Hepatitis C Virus Infection: Optimizing Diagnosis, Treatment, and Management

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Learning Objectives

- Identify evidence-based pathways to screen and test appropriate patients for HCV
- Summarize strategies for improving the quality of patient-provider communication and collaboration surrounding HCV diagnosis, treatment, and management
- Incorporate recommendations for managing HCV treatment and its associated side effects and drug-drug interactions into clinical practice
- Distinguish new and emerging HCV agents and treatment strategies that are likely to be incorporated into future standards of care
Disclosure Slide

▪ Dr. Bacon:
  - Grants/Research Support: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Kadmon, Merck
  - Consultant: Merck
  - Speakers’ Bureau: Gilead, Kadmon, Merck, Salix, Janssen, AbbVie

▪ Planners and managers for this activity have no relevant relationships to disclose
Commercial Support Statement

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Approximately 3.2 Million People in the United States Have Chronic Hepatitis C Virus (HCV) Infection

- ~3.2 million people are chronically infected with HCV, based on the NHANES (1999–2002) population survey\(^1,2\)
  - ~70% born between 1945 and 1964 (“Baby Boom” population)\(^1\)
- The number of persons chronically infected with HCV in the United States may be even higher\(^3\)
  - Populations not sampled in NHANES:
    - Incarcerated
    - Homeless
    - Nursing home residents
    - Hospitalized patients
    - Active military duty

NHANES = National Health and Nutrition Examination.

Distribution of HCV Genotypes in the United States

- Genotypes 1a and 1b account for 79%
- Genotype 2 accounts for 15%

Natural History of HCV Infection

- Acute Infection: 20%−30% of patients are symptomatic. HCC = hepatocellular carcinoma.
- Chronic Infection 75%−85%: Clearance of HCV RNA 15%−25%, Extrahepatic Manifestations
- Cirrhosis 10%−20% over 20 years: HCC 1%−4% per year, Decompensated Cirrhosis 5-yr survival rate, 50%

Current Estimates Show a Significant Gap in HCV Care

~3.2 million people in the United States have chronic HCV infection\(^1,2,\ast\)\(^a\)

~1.6 million (50%) diagnosed\(^3,4\)

170,000 – 200,000 (5%–6%) successfully treated\(^4\)

\(*\)Prevalence estimate based on NHANES data from 1999 through 2002.\(^1,2\) NHANES data underestimate the actual prevalence of HCV in the United States, as they do not account for incarcerated, homeless, hospitalized, nursing home, and active military duty populations.\(^6,7\)

1998 CDC Risk-Based HCV Screening Recommendations

Screening is recommended in persons who:

- Have ever injected illegal drugs
- Received clotting factors produced before 1987
- Received blood/organs before July 1992
- Have ever been on long-term hemodialysis
- Have evidence of liver disease (elevated ALT)
- Were born to an HCV-infected mother
- Have HIV infection
- Received a needle-stick injury or had mucosal exposure to HCV-positive blood (healthcare, emergency medical, and public safety workers)

ALT = alanine aminotransferase; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus.

2012 CDC Recommendations for Birth Cohort (1945–1965) Screening

- **Recommendation 1**
  - Adults born between 1945 and 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk
    
    *Grade: strong recommendation*  
    *Evidence: moderate-quality*

- **Recommendation 2**
  - All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated
    
    *Grade: strong recommendation*  
    *Evidence: moderate-quality*

In June 2013, the USPSTF issued its Grade B recommendations regarding who should have HCV screening:

- Those at high risk for HCV infection
- Those born from 1945 to 1965 (one-time screening of “Baby Boomers,” regardless of risk)

For this update, the USPSTF reviewed the indirect chain of evidence showing benefits of screening through:

- Improvements in SVR with current treatments
- Reductions in all-cause and liver-related mortality, and HCC associated with SVR

The USPSTF gave this recommendation a B Grade:

- Grade B means that a high certainty exists that the net benefit is moderate or that moderate certainty exists that the net benefit is moderate to substantial

The Affordable Care Act:

- Requires non-grandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing
- Provides incentives for Medicaid programs to cover these services

HCC = hepatocellular carcinoma; SVR = sustained virologic response; USPSTF = United States Preventive Services Task Force.

## 2014 AASLD/IDSA Guidelines

- HCV testing is recommended at least once for persons born between 1945 and 1965
- Other persons should be screened for risk factors for HCV infection, and testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection

### Risk behaviors
- Injection drug use (even if only injected once)
- Intranasal illicit drug use

### Risk exposures
- Long-term hemodialysis (ever)
- Tattoo from unregulated setting
- Healthcare/emergency/public safety workers after needle sticks, sharps, or mucosal exposure to HCV-infected blood

### Other medical conditions
- Children born to an HCV-infected mother
- Prior recipients of transfusions or organ transplants
- HIV infection
- Unexplained chronic liver disease, chronic hepatitis, including elevated ALT levels

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; IDSA = Infectious Diseases Society of America.

