Challenges in the Management and Treatment of HIV/Hepatitis C Virus Coinfection

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Financial Relationships With Commercial Entities

- Dr Kim has no relevant financial affiliations to disclose.
  (Updated 04/15/16)
- In this presentation I will discuss the off-label use of investigational direct-acting agents (velpatasvir/sofosbuvir)

Learning Objectives

After attending this presentation, participants will be able to:

- Describe modifiable risks for liver disease progression in HIV/hepatitis C virus(HCV)-coinfected individuals
- Optimize choice of antiviral regimens
- Describe rationale for enhanced screening, prevention, and treatment of HCV in HIV-infected individuals
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!

The continuum of care in HCV infection in the U.S.
At least 3 million persons infected

Mechanisms of accelerated HCV-related fibrosis in HIV

Kim and Chung Gastroenterology 2009
Fatty Liver and HIV

- HCV (particularly GT3) a risk factor for steatosis
- Increasing appreciation for nonalcoholic fatty liver/NASH in HIV-infected patients (E. Verna, Columbia)

Coffee tied to lower mortality in French HIV/HCV coinfected patients

- French ANRS HEPAVH cohort
- n=1035 followed for median 5 years
- deaths (N=77)
  - HCV-related causes 42.8%
  - non-AIDS, non-HCC cancer 11.7%
  - AIDS 10.4%
- shift for death:
  - unstable housing 3.7
  - CD4 =< 200 3.2
  - HCV cured 0.2
  - female gender 0.6
  - 1 or fewer EtOH drinks 0.5
  - 3 or more coffee 0.5

Nonhepatic effects of HCV in HIV

- HCV increased CV risk in DAD study
- HCV increased stroke risk in co-infected patients
- HCV increases renal disease risk
- HCV associated with risk of fractures in EuroSIDA & Swiss cohort study
- HCV RNA in CSF increased neuroinflammation in HIV patients

Will these effects reverse as HCV is cured?

Borges et al. CROI 2016 Abstract #46; Antinori et al. CROI 2016 Abstract #413; Kovari et al. CROI 2016 Abstract #612; Berenguer et al. CROI 2016 Abstract #639; Clement et al. CROI 2016 Abstract #642
Potential Therapeutic Targets in the HCV Replication Cycle

Translation
- HCV NS proteins
- Polyprotein processing
- NS3
- NS4B
- NS5A
- NS5B

Viral assembly
- Fusion and uncoating
- RNA replication
- CypA
- NS5A
- NS5B
- NS2
- NS3
- NS4B

Transport and release
- NS3/4A protease inhibitors
- NS5A inhibitors
- NS5B polymerase inhibitors
- NS5A inhibitors

Adapted from slide courtesy Ray Chung

Possible combinations of HCV treatments are then applied to different viral genotypes

PEG IFN
- RBV
-BOC
- LED
- DCV
- DSV
- PRV/r
- OBV
- BCV
- ASV
- GZR
- GS

Possible combinations of HCV treatments are then applied to different viral genotypes

PEG IFN
- RBV
- SOF
- TLV
- GT1
- 77%
- GT2
- 9%
- GT3
- 10%
- GT4
- 4%

Antiviral HCV treatments (FDA-approved as of February 12, 2016)

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

Combination Therapies
- Daclatasvir + Sofosbuvir
- Ledipasvir + Simeprevir
- Ledipasvir + Velpatasvir (FDC)
- Ledipasvir + Velpatasvir (FDC, GT1b, 4, 5, 6)*
- Ledipasvir + Simeprevir
- Ledipasvir + Simeprevir (FDC)
- Ledipasvir + Simeprevir (FDC, GT1b, 4, 5, 6)*

*approved for HIV/HCV coinfection
§approved for GT1-decompensated and post
- Paritaprevir/ritonavir/ombitasvir/dasabuvir (FDC, GT1)
- Paritaprevir/ritonavir/ombitasvir/dasabuvir (FDC, GT4)

