Learning Objectives

- know appropriate test to use to diagnose HCV
- Understand the natural progression of HCV and in HIV patients
- List 3 HCV treatments that can be used for genotype 1
- Identify general patterns of differences in treatment based on genotype, presence of cirrhosis, and prior anti-HCV treatment
- List several common side effects of HCV medications
HCV Mortality Exceeds HIV

The Increasing Burden of Mortality From Viral Hepatitis in the United States Between 1999 and 2007

Incidence of HCC in the United States

Who Should be Tested?

- Injection drug users
  - Active or previously used
- Internasal drug uses who share paraphernalia
- Received blood or blood component transfusion or organ transplant prior to 1992
- Hemophiliacs
- Unexplained LFT elevation
- Hemodialysis
- Children born to HCV-infected mothers
- Everyone at the age of 50 (new CDC recommendations)
HCV Sexual Transmission
Phylogenetic Tree Analysis in Acute HCV

- Acute HCV in MSM
- Associated with STDS
- Unprotected anal sex with trauma
- Risk of sexual transmission of HCV in MSM
Counseling for IDU

- Stop use of illicit drugs
- Avoid reusing or sharing syringes, needles, water, cotton, or other paraphernalia
- Clean injection site with new alcohol swab
- Dispose needles in puncture-proof container
Counseling to prevent transmission

HCV infected persons should be counseled on how to avoid HCV transmission (class 1, level C)

- Avoid sharing tooth brushes and dental or shaving equipment
- Cover any bleeding wound to prevent contact with blood to others
- Do not donate blood, body organs, or tissue or semen
- Risk of sexual transmission low (in monogamous heterosexual couples)
HIV/HCV

Natural History
## Spontaneous HCV Viral Clearance in HIV Patients

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Viral Clearance (%) (n=353 IDU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>5%</td>
</tr>
<tr>
<td>200 to 500</td>
<td>8.6%</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>8.3%</td>
</tr>
<tr>
<td>Total</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Comparison of Serial HCV RNA

Survival in Persons with HIV
1995-2005 from age 25 years

Survival in Persons with HIV HIV vs. HIV/HCV and by Time Periods

HCV Disease in HIV-infected
Accelerated Progression

Progression to cirrhosis:
HIV/HCV 3 x than HCV alone

Effect of HAART
Liver-Related Mortality in HIV/HCV

Qurishi. Lancet 2003; 362: 17-8-13
Impact of HAART on Fibrosis

Treatment of HIV critical in slowing HCV progression

HCV Treatment
Evolving HCV Treatment Paradigm

Duration of therapy
- IFN 24 weeks
- IFN 48 weeks
- IFN+ RBV 28 weeks
- Peg-IFNa+RBV 48 weeks
- TVR/BOC+ Peg-IFNa+RBV
- SOF + Peg-IFNa+RBV 12 weeks
- Oral therapy for 12 wks or less

SVR= Sustained Viral Response

SVR%:
- 1991: 6%
- 2014: 99%
HCV Genotype 1a: Most common in US and at Parkland

- 1a: 58%
- 1b: 19%
- 2: 10%
- 3: 4%
- 4: 3%
- 6: 1%
- Co-infection: 5%

n= 280
Directly Acting Antivirals

- **NS5A polymerase inhibitors** (-asvir)
  - High potency
  - Pan-genotypic, but inhibition by genotype may vary by molecule
  - Intermediate barrier to resistance (Barrier is how many mutations it takes to develop resistance; low barrier is 1 mutation and high barrier is multiple mutations)

- **NS5B polymerase inhibitors** (-busvir)
  - Intermediate potency
  - Some are pan-genotypic, others not
  - High barrier to resistance, but some are not

- **NS3/4A Protease Inhibitors** (-evir)
  - High potency
  - Limited genotypic coverage
  - Low barrier to resistance
Because of risk of HCV developing resistance, combination therapy should be used when treating hepatitis C
Definition of Cure

A person is considered to be cured of hepatitis C if the HCV RNA is undetectable 12 weeks after the completion of therapy.
Staging Liver Disease is key step prior to HCV treatment. Duration of treatment can vary depending on fibrosis stage

Treatment experienced refers to having taken interferon/ribavirin before. If a patient has taken newer therapies, then you should refer to specialist for treatment.
Four stages of liver fibrosis

- Minimal fibrosis
- Moderate fibrosis
- Severe fibrosis: Cirrhosis

Mild fibrosis
Staging liver fibrosis

- Liver biopsy is gold standard but excluding cirrhosis may also be possible with noninvasive estimates of liver fibrosis
  - **Fib-4 or APRI score** or equivalent serum tests are widely available.
  - FibroSure (# 550123 thru Labcorp)
  - Imaging helpful (liver ultrasound)
  - Fibroscan in special centers
  - MRI elastography but not widely available.
Calculating FIB-4

