Therapeutic Update:
New and Emerging Therapies for Hepatitis C

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Disclosures/Conflicts of Interest

• No actual or potential conflicts of interest in relation to this program

Objectives

1. Describe the pathophysiology of acute and chronic hepatitis C virus (HCV) infections
2. Compare and contrast new therapeutic agents to treat HCV
3. Discuss current treatment guidelines for the management of HCV
4. Determine the most appropriate HCV therapy based on specific patient characteristics.
Abbreviations

- HCV (hepatitis C virus)
- GT (genotype)
- SVR (sustained viral response)
- SOF (sofosbuvir)
- LDV (ledipasvir)
- SMV (simeprevir)
- OMV (ombitasvir)
- PTV (paritaprevir)
- DSV (dasabuvir)
- DCV (daclatasvir)
- RBV (ribavirin)
- PEG-IFN (pegylated interferon)
- OMV (ombitasvir)
- PTV (paritaprevir)
- DSV (dasabuvir)
- DCV (daclatasvir)
- RBV (ribavirin)
- PEG-IFN (pegylated interferon)

Hepatitis C Virus

- Single-stranded RNA virus
- Acute or chronic infection
- Blood borne transmission
- Complications
  - Cirrhosis
  - Liver cancer
  - Death

HCV Transmission

- Injection Drug Use 60%
- Transfusion (before 1992) 10%
- Other (HD, health care work, perinatal) 5%
- Sexual 15%
- Unknown 10%


HCV Epidemiology

• In the United States
  • 30,000 new infections annually
  • 3.2 million chronically infected
  • 15,000 HCV related deaths annually


Genotypes

• 6 HCV genotypes
• In US, genotype 1 is most common
  • 1a = 1b >> 2 > 3
• Genotype helps determine treatment options and duration

HCV Genotype Distribution

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Predominant Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>North America, Europe, East Asia</td>
</tr>
<tr>
<td>2</td>
<td>North America, Europe, East Asia</td>
</tr>
<tr>
<td>3</td>
<td>North America, Europe, East Asia</td>
</tr>
<tr>
<td>4</td>
<td>Middle East, Central America</td>
</tr>
<tr>
<td>5</td>
<td>South Africa, Southeast Asia</td>
</tr>
<tr>
<td>6</td>
<td>South Africa, Southeast Asia</td>
</tr>
</tbody>
</table>


HCV Life Cycle

Liang Ti, Ghany. NEJM. 2013;368:1907-1917
Clinical Progression of HCV

**Acute Infection**
- Usually asymptomatic
- Fatigue
- Weakness
- Abdominal pain
- N/V
- Jaundice
- Fever
- Muscle/joint pain

6 months
- 85%

20-30 yrs
- 20%

**Chronic Infection**
- Asymptomatic
- Persistent fatigue
- Abdominal pain
- Decr. appetite

**Cirrhosis/ESLD**
- Portal HTN
- Hepatic encephalopathy
- Ascites
- Coagulopathy
- Spider angioma
- Hepatocellular carcinoma

Who needs screening for HCV?

- One time screening
  - All individuals born between 1945 and 1965
  - Persons with risk factors for infection
    - Illicit drug use (IV or intranasal)
    - Hemodialysis
    - Children with HCV+ mother
    - Recipients of blood transfusions/organ transplant prior to HCV screening
    - Unregulated tattoos
    - HIV positive patients

- Annual screening
  - Patients with ongoing risk factors above
Historical Perspective of HCV

- 1975: Non-A, non-B hepatitis described
- 1989: HCV discovered
- 1991: IFN alfa-2b approved
- 1998: PEG-IFN alfa-2b approved (+ ribavirin)
- 2001: IFN alfa-2b + ribavirin approved
- 2011: Sofosbuvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir/dasabuvir approved
- 2013: Boceprevir and telaprevir approved
- 2014: Daclatasvir approved


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**Peg-interferon alfa**

- PEG-IFN alfa 2a (Pegasys®)
  - 180mcg SQ weekly
- PEG-IFN alfa 2b (PegIntron®)
  - 1.5mcg/kg SQ weekly

