HCV Treatment Recommendations
2014: Highlights from the
AASLD-IDSA Guidelines Panel

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Disclosures

- **Consulting**: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Genentech, Janssen, and Merck (none since April 2013)

- **Research**: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead, Janssen, and Idenix
Testing and linkage to care recommendations

**Simeprevir**
- QUEST trials

**Sofosbuvir**
- NEUTRINO, FISSION, FUSION, POSITRON, VALENCE trials

**Simeprevir + sofosbuvir**
- COSMOS trial

**Guidelines**
Testing and Linkage to Care
HCV Testing Recommendations

- Recommended at least once for persons born between 1945 and 1965.
  - Other persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

- Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men.

- An anti-HCV test is recommended for HCV testing.
  - If the result is positive, current infection should be confirmed by a sensitive RNA test.

- Among persons with a negative anti-HCV test who are suspected of having liver disease:
  - Testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months.
  - Testing for HCV RNA can also be considered in persons who are immunocompromised.
Quantitative HCV RNA testing is recommended before starting antiviral therapy to document baseline viral load.

Testing for HCV genotype is recommended to guide selection of antiviral regimen.

If anti-HCV positive and HCV RNA negative, persons should be informed that they do not have evidence of current (active) HCV infection.

Persons with current (active) HCV infection should receive
- Education and interventions to reduce progression of liver disease and prevent transmission of HCV
- Evaluation by a practitioner who can provide comprehensive management
HCV Treatment 2014
A Short History of HCV Therapy

- 1989: HCV Discovered (Chiron)
- 1992: HCV Antibody Testing
- 1996: Ribavirin Added
- 2000: PEG Interferon + RBV Trials
- 2005: Genotype-Specific RGT
- 2011: Telaprevir Boceprevir Approval
- 2014: Simeprevir Sofosbuvir Approval

SVR:
- 1989: 6%
- 1992: 12%
- 1996: 20%
- 2000: 40%
- 2005: 54%
- 2011: 70%
- 2014: 90%
Recently FDA Approved

- **Simeprevir (Olysio™)**
  - NS3/4a serine protease inhibitor
  - 150 mg once-daily administration x 12 weeks with PEG/RBV x 24-48 weeks
  - Accumulation and possible toxicity may occur in those with impaired hepatic function

- **Sofosbuvir (Sovaldi™)**
  - NS5b nucleotide inhibitor
  - 400 mg once-daily administration
    - With PEG/RBV for genotype 1 x 12 weeks
    - With RBV only for genotypes 2 and 3 x 12-24 weeks
  - Safety not established in those with GFR < 30 mL/min
What’s the Evidence?
Simeprevir

**Phase 2a**

- **Status:** Completed
  - C201 OPERA-1: treatment-naive and treatment-experienced HCV GT 1 infected patients - dose ranging study
  - C202 (GT 2-6): antiviral activity, safety, tolerability, PK in treatment-naive patients infected with HCV GT 2-6

**Phase 2b**

- **Status:** Completed
  - C205 PILLAR: treatment-naive HCV GT 1-infected patients
  - C206 ASPIRE: treatment-experienced HCV GT 1-infected patients

**Phase 3**

- **Status:** Data primary efficacy endpoint available
  - C208 QUEST-1: treatment-naive HCV GT 1-infected patients
  - C216 QUEST-2: treatment-naive HCV GT 1-infected patients

- **HPC3007 PROMISE:** prior relapser HCV GT 1-infected patients
Simeprevir

Phase 3

- C212 (HCV GT 1/HIV-1 co-infection)*
  - treatment-naïve and experienced HCV GT 1/HIV-1 co-infection

- HPC3011 (HCV GT 4)*
  - treatment-naïve and experienced HCV GT 4 infected patients

- C213 (Roll Over)
  - treatment-experienced HCV GT 1 infected patients from Phase 2/3 program (control group)

