HIV/HCV Coinfection Update 2010

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Seroprevalence of Hepatitis C: 170 to 200 Million Worldwide

2. Edlin B et al. AASLD; November 11-15; 2005 San Francisco, California. Oral Presentation #44.
Why Is Your Liver So Important to Your Health?

- Your liver is one of the largest and most important organs in your body. It is about the size of a football!
- Your liver plays a central role in many vital life processes
- Your liver is an important part of your digestive system
- Your liver helps your body process medicines, including your HIV medicines
- Your liver is responsible for so many things that any damage to it can cause problems in other parts of your body
Your Liver Is Your Body’s Factory

- It makes important substances called proteins that assist with many body functions (such as helping with clotting of your blood)
- It plays an important role in blood circulation
- It removes wastes and breaks down harmful substances, such as alcohol
  - A healthy liver filters about 1.5 quarts of blood per minute... that’s 540 gallons a day!!!
What Is Hepatitis?

- Hepatitis – inflammation (swelling) of the liver
  - There are over 100 causes of hepatitis and the most common one in the U.S. is alcohol!
    - Can be caused by medications, alcohol, viruses, genetic diseases or chemicals

- If hepatitis is caused by a VIRUS, it is given a letter like hepatitis A, hepatitis B or hepatitis C

- Hepatitis C is also referred to as hep C or HCV (hepatitis C virus)
Hepatitis C Infection

- Most people infected with hepatitis C end up with the chronic (long-term) form of the disease
  - Occurs in 80-85% of infected persons
- In the U.S., it is the most common infection that is spread from blood-to-blood contact
- About 35,000 new cases of hepatitis C are estimated to occur in the U.S. each year
- Untreated hepatitis C can cause many health problems. Since it affects your liver, it can affect your whole body
  - End-stage liver disease is the #1 cause of death among patients with HIV
What Is Fibrosis?

- The beginning of scarring in the liver
- Caused by infection, inflammation (swelling) or injury to liver cells
- Can prevent the liver from working well
  - Slows down the liver’s ability to circulate blood and remove toxins
- Can lead to severe scarring (cirrhosis)
What Is Cirrhosis?

- Means severe “scarring of the liver”
- Scar tissue has begun to replace normal liver cells. Once the liver has scar tissue, it cannot heal itself completely
- The more scar tissue present, the harder it is for the liver to do its many jobs
- Cirrhosis may put someone at risk for liver failure or liver cancer
What Is Advanced Liver Disease?

- Also called *end-stage liver disease*
  - The #1 cause of death in patients with HIV who also have hepatitis C
- Occurs when a lot of severe scarring (cirrhosis) is present in the liver
- Symptoms of this include:
  - Fatigue (extreme tiredness)
  - Difficulty thinking clearly or concentrating
  - Yellowing of skin and the white part of the eyes (jaundice)
  - Swelling of the lower extremities (ankles and feet)
  - Fluid in the abdomen (stomach area)
  - Gastrointestinal bleeding (bleeding from stomach or intestines)
  - Poor blood clotting
HCV Sexual Transmission
Unlikely in Heterosexual Monogamous Couples

- 895 monogamous heterosexual partners of HCV-infected patients
  - 10-year prospective follow-up study
- 3 HCV infections observed during follow-up (0.37 per 1000 person-years)
  - None were sexually transmitted from partner
  - In 1 couple, patient had HCV GT 2a; spouse GT 1b
  - In 2 couples, partners had the same GTs but different strains

Significant Increase in New Acute HCV Infections in 2003

- Test for trend p-value using Poisson regression $p<0.001$
- Error bars = 95% CI

