Hepatitis C for Internists – What’s New?

March 3, 2016

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No commercial or other conflicts of interest
What’s New with Hepatitis C

Objectives

• Brief review of epidemiology, populations affected, course of disease, HCV testing;
• Overview of candidate patients for treatment with new agents, pre-therapy assessments;
• Review of direct acting antivirals (DAA), drug resistance, adverse drug reactions during therapy;
• Overview of Case studies and success of therapy options;
• Brief synopsis about testing for Resistance-Associated Variants (RAVs) and drug interactions;
• Brief comments about monitoring during and after therapy and special populations.
Primary Causes of Chronic Liver Disease*

- Hepatitis C Virus (26%)
- Alcohol (24%)
- Unknown (17%)
- Other (5%)
- Hepatitis B Virus (11%)
- Hepatitis B Virus and Alcohol (3%)

*Jefferson County, Alabama, USA
The Phylogeny of the 6 Major HCV Genotypes
Natural History of HCV Infection

- Exposure (Acute Phase)
  - 15% (15) Resolved
  - 85% (85) Chronic
    - 80% (68) Stable
    - 20% (17) Cirrhosis
      - 75% (13) Slowly Progressive
      - 25% (4) HCC
- HIV and Alcohol
  - Transplant Death
Natural History of HCV Infection

- Exposure (Acute Phase)
  - 15% (15)
- Resolved
  - 90-100%
- Stable
- Chronic
  - 85% (85)
  - 80% (68)
- Cirrhosis
  - 20% (17)
  - 75% (13)
- Slowly Progressive
- HCC Transplant Death
  - 25% (4)

Factors:
- HIV and Alcohol
Scheme of Typical Laboratory Features During Acute Hepatitis C Progressing to Chronicity


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Extrahepatic Manifestations of Chronic Hepatitis C Virus Infection

- Lethargy
- Arthralgias (23%), myalgias (15%)
- Membranous glomerulonephritis with HTN
- Cutaneous vasculitis
- Pruritis (15%)
- Porphyria cutanea tarda
- Cryoglobulininemia

MMWR, Recommendations and Reports August 17, 2012 ;61(RR04):1-18
Projected Incidence of HCV-Related Sequelaes: USA, 1950-2030

Who should be tested for HCV infection?

HCV testing is recommended for anyone at increased risk for HCV infection, including:

Persons born from 1945 through 1965,

Persons who have ever injected or intranasally inhaled illegal drugs, including those who injected only once many years ago,

Recipients of clotting factor concentrates made before 1987,

Recipients of blood transfusions or solid organ transplants before July 1992,

Patients who have ever received long-term hemodialysis treatment,

Persons with known exposures to HCV, such as
  - health care workers after needlesticks involving HCV-positive blood,
  - recipients of blood or organs from a donor who later tested HCV-positive,

All persons with HIV-1 infection,

Patients with signs or symptoms of liver disease (e.g., abnormal serum enzyme tests),

Children born to HCV-positive mothers (to avoid detecting maternal antibody, these children should not be tested before age 18 months), and

Persons who were ever incarcerated.

CDC; ASSLD and IDSA, October, 2016
CDC Recommended Testing Sequence for Identifying Current HCV Infection

Recommendations for Counseling Those with Current (Active) HCV Infection

Persons with **current (active) HCV infection** should receive education and interventions aimed at **reducing progression** of liver disease and **preventing transmission** of HCV.

**Abstinence from alcohol** and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.

**Immunization against pneumococcal infection** is recommended to all patients with cirrhosis.

All persons with HCV infection should be provided **education on how to avoid HCV transmission** to others.
Measures to Prevent Transmission of HCV

Persons with HCV infection should be counseled:

• to **avoid sharing toothbrushes and dental or shaving equipment**, and be cautioned to **cover any bleeding wound** to prevent the possibility of others coming into contact with their blood.

• to **stop using illicit drugs** and enter substance abuse treatment.

