Hepatitis C Treatment: 2016

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What is HCV?
HCV History

• An RNA virus that used to be known as non-A, non-B hepatitis until it was discovered in 1988¹

• No vaccine available

• First therapy approved in 1991²

• Before 2011, HCV treatment could last as long as a year, with cure* (SVR) rates of 40%–50% for the most common genotype in the US³

• Since that time, scientific advances have made HCV treatment shorter and more effective

• There are interferon-free treatment options available that have shown cure (SVR) rates of 90% and greater in clinical studies⁴

*Cure, also known as sustained virologic response (SVR), is defined as no detectable HCV in the blood at 12 or more weeks after therapy is complete⁴,⁵

HCV Treatment Advances Through The Years

- **1991**: Interferon approved
- **1998**: Ribavirin approved
- **2001**: PEGylated interferon approved
- **2011-Present**: Direct-acting antiviral agents approved
HCV Genotypes

• 6 HCV genotypes\(^1\)
• Genotypic prevalence varies by geography\(^1\)
• Genotype 1 is the most common in the US and accounts for approximately 79% of HCV infections\(^1\)

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HCV GENOTYPE (GT) PREVALENCE VARIES GLOBALLY, BUT IS PREDOMINANTLY GT 1, GT 2, AND GT 3 IN THE US$^{1,2}$

HCV is a systemic disease that may affect organs other than the liver\textsuperscript{1-16}

**Extrahepatic Manifestations**

Mixed cryoglobulinemia vasculitis
Lymphoproliferative disorders
Peripheral neuropathy\textsuperscript{a}
Membranoproliferative glomerulonephritis\textsuperscript{a}
Insulin resistance
Cutaneous manifestations

* (eg, lichen planus, porphyria cutanea tarda, palpable purpura\textsuperscript{a})*

HCV may increase risk for diseases and conditions outside the liver\textsuperscript{1-16}

Associated Extrahepatic Conditions

**INCREASED RISK FOR:**

- Depression
- Carotid atherosclerosis/atherothrombosis
- Type 2 diabetes mellitus
- Hypertension
- Congestive heart failure
- Chronic kidney disease
- End-stage renal disease
- Kidney cancer
- Other renal manifestations (\textit{eg}, glomerulonephritis, proteinuria)\textsuperscript{a}
- Low bone mineral density (BMD)
- Rheumatologic manifestations (\textit{eg}, polyarthralgia, polyarthritis)\textsuperscript{a}
- Fatigue

**POSSIBLE INCREASED RISK FOR\textsuperscript{b}:**

- Neurologic impairment/disorders
- Stroke
- Coronary artery disease/ischemic heart disease

\textsuperscript{a}Secondary to mixed cryoglobulinemia vasculitis
\textsuperscript{b}Conflicting or equivocal data from studies

Impact of HCV
More Americans Die of HCV Than Any Other Infectious Disease.

19,659 deaths in 2014
An average annual increase of 865 deaths (6.2%) from 2003 to 2014

Estimated number of new infections is 30,000 per year
Deaths Associated with HCV

- 2003: 17,915
- 2013: 19,368

- HCV
- 60 other infectious conditions

Source: Healio.com
HCV Has a Mortality Rate That Exceeds HIV$^{1,2,a}$

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HCV Is Underdiagnosed and Undertreated

AN ESTIMATED 3.5 MILLION AMERICANS HAVE CHRONIC HCV\(^1\)

- It is estimated that 3.5 million Americans have chronic hepatitis C\(^1\)
- Approximately 9% of infected individuals successfully treated\(^1\)

In a study, approximately 45% of untreated HCV patients were projected to develop cirrhosis by 2030\(^2\).

HCV is a progressive disease.\(^2\) Patients who develop cirrhosis are at greater risk for developing liver cancer and other liver-related complications\(^3\).

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In the US, HCV is the Leading Cause of Liver Transplantation$^1$ and Liver Cancer$^2$

Liver Complications in HCV Patients Contribute to a Shorter Lifespan$^3$

Pregnancy, Vertical Transmission of HCV

• Women with HCV generally do well and don’t have a lot of complications.

• The big issue for HCV-infected pregnant women is the risk of transmission to their infants.
  – While the overall rate is between 3% and 15% depending on how and when you calculate.

• Cannot predict who will transmit

• If a mother does not have active virus in her blood, she will not transmit HCV.
HCV Can Be Cured
Unlike Some Chronic Conditions, HCV Can Be Cured
**Why Is Cure Possible?**

HCV does not integrate into the nuclei of infected cells, while HBV and HIV DNA are incorporated into the nucleus of the cell\(^1\)

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*HBV cccDNA (covalently closed circular DNA): accumulates in hepatocyte nuclei, acting as a template for viral messenger RNA transcription.*

†*HIV proviral DNA: integrates into the chromatin of infected cells, acting as the template for the transcription of viral genes.*

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What Defines HCV Cure?

