INDIVIDUALIZING TREATMENT REGIMENS FOR HEPATITIS C: A 2016 Update for Specialty Pharmacists

Monday, May 2, 2016
1:00 – 2:30 PM • Interactive CPE Activity

Encore at Wynn Las Vegas
Encore Ballroom 1-3

This symposium will provide live credit (L) for those states requiring it.

Supported by an educational grant from Merck & Co Inc.
Disclaimer

The following presentation was recorded in May 2016. Since then the following changes have occurred:

- Sofosbuvir/velpatasvir was approved in June 2016
- It is the first FDA approved pan-genotypic Hepatitis C therapy and is recommended by the AASLD guidelines as a treatment option for all HCV genotypes
Participating Faculty

Pamela S. Belperio, PharmD, BCPS, AAHIVE
National Public Health Clinical Pharmacist
VA Office of Public Health/Population Health
Department of Veterans Affairs
Los Angeles, California

Brittany Mills, PharmD, MBA, BCACP, AAHIVE
Clinical Pharmacist, Pharmacy Manager
Walgreens at Howard Brown Health Center
Chicago, Illinois
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Pamela S. Belperio, PharmD, BCPS, AAHIVE, reports having no relevant financial or advisory relationships with corporate organizations related to this activity.

Brittany Mills, PharmD, MBA, BCACP, AAHIVP, reports having no relevant financial or advisory relationships with corporate organizations related to this activity.
Agenda

1:00–1:05 PM  Welcome and Conference Goals
   Pamela S. Belperio, PharmD, BCPS, AAHIVE

1:05–1:15 PM  Current Status of HCV Therapy
   Brittany Mills, PharmD, MBA, BCACP, AAHIVP

1:15–1:25 PM  Considerations for Individualized Treatment
   Brittany Mills, PharmD, MBA, BCACP, AAHIVP

1:25–1:40 PM  Latest Guideline-Based Therapy Recommendations
   Pamela S. Belperio, PharmD, BCPS, AAHIVE

1:40–1:55 PM  Emerging Treatment Options and Trends
   Pamela S. Belperio, PharmD, BCPS, AAHIVE

1:55–2:15 PM  Pharmacist-Led Education Strategies
   Brittany Mills, PharmD, MBA, BCACP, AAHIVP

2:15–2:25 PM  Q&A Session
   Pamela S. Belperio, PharmD, BCPS, AAHIVE, and
   Brittany Mills, PharmD, MBA, BCACP, AAHIVP

2:25–2:30 PM  Closing Remarks and Educational Outcomes Activity
   Pamela S. Belperio, PharmD, BCPS, AAHIVE
Learning Objectives

- **ASSESS** individualized treatment plans for HCV treatment and associated monitoring parameters.
- **RECOGNIZE** patient-specific disease state complications relevant to drug therapy selection and modifications.
- **EVALUATE** benefits, risk, and characteristics of drugs in the HCV pipeline.
- **RECOMMEND** strategies to cope with social challenges and increase patient adherence with therapy.

HCV = hepatitis C virus.
CPE Information

**INTENDED AUDIENCE** – This activity is designed for specialty pharmacists in attendance at the 2016 Armada Specialty Pharmacy Summit. No prerequisites required.

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DISCLAIMER – The opinions and recommendations by faculty and other experts whose input is included in this educational activity are their own. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

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Educational Grant

The University of Tennessee College of Pharmacy would like to acknowledge an educational grant from Merck & Co., which helped to make this activity possible.
Current Status of HCV Therapy

Brittany Mills, PharmD, MBA, BCACP, AAHIVP
Clinical Pharmacist, Pharmacy Manager
Walgreens at Howard Brown Health Center
Chicago, Illinois
Hepatitis C Virus (HCV) in the US

- Most common blood-borne infection
  - Estimated 2.5 to 4.7 million infected in the United States
- Chronic, slow disease progression
  - Most patients remain undiagnosed.
  - Prevalence estimated to be as high as 11% in 1945–1965 cohort.
- Leading cause of:
  - Liver disease: cirrhosis, liver cancer
  - Liver transplantation
  - Liver-related mortality
- High financial burden

Goal of HCV Treatment

Sustained virologic response (SVR) = Viral Cure
HCV Genotypes

- Six genotypes: GT1–6
  - Subtypes (a, b, c)
- GT1a and GT1b: most common
- GT1–3: broad geographic representation
- GT4–6: cluster geographically
- Treatment regimen differs based on genotype.

