Hepatitis C
Something We Can Cure

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Figure 4.1. Reported number of acute hepatitis C cases — United States, 2001–2016

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Figure 4.4. Incidence of acute hepatitis C, by race/ethnicity — United States, 2001–2016

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Figure 4.3. Incidence of acute hepatitis C, by sex — United States, 2001–2016

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Figure 4.2. Incidence of acute hepatitis C, by age group — United States, 2001–2016

Reported cases/100,000 population

- 0-19 yrs
- 20-29 yrs
- 30-39 yrs
- 40-49 yrs
- 50-59 yrs
- > 60 yrs

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

*Includes case reports indicating the presence of at least one of the following risks 2 weeks to 6 months prior to onset of acute, symptomatic hepatitis C: 1) using injection drugs; 2) having sexual contact with suspected/confirmed hepatitis C patient; 3) being a man who has sex with men; 4) having multiple sex partners concurrently; 5) having household contact with suspected/confirmed hepatitis C patient; 6) having had occupational exposure to blood; 7) being a hemodialysis patient; 8) having received a blood transfusion; 9) having sustained a percutaneous injury; and 10) having undergone surgery.
Injection-drug use
- Yes: 767
- No: 351
- Missing: 1,849

Men who have sex with men
- Yes: 26
- No: 233
- Missing: 1,368

Sexual contact
- Yes: 4
- No: 5
- Missing: 2,958

Multiple sex partners
- Yes: 176
- No: 298
- Missing: 2,493

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

* A total of 2,967 case reports of acute hepatitis C were received in 2016.
† More than one risk exposure/behavior may be indicated on each case report.
§ No risk data reported.
¶ A total of 1,627 acute hepatitis C cases were reported among males in 2016.
Figure 4.6b. Acute hepatitis C reports*, by risk exposure/behavior† — United States, 2016

<table>
<thead>
<tr>
<th>Risk Exposure/Behavior</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>5, 967, 1,995</td>
</tr>
<tr>
<td>Dialysis patient</td>
<td>7, 991, 1,969</td>
</tr>
<tr>
<td>Surgery</td>
<td>96, 746, 2,125</td>
</tr>
<tr>
<td>Needle stick</td>
<td>64, 654, 2,249</td>
</tr>
</tbody>
</table>

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
*A total of 2,967 case reports of acute hepatitis C were received in 2016.
†More than one risk exposure/behavior may be indicated on each case report.
§No risk data reported.
Hepatitis C

Hepatitis C virus infection is the most common bloodborne infection in the United States and South Dakota.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Cases</th>
<th>Rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sioux Falls MSA</td>
<td>153</td>
<td>59.8</td>
</tr>
<tr>
<td>Rapid City MSA</td>
<td>80</td>
<td>58.4</td>
</tr>
<tr>
<td>Northeast</td>
<td>47</td>
<td>27.2</td>
</tr>
<tr>
<td>Southeast</td>
<td>44</td>
<td>38.8</td>
</tr>
<tr>
<td>Central</td>
<td>105</td>
<td>112.4</td>
</tr>
<tr>
<td>West</td>
<td>70</td>
<td>75.0</td>
</tr>
<tr>
<td>South Dakota</td>
<td>499</td>
<td>57.7</td>
</tr>
</tbody>
</table>

†Rate: cases per 100,000 population.
MSA: Metropolitan Statistical Area.


Disease fact sheets: [http://doh.sd.gov/diseases/infectious/diseasefacts](http://doh.sd.gov/diseases/infectious/diseasefacts)

