**Viral Hepatitis**

- Partially double-stranded DNA Virus
- Replicates by reverse transcription
- Transmitted in blood products and mother to child
- Associated with liver cancer
- Effective vaccine available

**Comparative Features of Hepatitis Viruses**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus structure</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Transmissibility</td>
<td>Blood,粪便</td>
<td>Blood,粪便</td>
<td>Blood,粪便</td>
<td>Blood,粪便</td>
<td>Blood,粪便</td>
</tr>
<tr>
<td>Incubation period (days)</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>150-180</td>
<td>70-160</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Mortality</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Characteristic symptoms</td>
<td>Jaundice</td>
<td>Jaundice</td>
<td>Jaundice</td>
<td>Jaundice</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Other disease associations</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
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<tr>
<td>Laboratory diagnosis</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Hepatitis B Virus**

- Partially double-stranded DNA Virus
- Replicates by reverse transcription
- Transmitted in blood products and mother to child
- Associated with liver cancer
- Effective vaccine available
Hepatitis B virus (Dane particle) and hepatitis B surface antigen (HBsAg) particles. The spherical HBsAg consists mainly of the S form of HBsAg with some M. The fiber HBsAg has S, M, and L forms.

Take home messages:
1) Multiple mRNAs are made from the same genetic information
2) Mutation in 1 position likely affects multiple proteins
3) Only 1 drug is needed to stop this virus.

Hepatitis B viral genome

Take home messages:
1) Reverse transcription takes place on the way out of the cell
2) Inhibition of reverse transcription blocks production of infectious virus
Outcomes after infection with HBV

- **Acute hepatitis B**
  - Resolution (50%)
  - Fulminant hepatitis (1%)

- **Asymptomatic carrier state**
  - Chronic persistent hepatitis
  - Chronic active hepatitis

- **Extrahepatic disease**
  - Polyarteritis nodosa
  - Glomerulonephritis
  - Hepatic cell carcinoma

- **Fever, rash, arthritis**
  - Jaundice
  - Dark urine
  - Malaise 95%
  - Anorexia 90%
  - Nausea 80%
  - RUQ pain 60%
  - Itching 10%

**Exposure**
- Incubation period
- Pre-icteric phase
- Acute disease
- Convalescent period
- Healthy

Acute Self-limiting HBV Infection

- **Incubation**
  - Acute viremia
  - Convalescence
  - Healthy

**Antigen**
- HBsAg
- HBeAg

**Antibody**
- Anti-HBs
- Anti-HBe

**Time**
- 4-12 wk
- 4-12 wk
- 2-16 wk
- Years
Chronic Active HBV Infection

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation</th>
<th>Acute viremia</th>
<th>Chronic viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>4-12 wk</td>
<td>6 month</td>
<td>Years</td>
</tr>
<tr>
<td>Antigen</td>
<td>HbsAg</td>
<td>HbsAg</td>
<td>Anti-Hbc</td>
</tr>
<tr>
<td>Antibody</td>
<td>Anti-HBc</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease:
- Jaundice

Symptoms:
- Virus Shedding
- Liver Enzymes

Five million Americans have hepatitis. Do you?

Get tested: 1-800-222-3773
Interpretation of Serologic Assays for Hepatitis B Virus (HBV)

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No evidence of present or past HBV infection</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Incubation period of HBV</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Early in acute infection with HBV or chronic HBV infection with high infectivity</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Later in acute infection, or chronic HBV infection with lower infectivity</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;Window&quot; period late in acute HBV infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Convalescent from HBV</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Later in convalescence (anti-HBe has waned)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Response to HBV vaccine</td>
</tr>
</tbody>
</table>

Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016
(Razavi-Shearer et al., Lancet Gastroenterol Hepatol 2018; 3(6): 383-403)
Therapy for HBV Infection

- **Lamivudine (1995)**
  - Nucleoside analogue, inhibits reverse transcription, reduction in HBV DNA,
  - Well tolerated, esp. compared to interferon

