Management of Hepatitis C (HCV) in the HIV/HCV Co-Infected Patient

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Liver and HIV Disease

- Opportunistic Diseases
- Hepatitis viruses B, C, D
- Immune Reconstitution
- Type 2 DM
- Dyslipidemia
- Alcohol

- HCV Treatment
- HIV Treatment/ hepatotoxicity
  - NNRTIs
  - PIs
  - NRTIs
Outline

- Epidemiology in co-infected patients - including fibrosis progression, mortality.
- HCV treatment in co-infected patients
- Barriers to treatment.
- CORE center hepatitis clinic model.
- Take home messages
- Open up for discussion.
Epidemiology
# HIV and Hepatitis C Co-infection in the United States

<table>
<thead>
<tr>
<th></th>
<th>HIV Infected</th>
<th>Hep C Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in U.S.</td>
<td>~1 million</td>
<td>~4 million</td>
</tr>
<tr>
<td>New dx per year</td>
<td>40,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Deaths per year</td>
<td>15,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Co-infection</td>
<td>15 - 45% +Hep C</td>
<td>10% +HIV</td>
</tr>
</tbody>
</table>
Epidemiology

- About 400,000 HIV/HCV + in U.S.
  - overall 30-50% of HIV+ are co-infected
- Prevalence of HCV in HIV+ individuals:
  - approx. 90% in IVDU
  - 60-85% in hemophiliacs
  - 4-8% in HIV+ MSM
Natural History of HCV Infection

Exposure (Acute phase)

- 15% (15) Resolved
- 85% (85) Chronic

Chronic

- 80% (68) Stable
- 20% (17) Cirrhosis

Cirrhosis

- 75% (13) Slowly Progressive
- 25% (4) HCC
  - HIV and Alcohol
    - Transplant
    - Death

Fibrosis progression in HCV

- Increases fibrosis risk
- Male sex
- Older age at infection
- Alcohol
- HIV co-infection
- Steatosis on biopsy
- ? Smoking
- ?HAART

- May delay fibrosis progression
- Younger age
- Female gender-estrogen
- ? HAART- virologic control
Influence of HIV on HCV Infection

- Increased risk of perinatal and sexual transmission of HCV
- Increased rate of HCV chronicity (Less likely to clear acute infection)
- HCV RNA level increases as immune deficiency progresses
- Natural history of HCV accelerated
- HCC at younger age and shorter duration of HCV
Progression to Hepatocellular Carcinoma in Co-Infected Patients – 1992-2004

- Co-infected pts progress more rapidly to HCC than mono-infected pts

<table>
<thead>
<tr>
<th>Spanish Study</th>
<th>HIV/HepC (n = 41)</th>
<th>HepC only (n = 119)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of HCV infection at time of HCC diagnosis (years)</td>
<td>26.4 (n = 30)</td>
<td>35.2 (n = 62)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>52.4</td>
<td>61.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median AFP level, ng/mL</td>
<td>1274</td>
<td>192</td>
<td>.002</td>
</tr>
<tr>
<td>Excessive alcohol use %</td>
<td>48.7 (n = 39)</td>
<td>71.0 (n = 100)</td>
<td>.005</td>
</tr>
<tr>
<td>Received HCC therapy %</td>
<td>56</td>
<td>36</td>
<td>.025</td>
</tr>
</tbody>
</table>

- Coinfected patients
  - Younger age at hepatocellular carcinoma diagnosis
  - Higher AFP levels
  - More likely to receive HCC treatment

Higher Mortality on OLT Waiting List Among Coinfected vs HepC Monoinfected Patients

0%

Madrid (n=16) [1]
Barcelona (n=13) [2]
Pittsburgh (n=58) [3]

Liver-related Mortality in HIV+ Patients in the HAART Era

1. 1997-2003, 124 deaths, Canada. 41 (33%) non-AIDS related

2. yr 2000, 964 deaths, France


4. D:A:D cohort, 1246 deaths; 14.5% LRD


<table>
<thead>
<tr>
<th>Factor</th>
<th>RR (CI)</th>
</tr>
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<tbody>
<tr>
<td>CD4&lt;50</td>
<td>16 (8-31)</td>
</tr>
<tr>
<td>HCV+</td>
<td>6.7 (4-11.2)</td>
</tr>
<tr>
<td>HBV+</td>
<td>3.7 (2.4-5.9)</td>
</tr>
<tr>
<td>IDU</td>
<td>2 (1.2-3.4)</td>
</tr>
<tr>
<td>Age/5yrs</td>
<td>1.3 (1.2-1.4)</td>
</tr>
</tbody>
</table>
Why Do We Need to Treat HIV/HCV Coinfected Patients?