- Nonspecific MOA
- ADRs
  - FATTY FATigue!!!
  - Flu-like symptoms
  - Injection site reactions
  - N/V
  - Insomnia
  - Depression
  - Cognitive dysfunction
  - Hematologic abnormalities

Pegasys Package Insert
PegIntron Package Insert

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**Ribavirin**

- Copegus®, Rebetol®, Riba-Pak®, generic ribavirin

- Unknown mechanism in HCV
- Used in all genotypes
- Pregnancy category: X

- Weight-based dosing
  - ≤ 75kg: 1000mg/day PO in 2 divided doses
  - 40mg/600mg
  - > 75kg: 1200mg/day PO in 2 divided doses
  - 600mg PO BID

- ADRs
  - Hemolytic anemia (10-15%)
    - Dose dependent
  - Itching
    - Continue treatment
    - Use topical corticosteroids
  - Rash
  - Fatigue

Downfall of IFN-based Regimens

- **Efficacy issues in GT 1**
  - IFN monotherapy SVR <10%
  - Peg-IFN + Ribavirin SVR 38-56%
  - GT 2/3 had improved SVRs of 80-90%

- **Tolerability/Safety issues**
  - Profound, debilitating fatigue, flu-like symptoms
  - Hematologic abnormalities (anemia, neutropenia, thrombocytopenia)

- **Current uses**
  - Co-1st line therapy for GT 3
  - Alternative options for GT 4, 5, 6

Out with the New...

- **Boceprevir and telaprevir**
  - First oral HCV drugs
  - 1st generation NS3/4A protease inhibitors
  - Only used in combo with ribavirin + Peg-IFN alfa
  - Boceprevir (Viekirax)
    - Approved 05/2011; Discontinued 12/2015
  - Telaprevir (Incivek)
    - Approved 05/2011; Discontinued 10/2014

In with the Newer

- Simeprevir (SMV)
- Sofosbuvir (SOF)
- Ledipasvir + Sofosbuvir (LDV/SOF)
- Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (OMV/PTV/RTV + DSV)
- Daclatasvir (DCV)

***Direct Acting Antivirals (DAA)***
Ledipasvir/Sofosbuvir (Harvoni®)

- LDV  NSSA Inhibitor
- SOF  NS5B Polymerase inhibitor
- 1 tablet PO daily (± food)
- 1st line treatment of genotype 1a/1b
  - Tx-naïve: 12 weeks
  - Tx-experienced + cirrhosis: 24 weeks
- SVR: 94-99%

Harvoni Package Insert
Hepatitis C Online. http://www.hepatitisc.uw.edu/page/treatment/drugs/ledipasvir-sofosbuvir

Ledipasvir/Sofosbuvir (Harvoni®)

- Adverse Effects
  - Well tolerated
  - Fatigue
  - Headache
  - Nausea

- Cost
  - 12 weeks: $94,000
  - 24 weeks: $189,000

- Drug Interactions- LOTS!!
  - Antiretroviral therapy
  - Amiodarone
  - Digoxin
  - P-glycoprotein Inhibitors
  - St. John’s Wort
  - Rifampin
  - Acid Reducing Agents
  - Rosuvastatin

Harvoni Package Insert
Hepatitis C Online. http://www.hepatitisc.uw.edu/page/treatment/drugs/ledipasvir-sofosbuvir
Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (Viekira Pak™)

- OMV: NS5A Inhibitor
- PTV: NS3/4A Protease Inhibitor (ritonavir boosted)
- DSV: NS5B Polymerase Inhibitor

- 1st line therapy for genotype 1a/1b

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (no cirrhosis)</td>
<td>Viekira Pak + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a (+ cirrhosis)</td>
<td>Viekira Pak + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>1b (no cirrhosis)</td>
<td>Viekira Pak</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1b (+ cirrhosis)</td>
<td>Viekira Pak + ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

- SVR: 91-100%

Viekira Pak Package Insert
Hepatitis C Online: [http://www.hepatitisc.uw.edu/page/treatment/drugs/3d](http://www.hepatitisc.uw.edu/page/treatment/drugs/3d)