HCV Therapy: Past, Present, and Future

IFN + ribavirin

Pegylated IFNs + ribavirin

Boceprevir and telaprevir

Simeprevir and sofosbuvir with IFN (GT1)

Sofosbuvir + RBV (GT2, 3)

Simeprevir + sofosbuvir (off-label use)

Daclatasvir

Ledipasvir/sofosbuvir

Paritaprevir/rit/ombitasvir/dasabuvir ± RBV

Simeprevir + sofosbuvir

Sofosbuvir/velpatasvir

Elbasvir/grazoprevir

6%–26% Interferon

34%–42%

40%–50%

50%–75%

85%–93%

90%–100%

94%–100%


GT = genotype; IFN = interferon; RBV = ribavirin.
HCV Treatment: Paradigm Shift

1 DAA + Peg-IFN/RBV (Triple Therapy)
2011–2014

- Boceprevir
- Telaprevir
- Simeprevir
- Sofosbuvir

IFN-Free Oral Regimens
Late 2014–2015

- SOF + simeprevir ± RBV
- SOF/LDV (fixed-dose combination) ± RBV
- Ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV

DAA = direct-acting antiviral; LDV = ledipasvir; SOF = sofosbuvir.
HCV Therapy Continues to Evolve into 2016

- Daclatasvir
  - August 2015: GT3, must be used with sofosbuvir
  - February 2016: GT1, must be used with sofosbuvir

- Elbasvir/grazoprevir
  - January 2016: GT1 and GT4
**NS3/4A Protease Cleaves the HCV Polyprotein**

**NS3/4A Protease**

Cleavage

**NS3 protease inhibitors:**
boceprevir, telaprevir, simeprevir, paritaprevir, grazoprevir

Inhibition of the NS5B Polymerase or NS5A Halts HCV Replication

RNA template

NS5B Polymerase inhibitor

NS5A Replication Complex

NS5A inhibitor

Polymerase

Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir

NRTI: Sofosbuvir
NNRTI: Dasabuvir

NNRTI = non-nucleoside reverse transcription inhibitor; NRTI = nucleoside reverse transcription inhibitor.

## Classes of DAAs in Available Products

<table>
<thead>
<tr>
<th></th>
<th>NS3/4A (protease inhibitor)</th>
<th>NS5A</th>
<th>NS5B (polymerase inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td></td>
<td>Ledipasvir</td>
<td>Sofosbuvir (NRTI)</td>
</tr>
<tr>
<td>OPrD</td>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
<td>Dasabuvir (NNRTI)</td>
</tr>
<tr>
<td>EBR/GZR</td>
<td>Grazoprevir</td>
<td>Elbasvir</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td></td>
<td>Daclatasvir</td>
<td></td>
</tr>
<tr>
<td>Genetic barriers to resistance</td>
<td>Low</td>
<td>Lowest</td>
<td>High (uncommon)</td>
</tr>
</tbody>
</table>

EBR/GZR = elbasvir/grazoprevir; OPrD = ombitasvir, paritaprevir, ritonavir, and dasabuvir.

AASLD/IDSA HCV Guidelines; FDA package labeling.
Considerations for Individualized Treatment

Brittany Mills, PharmD, MBA, BCACP, AAHIVP
Clinical Pharmacist, Pharmacy Manager
Walgreens at Howard Brown Health Center
Chicago, Illinois
Baseline Factors That May Influence Response

| Viral Factors | • HCV RNA level  
|              | • HCV genotype (GT1, 2, 3, 4, 5, 6)  
|              | • Genotype subtype (GT1a vs 1b)  
| Host Factors | • Race/ethnicity  
|              | • Gender  
|              | • IL28B (CC, CT, TT)  
|              | • BMI  
| Stage of Liver Disease | • Compensated vs decompensated  

BMI = body mass index.  
AASLD/IDSA HCV Guidelines.
Patient Considerations for Selecting HCV Treatment

- Treatment history
  - Peg-IFN/RBV, HCV protease inhibitor, SOF
- Comorbidities
  - Potential for drug-drug interactions
- Ability to adhere to treatment goals and monitoring
- Active substance use disorders
- Insurance
Drug Characteristics: Availability of All-Oral Regimens by Genotype

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3</th>
<th>GT4</th>
<th>GT5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>√</td>
<td></td>
<td></td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir and dasabuvir</td>
<td>√</td>
<td></td>
<td></td>
<td>No dasabuvir</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir + sofosbuvir</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>√</td>
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</tbody>
</table>

AASLD/IDSA HCV Guidelines; FDA package labeling.
## Comparison of Drug Profiles

<table>
<thead>
<tr>
<th></th>
<th>NS3/4A PIs, 1st Generation</th>
<th>NS3/4A PIs 2nd Generation</th>
<th>NS5A Inhibitor</th>
<th>Nucleoside NS5B Inhibitor</th>
<th>Nonnucleoside NS5B Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
</tr>
<tr>
<td><strong>Pan-genotypic efficacy</strong></td>
<td><img src="red.png" alt="Red" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="red.png" alt="Red" /></td>
</tr>
<tr>
<td><strong>Resistance profile</strong></td>
<td><img src="red.png" alt="Red" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="red.png" alt="Red" /></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td><img src="red.png" alt="Red" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
<td><img src="green.png" alt="Green" /></td>
</tr>
<tr>
<td><strong>Drug-drug interactions</strong></td>
<td><img src="red.png" alt="Red" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
<td><img src="yellow.png" alt="Yellow" /></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>tid</td>
<td>qd-bid</td>
<td>qd</td>
<td>qd</td>
<td>bid</td>
</tr>
</tbody>
</table>

