Overview

- Impact of chronic HCV Infection
- Current treatment recommendations
- Challenges
  - Access
  - HIV/HCV co-infection
  - HCV in CKD patients
  - Post-transplant and decompensated patients
  - DAA failures
Overview

- **Impact of chronic HCV Infection**
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Over 5.2 Million People Living With Chronic HCV in the United States

<table>
<thead>
<tr>
<th></th>
<th>Estimated Total HCV Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES Estimate</td>
<td>3.2</td>
</tr>
<tr>
<td>HCV Cases Not Included in NHANES*</td>
<td>1.9</td>
</tr>
<tr>
<td>Estimated Total HCV Cases</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Upper limit of estimate</td>
</tr>
<tr>
<td></td>
<td>7.1</td>
</tr>
</tbody>
</table>

*Homeless (n=142,761-337,610); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

1998 CDC Risk-Based HCV Screening Recommendations

Screening is recommended in persons who:

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


Is Risk-Based HCV Screening the Best Approach?

- High HCV prevalence in “baby boomer” population (born 1946-1964)
  - HCV may have been acquired decades ago
  - Individuals no longer identified as high risk
  - Aging of population anticipated to yield ↑ advanced liver disease
- Study investigated impact of targeted “birth cohort screening”
  - 1-time screening of all US persons born 1946-1964 vs risk-based screening through 70 yrs of age
  - Utilized Markov model of natural history of HCV and liver disease, incorporating diagnosis and treatment, to estimate HCV-associated outcomes for both screening approaches

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>238,500</td>
<td>291,200</td>
<td>-52,700</td>
</tr>
<tr>
<td>HCC</td>
<td>137,400</td>
<td>166,000</td>
<td>-28,600</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>28,700</td>
<td>34,700</td>
<td>-6000</td>
</tr>
<tr>
<td>HCV death</td>
<td>233,200</td>
<td>281,200</td>
<td>-48,000</td>
</tr>
</tbody>
</table>

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


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

- Recommendation 1
  - Adults born from 1945 to 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

2013 Updated USPSTF HCV Screening Recommendations

• In June 2013, the USPSTF issued its Grade B recommendations regarding 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 Grade B:
  – Grade B means there is high certainty that the net benefit is moderate or there is moderate certainty 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

2014 AASLD/IDSA Guidelines

• HCV testing is recommended at least once for persons born between 1948 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 HCV infection risk
  – 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
    • Children born to HCV-infected women
    • Prior recipients of transfusions or organ transplants
  – Other medical conditions
    • HIV infection
    • Unexplained chronic liver disease, chronic hepatitis, including elevated ALT levels

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

AASLD/IDSA. Available at: www.hcvguidelines.org.
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).


The Evolution of HCV Therapy

Overview

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- Challenges
  - Access
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  - HCV in CKD patients
  - Post-transplant and decompensated patients
  - DAA failures

General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 1 Patients

<table>
<thead>
<tr>
<th>Treatment, No Cirrhosis</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ledipasvir/sofosbuvir</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>97 (119/123)</td>
<td>2 (2/123)</td>
<td>0 (0/123)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>97 (385/385)</td>
<td>&lt;1 (3/385)</td>
<td>&lt;1 (2/385)</td>
</tr>
<tr>
<td><em>Elbasvir/grazoprevir</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks (non-cirrhotics and cirrhotics combined)*</td>
<td>97 (271/279)*</td>
<td>4 (10/279)*</td>
<td>1 (4/279)*</td>
</tr>
<tr>
<td><em>Ombitasvir/paritaprevir + dasabuvir</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1a (with RSV), 12 weeks</td>
<td>97 (97/100)</td>
<td>1 (1/100)</td>
<td>0 (0/100)</td>
</tr>
<tr>
<td>Genotype 1b (no RSV), 12 weeks</td>
<td>99 (207/207)</td>
<td>0 (0/207)</td>
<td>0 (0/207)</td>
</tr>
<tr>
<td><em>Simeprevir + sofosbuvir</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>97 (112/115)</td>
<td>3† (4/154)</td>
<td>0 (0/115)</td>
</tr>
<tr>
<td><em>Daclatasvir + sofosbuvir</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>98 (111/113)</td>
<td>&lt;1 (1/113)</td>
<td>0 (0/113)</td>
</tr>
</tbody>
</table>

