By 2020, it is estimated that 1,000,000 million HCV-infected individuals will have cirrhosis

Davis et al. GASTROENTEROLOGY 2010;138:513-521
Liver Transplant Projection From 2013 to 2043

- Model to forecast the effect of birth cohort screening and new therapies on need for liver transplants for the next 30 years
- Based on model previously developed by Davis et al and adapted to include only those born 1945-1965
- Some assumptions:
  - All stages of fibrosis treated at same rate; response to new therapies assumed to be 90% for all individuals
  - All patients with decompensated cirrhosis or HCC within Milan criteria considered as potential transplant candidates

Potential Transplant Need: Treatment of all candidates and SVR of 90% will still require ≈22,000 transplants/year in 2033

- No treatment
- 25% treated
- 50% treated
- 75% treated
- All treated

1. Desai et al. AASLD 2013. Abstract 1427

Therapeutic options for HCV infected individuals with cirrhosis
### Preferred Treatment Recommendations:

**Initial Therapy or Relapsed after Prior PR**

**AASLD-IDSA**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>Sofosbuvir + Ledipasvir 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + simeprevir 12 weeks-24 weeks†</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/r+Ombitasvir+Dasabuvir±RBV 12-24 weeks²</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Sofosbuvir + RBV 12 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Sofosbuvir + RBV 24 weeks</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>IFN eligible: Sofosbuvir + PR 12 weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: Sofosbuvir + RBV 24 weeks</td>
</tr>
<tr>
<td>Genotype 5 or 6</td>
<td>Sofosbuvir + PR 12 weeks</td>
</tr>
</tbody>
</table>

| PR: Pegylated interferon + Ribavirin. |
| † Currently recommended only for patients who require immediate treatment. |
| ‡1 Naïve or treatment experienced patients without cirrhosis receive 12 weeks, cirrhotic patients all receive 24 weeks. |
| 2. Genotype 1a with ribavirin, genotype 1b without cirrhosis do not require ribavirin. Cirrhotic patients with genotype 1a should receive 24 weeks though some populations can be considered for shorter duration. |

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### Study Design

**GT 1 Treatment-Naïve (ION-1)**

- GT 1 HCV treatment-naïve patients in Europe and USA
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥50,000/mm³, no neutrophil minimum
- 865 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b) and cirrhosis

---

*References*


ACG 2015 Boston Hepatitis School
Copyright 2015 American College of Gastroenterology
SVR12: Cirrhosis
GT 1 Treatment-Naïve (ION-1)

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>94/324</td>
<td>94/313</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/333</td>
<td>100/363</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.


Results: Reasons For Not Achieving SVR
GT 1 Treatment-Naïve (ION-1)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV/SOF</td>
<td>LDV/SOF+RBV</td>
</tr>
<tr>
<td>SVR12</td>
<td>211 (99)</td>
<td>211 (97)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>2 (&lt;1)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

- Single on-treatment breakthrough was due to non-compliance.
- Patient had no detectable levels of LDV or SOF at the time of virologic failure.
TURQUOISE-II Study Design: Phase 3 Trial Conducted Exclusively in GT1-Infected Cirrhotic Patients (N=380)

3D + RBV
(N=208)

3D + RBV
(N=172)

All patients to be followed through 48 weeks post-treatment

Day 0 Week 12 Week 24

3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID

RBV: 1000-1200 mg daily according to body weight (<75 kg and ≥75kg, respectively)

TURQUOISE-II Results: Naïve ITT SVR12 Rates
HCV Subtype 1a and 1b

SVR12, % Patients

HCV Subtype 1a

59/64 52/56

HCV Subtype 1b

100 100

3D + RBV

12-week arm

24-week arm
**TURQUOISE-II: Patients Not Achieving SVR12**

<table>
<thead>
<tr>
<th>Event, n/N (%)</th>
<th>12-Week Arm (N=208)</th>
<th>24-Week Arm (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not achieving SVR12</td>
<td>17/208 (8.2)</td>
<td>7/172 (4.1)</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>4/208 (1.9)</td>
<td>3/172 (1.7)</td>
</tr>
<tr>
<td>Adverse event, n</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Withdraw consent/other, n</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakthrough</td>
<td>1/208 (0.5)</td>
<td>3/172 (1.7)</td>
</tr>
<tr>
<td>Relapse through PTW12</td>
<td>12/203 (5.9)*</td>
<td>1/164 (0.6)**</td>
</tr>
</tbody>
</table>