*bid = twice a day; PI = protease inhibitor; qd = every day; tid = 3 times a day.*

Multiple Factors

- HCV Genotype
- Fibrosis Stage
- Extrahepatic Manifestations
- Comorbidities
- Contraindications Drug Interactions
- Treatment History
- Occupation
- Social and Behavioral Support
- Personal Plans
Individualized Treatment Strategy

Genotype
- 1a or 1b
- 2
- 3
- 4
- 5/6

Treatment History
- Naïve
- Experienced

Cirrhosis
- Yes
- No

Regimen
- NS3/4 PI
- NS5A
- NS5B

Variables
- Baseline HCV RNA
- Renal/Hepatic impairment
- Drug interactions
- Need for ribavirin

Duration
- 8 weeks
- 12 weeks
- 24 weeks
Latest Guideline-Based Therapy Recommendations

Pamela S. Belperio, PharmD, BCPS, AAHIVE
National Public Health Clinical Pharmacist
VA Office of Public Health/Population Health
Department of Veterans Affairs
Los Angeles, California
Guideline-Based Therapy Recommendations

- AASLD-IDSA guidelines
  http://www.hcvguidelines.org/

- Department of Veterans Affairs
  Treatment Considerations

AASLD = American Association for the Study of Liver Diseases; IDSA = Infectious Diseases Society of America.
Highlights

- Testing and Linkage to Care
- When and In Whom to Initiate Therapy
- Overview of Cost, Reimbursement, and Cost-effectiveness Considerations for Hepatitis C Treatment Regimens
- Initial Treatment and Retreatment
- Unique Patient Populations
  - HIV/HCV Coinfection
  - Decompensated Cirrhosis
  - Post-Liver Transplant
  - Renal Impairment
- Acute HCV Infection

AASLD/IDSA HCV Guidelines.
Approach to Treatment

- All patients are candidates for treatment unless limited life expectancy.

- Treatment urgency
  - Advanced liver disease
  - Post-liver transplant
  - HIV/HCV coinfection
    - Same treatment for HCV and HIV/HCV coinfection
  - Extrahepatic manifestations

- Non-FDA–indicated recommendations

**Note:**
- FDA = US Food and Drug Administration
- HIV = human immunodeficiency virus
- AASLD/IDSA HCV Guidelines
Efficacy of LDV/SOF in GT1

Excluding 1 subject with GT4 infection; error bars represent 95% confidence intervals.

SVR12 = sustained virologic response at 12 weeks.

Eight weeks of LDV/SOF was noninferior to 12 weeks for patients with HCV RNA <6M IU/mL and in the overall population.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPPHIRE-1</td>
<td>Treatment (Tx)-naïve HCV GT1 patients without cirrhosis</td>
<td>OPrD + RBV x 12 weeks</td>
<td>GT1a: 96% (308/322)</td>
</tr>
<tr>
<td>SAPPHIRE-II</td>
<td>Tx-experienced HCV GT1 patients without cirrhosis</td>
<td>OPrD + RBV x 12 weeks</td>
<td>GT1a: 96% (166/173)</td>
</tr>
<tr>
<td>PEARL-II</td>
<td>Tx-experienced HCV GT1b patients without cirrhosis</td>
<td>OPrD x 12 weeks</td>
<td>GT1b: 100% (91/91)</td>
</tr>
<tr>
<td>PEARL-III</td>
<td>Tx-naïve HCV GT1b patients without cirrhosis</td>
<td>OPrD for 12 weeks</td>
<td>GT1b: 100% (209/209)</td>
</tr>
<tr>
<td>PEARL-IV</td>
<td>Tx-naïve HCV GT1a patients without cirrhosis</td>
<td>OPrD + RBV for 12 weeks</td>
<td>GT1a: 97% (97/100)</td>
</tr>
<tr>
<td>TURQUOISE-II</td>
<td>Tx-naïve and Tx-experienced HCV GT1 patients with cirrhosis</td>
<td>OPrD + RBV x 12 weeks</td>
<td>GT1a: 89% (124/140)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OPrD + RBV x 24 weeks</td>
<td>GT1a: 95% (115/121)</td>
</tr>
</tbody>
</table>

