Co-infection with Hepatitis C Virus in Women

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6th International Workshop on HIV and Women
Colonnade Hotel
February 21, 2016
Disclosure Statement for Arthur Kim

Grant/research support from Gilead
Consultant: None
(Updated 2/21/16)

Off-label use: Any mention of antivirals during pregnancy

Funding: National Institutes of Health
(National Institute of Allergy and Infectious Diseases,
National Institute of Drug Abuse)
A tale of two viruses

<table>
<thead>
<tr>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex &gt; Blood</td>
<td>Blood &gt; Sex</td>
</tr>
<tr>
<td>Targets immune cells</td>
<td>Targets hepatocytes</td>
</tr>
<tr>
<td>Years to clinical illness</td>
<td>Decades to clinical illness</td>
</tr>
<tr>
<td>High levels of viremia</td>
<td>High levels of viremia</td>
</tr>
<tr>
<td>$10^9$ particles/day</td>
<td>$10^{12}$ particles/day</td>
</tr>
<tr>
<td>Low fidelity of reverse transcriptase (RNA-DNA)</td>
<td>Low fidelity of RNA-RNA polymerase</td>
</tr>
<tr>
<td>Frequently mutates</td>
<td>Frequently mutates</td>
</tr>
<tr>
<td>1 cure after BMT</td>
<td>&gt;90% Curable</td>
</tr>
</tbody>
</table>
Natural history of HCV

- **Acute infection**: ~20%
- **Chronic infection**: ~80%
- **Viral clearance**: ~20%
- **Cirrhosis**: Stable or slowly progressive
- **Liver failure**: HCC, Death
- **Other liver diseases**: (such as EtOH, NASH)
- **Coinfections**: (HIV, HBV)
HIV associated with higher rates of HCV-related liver fibrosis

Figure 3. Liver fibrosis and age among persons coinfectected with HIV and HCV (dashed line) and those with only HCV (solid line).

32% women
85% A-A

HIV+HCV
HCV

HIV / HCV co-infection is double trouble

Compared to HIV-negative individuals, those with HIV suffer from:

1. Higher rates of persistence (lower rates of spontaneous clearance)
2. Accelerated rate of fibrosis, higher rates of cirrhosis
3. Higher rates of decompensation & higher liver-related mortality

To reduce the burden of HIV/HCV co-infection we must test and cure!
Transmission of HCV: shared risk factors with HIV

- Parenteral
- Perinatal
- Sexual
Sexual transmission of HCV

- Eyster et al. examined 234 female partners of 231 hemophiliacs
  - In females, prevalence HCV 2.6%, HIV 12.8%
  - HCV in females associated with HIV transmission
  - for non-IDU females, HCV associated with sex with male IDU
- Monogamous heterosexual couples with discordant HCV sera: risk is ~1 in 190,000 sex contacts
  - Guidelines do not recommend barriers for discordant monogamous heterosexual couples
    - unless HIV in either partner
- Sexual transmission amongst HIV+ MSM

Rules of 3: risk after needlestick

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>30%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>3% (~1-2%)</td>
</tr>
<tr>
<td>HIV</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Likelihood of HCV infection: duration of IDU

Depends on context: much higher in areas of world without services for PWID

The number of users of heroin has grown over the last decade.

Overdose deaths began to rise sharply in the latter half of the previous decade among young whites. Death rates since 2010 have not yet been compiled.

Source: Centers for Disease Control and Prevention; Substance Abuse and Mental Health Services Administration

Graphic from “Heroin’s Small-Town Toll, and a Mother’s Grief” New York Times, 2/10/2014
Heroin use - shifts in demographics

- In 2012, about 669,000 Americans reported using heroin in the past year, compared to 404,000 ten years earlier.

- In 2011 179,000 new initiates of injecting opiates.

- 4.2 million Americans ages 12 or older (1.6 percent of Americans) have used the drug at least once in their lives.

National Survey on Drug Use and Health (NSDUH), National Institute on Drug Abuse (NIDA), Cicero et al. JAMA Psych 2014
HCV Surveillance in Massachusetts

• In 2002, data suggest a peak age in late 40s of HCV cases
• In recent years, there are ~2000 prevalent cases / yr of HCV annually aged 15-29, all of whom must have had aHCV in past

Source: Onofrey et al MMWR: May 6, 2011 / 60(17);537-541
Perinatal cases of HCV linked to increase of HCV in women of childbearing age

Data from MDPH, courtesy Dan Church

Data as of 13AUG2013 and subject to change
acute HCV is an iceberg

Only the tip is visible

Most cases are symptomatic
Cases not reported or classified (incomplete surveillance)
Cases not recognized (incomplete diagnosis)
Increasing population at risk
Fragmented care of high-risk-groups
HIV/HCV Co-infection Outbreak in the U.S.