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Ledipasvir/sofosbuvir: 8 weeks (ION-3, pre-treatment HCV RNA <6 M IU/mL), 12 weeks (ION-3 and ION-1).
Elbasvir/grazoprevir: 12 weeks (C-EDGE, C-WORTHY).
Ombitasvir/paritaprevir + dasabuvir: genotype 1a (PEARL-I), genotype 1b (PEARL-II).
Simeprevir + sofosbuvir: 12 weeks (OPTIMIST-1 [SVR12 rate for genotype 1a=Q80K: 56%, 44/80]).
Daclatasvir + sofosbuvir: (not FDA approved for genotype 1): 12 weeks (study 040 and ALLY-2).
*Genotype 1a, no baseline high fold-change NS5A RAVs for elbasvir (SVR12 rate for genotype 1a + these RAVs: 22%, 2/9).
†Includes treatment-naive and treatment-experienced patients.

## General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 1 Patients

### Treatment-Naïve, Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir 12 weeks</td>
<td>94 (32/34)</td>
<td>3 (1/34)</td>
<td>0 (0/34)</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir 12 weeks*</td>
<td>97 (96/99)</td>
<td>1 (1/99)</td>
<td>2 (2/99)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r + dasabuvir</td>
<td>100 (22/22)</td>
<td>0 (0/22)</td>
<td>0 (0/22)</td>
</tr>
</tbody>
</table>

*Genotype 1a: no baseline high fold-change NS5A RAVs for elbasvir.

Ledipasvir/sofosbuvir: 12 weeks (ION-3 and ION-1).
Elbasvir/grazoprevir: 12 weeks (C-EDGE, C-WORTHY).
Ombitasvir/paritaprevir/r + dasabuvir, genotype 1b (TURQUOISE-II).


## General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 2 Patients

### Treatment-Naïve

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (400 mg qd) + RBV 12 weeks*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir (60 mg qd)* + sofosbuvir (400 mg qd) Not eligible to receive RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ledipasvir/sofosbuvir: 12 weeks (ION-3 and ION-1).
Elbasvir/grazoprevir: 12 weeks (C-EDGE, C-WORTHY).
Ombitasvir/paritaprevir/r + dasabuvir, genotype 1b (TURQUOISE-II).

*Genotype 1a: no baseline high fold-change NS5A RAVs for elbasvir.

AASLD-IDSA: Recommended HCV Regimens for Treatment-Naïve, Genotype 2

<table>
<thead>
<tr>
<th>Duration of Therapy (weeks)</th>
<th>Sofosbuvir (400 mg qd) + RBV</th>
<th>Daclatasvir (60 mg qd)* + sofosbuvir (400 mg qd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td>16-24</td>
<td>16-24</td>
</tr>
</tbody>
</table>

* Dose may need to increase or decrease when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively. Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).


General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 3 Patients

<table>
<thead>
<tr>
<th>Treatment-Naïve, No Cirrhosis</th>
<th>Percent (n/N)</th>
<th>Treatment-Naïve, Compensated Cirrhosis</th>
<th>Percent (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR12 Rate</td>
<td>Relapse Rate</td>
<td>Discontinuations Due to Adverse Events</td>
</tr>
<tr>
<td>Sofosbuvir + PR: 12 weeks</td>
<td>96 (69/71)</td>
<td>5* (6/125)</td>
<td>1† (1/74)</td>
</tr>
<tr>
<td>Daclatasvir + sofosbuvir: 12 weeks</td>
<td>97 (73/75)</td>
<td>3 (2/75)</td>
<td>0 (0/75)</td>
</tr>
</tbody>
</table>

Daclatasvir + sofosbuvir: 24 weeks (+RBV)

85 (155/183) 7* (16/219) 1†‡ (3/468)

*Sofosbuvir + PR: 12 weeks (FISSION and VALENCE).
Daclatasvir + sofosbuvir: 12 weeks (ALLY-3); 24 weeks (French Compassionate Use Program).
*Includes genotype 3 treatment-naïve/experienced patients regardless of cirrhosis status.
†Also includes genotype 3, treatment-naïve cirrhotics and genotype 2, treatment-naïve cohort.
‡Combined data from the 12- and 24-week treatment groups.