- HCV is common in HIV patients (approx 25-40% in U.S.)
- HCV is a more serious disease in coinfected patients than in monoinfected.
- HCV has become one of the leading causes of death in the HIV population.
- HCV coinfection carries significant morbidity, limits ARV options, decreases QoL.
Treatment of HCV in Coinfected Patients
Potential Benefits of HCV Therapy in Patients Infected With HIV

- Viral eradication
- Delay fibrosis progression
- Prevent/delay bad clinical outcomes
  - Liver decompensation
  - Hepatocellular carcinoma
  - Death
- Improve tolerance and effectiveness of HAART
  - Permit aggressive antiretroviral drug therapy
  - Enhance immune reconstitution?
Treatment of HCV

Goals of Therapy

- **Primary goal**
  - Sustained virological response
    - >95% maintain response over 1-10 yrs

- **Secondary goals**
  - Reduce hepatic inflammation
  - Stabilize or decrease fibrosis
  - Reduce risk for hepatocellular carcinoma

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HCV/HIV Co-Infection

Treatment indicated:

- Detectable plasma HCV RNA and bridging or portal fibrosis on liver biopsy
- Consider other factors such as:
  - stage and stability of HIV disease
  - other co-morbidities
  - probability of adherence
  - possible contraindications to HCV medications
Defining Success

EVR = Early viral response, 12 week viral load is undetectable or decreased by 2 logs.

ETR = End of treatment response, undetectable viral load at end of treatment.

SVR = Sustained viral response, undetectable 6 or more months after therapy.
# 2004: Coinfected Hep C Treatment Trials

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<tr>
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<tbody>
<tr>
<td></td>
<td>PEG-IFN/RBV (600mg → 1000mg/d) n = 66</td>
<td>PEG-IFN/RBV (800mg/d) n = 289</td>
<td>PEG-IFN/RBV (800mg/d) n = 289</td>
</tr>
<tr>
<td>SVR</td>
<td>27%*</td>
<td>40%*</td>
<td>27%*</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>14%*</td>
<td>29% *</td>
<td>17% <strong>/</strong>*</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>73% *</td>
<td>62% *</td>
<td>44%</td>
</tr>
<tr>
<td>Discontinued (%)</td>
<td>12%**</td>
<td>25%</td>
<td>39%</td>
</tr>
</tbody>
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# Hep C Treatment Duration in HIV+ Patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Baseline HCV VL</th>
<th>Negative HCV VL Week 4</th>
<th>Length of Hep C Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/3</td>
<td>Low</td>
<td>-</td>
<td>24 wk</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>+</td>
<td>48 wk</td>
</tr>
<tr>
<td>1/4</td>
<td>Low</td>
<td>-</td>
<td>72 wk</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

% represent coinfected patients in PRESCO trial

- 10-15%
- 55-65%
- 25-30%

HIV/Hep C Co-infected Patients: Best Predictors of SVR

- HCV genotypes 2 or 3 – Predominant factor
- Low HepC viral load
- No cirrhosis
- Age <40 years
- Elevated ALT levels\(^1\)
- Adherence (80/80/80)
- Week 4 rapid virologic response\(^2\)
- Low or undetectable HIV viral load\(^3\)
- Preserved CD4 counts\(^3\)
  - CD4 >200


Side Effects of Interferon

- Flu-like symptoms
  - Headache
  - Fatigue
  - Myalgia, arthralgia
  - Fever, chills
- Nausea
- Diarrhea
- Leukocytopenia
- Thrombocytopenia

- Psychiatric symptoms
  - Depression
  - Insomnia
- Alopecia
- Injection-site reaction
- Thyroiditis
- Autoimmunity
- Weight loss*
Side Effects of Ribavirin