Birth Cohort vs Risk-Based HCV Screening

<table>
<thead>
<tr>
<th>Outcome Estimate, n</th>
<th>Birth Cohort Screening</th>
<th>Risk-Based Screening</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total screened</td>
<td>78,700,000</td>
<td>8,000,000</td>
<td>+70,700,000</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>1,312,391</td>
<td>427,030</td>
<td>+885,361</td>
</tr>
<tr>
<td>Treated</td>
<td>742,329</td>
<td>234,689</td>
<td>+507,640</td>
</tr>
<tr>
<td>SVR</td>
<td>404,274</td>
<td>124,650</td>
<td>+279,624</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>234,800</td>
<td>290,200</td>
<td>-55,400</td>
</tr>
<tr>
<td>HCC</td>
<td>135,400</td>
<td>165,500</td>
<td>-30,100</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>28,300</td>
<td>34,500</td>
<td>-6200</td>
</tr>
<tr>
<td>HCV death</td>
<td>229,900</td>
<td>280,200</td>
<td>-50,300</td>
</tr>
</tbody>
</table>

- Limitations of analysis: model is a simplified view of disease and treatment; validity is dependent on model assumptions; data are combined from various sources; incident infection and transmission are not included in model; new HCV treatments are not considered

HCC = hepatocellular carcinoma; SVR = sustained virologic response.

Counseling Recommendations for HCV-Infected Individuals

To Prevent HCV Transmission
- Avoid sharing toothbrushes and dental or shaving equipment
- Prevent blood contact with others
- Stop using illicit drugs; those who continue to inject drugs should take precautions to avoid viral transmission
- Risk of sexual transmission is low, but practice "safe sex"

Additional Recommendations
- Avoid alcohol consumption
  - Excess alcohol consumption may lead to progressive liver disease, increased HCV RNA replication, and reduced response to treatment
- Consider treatment for hepatitis C\(^a\)
- Vaccinate for hepatitis A and B
- Get tested for HIV
- Encourage family members to get screened

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\(^a\)If patient meets generally accepted indications for HCV treatment.
SVR Is Equivalent to Viral Cure

In nearly 100% of patients who achieve SVR, HCV remains undetectable during long-term follow-up\textsuperscript{1-4}

\[\begin{align*}
\text{Patients with SVR(%)} & \\
\text{Duration of follow-up} & \\
3.9 \text{ years (mean)} & 99^1 \\
3.5 \text{ years (median)} & 99^2 \\
3.3 \text{ years (median)} & 100^3 \\
5 \text{ years (median)} & 100^4
\end{align*}\]

SVR = sustained virologic response.

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

*International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n = 530).*

SVR = sustained virologic response.

The Evolution of HCV Therapy

DAA = direct-acting antiviral; IFN = interferon; PEG-IFN = pegylated interferon; PI = protease inhibitor; RVB = ribavirin.

Boceprevir and Telaprevir: No Longer Being Used as Standard Therapy

- Use of these initial DAAs as part of triple therapy with PEG-INF and ribavirin led to improvements in sustained SVR rates
- Multiple issues with these agents negatively impacted treatment
  - Adverse events/side effects
  - High pill burden
  - Drug–drug interactions

*These drugs are generally no longer in standard use in clinical practice in the United States*

- These first-generation DAAs have been rapidly eclipsed by newer antiviral agents
- Boceprevir/telaprevir remain important as “proof of concept” that DAAs in HCV are viable and effective

DAA = direct-acting antiviral agent; PEG-INF = pegylated interferon; SVR = sustained virologic response.

Goals for Hepatitis C Therapy

- As compared with traditional PEG-INF/RBV, new antiviral agents offer:
  - Improved efficacy
  - Efficacy in all patient types, including previously treated patients, those with cirrhosis, and African-Americans
  - Orally effective regimen, IFN-free
  - Shorter treatment duration
  - Improved side effect profile

IFN = interferon; PEG-INF = pegylated interferon; RBV = ribavirin.

Slide courtesy of Bruce Bacon, MD
HCV Genome and Potential Drug Targets

Characteristics Needed for DAA Performance

- Potency
- Genotype Coverage
- Resistance Barrier
- Safety/Tolerability
- Treatment Duration
- Half-life and Pills burden
- Drug–Drug Interaction
- Cost

DAA = direct-acting antiviral agent.
## Protease Inhibitors

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Company</th>
<th>Current Clinical Phase</th>
<th>Chemical Structure</th>
<th>Genetic Barriers</th>
<th>Dose Per Day</th>
<th>In Vitro Potency (IC₅₀ nM)</th>
<th>Drug–Drug Interactions</th>
<th>Duration of Therapy</th>
<th>Viral Response</th>
<th>Side Effects</th>
<th>Active Against HCV Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (VICTRELIS&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Merck</td>
<td>FDA/EMEA approved</td>
<td>Linear</td>
<td>Low</td>
<td>800 mg three times daily</td>
<td>600</td>
<td>Moderate</td>
<td>PI 24 wk + PR 24–48 wk (stopping rules, advanced fibrosis)</td>
<td>Naive G1: 63%–66%</td>
<td>Relapers: 75%</td>
<td>Partial Rs: 52%</td>
</tr>
<tr>
<td>Telaprevir INCIVO&lt;sup&gt;®&lt;/sup&gt; INCIVEK&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Janssen</td>
<td>FDA/EMA Approved</td>
<td>Linear</td>
<td>Low</td>
<td>1125 mg twice daily</td>
<td>300</td>
<td>High</td>
<td>PI 12 wk + PR 24–48 wk (Stopping rules, advanced fibrosis)</td>
<td>Naive G1: 72%–75%</td>
<td>Relapers: 83%–88%</td>
<td>Partial R: 54%–59%</td>
</tr>
</tbody>
</table>

