HEPATITIS C
EMERGING OPPORTUNITIES

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Disclosures & Investigational Medications

- No financial disclosures
- Slide 19 lists some FDA approved and investigational direct acting antiviral (DAA) medications
Hepatitis C Disease Burden: US

- Hepatitis C is the most common chronic blood-borne viral infection in the US\(^1\)
  - ~1/2 of cirrhotic patients\(^2\)
  - ~1/3 of HCC patients\(^3\)
  - #1 reason for liver transplants\(^4\)
  - #1 cause of death in HIV patients\(^5,6\)

It is estimated that 4 million Americans are infected with HCV\(^7\)

Future Burden of Hepatitis C Related Morbidity and Mortality in the US

- Markov model of health outcomes
  - Of 2.7 M HCV infected persons in primary care
    - 1.47 M will develop cirrhosis
    - 350,000 will develop liver cancer
    - 897,000 will die from HCV-related complications

Prevalence of HCV in Select Populations

- **Illicit drug users**: ~300,000 (80%-90%)²,³
- **Alcoholics**: ~240,000 (11%-36%)⁵
- **Incarcerated**: ~330,000 to 860,000 (16%-41%)¹
- **HIV-infected**: ~300,000 (30%)⁴
- **Living below poverty level**: ~940,000 (3.2%)⁶
- **Children (6-18 years old)**: ~100,000 (0.1%)⁹
- **Homeless**: ~175,000 (22%)⁷
- **Veterans**: ~280,000 (8%)⁸

Natural History of HCV Infection

Exposure (Acute Phase)
- 15% Resolved
- 85% Chronic

Cirrhosis
- ~20 year progression rate accelerated with HIV, HBV, alcohol
- 20%

ESLD: 6%/yr
HCC: 4%/yr
Transplant/death: 3-4%/yr

5-year survival in patients with HCC is <5%²

Time (yr) 10 20 30

HCC = hepatocellular carcinoma
ESLD = end-stage liver disease
Audience Question

On average, what percent of Americans are infected with HCV but NOT diagnosed?

A. More than 75%
B. About 50%
C. Less than 25%
D. We don’t have an accurate test to diagnose HCV infection
Hepatitis C Cascade

- Chronic HCV-Infected*: N=3,500,000.
- Diagnosed and Aware†: Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (49.8%); n=1,743,000.
- Access to Outpatient Care‡: Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient care (86.9%); n=1,514,667.
- HCV RNA Confirmed§: Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage HCV RNA confirmed (62.9%); n=952,726.
- Underwent Liver Biopsy‖: Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage who underwent liver biopsy (38.4%); n=581,632.
- Prescribed HCV Treatment¶: Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage prescribed HCV treatment (36.7%); n=555,883.
- Achieved SVR**: Calculated as estimated number prescribed HCV treatment (555,883) x estimated percentage who achieved SVR (58.8%); n=326,859.

Note: Only non-VA studies are included in the above HCV treatment cascade.
HCV Screening Recommendations

- Testing recommended at least once for persons born between 1945 and 1965
- Others: Screen for risk factors and perform one-time testing if risk factors present
- Annual HCV testing recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men
- Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV

Evaluation Issues

- *If HCV antibody positive, confirm infection with HCV RNA*
- *Assess liver function*
- *Vaccinate for hepatitis A&B as needed*
- Determine HCV genotype
- Assess stage of disease (extent of fibrosis)
  - Most health plans restrict treatment based on stage of disease
  - Guide decisions about treatment timing & duration
  - Identify cirrhosis
Need to identify cirrhotics

- Advise against drinking alcohol
- Liver cancer surveillance
  - Liver imaging test every 6 months
  - Alpha-fetal protein (AFP) test optional
- Identify liver transplant candidates
  - MELD score 15 or higher
- Upper endoscopy (EGD) to screen for esophageal varices
- Hepatology referral
- May alter anti-HCV treatment regimen & timing
HCV Genotypes in US

- HCV genotype 1
  - Comprise the majority of HCV patients in the United States

- HCV genotype 1a
  - Tend to have higher relapse rates than genotype 1b with certain regimens

- HCV genotype 1 infection that cannot be subtyped
  - Should be treated as genotype 1a

<table>
<thead>
<tr>
<th>HCV Genotypes in the United States</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>36-55</td>
</tr>
<tr>
<td>1b</td>
<td>15-24</td>
</tr>
<tr>
<td>2</td>
<td>13-16</td>
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<tr>
<td>3</td>
<td>8-13</td>
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<tr>
<td>4</td>
<td>1-2</td>
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<tr>
<td>5/6</td>
<td>1</td>
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</tbody>
</table>

