ACTHIV
THE AMERICAN CONFERENCE FOR THE TREATMENT OF HIV

ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
Pre-Treatment Evaluation of the Patient with Hepatitis C Virus Infection

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Disclosures

- I have no disclosures
Learning objectives

At the end of this presentation participants will be able to:

- Discuss basic epidemiology of HCV in HIV infected populations
- Explain clinical and laboratory evaluation of HCV infection in preparation for antiviral therapy
- Counsel a patient with HCV/HIV about health maintenance
- Describe indication for liver cancer surveillance
Epidemiology of HCV in HIV
High Prevalence of HCV infection among HIV infected individuals

Prevalence differs by HIV risk group

Liver disease remains 2nd leading cause of death in HIV-infected persons in D:A:D

- 33,308 participants from 1999-2008
  - 15.3% with HCV (Ab or RNA+)
  - 11.5% HBV (prior/active)
- 2,482 deaths
  - 29.9% AIDS-related
  - 13.7% liver-related
  - 11.6% CVD-related
Natural History of HCV Infection

Exposure (Acute Phase)
- Resolved (~15%)
- Stable (~85%)

Chronic
- ~80%

Cirrhosis
- Slowly Progressive (~75%)
- ~20%

ESLD: end-stage liver disease
- ~6%/yr
- ~4%/yr

HCC
- ~3%-4%/yr

Transplant/Death

Time (yrs)
- 10
- 20
- 30

5-year survival in patients with HCC is <5%*

Natural history of chronic liver disease

Chronic Liver Disease → Fibrosis → Compensated Cirrhosis → Decompensated Cirrhosis

Factors:
- Age
- HIV infection
- Hepatitis B
- Alcohol
- Obesity

Complications:
- Varices
- Ascites
- Encephalopathy
- Jaundice
- HCC
Case Study: Mr. A

- 67 year old African-American man with HIV, well controlled on HAART; hypertension, diabetes and prior injection drug use.
- Recently transferred to your care.
- On initial review of medical record:
  - CD4: 628, HIV RNA: < 20 copies/mL
  - HCV antibody: reactive

Medications:
- Darunavir, 800mg daily
- Norvir, 100mg daily
- TDF/ FTC, 1 tablet daily
- Metoprol XL, 50 mg daily
- Lisinopril, 20mg daily
- Metformin, 500mg BID
- Rosuvastatin, 10 mg daily
- Omeprazole, 20mg daily
Confirm infection in patients with positive HCV antibody test results

- Test for HCV RNA with a quantitative assay
- Interpretation of negative HCV RNA
  - Resolved infection
    - Spontaneously
    - Following successful therapy
Follow up of initial HCV testing

- If HCV antibody positive and HCV RNA negative by PCR, counsel patient that they do not have current (active) infection
  - However at risk for reinfection
- If ongoing risk factors for reinfection:
  - Screen for reinfection with HCV RNA testing

www.hcvguidelines.org
67 year old with well controlled HIV and a positive HCV antibody, HCV RNA 6.4 million IU/ml

What is your next step?

a. Additional testing, alcohol use screen, brief intervention and referral as needed.
b. Treat with sofosbuvir/ledipasvir to take 1 tablet daily for 12 weeks.
c. Refer to a gastroenterologist for further evaluation and management.
Clinical history to assess:

- Risk factor(s) for acquiring HCV infection
- Presence of significant medical co-morbidities
  - Coinfection with other viruses: hepatitis B
  - Potential to impact HCV treatment choice/course
    - E.g. ability to tolerate ribavirin induced anemia, advanced chronic kidney disease (sofosbuvir currently recommended if GFR >30ml/min/1.73m^2)
- History of complications of liver disease
  - Hepatic encephalopathy, jaundice, gastrointestinal bleeding, ascites
- History of prior HCV treatment
  - Prior HCV liver disease staging
History to assess for:

- Alcohol use
- Use of other liver toxic substances, e.g. herbal supplements, excessive tylenol
- Barriers to HCV treatment adherence
  - Transportation, stable housing
  - Ongoing substance use
  - HIV antiretroviral therapy adherence may be a prognosticator
- Risk factors for reinfection
  - Injection drug use
  - High risk unprotected sex with other men
Clinical exam

- Complete exam
- Height and weight to calculate BMI
- Evaluate for stigmata of chronic liver disease
  - Spider nevi (esp. on shoulders)
  - Palmar erythema
  - Ascites
  - Splenomegaly
  - Encephalopathy
Laboratory testing

- **General laboratory evaluation**
  - Complete blood count (CBC)
  - Serum creatinine
  - Pregnancy test if considering use of ribavirin