**IC<sub>50</sub>** = half maximal inhibitory concentration; **G1** = Genotype 1; **PI** = protease inhibitor; **PR** = peginterferon and ribavirin; **R** = responder; **QUEST-1** = simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; **QUEST-2** = simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; **RGT** = response-guided therapy; **SVR** = sustained virologic response; **DAA** = direct-acting antiviral agent.

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<tr>
<th>Protease Inhibitor</th>
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<th>Duration of Therapy</th>
<th>Viral Response</th>
<th>Side Effects</th>
<th>Active Against HCV Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danoprevir (ITMN-191, Roche 2</td>
<td>Macroyclic</td>
<td>Moderate</td>
<td>DAUPHINE: 200/r mg twice daily 100/r mg twice daily 50/r mg twice daily 100/r mg twice daily</td>
<td>1–10</td>
<td>Low</td>
<td>PI/r + PR 24 wk PIR + PR 24 wk</td>
<td>Naive G1: SVR24: 89% 79% G4: SVR12: 100% Partial R: SVR12: 56% G1b 91%, G1a 30% Nausea, diarrhea, Neutropenia ALT increase</td>
<td>1, 2, 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-5172 Merck 2</td>
<td>Macroyclic</td>
<td>High</td>
<td>100 mg daily</td>
<td>1–10</td>
<td>Low</td>
<td>MK-5172 100 mg + MK-5742 50 mg 12 wk</td>
<td>Naive G1: SVR12: 96% ~100% Not reported</td>
<td>1, 2, 4, 5, 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT-450 AbbVie 2</td>
<td>Macroyclic</td>
<td>Moderate</td>
<td>150/r mg daily</td>
<td>1–10</td>
<td>Low</td>
<td>PI + PR 12 wk + 12–36 wk PR ABT-450/RTV 150/100 mg QD; ABT-267 25 mg QD 12 wk</td>
<td>Naive G1: SVR12: 88% G1b, SVR12: 90% ~95% AE profile similar to PR</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sovaprevir (ACH-1625) Achillion 2</td>
<td>Macroyclic</td>
<td>Moderate</td>
<td>200–800 mg daily</td>
<td>1–10</td>
<td>Low</td>
<td>PI + PR 28 d + PR 44 wk PI + PR 12 wk + 36 PR wk</td>
<td>Naive G1: SVR: 63% ~86% G1b, EOT: 69% ~100% AE profile similar to PR</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asunaprevir (BMS-650032) Bristol-Myers Squibb 2</td>
<td>Macroyclic</td>
<td>Moderate</td>
<td>200–600 mg twice daily 600 mg + daclatasvir 60 mg QD ± PR 24 wk</td>
<td>1–10</td>
<td>Low</td>
<td>PI+ PR 48 wk PI + NSSA inhibitor 24 wk PI + NSSA inhibitor + PR 24 wk</td>
<td>Naive G1: SVR: 83%~92% Null-R G1: SVR: 36% SVR: 100% AE profile similar to PR</td>
<td>1, 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase; IC50 = half maximal inhibitory concentration; DAUPHINE = a randomized phase 2 study of danoprevir/ritonavir plus peginterferon alpha-2a/ribavirin in HCV genotypes 1 or 4; G1 = Genotype 1; PI = protease inhibitor; PR = peginterferon and ribavirin; R = responder; RGT = response-guided therapy; SVR = sustained virologic response.

New Protease Inhibitor: Simeprevir

PR = peginterferon and ribavirin; PROMISE = progesterone in recurrent miscarriages study; QUEST-1 = simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; QUEST-2 = simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; SMV = simeprevir.

Simeprevir in Treatment-Naïve Patients: QUEST-1 and QUEST-2 Results


**QUEST-1**

- **SMV 150mg qd + PR**
  - 210/264 (80%)
- **Placebo + PR**
  - 66/130 (50%)

**QUEST-2**

- **SMV 150mg qd + PR**
  - 209/257 (81.3%)
- **Placebo + PR**
  - 67/134 (50%)

**SVR12 %**

- **P<0.001**

**G1a** = Genotype 1a; **G1b** = Genotype 1b; **PR** = peginterferon and ribavirin; **QUEST-1** = simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; **QUEST-2** = simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; **SMV** = simeprevir.

