Overview

• What is viral hepatitis?
  – Broadly: inflammation of the liver due to any virus that targets the liver
  – A subset of viruses are tropic for the liver and require the liver for their lifecycle

• Five most common hepatotrophic viruses:
  – Hepatitis A (1973)
  – Hepatitis B (1970)
  – Hepatitis C (~1989)
  – Hepatitis D (~1970)
  – Hepatitis E (1983)
Clinical Manifestations of Viral Hepatitis

- Clinical presentation varies considerably
- Acute hepatitis:
  - Fatigue / malaise
  - Abdominal discomfort
  - Jaundice
  - Fulminant hepatic failure (primarily HAV, HBV)
- Chronic hepatitis:
  - Most commonly asymptomatic
  - Nearly 1/3 will have advanced fibrosis by time of clinical evaluation
Initial Evaluation: Acute hepatitis

Differential diagnosis of acute hepatitis:

- Drug-induced liver injury
- Autoimmune hepatitis
- Alcoholic hepatitis
- Ischemic hepatitis
- Acute biliary obstruction
- Viral Hepatitis:
  - Hepatotropic viruses
  - Non-hepatotropic viruses: HSV, CMV, HIV, EBV, VZV, adeno
- Other infectious causes (uncommon):
  - Erlichiosis, legionella, leptospirosis, Q fever
Initial Evaluation: Acute hepatitis

- Multi-center US study of causes of acute liver failure 1998-2008
- 300 patients enrolled
- DILI far and away the most common causes of acute liver failure
- Hepatitis A and hepatitis B comprised 11% of all cases

Initial Evaluation: Chronic Hepatitis

Differential diagnosis of chronic hepatitis

- Hepatotropic viruses: HBV, HCV, HDV
- Cholestatic diseases: PSC, PBC, AIDS cholangiopathy
- Steatohepatitis: NASH, alcoholic hepatitis
- Autoimmune hepatitis
- Wilson’s Disease
- Hereditary hemochromatosis
- Drug induced chronic hepatitis
- Alpha-1 antitrypsin deficiency
- Sarcoidosis, cryptogenic
Initial Evaluation: chronic hepatitis

- Series of ~1,000 U.S. patients from 1999-2001
- Chronic viral hepatitis comprised 67% of all causes of chronic liver disease
- U.K. study of NHS hepatology referrals in 2004 with 20% related to viral hepatitis, 29% related to NASH

The Hepatotropic Viruses

Viral genome
Transmission
Incubation period (days)
Progression to chronicity
Vaccine available
Treatment
Prophylaxis
ACUTE VIRAL HEPATITIS

Hepatitis A & E

AKA – Don’t eat that!
Hepatitis A
Hepatitis A Epidemiology

• Approximately 1.4 million new cases of acute hepatitis A occur yearly

• Presentation varies by geography:
  – Low prevalence: childhood, asymptomatic
  – High prevalence: adults, symptomatic, often severe

• Case in point: 2013 U.S. outbreak
  – 42% patients hospitalized, one transplant
  – All had a common exposure
Hepatitis A epidemiology

Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study

Hepatitis A Epidemiology

2005-2007 study of acute HAV
- Majority related to travel
  - Mexico & Americas most common
  - Caribbean, Africa
- Close contacts: 25-50% risk
- Daycare, outbreak

Since 2006, universal vaccination programs
- 2005: 4,488 cases reported
- 2009: 1,987 cases reported

Hepatitis A: Clinical Features

- Transmitted by the fecal-oral route
- Incubation period 15-45 days (mean – 30 days)
- Self limited hepatitis – but varies in severity and with age

Hepatitis A: epidemiology in resource-poor countries. Aggarwal, Rakesh; Goel, Ajit

DOI: 10.1097/QCO.0000000000000188
Hepatitis A: Clinical Features

- Viremia and shedding of antigen in the stool occur prior to clinical illness
- IgG response mounts after ~ 4 weeks
- Management is purely supportive
- Referral to transplant center if fulminant
- Vaccinate /IgG for contacts!
Hepatitis E
Hepatitis E Epidemiology

- HEV is also transmitted by fecal oral route
- Contaminated water remains most common source.
- Majority of clinically evident* cases of hepatitis E occur in endemic areas (*Stay tuned, more on this!)
  - Risk increases in times of flooding. Large outbreaks!
  - Children spared; high attack rates in pregnant women

Aggarwal & Naik, J Gastro Hep 2009.
Hepatitis E: Virology

- HEV is an RNA virus, with the least well characterized lifecycle of the hepatotropic viruses
- However, HEV is well known to have 4 distinct genotypes, which are important:
  - **Genotypes 1&2**: Endemic / epidemic virus
    - India, Asia, Africa, South America
    - Associated with outbreaks
  - **Genotypes 3&4**: sporadic disease
    - Swine thought to be a reservoir
Hepatitis E: Epidemiology, take 2!

