HCV Therapies: State of the Art

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Learning Objectives

• Evaluate the current treatment options for the management of treatment-naive patients with HCV genotype 1 infection
• Assess the current treatment options for the management of treatment-experienced patients with HCV genotype 1 infection
• Outline the major issues in the current treatment of HCV infection
Evolving Landscape of HCV Therapy

Discovery of HCV (Chiron) 1989
Approval Ribavirin 1992
Approval pegIFN- alfa-2b 1998
Genotype-Specific RGT 2001
Approval Telaprevir Boceprevir 2005
Approval Simeprevir 2011
Approval Ledipasvir/Sofosbuvir OBV/PTV/r + DAS 2013
Approval Daclatasvir OBV/PTV/r 2014
Approval Grazoprevir/Elbasvir Sofosbuvir/Velpatasvir 2015
Approval Ledipasvir/Sofosbuvir OBV/PTV/r + DAS 2016

SVR: 6% 12% 20% 40% 54% 65–75% >90%

Current Benchmark >95%

pegIFN-alfa 2b = peg-interferon alfa-2b; RGT = response-guided therapy; OBV/PTV/r + DAS = ombitasvir/paritaprevir and ritonavir + dasabuvir (or 3D).
FDA-Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes

- Ribavirin
- NS3 Protease Inhibitors: Boceprevir (BOC), Telaprevir (TVR), Simeprevir (SMV), Paritaprevir (PTV), Grazoprevir (GZR)
- NS5A Replication Complex Inhibitors: Daclatasvir (DCV), Ledipasvir (LDV), Ombitasvir (OMV), Elbasvir (EBR), Velpatasvir (VEL)
- NS5B NUC Inhibitors: Sofosbuvir (SOF)
- NS5B Non-NUC Inhibitors (NNI): Dasabuvir (DSV)

RNA structures: 3'UTR, Core, E1, E2, 5'UTR, 3'UTR
Proteins: NS2, NS3, NS4A, NS5A, NS5B
Enzymes: Polymerase, Replication Complex
Inhibitors: FDA-approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes
<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Protease Inhibitors</th>
<th>Nucleos(t)ide Polymerase Inhibitors</th>
<th>Non-nucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td></td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Ledipasvir</td>
</tr>
<tr>
<td>Boceprevir</td>
<td></td>
<td></td>
<td></td>
<td>Daclatasvir,</td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
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<td></td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td></td>
<td></td>
<td></td>
<td>Elbasvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td></td>
<td></td>
<td></td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Potency</td>
<td>High (varies by genotype)</td>
<td>Moderate-to-high (pangenotypic)</td>
<td>Variable (varies by genotype)</td>
<td>High (some pangenotypic)</td>
</tr>
<tr>
<td>Barrier to resistance</td>
<td>Low (1a&lt;1b)</td>
<td>High (1a =1b)</td>
<td>Very low (1a&lt;1b)</td>
<td>Low (1a&lt;1b)</td>
</tr>
<tr>
<td>Potential for drug</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low-to-moderate</td>
</tr>
<tr>
<td>Interactions</td>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash, anemia, jaundice, liver injury</td>
<td>Mitochondrial</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Dosing</td>
<td>qd to tid</td>
<td>qd to bid</td>
<td>qd to tid</td>
<td>qd</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd generation PIs (higher barrier to resistance, pangenotypic)</td>
<td>Single target active site</td>
<td>Allosteric Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
<tr>
<td>Predominant Metabolism</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

Sofosbuvir + simeprevir

- **Indications**
  - FDA
    - Genotype 1
  - AASLD/IDSA
    - Genotype 1

- **Benefits**
  - First IFN-free regimen available

- **Limitations**
  - May need baseline RAS testing and ribavirin
  - Not recommended for decompensated cirrhosis
Simeprevir + Sofosbuvir

SVR12 (%)

<table>
<thead>
<tr>
<th>Null responders, F0-F2, +/- ribavirin 12-24 weeks</th>
<th>Naïve &amp; non-responders, F3-F4, +/- ribavirin 12-24 weeks</th>
<th>No ribavirin 12 weeks</th>
<th>No ribavirin 8 weeks</th>
<th>Genotype 1b no ribavirin 12 weeks</th>
<th>Genotype 1a No Q80K no ribavirin 12 weeks</th>
<th>Genotype 1a + Q80K no ribavirin 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>94</td>
<td>97</td>
<td>83</td>
<td>84</td>
<td>92</td>
<td>74</td>
</tr>
</tbody>
</table>

