Treatment Initiation and Monitoring in HIV/HCV Co-infected Patients

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HCV Epidemiology

- NHANES IV 1999-2002\textsuperscript{[1]}
  - 1.6\% of the US \textit{household} population (incarcerated and homeless not included) positive for HCV antibodies
  - Estimated persons ever infected: 4,060,000
  - Estimated persons with chronic infection: 3,200,000
  - Risk factors: injection drug use, blood transfusion before 1992, higher number of sexual partners

- 15\% to 40\% prevalence of HCV in US prison population\textsuperscript{[2]}
  - 300,000-400,000 HCV-positive incarcerated at any time

In US and Europe, ~33% of all HIV-infected persons are HCV coinfected.

HIV coinfection exacerbates natural history of HCV infection:
- Higher levels of HCV viremia
- Less likely to clear HCV following acute HCV infection
- More rapid progression of HCV-related liver disease
- Less likely to clear HCV in response to treatment

Effect of HCV Coinfection on HIV Infection

- Some studies report impaired immune reconstitution on ART
  - However, effect is inconsistent and likely not clinically relevant[1]
- Patients more likely to experience hepatotoxicity on ART
- Patients 5x more likely to be admitted to hospital for liver complications[2]
- D:A:D study: liver disease second leading cause of death, after AIDS and before CV disease[3]
- With effective treatment of HIV, HCV has emerged as significant cause of morbidity and mortality

Counseling for Patients Who Are HCV Positive

- Avoid sharing toothbrushes and dental and shaving equipment; cover bleeding wounds to prevent contact of blood with others
- Stop using illicit drugs or avoid reusing or sharing syringes, needle or other paraphernalia; clean injection sites and dispose of sharps appropriately
- Do not get tattooed
- Do not donate blood, body organs, other tissues, or semen
- Limit alcohol intake

Weinbaum C, et al. MMWR. 2003; 52(No.RR-1)
Selecting Patients for HCV Treatment

- HCV antibody test positive
- Quantitative HCV RNA: confirms infection; gives information about potential response to therapy
- Genotype: gives information about potential response to therapy and duration of therapy
- Medical history, CBC, metabolic panel, PT/PTT, thyroid studies, pregnancy test for women
  - Anemia, low platelets, chronic renal disease are relative contraindications to therapy
  - Uncontrolled thyroid disease, autoimmune disease, or uncontrolled coronary artery disease are absolute contraindications to therapy
  - Ribavirin is a potent teratogen; pregnancy or inadequate contraception is an absolute contraindication to therapy

Assessment of Alcohol and Substance Abuse

- Ongoing Alcohol use? Amount?
- Ongoing Substance Abuse? Amount?
- How much use is acceptable?
- What are individual clinic protocols?
Evaluating and Modifying Obesity

- Obesity is associated with nonalcoholic fatty liver disease and steatosis
- Insulin resistance may diminish response to interferon
- Weight criteria for treatment initiation
- What are individual clinic protocols?
Indicators of Decompensated Cirrhosis

- Development of ascites
- Variceal hemmorhage
- Hepatic encephalopathy*
- Jaundice
- Hepatocellular carcinoma*
  - Screen via ultrasound every 6 months for patients with cirrhosis or bridging fibrosis
  - * can occur even in incomplete cirrhosis

Evaluation of Liver Status and Transplantation Referral

- Prognosis via MELD (Model for end stage liver disease) score should be assessed periodically

- Calculator available at:

- Score greater than 10 indicates need for possible liver transplantation referral
Factor Predicting Favorable Response

- HCV Genotype 2, 3
- HCV RNA level <400,000
- IL-28B genotype CC
- Non-African American race
- Absence of bridging fibrosis or cirrhosis
- Body weight <75 kg
- Age <40
- Baseline ALT > 3x ULN
Mental Health Assessment

- Mental Health Referral
- CES-D or PHQ-9 questionnaires
Factors Favoring Initiation of Therapy

- Patient motivation
- Biopsy with chronic hepatitis and greater than portal fibrosis
- Cryoglobulinemic vasculitis or kidney disease
- Stable HIV disease
- Compensated liver disease
- Acceptable hematologic parameters
- Serum creatinine <1.5
Absolute Contraindications to Therapy

