Hepatitis C Updates

Managing HIV/HCV in Primary Care Practice Conference
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• I have no financial disclosures or conflicts of interest
• Some slides courtesy of Cambridge Health Alliance’s Zinberg clinic (Deb Sarson, Carol Katz, Amy Colson, Linda Shipton)
Outline

- Epidemiology
- HCV screening
- Extrahepatic manifestations
- Staging
- Case study (HIV/HCV co-infection)
- Treatment
- Cost
- Project ECHO
Hepatitis C is a Global Health Problem

Hanafiah et al, *Hepatology* 2015
Prevalence of HCV among baby boomers

MMWR: Age distribution of newly reported confirmed cases of hepatitis C virus infection --- Massachusetts, 2002 and 2009

N = 6,281; excludes 35 cases with missing age or sex information.† N = 3,904; excludes 346 cases with missing age or sex information.

Source: MMWR: May 6, 2011; 60(17):537-541

MMWR 2011
Mortality Rates in the US, 1999-2007


<table>
<thead>
<tr>
<th>Year</th>
<th>HIV Rate</th>
<th>Hepatitis C Rate</th>
<th>Hepatitis B Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>6.0</td>
<td>3.0</td>
<td>0.9</td>
</tr>
<tr>
<td>2000</td>
<td>5.7</td>
<td>3.2</td>
<td>0.7</td>
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<td>2001</td>
<td>5.4</td>
<td>3.4</td>
<td>0.6</td>
</tr>
<tr>
<td>2002</td>
<td>5.0</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2003</td>
<td>4.6</td>
<td>3.6</td>
<td>0.4</td>
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<tr>
<td>2004</td>
<td>4.2</td>
<td>3.7</td>
<td>0.4</td>
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<tr>
<td>2005</td>
<td>3.8</td>
<td>3.8</td>
<td>0.4</td>
</tr>
<tr>
<td>2006</td>
<td>3.5</td>
<td>3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>2007</td>
<td>3.2</td>
<td>4.0</td>
<td>0.4</td>
</tr>
</tbody>
</table>
HIV/HCV co-infection

Compared to HIV or HCV monoinfection:

• More aggressive liver disease progression
• More likely to develop steatosis and fibrosis
• Other co-morbidities: CVD, chronic pain
• High mortality rates
  – Single-center, retrospective longitudinal cohort (n=105) found 25% mortality rate in co-infected patients

Malik, et al IDSA 2015
Tsui et al, *AIDS Care* 2012
Who Should You Screen for HCV?

- Born in the United States between 1945 and 1965
- Hx of IVDU or intranasal cocaine use, even if only used once
- Children born to HCV-infected mothers
- Needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partner of an HCV-infected person
- Evidence of liver disease (persistently elevated ALT)
- Chronic hemodialysis
- HIV, HIV+ MSM
- Incarcerated individuals
- Clotting factors made before 1987
- Blood/organs before July 1992
- Received blood from donor who later tested positive for HCV

CDC 2015
HCV Cascade of Care

- Chronic HCV-Infected*: 100%
- Diagnosed and Aware†: 50%
- Access to Outpatient Care‡: 43%
- HCV RNA Confirmed§: 27%
- Underwent Liver Biopsy‖: 17%
- Prescribed HCV Treatment¶: 16%
- Achieved SVR**: 9%

Yehia PLoS ONE 2014
Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

Nonreactive

- No HCV antibody detected
- STOP*

Reactive

- HCV RNA

  - 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.

Management

Patient Counseling

• Preventing HCV transmission
• HCV antibodies are not protective
• Avoid alcohol
• Avoid illicit drugs
• Avoid new medicines, including over the counter and herbal agents, without checking with their healthcare provider
• Maintain a healthy diet and lose weight if necessary
• Sources of support (e.g., social, emotional, financial)

Clinical Management

• HAV and HBV vaccinations
• Comorbidity management (depression, diabetes, hypertension)
• Medication assessment (for any products that may harm liver)
Extrahepatic manifestations of HCV

**Significant Prevalence**
- Mixed cryoglobulinemia/cryoglobulinemia vasculitis
- B-cell non-Hodgkins lymphoma

**High Prevalence**
- Diabetes mellitus type 2/insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Cardiovascular disorders
- Sicca syndrome
- Arthralgias/myalgias
- Auto-antibody production (ANA, anticardiolipin)
- Porphyria cutanea tarda
- Lichen planus