• **not to donate blood**

• to **use barrier precautions to prevent sexual transmission**

• **Household surfaces and implements contaminated with visible blood** from an HCV-infected person should be cleaned using a dilution of **1 part household bleach to 9 parts water**. **Gloves** should be worn when cleaning up blood spills.
Chronic Hepatitis C – Assessment

- **HCV quantitative real time PCR** (positive twice within 6 months) and **genotype**
- Thorough medical and psychiatric history
- Substance abuse history
- CBC, CMP, PT (INR), test for pregnancy
- TSH, **AFP, HIV-1 antibody, HBsAg, HBsAb, HBcAb, HAV Ab**
- Immunization for HBV and HAV if the patient is seronegative.
- **FibroSure, liver biopsy, (? IL28B gene polymorphism) and Q80K gene** (if simemprevir is to be used for HCV genotype 1a)
Noninvasive Tests for Hepatic Fibrosis

- **FibroSURE:**
  - FibroTest
  - $\alpha_2$-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, gamma glutamyl transpeptidase (GGT);

- **Acti-Test**
  - $\alpha_2$-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT
  - 66% sensitive, 92% specific

- **Transient elastography**

Scoring of FibroSure Test

Metavir scale /Fibrosis Stage (FibroTest)

• F0 - No fibrosis 0.00 - 0.21
• F0 - F1 0.21 - 0.27
• F1 - Portal fibrosis 0.27 - 0.31
• F1 - F2 0.31 - 0.48
• F2 - Bridging fibrosis with few septa 0.48 - 0.58
• F3 - Bridging fibrosis with many septa 0.58 - 0.72
• F3 - F4 0.72 - 0.74
• F4 - Cirrhosis 0.74 - 1.00

Activity/Necroinflammatory Grade (ActiTest)

• A0 - No activity 0.00 - 0.17
• A0 - A1 0.17 - 0.29
• A1 - Minimal activity 0.29 - 0.36
• A1 - A2 0.36 - 0.52
• A2 - Moderate activity 0.52 - 0.60
• A2 - A3 0.60 - 0.63
• A3 - Severe activity 0.63 - 1.00
Hepatic Transient Elastography

Fibroscan:

a: Fibroscan instrument;
b: Fibroscan probe;
c: diagram summarizing the principle of a measurement;
d: example of result produced by the device
Summary of Recommendations for When and in Whom to Initiate HCV Therapy

**Goal of Treatment**
The goal of treatment of HCV-infected persons is to **reduce all-cause mortality and liver-related health adverse consequences**, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (**SVR**).

**Recommendations for When and in Whom to Initiate Treatment**
Treatment is recommended for **all patients with chronic HCV infection**, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.
Benefits of Treatment and Cure of Hepatitis C Infection

• **Decrease of hepatic inflammation**, reflected by reduced AST, ALT;

• **Reduction of progression and reversal of hepatic fibrosis and necrosis** (39 to 73% of patients) and possible **cirrhosis resolution** (50% of patients);

• **Improvement of splenomegaly, portal hypertension, and a 90% reduction of hepatocellular carcinoma and liver-related deaths.**
Benefits of Treatment and Cure of Hepatitis C Infection (cont’d.)

• Reduction of symptoms and mortality/increased survival from extrahepatic manifestations of HCV infection, including fatigue, Porphyria Cutanea Tarda, cryoglobulinemia, lymphoproliferative disorders;
• Improved markers of insulin resistance and reduced incidence of type 2 diabetes mellitus;
• Decreased HCV transmission leads to Public Health benefits;
• Improved quality of life (physical, social, emotional)

Hepatitis C Virus Life Cycle

1. Receptor-virus binding
2. Endocytosis
3. Fusion and uncoating
4. Polyprotein processing

5. Cleavage
6. Formation of viral replication complex
7. Viral RNA replication
8. Assembly of progeny virions
9. Release

**NS5B** - Site of action of sofosbuvir, dasabuvir

**NS3/4a** - Site of action of (telaprevir, boceprevir), simeprevir, paritaprevir, grazoprevir, (asunaprevir, faldaprevir)