- Hemolytic anemia*
- Cough and dyspnea
- Insomnia
- Anorexia
- Rash and pruritus
- Teratogenicity
Are we treating HCV in our patients?
Barriers to HepC Treatment in Co-infected Patients in an Urban HIV Clinic

- Coinfection clinic opened at Johns Hopkins in 1998
  - Referral rate increased from 1% in 1998 → 28% in 2003
  - Initiation of Tx significantly decreased in Black patients, IDUs

![Bar graph showing the progression of patients through treatment stages from 1998 to 2001.]
ORGANIZATION TO ACHIEVE SOLUTIONS IN SUBSTANCE-ABUSE

Providing Comprehensive
Medical - Mental health - Vocational services
to underserved members of the community with

**Hepatitis C - HIV - Addiction**
and other serious medical conditions.

Diana Sylvestre, MD – Medical Director

- Most patients screened for HCV.
- 36% co-infected (271)
- Counseling: ETOH use rarely documented.
- Hep A & B vaccinations approx. 42%.
- Only 5 pts (1.8%) ever received IFN treatment with one SVR.
ACCESS: Westside Connect

- 5 year SAMHSA grant
- HIV, Hep C, substance abuse prevention programs
- Re-entry populations on the Westside
- Expand resources of existing buprenorphine program

Community and Correctional System Outreach and Education

Primary Outreach
- Safer Foundation, TASC, ACCESS health centers (4)

Secondary Outreach
- Family Guidance Center, Haymarket, Genesis House, Chicago Recovery Alliance, Cook County Furlough

HIV Rapid Testing at four ACCESS sites located in the targeted neighborhoods as a standard of care, as well as rapid testing onsite at our partner organizations.

Hepatitis Evaluation at ACCESS’ four health centers and through screening and outreach at Safer Foundation.

Substance Abuse Screening at ACCESS’ four health centers and by case managers at Safer Foundation and Chicago Recovery Alliance.

SA, HIV, Hepatitis Screening & Prevention Activities

Buprenorphine Group Intervention
ACCESS staff leads group sessions focusing on substance abuse, HIV, and hepatitis prevention education, screenings and interventions.
Barriers to HCV treatment- CORE center

HCV treatment eligibility in 182 HCV+ patients; 110 (60%) HIV+
Evaluated in the CORE hepatitis clinic 7/01-12/02.

AIDS pt Care&STDs 2004;18:239-245
Barriers to HCV treatment- CORE data

Treatment candidacy stratified by HIV status

AIDS pt Care&STDs 2004;18:239-245
HIV Clinics Know How to Support Adherence

Can we do better than traditional HCV treatment models in other care settings?
Elements of HCV/HIV Management

Phase I: Screening and diagnosis
Phase II: Counseling and health care maintenance
Phase III: Evaluation for treatment
Phase IV: Monitoring treatment
Phase V: Managing progressive liver disease

How far are you going in your practice?
Screening and Diagnosis

- Test all HIV patients for anti-HCV EIA ab.\(^1\)
- If IDU and neg HCV ab, check HCV PCR. (False-neg ab has been reported, 3.4% in one HIV cohort).\(^2\)
- If HCV pos., check PCR to confirm active infection (10-15% spontaneous clearance in monoinfected).

1. USPHS Guidelines for Preventing OI in PWHIV, 1999.
Counseling and HCM

Counseling Topics:

- Prognosis & treatment basics.
- Avoid EtOH, hepatotoxic meds.
- Limit acetaminophen < 2 gm/day.
- Limit Vitamin A and complementary meds.
- Prevent transmission (sex, drugs, needle exchange).

Counseling and HCM

Health Care Maintenance:

- Alcohol & drug treatment referral.
- Referral to peer support resources.
- Hep A and B vaccines
Phase III: Evaluating for Treatment
Whom Do We Treat?