**Fibrosis-4 (FIB-4) Calculator**

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

\[
\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10^9/L)} \times \sqrt{\text{ALT (U/L)}}}
\]

**Non-cirrhotic**
- 1.45

**Cirrhotic**
- 3.25

**Interpretation:**
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4–6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Sofosbuvir/Ledipasvir: Genotype targets

- **Sofosbuvir** = nucleoside NS5B inhibitor and pan-genotypic
- **Ledipasvir** = NS5A inhibitor with activity for genotypes 1, 4, 5, and 6
- Combination for genotypes 1, 4, 5, and 6
- One pill once a day
- Can not use with Cr Cl <30 ml/min

Harvoni
Sofosbuvir/Ledipasvir: Duration of Therapy

- Treatment naïve or non-cirrhotic treatment experienced
  - 12 weeks
  - Except: 8 weeks for genotype 1 with HCV RNA <6 million and early stage disease
  - Risk of relapse if patient has advanced fibrosis

- Treatment-experienced cirrhotic
  - 24 weeks
  - 12 weeks if you add ribavirin
Sofosbuvir/Ledipasvir: Efficacy

TN= Treatment naïve
TE= Treatment experienced

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
<th>SVR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN, non cirrhotic</td>
<td>Sof/LDV 12 wk</td>
<td>90</td>
</tr>
<tr>
<td>TN, with or without cirrhosis</td>
<td>Sof/LDV 8 wk</td>
<td>85</td>
</tr>
<tr>
<td>TE, with or without cirrhosis</td>
<td>Sof/LDV+ RBV 12 wk</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Sof/LDV 24 wk</td>
<td>90</td>
</tr>
</tbody>
</table>

TN= Treatment naïve
TE= Treatment experienced
Sofosbuvir/Ledipasvir: Drug Interactions

- Acid reducing medication: PPI (prescription strength) can reduce efficacy
  - Alternative - H2 blockers 12 hours apart
- Anticonvulsants: decrease efficacy
- Antimycobacterial therapy (including rifamycins): decrease efficacy
- HIV medications
  - Truvada and boosted PI combination
    - Increases tenofovir levels
  - Tipranavir
- St. John’s Wort: decrease efficacy
- Amiodarone - bradycardia
Sofosbuvir/Ledipasvir: Side Effects

- Fatigue (13-18%)
- Headaches (11-17%)
- Nausea (6-9%)
- Diarrhea (3-7%)
- Insomnia (3-6%)

Other side effects not in package insert
- Increased appetite
- Occasional increase in creatinine
Sofosbuvir and Ribavirin

- Sofosbuvir -- a NS5A inhibitor
- Ribavirin -- guansine anlong (mechanism of action unknown)
- Sofosbuvir: one pill once a day
- Ribavirin dose is weight-based
- If >75 kg give 1200 mg daily
  - 200 mg tablets give 3 in AM and 3 in PM
- If ≤75 kg give 1000 mg daily
  - 200 mg tablets give 3 in AM and 2 in PM
Sofosbuvir and Ribavirin: Duration of Therapy

- Genotype 2: Sofosbuvir 400 mg daily with weight-based ribavirin 12 weeks
  - With cirrhosis - treat for 16 weeks
- Genotype 3: Sofosbuvir 400 mg daily with weight-based ribavirin for 24 weeks
  - With cirrhosis, not as effective especially in treatment-experienced cirrhotics
Sofosbuvir and Ribavirin: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>SOF/RBV 12wk</th>
<th>SOF/RBV 24wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall</td>
<td>256</td>
<td>176</td>
</tr>
<tr>
<td>geno 2</td>
<td>73</td>
<td>183</td>
</tr>
<tr>
<td>geno 3</td>
<td>67</td>
<td>93</td>
</tr>
</tbody>
</table>

Zeuzem et al. *AASLD 2013 abstract 1085*
Sofosbuvir and Ribavirin:

- Sofosbuvir and ribavirin have renal clearance
- Do not use sofosbuvir in patients with cr cl <30 ml/min
- Ribavirin dosing should be modified for renal insufficiency

- Efficacy of Sofosbuvir will be decreased if used with
  - Rifampin
  - St. John’s Wort
Sofosbuvir and Ribavirin:

- Fatigue (30-38%)
- Headache (24-30%)
- Nausea (13-22%)
- Insomnia (15-15%)
- Pruritus (11-27%)
- Anemia (6-10%)
- Asthenia (6-21%)
- Irritability (10%)
- Rash (8-9%)
Sofosbuvir and Ribavirin: Side Effects

