HCV MANAGEMENT: CONSIDERATIONS FOR YOUR PRACTICE IN AN EVOLVING PATIENT LANDSCAPE

US Medical Affairs
Agenda

- HCV pathology and epidemiology in the United States
- Impact of hepatitis C on the liver and other organs
- Evolution of the HCV patient
- Screening, diagnosis, and linkage to care
- HCV treatment landscape
Hepatitis C is a contagious liver disease caused by a virus

Roughly 3.4 million individuals in the United States have chronic HCV\(^1\)

50% of patients with HCV are unaware they are infected\(^2\,\,4\)

Only 1 in 6 patients are referred to specialist care and prescribed treatment\(^4\)

There are at least 6 distinct HCV GTs, or strains, which are genetically distinct groups of the virus\(^1\)

Knowing the strain of the virus can help inform treatment recommendations

HCV GT Distribution in the United States\(^5\)

- 76% GT1
- 22% GT2 or 3
- ~2% GT4, 5, or 6

HCV Can Cause Progressive Liver Disease...¹,²

PROGRESSIVE LIVER DISEASE

Acute HCV infection
Chronic HCV infection
10–20% Cirrhosis
1-5% Annual risk of HCC*
3-6% Annual risk of hepatic decompensation
15-20% risk of death in the year following decompensation

EHMs³

...and may also affect other organ systems

Non-liver-related mortality

*HCC can occur in the absence of cirrhosis.
HCC, hepatocellular carcinoma; EHMs, extrahepatic manifestations.

HCV is a Systemic Disease
Up to 74% of patients develop at least 1 extrahepatic manifestation (EHM)\(^1\)

- EHM\(\text{\text{s}}\) may include immune-mediated, systemic, and organ-specific disorders, as well as neoplastic manifestations\(^1\)
- EHM\(\text{\text{s}}\) may develop at any time during the natural course of HCV infection\(^2\)


**All Causes (n=2394)**

- Cumulative Mortality, %
  - 35
  - 30
  - 25
  - 20
  - 15
  - 10
  - 5
  - 0

- Follow-Up, Years
  - 0 2 4 6 8 10 12 14 16 18 20

- P<0.001 for comparison between groups

**Liver Cancer (n=115)**

- Cumulative Mortality, %
  - 10.4

- Follow-Up, Years
  - 0 2 4 6 8 10 12 14 16 18 20

- P<0.001 for comparison between groups

**Extrahepatic Diseases (n=2199)**

- Cumulative Mortality, %
  - 19.8

- Follow-Up, Years
  - 0 2 4 6 8 10 12 14 16 18 20

- P<0.001 for comparison between groups

**Legend**

- Anti-HCV seropositive with detectable HCV RNA
- Anti-HCV seronegative

Case Studies: Patient History

Melvin: Middle-aged Baby Boomer
55 year-old African American male who visits PCP for follow up on diabetes

Chief Complaint: Diabetes management
Past Medical History: DM2 on insulin x 3 years, HTN. Status post cholecystectomy
Social History: 5 beers/day; ½ ppd tobacco x “many years”
Family History: CAD, HTN, father died of MI at age 60
Current Medications: Takes Humalog® (insulin lispro) 75/25, lisinopril, amlodipine, and HCTZ

Is this someone that you would routinely screen for HCV?
**Theresa: Young PWID**

25 year-old Caucasian female recently entered a rehabilitation program

<table>
<thead>
<tr>
<th>Chief Complaint:</th>
<th>Presents with GI distress/constipation; now establishing new PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Present Illness:</td>
<td>No symptoms</td>
</tr>
<tr>
<td>Past Medical History:</td>
<td>None</td>
</tr>
<tr>
<td>Social History:</td>
<td>History of IDU with heroin; recently entered a treatment program; no heroin use for 6 months; regular marijuana use; occasional alcohol use</td>
</tr>
<tr>
<td>Current medications:</td>
<td>Takes buprenorphine and naloxone</td>
</tr>
</tbody>
</table>

**Is this someone that you would routinely screen for HCV?**
In the United States, ~75% of people with chronic HCV infection are baby boomers (born 1945–1965) who became infected during the 1970s or 1980s.

However, reported cases of acute HCV infection increased ~3-fold from 2010 through 2016; this reflects rising rates of injection-drug use, mainly among young white persons who live in non-urban areas.

