Treatment of hepatitis C and hepatitis B

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Disclosures

• Grant/Research Support
  • Gilead
  • Genfit
  • Intercept
  • Tobira

• Advisory Committee/Board
  • Gilead
Learning objectives

• Overview epidemiology and natural history of chronic hepatitis C and chronic hepatitis B
• Describe relevant factors involved in treatment decision-making
• Review current treatment of chronic hepatitis C and chronic hepatitis B
Hepatitis C: Global Epidemiology

~200 million carriers worldwide
Hepatitis C Virus
Genotypes in the USA

Type 1: 72%
Type 2: 17%
Type 3: 10%
All others: 1%

Baby Boomers (Those Born From 1945 Through 1965) Account for 82% of HCV Cases in the United States

CDC guidelines recommend a one-time anti-HCV antibody test for all baby boomers (individuals born 1945-1965) in an effort to identify these undiagnosed individuals.
Chronic HCV Infection May Result in Liver Cirrhosis, HCC, and Liver-Related Death

Liver transplant
- HCV is the #1 cause of liver transplant in the United States
- Up to 45% of patients awaiting liver transplant have HCV

Liver cancer
- HCV is the leading cause of HCC

Death
- 4% annual death rate postcirrhosis
- CDC has identified the number of deaths from HCV now exceed those from HIV

The rate of progression of liver fibrosis accelerates as fibrosis advances and can vary from patient to patient
Deaths Due to HCV Infections Now Exceed Those Due to HIV Infections

- Mortality due to HCV infection may be vastly underestimated due to underreporting on death certificates

HCV Treatment Goals

Primary Goal
- Eradicate HCV infection

Secondary Goal
- Slow disease progression
- Improve histology
- Reduce risk of HCC
Studies Have Shown a Decreased Rate of Liver Complications in Patients Who Achieved SVR With Peg-IFN/RBV

- The HALT-C Trial was a multicenter study of 1145 subjects with advanced chronic HCV who were nonresponders to previous IFN-based treatment.
- The trial found that achieving SVR with Peg-IFN/RBV therapy significantly reduced HCV-associated complications and mortality.

Evolution of HCV treatment

- Interferon
- Interferon + ribavirin
- Peginterferon + ribavirin
- Peginterferon + ribavirin + PI
- Interferon-free combination

Sustained virological response rates (%)

- 1990: 7-10%
- 1998: 25%
- 2001: 40-50%
- 2011: 60-70%
- 2014: >90%
Direct acting antivirals

NS3/4A Protease Inhibitors (PI)
- High potency
- Multi-genotypic coverage
- Intermediate to high barrier to resistance

NS5A Inhibitors
- High potency
- Multi-genotypic coverage
- Low to intermediate barrier to resistance

NS5B Nucleoside Inhibitors (NI)
- Intermediate potency
- Pan-genotypic coverage
- High barrier to resistance

NS5B Non-Nucleoside Inhibitors (NNI)
- Intermediate potency
- Limited-genotypic coverage
- Low barrier to resistance
FDA approved treatments

- **2001**: PEG-IFN + RBV 24-48 semanas
- **5/2011**: PEG-IFN + RBV + Boceprevir o Telaprevir (Gt 1)
- **11/2013**: PEG-IFN + RBV + Simeprevir (Gt 1)
- **12/2013**: PEG-IFN + RBV + Sofosbuvir (Gt 1)
- **12/2013**: Sofosbuvir + RBV (Gt 2, 3)

http://hcvguidelines.org
FDA approved treatments

- **10/2014**: Ledipasvir + sofosbuvir (Gt 1)
- **11/2014**: Simeprevir + sofosbuvir ± RBV (Gt 1)
- **12/2014**: Paritaprevir/r + ombitasvir + dasabuvir ± RBV (Gt 1,4)
- **7/2015**: Daclatasvir + sofosbuvir (Gt 3)
- **7/2015**: Paritaprevir/r + ombitasvir (Gt 4)
- **1/2016**: Grazoprevir + elbasvir (Gt 1, 4)
- **6/2016**: Velpatasvir + sofosbuvir (Gt 1-6)

http://hcvguidelines.org
# Retail price

<table>
<thead>
<tr>
<th>Medication</th>
<th>28 days</th>
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<tbody>
<tr>
<td>Harvoni® (SOF/LDV)</td>
<td>$33,500</td>
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<tr>
<td>Sovaldi® (SOF)</td>
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<tr>
<td>Viekira® (3D)</td>
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<td>Epclusa® (SOF/VEL)</td>
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<tr>
<td>Olysio® (SMV)</td>
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<tr>
<td>Daklinza® (DCV)</td>
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<td>Zepatier® (EBR/GZR)</td>
<td>$19,350</td>
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</table>
Factors that impact DAA selection

- HCV genotype and genotype 1 subtype
- Presence/absence liver cirrhosis
  - Compensated vs. decompensated
- Treatment experience
- Viral load
- NS5A and other resistance-associated substitutions
- Renal function
- Drug-drug interactions
- Liver transplant status
### Recommended DAA treatment

