Update on Hepatitis C Treatment

Kara Chew, MD, MS
UCLA Center for Clinical AIDS Research & Education
Assistant Clinical Professor of Medicine
David Geffen School of Medicine at UCLA
Overview

• Review of hepatitis C epidemiology
• Review of hepatitis C complications
• Update on current treatment recommendations
Some terminology

- **HCV = hepatitis C virus**
- **SVR = sustained virologic response**
  (undetectable hepatitis C virus in blood 12-24 weeks after completing HCV treatment)
- **F0, F1, F2, F3, F4 = fibrosis score/stage**
  - Amount of scarring in the liver
  - F3 = advanced fibrosis
  - F4 = cirrhosis
Hepatitis C Virus (HCV)

• Infects hepatocytes (liver cells)
• Causes acute and chronic infection
The Burden of Hepatitis C

• ~170 million chronically infected worldwide
• ~2.3 million in the U.S.
  – Other estimates of up to 5.2 million in the U.S
• Most common bloodborne infection in the U.S.
• Leading indication for liver transplantation in the U.S.

¹WHO, J Clin Pharmacol 2004
²Ditah et al, J Hepatol 2014
³Chak et al, Liver International 2011
Long term Complications of HCV Infection

- Fibrosis $\rightarrow$ Cirrhosis $\rightarrow$ Liver failure
- Decompensated liver disease: ascites, variceal bleeding, hepatic encephalopathy
- Hepatocellular carcinoma (HCC)
- Death – increased mortality from both liver and non-liver diseases
Changes in the liver with HCV

**PROGRESSION OF LIVER DAMAGE**

<table>
<thead>
<tr>
<th>HEALTHY LIVER</th>
<th>FIBROTIC LIVER</th>
<th>CIRRHOTIC LIVER</th>
<th>LIVER CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Healthy Liver" /></td>
<td><img src="image2" alt="Fibrotic Liver" /></td>
<td><img src="image3" alt="Cirrhotic Liver" /></td>
<td><img src="image4" alt="Liver Cancer" /></td>
</tr>
</tbody>
</table>

A healthy liver is able to perform its normal functions effectively, e.g. aiding digestion and breaking down harmful drugs and poisons.  
Continuous inflammation of the liver caused by hepatitis C can lead to fibrosis – the formation of scar tissue within the liver.  
Extensive scarring can block the flow of blood through the liver and cause liver function to deteriorate over time - this is called cirrhosis.  
Hepatitis C is a leading cause of liver cancer – the formation of a malignant tumour in the liver.
Natural History of HCV Infection

1. **Acute Hepatitis C**
2. **Chronic Hepatitis** (75-85%)
   - Often asymptomatic
3. **Cirrhosis** (20%)
4. End stage liver disease
   - Hepatocellular carcinoma
   - Death (≥25%)

Duration: 20-30 years

References:
- Di Bisceglie et al, Hepatology, 2000
- Klevens et al, CID 2012
Hepatitis C and Mortality

- Increased all-cause mortality and death from hepatic diseases with HCV infection: REVEAL-HCV Study

HCV deaths now exceed HIV deaths in the U.S., 1999-2008

Klevens CID 2012;55(Suppl 1)

- Annual age-adjusted mortality rates and 95% CI, 1999-2008.
- Approximately 73% of HCV-related deaths in 45-64 y.o.
- 40-50% of decedents with HCV diagnosed by time of death
- 80% of decedents with HIV diagnosed by time of death
Other HCV-associated symptoms and complications

- Fatigue
- Arthralgia
- Depression/CNS
- Insulin resistance, diabetes mellitus
- Renal disease
- Lymphoma (NHL)
- Bone, ocular, vascular, peripheral nerve disease
- Increased hospitalizations, 15%/year
How to prevent liver disease progression (beyond treating HCV)

• Treat HIV
• Avoid alcohol
• Avoid smoking cigarettes
• Avoid marijuana
• Treat and vaccinate for co-infections (e.g. hepatitis A and hepatitis B)
• Weight loss may help
HEPATITIS C TREATMENT
The HCV Treatment Cascade, U.S.
Can we cure hepatitis C?