Virologic failure occurred in 17/380 patients (4.5%)

15 of these patients had at least 1 resistance-associated variant at the time of virologic failure

- D168V (NS3) and Q30R (NS5A) seen most frequently in GT1a-infected patients

The significance and persistence of these variants are under investigation

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**TURQUOISE-II: Safety Overview**

<table>
<thead>
<tr>
<th>Event, %</th>
<th>12-Week Arm (N=208)</th>
<th>24-Week Arm (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>91.8</td>
<td>90.7</td>
</tr>
<tr>
<td>Severe AE</td>
<td>6.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Serious AE</td>
<td>6.3</td>
<td>4.7</td>
</tr>
<tr>
<td>AE Leading to Drug Discontinuation</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Death*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*1 patient with a non-treatment emergent death (occurring 80 days after last dose of study treatment), not attributed to 3D or RBV.

- Hepatic decompensation events were rare (4 patients, 1.1%)
  - None were considered related to study drug
COSMOS: Study design: Simeprevir + Sofosbuvir ± RBV PEG IFN/RBV Null responders

Week
0 4 12 24 36 48

Arm 1: SMV + SOF + RBV
Arm 2: SMV + SOF
Arm 3: SMV + SOF + RBV
Arm 4: SMV + SOF

Post-treatment follow-up

Enrolment ratio 2:1:2:1

- Cohort 1: Prior null responders (METAVIR F0-F2)
  - Final SVR12
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)
  - Interim SVR4
- SMV 150 mg QD + SOF 400 mg QD +/- RBV 1000/1200 mg/day (BID)

COSMOS: Simeprevir + Sofosbuvir ± RBV in Genotype 1 Naïve Cirrhosis HCV Patients

- Randomized phase IIa study

Pts with GT1 HCV
Cohort 2: naïve F4 (N = 17)

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

**Preferred Treatment Recommendations:**

**Partial or Null Response to Prior PR†**

**AASLD-IDSA**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Prior PR</th>
<th>Sofosbuvir + ledipasvir 12-24 weeks ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>Prior PR-based triple therapy</td>
<td>Sofosbuvir + ledipasvir 12-24 weeks ¹</td>
</tr>
<tr>
<td>Genotype 2</td>
<td></td>
<td>Sofosbuvir + RBV 12-16 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td></td>
<td>Sofosbuvir + RBV 24 weeks</td>
</tr>
<tr>
<td>Genotype 4</td>
<td></td>
<td>Sofosbuvir + PR 12 weeks</td>
</tr>
<tr>
<td>Genotype 5 or 6</td>
<td></td>
<td>Sofosbuvir + PR 12 weeks</td>
</tr>
</tbody>
</table>

PR: Pegylated interferon + Ribavirin.

¹ sofosbuvir/ledipasvir for 12 weeks in non-cirrhotics, 24 weeks in cirrhotic patients
² sofosbuvir/simeprevir for 12 weeks in non-cirrhotics, 24 weeks in cirrhotic patients
³ Paritaprevir/r+Ombitasvir+Dasabuvir+RBV for 12 weeks in cirrhotic genotype 1b and non-cirrhotic patients. Genotype 1a null responders require 24 weeks of therapy, genotype 1a partial and relapsers may be considered for 12 or 24 weeks of therapy.