- Uncontrolled active major psychiatric illness
- Hepatic decompensation (hepatic encephalopathy, coagulopathy, or ascites)
- Uncontrolled HIV with advanced immunosuppression (CD4 < 100 cells/mm3)
- Known allergy or severe adverse reaction to interferon and/or ribavirin
Absolute Contraindications to Therapy

- Women who are pregnant, nursing, or are of child-bearing potential and not able to practice contraception

- Men who have pregnant partners or partners of child-bearing potential and unwilling to practice contraception during treatment and for 6 months after treatment ends

- Active, untreated autoimmune disease (e.g., systemic lupus erythematosis) known to be exacerbated by peginterferon and ribavirin

- Ribavirin is contraindicated if the creatinine clearance is less than 50 cc/min
Relative Contraindications to Treatment

- Significant hematologic abnormality: hemoglobin < 10.0 g/dl, absolute neutrophil count < 1,000/μl, or platelet count < 50,000/μl
- CD4 < 200 cells/mm3
- Uncontrolled diabetes mellitus
- Patients concurrently receiving zidovudine
Relative Contraindications to Treatment

- Autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis)
- Active substance use or ongoing alcohol use if interference with adherence is anticipated
- Untreated mental health disorder
- Hemoglobinopathies (e.g., thalassemia major and sickle cell anemia)
- Sarcoidosis
- Solid organ transplantation patients
Overcoming Barriers to Treatment Initiation

- Substance Abuse Counselors
- Opioid Dependence Treatment
- Patient Education
- Peer-Based Counseling
- Group Counseling
- Clinic Based Injections
Selecting Patients for Treatment

- Control other chronic diseases (asthma, hypertension, diabetes)
- If on antiretroviral therapy for HIV, should not be receiving zidovudine, stavudine, or didanosine
- Assess for depression
  - Interferon therapy is associated with depression and suicide has been reported in patients receiving interferon for HCV therapy

Selecting Patients for Treatment

- Need to differentiate between nonsignificant fibrosis and significant fibrosis
- International Association for the Study of the Liver scoring system for staging liver fibrosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Score</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Significance</td>
<td>Nonsignificant</td>
<td></td>
<td></td>
<td>Significant</td>
<td></td>
</tr>
</tbody>
</table>

- Assess liver fibrosis; options include
  - Liver biopsy
  - Noninvasive markers of hepatic fibrosis
  - Transient elastography

### PegIFN/RBV: Current Standard-of-Care Treatment for HCV-infected Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN</td>
<td></td>
</tr>
<tr>
<td>PegIFN alfa-2a</td>
<td>180 μg SQ q7d</td>
</tr>
<tr>
<td>PegIFN alfa-2b</td>
<td>1.5 μg/kg SQ q7d</td>
</tr>
<tr>
<td>Weight-based RBV</td>
<td></td>
</tr>
<tr>
<td>&lt; 75 kg</td>
<td>1000 mg PO divided BID</td>
</tr>
<tr>
<td>&gt; 75 kg</td>
<td>1200 mg PO divided BID</td>
</tr>
<tr>
<td>Genotype 2 and 3</td>
<td>800 mg PO divided BID</td>
</tr>
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</table>
## Response Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Time Point</th>
<th>HCV RNA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virologic response (RVR)</td>
<td>Wk 4 of therapy</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Early virologic response (EVR)</td>
<td>Wk 12 of therapy</td>
<td>$\geq 2 \log_{10} \text{IU decrease from baseline}$</td>
</tr>
<tr>
<td>Complete early virologic response (cEVR)</td>
<td>Wk 12 of therapy</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Slow to respond</td>
<td>Wk 24 of therapy</td>
<td>Undetectable (but with detectable HCV RNA at Wk 12)</td>
</tr>
<tr>
<td>End of treatment response (EOT or ETR)</td>
<td>End of therapy</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Sustained virologic response (SVR)</td>
<td>6 mos posttherapy</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>
HCV Response Rates in HIV+ and HIV- Patients Treated With PegIFN/RBV

APRICOT
HIV Positive
Overall SVR: 40%

PRESCO
HIV Positive
Overall SVR: 50%

FRIED
HIV Negative
Overall SVR: 56%

GT1/4 GT2/3
48 Wks of Therapy, 600 mg RBV
24, 48, or 72 Wks of Therapy, Weight-Based RBV
48 Wks of Therapy, Weight-Based RBV

