HIV AND HEPATITIS C: ENTERING A NEW ERA

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HIV CO-MORBIDITIES

• Neuropsychiatric Complications
  • Depression, bipolar disorder, anxiety disorders, cognitive dysfunction

• Metabolic and Renal Complications
  • Lipid changes, insulin resistance, fat redistribution → CAD, DM
  • Kidney dysfunction
  • Osteopenia/porosis/necrosis

• Malignancies

• Chronic Viral Hepatitis Co-Infections
  • Hepatitis B and C
VIRAL HEPATITIS CO-INFECTIONS

- **Hepatitis A**
  - Fecal-oral route
  - Usually self-limited
  - Prevention with vaccine

- **Hepatitis B**
  - Infected blood/body fluids
  - 10% of HIV patients chronically infected
  - Increased risk of liver-related disease and deaths
  - Prevention with vaccine, some ARV agents can be used to treat (3TC, FTC, tenofovir)

- **Hepatitis C**
## HIV/HCV Patients Have Significant Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV</th>
<th>HIV/HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug disorder</td>
<td>22%</td>
<td>58%</td>
</tr>
<tr>
<td>Alcohol disorder</td>
<td>24%</td>
<td>56%</td>
</tr>
<tr>
<td>Depression</td>
<td>28%</td>
<td>43%</td>
</tr>
<tr>
<td>Bipolar</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>Anemia</td>
<td>19%</td>
<td>27%</td>
</tr>
<tr>
<td>COPD</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37%</td>
<td>42%</td>
</tr>
</tbody>
</table>

WORLDWIDE PREVALENCE OF HCV

- Estimated 180 million infected worldwide
  - 60 million Russia
  - 32 million Africa
  - 30 million China
  - 20 million Eastern Europe/Middle East
  - 10 million South America
  - 9 million Western Europe
  - 4-5 million USA ~ 300,000 HIV/HCV co-infected
    - Prevalence about 2% in general population
    - Among those infected 10-30 yrs ago, nearly 75% undiagnosed
    - 15,000 deaths per year
    - Leading cause of deaths from liver disease and liver transplant

SOURCES OF NEWLY DIAGNOSED HCV INFECTION

Source: Centers for Disease Control and Prevention

Risk Factor

- Injecting Drug Use: 60%
- Sexual: 15%
- Transfusion: 10%
- Unknown: 10%
- Occupational: 4%
- Other (Hemodialysis, Mother-Infant): 1%
SEXUAL TRANSMISSION OF HCV

- Virus load (HCV RNA) in semen/vaginal secretions

- Risk of HCV transmission by sexual contact
  - Long-term monogamous partnerships: 0.6%/yr
  - Multiple partners/at risk for STDs: 1.8%/yr

- HIV infection increases rate of sexual transmission

- Recent rise in cases of acute HCV cases, especially among MSM

Terrault N. Hepatology 2002;36:S99-105
SEXUAL TRANSMISSION OF HCV

• Recent data presented at CROI 2012
• Swiss HIV Cohort Study, over 6,500 patients
• Twice as many HIV+ gay men infected compared to HIV+ injecting drug users
• 3,333 MSM followed
  • Incidence of new HCV infections in 2011 compared to 1998 increased 18-fold
• Identified risk factors
  • Unsafe anal sex
  • History of syphilis
  • Chronic HBV infection

19th CROI 2012 Abstract 743
HCV SCREENING RECOMMENDATIONS

- IDU in recent and/or remote past even if only once
- Persons with associated conditions*
- Prior recipients of transfusions or transplants prior to July 1992
- Children born to HCV + mothers
- Health care, emergency medical and public safety workers after an exposure
- Current sexual partners of HCV-infected persons
- Persons born between 1945-1965

Source: Centers for Disease Control and Prevention
HCV-ASSOCIATED CONDITIONS*

- HIV infection
- Hemophiliacs who received clotting factors prior to 1987
- Persons who have ever received hemodialysis
- Persons who have unexplained abnormal liver enzyme levels