Simeprevir in Genotype 1 Relapsed Patients: PROMISE Trial Results

G1 = Genotype 1; G1a = Genotype 1a; G1b = Genotype 1b; PROMISE = progesterone in recurrent miscarriages study.

Simeprevir in Genotype 1 Relapsed Patients: Phase 3 Safety Data

<table>
<thead>
<tr>
<th></th>
<th>QUEST-1 Placebo + PR, % (N = 130)</th>
<th>QUEST-1 SMV + PR, % (N = 264)</th>
<th>QUEST-2 Placebo + PR, % (N = 134)</th>
<th>QUEST-2 SMV + PR, % (N = 257)</th>
<th>PROMISE Placebo + PR, % (N = 130)</th>
<th>PROMISE SMV + PR, % (N = 264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AEs</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Discontinuation because of AEs</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>40</td>
<td>39</td>
<td>35</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>21</td>
<td>15</td>
<td>19</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Rash (any type)</td>
<td>25</td>
<td>27</td>
<td>11</td>
<td>24</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>16</td>
<td>14</td>
<td>16</td>
<td>20</td>
<td>17</td>
</tr>
</tbody>
</table>

AE = adverse event; PROMISE = progesterone in recurrent miscarriages study; QUEST-1 = simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection; QUEST-2 = simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection.

Simeprevir Recommended Therapy

- 150 mg once daily, with food
- Should be administered with both PEG-INF and ribavirin
- Recommended treatment duration is 12 weeks, followed by either 12 or 36 additional weeks of PEG-INF and ribavirin, depending on prior response status.

PEG-IFN = pegylated interferon.
New NS5B Nucleotide Inhibitor Sofosbuvir: NEUTRINO Trial

NEUTRINO = a phase 3, multicenter, open-label study to investigate the efficacy and safety of GS-7977 with peginterferon alfa 2a and ribavirin for 12 weeks in treatment-naïve subjects with chronic genotype 1, 4, 5, or 6 HCV infection; PR = peginterferon and ribavirin.

Sofosbuvir in Treatment-Naïve Patients: NEUTRINO Trial Results

# Sofosbuvir in Treatment-Naïve Patients: NEUTRINO Safety Data

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>NEUTRINO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF + PEG-IFN + RBV</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>(N = 327)</td>
</tr>
<tr>
<td>Any AE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>310 (95%)</td>
</tr>
<tr>
<td>Grade 3 AE</td>
<td>48 (15%)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>There were no Grade 4 AEs reported in this study.

AE = adverse event; PEG-IFN = pegylated interferon; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir.

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Other Sofosbuvir Trials – Patient Populations: FISSION, POSITRON, FUSION

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Intent-To-Treat</strong> SVR, n/N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>FISSION (Treatment-naïve)</td>
<td>SOF + RBV 12 weeks</td>
<td>171/256 (67%) 61%–73%</td>
</tr>
<tr>
<td></td>
<td>PEG-IFN + RBV 24 weeks</td>
<td>162/243 (67%) 60%–73%</td>
</tr>
<tr>
<td>POSITRON (Intolerant, ineligible, or unwilling to take interferon)</td>
<td>SOF + RBV 12 weeks</td>
<td>161/207 (67%) 71%–83%</td>
</tr>
<tr>
<td>FUSION (Treatment-experienced)</td>
<td>SOF + RBV 12 weeks</td>
<td>51/103 (67%) 40%–60%</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV 16 weeks</td>
<td>70/98 (71%) 61%–80%</td>
</tr>
</tbody>
</table>

FISSION = phase 3 study of sofosbuvir and ribavirin; FUSION = sofosbuvir + ribavirin for 12 or 16 weeks in treatment experienced subjects with chronic Genotype 2 or 3 HCV infection; PEG-IFN = pegylated interferon; RBV = ribavirin; POSITRON = sofosbuvir + ribavirin for 12 weeks in subjects with chronic Genotype 2 or 3 hepatitis C infection who are interferon intolerant, interferon ineligible or unwilling to take interferon; RBV = ribavirin; SOF = sofosbuvir.
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>SVR12 %</th>
<th>Primary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISSION (Treatment-naïve)</td>
<td>SOF + RBV 12 weeks</td>
<td>253</td>
<td>67%</td>
<td>Noninferiority demonstrated (SOF + RBV vs PEG-IFN + RBV; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td></td>
<td>PEG-IFN + RBV 24 weeks</td>
<td>243</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>POSITRON (Intolerant, ineligible, or unwilling to take interferon)</td>
<td>SOF + RBV 12 weeks</td>
<td>207</td>
<td>78%</td>
<td>Superiority demonstrated (SOF + RBV vs placebo; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td></td>
<td>Placebo 12 weeks</td>
<td>71</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>FUSION (Treatment-experienced)</td>
<td>SOF + RBV 12 weeks</td>
<td></td>
<td></td>
<td>Superiority demonstrated against 25% historical rate (SOF + RBV 12 weeks and 16 weeks; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV 16 weeks</td>
<td></td>
<td></td>
<td></td>
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FISSION = phase 3 study of sofosbuvir and ribavirin; FUSION = sofosbuvir + ribavirin for 12 or 16 weeks in treatment experienced subjects with chronic Genotype 2 or 3 HCV infection; PEG-IFN = pegylated interferon; RBV = ribavirin; POSITRON = sofosbuvir + ribavirin for 12 weeks in subjects with chronic Genotype 2 or 3 hepatitis C infection who are interferon intolerant, interferon ineligible or unwilling to take interferon; RBV = ribavirin; SOF = sofosbuvir.
Other Sofosbuvir Trials – Safety Data: FISSION, POSITRON, FUSION

