Chronic Hepatitis C: A Multifaceted Disease

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Disclosures

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• Mallinkrodt-Research grant
• Abbvie – Consulting
• Bristol Myers Squibb – Consulting
• Trio Healthcare Analystics- Consulting
Hepatitis C: A Global Health Problem
170 to 200 Million (M) Carriers Worldwide

- United States: 3-4 M
- Americas: 12-15 M
- Western Europe: 5 M
- Eastern Europe: 10 M
- Southeast Asia: 30-35 M
- Far East Asia: 60 M
- Africa: 30-40 M
- Australia: 0.2 M

Background

• 170-180 million people are infected with hepatitis C virus (HCV).

• Annual death rate attributed to HCV is 500,000-700,000

• Endemic areas are mostly in underdeveloped countries

• 2/3 of the world’s HCV population live in countries that cannot provide hepatitis tests
Modes of Transmission

Blood transfusion prior to 1992

Organ and tissue transplantation

Nosocomial

Sexual contact

Tattoos, body piercing

Intranasal drug use

Injection Drug Use

Occupational exposure

Mother-to-infant

Current Prevalence of HCV Infection in the United States - NHANES

Prevalence of HCV Infection

Does not include: >2,000,000 inmates + 300,000-600,000 homeless + 680,000 IV drug users

Source: Ditah et al., *J Hep*, 2014
Persons for Whom HCV Testing is Recommended (CDC)

- **Adults born from 1945 through 1965 should be tested once (without prior ascertainment of HCV risk factors)**
- **HCV testing is recommended for those who:**
  - Currently injecting drugs
  - Ever injected drugs, including those who injected once or a few times many years ago
  - Have certain medical conditions, including persons:
    - who received clotting factor concentrates produced before 1987
    - who were ever on long-term hemodialysis
    - with persistently abnormal alanine aminotransferase levels (ALT)
    - who have HIV infection
  - Were prior recipients of transfusions or organ transplants, including persons who:
    - were notified that they received blood from a donor who later tested positive for HCV infection
    - received a transfusion of blood, blood components, or an organ transplant before July 1992
- **HCV- testing based on a recognized exposure is recommended for:**
  - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
  - Children born to HCV-positive women

Increases in HCV Infection Among Young Persons Who Inject Drugs (<30 Years Old)

In the US, 1.6 Million Incarcerated Persons are Infected with Hepatitis C, and Represent Reservoir for New Infections Within Correctional Institutions and the Community Upon Release

- “From a public health standpoint, the High concentration of patients in Correctional institutions with hepatitis C - now a curable contagious disease - presents a critical opportunity to curtail this epidemic”

HCV seroconversion increased from an estimated rate of: 1991: 0.42/100 person-years to 2010: 1.09/100 person-years and 2012: 1.34/100 person-years

Infections were attributable to high-risk behaviors including traumatic sex and sex while on methamphetamines
Most Americans With Chronic HCV Have Not Been Diagnosed and Few Have Been Treated

Overall: 3.2 million of U.S. population with chronic HCV

50%

(1.6M)

32-38%

(1.0-1.2M)

7-11%

(220,000 - 360,000)

5-6%

(170,000 - 200,000)

Diagnosed  Referred to Care  Treated  Successfully Treated

Spectrum of Disease

Acute HCV Infection
15%-45%
Recovery

55%-85%
Chronic HCV Infection

Chronic Hepatitis C
Mild — Moderate — Severe

Cirrhosis

End-Stage Liver Disease
Liver Transplantation

Hepatocellular Carcinoma
Death

Adapted from Hoofnagle. *Hepatology*. 1997;26(3 suppl 1):15S-20S.
Progression of Fibrosis on Biopsy

Stage 1: Fibrous expansion of some portal areas

Stage 2: Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3: Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)

Stage 4: Fibrous expansion of portal areas with marked bridging (portal to portal and portal to central)

Stage 5, 6: Cirrhosis, probable or defined

Cirrhotic liver: Gross anatomy of cadaver

Courtesy of Gregory Everson, MD.
Extrahepatic Manifestations Associated With HCV

**Hematologic**
- Mixed cryoglobulinemia\(^1\)
- Aplastic anemia\(^2\)
- Thrombocytopenia\(^2\)
- Non-Hodgkin’s b-cell lymphoma\(^2\)