Cacoub et al *Digestive and Liver Disease* 2014
HCV and Cryoglobulinemia

Dermatitis

- Often occurs in dependent areas
- Deposition of cryoglobulins in small capillaries
- Ulcerations may develop
- Pruritic

Hellman, Johns Hopkins Vasculitis Center
http://www.hopkinsvasculitis.org/types-vasculitis/cryoglobulinemia/
HCV and Porphyria Cutanea Tarda (PCT)

- One of the primary drivers for PCT is hepatitis C.
- Patients may present with blisters, vesicles after sun exposure, trauma

http://hcvadvocate.org
How do you know if your patient has cirrhosis?
Assessing level of fibrosis

- Liver biopsy
- Serum biomarkers
- Fibroscan
Liver Biopsy Specimens

A

B

C

D

E

AASLD HEPATOLOGY, Vol. 49, No. 3, 2009
Serum Biomarkers

• APRI score
  • AST, platelet (<0.2, >2)

• FIB4
  • AST, ALT, platelet, age (<1.45, >3.25)

• Fibrosure ($$$$)
  • Age, gender, and 6 biochemical markers (<0.31, > 0.72)

• Others: Hyaluronic acid, YKL-40

Holmberg, et al CID 2013
Fibroscan

- Uses velocity of the sound wave passing through the liver and converts that into a liver stiffness measurement
- Results 0-75 kPa
- Score >15 gave a sensitivity of 84.5% and a specificity of 94.7% for cirrhosis
- Approved in USA in 2013
- Obese patients require special probe
Management of Cirrhosis

• Lifelong HCC screening with q 6 mo US
Management of Cirrhosis
Send for Transplant Evaluation

- MELD score of 10
  - INR, Cr, bilirubin

- Any sign of decompensation
  - ascites, bleeding varices, encephalopathy, coagulopathy (INR 1.4-1.5)

- Hepatocellular carcinoma
Case: 55 yo man with HIV/HCV co-infection

HCV history: Infected ~20 years ago through IVDU, treated 2011 with pegylated-interferon + ribavirin + for 24 wks with SVR during treatment then subsequent virologic relapse, course complicated by renal insufficiency


ROS: low energy but otherwise feels well. Denies abdominal pain, nausea, tarry or bloody stools

Social: IVDU and unhealthy alcohol use in past, sober from all substances for 10 years, not currently sexually active

Exam: mildly overweight, few spider angiomas on chest, no palmar erythema, liver not enlarged or tender, spleen not palpable
Case: Evidence for advanced fibrosis or cirrhosis

History: Infected ~20 years ago

Social: prior unhealthy alcohol use

Exam: few spider angiomas

Labs
- HCV genotype 1a
- HCV RNA 4.1 million
- ALT 178
- AST 246
- INR normal
- Albumin 3.3
- Plt 107
- Creatinine and UA normal
- Hemoglobin A1c 5.8

FIB-4 = 9.59 (>3.25 = advanced fibrosis likely)
Fibroscan confirms cirrhosis
Benefits of Curative Therapy in Patients with Advanced Fibrosis/Cirrhosis

- Improved fatigue and neurocognitive function
- Decrease risk of type 2 diabetes
- Improvement of non-hepatic complications: CV, renal, pain
- Eliminate risk of further transmission
- Improved quality of life
- Reduction in ESRD

ANRS CO13 HEPAVIH Cohort, AIDS 2015
Evolution of Treatment for HCV Genotype 1

Pre-2011
Non-specific Antiviral Drugs
Interferon and Ribavirin
48 weeks
Highly toxic

May 2011-October 2014
Interferon and Ribavirin
plus Oral Direct Acting Antiviral Drugs
12-48 weeks
Highly Toxic

Since Oct 2014...
All Oral Direct Acting Antiviral Drug Combinations
8-24 weeks
Well Tolerated
Therapeutic Targets of Direct Acting Antivirals (DAAs)

- Telaprevir
- Boceprevir
- Simeprevir
- Paritaprevir
- Sofosbuvir
- Ledipasvir
- Ombitasvir
- Daclatasvir

Diagram showing various stages of HCV RNA and the inhibition points targeted by different DAAs.
Multiple Classes of Direct-Acting Antiviral Agents

www.hcvguidelines.org

- Ribavirin
- NS3 Protease Inhibitors: Telaprevir approved 5/11, Boceprevir approved 5/11, Simeprevir approved 11/13, Asunaprevir, Paritaprevir, MK-5172, Faldaprevir, Sovaprevir, ACH-2684
- Ledipasvir approved 10/14, Daclatasvir, Ombitasvir, MK-8742, GS-5885, GS-5816, ACH-3102, PPI-668, GSK2336805, Samatasvir
- Sofosbuvir approved 12/13, VX-135, IDX21437, ACH-3422
- Dasabuvir, BMS-791325, PPI-383, GS-9669, TMC647055