## Genotype 1 and 4: Elbasvir/Grazoprevir Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-EDGE-TN</td>
<td>Tx-naïve HCV GT1 patients with or without cirrhosis</td>
<td>EBR/GZR x 12 weeks</td>
<td>273/288 (95%) 1a: 92%; 1b: 98%</td>
</tr>
<tr>
<td>C-EDGE-Coinfection</td>
<td>Tx-naive HCV/HIV GT1 patients with or without cirrhosis</td>
<td>EBR/GZR x 12 weeks</td>
<td>179/189 (95%)</td>
</tr>
<tr>
<td>C-EDGE-TE</td>
<td>Prior peginterferon/ribavirin Tx-experienced HCV GT1 patients with or without cirrhosis</td>
<td>EBR/GZR x 12 weeks, EBR/GZR + RBV x 16 weeks</td>
<td>90/96 (94%) 1a: 90%; 1b: 100% 93/96 (97%) 1a: 95%; 1b: 100%</td>
</tr>
<tr>
<td>C-SALVAGE</td>
<td>Prior peg/ribavirin + HCV protease inhibitor Tx-experienced HCV GT1 patients with or without cirrhosis</td>
<td>EBR/GZR + RBV x 12 weeks</td>
<td>76/79 (96%) 1a: 93%; 1b: 98%</td>
</tr>
<tr>
<td>C-SURFER</td>
<td>Tx-naive and prior peginterferon/ribavirin Tx-experienced GT1 patients with severe renal impairment, including hemodialysis</td>
<td>EBR/GZR x 12 weeks</td>
<td>115/122 (94%)</td>
</tr>
<tr>
<td>Pooled*</td>
<td>Tx-naïve HCV mono- and coinfected GT4 patients with or without cirrhosis</td>
<td>EBR/GZR x 12 weeks</td>
<td>64/66 (97%)</td>
</tr>
<tr>
<td>C-EDGE-TE</td>
<td>Prior peginterferon/ribavirin Tx-experienced HCV GT4 patients</td>
<td>EBR/GZR + RBV x 16 weeks</td>
<td>8/8 (100%)</td>
</tr>
</tbody>
</table>

* C-EDGE-TN, C-EDGE-Coinfection, C-SCAPE.

Elbasvir/Grazoprevir Efficacy for GT1

- Tx-naïve with or without cirrhosis
- Tx-experienced with or without cirrhosis x 12 weeks
- Tx-experienced with or without cirrhosis +RBV x 12 weeks
- Tx-experienced with or without cirrhosis +RBV x 16 weeks

SVR12 (%)

Daclatasvir + Sofosbuvir in Treatment-Naive and Experienced GT1 HCV Infection

Very few cirrhotics included (n = 14)

GT1 HCV Treatment Naive (N = 126)

- SOF (n = 15) 100%
- SOF + DCV (n = 14) 100%
- SOF + DCV + RBV (n = 15) 100%
- SOF + DCV (n = 15) 100%
- SOF + DCV + RBV (n = 41) 95%
- SOF + DCV (n = 41) 100%
- SOF + DCV + RBV (n = 41) 95%

GT1 HCV TVR/BOC Treatment Failures (N = 41)

- SOF + DCV (n = 21) 100%
- SOF + DCV + RBV (n = 20) 95%

BOC = boceprevir; DCV = daclatasvir; TVR = telaprevir.
Summary of Trials for GT1

12-week duration

DAC = daclatasvir; SIM = simeprevir.

## Recommendations for Genotype 1

<table>
<thead>
<tr>
<th>Genotype 1a (TN or TE) noncirrhotic</th>
<th>DAC+SOF</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>SOF+SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks</td>
<td>12 weeks; 8 weeks if TN and low VL</td>
<td>12 weeks + RBV</td>
<td>Test for NS5A RAV; (−)RAV, then 12 weeks; (+)RAV, then 16 weeks +RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1b (TN or TE) noncirrhotic</th>
<th>DAC+SOF</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>SOF+SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks</td>
<td>12 weeks; 8 weeks if TN and low VL</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cirrhosis, CTP A</th>
<th>DAC+SOF</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>SOF+SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 weeks</td>
<td>+RBV 12 weeks; -RBV 24 weeks</td>
<td>1b: 12 weeks; 1a: 24 weeks +RBV</td>
<td>12 weeks (1a: if NS5A RAV, then 16 weeks +RBV)</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cirrhosis, CTP B or C</th>
<th>DAC+SOF</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>SOF+SIM</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>12 weeks +RBV</td>
<td>12 weeks + RBV</td>
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<table>
<thead>
<tr>
<th>Renal insufficiency (eGFR &lt;30 mL/min)</th>
<th>DAC+SOF</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>SOF+SIM</th>
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<td></td>
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<td></td>
<td></td>
<td>12 weeks (1a: if NS5A RAV, then 16W + RBV)</td>
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</tr>
</tbody>
</table>

In CTP B or C initiate RBV at 600 mg/day.  CTP = Child Turcotte Pugh; eGFR = estimated glomerular filtration rate; RAV = resistance-associated variant; TE = treatment experienced; TN = treatment naïve; VL = viral load.  
AASLD/IDSA HCV Guidelines.
Impact of Baseline NS5A Resistance-Associated Polymorphisms

SVR in HCV GT1a patients with or without baseline NS5A polymorphisms (RAPs)

