Treatment in Special Clinical Populations

Jordan J. Feld MD MPH

Toronto Centre for Liver Disease
Sandra Rotman Centre for Global Health
University of Toronto
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
Impact of HIV on HCV Infection

- Decreased clearance of acute infection (5% to 10%)
- Increased HCV RNA level
- Increased liver disease progression → cirrhosis, ESLD
- Increased ART-associated hepatotoxicity
- Decreased response to HCV therapy
- No impact of HCV on HIV progression, ?
  Increased hepatotoxicity with ARVs
GESIDA Cohort: SVR Reduces Risk of Liver-Related Morbidity and Mortality

Rate/100 Person-Years (95% CI)  

<table>
<thead>
<tr>
<th>Event</th>
<th>No SVR</th>
<th>SVR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.12 (2.16-4.37)</td>
<td>0.46 (0.06-1.65)</td>
<td>0.003</td>
</tr>
<tr>
<td>Liver-Related Death</td>
<td>1.65 (0.98-2.61)</td>
<td>0.23 (0.01-1.27)</td>
<td>0.028</td>
</tr>
<tr>
<td>Liver Decompensation</td>
<td>4.33 (3.16-5.80)</td>
<td>0.23 (0.01-1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCC</td>
<td>0.83 (0.38-1.58)</td>
<td>0 (0-0.84)</td>
<td>0.099</td>
</tr>
<tr>
<td>Liver Transplantation</td>
<td>1.02 (0.50-1.82)</td>
<td>0 (0-0.84)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

N = 711 HCV/HIV patients

*P<0.05.

Similar data in mild fibrosis

Berenguer J AIDS Jul 2014
SVR=Benefits beyond the liver

1599 patients treated with P/R – 629 (39%) SVR

A

All Deaths

SVR

Non-SVR

Follow-up, mo

0 12 24 36 48 60 72 84 96

P<0.001

B

Liver-related Deaths

SVR

Non-SVR

Follow-up, mo

0 12 24 36 48 60 72 84 96

P<0.001

C

Non-Liver-related Deaths

SVR

Non-SVR

Follow-up, mo

0 12 24 36 48 60 72 84 96

P=0.002

D

Non-Liver, Non-AIDS-Related Deaths

SVR

Non-SVR

Follow-up, mo

0 12 24 36 48 60 72 84 96

P=0.007
Slow but steady progress

- Fixed dose RBV
- Weight-based RBV
- Direct Acting Antivirals

- G2/3 needs 48 wks
- EVR 100% NPV
- 72 wks not well tolerated

Martel-Laferriere J Clin Gastro 2014
Protease Inhibitors + Peg/ RBV in HIV-HCV co-infection

HIV-HCV Co-infection

- BOC/PR: 63%, 41/64
- TVR/PR: 74%, 28/38
- SIM/PR: 79%, 42/53

HCV Alone

- BOC/PR: 63%
- TVR/PR: 75%
- SIM/PR: 80%

Can you see the difference?
SOF/PR x 12 weeks for G1 Trt-naive

**NEUTRINO Single-Arm Study in HCV Monoinfection: SVR12**

- **HCV alone**
  - Overall: 90/295 (n/N = 295/327)
  - GT1: 89/261 (n/N = 261/292)

**P7977-1910 Single-Arm Study in HCV/HIV Coinfection: SVR12**

- **HIV-HCV**
  - GT1: 89/17 (n/N = 17/19)
  - GT1a: 87/13 (n/N = 13/15)
  - GT1b: 100/4 (n/N = 4/4)

HIV/HCV co-infection looking more and more like HCV monoinfection

Lawitz NEJM. 2013
PHOTON-1: Sofosbuvir + RBV in GT1-3 HCV Patients Co-infected With HIV

<table>
<thead>
<tr>
<th>HIV/HCV</th>
<th>HCV Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1: 76%</td>
<td>68%</td>
</tr>
<tr>
<td>GT2: 88%</td>
<td>97%</td>
</tr>
<tr>
<td>GT3: 67%</td>
<td>56%</td>
</tr>
<tr>
<td>GT2: 92%</td>
<td>97%</td>
</tr>
<tr>
<td>GT3: 94%</td>
<td>77%</td>
</tr>
</tbody>
</table>

ARVs: PI/NNRTIs/Integrase Inhibitors

- Cirrhosis 4-24%

- Similar results PHOTON-2 study
- AASLD Recommends: G2 12 weeks, G1 and G3 24 weeks

Sulkowski MS JAMA. 2014
What about the new agents?