**NS5A** - Site of action of daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir
<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic name(s)</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victrelis</td>
<td>Boceprevir (now discontinued in the US)</td>
<td>May 13, 2011</td>
</tr>
<tr>
<td>Incivek</td>
<td>Telaprevir (production discontinued 8/12/2014)</td>
<td>May 23, 2011</td>
</tr>
<tr>
<td>Olysio</td>
<td>Simeprevir</td>
<td>November 24, 2013</td>
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<tr>
<td>Sovaldi</td>
<td>Sofosbuvir</td>
<td>December 6, 2013</td>
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<tr>
<td>Harvoni</td>
<td>Ledipasvir, Sofosbuvir</td>
<td>October 10, 2014</td>
</tr>
<tr>
<td>Viekira Pak</td>
<td>Ombitasvir, paritaprevir/ritonavir with dasabuvir</td>
<td>December 19, 2014</td>
</tr>
<tr>
<td>Technivie</td>
<td>Ombitasvir, paritaprevir/ritonavir</td>
<td>July 24, 2015</td>
</tr>
<tr>
<td>Daklinza</td>
<td>Daclatasvir</td>
<td>July 24, 2015</td>
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<tr>
<td>Zepatier</td>
<td>Elbasvir, grazoprevir</td>
<td>January 28, 2016</td>
</tr>
<tr>
<td>Epclusa</td>
<td>Sofosbuvir, Velpatasvir</td>
<td>June 28, 2016</td>
</tr>
</tbody>
</table>

Schering-Plough/Vertex J&J/ Janssen/ Gilead// AbbVie// BMS/ Merck/ Gilead
Patterns of HCV RNA Response to 48 Weeks of Interferon and Ribavirin Therapy for Chronic Hepatitis C

A graph showing the Log_{10} HCV RNA level in IU/mL over weeks, with response types including Non, Rapid, Early, and Incomplete. The assay limit is indicated by a horizontal dashed line.
Interpretation of Virologic Response of HCV RNA during Antiviral Therapy

LLOQ/BLOQ - lower/below limit of quantification; LOD/BLOD - below/limit of detection; TND - target not detected.

Clin Liver Dis 2013; 17: 27-45
Comments about Agents for Hepatitis C

• Interferon α-2a and α-2b, and Pegalated forms of each (augments the immune system)

• Ribavirin (uncertain mechanism of action)

• **Protease (NS3/4a)** inhibitors – simeprevir, paritaprevir, grazoprevir - are generally genotype specific (genotype 1 - boceprevir, telaprevir; simeprevir has broader activity);

• **Polymerase (NS5B)** inhibitors – sofosbuvir, dasabuvir;

• **Replication complex (NS5A)** inhibitors – daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir - along with NS5B inhibitors, these DAAs have broader genotype activity