- NHANES III – 21% of the US population has anti-HEV antibodies
  - Higher in Midwest, men
  - Pet owners and consumers of liver and organ meats
Hepatitis E: The zoonotic reservoir

Detection and characterization of infectious Hepatitis E virus from commercial pig livers sold in local grocery stores in the USA


- 127 packages of commercially available pig livers were sampled
- 11% tested positive for HEV RNA!
- All were genotype 3
Sadly, this has been replicated

Frequent Hepatitis E Virus Contamination in Food Containing Raw Pork Liver, France

Nicole Pavio, Thiziri Merbah, and Anne Thébault

Food products containing raw pork liver are suspected to be vehicles for transmission of hepatitis E virus. Four categories of food products, comprising 394 samples, were analyzed to determine hepatitis E virus prevalence. Virus was detected in 3%-30% of the different categories. Phylogenetic analysis showed high identity with human and swine sequences.
Hepatitis E: Clinical Features

- Incubation period is 28-40 days, with ALT/AST peak at 42-46 days
- Disease severity varies widely:
  - Epidemic – genotypes 1 & 2 – may be severe
    - 15% have jaundice
    - Maternal mortality is high: 2% in first trimester, 8-10% in second trimester, 20% in third trimester
    - Mortality high with underlying liver disease
  - Sporadic – genotypes 3 & 4 – generally asymptomatic
    - Icteric hepatitis rare. One series found 3% DILI were HEV IgM+
- Clinical symptoms may persist 4-6 weeks

Chronic Hepatitis E (?!!)

- Although rare, chronic HEV has been recognized to occur in immunosuppressed individuals:
  - HIV/AIDS
  - Organ transplant recipients
  - Chemotherapy
- May cause active hepatitis, fibrosis or cirrhosis
- Diagnosis: viral RNA in serum or feces
- Treatment:
  - Reduction of immune suppression
  - Ribavirin *(limited data)*

CHRONIC VIRAL HEPATITIS

Hepatitis B, C, D
Hepatitis B
Hepatitis B

- Hepatitis B is a 3.2kB DNA *hepadnavirus*
- 350-400 million individuals worldwide have chronic hepatitis B infection
- Transmission occurs perinatally, percutaneously and sexually
- When transmission occurs before age 5, chronicity is near universal. In adults, chronicity is rare following exposure.
- Treatments include interferon, nucleoside inhibitors and nucleotide inhibitors, but cure is exceedingly rare
Hepatitis B viral lifecycle

- HBV circulates as a small, 42nm particle with viral surface proteins (surface Ag)
- The genome encodes 7 viral proteins
- The viral nucleocapsid enters the nucleus and the partially double stranded viral DNA is “repaired” to form a fully double stranded covalently closed circular DNA (cccDNA). This cccDNA plays an important role in chronicity and therapeutic challenges
- cccDNA also serves as a template for RNA transcription
Hepatitis B Epidemiology

• Worldwide: 2 billion exposed, 284 million with chronic disease
• United States: 850,000 – 2 million chronically infected
  – Higher prevalence rates in immigrant populations, particularly from Asia. One study found ~ 33% prevalence among Chinese immigrants.
  – Non-Hispanic Asians account for 50% of disease burden
• Incident rates rising with IDU
  – Recent documented rise in incidence of acute HBV in Kentucky, W. Virginia, Tennessee in 30-39 year olds with IDU as RF

**Natural History of Hepatitis B**

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

ALT
- Immune tolerant
- Immune clearance
- Inactive carrier state
- Reactivation

Natural history of chronic hepatitis B

“Immunotolerant”

- HBsAg+
- HBV DNA >> 20,000^+
- +eAg, -eAb
- ALT normal
- No necroinflammation

“Immunoactive”

- HBsAg+
- HBV DNA > 20,000^+
- +eAg, -eAb
- ALT increased
- Necroinflammation

8-12%/yr

“Inactive Carrier”