Source: Centers for Disease Control and Prevention
NATURAL HISTORY OF HCV INFECTION

Acute HIV → Chronic HCV → Hepatic Inflammation

Spontaneous Resolution 14-45%

55-86%

Hepatic Fibrosis (Scarring) 20% in 20 yrs

Cirrhosis 2-4%/year 2-5%/year

Hepatocellular Carcinoma

Hepatic Decompensation

Alcohol, HIV, and HBV may accelerate

Seef LB. Hepatology 2002;36 (suppl 1):S35-46
STAGES OF LIVER DISEASE

- Fatty Liver: Deposits of fat cause liver enlargement.
- Liver Fibrosis: Scar tissue forms.
- Cirrhosis: Growth of connective tissue destroys liver cells.

Normal liver vs. Liver with cirrhosis.
EPIDEMIOLOGY OF HCV IN HIV

- ARV therapy has decreased HIV-related complications
- Prolonged survival of HIV patients
- Chronic HCV is common in HIV patients
  - 25-35% of HIV patients are co-infected
  - In IDU or hemophiliacs, up to 80% co-infected
  - 300,000 patients in the U.S.
- HIV increases mortality in those coinfected with HCV, but not necessarily vice versa

IMPACT OF HIV ON HCV

- Decreased clearance of HCV
- Increased HCV RNA levels
- Increased risk of cirrhosis
- Increased risk of end-stage liver disease
- Increase risk of liver cancer

- Predictors of severe liver fibrosis
  - Older age (>35 yrs), excessive alcohol consumption (>50g/day), and CD4 <500

HCV COINFECTION AND MORTALITY IN HIV PATIENTS

- Liver disease is the second leading cause of death.
- Liver disease is primarily caused by viral hepatitis.
- Liver deaths occur at higher CD4 counts and despite ARV therapy.

HCV EVALUATION

• **Patient history**

  - Depression history, screening
  - Control of diabetes mellitus, complications
  - STD screening
  - Heart disease history, stress tests
  - OTC hepatotoxic drugs
  - History of HAV, HBV vaccination
  - Pregnancy testing if applicable

HCV LAB EVALUATION

• **HCV RNA level**
  • Predicts treatment response
  • Does NOT correlate with disease progression

• **HCV genotype**
  • Genetic heterogeneity within population
  • 6 distinct genotypes distributed throughout the world
  • Different HCV treatment responses

HCV LAB EVALUATION

• Other tests:
  • Liver function blood tests (albumin, bilirubin, INR)
  • ALT, AST levels but may not reflect liver damage
  • CBC
  • HAV past exposure (HAV IgG)
  • HBV screening (HBsAg, anti-HBs)
  • Liver cancer screen (abdominal ultrasound)
  • Urine pregnancy test if applicable

HCV GENOTYPE DISTRIBUTION IN U.S.

Figure 14. Distribution of HCV genotypes (1-6).
HCV EVALUATION: STAGING LIVER FIBROSIS

- Identify cirrhosis
  - Strongly consider ARV therapy
  - Increased cancer risk
  - Monitor for hepatic decompensation/failure (low albumin and clotting factors, encephalopathy, esophageal varices, portal hypertension)
  - Consider liver transplant evaluation

- Determine cirrhosis by
  - Liver biopsy
  - Non-invasive tests, biomarkers (i.e. FibroSure®) or elasticity echos

GOALS OF HCV THERAPY

Target Virus → Eradication (Viral Cure) = SVR at 6-12 months post tx

Target Disease: Prevent Complications → Delay Cirrhosis

→ Prevent Liver Cancer

FACTORS ASSOCIATED WITH BETTER RESPONSE TO HCV THERAPY

- Genetics: Interleukin-28b gene
- Female sex
- Non-black
- Younger age
- No Obesity
- Absence of HIV co-infection
- Abstaining from alcohol
- Adherence, adherence, adherence