- **Hepsera (adefovir, 2003)**
  - Nucleoside analogue, inhibits reverse transcription, reduction in HBV DNA,
  - Works against Lamivudine resistant HBV

### HBV Patients with Substantial Alanine Aminotransferase Responses after Treatment with Lamivudine

![Graph showing cumulative percentage of patients with sustained response over weeks for Lamivudine, 100 mg, Lamivudine, 25 mg, and Placebo.](image)

### HBV DNA Suppression and Resistance Rates Associated with Different Therapeutic Agents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pegylated Interferon</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Adefovir</th>
<th>Tenofovir</th>
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</thead>
<tbody>
<tr>
<td><strong>HBV DNA Suppression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
<td>31</td>
<td>NA</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 yr</td>
<td>NA</td>
<td>NA</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 yr</td>
<td>NA</td>
<td>NA</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
<td>34</td>
<td>0</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2 yr</td>
<td>—</td>
<td>12</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>3 yr</td>
<td>—</td>
<td>76</td>
<td>30</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resistance Rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
<td>40</td>
<td>72</td>
<td>40</td>
<td>79</td>
<td>20</td>
</tr>
<tr>
<td>2 yr</td>
<td>NA</td>
<td>NA</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 yr</td>
<td>NA</td>
<td>NA</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>2 yr</td>
<td>—</td>
<td>11</td>
<td>0</td>
<td>&lt;1</td>
<td>11</td>
</tr>
<tr>
<td>3 yr</td>
<td>—</td>
<td>NA</td>
<td>20</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>
HBV Vaccine

- HBsAg subunit vaccine
  HBsAg is produced in yeast cells and spherical aggregates form

Acute Disease
- Symptoms:
  - Jaundice
  - Release of enzymes
- Resolution

Chronic Disease
- Limited cell-mediated immune response
- Delta Agent
  - Fulminant Hepatitis
  - Primary Hepatocellular Carcinoma
  - Cirrhosis
Hepatitis D virus

- Circular RNA virus that encodes the delta antigen
- Co-infects with HBV to induce severe hepatitis
- Has ribozyme activity that cleaves and ligates RNA
- Vaccination with HBV protects from HDV!!
Hepatitis C Virus

• Positive strand RNA virus
• Causes persistent viral infection
• Associated with liver cancer

Hepatitis C Virus

• Identified by molecular methods in 1989
• Blood test available by 1991
• Direct acting antivirals (DAAs) can “cure” infection
Outcomes of hepatitis C virus infection

- **Acute infection**
  - Recovery and clearance: 5%
  - Chronic hepatitis: 15%
  - Persistent infection: 80%
  - Liver failure: 0%
- **Chronic infection**
  - Recovery and clearance: 5%
  - Chronic hepatitis: 40%
  - Cirrhosis: 20%
  - Hepatocellular carcinoma: 4%
- **Risk of hepatocellular carcinoma** per year: 1-4%

Mean Time (years) From Transfusion to Chronic Hepatitis

<table>
<thead>
<tr>
<th>Event</th>
<th>Mean (years)</th>
<th>Range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Persistent Hepatitis (27)</td>
<td>14</td>
<td>1-42</td>
</tr>
<tr>
<td>Chronic Active Hepatitis (30)</td>
<td>19</td>
<td>1-37</td>
</tr>
<tr>
<td>Cirrhosis (60)</td>
<td>21</td>
<td>3-42</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma (14)</td>
<td>28</td>
<td>8-42</td>
</tr>
</tbody>
</table>

Factors Influencing HCV Disease Progression

- Female sex, young age at infection
- Alcohol use, coinfection
- Normal liver, acute infection
- Normal liver, chronic hepatitis
- Liver failure, chronic hepatitis
- Cirrhosis develops in 20% of cases
- Risk of hepatocellular carcinoma: 1-4% per year
Diagnosis and Screening of HCV

**Serologic Assays**
- Screen for antibodies to HCV antigens

**Molecular Assays**
- Qualitative Tests for HVC RNA
- Quantitative Tests for Viral RNA
- HCV Genotype Tests

HCV Relapse After IFN Therapy

```
IFN
HCV RNA
ALT

weeks

20   40   60   80

10^2  10^3  10^4

500   400   300  200
```

