Overview of HCV and Strategies to Treat HCV Among Patients With Substance Use Disorders

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Program Overview

- Basic principles of viral hepatitis liver disease and treatment approaches in 2012
- Epidemiology considerations and significance of liver disease and hepatitis in HIV
- Special consideration for HCV-infected persons with substance use disorders
The Hepatitis C Epidemic

- Worldwide prevalence of chronic HCV: 170 million
- Most patients with HCV are asymptomatic until irreversible liver damage occurs
- Diagnosis depends on high index of suspicion and proper screening
- Screening recommended for:
  - IDUs
  - Blood transfusion
  - Tattoos (high risk settings)
  - Dialysis patients
  - Birth cohort (US)

Basic Principles

- Hepatic fibrosis is not reliably diagnosed by ultrasound or other imaging modalities
- Liver fibrosis rates are not predictable or linear
- Progression from compensated cirrhosis to decompensated liver disease occurs in 5% of patients per year
- Hepatocellular carcinoma develops in 1% to 2% of patients with hepatitis-related cirrhosis each year

Causes of Liver Disease in HIV Infection

Opportunistic Infections
- HCV
- HBV
- HAV

Immune Reconstitution

EtOH IDU

Fatty Liver Disease

NRTIs
NNRTI
PIs

Diabetes
Dyslipidemia
Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

Stage 1
Fibrous expansion of some portal areas

Stage 2
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3
Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4
Cirrhosis

Cirrhotic Liver

Fibrotic Progression in Viral Hepatitis

- Mild
- Moderate
- Severe
- Cirrhosis (mild)
- Cirrhosis (severe)
- Hepatocellular carcinoma

Duration of Hepatitis Infection (years)

0 10 20 30 40 50

15% to 33%

20% to 33%

Risk Factors for Progress Fibrosis in HCV Mono-Infected Patients

- Alcohol excess (>50 gm/day)
- Daily marijuana use
- Metabolic syndrome (↑ BMI, obesity, insulin resistance)
- Longer duration of infection
- Age >40 years at time of infection
- Male gender, post-menopausal women
- Coinfections: HBV, HIV, Schistosomiasis
- Organ transplantation

Modifiable

Poynard, Lancet, 1997
Mathurin, Hepatology, 1998
Benhamou, Hepatology, 1999
Kamal, Hepatology, 2006
Asselah, Gut, 2006
Ishida, J Clin Gastro Hep, 2008
HCV Treatment Goals (2012)

Viral Eradication (SVR)

- Sustained loss of HCV RNA 6 months post-Rx

Prevention of Disease Progression

- Normalization of LFTs
- Improved HRQoL
- Improved liver histology
- Decreased cirrhosis
- Decreased HCC
- Improved survival
### HCV Treatment Expectations (2012)

<table>
<thead>
<tr>
<th>GT</th>
<th>Medication Regimen</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG+RBV+Telaprevir</td>
<td>24-48 wks (RGT)</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>PEG+RBV+Boceprevir</td>
<td>24-48 wks (RGT)</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>PEG+RBV</td>
<td>24-48 wks (RGT)</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>PEG+RBV</td>
<td>24-48 wks (RGT)</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>PEG+RBV</td>
<td>48 wks</td>
<td>(~55%)</td>
</tr>
<tr>
<td>5</td>
<td>PEG+RBV</td>
<td>48 wks</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>PEG+RBV</td>
<td>48 wks</td>
<td>70%</td>
</tr>
</tbody>
</table>

Rationale for Treating HCV Infection

Favor
- Increased ability to ‘cure’ GT1
- Reduce disease progression to ESLD, cirrhosis and HCC
- Improve tolerability to other medications (e.g. ART)
- Decrease pool of HCV-infected persons

Against
- Poor tolerability
- Many often not treatment candidates
- Drug interactions
- Low physician comfort level
- Decreased response in HIV/HCV coinfectcd persons
SVR in GT1 Treatment Naïve Patients Receiving PI-containing Rx

**Telaprevir**
- PEG/RBV: 44
- TVR Combo: 69
- TVR Combo: 75

**Bocepravir**
- PEG/RBV: 38
- BCP Combo: 67
- BCP Combo: 75

**Results:**
- Telaprevir: 25-37%
- Bocepravir: 29-37%

*Jacobson IM, NEJM, 2011*  
*Poordad F, NEJM, 2011*
Futility Rules for PI-Based Therapy in Treatment-Naïve Patients

- Recommendation: All therapy should be discontinued in patients with the following:

<table>
<thead>
<tr>
<th>Boceprevir</th>
<th></th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Point</strong></td>
<td><strong>Criteria</strong></td>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>Wk 12</td>
<td>HCV RNA ≥ 100 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue all therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Telaprevir</th>
<th></th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Point</strong></td>
<td><strong>Criteria</strong></td>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>Wk 4 or 12</td>
<td>HCV RNA &gt; 1000 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>HCV RNA detectable</td>
<td>Discontinue pegIFN/RBV</td>
</tr>
</tbody>
</table>

Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.
Key Host and Viral Factors Affecting SVR Rates in HCV Mono-Infection