Cure, also known as sustained virologic response (SVR), is defined as no detectable HCV in the blood at 12 weeks after therapy is complete\(^1,2\)

- In some instances, HCV treatment does not result in cure, or SVR, because the virus does not reach undetectable levels or because it does not stay undetectable after therapy completion
- In one study, of those patients who reached SVR, 99% had undetectable levels of HCV RNA more than 4 years after treatment end\(^3\)
- These patients do not experience viral recurrence and may be considered to be cured\(^3\)

Cure Can Lead to Improvements in Disease Complications\textsuperscript{1,2} and Mortality\textsuperscript{3}

- Cure, or SVR, is associated with improvements in disease complications, such as rates of hepatocellular carcinoma, ascites, hepatic encephalopathy, and variceal bleeding\textsuperscript{1,2}

![Graph showing mortality percentage over years with and without SVR.]

SVR is also associated with reduced risk of all-cause mortality\textsuperscript{3}\textsuperscript{*}

\*These data are from an 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).

Limited Success With Risk-Based Screening

• Since 1998, the CDC has recommended screening individuals largely based on behavioral risk factors (eg, IV drug use, tattoos from unregulated environments)\(^1\)

• Risk-based screening has had limited success, as shown by the large number of undiagnosed individuals\(^1\)

• HCV is also much more prevalent among baby boomers, persons born between 1945–1965, than other age cohorts\(^1\)

• HCV screening guidelines include both risk-based and age-based factors
  • Expand screening to all baby boomers regardless of the presence of risk factors

CDC, USPSTF, and AASLD Recommend the One-Time Screening of All Baby Boomers, Regardless of Risk Factors\textsuperscript{1-3}

Baby boomers: born between 1945 and 1965

\textbf{~75\% OF ALL HCV PATIENTS ARE BABY BOOMERS}\textsuperscript{4}

Regardless of Any Symptoms, Screen Patients Who Have Any of These Risk Factors\(^1\-^3\)

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons who ever injected illegal drugs</td>
</tr>
<tr>
<td>HIV-infected patients</td>
</tr>
<tr>
<td>Persons who have received tattoos from unlicensed or unregulated environments</td>
</tr>
<tr>
<td>Those with certain medical conditions, including:</td>
</tr>
<tr>
<td>• Persons who received clotting factor concentrates produced before 1987</td>
</tr>
<tr>
<td>• Persons who were ever on long-term hemodialysis</td>
</tr>
<tr>
<td>• Persons with persistently abnormal alanine transaminase levels</td>
</tr>
<tr>
<td>Prior recipients of transfusions or organ transplants, including:</td>
</tr>
<tr>
<td>• Persons who were notified that they received blood from a donor who later tested positive for HCV infection</td>
</tr>
<tr>
<td>• Persons who received a blood transfusion, blood components, or an organ transplant before July 1992</td>
</tr>
<tr>
<td>Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-positive blood</td>
</tr>
<tr>
<td>Children born to an HCV-positive mother</td>
</tr>
</tbody>
</table>

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Screen Whether or Not Symptoms Are Present\(^1,2\)

- HCV is often asymptomatic
- Elevated liver enzymes are not present in all infected individuals
- USPSTF granted a grade B recommendation for HCV screening\(^2\)
  - Benefits of HCV screening outweigh the risks for appropriate individuals

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How to Screen

- HCV is screened using a simple blood test to detect the presence of antibodies against HCV
- A positive antibody test is an indicator of exposure to HCV
  - Elevated liver enzymes are not present in all infected individuals
- Talk with the patient before screening
  - Explain why he/she should be screened
  - Tell the patient that HCV is a progressive disease
  - Describe the screening process

Consider selecting a lab’s “reflex-testing” option at the screening step so an HCV RNA test will be run automatically if the antibody test is positive. (CPT CODE 86804)

Enable an EHR flag or standing order as a reminder to screen, diagnose, and refer patients.
Such reminders have proven helpful in improving outcomes.

Next Steps After HCV Antibody Test Results

**Antibody Negative**
- Patient not exposed to HCV
- No further action needed, unless exposure suspected in past 6 months
  - If suspected, consider re-testing for HCV antibodies or running an HCV RNA test

**Antibody Positive**
- Patient exposed to HCV
- An HCV RNA test is needed to confirm the chronic HCV diagnosis
  - If the reflex option was ordered for the screening test, the antibody and HCV RNA results will be returned at the same time
Diagnose
Prevalence in US population

Genotype 1: 74%
Genotype 2: 15%
Genotype 3: 7%
Genotypes 4-6: 4%

Assessing Candidates for Treatment
Pre-Treatment Assessment of Fibrosis

- Assess the degree of hepatic fibrosis
  - Liver biopsy
    - Diagnostic standard
    - Also provides assessment for other causes of liver disease
    - Subject to sampling error, observer variability
    - Invasive procedure
    - Major complications rare, but minor ones common

