Accessing Approaches to Managing HCV Infection

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Financial Relationships With Commercial Entities

- Dr Kim has no relevant financial affiliations to disclose. (Updated 08/17/17)
- Dr Kim will be discussing off-label use of certain drugs during this presentation. Please consult the prescribing information for full disclosure of approved uses.

Learning Objectives

After attending this presentation, learners will be able to:

- Describe modifiable risks for liver disease progression in HIV/HCV-coinfected individuals
- Optimize choice of antiviral regimens
- Describe rationale for enhanced screening, prevention, and treatment for HCV infection
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>Frequently mutates</td>
<td>Frequently mutates</td>
</tr>
<tr>
<td>1 cure after BMT</td>
<td>HCV &gt;90% curable</td>
</tr>
</tbody>
</table>

HCV deaths exceed those from 60 infectious conditions (death certificate data)

HCV associated with higher rates of HCV-related liver fibrosis
HIV associated with higher rates of HCV-related liver decompensation, even when on ART

Lo Re V et al. Annals of Internal Medicine 2014

HIV / HCV co-infection is double trouble

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

1. Susceptibility to mucosal transmission, higher rates of persistence
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 screen, test, and treat!

Audience Response Question

The greatest need for our practice to eliminate the burden of HCV infection is:

1. Enhanced screening
2. Effective harm reduction / preventive resources
3. Access to staging
4. Knowledge about novel therapies
5. Pharmacy support to review drug-drug interactions
6. Improving no-show rates to HCV-related clinic appointments
7. Capacity to fill out prior authorizations
Incidence, prevalence and sustaining an epidemic

Rising opiate use
Risky sex (HIV/MSM)
Unidentified infection
Lack of prevention services
Barriers to care, access restrictions and cost of treatment
Asymptomatic infection
Unknown serostatus

A perfect storm for sexual HCV transmission: HIV+MSM

Bloody practices
Semen exposure
Other STDs
Sildenafil
Internet

Higher levels of virus in plasma and semen
Immune deficiency, especially at GI mucosa
HCV reinfection incidence among HIV+ MSM

HCV Incidence Rising in a US HIV+ MSM Clinic in San Diego

Higher if crystal methamphetamine use

Heroin nationally

San Antonio, Texas, August 21-23, 2017
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!

"Toolbox" for HCV prevention for PWID

- HCV testing and counseling
- Drug treatment
- Reducing transmission from positive partners
- Vaccine

- Change injecting behavior
- Clean injecting equipment
- Syringes/needles
- "extra"
- Safe injecting locations

- Viral titer testing
- Antiviral treatment

Adapted from Kim Page, UNM

How well do we screen for incident HCV in HIV-clinics?

- Study at 7 U.S. HIV clinics
- Nearly all patients screened at enrollment
- Only half ever screened again
- Repeat screening poor even when ALT is elevated
- Site of care more predictive than reported risk behaviors

- MGH’s rate 4 years ago of HCV Ab within 12 months: 20%
- Increased to 50% by providing performance to each provider

Freiman et al. CID, 2015
Institution of EMR prompt for baby boomers with no prior testing at BIDMC, 2013

HCV Antibody Test Volume Increased after EMR Prompt

HCV in HIV+ MSM

- Screen for high-risk behaviors
  - Bloody practices, exposure to semen
  - Ulcer-genital STDs
- Screen those engaging in high-risk behaviors
  - Yearly antibodies recommended
  - Cost-effective
- React to minor changes in LFTs
  - HCV RNA for seronegative window
  - HCV RNA for re-infections


Audience Response Question

What is the greatest need in your clinic to prevent new cases of HCV?
1. Effective intervention to reduce high-risk sexual behavior
2. Access to substance abuse services
3. Patient awareness
4. Provider awareness
Natural history of HCV

Mechanisms of accelerated HCV-related fibrosis in HIV

San Antonio, Texas, August 21-23, 2017
Coffee tied to lower mortality in French HIV/HCV coinfected patients