COSMOS: naïve, experienced

OPTIMIST-1: Naïve and experienced, noncirrhotic

OPTIMIST-2: Naïve and experienced, cirrhotic

Extension to 24 weeks +/- ribavirin in cirrhosis, and Q80K testing if GT1a

Sofosbuvir + Ledipasvir

**Indications**
- FDA
  - Genotype 1
- AASLD/IDSA
  - Genotypes 1, 4, 5, 6

**Benefits**
- Regimen for many treatment failure patients
- Ribavirin-free for many
- Decompensated cirrhosis
- Low pill burden

**Limitations**
- Not recommended in advanced renal insufficiency
Sofosbuvir + Ledipasvir

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, 12 weeks</td>
<td>94</td>
</tr>
<tr>
<td>1b, 12 weeks</td>
<td>95</td>
</tr>
<tr>
<td>HCV RNA &lt; 6 MU/L, 8 weeks</td>
<td>90</td>
</tr>
<tr>
<td>LDV/SOF, 24 weeks</td>
<td>97</td>
</tr>
<tr>
<td>LDV/SOF + RBV, 12 weeks</td>
<td>96</td>
</tr>
</tbody>
</table>

ION3: treatment-naïve, noncirrhotic

SIRIUS: Protease inhibitor failures with compensated cirrhosis

Sofosbuvir/ledipasvir and NS5A RAVs

- Pooled analysis of 2,144 participants of phase 2/3 studies
- 16% with detectable NS5A RAS at baseline

Baseline NS5A RASs have minimal effects on SVR to LDV/SOF, and these effects may be overcome by extending treatment duration or through treatment intensification.

Ledipasvir/Sofosbuvir for 24 weeks for Previous Ledipasvir/Sofosbuvir Failures

- G1 treatment-experienced patients who failed prior LDV/SOF regimens
  - LDV/SOF +/- RBV: 33 (80%)
  - LDV/SOF + GS-9669: 8 (20%)

<table>
<thead>
<tr>
<th>Number of NS5A RAVs</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n = 11)</td>
<td>100%</td>
</tr>
<tr>
<td>1 (n = 16)</td>
<td>69%</td>
</tr>
<tr>
<td>≥2 (n = 14)</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of single NS5A RAV</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q30R or M28T (n = 5)</td>
<td>100%</td>
</tr>
<tr>
<td>L41M (n = 5)</td>
<td>80%</td>
</tr>
<tr>
<td>Y93H/N (n = 6)</td>
<td>33%</td>
</tr>
</tbody>
</table>

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir

**Indications**
- FDA:
  - Genotypes 1, 4 (no dasabuvir)
- AASLD/IDSA
  - Genotypes 1, 4 (no dasabuvir)

**Benefits**
- 3 agents against different targets
- Large development program, including cirrhosis
- Not renally metabolized

**Limitations**
- Ribavirin for genotype 1a
- Not recommended for decompensated cirrhosis
Paritaprevir/ritonavir + Ombitasvir + Dasabuvir ± Ribavirin for Genotype 1 HCV

PEARL III & IV: treatment-naïve, noncirrhotic

TURQUOISE II: compensated cirrhosis, naïve and experienced
100% SVR12 with PAR/r + OMB + DAS \textit{without} RBV for GT1b with Cirrhosis

- TURQUOISE III: phase IIIIB, open-label, single-arm trial
- 60 patients with compensated cirrhosis
- 55% treatment-experienced
- Most common AEs fatigue (20%), diarrhea (20%), headache (18%)
- One SAE: possible drug interaction with nisoldipine
- 20% with Grade 2 bilirubin elevation

PrOD \textit{without} ribavirin for GT 1b, regardless of prior treatment or the presence of cirrhosis

Impact of Baseline RASs on Efficacy of OBV/PTV/RTV + DSV ± RBV

- Analysis of data from 5 phase III trials using NGS; all pts treated with OBV/PTV/RTV + DSV ± RBV on label (based on subgenotype, previous treatment, and cirrhosis)
  - SVR12 rate 100% in pts with GT1b HCV, regardless of BL RAVs