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<tr>
<th></th>
<th>EBR/GZR for 12 Weeks SVR12</th>
<th>EBR/GZR + RBV for 16 Weeks SVR12</th>
<th>DAC+SOF ±RBV SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>No baseline NS5A polymorphisms</td>
<td>98% 441/450</td>
<td>100% 49/49</td>
<td>95% 142/149</td>
</tr>
<tr>
<td>(M28, Q30, L31, or Y93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of baseline NS5A</td>
<td>70% 39/56</td>
<td>100% 6/6</td>
<td>76% 13/17</td>
</tr>
<tr>
<td>polymorphism (M28, Q30, L31, or Y93)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA label recommends baseline testing for NS5A RAPs (For DAC, “consider” only in patients with cirrhosis)
RAP: Definition and How to Test (VA)

- RAP = resistance-associated polymorphism
  - Changes in amino acids that have been shown to emerge during treatment or that have been tested in vitro (replicon) and show a change in susceptibility ($EC_{50}$) of >2.5-fold
  - Sometimes referred to as RAV (resistance-associated variant)

- When to test
  - GT1a: for NS5A, before starting EBR/GZR
  - GT3: for NS5A, before starting daclatasvir
  - Retreatment of all-oral DAA failures: test for RAV to all drugs used in the proposed treatment regimen

- How to interpret
  - GT1a: if NS5A RAV present at position 28, 30, 31, or 93 and using EBR/GZR, then add RBV and Tx for 16 weeks
  - GT3: if NS5A RAV present at Y93, then add ribavirin to DCV+SOF or wait for next generation of DAAs

$EC_{50} = 50\%$ effective concentration.

Summary of Trials for GT2

- **SOF+RBV**
  - 12 wk: Naive (No cirrhosis)
  - 16 wk: Experience (No cirrhosis)
  - 16 wk: Experience (Cirrhosis)
  - 24 wk: Experience (No cirrhosis)

- **DAC+SOF**
  - 12 wk: Naive (No cirrhosis)
  - 24 wk: No cirrhosis

**SVR (%)**
- 92%–97%
- 88%–89%
- 78%–87%
- 100%
- 100%
- 92%

# Recommendations for Genotype 2

<table>
<thead>
<tr>
<th></th>
<th>Sofosbuvir + Ribavirin</th>
<th>Daclatasvir + Sofosbuvir*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naïve Noncirrhotic</strong></td>
<td>12 weeks</td>
<td>Use if ribavirin intolerant 12 weeks</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>16 weeks (no data)</td>
<td>Use if ribavirin intolerant 16–24 weeks</td>
</tr>
<tr>
<td><strong>Experienced Noncirrhotic</strong></td>
<td>16 weeks</td>
<td>Use if ribavirin intolerant 12 weeks</td>
</tr>
<tr>
<td><strong>Cirrhotic</strong></td>
<td>16–24 weeks</td>
<td>Use if ribavirin intolerant 16–24 weeks (VA: add RBV)</td>
</tr>
<tr>
<td><strong>Sofosbuvir failures</strong></td>
<td></td>
<td>Use with ribavirin 24 weeks</td>
</tr>
</tbody>
</table>

*Not FDA-approved.

**SVRs:** 87%–100%
Genotype 3: DCV + SOF for 12 Weeks in TN and TE, with and Without Cirrhosis

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Overall</th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>96 (105/109)</td>
<td>97 (73/75)</td>
<td>94 (32/34)</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (20/32)</td>
<td>58 (11/19)</td>
<td>69 (9/13)</td>
</tr>
</tbody>
</table>

# Recommendations for Genotype 3

<table>
<thead>
<tr>
<th>Population</th>
<th>SOF/PEG/RBV</th>
<th>DCV+SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive, no cirrhosis</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Naive, cirrhosis</td>
<td>12 weeks</td>
<td>24 weeks, ± RBV (VA: 12 weeks with RBV)</td>
</tr>
<tr>
<td>Experienced Peg/RBV failure, no cirrhosis</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Experienced Peg/RBV failure, cirrhosis</td>
<td>12 weeks</td>
<td>24 weeks, with RBV</td>
</tr>
<tr>
<td>Experienced, prior SOF failure</td>
<td></td>
<td>24 weeks, with RBV</td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV Guidelines.
## Genotype 4

<table>
<thead>
<tr>
<th></th>
<th>Paritaprevir/ Ritonavir/ Ombitasvir</th>
<th>Ledipasvir/ Sofosbuvir</th>
<th>EBR/GZR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve</td>
<td>12 weeks with RBV</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>with or without cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>12 weeks with RBV</td>
<td>12 weeks for cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>with or without cirrhosis CTP A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, CTP B/C*</td>
<td>Do not use</td>
<td>12 weeks with RBV or 24 weeks without RBV</td>
<td>Do not use</td>
</tr>
</tbody>
</table>

