<td>Lantus Scholar</td>
<td>$2,119,732,705</td>
<td>392,106</td>
<td>$2,573</td>
<td>$385</td>
</tr>
<tr>
<td>Januvia</td>
<td>$1,775,295,533</td>
<td>789,304</td>
<td>$2,247</td>
<td>$351</td>
</tr>
<tr>
<td>Lamisil</td>
<td>$1,725,355,624</td>
<td>787,204</td>
<td>$2,192</td>
<td>$379</td>
</tr>
<tr>
<td>Rivastad</td>
<td>$1,671,622,657</td>
<td>27,143</td>
<td>$61,586</td>
<td>$3,896</td>
</tr>
<tr>
<td>Dilacryl</td>
<td>$1,503,235,319</td>
<td>12,846</td>
<td>$69,891</td>
<td>$3,077</td>
</tr>
<tr>
<td>Levostrin</td>
<td>$690,952,572</td>
<td>11,718</td>
<td>$59,728</td>
<td>$3,921</td>
</tr>
</tbody>
</table>

Medicare Expenditures:
Aging Population

- HCV is a “baby boomer” epidemic
  - Peak prevalence among those born between 1945 to 1965
  - Majority of HCV-infected people age into Medicare
    - If not treated prior to Medicare, disease will progress, and future expenditures may rise.
  - Hepatitis C is curable
    - Curative treatment at earlier stages may reduce mortality
    - Affected members will live longer and incur Medicare expenses for a longer time
  - Dynamic situation

HCV in Managed Care
Maximize Outcomes & Minimize Costs

- Restrictions:
  - Treatment of chronic hepatitis C infection
  - Preferred formulary agent(s)
  - Advanced fibrosis (stage F3 and F4)
  - Prescribing by specialists only
  - No illicit drug use / alcohol consumption
- Use of specialty pharmacies
- Quantity limitations
- Re-authorization based on week-4, -8 viral load
- Adherence assessment

Authorization Criteria for Sofosbuvir:
Medicaid Fee-for-Service Programs

- Preferred status:
  - Non-preferred: 61%
  - Preferred: 33%
  - Not available: 6%
- Abstain from alcohol use:
  - Yes: 69%
  - No: 31%
- Abstain from drug use:
  - Yes: 67%
  - No: 33%
Authorization Criteria for Sofosbuvir: Medicaid Fee-for-Service Programs

- Minimum fibrosis score
  - F1: 1 (2%)
  - F2: 5 (10%)
  - F3*: 29 (57%)
  - F4: 4 (8%)
  - NA: 12 (23%)

- Restricted to specialist prescriber:
  - Yes: 30 (59%)
  - No: 21 (41%)

*Biopsy required (n=4)

Minimum Fibrosis Score

Adapted from Canary LA. Ann Intern Med. 2015;163:226.

Early vs. Delayed Treatment: Stages of Fibrosis Health Outcomes Lifetime Model of 10,000 Pts.

<table>
<thead>
<tr>
<th>Minimum Fibrosis</th>
<th>Number of cases of decompensated cirrhosis</th>
<th>Number of cases of HCC</th>
<th>Number of liver transplants</th>
<th>Number of HCV-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-1</td>
<td>36.7%</td>
<td>81.8%</td>
<td>74%</td>
<td>76.1%</td>
</tr>
<tr>
<td>F2</td>
<td>63.3%</td>
<td>45.9%</td>
<td>83%</td>
<td>84.5%</td>
</tr>
</tbody>
</table>

-Delaying treatment leads to more cases of advanced liver disease
-Initiating HCV treatment early (F0-1, F2) versus later (F3-4):
  -Reduces liver disease progression
  -Decreases downstream costs associated with advancing liver disease

Adapted from Ahmed A. AASLD 2014 Abstract # 1751

Number Need to Treat To Avoid a Negative Outcome

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Regimen</th>
<th>Avoid a case of DCC</th>
<th>Avoid a case of HCC</th>
<th>Avoid a liver transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>SOF+PEG+RBV</td>
<td>5</td>
<td>1</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>TPV+PEG+RBV</td>
<td>6</td>
<td>10</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>PEG+RBV</td>
<td>8</td>
<td>14</td>
<td>145</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>SOF+PEG+RBV</td>
<td>6</td>
<td>10</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>TPV+PEG+RBV</td>
<td>9</td>
<td>15</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>PEG+RBV</td>
<td>28</td>
<td>51</td>
<td>547</td>
</tr>
</tbody>
</table>

-DCC = decompensated cirrhosis, HCC = hepatocellular carcinoma
-SOF = sofosbuvir, PEG = Peginterferon, RBV = ribavirin, TPV = telaprevir
-NNT = Number needed to treat with a specific regimen, rather than remain untreated to avoid a negative outcome, for example, NNT to avoid a case of HCC for SOF+PEG+RBV:
  NNT=10 cases of HCC for SOF+PEG+RBV/10,000 - cases of HCC for no treatment/10,000

Adapted from Saab S. Aliment Pharmacol Ther 2014;40:657.