Fibrosis:
- F0-2: 67%
- F3-4: 41%

Race:
- Non-AA: 74%
- AA: 50%

IL-28B Polymorphisms:
- CC: 82%
- CT: 65%
- TT: 55%

Poordad F, NEJM, 2011; Bruno S, EASL 2011, Abstract 195
Adverse Events with PI-Based Treatment Compared to PEG/RBV Alone

- **Boceprevir**
  - Anemia (50% v 30%)
    - Managed with RBV reduction or Epo in 43%
  - Neutropenia (25% v 19%)
  - Dysgeusia (35% v 16%)

- **Telaprevir**
  - Rash (56% v 34%)
    - Severe rash in 4%; discontinuation in 6% (SJS-3; DRESS-11)
    - Most occurred in first 4 weeks, but may happen anytime
  - Anemia (36% v 17%)
  - Anorectal events (29% v 7%)
Key Elements of PI-Combination Rx

Similarities
- RGT: EVR determines Rx duration
- Futility rules used to minimize resistance
- Extended treatment in cirrhotics

Differences
- Lead-in with BCP; none with TLV
- Duration of triple vs dual therapy
- Rules for RGT and futility differ
- Potential for twice-daily Rx for TLV
Treatment of GT1 HCV Infection Using PI-Based Therapy Summary

- SVR rates superior to PEG/RBV, but several subtypes with suboptimal response
  - ~15% lower if cirrhotic, AA or unfavorable IL-B28
  - Prior partial or null response to PEG/RBV (SVR is ≤50% when treated with PI combo)

- RGT offers shorter treatment duration for ~50-60% of patients
  - EVR is highly predictive of SVR
  - Lead-in with PEG/RBV identified less responsive patient
  - Cirrhotics not eligible for shortened treatment
HCV Life Cycle and Targets for STAT-C/DAAs

- Prevent viral entry
  - Polyclonal and monoclonal antibodies
- Prevent translation of viral RNA
  - NS3/4 protease inhibitors
- Inhibit HCV-RNA polymerase
  - Nucleoside analogue NS5B polymerase inhibitors
  - Non-nucleoside analogue NS5B polymerase inhibitors
  - Replication complex inhibitor
  - Cyclophilin B inhibitors
- Viral assembly/release
  - Glucosidase inhibitor

Multiple Direct Antiviral Targets

Polyprotein

5’ UTR region

9.6 kb RNA

3’ UTR region

Polyprotein Processing

C E1 E2 p7 NS2 NS3 4A NS4B NS5A NS5B

C E1 E2 p7 NS2 NS3 4A NS4B NS5A NS5B

Core Envelope Glycoproteins Protease

Serine Protease Helicase Serine Protease Cofactor

NS3-4A protease inhibitors

Replication complex RNA and Zn binding

NS5A inhibitor

NS5B polymerase inhibitors

nucleoside analogs non-nucleoside analogs

RNA-dependent RNA polymerase

Terrault N, 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0104.
DAA Development Timeline

- **2010**: Treatment complexity
- **2012**: PEG-IFN + RBV
- **2014**: PEG-IFN + RBV + DAA
- **2015**: DAA combination (DAA combination)

GT1: PEG-Free Therapy
Boosted PI + NN Pol Inhibitor + RBV

Poordad, EASL, 2012
Considerations About Whether to Treat Now or Wait for New Therapies

- **Likelihood of response and risk of waiting**
  - Stage of fibrosis
  - Prior treatment history
    - Partial and null responders need better medications

- **Tolerability of PEG/RBV**
  - If previously treated, why was it stopped
  - Cirrhotics require 48 weeks – more risk of side side effects, especially cytopenias

- **Practical issues**
  - Insurance status & co-pays
  - Social support

- **Public health – secondary prevention**

Altice, personal opinion, 2012
Program Overview

- Basic principles of viral hepatitis liver disease
- Epidemiology considerations and significance of liver disease and hepatitis in HIV
- Special consideration for HCV-infected persons with substance use disorders
Liver Disease is the Second Leading Cause of Death in HIV-Infected Patients (1999-2004)

- D:A:D study (n=23,441)
  - Median follow-up: 3.5 years

- Baseline characteristics
  - Nadir CD4: 200 cells/µL
  - Previous AIDS: 26.5%
  - HCV positive: 22.5%
  - Active HBV infection: 6.8%
  - Inactive HBV infection: 21.4%
  - Receiving combination antiretroviral therapy: 88.7%

- Mortality
  - Total: 5.3%
  - Incidence: 1.62 per 100 person-years
  - Median age: 44 years

Independent Predictors of Liver-Related Death

Latest CD4 Cell Count (cells/µL)
- <50
- 50-99
- 100-199
- 200-349
- 350-499
- >500

HIV Acquisition via IDU

Hepatitis C Status
- Negative
- Positive

Hepatitis B Status
- Negative
- Positive

Relative Rate of Death

Multivariate analysis.
Not shown: Age per 5 years (1.32).