135 cases as of report

Investigation triggered by HIV surveillance

Injection of oxymorphone

Multigenerational use of injection drugs

84.4% (114/135) diagnosed with HCV infection

Need for HCV prevention and vaccine!
Take-home messages: epidemiology of HCV / HIV

• Incident cases of HCV are increasing in the U.S. due to opioid use
  • Target HIV prevention to this population
  • More HCV+ women of childbearing age
• For women living with HIV, more susceptible to HCV infection
• Finding acute HCV requires a high clinical suspicion because many underreport or may not be aware of risk
  • React to LFT abnormalities, especially as intervals between patient visits increase
• Yearly anti-HCV testing recommended
Natural history of acute HCV

Factors associated with clearance of virus during acute HCV
- Female
- Young age
- Race (non-African-American)
- Immunocompetence
- Jaundice
- Cell-mediated immunity
- Genes related to the immune system (HLA, interferon-lambda-4)
The Irish and East German anti-D outbreak

Anti-D used to prevent hemolytic disease of newborn

eyearly suspicious cases were not centrally reported

affected women:
400 in 1976-7 in Ireland
1018 in 1978-9 in East Germany

Higher rate of spontaneously clearing the virus (~45-50%)
Natural history of acute HCV: women more likely to spontaneously clear

Estimated HCV viral persistence probabilities (in months) among female and male young injection drug users with HCV infection.

Influence of gender on the natural history of HCV

- Women more likely to spontaneously clear virus
- Fibrosis progression rates tend to be lower in women
- Lower ALT than men
- Believed to be due to estrogen
  - Nulliparity and postmenopausal women higher progression rate, HRT protective
  - HRT associated with lower rates of progression

*Wiese et al. Hepatology 2000*
*Di Martino et al. Hepatology 2004*
Pregnancy’s influence on HCV outcomes

HCV ← Pregnancy

Maternal
- ALTs may improve during pregnancy (?: relaxation of immunity)
- Some studies associate nulliparity with faster fibrosis
- HCV RNA may rise, particularly during 3rd trimester
- Some groups have detected a drop in HCV RNA immediately postpartum

Postpartum surge in immunity and possible effect on HCV titers

Honegger et al. Nature Medicine 2013
HCV’s influence on pregnancy outcomes

HCV → Pregnancy

Maternal
- Occasional studies associated with gestational diabetes, preterm labor, antepartum hemorrhage, inconsistent findings

Infant
- One study of infants born to HCV+ women showed association with low birthweight, small for gestational age, need for assisted ventilation
- Not consistent finding

Studies may be confounded by concurrent drug use

Mother-to-child transmission of HCV

- Rates from mother to child ~ 5% (range quoted 2-8%)
  - HIV/HCV coinfected mothers are higher risk 19% (range 10-35%)
    - Recent systematic review suggests 10% in HIV coinfection
  - Related to magnitude of viral titer
    - Transmission much lower when <10^6 or when HCV RNA negative
  - Possibly increased risk: active injection drug use, premature rupture of membranes
  - Breastfeeding not associated with increased risk of neonatal HCV

- Amniocentesis risk unknown, but advisable to avoid inserting needle through the placenta

Perinatal transmission of HCV

No proven intervention
— Routine C-section not recommended
— Interferon is antiproliferative, effects on fetus unknown
— Ribavirin is teratogenic (category X)
— Newer direct-acting drugs are category B or C but are at times combined with ribavirin

Treat to reduce transmission

<table>
<thead>
<tr>
<th>At Elevated Risk of HCV Transmission* and in Whom HCV Treatment May Yield Transmission Reduction Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men (MSM) with high-risk sexual practices</td>
</tr>
<tr>
<td>Active injection drug users</td>
</tr>
<tr>
<td>Incarcerated persons</td>
</tr>
<tr>
<td>Persons on long-term hemodialysis</td>
</tr>
<tr>
<td><strong>HCV-infected women of child-bearing potential wishing to get pregnant</strong></td>
</tr>
</tbody>
</table>

**Rating:** Class IIa, Level C

*Patients at substantial risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.*

How do OBs do with HCV screening?