**SOF/LDV x 12 wks G1 HIV-HCV**

<table>
<thead>
<tr>
<th></th>
<th>ARV</th>
<th>No ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR4/12 (%)</td>
<td>100</td>
<td>100*</td>
</tr>
<tr>
<td>n/N</td>
<td>37/37</td>
<td>13/13</td>
</tr>
</tbody>
</table>

**Paritaprevir/r + ombitasvir + dasabuvir + RBV (3D + RBV) x 12 or 24 weeks**

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR4/12 (%)</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>n/N</td>
<td>29/31</td>
<td>31/32</td>
</tr>
</tbody>
</table>

Highly effective – only issue is drug-drug interactions

Osinusi EASL + AASLD 2014
Sulkowski AIDS 2014
Summary HIV-HCV

- HIV worsens HCV-related liver disease
- Liver disease major cause of mortality for HIV-infected individuals
- Reduced response to PegIFN
- DAAs, even with PegIFN, are making HIV no longer a special population
- Drug interactions still an issue
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
CHC & Renal Disease

- Increased risk → very high prevalence in HD populations
  - Industrialized countries mean 13.5%
  - Developing countries up to 70%
- Increased risk of chronicity with exposure
- Lower ALT
  - Must continue to screen for HCV over time – ongoing transmission risk
  - Fibrosis assessment important (non-invasive)
- Transplant may accelerate fibrosis progression BUT better outcomes than staying on HD

Chacko PMJ 2010
Peg/RBV Therapy: An RCT

Peg2a 135 µg/wk + RBV 200 mg/d (n=103) vs Peg2a alone (n=102) x 48 wks

- Change in Hemoglobin

  Peg/RBV
  Peg alone

Hb<8.5 g/dL: 72% vs 6%
DC for AE: 7% vs 4%

- SVR: 64% combo vs 33% mono
- Can be done in experienced centres

Liu Ann Int Med 2013
What about DAAs?

- Small numbers of patients treated with telaprevir/boceprevir
  - Significant anemia
  - Apparently reasonable rates of SVR
  - Very limited data

- New DAAs
  - **Sofosbuvir**: Metabolite accumulates – unknown significance
    - Should not be given to patients with GFR<30 mL/min yet
  - **Simeprevir**: Not renally cleared, likely not cleared by HD
  - **Paritaprevir/r/Ombitasivr + Dasabuvir (3D)** – Safe with mild/moderate or severe renal impairment (AASLD 2014)
  - Others – ongoing studies…

IFN-free, RBV-free therapy holds great promise
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
Low escalating dose of Peg/RBV in cirrhosis

124 pts treated with low escalating dose of PR

- Very low success rate, significant toxicity
- Therapy contraindicated in CPT-B/C

- 36 (29%) full dose & duration
- 22 SAEs
  - 21 CPT B/C
  - 4 deaths
How about with DAAs?
## Real-World Safety Findings