---

**GT 1 Treatment-Experienced (ION-2): Study Design**

- GT 1 HCV patients who had failed prior IFN-based therapy, including regimens containing a NS3/4A protease inhibitor
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥50,000/mm³, no neutrophil minimum
- 440 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b), cirrhosis, prior treatment response

SVR12: Absence of Cirrhosis vs Cirrhosis
GT 1 Treatment-Experienced (ION-2)

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>19/22</td>
<td>18/22</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>22/22</td>
<td>22/22</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.

Results: Reasons For Not Achieving SVR related to relapse
GT 1 Treatment-Experienced (ION-2)

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF n=109</td>
<td>102 (94)</td>
<td>108 (99)</td>
</tr>
<tr>
<td>LDV/SOF+RBV n=111</td>
<td>107 (96)</td>
<td>110 (99)</td>
</tr>
</tbody>
</table>

- Single on-treatment breakthrough was due to non-compliance.
- Patient had no detectable levels of LDV or SOF at multiple time points prior to and at the time of virologic failure.
LDV/SOF in Cirrhotic Patients Who Previously Failed PI-Based Triple Therapy

Double-blind, placebo-controlled study in cirrhotic GT1 patients who failed both PegIFN+RBV and PI+PegIFN+RBV regimens in France (null or partial responders)

- 30% of patients were previously enrolled in the CUPIC cirrhotic study
- RBV dosing was weight-based (<75 kg = 1000 mg; ≥75 kg = 1200 mg)
- Randomization was stratified by:
  - HCV genotype
    - 1a vs. 1b (mixed or other GT 1 results stratified as GT 1a)
  - Prior HCV therapy treatment response
    - Never achieved HCV RNA <LLOQ vs. Achieved HCV RNA <LLOQ
  - Cirrhosis was determined by: Biopsy, Fibroscan >12.5 kPa, or FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2

TURQUOISE-II Results: ITT SVR12 Rates by Prior Treatment Response in HCV Subtype 1a and 1b

3D + RBV
- 12-week arm
- 24-week arm

HCV Subtype 1a
- Relapse Partial Response Null Response
- 93 100 100 100 80 93 100 100 100

HCV Subtype 1b
- Relapse Partial Response Null Response
- 100 100 100 100 86 100 100 100 100
COSMOS: Simeprevir + Sofosbuvir ± RBV in Genotype 1 Null responding Cirrhosis HCV Patients

- Randomized phase IIa study

Wk 12

Wk 24 SVR 12

Pts with GT1 HCV Cohort 2: naives and previous null responders, F4 (N = 22)

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


Decompensated Cirrhosis
Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis

- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- Stratified by CTP class B [7-9] or C [score 10–12]*
- Broad inclusion criteria:
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing: dose escalation, 600–1200 mg/d

Results: SVR12

SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV
Change From Baseline to Follow-Up
Week 4

CPT B
12 wk (n=30)*
24 wk (n=29)*

CPT C
12 wk (n=23)*
24 wk (n=26)*

Flamm, AASLD, 2014, Oral #239

Genotype 2/3 options in cirrhosis

*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.
The current standard of care: Genotypes 2/3

- HCV genotype 2, regardless of eligibility for IFN therapy or treatment failure with PEG/RBV: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) for 12 weeks
  - cirrhotics may benefit from extension to 16 weeks
- HCV genotype 3, regardless of eligibility for IFN therapy or treatment failure with PEG/RBV: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) for 24 weeks
  - Alternative regimen: HCV genotype 2&3 PEG/RBV nonresponders: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) plus weekly PEG for 12 weeks in IFN eligible patients

FISSION Study: Treatment-Naïve, Genotype 2 or 3 Patients

<table>
<thead>
<tr>
<th>Week</th>
<th>SOF + RBV*, n=256</th>
<th>PegIFN + RBV* (SOC), n=243</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV n=256</th>
<th>Peg-IFN + RBV n=243</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>48 (20–72)</td>
<td>48 (19–77)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>171 (67)</td>
<td>156 (64)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>223 (87)</td>
<td>212 (87)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>108 (43)</td>
<td>106 (44)</td>
</tr>
<tr>
<td>GT 3, n (%)</td>
<td>183 (72)</td>
<td>176 (72)</td>
</tr>
<tr>
<td>Mean HCV RNA, log10 IU/mL (range)</td>
<td>6.0 (3.2–8.3)</td>
<td>6.0 (3.2–7.6)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>50 (20)</td>
<td>50 (21)</td>
</tr>
</tbody>
</table>