• ACOG recommends screening consistent with CDC
• Surveyed 1000+ Fellows
  – 80% providers routinely collect drug use/transfusion histories
  – 49% screened all with history of IDU
  – 35% screened all with blood transfusion before 1992
  – When HCV present,
    – 47% advised against breastfeeding
    – 70% recommended condom use with monogamous partner
• 40%-70% of pregnant HCV+ women reported no risk factor

Mechanisms of accelerated HCV-related fibrosis in HIV

Kim and Chung Gastroenterology 2009
African-American HIV/HCV connected women have improved liver-related survival in WIHS

- African-American women had lower risk of liver-related mortality; not linked to IFN-lambda genotypes

![Graph showing survival rates for different ethnic groups.](Sarkar Hepatology 2012; Sarkar J Viral Hepat 2015)
HIV/HCV coinfection and extrahepatic manifestations

- Increased rates of extrahepatic manifestations such as renal disease, bone disease, cardiovascular disease, neurocognitive disorders

- WIHS:
  - CD4 depletion associated with IL-7 levels in HCV
  - Neuropsychological function impaired in HCV/HIV women compared to HIV
  - Trend (not statistically significant) towards increased carotid intimate thickness in HIV/HCV connected women

- Increased Factor VIII% and D-dimer - ? increased coagulability

HIV/HCV coinfection associated with lower trabecular volumetric bone density in women

- Cross sectional study design; controlled for menopausal status, smoking
- TDF use similar in HIV infected patients
- Trabecular BMD lower but not cortical BMD
- Higher liver fibrosis levels linked to lower score

Lo Re et al. J Infect Dis 2015
Treatment of HCV

“Try jiggling the liver.”
Substantial benefit of SVR, all-cause mortality, liver-related mortality, hepatocellular carcinoma

All cause mortality

Liver-related mortality or OLT

5 year mortality without SVR is ~10%

Hepatocellular carcinoma

Liver failure

Van der Meer et al. JAMA 2012
Evolution of the Treatment for Chronic Hepatitis C

Poynard T et al. Gastroenterology. 2002

IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response
Potential Therapeutic Targets in the HCV Replication Cycle

Translation

HCV RNA

Polyprotein processing

Fusion and uncoating

RNA replication

NS3/4A protease inhibitors

NS5B polymerase inhibitors

NS5A inhibitors

Viral assembly

Transport and release

HCV NS proteins

NS3

NS4B

NS5A

NS5B

CypA

NSSA inhibitors

Courtesy Ray Chung
# Antiviral HCV treatments (FDA-approved as of February 19, 2016)

## Monotherapies
- IFN-2a
- IFN-2b
- PEG-IFN 2a
- PEG-IFN 2b

**PEG-IFN + ribavirin**
- IFN-2a + Ribavirin
- IFN-2b + Ribavirin
- PEG-IFN 2a + Ribavirin*
- PEG-IFN 2b + Ribavirin

**PEG-IFN + ribavirin plus either:**
- Boceprevir (GT1)
- Telaprevir (GT1)
- Simeprevir (GT1)

**In combination with other agents:**
- Sofosbuvir

## Combination Therapies

**Paritaprevir + ritonavir + ombitasvir (FDC) + dasabuvir (GT1)**

**Paritaprevir + ritonavir + ombitasvir (FDC) + (GT4)**

**Simeprevir + Sofosbuvir (GT1)**

**Daclatasvir + Sofosbuvir (GT 1,3)**

**Ledipasvir + Sofosbuvir (FDC, GT1,4,5,6)***

**Elbasvir + Grazoprevir (FDC, GT1,4)**

*approved for HIV/HCV coinfection
HCV versus HIV/HCV, genotype 1 in Clinical Trials
Not head to head comparison

**Graph:**
- SVR Rate
- Treatments: BOC, TLV, SMV (Naive), SMV (Relapser), SMV (Partial), SMV (Null), P/R/SOFx12, SOF/Rx24w
- HCV vs. HIV/HCV

**Data Sources:**
- Antiviral Drugs Advisory Committee Meeting, FDA review, 10/24/13
- C208, C216, C206, C212, HPC3007, Dieterich et al. Clin Infect Disease 2014 (epub ahead of print)
Treatment of HCV

Rapidly shifting paradigms - 2016 and beyond

Ideal regimen:
- High potency
- Little resistance
- Pangenotypic
- Tolerable
- Once daily
- Shorter duration
- Few DDIs
- Lower cost
Pangenotypic regimen - combination of NS5A inhibitor velpatasvir + NS5B inhibitor sofosbuvir

High efficacy of 12 weeks for GT 1, 2, 4-6

VEL/SOF 12 weeks versus SOF/RBV 24 weeks

Error bars represent 95% confidence intervals.