South Dakota Department of Health
<table>
<thead>
<tr>
<th>Disease/Agent</th>
<th>Cases YTD</th>
<th>Rate</th>
<th>5-Year Median YTD</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>33</td>
<td>3.8</td>
<td>15</td>
<td>+120%</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>6</td>
<td>0.7‡</td>
<td>4</td>
<td>+50%</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>695</td>
<td>80.3</td>
<td>727</td>
<td>-4%</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>7</td>
<td>0.8‡</td>
<td>14</td>
<td>-50%</td>
</tr>
<tr>
<td>E. coli, shiga toxin-producing</td>
<td>12</td>
<td>1.4‡</td>
<td>4</td>
<td>200%</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>7</td>
<td>0.8‡</td>
<td>14</td>
<td>-50%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>225</td>
<td>26.0</td>
<td>163</td>
<td>+38%</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>5</td>
<td>0.6‡</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hepatitis B, chronic</td>
<td>3</td>
<td>0.3‡</td>
<td>11</td>
<td>-73%</td>
</tr>
<tr>
<td><strong>Hepatitis C, acute and chronic</strong></td>
<td>84</td>
<td>9.7</td>
<td>86</td>
<td>-2%</td>
</tr>
<tr>
<td>HIV, including Stage III (AIDS)</td>
<td>3</td>
<td>0.3‡</td>
<td>5</td>
<td>-40%</td>
</tr>
<tr>
<td>Legionellosis</td>
<td>1</td>
<td>0.1‡</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>MRSA, invasive</td>
<td>28</td>
<td>3.2</td>
<td>20</td>
<td>+40%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>7</td>
<td>0.8‡</td>
<td>6</td>
<td>+17%</td>
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<tr>
<td>Pneumococcal disease, invasive</td>
<td>22</td>
<td>2.5</td>
<td>19</td>
<td>16%</td>
</tr>
<tr>
<td>Rabies, animal</td>
<td>2</td>
<td>NA</td>
<td>2</td>
<td>+0%</td>
</tr>
</tbody>
</table>

YTD: Year-to-Date      Rate: Cases per 100,000 population   5-Year Median: 2013–2017
‡ Unstable rate based on <20 observations
HCV Is Underdiagnosed and Undertreated

AN ESTIMATED 3.5 MILLION AMERICANS HAVE CHRONIC HCV

• It is estimated that 3.5 million Americans have chronic hepatitis C
• Approximately 9% of infected individuals successfully treated

PROGRESSION TO FIBROSIS IN HCV
In a study, approximately 45% of untreated HCV patients were projected to develop cirrhosis by 2030.

HCV is a progressive disease. Patients who develop cirrhosis are at greater risk for developing liver cancer and other liver-related complications.

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.
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


\sim75\% of all HCV patients are baby boomers\textsuperscript{4}
Why Test Baby Boomers?

- 75% of those with HVC were born between 1945 and 1965
- Baby boomers are 5X more likely to be infected than other adults
- Baby boomers with HCV face increasing morbidity and mortality
- About 45% to 85% of those with HCV do not know they are infected
- Testing baby boomers would identify ~800,000 infections, and with treatment, avert >120,000 HCV-related deaths.
- Savings of ~$1.5 to $7.1 billion in liver disease-related costs.
Testing Recommendations by Risk

- Baby boomer cohort (born between 1945-1965)
  - One-time screening for all members of baby boomer cohort
  - No prior HCV risk attainment recommended

- People who inject drugs
  - Those currently injecting drugs
  - Those who have ever injected drugs, even once

- HIV-positive persons
  - At initial HIV-related medical visit
  - Annually for all HIV-positive MSM

- Children born to HCV-positive mothers
  - After 18 months if using an antibody screening
  - At 1–2 months if using an RNA test, and repeated subsequently to confirm

3. CDC. Hepatitis C FAQ for Health Professionals. http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1
Appearances May Be Deceiving
When It Comes to Seniors With STIs

Nearly 75% Of those aged 57-64 and 26% Of those aged 75-85 Are sexually active.
Hepatitis C Testing Remains Low for Baby Boomers Despite Recent Increase

- Although small, there was a statistically significant increase in hepatitis C testing two years after the USPSTF recommendations were implemented
  - 12.3% to 13.8% (P=0.013)

- Only 10.5 million of the 76.2 million baby boomers in the country in 2015 were tested
CDC, USPSTF, and AASLD recommend screening for individuals with a high-risk of exposure to HCV.[1,2,3]

These include HIV-infected patients

3. AASLD/IDSA  https://www.hcvguidelines.org/evaluate/testing-and-linkage
Who Is Testing?

- People with just a high school diploma or less education had a lower testing rate than college graduates
  - (PR: 0.63, 95% CI: 0.48, 0.82 vs. PR 0.58, 95% CI: 0.48, 0.72)
- Insurance type was important in predicting if a baby boomer had been tested for hepatitis C or not.
  - Higher screening was found in the following (compared to privately insured):
    - **Medicare plus Medicaid** (PR: 1.83, 95% CI: 1.32, 2.53)
    - **Just Medicaid** (PR: 1.62, 95% CI: 1.16, 2.26)
    - **Military Insurance** (PR: 1.62, 95% CI: 1.16, 2.26)
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.¹
  – **Describe** the screening process.