- Ribavirin
  - Anemia
  - Rash
  - Irritability
  - Insomnia

Ribavirin rash
**Ribavirin rash management**

- Use topical steroids
- Reduce dose of ribavirin, reduce to 600 mg daily
- If severe, stop ribavirin and re-introduce 2 weeks later if rash resolved
- For pruritus, prescribe atarax
Ribavirin anemia monitoring and management

- Check CBC at 2 and 4 weeks and if stable then q4 weeks
- Reduce dose to 600 mg (monitor q 2 weeks)
  - If Hgb <10 g/dl without known cardiac disease
  - If >2 g/dl decrease within 4 weeks with history of stable cardiac disease
- Stop ribavirin
  - If Hgb <8.5 g /dL without known cardiac disease
  - If <12 g/dl after 4 weeks at reduced dose with known stable cardiac disease
Ombitasvir, paritaprevir/ritonavir and dasabuvir (O/P/D)

- Ombitasvir (NS5A)/Paritaprevir (PI), fixed dose combination
- Dasabuvir (NS5B)
- Combination therapy: 2 Ombitasvir/paritaprevir once a day plus 1 Dasabuvir twice a day
- Ritonavir has no HCV activity and is used to boost paritaprevir levels
- Used for genotype 1 and 4 (but not dasabuvir for genotype 4)
Ombitasvir, Paritaprevir/ritonavir and Dasabuvir (O/P/D): Duration of therapy

**Genotype**

1a: O/P/D + Ribavirin weight-based for 12 weeks

1a with cirrhosis: O/P/D & Ribavirin for 24 weeks

1b: O/P/D for 12 weeks

1b with cirrhosis: O/P/D for 12 weeks
Ombitasvir, Paritaprevir/ritonavir and Dasabuvir: Efficacy

GT1a, naïve  GT1a, TE  GT1a, cirrhosis/TE  GT1b, cirrhosis, TE

SVR %

O/P/D 12 wk  O/P/D 12 +RBV  O/P/D + RBV 24
Ombitasvir, Paritaprevir/ritonavir and Dasabuvir: Drug Interactions

- The following drugs or class of drugs will decrease efficacy
  - Anticonvulsants
  - HIV medication: Efavirenz
  - Rifamycins
  - Sedatives
  - St. John’s wort
- Do not use with ethinyl-estradiol as it can cause liver enzyme elevation
Ombitasvir, paritaprevir/ritonavir and Dasabuvir: Side effects

With ribavirin
- Fatigue (34%)
- Nausea (16-22%)
- pruritus (13-18%)
- skin reactions (16%)
- insomnia (12-14%)
- asthenia (9-14%)

Without ribavirin
- Nausea (8%)
- Pruritus (7%)
- insomnia (5%)
- Asthenia (4%)
Daclatasvir/Sofosbuvir

- Daclatasvir: NS5A
- Sofosbuvir: NS5B
- Both are pangenotypic: for all genotypes
- FDA Approved for genotype 3 and if HIV infected for genotype 1 and 3
- Daclatasvir 60 mg once a day
  - Strong CYP 3a inhibitors: use 30 mg (HIV PI)
    - Because HIV PI will boost level of daclatasvir
  - Moderate CYP 3a inducers: use 90 mg (HIV NNRTI such as efavirenz)
    - Because efavirenz will decrease daclatasvir levels
- Combination: 400 mg once a day
Daclatasvir/Sofosbuvir: Genotype and Duration

- **Genotype 1:**
  - Daclatasvir/sofosbuvir for: Treatment naive or Treatment experienced without cirrhosis or compensated cirrhotics → 12 weeks

- **Genotype 3:**
  - Daclatasvir/sofosbuvir: no cirrhosis → 12 week
  - Daclatasvir/sofosbuvir + Ribavirin: cirrhosis or decompensated → 12 weeks

Daklinza and Sovaldi:
Daclatasvir /Sofosbuvir:

- Drug Interactions:
  - amiodarone can cause bradycardia (sofosbuvir)
  - cyp 3A inhibitors/inducers (daclatasvir)
    - You have to adjust the dose of daclatasvir based on if you have a drug that is a strong inhibitor or inducer
Daclatasvir / Sofosbuvir:

- **Side effects**
  - Headache (8-14%)
  - Fatigue (14-15%)
  - Nausea (8-9%)
  - Diarrhea (5-7%)
Daclatasvir / Sofosbuvir: Efficacy

SVR %

- Dac/sof 12 wk (overall)
- Dac/sof (no cirrhosis)
- Dac/Sof (with cirrhosis)