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>FISSION</th>
<th>POSITRON</th>
<th>FUSION</th>
<th>FISSION, FUSION, POSITRON</th>
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<td></td>
<td>SOF + RBV 12 weeks</td>
<td>PEG-IFN + RBV 24 weeks</td>
<td>SOF + RBV 12 weeks</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n (%) (N = 253)</td>
<td>n (%) (N = 243)</td>
<td>n (%) (N = 207)</td>
<td>n (%) (N = 71)</td>
</tr>
<tr>
<td>Any AE</td>
<td>220 (86%)</td>
<td>233 (96%)</td>
<td>185 (89%)</td>
<td>55 (77%)</td>
</tr>
<tr>
<td>Grade 3 or higher AE</td>
<td>18 (7%)</td>
<td>45 (19%)</td>
<td>17 (8%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>7 (3%)</td>
<td>3 (1%)</td>
<td>11 (5%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>3 (1%)</td>
<td>26 (11%)</td>
<td>4 (2%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event; FISSION = phase 3 study of sofosbuvir and ribavirin; FUSION = sofosbuvir + ribavirin for 12 or 16 weeks in treatment experienced subjects with chronic Genotype 2 or 3 HCV infection; PEG-IFN = pegylated interferon; POSITRON = sofosbuvir + ribavirin for 12 weeks in subjects with chronic Genotype 2 or 3 hepatitis C infection who are interferon intolerant, interferon ineligible or unwilling to take interferon; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir
### Sofosbuvir Recommended Therapy

- 400 mg once daily, with or without food

<table>
<thead>
<tr>
<th>HCV Mono-infected and HCV/HIV-1 Co-infected</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 or 4</td>
<td>SOF + PEG-IFN alfa + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>SOF + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>SOF + RBV</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; PEG-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir.

A New Treatment Paradigm? Simeprevir and Sofosbuvir in Combination – The COSMOS Trial

- Phase 2 results from Cohort 1 (prior null responders only) demonstrated SVR8 rates of 96% and 93% after 12 weeks of treatment with 150 mg simeprevir and 400 mg sofosbuvir with and without ribavirin, respectively.

- Efficacy results combining Cohorts 1 and 2 (prior null responders and treatment-naïve patients):

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior null responder HCV patients (METAVIR score F0-F2)</td>
<td>Prior null responder and treatment naïve HCV patients (METAVIR score F3 or F4)</td>
</tr>
<tr>
<td>SMV/SOF + RBV (n = 27)</td>
<td>SMV/SOF (n = 14)</td>
</tr>
<tr>
<td>SVR12</td>
<td>26/27 (96%)</td>
</tr>
<tr>
<td>SVR12</td>
<td>26/27 (96%)</td>
</tr>
</tbody>
</table>

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

The COSMOS Trial

Features

- **Design**: Randomized, phase 2a, open-label, using sofosbuvir + simeprevir +/- ribavirin in treatment naïve or experienced, chronic HCV Genotype 1
- **Setting**: United States and Europe
- **Entry Criteria**
  - Chronic HCV Genotype 1
  - Cohort 1: prior null responders; METAVIR F0-F2
  - Cohort 2: treatment naïve and prior null responders; METAVIR F3-F4
- **Patient Characteristics** (range in different treatment arms)
  - N = 167 (n = 80 in Cohort 1 and n = 87 in Cohort 2)
  - Baseline Genotype 1a with Q80K: Cohort 1 = 50%; Cohort 2 = 40%
  - Non-CC IL28b Genotype: Cohort 1 = 94%; Cohort 2 = 79%
- **Endpoints**: primary = SVR12; secondary = safety

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; SVR = sustained virologic response.

Drug Dosing

SOF: 400 mg once daily
SMV: 150 mg once daily
RBV (weight-based and divided twice daily): 1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

COSMOS Study Results: Cohort 1

SVR12 by Regimen

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

Drug Dosing
SOF: 400 mg once daily
SMV: 150 mg once daily
RBV (weight-based and divided bid): 1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg²

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

COSMOS Study Results: Cohort 2 With F3-F4 Fibrosis

SVR 12 by Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>24-Week Treatment</th>
<th>12-Week Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + SMV + RBV</td>
<td>28/30</td>
<td>25/27</td>
</tr>
<tr>
<td>SOF + SMV</td>
<td>16/16</td>
<td>13/14</td>
</tr>
</tbody>
</table>

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

COSMOS Study Results: Cohort 2

COSMOS = Sofosbuvir + simeprevir +/- ribavirin in Genotype 1; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