- HBsAg+
- HBV DNA < 200^-
- -eAg, +eAb
- ALT normal
- No necroinflammation
- +/- fibrosis

20-30%

“Resolution”

- HBsAg=, HBsAb+
- HBV DNA Undetectable
- -eAg, +eAb
- ALT normal
- No necroinflammation
- +/- fibrosis

0.5%/yr

“eAg negative hepatitis”

- HBsAg+
- HBV DNA > 200^+
- eAg, +eAb
- ALT increased
- +/- necroinflammation

8-10%/yr

8-15% annual progression to cirrhosis

risk of HCC

DNA in IU/mL

* Not a candidate for therapy

* Unequivocal candidate for therapy

Pratt DS, 2008
Key Concept: Chronic hepatitis B carries an increased risk for development of hepatocellular carcinoma – even in the absence of cirrhosis.

• Cirrhosis is absent in up to 1/3 of patients with HBV-related HCC
• Mechanisms include direct mutagenic effects on human genome and inhibition of tumor suppressors by the HBV Protein X.
• Host factors also play a role: certain genes associated with risk, alcohol use, smoking
HCC Risk in Hepatitis B

• Non-cirrhotic: ~0.5% risk per year
  – Asian men > 40y, Asian women > 50y, Africans > 25y

• Cirrhotics: 2.2-3.7% risk per year

• Additional factors which increase risk:
  – **Viral factors**: Elevated viral DNA, viral genotype C
  – **Host factors**: Male gender, age > 40, HDV infection
  – Family history of HCC

• All of these groups merit q6 monthly screening with AFP and ultrasound (or alternating MRI if cirrhotic)

### When do you treat Hepatitis B?

#### Table 7  Treatment Guidelines for Chronic Hepatitis B

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver Biopsy</th>
<th>Management</th>
<th>Choice of First-Line Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>&gt; 20,000 IU/mL</td>
<td>&lt; 2 × ULN</td>
<td>None</td>
<td>Consider biopsy if age ≥ 40 yr, ALT high normal, or family history of HCC</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No inflammation</td>
<td>“Immune tolerant,” continue to monitor</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>&gt; 20,000 IU/mL</td>
<td>&gt; 2 × ULN</td>
<td>Inflammation or fibrosis</td>
<td>Treat</td>
<td>Entecavir, tenofovir, PEG interferon alfa × 48 wk</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt; 20,000 IU/mL</td>
<td>&gt; 2 × ULN</td>
<td>None Inflammation, fibrosis</td>
<td>Treat</td>
<td>Entecavir, tenofovir indefinitely; PEG interferon alfa × 48 wk</td>
</tr>
<tr>
<td></td>
<td>&gt; 2,000 IU/mL</td>
<td>&gt; 2 × ULN</td>
<td>None</td>
<td>Consider biopsy</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>&gt; 2,000 IU/mL</td>
<td>&gt; 2 × ULN</td>
<td>Moderate or severe inflammation, fibrosis</td>
<td>Treat</td>
<td>Entecavir, tenofovir indefinitely; PEG interferon alfa × 48 wk</td>
</tr>
<tr>
<td>&lt; 2,000 IU/mL</td>
<td>Normal</td>
<td>None</td>
<td>Continue to follow ALT, DNA</td>
<td>N/A</td>
<td>Entecavir, tenofovir indefinitely</td>
</tr>
<tr>
<td>±</td>
<td>Detectable</td>
<td>Any</td>
<td>Cirrhosis</td>
<td>Treat; consider referral to transplant center if decompensated</td>
<td>Entecavir, tenofovir indefinitely</td>
</tr>
</tbody>
</table>
### Treatment Options in HBV