- Elbasvir + Grazoprevir (FDC, GT1, 4)
- In combination with other agents:
- Sofosbuvir
- Daclatasvir
- Ledipasvir
- Velpatasvir

- Approved for GT1 – decompensated and post
HCV versus HIV/HCV, genotype 1 in Clinical Trials
Not head to head comparison

>90% cure rates for GT1

Extension of therapy beyond 12 weeks may be necessary for cirrhotic patients with GT1a

FDA warning issued regarding rare cases of decompensation in CTP-A cirrhosis
OPTIMIST 1 and OPTIMIST-2
SVR 12 of 12 weeks SMV/SOF by HCV subtype and Q80K
Q80K impacts on cirrhotic patients

SVR12 (%)

0 25 50 75 100

All Naive IFN-exp 1a + Q80K 1a w/o Q80K

SMV SOF RBV +/-

5/6 4/4 4/4 5/6

effect of Q80K

83 99 79 74 92

0 25 50 75 100

All Naive IFN-exp 1a + Q80K 1a w/o Q80K

OPTIMIST-1 Noncirrhotic

OPTIMIST-2 Cirrhotic

150/155 112/115 38/40 44/46 68/70 86/103

C-EDGE: RBV and nucleoside/nucleotide sparing 12-week regimen for genotype 1/4/6 HCV infection

% SVR12

0 25 50 75 100

All Patients GT 1a GT 1b GT 4 GT 6

Treatment naive Mean age 52 46% women 37% nonwhite 22% cirrhosis

Serious AE n=12, none drug-related

EBR/GZR - impact of RAVs

Effect of RAVs on specific baseline positions on likelihood to achieve SVR (Tables 7 and 8)

<table>
<thead>
<tr>
<th>Baseline Position</th>
<th>RAVs</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>


Mean age 52
46% women
37% nonwhite
22% cirrhosis

Serious AE n=12, none drug-related
EBR/GZR - impact of RAVs

Cirrhosis impact on SVR rates for 12 weeks of EBR/GZR

EBR/GZR - C-SURFER established safety and efficacy in patients with CKD stage 4-5
Summary of SVR rates for HIV/HCV

<table>
<thead>
<tr>
<th>Time</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 wk, GT1,4</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>12 wk, GT1,6</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>12-24 wk, GT1,4</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>12 weeks, GT2</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

ledipasvir + sofosbuvir (FDC)
ION-4 for HIV/HCV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Native or Experienced</th>
<th>Carbohydrate Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOV/SDV</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>LOV/SDV</td>
<td>12 patients</td>
<td>15%</td>
</tr>
</tbody>
</table>

Tenofovir Exposures

- TFV exposures are higher when TDF is coadministered with LDV/SOF compared to without LDV/SOF
- Compared to the range of TFV exposures with available safety data
- For NNRTIs: TFV exposure fell within the range
- For RTV-boosted PIs: TFV exposures partially exceeded the range

N = 30
15
17
14
12
24
23
24
23
Scorecard of ARV compatibility with combination DAAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efavirenz</th>
<th>Darunavir</th>
<th>Ledipasvir</th>
<th>Ritonavir</th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>TPV/r</th>
<th>EFV</th>
<th>RPV</th>
<th>TDF</th>
<th>QAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDI</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CAT 1</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
<td>No DDI</td>
</tr>
<tr>
<td>CAT 2</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
<td>Potential</td>
</tr>
<tr>
<td>CAT 3</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>CAT 4</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
<td>Unknown interaction</td>
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</tr>
</tbody>
</table>

Drug-Drug Interactions remain important for

- CAT 1 = no DDI
- CAT 2 = potential, may require dose reduction or monitoring
- CAT 3 = contraindicated
- CAT 4 = unknown interaction

Certain safety issues regarding regimens for HCV genotype 1

- Renal: Non-renal metastases
  - Monitor renal function
  - Avoid high doses with certain medications
  - Frequent cases of symptomatic kidney failure
  - GS-331007