• YES, we believe so
• No integration into host DNA as with HIV
• No known reservoirs as with HIV
• Very low rates of recurrent HCV after clearing with treatment (but re-infection is possible)
What are the benefits of HCV treatment?

• Decreased death from all causes
• Decreased death from liver-related causes
• Decreased risk of liver cancer
• Decreased risk of liver decompensation
SVR with interferon-based therapy is associated with reduced all-cause and liver mortality

Coverdale et al Am J Gastroenterol 2004;99:636-44
Veldt et al Ann Intern Med 2007;147:677-84
van der Meer et al JAMA 2012
Other treatment benefits

- Neurocognitive function
- Depression
- Fatigue
- Quality of life
Whom to treat

- **TREATMENT SHOULD BE CONSIDERED FOR ALL**
- Expected to benefit all HCV-infected persons, except those with limited life expectancy (<12 months)
- Treatment urgent if advanced fibrosis (F3/F4)
- Treatment options, with consideration of
  - Patient goals/willingness
  - Treatment history
  - Response rates with currently available therapies (particularly genotype 3)
  - Therapies to be available in the future (genotype 3)
  - Drug-drug interactions
  - Clinical trials
## Whom to treat: highest priority

### Highest Priority for Treatment Owing to Highest Risk for Severe Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rating:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced fibrosis (Metavir F3) or compensated cirrhosis (F4)</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td>Organ Transplant</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Type 2 or 3 essential mixed cyroglobulinemia with end-organ manifestations (e.g. vasculitis)</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis</td>
<td>Class IIa, Level B</td>
</tr>
</tbody>
</table>

### High Priority for Treatment Owing to High Risk for Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rating:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis (Metavir F2)</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>HIV-1 Coinfection</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Hepatitis B Virus (HBV) Coinfection</td>
<td>Class IIa, Level C</td>
</tr>
<tr>
<td>Other coexistent liver disease (e.g. NASH)</td>
<td>Class IIa, Level C</td>
</tr>
<tr>
<td>Debilitating fatigue</td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td>Type II Diabetes mellitus (insulin resistant)</td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Class IIb, Level C</td>
</tr>
</tbody>
</table>
Whom to treat: potential benefits for treatment as prevention

<table>
<thead>
<tr>
<th>Persons at Elevated Risk of HCV Transmission and in Whom HCV Treatment May Yield Transmission Reduction Benefits (Class IIa, Level C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men (MSM) with high-risk sexual practices</td>
</tr>
<tr>
<td>Active injection drug users</td>
</tr>
<tr>
<td>Incarcerated persons</td>
</tr>
<tr>
<td>HCV-infected women of child-bearing potential wishing to get pregnant</td>
</tr>
<tr>
<td>Persons on long-term hemodialysis</td>
</tr>
</tbody>
</table>

*Along with counseling on reducing risk of transmission and risk of reinfection*
How do we measure HCV treatment response?

- **Sustained virologic response (SVR)** = undetectable HCV viral load 12 weeks after end of HCV treatment
- Think of SVR as “Cure”
The New Drug Targets: Direct-Acting Antivirals (DAAs) for HCV

NS3/4A PROTEASE INHIBITORS
NS5A INHIBITORS
NS5B POLYMERASE INHIBITORS
Nucleotides and Non-nucleosides

Also non-DAAs:
Cyclophilin inhibitors (target a host enzyme)
MiR-122 inhibitors

Shimakami et al Curr Opin Pharmacol 2009
The old standard of care: pegylated interferon and ribavirin (PEG/RBV)

- SOC until 2011 for HCV monoinfected
- Inadequate response rates

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HCV</th>
<th>HIV/HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>40-50%</td>
<td>14-29%</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>80%</td>
<td>44-73%</td>
</tr>
</tbody>
</table>

Evolution of HCV treatment

>90% SVR, IFN-free (boceprevir or telaprevir)