Where Do We Go From Here? Investigational Agents in Phase 3 Trials

<table>
<thead>
<tr>
<th>Regimen With 1 DAA + PEG-IFN alfa/RBV</th>
<th>Regimen With 2 DAA + PEG-IFN alfa/RBV</th>
<th>IFN-Free Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir (NS5A)</td>
<td>Daclatasvir and asunaprevir</td>
<td>Sofosbuvir + RBV</td>
</tr>
<tr>
<td>Sofosbuvir (NI)</td>
<td></td>
<td>Sofosbuvir + GS-5885 (FDC) ± RBV</td>
</tr>
<tr>
<td>Simeprevir (PI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danoprevir (PI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alisporivir (CYP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK 5172 (PI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; DAA = direct-acting antiviral; IFN = interferon; NS5B inhibitor; NI = nucleotide inhibitor; PI = protease inhibitor; RBV = ribavirin.

Where Do We Go From Here?
Investigational Combination Agents

- Interferon-free combinations
  - Sofosbuvir/ledispavir (treatment-naïve and -experienced populations)
  - Sofosbuvir/daclatasvir with/without RBV
  - ABT-450/r, ombitasavir (ABT-267), dasabuvir (ABT-333) and RBV
  - Daclatasvir/asunaprevir combinations
  - MK-5172 and MK-8742 with/without RBV
  - Danoprevir/mericitabine with/without RBV

- “Interferon-free” regimens have the potential to change the “face” of therapy
  - Development of faldaprevir halted in June 2014, as drug was being developed to be used with interferon-based triple therapy

## Interferon-Free Combinations on the Horizon: Sofosbuvir/Ledipasvir in Untreated HCV Type 1


<table>
<thead>
<tr>
<th>Response</th>
<th>12-Wk Regimen</th>
<th>24-Wk Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV–SOF (N=214)</td>
<td>LDV–SOF + RBV (N=217)</td>
</tr>
<tr>
<td>HCV RNA &lt;25 IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment — no./total no. (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 2</td>
<td>174/213 (82)</td>
<td>181/217 (83)</td>
</tr>
<tr>
<td>At week 4</td>
<td>213/213 (100)</td>
<td>215/217 (99)</td>
</tr>
<tr>
<td>At week 12</td>
<td>213/213 (100)</td>
<td>214/214 (100)</td>
</tr>
<tr>
<td>After end of treatment — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 4</td>
<td>211 (99)</td>
<td>213 (98)</td>
</tr>
<tr>
<td>At week 12</td>
<td>211 (99)</td>
<td>211 (98)</td>
</tr>
<tr>
<td>Virologic failure during treatment — no.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse — no.</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up — no.</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Withdrew consent — no.</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

LDV = ledipasvir; SOF = sofosbuvir; RBV = ribavirin

Interferon-Free Combinations on the Horizon: Other DAA Combinations

- FDA has granted priority review to a 3-DAA combination for treatment of chronic Genotype 1 HCV
- Combination consists of protease inhibitor ABT-450 with ritonavir (150/100 mg) co-formulated with NS5A inhibitor ombitasvir (ABT-267) 25 mg, dosed once daily, and polymerase inhibitor dasabuvir (ABT-333) 250 mg, dosed twice daily
- Combination regimen is backed by six phase 3 studies
  - Studied in >2300 patients with HCV
  - Studied in >25 countries

DAA = direct-acting antiviral.

The Future: Interferon-Free Trials
(Genotype 1, Treatment Naïve Patients)

### Interferon-Free Trials for Treatment-Experienced Patients


<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Patients</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1b NR</strong>&lt;br&gt;ABT450/r ABT267</td>
<td>90/90</td>
<td>36/40</td>
<td>G1b NR&lt;br&gt;ABT450/r ABT267</td>
</tr>
<tr>
<td><strong>G1</strong></td>
<td>100/100</td>
<td>25/25</td>
<td>G1&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F3/F4</td>
</tr>
<tr>
<td><strong>G1</strong>&lt;br&gt;SOF&lt;br&gt;GS-5669</td>
<td>70/70</td>
<td>26/26</td>
<td>G1&lt;br&gt;SOF&lt;br&gt;GS-5669&lt;br&gt;12W&lt;br&gt;F3/F4</td>
</tr>
<tr>
<td><strong>G1 IP</strong>&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F4</td>
<td>95/95</td>
<td>18/19</td>
<td>G1 IP&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F0-F2</td>
</tr>
<tr>
<td><strong>G1 IP</strong>&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F0-F2</td>
<td>100/100</td>
<td>21/21</td>
<td>G1 IP&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F0-F2</td>
</tr>
<tr>
<td><strong>G1</strong>&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
<td>92.9/92.9</td>
<td>13/14</td>
<td>G1&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
</tr>
<tr>
<td><strong>G1</strong>&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
<td>93.3/93.3</td>
<td>14/15</td>
<td>G1&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
</tr>
<tr>
<td><strong>G1 IP</strong>&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F0-F2</td>
<td>96.3/96.3</td>
<td>26/27</td>
<td>G1 IP&lt;br&gt;SOF&lt;br&gt;LDV&lt;br&gt;RBV&lt;br&gt;12W&lt;br&gt;F0-F2</td>
</tr>
<tr>
<td><strong>G1</strong>&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
<td>79.3/79.3</td>
<td>19/24</td>
<td>G1&lt;br&gt;SMV&lt;br&gt;SOF&lt;br&gt;24W&lt;br&gt;F0-F2</td>
</tr>
</tbody>
</table>