PREDICTS SVR
TIME POINTS FOR ASSESSMENT OF HCV VIROLOGIC RESPONSE

- **Week 4**: RVR (rapid virologic response) = undetectable HCV RNA
- **Week 12**: 
  - Early virologic response (EVR) = 2 log drop in HCV RNA
  - Extended RVR (eRVR) = undetectable HCV RNA
- **Week 24**: undetectable HCV RNA
- **Week 48**: end-of-treatment undetectable HCV RNA
- **Week 72**: SVR (sustained virologic response) = undetectable HCV RNA = cure

INDICATIONS FOR HCV THERAPY

• HCV RNA +
• Chronic hepatitis with significant fibrosis
• Compensated liver disease (healthy bilirubin, INR, albumin, platelet count, no ascites or encephalopathy)
• Acceptable hematological and biochemical markers (hemoglobin, ANC, creatinine)
• HIV coinfection
  • Increases rate of fibrosis, so consider strongly
• Willingness to be treated and to adhere to treatment requirements
CONTRAINDICATIONS TO HCV THERAPY

- Active depression/psychosis
  - Hospitalization within prior year
  - Suicide attempt within prior year (some use ever)
- Decompensated cirrhosis
- Solid organ transplant (kidney, heart, lung)
- Severe coexisting medical condition (i.e. severe HTN, heart failure, COPD, poorly controlled DM, significant CAD)
- Pregnancy
- Untreated thyroid disease
- Age under 2 years (new PIs not approved for <18)
WHICH PATIENTS SHOULD BE TREATED?

- Disease Progression
- Treatment Response
- Adverse Effects
- Competing Comorbidities
HCV VIRAL LIFE CYCLE
HCV ANTIVIRAL AGENTS

- **Indirect Acting Agents**
  - Peginterferon (PEG-IFN) alfa
  - Ribavirin

- **Direct Acting Agents** (work directly on viral life cycle)- 27/6 phase III
  - NS3/4 Protease Inhibitors – only active genotype 1
    - Boceprevir, Telaprevir, Simeprevir*, multiple others*
  - NS5A Protein Inhibitors*
    - Daclatasvir
  - NS5B Polymerase Inhibitors*
    - Nucleoside and Non-nucleoside analogues
      - Sofosbuvir, multiple others
  - Cyclophilin Inhibitors*

* Non FDA-approved
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Therapeutic Option</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG-IFN-2b + Riba + Boceprevir</td>
<td>48 wks</td>
</tr>
<tr>
<td></td>
<td>PEG-IFN – 2a + Riba + Telaprevir</td>
<td>48 wks</td>
</tr>
<tr>
<td>2,3</td>
<td>PEG-IFN-2a or 2b + Ribavirin</td>
<td>48 wks</td>
</tr>
<tr>
<td>4</td>
<td>PEG-IFN-2a or 2b + Ribavirin</td>
<td>48 wks</td>
</tr>
</tbody>
</table>

**PEG-INTERFERON + RIBAVIRIN**

- **Pegylated IFN- alfa**
  - Suppress viral replication
  - Two formulations: 2a, 2b
    - Alfa-2a: 180 mcg/wk SQ
    - Alfa-2b: 1.5mcg/kg/wk SQ

- **Ribavirin**
  - Nucleoside analogue
  - Genotype 1,4:
    - ≤ 75 kg: 1,000 mg/d
    - > 75 kg: 1,200mg/d
  - Genotype 2,3: 800 mg/d
TELAPREVIR : HCV GENOTYPE 1

- NS3/4A protease inhibitor
- Indicated for genotype 1
- Use with PEG-IFN + ribavirin