Incidence of acute HCV infection/1000 pt yrs

# Sexual Transmission of HCV

<table>
<thead>
<tr>
<th>HCV Monoinfection</th>
<th>HIV/HCV Coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heterosexual, monogamous couples in Italy(^1)</td>
<td>• Acute HCV(^2)</td>
</tr>
<tr>
<td>- 3 infections</td>
<td>- 44 cases</td>
</tr>
<tr>
<td>• 0.37 per 1000 persons-years</td>
<td>• HIV-positive MSM</td>
</tr>
<tr>
<td>• Phylogenetic analysis: discordant virus</td>
<td>• Related to unprotected, receptive anal intercourse</td>
</tr>
<tr>
<td>- Sexual transmission</td>
<td>• San Francisco(^3)</td>
</tr>
<tr>
<td>• Extremely low</td>
<td>- 10 HCV seropositive cases among 833 MSM</td>
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</tbody>
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HCV Sexual Transmission
*Increased in HIV-Infected MSM*

- HCV(+) semen associated with HCV viremia ($P = .038$)\(^1\)
  - HCV(+) semen prevalence rates (%)
    - HCV monoinfection: 18.4%
    - HIV/HCV coinfection: 37.8% ($P = .033$)
- Risk factors for HCV transmission in HIV-infected MSM\(^2\)
  - Unprotected anal intercourse
  - Mucosally traumatic practices: fisting, sex toys
  - Group sex or sex under influence of “club” drugs
    - “Crystal meth”, ketamine, GHB, poppers, LSD, ecstasy

GHB, gamma hydroxybutyrate; MSM, men who have sex with men

Danta et al. CROI; February 5-8, 2006; Denver, CO. Abstract 86.
You Can’t Get Hepatitis C by:

- Sneezing
- Coughing
- Food or water
- Sharing drinking glasses or eating utensils
- Shaking hands
- Holding hands
- Hugging
- Kissing on the cheek
- Playing with children
- Donating blood
How Do You Know if You Have Hepatitis C?

- Hepatitis C is often known as a “silent” virus. Some people with hepatitis C may not have any symptoms at all!
  - Some people develop cirrhosis (severe scarring) from hepatitis C before they even have symptoms.

- Symptoms may include:
  - Feeling like you have the “flu”
  - General weakness or feeling tired
  - Loss of appetite
  - Joint pain
  - Problems sleeping
  - Mental tiredness
  - Poor digestion or diarrhea
  - Depression or mood swings
Extrahepatic Manifestations Associated With HCV

**Hematologic**
- Mixed cryoglobulinemia
- Aplastic anemia
- Thrombocytopenia
- Non-Hodgkin’s b-cell lymphoma

**Dermatologic**
- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotizing vasculitis

**Renal**
- Glomerulonephritis
- Nephrotic syndrome

**Endocrine**
- Hypothyroidism
- Diabetes mellitus

**Ocular**
- Corneal ulcer
- Uveitis

**Vascular**
- Necrotizing vasculitis
- Polyarteritis nodosa

**Neuromuscular**
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

**Autoimmune Phenomena**
- CREST syndrome

**Neuropsychiatric**
- Depression

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What Happens to People with Hepatitis C – WITHOUT HIV?

- Exposure (Acute Phase): 100 people
  - 15 people: Resolved
  - 85 people: Chronic HCV (Hepatitis C) Infection

- Cirrhosis: 20 people
  - 6 people/yr: End-stage Liver Disease
  - 4 people/yr: Hepatocellular Carcinoma (Liver Cancer)

- Transplant/Death: 3-4 people/yr

Approximate 20 year progression rate accelerated with HIV, hepatitis B or alcohol

Time (yr):
- 10
- 20
- 30
What Speeds the Progression of Hepatitis C?

- Drinking alcohol
- People who got hepatitis C when they were older than 40
- Being male
- Smoking cigarettes
- Hepatitis B infection
- Having HIV infection
- Having a weakened immune system
Alcohol content in specific beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>g/Drink</th>
<th>Drinks/50 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>11</td>
<td>4.5</td>
</tr>
<tr>
<td>12 oz at 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine</td>
<td>13</td>
<td>3.8</td>
</tr>
<tr>
<td>5 oz at 11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martini</td>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>3 oz at 40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
My Doctor said "Only 1 glass of alcohol a day". I can live with that.
What Happens to People with Hepatitis C and HIV?