Rates of HCV Infections are Rising Among Younger PWIDs

- Among people aged 18–29, HCV increased by 400% and admission for opioid injection by 622%¹
- Among people aged 30–39, HCV increased by 325% and admission for opioid injection by 83%¹
- HCV seroprevalence among PWIDs is ~55% in North America²

Who Should Be Tested for HCV?

One-time HCV testing is recommended for baby boomers (persons born between 1945 and 1965)\(^1\)

Annual or more frequent HCV testing based on risk behaviors
- PWID (People Who Inject Drugs)
- MSM (Men Who Have Sex with Men)

Universal HCV Screening for all pregnant women when initiating prenatal care

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### Who Should Be Tested for HCV?

#### Risk exposures:

- Persons who were ever on long-term hemodialysis
- Persons who were ever incarcerated
- Children born to HCV-infected women
- Health care workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Persons who received a tattoo in an unregulated setting
- Prior recipients of transfusions or organ transplants prior to 1992

#### Other considerations:

- Solid organ donors (deceased and living)
- HIV infection
- Unexplained chronic liver disease including elevated ALT levels

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Between 2012 and 2015, the mean anti-HCV prevalence in patients on hemodialysis was ~9% in 21 countries in Europe, Asia, the Middle East, Australia/New Zealand, and North America.

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ALT, alanine aminotransferase; HIV, human immunodeficiency virus.
Who Should Be Tested for HCV?

CDC Recommendations for HCV Diagnosis

**ELISA:** detects hepatitis C antibodies (seroconversion ~8-9 weeks after exposure)\(^1,2\)
- Always positive after exposure to HCV

**HCV RNA (viral load) by RT-PCR:** detects virus in the bloodstream\(^1,2\)
- Required to confirm HCV diagnosis

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**Diagram: HCV Testing Flow**

- **HCV antibody**
  - **Non-reactive**
    - No HCV antibody detected
    - No exposure to HCV
  - **Reactive**
    - **HCV RNA**
      - **Not detected**
        - No current HCV infection
      - **Detected**
        - Current HCV infection

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CDC, Centers for Disease Control and Prevention; ELISA, enzyme-linked immunosorbent assay; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction
Impact of Screening Initiatives in Primary Care

- CHI Health, comprising of 35 primary care clinics across eastern Nebraska and southwest Iowa, implemented an electronic health record prompt to screen baby boomers for HCV infection.
- A retrospective analysis examined ~36,000 baby boomers visits in both the 6 months pre- and post-alert.

**HCV Ab screened, n**

<table>
<thead>
<tr>
<th></th>
<th>Pre-alert</th>
<th>Post-alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Ab screened, n</td>
<td>625</td>
<td>8928</td>
</tr>
</tbody>
</table>

**HCV Ab+, n**

<table>
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<tr>
<th></th>
<th>Pre-alert</th>
<th>Post-alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Ab+, n</td>
<td>31</td>
<td>155</td>
</tr>
</tbody>
</table>

- Screening rate increased 14-fold
- Identification of HCV Ab+ patients increased 5-fold
- Among HCV Ab+ patients, more with early disease were identified who may have gone undiagnosed.

**Pre-alert**

<table>
<thead>
<tr>
<th>Normal ALT</th>
<th>Mean APRI</th>
</tr>
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<tr>
<td>45%</td>
<td>0.76</td>
</tr>
</tbody>
</table>

**Post-alert**

<table>
<thead>
<tr>
<th>Normal ALT</th>
<th>Mean APRI</th>
</tr>
</thead>
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<tr>
<td>75%</td>
<td>0.45</td>
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Pre-alert: June 1, 2016 – November 30, 2016. Post-alert: December 1, 2016 – May 31, 2017

The AASLD/IDSA Recommendation for Linkage to Care

General population
- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions
- All patients with active HCV infection should be linked to a clinician who is prepared to provide comprehensive management
- HCV-infected patients with decompensated cirrhosis (ie, ascites, hepatic encephalopathy) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center)

PWID population
- Active or recent injection drug use or a concern for reinfection is not a contraindication to HCV treatment
- Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with reflexive or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected
- Scale up of HCV treatment and harm reduction services among in PWID is necessary for HCV elimination

AASLD/IDSA Recommendations for Counseling Patients with HCV Infection

- Education on avoidance of transmission
- Abstinence from alcohol
- Evaluation for other conditions that may accelerate liver fibrosis (eg, HIV, HBV, NASH)
- Evaluation for advanced fibrosis
  - APRI, FIB-4, imaging
- Vaccination against HAV, HBV, and pneumococcal infection (in patients with cirrhosis)