Licensed

In Development

- Sofosbuvir and Ledipasvir approved 10/14
- Simeprevir + Sofosbuvir approved 11/14
- Daclatasvir + Sofosbuvir approved 07/15
- Ombitasvir + Paritaprevir + Ritonavir approved 7/15
- Dasabuvir + Ombitasvir + Paritaprevir + Ritonavir +/- Ribavirin (PrOD) approved 12/14
Considerations for HCV/HIV treatment

• Switching an optimized antiretroviral regimen carries risks: adverse effects/viral breakthrough

• Daclatasvir + Sofosbuvir is recommended for patients with substantial antiretroviral experience/known drug resistance

www.hcvguidelines.org
<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Paritaprevir, ombitasvir plus dasabuvir (PrOD)</th>
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<tbody>
<tr>
<td>Ritonavir-boosted</td>
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<tr>
<td>atazanavir</td>
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<td>No data</td>
<td>Ledipasvir ↑; atazanavir ↑</td>
<td>Daclatasvir ↑</td>
<td>Paritaprevir ↑; atazanavir ↑</td>
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<tr>
<td>Ritonavir-boosted</td>
<td>Simeprevir ↑; darunavir ↔</td>
<td>Sofosbuvir ↑; darunavir ↔</td>
<td>Ledipasvir ↑; darunavir ↔</td>
<td>Daclatasvir ↑</td>
<td>Paritaprevir ↓; darunavir ↓</td>
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<tr>
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<td>No data</td>
<td>No data</td>
<td>Daclatasvir ↑</td>
<td>Paritaprevir ↑; lopinavir ↔</td>
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<td>lopinavir</td>
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<tr>
<td>Rilpivirine</td>
<td>Simeprevir ↔; rilpivirine ↔</td>
<td>Sofosbuvir ↔; rilpivirine ↔</td>
<td>Ledipasvir ↔; rilpivirine ↔</td>
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<td>Paritaprevir ↑; rilpivirine ↑</td>
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<td>Raltegravir</td>
<td>Simeprevir ↔; raltegravir ↔</td>
<td>Sofosbuvir ↔; raltegravir ↔</td>
<td>Ledipasvir ↔; raltegravir ↔</td>
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<td>PrOD ↔; ↑ raltegravir</td>
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<tr>
<td>elvitegravir</td>
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<td>Daclatasvir ↔; dolutegravir ↑</td>
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<td>Tenofovir</td>
<td>Simeprevir ↔; tenofovir disoproxil fumarate ↔</td>
<td>Sofosbuvir ↔; tenofovir disoproxil fumarate ↔</td>
<td>Ledipasvir ↔; tenofovir disoproxil fumarate ↑</td>
<td>Daclatasvir ↔; tenofovir disoproxil fumarate ↔</td>
<td>PrOD ↔; tenofovir disoproxil fumarate ↔</td>
</tr>
</tbody>
</table>

Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.

http://www.hep-druginteractions.org
Consult with a pharmacist!
ION-2: Sofosbuvir/Ledipasvir
Genotype 1, Failed Prior Rx, With or Without Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Sofosbuvir/Ledipasvir 12 weeks N=109</th>
<th>Sofosbuvir/Ledipasvir 24 weeks N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR-12 (=virologic cure)</td>
<td>94% (102/109)</td>
<td>99% (108/109)</td>
</tr>
<tr>
<td>On treatment; virologic failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse after treatment</td>
<td>6% (7/108)</td>
<td>0</td>
</tr>
<tr>
<td>SVR-12 by Disease Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-No cirrhosis</td>
<td>95% (83/87)</td>
<td>99% (85/86)</td>
</tr>
<tr>
<td>-Cirrhosis</td>
<td>86% (19/22)</td>
<td>100% (22/22)</td>
</tr>
</tbody>
</table>
Case Conclusion

- Based on results of ION-2 study, you recommend treatment with Ledipasavir/Sofosbuvir for 24 weeks.

- Patient instructed to take omeprazole at the same time as the DAA.

- Medicare agrees to pay $189,000 for 24 weeks of therapy - patient undergoes treatment which he tolerates, and there is no detectable virus in blood 12 weeks after conclusion of therapy.