*DAC+SOF +RBV x 12 weeks may by used for CTP B/C; if RBV intolerant DAC+SOF x 24 weeks may be used.*

AASLD/IDSA HCV Guidelines.
Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected patients
- Do not use OPrD in coinfected patients not taking antiretroviral therapy
- Consider drug–drug interactions
  - Need to adjust or withhold ritonavir if receiving a boosted PI with OPrD
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Use cautiously in those with any CKD
  - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org

CKD = chronic kidney disease.
AASLD/IDSA HCV Guidelines.
Guidance for Renal Impairment

- If CrCl >30 mL/min, no dosage adjustment needed with:
  - Elbasvir/grazoprevir
  - LDV/SOF
  - OPrD
  - SMV
  - SOF

- If CrCl <30 mL/min
  - Elbasvir/Grazoprevir

CrCl = creatinine clearance.
AASLD/IDSA HCV Guidelines.
Key Monitoring Guidance

- Before and during treatment
  - HCV RNA before treatment and at Week 4
    - If detectable at Week 4, assess again at Week 6
  - ALT
    - OPrD: before treatment and at Week 4; if elevated at Week 4, assess again at Week 6 and Week 8
    - EBR/GZR: before treatment and at Week 8; if elevated at Week 8, assess again at Week 12 and as needed while treatment continues

- After treatment
  - If pretreatment Metavir ≥ F3, ultrasound for HCC every 6 months

ALT = alanine aminotransferase; HCC = hepatocellular carcinoma.
AASLD/IDSA HCV Guidelines; FDA package labeling.
Emerging Treatment Options and Trends

Pamela S. Belperio, PharmD, BCPS, AAHIVE
National Public Health Clinical Pharmacist
VA Office of Public Health/Population Health
Department of Veterans Affairs
Los Angeles, California
All-Oral DAAs: What’s Coming in 2016 and Beyond?

<table>
<thead>
<tr>
<th>Currently available</th>
<th>Protease Inhibitors</th>
<th>Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simeprevir</td>
<td>SOF</td>
<td>LDV</td>
<td>RBV</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/ritonavir</td>
<td>Dasabuvir</td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td>Expected in 2016</td>
<td>Grazoprevir</td>
<td>SOF</td>
<td>Velpatasvir</td>
<td></td>
</tr>
</tbody>
</table>

*Used with sofosbuvir.

All genotypes, prior PI failures, shorter treatment duration for some
ASTRAL-1: SVR12 with Sofosbuvir/Velpatasvir in GT1, 2, 4, 5, 6 HCV

- Key baseline characteristics: cirrhosis 19%; Tx-experienced 32%; baseline (BL) NS5A RAVs 42%
- No impact of cirrhosis, Tx-experience, BL NS5A RAVs on SVR rates

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>SVR12 (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>99/618/624</td>
<td>98/206/210</td>
</tr>
<tr>
<td>1a</td>
<td>99/117/118</td>
<td>100/104/104</td>
</tr>
<tr>
<td>1b</td>
<td>100/116/116</td>
<td>97/34/35</td>
</tr>
<tr>
<td>2</td>
<td>100/104/104</td>
<td>100/41/41</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASTRAL-3, Sofosbuvir/Velpatasvir in GT3

- SVR rate numerically lower with vs without BL NS5A RAPs (88% vs 97%)

VEL = velpatasvir.
## Combination Regimens for Treatment Failures

General principles: Resistance testing, add ribavirin, use longer duration

<table>
<thead>
<tr>
<th>Failed Regimen</th>
<th>Potential Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A Protease Inhibitors</td>
<td>LDV/SOF (+RBV if cirrhosis)</td>
<td>12 weeks</td>
<td>94%–98%</td>
</tr>
<tr>
<td></td>
<td>DAC+SOF (+RBV if cirrhosis)</td>
<td>12 weeks no cirrhosis; 24 weeks with cirrhosis</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>EBV/GZR ± RBV</td>
<td>12–16 weeks based on RAPs</td>
<td>96%</td>
</tr>
<tr>
<td>SOF+SIM</td>
<td>LDV/SOF +RBV or DAC+SOF+RBV</td>
<td>24 weeks</td>
<td>85%–91%</td>
</tr>
<tr>
<td>NS5A Inhibitor or SOF+SIM</td>
<td>SOF+EBV/GZR+RBV</td>
<td>12 weeks</td>
<td>100% (23/23)</td>
</tr>
<tr>
<td></td>
<td>SOF+OPrD ± RBV</td>
<td>GT1b: 12 weeks; GT1a: 24 weeks</td>
<td>93% (14/15)</td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV Guidelines.
Unanswered Questions

- “Real-world” results
  - Efficacy vs effectiveness
  - Comparative effectiveness
  - Retreatment of those who fail

- Resistance
  - Future implications

- Cost of treatments
  - Market competition
  - Disparities
Pharmacist-Led Education Strategies