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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.²
Initial Testing for Hepatitis C Has Three Parts

- HCV antibody testing
- Qualitative HCV RNA testing
- HCV Genotypic Testing

https://www.hepmag.com/basics/hepatitis-c-basics/hepatitis-c-testing
**Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection**

1. **HCV antibody**
   - **Nonreactive**:
     - **No HCV antibody detected**
       - **STOP**
   - **Reactive**:
     - **Not Detected**:
       - **No current HCV infection**
         - Additional testing as appropriate†
     - **Detected**:
       - **Current HCV infection**
         - Link to care

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* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

DATA NEEDED FOR TREATMENT

- Hep C Genotype
- Hep C RNA quantitative
- Fibrosis score
- Previously treated?
- Potential Direct Acting Antiviral and Antiretroviral Therapy Drug-Drug Interactions
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 ARE 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 \((\frac{\text{AST}}{40})/\text{Plts}*100\)
- Fib-4 score \((\frac{\text{AST}*\text{Age}}{\text{Plts}^*\sqrt{\text{ALT}}})\)

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
Unlike Some Chronic Conditions, HCV Can Be Cured

HIV
Diabetes
Hypertension

HCV

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

*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.

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\(^3\).

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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}

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).

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated

- PegIFN/RBV 12 Mos [5-8]
- IFN/RBV 12 Mos [5-7]
- IFN 6 Mos [5]
- IFN 12 Mos [5,6]
- Standard Interferon 1991 [1]
- Peginterferon 2001 [3]
- 2011 [4]
- 2013 [4]
- DAA Therapy
- PegIFN/RBV + DAA [9-10]
- DAA + RBV ± PegIFN [11]
- All-Oral DAA ± RBV [12-16]
- 90+
- 2013 [4]
- Current 95+

Sustained HCV Virologic Response (%)

References in slidenotes.

Slide credit: clinicaloptions.com
AASLD/IDSA Guidance on HCV Treatment

“Treatment recommended for all pts with chronic HCV infection, except those with short life expectancies who cannot be remediated by treating HCV, by transplantation, or by other directed therapy”
Benefits of Achieving SVR

- **Cure**
- **Decreased transmission**[^1]
  - **Hepatic**
    - ↓ Cirrhosis
    - ↓ Decompensation
    - ↓ HCC
    - ↓ Transplantation
- **Improved clinical outcomes**[^1,^2]
  - **Extrahepatic**
    - ↓ All-cause mortality
    - Improved QoL
    - Malignancy
    - Diabetes
    - CVD
    - Renal
    - Neurocognitive

HCV Cure Associated With Improved 15-Yr Survival in Pts With F0/F1 Disease

- Single-center cohort of consecutive pts since 1992 (N = 1381)
- Progression to F3/F4 was observed in 15.3% of F0/F1 pts with available liver biopsy (n = 157)
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
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
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Component Classes</th>
<th>Approved Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grazoprevir/elbasvir (Zepatier)</strong></td>
<td>Protease inhibitor + NS5A inhibitor</td>
<td>1, 4</td>
</tr>
<tr>
<td><strong>Ombitasvir/paritaprevir/ritonavir (Technivie)</strong></td>
<td>Protease inhibitor + NS5A inhibitor</td>
<td>4</td>
</tr>
<tr>
<td><strong>Ombitasvir/paritaprevir/ritonavir + dasabuvir (Vikera Pak)</strong></td>
<td>Protease inhibitor + NS5A inhibitor + polymerase inhibitor</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sofosbuvir + daclatasvir (Darvoni, Sovodak)</strong></td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>1, 3</td>
</tr>
<tr>
<td><strong>Sofosbuvir/ledipasvir (Harvoni)</strong></td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td><strong>Simeprevir + sofosbuvir</strong></td>
<td>Nucleotide polymerase inhibitor + protease inhibitor</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sofosbuvir/velpatasvir (Epclusa)</strong></td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td><strong>Glecasprevir/pibrentasvir (Mavyret)</strong></td>
<td>NS3/4A protease inhibitor + NS5A inhibitor</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td><strong>Sofosbuvir, Velpatasvir, and Voxilaprevir (Vosevi)</strong></td>
<td>Nucleotide analog NS5B polymerase inhibitor/NS5A replication complex inhibitor/NS3/4A protease inhibitor.</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