- Adverse Effects
  - Fatigue
  - Nausea
  - Pruritus/Rash
  - Insomnia
  - Asthenia
  - Elevated ALT w/ estrogen contraceptives

- Cost
  - 12 weeks: $83,000
  - 24 weeks: $168,000

- Drug Interactions- EVEN MORE!!
  - Alfuzosin*
  - Carbamazepine, phenytoin, phenobarb*
  - Gemfibrozil*
  - Ethinyl-estradiol contraceptives*
  - Lovastatin/simvastatin*
  - Antiretrovirals (efavirenz*)
  - Sildenafil*
  - Amlodipine
  - Antiarrhythmic drugs
  *= contraindicated

Viekira Pak Package Insert
Hepatitis C Online: [http://www.hepatitisc.uw.edu/page/treatment/drugs/3d](http://www.hepatitisc.uw.edu/page/treatment/drugs/3d)

Sofosbuvir (Sovaldi™)

- **MOA**: NS5B Polymerase inhibitor
  - Pangenotypic activity
  - Used in GT 1-4

- **400mg PO daily (± food)**
  - Role and combination therapy differ by GT
  - GT1: SOF + (SMV or DCV or LDV)

- **SVR**
  - Varies but usually >90%

Sofosbuvir (Sovaldi™)

- **ADRs**
  - Well tolerated
  - Fatigue
  - Headache

- **Cost**
  - 12 weeks: $84,000

Sofosbuvir (Sovaldi™)

- **Drug interactions**: P-gp inducers
  - Carbamazepine
  - Phenytoin
  - Rifampin, etc
  - St. John’s wort
  - Amiodarone (bradycardia)

Daclatasvir (Daklinza®)

- **MOA**: NS5A inhibitor
  - Pangenotypic activity
  - Used in GT 1, 2, 3

- **60mg PO daily (± food)**
  - In combination with sofosbuvir
  - GT 1: 12 weeks (no cirrhosis)
  - GT 1: 24 weeks (cirrhosis)

- **GT 1 SVR >96% (DCV+SOF)**
  - 63-76% in advanced cirrhosis
Daclatasvir (Daklinza®)

- **DRs**
  - Fatigue
  - Headache
  - Nausea
  - Bradycardia (amio+SOF)

- **Cost**
  - 12 weeks: $63,000

**Drug Interactions**
- **3A4 Drugs**
  - Strong 3A4 inhibitors
    - Decr. dose to 20mg
  - Moderate 3A4 inducers
    - Incr. dose to 60 mg
  - Strong 3A4 inducers
    - Contraindicated

- **Cost**
  - 12 weeks: $63,000

Drug Interactions: organic anion transporting polypeptide 1B1, 1B3, breast cancer resistance protein

Simeprevir (Olysio™)

- **MOA** - NS3/4A Protease Inhibitor (2nd gen)
  - Used in GT 1 only

- **150 mg PO daily with food**
  - In combination with SOF
  - 12 weeks (no cirrhosis)
  - 24 weeks (cirrhosis)

- **Q80K polymorphism testing prior to initiation**

- **SVR > 90% (SMV+SOF)**

**Drug Interactions**
- **3A4 Drugs**
  - Antiretrovirals
  - 3A4 Inducers
  - 3A4 Inhibitors
  - St. John’s Wort

**Cost**
- 12 weeks: $66,000

Drug Interactions: organic anion transporting polypeptide 1B1, 1B3, breast cancer resistance protein
### PRO
- Highly effective
- Well tolerated
- Lowest pill burden
- Good for HIV infection, post transplant

### CON
- Longer treatment duration for treatment experienced
- High pill burden
- Usual co-administration with ribavirin
- Major DDIs
- Cost