Nature Reviews | Drug Discovery
### FDA-approved agents for HCV

<table>
<thead>
<tr>
<th>NS3 Protease Inhibitors</th>
<th>NS5A Replication Complex Inhibitors</th>
<th>NS5B Nucleoside Inhibitors</th>
<th>NS5B Non-nucleoside Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Peginterferon</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Ombitasvir</td>
<td></td>
<td></td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IFN-FREE REGIMENS (will depend on genotype)**
- Sofosbuvir + RBV
- Sofosbuvir /ledipasvir fixed dose combination (FDC) +/- RBV
- Paritaprevir/ritonavir/ombitasvir FDC + dasabuvir +/- RBV
- Sofosbuvir + simeprevir +/- RBV
## HCV Genotype 1a Treatment: Treatment Experienced

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>PEG/RBV failure</th>
<th>HCV PI failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-cirrhotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG/RBV failure</td>
<td>LDV+SOF x 12 weeks</td>
<td>LDV+SOF x 12 weeks</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>Paritaprevir/ritonavir/ombitas vir + dasabuvir + RBV x 12 weeks</td>
<td>SOF+ SMV +/- RBV x 12 weeks</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV+SOF x 24 weeks</td>
<td>LDV+SOF x 24 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF+SMV +/- RBV x 24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

*Not FDA-approved*
### HCV Genotype 1b Treatment: Treatment Experienced

<table>
<thead>
<tr>
<th>Genotype 1b</th>
<th>PEG/RBV failure</th>
<th>HCV PI failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-cirrhotic</strong></td>
<td><strong>LDV+SOF x 12 weeks</strong></td>
<td><strong>LDV+SOF x 12 weeks</strong></td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/ritonavir/ombitas vir + dasabuvir x 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF+ SMV +/- RBV x 12 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Cirrhotic</strong></td>
<td><strong>LDV+SOF x 24 weeks</strong></td>
<td><strong>LDV+SOF x 24 weeks</strong></td>
</tr>
<tr>
<td></td>
<td><strong>LDV+SOF+RBV x 12 weeks</strong></td>
<td><strong>LDV+SOF+RBV x 12 weeks</strong></td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/ritonavir/ombitas vir + dasabuvir + RBV x 24 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF+SMV+/-RBV x 24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

*Not FDA-approved
Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
ION-1 Study: Results

ION-1: SVR12 by Treatment Regimen and Liver Disease

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Without Cirrhosis</th>
<th>With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV-SOF</td>
<td>100/179</td>
<td>99/181</td>
</tr>
<tr>
<td>LDV-SOF + RBV</td>
<td>100/178</td>
<td>100/31</td>
</tr>
<tr>
<td>12-Week Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV-SOF</td>
<td>100/179</td>
<td>100/36</td>
</tr>
<tr>
<td>LDV-SOF + RBV</td>
<td>100/33</td>
<td>100/32</td>
</tr>
<tr>
<td>24-Week Treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1
ION-2 Study: Results

ION-2: SVR12 by Treatment Regimen and Liver Disease

SOF/LDV in HIV/HCV: ION-4

Results: SVR12 by Prior Treatment Experience
HIV-HCV (ION-4)

Allowed ARV regimens:
Efavirenz, raltegravir, rilpivirine + FTC/TDF

Naggie et al, CROI 2015
Ledipasvir-Sofosbuvir for 8 or 12 Weeks in Treatment-Naïve HCV GT 1
ION-3 Study: Results

ION-3: SVR 12 by Treatment Duration and Regimen

<table>
<thead>
<tr>
<th>Patients with SVR 12 (%)</th>
<th>8-Week Regimen</th>
<th>12-Week Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV-SOF</td>
<td>202/215</td>
<td>206/216</td>
</tr>
<tr>
<td>LDV-SOF +RBV</td>
<td>201/216</td>
<td></td>
</tr>
<tr>
<td>LDV-SOF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