- HPC3002 (Long-Term FU)
  - patients treated with SMV

Interferon-free Phase 2

- HPC2002 (COSMOS)*
  - SMV + Sofosbuvir
  - prior null responders and naïve HCV GT 1 infected patients
QUEST 1 and 2: Simeprevir plus PegIFN/RBV for Treatment of Treatment-Naïve Patients with Genotype 1 Infection

- GT 1, treatment-naïve patients (n=785)
- Simeprevir 150 mg or placebo for 12 wks + PegIFN/RBV for 24 or 48 weeks (RGT)
- 88% had HCV RNA < 25 IU/mL at week 4 – stop after 24 weeks: **SVR 88%**

- In subjects with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates was observed*

- Q80K prevalence in 1500 clinical specimens sent to an US commercial lab‡
  - GT 1a, 32.5%
  - GT 1b, 0.1%

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*95% confidence intervals

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† TTGTG database, 2011-2012
‡ GTG database, 2012-2013

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* SVR12 rates were not statistically different within groups based on the Q80K polymorphism.
Sofosbuvir (SOF, GS-7977)

- HCV-specific uridine nucleotide NS5B polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
  - Renally cleared
  - No hepatic CYP450 metabolism
  - Limited potential for drug interactions
- Generally safe and well tolerated in clinical studies to date (>3,000 patients)
Sofosbuvir Phase 3 Study Designs

**Treatment-Naïve: NEUTRINO**
- GT 1,4,5,6
  - SOF + PegIFN + RBV, n=327
  - SVR12
  - SVR24

**Treatment-Naïve: FISSION**
- GT 2,3
  - SOF + RBV, n=256
  - PegIFN + RBV, n=243
  - SVR12

**PegIFN-Unable: POSITRON**
- GT 2,3
  - SOF + RBV, n=207
  - PegIFN + RBV, n=71
  - SVR12

**Treatment-Experienced: VALENCE**
- GT 2
  - SOF + RBV, n=73
  - SVR12
- GT 3
  - SOF + RBV, n=250
  - SVR12

**Treatment-Naïve and Treatment-Experienced: FUSION**
- GT 2,3
  - SOF + RBV, n=103
  - PBO
  - SVR12

**Treatment-Naïve: ALL-ORAL THERAPY**
- GT 2
  - SOF + RBV, n=68
  - SOF + RBV, n=114
  - SVR12

**IFN LIMITING**

SOF 400 mg/d; PegIFN 180 μg/wk; RBV 1000-1200 mg/d for SOF+RBV arms and 800 mg/d for PegIFN+RBV arm
Sofosbuvir Plus PEG/RBV
NEUTRINO: Treatment-Naïve GT1, 4, 5, 6

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
<th>G1</th>
<th>G4</th>
<th>G5,6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 %</td>
<td>90</td>
<td>92</td>
<td>80</td>
<td>89</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>295/327</td>
<td>252/273</td>
<td>43/54</td>
<td>261/292</td>
<td>27/28</td>
<td>7/7</td>
</tr>
</tbody>
</table>

Lawitz E, et al. NEJM 2013;368:1878-87
Treatment with SOF + RBV ± PegIFN for 12 weeks resulted in similarly high SVR rates across all HCV GT 2 patients regardless of presence of cirrhosis or treatment experience.

SVR12 Rates Across SOF-Based Studies: HCV Genotype 3 Patients

HCV GT 3 patients treated with SOF + RBV for 24 weeks or SOF + PegIFN + RBV for 12 weeks achieved high SVR rates regardless of presence of cirrhosis or treatment experience.

Simeprevir + Sofosbuvir Combination
**COSMOS: Simeprevir + Sofosbuvir ± RBV in Genotype 1 HCV Patients**

- Planned interim analysis of randomized phase 2a study
- 2 cohorts with same study design evaluating impact of duration and RBV
- Primary endpoint: SVR12

**Patients With GT1 HCV**

**Randomized 2:1:2:1**

**Wk 12**
- Simeprevir + Sofosbuvir + RBV
- Simeprevir + Sofosbuvir

**Wk 24**
- Simeprevir + Sofosbuvir + RBV
- Simeprevir + Sofosbuvir + RBV

**Cohort 1:**
- Previous null responders, F0-F2
  - (N = 80)

**Cohort 2:**
- Naïves and previous null responders, F3-F4
  - (N = 87)

Simeprevir 150 mg QD; sofosbuvir 400 mg QD; weight-based RBV 1000-1200 mg/day.