**Dermatologic**
- Porphyria cutanea tarda\(^1\)
- Lichen planus\(^2\)
- Cutaneous necrotizing vasculitis\(^2\)

**Renal**
- Glomerulonephritis\(^1\)
- Nephrotic syndrome\(^2\)

**Endocrine**
- Hypothyroidism\(^2\)
- Diabetes mellitus\(^2\)

**Ocular**
- Corneal ulcer\(^2\)
- Uveitis\(^2\)

**Vascular**
- Necrotizing vasculitis\(^2\)
- Polyarteritis nodosa\(^2\)

**Neuromuscular\(^2\)**
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

**Autoimmune Phenomena\(^2\)**
- CREST syndrome

**Neuropsychiatric**
- Depression\(^1\)

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Incidence and Predictors of Hepatocellular Carcinoma Following SVR

VA Study Cohort

- 22,197 with HCV RNA tests available to determine SVR12
- 10,817 with SVR
- 11,380 without SVR
- 10,638 without HCC and 100 with HCC
- 10,865 without HCC and 425 with HCC

- Incidence of HCC with SVR 3.27/1000 PY (0.327% PY) and with no SVR 13.2/1000 PY (1.32% PY) [HR 0.358]
- Age, DM, cirrhosis and G3 risk factors post SVR

HCC Incidence Following SVR: By Cirrhosis

Cumulative incidence of HCC

Years After SVR

El-Serag H, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 90.
HCV and cryoglobulins

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, clinicoserological, and virological features of 170 patients with mixed cryoglobulinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD; range) age (years)*</td>
<td>51 (11; 29-73)</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean (SD; range) disease duration (years)</td>
<td>11.9 (6.4; 1-34)</td>
</tr>
<tr>
<td>Purpura</td>
<td>91%</td>
</tr>
<tr>
<td>Weakness</td>
<td>89%</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>83%</td>
</tr>
<tr>
<td>Arthritis (non-erosive)</td>
<td>10%</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>34%</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>36%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>36%</td>
</tr>
<tr>
<td>Renal involvement†</td>
<td>31%</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>70%</td>
</tr>
<tr>
<td>B cell non-Hodgkin’s lymphoma</td>
<td>7.5%</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2.4%</td>
</tr>
<tr>
<td>Mean (SD) cryocrit (%)</td>
<td>3.7 (7.0)</td>
</tr>
<tr>
<td>Type II/type III mixed cryoglobulins</td>
<td>2/1</td>
</tr>
<tr>
<td>Mean (SD) CH50 (units; normal, 160-220)</td>
<td>83 (58)</td>
</tr>
<tr>
<td>Mean (SD) C3 (mg/l; normal, 600-1300)</td>
<td>770 (280)</td>
</tr>
<tr>
<td>Mean (SD) C4 (mg/l; normal, 200-550)</td>
<td>100 (150)</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>24%</td>
</tr>
<tr>
<td>Antimitochondrial antibodies</td>
<td>10%</td>
</tr>
<tr>
<td>Antismooth muscle antibodies</td>
<td>23%</td>
</tr>
<tr>
<td>Anti-extractable nuclear antigen antibodies</td>
<td>7%</td>
</tr>
</tbody>
</table>

| Anti-HCV antibodies | 90% |
| HCV RNA | 86% |
| Anti-HBV antibodies | 40% |
| HBsAg | 3.5% |

*At presumed disease onset; †variably membranoproliferative glomerulonephritis. HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.
Lichen Planus

- Antibodies to HCV are present in 10-40% of patients with lichen planus
- Causality has not been established
- Resolution and exacerbations have been reported with interferon therapies
- Oral LP resolved/improved in 7 of 7 treated with Asun/Dac

Porphyria Cutanea Tarde (PCT)

- 50% of patients with PCT have HCV
- Improvement and remission has been documented with eradication of HCV infection
- No reports of response to DAA therapies

Type 2 Diabetes Mellitus

• Complex and incompletely understood
• Prevalence of incidence of DM in HCV is increased
  – 3 fold increase risk of DM in 40 year olds with HCV
• DM and insulin resistance (IR) are independet risk factors for liver fibrosis
• DM and IR increase the risk of HCC
Veterans with HCV who Reported Psychiatric or Substance Use Disorders

<table>
<thead>
<tr>
<th>Psychiatric or substance use disorder</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>81%</td>
</tr>
<tr>
<td>PTSD</td>
<td>62%</td>
</tr>
<tr>
<td>Substance Use (any)</td>
<td>58%</td>
</tr>
<tr>
<td>Heavy Alcohol Use (AUDIT-C≥4)</td>
<td>21%</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>20%</td>
</tr>
<tr>
<td>Schizophrenia/Psychosis</td>
<td>17%</td>
</tr>
</tbody>
</table>