- Non-invasive testing
  - Indirect serum biomarkers: e.g. APRI, FIB-4
  - Direct serum biomarkers
  - Elastography (Fibroscan)

- Clinically evident cirrhosis
# Noninvasive Liver Tests May Be a Good Alternative to Liver Biopsy

## Magnetic Resonance Imaging
- Magnetic resonance elastography to estimate liver stiffness
- Computed tomography to identify complications of cirrhosis

## FibroScan® Transient Elastography (Ultrasound)
- Estimates liver stiffness
- Identifies complications of cirrhosis

## Blood Testing
- Fibrosure® uses biochemical marker levels to predict mild to significant fibrosis

## Computational Methods
- APRI score \((\frac{\text{AST}}{40})/\text{Plts} \times 100\)
- Fib-4 score \((\frac{\text{AST} \times \text{Age}}{\text{Plts} \times \sqrt{\text{ALT}}})\)

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APRI, AST to platelet ratio index; AST, aspartate aminotransferase; ALT, alanine transferase.

**FibroSure**

- The FibroSure score is calculated from the results of a 6-parameter blood test.
- Combines 6 serum markers with the age and gender of the patient:
  - Alpha-2 macroglobulin
  - Haptoglobin
  - Apolipoprotein A1
  - Gamma-glutamyl-transpeptidase (GGT)
  - Total bilirubin
  - Alanine transaminase (ALT)
# The Conversion of FibroSure Score Into Fibrosis Stages

<table>
<thead>
<tr>
<th>FibroSure</th>
<th>METAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75 – 1.00</td>
<td>F4</td>
</tr>
<tr>
<td>0.73 – 0.74</td>
<td>F3-F4</td>
</tr>
<tr>
<td>0.59 – 0.72</td>
<td>F3</td>
</tr>
<tr>
<td>0.49 – 0.58</td>
<td>F2</td>
</tr>
<tr>
<td>0.32 – 0.48</td>
<td>F1 – F2</td>
</tr>
<tr>
<td>0.28 – 0.31</td>
<td>F1</td>
</tr>
<tr>
<td>0.22 – 0.27</td>
<td>F0-F1</td>
</tr>
<tr>
<td>0.00 – 0.21</td>
<td>F0</td>
</tr>
</tbody>
</table>
The FibroSure Test Score (in this case 0.88) May Indicate the Presence of Cirrhosis
Treatment

Hepatitis C
What Are the Key Elements of an Ideal HCV Regimen?

- Highly Effective
- Safe and Tolerable
- Pan-Genotypic
- Easy Dosing, All Oral
- Few Drug-Drug Interactions
HCV Life Cycle and Direct Acting Antiviral (DAA) Targets

Direct-Acting Antiviral Agents (DAAs) - Key Characteristics

**NS3 /4A Inhibitors (Protease inhibitor PI):**
- High potency
- Limited genotypic coverage
- Low barrier to resistance

**NS5B Nucleos(t)ide Inhibitors (NI):**
- Intermediate potency
- Pan genotypic coverage
- High barrier to resistance

**NS5A Inhibitors:**
- High potency
- Multi-genotypic coverage
- Low barrier to resistance

**NS5B Non Nucleoside Inhibitors (NNI):**
- Intermediate potency
- Limited genotypic coverage
- Low barrier to resistance
DAA’s Available: 2016

- sofosbuvir (Sovaldi)
- simeprevir (Olysio)
- ombitasvir / paritaprevir / ritonavir / dasabuvir (Vikera Pak)
- ledipasvir / sofosbuvir (Harvoni)
- daclatasvir (Daklinza)
- ombitasvir / pritaprevir / ritonavir (Technivie)
- elbasvir and grazoprevir (Zepatier)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>n</th>
<th>Regimen</th>
<th>Duration, Wks</th>
<th>SVR12, %</th>
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</thead>
<tbody>
<tr>
<td>NEUTRINO[1]</td>
<td>Tx-naive GT 1</td>
<td>292</td>
<td>SOF + P/R</td>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 4</td>
<td>28</td>
<td>SOF + P/R</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 5/6</td>
<td>7</td>
<td>SOF + P/R</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>FISSION[2]</td>
<td>Tx-naive GT 2</td>
<td>70</td>
<td>SOF + RBV</td>
<td>12</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 3</td>
<td>183</td>
<td>SOF + RBV</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>FUSION[3]</td>
<td>Tx-experienced GT 2</td>
<td>36</td>
<td>SOF + RBV</td>
<td>12</td>
<td>86</td>
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<tr>
<td></td>
<td>Tx-experienced GT 3</td>
<td>64</td>
<td>SOF + RBV</td>
<td>12</td>
<td>30</td>
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<tr>
<td></td>
<td>Tx-experienced GT 2</td>
<td>32</td>
<td>SOF + RBV</td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Tx-experienced GT 3</td>
<td>63</td>
<td>SOF + RBV</td>
<td>16</td>
<td>62</td>
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<tr>
<td></td>
<td>IFN-UII GT 3</td>
<td>98</td>
<td>SOF + RBV</td>
<td>12</td>
<td>61</td>
</tr>
<tr>
<td>VALENCE[5]</td>
<td>Tx-naïve or experienced GT2</td>
<td>73</td>
<td>SOF + RBV</td>
<td>12</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Tx-naïve or experienced GT3</td>
<td>250</td>
<td>SOF + RBV</td>
<td>24</td>
<td>84</td>
</tr>
</tbody>
</table>