COSMOS: Cohort 1 Results
(Prior Nulls With F0-F2 Fibrosis)
COSMOS: Cohort 2 Results
(Naïves and Nulls: F3-F4)

12-week treatment

**Total**
- SVR4 (SMV/SOF): 100
- SVR4 (SMV/SOF/RBV): 96.3
- Relapse: 1/27

**Naïves**
- SVR4 (SMV/SOF): 100
- SVR4 (SMV/SOF/RBV): 100
- Relapse: 7/7

**Nulls**
- SVR4 (SMV/SOF): 100
- SVR4 (SMV/SOF/RBV): 93.3
- Relapse: 7/7
COSMOS Results

Excludes non-virologic failures

**SVR12**
- Cohort 1 (12 and 24 wk arms):
  - GT1a with Q80K: 88.9%
  - GT1a without Q80K: 100%
  - GT1b: 100%
- a3 relapsed (w/BL Q80K): 24/27

**SVR4**
- Cohort 2 (12 wk arm):
  - GT1a with Q80K: 90.9%
  - GT1a without Q80K: 100%
  - GT1b: 100%
- b1 relapsed (w/BL Q80K): 10/11

BL, baseline; GT, genotype; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR4, sustained virologic response 4 weeks after end of treatment; SVR12, sustained virologic response 12 weeks after end of treatment.
AASLD-IDSA HCV Guideline
Recommendations
(www.HCVguidelines.org)
# Treatment-Naïve HCV

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>IFN eligible: SOF + PEG/RBV x 12 weeks</td>
<td>IFN eligible: SMV x 12 weeks + PEG/RBV x 48 weeks*</td>
<td>TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks</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>Monotherapy with PEG, RBV, or a DAA Do not treat <em>decompensated cirrhosis</em> with PEG or SMV</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>SOF + RBV x 12 weeks</td>
<td>None</td>
<td>PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>SOF + RBV x 24 weeks</td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>IFN eligible: SOF + PEG/RBV x 12 weeks</td>
<td>SMV x 12 weeks + PEG/RBV x 24-48 weeks</td>
<td>PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: SOF + RBV x 24 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 or 6</strong></td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>PEG/RBV x 48 weeks</td>
<td>Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC</td>
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For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.
HCV Prior Treatment Experienced

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<tr>
<td><strong>Patients in whom previous PEG/RBV has failed</strong>*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>SOF + SMV ± RBV x 12 weeks</td>
<td>SOF x 12 weeks + PEG/RBV 12 weeks</td>
<td>PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SMV x 12 weeks + PEG/RBV x 48 weeks**</td>
<td>Do not treat <a href="#">decompensated cirrhosis</a> with PEG or SMV</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat <a href="#">decompensated cirrhosis</a> with PEG</td>
</tr>
<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 Monotherapy with PEG, RBV, or a DAA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not treat <a href="#">decompensated cirrhosis</a> with PEG</td>
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<td>4</td>
<td>SOF x 12 weeks + PEG/RBV 12 weeks SOF + RBV x 24 weeks</td>
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<td>Do not treat <a href="#">decompensated cirrhosis</a> with PEG</td>
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</table>

**Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed**

| | | | |
| 1a | SOF x 12 weeks + PEG/RBV x 24 weeks | SOF + RBV x 24 weeks | PEG/RBV ± telaprevir or boceprevir or SMV Monotherapy with PEG, RBV, or a DAA |
| 1b | SOF x 12 weeks + PEG/RBV x 12-24 weeks | SOF + RBV x 24 weeks | Do not treat [decompensated cirrhosis](#) with PEG or SMV |

*Non-responder is defined as partial or null response to treatment with PEG/RBV. Relapse to prior therapy should be treated the same as treatment-naive (see Initial Treatment section)

**For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present