Antiviral Research 2013; 99:12–17
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved for</th>
<th>Prescribed with</th>
<th>Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epclusa</strong> (sofosbuvir + velpatasvir)</td>
<td>genotypes 1, 2, 3, 4, 5, and 6 with or without cirrhosis</td>
<td>ribavirin in cases of decompensated cirrhosis and without ribavirin in all other cases</td>
<td>one tablet daily with or without food</td>
<td>12-16 weeks</td>
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<tr>
<td><strong>Zepatier</strong> (elbasvir + grazoprevir)</td>
<td>genotypes 1 and 4 with or without cirrhosis</td>
<td>with or without ribavirin, depending on genotype and treatment history</td>
<td>one tablet daily with or without food</td>
<td>12-16 weeks</td>
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<tr>
<td><strong>Daklinza</strong> (daclatasvir)</td>
<td>genotype 3 without cirrhosis</td>
<td>Sovaldi (sofosbuvir)</td>
<td>one tablet daily with food</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Technivie</strong> (ombitasvir + paritaprevir + ritonavir)</td>
<td>genotype 4 without cirrhosis</td>
<td>ribavirin</td>
<td>two tablets daily with food</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Viekira Pak</strong> (ombitasvir + paritaprevir + ritonavir, co-packaged with dasabuvir)</td>
<td>genotype 1 with or without cirrhosis</td>
<td>ribavirin or taken on its own, where indicated</td>
<td>two tablets of ombitasvir + paritaprevir + ritonavir taken once daily with food, plus one tablet of dasabuvir taken twice daily with food</td>
<td>12-24 weeks</td>
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<tr>
<td><strong>Harvoni</strong> (sofosbuvir + ledipasvir)</td>
<td>genotype 1 with or without cirrhosis</td>
<td>taken on its own</td>
<td>one tablet daily with or without food</td>
<td>12-24 weeks</td>
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<tr>
<td><strong>Sovaldi</strong> (sofosbuvir)</td>
<td>genotypes 1, 2, 3 and 4 with cirrhosis, including those with cirrhosis or hepatocellular carcinoma (HCC)</td>
<td>Peg-interferon + ribavirin, ribavirin alone, or Olysio (simeprevir) with or without ribavirin, where indicated</td>
<td>one tablet daily with or without food</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td><strong>Olysio</strong> (simeprevir)</td>
<td>genotype 1 with or without cirrhosis</td>
<td>peginterferon + ribavirin, or Sovaldi (sofosbuvir), where indicated</td>
<td>one capsule daily with food</td>
<td>24-48 weeks</td>
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## Comparison of DAAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>PI: 1st Generation</th>
<th>PI: 2nd Generation</th>
<th>NS5A Inhibitors</th>
<th>NS5B Nucleoside Inhibitor</th>
<th>NS5B Non-nucleoside Inhibitor</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Boceprevir</td>
<td>Simeprevir</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
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<td></td>
<td>Telaprevir</td>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
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<td>Grazoprevir</td>
<td>Daclatasvir</td>
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<td>Elbasvir</td>
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<td>Valpatasvir</td>
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<td>Efficacy</td>
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<td><img src="#" alt="Average profile" /></td>
<td><img src="#" alt="Good profile" /></td>
<td><img src="#" alt="Good profile" /></td>
<td><img src="#" alt="Average profile" /></td>
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<td>Resistance</td>
<td><img src="#" alt="Least favorable profile" /></td>
<td><img src="#" alt="Average profile" /></td>
<td><img src="#" alt="Good profile" /></td>
<td><img src="#" alt="Good profile" /></td>
<td><img src="#" alt="Least favorable profile" /></td>
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<td>Pangentotypic Efficacy</td>
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<td>Drug Interactions</td>
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<td><img src="#" alt="Good profile" /></td>
<td><img src="#" alt="Least favorable profile" /></td>
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- **Good profile**: Green circle
- **Average profile**: Yellow circle
- **Least favorable profile**: Red circle
## Adverse Drug Reactions > 5%

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<tr>
<th>Adverse Drug Reaction</th>
<th>VAL/SOF N=1035</th>
<th>Placebo N=166</th>
<th>GRZ/ELB</th>
<th>SIM+SOF</th>
<th>LED/SOF</th>
<th>DAS/OMB/PAR/rit N=401</th>
<th>DAC+SOF</th>
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<td>7</td>
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<td>Fatigue</td>
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<td>11</td>
<td>25</td>
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<td>Headache</td>
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<td>Insomnia</td>
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<td>14</td>
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<td>Nausea</td>
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<td>14</td>
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</table>
Selection of Treatment Regimen

Consider the following:

- Genotype
- History of prior treatment (naïve vs. experienced)
- Stage of fibrosis
- Adverse effect profile
- Drug interactions
- Duration of therapy
- Cost
Patient #1: 54 YO woman CW

- CW was diagnosed in 2004 with Chronic Active Hepatitis C. In 1992 she had surgery at an outpatient surgical center in Richmond. After the surgery, CW later developed symptoms associated with acute liver disease. After a lengthy investigation, the source of the infection was discovered, a scrub tech with HCV infection who used intravenous drugs and the same syringe used by the anesthesiologist for CW’s surgical anesthesia.

- After having been diagnosed through blood tests, CW then had a liver biopsy and was informed that she had chronic active hepatitis C with liver damage already evident. In addition, she was diagnosed with hypothyroidism and vitiligo, both on an autoimmune basis. She was tested for HIV-1 infection and Autoimmune Hepatitis, both of which returned negative. CW related that having autoimmune disorder and genotype 1 were felt by her PCP and consultants to have made Hep C more challenging to treat.

- Related to religious beliefs and the predicted side effects of available therapy, CW has deferred treatment up to the present.

- CW now presents to your office as a new patient desiring to reconsider therapy. She has Hepatitis C virus genotype 1a.
**Genotype 1a Treatment-Naïve Patients Without Cirrhosis**

Daily fixed-dose combination of **elbasvir** (50 mg)/**grazoprevir** (100 mg) (Zepatier) for 12 weeks is a Recommended regimen for patients in whom no baseline NS5A RAVs§ for elbasvir are detected (SVR12 = 92% for GT-1a and 99% for GT-1b without cirrhosis; SVR=97% with cirrhosis.).