The Good News
Advances in Raising Cure Rates of Chronic HCV Therapy (Genotype 1)

sofosbuvir (Sovaldi)

- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
  - No significant drug interactions
- Generally safe and well-tolerated in clinical studies to date (> 2,000 patients)
  - No safety signal in preclinical/clinical studies
### Sofosbuvir FDA Indication

<table>
<thead>
<tr>
<th>Patients with genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 4 CHC</td>
<td>Sofosbuvir + peginterferon + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2 CHC</td>
<td>Sofosbuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3 CHC</td>
<td>Sofosbuvir + ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

**Recommended regimens and durations for sofosbuvir combination therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients**

Sofosbuvir and ribavirin for 24 weeks in Geno 1 patients who are ineligible to receive an Interferon-based regimen.
FUSION: SVR by GT and Cirrhosis in Treatment-Experienced Patients

- Sofosbuvir + RBV 12 wks
- Sofosbuvir + RBV 16 wks

12 weeks sufficient for GT2
16 weeks better than 12 weeks for GT3… so what about 24 weeks?

simeprevir (Olysio)

- Approved for Genotype 1
- Dosage: Olysio 150mg QD and pegIFN 180 mcg SQ per week + Ribavirin (weight based)
- Treatment naïve and Prior Relapsers (including cirrhosis)
  - Olysio = 12 weeks with P/R then P/R for an additional 12 weeks (24 total weeks)
- Prior Non-responder and partial/null responders (including cirrhosis)
  - Olysio = 12 weeks with P/R and then P/R for an additional 48 weeks (48 total weeks)
ombitasvir / paritaprevir / ritonavir / dasabuvir
(Viekira Pak)

- Approved for Genotype 1
- Dosage: 2 - ombitasvir 12.5mg, paritaprevir 75mg, ritonavir 50mg daily. One dasabuvir 250mg bid with a meal and ribavirin (weight based)
- Genotype 1a, without cirrhosis – 12 weeks
- Genotype 1a, with cirrhosis – naïve and prior pegIFN/RBV – 24 weeks
- Genotype 1a with cirrhosis – naïve and prior pegIFN/RBV – 12 weeks
- Genotype 1b without cirrhosis – treatment experienced AND treatment naïve – 12 weeks
- Genotype 1b with cirrhosis – treatment experienced AND treatment naïve – 12 weeks
### AbbVie 3D Combination

ABT-450/ritonavir (150/100 mg) + ombitasvir (25 mg)  
Once Daily  
dasabuvir (250 mg) ± ribavirin  
Twice Daily

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Weeks</th>
<th>Riba?</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearl-II</td>
<td>Geno1b experienced</td>
<td>12</td>
<td>Yes n=88</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No n=91</td>
<td>99%</td>
</tr>
<tr>
<td>Pearl-III</td>
<td>Geno1b naive</td>
<td>12</td>
<td>Yes n=201</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No n=209</td>
<td>99%</td>
</tr>
<tr>
<td>Pearl-IV</td>
<td>Geno1a naive</td>
<td>12</td>
<td>Yes n=100</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No n=205</td>
<td>90%</td>
</tr>
<tr>
<td>Turquoise-II</td>
<td>Geno1 compensated cirrhosis</td>
<td>12</td>
<td>Yes n=208</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>Yes n=172</td>
</tr>
<tr>
<td>Sapphire-I</td>
<td>Geno1 naive</td>
<td>12</td>
<td>Yes n=473</td>
<td>96%</td>
</tr>
<tr>
<td>Sapphire-II</td>
<td>Geno1 experienced</td>
<td>12</td>
<td>Yes n=297</td>
<td>96%</td>
</tr>
</tbody>
</table>
Study design: TURQUOISE I was a phase II clinical trial evaluating VIEKIRA PAK + RBV in GT1 treatment-naïve or pegIFN/RBV treatment-experienced adults with HIV-1 coinfection. Patients received ombitasvir, paritaprevir, ritonavir (25/150/100 mg QD), and dasabuvir (250 mg BID) + RBV. RBV dose was determined by body weight (1000 or 1200 mg divided BID).
Sofosbuvir/velpatasvir (Harvoni)