Feld et al. NEJM 2015; Foster et al. NEJM 2015
<table>
<thead>
<tr>
<th></th>
<th>Simeprevir&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Sofosbuvir&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Ledipasvir&lt;sup&gt;3-5&lt;/sup&gt;</th>
<th>Daclatasvir&lt;sup&gt;6,7&lt;/sup&gt;</th>
<th>AbbVie 3D&lt;sup&gt;8-10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>↑ LDV, ↑ ATV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ABT450 ↑; ATV ↑</td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>SIM ↑; DRV ↔</td>
<td>SOF ↑; DRV ↔</td>
<td>↑ LDV, ↔ DRV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑</td>
<td>3D ↓↑; DRV ↓</td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>DCV ↑</td>
<td>ABT450 ↑; LPV ↔</td>
</tr>
<tr>
<td><strong>TPV/r</strong></td>
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<td>No data</td>
<td>No data</td>
<td>No data</td>
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<tr>
<td><strong>EFV</strong></td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>LDV ↓; EFV ↓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↓&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No PK data&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
<td>No data</td>
<td>ABT450 ↑; RPV ↑</td>
</tr>
<tr>
<td><strong>ETR</strong></td>
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<tr>
<td><strong>RAL</strong></td>
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<td>3D ↔; ↑ RAL</td>
</tr>
<tr>
<td><strong>EVG/cobi</strong></td>
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<td>SOF ↑; ELV/cobi ↑</td>
<td>LDV ↑; ELV/cobi ↑</td>
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<td><strong>TDF</strong></td>
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<td>SOF ↔; TFV ↔</td>
<td>LDV ↔; ↑TFV</td>
<td>DCV ↔; TFV ↔</td>
<td>3D ↔; TFV ↔</td>
</tr>
</tbody>
</table>

<sup>a</sup>Watch renal function, TFV levels increased,  
<sup>b</sup>Decrease DCV dose to 30mg QD with ATV, increase DCV dose to 90mg QD with EFV,  
<sup>c</sup>3D + EFV led to premature study discontinuation due to toxicities  
<sup>1</sup>Ouwerkerk-Mahadaven S IDWeek 2012,  
<sup>2</sup>Kirby B AASLD 2012,  
<sup>3</sup>Harvoni package insert,  
<sup>4</sup>German P 15<sup>th</sup> International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy 2014,  
<sup>5</sup>German P, CROI 2015,  
<sup>7</sup>Eley T HIVDART 2014,  
<sup>8</sup>Khatri ICAAC 2014,  
<sup>9</sup>Khatri ICAAC 2014,  
<sup>10</sup>Viekira Pak package insert

Slide Courtesy of J Kiser
HCV Treatment Cascade in HIV-infected patients
UCSD Owen Clinic

Figure 1: HCV cascade of care in HIV-Infected patients following HCV infection diagnosis, UCSD Owen Clinic: 2008-2012

- Total number of patients with access to HIV care with HCV antibody positive (n=748)
  - Chronic active HCV infection with access to HIV care 100% (n=562)
  - Referred for HCV treatment 54% (n=303)
  - Attended at least 1 clinic visit for HCV treatment evaluation 50% (n=283)
  - Final decision made regarding HCV therapy initiation 44% (n=250)
  - Initiated HCV treatment 16% (n=88)
  - HCV cure 7% (n=41)

Cure rates by era

Summary

• Epidemiology
  – Women less likely than men in baby-boomer population
  – **Emerging infection** in young adults, women of childbearing age. Equal gender ratio.

• Natural history of HCV in women
  – Women more likely to spontaneously clear
  – Pregnancy and menopause may affect the course of HCV
  – Liver disease in women generally progresses more slowly than men
  – HIV accelerates liver fibrosis, ? slower in African Americans

• Treatment of HIV/HCV co-infection
  – Equivalent efficacy of regimens thus far in DAA era
  – Treatment most limited by drug interactions & barriers to access
Future directions

• Future directions: HCV among young women
  – Prevention of HCV transmission, including “cure” as prevention
  – Screening of women of childbearing age / Prevention of mother-to-child transmission
  – HIV prevention paramount to avoid outbreaks (Indiana)

• HCV and HIV/HCV coinfected patients
  – Effect of menopause / aging
  – Cure to prevent liver disease progression
  – Does cure prevent extrahepatic manifestations (eg CVD, bone fracture)?