Wk 12*  
Telaprevir + PEG + RBV  

Wk 48  
PEG + RBV  
Total 48 wks

*If HCV RNA >1,000 IU/ml at week 4 or 12, stop tx

- Dosage: 750mg every 8 hrs
  - 375mg tablets
- Administer with 20 gm fat meal

INCIVEK® labeling information, Vertex Pharmaceuticals, 2011
TELAPREvir AND FATTY FOOD

Each telaprevir dose should be taken with food containing **20gms of fat**, such as

- Bagel with cream cheese
- 3 tbsp peanut butter
- 2 oz American or cheddar cheese
- 2 oz potato chips (about 30 chips)
- 1 cup ice cream
- ½ cup trail mix
- ½ cup nuts
## SVR Rates with Telaprevir for HCV Genotype 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE (Naïve)</td>
<td>TVR/PR x 12wks → PR x 12 wks</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>TVR/PR x 12wks → PR x 36 wks</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>PR x 48wks</td>
<td>44%</td>
</tr>
<tr>
<td>PROVE-2 (Prior Rx)</td>
<td>TVR/PR x 12wks → PR x 12wks</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>TVR/PR x 24wks → PR x 24wks</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>PR x 48 wks</td>
<td>14%</td>
</tr>
</tbody>
</table>

**BOCEPREVIR: HCV GENOTYPE 1**

- NS3/4A protease inhibitor
- Indicated for genotype 1
- Use with PEG-IFN + ribavirin

**Dosage:** 800mg every 8 hrs
- 200mg capsules

If HCV RNA >100 IU/ml at wk 12, stop tx

**PEG+RBV**

Wk 4

Boceprevir +

PEG+RBV

Wk 48

Total

48 wks

Boceprevir (Victrelis®)

Victrelis® labeling information, Roche Pharmaceuticals, 2011
SVR RATES WITH BOCEPREVIR FOR GENOTYPE 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT-2</td>
<td>PR x 4wks → BOC/PR x 24wk → PR x 20wk</td>
<td>63%</td>
</tr>
<tr>
<td>(Naïve)</td>
<td>PR x 4wks → BOC/PR x 44 wk</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>PR x 48wk</td>
<td>38%</td>
</tr>
<tr>
<td>RESPOND-2</td>
<td>PR x 4wks → BOC/PR x 32wk → PR x 12wk</td>
<td>59%</td>
</tr>
<tr>
<td>(Prior Rx)</td>
<td>PR x 4 wks → BOC/PR x 44 wk → PR x 44wk</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>PR x 48 wks</td>
<td>21%</td>
</tr>
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# SVR Rates in HIV/HCV Co-Infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>APRICOT $^1$</th>
<th>ACTG 5071 $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN + RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>62%</td>
<td>73%</td>
</tr>
<tr>
<td>TVR + PEG-IFN + RBV $^3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVR + PR</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>BOC + PEG-IFN + RBV $^4$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOC + PR</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

3. Dietrich D et al. 19$^{th}$ CROI 2012 Abst 46
4. Sulkowski M et al. 19$^{th}$ CROI 2012 Abst 47
ADVERSE EFFECTS OF HCV THERAPY

• Almost all treated will experience something
• Major reason for discontinuing meds (~ 25-30%)
• Interferons
  • Flu-like symptoms (fatigue, headache, fever, rigors)- 50%
  • Loss of appetite and weight loss -40%
  • Mild to moderate hair loss, rashes – 20%
  • Psychiatric (depression, irritability, insomnia, suicidal ideas)-20%
  • Lab abnormalities (drop in cell counts)- 20-25%
  • Thyroid disorders
• Ribavirin
  • Anemia – 20-25%
  • Birth defects

Slim J. Infect Dis Clin N Amer 2012;26:917-29
### ADVERSE EFFECTS OF HCV PROTEASE INHIBITORS IN HIV/HCV