Daily fixed-dose combination of **ledipasvir** (90 mg)/**sofosbuvir** (400 mg) (Harvoni) for 12 weeks (SVR12 = 97-99% without or with cirrhosis)

Daily fixed-dose combination of **paritaprevir** (150 mg)/**ritonavir** (100 mg)/**ombitasvir** (25 mg) plus twice-daily dosed **dasabuvir** (250 mg) (Viekira Pak) with weight-based **ribavirin** for 12 weeks (SVR12 = 95-97% for GT-1)

Daily **simeprevir** (150 mg; Olysio) plus **sofosbuvir** (400 mg; Sovaldi) for 12 weeks (SVR12 = 97% for GT-1a and 1b, regardless of Q80K resistance mutation to simeprevir)

Daily fixed-dose combination of **sofosbuvir** (400 mg)/**velpatasvir** (100 mg) for 12 weeks (Epclusa) (SVR12 = 98-99% with or without cirrhosis, regardless of presence of RAVs)

Daily **daclatasvir** (60 mg*; Daklinza) plus **sofosbuvir** (400 mg; Sovaldi) for 12 weeks (SVR12 = 96%)
Patient #2: 37 YO woman JW

- **JW is a 37 YO woman living in Alexandria.** When JW was 18 years of age she suffered a series of tragic events in her life which led to her trying heroin for the first time.
- During several years of using heroin on and off, she apparently contracted hepatitis C from her boyfriend who had introduced her to heroin.
- She stopped using the drugs when she was 20. For the next 12 years, while wanting to beat the virus, JW worked hard and lived a good life, but was also in denial of having the virus. Over these ten years JW started to feel the effects of hepatitis C, mainly fatigue.
- When she was in my early 30s, 13 years after contracting hepatitis C, JW finally had the support needed from a loving partner and an opportunity to beat the virus.
- In 2011 JW was accepted onto a drug trial. For the next six winter months she took interferon and ribavirin, along with a new protease inhibitor. The treatment made her very tired. While she was on the trial, her memory improved but she had a body rash and trouble sleeping.
- JW was fortunate while she was on the trial because she tested negative for the virus from week four and through the trial; she was able to stop treatment at six months. However, her HCV relapsed at 6 months after completion of therapy.
- GW has HCV **genotype 1b**; she has had a recent liver biopsy and it revealed grade 2 inflammation, stage 1 scaring.
Genotype 1 HCV - Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin
Treatment-Experienced Patients Without Cirrhosis

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (*Harvoni*) for 12 weeks (SVR12 = 94%)

Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) (*Epclusa*) for 12 weeks (SVR12 = 100% for GT-1a and 96.9% for GT-1b)

Daily daclatasvir (60 mg*; *Daklinza*) plus sofosbuvir (400 mg; *Sovaldi*) for 12 weeks (SVR12 = 98%)

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) (*Zepatier*) with weight-based ribavirin for 12 weeks. Genotype 1a patients who have baseline NS5A RAVs§ for elbasvir should have this treatment extended to 16 weeks. (SVR12 = 96% without NS5A RAV for elbasvir);
GM is a 56 year-old business development adviser living in Fairfax. Unexpectedly one evening in 1996 he received a call from his health provider telling him he had hepatitis C. He had given blood recently and they had detected the virus in his blood.

GM is married with two sons, now aged 18 and 24. He said that having hepatitis C made him worry if he would be around to see his kids grow up.

He has no idea how he contracted hepatitis C, but says he started showing symptoms when he was just 21-years-old. He had spent some time in the UK and was injured there. The hospital staff were very busy. He suspects that they used dirty instruments. He does recall while he was in the UK being very ill and turning yellow.

He also could have contracted hepatitis C when I worked in the prison service but he really has no idea. In more recent years subtle symptoms have surfaced. He often had trouble concentrating and says he would lose his train of thought. He would often feel really tired.

About 15 years ago he had the opportunity to receive interferon treatment. He declined the treatment after speaking to a chemist about the side-effects and the probability that he might not be cured.