<table>
<thead>
<tr>
<th>PRO</th>
<th>OMV/PTV/RTV + DSV (Viekira Pak)</th>
<th>SMV + SOF (Olysio + Sovaldi)</th>
<th>DCV + SOF (Daklinza + Sovaldi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO</td>
<td>Highly effective</td>
<td>Highly effective</td>
<td>Highly effective</td>
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<tr>
<td>Well tolerated</td>
<td>Well tolerated</td>
<td>Well tolerated</td>
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<tr>
<td>Similar duration for tx</td>
<td>Similar duration for tx</td>
<td>Similar duration for tx</td>
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<tr>
<td>experienced patients</td>
<td>experienced patients</td>
<td>experienced patients</td>
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</tr>
<tr>
<td>Good for HIV infection, post</td>
<td>Good for HIV infection, post</td>
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<tr>
<td>transplant</td>
<td>transplant</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>Long pill burden</td>
<td>High pill burden</td>
<td>Reduced SVR in cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Usually co-administration with</td>
<td>Usually co-administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ribavirin</td>
<td>with ribavirin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major DDIs</td>
<td>Major DDIs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cost</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polymorphism testing</td>
<td>Polymorphism testing</td>
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</tr>
<tr>
<td></td>
<td>Use in GT 1 only</td>
<td>Use in GT 1 only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cost</td>
<td>Cost</td>
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</tbody>
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### Self-Assessment Question 1

- All of the following are potential benefits of new direct acting antiviral HCV regimens over IFN-alfa-based regimens EXCEPT:
  a) All oral regimens
  b) Improved therapeutic efficacy
  c) Reduced drug interaction risk
  d) Improved tolerability

### Choosing an HCV Regimen

- Genotype?
  - Subtype if GT 1?

- Treatment naive vs. experienced?
  - What drugs were used if previously treated?

- Cirrhosis status?

- Most urgent for treatment
  - Compensated cirrhosis
  - Liver transplant patients
  - Advanced cirrhosis
  - Co: HIV or HBV
  - Extrahepatic symptoms

### Recommendations for Treatment-Naive with Genotype 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/1b</td>
<td>LDV/SOF x 12 weeks</td>
<td>LDV/SOF x 12 weeks</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td>1a</td>
<td>OMV/PTV/RTV + DSV + RBV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV + RBV x 24 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1b</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1a</td>
<td>SMV + SOF +/- RBV x 12 weeks</td>
<td>SMV + SOF +/- RBV x 24 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1b</td>
<td>SMV + SOF x 12 weeks</td>
<td>SMV + SOF +/- RBV x 24 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1a/1b</td>
<td>DCV + SOF x 12 weeks</td>
<td>DCV + SOF +/- RBV x 24 weeks</td>
<td>I,B (no cirrhosis) IIa,B (cirrhosis)</td>
</tr>
</tbody>
</table>

### Recommendations for Treatment-Experienced w/ prior PegIFN/RBV

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/1b</td>
<td>LDV/SOF x 12 weeks</td>
<td>LDV/SOF x 24 weeks</td>
<td>I, A (no cirrhosis) II, A/B (cirrhosis)</td>
</tr>
<tr>
<td>1a</td>
<td>OMV/PTV/RTV + DSV + RBV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV + RBV x 24 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1b</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1a/1b</td>
<td>SMV + SOF +/- RBV x 12 weeks</td>
<td>SMV + SOF +/- RBV x 24 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

### Recommendations for Treatment-Experienced w/ prior SOF or Protease Inhibitor

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/1b</td>
<td>LDV/SOF x 12 weeks</td>
<td>LDV/SOF x 24 weeks</td>
<td>I, A (no cirrhosis) II, A/B (cirrhosis)</td>
</tr>
<tr>
<td>1a</td>
<td>OMV/PTV/RTV + DSV + RBV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV + RBV x 24 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1b</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>OMV/PTV/RTV + DSV x 12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>1a/1b</td>
<td>SMV + SOF +/- RBV x 12 weeks</td>
<td>SMV + SOF +/- RBV x 24 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

Any NS5A Inhibitor Use: Defer treatment for addl data Test for resistance IIb, C (no cirrhosis) IIb, C (cirrhosis)
**Recommendations for Treatment-Naive with Genotype 2**

- **SOF + RBV x 12 weeks (no cirrhosis)**
  - SVR 94%
  - Extend therapy to 16 weeks with cirrhosis

- **DCV + SOF x 12 weeks (no cirrhosis)**
  - For patients who cannot take ribavirin
  - SVR 92%
  - Extend therapy to 24 weeks with cirrhosis