**Slide credit:** clinicaloptions.com/ Mavyret & Vosevi package inserts
HARVONI Offers Simple Once-daily Dosing for GT 1 Patients

HARVONI is the only HCV regimen that offers an 8-week course of therapy

**8 weeks**
- Can be considered in treatment-naïve patients without cirrhosis and with pretreatment HCV RNA <6 million IU/mL

**12 weeks**
- Treatment-naïve patients with or without cirrhosis
- Treatment-experienced patients without cirrhosis

**24 weeks**
- Treatment-experienced patients with cirrhosis

- The dosing information listed here does not include patients with decompensated cirrhosis (Child-Pugh B or C) or liver transplant recipients
- The recommended treatment duration for HCV GT 4, GT 5, or GT 6 treatment-naïve and treatment-experienced patients with or without cirrhosis is 12 weeks
- HARVONI + RBV for 12 weeks can be considered in treatment-experienced GT 1 patients with cirrhosis who are eligible for RBV
- For patients with HCV/HIV-1 coinfection, follow the dosage recommendations above. Refer to the Drug Interactions section of the HARVONI Prescribing Information for dosage recommendations for concomitant HIV-1 antiretroviral drugs

*aCirrhosis = compensated cirrhosis (Child-Pugh A).*
*bTreatment-experienced = patients who have failed a Peg-IFN alfa + RBV–based regimen with or without an HCV PI.*
*cThe daily dosage of RBV is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in 2 divided doses with food. Refer to the RBV Prescribing Information.*
Elbasvir and Grazoprevir (Zepatier)

- **Approval Status:** Approval by United States FDA on July 28, 2015
- **Indications and Usage**
  - HCV genotypes 1, 4 and 6
  - Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended
- **Class & Mechanism:** Protease inhibitor + NS5A inhibitor
- **Medication Form (Tablet):** 50 mg of elbasvir/ 100 mg grazoprevir in a single tablet
- **Dosing:** 1 tablet orally once daily with or without food
- **Adverse Effects (AE):** Most common fatigue and headache

Source: Zepatier Prescribing Information. Merck
sofosbuvir(SOF)/velpatasvir (VEL) (Epclusa)

Approval Status: Approval by United States FDA on June 28, 2016

Indications and Usage:
• treatment of chronic genotype 1-6 hepatitis C virus (HCV) infection for naïve and experienced with all stages of fibrosis. Can be used in HIV Co-infection

Class & Mechanism
• Sofosbuvir - nucleotide analog - NS5B inhibitor / Velpatasvir - NS5A inhibitor)

Medication Form (Tablet):
• Sofosbuvir 400mg (nucleotide analog NS5B inhibitor)
• Velpatasvir 100mg (NS5A inhibitor)

Dosing:
• Once daily fixed-dose combination with or without food

Adverse Effects (AE):
• most common headache and fatigue

Source: Epclusa Prescribing Information. Gilead, Inc.
Sofosbuvir, Velpatasvir, and Voxilaprevir (Vosevi)

- **Approval Status:** Approval by United States FDA on July 18, 2017
- **Indications and Usage**
  adults with chronic HCV genotypes 1-6 without cirrhosis (liver disease) or with mild cirrhosis.
- **Class & Mechanism**
  sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, velapatasvir, an NS5A replication complex inhibitor, and voxilaprevir, an NS3/4A protease inhibitor.
- **Medication Form (Tablet):** 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir.
- **Dosing:** 1 tablet once a day with food
- **Adverse Effects (AE):** most common headache and fatigue

Source: Vosevi Prescribing Information. Gilead, Inc.
Glecaprevir-Pibrentasvir (Mavyret)

• Approval Status: Approval by United States FDA on August 3, 2017

• Indications and Usage
  - Treatment-naïve patients with HCV genotypes 1-6 in without cirrhosis and with compensated cirrhosis (Child-Pugh A)
  - HCV genotype 1 previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both

• Class & Mechanism
  - Glecaprevir (GLE): HCV NS3/4A protease inhibitor
  - Pibrentasvir (PIB): HCV NS5A inhibitor