Changing Landscape

-Many payors prioritize HCV treatment to advanced liver fibrosis (F3-F4).
  -AASLD/IDSA updated guidelines October 20151. “Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies…”
  -CMS sent letter to Medicaid programs2. “Assuring Medicaid beneficiaries access to hepatitis C (HCV) drugs”

-Delay for illicit drug use / alcohol consumption2,3
-Criteria can vary by State/County
-Restrict to prescribing by specialists only2,3
-Access to limited number of specialist(s) may delay treatment

Cost-effectiveness Analysis Considerations

-How much more will we spend on a new intervention?
  -Cost of intervention over person’s lifetime
  -Cost savings from decreasing/preventing disease complications

-How much more benefit accrues from a new intervention?
  -Quality-adjusted life years (QALY)
    -Range: 0 (death) to 1 (perfect health)
    -How much more QALY will be gained with new medication?

-How much is society willing to pay (to gain 1 QALY)?
  -Willingness-to-pay (WTP) threshold ($50,000 to $100,000/QALY)
  -Budgets are finite
  -Spending on more on one disease state means less for another


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What is Cost Effective?

- CEA compares the relative costs of interventions
  - Budget limitations
  - Maximize public health benefits
- Incremental Cost Effective Ratio (ICER)
  - Incremental cost associated with measure of effect
  - Cost-utility analysis: Cost per QALY gained
- Historically "cost effective": ICER < $50,000\(^1\)
- World Health Organization (WHO)\(^2\)
  - Intervention cost < 1x annual GDP is highly cost effective
  - Intervention cost < 3x annual GDP is cost effective
- United States annual GDP per capita (2014) is $54,800\(^3\)

Cost Effectiveness and Budget Impact Sofosbuvir/ledipasvir

- Treatment will decrease the clinical burden of HCV disease
- $136 billion for all treatment-eligible patients during next 5 years
  - ~$61 billion paid for by government
  - ~$65 billion cost of using new treatments
  - Downstream offsets: ~$16 billion (24% of additional spending on new drugs)
- Better value in:
  - Genotype 1, cirrhosis, younger age
  - 35% probability of cost effectiveness ($50,000 WTP threshold)
  - 83% probability of cost effectiveness ($100,000 WTP threshold)
- May be cost effective with longer patient enrollment
  - Medicare, Medicaid, Veterans Health Administration
- Cost of treating: $27 billion/yr (~10% of prescription spend in 2012)

Incremental Cost Effective Ratio 10, 20, 30-Year Time Horizon

<table>
<thead>
<tr>
<th>ICER ($/QALY)</th>
<th>10 Years</th>
<th>20 Years</th>
<th>30 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>148,467</td>
<td>82,109</td>
<td>52,513</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>93,552</td>
<td>51,860</td>
<td>39,860</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>42,552</td>
<td>10,873</td>
<td>13,260</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>93,552</td>
<td>51,860</td>
<td>39,860</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>398,461</td>
<td>226,362</td>
<td>178,787</td>
</tr>
<tr>
<td>Non-Cirrhotic</td>
<td>174,243</td>
<td>87,803</td>
<td>73,618</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>174,243</td>
<td>87,803</td>
<td>73,618</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>758,237</td>
<td>423,214</td>
<td>336,489</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>263,778</td>
<td>131,904</td>
<td>110,958</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>263,778</td>
<td>131,904</td>
<td>110,958</td>
</tr>
</tbody>
</table>

Cost-effective ≠ Affordable

- CEA compares health-care costs and societal benefits
  - Allocate limited health-care resources
- Short-term budget impact ("today")
- Clinical events may take years to realize ("tomorrow")
  - DAAs FDA approved in 2013
  - Hepatic decompensation, HCC, liver transplant
  - Lower patient turnover (Medicaid/Federal Health System)\(^1,2\)
- New drugs coming to market
  - New drugs / treatment regimens
  - Free market competition
- Cost effectiveness is dependent of cost of treatment

Managed Care of HCV Opportunities

- Interdisciplinary team-care approach
- Access to specialized medications
- Coordinating services across the care continuum
- Plan benefit design

Clinician’s Conundrum

- Increased volume of patients seeking treatment
  - Affordable care act (ACA) = more access to care
  - Birth-cohort screening
- Resource intensive environment
  - More providers = more space = increased costs
  - Prior authorization / appeals / re-authorization / follow-up
- Family practitioner vs. specialist
  - Family (community) practitioner with limited resources
  - Project ECHO (Extension for Community Healthcare Outcomes)
- Changing landscape
  - New drugs / guidelines / reimbursement