Prevalence of extra-hepatic manifestations

Table 1. Pooled Prevalence and Odds Ratios for the Hepatitis C Extrahepatic Manifestations

<table>
<thead>
<tr>
<th>EHM</th>
<th>Prevalence in HCV, % (95% CI)</th>
<th>Prevalence in non-HCV, % (95% CI)</th>
<th>OR (95% CI)</th>
<th>No. of studies included in HCV and non-HCV (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MC</td>
<td>30.1 (21.4–38.9)</td>
<td>1.9 (0.4–3.4)</td>
<td>11.50 (4.56–29.00)</td>
<td>21 studies (n = 4145); 7 studies (n = 585)</td>
</tr>
<tr>
<td>Symptomatic MC (vasculitis)</td>
<td>4.9</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRD (including end-stage)</td>
<td>10.1 (6.7–13.4)</td>
<td>7.6 (4.7–10.5)</td>
<td>RR = 1.23 (1.12–1.34)</td>
<td>14 studies (n = 336,227 HCV; n = 2,665,631 non-HCV)</td>
</tr>
<tr>
<td>DM</td>
<td>15 (13–18)</td>
<td>10 (6–15)</td>
<td>1.58 (1.30–1.86)</td>
<td>31 studies (n = 61,843); 19 studies (n = 202,130)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>NA</td>
<td>NA</td>
<td>RR = 1.60 (1.34–1.86)</td>
<td>16 studies⁵</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>1.9 (1.2–2.5)</td>
<td>1.1 (0.3–1.8)</td>
<td>2.27 (1.41–5.66)</td>
<td>18 studies (n = 40,063); 8 studies (n = 138,811)</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>11.9 (7.6–16.2)</td>
<td>0.7 (0.00–3.3)</td>
<td>2.29 (0.19–27.09)</td>
<td>11 studies (n = 38,789); 2 studies (n = 136,845)</td>
</tr>
<tr>
<td>PCT</td>
<td>0.5 (0.1–0.8)</td>
<td>0.0 (0.0–0.1)</td>
<td>8.53 (4.15–17.52)</td>
<td>7 studies (n = 970,315); 3 studies (n = 18,763,644)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.0 (0.0–2.0)</td>
<td>0.09 (0.00–0.09)</td>
<td>2.39 (1.52–3.77)</td>
<td>4 studies (n = 10,970); 1 study (n = 199,568)</td>
</tr>
<tr>
<td>Depression</td>
<td>24.5 (14.1–34.9)</td>
<td>17.2 (13.4–21.0)</td>
<td>2.30 (1.31–4.01)</td>
<td>12 studies (n = 139,039); 3 studies (n = 127,506)</td>
</tr>
</tbody>
</table>

Younossi et al. Gastroenterology 2016;150:1599–1608
Patients with the following extrahepatic manifestations should be prioritized for HCV treatment:

- Severe renal impairment
- Type 2 diabetes and insulin resistance
- Fatigue
- Porphyria cutanea tarda
- Lichen Planus
Chronic HCV Infection Increases Mortality from Both Hepatic and Extrahepatic Diseases

All Causes (n=2394)

Liver Cancer (n=115)

Extrahepatic Diseases (n=2199)

* \( p < 0.001 \) for comparison among all 3 groups and \( p < 0.001 \) for HCV RNA detectable versus undetectable.

† \( p < 0.001 \) for comparison among all 3 groups and \( p = 0.002 \) for HCV RNA detectable versus undetectable.

Community-based, long-term, prospective study in Taiwan (REVEAL-HCV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer, 1991-2008).

Keeping your liver healthy

• Minimize alcohol consumption
• Exercise regularly and eat healthy
• Low salt diet
• Hepatitis A and B immunization if naive
HCV Therapy

- Successful hepatitis C treatment results in sustained virologic response (SVR) and is expected to benefit nearly all chronically infected persons.
- Treatment goal is to reduce all-cause mortality and liver-related complications, including end-stage liver disease, the need for liver transplantation, and hepatocellular carcinoma (HCC).

http://www.hcvguidelines.org/full-report-view
Sustained Virologic Response is Associated with a Reduction in Liver-Related Mortality and HCC

Liver-Related Mortality or Liver Transplantation

Hepatocellular Carcinoma

HCV Therapy

• Six highly potent DAA oral combination regimens are recommended for patients with HCV genotype 1 infection