## General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 4 Patients

### Treatment-Naïve, Treatment-Experienced

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir/sofosbuvir 12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>93 (39/42)</td>
<td>7 (3/42)</td>
<td>0 (0/42)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
<td>0 (0/10)</td>
</tr>
<tr>
<td><strong>Elbasvir/grazoprevir 12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>96 (54/56)</td>
<td>2 (1/56)</td>
<td>0 (0/56)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>100 (6/6)</td>
<td>0 (0/6)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td><strong>Ombitasvir/paritaprevir r + RBV 12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>100 (91/91)</td>
<td>0 (91/91)</td>
<td>0 (0/91)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>96 (52/54)</td>
<td>0 (0/52)</td>
<td>0 (0/52)</td>
</tr>
</tbody>
</table>

*Includes cirrhotics/non-cirrhotics.

## General Outcomes With AASLD-IDSA Recommended HCV Regimens for Genotype 5 and 6 Patients

### Genotype 5: Treatment-Naïve, Treatment-Experienced

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir/sofosbuvir 12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>97 (31/32)</td>
<td>3 (1/32)</td>
<td>0 (0/32)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>89 (8/9)</td>
<td>11 (1/9)</td>
<td>0 (0/9)</td>
</tr>
</tbody>
</table>

### Genotype 6: Treatment-Naïve, Treatment-Experienced

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 Rate</th>
<th>Relapse Rate</th>
<th>Discontinuations Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir/sofosbuvir 12 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis/compensated cirrhosis</td>
<td>96 (24/25)</td>
<td>4 (1/25)</td>
<td>0 (0/25)</td>
</tr>
</tbody>
</table>

Ledipasvir/sofosbuvir: 12 weeks (study 1119 and ION-4 [no cirrhosis]).
Elbasvir/grazoprevir: 12 weeks (pooled analysis of phase 2-3 studies).
Ombitasvir/paritaprevir r + RBV: 12 weeks (PEARL-I [non-cirrhotics] and AGATE-1 [cirrhotics]).

*Includes cirrhotics/non-cirrhotics.

Ledipasvir/sofosbuvir (12 weeks): genotype 5 (study 1119) and genotype 6 (ELECTRON).
Sofosbuvir/Valpatasvir Delivered High Cure (SVR12) Rates Among Gt 1 Subjects In Astral-1\textsuperscript{1,2}

- Of 328 GT 1 subjects in ASTRAL-1, there were 2 relapses: 1 GT 1a subject (1/209) and 1 GT 1b subject (1/118)\textsuperscript{1,2}

\textsuperscript{1} The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

\textsuperscript{2} EPCLUSA US full Prescribing Information, Gilead Sciences, Inc. Foster City, CA. June 2016.


Sofosbuvir/Valpatasvir Delivered High Cure (SVR12) Rates Among Gt 2 Subjects In Astral-1 And Astral-2

- The relapse rate was 0% (0/238) among subjects receiving EPCLUSA for 12 weeks and 5% (6/132) among subjects receiving SOF + RBV for 12 weeks.
Sofosbuvir/Valpatasvir Delivered High Cure (Svr12) Rates Among Gt 3 Subjects In Astral-3

- The relapse rate was 4% (11/276) among subjects receiving EPCLUSA for 12 weeks and 14% (38/272) among subjects receiving SOF + RBV for 24 weeks

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    - HIV/HCV co-infection
    - HCV in CKD patients
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    - DAA failures
The Challenge of Access

