HIV/HCV Co-infection

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### Major Hepatitis Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Means of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Fecal-oral: Contaminated food or water</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Sexual, mother-to-child, blood exposure (transfusion, IDU, tattoo)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Blood exposure (transfusion, IDU, tattoo); sexual, mother-to-child less common</td>
</tr>
</tbody>
</table>
Hepatitis C: A Global Health Problem
170-200 Million (M) Carriers Worldwide

- United States: 3-4 M
- Americas: 12-15 M
- Western Europe: 5 M
- Eastern Europe: 10 M
- Southeast Asia: 30-35 M
- Far East Asia: 60 M
- Africa: 30-40 M
- Australia: 0.2 M

Hepatitis C: United States

- 3.7 million infected in U.S. (1.8% of population)
- 25,000-35,000 new infections per year
  - Sixty percent due to injection drug use (IDU)
- A leading cause of cirrhosis and liver cancer and the most common reason for liver transplantation in the United States
- 8,000-10,000 deaths from HCV annually
- HCV-related deaths and transplants projected to triple in next decade

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002
Hepatitis C Statistics

U.S. Population

• 1.6% overall
  – ~4 million Americans infected

• 3.2 million chronically infected
  – 2.1% Mexican Americans
  – 3.4% African Americans

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HCV Diagnostics: Genotype Test

• Genotypes (1,2,3,4,5,6)
  – U.S. population
    • 70% genotype 1
    • 30% genotypes 2 & 3

• Why Is a Genotype Test Important?
  – Helps predict treatment response
  – Dictates treatment duration of 24 or 48 weeks

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Genotype Distribution

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Prevalence of HCV infection in selected subgroups in the U.S.

- Injection drug users 52-90%
- Hemophiliacs 60-85%
- HIV infected individuals 9-40%
- Incarcerated HIV+ 50%
- MSM 4-8%
Risk factors for Hepatitis C infection

- 55% IVDU
- 20% Cocaine
- 10% Exposure to infected sex partner or multiple partners
- 10% Occupational, hemodialysis, household, perinatal
- 5% No recognized source

Natural History of Hepatitis C

Most patients with chronic HCV infection are asymptomatic

10-20 years

Acute Hepatitis C

Chronic Hepatitis
75%-85%

Cirrhosis 20%

Hoofnagle JH Hepatology. 1997;26 (suppl 1): 15S-20S
Di Bisceglie, Hepatology, 2000
Hepatitis C: Diagnosis

- Antibody test (EIA)
  - Indicates past or active infection
  - Unlike hepatitis B, presence of antibodies does not confer immunity

- HCV RNA test (PCR)
  - Confirms active infection, infectivity to others
  - Quantitative or qualitative RNA tests exist; the former is more often used because it provides a potentially useful viral load measurement
Histologic Staging

Stage 0: No Fibrosis
Stage 1: Portal Fibrosis
Stage 2: Few septa
Stage 3: Numerous septa
Stage 4: Cirrhosis
Treatment: is there a cure?

Yes, for many but not all.
Predictors of Virologic Response

Viral Factors
- Genotype
- Viral Load

Host Factors
- Age
- Cirrhosis
- Race
- Gender
- Weight

[Diagram showing viral factors and host factors with specific components like nucleocapsid, single-stranded RNA, envelope, protein E1, and protein E2]
Vaccinations

- Test all HIV+ and Hepatitis C patients for antibodies to hepatitis A and B

- Vaccinate as needed
Antibody Testing

• Hepatitis A: order only IgG unless the patient is acutely ill

• Hepatitis B:
  • HBV surface antibody IgG
  • HBV core antibody IgG
  • HBV surface Antigen
Hepatitis B

- Vaccinate if: surface antibody is less than 10 units and core antibody is absent

- Vaccinate if: HBV core and surface IgG antibody negative

- Patients who have had HBV infection in the distant past will often have no surface antibodies but will have immunity because they have core antibodies.
Hepatitis C

Treatment Decisions

• Who to treat?
  – People w/bridging fibrosis or cirrhosis
  – People with symptoms
  – Acute hepatitis
    • Decreased rate of developing chronic infection in 2 small studies
Hepatitis C

Treatment Decisions

• Do not treat patients with
  – Advanced cirrhosis
  – Severe depression/psychiatric disorder
  – Low blood counts
  – Thyroid disease, untreated
  – Autoimmune diseases
  – Alcohol/drug dependency
  – Pregnancy
Hepatitis C / HIV coinfection
Hep C and HIV Topics