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Boceprevir&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TVR+PR</td>
<td>PR</td>
</tr>
<tr>
<td>Itching</td>
<td>39%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>37%</td>
<td>27%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>23%</td>
</tr>
<tr>
<td>Rash</td>
<td>34%</td>
<td>23%</td>
</tr>
<tr>
<td>Fever</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Depression</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Anemia</td>
<td>39%</td>
<td>27%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Decr appetite</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Decr weight</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

1. Dietrich E et al. CROI 2012 Abstr 46%  
2. Sulkowski M et al. 29<sup>th</sup> CROI 2012 Abst 47
MANAGING TOXICITIES

• **Close follow up**: have patients call with concerning events
• Rash: assessment, antihistamines, topical steroids
• Flu-like symptoms: NSAIDs, hydration
• Depression: B-med referral, antidepressants
• Weight loss: appetite stimulants (Megace®, Marinol®)
• Anal discomfort: topical steroids, lidocaine
• Anemia: decr ribavirin dose, erythropoetin

Slim J. Infect Dis Clin N Amer 2012;26:917-29
SELECTED DRUG INTERACTIONS WITH HCV PROTEASE INHIBITORS

- Anticonvulsants
- Antidepressants
- Benzodiazepines
- Calcium channel blockers
- Colchicine
- Systemic steroids
- Ergot derivatives
- Statins
- Opioids, methadone
- Oral contraceptives
- Erectile dysfunction agents
- St. Johns Wort
- Warfarin
- Zolpidem
NRTI CHOICE WITH HCV THERAPY

• Avoid zidovudine (AZT) with ribavirin
  • Greater decrease in hemoglobin → higher risk of anemia

• Avoid didanosine (ddI) with ribavirin
  • Risk of mitochondrial toxicity → lactic acidosis, peripheral neuropathy, pancreatitis

• Questions remain with abacavir
  • May compete intracellularly with ribavirin → decrease ribavirin effectiveness?

Yee HS. Hepatitis C Treatment. The Rx Consultant. 2012; 21(2):1-8
HCV PI AND ARV DRUG INTERACTIONS

- Phase 1 studies in healthy volunteers

- Telaprevir drug levels:
  - Decr 30-50% with lopinavir, darunavir, fosamprenavir
  - Decr with efavirenz (requires incr. dosage)
  - No change with tenofovir, raltegravir

- Boceprevir drug levels:
  - Decr 40% on efavirenz, PIs
  - No change with tenofovir, raltegravir
MEASURES TO AVOID HCV TRANSMISSION

• Avoid sharing toothbrushes, nail clippers and dental or shaving equipment, and be cautioned to cover any bleeding wounds
• Stop using illicit drugs. If continued, avoid reusing or sharing “works”, use safe disposal
• Do not donate blood, body organs, tissue or semen
• Practice safe sex by using condoms

Source: Centers for Disease Control and Prevention
SOME OTC AND HERBAL SUPPLEMENTS THAT MAY CAUSE LIVER DAMAGE

• Acetaminophen
• Black cohosh
• Chinese herbal medicines
  • Chaso, Onshido, Sho (do)-saiko-to, Jin Bu Huan, Ma Huang (ephrnea)
• Kava
• Mistletoe
• Pennyroyral
• Skullcap
• Valerian

Yee HS. Hepatitis C Treatment. The Rx Consultant. 2012; 21(2):1-8
INTEGRATING HEPATITIS C CARE INTO HIV PRACTICE

• Multidisciplinary management team
• Provide support and education
• Treat psychiatric co-morbidities/substance abuse
• Vaccinate against Hepatitis A and B
• Counsel regarding ways to avoid transmission, especially safer sex/condom use and IDU
• Avoid other hepatotoxins, including alcohol, acetaminophen and certain herbal meds
• Provide HCV therapy
• Focus on adherence!!!
CAMC RYAN WHITE HIV PROGRAM

Contact Information: Call toll free 1-877-565-4423
www.camc.org/ryanwhite
HEPATITIS AWARENESS

May 19th is National Hepatitis Testing Day