• Estimated 5,200,000 patients
  – 50% Identified
  – <10% cured

• Treated
  – 2014 – 130,000 to 146,000
  – 2015 – 243,000 to 268,000
  – 2016 – 227,000 to 264,000

The Challenge of Access

• Identify all with the disease
  – Screen baby boomer population, those with risk factors

• Of those with the disease
  – Barriers to treatment
  • Limitations by private insurance and by state Medicaid programs due to cost
  • Only stage 3 and 4 eligible
  • Negative substance abuse screenings
  • Numerous studies have identified cost-effectiveness of treatment at all stages
  – Lawsuits – generally effective
  – Several private insurers and state Medicaid programs have loosened restrictions
Overview

- Impact of chronic HCV Infection
- Current treatment recommendations

**Challenges**
- Access
- **HIV/HCV co-infection**
  - HCV in CKD patients
  - Post-transplant and decompensated patients
  - DAA failures

Challenges – HIV-HCV Co-infection

- With interferon-based treatments response rates were diminished
- With DAA’s co-infected patients do as well as mono-infected patients
- Access is often easier regardless of severity of disease
- DDI’s main obstacles
- HIV-HCV co-infection essentially no longer a challenge
Overview

- Impact of chronic HCV Infection
- Current treatment recommendations

**Challenges**

- Access
- HIV/HCV co-infection

**HCV in CKD patients**

- Post-transplant and decompensated patients
- DAA failures

Challenges – HCV in CKD Patients

- Elbasvir – Grazoprevir with or without ribavirin highly effective (95%) and safe in CKD patients, including on dialysis
- Ombitasvir/paritaprevir and dasabuvir without ribavirin in Gt 1b, with ribavirin in Gt 1a highly effective (95-100%) and safe in CKD patients
- Sofosbuvir safe and effective in CKD patients
- Treatment of CKD patients essentially no longer a challenge
Overview

• Impact of chronic HCV Infection
• Current treatment recommendations

• Challenges
  – Access
  – HIV/HCV co-infection
  – HCV in CKD patients
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  – DAA failures

Challenges – Post-transplant and Decompensated Patients

• More patients being effectively treated prior to transplant
• Some patients waiting until after transplant due to timing and concern about “MELD purgatory”
• Treatment highly effective and this is less of a challenge
HCV-TARGET: DAA Regimens in Kidney and Liver Transplant Recipients With HCV

- Prospective, observational cohort undergoing HCV treatment per the regional standards of care
  - 44 academic and 17 community medical centers in North America and Europe
  - Kidney, liver, or kidney/liver transplant recipients
  - Information collected from medical records and abstracted into a centralized data core

- Regimens (started before 9/2015)
  - Ledipasvir/sofosbuvir + RBV (95%)
  - Daclatasvir + sofosbuvir + RBV (1%)
  - Ombitasvir/paritaprevir/r + dasabuvir + RBV (4%)


Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Kidney (n=23)</th>
<th>Liver (n=229)</th>
<th>Kidney/Liver (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>≥65 years of age (%)</td>
<td>16</td>
<td>30</td>
<td>52</td>
</tr>
<tr>
<td>White/black (%)</td>
<td>45/32</td>
<td>78/8</td>
<td>57/17</td>
</tr>
<tr>
<td>HCV genotype (%)</td>
<td>2a/2b/3/4/5/6</td>
<td>52/32/10</td>
<td>56/35/9</td>
</tr>
<tr>
<td>Treatment experienced (%)</td>
<td>32</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Prior DAA failure (%)</td>
<td>3</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>HCV RNA (log_{10} IU/mL)</td>
<td>5.9</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>32</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.6</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Platelets (x10^9/µL)</td>
<td>180</td>
<td>142</td>
<td>128</td>
</tr>
<tr>
<td>Creatinine clearance (%)</td>
<td>≤30 mL/min</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;30 mL/min</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>


HCV-TARGET: Treatment Outcomes With DAA Regimens in Kidney and Liver Transplant Recipients

- Overall SVR12 rates ranged 83% to 93%
  - Higher SVR12 rates seen among liver transplant recipients