• Interactions of viruses

• Treatment decisions

• Drug interactions
HCV

- *Flaviviridae* family
- Single-stranded RNA
- Large heterogeneity leading to ‘quasispecies’
- $10^{12}$ virions/day
- Stays in cytoplasm and HCV genome does not integrate into cell’s genome.
- 6+ genotypes

HIV

- *Retroviridae* family
- Double-stranded RNA
- Large heterogeneity leading to ‘quasispecies’
- $10^9 - 10^{10}$ virions/day
- RNA transcribed to DNA by RT and integrates into viral genome
- 11+ clades
### Comparisons

<table>
<thead>
<tr>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly infects CD 4 cells</td>
<td>Mainly infects liver cells</td>
</tr>
<tr>
<td>Daily – replicates billions</td>
<td>Daily – replicates trillions</td>
</tr>
<tr>
<td>High mutation rate</td>
<td>Very high mutation rate</td>
</tr>
</tbody>
</table>

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Comparisons

**HIV**
- Chronic – 100%
- US – 1 major strain
- High sexual transmission rate
- High IDU transmission rates (Blood)

**HCV**
- Chronic rates - 55-85%
- US – 3 major strains
- Low Sexual transmission rate
- Very high IDU transmission rates (Blood)

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Comparisons – Con’t

<table>
<thead>
<tr>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cure?</td>
<td>• Cure?</td>
</tr>
<tr>
<td>– No</td>
<td>– Virological Cure</td>
</tr>
<tr>
<td>• Treatment - lifelong</td>
<td>• Treatment 24 to 48 weeks</td>
</tr>
<tr>
<td>• Can become resistant</td>
<td>– New direct antivirals will lead to resistance</td>
</tr>
</tbody>
</table>

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Comparisons – Prevalence

HIV

U.S. –
• ~1,000,000

HCV

U.S. –
• ~4,000,000

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Serologic Tests

• **EIA**
  - Main screening assay
  - 95% sensitive and specific
  - Mean time to seroconversion: 10 weeks
  - May exhibit false (+) results

• **RIBA-2**
  - Confirmatory assay to distinguish between a false-positive EIA-2 and a true previous exposure to HCV
  - Positive response for both active and resolved disease

HIV/HCV COINFECTION

• 10%-30% of HIV+ patients are coinfected with HCV

• Rate of HCV depends on risk factor
  – Hemophiliacs >90%
  – IDUs 70%-90%
  – MSM 5%-10%
HCV/HIV Coinfection

- HIV accelerates Hep C liver disease (may cut time to cirrhosis in half!)
- HCV may impair immune reconstitution after HAART
- HCC may occur at an earlier age in coinfected patients
Molecular Virologic Assays

- Detect, quantify, and/or characterize HCV RNA genomes
- > 90% sensitive and specific
  - **Qualitative PCR (Viral load)**
    - Most sensitive test
    - Detects virus as early as 1-2 weeks after exposure
    - Confirms a positive anti-HCV; assesses sustained virologic response (SVR)

HIV/HCV COINFECTION

• HCV liver disease is more severe in HIV+ patients
• HCV liver disease is now more important
  – HIV deaths are decreasing
  – Deaths related to liver disease are increasing
• Effect of HCV infection on HIV/AIDS progression is not known
Does HIV Make HCV Worse?

• HIV accelerates HCV disease progression – doubles the risk for cirrhosis and increases the chance for liver cancer

• Some evidence suggests that when HIV is stable – HCV disease progression is slowed in people with HIV/HCV coinfection
Effect of HCV/HIV Co-infection on HCV Diagnosis

- Single negative antibody test does not rule out HCV in HIV-positive patients
- Sensitivity of anti-HCV tests can be lower in HIV-infected patients
- Diagnosis should be confirmed by detecting HCV RNA

When and Which to Treat?