• Medicaton Form (Tablet): 100 mg Glecaprevir and 40 mg Pibrentasvir

• Dosing: Three tablets orally once daily, with food (total daily dose of Glecaprevir 300 mg and Pibrentasvir 120 mg)

• Adverse Effects (AE): most common headache and fatigue

Source: Mavyret Prescribing Information. AbbVie., Inc.
## Overall Cure Rates Of Commonly Used Treatment Regimens for Hepatitis C

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Overall Cure</th>
<th>Genotype</th>
<th>Length Of Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>sofosbuvir/Velpatasvir – (Epclusa)</td>
<td>99%</td>
<td>GT 1-6</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ledipasvir/sofosbuvir – (Harvoni)</td>
<td>99%</td>
<td>GT1,4,5,6</td>
<td>12 weeks</td>
</tr>
<tr>
<td>glecasprevir/pibrentasvir – (Mavyret)</td>
<td>98%</td>
<td>GT1-6</td>
<td>8 weeks</td>
</tr>
<tr>
<td>elbasvir/grazoprevir - (Zepatier)</td>
<td>97%</td>
<td>GT1</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>GT4</td>
<td></td>
</tr>
<tr>
<td>sofosbuvir, vlepatasvir and voxilaprevir (Vosevi)#</td>
<td>96-97%</td>
<td>GT 1-6</td>
<td>12 weeks</td>
</tr>
<tr>
<td>paritaprevir/r/ombitasvir + dasabuvir + ribavirin - (Viekira Pak)**</td>
<td>90%</td>
<td>GT1</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

# - for those with GT1-6 who have been previously treated with the DAA drug sofosbuvir or other drugs for HCV that inhibit NS5A

** - includes compensated cirrhosis. Limitations of use include decompensated liver disease.

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

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).

Benefits of HCV Therapy Extend Beyond the Liver: Diabetes

- HCV cure significantly reduces incidence of type 2 DM[1]
  - HCV pts have 2-3 x greater odds of DM[2]
- SVR may prevent and improve IR[3]
  - IR and DM increase risk and rate of fibrosis[2]
- PegIFN + RBV associated with improved renal/cardiovascular outcomes in pts with DM + HCV[4]


ESRD in DM Pts Treated or Untreated With PegIFN + RBV[4]

Cumulative incidence of ESRD (%) vs. Yrs

- Treated pts (DM + HCV; n = 1411)
- Untreated pts (DM + HCV; n = 1411)
- Untreated pts (DM only; n = 5644)

P < .001

Slide credit: clinicaloptions.com
### HIV/HCV COINFECTION

#### Epidemiology in the U.S.
- About 25% of HIV-infected persons have Hepatitis C virus (HCV). [1]
- 75% of HIV-infected injected drug users have HCV. [1]
- HCV-related liver disease is a leading cause of death in HIV patients. [2]
- The USPSTF /IDSA/CDC recommend that all HIV-infected persons be screened for HCV infection. [3,4]

#### Compared to HCV mono-infection
- Higher rates of persistence
- Faster rates of fibrosis
- Higher rate of cirrhosis
- Increased liver related mortality

---

“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
Pts With Minimal Liver Disease Denied HCV Treatment Access in Many Settings

- Medicaid reimbursement criteria for DAAs based on documented liver fibrosis stage required for reimbursement

Treatment Cost

Wholesale acquisition cost
- Transparent; static
- Relevant in “relative terms” only

What payers actually pay
- Most relevant, most opaque
- Clearly coming down

“Deals” with specialty pharmacies

Discounts for the large payers; VA

Government-negotiated plans
- Egypt, Brazil, Spain, Australia

Production cost
- Not officially known
- Estimates suggest VERY low (100-300 USD per course!)

References in slide notes.

Slide credit: clinicaloptions.com
## Cost of Medication Regimens
### Wholesale Acquisition Cost (WAC)