• There are differences in the recommendation based on HCV subtype, the presence of cirrhosis, and the presence of baseline resistance-associated variants

http://www.hcvguidelines.org/full-report-view
## DAA Regimens for HCV

<table>
<thead>
<tr>
<th>Regimen</th>
<th>G1</th>
<th>G 2</th>
<th>G 3</th>
<th>G 4</th>
<th>G 5</th>
<th>G 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>✔️</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir/dasabuvir</td>
<td>✔️</td>
<td></td>
<td></td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir/sofosbuvir</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velpatasvir/sofosbuvir</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Daclatasvir/sofosbuvir</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Treatment of Genotype 1 Patients
### Sustained Viral Response Rates

<table>
<thead>
<tr>
<th>Regiment*</th>
<th>Cohort</th>
<th>Non cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LED (duration)</td>
<td>Treatment naïve</td>
<td>96-99% (8-12 wks)</td>
<td>94% (12 wks)</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced</td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
</tr>
<tr>
<td>SOF/SIM (duration)</td>
<td></td>
<td>95% (12 wks)</td>
<td>100% (24 wks)</td>
</tr>
<tr>
<td>3-D ± R (duration)</td>
<td>Genotype 1a</td>
<td>96% (12wks)</td>
<td>89-95% (12-24wks)</td>
</tr>
<tr>
<td></td>
<td>Genotype 1b</td>
<td>100% (12 wks)</td>
<td>99% (12 wks)</td>
</tr>
<tr>
<td>GZR/EBR</td>
<td>Genotype 1</td>
<td>94% (12 wks)</td>
<td>97% (12wks)</td>
</tr>
</tbody>
</table>

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; SIM – simeprevir; 3-D – ombitasvir, paritaprevir + ritonavir, dasabuvir; R-ribavirin; GZR – Grazoprevir; EBR – Elbasvir

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205834s000lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf

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ASTRAL-1: SVR12 by HCV Genotype

Feld J, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-2.
TRIO: Effectiveness of 8 or 12 week LDV/SOF in GT1, Treatment-naïve, Non-cirrhotic

Patient Disposition
TN, non-cirrhotic (n=895)

8 wks LDV/SOF (n=263)
- Death (n=0)
- LTFU (n=6)
- D/C (n=3)
- SVR achieved (n=251)
- SVR not achieved (n=3)

12 wks LDV/SOF ± RBV (n=632)*
- Death (n=2)
- LTFU (n=16)
- D/C (n=4)
- SVR achieved (n=604)
- SVR not achieved (n=6)

SVR12 by Fibrosis

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>95</td>
<td>98</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td></td>
<td>76</td>
<td>95</td>
</tr>
<tr>
<td>LTFU</td>
<td>42</td>
<td>52</td>
<td>143</td>
<td>31</td>
</tr>
<tr>
<td>D/C</td>
<td>53</td>
<td>81</td>
<td>203</td>
<td>144</td>
</tr>
</tbody>
</table>

| 12 wks   |    |    |    |    |
| Relapse  | 96 | 97 | 76 | 95 |
| Death    | 2  |    | 8  |    |
| LTFU     | 43 | 76 | 162|    |
| D/C      | 53 | 203| 170|    |

SVR12 Rates by Baseline Viral Load

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>&lt;6MM</th>
<th>6MM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td>242/254</td>
<td>8/8</td>
</tr>
<tr>
<td>12 wks</td>
<td>436/456</td>
<td>162/170</td>
</tr>
</tbody>
</table>

*21 Patients were on 12 weeks of LDV/SOF+RBV

Curry M, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 1046.
Recommendations for Decompensated Cirrhosis

• Most patients with decompensated cirrhosis receiving DAA therapy experienced improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12

## Decompensated G1 or 4 cirrhosis

<table>
<thead>
<tr>
<th>Geno 1 and 4 cirrhosis</th>
<th>Treatment naïve and ribavirin eligible</th>
<th>Treatment naïve and ribavirin ineligible</th>
<th>Treatment experience (prior Sofosbuvir treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ledipasvir and Sofosbuvir with initial low dose ribavirin increased as tolerated for 12 weeks</td>
<td>Velpatasvir and Sofosbuvir with weight based Ribavirin for 12 weeks</td>
<td>Ledipasvir and Sofosbuvir with initial low dose increased as tolerated for 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Velpatasvir and Sofosbuvir with weight based Ribavirin for 12 weeks</td>
<td>Daclatasvir and Sofosbuvir with initial low dose increased as tolerated for 12 weeks</td>
<td>Velpatasvir and Sofosbuvir with weight based Ribavirin for 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Ledipasvir and Sofosbuvir for 24 weeks</td>
<td>Velpatasvir and Sofosbuvir for 24 weeks</td>
<td>Daclatasvir and Sofosbuvir for 24 weeks</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org/full-report-view
Decompensated G2 or 3 cirrhosis