#### Table 8: Antiviral Drugs for Hepatitis B

<table>
<thead>
<tr>
<th>Class</th>
<th>Pegylated Interferon</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Adefovir</th>
<th>Tenofovir</th>
<th>Entecavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose*</td>
<td>Biologic agent</td>
<td>L-nucleoside</td>
<td>L-nucleoside</td>
<td>Acyclic nucleotide</td>
<td>Acyclic nucleotide</td>
<td>Guanosine analogue</td>
</tr>
<tr>
<td></td>
<td>180 µg once weekly, subcutaneous injection</td>
<td>100 mg daily</td>
<td>600 mg daily</td>
<td>10 mg daily</td>
<td>300 mg daily</td>
<td>0.5 mg daily</td>
</tr>
<tr>
<td>Duration</td>
<td>48 wk</td>
<td>Variable - indefinite</td>
<td>Variable - indefinite</td>
<td>Variable - indefinite</td>
<td>Variable - indefinite</td>
<td>Variable - indefinite</td>
</tr>
<tr>
<td>Log10 HBV DNA decline (48 wk)</td>
<td>4.5</td>
<td>5.5</td>
<td>6.4</td>
<td>3.5</td>
<td>6.2</td>
<td>6.9</td>
</tr>
<tr>
<td>HBeAg loss (48–52 wk)</td>
<td>27%</td>
<td>21%</td>
<td>22%</td>
<td>12%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>HBsAg loss (48–52 wk)</td>
<td>3%</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
<td>0%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Frequency of resistance</td>
<td>—</td>
<td>30% at 1 yr</td>
<td>4.4% at 1 year</td>
<td>0% at 1 yr</td>
<td>0% at 1 yr</td>
<td>0.2% at 1 yr</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>80% at 5 yr</td>
<td>29% at 5 yr</td>
<td>0% at 5 yr</td>
<td>1.2% at 5 yr</td>
<td></td>
</tr>
<tr>
<td>Frequency of resistance (LMV resistant)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>≤ 18% at 1 yr</td>
<td>—</td>
<td>6% at 1 yr</td>
</tr>
<tr>
<td>Adverse effects/monitoring</td>
<td>Poorly tolerated: flulike symptoms, myalgias, leukopenia, thrombocytopenia; contraindicated in decompensated cirrhosis</td>
<td>High rates of resistance</td>
<td>Asymptomatic creatinine kinase elevations</td>
<td>3 Impaired renal function (rare); periodic creatinine monitoring recommended</td>
<td>Associated with rare renal impairment; periodic creatinine monitoring recommended</td>
<td>Well tolerated; safety profile similar to lamivudine</td>
</tr>
</tbody>
</table>
What about PEG-IFN?

• Recent data have suggested that combining PEG-IFN with tenofovir may have benefit:
  – 9% achieved surface Ag loss at 72 weeks
  – Greatest response in those with genotype A HBV and in e-antigen positive patients
    • 37.5% loss in genotype A, E-antigen positive

• Patients must be carefully selected due to risks associated with PEG-IFN
  – Non-cirrhotics
  – Best results in genotype A, female, high ALT and relatively low DNA

Does Viral Suppression make a Difference?

- Over 50% of patients will have improvement in degree of liver fibrosis
- There can even be regression of complete cirrhosis
- HCC risk is markedly reduced
  - Includes cirrhotics & non-cirrhotics
  - Data pooled from 3 studies

Hepatitis C
HCV Epidemiology

115 million individuals infected worldwide
3-4 million chronically infected in the US alone
Leading indication for liver transplantation (currently)

The evolving epidemiology...

- Since 2010, there has been a dramatic rise in incident HCV in the US.
- Some regions have had over 200% increase in acute HCV infections.

May 18, 2012: CDC issues a recommendation that **all** individuals in the “baby boomer” generation should be tested for hepatitis C

- Anyone born between 1945 – 1964
- Estimated that 1 in 30 harbor chronic HCV infection
- 75% of all U.S. HCV carriers thought to be in this group
- One-time antibody test, HCV RNA if positive
Implementing CDC Screening?

• How to best encourage birth cohort testing?
• One study randomized patients to no “trigger” versus three interventions:
  – Letters inviting patients to undergo screening
    • Resulted in an 8-fold increase in detection
  – Best Practice Alert:
    • Resulted in a 3-fold increase in detection
  – Trained recruiter:
    • Resulted in a 5-fold increase in detection

Smith, et al. AASLD 2014, #194
Acute HCV infection is most commonly silent (90%). Between 15-20% will spontaneously clear. The majority will go on to develop chronic infection.

When acute HCV presents clinically:
- Aminotransferase elevation
- Jaundice
- Abdominal pain
- Malaise/rash/fevers

Spontaneous clearance is more common with symptomatic presentation, and with jaundice in particular. Genetics are key!
HCV Natural History

- After exposure, chronicity is likely (only 15% clear)
- Fibrosis progresses slowly: one stage every 7-10 y
- HIV, alcohol accelerate progression

Fig. 4. Natural history of hepatitis C. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma. Percentage values refer to patients.
Complications of HCV

Chronic hepatitis C has a number of manifestations that extend beyond liver injury

• **Common complications:**
  – Insulin resistance (32-70%)
  – Metabolic Syndrome (26-51%)
  – Type 2 Diabetes (14-50%)
  – Mixed Cryoglobulinemic Vasculitis (19-50%)

• **Other complications**
  – Renal disease
  – Lymphoma
  – Autoimmune disease

Bear with me…!