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Managed Care of HCV

It Takes a Team
- Interdisciplinary team-care approach
  - MD, NP/PA, Pharm.D., CPhT, MA
- Pharmacy technician
  - Tracking of patient from start to finish
  - Follow up prior authorizations/re-authorizations
- Pharmacist
  - Review regimen for appropriateness, drug-drug interactions
  - Triage prescriptions to pharmacies
  - Initiation visit
    - Medication reconciliation
    - Counsel patient/care providers
- Access to specialized medications
  - Review medication regimen for appropriateness
  - Manage drug-drug, drug-disease interactions
  - Formulary preferences
  - SOF/LDP 8 week regimen (if appropriate)
  - Prior authorization / Peer to peer / Independent reviewer
  - Minimize gaps in treatment
  - Patient assistance programs
  - Partner with specialty pharmacies
- Facilitate authorization (designated specialty pharmacy)
  - Coordinate delivery of medications and blister packing
  - Communications about clinical/adherence issues

HCV-TARGET: SVR-12 & Relapse

Sofosbuvir/ledipasvir by Duration

- 97% SVR after 8 weeks
- 97% SVR after 12 weeks
- 95% SVR across the 24 weeks

- HCV-TARGET: Observational study
- Sofosbuvir/ledipasvir containing regimens are highly effective (genotype 1)
- Response rates comparable to clinical trials

1. Adapted from Terrault N. AASLD 2015. Abstract 94.

HCV-TARGET: SVR-12

8 Week Treatment is Underutilized

- 323 Qualified for 8 weeks of therapy:
  - 131 received 8 weeks
  - 192 received 12 weeks
- 8 Weeks of therapy:
  - Genotype 1
  - NO cirrhosis
  - Treatment naïve
  - HCV VL < 6 million IU/mL
- Sofosbuvir/ledipasvir is highly effective
- 8 weeks is underutilized

1. Adapted from Terrault N. AASLD 2015. Abstract 94.

Managed Care of HCV

The Pharmacy Team
- Coordinating services across the care continuum
  - Transitions of care (to/from hospital)
  - Counsel patients to bring HCV meds with them to the hospital
  - Ensure continuation of therapy when hospitalized
  - Start date, end of treatment (EOT) date
  - Patient’s own medication (within hospital)
- Alternative regimens (organ function, drug interactions)
  - Renal failure: SOF/LDP->SIM/SOF or SOF/DAC
  - Minimize PPI/H2RA with SOF/LDP (or time meds appropriately)
- New drug request (in electronic medical record)
  - Formulary review (P&T Committee)

Managed Care of HCV

- Plan benefit design
  - Formulary
  - Preferred drug(s)
  - Drug utilization criteria
  - Practice guidelines
  - Contract negotiation with manufacturers for discount pricing
  - Clinical program development
  - Disease state management
  - Adherence indicators (e.g. refill history)
  - Pharmacoeconomic analysis
  - Utilization of specialty pharmacies
Conclusions

- Hepatitis C infection is a global health problem
  - 150 million worldwide with chronic hepatitis C infection
  - Enormous cost to health care system and society
- Treatment of hepatitis C infection is rapidly evolving
  - New drugs are very effective
  - Treatment is expensive
- Expert-developed, evidence-based treatment guidelines
  - Recommendations for treatment of hepatitis C
  - Constantly changing, based on new drugs and emerging data
- Managed care is in a unique position
  - Manage costs (pharmaceutical and medical benefits)
  - Optimize patient outcomes and prevent disease progression

Which of the following is not a benefit associated with the early initiation of HCV treatment?

A. Prevent progression to end stage liver disease
B. Reduction in liver disease-related morbidity and mortality
C. Ability to shorten the duration of treatment with direct-acting antiviral drugs to 8 weeks in all patients regardless of genotype and treatment experience
D. Reduction in the incidence of HCV disease transmission

Which HCV antiviral medication is no longer recommended alone or in combination as treatment for an HCV genotype 1 infection?

A. Ribavirin
B. Pegylated interferon
C. Simeprevir
D. Ledipasvir

HCV Treatment guidelines can assist the practitioner to help manage patients with chronic HCV infection because:

A. Only FDA approved regimens are included in the guidelines
B. Only the least expensive treatment regimens are included in the guidelines
C. Provides concise treatment recommendations based on the most current information from clinical trials
D. Includes experimental treatments and investigational protocols

Considerations for the treatment of HCV infection in a managed care situation include:

A. Due to the high cost of antivirals, treatment of HCV infection should be restricted only to patients with stage F4 fibrosis (cirrhosis)
B. Pharmacoeconomic models can be used to determine the cost-effectiveness of various HCV treatment regimens
C. Treatment cure is associated with an immediate cost savings by preventing liver-disease related complications
D. Expensive new antivirals are no more effective than previously used treatments such as peginterferon + ribavirin