• Generally, HIV should be under control
  – Most recommend treat HIV first

• HCV – People with HIV/HCV should be considered for HCV treatment
  – Unless:
    • CD4 counts less than 200
    • Active opportunistic illness

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HIV Meds and the Liver

• Generally, some medications including HIV medications can be difficult for a liver to process

• HIV meds temporarily increase liver enzymes and HCV viral load – usually stabilize over time
  – If ALT’s 4 to 5 times baseline –
    • Change to more liver friendly HIV medications

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Recommendations

- HIV specialist and liver specialist should closely follow co-infected people
- Monitor liver functions especially when on HIV treatment
- Switch to more liver friendly HIV medications
Counseling HCV Infected Persons

HCV-positive persons:

- Can work in food service
- Are considered potentially infectious
- Should keep cuts and skin lesions covered
- Need to be informed of the potential for sexual transmission
- Need to be informed of the potential for perinatal transmission
  - no evidence to advise against pregnancy or breastfeeding
  - should consider testing child after birth

HCV-positive persons should NOT:

- Donate blood, organs, tissue or semen
- Share household articles (e.g., toothbrushes, razors)
Natural History of HCV Infection: HIV Co-infection Increases Progression

Management of Hepatitis C. *NIH Consensus Statement.* 1997; March 24-26: 15(3).
Factors Influencing HCV Progression

- Heavy alcohol intake
- Male gender
- >40 years of age at time of infection, particularly if contracted via blood transfusion
- Coinfection with HIV
- Coinfection with HBV

*Note:* HCV progression has NOT been demonstrated to be influenced by genotype, viral load, serum ALT, or mode of transmission

Effect of HIV on HCV

• In hemophiliac series, simultaneous acquisition of HIV and HCV increased risk of hepatic failure 21 times.

• Chronic hepatitis C leads to increased mortality in HIV-infected patients.

Effect of HCV on HIV

- Most studies have not found an effect of chronic hepatitis C infection on the course of HIV infection.
- Chronic HCV infection has been associated with more accelerated HIV infection progression in patients co-infected with HCV genotype 1 and was associated more rapid CD4 cell decline.

Effect of HAART on HCV

• Initiation of HAART appears to have minimal effect on HCV replication.
• Several studies have suggested the possibility of a ‘reactivation’ of HCV shortly after initiation of HAART - ? Consequence of immune reconstitution.

HCV/HIV Coinfection

• The Issues
  – Patients infected with HIV are living longer
  – Hepatitis C is present in approximately 40% of HIV infected patients
  – Coinfected patients are at high risk for developing end stage liver disease
  – Lack of results from large clinical studies with coinfectected patients
  – Coinfected patients present additional challenges compared to the HCV monoinfected patients
HIV/HCV COINFECTION

• HIV treatments (ARV) can cause fatty liver/liver enzyme elevations
  – In some studies these liver problems are increased in those w/HCV

• Some report worsening of HCV liver disease after HIV treatment is started
WHEN TO TREAT?

Treat HCV before HIV treatment?

- Likely to help avoid Hepatotoxicity
- Less drug interactions – toxicity (TDM), adherence
- Response to HAART – better immune reconstitution
HIV/HCV Treatment

- Predictors of success in achieving a sustained viral response:
  - CD4 count greater than 500
  - HIV RNA levels below 10,000 copies
  - No alcohol consumption
HCV Treatments

• Treatment response rates lower in people with HIV
  – Genotype 1 up to 29%; Genotype 2,3 up to 62%

• Closely monitored for:
  – Anemia rates up to 50% caused by ribavirin
  – Thrombocytopenia (low platelets) caused by interferon

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Ribavirin and HIV Medications

- Ribavirin originally developed for HIV, but not effective

- HIV medications that should be avoided or used with caution when combined with ribavirin:
  - D4T (Zerit)
  - AZT (Retrovir)
  - DDI (Videx)

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Drug interactions in Co-infection

- ddI and d4T plus interferon/ribavirin appear to cause mitochondrial toxicity
- result: lactic acidosis, peripheral neuropathy
- Avoid starting these drugs if plan to treat HCV later
ADVANCES IN HCV: TREATMENT

• IL28B
  • A variation in IL28B called CC genotype = 2-fold increase in response
    • ~80% of those who achieved response (SVR) had CC genotype
    • Partly explained SVR differences in African Americans and Hispanics
  • Test commercially available in August 2010?
ADVANCES IN HCV: TREATMENT

- HCV Protease Inhibitors
  - Telaprevir and boceprevir - genotype 1 - in combination with pegylated interferon and ribavirin
    - Increase efficacy by 10 to 30%
    - Treatment duration - response guided therapy
    - Telaprevir – skin rash – may be whole body rash
    - Boceprevir – higher rates of anemia
• Medication burden:
  • Telaprevir – every 8 hours
  • Pegylated interferon (sq) once-a-week
  • Ribavirin – taken twice a day

• Adherence
• Resistance
Some unanswered questions – are all oral medications viable?