Patients With SVR (%)

Sequencing HCV and HIV Treatment

- If HIV treatment is indicated, treat HIV infection first
- Consider treating HCV first if
  - CD4+ count > 500 cells/mm³ and antiretroviral therapy is not being initiated
  - Patient cannot tolerate antiretroviral therapy due to hepatotoxicity, since HCV coinfection may increase likelihood of antiretroviral therapy–associated hepatotoxicity
Monitoring HCV During Treatment

- CBC and differential blood count every 2-4 wks
- TSH every 12 wks
- Pregnancy test (female)
- HCV RNA
  - 4 wks (RVR)
  - 12 wks (EVR, cEVR)
  - 24 wks (STR)

Managing Adverse Effects: PegIFN/RBV

- When initiating pegIFN/RBV, tell patients what to expect prior to starting therapy
- In all cases, consider coaching and encouragement particularly if response looks promising

<table>
<thead>
<tr>
<th>RBV</th>
<th>Surveillance/Treatment</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>- Monitor CBC frequently</td>
</tr>
<tr>
<td></td>
<td>- Ask about fatigue, SOB, chest pain</td>
</tr>
<tr>
<td></td>
<td>- If Hb &lt; 10 g/dL, use erythropoietin (preferred) or reduce RBV dose</td>
</tr>
</tbody>
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## Managing Adverse Effects: PegIFN

<table>
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<tr>
<th>PegIFN</th>
<th>Surveillance/Treatment</th>
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| Depression              | - Assess mood prior to treatment and during treatment  
                          - Ask about mood, sleep, suicidal thoughts  
                          - Consider SSRI to treat baseline or new depression  
                          - Ask mental health services to follow high-risk patients during HCV treatment                                                                 |
| Decreased WBC and platelets | - Monitor CBC frequently  
                          - Ask about symptoms of infection or bleeding  
                          - Reduce dose of interferon                                                                                                                              |
| Influenzalike symptoms  | - Acetaminophen  
                          - Hydration  
                          - Reduce dose of interferon                                                                                                                             |
| Dry, itchy skin         | - Moisturizing lotion  
                          - Antihistamines                                                                                                                                           |
| GI upset                | - Antiemetics  
                          - Dietary supplements  
                          - Appetite stimulants                                                                                                                                      |
| Hair loss               | - Encouragement                                                                                                                                             |
| Insomnia                | - Diphenhydramine or other sleep aid                                                                                                                           |
| Injection-site reactions| - Alternate injection sites; stomach and thighs are good places to inject  
                          - Inject at 45-90 degree angle to skin  
                          - Warm interferon in hand prior to injecting                                                                                                           |
Safety Considerations When Managing HCV/HIV-Coinfected Patients

- RBV-related anemia more common in HCV/HIV-coinfected patients than in HCV-monoinfected patients
  - Particularly common in patients also receiving the antiretroviral, zidovudine

- RBV potentiates the toxic effects of the antiretrovirals, didanosine and stavudine
  - Mediated by mitochondrial toxicity
  - Can result in fatal lactic acidosis and pancreatitis
  - Combination contraindicated

Drug/Toxicity Links

- Anemia – Ribavirin
- Thrombocytopenia – Pegylated Interferon
- Neutropenia – Pegylated Interferon
Management of Treatment Related Anemia

- For Symptomatic Anemia or Hgb <10 g/dL

- **STEP 1:**
  - Reduce Ribavirin by 200 mg for patient receiving 800-1200 mg/d
  - Reduce Ribavirin dose by 400 mg for patients receiving 1400 mg/d

- **STEP 2:**
  - Reduce Ribavirin by another 200 mg for patients who have not responded 2 weeks after dose reduction (provided current dose is 800mg/d or greater)
Management of Treatment Related Anemia – Special Situations

- Immediately reduce ribavirin dose to 600 mg/d for the following situations:
  - A sharp decline in hemoglobin in the first 4 weeks of treatment
  - Moderate to severe symptoms of anemia
  - High Cardiovascular Risk
- Dose should not be reduced below 600 mg/d
Management of Treatment Related Anemia – Special Situations