…Understanding the virology helps demystify the medications!
HCV Lifecycle: an overview
HCV Virology

- Hepatitis C is a positive strand, RNA virus
- The viral genome encodes 4 structural proteins, and six non-structural proteins
HCV Virology

Developed countries

Americas + Western Europe

South Africa

Middle East

North Africa

IDU

Asia

U.S.
1 75%
2,3 25%

Simmonds P, Journal of Hepatology, 1999
The good news: a sustained response means *sustained*

- **Sustained Virologic Response (%)**
  - All: 99.1%
  - PEG Mono therapy: 98.8%
  - PEG RBV Abnormal ALT: 99.1%
  - PEG RBV Normal ALT: 100%
  - PEG +/− RBV HCV HIV: 99.0%

- **Mean F/U:** 0.8-7.1 yrs

Swain M, et al. *Gastroenterology* 2010;139:1593
More good news: SVR translates into decreased all-cause and liver related death.

Van der Meer. JAMA 2012.
More good news: SVR translates into decreased all-cause and liver related death.
<table>
<thead>
<tr>
<th>Target</th>
<th>Structural / Functional Considerations</th>
<th>Function in viral life cycle</th>
<th>Drugs in clinical Development?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>3 functional domains: RNA binding domain, hydrophobic domain, and C-Terminal domain</td>
<td>RNA binding and core-core interactions, nucleocapsid assembly, association with cytoplasmic lipid droplets, replication; may play a role in steatosis</td>
<td>None</td>
</tr>
<tr>
<td>E1</td>
<td>Glycosylated transmembrane protein</td>
<td>Envelope protein, facilitates entry</td>
<td>None</td>
</tr>
<tr>
<td>E2</td>
<td>Glycosylated transmembrane protein</td>
<td>Envelope protein, facilitates entry</td>
<td>None</td>
</tr>
<tr>
<td>p7</td>
<td>Two transmembrane domains linked by cytoplasmic loop</td>
<td>Creates an ion channel (viroporin) across ER membrane, important for viral assembly and release</td>
<td>None</td>
</tr>
<tr>
<td>NS2</td>
<td>N-terminal membrane anchor domain and C-terminal Zn-dependent cysteine protease</td>
<td>Autoprotease, required for assembly and infectivity</td>
<td>None</td>
</tr>
<tr>
<td>NS3</td>
<td>Serine-type protease, RNA helicase, NTPase</td>
<td>Viral polyprotein processing (with NS4A), cleavage of proteins of innate immune response (with NS4A), RNA replication, and virion assembly</td>
<td>Yes</td>
</tr>
<tr>
<td>NS4A</td>
<td>Forms heterodimer with NS3</td>
<td>Protease activity (with NS3); may play a role in viral persistence</td>
<td>None</td>
</tr>
<tr>
<td>NS4B</td>
<td>Integral membrane protein</td>
<td>Directs formation of the membranous web, interacts with viral RNA during replication</td>
<td>Yes*</td>
</tr>
<tr>
<td>NS5A</td>
<td>Three or four distinct domains; 2 states of phosphorylation</td>
<td>Essential for replication, and likely for assembly; may inhibit interferon signaling. Function may depend on phosphorylation state</td>
<td>Yes</td>
</tr>
<tr>
<td>NS5B</td>
<td>R-handed polymerase structure</td>
<td>RNA-dependent RNA polymerase</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Host Factors: What has been targeted for drug development?