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Telaprevir n=296</th>
<th>BOC n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (SAEs)*</td>
<td>144 (48.6%)</td>
<td>61 (38.4%)</td>
</tr>
<tr>
<td>Premature discontinuation Due to SAEs</td>
<td>77 (26.0%)</td>
<td>38 (23.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>43 (14.5%)</td>
<td>12 (7.4%)</td>
</tr>
<tr>
<td>Septicemia, Septic shock, Pneumopathy, Oesophageal varices Bleeding, Encephalopathy, Lung carcinoma</td>
<td>6 (2.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Infection (Grade 3/4)</td>
<td>26 (8.8%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>20 (6.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4 (SCAR)</td>
<td>13 (4.4%)</td>
<td>7 (4.4%)</td>
</tr>
<tr>
<td>Blood Transfusions</td>
<td>45 (15.2%)</td>
<td>17 (10.7%)</td>
</tr>
</tbody>
</table>
## Predictors of Severe Complications

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count ≤100,000/mm³</td>
<td>3.11</td>
<td>1.32-7.73</td>
<td>0.0098</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L</td>
<td>6.33</td>
<td>2.66-15.07</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Death, severe infection and hepatic decompensation, n=32 (6.4%)
All Oral Therapies

• CPT-A
  – Response rates fairly similar to non-cirrhotic
  – Longer duration needed for cirrhotic, treatment-experienced
  – Safety, tolerability remarkably good

What about CPT-B & C?
Decompensated cirrhosis

SOF + RBV x 48 wks vs observation

### Clinical Events, n

<table>
<thead>
<tr>
<th></th>
<th>Ascites</th>
<th>Hepatic Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF + RBV (n = 25)</td>
<td>Observation (n = 25)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Week 12</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Week 24</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

- Will SVR really benefit these patients?
- Is there a point of no return...

Afdahl et al EASL 2014 Abst 68
Hopefully this is not the future...

SVR but far from cured...
Treatment pre-transplant for HCC (low MELD)

Curry MP, et al. Gastroenterology In Press

Days With HCV RNA Continuously TND Prior to Liver Transplant

- > 30 days TND
- No Recurrence (n = 28)
- Recurrence (n = 10)

SOF + RBV x up to 48 wks

Median days undetectable
- No recurrence: 95
- Recurrence: 5.5
  \((P < .001)\)

Only 1 of 24 with HCV RNA neg > 30 days with recurrence
Life Saving Therapy

Fibrosing Cholestatic Hepatitis Diagnosed 2 Mo After OLTx

- LT: TE 17 kPa, Ascites
- No Ascites: TE 9.6 kPa

HCV RNA: 541,000,000 IU/mL

Bilirubin normalized at Wk 9.

After LT: SOF + RBV Treatment

Treatment Post-Transplant

SOF/RBV x 24 wks post OLTx

- SVR4/12 (%): 70
- n/N = 28/40
- 40% cirrhosis
- 83% G1
- 88% prev Trt

Paritaprevir/r/Ombitasivr + Dasabuvir + RBV x 12 wks post OLTx

- SVR4/12 (%): 96
- n/N = 25/26
- **DDIs

More data at AASLD...

Charlton Gastro In Press
Kwo EASL 2014
Cirrhosis & Peri-transplant

• **CPT-A**
  – High efficacy & safety
  – May need longer duration
  – Lots more data at AASLD…

• **CPT-B/C**
  – Good on-treatment responses…long-term data unclear
  – Benefit needs to be proven

• **Pre-transplant**
  – Suppression can prevent re-infection

• **Post-transplant**
  – Can be life-saving (FCH)
  – DDIs but otherwise looks good
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
Hemoglobinopathies

• High prevalence
  – Multiply transfused
• No data but really RBV is the only issue
• Likely to disappear as a ‘special population’ wherever IFN-free and RBV-free therapy available
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemoglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, aboriginals, incarcerated)
HCV in the Elderly

• Many unaware until present with advanced disease
• Will find more HCV with screening initiatives

More than 75 percent of American adults with hepatitis C are baby boomers
Not all elderly are the same

- Must consider the whole patient
- How relevant is HCV to overall health?
CHC in the Elderly

Favour Treatment
- Healthy – few con meds
- Advanced fibrosis
- Extra-hepatic HCV
- Access to IFN-Free option

Favour No Treatment
- Co-morbidities
  - Renal impairment
  - Anemia
- Mild fibrosis
- ? Previous failed therapy
IFN-based Therapy in the Elderly