**Legend:**
- **Red:** Pearl-1, ABT450/r + ABT 267; Lawitz et al. AASLD 2013, A75.
- **Orange:** Electron: sofosbuvir (SOF)/ledipasvir (LDV) + RBV; Gane et al. AASLD 2013, A73.
- **Dark Grey:** Lonestar: sofosbuvir (SOF)/ledipasvir (LDV) + RBV; Lawitz et al. AASLD 2013, A215/1844.
- **Green:** Cosmos: sofosbuvir (SOF)/simeprevir (SMV) + RBV; Jacobson et al. AASLD 2013, ALB3.

## 2014 AASLD/IDSA Guidelines for Therapy: Initial Therapy or Relapse After Prior PEG-IFN/RBV Therapy

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IFN eligible: SOF + PEG-IFN/RBV x 12 weeks</td>
<td>IFN eligible: SMV x 12 weeks + PEG-IFN/RBV x 24 weeks</td>
<td>TVR + PEG-IFN/RBV x 24 or 48 weeks (RGT)</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: SOF + SMV ± RBV x 12 weeks</td>
<td>IFN ineligible: SOF + RBV x 24 weeks</td>
<td>BOC + PEG-IFN/RBV x 28 or 48 weeks (RGT)</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV x 12 weeks</td>
<td>None</td>
<td>PEG-IFN/RBV x 24 weeks</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
<td>None</td>
<td>PEG-IFN/RBV x 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Monotherapy with PEG-IFN, RBV, or a DAA. Do not treat decompensated cirrhosis with PEG-IFN or SMV.</td>
<td>Any regimen with TVR, BOC, or SMV</td>
<td></td>
</tr>
</tbody>
</table>
### 2014 AASLD/IDSA Guidelines for Therapy: Initial Therapy or Relapse After Prior PEG-IFN/RBV Therapy (cont’d)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>SOF + RBV x 24 weeks</td>
<td>SOF + PEG-IFN/RBV x 12 weeks</td>
<td>PEG-IFN/RBV x 24-48 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monotherapy with PEG-IFN, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td>4</td>
<td>IFN eligible: SOF + PEG-IFN/RBV x 12 weeks</td>
<td>SMV x 12 weeks + PEG-IFN/RBV x 24-48 weeks</td>
<td>PEG-IFN/RBV x 48 weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: SOF + RBV x 24 weeks</td>
<td></td>
<td>Monotherapy with PEG-IFN, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any regimen with TVR or BOC</td>
</tr>
<tr>
<td>5</td>
<td>SOF + PEG-IFN/RBV x 12 weeks</td>
<td>PEG-IFN/RBV x 48 weeks</td>
<td>Monotherapy with PEG-IFN, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any regimen with TVR or BOC</td>
</tr>
</tbody>
</table>

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; BOC = boceprevir; DAA = direct-acting antiviral; IDSA = Infectious Diseases Society of America; IFN = interferon; PEG-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SMV = simeprevir; TVR = telaprevir.
## 2014 AASLD/IDSA Guidelines for Therapy: Retreatment After Treatment Failure

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOF + SMV ± RBV x 12 weeks</td>
<td>SOF x 12 weeks + PEG-IFN/RBV x 12-24 weeks</td>
<td>PEG-IFN/RBV ± TVR or BOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF + RBV x 24 weeks</td>
<td>Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SMV x 12 weeks + PEG-IFN/RBV x 48 weeks</td>
<td>Do not treat decompensated cirrhosis with PEG-IFN or SMV</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
<td>SOF + PEG-IFN/RBV x 12 weeks</td>
<td>PEG-IFN/RBV ± telaprevir or boceprevir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monotherapy with PEG-IFN, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat decompensated cirrhosis with PEG-IFN</td>
</tr>
</tbody>
</table>

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; BOC = boceprevir; DAA = direct-acting antiviral; IDSA = Infectious Diseases Society of America; IFN = interferon; PEG-IFN = pegylated interferon; RBV = ribavirin; RGT = response-guided therapy; SOF = sofosbuvir; SMV = simeprevir; TVR = telaprevir.

AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: [www.hcvguidelines.org](http://www.hcvguidelines.org).
### 2014 AASLD/IDSA Guidelines for Therapy: Retreatment After Treatment Failure (cont’d)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>SOF + RBV x 24 weeks</td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>PEG/RBV ± any current protease inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat decompensated cirrhosis with PEG</td>
</tr>
<tr>
<td>4</td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>SOF + RBV x 24 weeks</td>
<td>PEG/RBV ± any current HCV protease inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat decompensated cirrhosis with PEG</td>
</tr>
<tr>
<td>5</td>
<td>SOF x 12 weeks + PEG/RBV 12 weeks</td>
<td></td>
<td>PEG/RBV ± any current HCV protease inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat decompensated cirrhosis with PEG</td>
</tr>
</tbody>
</table>

AASLD = American Association for the Study of Liver Disease; IDSA = Infectious Diseases Society of America; ALT = alanine aminotransferase; IFN = interferon; SOF = sofosbuvir; PEG = pegylated interferon; RBV = ribavirin; SMV = simeprevir; DAA = direct-acting antiviral.

AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: [www.hcvguidelines.org](http://www.hcvguidelines.org).
New DAAs in HCV: The Cost Conundrum

- With tremendous success of new DAAs come increased costs\(^1\)
  - Substantially higher drug costs
  - Increased costs to the healthcare system
- Demand for these drugs is high\(^1\)
  - Greater than expected by physicians/patient
  - Underestimated by payers
- However, the fact that these drugs/combinations are providing cures must also be considered\(^1\)
  - Cure equals no need for further therapy
  - Cure removes the patient from the healthcare system for this condition
- Large scale production of new DAAs/combinations over the next 15 years may be feasible\(^2\)
  - Lowering drug costs overall
  - Making SVR/cure more globally accessible and achievable

Antiviral activity in all HCV genotypes
All-oral combination regimen
Daily or twice-daily dosing
No selection of resistance
Short treatment duration
Excellent safety and tolerability

Applicable in difficult-to-treat populations:
• Transplant
• Co-infection
• End-stage renal disease, etc.
FDA has approved the first combination therapy (ledipasvir and sofosbuvir) to treat chronic HCV genotype 1 infection\(^1,2\)

- First approved regimen that does not require administration with interferon or ribavirin\(^1\)

- Efficacy was evaluated in three clinical trials enrolling 1,518 participants (treatment-naïve or treatment-experienced including participants with cirrhosis)\(^1,2\)
  - ION 1, treatment-naïve, patients with or without cirrhosis: 99% achieved SVR after 12 weeks of treatment
  - ION 2, treatment-experienced, patients with or without cirrhosis: 94% achieved SVR at 12 weeks of therapy with 99% achieving SVR at 24 weeks
  - ION 3, treatment-naïve, non-cirrhotic: 94% treated for 8 weeks achieved SVR with 96% of those treated for 12 weeks also achieving SVR
  - Within these trials, ribavirin was not shown to increase response rates

- Use of the combination therapy for only 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL\(^3\)

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Pursuit of FDA approval for combined daclatasvir and asunaprevir therapy for patient with HCV genotype 1b discontinued

- New drug application (NDA) for NS3/4A protease inhibitor asunaprevir withdrawn
- Manufacturer will continue to seek FDA approval for the pan-genotypic NS5A complex inhibitor daclatasvir for difficult-to-treat HCV patients, including those with HCV genotype 3, patients pre- and post-liver transplant, and patients co-infected with HIV

On December 19th, 2014, the FDA approved a new 4-drug combination therapy regimen to treat chronic HCV genotype 1 infection

- Regimen combines ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets
- Ombitasvir, paritaprevir, and dasabuvir work together to inhibit the growth of HCV
- Ritonavir acts to increase blood levels of paritaprevir
- Combination was evaluated in six clinical trials encompassing 2,308 participants with chronic HCV infection with and without cirrhosis
  - Primary endpoint was achievement of SVR after 12 weeks of therapy
  - Results from multiple patient populations, including difficult-to-treat patients, demonstrated 90% to 100% of participants treated with this combination at recommended dosing levels achieved SVR
- Recommended dosing is 2 ombitasvir, paritaprevir, ritonavir 12.5 milligrams (mg)/75 mg/50 mg tablets once daily combined with one dasabuvir 250 mg tablet twice daily
New HCV Therapies and The Pharmacy Benefit Coverage Conundrum: Price Wars?

- Approval of new therapies has led to different pharmacy benefit programs approving preferred status for different therapies
  - Approval of the new 4-drug combination (ombitasvir, paritaprevir, ritonavir, dasabuvir) has led Express Scripts to offer this therapy regimen as its “exclusive” option for treatment of HCV genotype 1
  - Subsequently, Aetna has declared similar status for sofosbuvir or combined ledipasvir/sofosbuvir as preferred treatments
  - Anthem, Inc. will offer ledipasvir/sofosbuvir as its preferred therapy
  - CVS Health Corp. has negotiated a similar preferred status for the ledipasvir/sofosbuvir combination
  - Other arrangements are also ongoing, and continual changes are likely in this ever-evolving therapy and coverage dynamic

- Critical questions and issues for clinicians and patients
  - How do you best approach cost vs benefit in HCV therapy?
  - Should cost override clinician/patient choices for treatment?
  - Not all treatments are necessarily equal nor alike: keeping efficacy and safety data at the forefront of therapy