Hepatitis C: A silent and potentially deadly but curable epidemic

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Disclosure

• No real or potential conflict of interest to disclose
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives

• Upon completion of the learning activity the participant will be able to:
  – Assess risk factors for the becoming infected with Hepatitis C.
  – Analyze appropriate diagnostic tests for the diagnosis of Hepatitis C.
  – Describe the extrahepatic manifestations of Hepatitis C.
Hepatitis

- Inflammation of the liver
  - Presents with elevation of liver enzymes
- Infectious or noninfectious
  - Acute or chronic
Infectious Hepatitis

- Hepatitis A
- Hepatitis B
- Non-A; non-B
  - Hepatitis C
  - Hepatitis D
  - Hepatitis E
  - Hepatitis G
  - Hepatitis ?

Scope of the Problem

- ~3.2 million people are chronically infected with HCV based on NHANES (1999-2002) population\(^1,2\)
  - 1945-1964\(^1\)
Approximately 3.2 Million People in the US Have Chronic HCV Infection (continued)

- The number chronically infected with HCV in the US may be even higher\(^3\)
  - Accounting for populations not sampled in NHANES
    - Incarcerated
    - Homeless
    - Nursing home residents
    - Hospitalized
    - Those on active military duty

Hepatitis C

- The most common chronic blood-borne infection in the US.
  - #1 reason for liver transplant in the US
- 10–20% will develop cirrhosis 20–30 years after exposure.
- Up to 5% will develop liver cancer

Hepatitis C (continued)

- 15% of those exposed will clear spontaneously but retain the hepatitis C antibody.
  - 85% will remain viremic (chronically infected).
- Leading cause of death in patients with HIV
Natural History of HCV Infection

*20%–30% of individuals are symptomatic.

HCC = Hepatocellular carcinoma


Extrahepatic Manifestations of HCV

**Strongly associated**

- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis

**Possibly associated**

- Corneal ulcers
- Thyroid disease
- Lichen planus
- Pulmonary fibrosis
- Type 2 diabetes
- Systemic vasculitis (polyarteritis nodosa, microscopic polyangiitis)
- Arthralgias, myalgias, inflammatory polyarthritis
- Autoimmune thrombocytopenia


Insulin Resistance

- Specific feature of chronic HCV infection (but not HBV)¹
  - Associated with genotypes 1 and 4, high serum HCV RNA level, and fibrosis¹
  - More common in carriers of the “T” IL28B allele²

In a retrospective cohort study of patients treated with interferon therapy (± RBV), SVR was associated with a two-thirds reduction in development of type 2 diabetes mellitus.³

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Symptoms of HCV

- Acute infection (<6 months)
  - Generally asymptomatic, but jaundice occurs in 20% of cases.

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The Majority of Patients Are Asymptomatic

- Symptoms of HCV include¹ ²
  - Fatigue
  - Nausea
  - Poor appetite/weight loss
  - Muscle and joint pains/muscle weakness
  - Jaundice
  - Abdominal pain or swelling
  - Dark urine
  - Itching
  - Fluid retention

- However, symptoms differ from patient to patient and some patients may not have any symptoms for up to 20 years, yet their liver disease may be progressing¹

- 80% of patients with HCV have no signs or symptoms²
Hepatitis C Virus
High Risk Profile

Transmission Factor

<table>
<thead>
<tr>
<th>Transmission rate (%)</th>
<th>Recipients of clotting factors made before 1987</th>
<th>Injection drug use</th>
<th>Long-term dialysis</th>
<th>Individuals with multiple sex partners</th>
<th>Recipients of blood transfusions prior to July 1992</th>
<th>Infants born to infected women</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td></td>
<td>10-20</td>
<td>4-6</td>
<td>5</td>
<td>4-7</td>
<td></td>
</tr>
</tbody>
</table>


Additional Risk Factor

• Those born between 1945–1965 (baby boomers) should be offered a 1 time screening for hepatitis C.
  – 5 times more likely than other adults to have hepatitis C
  – 75% of adults with hepatitis C are baby boomers.
    – Source: http://www.cdc.gov/features/HepatitisCTesting/index.html
Possible Risk Factor

Who to Screen

• Anyone with a risk factor for hepatitis C
• Anyone with elevated liver enzymes

Diagnosis of Hepatitis C

• Health history
  – Most reliable method available to assess risk
• Physical exam
  – Not reliable!!!
• Abnormal liver enzymes (ALT)
  – Not reliable!!!
Diagnostic Studies

• Hepatitis C antibody
• Hepatitis C RNA
• Hepatitis C genotype
• Liver biopsy

Diagnostic Tests

• Hepatitis C antibody
  – Screening test for exposure to HC
  – Immune cell that is made to fight off HC
  – All of those exposed will generate an antibody but 15% will clear the virus.
  – 85% of those with an antibody will be currently infected if not previously treated.