- HIV stable (No ddl in regimen, may need to d/c AZT.)
- If HIV not stable, needs to be addressed first (judgment call!)
- Treatment/follow-up adherence
- Drug & alcohol free (methadone okay)
- Willing to undergo treatment
- Pre-treatment liver biopsy necessary in most patients.
Whom Do We Treat (2)

- Depression under control
- No other contraindications for treatment (renal failure, severe cardiac disease, severe anemia/neutropenia/thrombocytopenia, uncontrolled diabetes, autoimmune diseases)
- Compensated liver disease
- Pretreatment vaccine for Hep A/Hep B
Utility of Liver Biopsy

Confirm presence of chronic hepatitis

Role of Liver Biopsy

Assess severity of necroinflammation

Evaluate possible concomitant disease processes

Assess fibrosis

Assess therapeutic intervention

Progression of Fibrosis on Biopsy

No Fibrosis

Stage 1: Fibrous expansion of some portal areas

Stage 3: Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 4: Fibrous expansion of portal areas with marked bridging (portal to portal and portal to central)

Stage 5,6: Cirrhosis, probable or defined

Cirrhotic liver: Gross anatomy of cadaver

Courtesy of Gregory Everson, MD.
When to Delay or Avoid Treatment

- CD4+ cells < 100/mm³, active opportunistic infections
- Uncontrolled HIV viral load
- Decompensated liver disease
- Untreated depression
- Ongoing substance abuse
- Nonadherence
- Active ischemic heart disease
- Untreatable malignancy
- Severe autoimmune disease
- Pregnancy plans
The Co-infected patient in the Hepatitis Clinic

The STAR/KEY players
- Maureen Gallagher
- Debbie Wolen
- Rebecca Goldberg

Graph:
- HIV/HCV+ patient
  - Psychiatrist/MH provider
  - Physicians/NPs
  - Nutritionist
  - Pharmacist
  - Peer educators
  - Nursing staff
  - Educational materials
  - Social support
  - Primary care provider
Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

<table>
<thead>
<tr>
<th>Week</th>
<th>During the Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely or none of the time (less than 1 day)</td>
<td>Some or a little of the time (1-2 days)</td>
</tr>
<tr>
<td>1. I was bothered by things that usually don't bother me.</td>
<td>☐</td>
</tr>
<tr>
<td>2. I did not feel like eating; my appetite was poor.</td>
<td>☐</td>
</tr>
<tr>
<td>3. I felt that I could not shake off the blues even with help from my family or friends.</td>
<td>☐</td>
</tr>
<tr>
<td>4. I felt I was just as good as other people.</td>
<td>☐</td>
</tr>
<tr>
<td>5. I had trouble keeping my mind on what I was doing.</td>
<td>☐</td>
</tr>
<tr>
<td>6. I felt depressed.</td>
<td>☐</td>
</tr>
<tr>
<td>7. I felt that everything I did was an effort.</td>
<td>☐</td>
</tr>
<tr>
<td>8. I felt hopeful about the future.</td>
<td>☐</td>
</tr>
<tr>
<td>9. I thought my life had been a failure.</td>
<td>☐</td>
</tr>
<tr>
<td>10. I felt fearful.</td>
<td>☐</td>
</tr>
<tr>
<td>11. My sleep was restless.</td>
<td>☐</td>
</tr>
<tr>
<td>12. I was happy.</td>
<td>☐</td>
</tr>
<tr>
<td>13. I talked less than usual.</td>
<td>☐</td>
</tr>
<tr>
<td>15. People were unfriendly.</td>
<td>☐</td>
</tr>
<tr>
<td>16. I enjoyed life.</td>
<td>☐</td>
</tr>
<tr>
<td>17. I had crying spells.</td>
<td>☐</td>
</tr>
<tr>
<td>18. I felt sad.</td>
<td>☐</td>
</tr>
<tr>
<td>19. I felt that people dislike me.</td>
<td>☐</td>
</tr>
<tr>
<td>20. I could not get &quot;going.&quot;</td>
<td>☐</td>
</tr>
</tbody>
</table>

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.
Hepatitis treatment evaluation - Timeline of events

Visit 1 (To)
- Medical and Psychiatric history
- Social history
- Labs - HCVRNA, genotype, etc
- Educational materials - on HCV; Transmission, prevention, treatment
- Liver biopsy, etc.
- Need for adherence, long process before treatment started.