- **NOT RECOMMENDED**
  - Peg-IFN + RBV
  - Monotherapy of any kind
  - Regimens with ledipasvir (or boceprevir/telaprevir)

**Recommendations for Treatment-Naive with Genotype 3**

- **DCV + SOF x 12 weeks (no cirrhosis)**
  - SVR 95%
  - If cirrhosis: +/- RBV and extend therapy to 24 weeks (SVR 88%)

- **SOF + PegIFN + RBV x 12 weeks**
  - SVR 95%

- **SOF + RBV x 24 weeks**
  - For IFN ineligible patients (SVR 94%)

- **NOT RECOMMENDED**
  - Peg-IFN + RBV
  - Monotherapy of any kind
  - Regimens with simeprevir (or boceprevir/telaprevir)

**Considerations for HIV Co-infections**

- Do NOT interrupt HIV therapy to treat HCV
- OMV/PTV/RTV + DSV
  - Adjust or stop RTV if receiving boosted protease inhibitor as part of HIV regimen
  - Avoid use with darunavir, efavirenz, lopinavir/r, ritopivirine
  - Avoid if co-infected patients are not on antiretroviral therapy
- LDV regimens
  - Increases tenofovir levels, increasing renal toxicity risk
  - Avoid if CrCl <60 or if receiving tenofovir + (ritonavir or cobicistat)
- SMV cannot be used with HIV protease inhibitors and most NNRTIs
  - Integrase inhibitors or rilpivirine: OK
- DCV + SOF preferred in HIV regimen cannot be changed
  - Decr. DCV dose to 30mg if using atazanavir/r
  - Incr. DCV dose 90mg if using efavirenz or etravirine

Drugs in the Pipeline

- **Phase 3**
  - Grazoprevir/Elbasvir
  - GS-5816 (NS5A inhibitor)
    - Studied in combo with SOF
- **Phase 2**
  - Odalasvir (NS5A inhibitor)
  - Studied in combo with SOF
  - Sovaprevir (NS3/4A protease inhibitor)
  - Samatasvir (NS5A inhibitor) and TMC-647055 (NS5B inhibitor)
    - Studied in combo with DCV and RTV

Clinicaltrials.gov

Self-Assessment Case

- GT is a 31 year old female presenting to your ID clinic for evaluation and initiation of HCV treatment.
- **PMH**
  - HCV Genotype 1b x 10 years (not previously treated)
  - GERD
- **Social History**
  - Former IV drug user in early 20s.
  - Lives with husband
  - Works as waitress at local restaurant
  - No known drug allergies

Self-Assessment Case

- **Home Medications**
  - Omeprazole 20 mg daily
  - Desogestrel/ethinyl estradiol 0.15mg/0.03mg
- **ROS**
  - Mild fatigue; no abdominal pain; no N/V/D; no rashes
- **Phys. Exam**
  - No jaundice; no hepatomegaly; no ascites
- **Labs (1 month ago)**
  - BMP: within normal limits
  - AST 20; ALT 25; AlkPhos 60; Tbilii 0.5; INR 1.01
  - HCV RNA: 14 million copies/mL
- **Advanced diagnostics**
  - No fibrosis
Self-Assessment Question 2

• How might GT's home medications impact the selection of an HCV regimen?

Self-Assessment Question 3

• What would be the best HCV regimen to start in GT at this time?
  a) LDV/SOF  
  b) SOF + RBV  
  c) OMV/PTV/RTV + DSV  
  d) SOF + PegIFN + RBV  
  e) DCV + SOF

Self-Assessment Question 4

• How long should GT be treated for her chronic HCV?
  a) 8 weeks  
  b) 12 weeks  
  c) 24 weeks  
  d) 48 weeks
Conclusions

- Chronic HCV is now curable!
- Every growing therapeutic armamentarium
  - Frequent changes to guidelines
- Pharmacist roles
  - Adverse effect monitoring and mitigation
  - Cost containment
  - Evaluating for drug interactions
  - Patient education and counseling

Therapeutic Update:
New and Emerging Therapies for Hepatitis C

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November 8th, 2015