Staging of Liver Disease: Liver Biopsy

- Gold standard
  - Invasive
  - Morbidity (3/1,000)
  - Mortality (1/10,000)
  - Observer variability
  - Sampling error
  - Costly
# Staging: Non-invasive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Components</th>
<th>Requirements</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>AST, platelets</td>
<td>Simple serum and haematology tests</td>
<td>+</td>
</tr>
<tr>
<td>FIB4</td>
<td>Age, AST, ALT, platelets</td>
<td>Simple serum and haematology tests</td>
<td>+</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>gGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin</td>
<td>Specialized tests. Testing at designated laboratories</td>
<td>++</td>
</tr>
<tr>
<td>Fibroscan</td>
<td>Transient elastography</td>
<td>Dedicated equipment</td>
<td>+++</td>
</tr>
</tbody>
</table>

APRI: aminotransferase/platelet ratio index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; gGT: gamma glutamyl transpeptidase
Hepatitis C: Goals of Therapy

Primary goal: Eradicate HCV infection

Secondary goals:
- Improve histology
- Slow progression to ESLD, including HCC
- Improve health-related quality of life

ESLD = end-stage liver disease
HCC = hepatocellular carcinoma

SVR Decreases All Cause Mortality

- General: 18 studies, n=29,269, Avg. FU=4.6 years
- Cirrhotic: 9 studies, n=2,734, Avg. FU=6.6 years
- HIV/HCV: 5 studies, n=2,560, Avg. FU=5.1 years

5-Year All Cause Mortality:

- General: 4.5% (SVR), 10.5% (No SVR)
- Cirrhotic: 3.6% (SVR), 11.3% (No SVR)
- Co-infected: 1.3% (SVR), 10.0% (No SVR)

Saleem, Abst# 44
Audience Question

With current HCV treatment, about what percent of people can we cure?

A. Less than 25%
B. 50%
C. 70%
D. 90% and higher
E. There is no current cure for HCV infection
SVR Rates in HCV Genotype 1 Treatment-Naïve Patients


IFN 6 mo: 6%
IFN 12 mo: 16%
IFN+RBV 6 mo: 34%
IFN+RBV 12 mo: 42%
PEG 12 mo: 39%
PEG+RBV 12 mo: 54.56%
PI+PEG+RBV 6-12 mo: 68.75%
SMV+PEG+RBV 6-12 mo: 80-81%
SOF+PEG+RBV 3 mo: 90%
LDV/SOF 2-3 mo: 94.99%

*Year of data presentation at EASL 2014 and publication in NEJM

# Overview of Oral DAAs (Direct Acting Antivirals)

<table>
<thead>
<tr>
<th>Function</th>
<th>NS3/4A</th>
<th>NS5A</th>
<th>NS5B</th>
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</thead>
<tbody>
<tr>
<td><strong>Core</strong></td>
<td>Serine Protease</td>
<td>Component of HCV</td>
<td>RNA-dependent RNA</td>
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<tr>
<td></td>
<td></td>
<td>Replication Complex</td>
<td>polymerase</td>
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<tr>
<td><strong>Envelope Glycoproteins</strong></td>
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<tr>
<td><strong>Protease</strong></td>
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<tr>
<td><strong>Serine Protease</strong></td>
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<tr>
<td><strong>Helicase</strong></td>
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<tr>
<td><strong>NS3</strong></td>
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<tr>
<td><strong>NS4A</strong></td>
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<td></td>
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<tr>
<td><strong>Serine Protease Cofactor</strong></td>
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<tr>
<td><strong>NS5A</strong></td>
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<tr>
<td><strong>Component of HCV Replicase</strong></td>
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<tr>
<td><strong>NS5B</strong></td>
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<tr>
<td><strong>RNA-dependent RNA polymerase</strong></td>
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**Drugs**
- **Covalent**
  - Ledipasvir
  - Daclatasvir
  - Ombitasvir
  - MK-8742
  - PPI-668
- **Non-covalent**
  - Nucleoside analogs
    - Sofosbuvir
    - Non-nucleoside
      - BMS-791325
      - Dasabuvir
      - Deleobuvir
  - Faldaprevir
  - Simeprevir
  - ABT-450
  - Asunaprevir
  - MK-5172
Treatment: What’s changed?

 THEN

- 24-48 week duration
- PEG-interferon + ribavirin
- Many side-effects
- Some side-effects severe
- 40-50% effective

 NOW

- 8-12 weeks
- Oral direct acting agents (DAAs)
- Fewer side-effects
- Side-effects mild
- 90+ % effective
http://www.hcvguidelines.org/
Remaining Treatment Challenges

- Identify and prepare patients for treatment
- Treatment options for special populations
  - Cirrhosis
  - Prior oral DAA failure with resistance
  - Advanced renal disease
  - Genotype 3 infection
- Cost of treatment & restricted access
What can the PCP do?

- Test and diagnosis HCV infection
- Vaccinate for hepatitis A and B if indicated
- Encourage abstinence from alcohol
- Refer for HCV evaluation and treatment
  - Be aware of long wait-time and other barriers
- Assist with ongoing care of patients with cirrhosis
- Consider opportunities to partner with specialists around HCV care & treatment