Prior to starting therapy, AASLD/IDSA recommends:

- Fibrosis staging
- Laboratory tests (INR, hepatic function panel, eGFR)
- HCV genotype and subtype
- Quantitative HCV viral load
- Assessment for HBV co-infection (HBsAg) and prior HBV infection (anti-HBs and anti-HBc)
Options for Liver Fibrosis Assessment

Liver biopsy:
- Gold standard
- Rarely performed now

Elastography:
- Approved in the United States

Axial CT/MRI:
- Can demonstrate cirrhotic morphology and portal hypertension

Serum markers of fibrosis:
- FIBROSpect® (Prometheus, San Diego, CA)
- FibroSure® (LabCorp, Raritan, NJ)
- APRI; FIB-4

AASLD/IDSA: If direct biomarkers or transient liver elastography are not available, the APRI or FIB-4 index score can prove helpful for fibrosis assessment—although neither is sensitive enough to rule out substantial fibrosis.

CT, computed tomography; MRI, magnetic resonance imaging.

AASLD/IDSA: Evaluation for advanced fibrosis is recommended for all persons with HCV infection to facilitate an appropriate care

- Some DAA regimens are contraindicated for patients with decompensated liver disease
- Long-term HCC screening every 6 months is recommended in patients with advanced fibrosis (F3 and F4)

AASLD/IDSA: If direct biomarkers or transient liver elastography are not available, the APRI or FIB-4 index score can prove helpful for fibrosis assessment—although neither is sensitive enough to rule out substantial fibrosis¹

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CT, computed tomography; MRI, magnetic resonance imaging.
The Current HCV Treatment Landscape
HCV can be virologically cured: Cure is defined as Sustained Virologic Response (undetectable serum HCV RNA) 12 weeks after treatment (SVR12)

- Treatments have shifted from a combination of interferon injections with ribavirin to all-oral Direct-Acting Antivirals (DAAs)
- Cure rates have risen in the era of DAA therapy\(^1\) while treatment duration has decreased from 48 weeks to as low as 8 weeks
- While initial DAA options targeted one or a few genotypes,\(^1\) the most recently approved regimens are pangenotypic (GT 1–6)\(^5-7\)

HCV Treatment Landscape, 1991 – 2018


DAA, direct-acting antiviral; IFN, interferon; PegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

*Use with RBV approved in 1998. †Discontinued.
# HCV Landscape: Select All-Oral DAA Options for Treatment-Naïve Non-Cirrhotic Patients

These products differ with respect to indications, patient populations studied, and clinical safety and efficacy profile. No conclusions regarding comparative safety or efficacy should be drawn from the information presented.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Approval</th>
<th>Boxed warning</th>
<th>Genotype coverage</th>
<th>Duration</th>
<th>Dosing and administration</th>
<th>Use in compensated cirrhosis</th>
<th>Use in decompensated cirrhosis</th>
<th>Use in renal disease: Severe or ESRD</th>
<th>HIV coinfection data in label</th>
<th>Concomitant ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>Gilead</td>
<td>RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV: Test all patients for current or prior HBV infection before initiating treatment. HBV reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death.</td>
<td>1 2 3 4 5 6</td>
<td>(8*) 12–24 weeks</td>
<td>1 tablet once daily, with or without food</td>
<td>Yes</td>
<td>Yes</td>
<td>No recommendation in severe CKD</td>
<td>No recommendation in severe CKD</td>
<td>Decompensated cirrhosis, liver transplant</td>
</tr>
<tr>
<td>EBR/GZR</td>
<td>Merck</td>
<td></td>
<td>1 2 3 4 5 6</td>
<td>12–16 weeks</td>
<td>1 tablet once daily, with or without food</td>
<td>Yes</td>
<td>No</td>
<td>GT1a with resistance to P/R-experienced</td>
<td>Yes</td>
<td>GT1 and 4 P/R-experienced</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>Gilead</td>
<td></td>
<td>1 2 3 4 5 6</td>
<td>12 weeks</td>
<td>1 tablet once daily, with or without food</td>
<td>Yes</td>
<td>Yes</td>
<td>No recommendation in severe CKD</td>
<td>Yes</td>
<td>No, except in decompensated cirrhosis</td>
</tr>
<tr>
<td>G/P</td>
<td>AbbVie</td>
<td></td>
<td>1 2 3 4 5 6</td>
<td>8–12 weeks</td>
<td>3 tablets once daily, with food</td>
<td>Yes</td>
<td>Yes</td>
<td>No recommendation in severe CKD</td>
<td>Yes</td>
<td>No</td>
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- **ESRD**, end-stage renal disease; **HBV**, hepatitis B virus; **P/R**, pegylated interferon + ribavirin
- **8 weeks** can be considered in GT1 treatment naïve, non-cirrhotic patients with <6 million IU/mL baseline viral load.

