ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals
Epidemiology & Pathogenesis of HCV 2016
Focusing on HIV and Co-morbidities

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Learning Objectives

• Identify who is at risk for HIV/HCV co-infection and HCV re-infection
• Recognize co-factors and co-morbidities that contribute to liver disease progression in HIV/HCV co-infection which are amenable for intervention
• Appreciate the emerging need for HCV treatment in co-infected populations
Is HIV infection still an important consideration for persons infected with HCV in the era of effective treatments for HCV?

1. Yes
2. No
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-o81fsx
Estimated numbers of Co-infected persons (worldwide)

Canada: 30% HIV+ (est. 12-15,000) co-infected*

USA: 25% HIV+ (est. 12-15,000) co-infected**

Sources: *Public Health Agency of Canada, 2011; ** CDC 2014
Global prevalence of HIV-HCV Co-infection

% HIV+ persons co-infected with HCV

Peters & Klein  Curr Opin HIV/AIDS, 2015
HCV in Young Nonurban Injection Drug Users

- Rising rates of HCV infection among young adults who started prescription opioid use before transitioning to heroin injection

Massachusetts – changing epidemiology of HCV; MMWR May 6, 2011
HCV is a sexually transmitted disease among HIV-infected MSMs

- 74 HIV-positive MSM diagnosed with recent HCV between 2005 and 2010
  - No IDU
  - Antiretroviral therapy, 74%
  - HCV associated with receptive anal intercourse (AOR: 23) and sex while on methamphetamine (AOR: 29)
- NS5B sequences were obtained in 50 men
  - Phylogenetic analysis revealed 5 clusters of genotype 1a

Incidence of HCV in HIV-infected MSM from 12 cohorts within CASCADE

Fierer DS et al. MMWR July 22, 2011; van der Helm JJ et al. AIDS 2011
Saskatchewan: An Emerging Epidemic

HIV Cases by Selected Self-reported Ethnicity in Saskatchewan, 2000 to 2009

Ministry on Health - PHB, 2010
Public Health Agency of Canada, 2009
The Canadian Coinfection Cohort 2003-2015 (n=1595)

Cohort Demographic Information
- Aboriginal Female
- Non-aboriginal Female
- Aboriginal Male
- Non-aboriginal Male

Risk Factors for HCV
- IDU ever
- MSM
- Blood
- Other

British Columbia
A - Oak Tree (n=101)
B - Pender (n=207)
E - BCCFE (n=109)
U - Native BC (n=63)

Alberta & Saskatchewan
G - South Alberta Clinic (n=47)
F - Regina (n=113)
X - Saskatchewan (n=19)

Ontario
J - Windsor (n=30)
M - McMaster (n=59)
R - Sunnybrook (n=19)
S - Sudbury Haven (n=83)
T - Toronto General (n=112)
W - Ottawa (n=63)

Quebec & Nova Scotia
K - Montreal Chest Institute (n=189)
C - Montreal General (n=52)
H - Quartier Latin (n=16)
N - Notre Dame (n=262)
Q - Quebec (n=38)
H - Halifax (n=15)
Canadian Coinfection Cohort, unpublished
Burgeoning Epidemic of Liver disease

The number of patients with cirrhosis will peak in the next 7-10 years

- In US, 3.2 million people with chronic HCV
  - 50% diagnosed
  - ~170,000 – 200,000 cured
  - >450,000 may get insurance between 2014 and 2020

- Without changes to historical diagnosis and treatment paradigm, annual medical costs expected to rise to $85 billion in 5 years

Holmberg NEJM, 2013
Mortality from Chronic HCV

Mortality Rates of HBV, HCV, HIV: United States, 1999 – 2007\(^1\)

Predictions for HCV Mortality: United States\(^2\)

\(^1\)Ly KN. Ann Intern Med 2012

\(^2\)Rein RB. Dig Liver Dis 2011
Mortality in the Canadian Co-infection Cohort 2005-2015

SMR: 12.1 (95% CI: 10.1, 14.2) overall
9.3 (95% CI: 7.5, 11.1) for men
19.4 (95% CI: 12.7, 26.2) for women

Klein et al. HIV Medicine, 2012 and submitted

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESLD</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>OVERDOSE</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>CANCER</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>AIDS</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>CVD</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Trauma/suicide</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>178</td>
<td>100</td>
</tr>
</tbody>
</table>
Cause Specific Event Rates by Period and Baseline Age

Canadian Coinfection Cohort, unpublished
Which of the following interventions will have the MOST impact on preventing ESLD in HIV/HCV co-infected?