- genotype 3
- genotype 1
Elbasvir/Grazoprevir:

- Elbasvir is a NS5A polymerase inhibitor
- Grazoprevir is a NS3/4A protease inhibitor
- One pill once a day
- Effective for genotype 1 and 4
Elbasvir/Grazoprevir: Duration of Therapy

- Genotype 1a Treatment Naïve or Experienced:
  - without NS5A mutations: 12 weeks
  - with NS5A mutations: + ribavirin for 16 weeks
- Genotype 1b Treatment naïve/experienced: 12 weeks
- Genotype 1a or 1b Treatment experience with PI: + ribavirin for 12 weeks
- Genotype 4 Treatment naive: 12 weeks
- Genotype 4 Treatment experienced: + ribavirin for 16 weeks
Elbasvir/Grazoprevir: Efficacy

SVR %

0 10 20 30 40 50 60 70 80 90 100

overall 1a 1b non-cirrhotic cirrhotic

TN= Treatment naïve  TE= Treatment experienced

Elbasvir/Grazoprevir: Use in renal disease and drug interactions

- Can be used with renal insufficiency or dialysis
- Avoid with the following drugs due to drug interactions which will decrease efficacy:
  - Anticonvulsants
  - Antimycobacteria agents such as rifamycins
  - St. John’s Wort
  - HIV medications such as Efavirenz, HIV Protease Inhibitor
  - Cyclosporine
Elbasvir/Grazoprevir: Side Effects

- Without ribavirin:
  - Fatigue (5-11%)
  - Headache (10%)
  - Abd pain/diarrhea (2%)
  - Irritability (1%)
  - Depression (1%)

- With ribavirin:
  - Anemia (8%)
  - Headache (6%)
  - Fatigue (4%)
  - Dyspnea (4%)
  - Rash & Pruritus (4%)
  - Irritability (3%)
  - Abd pain (2%)
  - Depression (1%)
  - Arthralgia (2%)
Sofosbuvir/Velpatasvir:

- Sofosbuvir is nucleoside NS5B inhibitor and pan-genotypic
- Velpatasvir is NS5A inhibitor and pangenotypic
- Can be used for all genotypes 1, 2, 3, 4, 5, and 6
- One pill once a day
Sofosbuvir/Velpatasvir: Indications

- Without cirrhosis or with compensated cirrhosis (Child-Pugh A): 12 weeks (regardless of genotype)

- Decompensated cirrhosis (Child-Pugh B and C) + ribavirin (weight-based) for 12 weeks

- Can not use with Cr Cl <30 ml/min
Sofosbuvir/Velpatasvir: Efficacy

SVR (%)

- Genotype 1a
- Genotype 1b
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5
- Genotype 6

- Epclusa 12 wk
- sof + RBV 12 wk
- Sof+ RBV 24 wk
Sofosbuvir/Velpatasvir: Drug Interactions

- Amiodarone - symptomatic bradycardia
- Rifampin, St. John’s wort, carbamazepine: may decrease concentration of drug
- Drugs decreasing velpatasvir dose
  - Antacids: take least 4 hours apart
  - H2 blockers: take 12 hours apart
  - No PPI: except take this drug with food at least 4 hours before omeprazole 20 mg
- HIV meds: do not use with Efavirenz, Tipranavir/ritonavir
Sofosbuvir/Velpatasvir: Side Effects

Sofosbuvir/Velpatasvir
- Headache (22%)
- Fatigue (15%)
- Nausea (9%)
- Asthenia (5%)
- Insomnia (5%)

With Ribavirin
- Fatigue (32%)
- Anemia (26%)
- Nausea (15%)
- Headache (11%)
- Diarrhea (10%)
Effectiveness of HCV medications at Parkland

Including 16% who failed to return for the last HCV viral load 12 weeks after completing treatment

Including those who completed all follow-up testing

- SVR 12: 76%
- Relapse: 16%
- Lost to F/U: 2%
- Other: 6%

n= 178

- SVR 12: 90%
- Relapse: 3%
- Other: 7%

n= 150
HCV Treatment: Labs

- Baseline HCV RNA, LFTS, electrolytes, Bun, cr, CBC
- Week 2 CBC (if on ribavirin)
- 4 week HCV RNA, LFTS, (add CBC if on ribavirin)
- 8 week HCV RNA, LFTS, (add CBC if on ribavirin)
- 12 week HCV RNA, LFTS, (add CBC if on ribavirin)
- 12 week post-treatment HCV RNA, LFTS, CBC

- Can omit week 8 and 12 if cost is an issue
- But must obtain CBCs if on ribavirin
Thank you for your Attention!

STOP HCC by Treating HCV