<table>
<thead>
<tr>
<th>Medication Regimen</th>
<th>Trade Name</th>
<th>12 Weeks - WAC</th>
<th>24 Weeks - WAC</th>
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</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>$84,000</td>
<td>$168,000</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Olysio</td>
<td>$66,360</td>
<td>$132,720</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir/ + dasabuvir</td>
<td>Vikera Pak</td>
<td>$83,300</td>
<td>$166,600</td>
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<tr>
<td>Ledipisvir/sofosbuvir</td>
<td>Harvoni</td>
<td>$147,000</td>
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<td>Daclatasvir</td>
<td>Daklinza</td>
<td>$63,000</td>
<td>-NA-</td>
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<tr>
<td>Ombitasvir/pritaprevir/ritonavir</td>
<td>Technivie</td>
<td>$76,653</td>
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<td>Elbasvir/grazoprevir</td>
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<td>Sofosbuvir/velpatasvir</td>
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<td>$74,760</td>
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<tr>
<td>Glecaprevir-Pibrentasvir</td>
<td>Mavyret</td>
<td>$39,600</td>
<td>-NA-</td>
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<tr>
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http://www.hepatitisc.uw.edu/page/treatment/drugs/
## Cost of Medication Regimens

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http://www.hepatitisc.uw.edu/page/treatment/drugs.
http://hcp.harvoni.com/SOFLDV_STR/hcp_harvoni_com/mm_pdfs/Pricing_Flashcard_060916.pdf
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.

Most iatrogenic HCV Cases Unidentified Until Symptom Onset

- Between 2001 and 2011 more than 130,000 patients may have been exposed to hepatitis C virus infection because of medical errors
- Only 37% were proactively notified before the onset of symptoms
- By the time of symptom onset, diagnosis, alert and screening of anyone else connected to that facility, 1,000’s more might have been infected.

Discriminatory HCV Treatment Practices Need to End!

“We should be celebrating that there is a cure for HCV as I think we would if there was a similar priced cure for HIV, Alzheimer’s disease, multiple sclerosis or cancer. However, in the case of HCV, we still have a significant number of public and private insurers denying access”

- Robert Greenwald, JD, Clinical professor of law, Faculty director, Center for Health Law and Policy Innovation, Harvard Law School

Source: Healio.com/HCV
Unrestricted access to HCV Therapy Cost-effective for Medicaid Beneficiaries

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

Projected End Stage Liver Disease Related to Hepatitis C *(if not treated)*

There would be approximately 1.76 million persons with chronic HCV infection...

- They will develop cirrhosis during the next 40 to 50 years, with a peak prevalence of about 1 million in the mid-2020’s.
- The projected incidence peak (new cases) of end-stage liver disease will occur in 2030, with about 38,600 cases per year.
- The prevalence (number of people living) with end-stage liver disease also is predicted to peak in 2030, with an estimated 131,300 persons living with end-stage liver disease.
- Transplants would be expected to peak in 2032 to 2033 at level of 3200 HCV-related transplants per year.

http://www.hepatitisc.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all
Global Call for HCV Elimination

- Vision: “A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable, and effective treatment and care”
  - 2020 target: 3 million HCV infections treated

- Feasible by scaling up 6 key interventions to high coverage:
  - Hepatitis B vaccination (including birth dose)
  - Safe injection practices and safe blood
  - Harm reduction for injecting drug users
  - Safer sex (including condom promotion)
  - Hepatitis B treatment
  - Hepatitis C cure

2030 Targets

- 90% Diagnosed
- 80% Treated
- 65% Reduced Mortality

Resources

AASLD/IDSA Guidelines
http://hcvguidelines.org

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

Hepatitis Education Project
http://hepeducation.org
# HIV / HCV Drug-Drug Interactions

## Direct-Acting Antivirals for the Treatment of Hepatitis C Virus

<table>
<thead>
<tr>
<th>Interactions</th>
<th>SOF</th>
<th>LDV</th>
<th>VEL</th>
<th>SMV</th>
<th>DCV</th>
<th>ELB/GRZ</th>
<th>GLE/PIB</th>
<th>PrOD</th>
<th>PrO</th>
<th>SOF/VEL/VOX</th>
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</thead>
<tbody>
<tr>
<td>DTG/ABC/3TC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>DTG + TDF/FTC or TAF/FTC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
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### First-line recommended HIV treatment regimens

<table>
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<tr>
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</tr>
</tbody>
</table>

### Notes:

- **✓** = No clinically significant drug–drug interactions exists, safe to coadminister
- **✓** = Use TDF/FTC with caution, may be associated with increased TDF levels
- **✗** = Concomitant use USE NOT recommend; significant drug–drug interactions exists or no data
- **✗** = Concomitant use NOT recommended unless there are no darunavir resistance-associated mutations; then darunavir 800 mg can be administered without ritonavir and coadministered with PrOD or PrO

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