Learning Objectives

After attending this presentation, participants will be able to:

- Summarize hepatitis C virus (HCV) screening recommendations and rationale for screening
- Describe the natural history of HCV infection
- Describe emerging treatments for HCV and how the changing landscape will impact treatment decisions in the near future

Objectives

- Hepatitis C epidemiology and screening
- Natural History
- Evaluation
- Genome and Drug Targets
- Current Treatments
- What Does SVR Really Mean?
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HCV Worldwide

- 170 million infected
- Highest Asia & Africa
- Egypt > 15%
- USA 1.6%
- 3-4 million infected

Worldwide prevalence of each HCV genotype by GBD

- HCV genotype 1 (60.4 million cases: 46.2%): one-third of which are in East Asia
- Genotype 3 (54.3 million: 39.1%): genotypes 2, 4, and 6 (20.4%): genotype 5 <1%
- While genotypes 1 and 3 dominate in most countries irrespective of economic status; largest proportions of genotypes 4 and 5 are in lower-income countries
HCV-related deaths exceed HIV-related deaths

Excess HCV associated Hepatic and Extra-hepatic mortality

The REVEAL HCV Cohort Study

- 2394 deaths after an average follow-up of 16.2 years

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Multivariate-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1.89 (1.66 – 2.15)</td>
</tr>
<tr>
<td>All liver-related</td>
<td>12.48 (9.34 – 16.66)</td>
</tr>
<tr>
<td>HCC</td>
<td>21.63 (14.83 – 31.54)</td>
</tr>
<tr>
<td>All extra-hepatic diseases</td>
<td>1.35 (1.15 – 1.57)</td>
</tr>
<tr>
<td>All cancers, except HCC</td>
<td>1.32 (1.00 – 1.74)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.49 (0.91 – 2.42)</td>
</tr>
<tr>
<td>Liver and biliary</td>
<td>2.77 (1.49 – 5.15)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio

Most Americans With Chronic HCV Have Not Been Diagnosed and Few Have Been Treated

Overall: 3.2 million of U.S. population with chronic HCV
HCV Screening

HCV testing is recommended at least once for persons born between 1945 and 1965.

1. Risk factors
   - Intravenous drug use
   - Transfusion
   - Occupational exposure
   - Household contact
   - Sexual contact

2. Follow-up
   - If reactive, confirm with second test
   - Follow up for treatment

3. Other medical conditions
   - Cirrhosis
   - Liver disease
   - Family history

Hepatitis C Tests

- Hepatitis C antibody tests
  - Turn positive 8 weeks after exposure
  - Sensitivity 99%, Specificity 100%
  - Rapid immunosassays
  - HCV Rapid antibody test
  - Sensitivity and specificity >99% on blood
  - Home-based self-collected tests

- HCV RNA test
  - Confirm presence or absence of infection
  - Quantify HCV RNA

HCV testing algorithm

- Consider simultaneous anti-HCV and HCV RNA
  - Immunocompromised patients
  - Patients on hemodialysis
  - Transplant recipients
  - Advanced HIV

- Acute HCV / Recent exposure
Objectives

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Natural History of HCV Infection

- Exposure (acute Phase)
- Chronic
- Transplant/Death

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


Evaluation of liver disease: Cirrhosis

- Serum markers
  - Low platelets, low albumin
  - Elevated PT/PTT
- Clinical exam
  - Spider nevi (esp. on shoulders)
  - Ascites
  - Splenomegaly
  - Encephalopathy
- Imaging
  - CT
  - MRI
- Invasive tests
  - Liver biopsy

Liver disease staging no longer a barrier to HCV care

- Liver Biopsy
- Serum Biomarkers
- Elastography

Evaluation of liver disease: Cirrhosis

- Serum markers: APRI & FIB-4
  - Fibrosure
  - Fibrospect
Transient Elastography