Visit 2 (3-6 weeks post To)
- Review labs
- Schedule liver biopsy
- Psychiatry evaluation
- Other testing - Cardiac stress scheduling
- Eye exam, Ultrasound
- Benefits assessment, apply for MAP

Visit 3 (3-6 weeks post V2)
- Liver biopsy

Visit 4 (Biopsy + 3 weeks)
- Review biopsy results
- Discuss treatment, side effects in more detail.
- Decide on timing of treatment start
- Nutritionist evaluation

Visit 5, 6
- Teaching session(s)
- Start treatment
- Treatment package of lab slips, Clinic appoints.
- Frequent clinic visits - medicine, Psych, nutrition..
HIV and Hepatitis C Newsletter

The Ins and Outs of Hepatitis C Treatment

What is the Hepatitis C Virus and why is it important to me?

Hepatitis C Virus (HCV) causes inflammation to the liver. This virus is normally spread by blood from an infected person. The highest risk for being infected is primarily through IV drug use. This includes sharing contaminated needles, syringes, or even cotton. People who inject drugs for at least 5 years have a 60-80% chance of getting the HCV infection. Other sources of HCV include contaminated blood with blood transfusions, unsafe sex practices, men having sex with men, and tattoos done unprofessionally.

HCV is estimated to affect 4 million people in the United States. Non-Hispanic blacks and men are most likely to be infected. Right now, hepatitis C is the leading cause of liver transplants.

Possible Symptoms of Hepatitis C
- Fatigue (tiredness, exhaustion)
- Loss of appetite
- Jaundice (yellow skin and yellow eyes)
- Fever
- Dry coughs
- Body aches
- Itching, nausea
- Stomach pains

Reasons for treating my Hepatitis C (and more importantly if I have HIV too)

About 80% of the people infected with HCV show no signs or symptoms of the disease. However, this does not mean there is no damage to the liver. If left untreated, HCV can lead to serious conditions such as cirrhosis (scarring of the liver) or even liver cancer. Today, treatment is available for people who have HCV. The chance in getting rid of the HCV infection is about 50%. People having both HIV and HCV are at greater risk of developing cirrhosis than people who are only infected with HCV alone.

The History of Hepatitis C Treatment

The treatment for hepatitis C has improved over the last 15 years. Interferon (IFN) injection was the first treatment available for HCV, however response rates were poor. Since then, response has improved significantly to 35-40% with the addition of ribavirin to IFN. The most recent improvement to the treatment of HCV was in 2001 when polyethylene glycol (PEG) was attached to IFN. PEGIFN is different from IFN as it is a larger size drug so it stays in the body longer to fight off the HCV infection and only requires once weekly injections. At present, the only treatment for HCV in HIV positive patients is the combination of PEGIFN and ribavirin.
Practical Lessons: HCV Rx in the HIV Clinic

- Severe anemia is common, start epo early, monitor often.
- Monitor closely for depression. SSRI’s use early
- Warn pts that abs CD4 will fall due to IFN (%CD4 is preserved).
- Water (2-3 liters per day) is the best side effect management tool. Exercise too!
Practical Lessons: HCV Rx in the HIV Clinic

- Peer education and support very important
- Educational materials for patients and family.
- Group appointments for new patients, teaching sessions.
- Multidisciplinary approach to care at all stages- evaluation, treatment/side effect management and adherence counseling.
Take Home Messages

- Consider early treatment of hepatitis C in co-infected patients with stable HIV infection
- Vaccinate for hepatitis A and B
- Advocate for safe sex practices to prevent transmission
- Counsel for ETOH and substance abuse
- Utilize strengths of community clinic approach in high-risk populations
  - Partnerships
  - Intensive peer interventions
  - Adherence tools to overcome barriers to treatment
Future HCV Therapies

- Combination treatments with pegInterferon
  - $\gamma$-interferon – anti-fibrotic agent
  - Viramidine, VX 497, CSA
- Immune modulation therapies
  - Thymosin
- Newer antiviral agents
  - Helicase, protease, polymerase inhibitors
  - Anti-sense nucleotides (ISIS 14803), SiRNAs
  - Pegylated consensus interferon
Pipeline for Future HCV Therapies

- pegInterferon + RBV
- pegInterferon + Viramidine
- pegInterferon + VX 497 (?)
- pegInterferon + protease inh
- Dual Inhibitors