*RBV dose 1,000-1,200 mg/day for SOF + RBV and 800 mg/day for PegIFN + RBV

Gane E, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 5.
Results: SVR12 by Genotype and Cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cirrhosis</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
<th>No cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td>91/111</td>
<td>82/84</td>
<td>62/26</td>
<td>71/26</td>
</tr>
<tr>
<td>GT 3</td>
<td>89/145</td>
<td>99/139</td>
<td>34/30</td>
<td>30/30</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.

FUSION Study: Treatment-Experienced, Genotype 2 or 3 Patients

<table>
<thead>
<tr>
<th>Week</th>
<th>SOF + RBV, n=103</th>
<th>Placebo</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>73 (71%)</td>
<td>67 (68%)</td>
<td>54 (24–70%)</td>
</tr>
<tr>
<td>16</td>
<td>64 (62%)</td>
<td>63 (64%)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>36 (35%)</td>
<td>32 (33%)</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>78 (76%)</td>
<td>73 (75%)</td>
<td></td>
</tr>
</tbody>
</table>

SOF dose 400 mg once daily; RBV dose 1,000-1,200 mg/day

* Nelson D, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 6.
Results: SVR12 by HCV Genotype/Cirrhosis

- **SOF + RBV 12 weeks**
  - No cirrhosis: 96/25/26
  - Cirrhosis: 100/23/23

- **SOF + RBV 16 weeks**
  - No cirrhosis: 60/6/16
  - Cirrhosis: 78/7/19

Error bars represent 95% confidence intervals.

Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients With HCV Genotype 2 or 3

- **GT 2/3**
  - SOF + RBV (n=334)
  - SVR12
  - Placebo (n=85)
  - SVR12

- **GT 2**
  - SOF + RBV (n=73)
  - SVR12

- **GT 3**
  - SOF + RBV (n=250)
  - SVR12

- Study amended due to data suggesting GT 3 patients would benefit from >12 weeks of treatment
  - Treatment extended to 24 weeks for GT 3 patients, irrespective of treatment history
  - Patients randomized to placebo offered treatment in alternative protocol

Zeuzem et al. AALSD 2013 LB-28
SVR12 in GT 3 Patients Treated for 24 Weeks

Zeuzem et al. AALSD 2013 LB-28

LONESTAR-2: 12 weeks PR/Sofosbuvir
SVR12 by Cirrhosis Status

Error bars represent 95% confidence intervals

**ALLY-3: Study Design**

**GT 3**
- Treatment-naive
  - N = 101
- Treatment-experienced
  - N = 51

**Follow-up**
- DCV 60 mg + SOF 400 mg QD
- Day 1
- Week 12
- Week 24
- Week 36

- **Primary endpoint:** SVR12
  - HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12

- **Eligible patients**
  - Age ≥18 years with chronic GT 3 infection and HCV RNA ≥10,000 IU/mL
  - Treatment-naive or -experienced (prior treatment failures), including patients with cirrhosis
  - Those who received prior treatment with NS5A inhibitors were excluded

*Assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).
SVR12 in Patients With Cirrhosis

Among patients with cirrhosis, 34% (11/32) had baseline platelet counts < 100,000/mm³.

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**Summary**

- **All oral therapies for genotype 1 subjects are approved in 2014**
  - Expect > 90% SVR, 12-24 week duration
  - Cirrhotic patients: Some will require 24 weeks
  - Interferon will not be required
  - RBV free therapies also desirable
  - Initial data in decompensated liver disease
- **Genotype 2 High SVR rates regardless of cirrhosis**
- **Genotype 3 High SVR rates in treatment naïve patients**
  - Additional strategies for cirrhotic non-responders