<table>
<thead>
<tr>
<th>Host Target</th>
<th>Cellular Function</th>
<th>Viral Interaction</th>
<th>Drugs in clinical development?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophilin</td>
<td>Peptidyl-prolyl cis-trans isomerase, molecular chaperone</td>
<td>Interacts with NS5A and supports replication</td>
<td>Yes^</td>
</tr>
<tr>
<td>MicroRNA-122 (miR-122)</td>
<td>Comprises over 70% of hepatic miRs; Exact cellular functions unknown</td>
<td>Binds two sites in 5' UTR of HCV genome, promotes replication</td>
<td>Yes</td>
</tr>
<tr>
<td>HMG-Co-A Reductase</td>
<td>Rate-limiting enzyme in mevalonate pathway of cholesterol biosynthesis</td>
<td>Generates geranylgeraniol; host FBL2 protein requires geranylgeranylation to support replication</td>
<td>No*</td>
</tr>
<tr>
<td>Phosphatidylinositol-4-kinase-I1a</td>
<td>Kinase, converts phosphatidylinositol (PI) to PI 4-phosphate</td>
<td>Supports generation of the membranous web</td>
<td>No</td>
</tr>
</tbody>
</table>
May 2011: FDA approves two new drugs for the therapy of chronic hepatitis C

- **Telaprevir** and **Boceprevir**
- Both are **NS3/4A protease inhibitors**
  - Target the GENOTYPE 1 viral protease
  - Block the cleavage of the viral polypeptide
  - Non-structural proteins of the replicase complex are therefore blocked as well
- But had lower SVR rates in “real world” and associated with significant adverse effects
- No longer in clinical use
## HCV-TARGET: The Real World Experience with BOC/TPR

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir (n=262)</th>
<th>Telaprevir (n=838)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex</strong></td>
<td>60.3%</td>
<td>60.7%</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>56 (20-76)</td>
<td>56 (18-75)</td>
</tr>
<tr>
<td><strong>Black race</strong></td>
<td>15.7%</td>
<td>15.9%</td>
</tr>
<tr>
<td><strong>Genotype 1, no subtype</strong></td>
<td>22.1%</td>
<td>22.3%</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>29.8%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>SVR, Treatment-naïve patients</strong></td>
<td>58%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Premature Discontinuations</strong></td>
<td>41.6%</td>
<td>34.7%</td>
</tr>
<tr>
<td><strong>Epoetin alfa use</strong></td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Transfusion</strong></td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Skin Rash</strong></td>
<td>32%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Serious Adverse Events (SAE)</strong></td>
<td>15%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Di Bisceglie AM et al. The Liver Meeting 2013; Abstract 41
Therapy of Chronic Hepatitis C: 2016

Who are the players in the game now?

• “Second Generation” **NS3/NS4A** protease inhibitors

• **NS5B** RNA-dependent RNA Polymerase inhibitors
  – Nucleos(t)ide analogs
  – Non-nucleoside inhibitors

• **NS5A** inhibitors
Limitations of PIs: Viral Resistance.

- HCV circulates as a quasispecies
- It is estimated that any infected individual generates *every possible* single and double mutation *every day*
- Viral resistance, therefore, is inevitable. *In vivo*, monotherapy results in resistance within days, and is near universal within two weeks
- In TPV/BOC testing, resistance associated with lower trough levels. Thus, q8h dosing
“Second Generation” NS3/4A Protease Inhibitors

- More favorable pharmacokinetics / dosing
- Potency against additional genotypes (2-6)
- Improved side effect profiles
- Maintain antiviral effect against viral variants that have developed resistance to telaprevir and boceprevir
- Drugs in this class:
  - Simeprevir
  - Paritaprevir
  - Grazoprevir
NS5B: RNA-dependent RNA Polymerase

Two Broad Classes of NS5B Polymerase Inhibitors:

**Nucleoside Inhibitors (NI)**
- Bind at the catalytic or “active” site of the RNA polymerase (Sofosbuvir)

**Non nucleoside Inhibitors (NNI)**
- Bind at away from the catalytic site, at an allosteric site
# HCV Drugs: NS3A/4A PI, NS5B

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>HCV Genotype with Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3A/4A Protease Inhibitors</td>
<td>Simeprevir</td>
<td>Olysio®(45)</td>
<td>1, 4</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir (fixed dose combination product with ritonavir, ombitasvir, and copackaged with dasabuvir)</td>
<td>Viekira Pak®(40)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir (fixed dose combination product with ombitasvir, ritonavir)</td>
<td>Technivie®(44)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir (fixed dose combination product with elbasvir)</td>
<td>Zepatier™(41)</td>
<td>1 and 4</td>
</tr>
<tr>
<td>NS5B Polymerase Inhibitors- nucleotide</td>
<td>Sofosbuvir</td>
<td>Sovaldi®(37)</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>NS5B Polymerase Inhibitors- non-nucleoside</td>
<td>Dasabuvir (copackaged with fixed dose combination product - ombitasvir, paritaprevir, ritonavir)</td>
<td>Viekira Pak®(40)</td>
<td>1</td>
</tr>
</tbody>
</table>