- Approved for Genotype 1
- Dosage: ledipasvir 90mg / sofosbuvir 400mg
- Treatment naïve
  - Without cirrhosis and pre treatment HCV RNA of < 6 million IU/mL = 8 wks
  - With or Without cirrhosis and pre treatment HCV RNA of ≥ 6 million IU/mL = 12 weeks
- Treatment experienced
  - Without Cirrhosis = 12 weeks
  - With Cirrhosis = 24 weeks
Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection
NIAID ERADICATE Trial: Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledipasvir-Sofosbuvir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretroviral Untreated ($n = 13$)</td>
<td></td>
<td></td>
<td>SVR12</td>
</tr>
<tr>
<td>CD4 count stable &amp; HIV RNA &lt; 500 copies/ml or CD4 &gt; 500 cells/mm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Ledipasvir-Sofosbuvir** | | | SVR12 |
| *Antiretroviral Treated ($n = 37$) | | | |
| CD4 > 100 cells/mm$^3$ | | | |
| HIV RNA < 40 copies/ml | | | |
| Current ARVs $\geq$ 8 weeks | | | |

**Drug Dosing:** Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

*Antiretrovirals: tenofovir-emtricitabine with one or more of following: efavirenz, rilpivirine, or raltegravir

<table>
<thead>
<tr>
<th>HCV RNA &lt; LLOQ, %</th>
<th>ARV Untreated (n=13)</th>
<th>ARV Treated (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>100 (n =13)</td>
<td>100 (n=37)</td>
</tr>
<tr>
<td>Week 8</td>
<td>100 (n =13)</td>
<td>100 (n=37)</td>
</tr>
<tr>
<td>Week 12 (EOT)</td>
<td>100 (n =13)</td>
<td>100 (n=37)</td>
</tr>
<tr>
<td>SVR 4</td>
<td>100 (n =13)</td>
<td>97 (n=36)</td>
</tr>
<tr>
<td>SVR 8</td>
<td>100 (n =13)</td>
<td>97 (n=36)</td>
</tr>
<tr>
<td>SVR 12</td>
<td>100 (n =13)</td>
<td>97 (n=36)</td>
</tr>
</tbody>
</table>

Harvoni Dosage and Administration

RBV was not shown to increase the response rates observed with HARVONI in ION-1. Therefore, the HARVONI + RBV arm is not presented.\(^1\)

\(^{a}\)SVR12 was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment.\(^1\) Achieving SVR is considered a virologic cure.\(^2\)
HARVONI delivered high cure (SVR) rates in GT 1 treatment-naïve adult subjects without cirrhosis\textsuperscript{1,a}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{\% SVR12 in treatment-naïve GT 1 subjects without cirrhosis in ION-3\textsuperscript{1,b}}
\end{figure}

RBV was not shown to increase the response rates observed with HARVONI in ION-3. Therefore, the HARVONI + RBV arm is not presented.\textsuperscript{1}
Hepatitis C: Genotype 3

- 1/8 of Hepatitis C in US = genotype 3
- Higher Progression rate of fibrosis
- Higher rate of cirrhosis at diagnosis with GT3

**SVR12**

- 96% noncirrhotic
  vs.
- 63% with cirrhosis

- 24 weeks of treatment recommended with cirrhosis
Daclatasvir (Daklinza) Studied in Adults With Chronic HCV in Multiple High-Unmet-Need Patient Populations

Daclatasvir + sofosbuvir has been studied in chronic HCV patients in three Phase III clinical trials; one study included use with ribavirin.

- **ALLY 1**
  - Patients with advanced cirrhosis or post-liver transplant
  - Permitted to enroll GT1–6
  - Daclatasvir + sofosbuvir + ribavirin, 12 weeks

- **ALLY 2**
  - Patients with HIV-1 co-infection
  - Permitted to enroll GT1–6
  - Daclatasvir + sofosbuvir, 12 weeks

- **ALLY 3**
  - Patients with GT3 infection
  - Treatment-naïve or treatment-experienced
  - Daclatasvir + sofosbuvir, 12 weeks

Daclatasvir is indicated for use with GT1 and GT3.

GT = genotype; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus.