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1. LDV/SOF Prescribing Information; 2. EBR/GZR Prescribing Information; 3. SOF/VEL Prescribing Information; 4. G/P Prescribing Information.
HCV Landscape: Select DAA Options for Treatment-Naïve Non-Cirrhotic GT1-Infected Patients (Melvin)

55 year-old African American male with diabetes was diagnosed with chronic HCV GT1 infection with mild fibrosis

### Melvin

**G/P 8 weeks**
- GT1 treatment-naïve and PRS-experienced patients
  - 99%
  - Common AEs (≥10%): Headache, fatigue
  - D/C due to AEs: <1%

### LDV/SOF 12 weeks*
- GT1 treatment-naïve patients
  - 98%
  - Common AEs (≥10%): Headache, fatigue, asthenia
  - D/C due to AEs: <1%

### SOF/VEL 12 weeks
- GT1 treatment-naïve and PR-experienced patients
  - 98%
  - Common AEs (≥10%): Headache, fatigue
  - D/C due to AEs: <1%

No head-to-head clinical trials exist comparing G/P, LDV/SOF, and SOF/VEL. The studies shown differ with respect to patient population and enrollment criteria; direct head-to-head comparisons cannot be made.

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*LDV/SOF for 8 weeks can be considered in treatment-naïve patients with HCV GT1 without cirrhosis who have pretreatment HCV RNA <6 million IU/mL.

AE, adverse event; D/C, discontinued; PRS, prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor; PR, prior treatment experience with peginterferon/ribavirin based regimens with or without an HCV protease inhibitor.

1. G/P US Prescribing Information
3. LDV/SOF US Prescribing Information
4. SOF/VEL US Prescribing Information.
Important Information for Glecaprevir/Pibrentasvir (G/P)

Warnings and Precautions

**BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV**
Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with G/P. HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV co-infected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

**RISK OF REDUCED THERAPEUTIC EFFECT DUE TO CONCOMITANT USE OF G/P**
- Carbamazepine, efavirenz, and St. John’s Wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of G/P. The use of these agents with G/P is not recommended.

**Contraindications**
- Patients with severe hepatic impairment (Child-Pugh C).
- Atazanavir and rifampin.

**Indications and Usage**
- G/P is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). G/P is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

**Dosage and Administration**
- G/P is a fixed-dose combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet.
- The recommended oral dosage of G/P is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food.

**Prescribing Information**
- Review G/P full prescribing information for additional information at www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110.
HCV Landscape: Select DAA Options for Treatment-Naïve Non-Cirrhotic GT3-Infected Patients (Theresa)

25 year-old Caucasian female in rehab for heroin was diagnosed with chronic HCV GT3 infection with no fibrosis

G/P 8 weeks
GT3 treatment-naïve patients without cirrhosis

SOF/VEL 12 weeks
GT3 treatment-naïve subjects without cirrhosis

No head-to-head clinical trials exist comparing G/P and SOF/VEL.
The studies shown differ with respect to patient population and enrollment criteria; direct head-to-head comparisons cannot be made.

- Common AEs (≥10%): Headache, fatigue
- 0.1% discontinued due to adverse reactions
- 8 weeks G/P was non-inferior to 12 weeks G/P
- Common AEs (≥10%): Headache, fatigue
- 0.2% discontinued due to adverse reactions

GLE, glecaprevir; PIB, pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir.

1. G/P US Prescribing Information;
3. SOF/VEL US Prescribing Information.
You play a critical role in the screening and diagnosis of HCV patients in order to provide appropriate treatment or referral to a specialist.

Call to action

• **Screen** for HCV in all baby boomers and patients with risk behaviors or risk exposures

• **Treat or refer** – Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions
  • There are all-oral DAA treatment options for patients with all major GTs

Additional considerations

• **Vaccinate** HCV-infected patients against HAV, HBV, and (in patients with cirrhosis) pneumococcal infection

• **Educate** HCV-infected patients on prevention of HCV transmission

• **Screen** HCV-infected patients with advanced fibrosis for primary liver cancer

HAV, hepatitis A virus