Probably a combination of different HCV protease and polymerase inhibitors

At least 5 to 10 years away
Drug interactions

• Clinical manifestations: pancreatitis, hepatitis, myopathy, peripheral neuropathy and lactic acidosis
Drug interactions

- Monitor serum lactate and amylase monthly
- Consider changing HAART before starting combination therapy
- Discontinue all meds immediately if lactate rising
On HAART and HCV treatment

Drug interactions

• Anaemia (AZT & ribavirin)
• Mitochondrial toxicity-Lactic acidosis, pancreatitis, lipodystrophy (ddl & ribavirin)
• Possible reduction in CD4 (due to interferon)

Compromise adherence
Hepatitis C/HIV

SUMMARY

• HIV+ patients have worse liver disease
  – Treatment should be considered
  – Expect greater side effects, possible interactions with HIV medications
Primary Care Role

- HCV antibody testing/ PCR testing
- Hepatitis A and B testing and vaccination
- Patient education
- HIV testing
- Referral for liver evaluation
- Referral for drug and alcohol treatment
Specialist Role

• Special tests: abdominal ultrasounds/EGD/Liver biopsy
• Combination therapy management
• Vaccinations: HAV, HBV, pneumovax?
• Education
Team Work

- Physician/PA/NP providers
- Nurses
- Nutritionists
- Social workers
- Mental health: psychiatrist/counselors
- Pharmacists
- Advocates
Investigational Drugs

• Protease inhibitors
• Helicase inhibitors
• Anti-fibrotic agents
Data from CROI 2013

• Investigational drugs for HCV in patients coinfected with HIV
Results of two French studies suggest that adding the protease inhibitors boceprevir or telaprevir to standard hepatitis C therapy improved treatment outcomes in people with HIV and hepatitis C co-infection who had characteristics associated with a poor hepatitis C treatment response.

The safety profile of the two drugs was also acceptable.

Large numbers of people living with HIV are co-infected with hepatitis C, and liver disease is an important cause of death in people with this co-infection.

Some people with hepatitis C are delaying starting treatment until newer drugs become available, in particular interferon-free regimens, because of the unpleasant side-effects caused by interferon.

However, people with HIV and hepatitis C co-infection who have serious liver disease are in urgent need of new hepatitis C treatment options, such as boceprevir or telaprevir.

French investigators therefore designed two separate studies examining the safety and efficacy of adding boceprevir or telaprevir to interferon-based treatment.

CROI 2013
The study populations involved people with co-infection who had hepatitis C genotype 1 infection and who had not responded to a previous course of interferon-based therapy.

Between 70 and 75% of the study participants had the difficult-to-treat genotype 1a infection, and up to 25% had liver cirrhosis.

Interim results from the boceprevir study showed that 63% of patients had an undetectable hepatitis C viral load after 16 weeks of therapy. Surprisingly, 73% of patients with cirrhosis had a good treatment response at this point.

Almost all the participants in this study reported side-effects. These were categorized as serious in 30% and a small number of individuals stopped therapy early because of adverse events.

Laboratory abnormalities were also common, with 42% developing anemia and 70% neutropenia.

Interim 16-week data were also presented for the telaprevir study.

Some 88% of patients had a good treatment response at this point. However, skin reactions were common and were observed in 70% of patients. Approximately 30% of patients developed anaemia and 84% developed neutropenia.

A number of promising new anti-hepatitis drugs are in the pipeline and they offer the prospect of high treatment-response rates without the need for interferon.

However, the results of these studies will offer hope for people with HIV and hepatitis C co-infection whose liver disease means that early treatment is a priority.
The ELECTRON study

- A combination of three direct-acting anti-hepatitis C drugs has achieved a 100% response rate.
- The study involved treatment-naïve and null-responders who previously failed to respond to therapy with pegylated interferon and ribavirin.
- The ELECTRON study involved 25 treatment-naive participants and nine null-responders. All had genotype 1 infection, the majority having the more difficult-to-treat 1a genotype.
- They were treated with a combination of sofosbuvir (HCV polymerase inhibitor), ledipasvir (NS5A inhibitor) and ribavirin.
- Therapy lasted for twelve weeks. At this point, all the participants had an undetectable hepatitis C viral load. This was also the case 4 and 12 after the completion of therapy.
- The treatment was safe and well-tolerated. Only 4% of participants discontinued their therapy because of side-effects.
- Anemia, depression and headache were the most common side-effects.