Diagnostic Tests (continued)

• Hepatitis C RNA
  – “Viral load”
  – Indicates current infection
  – Value does not correlate with degree of liver damage or clinical symptoms
Laboratory Diagnosis of Chronic HCV Infection

- RNA testing identifies active disease in HCV-seropositive patients
- HCV antibodies appear by 6–8 weeks following infection\(^1\)
  - Can be detected by EIA\(^2\)
- Serum ALT is not a reliable indicator of liver damage\(^1\)
- FDA-approved rapid point-of-care testing is available\(^3\)
  - OraQuick® HCV Test

ALT=Alanine aminotransferase; EIA=Enzyme immunoassay; RNA=Ribonucleic acid; ULN=Upper limit of normal

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Diagnostic Tests

- **Hepatitis C genotype**
  - There are 6 forms (genotypes) of HCV.
  - Genotype 1 is the most common in the US.
  - With current therapies the response rates are similar regardless of genotype

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Diagnostic Tests (continued)

- **Patented biomarker test (FibroSure\(^a\))**
  - Serologic markers to predict stage of fibrosis and inflammation
- **Transient elastography (FibroScan\(^a\))**
  - Imaging that can be done in the office
  - Until recently it was deemed experimental
- **Liver biopsy**
  - Allows staging of liver disease
  - Rules out autoimmune hepatitis
Factors Causing Rapid Progression of Liver Disease in HC

- Alcohol use
- Obesity/fatty liver
- HIV infection
- Hepatitis B infection
- Male gender


Historical Management of Hepatitis C
SVR was associated with improved long-term liver-related outcomes in the HALT-C trial database.


Analysis of liver outcomes (decompensation, HCC, or death) in the HALT-C trial database. All comparisons P<0.001.

*Detectable HCV RNA at treatment week 20 (combination therapy was discontinued at week 4).

HALT-C = Hepatitis C Antiviral Long-term Treatment against Cirrhosis.

SVR was associated with reduced long-term risk of all-cause mortality in an international, multicenter study.


International, multicenter, long-term followup study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).


Non-SVR

SVR

P<0.001

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**Historic Management of Hepatitis C**

- **Interferon**
  - Innate immune chemical that has antiviral properties
  - “Boosts” the immune system and recruits other immune cells
    - Histamine, interleukins, bradykinins, etc.
  - <10% effective as a solo agent in eradicating HC

- **Ribavirin (1998)**
  - Mechanism of action unknown
  - 1000 mg/day (<75 kg), 1200 mg/day (>75 kg)
  - Ineffective as monotherapy
  - Close to 50% effective in eradicating HC when used in combination with interferon

- **Pegylated interferon**
  - 2001
  - Used in combination with ribavirin
  - A molecule of polyethylene glycol was added to the interferon, prolonging its action.
  - <50% effective in eradicating genotype 1 HC and >70% effective at eradicating genotype 2/3
Historic Management of HC (continued)

- Direct acting antivirals
  - 2011
  - Boceprevir (Victrelis®), telaprevir (Incivek®)
  - Approved for genotype 1 virus only
  - Approved only in combination with pegylated interferon and ribavirin
  - Up to 80% cure rate in genotype 1 disease


Drawbacks of Boceprevir and Telaprevir

- Approved for genotype 1 only
  - Must be used in combination with pegylated interferon/ribavirin
- Adverse effects
  - Profound anemia
  - High rate of viral resistance if doses were missed
  - CYP P450 pharmaceutical interactions

Drawbacks of Boceprevir and Telaprevir (continued)

- Severe reactions
  - Toxic epidermal necrolysis (TEN) syndrome
  - Stevens-Johnson syndrome
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)

Image source: https://en.wikipedia.org/wiki/Stevens%E2%80%93Johnson_syndrome
Olysio (Simeprevir®)

- HCV-specific NS3/4A protease inhibitor
- Approved in combination with pegylated interferon and ribavirin for genotype 1 HC
  - Decreased effectiveness with the NS3 Q80K polymorphism in Genotype 1a
- Dose
  - 150 mg daily with food