Sofosbuvir + Daclatasvir

**Indications**
- FDA:
  - Genotype 3
- AASLD/IDSA:
  - Genotypes 1, 2, 3

**Benefits**
- Pangenotypic
- Flexibility with DDIs
- Decompensated cirrhosis

**Limitations**
- Access outside genotype 3
- Not recommended in advanced renal insufficiency
ALLY 3+: Daclatasvir + Sofosbuvir + Ribavirin for GT3

- No virologic breakthroughs
- Relapse (n = 4)
  - All cirrhotics (2 in each arm)
  - All had Y93H RAV at relapse
- Overall well tolerated
  - No discontinuations
  - RBV dose reduction in 12%
  - Treatment-emergent grade 3/4 laboratory abnormalities
    - Hemoglobin <9.0 g/dL 2%
    - Total bilirubin >2.5x ULN 4%

European Compassionate Use Program: Daclatasvir + Sofosbuvir ± RBV in HCV Genotype 3 Cirrhosis

Extension to 24 weeks +/- ribavirin is recommended for cirrhosis

Elbasvir + Grazoprevir

**Indications**
- FDA:
  - Genotype 1, 4
- AASLD/IDSA:
  - Genotypes 1, 4

**Benefits**
- Approved for use with advanced renal insufficiency
- Low pill burden

**Limitations**
- May need baseline RAS testing and ribavirin
- Not recommended for decompensated cirrhosis
C-EDGE: Final SVR24 Data with Elbasvir/Grazoprevir in TN, HCV GTs 1, 4, or 6

- Phase 3, double-blind, randomized to ELB/GRZ for 12 weeks (n = 316) or placebo and delayed treatment (n = 105)
- Overall SVR24 rate: 94%
  - Genotype 1a/1b: 93%/99%
  - Genotype 4/6: 100%/62%
- Overall relapse rate: 4%
  - 1 confirmed relapse between SVR12 and SVR24
- Lower SVR24 rates in genotype 1a with RAVs at positions 28, 30, 31

Prolong treatment to 16 weeks with ribavirin for TN and TE genotype 1a patients with baseline NS5A RAVs

C-SURFER: Grazoprevir + Elbasvir in Stage 4 and 5 Chronic Kidney Disease

- 224 patients
- GT 1 HCV
- 12 weeks (randomized to immediate or delayed)
- 6% cirrhotic, 20% TE
- 75% on HD
- Well tolerated, no evidence of worsening of renal function

Sofosbuvir + Velpatasvir

• **Indications**
  - FDA:
    - Genotypes 1, 2, 3, 4, 5, 6
  - AASLD/IDSA:
    - Genotypes 1, 2, 3, 4, 5, 6

• **Benefits**
  - Pangeneotypic
  - Regimen for many treatment failure patients
  - Ribavirin-free for many
  - Decompensated cirrhosis
  - Low pill burden

• **Limitations**
  - Access outside genotype 3
  - Not recommended in advanced renal insufficiency
Sofosbuvir + Velpatasvir for 12 Weeks

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5</th>
<th>GT 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98</td>
<td>98</td>
<td>99</td>
<td>95</td>
<td>100</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>1015/1035</td>
<td>323/238</td>
<td>237/238</td>
<td>264/277</td>
<td>116/116</td>
<td>34/35</td>
<td>41/41</td>
</tr>
</tbody>
</table>

2 relapse 2 LTFU 1 D/C 11 relapse 2 D/C 1 death

Agarwal, EASL 2016.
SOF/VEL 12 wks vs SOF/RBV 24 wks G3

2016: Add ribavirin?

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncirrhotic</td>
<td>98/160/163</td>
<td>90/141/156</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>93/40/43</td>
<td>73/33/45</td>
</tr>
<tr>
<td>Noncirrhotic</td>
<td>91/31/34</td>
<td>71/22/31</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>89/33/37</td>
<td>58/22/38</td>
</tr>
</tbody>
</table>