Transient Elastography: HCV

- Absent or mild fibrosis (F0-F1)
- Significant fibrosis (F2)
- Severe fibrosis (F3)
- Cirrhosis (F4)

Affected by weight, access of probe (2 cm), steatosis

Evaluation of liver disease: Cirrhosis

- Compensated
  - Asymptomatic
- Decompensated
  - Symptomatic: ascites, encephalopathy
Calculate the CTP for all cirrhotics

Child-Turcotte-Pugh Classification for Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Mild to moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
</tr>
<tr>
<td>Asites</td>
<td>None</td>
<td>Mild to moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2.5</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.5-3.5</td>
<td>&lt;2.5</td>
</tr>
<tr>
<td>Prothrombin time (seconds prolonged)</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)*

Class A: 5-6 points (mild liver disease)
Class B: 7-9 points (moderate liver disease)
Class C: >10 points (severe liver disease)

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Potential Therapeutic Targets in the HCV Replication Cycle

Adapted from slide courtesy of Ray Chung
### HCV Armamentarium 2016

#### Antiviral Agent Class

<table>
<thead>
<tr>
<th>NS3</th>
<th>NS5A</th>
<th>NS5B</th>
<th>Nuc</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir FDC</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paritaprevir/ritonavir FDC + dasabuvir</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sofosbuvir + ribavirin</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir FDC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/grazoprevir FDC</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir FDC</td>
<td></td>
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</tbody>
</table>

### Velpatasvir/Sofosbuvir highly effective in patients with HCV genotype 1, 2, 3, 4 ,5 and 6 infection

**SVR12 (%)**

<table>
<thead>
<tr>
<th>Total</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>98%</td>
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<td>99%</td>
<td>95%</td>
<td>100%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Jacobson IM. HEPDART 2015

### Participants taking velpatasvir/sofosbuvir and placebo reported similar adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SOF/VEL 12 wk n=1035</th>
<th>Comparator Regimens Placebo 12 Week N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>296 (29)</td>
<td>33 (28)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>217 (21)</td>
<td>23 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>135 (13)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>87 (8)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>121 (12)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>73 (7)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>57 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Irritability</td>
<td>49 (5)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>56 (5)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>56 (5)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (6)</td>
<td>9 (8)</td>
</tr>
</tbody>
</table>

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HCV RAVs

- Resistance-associated variants (RAV) arise when a specific amino acid change occurs at a position that modifies the interaction with a drug
- RAVs lead to decreased viral replication ("fitness")
- Baseline prevalence of NS5A RAVs: up to 12%, depending on sequencing methodology
- RAVs increase the concentration of drug needed to inhibit viral replication (EC\textsubscript{50}) ("resistance")
  - \(<2\) - >1000-fold more drug needed to inhibit virus

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Effect of Baseline NS5A Resistance-Associated Polymorphisms on SVR

ION Phase 3 Program (ION-1, ION-2, ION-3)


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97% SVR

Effect of Baseline NS5A Resistance-Associated Polymorphisms on SVR

93% SVR

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NS5A RAVS impact on GT1a HCV

- NS5A RAVS in C-EDGE
- Elbasvir/grazoprevir x 12 weeks
- 12% (19/154) GT 1a with baseline NS5A RAVS
  - 11/19 (58%) achieved SVR 12
- NS5A RAVS with ≥5 fold shift to elbasvir
  - 2/9 (22%) achieved SVR 12
- C-EDGE Treatment Experiencded trial
  - Elbasvir + Grazoprevir x 16 weeks plus ribavirin
  - 6/6 (100%) with SVR 12

Predictors of SVR 12 with 22 weeks of elbasvir/grazoprevir in treatment naive pooled efficacy population (TN-PFP)


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SVR Impact on Liver-Related Outcomes

- Therapy is effective:
  - SVR associated with decreased rates of hepatic decompensation, hepatocellular carcinoma, and liver-related mortality

Mira JA et al, CID 2013;56:1646-1653

Hepatic Decompensation**