Fibrosis progression is faster and less predictable in patients with HIV.
Change in Fibrosis Stage in HCV/HIV Coinfected Patients

- 67 patients with no or minimal fibrosis underwent a second biopsy (Ishak score)
- Median time between biopsies was 2.84 years
- 37% with 2 or more stage progression

What Happens to People with Hepatitis C and HIV?

Mean time to cirrhosis (years)

- HIV -: 23.2 years (n = 431)
- HIV +: 6.9 years (n = 116)

Progression to cirrhosis can occur in as little as 7 years in patients with HIV

$P < 0.001$
Increased Risk of Cirrhosis and ESLD in HCV/HIV Coinfected Patients

- Histological Cirrhosis
- Decompensated Liver Disease

CI = Confidence interval
ESLD = End stage liver disease
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus
HCV and HIV Coinfection

- Coinfection – a medical term meaning that there are two or more infections in your body at the same time

- HIV and HCV are very different, so it is important that you learn about both of them

- About 1 million Americans have HIV – 1 out of 3 also has hepatitis C
  - It has been estimated that about 90% of HIV-infected intravenous drug users (IVDU) are coinfectected with HCV
Worldwide Prevalence: % of HIV Patients Who Are Coinfected With HCV

1. United States 30%¹
2. Spain 50%¹
3. Western Europe 33%¹
4. Thailand ~50%²

¹Soriano V, et al. AIDS. 2002;16:813-826
US Prevalence of Comorbid HCV Infection in HIV-Infected Patients

Overall: 30%

Among IVDU: 90%

83% HCV GT 1 infection

IVDU, intravenous drug users

How Does HIV Affect Hepatitis C?

- HIV can make hepatitis C worse. People with HIV tend to have hepatitis C that *gets worse, faster*.
- Some medicines that are used to treat HIV may cause damage to your liver.
- HIV affects your entire immune system, including your body’s ability to fight off hepatitis C.
How Does HIV Affect Hepatitis C?

- When you have HIV, it is harder for your body to fight the hepatitis C virus. That is why people with HIV tend to have hepatitis C that gets worse faster.

- Without treatment, people may progress to fibrosis (scarring), cirrhosis (severe scarring) or end-stage liver disease. They may also die from untreated hepatitis C and its complications.
HIV Infection Is Associated With Increased HCV RNA Concentrations

Increased HCV viral production
Decreased immune clearance

![Graph showing mean HCV RNA concentrations for HCV monoinfected and HCV/HIV coinfect ed individuals.](image)

- **HCV Monoinfected**: 6 million (X 10^6 Copies/mL)
- **HCV/HIV Coinfected**: 14 million (X 10^6 Copies/mL)

HIV Viremia Is Associated With Increased Fibrosis Progression Rates in Coinfection

Low CD4\(^+\) Cell Count Is Associated With Increased Fibrosis Progression Rates in Coinfection

Most Common Causes of Death in HCV/HIV Coinfected Patients

- **End-Stage Liver Disease**: 31%
- **AIDS**: 29%
- **Cancer**: 9%
- **Cardiovascular Disease**: 8%
- **Bacterial Infection**: 7%

Now that HIV medications work so well, more patients are dying from liver related disease.

Liver disease is the #1 cause of death in patients with HCV/HIV coinfection.
Current Treatment Options

The Centers for Disease Control (CDC) Recommends that Antiviral Treatment Be Considered for All HIV Patients Coinfected with Chronic Hepatitis C Infection
Why Is It Important That You Talk to Your Healthcare Provider about Hepatitis C Treatment?

- The longer hepatitis C goes untreated, the greater the risk for further liver damage.
- Starting therapy earlier, rather than later, may help your liver by stopping the virus from causing more damage.
- Hepatitis C medication may work better if used before there is serious liver damage.
- If you have hepatitis C and HIV coinfection, ask your healthcare provider if treatment is right for you.
What Are the Treatment Goals of Hepatitis C Medication?