Gane E et al. ELECTRON: 100% suppression of viral load through 4 weeks’ post-treatment for sofosbuvir + ledipasvir (GS-5885) + ribavirin for 12 weeks in treatment-naive and -experienced hepatitis C virus GT 1 patients. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 41LB, 2013.
4-Drug Oral Regimen Cures More than 90% of Chronic Hepatitis C Patients

- Abbott's Investigational Interferon-Free Hepatitis C Treatment Regimen Achieved SVR12 (Observed Data) Rates in 99 Percent of Treatment-Naive and 93 Percent in Prior Null Responders for Genotype 1 Patients in Phase 2b Study
### Study M11-652 (Aviator)

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naive</th>
<th>Null responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=79)</td>
<td>(N=45)</td>
<td></td>
</tr>
<tr>
<td>BL HCV RNA (log\textsubscript{10} IU/mL)</td>
<td>6.5±0.6</td>
<td>6.6±0.5</td>
</tr>
<tr>
<td>BL IL28B non-CC genotype</td>
<td>72%</td>
<td>96%</td>
</tr>
<tr>
<td>SVR\textsubscript{4}</td>
<td>(99%) 78/79</td>
<td>(93%) 42/45</td>
</tr>
<tr>
<td>OD SVR\textsubscript{12}</td>
<td>(99%) 76/77</td>
<td>(93%) 38/41</td>
</tr>
<tr>
<td>PTW12 data missing*</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>OD SVR\textsubscript{12} (GT1a)</td>
<td>(98%) 52/53</td>
<td>(89%) 24/27</td>
</tr>
<tr>
<td>OD SVR\textsubscript{12} (GT1b)</td>
<td>(100%) 24/24</td>
<td>(100%) 14/14</td>
</tr>
<tr>
<td>OD SVR\textsubscript{12} (IL28B non-CC)</td>
<td>(98%) 54/55</td>
<td>(92%) 36/39</td>
</tr>
</tbody>
</table>
Mother-Infant Transmission
Role of HCV/HIV Co-infection

• HIV co-infection ↑ HCV transmission
  – HCV only → 5% (3 - 8%)
  – HCV/HIV → 17% (7 - 36%)
  – Mechanism - increased HCV viremia

• HCV co-infection may ↑ HIV transmission
  – HIV only → 16.3%
  – HIV/HCV → 26.1% (OR 1.82)

Zanetti AR. Lancet 1995;345:289
Hershow RC. J Infect Dis 1997;176:414
### Transmission & Prevention

<table>
<thead>
<tr>
<th>Source of Transmission</th>
<th>Risk Groups</th>
<th>Pathway Before 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared Needles</td>
<td>All Drug Paraphernalia</td>
<td>Blood transfused, products, procedures</td>
</tr>
<tr>
<td>Sexual Transmission</td>
<td>Healthcare Workers - needle sticks</td>
<td>Shared Household items - razors &amp; toothbrushes</td>
</tr>
<tr>
<td>Mother to Child</td>
<td>Tattoos / Piercing</td>
<td>&lt;10% of routes can not be identified</td>
</tr>
</tbody>
</table>

Source: www.hcvadvocate.org
Transmission & Prevention

• HCV is **not** spread by breast feeding, sharing eating utensils or drinking glasses, kissing, hugging

• Direct blood to blood transmission route

www.hcvadvocate.org
Transmission & Prevention: Tips

• Safer Sex
  – For so called “high risk groups”

  • Multiple sexual partners, people with sexually transmitted diseases, coinfection with HIV or HBV

  • Any situation where blood is present
Transmission & Prevention: Tips

• Mother to Child Transmission
  – Low risk – about 5-6%
  – Given the low rate of transmission, pregnancy should not be avoided.
    • Note: pregnant women can not take interferon or ribavirin

• Health-Care Settings
  – Follow standard/universal precautions
Transmission & Prevention: Tips

• Tattoos & Piercing
  – Considered a low risk in commercial setting
  • Make sure disposable needles and separate ink pots are used and that general safety precautions are followed
  – Considered a higher risk in other settings
    • Non-commercial settings such as in prison or on the streets

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**HCV Transmission & Prevention: Tips**

- **Household**
  - Cover cuts or sores
  - Do not share personal hygiene items (toothbrushes, razors, etc.)

- **Professional Personal Care Settings**
  - Standard precautions
  - Disposable equipment
  - Bring own equipment

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