## AASLD/IDSA Guidance

<table>
<thead>
<tr>
<th></th>
<th>SOF + PEG + RBV</th>
<th>SOF + RBV</th>
<th>SIM + SOF</th>
<th>LDV + SOF</th>
<th>PAR/r + OMB + DAS</th>
<th>DAC + SOF</th>
<th>ELB + GRZ</th>
<th>VEL + SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT</td>
<td>NS5B</td>
<td>NS5B</td>
<td>PI + NS5B</td>
<td>NS5A + NS5B</td>
<td>PI + NS5A + NS5B</td>
<td>NS5A + NS5B</td>
<td>PI + NS5A</td>
<td>NS5A + NS5B</td>
</tr>
<tr>
<td>4</td>
<td>Naïve PEG/R Exp</td>
<td>Naïve PEG/R Exp (no DAS)</td>
<td></td>
<td>Naïve PEG/R Exp</td>
<td></td>
<td>Naïve PEG/R Exp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Naïve PEG/R Exp</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Naïve PEG/R Exp</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Recommended** — Green  
**Alternative** — Yellow

[www.hcvguidelines.org](http://www.hcvguidelines.org), accessed March 2017
NS5A resistance
DAA Failures (prior NS5A Inhibitor)

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>Retreatment Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV +/- PEG</td>
<td>SOF/LDV + RBV</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td>PI + PEG + RBV</td>
<td>SOF/LDV +/- RBV</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + DAC +/- RBV</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td></td>
<td>ELB/GRZ + RBV</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td>SOF + SIM</td>
<td>• Defer treatment unless urgent, pending additional data and availability of newer regimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Test for NS3 protease and NS5A inhibitor resistance-associated substitutions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Use of SOF-based therapy for extended duration (24 weeks), add RBV if can tolerate; consider triple or quadruple DAA regimen if possible</td>
<td></td>
</tr>
</tbody>
</table>

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir in cirrhosis

• FDA Drug Safety Communication
• 26 worldwide cases
  – 10 hepatic failure resulting in transplantation or death
  – 16 patients with liver dysfunction
• In most, liver injury within 1 to 4 weeks of starting
• “Transaminase elevations did not appear to be a predominant presentation in the cases with advanced liver disease”

Contraindicated in moderate to severe hepatic impairment (CTP B and C) and monitored closely in compensated cirrhosis (labs at least every 4 weeks)
# HBV Reactivation Associated with HCV DAA Therapy

Query of the FDA Adverse Event Reporting System (FAERS) for cases of HBV-R associated with HCV DAAs from 11/22/2013–10/15/2016

<table>
<thead>
<tr>
<th>Descriptive Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td># of cases/geography</td>
<td>29 cases (5 in US, 19 Japan, 5 in other)</td>
</tr>
<tr>
<td>Timing</td>
<td>Temporally related to HCV therapy and occurred within 4-8 weeks (mean time to HBV-R was 53 days)</td>
</tr>
<tr>
<td>Baseline HBV viral parameters</td>
<td>HBsAg+ (n = 13) (n = 12 not reported); HBCab+ (n = 6) (n = 23 not reported); HBV DNA undetectable/detectable (n = 16/9)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death (n = 2) (due to decompensated liver failure); transplant (n = 1); hospitalization (n = 6); other (n = 20)</td>
</tr>
<tr>
<td>Specific DAAs used</td>
<td>SOF-based (n = 16); DCV+ASV (n = 11); PI-based (n = 2)</td>
</tr>
<tr>
<td>HBV treatment</td>
<td>In 16 patients who received HBV treatment, treatment was delayed in ≥7 cases (44%); 1 of these 7 patients died; possible delay in ≥7 other cases (1 had a liver transplant)</td>
</tr>
</tbody>
</table>

**Health care professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.**

*HBV-R is defined as the abrupt increase in HBV replication in a patient with inactive or resolved HBV (HBsAg positive or negative, respectively), and hepatitis B core antibody (HBCab) positive*
Remaining Challenges

• Patients who require ongoing optimization:
  – Genotypes non-1
  – High-level resistance
  – Advanced renal insufficiency
  – Decompensated cirrhosis

• Regimen questions:
  – Shorter duration
  – One pill daily, ribavirin-free for all
Grazoprevir/Elbasvir + Sofosbuvir

Treatment-naïve, GT 1 and 3

C-ISLE: EBR/GZR + SOF in GT 3 and Cirrhosis

Treatment-naïve

Treatment-experienced

• Modified full analysis set includes excludes patients who discontinued treatment for reasons unrelated to study medication
• Baseline NS5A RAS did not impact SVR