- **Assess for:**
  - Hepatic inflammation
    - Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)
  - Hepatic synthetic function
    - Bilirubin, PT, INR, albumin
  - HCV RNA, “Viral load”
    - Establish pre-treatment baseline
  - HCV genotype
  - Coinfections
    - Hepatitis A: Hepatitis A total antibody or IgG
    - Hepatitis B: Hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody

www.hcvguidelines.org
## Hepatitis B and HCV

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>HB core antibody</th>
<th>Meaning</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Susceptible</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Immune, vaccine</td>
<td>Nothing with regards to HCV</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Hepatitis B</td>
<td>Risk of HBV reactivation during oral DAA therapy</td>
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<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Isolated core antibody</td>
<td>Consider HBV DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low risk of HBV reactivation with oral DAA</td>
</tr>
</tbody>
</table>
Monitoring for reactivation of HBV in patients initiating HCV DAA therapy

- All patients should be assessed for HBV coinfection
  - HBsAg, anti-HBs and anti-HBc
  - HBV vaccination for all susceptible individuals

- In sAg positive patients
  - Test for HBV DNA
  - Start HBV therapy in patients who meet criteria for treatment of active HBV
  - Monitor patients with low or undetectable HBV DNA at regular intervals with HBV DNA
  - Consider possibility of HBV reactivation in patients with past or current HBV in the event of unexplained increase in liver enzymes during and/or after HCV treatment
Screen for other causes/contributors of liver disease

- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Alpha-1 antitrypsin deficiency
- Hemochromatosis
- Autoimmune hepatitis
Liver Disease Staging
HCV disease progression is measured by the magnitude of liver fibrosis: METAVIR stages

**Stage 0:** No Fibrosis

**Stage 1:** Fibrous expansion of some portal areas

**Stage 2:** Fibrous expansion of most portal areas with occasional portal to portal bridging

**Stage 3:** Fibrous expansion of portal areas with marked bridging (portal to portal and portal to central)

**Stage 4:** Cirrhosis, probable or defined
Clinical role of staging is to assess for presence or absence of cirrhosis.
Detection of cirrhosis is important

- Risk of hepatic decompensation in patients with cirrhosis
- Increased risk of liver cancer with cirrhosis even after HCV cure
  - Imaging to assess for hepatocellular cancer
  - Ongoing hepatocellular cancer screening every 6 months (life long)
- Cirrhosis may impact HCV treatment regimen and duration
- Esophagogastroduodenoscopy (EGD) required to screen for varices
Case Study: Mr. A

- 67 year old African-American man with HIV, well controlled on HAART; hypertension, diabetes
- Acquired HIV/HCV through IDU
- H/o endocarditis with valvular heart disease
- No previous evaluation or treatment for HCV
- ROS: + Fatigue

- Social history
  - Drinks 2-3 beers daily
  - Reports intermittent injection drug use
  - Denies sharing drug use paraphernalia

- PE: + for cardiac murmur

- Labs
  - CD4 628, HIV RNA < 20 copies
  - HCV RNA: 6.4 million IU
  - HCV Genotype 1a
  - ALT 48; AST 90; pltts 125k; INR 1.0; T, bilirubin 1.2; Albumin 3.3, Hb 13.6; Cr 1.4
Evaluation of liver disease with serum markers

APRI

AST to Platelet Ratio Index (APRI) Calculator
This is an AST to Platelet Ratio Index (APRI) calculator tool. Enter the required values to calculate the APRI.

APRI = \frac{\text{AST Level (U/L)}}{\text{Platelet Count (10^9/L)}} \times 100

\text{APRI} = \frac{90}{40} \times 100 = 1.800

APRI > 1.0
76% sensitive, 72% specific for cirrhosis

FIB-4

Fibrosis-4 (FIB-4) Calculator
The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4.

FIB-4 = \frac{\text{Age (years)} \times \text{AST Level (U/L)} \times \sqrt{\text{Platelet Count (10^9/L)}}}{\text{ALT (U/L)}}

FIB-4 = \frac{67 \times 90 \times \sqrt{125}}{48} = 6.96

FIB 4 >3.25
97% specificity for cirrhosis

http://www.hepatitisc.uw.edu/pageclinical-calculators/ctp
Non-invasive blood test to stage fibrosis

- Fibrosis index (HCV FibroSURE)
  - GGT
  - Bilirubin
  - Haptoglobin
  - Apolipoprotein A1
  - α2 macroglobulin

- Necroinflammatory activity
  - Markers + ALT

- Should not be used for patients with Gilbert disease, acute hemolysis, acute viral hepatitis, drug-induced hepatitis, genetic liver disease, autoimmune hepatitis, or extrahepatic cholestasis