“Old” Antiviral Therapy to Combat HCV

- “Rebetron” Therapy
  - Ribaviron
  - Interferon
- Serious side effects
- Sustained virologic response (SVR) rate generally less than 50%
New Antiviral Agents to Combat HCV

- Protease Inhibitors (NS3)
- Phosphoprotein inhibitors (NS5A)
- Polymerase Inhibitors (NS5B)

Multiple Drug Regimen Most Effective

Current DAAs

Viral targets

<table>
<thead>
<tr>
<th>NS3</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td>The NS3/4A serine protease</td>
<td>Multifunctional phosphoprotein, component of the HCV-RNA replication complex</td>
<td>RNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Velpatasvir</td>
<td>Nucleoside analogues</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>

Chronic HCV Therapy (Genotype 1): Advances in Raising Cure Rates
Hepatitis C Virus

- Positive strand RNA virus
- Causes persistent viral infection
- Associated with liver cancer
- Use of DAAs leads to a sustained virologic response (cure)!

| Drug | Cost per Unit | Treatment Cost | SVR%
|------|--------------|----------------|--------|
| Episud® (sofosbuvir/velpatasvir) | $890 | $74,760 | 94-98%
| Zepat® (ribavirin/paraprevir) | $650 | $54,600 | 94-97%
| Harvok® (ribavirin/sofosbuvir) | $1,125 | $94,500 | 96-99%
| Viokira P® (omivitras/paracetamol/monamin/ distubir) | $27,773 (28-day pack) + $3,400–$3,600 (28-day pack) | $81,319 + $4,200–$5,000 | 97%
| Ribavirin | $700 + $1,000 | $64,160 + $84,000 | 95-97%

2016 cost for 12 week treatment of Genotype 1; SVR = undetectable HCV 12-24 weeks after stopping treatment.

- Sofosbuvir – nucleotide analog inhibitor of HCV NS5B polymerase
- Velpatasvir – direct acting antiviral for HCV NS5A
- This combination works against all 6 major genotypes of HCV

Sofosbuvir and Velpatasvir, when used in combination, offer a cure rate of 97% for Hepatitis C patients.
**Hepatitis E Virus**

- Positive strand RNA virus, rarely seen in the USA, mostly in southeast Asia (India, Nepal)
- Causes acute viral infection
- High mortality in pregnant women
- Killed virus vaccine elicits protective immunity (not yet FDA approved)

---

**Comparative Features of Hepatitis Viruses**

<table>
<thead>
<tr>
<th>Feature</th>
<th>HAV</th>
<th>HEV</th>
<th>HBV</th>
<th>HDV</th>
<th>HCV</th>
</tr>
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<tbody>
<tr>
<td>Common name</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Virus structure</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Transmission</td>
<td>Faecal</td>
<td>Faecal</td>
<td>Faecal</td>
<td>Faecal</td>
<td>Faecal</td>
</tr>
<tr>
<td>Incubation period</td>
<td>5-50</td>
<td>5-50</td>
<td>5-50</td>
<td>15-60</td>
<td>15-60</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Mortality</td>
<td>&lt;5%</td>
<td>1% - 2%</td>
<td>5% - 10%</td>
<td>High to Very high</td>
<td>High to Very high</td>
</tr>
<tr>
<td>Chronicity/Carrier state</td>
<td>None</td>
<td>Faecal</td>
<td>Hepatitis B</td>
<td>Hepatitis B</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Antivirals</td>
<td>None</td>
<td>RT inhibitors</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Killed virus</td>
<td>HBsAg subunit</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Viral Hepatitis**

- **HAV, HEV** acute
- **HBV/HDV** and **HCV** potentially chronic
- RT inhibitors for **HBV**; DAA for **HCV**
- Killed virus vaccines for **HAV** and **HEV**; subunit HBsAg vaccine for **HBV/HDV**