Over the last 20 years has had several liver biopsies and developed mild fibrosis in his liver. He credits a healthy lifestyle for keeping the virus at bay. No alcohol and eating well. GM has HCV genotype 2.
Daily fixed-dose combination of **sofosbuvir** (400 mg)/**velpatasvir** (100 mg) (**Epclusa**) for 12 weeks (SVR12 = 99%)

**Genotype 2 Treatment-Naïve Patients Without Cirrhosis - Alternative**

Daily **daclatasvir** (60 mg*; **Daklinza**) plus **sofosbuvir** (400 mg; **Sovaldi**) for 12 weeks (SVR12 = 93%)
Is the Genotype 3 of the Hepatitis C Virus the New Villain?

Goossens N, Negro F

**Conclusion**: Hepatitis C genotype 3 is associated with more frequent and advanced steatosis than other Hepatitis C genotypes.
Case Study #4: 41 YO woman JG

JG has been fighting Hepatitis C virus for over 30 years, having been infected through blood transfusions during open heart surgery when she was 8 years old. She was diagnosed in 2003 and by biopsy she was told that she was stage 3 fibrosis.

JG was initially treated on a clinical trial for six months and the end result was that she was a non-responder. She then immediately switched to another trial which was available (daily interferon and ribavirin) and, while she was on the treatment, she cleared the virus. Unfortunately, after a year JG relapsed. Even though the doctors were not hopeful, JH decided to give the same treatment one more try. Unfortunately, she again did not respond to the treatment.

JG is hoping that the new oral treatments now available will be a success since she may have little time to wait. Her HCV is genotype 3.
Genotype 3: PEG-IFN/Ribavirin Treatment—Experienced Patients Without Cirrhosis

Daily daclatasvir (60 mg; Daklinza) plus sofosbuvir (400 mg; Sovaldi) for 12 weeks.¶
(SVR12 = 94%)

Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) (Epclusa) for 12 weeks ¶.

¶ RAV testing for Y93H is recommended and ribavirin should be included in regimen if present.
When to Test for Resistance-Associated Variants (RAVs) of HCV **Genotype 1**

- When use of daily fixed-dose combination of **elbasvir/grazoprevir (Zepatier)** is chosen for HCV **genotype 1a** infection - test for **NS5A resistance variants**;

- When shortening therapy to 8 weeks is considered for **ledipasvir/sofosbuvir** instead of 12 weeks for GT-1 infection - test for **IL28B polymorphism CT or TT**;

- Test for **Q80K NS3 mutation** when considering use of **simeprevir/sofosbuvir** for treatment naïve GT-1a patients (with cirrhosis);

When to Test for Resistance-Associated Variants (RAVs) of HCV **Genotype 1** (cont’d.)

- for those patients whose prior treatment regimen containing an NS5A inhibitor failed, testing for RAVs that confer decreased susceptibility to NS3 protease inhibitors (e.g. Q80K) and to NS5A inhibitors should be performed using commercially available assays
- Other circumstances according to guidelines.
Testing for Resistance-Associated Variants (RAVs) of HCV

• In the future resistance testing may become essential for treatment failures following multiple DAA regimens (Monogram, Quest);

• To avoid such problems,
  - choose a correct regimen the first time,
  - assure patient compliance during therapy, and
  - avoid drug-drug interactions.
### Concomitant Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Daclatasvir</th>
<th>Ledipasvir</th>
<th>Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir</th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Elbasvir / Grazoprevir</th>
<th>Velpatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-reducing agents*</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Alfaosin/tamsulosin</td>
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<td>X</td>
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<tr>
<td>Antidystrophic agents**</td>
<td>X**</td>
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<tr>
<td>Antiretrovirals*</td>
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<tr>
<td>Azole antifungals*</td>
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<tr>
<td>Buprenorphine/naloxone</td>
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<td>Calcineurin inhibitors*</td>
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<tr>
<td>Calcium channel blockers*</td>
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<tr>
<td>Cisapride</td>
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<td>Ergot derivatives</td>
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<td>Ethyl estradiol-containing products</td>
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<td>Glucocorticoids*</td>
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<td>Herbals</td>
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<tr>
<td>St. John’s wort</td>
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<td>Milk thistle</td>
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<td>HMG-CoA reductase inhibitors (statins)*</td>
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<td>X</td>
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<tr>
<td>Macrolide antimicrobials*</td>
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<td>X</td>
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<tr>
<td>Other antiarrhythmics*</td>
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<td>Phosphodiesterase inhibitors*</td>
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<td>Pimozide</td>
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<tr>
<td>Rifamycin antimicrobials*</td>
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<td>Salmeterol</td>
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<tr>
<td>Sedatives*</td>
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</tbody>
</table>