FibroSURE Technical Report, 2006
Transient Elastography
Transient Elastography: HCV

2.5 kPa

- Absent or mild fibrosis (Metavir F0-F1)
- Significant fibrosis (F2)
- Severe fibrosis (F3)
- Cirrhosis (F4)

Affected by weight, access of probe (2 cm), steatosis
Management of HCV+ patients with cirrhosis

- Screen for hepatocellular carcinoma
- Screen and manage varices
- Stage with CPT and MELD score
  - Prognosis
  - Indication for liver transplant referral
Screening for hepatocellular carcinoma

- All patients with cirrhosis, also consider in those with stage F3 disease
- Surveillance using ultrasound (US)
- Alpha fetoprotein (AFP) should not be used alone
- 6 month intervals

Evaluation of liver disease: Cirrhosis

- Compensated
  - Asymptomatic
- Decompensated
  - Symptomatic: ascites, encephalopathy
Calculate the CTP for all cirrhotics

### Child-Turcotte-Pugh Classification for Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Mild to moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild to moderate (diuretic responsive)</td>
<td>Severe (diuretic refractory)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2-3</td>
<td>&gt;3</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
<td></td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
<td></td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

**Criteria**

- No encephalopathy: 1
- No Ascites: 1
- Bilirubin: 1.2 mg/dl: 1
- Albumin: 3.3 g/dl: 2
- INR: 1.2: 1

**Total Score**: 6

**CTP Class**: A

**Compensated Cirrhosis**

CTP Class B and C considered decompensated liver disease

http://www.hepatitisc.uw.edu/page/clinical-calculators/ctp
Calculate the MELD score

Model For End-Stage Liver Disease (MELD) for ages 12 and older

The Model for End Stage Liver Disease (MELD) predicts survival for patients with advanced liver disease.

The United Network for Organ Sharing (UNOS) made a policy change regarding a revision in the MELD scoring system on January 11, 2016 that is related to transplant listing. The new MELD scores are calculated first by determining the traditional MELD score as an initial score (MELD), if the initial MELD score is 12 or greater, the score is adjusted by incorporating the serum sodium value.

3-Month Mortality Based on MELD Scores

The estimated 3-month mortality is based on the MELD score highlighted in yellow above.

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>Mortality Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>6.0% mortality</td>
</tr>
<tr>
<td>10-19</td>
<td>6.0% mortality</td>
</tr>
<tr>
<td>20-29</td>
<td>19.6% mortality</td>
</tr>
<tr>
<td>30-39</td>
<td>52.6% mortality</td>
</tr>
<tr>
<td>≥40</td>
<td>71.3% mortality</td>
</tr>
</tbody>
</table>

Based on liver transplant survival data, patients with MELD score \( \geq 15 \) have improved survival after liver transplantation.

http://www.hepatitisc.uw.edu/page/clinical-calculators/ctp
Patients with decompensated liver disease should be treated for HCV in specialized centers with access to liver transplant services.
Counseling for Health Maintenance
Alcohol and Hepatitis C

*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men

Alcohol counseling

➢ Alcohol use screening, brief intervention and referral for treatment (SBIRT) recommended as part of HCV care

http://www.niaaa.nih.gov/guide#powerpoint
Patient Education

- Natural history of hepatitis C
- Regarding HCV transmission
  - Do NOT share razors, nail clippers, toothbrushes
  - Sexual transmission among MSM
  - Do not share needles or injection drug use paraphernalia
    - Link to harm reduction services
- Liver healthy lifestyle
  - Recommend alcohol abstinence
  - Avoid OTCs or complimentary medications unless cleared by a clinician
  - Achieve and/or maintain a normal body mass index
  - Drink coffee???
- Discuss new HCV treatments: **Cure is possible!**
- Risk of reinfection after cure
It takes a village....

• The whole health care team is needed to ensure HCV treatment success
  • Clinicians
  • Nurses
  • Case managers
  • Support staff
  • Pharmacy staff
67 year old with HIV, Genotype 1a, chronic HCV, treatment naïve with compensated cirrhosis

Do we have everything we need to make a treatment decision?

a. Yes
b. No
When to get HCV resistance testing?