NO DATA FOR HIV/HCV – SHORT COURSE NOT RECOMMENDED

No cirrhosis

3D + Ribavirin in GT1 and Compensated Cirrhosis
TURQUOISE-II: Results

TURQUOISE II: SVR12 Based on Prior Treatment

3D + RBV x 12 Weeks  3D + RBV x 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th>3D + RBV x 12 Weeks</th>
<th>3D + RBV x 24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior Treatment</td>
<td>94/86</td>
<td>95/74</td>
</tr>
<tr>
<td>Prior Relapser</td>
<td>97/28</td>
<td>100/23</td>
</tr>
<tr>
<td>Partial Responder</td>
<td>94/17</td>
<td>100/13</td>
</tr>
<tr>
<td>Null Responder</td>
<td>87/65</td>
<td>95/59</td>
</tr>
</tbody>
</table>

3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; RBV = ribavirin

Abbvie 3D Interferon-Free Regimen in HIV/HCV

**TURQUOISE-I Results:**
**ITT Virologic Response Rates**

- RVR (Week 4): 31/31, 32/32
- EOTR (Week 12 or 24): 30/31, 31/32
- SVR4: 29/31, 31/32
- SVR12: 29/31

**ART:** Atazanavir, raltegravir

Sulkowski et al. International AIDS Conference 2014, Melbourne
Safety and Tolerability of IFN-free regimens

- Well tolerated
- Few discontinue treatment due to side effects
- Common side effects: fatigue, insomnia, headache, nausea, diarrhea, irritability
- Lab abnormalities: elevated bilirubin
- Anemia with ribavirin
Drug-Drug Interactions/Toxicity

- Acid-suppressing medications and SOF/LDV
  - Decreased absorption of ledipasvir
- Salmeterol and paritaprevir/ritonavir/ombitasvir + dasabuvir
  - Prolonged QT
- St. John’s Wort
  - St John’s wort will decrease ombitasvir/paritaprevir/ritonavir + dasabuvir levels and SOF/LDV levels
- HIV Antiretrovirals
  - DDIs with protease inhibitors
  - Effects on tenofovir levels and renal toxicity
- Statins
  - Increased levels with both SOF/LDV and paritaprevir/ritonavir/ombitasvir/dasabuvir
- AMIODARONE: RECENT FDA WARNING
  - SOF/LDV or SOF + another HCV DAA (daclatasvir or simeprevir)
  - Serious symptomatic bradycardia, including fatal cardiac arrest and cases requiring pacemaker intervention
More HCV treatments coming

- Pan-(or multi-) genotypic regimens
- Daclatasvir + Sofosbuvir +/- Ribavirin for Genotype 3
- Asunaprevir/Daclatasvir/Beclabuvir +/- Ribavirin
- Sofosbuvir + GS-5816
- Grazoprevir/Elbasvir + MK-3682
Remaining gaps and questions

- Identifying the HCV-infected population: Diagnosing and confirming HCV infection
- Linking to care
- Accessing HCV treatment
- How to treat HCV genotype 3
- Even shorter therapies?
- How to treat DAA failures (failures of the new drugs)
- Implications of HCV resistance mutations for re-treatment
- Ongoing role of pegylated interferon
- Improving liver outcomes post-treatment in patients with advanced fibrosis/cirrhosis
HIV/HCV resources for patients and educators

- IDSA/AASLD/IAS-USA HCV Guidelines: [www.hcvguidelines.org](http://www.hcvguidelines.org)
 CURRENT STUDIES

• CTSI-PLACE Study - HIV/Hepatitis C (HCV) and Heart Disease
  – Study of endothelial function and cardiovascular disease blood markers in HIV/HCV vs HIV

• ACTG A5320 (V-HICS) HIV/HCV or HCV only
  – Study of long-term outcomes following HCV treatment

• ACTG A5329 – HIV/HCV Interferon-FREE HCV treatment
  – HCV treatment naïve

• HCV Treatment Barriers Survey – HCV or HIV/HCV
  – Survey study of barriers patients are experiencing to accessing HCV treatment

COMING STUDIES: ADDITIONAL INTERFERON-FREE REGIMENS for HIV/HCV COINFECTED, treatment-naïve and experienced

Call us! CARE Center Outreach Line: 310-557-9062
Thank you for your attention!