Simeprevir Cure Rates

<table>
<thead>
<tr>
<th>Cure</th>
<th>Simeprevir + PEG/Riba N=521 % (n/N)</th>
<th>Placebo + REG/Riba N=264 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cure 1a + 1b</td>
<td>80 (419/521) 75 (191/254)</td>
<td>50 (132/264) 47 (62/131)</td>
</tr>
<tr>
<td>Genotype 1a without Q80K</td>
<td>84 (138/165) 58 (49/84)</td>
<td>43 (36/83) 52 (23/44)</td>
</tr>
<tr>
<td>Genotype 1b with Q80K</td>
<td>85 (228/267)</td>
<td>53 (70/133)</td>
</tr>
</tbody>
</table>

Simeprevir Dosage Regimens

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Treatment regimen and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive and prior relapsers</td>
<td>12 weeks of simeprevir in combination with PEG/Riba followed by an additional 12 weeks of PEG/Riba (24 weeks total)</td>
</tr>
<tr>
<td>Prior non-responders</td>
<td>12 weeks of simeprevir in combination with PEG/Riba followed by an additional 36 weeks of PEG/Riba (48 weeks total)</td>
</tr>
</tbody>
</table>
Sofosbuvir

- HCV-specific polymerase inhibitor
  - Potent pan-genotypic antiviral activity against HCV GT1–6
  - High barrier to resistance
  - Used in combination with PEG/Riba for G1,4,5,6
- Dose
  - Once daily, oral, 400 mg tablet

Sofosbuvir (continued)

- Used in combination with Riba for G2,3
- Favorable clinical pharmacology profile
  - No food effect
  - No clinically significant drug interactions
- Generally safe and well-tolerated in clinical studies to date (>2,000 patients)
  - No safety signal in preclinical/clinical studies

SVR 12 Across Treatment-naïve Patients Genotypes 1, 2, 3, 4, 5, 6

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR 12 (%)</th>
</tr>
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<tbody>
<tr>
<td>GT 1</td>
<td>89%</td>
</tr>
<tr>
<td>GT 2</td>
<td>97%</td>
</tr>
<tr>
<td>GT 3</td>
<td>93%</td>
</tr>
<tr>
<td>GT 4</td>
<td>96%</td>
</tr>
<tr>
<td>GT 5/6</td>
<td>100%</td>
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</table>

Patients with HCV RNA < LLOQ (%)

- GT 1: NEUTRINO SOF + Peg-IFN + RBV x12 weeks
- GT 2: FISSION & VALENCE SOF + RBV x12 weeks
- GT 3: VALENCE SOF + RBV x24 weeks
- GT 4: NEUTRINO SOF + Peg-IFN + RBV x12 weeks
- GT 5/6: NEUTRINO SOF + Peg-IFN + RBV x12 weeks

SVR Rates in Patients With HCV

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6 mo</th>
<th>IFN 12 mo</th>
<th>IFN/RBV 6 mo</th>
<th>IFN/RBV 12 mo</th>
<th>PEG-IFN 12 mo</th>
<th>PEG-IFN/RBV 12 mo</th>
<th>PI/PEG-IFN/RBV 6-12 mo</th>
<th>SOF/PEG-IFN 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>6</td>
<td>16</td>
<td>34</td>
<td>42</td>
<td>39</td>
<td>54-56</td>
<td>68-75</td>
<td>80-81†</td>
</tr>
<tr>
<td>1998</td>
<td>6-12 mo</td>
<td>80-81</td>
<td>12 mo</td>
<td>6-12 mo</td>
<td>3 mo</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Year of presentation of QUEST-1, QUEST-2, and NEUTRINO
†SVR12 rate of 80-81% among GT 1 patients in the Phase 3 studies QUEST-1 and QUEST-2 (24-48 weeks of SMV+PEG-IFN-RBV)
‡SVR12 rate of 90% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN-RBV)


Sofosbuvir/ Ledipasvir (Harvoni®)

- Fixed-dose drug combination
  - Sofosbuvir 400 mg/ledipasvir 90 mg
- An all oral, interferon and ribavirin free regimen for the management of genotype 1 Hepatitis C

Dosage and Administration

The recommended dosage of ledipasvir/sofosbuvir (HARVONI®) for adults is one tablet taken orally once daily with or without food.

**RECOMMENDED REGIMEN AND TREATMENT DURATION IN GT1 CHC PATIENTS**

- Treatment naïve patients with or without cirrhosis: 12 weeks* (HARVONI® for 8 weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than 6 million international units/mL)
- Treatment naïve patients with cirrhosis: 24 weeks
- Treatment experienced patients who have failed treatment with other peginterferon (Peg-IFN) + RBV or an HCV protease inhibitor (PI) + Peg-IFN + RBV:
  - 12 weeks

*No dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR]<30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite
Mechanism of Action

- A fixed-dose combination of ledipasvir and sofosbuvir which are direct-acting antiviral agents against the hepatitis C virus.