- Low uptake, high D/C rates, slightly lower SVR
- **HCV-TARGET (1st gen PIs)**
  - 73 over age 65: 17 BOC & 56 TVR
  - Similar rates of treatment completion and SVR
Limited data with new therapies

- Relatively few patients over 65 in trials
  - 90 in SOF Phase 3 trials
  - No apparent difference in tolerability or SVR
  - Appears true with other regimens as well

- Clearly need more data

- DDIs likely the major issue

- Balance individual vs. societal benefit (cost)
Special Clinical Populations

- HIV-HCV co-infected
- Renal impairment
- Cirrhosis
- Peri-transplant
- Hemiglobinopathies
- Elderly + Comorbidities
- Marginalized populations (PWID, Aboriginals, incarcerated)
Marginalized populations

• Treatment success similar
• But…
  – Diagnosis rate low
  – Treatment access low
  – Treatment acceptance low (may be changing…)
  – Treatment coverage low
• Lots of ‘excuses’
  – Re-infection
  – Non-adherence
  – “Self-inflicted” disease…
HCV is a disease of the marginalized

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug users &gt; 10 yrs of use</td>
<td>90%</td>
</tr>
<tr>
<td>Injection drug users &lt; 10 yrs of use</td>
<td>50%</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>35%</td>
</tr>
<tr>
<td>Prisoners</td>
<td>29%</td>
</tr>
<tr>
<td>Severely mentally ill people</td>
<td>19%</td>
</tr>
<tr>
<td>Hospital patients</td>
<td>17%</td>
</tr>
<tr>
<td>African-American men 50–59 yrs</td>
<td>14%</td>
</tr>
<tr>
<td>US population</td>
<td>2%</td>
</tr>
</tbody>
</table>

Edlin Nature 2011
The consequence

US RESPONSE TO HIV AND VIRAL HEPATITIS EPIDEMICS
Hepatitis C infection is at least five times more prevalent as HIV infection in the United States, yet funding lags far behind.

Prevalence

Undiagnosed Infections

Dollars Spent (Billion USD)

Funding

Number of people (millions)

HIV HBV HCV

Edlin Nature 2011
What needs to change...

HIV Lobby

HCV Lobby
Impact of IDU and adherence on SVR

Australian Trial in Acute Hepatitis C Study (n=109), 74 HCV, PEG-IFN

Incarceration

Prison Pop’n
- Male
- IDU
- ETOH
- African American

Peg/RBV x 24-48 weeks

SVR (%)

0 20 40 60 80 100

n/N = 43
97/234

n/N = 38
115/319

- Incarceration not associated with response to therapy
- Treatment uptake continues to be low...

Rice Hepatology 2012
Barriers to treatment

Modeled data for non-VA US population

Should improve with IFN-free therapy but long way to go…

Yehia PLoS One 2014
## Treatment uptake among PWID very low

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Cohort</th>
<th>HCV Treatment Uptake/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada (Vancouver)(^1)</td>
<td>1,360</td>
<td>Community-based inner city residents</td>
<td>1-2%</td>
</tr>
<tr>
<td>United States (Baltimore)(^2)</td>
<td>597</td>
<td>Community-based IDUs</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Australia(^3)</td>
<td>2,500</td>
<td>Needle exchange participants</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

---

1) Grebely J. J Viral Hep 2009  
Uptake more important than SVR

Improved therapy of no benefit unless treatment rates increase

Thomas Lancet 2010
Treatment as prevention for HCV

Implementation in PWID/incarcerated pop’ns
Important for reducing prevalence in high income countries

Summary

• Treatment improving rapidly
• Most ‘difficult to cure’ populations will soon be ‘easy to cure’
• Likely few ‘special populations’
• Cirrhosis will likely remain a challenge
• Access to therapy will remain in a challenge
• The most difficult clinical population remains those who are not yet diagnosed...