1. HIV Treatment
2. Lifestyle modification (e.g. reduction of alcohol, smoking, drug use)
3. Management of insulin resistance
4. HCV Treatment
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/spn77sui
ART IS NOT ENOUGH
Hypothetical multifactorial progression of liver disease in aging HIV mono-infected populations

- **Normal**
- **Steatosis/Fibrosis**
- **NASH or Significant Fibrosis**
- **Cirrhosis**
- **HCC**

**Metabolic risk factors**
- Abdominal obesity
- Insulin resistance
- Diabetes
- Menopause

**HIV-related risk factors**
- HIV viral load
- Pro-apoptotic effect of HIV on hepatocytes

**Prolonged cART use**
- Lipodystrophy
- Hepatotoxicity
- Insulin resistance

**Aging HIV**

**Patient related-risk factors**
- Age / Gender
- Excessive Alcohol
- Elicit Drugs

Sebastiani, unpublished
HCV disease progression remains faster in HIV infected patients -- despite effective ART

- If HIV RNA < 1000 copies/mL: +65% excess risk
- If HIV RNA > 1000 copies/mL: +82% excess risk
- If CD4 < 200/mm²: +203% excess risk
- If CD4 > 200/mm²: 56–63% excess risk

## Baseline Characteristics: NA-ACCORD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No ESLD N=33739</th>
<th></th>
<th>ESLD N=380</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>26,559</td>
<td>79%</td>
<td>325</td>
<td>86%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13,763</td>
<td>41%</td>
<td>186</td>
<td>49%</td>
</tr>
<tr>
<td>Black</td>
<td>11,955</td>
<td>35%</td>
<td>122</td>
<td>32%</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>8,021</td>
<td>24%</td>
<td>72</td>
<td>19%</td>
</tr>
<tr>
<td>History of injection drug use</td>
<td>4,842</td>
<td>14%</td>
<td>109</td>
<td>29%</td>
</tr>
<tr>
<td>Hepatitis C infection</td>
<td>3,741</td>
<td>11%</td>
<td>102</td>
<td>27%</td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td>1,177</td>
<td>3%</td>
<td>43</td>
<td>11%</td>
</tr>
<tr>
<td>CD4 &lt;200 cells/mm³</td>
<td>8,646</td>
<td>26%</td>
<td>146</td>
<td>38%</td>
</tr>
<tr>
<td>HIV RNA ≥500 copies/mL</td>
<td>18,620</td>
<td>55%</td>
<td>226</td>
<td>59%</td>
</tr>
</tbody>
</table>

Klein et al. CROI Seattle 2015. Presentation #638 and submitted
Incidence rates (95% CI) of ESLD by Hepatitis Status & ART Era NA-ACCORD

Klein et al. CROI Seattle 2015. Presentation #638 and submitted
START Study implications

• Median baseline CD4 647 [583,758] cells/ul
• HCV co-infected: 14%; HBV co-infected: 11%
• Median liver stiffness measure: 4.9 kPa; 8% > 7.2
• Baseline factors associated with fibrosis:
  – HCV infection, alcohol in univariable analyses
  – HIV RNA, ALT and Hispanic/Latino ethnicity but NOT HCV or Alcohol in MVA
• Is this inflammation or fibrosis?
• Will Early ART change rate of progression?
Progression of Liver Fibrosis and Modern Combination Antiretroviral Therapy Regimens in HIV-Hepatitis C–Coinfected Persons

CCC participants
N=1321

- No chronic HCV infection (n=216)
- Not on 1st anchor class (n=334)
- On HCV treatment (n=23)
- Not on PI or NNRTI (n=192)
- Not on recommended backbone (n=177)
- Not on 1st line anchor agent (n=21)
- Hepatitis B infection (n=8)

Unmatched sample
N=348

- Unmatched NNRTI users (n=9)
- Unmatched PI users (n=25)

Matched sample
N=314
N=628 including repeats

Median rates of change in APRI score per 5 years by regimen

- PI + ABC/3TC: 1.16 (1.04, 1.29)
- PI + TDF/FTC: 1.03 (0.93, 1.12)
- NNRTI + ABC/3TC: 1.11 (1.02, 1.20)
- NNRTI + TDF/FTC: 1.08 (0.97, 1.19)

Significant liver fibrosis

Brunet Clin Inf Dis, 2016
Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/hepatitis C virus-coinfected patients

Mark W. Hull\textsuperscript{a}, Kathleen Rollet\textsuperscript{b}, Erica E.M. Moodie\textsuperscript{c}, Sharon Walmsley\textsuperscript{d}, Joseph Cox\textsuperscript{c,e}, Martin Potter\textsuperscript{f}, Curtis Cooper\textsuperscript{g}, Neora Pick\textsuperscript{b}, Sahar Saeed\textsuperscript{b}, Marina B. Klein\textsuperscript{b}, the Canadian Co-infection Cohort Study Investigators

Adjusted HR: 7.33 (95\% CI 2.55–23.36)
Marijuana Smoking Does Not Accelerate Progression of Liver Disease in HIV–Hepatitis C Coinfection: A Longitudinal Cohort Analysis

Laurence Brunet,1 Erica E. M. Moodie,1 Kathleen Rollet,2 Curtis Cooper,3 Sharon Walmsley,4 Martin Potter,2 and Marina B. Klein,2 for the Canadian Co-infection Cohort Investigators