Sofosbuvir
An inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication.

Ledipasvir
An inhibitor of the HCV NS5A protein, which is required for viral replication.

Ledipasvir/Sofosbuvir (HARVONI®) in Treatment-naïve, GT1 CHC Adults with or without Compensated Cirrhosis

ION-1 SVR12 by Cirrhosis Status

- SVR12, %
  - 99% 176/177
  - 94% 32/34

Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir (Viekira Pak™)

- Combination regimen
  - Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg combination tablet
    - 1 pill every morning
  - Dasabuvir 250 mg tablet BID
    - With or without ribavirin
- 97% cure rate

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Daclatasvir

- Direct-acting HCV specific antiviral
- 60 mg for 12 weeks
  - Dose can be adjusted for concomitant use of CYP3A inhibitors/ moderate enhancers
  - Contraindicated with severe CYP3A enhancers
- Used with sofosbuvir with or without ribavirin for treatment of Genotype 1 and 3 HCV

Elbasvir/Grazoprevir (Zepatier®)

- Elbasvir 50 mg/grazoprevir 100 mg
  - 1 pill daily with or without ribavirin for 12–16 weeks for genotype 1 and genotype 4 HCV
- Special issues
  - Must check for viral resistance
Current Management of Hepatitis C

- Frequently changing guidelines
- [www.aasld.org](http://www.aasld.org)
  - Click on "Practice guidelines"
  - Click on "See all guidelines"
  - Click on "Hepatitis C guidance"

Genotype 1a Treatment Naïve

- Elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks in noncirrhotics and those with compensated cirrhosis and in whom no baseline resistance for elbasvir are detected.

Genotype 1a Treatment Naïve (continued)

- Elbasvir (50 mg)/grazoprevir (100 mg) with weight based ribavirin for 16 weeks in noncirrhotics and those with compensated cirrhosis and in whom baseline resistance for elbasvir are detected.
Genotype 1a Treatment Naïve
(continued)
• Ledipasvir/sofosbuvir (HARVONI 
  – 1 pill daily for 12 weeks
• Dasabuvir/ombitasvir/paritaprevir/
  ritonavir (Viekira Pak™) + weight based ribavirin for
  – 12 weeks (noncirrhotic), 24 weeks (cirrhotic)
• Sofosbuvir and simeprevir +/− ribavirin for
  – 12 weeks (noncirrhotic), 24 weeks (cirrhotic)

Genotype 1a Treatment Naïve
(continued)
• Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)
  for 12 weeks (noncirrhotic).
• 24 weeks +/− ribavirin for compensated cirrhotics

Genotype 1b Treatment Naïve
• Elbasvir (50 mg)/grazoprevir (100 mg) for 12
  weeks in noncirrhotics and those with
  compensated cirrhosis.
• Daily daclatasvir (60 mg) plus sofosbuvir (400
  mg) for 12 weeks (noncirrhotic). 24 weeks +/−
  ribavirin for compensated cirrhotics
Genotype 1b Treatment Naïve (continued)
• Ledipasvir/sofosbuvir (HARVONI®)
  – 1 pill daily for 12 weeks
• Dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira Pak™) for
  – 12 weeks (noncirrhotic), add ribavirin if cirrhotic
• Sofosbuvir and simeprevir for
  – 12 weeks (noncirrhotic), 24 weeks (cirrhotic)

Genotype 2 Treatment Naïve
• Sofosbuvir and ribavirin for
  – 12 weeks (noncirrhotic), 16–24 weeks (cirrhotic)
• Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for
  – 12 weeks (noncirrhotic), 16–24 weeks (cirrhotic) for those who are not eligible to receive RBV.

Genotype 3 Treatment Naïve
• Sofosbuvir 400 mg and daclatasvir 60 mg for 12 weeks (24 weeks +/- ribavirin)
• Sofosbuvir 400 mg and weight based ribavirin with weekly pegylated interferon for 12 weeks (noncirrhotic and those with compensated cirrhosis)
Genotype 1a Treatment Experienced

- Elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks in noncirrhotics and those with compensated cirrhosis and in whom no baseline resistance for elbasvir are detected.

Genotype 1a Treatment Experienced (continued)

- Elbasvir (50 mg)/grazoprevir (100 mg) with weight based ribavirin for 16 weeks in noncirrhotics and those with compensated cirrhosis and in whom baseline resistance for elbasvir are detected.