- French ANRS HEPAVIH cohort
- n=1035 followed for median 5 years
- deaths (N=77)
  - HCV-related causes 42.8%
  - non-AIDS, non-HCV cancer 11.7%
  - AIDS 10.4%
  - arrest or death
  - Unstable housing 3.7
  - CD4 =< 200 3.2
  - HCV cured 0.2
  - female gender 0.3
  - 1 or fewer EtOH drinks 2.5
  - 3 or more coffee 0.5

Cannabis use neutral for HIV/HCV coinfect ed patients

- Hepatocytes receptors for cannabinoids
  - CB1 - increases inflammation
  - CB2 - decreases fibrogenesis
- Study suggested more steatosis with daily marijuana smoking
  - Canadian study
    - n=690, 53% marijuana smokers, no association with progression to cirrhosis
  - Women Interagency HIV Study
    - n=575, 44% marijuana use, no association with progression to cirrhosis
  - French study HEPAVIH
    - n=703 - decreased insulin resistance

Nonhepatic effects of HCV in HIV

- HCV increased CV risk
- HCV increased stroke risk
- HCV increases renal disease risk
- HCV associated with risk of fractures
- HCV RNA in CSF increased neuroinflammation in HIV patients

Will these effects reverse as HCV is cured?
Audience Response Question

Which of the following 8-week antiviral combinations is >95% effective for all genotypes of HCV infections if applied to never-treated patients without cirrhosis?

A. Sofosbuvir/velpatasvir
B. Ledipasvir/sofosbuvir
C. Glecaprevir/pibrentasvir
D. Simeprevir/sofosbuvir

Treatment of HCV

“First we’re going to run some tests to see how your insurance reacts.”
**Possible combinations of HCV treatments**

then are applied to different viral genotypes

- **PEG IFN**
- **RBV**
- **BOC**
- **SOF**
- **SMV**
- **TLV**

**GT1**
- 77%

**GT2**
- 9%

**GT3**
- 10%

**GT4**
- 4%

**Abbreviations:** GT = genotype; PEG IFN = pegylated interferon; RBV = ribavirin; BOC = boceprevir; TLV = telaprevir; SMV = simeprevir; SOF = sofosbuvir; TLV = voxilaprevir; PIB = paritaprevir; GZR = grazoprevir; GLE = glecaprevir.

**Pharmacologic booster:** r = ritonavir.

**NS5A:**
- **LDV** = ledipasvir
- **VEL** = velpatasvir
- **OBV** = ombitasvir
- **DCV** = daclatasvir
- **EBR** = elbasvir
- **PIB** = pibrentasvir

**NS5B nonnucleoside:**
- **DSV** = dasabuvir

**NS5B nucleotide:**
- **SOF** = sofosbuvir

**Antiviral HCV treatments**

(FDA-approved as of August, 2017)

**Monotherapies**

<table>
<thead>
<tr>
<th>Combination</th>
<th>IFN-2a</th>
<th>PEG-IFN 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG-IFN 2a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **IFN-2a**
- **PEG-IFN 2a**

**In combination with other agents:**

- **Boceprevir** (GT1)
- **Telaprevir** (GT1)
- **Simeprevir** (GT1)

**In combination with other agents:**

- **Sofosbuvir**
  - Ledipasvir (LDV) / Sofosbuvir (SOF) (FDC, GT1,4,5,6)*
  - Paritaprevir / ritonavir / ombitasvir / dasabuvir
  - Daclatasvir (DCV) + Sofosbuvir (SOF) (GT1,3)*
  - Elbasvir (EBR) / Grazoprevir (GZR) (FDC, GT1,4)*
  - Sofosbuvir (SOF) / Velpatasvir (VEL) (FDC, All GTs)*

**Recommended regimens for HIV/HCV-coinfected individuals.**

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections).