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Clinical Pharmacist, Pharmacy Manager
Walgreens at Howard Brown Health Center
Chicago, Illinois
HCV Drug Management Challenges

- High cost of therapy
- Over 3.2 million people chronically infected
- Treatment regimens vary in duration, pill burden, need for ribavirin, baseline resistance testing, and cost.
- Less than optimal medication adherence may lead to treatment failure and drug resistance.
- Medication waste if patient does not start or complete treatment
- Transient patients – lose or gain patients in the middle of treatment due to changing health plan
Collaborative Approach to Treatment

- Prescriber
- Specialty Pharmacy
- Pharmaceutical Manufacturer
- Health Insurer
- Patient
Role of the Clinical Pharmacist in HCV Management

- HCV screening
- HCV medication selection
- Treatment plan and monitoring
- HCV med management (ie, initiate treatment, adjust dose, discontinue under pharmacist scope of practice)
- Management of adverse drug events related to therapy
Role of the Clinical Pharmacist in HCV Management (cont’d)

- Patient adherence assessment
- E-consult services
- Telemedicine services to outlying clinics (ie, Clinical Video Telehealth [CVT])
- Population management to identify patients requiring treatment
Role of the Specialty Pharmacist in HCV Management

- Medication reconciliation
- Verify regimen selection against guidelines
- Advise HCV provider of existing drug-drug interactions
- Advise patient of potential OTC drug-drug interactions
- Patient adherence assessment
- Support for medication acquisition (ie, co-pay assistance, foundation assistance)
- Connect patient with local support (ie, case management, support group)
- HAV/HBV vaccination recommendations
- End of treatment education (SVR, HCC monitoring when applicable, reinfection risk, antibody positivity)

HAV = hepatitis A virus; HBV = hepatitis B virus; OTC = over the counter.
Critical to Success…

- Pretreatment assessment
  - Patient understanding of treatment goals
  - Provision of education on adherence and follow-up
- Well-established therapeutic relationship between practitioner and patient
- Ensure accessibility to treatment for duration
# Sample Pharmacist Clinical Interventions

<table>
<thead>
<tr>
<th>Pharmacist Intervention</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Baseline assessment**  | • Patient demographic and clinical laboratory data collection (eg, HCV genotype/subtype, prior Tx history and outcome, baseline VL, liver fibrosis stage, hemoglobin, CrCl)  
• Comorbidities, allergies, concomitant medications  
• Evaluation of HCV regimen appropriateness (safety, efficacy, drug interactions, contraindications) |
| **Initial and ongoing patient education, treatment monitoring, adherence support** | • Pharmacist counseling (disease, drug regimen, adverse event management, adherence)  
• Educational brochures |
| **Referral to patient assistance programs** | • Manufacturer financial assistance programs or supportive organizations (eg, substance abuse counseling) |
| **Adherence and distribution outreach** | • Arrange timely refills based on Tx start date  
• Assess Tx tolerance, administration technique |
| **On-treatment monitoring** | • Obtain VL at Week 4 (and as required, if applicable) for response and adherence  
• Gather SVR12 data |
Factors Affecting Adherence

- **Patient characteristics**
  - Lack of understanding of the disease, complications, low motivation, forgetfulness

- **Antiviral treatment**
  - Regimen complexity, treatment duration, prior treatment failure, side effects

- **Social and economic conditions**
  - Unstable living conditions, lack of familial support, cultural beliefs, medication cost, substance abuse

- **Health care system**
  - Poor patient-provider relationship, medication distribution systems, adherence support
### Drug-Specific Treatment Considerations

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>EBR/GZR</th>
<th>DAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pill burden</strong></td>
<td>1 pill</td>
<td>4 pills</td>
<td>1 pill</td>
<td>1 pill*</td>
</tr>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>qd</td>
<td>bid (with food)</td>
<td>qd</td>
<td>qd</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>8–12 wks</td>
<td>12–24 wks</td>
<td>12–16 wks</td>
<td>12–24 wks</td>
</tr>
<tr>
<td><strong>Drug interaction</strong></td>
<td>Low (PPIs/H2RA)</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate†</td>
</tr>
<tr>
<td><strong>Special monitoring</strong></td>
<td>None</td>
<td>LFTs including bilirubin</td>
<td>LFTs</td>
<td>None</td>
</tr>
<tr>
<td><strong>Use in decompensated cirrhosis</strong></td>
<td>OK</td>
<td>Do not use in CPT B or C</td>
<td>Do not use in CPT B or C</td>
<td>OK</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Fatigue, headache, nausea</td>
<td>Nausea, pruritus, insomnia</td>
<td>Fatigue, headache, nausea</td>
<td>Headache, fatigue, nausea, diarrhea</td>
</tr>
</tbody>
</table>

*Must be used with sofosbuvir; †Dose adjustments of DAC required with strong CYP3A inducers and inhibitors.