Daklinza™ (daclatasvir) Prescribing Information. Bristol-Myers Squibb Company, Princeton, NJ.
DAKLINZA™ (daclatasvir) Regimens: A 12-week, all-oral therapy for difficult-to-treat GT3 patients, including HCV/HIV-1 co-infection, advanced cirrhosis, and post-liver transplant

### Efficacy

<table>
<thead>
<tr>
<th><strong>High SVR&lt;sub&gt;12&lt;/sub&gt; rates in GT3 in 3 clinical studies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without RBV:</strong></td>
</tr>
<tr>
<td>• 96% (115/120) in non-cirrhotics</td>
</tr>
<tr>
<td>- 63% (20/32) in cirrhotics in ALLY 3</td>
</tr>
<tr>
<td>• 100% (10/10) in HCV/HIV-1 co-infection in ALLY 2</td>
</tr>
<tr>
<td><strong>With RBV:</strong></td>
</tr>
<tr>
<td>• 83% (5/6) in Child-Pugh B,C in ALLY 1</td>
</tr>
<tr>
<td>• 91% (10/11) in post-transplant in ALLY 1</td>
</tr>
</tbody>
</table>

### Safety Profile

<table>
<thead>
<tr>
<th><strong>No treatment-related serious AEs in all 3 studies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 0% discontinuation due to AEs in ALLY 3 and ALLY 2</td>
</tr>
<tr>
<td>• Discontinuation due to AEs in ALLY 1: 2% all study drugs; 12% ribavirin only</td>
</tr>
</tbody>
</table>

### Drug-Drug Interactions

<table>
<thead>
<tr>
<th><strong>Well-studied drug-interaction profile</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• No need to change or adjust HAART regimen for co-infected patients; DAKLINZA dose adjustment may be needed</td>
</tr>
<tr>
<td>• No need to change/adjust commonly used immunosuppressives</td>
</tr>
<tr>
<td>• DAKLINZA is contraindicated with strong inducers of CYP3A</td>
</tr>
</tbody>
</table>

Daklinza™ (daclatasvir) Prescribing Information. Bristol-Myers Squibb Company, Princeton, NJ.
daclatasvir (Daklinza)

- Approved for Genotype 3
- Both treatment naïve and treatment experienced
- Dosage – Daclatasvir 60mg daily with sofosbuvir 400 mg
- 12 weeks
Ombitasvir, pritaprevir, ritonavir

(Technivie)

- Approved for genotype 4 (without cirrhosis)
- Used with ribavirin
- Once daily in the am with a meal
- 12 weeks
- 100% SVR (91% without ribavirin)
elbasvir and grazoprevir (Zepatier)

- Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended.

**Recommended dosage:**
- 50 mg of elbasvir / 100 mg of grazoprevir in a single tablet.
- One tablet taken orally once daily with or without food.
elbasvir and grazoprevir (Zepatier)

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced*</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>NS5A polymorphisms†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced*</td>
<td>ZEPATIER +</td>
<td>16 weeks</td>
</tr>
<tr>
<td>with baseline NS5A polymorphisms†</td>
<td>ribavirin</td>
<td></td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a or 1b: PegIFN/RBV/PI-experienced†</td>
<td>ZEPATIER +</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ribavirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 4: Treatment-naïve</td>
<td>ZEPATIER</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced*</td>
<td>ZEPATIER +</td>
<td>16 weeks</td>
</tr>
<tr>
<td>ribavirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Peginterferon alfa + ribavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.
sofosbuvir/velpatasvir
400 mg/100 mg tablets
(Epclusa)
SOFUSBUVIR/VELPATASVIR (EPCLUSA) is the first and only pan-genotypic, once-daily, single-tablet regimen for chronic HCV patients

<table>
<thead>
<tr>
<th>Sofusbufvir/velpatasvir (Epclusa) for the treatment of HCV GT 1-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GT 1-6, treatment-naïve and treatment-experienced&lt;sup&gt;a&lt;/sup&gt; patients without cirrhosis or with compensated cirrhosis</td>
</tr>
<tr>
<td>12 weeks</td>
</tr>
</tbody>
</table>

• offers simple dosing as the first and only once-daily single-tablet regimen for HCV GT 2 and GT 3 patients

• The dosing information listed here does not include patients with decompensated cirrhosis (Child-Pugh B or C)

• No baseline resistance testing is required

<sup>a</sup>Treatment-experienced = patients who have failed a Peg-IFN alfa + RBV–based regimen with or without an HCV PI.
### ASTRAL-1 STUDY DESIGN:
GT 1, 2, 4, 5, 6, TREATMENT-NAÏVE AND -EXPERIENCED, WITHOUT CIRRHOSIS OR WITH COMPENSATED CIRRHOSIS