**Rating:** Class I, Level B
ledipasvir + sofosbuvir (FDC) 
ION-4 for HIV/HCV

ASTRAL-5: SVR12 rates for 12 weeks of Sofosbuvir/velpatasvir in HIV/HCV

EXPEDITION-2: glecaprevir/pibrentasvir for HIV/HCV co-infected patients
**Baseline Demographics & Disease Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Untreated Cohort</th>
<th>GLECAP/PIB</th>
<th>GLECAP/PIB/IDV</th>
<th>GLECAP/PIB/IDV/DDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 (10)</td>
<td>44 (10)</td>
<td>44 (10)</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>48/52</td>
<td>48/52</td>
<td>48/52</td>
<td>48/52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (22.9-31.0)</td>
<td>27.1 (22.9-31.0)</td>
<td>27.1 (22.9-31.0)</td>
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</tr>
<tr>
<td>CD4 count (cells/µL)</td>
<td>77 (20-490)</td>
<td>77 (20-490)</td>
<td>77 (20-490)</td>
<td>77 (20-490)</td>
</tr>
<tr>
<td>HIV RNA (copies/mL)</td>
<td>37,500 (20,000-150,000)</td>
<td>37,500 (20,000-150,000)</td>
<td>37,500 (20,000-150,000)</td>
<td>37,500 (20,000-150,000)</td>
</tr>
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**Identifying and Managing Interactions**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Increase/Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>ELB ↑, ATV ↑</td>
</tr>
<tr>
<td>DRV/r</td>
<td>ELB ↑, DRV ↑</td>
</tr>
<tr>
<td>LPV/r</td>
<td>ELB ↑, LPV ↑</td>
</tr>
<tr>
<td>TPV/r</td>
<td>ELB ↑, TPV ↑</td>
</tr>
<tr>
<td>ATV/r</td>
<td>GP ↑, ATV ↑</td>
</tr>
<tr>
<td>DRV/r</td>
<td>GP ↑, DRV ↑</td>
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<td>TPV/r</td>
<td>GP ↑, TPV ↑</td>
</tr>
</tbody>
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**Slide courtesy of Jennifer Kiser**

Late 2015: unrestricted access with very rapid uptake in Dutch HIV/HCV coinfection - ~70% treated
• No associated decrease in syphilis or LGV so behavior unlikely explanation
• Indirect evidence of “cure as prevention” for HCV

What were the effects of de-restricting access to DAAIs in the Netherlands?


“Eliminating the public health problem of hepatitis B and C is a bold goal, and reaching it will require more money of prevention and treatment”

National Academies Hep B & C Phase 2 Study Results

Recommendation 5-3: The Department of Health and Human Services should work with states to build a comprehensive system of care and support for special populations with hepatitis B and C on the scale of the Ryan White system.

Attacking the HIV/HCV epidemic

Prevention / harm reduction
Cure as prevention
Screening / testing
Access to Staging
Promote liver health
Drug-drug interactions
Improve capacity and access to curative treatment
Assessing your approach to HIV/HCV co-infection

- Improving cascade of care
  - Prevention and screening for both HIV MSM & PWID
  - Possibility of curing HCV for transmission benefits
  - Removal of restrictions
- Improving liver health
  -- Reduction of alcohol
  -- Coffee potentially beneficial
- Treatment access and capacity
  - Drug interactions: http://www.hep-druginteractions.org
  - Multidisciplinary team
  - Addressing substance use
- Resources
  - Guidelines: http://hcvguidelines.org/
  - IDSA Webinars: http://www.idsociety.org/HCVKN/
    - http://natap.org/
    - http://hivandhepatitis.com/
    - http://www.hepeducation.org/
  - Hepatitis C Online Course: http://www.hepatitisc.uw.edu/
  - Liverpool website for drug interactions:
    - http://www.hep-druginteractions.org/
  - UCSF Hep C Warmline 844-HEP-INFO

The Clinician Consultation Center (CCC) provides expert clinical advice to support clinicians managing patients with hepatitis C (HCV) and/or co-infections such as HIV or substance use disorders. Advice provided is based on federal treatment guidelines, current medical literature, and clinical best practices.

The Clinician Consultation Center is a component of the AIDS Education and Training Centers, located at UCSF and funded by the Health Resources and Services Administration.

Consultation topics include:
- HCV transmission & prevention
- HCV screening & diagnostic testing
- HCV staging & monitoring
- HCV infection & staging
- HCV treatment
- HCV/HIV management strategies
- Prior HCV treatment failure
- HCC/HIV linked disease
- Management of clinical problems— including cirrhosis and anemia
- HCV in pregnancy
• Use the microphones or Q-cards for questions
• If you are participating via the live webcast, please email your questions to RWCCwebcast@iasusa.org