- Predictors of SVR12 with ledipasvir/sofosbuvir + RBV (odds ratios)
  - Albumin ≥3.5 g/dL: 4.1 (P<0.001)
  - Bilirubin ≤1.2 mg/dL: 3.8 (P<0.001)
  - No cirrhosis: 3.2 (P<0.001)
  - No decompensation: 3.9 (P<0.001)

- Regimens were well tolerated
  - Discontinuations due to adverse events (n=1)
  - Deaths (n=1)
  - Rejection episodes (n=1)
  - Kidney recipient (not related to HCV therapy)

SOLAR-1 and -2: Ledipasvir/Sofosbuvir + RBV in Decompensated Cirrhosis or Liver Transplantation

Phase 2, Exploratory Studies
Combined Analysis

Open-label studies
Genotype 1 or 4
Treatment-naïve or -experienced
Creatinine clearance >40 mL/min
Platelets >30K X 10³/µL
CPT ≤12

Impact of baseline RAVs on the primary endpoint (SVR12)
RBV dosing: fibrosing cholestatic hepatitis, Metavir F0-F3, CPT A (weight-based 1000-1200 mg/day); CBT B and C pre- and post-transplant (dose escalation 600-1200 mg/day).
Baseline demographics (CBT B and C):
Male: 69%-80%.
Mean age: 58-60 years.
White: 90%-93%.
Genotype 1a: 58%-62%.
Genotype 4: 6%.
HCV RNA: 5.5-6.4 log₁₀ IU/mL.
Prior HCV treatment: 69%-84%.
Median eGFR: 64-85 mL/min.
MELD >15: 25%-35%.

SOLAR-1 and -2: SVR12 Rates With Ledipasvir/Sofosbuvir + RBV in Decompensated Cirrhosis or Liver Transplantation

12-Week Regimen

No NSSA RAVs
93% 83%

Decompensated Cirrhosis*
(n=124/12)

Decompensated Cirrhosis†
(n=148/13)

NSSA RAVs
98% 100%

24-Week Regimen

No NSSA RAVs
95% 100%

Decompensated Cirrhosis*
(n=121/18)

Decompensated Cirrhosis†
(n=139/14)

NSSA RAVs
100% 100%

*Pre-and post-transplant; †post-transplant only.
Analysis with 15% assay cutoff.

**SOLAR-1 and -2: Ledipasvir/Sofosbuvir + RBV in Decompensated Cirrhosis or Liver Transplantation**

- RAVs at time of virologic failure
  - NS5A: 91%; NS5B: 16%

- Baseline NS5A RAVs and SVR12 rates
  - Total treated (n=622)
    - 80 had baseline NS5A RAVs and of these 5 did not achieve SVR12
    - No clinically meaningful impact on SVR12 rates for the majority of genotype 1 or 4 patients
    - Impact of baseline NS5A RAVs was greatest in those with decompensated cirrhosis who were treated for 12 weeks
  - Baseline NS5B RAVs had no impact on SVR12 rates


**European Compassionate Use Program: Daclatasvir + Sofosbuvir + RBV in Decompensated Cirrhosis**

- HCV patients with Child-Pugh B or C and no other treatment options (n=165)
  - Creatinine clearance >30 mL/min
  - Daclatasvir 60 mg + sofosbuvir 400 mg qd for 24 weeks (addition of RBV or shorter duration of treatment at the physician’s discretion)
  - Prior HCV treatment: 67%

- Safety
  - Overall well tolerated, most safety events related to pre-existing liver disease
  - Treatment-emergent serious adverse events (4%)
  - Discontinuations due to adverse events: 12%
  - Deaths: 5% (9/185; not related to study drugs)
    - Liver-related events (n=3), other (n=6)