**ASTRAL-1**
Randomized, double-blind placebo-controlled

**Sofusbuvir/velpatasvir for 12 weeks**

**Placebo for 12 weeks**

Primary endpoint = SVR12

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>ASTRAL-1 (N=740)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>56 (18-82)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>60%</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79%</td>
</tr>
<tr>
<td>Black</td>
<td>9%</td>
</tr>
<tr>
<td><strong>HCV GT 1</strong></td>
<td>53%</td>
</tr>
<tr>
<td><strong>HCV GT 2</strong></td>
<td>17%</td>
</tr>
<tr>
<td><strong>HCV GT 4</strong></td>
<td>19%</td>
</tr>
<tr>
<td><strong>HCV GT 5</strong></td>
<td>5%</td>
</tr>
<tr>
<td><strong>HCV GT 6</strong></td>
<td>7%</td>
</tr>
<tr>
<td><strong>HCV RNA ≥800,000 IU/mL</strong></td>
<td>74%</td>
</tr>
<tr>
<td><strong>BMI ≥30 kg/m²</strong></td>
<td>21%</td>
</tr>
<tr>
<td><strong>HCV treatment–experienced</strong></td>
<td>32%</td>
</tr>
<tr>
<td><strong>Compensated cirrhosis</strong></td>
<td>19%</td>
</tr>
</tbody>
</table>

Demographics and baseline characteristics were balanced across the treatment groups.

*Treatment experienced = patients who have failed a Peg-IFN alfa + RBV–based regimen with or without an HCV PI.*
The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

SOFUSBUVIR/VELPATASVIR DEMONSTRATED SAFETY WITH LOW RATES OF ADVERSE EVENTS IN ASTRAL-1

Adverse Reactions (All Grades) Reported in ≥5% of Subjects Receiving 12 Weeks of Treatment with EPCLUSA in ASTRAL-1

<table>
<thead>
<tr>
<th>ASTRAL-1 Adverse Events for GT 1, 2, 4, 5, 6</th>
<th>Sofusbuvin/velpatasvir 12 Weeks N=624</th>
<th>With the exception of asthenia, a each of these adverse reactions occurred at a similar frequency or more frequently in subjects treated with placebo compared to subjects treated with SOF/VEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

- The majority of the adverse reactions were grade 1 in severity
- 0.2% discontinuations due to adverse events for EPCLUSA
- The adverse reactions observed in GT 2 and GT 3 subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was observed in ≥5% of subjects treated with EPCLUSA in ASTRAL-3
- No hepatic or hematologic monitoring is required when EPCLUSA is used alone

aAsthenia: 3% versus 5% for the placebo and EPCLUSA groups, respectively.
### OTHER DRUG INTERACTIONS WITH SOFUSBUVIR/LEDEPASVIR (SOF/LED, HARVONI) AND/OR SOFUSBUVIR/VELPATASVIR (SOF, VEL, EPCLUSA)

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td>Monitor patients during HARVONI or EPCLUSA treatment. Coadministration may increase digoxin levels</td>
</tr>
<tr>
<td><strong>Rosuvastatin and Atorvastatin</strong></td>
<td>SOF/LED coadministration with rosuvastatin is not recommended due to increased concentrations of rosuvastatin. Coadministration with SOF/VEL may increase rosuvastatin or atorvastatin concentrations, which may increase the risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis. Rosuvastatin dose should not exceed 10 mg</td>
</tr>
</tbody>
</table>
DRUGS NOT RECOMMENDED FOR
COADMINISTRATION WITH SOF/LED
(HARVONI) OR SOF/VEL (EPCLUSA)

Coadministration is not recommended with oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir due to decreased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

Coadministration of is not recommended with co-formulated elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (STRIBILD) due to increased concentrations of tenofovir; or with simeprevir due to increased concentrations of ledipasvir and simeprevir; or with rosvastatin due to increased concentrations of rosvastatin.

Coadministration of EPCLUSA is not recommended with proton-pump inhibitors or efavirenz due to decreased concentrations of velpatasvir; or with topotecan due to increased concentrations of topotecan.
Ledipasvir and velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of ledipasvir and velpatasvir.

<table>
<thead>
<tr>
<th>Antacids&lt;sup&gt;a&lt;/sup&gt;</th>
<th>It is recommended to separate antacid and HARVONI or EPCLUSA administration by 4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&lt;sub&gt;2&lt;/sub&gt;-receptor antagonists&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>H&lt;sub&gt;2&lt;/sub&gt;-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI or EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily</td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions</td>
</tr>
</tbody>
</table>

Coadministration of omeprazole or other proton-pump inhibitors is not recommended with EPCLUSA

- If it is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied

<sup>a</sup>Eg, aluminum and magnesium hydroxide.

<sup>b</sup>Eg, famotidine.