- Monitoring: AST/ALT increases ~8 weeks
  - GS-331007

- C-T-P-B-C
  - C: Child Turcotte Pugh A
  - T: Tenofovir levels with certain antiretrovirals
  - P: Rare cases of symptomatic bradycardia
  - B: Child Turcotte Pugh A - scattered reports of hepatotoxicity/decompensation
  - C: Ribavirin frequently used

- Ribavirin: Increased bilirubin, especially in East Asians
A menu of options

A menu of options

Potential Therapeutic Targets in the HCV Replication Cycle

Treatment of HCV

Notice: The consumption of raw or undercooked eggs, meat, poultry, seafood or shellfish, and certain combinations are not approved by the FDA for Hepatitis C. Please ask your server whether Ribavirin is suggested.

Due to regulations, no alcohol will be served.

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Potential Therapeutic Targets in the HCV Replication Cycle

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Notice regarding protease inhibitors: boceprevir and telaprevir will no longer be offered due to high calories, dysgeusia and/or allergic reactions.

Merck Medley (nuc-free option)

12 weeks of sous-vide grazoprevir topped with fresh elbasvir salsa

Bristol-Myers Squab

12 weeks of grilled asunaprevir marinated in daclatasvir with beclabuvir Béchamel sauce

Gilead Goose

6 weeks of GS-9857, pan-seared topped with velpatasvir flakes on a sofosbuvir backbone

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Response rates for pangenotypic regimen in development: Genotypes 1-6

- 12 weeks for GT1, 2, 3, 4, 5, 6
- 100% compensated cirrhosis
- No cirrhosis

- SVR 12
  - GT3
    - 38/39 (97%)
    - 93/93 (100%)
    - 91/91 (100%)
  - No cirrhosis
    - 99/100 (99%)

- Emergent results as of June 2016

8 week arms of phase II trial using 3 arms at 100 mg VEL dos (81-88%)


Pangenotypic regimen - velpatasvir / sofosbuvir

drug-drug interactions

- Evaluation of DDIs between SOF/VEL and:
  - EFV/FTC/TDF
  - RPV/FTC/TDF
  - DTG
  - RAL/FTC/TDF

- No effect on SOF exposures
- No effect on ARV levels

Mogalian et al. CROI 2016 Abstract #100

Incidence, prevalence and sustaining an epidemic

- Rising opiate use
- Lack of prevention services
- Asymptomatic infection
- Unknown serostatus
- Barriers to care, access restrictions and cost of treatment

Health
- Cures
- Obtaining patients to care
- Access
- Prevention and treatment
- Treatment and care
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!

Treatment of recently active PWID with elbasvir/grazoprevir; on opiate agonist therapy, made 80% appointments

A perfect storm for sexual HCV transmission

- Bloody practices
- Semen exposure
- Other STDs
- Sildenafil
- Intral
- Crystal methamphetamine

--Higher levels of virus in plasma and semen
--Immune deficiency, especially at GI mucosa
How do we screen for incident HCV among HIV-infected?

- 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 2 years ago of HCV Ab within last year: 20%

Freeman et al. CID, 2015

6 weeks of LDV/SOF achieved high SVR rates in acutely infected HIV+ MSM

85% SVR rate (22/26) - 3 relapses occurred in patients with HCV RNA > 9,000,000 IU/mL at initiation
**HIV/HCV coinfection**

- Novel interferon-free and ribavirin-free paradigms
  - Potent combinations can overcome prior barriers (e.g. cirrhosis, IFN-treatment experience)
  - Drug-drug interactions remain for HIV/HCV co-infection
  - 12 week regimens available for many patients
- Special populations
  - CKD stage 4/5, decompensation, acute disease
- Improving cascade of care
  - Prevention and screening
  - Possibility of curing HCV for transmission benefits
  - Removal of restrictions