Foster et al AASLD 2016
# DAAs in Late-Stage Clinical Development

<table>
<thead>
<tr>
<th>NS3/4A Protease Inhibitors</th>
<th>Nucleotide NS5B Polymerase Inhibitors</th>
<th>Non-nucleoside NS5B Polymerase Inhibitors</th>
<th>NS5A Replication Complex Inhibitors</th>
<th>Cyclophilin Inhibitors</th>
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</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
<td></td>
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<tr>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Ledipasvir</td>
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<tr>
<td>Boceprevir</td>
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<td></td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td></td>
<td></td>
<td>Daclatasvir</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/r Grazoprevir</td>
<td></td>
<td></td>
<td>Elbasvir</td>
<td>Velpatasvir</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voxilaprevir</td>
<td>MK-3682</td>
<td>Beclabuvir</td>
<td>Pibrentasvir</td>
<td>Ruzasvir</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Glecaprevir</td>
<td></td>
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<tr>
<td><strong>Phase 2</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GS-9256 Sovaprevir</td>
<td>ACH-3422</td>
<td>ABT-072</td>
<td>Odalasvir</td>
<td>SCY-635</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GS-9669 TMC-647055</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Not all-inclusive.</em></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Sofosbuvir/Velpatasvir/Voxilaprevir

SOF/VEL/VOX for 12 weeks provides a STR for all DAA-experienced patients and SOF/VEL for 12 weeks provides a STR for DAA-naive patients regardless of cirrhosis status.

Bourliere M, AASLD 2016; Zeuzem S, AASLD 2016; Jacobson IM, AASLD 2016; Foster GR, AASLD 2016.
POLARIS-1: SOF/VEL/VOX for 12 Wks in NS5A Inhibitor-Experienced HCV GT 1–6

SVR12, %

<table>
<thead>
<tr>
<th>GT</th>
<th>SVR12</th>
<th>Relapse</th>
<th>Breakthrough</th>
<th>Withdrew Consent</th>
<th>LTFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>97</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GT 1a</td>
<td>96</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GT 1b</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GT 2</td>
<td>100</td>
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<td>1</td>
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<tr>
<td>GT 3</td>
<td>95</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 4</td>
<td>91</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GT 5</td>
<td>100</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
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<tr>
<td>GT 6</td>
<td>100</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Bourliere M, AASLD 2016.
2 patients had S282T at baseline; both achieved SVR12
C-CREST: MK-3682/Grazoprevir/Ruzasvir (MK3)

- No difference with ribavirin or based on cirrhosis or prior P/R Rx
- One GT2 patient treated with 8 weeks + RBV discontinued at Day 5 due to drug-related AEs (fatigue, malaise)

Lawitz et al, AASLD 2016.
ENDURANCE-1: G/P for 8 or 12 Weeks
GT1 Noncirrhotics, no NS5A

GT1 noncirrhotic ±HIV-1
TN or TE (IFN / peg-IFN ± RBV / SOF + RBV ± peg-IFN)

G/P 300 mg/120 mg QD (n = 351)
G/P 300 mg/120 mg QD (n = 352)

0 4 8 12
Time (weeks)

Zeuzem et al, AASLD 2016.

- One virologic failure (Wk 8)
- No impact of preexisting RAS (NS5A ~25%)
EXPEDITION-IV: G/P for 12 Weeks in Renal Impairment (GFR <30 mL/min)

- 104 patients with GT1–6 ± compensated cirrhosis TN or TE (IFN- or SOF-based regimens)
- eGFR <30 mL/min/1.73 m

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Patients N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-experienced</td>
<td>42%</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>19%</td>
</tr>
<tr>
<td>GT1/2/3/4/5/6</td>
<td>52%/16%/11%/19%/1%/1%</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>13%</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>87%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>82%</td>
</tr>
</tbody>
</table>

- The patient not achieving SVR4 prematurely discontinued treatment
- 4 AEs (4%) led to study drug discontinuation
- 1 patient died after achieving SVR4 due to a serious AE not related to study drug (intracerebral hemorrhage)

Gane et al, AASLD 2016.
Conclusions

- HCV treatment continues to rapidly evolve
- Pangenotypic regimens are now available, with additional options on the horizon
- Progressively smaller groups of patients remain underserved by the regimens available
- Controversies remain: impact on liver function, HCC risk, treatment in renal failure, drug-drug interactions
- Expanding access will be the key to realizing the full potential of these DAA regimens to impact HCV-related morbidity and mortality