<sup>c</sup>Eg, omeprazole.
Sustained Virologic Response (SVR) Leads to Improved Outcome

- Viral Eradication
- Improved Clinical Outcomes
- Improved Liver Histology

Decreased

- Decompensation
- Hepatocellular Carcinoma
- Mortality

SVR is Significantly Associated With Reduction in All-Cause Mortality

Genotype 1
(n=12,166)

SVR rate: 35%

Cumulative Mortality (%)

P<0.0001

Years

Genotype 2
(n=2904)

SVR rate: 72%

Cumulative Mortality (%)

P<0.0001

Years

Genotype 3
(n=1794)

SVR rate: 62%

Cumulative Mortality (%)

P<0.0001

Years

Retrospective analysis of veterans who received pegIFN + RBV at any VA medical facility (2001-2008).
Impact of SVR on HCC and Liver-Related Complications

Single-center cohort. Non-SVR in 67% of patients treated with pegIFN + RBV. Median follow-up: 3.5 years. Total patients (n=307). Number of events: HCC (n=46); liver-related complications (n=31).

“HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications.”

Source: hcvguidelines.org
HCV Treatment for HIV-Coinfected Patients – Getting Better

- Two open-label studies confirm that a once-daily combination of sofofvir plus either ledipasvir or daclatasvir cures hepatitis C virus infection in most such patients
  - SVR at post treatment week 12 – 96.1%
  - Treatment-naïve with 12 weeks – 97%
  - Treatment experienced with 12 weeks – 98.1%

- Side effects generally mild

- No patients stopped therapy because of adverse events
Adverse Effects of New Therapies

- **PegIFN/RBV**: well-established AE profiles

- **Sofosbuvir**[^1-3]
  - Mild fatigue
  - Mild headache

- **Simeprevir**[^4,5]
  - Mild, reversible hyperbilirubinemia
    - Due to transporter inhibition and not associated with hepatotoxicity
  - Mild photosensitivity

---

[^3]: Sofosbuvir [package insert].
[^5]: Simeprevir [package insert].
Other Issues for Therapy

• Contraindications
  - Do not use NS3/4A protease inhibitors (simeprevir, grazoprevir, paritaprevir) if decompensated cirrhosis [Use Harvoni]
  - Avoid sofosbuvir in renal failure (CrCL <30) [Use Zepatier or Viekira Pak]

• Drug-Drug Interactions
  - Avoid acid suppression with ledipasvir & Viekira Pak
  - PrOD contains ritonavir; take into account if patient has HIV on boosted PI
  - NS3/4A protease inhibitors and many NS5A inhibitors metabolized by CYP3A

• Laboratory Monitoring
  - Baseline: CBC, CMP, Hep C RNA, [NS5A genotype, TSH]
  - 4-week: CBC, CMP, and Hep C RNA
  - 12-weeks after therapy: Hep C RNA
  - Monitor more closely if ribavirin and/or interferon

• Discontinuation of Therapy
  - 10-fold increase in ALT
  - Symptomatic hepatitis
  - If detectable Hep C RNA at week 4 and then >10-fold increase thereafter
Unrestricted access to HCV Therapy Cost-effective for Medicaid Beneficiaries

“A cost-effective analysis revealed that for current Medicaid beneficiaries, the increased short-term costs of unrestricted access to care can be offset by savings from reduced complications in 9 - 16 years, depending on the treatment strategy and age of the cohort.”

Alexis P. Chidi, PhD, MSPH of the University of Pittsburgh School of Medicine, said in a press release.

The researchers concluded:

- In a multi-payer health care system, efforts to minimize costs for individual payers can result in cost shifting and economic efficiency for the system as a whole.
- Collaborative efforts between state and federal payers may be needed to realize the full public health impact of recent advances in hepatitis C therapy.
## Cost of Medication Regimens
### Wholesale Acquisition Cost (WAC)

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Granzyme B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + daclatasvir</td>
<td>$166,600</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>$84,000</td>
<td>$168,000</td>
</tr>
<tr>
<td>Sofosbuvir/Ledipasvir</td>
<td>$94,500</td>
<td>$189,000</td>
</tr>
<tr>
<td>Sofosbuvir + Daclatasvir</td>
<td>$147,000</td>
<td>$294,000</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>$150,360</td>
<td>$300,720</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir</td>
<td></td>
<td>$76,653</td>
</tr>
</tbody>
</table>

**Edit:** add Harvoni and Epclusa
The Price of a Cure...

Sofosbuvir is $1,000 a pill ($84,000 for a 12-week treatment course)
Simeprevir is $66,000 for a course of treatment

Ledipasvir/sofosbuvir $100,000 for 12 week treatment

Both are excluding the cost of other concomitant therapies and possible need for longer therapy

SVR is priceless

Source: Healio.com/HCV
The annual health care costs of chronic HCV were estimated at:

$24,176

$17,277 = no cirrhosis

$22,752 = compensated cirrhosis

$59,995 = end-stage liver disease

Source: Healio.com/HCV
Resources

AASLD/IDSA Guidelines
http://hcvguidelines.org

UW Hepatitis Online Modular Course
http://hepatitisc.uw.edu

Hepatitis Education Project
http://hepeducation.org