*AASLD and IDSA - HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C: October, 2016*
**Potentially Significant Acid-reducing Drug Interactions with Epclusa and Harvoni**

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration</th>
<th>Clinical Effect - Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acid Reducing Agents:</strong></td>
<td>↓ velpatasvir, ledipasvir</td>
<td>Velpatasvir and ledipasvir solubility decrease as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir and ledipasvir.</td>
</tr>
<tr>
<td><strong>Antacids (e.g., aluminum and magnesium hydroxide)</strong></td>
<td></td>
<td>Separate antacid and Epclusa/Harvoni administration by 4 hours</td>
</tr>
<tr>
<td><strong>H2-receptor antagonists (e.g., famotidine)</strong></td>
<td></td>
<td>H2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily</td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors (e.g., omeprazole)</strong></td>
<td></td>
<td>Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If necessary to co-administer, Epclusa should be administered with food and taken 4 hours before omeprazole 20 mg. Omeprazole 20 mg or lower can be administered simultaneously with Harvoni under fasted conditions.</td>
</tr>
</tbody>
</table>
Potentially Significant Drug Interactions with Epclusa and Harvoni (cont’d.)

• Coadministration of amiodarone with Epclusa or Harvoni may result in serious symptomatic bradycardia. The mechanism of this effect is unknown.

• Anticonvulsants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine) cause decreased sofosbuvir, ledipasvir and velpatasvir concentrations; co-administration is not recommended.

• Herbal supplements (St. John’s wort) cause decreased sofosbuvir, ledipasvir and velpatasvir concentrations;
Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.

**Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel** are recommended after 4 weeks of treatment and as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).

A 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy. Any increase in ALT of less than 10-fold at week 4 and accompanied by symptoms of weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio, should also prompt discontinuation of therapy. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.
Recommended Monitoring During Antiviral Therapy (cont’d.)

- **Quantitative HCV viral load** testing is recommended after **4 weeks** of therapy and at **12 weeks following completion of therapy**. Antiviral drug therapy should not be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.

- **Quantitative HCV viral load** testing can be considered at the **end of treatment** and **24 weeks or longer following the completion of therapy**.

- For **HBsAg+ patients** who are not already on HBV suppressive therapy, monitoring of **HBV DNA levels** during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met.
**Recommended Follow-up for Patients Who Achieve a Sustained Virologic Response (SVR)**

For patients who *do not have advanced fibrosis* (i.e., those with Metavir stage F0-F2), recommended follow-up is *the same as if they were never infected* with HCV.

Assessment for HCV recurrence or reinfection is recommended only if the patient has *ongoing risk* for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection.

Surveillance for hepatocellular carcinoma with *twice-yearly ultrasound* examination is recommended for patients with *advanced fibrosis* (i.e., Metavir stage F3 or F4) who achieve an SVR.

A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated.

Assessment of other causes of liver disease is recommended for patients who develop *persistently abnormal liver tests* after achieving an SVR.
Drug Interactions between Antiretrovirals and HCV DAAs in HIV-1/Hepatitis C Virus Coinfected Patients

• The most frequent interactions are between HCV DAAs and ritonavir-boosted and cobicistat-boosted drug regimens;
• Interactions are also seen with efavirenz, rilpivirine, raltegrevir, dolutegrevir, and tenofovir containing regimens;
• General rule is not to change ART and carefully to select appropriate HCV DAA based upon anticipated drug interactions.
HCV Therapy for Special Populations (cont’d.)

- Dosage Adjustments for Patients with Mild, Moderate and Severe Renal Impairment

- Medical Management and Monitoring of patients with Acute HCV Infection

- Treatment for Patients with Acute HCV Infection
“We have an opportunity to make a real dent in the impact of the (chronic Hepatitis C) disease”

Kimberly Page, Epidemiologist,
University of California, San Francisco

Nature 2013; 497: 18–19
Thank you!

Questions?