H2RA = H2-receptor antagonist; LFT = liver function test; PPI = proton pump inhibitor.
All Oral: Pill Burden

LDV/SOF:
1 tablet once a day

WITH or WITHOUT

OPrD:
2 tablets AM and 1 tablet twice daily

EBR/GZR:
1 tablet once a day

RBV:
Up to 3 tablets twice daily

DAC + SOF:
2 tablets once a day

FDA package labeling.
Ledipasvir/Sofosbuvir

- Ledipasvir 90 mg/sofosbuvir 400 mg
  - One pill once a day for most patients
  - Some patients will require ribavirin
  - 8-week regimen can be considered for naïve, noncirrhotic, low viral load patients
- Special administration with PPIs and H2RAs

FDA package labeling.
Ombitasvir, Paritaprevir/Ritonavir + Dasabuvir

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Ombitasvir (OBV)</th>
<th>Paritaprevir/r (PTV/r)*</th>
<th>Dasabuvir (DSV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5A inhibitor</td>
<td></td>
<td>NS3/4A protease inhibitor (ritonavir: prolongs half-life)</td>
<td>Non-nucleos(t)ide NS5B-palm polymerase inhibitor</td>
</tr>
<tr>
<td>Dosing</td>
<td>25 mg qd</td>
<td>150 mg qd</td>
<td>250 mg bid</td>
</tr>
</tbody>
</table>

* r = ritonavir, a CYP3A inhibitor; † Each OBV/PTV/r tablet contains 12.5/75/50 mg of each component, respectively.

- LFT monitoring required (cirrhosis)
- High drug-interaction potential

To maximize absorption, should be taken with a meal without regard to fat or calorie content.
Daclatasvir

- Daclatasvir 60 mg
  - NS5A inhibitor
  - GT1 and GT3
  - MUST be used with sofosbuvir
  - Two pills (daclatasvir + sofosbuvir) once a day for 12 weeks (for most patients)
  - NS5A baseline resistance testing for GT1a with cirrhosis
  - ? 16 weeks + ribavirin for those with baseline NS5A RAVs
  - Dose adjust daclatasvir with CYP3A inhibitors and inducers

<table>
<thead>
<tr>
<th>Strong CYP3A inhibitors</th>
<th>30 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate CYP3A inducers</td>
<td>90 mg daily (3 x 30 mg or 30 mg +60 mg)</td>
</tr>
<tr>
<td>Strong CYP3A inducers</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Once a day for 12 weeks

FDA package labeling.
Elbasvir/Grazoprevir

- **Elbasvir 50 mg/grazoprevir 100 mg**
  - NS5A inhibitor/NS3 protease inhibitor
  - One pill once a day (for most patients)
  - 12 weeks for most patients
  - 16 weeks + ribavirin for some GT1a and GT4 patients
  - Moderate drug interaction potential

FDA package labeling.
Elbasvir/Grazoprevir

**Benefits**
- Can be used in renal failure and dialysis
- Same regimen/duration with and without cirrhosis

**Issues**
- GT1a: test for RAV before prescribing
  - Positions 28, 30, 31, and 93
  - Ribavirin needed in ~6%–12% of patients with GT1a
- Do not use in CPT B or C (decompensated; CTP ≥7)
- Monitor LFTs at Week 8 (and Week 12 for 16-week regimen)
  - Elevated ALT in ~1% (2% Asian or >65 years of age or CTP A)
  - Stop if ALT >10x, symptoms, increase in bilirubin or INR

INR = international normalized ratio.
FDA package labeling.
Drug Interaction Assessment

- **http://www.hep-druginteractions.org/**
- Drug-drug interactions must be considered when selecting a treatment regimen.
- Providers should consult a knowledgeable clinical pharmacist for specific questions regarding drug-drug interactions.
Common Side Effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>DAC+SOF</th>
<th>EBR/GZR</th>
<th>LDV/SOF</th>
<th>OPrD</th>
<th>SOF+SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Fatigue</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Nausea</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>ALT ↑</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Lipase ↑</td>
<td></td>
<td>Lipase ↑</td>
<td></td>
<td>Skin reactions; pruritus; Bili ↑; pruritus; photosensitivity</td>
</tr>
</tbody>
</table>

Bili = bilirubin.
Summary

- Rapidly evolving treatment landscape
  - IFN-free cure rates >90%
  - More tailored approach in the near future
- Rising demand for treatment anticipated
  - Increased screening
  - Accessibility of oral regimens
- Pharmacist interventions play a key role in promoting the use of cost-effective regimens and improving treatment outcomes.
INTERACTIVE CPE SYMPOSIUM

INDIVIDUALIZING TREATMENT REGIMENS FOR HEPATITIS C:
A 2016 Update for Specialty Pharmacists

Monday, May 2, 2016  
1:00 – 2:30 PM  •  Interactive CPE Activity

Encore at Wynn Las Vegas  
Encore Ballroom 1-3

This symposium will provide live credit (L) for those states requiring it.

Supported by an educational grant from Merck & Co Inc.