<table>
<thead>
<tr>
<th>Geno 2 and 3 cirrhosis</th>
<th>Velpatasvir and Sofosbuvir with weight based Ribavirin for 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve and ribavirin eligible, may or may not be candidate for LT including HCC</td>
<td>Daclatasvir and Sofosbuvir with initial low dose increased as tolerated for 12 weeks</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org/full-report-view
Sofosbuvir/Velpatasvir Fixed-Dose Combination for the Treatment of HCV in Patients With Decompensated Liver Disease: the Phase 3 ASTRAL-4 Study


1 Intermountain Medical Center, Murray, UT; 2 Baylor Research Institute, Dallas, TX; 3 Ochsner Medical Center, New Orleans, LA; 4 Duke University, Durham, NC; 5 Washington University School of Medicine in Saint Louis, MO; 6 Thomas Jefferson University, Philadelphia, PA; 7 University of Pennsylvania School of Medicine, Philadelphia, PA; 8 Texas Liver Institute, San Antonio, TX; 9 Mount Sinai Hospital, New York, NY; 10 NYU School of Medicine, New York, NY; 11 University of Michigan, Ann Arbor, MI; 12 University of Miami, Coral Gables, FL; 13 University of North Carolina at Chapel Hill-School of Medicine; 14 Gilead Sciences, Inc., Foster City, CA; 15 Columbia University Medical Center, New York-Presbyterian, New York, NY; 16 Beth Israel Deaconess Medical Center, Boston, MA

- The number of patients with decompensated cirrhosis caused by HCV is expected to increase
- Liver transplantation has been the only treatment available for such patients
- Recent trials with Sofosbuvir based treatments have shown it is possible to treat patients with HCV genotype 1 and 4 related decompensated cirrhosis
Overall SVR12

P-value < 0.001 for comparison of SVR12 rate to 1% for each treatment group. Error bars represent 95% confidence intervals.

CPT Shift: Baseline to Follow-up Week 12 Patients With SVR12

<table>
<thead>
<tr>
<th></th>
<th>Follow-up Week 12, % (n/n)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CPT A</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>CPT A</td>
<td>71 (10/14)</td>
</tr>
<tr>
<td>CPT B</td>
<td>17 (34/205)</td>
</tr>
<tr>
<td>CPT C</td>
<td>10 (1/10)</td>
</tr>
</tbody>
</table>

n=234; 5 patients had no follow-up Week 12 assessment.

MELD Change: Baseline to Follow-up Week 12
Patients With SVR12

No follow-up Week 12 assessment for 5 patients.

**TARGET Data and TRIO Data**

**HCV-TARGET: SVR12 by Use of PPI at Baseline with LDV/SOF**

- **No PPI at baseline**
- **With PPI at baseline**

**SVR12 Rates by PPI Usage – Intent to Treat**

*Reasons for DC include 10 patients with clinical issues, 2 patients that wished to stop treatment, 1 patient who was directed by the clinician to stop, and 5 patients whose reasons were not reported.*

**PPI Frequency**

- Once Daily (n=420)
- Twice Daily (n=34)

**Drug name**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dexlansoprazole</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>30</td>
<td>20</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>High dose</td>
<td>≥60</td>
<td>≥40</td>
<td>≥30</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Completed treatment as of 7/1/15 and have available virological outcomes. Patients who discontinued due to AE or were lost to follow-up are excluded.
98 patients with treated HCC before DAA and with CR

Excluded
3 HCC within week of DAA
9 absence of CR
2 treated with IFN
2 prior LT
8 Non characterized nodules
7 no radiological followup before DAA

58 confirmed HCC radiological assessment after DAA

16 HCC recurrence

42 HCC CR

• 7/16 had been treated initially with resection and 9/16 with ablation
• Median time from HCC treatment to DAA was 11.2m (25%-75%: 3.6-23.2)
• Median time from CR to DAA was 1.7 and 1.3 for HCC recurrent patient
• Median time from CR to recurrence was 3.5 months (1.1-8)
• Recurrence rate is higher than observed in historical non DAA treated controls
Financial denials

- Multivariable analysis identified Medicaid insurance, absence of cirrhosis and DAA prescription in the initial 3 months associated with higher risk of denial.
- Older age and Medicare coverage were associated with lower risk of denial.
- Median time for prescription fill was longer for Medicaid patients.

Lo Re et al. Clinical Gastroenterology and Hepatology 2016, doi: 10.1016/j.cgh.2016.03.040