Table 3. Effect of Marijuana Smoking on Progression of Liver Diseases

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI ≥ 1.5</td>
<td>10 joints/wk, current&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.02 (0.93, 1.12)</td>
</tr>
<tr>
<td></td>
<td>Lagged exposure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.95 (0.85, 1.07)</td>
</tr>
<tr>
<td>APRI ≥ 2</td>
<td>Current exposure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.99 (0.88, 1.12)</td>
</tr>
<tr>
<td></td>
<td>Lagged exposure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.96 (0.85, 1.10)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Current exposure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.33 (1.09, 1.62)</td>
</tr>
<tr>
<td></td>
<td>Lagged exposure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.12 (0.94, 1.34)</td>
</tr>
<tr>
<td>ESLD</td>
<td>Current exposure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.08 (0.90, 1.28)</td>
</tr>
<tr>
<td></td>
<td>Lagged exposure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.07 (0.85, 1.34)</td>
</tr>
<tr>
<td>Cirrhosis or ESLD</td>
<td>10 joints/wk, current&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.13 (1.01, 1.28)</td>
</tr>
<tr>
<td></td>
<td>Lagged exposure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.10 (0.95, 1.26)</td>
</tr>
</tbody>
</table>
THE POTENTIAL OF HCV TREATMENT
HCV cure is associated with survival in HIV/HCV coinfected patients

Limketkai et al. JAMA 2012
Metanalysis: Long term outcomes after SVR

Figure 1. Five-year mortality rates (95% confidence interval) for sustained virologic response (SVR) vs non-SVR groups for each cohort.

Simmons et al Clin Inf Dis 2015
Quality of Life (EQ5D)
SVR-achievers increase and plateau above baseline scores

SVR was significantly associated with improved VAS scores at one year (+11.4 units (95% CI: 2, 21))

Yeung et al. HIV Clin Trials 2015
Figure 6b: Proportion of patients reporting substance use over time

At cohort entry, before treatment (Pre-tx), six months and one year after treatment comparing SVR-achievers and non-responders.
Advanced Liver Fibrosis (FIB-4 ≥ 3.25), By Level of Alcohol Use and HIV/HCV

Prevalence of Advanced Fibrosis

Odds Ratio of Advanced Fibrosis

Lim JK. Clin Infect Dis 2014
Regression of liver fibrosis despite alcohol

SVR remained significantly associated with APRI improvement after adjusting for baseline APRI and alcohol use 6 months (-0.4; 95% CI: -0.7, -0.2) and 1 yr post-treatment (-0.6; 95% CI: -1.1, -0.2).

Yeung et al. HIV Clin Trials 2015
Risk of Re-Infection or Late Relapse

5-year cumulative risk: 21% (95% CI: 13%, 34%)

Overall incidence rate: 18 events / 443 PYFU = 4.1 per 100 PY (95% CI: 2.6, 6.4)

Rossi et al 2015, accepted for presentation
Among HIV+ MSM

HCV Reinfection Incidence

Second reinfection: 23.2 per 100 py (95% CI 11.6-43.4 per 100py)

Overall reinfection rate
Reinfection post-treatment
Reinfection post-spontaneous clearance
Second reinfection rate

Kaplan-Meier survival estimates

Martin, IAS 2013: 7th IAS Conference on HIV Pathogenesis Treatment and Prevention
June 30 - July 3 2013 Kuala Lumpur, Malaysia
Who to target within PWID populations

**INFECTION PREVENTION**
- Risk of HCV transmission

**LIVER DISEASE BURDEN REDUCTION**
- Risk of liver-related morbidity and mortality

Years of age

**Results**

A. Incidence at 10 years (100 PY)

B. RNA-prevalence at 10 years (%)

Scenario

**S4:** Improve adherence to treatment

**S5:** Improve treatment initiation rate to 10%/y

**S6:** Improve treatment initiation rate to 20%/y

**S7:** Combined scenario: S2 & S3 & S4 & S6

Anthony Cousien, IAS Vancouver 2015
5g of diamonds
25 1-carat ($1900 each)
Cost = $48,000

5g of daclatasvir
12 weeks of treatment, 60mg/day
Cost = $53,000 (UK price)

Andrew Hill
2nd International Coinfection Meeting
Vancouver July, 2015
Audience Question #3

• In 10 years, what will be the most important factor leading to end-stage liver disease in HIV co-infected patients?
  1. HIV
  2. HCV
  3. NAFLD
  4. Alcohol
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/splk1a2y
Take Home Points

• Reducing liver disease in HIV-HCV coinfectected persons will require a comprehensive and targeted approach
  – Early use of HIV treatment
  – Screen for HCV and stage for treatment
  – Dramatically increase number of patients receiving HCV therapy
  – Aggressively deal with contributing co-morbidities especially alcohol use
  – Identify new interventions to reduce harm from NAFLD
Acknowledgments

- The participants of HIV-HCV Canadian Cohort (CTN 222)
- The study coordinators and nurses
- Sahar Saeed
- Visit us at www.cocostudy.ca
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