- In treatment naïve patients
  - Genotype 1a patient
  - When considering use of Grazoprevir/Elbasvir
  - Test for NS5A resistance associated substitutions (RASs)
    - 10%-15% of HCV genotype 1 patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RASs prior to treatment
    - If NS5A resistance RASS present, it changes treatment duration and requires addition of ribavirin in patients with HCV genotype 1a infection
Case Study: Mr. A

- 67 year old African-American man with HIV, well controlled on HAART; hypertension, diabetes and valvular heart disease. HCV treatment naive
  - CD4 628, HIV RNA < 20copies
  - HCV RNA: 6.4 million IU
  - HCV Genotype 1a
  - Fibrosure F4-cirrhosis, Fibroscan score 26KPA
  - CTP score 6 c/w compensated cirrhosis
  - Liver ultrasound: No mass
  - EGD: small varices

- Medications:
  - Darunavir, 800mg daily
  - Norvir, 100mg daily
  - TDF/FTC, 1 tablet daily
  - Metoprol XL, 50 mg daily
  - Lisinopril, 20mg daily
  - Metformin, 500mg BID
  - Rosuvastatin, 10 mg daily
  - Omeprazole, 20mg daily
67 year old with HIV, Genotype 1a, chronic HCV, treatment naïve with compensated cirrhosis

Are you ready to initiate HCV therapy?

a. Yes, I’m ready to initiate HCV therapy
b. Yes, but I need more information
c. Probably not
Assessment for Potential Drug Interactions
<table>
<thead>
<tr>
<th></th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Velpatasvir</th>
<th>Simeprevir</th>
<th>Daclatasvir</th>
<th>EBR/GZP</th>
<th>P/r/O + D</th>
<th>P/r/O</th>
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<td>LDV ↑; ATV ↑⁸</td>
<td>VEL↑; ATV ↑⁸</td>
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<td>↓DCV to 30mg</td>
<td>EBR &amp; GZP↑; ATV ↑</td>
<td>PAR ↑; ATV ↑</td>
<td>PAR ↑; ATV ↔</td>
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<tr>
<td>DRV/r</td>
<td>SOF ↑; DRV ↔</td>
<td>LDV ↑; DRV ↔⁸</td>
<td>VEL↔; DRV↔⁸</td>
<td>SMV↑; DRV↔</td>
<td>DCV ↑; DRV ↔</td>
<td>EBR &amp; GZP↑; DRV ↔</td>
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<tr>
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<td>PAR ↑; LPV ↔</td>
<td>PAR ↑; LPV ↔</td>
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<td>EFV</td>
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<td>LDV↓; EFV↓⁸</td>
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<td>SMV↔; RPV↔</td>
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<td>EBR &amp; GZP↔; RPV ↔</td>
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<td>↑DCV to 90mg</td>
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<td>RAL</td>
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Footnotes:

⁸ DCV to 30mg for the DRV/r combination.
⁹ DCV to 90mg for the DRV/r combination.
¹⁰ DCV to 90mg for the DRV/r combination.
¹¹ DCV to 90mg for the DRV/r combination.
¹² DCV to 90mg for the DRV/r combination.
¹³ DCV to 90mg for the DRV/r combination.
¹⁴ DCV to 90mg for the DRV/r combination.
¹⁵ DCV to 90mg for the DRV/r combination.
¹⁶ DCV to 90mg for the DRV/r combination.
¹⁷ DCV to 90mg for the DRV/r combination.
¹⁸ DCV to 90mg for the DRV/r combination.
¹⁹ DCV to 90mg for the DRV/r combination.
²⁰ DCV to 90mg for the DRV/r combination.
²¹ DCV to 90mg for the DRV/r combination.
²² DCV to 90mg for the DRV/r combination.
²³ DCV to 90mg for the DRV/r combination.
²⁴ DCV to 90mg for the DRV/r combination.
²⁵ DCV to 90mg for the DRV/r combination.
²⁶ DCV to 90mg for the DRV/r combination.
²⁷ DCV to 90mg for the DRV/r combination.
²⁸ DCV to 90mg for the DRV/r combination.
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³³ DCV to 90mg for the DRV/r combination.
³⁴ DCV to 90mg for the DRV/r combination.
³⁵ DCV to 90mg for the DRV/r combination.
³⁶ DCV to 90mg for the DRV/r combination.
³⁷ DCV to 90mg for the DRV/r combination.
³⁸ DCV to 90mg for the DRV/r combination.
³⁹ DCV to 90mg for the DRV/r combination.
⁰ DCV to 90mg for the DRV/r combination.

www.hcvguidelines.org
Drug Interactions with oral DAA

Other major classes
- Acid blockers
- Antiseizure medications
- Statins

- Get help with assessing for drug interactions

http://www.hep-druginteractions.org/
Conclusion

• Evaluation of the patient with HCV requires a history, physical exam and laboratory testing
• Liver disease staging is indicated primarily to assess for presence of liver cirrhosis
• Patients with cirrhosis require screening for hepatocellular cancer with imaging (ultrasound)
• Address alcohol use and ongoing risk factors for reinfection
• Assess for drug interactions
• It takes a village....
Treatment of HCV

Acknowledgements:
Dr. Mark Sulkowski

Thank you!
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