Nucleoside vs. Non-nucleoside Inhibitors

• **Nucleos(t)ide Inhibitors (NI): Sofosbuvir**
  – Mechanism: mimic natural nucleosides, bind the catalytic site, and are incorporated into the viral genome, prompting chain termination
  – Catalytic site conserved across genotypes (thus, may have pan-genotypic effects)
  – Mutations at the catalytic site comes at a high cost of fitness (higher barrier to resistance)
Nucleoside vs. Non-nucleoside Inhibitors

- **Non-nucleoside Inhibitors (NNIs): Dasabuvir**
  - Mechanism: bind away from the catalytic site, leading to conformational changes in the polymerase preventing chain elongation
  - Allosteric sites not conserved across genotypes
  - Mutations at the allosteric sites do not come at a significant fitness cost
NS5A Inhibitors:

• NS5A has several functions in the HCV lifecycle
  – Required for replication
  – Thought to bridge replication and assembly
  – May subvert the host interferon response
• No enzymatic structure to target (like a protease or polymerase) – making drug development difficult
• First drug against NS5A found by a small molecule screen, then chemically modified
• Many treatment failures will have pre-existing NS5A resistance mutation
• Now: Ledipasvir, Daclatasvir, Ombitasvir, elbasvir, velpatasvir
## HCV Drugs: NS5A Inhibitors

<table>
<thead>
<tr>
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<th>Generic Name</th>
<th>Trade Name</th>
<th>HCV Genotype with Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5A Inhibitors</td>
<td>Ledipasvir (fixed dose combination product with sofosbuvir)</td>
<td>Harvoni®(39)</td>
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<tr>
<td></td>
<td>Ombitasvir (fixed dose combination product with paritaprevir, ritonavir and copackaged with dasabuvir)</td>
<td>Viekira Pak®(40)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir (fixed dose combination product with paritaprevir, ritonavir)</td>
<td>Technivie®(29)</td>
<td>4</td>
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<tr>
<td></td>
<td>Daclatasvir</td>
<td>Daklinza™(42)</td>
<td>1 and 3</td>
</tr>
<tr>
<td></td>
<td>Elbasvir (fixed dose combination product with grazoprevir)</td>
<td>Zepatier™(41)</td>
<td>1 and 4</td>
</tr>
<tr>
<td></td>
<td>Velpatasvir (fixed dose combination product with sofosbuvir)</td>
<td>Epclusa®(43)</td>
<td>1, 2, 3, 4, 5 and 6</td>
</tr>
</tbody>
</table>
Other steps in viral lifecycle:

- **NS4B**: Inhibitor identified, not currently in drug development
- **Entry**: Numerous entry factors required
  - SRB1 Inhibitor (ITX 5061)
  - Anti-E3 antibodies
  - EGFR inhibitor (Erlotinib/Tarceva)
  - NPC1L1 inhibitor (ezetimibe/Zetia)
- **Host Factors**
Treatment of HCV: then and now

Hepatitis D

The naked one
Hepatitis D: overview

- Hepatitis D is a small, “defective” RNA virus
  - Smallest genome of any human virus
  - The genome encodes a single protein (delta Ag)
  - The virus is encapsulated by HBV surface Ag
  - Thus, HDV is dependent on HBV for infection and replications

- Epidemiology parallels HBV – but transmission is only parenteral.
Hepatitis D: Epidemiology

Figure 2. Schematic representation of the main areas of HDV globally onto which the predominant hepatitis D virus (HDV) genotype for each geographical area has been superimposed. (From Negro 2014; reproduced from © 2013 John Wiley and Sons.)
Hepatitis D: Clinical Features

• Clinical features depend on whether HDV was acquired after or simultaneously with HBV
  – Acute coinfection – often resolves as HBV is most commonly cleared by adults.
  – Superinfection: viral persistence is the rule
    • Presents as an acute hepatitis or decompensation
    • Often have lower HBV DNA levels

• Accelerates disease progression in HBV
  – Cirrhosis develops in 70% of cases
    • 15% may occur within two years of coinfection
  – Increased risk of hepatocellular carcinoma
Questions?

Homer Simpson Quotes

"All right, let's not panic. I'll make the money by selling one of my livers. I can get by with one."

Esperance Schaefer, MD, MPH
Massachusetts General Hospital, MGH Liver Center