**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patients (n=165)</th>
<th>Median age (years)</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Genotype (%)</td>
<td>26/35</td>
<td></td>
</tr>
<tr>
<td>1a/1b</td>
<td>26/35</td>
<td></td>
</tr>
<tr>
<td>3/other</td>
<td>27/12</td>
<td></td>
</tr>
<tr>
<td>Median HCV RNA log_{10} (IU/mL)</td>
<td>5.3-6.0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MELD score (%)</th>
<th>&lt;10</th>
<th>22</th>
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</thead>
<tbody>
<tr>
<td>10-15</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>&gt;21</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;1.2 mg/dL (%)</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;100 x10^9/L (%)</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt;35 g/L (%)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Liver transplant recipients (%)</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

European Compassionate Use Program: SVR12 Rates With Daclatasvir + Sofosbuvir + RBV in Decompensated Cirrhosis

- MELD scores were stable or improved at SVR12 in the overall Child-Pugh B/C subgroup
- SVR rates in patients with renal insufficiency
  - Child-Pugh B
    - Mild (n=29): 92%-100%
    - Moderate (n=10): 75%-100%
    - Severe (n=1): 100%
  - Child-Pugh C
    - Mild (n=3): 66%
    - Moderate (n=1): 50%

SVR12: Liver Transplant Subanalysis

Overview

• Impact of chronic HCV Infection
• Current treatment recommendations

• Challenges
  – Access
  – HIV/HCV co-infection
  – HCV in CKD patients
  – Post-transplant and decompensated patients
  – DAA failures

Challenges – DAA Failures

• Primary virologic failures – nonresponder while on treatment – infrequent
• Response with relapse – usually due to NS5A RAVs – occurs in a few percent of patients
• With continued use of DAAs, failures are beginning to increase in numbers
Ongoing Real-World Study: SVR12 Rates With Retreatment of Prior DAA Failures (Genotype 1)

- RAVs in simeprevir + sofosbuvir failures (n=27)
  - No RAVs: 18%
  - NS3/NS5B: 52%/15%
  - NS3 plus
    - NS5A: 4%
    - NS5B: 7%

- Retreatment regimens
  - Ledipasvir/sofosbuvir + RBV for 12 (n=10) or 24 (n=3) weeks
  - Ombitasvir/paritaprevir + dasabuvir + RBV for 12 (n=3) or 24 (n=1) weeks


Interim SVR12 Rates (ITT)

- 12 Weeks:
  - Ledipasvir/sofosbuvir + RBV: 100%
  - Ombitasvir/paritaprevir + dasabuvir + RBV: 90%

- 24 Weeks:
  - Ledipasvir/sofosbuvir + RBV: 100%
  - Ombitasvir/paritaprevir + dasabuvir + RBV: 75%

Ongoing Real-World Study: SVR12 Rates With Retreatment of Prior DAA Failures (Genotype 1)

- RAVs in ledipasvir/sofosbuvir and daclatasvir + sofosbuvir failures (n=22)
  - No RAVs: 5%
  - NS5A: 77%
  - NS5A plus either NS3 (5%), NS5B (9%) or NS3 + NS5B (5%)

- Retreatment regimens
  - Simeprevir + sofosbuvir + RBV
    - 12/24 weeks (n=6/11)
  - Ombitasvir/paritaprevir/r + dasabuvir + RBV
    - 12/24 weeks (n=4/1)


Interim SVR12 Rates (ITT)

- 12 Weeks:
  - Simeprevir + sofosbuvir + RBV: 100%
  - Ombitasvir/paritaprevir/r + dasabuvir + RBV: 75%
Ongoing Real-World Study: SVR12 Rates With Retreatment of Prior DAA Failures (Genotype 3)

- RAVs in sofosbuvir + RBV failures (n=14)
  - No RAVs: 79%
  - NS5A (A30K/S): 21%
- Retreatment regimens
  - Daclatasvir + sofosbuvir ± RBV for 12 (n=3) or 24 (n=10) weeks
  - Ledipasvir/sofosbuvir + RBV for 24 weeks (n=1)


**Summary**

- Excellent, effective treatments available in 2016 for the vast majority (>90%) of HCV patients
- HIV-HCV co-infection, CKD patients, post-transplant patients no longer considered a challenge
- DAA failures, decompensated patients still present some challenges
- Biggest challenge is limited access