- You inform him that prospective studies have shown < 1% risk of virologic relapse (5 years follow up) if HCV is absent from blood 12 weeks after completing therapy.
# Summary of Current Treatment Recommendations

## Genotype 1, Treatment

**Experienced, Cirrhosis**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td>Paratasvir/r/Ombitasvir + Dasabuvir + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Paratasvir/r/Ombitasvir + Dasabuvir</td>
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</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

*Cannot use with Q80K mutation*

**Naïve OR Experienced, NO Cirrhosis**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir + Sofosbuvir</td>
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<td>12 weeks</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*PI failures

**PI or SOF failures

***Shortening to 8 weeks done at “discretion of provider” (HCV VL <6 million, HCV monoinfected, no cirrhosis)*

## Genotype 2

**Treatment naïve**

- **No Cirrhosis**
  - Sofosbuvir + R 12 wks
  - Daclatasvir + Sofosbuvir 12 wks
  - Sofosbuvir + R 12 wks
- **Cirrhosis**
  - Sofosbuvir + R 16 wks
  - Daclatasvir + Sofosbuvir + R 16 wks
  - Sofosbuvir + R + IFN 12 wks
- **Treatment experienced**
  - **No Cirrhosis**
    - Sofosbuvir + R 16-24 wks
    - Daclatasvir + Sofosbuvir 12-24 wks
    - Sofosbuvir + R + IFN 12 wks
  - **Cirrhosis**
    - Sofosbuvir + R + IFN 12 wks

## Genotype 3

**Daclatasvir + Sofosbuvir 12 wks**

- Daclatasvir + Sofosbuvir + R 24 wks
- Sofosbuvir + R + IFN 12 wks
- Sofosbuvir + R 24 wks*

## Genotype 4

- Ledipasvir/Sofosbuvir 12 wks
- Ombitasvir/paritaprevir/r + R 12 wks
- Sofosbuvir + R 24 wks
- Sofosbuvir + R + IFN 12 wks

*IFN = interferon*
Prioritization by Insurance Companies

**Highest Priority=Highest Risk for Severe Complications**

- Advanced fibrosis (F3)
- Compensated cirrhosis
- Pre/post liver transplant
- Cryoglobulinemia with end organ manifestation (vasculitis)
- Glomerular Disease secondary to immune complex deposition

**High Priority=High Risk for Complications**

- Moderate Fibrosis (F2)
- HIV co-infection
- HBV co-infection
- Co-existent liver disease (NASH)
- Debilitating fatigue
- Insulin resistant
- Porphyria cutanea tarda

Restrictions in several states if patients not abstinent from IV drug, marijuana, alcohol use for 6-12 months – though treatment has been effective in people who inject drugs
### Cost Per SVR

Hepatitis C is associated with hospitalizations & emergency department visits. Treatment of hepatitis C is cost-effective and may prevent unnecessary acute care visits.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Weeks</th>
<th>SVR Rate</th>
<th>2014 WAC* Price</th>
<th>Cost per SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN+RBV</td>
<td>48</td>
<td>41%</td>
<td>$41,758</td>
<td>$101,849</td>
</tr>
<tr>
<td>TVR+ Peg-IFN+RBV</td>
<td>24</td>
<td>75%</td>
<td>$86,843</td>
<td>$115,791</td>
</tr>
<tr>
<td>Sofosbuvir+Peg-IFN+RBV</td>
<td>12</td>
<td>90%</td>
<td>$94,421</td>
<td>$104,912</td>
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<tr>
<td>Sofosbuvir+Ledipasvir</td>
<td>8</td>
<td>94%</td>
<td>$63,000</td>
<td>$67,021</td>
</tr>
<tr>
<td>Sofosbuvir+Ledipasvir</td>
<td>12</td>
<td>99%</td>
<td>$94,500</td>
<td>$95,454</td>
</tr>
</tbody>
</table>


*Wholesale Acquisition Cost

Bridging the gap
HCV as an iceberg

Only the tip is visible due to asymptomatic or minimally symptomatic transmission, fragmented care of high-risk groups

Increasing opiate use
Increasing high-risk sexual behaviors

A. Kim, CROI 2015 (modified)
Take-Home Points

- HIV-infected individuals no longer considered “special population” for HCV treatment outcomes, but HIV/HCV patients do have higher risk of more severe liver disease

- Recognize that ART and DAA drug interactions exist

- Despite prioritization by insurance companies, HCV treatment should be offered to people w/ all stages of liver disease and is cost-effective

- HCV treatment is effective in people who inject drugs; integration of HCV treatment and treatment of opioid use disorders also effective in primary care practice.