#### Patients without cirrhosis

<table>
<thead>
<tr>
<th>Gt</th>
<th>Prior Tx</th>
<th>LDV/SOF</th>
<th>DCV+SOF</th>
<th>SMV+SOF</th>
<th>PTVr/OBV +DSV</th>
<th>EBR/GZ R</th>
<th>SOF/VEL</th>
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<tbody>
<tr>
<td>1a</td>
<td>TN</td>
<td>12 wk</td>
<td>12 wk</td>
<td>12 wk</td>
<td>12 wk+R</td>
<td>12 wk+16 wk+R</td>
<td>12 wk</td>
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<tr>
<td></td>
<td>TE</td>
<td>12 wk</td>
<td>12 wk</td>
<td>12 wk</td>
<td>12 wk+R</td>
<td>12 wk+16 wk+R</td>
<td>12 wk</td>
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<tr>
<td>1b</td>
<td>TN</td>
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<td>TE</td>
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<td>12 wk</td>
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<td>TN</td>
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<td>12 wk</td>
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<td>12 wk</td>
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<tr>
<td>3</td>
<td>TN</td>
<td>12 wk</td>
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<td>TE</td>
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<td>12 wk</td>
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</tbody>
</table>

TN: treatment-naïve  
R: ribavirin  
TE: treatment-experienced
<table>
<thead>
<tr>
<th>Gt</th>
<th>Prior Tx</th>
<th>LDV/SOF</th>
<th>DCV+SOF</th>
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<th>PTVr/OBV +DSV</th>
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<tr>
<td>1a</td>
<td>TN</td>
<td>12 wk</td>
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<td>12 wk</td>
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<tr>
<td></td>
<td>TE</td>
<td>12 wk+R</td>
<td></td>
<td></td>
<td></td>
<td>12 wk+R</td>
<td>12 wk</td>
</tr>
<tr>
<td>1b</td>
<td>TN</td>
<td>12 wk</td>
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<tr>
<td></td>
<td>TE</td>
<td>12 wk+R</td>
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<td>12 wk</td>
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<td>12 wk</td>
<td>12 wk</td>
</tr>
<tr>
<td>2</td>
<td>TN</td>
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<td>12 wk</td>
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<td>TE</td>
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<td></td>
<td>12 wk</td>
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<tr>
<td>3</td>
<td>TN</td>
<td>24 wk±R</td>
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<td></td>
<td></td>
<td></td>
<td>12 wk</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>24 wk+R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 wk+R</td>
</tr>
</tbody>
</table>

TN: treatment-naïve  
R: ribavirin  
TE: treatment-experienced
### Recommended DAA treatment for Decompensated cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>LDV/SOF</th>
<th>DCV+SOF</th>
<th>SOF/VEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 wk+R</td>
<td>12 wk+R</td>
<td>12 wk+R</td>
</tr>
<tr>
<td>Ribavirin-inelegible</td>
<td>24 wk</td>
<td>24 wk</td>
<td>24 wk</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>12 wk+R</td>
<td>12 wk+R</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>12 wk+R</td>
<td>12 wk+R</td>
</tr>
</tbody>
</table>

R: ribavirin
Worldwide chronic HBV prevalence (~250 million)

US: 1-2 million chronic HBV
~800,000 deaths/year worldwide
Natural history of HBV infection

- Acute infection
  - >90% of infected children progress to chronic disease
  - <5% of infected adults progress to chronic disease

- Chronic Infection

- Liver cancer (HCC)
  - 4-6% of people with chronic HBV infection develop HCC

- Cirrhosis
  - 30% of people with chronic HBV infection develop cirrhosis

- Liver failure (decompensation)
  - 23% of patients decompensate within 5 years of developing cirrhosis

- Liver transplantation
- Death
Factors associated with cirrhosis and HCC in HBV

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Host</strong></td>
<td>&gt;40 years of age</td>
<td>&gt;40 years of age</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td></td>
<td>Immune compromised</td>
<td>Immune compromised</td>
</tr>
<tr>
<td><strong>Viral/disease</strong></td>
<td>High serum HBV DNA (&gt;2,000 IU/mL)</td>
<td>Presence of cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Elevated ALT levels</td>
<td>High serum HBV DNA (&gt;2,000 IU/mL)</td>
</tr>
<tr>
<td></td>
<td>Prolonged time to HBeAg seroconversion</td>
<td>Elevated ALT</td>
</tr>
<tr>
<td></td>
<td>Development of HBeAg-negative CHB</td>
<td>Prolonged time to HBeAg seroconversion</td>
</tr>
<tr>
<td></td>
<td>Genotype C</td>
<td>Development of HBeAg-negative CHB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genotype C</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td>Concurrent viral infections (HCV, HIV, and HDV)</td>
<td>Concurrent viral infections (HCV, HIV, and HDV)</td>
</tr>
<tr>
<td></td>
<td>Heavy alcohol use</td>
<td>Heavy alcohol use</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>(obesity, diabetes)</td>
<td>(obesity, diabetes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aflatoxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking</td>
</tr>
</tbody>
</table>
HBV Treatment Goals