• The most important goal is to achieve a sustained virologic response (SVR)
  – This means that the medication was successful because the virus cannot be measured in your blood 6 months after you finish treatment

• Another possible goal of treatment is:
  – To stop more liver damage from occurring
Current Treatment for HCV Infection

- Peginterferon Alpha 2 a/b once a week with Ribavirin.
- In genotype 2 treat for 24 to 48 weeks.
- In genotype 1-4 treat for 48 weeks or longer if needed.
- Ribavirin dose will be 400mg in AM and 600mg in PM if the weight is <75 KG and if the patient is >75 KG, the dose would be 600mg twice a day.
Multiple Anti-HCV Drugs Are In Development

**Linear class**
- Telaprevir
- Boceprevir
- Narlaprevir

**Active site**
- RG7128
- IDX184
- PSI-7977

**NS3 Protease**
- Macrocyclic class
  - RG7227/ITMN-191
  - TMC 435350
  - MK 7009
  - BI 201335
  - BMS-650032

**NS5A**
- BMS-790052

**NS5B Polymerase**
- Palm
  - ABT-333
  - ABT-072
  - GS 9190
  - ANA598
- Thumb
  - VCH-759
  - VCH-916
  - VX-222
  - BI 207127
  - Filibuvir

**Cyclophilin**
- Debio 025
- NIM 811

Compounds in Ph2/3 trials (Cct-2009)
Contribution Of Peg-IFN/RBV To SVR

- NS3 Protease Inhibitor + Peg-IFN+RBV: SVR~70%
- NS3 Protease Inhibitor + Peg-IFN: SVR~46%
- Baseline contains WT + resistant variants in treatment naïve individuals: SVR~36%

Kwo PY. Hepatology 2008;48:1027A
Peg-IFN/RBV Treatment Experienced Patients Can Be Re-treated

Relapsers

New regimen: NS3 Protease Inhibitor + Peg-IFN+RBV

Viral breakthroughs

SVR~69%

Non-responders

SVR~39%

Peg-IFN/RBV treatment failure

SVR~57%
Patient Factors Can Affect Ability To Respond To Therapy

- SVR
- Age >50yrs
- Non-adherence
- Unmanaged Depression
- Male
- Insulin resistance
- African American
- Fatty Liver
- Genetics IL28B
Multiple Factors Can Increase Response To Antiviral Therapy

SVR

- Complete therapy
- Adherence
- Tolerability
- Potent viral suppression
- Overcome virologic resistance
- Combination regimens
Resistant Variants Occur Naturally
Resistant Variants Are Present Before Treatment

- HCV exists as a mixture of populations of genetically distinct, but closely related, virions in every patient\(^1\)
  - \(\sim 10^{12}\) viruses produced per day
  - \(\sim 1\) mutation per virus produced

- Most resistant variants are relatively unfit and are undetectable prior to therapy with current technology\(^2,3\)

References:
1. Pawlotsky JM. *Clin Liver Dis* 2003; 7:45-66
Resistant Variants Can Be Selected During Treatment

Antiviral

Potent antiviral therapy eliminates sensitive variants

Resistant variants are uncovered which can then expand
Frequent Monitoring Of HCV RNA Levels Can Detect Treatment Failure And Resistance

Baseline HCV RNA → Start treatment → Viral breakthrough

HCV RNA

Before treatment
Time on treatment
Patients have viral variants with different levels of resistance to a drug
Summary

• HCV makes HIV worse and HIV makes HCV liver damage worse
• HCV is a multisystem disease
• Liver biopsy helps in deciding if you need HCV treatment or not
• HCV is treated with Peginterferon and Ribavirin at present time but many drugs in development
• Future treatment may be less toxic and shorted duration with better success rates!!!
• HIV CAN BE CURED!!!
TO TREAT NOW OR TREAT LATER?

THAT IS THE QUESTION!
Thank you

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