- Ribavirin dose should remain at reduced level if patient is not receiving erythrocye-stimulating agents.
- If the patient is given an erythrocye-stimulating agent, the ribavirin dose can be slowly increased when Hgb approaches or exceeds 10 g/dL.
- If Hgb persist at a level less than 8.5 g/dL despite dose reduction and erythrocye stimulating factors, ribavirin should be discontinued.
Use of Erythrocyte-Stimulating Agents

- **Dosing:**
  - Epoetin alfa – 40,000 IU SC/ week
  - Darbepoetin alfa 200 mcg SC every other week
- **Goal:** 1g/dL or more increase in Hgb in 2 weeks
  - If goal not achieved, change epoetin alfa to 60,000 IU/week, darbepoetin to 300 mcg/ every other week
Use of Erythrocyte-Stimulating Agents

- Outcome goal:
  - Hgb between 10-12 g/dL but not exceeding 12 g/dL
    - Hgb of >13 g/dL resulting from erythrocyte stimulating agents has been linked to increased mortality and cardiovascular complications
  - Some experts will maintain the use of erythrocyte stimulating agents and slowly increase ribavirin dose when Hgb is between 10-12 g/dL
Management of Thrombocytopenia

- Primary strategy is pegylated interferon dose reduction
- Therapy should be discontinued for platelet count less than 25,000 cell/mm³
Management of Neutropenia

- Primary strategy is peginterferon dose reduction
- Permanent discontinuation rarely necessary, but temporary discontinuation necessary for:
  - ANC < 400 cells/mm³
  - Active bacterial infection AND ANC < 500 cell/mm³
- Permanent discontinuation for neutropenia which is refractory to peginterferon dose reduction and filgrastim (G-CSF)
Use of Filgrastim (G-CSF)

- For ANC <500 cells/mm³
- Neutropenia which dose not respond to level 1 peginterferon dose reduction
- G-CSF 300 mcg SC once or twice weekly
- Monitor ANC at least 1-2X weekly
- Redose based on response
- G-CSF may need dosed 2-3x/week in some cases to maintain ANC >500 cells/mm³
- Hold G-CSF for ANC > 750 cells/mm³
What Is New in HCV Evaluation and Treatment

- **IL28B** haplotype testing
  - Predicts response rate to pegIFN/RBV
  - Commercially available

- Protease inhibitors for genotype 1 HCV
  - FDA approved first HCV protease inhibitors in May 2011
  - HCV protease inhibitors in combination with pegIFN and RBV may increase response rate and potentially decrease length of therapy in genotype 1 patients
SVR Rates With BOC and TVR in GT1 Treatment-Naive and -Experienced Pts

*Overall rates in protease inhibitor–containing arms, not stratified by type of prior nonresponse.

Study 110: High Rates of Early Response With TVR + PR in Coinfected Patients

- Similar efficacy results observed with or without concurrent ART
- Nausea, pruritus, dizziness, fever more common with TVR vs placebo
- Pharmacokinetic interactions with ATV or EFV not clinically significant

Undetectable HCV RNA, Week 4 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir + PR</th>
<th>PR</th>
</tr>
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<tbody>
<tr>
<td>No ART</td>
<td>71/7</td>
<td>12/16</td>
</tr>
<tr>
<td>ATV/RTV-based ART</td>
<td>64/14</td>
<td>0/8</td>
</tr>
<tr>
<td>Total</td>
<td>70/37</td>
<td>5/22</td>
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Undetectable HCV RNA, Week 12 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir + PR</th>
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Key Points About HCV Protease Inhibitors

- FDA approved in May 2011
- Only tested in genotype 1
- Will be used in combination with pegIFN and RBV
- Expected to reduce total duration of treatment and increase SVR in significant number of patients
- Will also increase adverse effects and regimen complexity
- Drug interactions with many antiretroviral drugs
Summary

- HCV and HCV/HIV coinfection are common
- Targeted screening for those at high risk of HCV infection is an effective means of diagnosis
- All HCV-positive patients should receive education regarding prevention of transmission of HCV to others
- HCV infection treatment in the setting of HIV coinfection requires careful patient selection and treatment monitoring