**Primary Goal**
- Control HBV replication

**Secondary Goal**
- Slow disease progression
- Improve histology
- Reduce risk of HCC
## Definitions of HBV cure

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBs Ab</th>
<th>Viraemia</th>
<th>cccDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional cure</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Complete cure</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Ab, antibodies; cccDNA, covalently closed circular DNA.
AASLD guidelines chronic HBV

• Treatment recommended immune active phase HBV
  – ALT >2 ULN (men: 30 U/L, women: 19 U/L) or “significant” histological disease (including cirrhosis)
  – HBV DNA >2,000 IU/mL (HBeAg negative)
  – HBV DNA >20,000 IU/mL (HBeAg positive)

• Consider treatment immune active phase ALT <2 ULN
  – Age >40 years (increased risk of advanced fibrosis)
  – Family history of HCC
  – Extrahepatic manifestations
AASLD guidelines chronic HBV

- Treatment not recommended for immune tolerant phase HBV
  - Normal ALT (men: 30 U/L, women: 19 U/L)
  - Monitor ALT every 6 months
- Treatment suggested in patients >40 years old with normal ALT and HBV DNA >1,000,000 IU/mL and liver biopsy with significant necroinflammatory activity or fibrosis
- Treatment suggested for patients with compensated cirrhosis and HBV DNA <2,000 IU/mL regardless of ALT levels
AASLD guidelines chronic HBV Pregnancy

- Treatment suggested to reduce risk perinatal transmission in HBsAg positive pregnant women with HBV DNA >200,000 IU/mL
- Antivirals studied: lamivudine, telbivudine and tenofovir
- Start treatment 28-32 weeks of gestation
- Discontinue treatment at birth to 3 months postpartum
- C-section not indicated to prevent transmission
- Breastfeeding not contraindicated
## Efficacy FDA-approved treatment chronic HBV

<table>
<thead>
<tr>
<th></th>
<th>Peg-IFN* (%)</th>
<th>Entecavir† (%)</th>
<th>Tenofovir† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg-Positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA suppression†</td>
<td>30-42 (&lt;2,000-40,000 IU/mL)</td>
<td>61 (&lt;50-60 IU/mL)</td>
<td>76 (&lt;60 IU/mL)</td>
</tr>
<tr>
<td></td>
<td>8-14 (&lt;80 IU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>32-36</td>
<td>22-25</td>
<td>–</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>29-36</td>
<td>21-22</td>
<td>21</td>
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<tr>
<td>Normalization ALT↑</td>
<td>34-52</td>
<td>68-81</td>
<td>68</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>2-7 (6 mos post-treatment)</td>
<td>2-3 (1 yr)</td>
<td>3 (1 yr)</td>
</tr>
<tr>
<td></td>
<td>11 (at 3 yrs post-treatment)</td>
<td>4-5 (2 yrs)</td>
<td>8 (3 yrs)</td>
</tr>
<tr>
<td></td>
<td>31.33-35</td>
<td>36-38</td>
<td>30-39</td>
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<tr>
<td><strong>HBeAg-Negative</strong></td>
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<tr>
<td>HBV DNA suppression§</td>
<td>43 (&lt;4,000 IU/mL)</td>
<td>90-91</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>19 (&lt;80 IU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalization ALT↑</td>
<td>59</td>
<td>78-88</td>
<td>76</td>
</tr>
<tr>
<td>HBsAg loss (%)</td>
<td>4 (6 mos post-treatment)</td>
<td>0-1 (1 yr)</td>
<td>0 (1 yr)</td>
</tr>
<tr>
<td></td>
<td>6 (at 3 yrs post-treatment)</td>
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</tr>
</tbody>
</table>
HBV life cycle and therapeutic targets
Therapeutic strategies to control HBV

- NUCs
- CRISPR/Cas9
- RNAi
- Entry inhibitors
- Core/capsid inhibitors

Interfering with the viral life cycle including spread

Modulation of immune system

IFNα
- TLR7 agonists
- DNA vaccines
- PD-1/PDL-1 inhibitors

cccDNA elimination

CRISPR/Cas9
- Small molecules
- LTβR agonists
- TDP2 inhibition

Liver International 2016; 36: 775-82
Conclusions HCV

- ~4 million chronic HCV in United States
- ~50% unaware of HCV infection
- Burden of cirrhosis estimated to peak 2020 with ~1 million cases
- **HCV is curable & treatment more likely to succeed if started early**
- Current direct-acting antiviral combinations provide safe and effective interferon-free options to treat hepatitis C
- Newer regimens in development for HCV:
  - Treat all genotypes
  - Shorter duration treatment
Conclusions HBV

- **~1-2 million** chronic HBV in United States
- **HBV is treatable, but “cure” is uncommon**
- Current treatments for hepatitis B are safe and effective
  - Peg-interferon
  - Entecavir
  - Tenofovir
- Multiple therapeutic targets in HBV and active development new therapies with goal to “cure” HBV