Standardized Cumulative Incidence of Hepatic Decompensation

Hepatic decompensation risk 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)

Lo Re V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0102.
Summary of Findings for PI-based Treatment for HIV/HCV Co-Infection

- Improved efficacy ➔ 30% over PEG/RBV
  - Similar to HCV monoinfected
  - Tolerability similar to monoinfected

- BUT ............
  - Only applicable to GT1, treatment-naïve patients
  - Still requires 48 weeks of treatment
  - Limited number of ART regimens studied
  - May use either if on no ART or RAL+2NRTIs
  - Use TLV if on ATV/r+2NRTIs
  - Use increased TLV 1125 Q8h if on EFV+2NRTIs
Increased Potential for Pharmacokinetic Drug Interactions

● **Telaprevir**
  - CYP3A4 and P-gp substrate
  - Non-cytochrome P450 metabolism as well
  - CYP3A4 inhibitor

● **Boceprevir**
  - Aldoketoreductase (AKR) and CYP3A4/5 substrate
  - CYP3A4 and P-gp inhibitor

● **HIV PIs or NNRTIs, statins, antiarrhythmic drugs, others**
Program Overview

- Basic principles of viral hepatitis liver disease
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Treating HCV Among Drug & Alcohol Users

- Can reduce treatment duration
- Relatively few drug interactions
- Providers, however, unlikely to treat
- Many substance use disorders can be effectively treated with medication-assisted therapy
  - Opioids (methadone, buprenorphine, XR-NTX)
  - Alcohol (XR-NTX, acamprosate)
- Creative delivery of health services may be needed to overcome existing obstacles
Not Prescribing ART to Drug Users

- CD4=200
  - No IDU: 1
  - Abstinent 3 mo: 2.4
  - Occasional IDU: 23
  - Daily IDU: 52

- CD4=350
  - No IDU: 11
  - Abstinent 3 mo: 13
  - Occasional IDU: 49
  - Daily IDU: 70

- CD4=500
  - No IDU: 61
  - Abstinent 3 mo: 67
  - Occasional IDU: 86
  - Daily IDU: 92
How to Increase Treatment of HCV

1° Care Clinics
Community Outreach NSEPs
Specialized Drug Rx
Prisons

Community
Integration into Specialty Drug Treatment Programs

Developing a Modified Directly Observed Therapy Intervention for Hepatitis C Treatment in a Methadone Maintenance Program: Implications for Program Replication

R. Douglas Bruce, M.D., M.A., M.Sc\textsuperscript{1,2}, Julie Eisman, M.A.\textsuperscript{1}, Angela Acosta, B.S.\textsuperscript{1}, Ceilia Gote, APRN\textsuperscript{3}, Joseph K. Lim, M.D.\textsuperscript{4}, and Frederick L. Altice, M.D., M.A.\textsuperscript{1,2}

- Supervised dosing enhances adherence
- Evidence for success in treating TB & HIV

<table>
<thead>
<tr>
<th></th>
<th>Integrated</th>
<th>Referral</th>
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<tbody>
<tr>
<td>Started Rx</td>
<td>100%</td>
<td>36.4%</td>
</tr>
<tr>
<td>EVR</td>
<td>83.3%</td>
<td>27.2%</td>
</tr>
<tr>
<td>SVR</td>
<td>50.0%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>
Impact of Telaprevir on Methadone and Buprenorphine/NLX

- No significant change in BPN/NLX AUC
- No clinical symptoms of opioid withdrawal for either

*Van Heeswijk, EASL, 2012, Abs 654
Luo, Antimicrob Agents Chemo, 2012*
Project ECHO: Increasing Primary Care Treatment of HCV Infection

- Challenge: rural and non-specialists are unlikely to treat HCV
- Increased HCV screening, evaluation for Rx, self-efficacy and initiation of HCV treatment
- Weekly telemedicine clinical conferences with didactics, case presentations and discussions
- RCT of specialty HCV treatment versus ECHO:
  - SVR: 57.5% v 58.2%
  - SVR GT1: 45.8% v 49.7%
  - Serious adverse events: 13.7% v 6.9%

Arora, Hepatology, 2010
Arora, NEJM, 2011
HCV Treatment Outcomes in Prisons

- Prisons are structured settings to initiate and treat diseases
- Pilot study of HCV treatment outcomes
- SVR=51%
- Having depression and cirrhosis associated with no SVR

Table 3. Reasons for deferral of hepatitis C therapy.

<table>
<thead>
<tr>
<th>Reason for deferral</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's release was too soon</td>
<td>40 (57.1)</td>
</tr>
<tr>
<td>Normal liver function test results</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Normal biopsy findings</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Patient refused consent/change of facilities</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Patient refused consent/other</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Patient deemed to be noncompliant</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Patient had uncontrolled HIV disease</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Patient had uncontrolled diabetes</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Unclear</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

Maru, CID, 2008
Outreach
Medical Care
Drug Treatment
Mental Health
HIV Care
Case Management
HCV Treatment

Community Health Care Van
Summary

● Newer treatments have emerged that can “cure” HCV infection with shorter duration, but with increased complexity, cost and side effects

● Substance use disorders and psychiatric illnesses can be effectively treated with existing pharmacotherapies

● Innovative solutions are urgently needed if we intend to expand treatment and reduce negative health consequences to individuals and society