Genotype 1a Treatment Experienced (continued)

- Ledipasvir/sofosbuvir (HARVONI®) – 1 pill daily for 12 weeks (noncirrhotic), 24 weeks (cirrhotic)
- Ledipasvir/sofosbuvir (HARVONI®) + ribavirin for 12 weeks (cirrhotic)
- Dasabuvir/ombitasvir/paritaprevir/ ritonavir (Viekira Pak™) + weight based ribavirin for – 12 weeks (noncirrhotic), 24 weeks (cirrhotic)
Genotype 1a Treatment Experienced (continued)

• Sofosbuvir and simeprevir +/- ribavirin for
  – 12 weeks (noncirrhotic),
  24 weeks (cirrhotic)
• Daclatasvir and sofosbuvir for 12 weeks
  (noncirrhotics) +/- ribavirin for 24 weeks
  (compensated cirrhotics)

Genotype 1b Treatment Experienced

• Elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks in noncirrhotics and those with
  compensated cirrhosis and in whom no baseline resistance for elbasvir are detected.

Genotype 1b Treatment Experienced (continued)

• Elbasvir (50 mg)/grazoprevir (100 mg) with weight based ribavirin for 16 weeks in
  noncirrhotics and those with compensated cirrhosis and in whom baseline resistance for
  elbasvir are detected.
Genotype 1b Treatment Experienced (continued)

- Ledipasvir/sofosbuvir (HARVONI®)
  - 1 pill daily for 12 weeks (24 weeks for cirrhotics, add ribavirin for 12 weeks)
- Dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira Pak™) for
  - 12 weeks

Genotype 1b Treatment Experienced (continued)

- Sofosbuvir and simeprevir +/- ribavirin for
  - 12 weeks (noncirrhotic), 24 weeks (cirrhotic)
- Daclatasvir and sofosbuvir for 12 weeks (noncirrhotics) +/- ribavirin for 24 weeks (compensated cirrhotics)

Genotype 1 Treatment Experienced

- For additional recommendations for retreatment of genotype 1 patients based on previous regimen failures, please refer to the Hepatitis C treatment guidelines on the AASLD website: [www.aasld.org](http://www.aasld.org)
Genotype 2 Treatment Experienced

- Sofosbuvir and ribavirin for 12 weeks (noncirrhotic), 16–24 weeks (cirrhotic)
- Sofosbuvir and daclatasvir plus weekly pegylated interferon for 12 weeks (16–24 weeks if cirrhotic)

Genotype 2 Treatment Experienced (continued)

- For additional recommendations for retreatment of genotype 1 patients based on previous regimen failures, please refer to the Hepatitis C treatment guidelines on the AASLD website: [www.aasld.org](http://www.aasld.org)

Genotype 3 Treatment Experienced

- Daclatasvir and sofosbuvir for 12 weeks (+ ribavin for 24 weeks for cirrhosis)
- Sofosbuvir and ribavirin with weekly pegylated interferon for 12 weeks
Genotype 3 Treatment Experienced (continued)

• For additional recommendations for retreatment of genotype 1 patients based on previous regimen failures, please refer to the Hepatitis C treatment guidelines on the AASLD website: www.aasld.org

Additional Measures to Consider in the Management of Chronic Hepatitis C

• Hepatoma screening
  – Cirrhotic or chronic hepatitis B
  • Ultrasound and alpha-fetoprotein? q 6 months
  • Continue to screen cirrhotics even after they are cured of their Hepatitis C.
• Alcohol avoidance
• Weight reduction

Additional Measures to Consider in the Management of Chronic Hepatitis C (continued)

• Nonalcoholic fatty liver disease can worsen fibrosis in those with Hepatitis C
• There are no contraindications to treating those who are actively using drugs or alcohol but each patient must be considered individually
Case Study

• MS is a 52-year-old male who received a blood transfusion in 1972.
• He has applied for life insurance and a hepatitis C antibody has been found to be positive.
  – What % chance does he have of having hepatitis C?
  – What test would confirm the diagnosis?

Case Study (continued)

• A hepatitis C RNA study confirms the presence of hepatitis C
  – What tests would determine how much damage has occurred in his liver?
  – What test would determine course and duration of treatment?
Case Study (continued)

• Blood work indicated genotype 1a hepatitis C
• Liver biopsy indicates stage 3 of 4 fibrosis
• What now?

Case Study (continued)

• He is treated with a course of antivirals and had no evidence of hepatitis C upon completion of treatment.
  — At what point will he be considered to be cured?
  — If cured is he immune to hepatitis C?

Questions?
End of Presentation
Thank you for your time and attention.
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